Transurethral microwave thermotherapy and transurethral resection of the prostate

Evaluation and development

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Cover illustration: the Schelin Catheter™ (ProstaLund AB, Lund, Sweden). Permission granted.

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To my beloved sons Erik, Filip and Johan

En gång
gjorde jag matchens enda mål.
Motståndaren vann.
Trots idiotförklaring
var jag lycklig.
För det var en
vacker lobb!

Dikten Bakåtpassningen av Bengt Cidden Andersson
Ur diktsamlingen Hela bollen ska ligga still…

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ABSTRACT

Lower urinary tract symptoms (LUTS) are common among men and become more prevalent with increasing age. One frequent cause is benign prostatic obstruction (BPO). Patients with LUTS/BPO can be ameliorated if the obstructive tissue is removed. The surgical reference methods are transurethral resection of the prostate (TURP) in prostates 30-80 ml, and transvesical (or transcapsular) adenoma enucleation (TAE) in prostates >80-100ml. An outpatient alternative to TURP and TAE is transurethral microwave thermotherapy (TUMT).

In **Paper I**, we evaluated the accuracy of the calculated cell kill (CK) using advanced TUMT, the CoreTherm Concept (CoreTherm®, ProstaLund AB, Lund, Sweden). A total of 278 treatments were retrospectively analysed. It was apparent that CK calculated by the software during treatment underestimated the actual prostate volume reduction. For prostate volumes <100 ml before treatment the prostate volume reduction measured by transrectal ultrasound (TRUS) was 26% ($p=0.003$), and for prostate volumes ≥100 ml the prostate volume reduction measured by TRUS was 31% ($p<0.001$).

Paper II was a study with the primary objective of evaluating pretreatment parameters in order to estimate an appropriate thermal dose for each case. It was evident that energy delivery was correlated to prostate volume ($p<0.001$), the larger the prostate, the more energy was needed to achieve the desired volume reduction. The study also showed that age correlated to energy consumption ($p=0.01$), where older men required less energy, despite having the same prostate size. Consequently, it is possible to calculate the thermal dose before treatment and use this as an alternative treatment endpoint.

In **Paper III**, the short- and long-term efficacy of the CoreTherm Concept and CoreTherm in prostates ≥ 80 ml were evaluated in 570 patients. Patients treated 1999-2015 were included and followed up until the end of 2019. A total of 17 patients (3.0%) were retreated with TAE and 54 patients (9.5%) with TURP. The conclusion was that the CoreTherm Concept is a valuable outpatient option to surgery for patients with large prostates.

Paper IV was an open, prospective, controlled, randomised multicenter study of TURP after intraprostatic injections of mepivacaine and adrenaline (MA) versus regular TURP in patients with LUTS/BPO. The primary objective of this study was to determine whether injections of MA, administered via the Schelin Catheter (Schelin Catheter™, ProstaLund AB, Lund, Sweden) before and during TURP, reduced perioperative bleeding. The results indicate that it might be beneficial to apply intraprostatic injections of MA in conjunction with TURP, although further studies are deemed necessary.

Keywords: TUMT, CoreTherm, the CoreTherm Concept, TURP, adrenaline

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SAMMANFATTNING PÅ SVENSKA

Godartad prostataförstoring är vanligt bland medelålders och äldre män och kan medföra lätta, måttliga eller svåra vattenkastningsbesvär. Orsaken kan vara att den förstorade prostatan hindrar urinflödet. Det innebär att behandlingen för dessa män är att avlägsna den körtelvävnad som helt eller delvis är orsaken till besvären. Den klassiska metoden, som använts i decennier med goda resultat, är att hyvla bort prostatavävnaden via ett instrument som förs in i urinröret. Denna metod, transuretral resektion av prostata (TURP), är vida använd i världen och betraktas som standardmetod. Vanligen anser man att TURP kan användas på körtlar som är måttligt förstorade och att andra alternativ bör användas på de allra minsta respektive största körtlarna.

Transuretral (via urinröret) mikrovågsterapi (TUMT) är ett alternativ till operation och kan enkelt utföras i samband med ett besök på en öppenvårdsmottagning. Metoden utförs under lokalbedövning. En utvecklad form av TUMT, med intraprostatisk temperaturmätning, är behandling med CoreTherm (CoreTherm®, ProstaLund AB, Lund, Sweden). Denna behandling föregås, sedan början av 2000-talet, av injektion med lokalbedövning med mepivakain och adrenalin (MA) och benämns *the CoreTherm Concept*. Det övergripande syftet med denna avhandling var att utvärdera och utveckla behandlingsmetoderna TURP och avancerad TUMT.

Syftet med **Studie I** var att utvärdera volymreduktionen i samband med att man använder sig av injektioner med MA, vilket inte var fallet under de första årens behandlingar med CoreTherm, i slutet av 1990-talet och början på 2000-talet. Studien visade att mjukvaran underskattar volymreduktionen i samband med dessa injektioner. Detta är en högst väsentlig slutsats, som har en direkt inverkan på hur behandlingen utförs.

Studie II visade att det finns ett samband mellan prostatavolym och ålder gentemot energibehov då man använder injektioner med MA vid behandling med CoreTherm. Energibehovet ökade med ökande prostatavolym och minskade med ökande ålder. Detta innebär även att det är möjligt att använda sig av energiberäkning innan behandling påbörjas, som ett alternativt slutmål.

Studie III utvärderade behandlingsresultaten för CoreTherm, med och utan MA bland män med stora prostatakörtlar. Totalt 570 män, behandlade 1999-2015 utvärderades, främst avseende eventuell ombehandling fram till och med år 2019. Denna studie, med en medeluppföljningstid på 10 år visade att endast 12.5% behövde ombehandlas med operation.

Studie IV hade som syfte att utvärdera effekten av injektioner med MA i samband med TURP. Det primära behandlingsmålet var att beräkna skillnaden i blödning per gram avlägsnad vävnad. Vi fann att resultaten pekar mot att det kan vara fördelaktigt att använda sig av intraprostatiska injektioner av MA vid TURP.

LIST OF PAPERS

This thesis is based on the following papers, referred to in the text by their Roman numerals.

I. **Stenmark F**, Brudin L, Stranne J, Peeker R. High-energy feedback microwave thermotherapy and intraprostatic injections of mepivacaine and adrenaline: an evaluation of calculated cell kill accuracy and responder rate. Scand J Urol. 2014;48(4):374-8.

II. **Stenmark F**, Brudin L, Kjölhede H, Peeker R, Stranne J. Prostate volume and age are predictors of energy delivery using the CoreTherm Concept in patients with LUTS/BPO: a study on thermal dose. Scand J Urol. 2020;54(3):248-52.

III. **Stenmark F**, Brudin L, Kjölhede H, Peeker R, Stranne J. Transurethral microwave thermotherapy in 570 patients with prostate volumes of 80-366 ml: an evaluation of short- and long-term efficacy. *In manuscript.*

IV. **Stenmark F**, Brudin L, Gunnarsson O, Kjölhede H, Lekås E, Peeker R, Richthoff J, Stranne J. A randomised study of TURP after intraprostatic injections of mepivacaine and adrenaline versus regular TURP in patients with LUTS/BPO. *In manuscript*.

CONTENTS

ABBREVIATIONS

AUA	American Urological Association
AUR	Acute urinary retention
BPE	Benign prostatic enlargement
BPH	Benign prostatic hyperplasia
BPO	Benign prostatic obstruction
CK	Cell kill
CUR	Chronic urinary retention
EAU	European Association of Urology
IPSS	International Prostate Symptom Score
LUTS	Lower urinary tract symptoms
MA	Mepivacaine and adrenaline
MIS	Madsen-Iversen Score
PLFT	ProstaLund Feedback Treatment
TAE	Transvesical (or transcapsular) adenoma enucleation
TRUS	Transrectal ultrasound
TUMT	Transurethral microwave thermotherapy or transurethral microwave therapy
TURP	Transurethral resection of the prostate

DEFINITIONS IN SHORT

Adrenaline	A hormone and neurotransmitter that causes constriction of arteries via sympathetic nerve fibres. The same as epinephrine.
Cell kill	During treatment with CoreTherm the estimated volume reduction in percent is continuously calculated, named cell kill.
CoreTherm	TUMT with feedback technique (the same as PLFT).
Epinephrine	A hormone and neurotransmitter that causes constriction of arteries via sympathetic nerve fibres. The same as adrenaline.
Intraprostatic sensor	IP sensor. A sensor that is inserted into the prostate via the treatment catheter and measures temperatures within the prostate during treatment.
Logical temperature curves	When the treatment catheter is correctly placed, the temperature input from the IP sensor is correctly measured, leading to logical temperature curves.
Microwaves	Electromagnetic waves of a specific wavelength.
PLFT	ProstaLund Feedback Treatment. TUMT with feedback technique (the same as CoreTherm).

