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# **Development of Feedback Microwave Thermotherapy in Symptomatic Benign Prostatic Hyperplasia**

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## **ABSTRACT**

The purpose of this thesis was to evaluate ProstaLund Feedback Treatment® (PLFT®) and the CoreTherm® device with regard to biophysics, mechanisms of action, treatment indications, additional techniques, efficacy and safety in the treatment of patients with benign prostatic hyperplasia (BPH).

The application of two biophysical equations in the PLFT software is explained. The calculations provide the intraprostatic "blood flow index" and amount of accumulated coagulation necrosis during treatment. The accuracy of the "cell kill" calculations is compared to gadolinium-enhanced magnetic resonance imaging (MRI) and histology. The accumulated "cell kill" monitored on-line during PLFT is considered a useful tool for helping the doctor to tailor the individual "thermal dose" to each patient.

The clinical efficacy, 1 and 5 years after PLFT and Transurethral Resection of the Prostate (TURP), is compared showing no statistically significant differences. Serious adverse events were more frequent after TURP. Expanded treatment indications for PLFT, to including patients with persistent urinary retention and patients with heavily enlarged prostates (>100 g), were studied in a retrospective survey and in a prospective randomized multicentre study comparing PLFT with surgery (TURP and open surgery). Responder rate after PLFT was close to 80% and statistically equivalent to surgery after 6 months. Serious adverse events were less frequent after PLFT.

The intraprostatic blood flow works like a heat sink by transporting heat away from the treatment area during thermotherapy. This is the explanation for the unpredictable outcome and frequent treatment failures described after low-energy transurethral microwave thermotherapy. High-energy TUMT can compensate for this in many ways but results in significant patient discomfort from micturition urge, burning sensations and pain.

A new device, the Schelin Catheter<sup>®</sup>, makes it possible to inject and infiltrate the prostate by the transurethral route. Injections in several locations with local anaesthetics containing epinephrine have a twofold aim: 1) to minimize the intraprostatic blood flow and 2) to achieve good analgesia. Treatment time was reduced by 50% and the total energy required was reduced by 60% when using this technique. The effects of the epinephrine on the intraprostatic blood flow were also verified with positron emission tomography, [<sup>15</sup>O]H<sub>2</sub>O-PET.

The results in this thesis show that the efficacy, safety and methodological improvements of PLFT now make it a challenger to surgery (TURP and open surgery) as a convenient, office based and more available option. This truly minimally invasive treatment is an attractive option for patients that can replace surgery for the majority of patients with clinical BPH. It also reduces the cost to the taxpayer.

## LIST OF ORIGINAL PAPERS:

**I Cell-kill modeling of microwave thermotherapy for treatment of benign prostatic hyperplasia.**

Bolmsjö M, Schelin S, Wagrell L, Larson T, de la Rosette JJ and Mattiasson A.

J Endourol, 14:627-635, 2000

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**II Evaluation of microwave thermotherapy with histopathology, magnetic resonance imaging and temperature mapping.**

Huidobro C, Bolmsjö M, Larson T, de la Rosette JJ, Wagrell L, Schelin S, Gorecki T, and Mattiasson A.

J Urol, 171:672-678, 2004

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**III Feedback microwave thermotherapy versus TURP for clinical BPH – a randomized controlled multicenter study.**

Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, Schain M, Larson T, Boyle E, Duelund J, Krøyer K, Ageheim H and Mattiasson A.

Urology, 60:292-299, 2002

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**IV Microwave thermotherapy in patients with benign prostatic hyperplasia and chronic urinary retention.**

Schelin S.

Eur Urol, 39:400-404, 2001

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- V Mediating transurethral microwave thermotherapy by intraprostatic and periprostatic injections of Mepivacaine Epinephrine: Effects on treatment time, energy consumption and patient comfort.**  
Schelin S.  
J Endourol, 16:117-121, 2002  
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- VI Effects of intraprostatic and periprostatic injections of Mepivacaine Epinephrine on intraprostatic blood flow during transurethral microwave thermotherapy; Correlation with. [<sup>15</sup>O] H<sub>2</sub>O-PET.**  
Schelin S, Claeson A, Sundin A and Wagrell L.  
J Endourol, Vol. 18:965-970. 2004  
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- VII Feedback microwave thermotherapy vs TURP/ prostate enucleation surgery in patients with benign prostatic hyperplasia and persistent urinary retention; a prospective randomized multicenter study.**  
Schelin S, Geertsen U, Walter S, Spångberg A, Duelund-Jacobsen J, Krøyer K, Hjertberg H, Vatne V, Richthoff J and Nordling J.  
Submitted
- VIII Five-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study.**  
Mattiasson A, Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, Schain M, Larson T, Boyle E, Duelund J, Krøyer K, and Ageheim H.  
Submitted

## **ABBREVIATIONS:**

AFM	Anterior fibro-muscular stroma
ASA	American Society of Anesthesiologists
AUA	American Urological Association
AUR	Acute urinary retention
BOO	Bladder outlet obstruction
BNC	Bladder neck catheter
BPH	Benign prostatic hyperplasia
BS	Bother score
CZ	Central zone
DUA	Detrusor under-activity
EAU	European association of urology
EIP	Ethanol injection of the prostate
FDA	Food and drug administration
HE-TUMT	High energy transurethral microwave thermotherapy
HIFU	High intensity focused ultrasound
ILC	Interstitial laser coagulation
IPSS	International prostate symptom score
LA	Local anaesthetic
LE-TUMT	Low energy transurethral microwave thermotherapy
LUTS	Lower urinary tract symptoms
MRI	Magnetic resonance imaging
NSAID	Non-steroid anti-inflammatory drug
OAB	Over-active bladder

PC	Personal computer
PET	Positron emission tomography
PLFT	ProstaLund Feedback Treatment
PSA	Prostate specific antigen
PUR	Persistent urinary retention
PVR	Postvoid residual urine
PZ	Periferal zone
QOL	Quality of life
TRUS	Transrectal ultrasound
TUMT	Transurethral microwave thermotherapy
TUNA	Transurethral needle ablation
TUR	Transurethral resection
TURP	Transurethral resection of the prostate
TZ	Transition zone
UAB	Under-active bladder
UTI	Urinary tract infection
WIT	Water induced thermotherapy

## **INTRODUCTION**

The term, lower urinary tract symptoms (LUTS), was introduced in 1994 by Abrams as a non-organ specific term to replace the previous term “prostatism” (Andersen 1982). LUTS may be used to describe all kinds of symptoms due to lower urinary tract dysfunction - irrespective of its character and origin (Sirls et al 1996). It is necessary to rule out organic disorders such as inflammation, neoplasia and stone diseases with e.g. hematuria, infection and other signs indicating the presence of non-dysfunctional disorders before the term LUTS can be used. Benign prostatic hyperplasia (BPH) is the most common male condition causing LUTS. The aetiology and pathophysiology of BPH is poorly understood. The hyperplasia very often causes an enlargement of the prostate, which can eventually lead to lower urinary tract problems due to bladder outlet obstruction (BOO). BOO can be either restrictive “epithelial” and/or constrictive “stromal” in origin. The result is increased urethral resistance. The increased functional demands on the bladder detrusor muscle, induced by the obstruction, will lead to hypertrophy of the bladder wall as a consequence of the increased bladder pressure. Operations that debulk the prostate and thus relieve the obstruction are the classical treatment for BPH and BOO.

Several new minimally invasive treatments (MIT) have been launched in the last 15 years. They all have been compared with transurethral resection of the prostate (TURP) which for many years has been considered the “golden standard”. Different kinds of laser, transurethral needle ablation (TUNA), high-intensity focused ultrasound (HIFU), water- induced thermotherapy (WIT) and transurethral microwave thermotherapy (TUMT) have all emerged. TUMT is the only one of all these techniques that has been developed continuously and consequently has now been recommended for the treatment of symptomatic BPH in the recent guidelines of the American and European Urological Associations (AUA and EAU, respectively), (Roehrborn et al 2003, de la Rosette et al 2001).

As shown in this thesis feedback TUMT, the ProstaLund Feedback Treatment (PLFT), is now challenging surgery in terms of efficacy, safety and ease of use.

## Background

TUMT was introduced in Europe less than 15 years ago and there was great hope for this new technique as an alternative treatment for BPH and BOO. Soon it proved to be unable to meet the high expectations. Many patients reported symptomatic improvement but no objective response could be registered. At that time it did not replace surgery as had been anticipated by many early adopters. An early TUMT device (Comair AB) was used in 13 patients scheduled for TURP at the clinic in Kalmar. No objective treatment effect was seen in 9 patients, there was obvious improvement in another 2 and serious adverse events were seen in 2 patients. The early TUMT-devices used a fixed treatment time – usually one hour. A temperature sensor in the treatment catheter monitored the catheter temperature, but there were no means to actually measure the temperature in the prostate and thereby tailor the treatment to each individual.

One important observation from the early TUMT was the large variation in treatment outcome; some patients responded quite well, whereas the majority did not and there was no way to predict the outcome. All patients were treated in the same way irrespective of prostate size, shape, tissue composition, vascularity and patient age. To understand the mechanisms involved, we conducted a small test series of cases in 1994 where the intraprostatic temperature was measured by thermosensors inserted by the transperineal route. There were large individual variations in the amount of energy needed to achieve a rise in temperature during treatment. Many patients had a temperature plateau around 45°C for 15 to 35 minutes, despite the use of maximum energy (80W) before the temperature increased to a therapeutic level. In other cases, patients showed a quick rise in temperature without any delay even at quite low energy levels (30–40W). Differences in the intraprostatic blood flow were believed to be the reason for this great variation. We therefore performed transrectal colour-doppler before and during TUMT. As later described by Tubaro et al in 1995, a great individual variation in prostatic blood flow at baseline and as a response to heat exposure was also found.

In a prospective study intraprostatic thermosensors were introduced by the transperineal route in 30 patients. These first microwave feedback treatments provided extremely valuable knowledge and understanding of thermotherapy. Both net energy and treatment time could be adapted for each patient and the treatment outcome was convincing for both subjective and objective clinical

variables (Wagrell et al 1998). These experiences led to the crucial realization by ProstaLund and our research group that the treatment catheter itself could be used as a delivery device with implantable thermosensors. This made it possible to establish a simple application easily repeated for routine use, the feedback treatment for clinical routine use was realized in 1996. One question remained unsolved; intraprostatic temperature monitoring results in a large amount of data being displayed during treatment. What do all these data mean, for how long time should treatment last and what is the ideal treatment temperature? Is there a way to condense all these temperature data into one easily interpretable unit that describes the treatment? Is it possible to establish a “thermal dose concept” that translates temperature and time into an estimated amount of tissue that is necrotized?

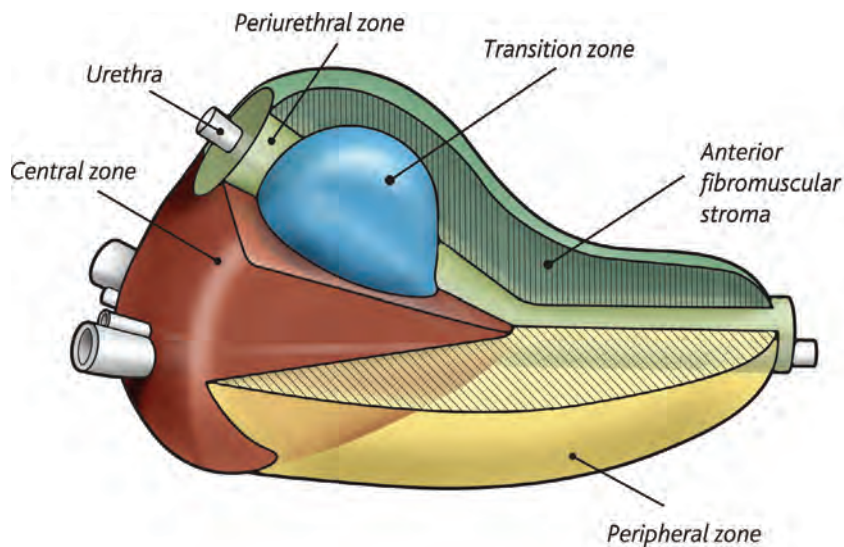
Over the next two years, researchers at ProstaLund developed a software algorithm to calculate the amount of coagulated tissue from the measured intraprostatic temperatures. The idea was based on a novel approach to combine the Bioheat Equation, proposed by Pennes, for assessing the temperature distribution in the prostate, with the heat sensitivity of tissue described by Henriques (Pennes 1948, Henriques 1947). Two quantities could be derived in this way during ongoing treatment and in real time: an intraprostatic blood flow index and the amount of coagulated tissue (Bolmsjö et al 1998).

This augmented feedback technique has been available for routine use since 1998. It soon gave new understanding of the TUMT procedure itself. These experiences indicated the need to reduce and control the intraprostatic blood flow during the treatment. A specially designed catheter was invented, making it possible to administrate local anaesthetics containing epinephrine into the prostate prior to TUMT.

## **Benign Prostatic Hyperplasia (BPH)**

The prostate is a secretory gland located around the proximal urethra and is a part of the male bladder neck. The juvenile prostate is cylindrical and somewhat cone-shaped and surrounds the 3 cm urethra proximal. The average weight of a normal adult prostate is about 20 g (Berry 1984). Prostate secretion contains several biochemically active substances with essential fertility functions. Both the quantity and composition of the prostate secretion seem to be of great importance to male fertility.

The anatomy of the prostate gland was poorly understood before 1981 when McNeal described a three-dimensional model. Four anatomic regions could be identified. These regions correlate to the glandular arrangements and their secretory ducts which empty into the urethra and the ejaculatory ducts. This zonal anatomy can be identified and is of paramount importance during transrectal ultrasound (TRUS): 1) The peripheral zone (PZ) is the superficial U-formed outer part covered by the prostate capsule. 2) The central zone (CZ) surrounds the two vasa deferentia and ejaculatory ducts and is the origin of a possible median lobe. 3) The transition zone (TZ) surrounds the urethra proximal to the verumontanum and represents just a small part of the prostate in the young adult male. These peri-urethral glands and small ducts that empty directly into the urethra are the main origin of BPH. 4) The anterior fibro-muscular stroma (AFM) contains no glandular tissue and functions only as a supporting anterior wall of the prostate (see figure).



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## **Aetiology and pathophysiology**

Hyperplasia of the prostate gland is very common in the aging male. The aetiology is obviously multifactorial. One factor that is believed to be essential is long-term exposure to testosterone. Epidemiological and genetic studies have suggested age, hormonal and genetic risk factors. Other potential risk factors that have been considered include race, ethnicity, diet, vitamin intake, baldness and obesity. Oestrogen synergism with androgen exposure, particu-

larly dihydro-testosterone, has been suggested as another potentially important factor following interpretation of animal studies. It has been suspected that dysregulation of different factors stimulating growth promotes cellular proliferation and prostatic growth (Lee et al 1995). However, very little is known about these mechanisms.

A decreased endogenous rate of apoptosis has also been suggested to explain abnormal tissue growth (Kyprianou et al 1996). BPH as a hereditary condition was vaguely supported by Roberts et al in 1995 and by a twin study performed by Partin in 1994. “Early onset BPH” is suspected to be a hereditary condition (Sanda et al 1997). No significant correlations to smoking habits, alcohol consumption or sexual activity have been found. In 2002 Hammarsten et al found a correlation between a fast growing BPH and the male metabolic syndrome. BPH is a histological diagnosis that can be demonstrated in 60–80% of the 60–80 year old men and in 80-90% of men over the age of 80 (Berry et al 1984). In hyperplastic prostates the stroma-to-epithelia ratio increases from 2:1 to 5:1 (Cabelin et al 2000). PSA elevation also corresponds to prostate enlargement and is a sensitive but not specific test for prostate disease. Normally, a PSA elevation 2–9 ng/ml is often related to BPH but there is a risk of over-diagnosis of prostate cancer (Stamey et al 2002). Most urologists consider BPH to be a progressive disease (Djavan et al 2002). In a community-based study in the Netherlands the annual average prostate growth was 2% (Bosch et al 1994).

There is no absolute correlation between the degree of prostate enlargement and BOO. Some old men have a very large (“grapefruit”) prostate without BOO and LUTS while others may demonstrate severe LUTS and BOO whilst having a small prostate (“walnut”). There is, however, a strong correlation between prostate volume, PSA elevation and risk of acute urinary retention needing surgical intervention over time (Roehrborn et al 1999). This could be explained hypothetically by three components:

- 1) Restrictive compression of the urethra.
- 2) Smooth muscle constrictive compression.
- 3) Prostate secretion retention.

There is poor correlation between the degree of obstruction and LUTS measured by means of the International Prostate Symptom Score (IPSS) and Bother Score (BS) or Quality of Life Score (QOL) (Abrams 1994, Yalla 1995, Atan



1996, Graeme et al 2000). One-third of men with LUTS do not have BOO. Selective use of pressure-flow studies can help to differentiate between obstruction and non-obstruction and improve diagnosis before treatment decisions are made (Jensen 1989). LUTS as well as bother and discomfort induced by the symptoms bring the patient to the doctor. The character and intensity of symptoms influence treatment decisions. A low symptom score will probably end up in watchful waiting, medication or MIT. Severe symptoms will more often lead to MIT or surgery.

During the last four decades most patients with moderate or severe symptoms underwent TURP or open surgery. Treatment decisions were often made based on symptoms and only the presence of an enlarged prostate. Hald (1989) presented a model with three overlapping and interacting rings explaining the interaction and complexity of BPH, BOO and LUTS. By his definition of “clinical BPH” the patient had to fulfill all of the following three criteria: 1) Prostate enlargement shown by digital rectal examination (DRE) and/or TRUS. 2) Verified obstruction found by urodynamics (pressure- flow study). 3) Symptom score verification of significant LUTS.

In the case of obstruction, the development of symptoms can be divided into two categories:

1. Storage symptoms: If an obstruction builds slowly due to BPH the bladder will adjust to the increased work load. The opening pressure needs to increase to initiate micturition. Detrusor pressure must also be at a high level to maintain the flow throughout the whole emptying phase. The detrusor adapts to this extra demand via hypertrophic thickening of the bladder wall. This will result in a reduced functional capacity, reduced compliance and an over-active bladder – altogether experienced as urgency and frequency.
2. Emptying symptoms: Increased resistance to flow through urethra will demand increased pressure to compensate. If and when the detrusor fails to adequately increase the tension of the bladder wall – e.g. the pressure is insufficient to overcome and compensate for the increasing resistance to flow – a slow stream, hesitancy, intermittency and increasing residual urine will occur.

Yet the static-dynamic paradigm of BPH fails to account for all bladder effects on LUTS. In more than 50% of patients with BPH, involuntary detrusor

contractions are seen. With increasing age histological changes occur in bladder musculature together with altered compliance and decreased contractile strength of the detrusor. Irritative symptoms do not statistically correlate to prostate morphology such as volume, prostate inflammation and hyperplasia found on histopathology after TURP. These symptoms should probably be attributed to extra-prostatic factors such as bladder reaction (Atan et al 1996). A three-component mechanism of LUTS for the “clinical BPH” is more comprehensive: static, dynamic and detrusor-related (Zaida A. et al 1999).

The term “over-active bladder” has been accepted by the International Continence Society and replaces the old term “unstable bladder” (Garnett et al 2002). Overactive bladder (OAB) was found in 45% of patients with verified BOO. Patients with BOO and OAB were older and were more obstructed than patients with BOO without concomitant OAB (Knutson et al 2001). The severity of symptoms and obstruction differ from very light and intermittent discomfort all the way to chronic urinary retention. About 70% of all men have some voiding troubles during their life time and approximately 30% will need surgery or another active treatment (Glynn et al 1985). Many patients still have LUTS for a long period of time or permanently following surgical alleviation of obstruction due to bladder dysfunction (Abrams et al 1979). Long-standing symptoms seem to increase the risk of bladder decompensation (Andersen 1982).

## **Epidemiology**

Epidemiology is difficult to address while “clinical BPH” is defined differently (Boyle et al 2000). BPH is a histological entity and LUTS just is a collective name for symptoms related to storage and voiding (Guess 1990). There is a huge variation in BPH prevalence both in specific age groups and in different countries. This is partly explained by the different definitions that are used. BPH, clinical symptoms and verified obstruction as defined by Hald in 1989 comprise the clinical condition that should be addressed but this is seldom the entity presented in the literature. Mortality rate, correlated to BPH, has fallen more than ten-fold during the last 50 years in the developed countries (Boyle et al 1996). A LUTS prevalence study performed in two Swedish counties in 1997, including almost 40.000 men aged 45–79, showed 18.5% of the men to have moderate symptoms and 4.8% to have severe symptoms. The symptomatic men reported a bad QOL in 36% of the cases (fairly bad, very bad or terrible). Only 29% were previously diagnosed and 11% were on medication

for LUTS (Andersson et al 2004). As the male life expectancy approaches 80 in the developed part of the world, more men live long enough to encounter symptomatic BPH (Berry et al 1984). Increasing prevalence and costs are two of the reasons that explain the demand for new, alternative and cheaper treatments.

## Health economics

Symptomatic BPH is causing a growing health economic burden on the developed countries due to rising life expectancy and new treatments even for mild and moderate symptoms. Medication is often only a symptomatic therapy that in many patients leads to symptomatic relief as long as treatment is continued. For some patients compliance is poor. In particular,  $\alpha$ -receptor blockers can cause side effects such as low blood pressure, headaches, dizziness and fatigue. Medication for symptomatic BPH is very expensive and the annual cost of treatment with a  $5\alpha$ -reductase inhibitor or  $\alpha$ -receptor blocker is USD 500–600. Combination therapy as advocated recently by some investigators will thus cause double the cost. Many patients on medication will eventually need “curative” treatment (debulking) such as minimally invasive treatment or surgery. In this “treatment cascade”, medication adds extra costs that could have been avoided if the patient received a definitive, i.e. an invasive/minimally invasive treatment earlier. Ackerman calculated the treatment costs of the Targis TUMT System (Urologix) and compared it to TURP using US costs reports from 1999. The primary cost for treatment without complications was estimated to USD 2.639 for TUMT and USD 4.597 for TURP. In the risk-inclined patient group TUMT was preferred and in the risk-averse group medication was preferred. TURP was the least preferred therapy (Ackerman et al 2000). Calculations of the 5-year costs for the same hypothetical patient cohort of 65-year-old men with moderate to severe BPH symptoms showed the lowest expenditure for TUMT when compared to TURP or medication with alpha blockers (Blute et al 2000). de la Rosette compared the costs for TURP and high energy TUMT (HE-TUMT - Prostatsoft 2.5) in a prospective randomized 3- year follow-up study. The costs were almost 50% higher for TURP compared to TUMT, including re-treatments (de la Rosette et al 2003). Some new alternative therapies such as non-contact laser therapy are even more expensive than TURP (Noble et al 2002). As an outpatient procedure PLFT is less costly than TURP but cost - effectiveness depends on the clinical effect over time and is hard to estimate for a new treatment modality. Kobelt et al investigated the 1-year costs comparing PLFT to TURP for the

patients treated in the “FDA – study” (Kobelt et al 2004). The mean 1–year costs for PLFT were EUR 1.763 and EUR 3.209 for TURP. Both groups will face additional costs for re-interventions after treatment over the years. The 3–year follow-up to the “FDA” study, with equivalent clinical outcome suggests lasting economic advantage for PLFT (Wagrell et al 2004).

## **Investigations and diagnosis**

The character and severity of LUTS and the bother score (BS) determines when the patient will consult his doctor. While the severity of symptoms usually varies over time BPH patients often have a long past history before they first take contact with their doctor. A short history typically raises a suspicion of cancer, stone or infection. The urologist takes the IPSS, BS, Qmax, post void residual urine (PVR) together with urine and blood laboratory tests into account. There is no absolute correlation between the number of symptoms and BS. Nocturia and urgency have the greatest impact on bother score and thus are least tolerated by the patients. In 1992 Meyhoff et al advocated a more developed symptom score that also included questions about sexual function and an evaluation of bother score for every symptom. Irritative symptoms were found to have greater impact on the BS than obstructive symptoms. Investigations of patients with probable BPH have two aims: 1) Differential diagnosis-exclusion of other disorders. 2) To confirm the presence of BPH, BOO and LUTS. Besides BPH, alternative causes to LUTS from the bladder level and downwards can be:

- 1) Detrusor insufficiency due to both muscular and neuropathic disorders.
- 2) Organic bladder disorders, e.g. stones, diverticula, inflammation, infection and cancer.
- 3) Detrusor over-activity/over-active bladder.
- 4) Detrusor sphincter (bladder neck) dyssynergia.
- 5) Bladder neck sclerosis – a restrictive obstruction due to scarring.
- 6) Other prostate disorders such as cancer and prostatitis.
- 7) Urethral stricture, inflammation and diverticula.
- 8) Meatal stenosis.

Patients with long-standing high blood pressure may end up with, natriuresis due to tubular kidney damage and nocturia owing to increasing urine volumes. Nocturia is also quite common together with oedema due to cardiac conditions. Habitual polydipsia can cause increased frequency and nocturia.

Mandatory routine investigations are:

A medical history: Hereditary disposition towards genito-urinary disease (early onset of BPH, cancer and stone), previous illnesses, ongoing medications, previous surgery and possible allergy, IPSS, QOL and questions about sexual function are routine. What are the patient's major complaints and expectations?

Laboratory tests: Blood tests: Creatinine, haemoglobin. PSA should be taken in all patients where a prostate cancer diagnosis may change therapy. Urine test: Dip-slide.

Physical examination: Estimation of the general health condition and performance status. Careful abdominal palpation is performed to detect tenderness, a distended bladder or abdominal mass and flank palpation to detect hydronephrosis or kidney tumour. Scrotal inspection and palpation are carried out to reveal any abnormalities. DRE is crucial to evaluate prostate size, shape, consistency and tenderness.

Flow rate recordings: Should initially be done for all LUTS patients. It may give suspicion of other disorders such as urethral stricture, detrusor sphincter (bladder neck) dyssynergia or neurogenic bladder. A retarded flow rate can not distinguish between BOO or a weak bladder. A single poor flow rate registration does not even confirm a micturition problem because of poor reproducibility. To minimize false tests, the Qmax should be measured twice with voided volumes exceeding 150 ml each time. Some patients find it impossible to urinate in the office and may be evaluated by time-flow registrations performed at home.

PVR is the residual urine volume left in the bladder immediately after emptying. It varies considerably over time. Increased PVR may be a sign of incomplete emptying due to BOO or a weak detrusor.

Voiding diary: This registration performed by the patient should be repeated for at least two complete 24-hour periods. Voiding diaries give information about frequency and voided volumes during the day and during the night, which is of special interest. It gives information about the total intake of fluid and nocturnal polyuria.

TRUS is a valuable tool for differential diagnostic considerations. Prostate cancer can be diagnosed by TRUS guided biopsies. Secretion congestion and calcifications can be seen and correlated to the findings from palpation. Adenoma size can be measured. TRUS is mandatory before PLFT. Therapy instructions define and exclude treatment indications according to prostate measurements and also recommend a therapeutic goal, which is to achieve a coagulation necrosis to a certain percentage of the total prostate volume.

Nowadays equipments for TRUS are standard in almost every urology office. Most urologists who are handling BPH patients have the skill to perform TRUS routinely on every patient before MIT or surgery. Prostate size is easily measured and calculated with acceptable accuracy by the equation (width x length x height x 3.14/6) (Terris et al 1991). This information is a cornerstone in the evaluation of BPH patients since the prostate size can neither be estimated with acceptable accuracy by palpation nor by cystoscopic measurement of the urethral length. Prostate volume in BPH patients can also be estimated by its correlation to the total PSA elevation (Mochtar et al 2003). The prostate shape is also of interest and influences the choice of appropriate therapy. When a pronounced mid-lobe is detected, increasing the failure risk after TUMT, TURP should be the treatment of choice.

Urodynamic studies (pressure-flow): will discriminate between an increased outflow resistance and a weak bladder in patients with LUTS. One-third of the men with LUTS do not have BOO. Pressure-flow studies are not considered for routine evaluations but are greatly recommended before interventions (Jensen 1989). In one study there was no correlation between detrusor pressure at maximum flow rate (Pdet, Qmax) and patient age, IPSS or Qmax. However, a weak correlation to prostate volume was found (Tammela et al 1999).

## **Treatments for symptomatic BPH**

### ***Drug treatments***

Several drugs have the capacity to reduce prostate volume by inducing apoptosis in the gland using endocrine mechanisms. GnRH agonists, antagonists and androgen receptor antagonists work effectively but are not used for BPH. However, finasteride and dutasteride, which are 5-alpha reductase inhibitors, are frequently used for BPH. Alpha receptor blockers work by reducing the tone in prostatic smooth muscle, thus relieving a constrictive factor contributing to obstruction (Lepor et al 1988). Alpha receptor blockers have an im-

mediate onset of action while 5-alpha-reductase inhibitors induce prostate volume reduction more slowly and symptom relief comes gradually in 30–50% of the patients (Andersen 1995). Finasteride does not have a better effect than sham treatment in small and moderately enlarged glands (<40g) (Lepor et al 1996). In large glands, a significant volume reduction (>30% in 42% of the patients), increased flow rate (+2.3 ml/s) and reduced IPSS (-3.6p) were found after 36 months of finasteride treatment (Stoner et al 1994). In the “MTOPS” study after four years the IPSS had decreased by 5 points in the finasteride group and by 4 points in the placebo group compared to the baseline. Qmax was only 0.8ml/s higher in the finasteride group compared to the placebo group (McConnell et al 2003). Pressure flow variables may also improve after finasteride treatment in prostate glands >40 cc (Abrams et al 1999).

In the small glands alpha receptor blockers are advocated whereas a combination therapy is often recommended in the large glands to start up medication. Alpha blockers can often be abandoned after a while when finasteride is fully effective. Prostate volume and PSA are predictors for an increased risk of developing acute urinary retention (AUR) and this risk is reduced by about 60% with finasteride treatment (Marberger et al 2000). Djavan used alpha-blockers together with TUMT to speed up symptom relief after microwave treatment (Djavan et al 1998). Symptoms of over-active bladders bother almost every second patient with BPH and BOO (Knutsson et al 2001). Drugs like tolterodine reduce urgency and frequency, which are both symptoms that have a great impact on the daily life and bother score of patients. There are no urodynamic prognostic factors to tell who will respond favourably to tolterodine (Wagg et al 2003). Over-active bladder symptoms can continue in 30% of the patients even after surgery (Andersen 1982). Bladder training could supplement the medication and improve symptoms even further (Mattiasson et al 2003).

There has been a major shift in BPH treatment attitudes during the last 15 years. Almost all patients presenting LUTS in the recent years have been prescribed medical management as initial therapy almost by default. Does this represent good quality care (Wei et al 2005)? There is growing concern among many urologists in the United States and Europe that the grand scale of drug prescription creates a “mountain” of patients who will eventually need a more definite treatment – the hypothesis is that it is cheaper for the society and better for the patient to promote a definite (curative?) treatment early on than to offer a pill a day (palliative?) for the rest of their lives. The

answer to the question posed by Wei et al. is NO- medication for symptomatic BPH is only good quality care as a temporary palliative therapy for the majority of patients.

### ***Surgical treatments***

#### *Transurethral resection of the prostate (TURP)*

Most patients underwent open surgery before the 1970s when transurethral resection of the prostate, TURP, became widespread as the new “golden standard” for treating symptomatic BPH. Prior to this surgery was in fact often delayed until an “absolute indication” requiring treatment was present, e.g. persistent urinary retention or uremia. This reluctance to operate was due to the quite common serious adverse events and mortality caused by severe bleeding and thrombo-embolism. TURP was introduced in Sweden by Ridell in 1933 (Knutson 2000). It was soon recognized as a safe procedure and indications were gradually widened to include even patients with light symptoms at the end of the 1980s. Chen et al determined the residual prostate weight ratio after TURP (at baseline and after 16 weeks). There was good correlation between the TRUS measurements and the weight of the TURP specimen (Chen et al 2000). Almost 400.000 operations were carried out annually in the United States. As a comparison, 12.200 TURP operations were performed in Sweden in 1993 (Brehmer et al 1996).

In the beginning of the 1990s TURP frequency slowly decreased for several reasons. In 1999 it had decreased to 5000 operations and 2 years later only 4400 TURP procedures were done in Sweden (Kobelt et al 2004). This could be due to more stringent indications, increased use of medications and minimally invasive treatments, but also as a consequence of the scarcity of resources. Hospital beds have increasingly been needed for radical prostatectomy patients. Greater knowledge of the definition of “clinical BPH” has clarified indications for surgery. With urodynamic assessment before surgery a certain number of patients with detrusor under-activity (DUA) will be detected. This saves many patients from unnecessary and ineffective operations (Thomas et al 2004). Lepor et al described the efficacy of TURP. Mean peak flow increased by 108%, and obstructive and irritative symptom scores decreased 88% and 65% respectively. The responder rate was 84% (Lepor et al 1990).



Even if TURP is considered an effective and safe procedure, there are still complications and treatment failures. In an early publication postoperative mortality was reported as 2.5% and the morbidity rate as 18% (Holtgrave et al 1962). In a retrospective U.S. study of 218.127 Medicare patients operated on between 1984 to 1990, mortality following TURP was calculated as 0,4% for patients aged between 65-69 years and 3.5% for patients aged 85 years and older (Lu-Yao et al 1994). In other contemporary papers the postoperative mortality was 0.2% and even 0.0% (Mebust et al 1989, Borboroglu et al 1999). Horninger reported on a retrospective study of 1.211 consecutive TURP operations from 1988–1991 in Austria. The intra-operative complication rate was 8.9% and early postoperative complications were 15.9% but there was no mortality reported. Late complications were 11.2% and there was a 2.5% re-resection rate over the first 3 years (Horninger et al 1996).

The risk of the dangerous TUR-syndrome is almost eliminated when new techniques are used e.g. alcohol tracing, better operating equipments and safe irrigating fluids (Hjertberg et al 1991). According to Bruskewitz et al the occurrence of TUR-syndrome was 0.8%, transfusion rate 2.5%, urethral strictures within one year 6.5% and treatment failures were 6.3% (Bruskewitz et al 1997). There was an 18% immediate postoperative morbidity in almost 4.000 patients according to Mebust et al. Re-operations for postoperative bleeding and evacuation of clot retention are not frequent but needed regularly and reported in 3.3% of the cases (Mebust et al 1989). Serious adverse events also include septicaemia and sepsis that can complicate a urinary tract infection (UTI) in the postoperative period. Preoperative antibiotic prophylactics and treatment of UTI in the post-operative phase can avoid this problem in most cases (Grabe et al 1984, Hellsten et al 1989).

The outcome after TURP and transvesical prostatectomy was found to be equally good in a 5-year randomized study. About 25% of the patients needed a secondary operation during the first 5 postoperative years in both groups (Meyhoff et al 1986). Pressure flow studies can be helpful in determining the need for a repeated TURP because of unimproved symptoms, since in one study 16% of the patients had residual obstruction (Nitti et al 1997).

Impotence is a known but fortunately not common consequence of TURP. Retrograde ejaculation is a frequent postoperative consequence and the patients should always be informed about the risk before surgery. Mild to moderate erectile dysfunction was reported from 26.5% of the patients after TURP. Eja-

ulation loss or severe decrease in ejaculate volume was reported by 48.6% of the patients. There was a significant negative impact due to ejaculatory dysfunction on sexual activity (Arai et al 2000).

In short, TURP is not the perfect treatment. The efficacy is very good but TURP is an expensive inpatient procedure with a high frequency of serious adverse events.

#### *Transurethral incision of the prostate (TUIP)*

The incision can either be done from the area distal to the ureteral opening in the bladder down to the verumontanum, in one or two sides, or in the midline in the 6 o'clock position. This is a quick, safe and low-risk procedure mainly suitable for younger patients with smaller prostates (<30 cc) and an interest in future fertility because the operation has a lower risk of retrograde ejaculation. In addition, many urologists use this operation as an alternative to TURP for elderly, fragile and high-risk patients. Short-term results are almost as good as for TURP and the durability is of less interest for that patient category. Functional bladder neck obstruction verified by urodynamic examination can be treated with excellent symptomatic and urodynamic results (Christensen 1985). TUIP is the preferred treatment for patients with "clinical BPH" in the small glands (<30-35cc).

#### *Open prostatectomy*

This operation can either be done by the transvesical (Hryntschak 1951) or retropubic (Millin 2002) route and is the proper alternative for large glands (>80-100 cc). The risks and morbidity surpass TURP and the need for hospitalization is often 1 week. The clinical outcome and durability are superior even to TURP. In selected cases this method is an effective and good treatment, but inconvenient for the patient. (Debruyne et al 2000).

#### *Minimally invasive treatments (MIT)*

Almost all MITs, except for prostate stents and alcohol injections, work by the same mechanism – tissue destruction by the means of heat. Several new approaches, for example HIFU, different kinds of laser treatments, TUNA and WIT (Corica et al 2000) have been launched but not developed to replace or compete with TURP and open surgery. Microwave treatment alone has developed continuously, past "adolescence" and reached widespread application and is now used as an alternative to surgery (de la Rosette et al 1997).