Primary treatment endpoint	The treatment is ended when the primary treatment of 20% cell kill is achieved.
The CoreTherm Concept	A treatment concept using CoreTherm with intraprostatic injections of mepivacaine and adrenaline via the Schelin Catheter.
The Schelin Catheter	A catheter with a plastic injection needle that enables intraprostatic injections.

1 INTRODUCTION

If you can't explain it simply, you don't understand it well enough.
Albert Einstein

Curative treatment in men with lower urinary tract symptoms (LUTS) due to benign prostatic obstruction (BPO) is one of the cornerstones of urology. Although LUTS due to BPO is a benign condition that, today, most commonly do not lead to severe disease or death, they might cause bother that can reduce the quality of life (QoL) substantially. To cure men with LUTS/BPO, the enlarged prostate that causes the obstruction must be reduced in volume. To achieve this, the prostate can be reached through an incision in the abdominal wall or transurethrally. Volume reduction of the adenomatous tissue in the transition and central zone is then possible via the prostatic capsule, the urinary bladder or the prostatic urethra. Deciding on the best approach as well as modality in each case is not always easy or straightforward. Throughout the centuries, the enlarged prostate has been handled in many different ways, or as Harry W. Herr wrote in a historical review article: the prostate has been "lanced, punctured, punched, incised, cut, crushed, scarified, sliced, enucleated, whittled, and burned" [1].

Debulking of the prostate can be achieved immediately, as for example in transurethral resection of the prostate (TURP) or delayed, as in transurethral microwave thermotherapy (TUMT). CoreTherm (CoreTherm®, ProstaLund AB, Lund, Sweden), or ProstaLund Feedback Treatment (PLFT), was developed from regular TUMT and provides unique features, such as an intraprostatic temperature sensor (IP sensor) and a software that calculates cell kill (CK) in real-time during treatment [2-4]. The CK-calculation enables tailoring of treatment, by adjusting the effect and accomplishing appropriate temperatures, adequate volume reduction can be achieved. The prerequisite for a correctly calculated CK is an accurate temperature input, by means of a properly placed IP sensor. In those cases where the IP sensor is incorrectly positioned, the CK-calculation is unreliable. Furthermore, during treatment, the rise in temperature causes increased blood flow, which is counterproductive, as this leads heat away from the prostate [5]. The means to overcome a high blood flow was, and is, intraprostatic injections of mepivacaine and adrenaline (MA) via the Schelin Catheter (Schelin Catheter™, ProstaLund AB, Lund, Sweden), a device that was approved some 20 years ago.

The CoreTherm Concept is the same treatment as CoreTherm, however also including intraprostatic injections of MA, which reduce blood flow. When injections were first used, it was evident that this technique brought about a more pronounced prostate volume reduction at clinical follow-up. It was also apparent that energy delivery was almost consistently lower due to the minimised or abolished blood flow, meaning that the energy remained within the prostate. Furthermore, clinical follow-up showed results that were judged equally favourable irrespective of prostate size. Treatments were therefore continuously performed without an upper size limitation.

TURP is the gold standard treatment for patients with LUTS/BPO and prostate volumes of 30-80 ml, and transvesical (or transcapsular) adenoma enucleation (TAE) is the gold standard in prostates >80-100 ml [6-8]. A TURP can be performed with monopolar (M-TURP) or bipolar (B-TURP) technique. The B-TURP has some advantages compared to M-TURP, such as reduced bleeding and clot retention, shown by Treharne et al. [9] and reduced risk for the TUR-syndrome, demonstrated by Sagen et al. [10], but both methods are considered standard procedures.

This thesis aims to tie up some loose ends and complete the development of the CoreTherm Concept by evaluating prostate volume reduction when using MA and analysing the data that indicates a possibility to introduce an alternative treatment endpoint when the CK-calculation is unreliable. In addition to these developmental issues, CoreTherm and the CoreTherm Concept have been used as a treatment alternative in prostates >80 ml, but no studies have been published on the subject. Therefore, it is considered important to evaluate the short- and long-term efficacy of the CoreTherm Concept and CoreTherm, since these could be outpatient alternatives for patients with large prostates. Finally, the use of the Schelin Catheter for injections of MA before treatment with CoreTherm gave birth to the idea that injections of MA before a TURP could reduce bleeding and increase the efficacy of the procedure.

1.1 THE LOWER URINARY TRACT

In males, the lower urinary tract anatomically consists of the urinary bladder, the bladder neck, the internal urinary sphincter, the prostate, the prostatic urethra, the external sphincter, the striated muscles of the pelvic floor and the membranous and penile (spongy) urethra. The primary function of the lower urinary tract, during the storage phase, is for the urinary bladder to hold a certain amount of urine and be filled at a low pressure, while the detrusor should be relaxed and the sphincters closed. A preserved sensation of bladder fullness and maintaining continence, and postponing micturition until practically and socially acceptable, are fundamental requirements of functionality. During the voluntary voiding phase, the detrusor should contract and pass urine through relaxed sphincters, thereby allowing an uninterrupted and complete emptying of the urinary bladder under normal pressure.

The nervous control of the lower urinary tract is complex, with cerebral, spinal and peripheral ganglia and the pontine micturition centre as a relay centre controlling tonus in the sympathetic and parasympathetic nervous systems (SNS and PNS) [11]. The SNS facilitates the storage phase, innervates the urinary bladder, and controls the detrusor and urethral smooth muscle via hypogastric nerve fibres originating from Th10-12. Stimulation of the SNS maintains detrusor relaxation and the sphincters contracted. The PNS controls the voiding phase via pelvic nerve fibres originating from S2-3.

In addition to these involuntary systems, voluntary control is generated via pudendal and sacral nerve fibres originating from the nucleus of Onuf, at the level of S1-3, governing the striated musculature in the urethral sphincter and pelvic floor. Detrusor relaxation is controlled by the SNS and mediated by noradrenaline on the β-3 receptors at the receptor level, also stimulating α-1 receptors in the bladder neck to keep it closed. In the PNS, the cholinergic control of the detrusor is mediated by acetylcholine, mainly on the muscarinic receptor M3. Thus, the mechanisms for the medical treatment of overactive bladder are mediated by agonists in the SNS and antagonists in the PNS [12].

1.2 THE PROSTATE

The prostate is shaped like a chubby cone with the base area tightly stuck to the bladder and the apical part in continuum with the membranous urethra. Although the prostate is part of the lower urinary tract, it deserves more attention, and a subchapter in this thesis highlights the prostate as the lead character. This gland has an essential role when a man might intend to reproduce, but later on in life, its presence is seldom noted, at least until daily suffering from LUTS is evident.

The prostate has both endocrine and exocrine functions and is deeply hidden in the darkness of the pelvis, surrounded by the bladder, rectum and pelvic floor, also containing a channel from base to apex, named the prostatic urethra. It was first described by the father of anatomy, Herophilus of Chalcedon [13, 14]. He probably performed vivisections of criminals and is acknowledged as the “Father of Anatomy” or the “Vesalius of Antiquity” [15]. Vesalius himself is most often considered the “Father of modern Anatomy”. The name prostate is derived from Greek, meaning something that stands before [16]. In 1981, McNeal thoroughly described the anatomy of the adult prostate and its main features [17]. He described four distinct anatomic regions: the peripheral and central zone, the preprostatic region (containing the transition zone) and the anterior fibromuscular stroma (Figure 1). Dividing the prostate into these zones has important clinical implications. In patients with LUTS/BPO, the transition and central zones are the most important, as benign hyperplasia occurring in these areas is the most frequent cause of obstruction of urinary flow.