### *Ethanol injection therapy of the prostate (EIP)*

Ethanol injection therapy of the prostate (EIP) is one of the most novel contributions to the MIT family. Moderate improvements in urinary flow rate, IPSS and BS as well as re-treatment rates of 41% after 3 years of follow-up have been shown (Goya et al 2004). Serious adverse events are reported in 2 out of 115 patients due to bladder necrosis (Grise et al 2004)

### *TUNA*

TUNA uses radio frequency energy to create several spots of coagulation necrosis inside the prostate. The urologist has to place the needle one spot at a time under endoscopic vision and wait a moment (5 minutes) for it to heat up (60–100°C). Treatments are carried out under a local anaesthesia as an outpatient procedure. After the 5-year follow-up, 23% had additional treatment. However, in the study by Zlotta et al. 2003, the responder rates, when including all treated patients were according to the definition by de Wildt (the percentage of patients with improved Qmax and IPSS of at least 50%) 18% and 58% respectively.

### *Laser treatments*

Laser treatments need endoscopic instrumentation and anaesthesia equivalent to TURP. There are three principally different approaches: 1) Interstitial lasers (ILC) create spots of coagulation necrosis. 2) Holmium lasers cut pieces of tissue basically without bleeding but have the disadvantage of tissue evacuation. 3) Superficial lasers (e.g. Green Laser) evaporate tissue from the surface but have the disadvantage of being expensive, time-consuming and can only be applied for small glands (<50 cc). ILC has had variable outcomes reported and a 40% 3-year retreatment rate according to literature. Long-term durability has not been properly documented (Laguna et al 2003).

The ability to debulk obstructive tissue is crucial to achieving good results. There is a fundamental difference between microwaves and the HIFU, TUNA, EIP and ILC treatments. They all create more or less deep focal spots of coagulation necrosis. Microwaves create a symmetrical cylindrical and cone-shaped coagulation necrosis around the urethra with the widest diameter towards the bladder neck (Larson et al 1994, 1998). After sloughing and absorption of necrotic tissue the result mimics a partial TURP.

## ***Microwaves***

### *Physical characteristics*

TUMT (Transurethral Microwave Thermotherapy) uses a special transurethral catheter with a microwave antenna which transmits energy into the prostate. Microwaves are electromagnetic radiation; heat is produced when the microwaves are absorbed into the tissue. This chiefly occurs through two processes: 1) electric dipoles, water molecules for example, oscillate in the microwave field. 2) electric charge carriers, ions for example, move back and forth in the field. These movements transfer energy to the tissue in the form of heat. The depth of the penetration increases as the frequency decreases and fatty tissue absorbs less microwaves than wet tissue (Goldfarb et al 1995). At the frequencies used by TUMT, between 900 and 1300 MHz, the penetration in water-rich tissue (typically muscle and prostate tissue) is about 15 mm. At 100 MHz the penetration is 100 mm and at 2450 MHz (microwaves for household use) the penetration is only 10 mm. Most TUMT devices use either 915 or 1296 MHz. Microwaves at 915 MHz penetrate a few mm deeper into the tissue than 1296 MHz, but this difference is of no importance to efficacy or TUMT safety.

Hyperthermia is defined as maximal temperatures  $< 45^{\circ}\text{C}$ . Hyperthermia does not kill the living cells but damages cellular transport mechanisms and induces an inflammatory response with lymphocyte migration. The damage is reversible and can not be detected in the microscope by histology. Thermotherapy, which aims for coagulation necrosis, uses temperatures between  $45^{\circ}\text{C}$ - $70^{\circ}\text{C}$ . An urge and pain threshold at  $45^{\circ}\text{C}$  is regularly seen as described by Devonec et al in 1990. Treatment temperatures  $>70^{\circ}\text{C}$  are called thermo-ablation.

### *The history of technical development*

The first attempt to treat BPH with microwaves was made by Yerushalmi in Israel in the early 1980s (Yerushalmi et al 1986, 1990). He studied applied hyperthermia ( $<45^{\circ}\text{C}$ ) heating to the prostate transrectally. The results were not conclusive and the approach was quickly abandoned. In 1985 Harada suggested using a transurethrally-inserted microwave antenna to heat the prostate. Soon afterwards Astrahan introduced and advocated the transurethral approach for hyperthermia treatment of BPH (Astrahan et al 1989). Only limited microwave power was used (20 Watt) and thermometry showed a temperature drop of  $6^{\circ}\text{C}/\text{cm}$  radially from the antenna in 5 patients (Astrahan et al 1991). Simultaneous transrectal and transurethral microwave hyperthermia

treatments were also performed (Debicki et al 1992). Microwave antennas progressed from a simple dipole antenna to a narrower, more flexible and effectively insulated helical antenna (Astrahan et al 1991). The Prostatron device, for example, uses a microwave antenna designed as a simple coaxial cable with an exposed inner conductor at the tip (monopole antenna) that has an inherently high degree of back-heating, or as in the CoreTherm (Prosta-Lund) and Targis (Urologix), a combination of folded dipoles and a helix that has a more well-defined heat pattern (Bolmsjö et al 1996; Larson et al 1998). Sapozink and Devonec introduced cooling of the treatment catheter and could thereby increase energy from 20 Watts to 60 Watts (Devonec et al 1991, Blute et al 1991).

### *Clinical documentation and user acceptance*

In the beginning of the 1990s there was a lot of enthusiasm for and also high expectations of these new minimally invasive treatments for BPH, e.g. various forms of laser treatment and microwave thermotherapy. The reception of first introductory phase of microwave treatment was similar to what usually happens when new technologies breaks through – technology that is about to induce a shift: enthusiasm among a small group of people coupled with suspicion and an anti-attitude amongst the majority. For example the introduction of the TURP operation and the PC (personal computer) – in the beginning the latter was seen as a useless toy except by a small group of users – the enthusiasts. With the first TUMT devices, several manufacturers sold different devices basically without any valid clinical documentation. At that time, there was no common legislation for the introduction of new medical devices in Europe. Manufacturers really only needed to demonstrate that the device was electrically safe. That changed in 1998 when the new EU medical device directive became mandatory. In an instant, the requirements and burden of proof multiplied for the manufacturers.

Very soon after the introduction of TUMT there was great deal of disappointment due to frequent treatment failures and TUMT got a bad reputation. This scepticism about TUMT remained to some extent even until the last few years despite many positive studies, greater understanding of thermotherapy and plenty of clinical documentation. Several TUMT vs. SHAM studies were performed that showed significant TUMT superiority (Carter et al 1992, Ogden et al 1993). In 1993 Devonec suggested basic definitions for thermoregulation in TUMT. Extrinsic factors are microwave energy and catheter cooling. Intrinsic factors are organ specific e.g. anatomy, tissue composition and vascu-

larization in different parts (zones) of the gland, conductivity and variability in blood flow. In 1993 Devonec also documented a quite good symptomatic effect but no effect on prostate volume using the Prostatron 2,0 (Devonec et al 1993). The same experiences without any observed prostate volume reduction, using the early low energy TUMT (LE-TUMT - Prostatron 2, 0), were documented by others (Goldfarb et al 1995, de Wildt et al 1995). The symptom improvement was very good after LE-TUMT (IPSS decreased 8-10 p e.g. 100% superior to the effect of finasteride).

In 1994 Thayne Larson introduced thermo-mapping during TUMT and defined the resulting coagulation necrosis using histopathology. This was important basic science for understanding the effects of microwave thermo-therapy. Many studies showed an inconstant and unpredictable outcome. No predictive factors could be ascertained, although it was suggested that a high epithel/stroma ratio would be beneficial for good treatment. One study, however, showed a predictive outcome from pressure-flow analysis before TUMT. 68% responders were found among constrictive BOO patients compared to 15% among compressive patients (Tubaro et al 1995). No correlations were found between the temperature in the rectum, urethra and inside the prostate during treatment (Goldfarb et al 1995, Venn et al 1996). Durability after LE-TUMT was a major disappointment as two-thirds of the patients had received supplementary BPH treatment four years after the Prostatron 2,0 (Hallin et al 1998).

Further development of high-energy TUMT (HE-TUMT) and feedback TUMT has resulted in effective minimally invasive treatments. Objective results close to what is regularly seen after surgery have been reported in randomized studies. Just like the second breakthrough for the TURP-operation and the PC (personal computer), the combination of further technical development and improved clinical efficacy has started a second enthusiastic phase driven by the urologists. Increasing the energy deliverance during TUMT resulted in a better outcome. Efficacy improvements were reached gradually; in 1995 Devonec started to use HE-TUMT (Prostatron 2.5 - 70 Watts) (Devonec et al 1995). These treatments resulted in 60% responders according to the definition by de Wildt (de Wildt et al 1995) and a re-treatment rate of about 10% within 1 year (de la Rosette et al 1997). A prospective randomized study comparing HE-TUMT (Prostatron 2.5) to TURP in 60 patients showed an equally good clinical subjective response but no objective improvement after TUMT (Ahmed et al 1997). In 1998 D'Ancona et al compared the outcome

of 21 TURP and 31 TUMT (Prostasoft 2.5) treatments after 2.4 years. They found that 78% of the patients were obstructed according to urodynamic investigation before TURP and 14% remained obstructed after the operation. In the TUMT group 67% were obstructed before and 33% remained obstructed afterwards.

Another study comparing TUMT to TURP showed both subjective and objective response in a 2-year follow-up study (Dahlstrand et al 1995). Many authors suspected the intraprostatic blood flow to be the reason for frequent treatment failures. 47 high risk patients (ASA III/IV) with persistent urinary retention for more than 1 month were treated with the Prostasoft 2.5. 81% of the 26 patients followed up 6 months later were free from catheter use with good QOL (Chaussy et al 1996). In 2004 Kellner et al treated 39 patients with chronic urinary retention with the Targis device. He reported an 82% success rate in catheter removal after  $4.1 \pm 2$  weeks. However, 85% of the patients needed continuous medication. Djavan et al. treated 31 patients in acute urinary retention with targeted HE-TUMT. The success rate of catheter removal was 94% with a mean catheter time of 3 weeks (Djavan et al 1999). de la Rosette established transurethral microwave thermotherapy to be so effective, safe and cost-efficient and enhanced that its position as a standard treatment for BPH was strengthened (de la Rosette et al 2003). Khair et al performed microwave thermotherapy just before radical prostatectomy in 7 patients with localized prostate cancer. There was no obvious difference in heat sensitivity for benign prostate tissue, hyper-plastic tissue or cancer (Khair et al 1999). Increasing the net energy improved efficacy but at the cost of more patient discomfort and adverse events. Most papers on HE-TUMT mention the need for medication with sedatives and analgesics. Mild to moderate erectile dysfunction was reported in 18.2% of the patients after TUMT. Loss of ejaculation or severe decrease in ejaculate volume was reported in 28.1% of the patients (Arai et al 2000).

Carter et al compared the actual intraprostatic temperatures to the clinical outcome. They found, just like our group, greater improvements both in terms of symptomatic and objective efficacy when the intraprostatic temperatures were above 50°C than when they were below 50°C. Their conclusion was that this data provided a sound rationale for monitoring the intraprostatic temperatures and developing invasive thermometry feedback mechanisms of thermal treatment of BPH (Wagrell et al 1998, Carter et al 2000).

### *PLFT*

In 1993 we discussed why some patients benefit from LE-TUMT whilst others do not. During those discussions, variation in prostate temperatures was suggested as one mechanism. We then decided to use intra-prostatic thermosensors to guide microwave treatment and we carried out a pilot study in 1994. Transrectal Doppler ultrasound revealed that the blood flow increased during treatment and was possibly cooling the prostate in many patients so that the temperature did not reach therapeutic levels. At our clinic in 1995, we started a prospective study of feedback TUMT, using transperineal placement of thermosensors, where the microwave power was adjusted to achieve temperatures above 55° C. The first promising results were published in 1998 (Wagrell et al 1998). This first experience from a clinical feedback microwave thermotherapy technique showed much better results than before; about 2/3 of the treated patients responded satisfactorily (Wagrell et al 1998, de Wildt et al 1995). Although temperature monitoring obviously led to better treatment results, it was also evident that thermosensor placement from the perineum was cumbersome and time-consuming. Bolmsjö and co-workers then suggested a technical solution that resulted in a clinically usable set-up. They invented a device with a thermosensor needle harboured in the treatment catheter, leaving the catheter in the apex part of the prostate, penetrating the urethra and measuring the temperatures in three spots inside the prostate (Bolmsjö et al 1998).

ProstaLund Feedback TUMT was introduced commercially in 1997 and one year later the “cell kill” concept was added. The intraprostatic blood flow and amount of coagulated tissue were calculated in real time by the software of the machine and monitored on-line to guide the operator during treatment. In 1998 this improved system - ProstaLund Feedback Treatment (PLFT) - was available commercially. The development of a working feedback system has greatly contributed to better security, treatment results and an understanding of prostate thermotherapy in general.



Feedback microwave thermotherapy using the PLFT (CoreTherm device) works by:

- measuring the temperatures in 3 spots inside the prostate, which are displayed on line, during the whole treatment.
- calculating the heat distribution in the whole prostate gland using the heat pattern known from in vitro phantoms.
- calculating and displaying the intraprostatic blood flow index using “Penne’s bioheat equation”.
- calculating the amount of coagulation necrosis, by using Henriques’ cell kill integral and displaying it on-line to guide the doctor running the treatment (Henriques 1947).
- continuously checking the safety temperatures in the catheter, rectum and outside the urethra and shutting off treatment automatically if any safety temperature is exceeded.

According to Penne’s bioheat equation from 1948, only 3 factors influence the resulting heat build up in tissue during thermotherapy:

$$\rho c \frac{dT}{dt} = \lambda \Delta T - \omega_b \rho_b c_b \rho (T - T_a) + Q_s + Q_m$$

Temperature change

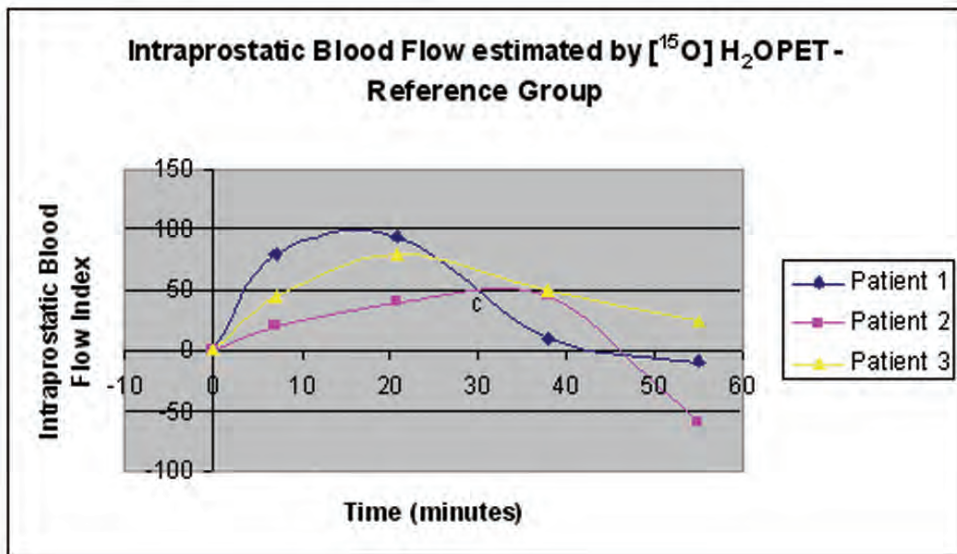
*Penne’s bioheat equation with the 3 factors underlined.  $Q_m$  is metabolically generated heat - of less importance here.*

Microwaves add heat. Heat conduction varies individually, but is a fairly constant factor in one and the same person. The intraprostatic blood flow works like a heat sink and transports heat away from the treatment area.

### *Blood flow problems*

As early as 1993 when we were coming up with the idea of feedback thermotherapy, we suspected the intraprostatic blood flow to be of great importance for the distribution and the building up of heat during TUMT. We performed TUMT in 5 patients under simultaneous transrectal colour-doppler examination. This semi-quantitative method showed a tremendous increase of the

intraprostatic blood perfusion starting some 5–10 min into the treatment in all 5 patients. This phenomenon seemed to be a reaction and a physiological defence mechanism to heat exposure. In one patient an intraprostatic injection, by the perineal route, of local anaesthetics containing epinephrine, was performed during ongoing TUMT. Colour Doppler showed an immediate shut-off of the blood flow in the injected lobe. Inaba found, when investigating prostate blood flow, using Positron Emission Tomography (PET), in normal glands a blood flow of  $15.7 \pm 7.5$  ml/min/100g, in BPH glands  $17.7 \pm 5.2$  ml/min/100g and in prostate cancer  $29.4 \pm 7.8$  ml/min/100g (Inaba 1992). In 1995 Thayne Larson et al found, using simultaneous thermal mapping and doppler ultrasound, a 99% increase in blood perfusion by analyzing wave-forms in blood flow measured during TUMT.



Reprinted from *J of Endourology* 18:968, Schelin S, Claeson A, Sundin A and Wagrell L, Effects of intraprostatic and periprostatic injections of Mepivacaine Epinephrine on intraprostatic blood flow during transurethral microwave thermotherapy: Correlation with (<sup>15</sup>O)H<sub>2</sub>O-PET, Copyright 2004, with permission from Mary Ann Liebert, Inc publishers.

L Wagrell did PETscans in 3 patients during PLFT and compared it to the blood flow calculations in the PLFT software. He found quite a good correlation. He also found a pronounced increase in blood perfusion by 50%, 80% and 100% compared to the baseline. It started a few minutes into the treatment and lasted for 20–40 minutes (Wagrell et al 2005). Tubaro observed a 12.5-fold blood flow increase compared to the baseline when performing a Dopp-

ler ultrasound during TUMT (Tubaro et al 1994). The intraprostatic blood perfusion varies considerably between individuals at the baseline and also in how patients react to heat exposure. The prostate blood perfusion transports heat away from the treatment area. Two major problems with standard HE-TUMT as a result of prostate blood flow are recognized:

- 1) The unpredictable outcome and lack of predictive diagnostic factors. The blood flow has a much greater impact on the needed “thermal dose” than any other factor e.g. prostate shape and volume, tissue composition etc.
- 2) Treatment failures in 15-30% of the patients. The explanation of the actual shortcomings of TUMT is thus too high intraprostatic blood flow. PLFT also has the same problem but the urologist will be aware of the difficulty and can cope with it during PLFT. If there is still no or insufficient “cell kill” you will realize the failure immediately.

There is no correlation between the static (baseline) blood flow and the treatment outcome while the dynamic reaction to heat exposure seems to react without any correlation (Wagrell et al 2005).

#### *Previously unsolved TUMT issues*

Other substantial TUMT problems:

- 1) Treatment time
  - 2) Patient discomfort
  - 3) Inappropriate technique for small or too large glands, ball-like mid-lobes and heavily protruding side-lobes.
  - 4) Need for indwelling catheter for variable period after treatment
  - 5) Post-treatment bothers such as pain, urge and frequency
  - 6) Durability of the treatment effect
- 1) Empirically, a treatment time of 60 minutes has been recommended for all devices. HE-TUMT leads to quite substantial discomfort and for the patient the treatment is very long. Drawn-out treatments also increase the treatment costs. Attempts to shorten treatment time have been launched. ProstaSoft 3.5 (Edap-Technomed, Lyon, France) is the last generation 30-min algorithm for HE-TUMT. de la Rosette found an equivalent outcome comparing it to ProstaSoft 2.5 (60 min) in 108 patients after 1 year (de la

Rosette et al 2000). Urologix is marketing a corresponding device – the CTC (Cooled Thermocath) – a 28.5 minutes high-energy protocol treatment presumably almost equipotent to their Targis 60 min protocol according to a multicentre trial (Huidobro et al 2003).

- 2) Patient discomfort is reported and mentioned in almost every paper about HE-TUMT. Sedatives and analgesics are given both as a pre-medication cocktail and extra during treatments on demand. There are no randomized prospective studies of this topic. A great many high-energy treatments today are performed either by trans-perineal or transrectal (TRUS-guided) peri-prostatic blocks with local anaesthetics together with sedative medication. Trans-perineal blocks are difficult and sometimes troublesome to perform and nasty for the patient. Transrectal blocks are easy to do but hazardous due to the risk of contracting septicaemia through germ inoculation.
- 3) Prostate size over 100g has been a common contraindication to TUMT. A retrospective survey from several clinics in Sweden found PLFT to be just as successful as in smaller glands (Ahl et al 2004). In small glands <30g HE-TUMT and PLFT is a less appropriate option. The margin for over- and/or under-treatment is too narrow. A TUIP is the preferred procedure in the small glands. A large mid-lobe was held as an absolute contraindication to TUMT. Experience has shown this is not always true. If there is a vertical opening anterior to the mid-lobe, through the bladder neck on cystoscopy, TUMT can be successful in most patients. In the very large glands or if there is a protruding mid- or side-lobe the treatment could be planned as a 2-step procedure. If the outcome after PLFT is unsatisfactory an easy supplementary TURP can be performed.
- 4) HE-TUMT and PLFT have documented substantial debulking effects initially producing a huge tissue necrosis. After HE-TUMT and PLFT there is a 100% retention risk due to a pronounced oedema soon appearing in the dead tissue left behind. An indwelling catheter is required for 1–3 weeks after treatment. Patients with chronic urinary retention have a longer postoperative need for a catheter – on average a period of 4 weeks. Persistent urinary retention was previously an absolute contraindication of TUMT. Several papers from the last 10 years describe successful outcomes after HE-TUMT and PLFT in small retrospective series for this patient category (Chaussy et al 1996, Kellner et al 2004). The need for an indwelling catheter for several weeks after microwave thermotherapy is the most negative factor from the patient's perspective. The catheter is

responsible for substantial patient discomfort. The first 2-3 days after the insertion of the catheter sees accompanying troublesome urethral irritation. Catheter-induced UTI is also a frequent problem. Catheter care also has strong negative connotations and is a psychological drawback when patients consider microwave thermotherapy as a treatment option. A temporary stent could be the solution to this problem.

- 5) The large tissue infarction and coagulation necrosis as a result of PLFT will cause a massive inflammatory response. Many patients experience substantial discomfort in the first weeks after treatment. Most of the dead tissue will be absorbed inwards but the rest will be discharged as sloughing. This inflammation in the prostate and the local irritation from the catheter will lead to most patients experiencing initially pronounced but decreasing suffering from urgency, frequency and pain. NSAID or COX 2-inhibitors are commonly used to reduce these bothers. Detrusitol® or antimuscarinic drugs are also helpful.
- 6) The durability after initially successful microwave thermotherapy is now documented. Durable results for PLFT after 3 years were published in the “FDA study” (Wagrell et al 2004). 5% of the patients had additional treatment in the PLFT group and 2.6% in the TURP group during the 12 to 36 month period. HE-TUMT (Targis 60) also seems to have quite good durability in a long-term pooled analysis of multicentre studies of cooled thermotherapy over 4 years. Improvements in AUA symptom score, Qmax and QOL were 43%, 35% and 50% (Trock BJ et al 2004).

#### *Methodological improvements*

The PLFT technique assess a clinically useful figure - “cell kill” to guide the urologist adapting the individually optimized microwave thermotherapy. These calculations show quite good correlation between calculated blood flow and PETscans (Wagrell et al 2005). The cell kill calculation and volume reduction measured by TRUS were also found to correlate quite well on 3D TRUS as well (de la Rosette et al 2003). Extensive thermo-mapping comparing the estimated cell kill to the findings on Gadolinium-enhanced MRI showed fairly good correlation in 13 patients (Osman et al 2000).

The Schelin Catheter® is a new invention for intraprostatic administration of medications by the transurethral route. This device has almost the same look and working principle as the IP-sensor introduced through the PLFT treatment catheter. Instead a hard plastic needle, with 2 side holes behind the tip, deviate from the catheter 45 mm distally to the catheter balloon at an angle of 30°. It protrudes 45mm deep into the prostate and hits the base area, where



*The Schelin Catheter®*

the large vessels enter the prostate. As the injection needle position always correlates to the balloon and thereby the bladder neck it will always reach the base of the prostate irrespective of its size. With the infiltration of local anaesthetics containing epinephrine a double purpose is reached. Analgesia of the prostate and blockage of its blood flow are attained using the astringent effect of epinephrine on the blood vessels. Successful transurethral administration of local anaesthetics under visual control together with urological endoscopic operations such as prostate incision, TURP, visual urethrotomy, ureteral meatotomy and resection of bladder tumours have been described previously (Orandi 1994).

Sinha et al performed 100 TURP operations using only either transurethral injections or a combination with transperineal administration of local anaesthesia (Sinha et al 1986). Mutaguchi et al found intraprostatic administration of local anaesthesia before prostate



*Transverse section of prostate showing one example of possible locations of injections of drugs.*

biopsies superior to periprostatic nerve block (Mutagushi et al 2005). Sturesson et al found a 47% larger necrosis by thermotherapy after blood inflow occlusion in the rat liver. He also found quick and continuously increasing temperatures. Low tissue pH, nutritional deprivation and hypoxia increase thermal sensitivity (Sturesson et al 1997). Using epinephrine before thermo-therapy, blood flow is not occluded but minimized.

## PRESENT INVESTIGATION

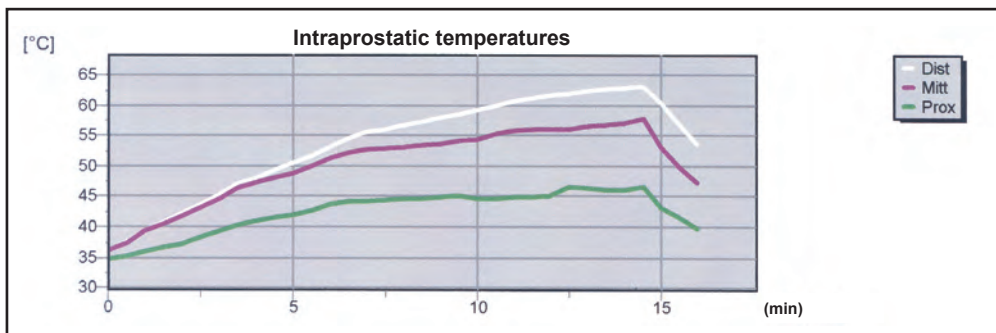
### Aims of the study

- To investigate the cell kill modelling with the aim of predicting the reduction in prostate volume after microwave thermotherapy of benign prostate hyperplasia.
- To compare the cell kill assessment obtained from the CoreTherm (ProstaLund – PLFT) device with the pattern and extent found using extensive thermo-mapping, Gadolinium-enhanced magnetic resonance imaging (MRI) and histopathology.
- To compare the outcome and safety of feedback microwave thermotherapy that is based on intraprostatic temperature measurements during treatment (PLFT) with transurethral resection of the prostate (TURP) in a randomized controlled multicentre study for clinical benign prostatic hyperplasia (BPH).
- To evaluate microwave thermotherapy as a treatment option for benign prostate hyperplasia (BPH) in patients with chronic urinary retention and fitted with an indwelling catheter.
- To compare the effects of Mepivacaine–Epinephrine injections into the prostate prior to PLFT at the time of treatment, intraprostatic blood flow, energy deliverance and patient comfort with a reference group in a retrospective survey.
- To study the intraprostatic blood flow by using positron emission tomography (PET), before and after intraprostatic injections of Mepivacaine–Epinephrine, during PLFT and comparing with a reference group of patients without injections.
- To compare efficacy and safety of ProstaLund Feedback Treatment (PLFT) with surgery, both transurethral resection (TURP) and open surgery, for BPH patients with persistent urinary retention in a randomized controlled multicentre study.
- To compare the long-term efficacy and safety of feedback microwave thermotherapy vs. TURP in a 5-year prospective international study.

## Materials and methods

The inclusion and exclusion criteria for participating patients in the different studies are described in more detail in the individual papers. Treatments with PLFT were performed according to the “Clinical instructions for use” recommended by ProstaLund and without local anaesthesia and epinephrine for Papers I, II, III, IV, VII and VIII. Surgery was performed according to the routine at each centre for Papers III, VII and VIII. All prospective studies were approved by the Ethical Committees concerned. Study II was approved by the Ethical Committee of the University, Santiago de Chile. Study III was also supervised by the American Food and Drug Association (FDA). All participating patients in the prospective studies provided written informed consent (II, III, VI, VII and VIII). The multicentre studies, Papers III, VII and VIII, were controlled by external monitoring. Statistical analyses were supervised (both at protocol design and at work up) by external experts.

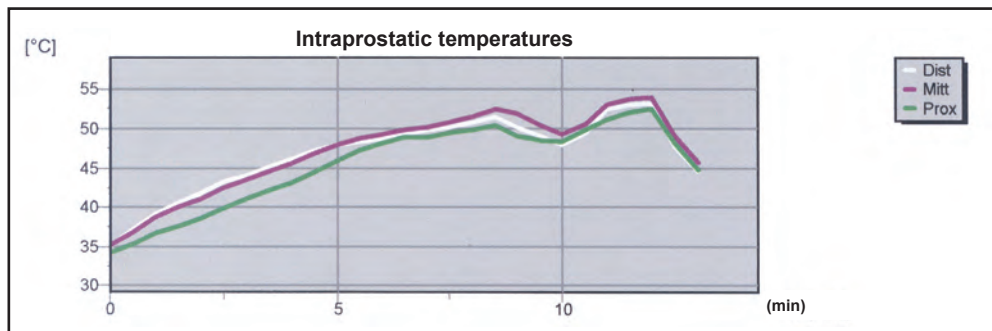
The reliability of the calculations delivered by the PLFT machine and its software of course very much depends upon the accuracy of the intraprostatic temperature measurements. If the intraprostatic PLFT thermosensor (IP sensor) hits perfectly between 2 and 4 o’clock in the left prostate lobe, there will be logical temperatures (see figure below).



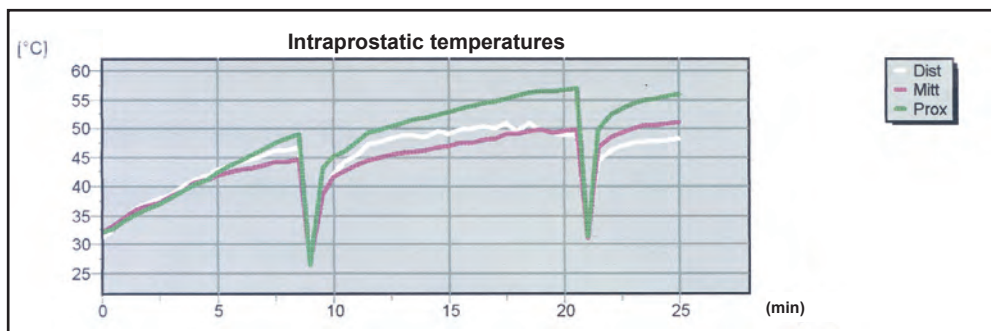
The white line represents the tip of the IP sensor measuring the temperature closest to the bladder neck and 15mm down from the microwave antenna. The red line reads the mid-point temperature 10mm deep into the prostate. The green line registers the temperature closest to the apex of the prostate at a depth of 6 mm. To find the logical temperatures the curves must be separated and the white or red line records the highest temperatures. If the treatment catheter harbouring the IP sensor is wrongly rotated anti-clockwise, the IP



sensor will hit too ventrally (12–2 o'clock). Due to the urethral curvature through the prostate the IP sensor will then be positioned parallel to the microwave antenna and all 3 measuring spots (white, red and green) will be at almost the same depth in the gland. In this situation all 3 curves will go close together (see figure below).



If the treatment catheter is wrongly rotated clockwise (4–6 o'clock), the IP sensor will follow the tangent of the urethral curvature backwards and leave the antenna too far out into the prostate. The tip (white) can even hit beyond the microwave irradiation field. In this situation the curves will be separated and go in inverted order (see figure below).



It is essential to evaluate the registered temperatures in the beginning of PLFT and if they are illogical the IP sensor must be repositioned! If the temperature curves are illogical one cannot rely on the cell kill calculations. In most cases it is easy to check the position of the IP sensor using TRUS. If it is difficult to visualize the IP sensor using TRUS, it can easily be identified when an assistant moves it in and out with small quick movements during the TRUS examination. If the IP sensor is in the correct position but the curves are still illogical, you cannot fully rely on the calculations. The measuring spots will come closer to the microwave antenna when the IP sensor is wrongly posi-

tioned anti-clockwise (12–2 o'clock) and falsely high temperatures will be registered. This will result in an overestimation of the resulting "cell-kill". The opposite situation will occur when there is too much clockwise rotation (4-6 o'clock). The measuring spots will go too far out from the antenna and register false low temperatures. The result will be an underestimation of the treatment effect. Illogical curves must be considered during every PLFT and the treatment strategy adjusted accordingly.

## **Results**

### ***Paper I***

The average prostate volume reduction measured by TRUS 3 months after PLFT was 26 ml. The on-line cell kill calculation according to Henriques' "damage integral" was 27ml. The uncertainty in TRUS measurements according to Terris was a calculated standard deviation of 15.6 (Terris et al 1991). According to Bates et al. the difference in volume determination between investigators was <10% (Bates et al 1996). In this study the 95% two-sided confidence interval for the cell kill calculation was 16.0%. The hypothesis was that the two methods have equal standard deviations. There is statistically no evidence that the cell kill modelling is less accurate than the ultrasound measurements. Simulating different tissue heat sensitivity or positioning the IP-sensor slightly incorrectly did not significantly alter the calculated cell kill. This study shows that it is possible to calculate cell kill estimations on-line during feedback microwave thermotherapy with reasonable accuracy.

### ***Paper II***

Extensive interstitial thermal mapping (30–40 measuring points) in eight patients showed therapeutic temperatures in a bowl-like shape with a wide circumference of highest temperatures at the base of the prostate. The temperatures and circumference decreased toward the apex. Comparing the cell kill calculations of the CoreTherm (PLFT) device with histopathology, Gadolinium-enhanced MRI and calculations on extensive thermal mapping showed relatively close mean values: 18 ml, 19 ml, 20 ml and 23 ml. In most patients a huge coagulation necrosis close to the calculated prediction was verified by histopathology. 16 biopsies from the urethra in 4 patients 3 weeks after PLFT verified by histopathology that the prostatic urethra was destroyed by the treatment.

### ***Paper III***

91/100 of the PLFT-treated and 42/46 TURP-operated patients completed the 12 months follow-up. According to the definition by de Wildt et al 82% were responders in the PLFT group and 86% in the TURP group. The difference was not statistically significant. In this first randomized controlled study comparing PLFT with TURP, there were no statistically significant differences either symptomatically or urodynamically. As expected more prostate tissue was removed after TURP than with PLFT. Median catheter time after treatment was 12 days (7–56) in the PLFT group and 2 days (1–26) in the TURP group. Serious adverse events related to treatment were 2% after PLFT and 17% after TURP (1 patient died after 27 days). Mild and moderate adverse events, e.g. urgency, urinary retention, hematuria and urinary tract infections (UTI), were common in both treatment groups. Micturition urgency was more frequent after PLFT and hematuria more frequent after TURP.

### ***Paper IV***

Due to very long waiting time for surgery, all 24 patients with persistent urinary retention on the hospital waiting list for TURP were offered PLFT as a quicker alternative. All patients accepted microwave thermotherapy in spite of reservations about the outcome. No patient was excluded due to contraindications such as median lobe, weak detrusor etc. 19 out of 24 (80%) of the patients had a satisfactory treatment result after 3 months e.g. free from catheter. Mean catheter time after treatment = 26 (9–54) days, mean values for: Qmax = 12.5 ml/s, PVR = 47 ml, IPSS = 4.8 p and BS = 0.8 p. At the 1-year check up 16 patients had even better results; Qmax = 14.7 ml/s was registered. A prostate volume reduction of 32% and 42% compared to the baseline was found on TRUS after 3 and 12 months respectively. The reason for treatment failure could be identified in all 5 cases of failure.

### ***Paper V***

Prior to PLFT 15 consecutive patients had Mepivacaine–Epinephrine (Carbocaine- Adrenalin®) infiltrated into 3 locations (4, 8 and 12 o'clock) by the transurethral route, using a new specially designed catheter device. They were compared to 35 consecutive regular PLFT treatments without intraprostatic injections. A comparison of the mean values in the Mepivacaine group compared with the reference group showed that treatment time was reduced about 50% from 61 to 32 minutes and energy delivery was reduced about 60% from 172 to 65 KJ. Calculated intraprostatic blood flow was reduced 50%, from 26 to 13 units/min. The need for sedatives was reduced by 50% and analgesics

by 80%. The clinical outcome in the two groups in terms of subjective variables (IPSS and BS) and objective registrations (Qmax and prostate weight reduction), was equivalent after 3 months.