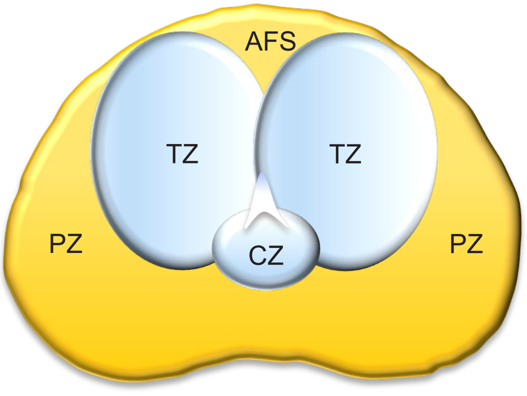

Figure 1. The prostate in an axial view with the peripheral zone (PZ), the central zone (CZ), the transition zone (TZ) and the anterior fibromuscular stroma (AFS).

1.3 LOWER URINARY TRACT SYMPTOMS

Urine is produced by the kidneys and transported to the urinary bladder via the ureters. The processes of storing and disposing of urine are, in a normal and ideal situation, uncomplicated and unbothersome. Thus, one seldom has to pay much attention to it, other than to decide where and when to void. This despite the fact that the lower urinary tract is a highly complicated system.

Dysfunction or pathological conditions at any level in this complex system can be very bothersome and cause severe impairment to QoL [18, 19]. Problems can range from total incontinence and loss of voluntary control to complete obstruction and urinary retention with subsequent renal failure. However, most often, the effects are not life-threatening and seldom encumbered with irreversibly long-term complications.

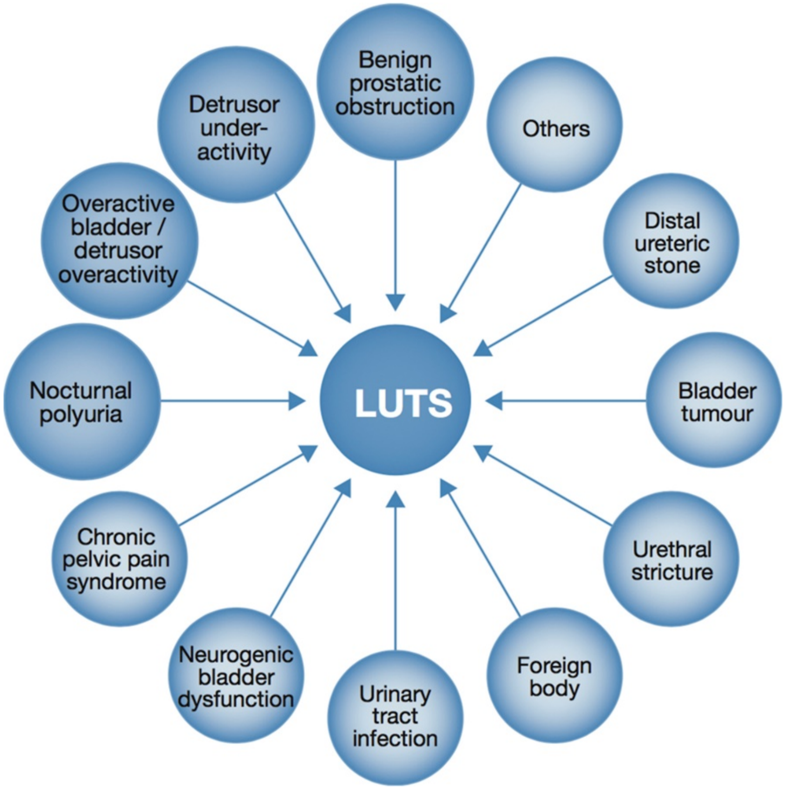

Figure 2. The possible causes of male LUTS. EAU Guidelines on Management of Non-Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) 2020 by Gravas et al. [6]. Permission granted.

The term LUTS was initially presented as a concept in order to deepen the understanding and complexity of voiding or storing dysfunctionality [20], and most importantly to avoid using terms such as “prostatism”, indicating dysfunction in a single specific organ (the prostate), as was otherwise often the case [21-23].

LUTS can be divided into three symptom complexes, encompassing voiding, storage and post-micturition symptoms, respectively [24]. LUTS cover patients with BPO, but LUTS can also be caused by dysfunction or diseases in other organs or structures (Figure 2) [25]. LUTS are common in men ≥40 years of age, and in a study of 14139 men from the USA, UK and Sweden, both voiding and storage symptoms were frequent [26]. The prevalence of LUTS in men also increases with age, the most bothersome symptoms being urgency, nocturia and post-micturition dribble [27]. In the EpiLUTS study [28], the prevalence of LUTS in three countries, including Sweden, was investigated. It showed that 48% of men frequently had at least one symptom from the lower urinary tract. It was also quite common that many men had voiding symptoms, indicative of BPO. In another study, the prevalence of LUTS in Swedish men >50 was 33% [29]. In that study, it was also apparent that symptoms increased with age, and that less than half had consulted a physician for their symptoms.

1.4 BENIGN PROSTATIC OBSTRUCTION

The term BPO indicates, with clarity, that the prostate gland obstructs the flow of urine from the urinary bladder. This obstruction can, in turn, lead to LUTS. However, the relationship between BPO and discomfort is not unequivocal, which means that it is impossible to link an increased prostate volume to increased bother from LUTS, although it is more likely that a larger gland will cause difficulties eventually, compared to a smaller gland.

The most common underlying cause of BPO is benign prostatic hyperplasia (BPH), which is a histological diagnosis predominantly located in the transition zone of the prostate. That the term BPH is to be used only on a histopathological basis has been emphasised by Paul Abrams in his article: "LUTS, BPH, BPE, BPO: A Plea for the Logical Use of Correct Terms" [30]. Furthermore, it must be stated that BPH is not a prostatic disease, as prostate cancer. The term BPH instead reflects changes in the gland's microscopic appearance as a part of normal ageing, consisting of an increased number of cells, hence hyperplasia. Thus, BPH can, via benign prostatic enlargement (BPE) and subsequently BPO, cause urinary retention and renal failure, but BPH in itself is just histological changes in the gland due to ageing (Figure 3).

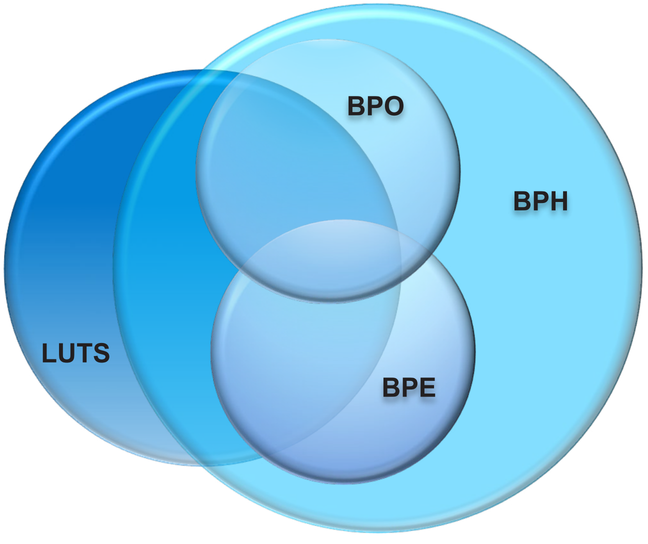

Figure 3. A diagram presenting the relationship between benign prostatic hyperplasia (BPH), benign prostatic enlargement (BPE), benign prostatic obstruction (BPO) and lower urinary tract symptoms (LUTS).

One of the first described cases of BPH was no other than Pandolfo III Malatesta (1370-1427). He became the Prince of Fano, a town in the northeast of Italy. He was a high-ranking soldier and fought against the Visconti of Milan and the Hungarians, among others. Paleopathologists have thoroughly investigated his mummified corpse, and the microscopic examination of his prostate showed BPH [31]. He died of “fever” at the age of 57, speculatively due to urinary retention, secondary to BPO, followed by urinary tract infection and septicaemia.