### ***Paper VI***

Positron emission tomography (PET) using [<sup>15</sup>O] H<sub>2</sub>O was performed before and during PLFT in 7 patients. PET in 3 reference patients showed a 50, 80 and 100% increase in blood flow during PLFT compared to the baseline. Four patients, using the Schelin Catheter<sup>®</sup>, had prostatic infiltrations with Mepivacaine–Epinephrine (ME) in 3 locations (4, 8 and 12 o'clock) prior to PLFT. Two of them had a second baseline PET scan after the injections but before treatment. Blood perfusion dropped about 60% in one of the patients but less in the other presumably due to technical problems and a delayed PET. The other 2 patients started PLFT immediately after the ME injections and had blood perfusions close to or considerably below the baseline during their treatments. Medicine wash-out seemed to have reduced the astringent effect from epinephrine when treatments were delayed as seen in two of the patients. In the reference patients the intraprostatic temperatures of 50°C were never reached in 1 patient and after 30 and 43 minutes in the two others. After intraprostatic ME injections the temperature of 50°C was reached 10, 30, 5 and 6 minutes into PLFT. The mean treatment time was 61 minutes and net energy was 223 KJ in the reference group, compared to 34 minutes and 94.5 KJ respectively in the ME group.

### ***Paper VII***

This Scandinavian prospective controlled randomized multicentre study compared PLFT with surgery (TURP if prostate weight was ≤80g and open surgery for the large glands >100g) as treatment for patients with persistent urinary retention due to BPH. 125 patients were included and randomized 1:1. 49 patients were treated with TURP and 10 underwent open surgery compared to 61 patients who received PLFT (49 + 12 with glands >100g). Primary endpoints showed at the 6-month follow-up that 8/10 patients after PLFT and 9/10 after surgery were catheter-free. IPSS was 7.3 points after PLFT and 4.4 points after surgery. Secondary endpoints after 6 months: BS was 1.4 point after microwaves and 0.8 point after surgery. Qmax was 13.4 ml/s in the PLFT group and 18 ml/s after surgery. Prostate volume reduction was 22% after PLFT compared to 59% after surgery. Serious adverse events happened in 1 patient following PLFT and in 5 patients after surgery.

### ***Paper VIII***

No statistically significant differences were found in IPSS, BS, Qmax and PVR between PLFT and TURP in the 1-5 years follow-up of the “FDA study”. Adverse events were more frequent after TURP. Retreatment rate was 10% after PLFT and 4.3 % after surgery.

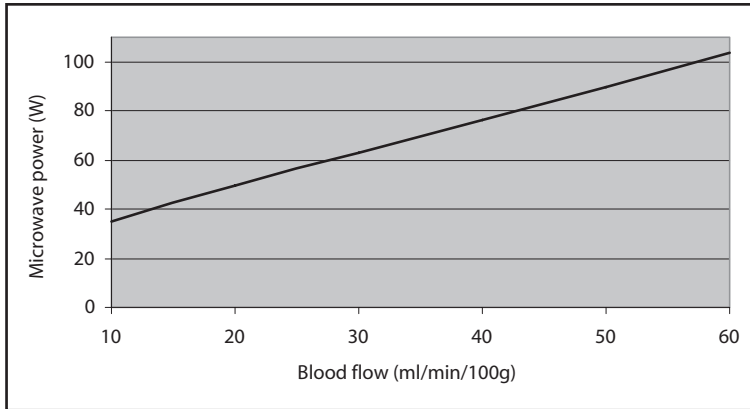
## **General discussion**

Transurethral microwave thermotherapy (TUMT) is the only minimally invasive method for treatment of clinical BPH that has been introduced in the last 15 years and has succeeded in staying in common clinical use. The technique has been a subject of continuous development. Of the available techniques for TUMT, the feedback-technique, PLFT, which was introduced in 1998, is described in this thesis. This method can now obviously be regarded as a natural alternative to surgery in the majority of patients with symptomatic BPH requiring invasive treatment (Papers III, VII and VIII). Efficacy has improved all the time since the end of the 1980s. Criteria for responders to treatment were presented by de Wildt et al in 1995. A responder rate of 40% was reported using a Prostatron device but no objective response was found in the investigation by Ahmed (1997). The first treatments with feedback technique and with protocols for high energy TUMT improved the responder rate to 60% (Wagrell et al 1998). At present, on-line monitoring of the calculated blood flow index and cell kill estimations make it possible to tailor for every treatment using the PLFT technique and thus to adapt and compensate for the effects of the prostatic blood flow. There are, however, still some partial or even complete treatment failures also seen with the feedback technique. This might be due to very high blood flow and a possible mechanism for this phenomenon was described by Bolmsjö et al in 1998. With the addition of intraprostatic injections of epinephrine in order to reduce the intraprostatic blood flow it seems possible to avoid such treatment failures and even better responder rates can now be anticipated (Papers V and VI).

The individual response to heat exposure varies greatly. Elderly men seem to have lower blood flow at the baseline and their blood flow increases much less in response to heat exposure. Perhaps this is due to pelvic atherosclerosis. Younger men often have quite high blood flow even before treatment and during the treatment procedure react with an increase of the blood flow index with more than 100%. The most important variables for the amount of cell kill achieved are the interdependence on temperature and time. Thermal inju-

ries are linearly-related to time but exponentially-related to temperature. As a consequence, higher temperatures result in much quicker treatments. Blood flow, heat conduction, tissue composition, energy applied and catheter cooling are all secondary parameters that influence the way the therapeutic temperature is reached. Once a target cell has reached the therapeutic temperature it is the actual temperature and time of exposure that determine whether or not the cell will survive (Wagrell et al 2000). The first PLFT software version used Henriques' tissue destruction integral and the assumption that heat sensitivity was the same with BPH tissue and pig skin (Henriques 1947). The Bischof group determined the time-temperature relationship for the destruction of prostate stromal and glandular tissue in a study that was initiated by our research group (Bhowmick et al 2004). These data are now considered in the new PLFT software. This study interestingly supports the early observations that prostates with a high epithelial/stroma ratio are more sensitive to heat.

The first comparison between the *in vitro* phantom temperature response and what was found in a canine model, using "Penne's bioheat equation", calculates that the blood flow rate to increases by 2.5 times as a response to heat (Xu et al 1993).



Mathematical calculations according to the same equation describe the relation between the prostate blood flow and the energy required to achieve a temperature elevation.

The intraprostatic blood flow is the most important factor during microwave thermotherapy that is responsible for the unpredictable outcome and failure to find any prognostic factors before a standard TUMT. In a typical PLFT procedure, the prostate blood flow which is calculated and displayed on-line shows a pronounced and rapid increase 5–8 minutes after the treatment is started.

It is then stabilized at a high level and this is the case even when maximum power (80W) continues to be delivered. The blood flow suddenly starts to decrease after 15–35 minutes at this level and the temperature increases to therapeutic levels ( $>48^{\circ}$ ), a phenomenon which has also been described by Goldfarb et al (1995). This diminished perfusion of the intraprostatic blood flow is thought to result from swelling of the prostate (oedema) and thrombosis of small vessels. The experiences from several hundred PLFT procedures tell us that there are about 15% treatment failures either partial or complete (no or too little “cell kill” obtained). Most of these failures seem to be due to a very high intraprostatic blood flow that is not reduced during a total treatment time of 60–70 minutes at maximum energy deliverance, i.e. 80W.

Treatment results with TUMT have significantly improved using the feedback technique. The categorization of TUMT into low and high energy treatments has no relevance in this context. Some patients with low blood flow only need very little energy to end up with a huge coagulation necrosis, while, as discussed above, even maximum energy output might be insufficient to induce any “cell kill” at all in other patients (Bolmsjö et al 1998). In Paper III the outcome for PLFT is equal to TURP at 12-month follow-up as regards IPSS, Qmax, QOL and detrusor pressure. After 1 year the prostate volumes, measured by transrectal ultrasound (TRUS), were reduced by 30% and 51% after PLFT and TURP respectively. Responder rates were 82% and 86% in the PLFT and TURP group.

A randomized single-centre study in Switzerland comparing PLFT to TURP showed at the 1 year follow-up even more pronounced improvements than the ones mentioned in Paper III for IPSS, Qmax, PVR, prostate volume reduction and detrusor pressure after PLFT. The responder rate was approximately 90%. (Graber et al 2002). Another prospective open single-centre study in Holland showed an 88% responder rate and 34.4% prostate volume reduction measured by TRUS after 1 year. This study also shows statistically significant improvements in IPSS, BS and Qmax from 8.4 to 17.8 ml/s (Gravas et al 2003). Sexual functions such as potency and libido remained unchanged after PLFT but the capacity to ejaculate decreased from 78% to 51.4%. The responder rate seems to increase from a level of 60–70% described in studies using high energy protocols with traditional TUMT technique to a level above 80% for PLFT. The first short (5.6 months) multicentre study of 102 patients from the U.S. shows satisfactory outcome (David et al 2004).

The 3-year follow-up for the “FDA – study” shows a durable situation with no

statistical differences between PLFT and TURP in BS and Qmax, even though there was an advantage for TURP in IPSS – 5.0 points compared to 8.2 points for PLFT (Wagrell et al 2004). An initial substantial prostate volume reduction ( $\geq 30\%$ ) is regularly seen after PLFT (Papers I, II, III and IV). Since the “cell kill” concept estimates the correct amount of coagulation necrosis with acceptable accuracy (if the intraprostatic temperatures are logical during the PLFT procedure) the thermal dose can be optimized individually for each patient. Problems that could be related to tissue composition, prostate volume and the variable blood flow thus can be overcome with the feedback technique (Bolmsjö et al 1998). The urologist performs a “heat operation” with a defined endpoint, e.g. an estimated certain percentage of destroyed tissue in relation to the whole prostate volume. A great deal of effort has been spent on identifying reliable predictive parameters, but no such measures have been found. It is only temperature and time that will determine the outcome (Henriques 1947). Unpredictable outcome and too low success rates have been drawbacks accompanying the different “blind” TUMT devices (without feedback technique) when only a treatment catheter and rectal temperatures were available. No correlations have been found between the intraprostatic temperature and the rectal or catheter temperature (Goldfarb et al 1995).

In a review article from 1997 de la Rosette pointed out some unsolved issues about microwave thermotherapy. He called for:

- 1) Shorter treatment times
- 2) Less painful treatments
- 3) Replacement of postoperative catheter with a temporary stent
- 4) The option of adapting the optimal “thermal dose”
- 5) Improved patient selection

While a regular PLFT procedure seems able to solve issues 4 and 5, the use of intraprostatic injections of local anaesthetics containing epinephrine (in 4 sites) prior to PLFT will probably also solve the first two problems, thus adding important methodological improvements to microwave thermotherapy.

The following advantages can be seen with this technique:

- a) Pain control – almost no need for sedative or analgesic medication.
- b) Shortened treatment time - by about 80%.
- c) Efficacy – even patients with very high blood flow could be turned into responders.

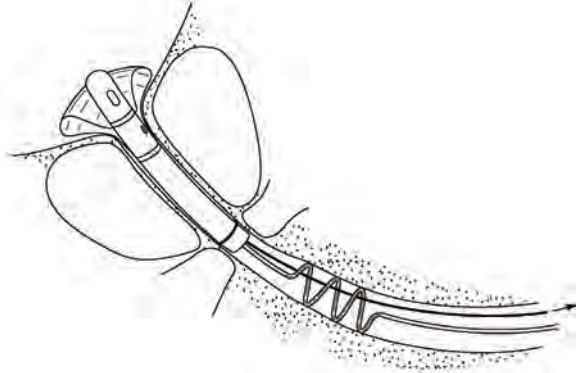


- d) Safety – only 20% of the energy and time is used for a complete treatment.
- e) Clinical result – cell kill calculations seem to be more accurate and reliable.
- f) Savings – less time and medications are needed.
- g) Shortening of the whole procedure – analgesia lasts for several hours after the procedure. The patient can leave the office immediately after treatment.

Perineal or trans-rectal blocks with local anaesthetics prior to TUMT result in an effective analgesia that reduces patient discomfort during treatment. The perineal route is sterile but involves bothersome and uncomfortable handling of the patients. The transrectal route is easy to perform and less inconvenient to the patients but there is a risk of serious infection due to germ inoculations. Neither of these methods with periprostatic blocks can control the intraprostatic blood flow effectively if epinephrine is used. Intraprostatic injections and medication of the prostate, by the transurethral route using the Schelin Catheter® achieve an effective blood perfusion blockage together with an almost perfect analgesia. This sterile technique is easy quick and reproducible with a short learning time. The patient lays flat and does not have to roll over. The catheter device has two functions - to harbour and mediate the injection needle and to drain the bladder before PLFT. No additional catheterization will be needed. Analgesia seems to be more effective after intraprostatic injections compared to periprostatic blocks with local anaesthesia (Mutagushi et al 2005). When using epinephrine it is essential to carry out TUMT with feedback technique – otherwise there is an obvious risk of serious over-treatments and complications.

The combination of PLFT and prostate injections of local anaesthetics with epinephrine seem to address four of the five issues raised by de la Rosette in 1997. The remaining issue is the need for an indwelling catheter for some weeks after microwave thermotherapy. Temporary urethral stenting would be the next logical step. A cheap temporary stent, which could be positioned easily without the help of endoscopy and with high performance, would solve this problem. Devonec reported positive experiences of using two types of stents after HE-TUMT (Devonec et al 1998). The Spanner™ is a new, short catheter-like stent that seems to work quite well in ordinary BPH and BOO patients (Corica et al 2004).

A new invention, by Bolmsjö and Schelin, now CE-marked according to the EU medical device directive, is the “Bladder Neck Catheter” (BNC). The BNC works like a short indwelling catheter and by means of pulling a thread it is also a device for ante-grade self-catheterization. This device can be inserted directly after PLFT and provides for immediate patient-controlled micturition and full continence. So far there have been no urinary tract infections (UTI) during the postoperative period when using this device. Patient discomfort also seems to be minor compared to the regular indwelling catheter situation according to interviews with several patients. A number of the patients that used the BNC have returned to work the day after PLFT.



*The Bladder Neck Catheter*

Persistent urinary retention was previously regarded as an absolute contraindication for TUMT. TUMT with Prostatsoft 2.0 and 2.5 were performed on 9 acute and 16 chronic urinary retention patients with a responder rate of 13/25 (52%) (Nørby et al 2000). Improved objective treatment results and substantial debulking in highly obstructed patients treated with PLFT led to the logical insight that even patients with persistent urinary retention (PUR) could be treated successfully. The difference is only the severity and degree of obstruction. This idea corresponds with the findings after PLFT in PUR patients treated for BPH. Post-treatment retention and the need for a catheter were lasting longer compared to patients without retention, i.e. a mean period of 4 weeks (Papers IV and VII). More tissue needs to be absorbed and discharged before the obstruction is resolved. The main difference to surgery is time for the alleviation of obstruction. Surgery ideally results in the immediately free and unobstructed passage of urine. PLFT needs 2–3 months before the corresponding unobstructed condition is achieved. Thus the urinary bladder can start earlier to adapt to the removal of obstruction after surgery. These differences should be taken into account when outcome is evaluated shortly after treatment. Paper VII is the first controlled, prospective and randomized study verifying that the outcome after PLFT in PUR patients almost equals the results after regular PLFT (Paper III) and surgery. In Paper VII the responder rate was approximately 80%. It seems that PLFT, at least in the short term,

has almost as good an outcome as surgery in relieving PUR patients from the catheter. Even PUR patients with large glands  $\geq 100\text{g}$  had successful outcome after PLFT.

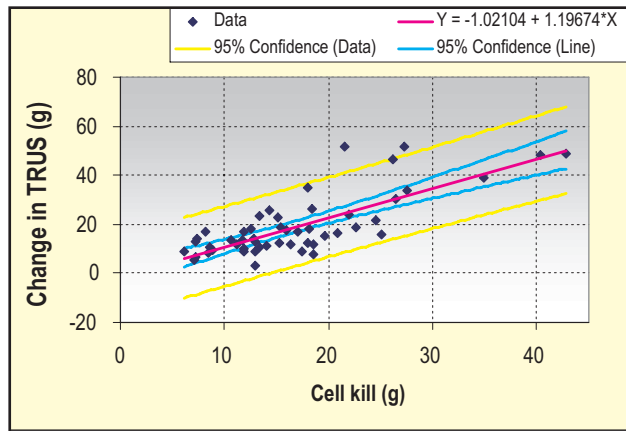
For high risk patients (ASA III and IV) PLFT could fill a hole in the therapeutic arsenal, where these patients previously had to carry an indwelling urinary catheter for the rest of their life. D'Ancona showed, for high risk patients classified as ASA III and IV, that outcome after HE-TUMT was just as good as for ordinary patients (D'Ancona et al 1999).

Another previous contraindication for TUMT was large glands. In a retrospective survey in four Swedish clinics, 122 PLFT treatments performed on prostates  $\geq 100\text{g}$  showed equally good treatment results as those seen after the regular indications for treatment (Ahl et al 2004). It seems that the main obstruction due to BPH is located in the bladder neck and proximal part of the urethra. Wagrell studied this by using video-urodynamics. The cross-sectional area at the internal meatus correlated to the voiding pressure and outcome 3 years after feedback TUMT (Wagrell et al 1999). This could explain the positive outcome in the large glands as well when using the regular relatively short microwave antenna in this connection. Papers IV and VII showed that glands  $\geq 100\text{g}$  and simultaneous PUR were also treated with equal success. The larger gland, the wider is the margin for a safe microwave thermotherapy. The goal of PLFT is to destruct 20-30% of the prostate volume at baseline. In glands  $\geq 100\text{g}$  the ideal resultant coagulation necrosis is  $\geq 30\text{g}$ . This substantial debulking offers a wide passage through the prostate, which could explain even better  $Q_{\text{max}}$  improvements after PLFT in the large glands than for TURP. Six months after treatment the mean  $Q_{\text{max}}$  was 18.2 ml/s for the 12 PLFT patients with prostate volumes  $\geq 100\text{g}$  (Paper VII). The corresponding mean  $Q_{\text{max}}$  in the TURP group was 16 ml/s.

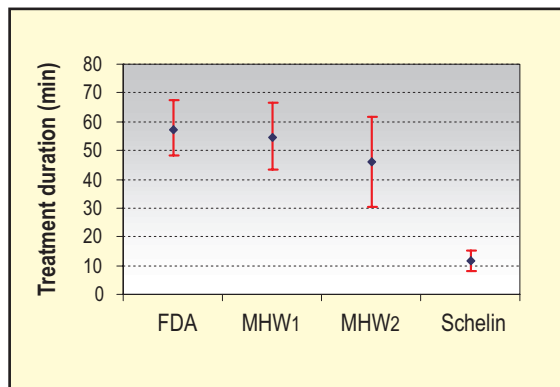
Regular PLFT has improved efficacy and safety, widened indications, individualized treatment, quantified the blood flow and cell kill of treatment and tailored the “thermal dose”. There have been plenty of discussions about the reliability of the cell kill calculations of PLFT. Paper I describes the theoretical background and Paper II evaluates the calculations compared to Gadolinium-enhanced MRI and histopathology examinations. The mean values correlated quite well, but some individual measurements differed. The standard error was calculated to be  $\pm 8\text{g}$ . The accuracy of the “cell kill” calculation was suspected to be negatively influenced by huge blood flow variations during

PLFT. Paper IV shows significant reduction in treatment time and energy consumption using LA + epinephrine in 3 injection sites compared to a regular PLFT. Later when the paper by Clegg in 1956, describing the “vascular arrangements in the human prostate gland” was considered, it was obvious that all 4 quadrants of the prostate had to be infiltrated and medicated to achieve a complete and reproducible effect. That factor was evaluated by a retrospective look at the last 72 consecutive patients all having intraprostatic injections of Mepivacaine-Epinephrine in 4 sites prior to PLFT (see figure below).