1.5 EVALUATION OF LUTS AND BPO

Men do not seek medical care for LUTS due to BPO, but for LUTS. Most bothersome in male LUTS are storage symptoms such as urgency, frequency and nocturia [32, 33]. There are no symptoms or findings in the clinical evaluation that are pathognomonic to BPO. Instead, men with BPO, impaired detrusor contractility or overactive bladder can display the same symptoms and findings, as well as a similar chronic course. Pressure-flow studies are, at present, the only way to discriminate between these conditions. Also, nocturia and other symptoms may not be related to the urinary tract but may instead be a consequence of systemic disease [34, 35]. In addition, many men have LUTS and BPH or BPE, but not BPO. This means that there must be sufficient certainty that the clinical evaluation, leading to determine that BPO is present, must be correct so that the patient will benefit from an eventual irreversible treatment.

The importance of taking a thorough medical history applies to all consultations in patients seeking a professional evaluation. This is also the case in patients with LUTS or chronic urinary retention (CUR), where relevant previous surgical procedures and general history also are essential. The reason for this might be apparent but is nevertheless important to emphasise. The clinical evaluation, beginning with the patient's general history, has several important purposes. Listening to the patient with an open mind and letting the patient bring forward his concerns, problems, and worries is crucial in several aspects. Then, and only then, through knowledge, experience and expertise, it is time to penetrate specific areas and complete the information that is judged relevant.

Heredity for prostate cancer, stone formation in the urinary tract, history of urinary bladder cancer, neurological disease, cardiovascular disease or diabetes mellitus are examples of areas that must be included in a medical history. When these areas are covered, it is possible to continue. Men with LUTS are, in many cases, concerned about having prostate cancer. Accurate information is an essential part of the consultative process. Men with LUTS often require thorough information that prostate cancer is not suspected, as it has no apparent connection to neither LUTS nor BPH, as shown in several studies from Sweden and Norway [36-38]. Moreover, men with LUTS do not have an increased risk of malignancy of the upper urinary tract [39, 40]. When these steps are completed, it is possible to continue with further clinical evaluation.

Symptom evaluation using questionnaires is recommended in guidelines [6-8]. The International Prostate Symptom Score (IPSS) is the most used questionnaire and is self-administered [41]. It consists of seven symptom questions covering: a sensation of incomplete emptying after urination, frequency, intermittency, urgency, weak stream, straining, nocturia and an eighth question about overall bother, the QoL question. The first seven symptom or core questions are scored with 0-5 points, leading to a maximum score of 35 points, with a scale of 0-6 points regarding QoL. The IPSS is most often trichotomised into mild (1-7 points), moderate (8-19 points) and severe (20-35 points) symptoms, if excluding 0 points (asymptomatic).

Another score is the American Urological Association Symptom Score (AUASS) or American Urological Association Symptom Index (AUASI), which is precisely the same as the IPSS for the first seven questions. In fact, the IPSS was constructed using the AUASS/AUASI as a template. Neither the IPSS nor the AUASS/AUASI grade individual symptoms nor cover incontinence or post-micturition variables. The Danish Prostate Symptom Score (DAN-PSS), initially presented in a study by Hald et al. [42, 43], is a scoring system that contains more questions than the IPSS, and it also addresses incontinence and bother of each symptom.

There are also symptom scores that were primarily intended to be used in an interview setting, as the Boyarsky [44] and Madsen-Iversen Score (MIS) [45]. The initial purpose of the MIS was to create a scoring system to discriminate patients that required debulking surgery, from those that did not show an absolute indication for surgery. Besides questions regarding symptoms, it also includes a clinical evaluation sheet with trabeculation assessment points by cystoscopy and other parameters.

A form where the time of micturitions and micturition volumes for each occasion are registered is labelled a frequency–volume chart (FVC) [24]. This is a valuable and relatively simple self-administered tool that is recommended to be used for at least one day and night, but recordings during several days and nights are to prefer. The FVC is a valuable tool for evaluating nocturia [46-48]. The simpler micturition time chart, in which only the time for each micturition is registered, is another option, but seldom used. The addition of time in seconds per voided deciliter can also be included in the chart. If a chart also contains information about fluid intake, incontinence, activities and sensations from the lower urinary tract, it is named bladder diary [24], although the term voiding diary is also used [49].

Uroflowmetry is a standard method used to evaluate micturition and provides a flow curve and maximum urinary flow (Q_{max}), measured in ml/s. The typical flow pattern is a "bell-shaped" curve, and a voided volume of >150 ml is considered the minimum volume in order to use the results from the uroflowmetry [6]. Repeated measurements are recommended as Q_{max} has shown significant intraindividual variations [50] and also to reduce the risk for overinterpretations of abnormalities. It cannot discriminate between BPO, a weak detrusor, or an under-filled bladder but is a valuable tool when evaluating patients after intervention [51-53].

Measurement of the urine volume that remains in the urinary bladder after voiding or attempting to void, the post-void residual volume (PVR) can be assessed using ultrasound, a bladder scanner or catheterisation. There is no consensus on how to interpret and handle the PVR result, *e.g.*, at which volume it should be considered pathological and demand intervention [54, 55]. A PVR can result from bladder outlet obstruction, such as BPO, or detrusor underactivity [56]. However, the most common cause of urinary retention in men is BPO [57], and a high PVR implies an increased risk of progression of LUTS [58, 59]. Measuring PVR during a longer period can help identify men at risk for acute urinary retention (AUR) [60]. Men with AUR cannot pass urine and have a painful urinary bladder that is palpable or percussible, in contrast to those having CUR, where the urinary bladder is painless [24].

Evaluation of the prostate gland regarding size, shape, symmetry or asymmetry, architecture, consistency, pain and areas suspect for cancer can be made using digital rectal examination and transrectal ultrasound (TRUS) of the prostate. These are both essential tools in evaluating male patients with LUTS. When it comes to deciding the most appropriate treatment for patients with LUTS/BPO, it is crucial to determine the volume of the gland. Digital rectal examination can appreciate prostate volume to some extent [61-63], but not nearly as accurate as TRUS, especially in larger prostates [62]. Other options to evaluate prostate size are transabdominal ultrasound [64], computed tomography and magnetic resonance imaging. Prostate volume is a predictor of disease progression, both regarding symptoms, complications, and the risk for surgery [65-67].

Besides the presence of BPE, evaluating if the enlargement is bilobal or trilobal is also necessary in some cases. If there is an intention to consider treatment with TUMT, it has previously been suggested that a trilobal enlargement is an absolute contraindication. This contention, however, does not hold true any longer, as some patients may benefit from a wider bladder neck despite the presence of a third lobe enlargement. If a third lobe is apparent on TRUS and treatment with microwaves is an option, urethrocystoscopy is mandatory. If a vertical opening is present in the bladder neck, treatment with the CoreTherm Concept is possible. Otherwise, urethrocystoscopy is mainly indicated as part of the clinical evaluation if other diseases are suspected.

Analysis of urine with a urine stick should be included in the evaluation as bacteriuria and glucose can be easily detected. Although there are some limited studies on benefits, the cost is low, and as it is a straightforward method, its use is considered mandatory in guidelines [6, 68].

The European Association of Urology (EAU) strongly recommends measuring serum prostate-specific antigen (PSA) if a diagnosis of prostate cancer would change the management or if the measurement of PSA is deemed of value in the process from evaluation to treatment [6]. PSA can be used as a proxy to forecast prostate volume [66, 69] and an increasing prostate volume [70]. It has also been shown, in a study by Patel et al. in 1534 men, that PSA can be used to predict the risk for future LUTS [71]. Renal insufficiency can be appraised by measuring serum creatinine or estimated glomerular filtration rate and is of value as renal function impairment increases the risk for postoperative complications [71]. In men where decreased renal function is suspected or when surgery is an alternative, serum creatinine or estimated glomerular filtration rate should therefore always be included in the evaluation [6].

The most commonly used invasive urodynamic investigation is filling cystometry with pressure-flow studies. It is recommended by the EAU to be used in specific patients before curative treatment, in unclear cases, in men previously treatment invasively, in those who cannot void >150 ml during uroflowmetry, voiding symptoms and Q_{max} >10 ml/s, a PVR >300 ml and voiding LUTS or age >80 or <50 years [6].

1.6 NON-CURATIVE TREATMENTS

In some men with LUTS/BPO, a non-curative treatment can be an option, at least for a period. Conservative treatment, as well as medications, can be used to reduce symptoms and occasionally bother. In men with significant CUR, an indwelling catheter or clean intermittent catheterisation can be an option, preferably as a bridge to curative treatment. Watchful waiting and lifestyle adjustments constitute conservative treatment [6]. In the EAU guidelines, watchful waiting is strongly recommended in men with minimal bother [6]. It is also stated that lifestyle adjustments are to be offered in men before or at treatment initiation. That conservative treatment is an option in male LUTS, since not all patients progress to more cumbersome symptoms, has been known for decades, the first study being published on the subject in 1969, by Craigen et al. [72]. In that study, 212 men with LUTS/BPO or AUR were followed up for four to seven years, and nearly 50% had symptom improvement or became non-bothered during that time.

Although some symptoms can be managed with conservative treatment, there are certain risk factors for symptom progression, AUR and surgery. In the Baltimore Longitudinal Study of Aging, Arrighi et al. [73] identified a weakened urinary stream, a perception of incomplete bladder emptying, and an enlarged prostate volume as risk factors. Having all three risk factors amplified the risk for AUR or surgery by almost 40%, with a profoundly amplified risk in older men. Similar risk factors were seen in the Olmsted County study of 2115 men by Jacobsen et al. [74]. They concluded that reduced urinary flow, moderate to severe LUTS and an enlarged prostate increased the risk for surgery at the same magnitude as for those with AUR. The most apparent non-modifiable risk factor in male LUTS is age. Modifiable risk factors that can be addressed to reduce bother are reduced fluid intake, exercise, double voiding, pelvic floor muscle training, reduced alcohol and caffeine intake, among several other options [6]. Components of the metabolic syndrome, such as visceral obesity and dyslipidemia, are also linked to benign enlargement of the prostate [75]. That obesity increases urinary frequency in men was shown by Vaughan et al. in a study in Finnish men [76].

There are α-adrenoreceptors (α-receptors) throughout the body, and they can be found in the smooth muscle of blood vessels, the bladder neck and the prostate. They are receptors involved in the regulation of blood pressure and abundant in both arteries and veins. In a study from 1974, Awad et al. concluded that α-receptors frequently occur in the bladder neck [77]. In BPH, there is an increase in stromal and epithelial components, where 40% of proliferation consists of smooth muscle [78, 79]. Although the α1a- receptor is responsible for smooth muscle contraction [80] and α1-blockers, mediate relaxation of smooth muscle, hence reducing bladder outlet obstruction [81], the effect of α1-blockers is due to antagonism on all α1-receptor subtypes (1a, 1b, 1d) [82]. They are located in the prostate and the trigone, bladder neck, and urethra [81]. Several unselective, long-acting α-blockers that inhibit the effect of endogenic noradrenaline on the receptor are available. The effects are similar [83], such as reducing symptoms and increased peak urinary flow [84]. They are usually well-tolerated, although side effects such as hypotension and dizziness occur relatively frequently. In patients with AUR, they might reduce the risk for recatheterisation after removing the catheter [85]. Most often, α1-blockers are used as second-line treatment after watchful waiting, but they reduce neither the need for surgery nor the risk for AUR, nor do they reduce prostate volume [86, 87].

The main androgenic effect on the prostate is mediated by dihydrotestosterone, which is converted from testosterone by the enzyme 5α-reductase [88]. There are two subtypes of 5α-reductase, of which type two is located within the prostate, and type one is located in the skin and liver. Mutations in the gene responsible for the 5α-reductase type two can cause a deficiency syndrome, resulting in a rudimentary prostate, and these men will never develop BPH or prostate cancer. Two enzyme inhibitors are available on the market, dutasteride inhibits subtype one and two, and finasteride inhibits subtype two. These medications induce epithelial cell death [89], reduce prostate volume by about 30% and reduce circulating PSA in blood by about 50% after 6-12 months of treatment [90]. Despite differences at the receptor level, the two available antagonists are equally effective at reducing symptoms and increasing peak urinary flow [90, 91]. Both drugs have a slow onset of action, >6 months and the most frequent side effects are reduced libido and erectile dysfunction [92]. Finasteride and dutasteride reduce the long-term risk for disease progression and risk for acute urinary retention and the need for surgery [58, 93].

The muscular wall of the bladder, the detrusor, consists of smooth muscle and is innervated by parasympathetic nerve fibres. Acetylcholine has an agonistic effect, and there are several drugs that bind to the receptor and have an antagonistic effect, leading to impairment of detrusor contraction. There are five muscarinic receptors (M1-M5), and the available drugs affect all these five receptors. Receptors frequently distributed in the bladder are the M2 and M3. The effect of the medications is reduced daytime frequency, reduced nocturia and increased bladder capacity and reduction of symptoms [94]. Side effects, which occur relatively often, are constipation, dizziness, dry mouth, abdominal pain, dry eyes, headache and anxiety. Muscarinic receptor antagonists have been used for decades in women, but they have not been used frequently in male LUTS. The reluctance to use these medications in men has been an exaggerated fear of urinary retention. Despite increased bladder capacity and potential theoretical risk for acute urinary retention, only minimally increased PVR has been noted [95]. However, some caution is recommended, especially in older patients and in men where the initial PVR is substantial since no studies have thoroughly examined this.

In addition to α1a-receptors in the lower urinary tract, β-receptors are common in the smooth muscle of the detrusor. Especially abundant is the β3-receptor, and stimulation of this receptor leads to smooth muscle relaxation. The agonistic effect has not been determined in detail [96]. As for the muscarinic receptor antagonists, some caution is recommended when the PVR >150 ml, according to the EAU guidelines [6]. Common side effects for mirabegron, the only available drug on the market, are hypertension and headache. The use of mirabegron in men with severe uncontrolled hypertension is contraindicated.

The mode of action for phosphodiesterase inhibitors is that they lead to increased cyclic guanosine monophosphate levels, resulting in smooth muscle relaxation in the detrusor, prostate and urethra [97]. They are mainly used by men having erectile dysfunction, but they also reduce IPSS and improve bother from LUTS [98, 99]. In Sweden, the most commonly used phosphodiesterase inhibitors are sildenafil and tadalafil. In men with LUTS and erectile dysfunction, tadalafil has been shown to improve both erectile dysfunction and LUTS [100], with common adverse effects as flushing, headache, and nasal congestion [101].

Combination therapy with two or more pharmacological agents is a possibility, and the most frequently used combination therapy is the use of an α1-blocker and a 5α-reductase inhibitor [58, 102, 103]. In men with moderate symptoms without complicating factors, combination therapy can be offered if there is a reluctance to a surgical procedure or a minimally invasive treatment option. It is also feasible to use an α1-blocker and a 5α-reductase inhibitor for six months, and hereafter only the 5α-reductase inhibitor [104, 105]. In addition, treatment with finasteride before TURP has been shown to reduce bleeding [106, 107] and can be an option in selected cases.

Another option is to use an 5α-reductase inhibitor for six months in a high-risk patient to reduce prostate size and possibly avoid a TAE in favour of a TURP or using a muscarinic receptor antagonist until the urgency and frequency subside after treatment with TUMT in patients with pronounced storage symptoms secondary to BPO.

In the Medical Therapy of Prostatic Symptoms (MTOPS) study [93], the combination of the α1-blocker doxazosin and the 5α-reductase inhibitor finasteride was elucidated. That study showed superiority for combination therapy compared to monotherapy regarding reduced risk for long-term progression, AUR and surgery. In 2006, Kaplan et al. concluded, based on data from the MTOPS study, that combination therapy with doxazosin and finasteride reduced the risk for clinical progression in med with prostate volume >25 ml [108]. The 4-year results from the Combination of Avodart and Tamsulosin (CombAT) study showed that combining the α1-blocker tamsulosin and the 5α-reductase inhibitor dutasteride gave better symptom reduction and also reduced the risk for clinical progression, compared to monotherapy [109]. In patients with overactive bladder, the SYNERGY II study showed that combination therapy with the muscarinic receptor antagonist solifenacin and mirabegron could be used in patients with or without obstruction [110].