The correlation between the PLFT-calculated cell kill compared to the volume reduction measured by TRUS showed 1/1 relation after 3 months. The standard error was calculated to be  $\pm 4g$ . It seems that the block of prostate blood flow by epinephrine prior to PLFT enhanced the effect of micro-

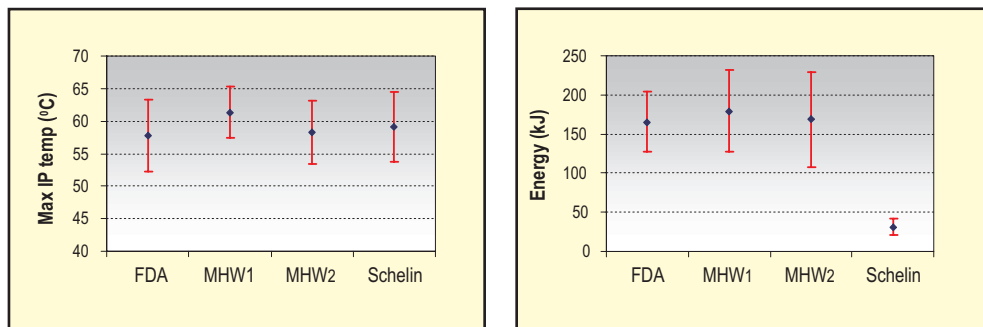


waves. More homogenous conditions with less variability in blood flow seem to create more reliable cell kill calculations, by stabilizing one otherwise very variable factor in the heat equation by Penne. Looking at the treatment time and energy required in the 72 patients described above, additional savings in comparison with regular PLFT in three prospective studies were found (see figures below).



The three prospective studies; FDA (paper III), MHW1 (Graber et al 2002), MHW2 (Gravas et al 2003).

Mean treatment time was reduced to 11.6 min with a mean energy consumption of only 31.6 KJ.



The three prospective studies; FDA (paper III), MHW1 (Graber et al 2002), MHW2 (Gravas et al 2003).

PLFT has further developed TUMT to be a “heat operation” which is adapted and tailored to deliver the right “thermal dose” for each patient. The urologist has a treatment plan for each patient, e.g. how many grams of tissue he wants to destroy before the treatment is finished. Treatment time or power can not be predetermined. The treatment is adjusted to the individual response and the heat is raised over time. A great deal of experience has been gathered in 7 years since PLFT was introduced. According to experience, the perfect treatment is a balance between efficacy, safety and patient comfort. Making use of the transurethral intraprostatic block with local anaesthetics and epinephrine the treatment is very quick and convenient for the patient: it is a true, minimally invasive and office-based outpatient procedure. So far no prospective randomized study has been performed using epinephrine in combination with PLFT in comparison with surgery. By adding epinephrine non-responders to regular PLFT, due to too high blood flow, hopefully they would be converted to responders. This might fill a small theoretical efficacy gap for regular PLFT?

The 5-year data show sustained efficacy and safety. PLFT shows good durability comparable to TURP which is a very important argument when challenging surgery as the new “Golden standard” treatment for clinical BPH and BOO (Paper VIII). The remaining challenge is to abolish the need for a post-treatment indwelling catheter.

Djavan et al in 1998 questioned drug treatment for symptomatic BPH and recommended TUMT as a better treatment alternative. In 2005 Wei et al questioned the actual therapeutic management for clinical BPH – “As a consequence of physicians prescribing increasingly more oral therapies for BPH, there has been an extraordinary shift in BPH management from surgical to medical care. The net effect of this phenomenon is that BPH has transformed from a pseudo-acute condition (that is a symptomatic condition that was promptly treated with surgery) to a bone fide chronic condition requiring ongoing medication and medical care. The public health impact of this paradigm shift on the American population is wholly unclear but unlikely trivial... In fact there are ample data to suggest that symptomatic improvement in surgical patients is much greater than in those on medical management.” (Wei et al 2005).

## **Conclusions**

- The biophysics works like a digital system – either the heat exposed cell has acquired the “activation energy” or not – it will live or die. This is the rationale of cell kill modelling, making it possible to condense all dynamic information into one single useful number - the amount of accumulated coagulation necrosis.
- PLFT, using the CoreTherm device, calculates and displays on-line the blood flow index and the accumulated coagulation necrosis (“cell kill”) with acceptable accuracy. This will help the urologist to perform a “heat operation” and tailor the “thermal dose” to each patient.
- 1-year follow-up in a prospective, randomized, controlled multicentre study in Scandinavia and the U.S. comparing PLFT to TURP in clinical BPH, shows equally good symptomatic and urodynamic results. Serious adverse events were less frequent after PLFT.
- PLFT, applied as an alternative to TURP for BPH patients with persistent urinary retention and scheduled for surgery, shows responder rate equal to the outcome after regular PLFT.

- Transurethral injections of local anaesthetics with epinephrine, using a specially designed catheter harbouring an injection needle, in the prostate before PLFT improve microwave thermotherapy. An easy sterile management, good analgesia, substantially reduced applied energy and shortened treatment time are gained.
- Blood flow in the prostate is of paramount importance during thermotherapy and is the key factor preventing the build up of heat. There is huge individual variation both at the baseline and in the response to heat. Local anaesthetics containing epinephrine minimize, via astringent effect, the blood flow - cooling of the treatment area, thereby facilitating thermotherapy.
- 6-month follow-up in a prospective randomized controlled Scandinavian multicentre study comparing PLFT to surgery (TURP/enucleation surgery) in BPH patients with persistent urinary retention shows equally good treatment outcome for both groups. Serious adverse events were more frequent after surgery.
- 5 years follow-up, in a prospective randomized controlled multicentre study in Scandinavia and the U.S. shows consistent clinical outcome for PLFT and TURP with 10% and 4.3% re-treatment rates, respectively.
- Intraprostatic infiltration of local anaesthetics containing epinephrine in 4 sites (all 4 quadrants) of the prostate provides perfect analgesia (no need for sedative or analgesic medication) and will shorten treatment time by 80% compared to 3 randomized studies.
- Intraprostatic infiltration of local anaesthetics containing epinephrine eliminates former treatment failures due to too high and persistent prostate blood flow. It also seems to improve the accuracy of the cell-kill calculation in the PLFT software by stabilizing an important factor.

- Treatment indications for PLFT have widened to include BPH patients in persistent urinary retention and large glands (>100g) unsuitable for TURP. PLFT is an attractive option replacing open surgery and thereby helping also high risk BPH patients to get rid of a persistent catheter.
- PLFT is a true, office-based minimally invasive treatment for clinical BPH that should, according to several good prospective multi-centre studies besides surgery be the new “golden standard” for the majority of patients with obstruction due to BPH. The efficacy, safety, durability and cost-effectiveness emphasize and support this statement.

**This thesis offers three important and provocative general conclusions and statements:**

- Drug therapy, either as mono-therapy (alpha-blockers or alpha-reductase inhibitors) or as combination therapy, transforms the condition of symptomatic BPH into a chronic disease requiring life-long and very expensive medication, which in many cases provides only moderate symptomatic improvement and the risk of on-going side effects.
- Surgical treatment (TURP/open surgery) as a “golden standard” has been taken for granted but has not been questioned for many years. Efficacy is now challenged by PLFT and the unavailability, discomfort, costs and quite frequent serious adverse events together with surgical treatments are recognized as very negative factors from the perspective of both patients and society.
- It is unethical to offer surgical treatment to the ordinary symptomatic BPH patient (without a bladder stone, history of irradiation or a large median lobe) without informing them of the possibility of achieving equivalent outcome using less risky treatment, i.e. the PLFT technique.



# POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

## Introduktion och bakgrund

Åldersförstorad prostata (BPH) utvecklas hos de flesta män vid tilltagande ålder. Många män får emellertid inga eller endast måttliga besvär under sin livstid. Påtagliga vattenkastningsbesvär utvecklas dock hos 30 % av den grad att de kommer att behöva en aktiv behandling. Vid ökad tillväxt klämmer prostatakörteln runt urinröret så att passagen förträngs. Urinblåsan kan till en början kompensera för detta genom att arbeta med högre tryck, som krävs för att starta men också vidmakthålla en urintömning. När urinblåsan inte längre orkar med detta kommer ökande symtom: i) tömningsbesvär som innebär startsvårigheter, klen stråle, portionsvis tömning och ökande mängd urin kvar i blåsan ii) lagringsbesvär som innebär urinträngningar och frekventa tömningar både dag och natt. Den klassiska behandlingen har varit att operera bort förträngningen genom en så kallad ”hyvling” eller TURP (den lilla operationen). Stora prostatakörtlar är olämpliga för denna metod och har vanligtvis opererats genom öppen operation (den stora operationen). Båda metoderna kräver sjukhusvård och är förenade med komplikationsrisker och stora kostnader. Medellivslängden för män i västvärlden ökar och närmar sig nu 80 år. Med ökad livslängd ökar behovet av behandling för åldersförstorad prostata och därmed kostnaderna i en alltmer ansträngd sjukvårdsekonomi.

Ett flertal minimalinvasiva behandlingsmetoder har lanserats under de senaste 15 åren. Olika typer av värmebehandlingar med exempelvis laserteknik har provats med viss framgång. Dessa behandlingar har kunnat göras polikliniskt men haft begränsade användningsområden och kräver bedövning och sjukhusresurser motsvarande operationsbehandling. Kostnaderna har till och med i vissa fall blivit större än för operationsbehandling. Värmebehandling med radiofrekvensvågor, fokuserat ultraljud och varmvatten har lanserats men ingen av dessa behandlingar har kunnat ersätta kirurgisk behandling. Värmebehandling med mikrovågor (TUMT) lanserades i början på 90 – talet, men med endast måttliga symptomatiska effekter mest på lagringsbesvär d.v.s. urinträngningar och täta vattenkastningar. Den gynnsamma effekten på en del patienter bedömdes bero på värmeskador på känselnerv och nerver som stimulerar den glatta muskulaturen att knipa runt urinröret. Den första lanseringen drevs av entusiastiska tekniker men blev ett misslyckande på grund av brist på vetenskaplig dokumentation, en outvecklad teknik och alltför dåliga

behandlingsresultat. TUMT fick dåligt rykte då många som satsat på denna nya behandling blev besvikna och ångrade sin investering. Vid urologienheten i Kalmar prövades ett svenskt motsvarande behandlingssystem. Ett lyckat resultat uppnåddes endast hos 2 av 13 patienter. Dessutom fick två av patienterna allvarliga behandlingskomplikationer.

Det föreföll märkligt att behandla alla patienter oberoende av prostatastorlek på samma sätt. Ett stort antal kliniska resultat redovisades på 90-talet utan några fynd av tydliga prognostiska faktorer. Vid kliniken diskuterades varför enstaka patienter svarade bra på behandlingen men flertalet inte alls. Då föddes idén att kunna styra behandlingen genom temperaturmätning inne i prostatakörteln. Vi fann vid TUMT behandlingar med samtidig temperaturmätning en stor variation mellan olika patienter. De flesta patienterna krävde en stor mängd värmeenergi under lång tid innan temperaturen i prostatakörteln nådde över 45 grader, vilket är den nedre gränsen för en verksam värmebehandling. Enstaka äldre patienter reagerade dock med en snabb temperaturstegring även vid låg energitillförsel. Detta fick oss att misstänka att blodflödet i prostatakörteln fungerade som en ”kylare i en bilmotor” och var orsaken till denna stora variation. Blodflödesmätning genom ultraljud (färgdoppler), före och under TUMT behandling, bekräftade en stor individuell variation av blodgenomströmningen. Många patienter fördubblade sitt blodflöde i prostata efter 5 – 8 minuters värmebehandling. Efter 15 – 40 minuters behandling med hög energitillförsel minskade plötsligt blodflödet och temperaturen i prostata steg till en effektiv behandlingsnivå. Den plötsliga blodflödesminskningen bedömdes vara en effekt av svullnad och tilltäppning av små blodkärl i prostata.

Under 90-talet utvecklades TUMT fortlöpande. Genom en effektiv genomspolning och därmed kylning av behandlingskatetern kunde energitillförseln ökas. Mikrovågsantennen i behandlingskatetern modifierades och en förbättrad avgränsning av värmeförseln uppnåddes. Högenergi TUMT lanserades och antalet lyckade behandlingar ökade med också objektiva förbättringar såsom kraftigare urinflöde och storleksminskning av prostatakörteln vid kontrollundersökning. En studie gjordes i mitten av 90-talet på 30 patienter i Kalmar där man genom temperaturmätning med hjälp av termometrar, som införts i prostatakörteln, kunde styra behandlingen till minst 55 grader i de flesta fall. Man fick då ett mycket bra behandlingsresultat i ca 60 % av fallen. Denna feedback TUMT kunde i flertalet fall kompensera för höga blodflöden genom hög energitillförsel och förlängd behandlingstid. Med ökande ener-

gitillförsel ökade också patientobehaget under behandling i form av kraftiga urinträngningar, brännande värmekänsla och smärta. Före behandling krävdes medicineringsmedel med smärtstillande och avslappnande medel och ofta ytterligare vid behov under själva behandlingen. Högenergi TUMT orsakar regelmässigt en tillfällig oförmåga att kasta vatten och urinvägskateter krävs under några veckor efter behandlingen. Samtidigt som behandlingsresultaten förbättrades kvarstår sålunda flera olösta problem med TUMT.

- 1) Behandlingen misslyckas mer eller mindre i 30-40% av fallen.
- 2) Behandlingstiden är lång (vanligtvis 1 timme).
- 3) Behandlingen är plågsam för många patienter.
- 4) Behandlingen har begränsat användningsområde – passar ej för inbuktande, alltför stora och alltför små prostatakörtlar. Ej heller för patienter i kronisk urinstämning (kateterbärare).
- 5) Kateter krävs under 1-3 veckor efter behandling.
- 6) Obehag av urinträngningar, smärta och frekventa urintömningar under perioden efter TUMT
- 7) Behandlingseffektens varaktighet efter TUMT är ifrågasatt.

## **ProstaLund Feedback Treatment (PLFT)**

1998 lanserades en uppfinning av Magnus Bolmsjö och medarbetare i ProstaLund där ett temperaturmätningssystem kunde införas direkt i prostata via behandlingskatetern. Denna patenterade teknik har fått namnet ProstaLund Feedback Treatment (PLFT). PLFT-tekniken gör det möjligt att rutinmässigt följa temperaturutvecklingen i prostata under värmebehandlingen och anpassa energitillförseln till varje patient. PLFT-systemet integrerar 2 viktiga parametrar - temperatur och tid i två biofysiska ekvationer. Dessa beräkningar bedömer om en värmebehandlad cell överlever eller dör. Systemets mjukvara beräknar blodflödet i prostata, men också den sammanlagda vävnadsdöden under pågående behandling.

Schelinkatetern<sup>®</sup> är en CE-märkt utrustning som gör det möjligt att via en kateter genom urinröret införa en injektionskanyl i prostatakörteln. Injektioner, med en blandning av lokalbedövningsmedel och adrenalin, kan ges på flera ställen i prostatakörteln före PLFT. Injektionerna har dubbla funktioner.

Lokalbedövningsmedel ger ett reducerat patientobehag under behandling och adrenalin minimerar blodflödet genom sin sammandragande effekt på blodkärnen.

## **Denna avhandling**

De studier som presenteras i denna avhandling tillkom för att ge svar på följande frågor:

- 1) Är det möjligt att sammanfatta all efterhandsinformation avseende temperatur och tid under en värmebehandling, genom att använda 2 biofysiska ekvationer, till kliniskt användbara beräkningar av blodflödet och den sammanlagda vävnadsdöden?
- 2) Hur väl överensstämmer PLFT systemets beräknade vävnadsskada med beräkningar efter utvidgad temperaturmätning i prostata, magnetröntgenundersökning med kontrastmedel som visar vävnadsdöd och mätning av vävnadsskadans storlek med mikroskopi efter avlägsnande av hela prostatakörteln?
- 3) Hur väl står sig behandlingsresultat och komplikationer efter PLFT jämfört med TURP efter 1 år i en kontrollerad, slumpvis fördelad studie utförd på flera sjukhus?
- 4) Hur fungerar PLFT som alternativ till operationsbehandling för BPH patienter med kvarkateter på grund av kronisk urinstämna?
- 5) Hur påverkas behandlingstiden, blodflödet i prostata, energiåtgången samt patientobehaget under PLFT av injektioner med lokalbedövningsmedel och adrenalin i prostatakörteln före behandling?
- 6) Hur påverkas blodflödet i prostatakörteln under PLFT av adrenalininjektioner före behandlingen och hur väl överensstämmer PLFT systemets blodflödesberäkning med blodflödesmätning enligt en referensmetod (PET- kamera)?
- 7) Hur klarar sig PLFT mot kirurgisk behandling (TURP/öppen operation) vid behandling av kateterbundna BPH patienter i kronisk urinstämna i en kontrollerad, jämförande, slumpvis fördelad studie vid flera Skandinaviska sjukhus?
- 8) Hur effektiv och säker är PLFT vid långtidsuppföljning (5 år) jämfört med TURP?

**Delarbete I:** Detta arbete förklarar hur man genom att applicera två biofysiska ekvationer kan i ett första steg beräkna blodflödet i prostatakörteln (Pennes värmeeckvation) och i ett andra steg beräkna vävnadsdöden (Henriques vävnadsskadeintegral) under en pågående värmebehandling. Dessa beräkningar görs fortlöpande under behandling i PLFT systemets mjukvara. Bakgrunden till denna möjlighet är det faktum att en levande cell dör när den utsatts för en kritisk mängd värmeenergi. Beroende på tillförd mängd värmeenergi finns bara två möjliga situationer – cellen överlever eller dör. Detta utgör i praktiken ett ”digitalt” system som gör en matematisk beräkning möjlig. I detta arbete tillämpas denna beräkningsteknik på ett patientmaterial där hypotesen är att beräkningens tillförlitlighet är lika säker som beräkning av prostatakörteln storlek med hjälp av transrektal ultraljudteknik. Denna hypotes bekräftas och även vid hypotetiska beräkningar vid varierande värmekänslighet i vävnaden samt vid måttlig felplacering av temperaturmätningen är överensstämmelsen relativt god. Felberäkningen i systemet uppskattas till som mest  $\pm 8\%$ . Slutsatsen är att metoden är användbar i klinisk tillämpning.