Even though there are numerous different options when considering pharmacological treatment, the long- and short-term results are often moderate. In many cases, medications reduce IPSS by a few points and perhaps even reduce bother. Thus, although no combination therapy should be excluded, a curative treatment is, in many cases, preferable instead of life-long medication, especially in older or fragile men, with comorbidity.

1.7 CURATIVE TREATMENTS

From an historical perspective, there has been a progression from mere symptom relief to a smorgasbord of options for men with LUTS/BPO, including cure. As early as 1500 BC, the Eber and Edwin Smith papyri from ancient Egypt described various decoctions to reduce LUTS symptoms [111, 112]. Moreover, bladder emptying as a relief for patients with urinary retention was also commonly practised. Hippocrates was pessimistic regarding a cure for LUTS and urinary retention and believed that focus on alleviating symptoms and temporary relief of urinary retention was the only possible solution [113]. When, thousands of years later, insight was gained into the existence of the prostate and the causality between BPO, enlargement and obstruction with the subsequent effect on urination in older men, cure became an option.

To cure men with LUTS/BPO, it is possible to enucleate, resect, vaporise or thermoablate the prostate gland. The goal is always to liberate the patient from the obstructive glandular tissue, and the decision making involves several different steps. The choice stands between different surgical approaches and modalities, which is dependent on several other factors. The availability of methods and surgical competence in the organisation are essential puzzle pieces. A risk versus benefit assessment must, of course, always be made. Most importantly, the indispensability of a thorough discussion with the patient in each case must be firmly emphasised. Surgery, or another debulking treatment, should be strongly recommended in patients with renal insufficiency, persistent urinary retention, recurrent urinary tract infection, recurrent bladder stones, gross haematuria, refractory symptoms despite other therapy or willingness to be cured.

1.7.1 ENUCLEATION

The complete removal of the prostate, as is presently the remedy for localised prostate cancer, definitely differs from the so-called prostatectomy introduced by surgeons some 150 years ago. The denomination simple prostatectomy is sometimes used for this kind of surgery and means removing the transitional zone, and if there is a trilobal enlargement, the central zone as well. Simple prostatectomy is enucleation surgery (TAE), and what the early surgeons and urologists wrongly believed was a complete, or radical prostatectomy.

The first perineal simple prostatectomy was performed in 1867 by Billroth. Sir Peter Freyer was the first surgeon to perform and publish an extensive series of suprapubic prostatectomies in patients with LUTS/BPO. He published his first four cases in 1901 [114], only about a year after promoting a perineal approach [115]. However, Freyer was not the first to use and conduct a suprapubic enucleation of the prostate. The procedure was both described and done on several patients in the 1880s by McGill in Leeds and Belfield in Chicago [116, 117]. In 1909, Van Stockum published an article where he performed the enucleation suprapubically, but it was not until decades later, when Millin published his article about 20 cases, that this approach became popular [118].

In a study of 902 men by Gratzke et al., a total of 68 men (7.5%) required transfusion and 33 (3.7%) a second operation due to profuse bleeding after TAE [119]. Open enucleation surgery reduces IPSS and PVR, increases QoL and Q_{max} with durability up to six years after surgery [120]. Madersbacher et al. evaluated short-, mid-, and long-term results in 2452 interventions. The reoperation rate was 1.0%, 2.7% and 3.4%, respectively [121]. TAE is recommended by the EAU in prostates >80-100 ml, due to its efficacy and durability, but it is stressed that it is the most invasive option of all surgical procedures for BPE [6], with mortality rates <0.5% [122].

The acronym minimal invasive simple prostatectomy (MISP) includes laparoscopic simple prostatectomy and robot-assisted simple prostatectomy. The first laparoscopic simple prostatectomy was performed in Brazil in 1999, later published by Mariano et al. as a case report [123]. This patient had a prostate volume, measured by TRUS, of 173 ml, and the incision was made longitudinally in the urinary bladder into the prostatic capsule, thereby also dividing the bladder neck. The hospital admission time was short, and at the five-month follow-up, no significant complications had occurred, and the results were satisfactory.

The first paper on robot-assisted simple prostatectomy was published in 2008 by Sotelo et al. on seven men with no adverse events, except for transfusion in one patient [124]. In a systematic review and meta-analysis, including 764 patients, the conclusion was that MISP is effective and safe. EAU concludes that MISP appears feasible in men with a prostate size >80 ml, but RCTs are needed [6].

Another possibility for complete removal of the transitional zone is by laser, thereby performing a transurethral enucleation. Holmium laser enucleation of the prostate (HoLEP) is a surgical procedure where a YAG laser covered with holmium (Ho:YAG) is used. This device creates a beam of 2100 nm and a penetration depth of 0.4 mm. The energy is absorbed by water molecules, leading to immense heating of water and subsequent vaporisation, followed by expansion and tissue splitting. Since it is used transurethrally, there is no need for a skin incision, opening of the urinary bladder or the prostatic capsule.

The first study published using the Ho:YAG laser for enucleation was published in 1998 by Fraundorfer et al. [125]. In that study, 14 patients with a mean prostate volume of 98.6 ml were included. HoLEP is strongly recommended as an alternative to TURP and TAE in the EAU guidelines [6]. HoLEP has also shown superior symptom improvement compared to TURP [126]. In a meta-analysis versus TURP, HoLEP was superior regarding outcome variables such as IPSS, Q_{max}, time with catheter, hospital stay, blood loss and transfusion rate [127]. In a long-term follow-up, it was evident that complications were few, and the procedure has also proven durable, with a low retreatment surgical intervention rate for regenerated adenoma of 0.7% [128].

An RCT from 2008 showed equal efficacy for voiding improvement parameters and retreatment rate after five years in HoLEP versus TAE [129]. In addition, HoLEP also showed reduced blood loss, shorter catheterisation time and hospital stay compared to TAE in that study. It has excellent haemostatic properties and can be performed during medication with antithrombotic agents, even in larger prostates [130]. The drawback of HoLEP is the relatively complicated procedure with difficulties learning the enucleation technique and, despite training, also relatively long operating times [131, 132].

The thulium prostate enucleation laser (Tm:YAG) differs from the Ho:YAG laser in wavelength and a slightly smaller penetration depth, of 0.2 mm, besides being covered with thulium instead of holmium. It is a continuous laser, in contrast to the pulsatile HoLEP laser. The fact that it is continuous and uses higher amounts of energy may lead to more efficient vaporisation [133].

Another option for laser enucleation is “greenlight” laser surgery, where the laser energy from the potassium-titanyl-phosphate (KTP) or lithium triborate (LBO) laser is absorbed by haemoglobin. The effect is tissue vaporisation, and different techniques to remove the adenoma can be used [134]. The most used device at present is the 180-W XPS laser. In a study by Elshal et al. [135], symptom reduction was comparable to HoLEP, but the prostate volume reduction was more pronounced in the HoLEP group at four months follow-up.

1.7.2 RESECTION

The first modern resectoscope was constructed by the American urologist Maximilian Stern, who presented his invention in 1926 [136]. This made it possible to resect tissue via an electrified wire under visualisation of the prostate. The wire was better in cutting than coagulating, for which he received some criticism. Several improvements were made in the years to come. Another American urologist, Theodore Davis, made improvements to the diathermy and introduced the foot pedal, with the cutting and coagulation functions, familiar to every urologist [137].

Further improvements were added by McCarthy and Wappler, such as better lenses and electrical insulation by a sheet of Bakelite [138]. The Stern-McCarty resectoscope thereby saw the light of day, making it possible to perform TURP with a certain resemblance of today. However, considerable improvements have been made since then.

In most cases, a TURP begins with inspection and identification of landmarks. The cutting loop is then used to, chip by chip, resect the adenoma. More shallow in the beginning and at the end of each chip, creating tissue that longitudinally resembles a kayak. This is repeated until complete resection, which most often is finished in the apical parts of the prostate. Coagulation is performed at demand during the surgery, especially targeting Badenoch's and Flocks' arteries. Several others have described different techniques with sometimes modifications of existing procedures, *e.g.*, Nesbit [139] and Flocks [140]. Regardless of technique, the final result is the same, a reduced prostate volume and reduced obstruction.