**Delarbete II:** Denna studie gjordes för att undersöka tillförlitligheten av PLFT systemets beräkning av vävnadsdöd. Genom att jämföra med beräkningar efter utvidgad temperaturmätning i 30 – 40 mätpunkter i prostatakörteln hos 8 patienter studeras tillförlitligheten av systemets mätning på 3 ställen. Man jämför också mot kontrastförstärkt magnetrontgen som visar vävnadsskadans storlek indirekt i form av områden med upphävd blodcirkulation. Den verkliga vävnadsskadans storlek undersöktes med mikroskopi på ”storsnitt” av hela prostatakörteln från 5 patienter där prostata bortopererats en tid efter värmebehandlingen. Man fann stora områden med död vävnad och en god överensstämmelse mellan de olika mätningarna vad gäller medelvärden för vävnadsskadans storlek.

**Delarbete III:** Här undersöktes det kliniska utfallet efter 3, 6 och 12 månader i en jämförande studie mellan PLFT och TURP. Patienterna lottades till respektive behandling i förhållandet 2:1. I studien deltog 2 amerikanska, 2 danska och 6 svenska kliniker. Studien gjordes under överinseende av amerikanska Food and Drug Administration (FDA). Man fann ej några statistiskt signifikanta skillnader mellan behandlingarna vad gäller symptomförbättring, livskvalitetsfrågor, urinflödesförbättring eller tryck-flödes förhållande. Storleksminskningen av prostata efter behandling var som förväntat större efter TURP. Antalet lyckade behandlingar enligt vedertagen definition var 82 % efter PLFT och 86 % efter TURP. Behovet av kateter efter behandling var 12

(7-56) dagar efter PLFT och 2 (1-26) dagar efter TURP. Allvarliga komplikationer inträffade i 2 % avfallen efter PLFT och i 17 % efter TURP. Lindriga och måttliga komplikationer såsom urinträngningar och urinstopp var vanligare efter PLFT. Blödningsbesvär var däremot vanligare efter TURP.

**Delarbete IV:** Denna artikel redovisar behandlingsresultatet vid uppföljning av ett kliniskt patientmaterial, där behandlingsindikationen för PLFT har utvidgats till att omfatta även BPH patienter med kronisk urinstämma. På grund av en omänskligt lång väntetid (>1 år) till operationsbehandling, erbjöds 24 patienter på klinikens väntelista PLFT som en snabbare lösning. Samtliga patienter accepterade erbjudandet. Ingen patient exkluderades från behandling på grund av klen urinblåsa eller någon annan kontraindikation. (80 %) 19/24 av patienterna kunde kateterbefrias och hade vid 3 månaders kontroll en tillfredsställande vattenkastning och symptomfrihet. Behovet av en avlastande urinvägskateter efter PLFT var i genomsnitt 26 (9 – 54) dagar. Man fann en ytterligare förbättring av urinflödes hastigheten efter 1 år. Storleksminskningen av prostatakörteln fortsatte efter 3 månader och den var i genomsnitt 42 % mindre än ursprungsstorleken före behandling vid kontroll efter 1 år. Hos samtliga 5 patienter, som inte kunde kateterbefrias efter PLFT, kunde orsaken till de misslyckade behandlingarna identifieras och förklaras.

**Delarbete V:** I denna rapport jämfördes behandlingsdata från 15 patienter som behandlats, enligt klinikens nya rutinmetod PLFT, direkt efter injektioner av lokalbedövningsmedel och adrenalin i prostata med 35 tidigare behandlingar utan denna premedicinering. Man fann att behandlingstiden i medeltal hade halverats och den totala energiåtgången hade minskat med 60 % hos patienterna som fått injektionsmedicinering före mikrovågsbehandlingen. Det uppskattade blodflödet var också halverat. Behovet av lugnande medicin var 50 % lägre och behovet av smärtstillande hade minskat med ca 80 %. Uppföljningsresultaten 3 månader efter behandling var likvärdiga mellan grupperna.

**Delarbete VI:** Denna studie undersöker blodflödet i prostatakörteln med hjälp av radioaktivt vatten [ $^{15}\text{O}$ ]  $\text{H}_2\text{O}$  (PET-kamera) före och under PLFT. I en referensgrupp gavs behandling med PLFT till 3 patienter utan föregående injektioner av lokalbedövningsmedel med adrenalin. Den genomsnittliga behandlingstiden var 61 minuter med en ökning av blodflödet med 50 %, 80 % och 100 % under behandling jämfört med utgångsläget. Till 4 patienter gavs via en specialkateter injektioner med lokalbedövningsmedel innehållande adrenalin på 3 ställen i prostatakörteln före PLFT. Blodflödesbestämning gjordes

på 2 patienter före och efter prostatainjektionerna innan PLFT. Man fann en kraftig minskning med 60 % hos den ene patienten och en mindre uttalad sänkning hos den andra. På ytterligare 2 patienter startades PLFT omedelbart efter lokalbedövning med adrenalin, och man fann vid undersökning under pågående PLFT ingen blodflödesökning i det ena fallet och en kraftig minskning av blodflödet jämfört med utgångsläget i det andra fallet. Genomsnittlig behandlingstid var 34 minuter och energiåtgången minskade kraftigt i gruppen som fick injektioner före PLFT. Det tycks angeläget att behandlingen med PLFT startar omedelbart efter injektionerna då adrenalineffekten på blodcirkulationen i prostatakörteln förefaller att börja minska efter ca 15 min.

**Delarbete VII:** Denna studie är en skandinavisk kontrollerad och jämförande undersökning av kateterberoende BPH patienter (i kronisk urinstämna), där behandlingsresultaten efter PLFT och operationsbehandling (TURP/öppen operation) redovisas efter 6 månaders uppföljning. 125 patienter ingick i studien fördelad på 17 kliniker och patienterna lottades i förhållande 1:1 till respektive behandling. I den ena gruppen opererades 49 patienter med TURP och 10 opererades med öppen operation. I den andra gruppen behandlades 62 patienter med PLFT (12 av dessa hade prostatastorlek >100g). Patienterna kateterbefriades i 80 % av fallen i PLFT gruppen och 90 % i operationsgruppen. Vid jämförelse av kateterbefrielse, symptomlindring, urinflödes hastighet och livskvalitetsfrågor framkom inga statistiskt signifikanta skillnader mellan grupperna. En allvarlig komplikation rapporterades efter PLFT och 5 efter operationsbehandling.

**Delarbete VIII:** Denna studie redovisar uppföljning efter 5 år i "FDA studien" (delarbete III). Man fann inga statistiskt signifikanta skillnader avseende symptombild, urinflödes hastighet och livskvalitetsfrågor. Ytterligare behandling för BPH hade getts till 10 % av patienterna i PLFT - och till 4,3 % i TURP -gruppen. Sena komplikationer var vanligare efter TURP.

## **Sammanfattande slutsatser i avhandlingen**

ProstaLund Feedback Treatment (PLFT) är en vidareutvecklad och förbättrad mikrovågsmetod för värmebehandling av symptomgivande åldersförstorad prostata. Metoden att beräkna mängden avdödad vävnad gör att behandlingen, med kliniskt acceptabel noggrannhet, kan anpassas till varje patient. Jämförande studier mot operationsbehandling visar att PLFT är lika effektiv men har färre allvarliga biverkningar. PLFT kombinerat med injektioner av lokalbedövningsmedel med adrenalin före behandling ger ytterligare fördelar med korta och smärtfria behandlingar. Lyckade behandlingar uppnås sannolikt även hos patienter med höga blodflöden i prostatakörteln där det annars finns risk för misslyckad behandling utan denna teknik. Behandlingsindikationerna för PLFT kan vidgas att även omfatta BPH patienter i kronisk urin-stämning och patienter med mycket stora prostatakörtlar (>100g).

PLFT, som är en minimalinvasiv poliklinisk metod att behandla symptomgivande åldersförstorad prostata, är ur både patient- och samhällsperspektiv en mer attraktiv behandling än operationsbehandling. PLFT borde som lindrigare, lättillgängligare, billigare och mindre riskabel men lika effektiv behandling för patienten kunna ersätta många TURP ingrepp och flertalet öppna operationer.





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## REFERENCES

- Abrams P, Schafer W, Tammela TL, Barrett DM, Hedlund H, Rollema P, Matos-Ferreira A, Nordling J, Bruskewitz R, Andersen JT, Hald T, MUIP, Kirby R, Mustonen S, Cannon A, Jacobsen CA, Gormley GJ, Malice MP, Bach MA. Improvement of pressure flow parameters with finasteride is greater in men with large prostates. Finasteride Urodynamics Study Group. *J Urol*. 1999; 161(5): 1513-7.
- Abrams P. New words for old: lower tract symptoms for "prostatism". *BMJ*. 1994; 308(6934): 929-930.
- Ahl A, Schelin S, Madsen M, Lagerkvist M, Mattiasson A. Initial experiences of microwave thermotherapy of patients with prostate size of or above 100g. *EAU 2004*; Abstract 563.
- Ackerman SJ, Rein AL, Blute M, Beusterien K, Sullivan EM, Tanio CP, Manyak MJ, Strauss MJ. Cost effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: part I-methods. *Urology*. 2000; 20;56(6): 972-80.
- Ahmed M, Bell T, Lawrence WT, Ward JP, Watson GM. Transurethral microwave thermotherapy (Prostatron® version 2.5) compared with transurethral resection of the prostate for the treatment of benign prostatic hyperplasia: a randomized, controlled, parallel study. *BJU* 1997; 79: 181-185.
- Andersen JT. Prostatism. III. Detrusor hyperreflexia and residual urine. Clinical and urodynamic aspects and the influence of surgery on the prostate. *Scand J Urol Nephrol*. 1982;16(1): 25-30.
- Andersen JT. Prostatism: Clinical, clinical radiological and urodynamic aspects. *Neurourol. Urodyn* 1982; 1: 241-293.
- Andersen JT. Alpha 1-blockers vs 5 alpha-reductase inhibitors in benign prostatic hyperplasia. A comparative review. *Drugs Aging*. 1995; 6(5): 388-96.
- Andersson SO, Rashidkhani B, Karlberg L, Wolk A, Johansson JE. Prevalence of lower urinary tract symptoms in men aged 45-79 years: a population-based study of 40 000 Swedish men. *BJU* 2004; 94: 327-331.
- Arai Y, Aoki Y, Okubo K, Maeda H, Terada N, Matsuta Y, Maekawa S, Ogura K. Impact of interventional therapy for benign prostatic hyperplasia on quality of life and sexual function: a prospective study. *J Urol*. 2000; 164(4): 1206-11.

Astrahan MA, Sapozink MD, Cohen D, Luxton G, Kampp TD, Boyd S, Petrovich Z. Microwave applicator for transurethral hyperthermia of benign prostatic hyperplasia. *Int J Hyperthermia*. 1989; 5(3): 283-96.

Astrahan MA, Ameye F, Oyen R, Willemen P, Baert L and Petrovich Z. Interstitial Temperature Measurements during Transurethral Microwave Hyperthermia. *J Urol*. 1991; 145: 304 – 308.

Astrahan M, Imanaka K, Jozsef G, Ameye F, Baert L, Sapozink MD, Bo S, Petrovich Z. Heating characteristics of a helical microwave applicator for transurethral hyperthermia of benign prostatic hyperplasia. *Int J Hyperthermia*. 1991; 7(1): 141-55.

AUA Practice Guidelines Committee: Chapter 1; Diagnosis and treatment recommendations. *J Urol* 2003; 170: 530-547.

Bakke A, Myhr KM, Gronning M, Nyland H. Bladder, bowel and sexual dysfunction in patients with multiple sclerosis—a cohort study. *Scand J Urol Nephrol* 1996; (Suppl 179): 61.

Bates TS, Reynard JM, Peters TJ, Gingell JC. Determination of prostatic volume with transrectal ultrasound; a study of intra-observer and interobserver variation. *J Urol* 1996;155: 1299-300.

Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol* 1984; 132: 474-9.

Bhowmick P, Coad JE, Bhowmick S, Pryor JL, Larson T, De La Rosette JJ, Bischof JC. In vitro assessment of the efficacy of thermal therapy in human benign prostatic hyperplasia. *Int J Hyperthermia*. 2004; 20(4): 421-39.

Blute ML, Lewis RW. Local microwave hyperthermia as a treatment alternative for benign prostatic hyperplasia. *J Androl*. 1991; 12(6): 429-34.

Blute M, Ackerman SJ, Rein AL, Beusterien K, Sullivan EM, Tanio CP, Strauss MJ, Manyak MJ. Cost effectiveness of microwave thermotherapy in patients with benign prostatic hyperplasia: part II—results. *Urology*. 2000; 56(6): 981-7.

Bolmsjö M., Wagrell L., Hallin A., Eliasson T., Erlandsson B-E., Mattiasson A: The heat is on - but how? A comparison of TUMT devices. *Br J Urol* 1996; 78: 564.

Bolmsjö, M., Stuesson, C., Wagrell, L., Andersson-Engels, S. Mattiasson, A.: Optimizing transurethral microwave thermotherapy a model for studying power, blood flow, temperature variations and tissue destruction. *Br J Urol*, 1998; 81: 811-6.

Borboroglu PG, Kane CJ, Ward JF, Roberts JL, Sands JP. Immediate and postoperative complications of transurethral prostatectomy in the 1990s. *J. Uro.* 1999; 162: 1307-1310.

Boyle P, Maisonneuve P, Steg A. Decrease in mortality from benign prostatic hyperplasia: a major unheralded health triumph. *J. Urol.* 1996; 155: 176-180.

Boyle P, Fang Liu GU, Jacobsen S, Ogawa O, Oishi K, O'Reilly P. Epidemiology and Natural History. 5th International Consultation on Benign Prostatic Hyperplasia (BPH) - June 25- 28, 2000, Paris.

Bruskewitz RC, Reda DJ, Wasson JH, Barret L, Phelan M. Testing to predict outcome after transurethral resection of the prostate. *Journal of Urology* 1997; 157: 1304-1308.

Bruskewitz et al: From Proceedings 4th International Consultation on Benign Prostatic Hyperplasia, Paris 1997; 523.

Cabelin MA, E. Te A, Kaplan SA. Benign prostatic hyperplasia: challenges for the new millennium. *Cur Op Urol Vol* 2000; vol 10. 4: 301-6.

Carter S, Tubaro A. Relation between intraprostatic temperature and clinical outcome in microwave thermotherapy. *J Endourol.* 2000; 14(8): 617-25.

Chaussy C, Thuroff S. Is high temperature-TUMT an effective and riskless option for obstructed ASA III/IV BPH patients? *Eur Urol* 1996; 30 suppl.2: 368.

Chen SS, Hong JG, Hsiao YJ, Chang LS. The correlation between clinical outcome and residual prostatic weight ratio after transurethral resection of the prostate for benign prostatic hyperplasia. *BJU Int.* 2000; 85(1): 79-82.

Christensen MG, Nordling J, Andersen JT, Hald T. Functional bladder neck obstruction. Results of endoscopic bladder neck incision in 131 consecutive patients. *Br J Urol.* 1985; 57(1): 60-2.

Chute CG, Stephenson WP, Guess HA et al Benign prostatic hyperplasia: A population based study *Eur Urol* 1991; 20 (suppl 2): 11-17.

Clegg EJ. The vascular arrangements within the human prostate gland. *Br J Urol.* 1956; 28(4): 428-35.

Corica FA, Cheng L, Ramnani D, Pacelli A, Weaver A, Corica AP, Corica AG, Larson TR, O'Toole K, Bostwick DG. Transurethral hot-water balloon thermoablation for benign prostatic hyperplasia: patient tolerance and pathologic findings. *Urology* 2000; 56(1): 76-80; discussion 81.

Corica AP, Larson BT, Sagaz A, Corica AG, Larson TR. A novel temporary prostatic stent for the relief of prostatic urethral obstruction. *BJU Int.* 2004; 93(3): 346-8.

Dahlstrand C, Walden M, Geirsson G, Pettersson S. Transurethral microwave thermotherapy versus transurethral resection for symptomatic benign prostatic obstruction: a prospective randomized study with a 2-year follow-up. *Br J Urol.* 1995; 76(5): 614-8.

D'Ancona FC, Francisca EA, Witjes WPJ, Welling L, Debruyne FM, De La Rosette JJ. Transurethral resection of the prostate vs high-energy thermotherapy of the prostate in patients with benign prostatic hyperplasia: long-term results. *BJU* 1998; 81: 259-264.

D'Ancona FC, van der Bij AK, Francisca EA, Kho H, Debruyne FM, Kienemeney LA, de la Rosette JJ. Results of high-energy transurethral microwave thermotherapy patients categorized according to the American Society of Anesthesiologists operative risk classification. *Urology.* 1999;53(2): 322-8.

David RD, Grunberger I, Shore N and Swierzewski S. Multicenter initial U.S. experience with CoreTherm-monitored feedback transurethral microwave thermotherapy for individualized treatment of patients with symptomatic benign prostatic hyperplasia. *J Endourol.* 2004; 18(7): 682-685.

Debruyne FMJ et al. Proceedings 5th International Consultation on Benign Prostatic Hyperplasia; Interventional Therapy; Paris 2000.

Debicki P, Astrahan MA, Ameye F, Oyen R, Baert L, Haczewski A, Petrovich Z. Temperature steering in prostate by simultaneous transurethral and transrectal hyperthermia. *Urology.* 1992; 40(4): 300-7.

de la Rosette JJ, D'Ancona FCH, Debruyne FMJ. Current status of thermoherapy of the prostate. *J Urol* 1997 (A); 157: 430.

de la Rosette JJ, Alivizatos G, Madersbacher S et al: EAU Guidelines on benign prostatic hyperplasia (BPH). *Eur. Urol* 2001; 40(3): 256-263.

de la Rosette JJ, Laguna MP, Gravas S, de Wildt MJ. Transurethral microwave thermotherapy: the gold standard for minimally invasive therapies for patients with benign prostatic hyperplasia? *J Endourol.* 2003; 17(4): 245-51.

de la Rosette JJ, Floratos DL, Severens JL, Kiemeny LA, Debruyne F: Pilar Laguna M. Transurethral resection vs microwave thermotherapy of the prostate: a cost-consequences analysis. *BJU Int.* 2003; 92(7): 713-8.

Devonec M, Cathaud M, St. Carter S, et al.: Transurethral microwave application: Temperature sensation and thermokinetics of human prostate [abstract1713]. *J Urol* 1990; 143(pt 2): 414A.

Devonec, M., Berger, N. and Perrin, P.: Transurethral microwave heating of the prostate - or from hyperthermia to thermotherapy. *J. Endourol* 1991; 5: 129.

Devonec M, Tomera K, Perrin P. Review: Transurethral microwave thermotherapy in benign prostatic hyperplasia. *J Endourol* 1993; (7) 3: 255-259.

Devonec M, Berger N, Fendler JP, Joubert P, Nasser M, Perrin P. Thermoregulation during transurethral microwave thermotherapy: experimental and clinical fundamentals. *Eur Urol.* 1993; 23 Suppl 1: 63-7.

Devonec, M., Carter, S. St. C., Tubaro, A., de la Rosette, J. J. M. C. H., Hofher, K. and Perrin, P. Microwave therapy. *Curr. Opin. Urol* 1995; 5: 3.

Devonec M, Dahlstrand C. Temporary urethral stenting after high-energy transurethral microwave thermotherapy of the prostate. *World J Urol.* 1998; 16(2): 120-3.

Djavan B, Larson TR, Blute ML, Marberger M. Transurethral microwave thermotherapy: what role should it play versus medical management in the treatment of benign prostatic hyperplasia? *Urology* 1998; 52(6): 935-4.

Djavan B, Seitz C, Ghawidel K, Basharkhah A, Bursa B, Hruby S, Marberger M. High- energy transurethral microwave thermotherapy in patients with acute urinary retention due to benign prostatic hyperplasia. *Urology* 1999; 54(1): 18-22.

Djavan B, Nickel JC, de la Rosette J, Abrams P. The urologist view of BPH progression: results of an international survey. *Eur Urol.* 2000; 41(5): 490-6.



de Wildt MJ, de la Rosette JJ. Transurethral microwave thermotherapy: an evolving technology in the treatment of benign prostatic enlargement. *BJU* 1995; 76: 531-538.

de Wildt MJ, Tubaro A, Hofner K, Carter SS, de la Rosette JJ, Devonec M. Responders and nonresponders to transurethral microwave thermotherapy: a multicenter retrospective analysis. *J Urol*. 1995; 154(5): 1775-8.

Garnett S, Abrams P. Clinical aspects of the overactive bladder and detrusor overactivity. *Scand J Urol Nephrol Suppl*. 2002;(210): 65-71.

Garraway WM, Collins GN, Lee RJ. High prevalence of benign prostatic hypertrophy in the community. *The Lancet* 1991; 338: 469-71.

Goldfarb B, Bartkiw T, Trachtenberg J. Microwave therapy of benign prostatic hyperplasia. *Urol Clin North Am* 1995; 22: 431.

Goya N, Ishikawa N, Ito F, Kobayashi C, Tomizawa Y, Toma H. Transurethral ethanol injection therapy for prostatic hyperplasia; 3-year results. *J Urol*. 2004; 172(3): 1017-20.

Grabe M, Forsgren A, Hellsten S. The effect of a short antibiotic course in transurethral prostatic resection. *Scand J Urol Nephrol*. 1984; 18(1): 37-42.

Grise P, Plante M, Palmer J, Martinez-Sagarra J, Hernandez C, Schettiin M, Gonzalez-Martin M, Castineiras J, Ballanger P, Teillac P, Rolo F, Baena V, Erdmann J, Mirone V. Evaluation of the transurethral ethanol ablation of the prostate (TEAP) for symptomatic benign prostatic hyperplasia (BPH): a European multi-center evaluation. *Eur Urol*. 2004; 46(4): 496-501; discussion 501-2.

Graber S, Schmid DM, Tscholl RRF. ProstaLund Feedback Thermotherapy vs TUR-P in BPH: A prospectively randomized study of a novel method in comparison to the standard treatment. *J Endourol*. 2002; 16, suppl. 1, P 11-13.

Gravas S, Laguna MP, de la Rosette JJ. Efficacy and safety of intraprostatic temperature-controlled microwave thermotherapy in patients with benign prostatic hyperplasia: results of a prospective, open-label, single-center study with 1-year follow-up. *J Endourol*. 2003; 17(6): 425-30.

Guess HA, Arrighi HM, Metter EJ, et al. The cumulative prevalence of prostatism matches the autopsy prevalence of benign prostatic hyperplasia. *Prostate* 1990; 17: 241-246.

Hald T. Urodynamics in benign prostatic hyperplasia: a survey. *Prostate Suppl.* 1989; 2: 69-77.

Hallin A, Berlin T. Transurethral microwave thermotherapy for benign prostatic hyperplasia: clinical outcome after 4 years. *J Urol.* 1998; 159(2): 459-64.

Hammarsten J, Hogstedt B. Calculated fast-growing benign prostatic hyperplasia—a risk factor for developing clinical prostate cancer. *Scand J Urol Nephrol.* 2002; 36(5): 330-8.

Hellsten S, Forsgren A, Bjork T, Grabe M. Use of ciprofloxacin in patients undergoing transurethral prostate surgery. *Scand J Infect Dis Suppl.* 1989; 60: 104-7.

Henriques FC. Studies of thermal injury. *Arch Pathol* 1947; 43: 489.

Hjertberg H, Jorfeldt L, Schelin S. Use of ethanol as marker substance to increase patient safety during transurethral prostatic resection. Screening investigation of irrigating fluid absorption in four hospitals and comparison of experienced and inexperienced urologists. *Urology.* 1991; 38(5): 423-8.

Holtgrave H, Valk W. Factors influencing the mortality and morbidity of transurethral prostatectomy. *J. Urol* 1962; 87: 450-459.

Horninger W, Unterlechner H, Strasser H, Bartsch G. Transurethral prostatectomy: mortality and morbidity. *Prostate.* 1996; 28(3): 195-200.

Hryntschak T. Suprapubic transvesical prostatectomy with primary closure of the bladder; improved technic and latest results. *J Int Coll Surg.* 1951; 15(3): 366-8.

Fitzmaurice H, Fowler CJ, Rickhards D, Kirby RS, Quin NP. Micturition disturbances in Parkinson's disease. *Br J Urol* 1985; 57: 652.

Inaba T., Quantitative Measurement of Prostatic Blood Flow and Blood Volume by Positron Emission Tomography, *J. Urol,* 1992; 148: 1457.

Jensen KME. Clinical evaluation of routine urodynamic investigations in prostatism. *Neurourol Urodyn* 1989; 8: 545-578.

Jung HA. generalized concept for cell killing by heat, *Radiat. Res* 1986; 106: 56-72.

Jung HA. generalized concept for cell killing by heat, effect of chronically induced thermotolerance, *Radiat. Res* 1991; 127: 235-242.

Kellner DS, Armenakas NA, Brodherson M, Heyman J, Fracchia JA. Efficacy of high-energy transurethral microwave thermotherapy in alleviating medically refractory urinary retention due to benign prostatic hyperplasia. *Urology* 2004; 64: 703-706.

Khair AA, Pacelli A, Iczkowski KA, Cheng L, Corica FA, Larson TR, Corica A, Bostwick DG. Does transurethral microwave thermotherapy have a different effect on prostate cancer than on benign or hyperplastic tissue? *Urology*. 1999; 54(1): 67-72.

Knutson T. On investigations of patients with Lower Urinary Tract Symptoms due to suspected Bladder Outlet Obstruction. 2000; Thesis: Sahlgrenska University hospital, Sweden.

Knutson T, Edlund C, Fall M, Dahlstrand C. BPH with coexisting overactive bladder dysfunction – an every day urological dilemma. *Neurourol Urodyn*. 2001; 20(3): 237-247.

Kobelt G, Spångberg A, Mattiasson A. The cost of feedback microwave thermotherapy compared with transurethral resection of the prostate for treating benign prostatic hyperplasia. *BJU* 2004; 93: 543-548.

Koskimäki J, Hakama M, Huhtala H and Tammela T.L.J. Association of non-urological diseases with lower urinary tract symptoms. *Scand J Urol Nephrol* 2001; 35: 377-381.

Kyprianou N, Tu H, Jacobs SC. Apoptotic versus proliferative activities in human benign prostatic hyperplasia. *Human Path* 1996; 27: 668-675.

Laguna MP, Alivizatos G, De La Rosette JJ. Interstitial laser coagulation treatment of benign prostatic hyperplasia: is it to be recommended? *J Endourol*. 2003; 17(8): 595-600.

Lee C, Kozlowski JM, Grayhack JT. Etiology of benign prostatic hyperplasia. *Urol Clin North Am* 1995; 22: 237-246.

- Larson BT, Bolmsjö M, Wagrell L, Larson TR. ProstaLund Feedback Thermotherapy: A Review. *Current Urology Reports* 2003; 4: 292-296.
- Larson TR, Coricka A, Bostwick D. Extent of thermal cell death correlated to accurate interstitial temperatures of ten pathologic prostate specimens using Urologix T3 microwave transurethral thermal therapy unit. In: Proc X:th congr Eur Assoc Urol, Berlin 1994: 335.
- Larson TR, Collins JM. Increased prostatic blood flow in response to microwave thermal treatment: preliminary findings in two patients with benign prostatic hyperplasia. *Urology* 1995; 46(4): 584-90.
- Larson TR, Blute ML, Tri JL, Whitlock SV. Contrasting heating patterns and efficiency of the Prostatron and Targis microwave antennae for thermal treatment of benign prostatic hyperplasia. *Urology* 1998; 51(6): 908-15.
- Larson TR, Collins JM, Corica A. Detailed interstitial temperature mapping during treatment with a novel transurethral microwave thermoablation system in patients with benign prostatic hyperplasia. *J Urol.* 1998; 159(1): 258-64.
- Lepor H, Gup DI, Baumann M, et al. Laboratory assessment of terazosin and alpha-1 adrenergic receptor in human benign prostatic hyperplasia. *Urology* 1988; 32(Suppl 6): 21-26.
- Lepor, H. and Rigaud, G. The efficacy of transurethral resection of the prostate in men with moderate symptoms of prostatism. *J. Urol.* 1990; 143: 533.
- Lu-Yao G, Barry MJ, Chang CH, Wasson JH, Wenneberg JE. Transurethral resection of the prostate among Medicare beneficiaries in the United States: Time trends and outcomes. *Urology* 1994; 44: 692-698.
- Marberger MJ, Andersen JT, Nickel JC, Malice MP, Gabriel M, Pappas Meehan A, Stoner E, Waldstreicher J. Prostate volume and serum prostate-specific antigen as predictor of acute urinary retention. Combined experience from three large multinational placebo-controlled trials. *Eur Urol.* 2000; 38(5): 563-8.
- Mattiasson A, Blaakaer J, Hoye K, Wein AJ; Tolterodine Scandinavian Study Group. Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder. *BJU Int.* 2003; 91(1): 54-60.

McConnell et al. Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. The long-term effect of doxazosin, finasteride and the combination therapy on clinical progression of benign prostatic hyperplasia. *N Engl J Med.* 2003; 349(25): 2387-98.

McNeal JE. The zonal anatomy of the prostate. *The Prostate* 1981; 2: 35-49.

Mebust WK, Holtgrewe HL, Cockett ATK, Peters PC, and Writing Committee: Transurethral prostatectomy: Immediate and postoperative complications. A cooperative study of 13 participating institutions evaluating 3.885 patients. *J Urol* 1989; 141: 243.

Meyhoff, HH and Nordling J. Long term results of transurethral and transvesical prostatectomy. A randomized study. *Scand. J. Urol. Nephrol.* 1986; 20: 27.

Meyhoff HH, Hald T, Nordling J, Andersen JT, Bilde T and Walter S. A new weighted symptom score system (DAN-PSS-1). Clinical assessment of indications and outcomes of transurethral prostatectomy for uncomplicated benign prostatic hyperplasia. *Scand J Urol Nephrol.* 1993; 27(4): 493-499.

Millin T. Retropubic prostatectomy: a new extravesical technique report on 20 cases 1945. *J Urol.* 2002; 167: 976-979.

Mochtar CA, Kiemeny LA, van Riemsdijk MM, Barnett GS, Laguna MP Debruyne FM, de la Rosette JJ. Prostate-specific antigen as an estimator of prostate volume in the management of patients with symptomatic benign prostatic hyperplasia. *Eur Urol.* 2003; 44(6): 695-700.

Mutagushi K, Shinohara K, Matsubara A, Yasumoto H, Mita K and Usui T. Local Anesthesia during 10 core biopsy of the prostate: comparison of 2 methods. *J Urol* 2005; 173: 742-745.

Nitti VW, Kim Y, Combs AJ. Voiding dysfunction following transurethral resection of the prostate: symptoms and urodynamic findings. *J Urol* 1997; 157: 600-603.

Noble SM, Coast J, Brookes S, Neal DE, Abrams P, Peters TJ, Donovan JL. Transurethral prostate resection, noncontact laser therapy or conservative management in men with symptoms of benign prostatic enlargement? An economic evaluation. *J Urol.* 2002; 168(6): 476-82.

Ogden CW, Reddy P, Johnson H, Ramsay JW, Carter SS. Sham versus transurethral microwave thermotherapy in patients with symptoms of benign prostatic bladder outflow obstruction. *Lancet*. 1993; 341(8836): 14-7.

Orandi A. Urological endoscopic surgery under local anesthesia: A cost-reducing idea. *J Urol*. 1984; 132: 1146-47.

Osman YM, Larson TR, El-Diasty T, Ghoneim MA. Correlation between central zone perfusion defects on gadolinium enhanced MRI and intraprostatic temperatures during transurethral microwave thermotherapy. *J Endourol*. 2000; 14(9): 761-6.

Partin, A, Page, B, Lee, et al. Concordance rates for benign prostatic disease among twins suggest hereditary influence. *Urology* 1994; 44(5): 646-50.

Pennes HH. Analysis of tissue and arterial blood temperatures in the resting human forearm. *J Appl. Physiol*. 1948; 1: 93-122.

Roberts RO, Rhodes T, Panser LA, et al. Association between family history of benign prostatic hyperplasia and urinary symptoms: results of a population-based study. *Am J Epidemiol* 1995; 142: 965-973.

Roehrborn CG, McConnell JD, Lieber M, Kaplan S, Geller J, Malek GH, Castellanos R, Coffield S, Saltzman B, Resnick M, Cook T, Waldstreicher J. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS study group. *Urology* 1999; 53: 473-480.

Roehrborn CG, McConnel JD, Barry MJ et al: Guideline on the management of benign prostatic hyperplasia (BPH). 2003: AUA Education and Research, Inc®.

Sanda MG, Doehring CB, Binkowitz B, Beaty TH, Partin AV, Hale E, Stoner E and Walsh PC. Clinical and biological characterization of familial benign prostatic hyperplasia. *J Urol* 1997; 157: 876-879.

Sinha B, Haikel G, Lange PH, Moon TD, Narayan P. Transurethral resection of the prostate with local anesthesia in 100 patients. *J Urol*. 1986; 135: 719-21.

Sirls LT, Kirkemo AK, Jay J. Lack of correlation of the American Urological Association symptom 7 Index with urodynamic bladder outlet obstruction. *Neurourol Urodyn* 1996; 15(5): 447-456.

Stoner E, Three-year safety and efficacy data on the use of Finasteride in the treatment of benign prostatic hyperplasia. *Urology* 1994; 43: 284-294.

Sturesson C, L Liu D, Stenram U, Andersson-Engels S. Hepatic inflow occlusion increases the efficacy of interstitial laser-induced thermotherapy in rat. *J Surg Res* 1997; 71: 67-72.

Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991; 145: 984-987.

Thomas AW, Cannon A, Bartlett E, Ellis-Jones J, Abrams P. The natural history of lower urinary tract dysfunction in men: the influence of detrusor underactivity on the outcome after transurethral resection of the prostate with a minimum 10-year urodynamic follow-up. *BJU Int.* 2004; 93(6): 745-50.

Trock BJ, Brotzman M, Ute WJ, Ugarte RR, Kaplan SA, Larson TR, Blute ML, Roehrborn CG, Partin AW. Long-term pooled analysis of multicenter studies of cooled thermotherapy for benign prostatic hyperplasia results at three months through four years. *Urology* 2004; 63(4): 716-21.

Tubaro A, Carter SS, de la Rosette J, Hofner K, Trucchi A, Ogden C, Miano L, Valenti M, Jonas U, Debruyne F. The prediction of clinical outcome from transurethral microwave thermotherapy by pressure-flow analysis: a European multicenter study. *J Urol.* 1995; 153(5): 1526-30.

Venn SN, Hughes SW, Montgomery BSI, Timothy A. Heating characteristics of a 434 MHz transurethral system for the treatment of BPH and interstitial thermometry. *Int. J. Hyperthermia* 1996; 12; 2: 271-278.

Wagrell L, Schelin S, Bolmsjö M, Brudin L: Intraprostatic temperature monitoring during transurethral microwave thermotherapy for the treatment of benign prostatic hyperplasia. *J Urol* 1998; 159: 1583.

Wagrell L, Schelin S, Bolmsjö MB, Mattiasson A. Aspects on transurethral microwave thermotherapy of benign prostatic hyperplasia. *Tech Urol.* 2000; 6(4): 251-5.

Wagrell L, Schelin S, Nordling J, Richthoff J, Magnusson B, Schain M, Larson T, Boyle E, Duelund J, Krøyer K, Ageheim H, Mattiasson A. Three-year follow-up of feedback microwave thermotherapy versus TURP for clinical BPH: a prospective randomized multicenter study. *Urology* 2004; 64(4): 698-702.

Wagrell L, Sundin A, Norlén BJ. Intraprostatic blood-flow changes during Prostalund Feedback Treatment measured by positron emission tomography. *J Endourol.* 2005; 19(7): 873-877.

Xu LX, Rudle E, Holmes KR. Transurethral thermal therapy (T3) for the treatment of benign prostatic hyperplasia (BPH) in the canine: analyses using the Pennes bio heat equation. *HTD-ASME* 1993; Vol. 268: 31-35.

Yerushalmi A, Shani A, Fishelovitz Y, Arielly J, Singer D, Levy E, Katsnelson R, Rakowsky E, Stein JA. Local microwave hyperthermia in the treatment of carcinoma of the prostate. *Oncology.* 1986; 43(5): 299-305.

Yerushalmi A. Use of local hyperthermia for the treatment of benign prostatic hyperplasia. *Adv Exp Med Biol.* 1990; 267: 167-76.

Zaida A, Rosenblum M, Crawford ED. Benign prostatic hyperplasia: an overview. *Urology* 1999; 53(3A): 1-6.

Zlotta AR, Giannakopoulos X, Maehlum O, Ostrem T, Schulman CC. Long-term evaluation of transurethral needle ablation of the prostate (TUNA) for treatment of symptomatic benign prostatic hyperplasia: clinical outcome up to five years from three centers. *Eur Urol.* 2003; 44(1): 89-93.