M-TURP or B-TURP is strongly recommended in the EAU guidelines in men with a prostate volume of 30-80 ml and moderately to severe LUTS due to BPO [6]. The difference between M-TURP and B-TURP is that the electrical current travels to the resectoscope, through the body, via a grounding pad and back in M-TURP and locally between instrument parts in B-TURP. There is no risk for the TUR-syndrome [141] in B-TURP, other than fluid overload, as the instrument can be used with the urinary bladder filled with physiological saline. The TUR-syndrome during M-TURP is, partially caused by absorption of hypotonic irrigation fluid through venous sinuses opened during surgery. This leads to hyponatremia and hypoosmolality with brain oedema, pulmonary oedema, bradycardia and hypoxemia; symptoms such as dizziness and confusion are also common. The recognition of the TUR-syndrome is of paramount importance. Failure or neglect in this respect may lead to an aggravation of cerebral oedema, which will bring about an increased intracranial pressure, eventually resulting in circulatory arrest.

In a meta-analysis of transurethral procedures in men with LUTS/BPO, by Reich et al. [142], a total of 20 RCTs included data for M-TURP. The maximum follow-up was five years, IPSS and the PVR were reduced, QoL and Q_{max} increased. Madersbacher et al., in 2005, presented short-, mid-and long-term data for 20671 men who had undergone M-TURP in Austria [121]. At one, three and eight years, the reoperation rate was 2.9%, 5.8% and 7.4%, respectively. Thomas et al. [143], showed, in a study of 1018 men, that the main reason for failure after surgery was detrusor underactivity and not obstruction.

The incidence of the TUR-syndrome has been declining in the last decades. In a study by Rassweiler from 2006, the risk was 1.1% [144], similar results as in a systematic review of RCTs, showing a risk of 0.8% [145]. During surgery, bleeding is quite common, which sometimes can be troublesome and continue after surgery. In severe cases, profound bleeding can lead to cardiovascular events, reoperation and, in a worst-case scenario, death. The 30-day mortality was reported to be 0.1%, as shown in a study of 20388 men [122]. In another study of 10654 patients, bleeding requiring transfusion occurred in 2.9% [146]. B-TURP has equal short-, mid- and long-term efficacy [147-149] as M-TURP. B-TURP, though, has shown lower rates of clot retention and transfusion events [9, 150].

There is no doubt that much water has flowed under the bridge since Maximilian Stern presented his resectoscope more than 100 years ago [136]. The reason why TURP is still a strong contender in the race for the best curative option in patients with LUTS/BPO is not that Stern created the perfect surgical tool. Instead, since the development of TURP has taken place in parallel to development in other areas, the method has constantly improved, and the TURP has therefore retained and strengthened its place as an excellent curative alternative.

Hence, there is currently no reason to go berserk and throw TURP as a treatment method to the wolves. Instead, it would be more appropriate to jump on the train and improve the method further. Despite all previous development and refinement of the method, a severe problem remains, namely bleeding during and after the operation. Of course, there have been changes over time, with reduced bleeding and reduced need for transfusions, but bleeding during and after a TURP remains a significant problem for all parts involved. Not only can bleeding *per se* be problematic, with the risk of myocardial infarction and death, but the operation can rarely be performed as initially intended if vision during surgery is suboptimal.

1.7.3 TUMT AND THE CORETHERM CONCEPT

The possibility of using microwaves to reduce prostate volume was first shown in a paper by Magin et al. in 1980 [151]. They heated the prostate in eight canines in 15 minutes to >60 °C, leading to necrosis of prostatic tissue. The first study where prostates in men were treated with microwaves was published by Yerushalmi et al. in 1982 [152]. In total, 15 men with prostate cancer were included, and reduced obstruction of urinary flow was noted. A study on treatment in men with LUTS/BPO was published some years later, in 1985, by Yerushalmi et al. [153]. In that study, 29 men were treated, and the prostate tissue reached 42-43 °C, corresponding to hyperthermia. In these papers and a later study by Lindner et al., the transrectal route was used to apply microwaves to the prostate [154].

Microwaves are electromagnetic radiation, as well as visible light, radio waves, and gamma rays. Applying microwaves to the prostate leads to a temperature rise whereby microwaves make dipoles, as water change direction in the electromagnetic field and ions oscillate, thereby creating energy and heat. The same year as Yerushalmi et al. published his study on patients with LUTS/BPO, in 1985, Harada et al. [155] not only heated ham, but also treated nine men with LUTS/BPO or prostate cancer transurethrally, showing that this was a possible route to reach the prostatic tissue with microwaves.

In the following years applying microwaves to the prostate was continuously tested in different settings, for example, in preclinical studies, in canine studies, using different antennas, transrectally or transurethrally, and in men with different prostatic diseases. In 1987 Servadio et al. [156] published a paper where patients with prostate cancer, LUTS/BPO and prostatitis were treated. In those patients with LUTS/BPO, results included relief of symptoms, increased peak urinary flow, reduced PVR and also catheter removal in some of the patients that had a permanent indwelling catheter before treatment.

Studies comparing the transrectal route to the transurethral were also made, with results indicating that the transurethral route was preferable, because of superior clinical results [157]. The temperature distribution within the prostate and the heating pattern is dependent on the microwave antenna design. The first antennas produced had a straight dipole design, with a heat pattern that differentiated them from the helical coil antennas constructed later [158, 159].

Some early studies showed that the helical coil construction leads to a power distribution closer to the tip of the antenna than did the simpler dipole antennas [160, 161]. The localisation of the antenna in relation to the prostate is also crucial in order to deploy the energy at the bladder neck area. Many of the earlier studies did not use Foley catheters to anchor the catheter at the bladder neck, as in the study by Harada et al. [155], where ultrasound was used. When temperatures were measured it was often done inside the urethra, and most often only moderate hyperthermia with temperatures <45 °C was achieved.

Objective and subjective voiding parameters were often improved [162], and prostate volume reduction was reported, in occasional papers [163]. In addition to the clinical evaluation after treatment, also histopathology after treatments were undertaken, as in the study by Baert et al. [164]. In that study, from 1991, it was evident that the microwave effect was mainly located on the lateral lobes, with no effect on middle lobe enlargement, also suggested earlier [165, 166].

An important study was published in 1991 by Devonec et al. [167]. In that study, thermotherapy (>45 °C), in contrast to hyperthermia (<45 °C), was defined. Thus, this is an essential division between hyperthermia and thermotherapy. Macroscopic and microscopic examinations of the prostate after thermotherapy and subsequent prostatectomy showed tissue necrosis and prostate volume reduction. That prostate volume reduction could be achieved after treatment with microwaves had been shown before, at follow-up with TRUS, but not with the histopathological examination of human prostates. Also, although the term thermotherapy had been used in one previous study, where temperatures were <45°C, and thus, by definition, was not thermotherapy [168].

In 1993, in another study by Devonec et al. [169], it was demonstrated that the prostate in younger patients required a higher thermal dose to achieve the same temperatures than older patients, despite the same prostate volume. This was probably due to a more viable blood supply. With an increasing number of studies, and as time went by, it became more and more evident that transrectal heating was inferior to transurethral heating and that hyperthermia only gave acceptable short term results. In a study by Montorsi et al. in 1995, poor long term results were presented for transrectal hyperthermia, concluding that the method should not be recommended [170].

CoreTherm has components that should mean that it ought to be considered a different method, as opposed to regular TUMT. Although the general principle of heating the prostatic tissue via a device creating microwaves is shared, the fact that temperatures are measured continuously during treatment is a crucial difference. While some manufacturers focused on the transition from low-energy TUMT to high-energy TUMT one manufacturer chose to measure intraprostatic temperatures and developed the feedback technique, which later became named CoreTherm. Thus, it would be appropriate to regard CoreTherm versus other variations of TUMT as different methods (Figure 4). This opinion is reminiscent of how M-TURP and B-TURP are viewed. However, these methods have more in common compared to different microwave treatments.

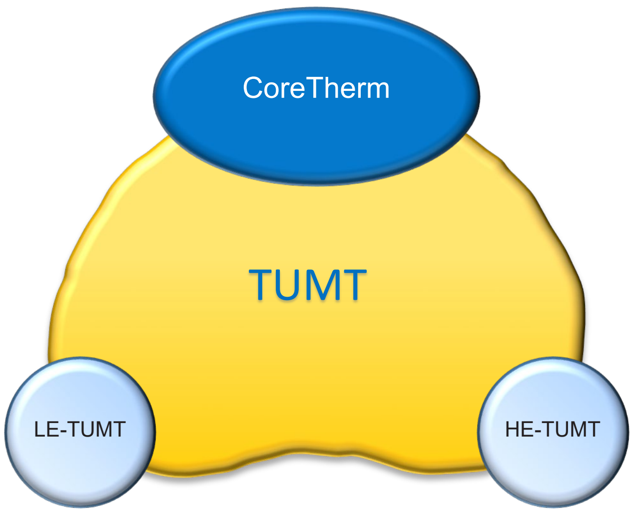

Figure 4. Illustration of transurethral microwave thermotherapy (TUMT) as the common denominator for all treatments using microwaves. Low-energy TUMT (LE-TUMT), high-energy TUMT (HE-TUMT) and CoreTherm.

There is an extra channel within the treatment catheter wall where the intraprostatic sensor (IP sensor), which continuously measures the intraprostatic temperatures, is inserted. This sensor has three different points where intraprostatic temperatures are measured. When the catheter is correctly placed, and the distance and angle between the sensor and antenna are adequate, logical temperature curves are received. Those are presented as curves with different colours (white, red and green) on the treatment computer monitor.

Measuring the intraprostatic temperatures *per se*, as general information, is not the quintessence. It is the steps that can be taken when the temperature is measured that are important, and the key to a successful treatment. With the knowledge of the microwave power distribution via the helical coil and the temperatures within the prostate, the intraprostatic blood flow is calculated by the software using Penne's bioheat equation (Equation 1) [171]. This equation shows that the temperature rise within the prostate mainly depends on heat spread by conduction, blood flow and microwave power (Figure 5). Hereafter, with the knowledge of the calculated blood flow, the temperature distribution within the prostate is derived by using Penne's bioheat equation backwards.

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

Equation 1. Penne's bioheat equation. The temperature change [$\rho c(dT/dt)$] is dependent on heat conduction [$\lambda\Delta T$], blood flow [$\lambda\Delta T-\omega_b\rho_b c_b\rho(T-T_a)$], microwave power [$Q_s$] and heat as a consequence of tissue metabolism [Q_m].

The final step for calculating CK is by using Henriques' damage integral [$\Omega=A\int e\text{-}Eal(RT)dt$] [172] and Jung's compartment model [173], making it possible for the software to determine the amount of tissue destructed due to heat damage and subsequent coagulative necrosis. This calculation is continuously updated in real-time and presented on the treatment computer monitor. The treatment with CoreTherm is terminated when the primary treatment endpoint of a calculated CK of 30% is achieved.

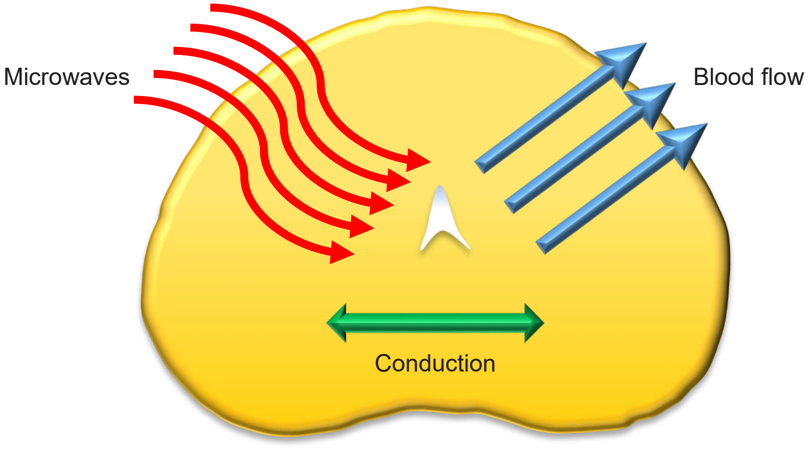

Figure 5. Illustration of the different principal components that affect heat build-up in the prostatic gland. Axial view of the prostate. Microwaves increase the temperature while the blood flow transports heat away from the adenoma. The heat is spread beyond the reach of the microwaves, within the gland, by means of conduction.

In a study by Bolmsjö et al., the CK-calculation by the computer software in 22 patients was evaluated and compared to volume reduction three months after treatment [2]. In that study, it was concluded that the CK-calculation was precise and matched volume reduction measured by TRUS, the mean calculated CK being 27 ml compared to a prostate volume reduction of 26 ml. Huidobro et al. conducted a study that evaluated the volume reduction in 12 patients after CoreTherm [174].

Evaluation with both histopathology and magnetic resonance imaging showed conformity with the CK-calculation, that is, similar volume reduction. Vesely et al. [175] conducted a study where 13 patients with catheter due to CUR were treated with CoreTherm, and 12 patients were evaluated with magnetic resonance imaging after one week and six months. Volume reduction was, in that study, found to be in concordance with the CK-calculation.

Thus, the cell kill has been demonstrated to correspond to volume reduction after treatment. Nevertheless, the IP sensor may be placed incorrectly, which leads to incorrect temperature input and a situation where illogical temperature curves will be present. Figure 6 illustrates an example of illogical temperature curves (inverted).

The interpretation of these curves is that the temperature sensor is positioned backwards, and the solution is to pause treatment and rotate the treatment catheter counter-clockwise 45° or more. There is a risk of underestimating cell kill in that specific case, where too much energy could be deployed, in a worst-case scenario.

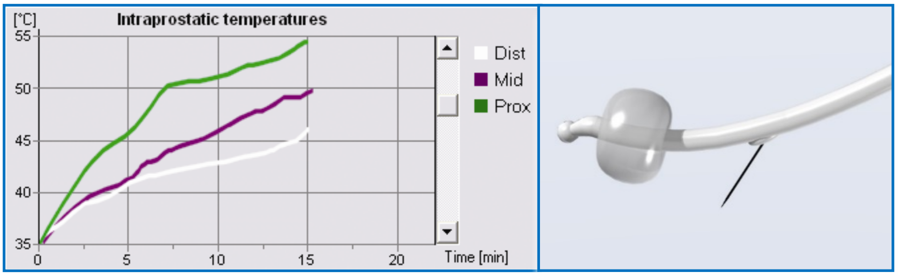

Figure 6. Illustration of illogical temperature curves, or in more detail inverted temperature curves, as illustrated on the left. The interpretation of these curves is that the intraprostatic temperature sensor points backwards at the six o'clock position, as displayed at the right. Permission from ProstaLund AB.

The presence of illogical temperature curves during treatment is a major problem. However, it can usually be solved by pausing the treatment and hereafter by repositioning the treatment catheter. However, this means inconvenience to the patient and a rapid temperature decrease in the prostate, resulting in a reduced cell kill. Also, there is a substantial risk for an incorrect CK-calculation due to the interruption of treatment.

Thus, even if a situation with an incorrectly placed IP sensor can be handled, it would be highly valuable if treatment could commence and be finalised using a treatment goal other than the primary treatment endpoint. This would mean less inconvenience for future patients, as well as a simplified treatment.

Despite the possibility to measure temperatures within the prostate, and adjust the effect accordingly during treatment with CoreTherm, the intraprostatic blood flow transports heat away from the adenoma. The arterial blood flow to the prostate comes from branches that arise from the internal iliac arteries. The arterial vascular supply to the prostatic gland was thoroughly examined by Clegg in 1955 [176]. He studied the arteries that emerge to the prostate by dissection of human corpses and radiologic examination of these corpses after contrast injection. In all cases studied he found a prostatic artery that originated directly from the internal iliac artery or branches more distally. In about 30% of the cases blood flow to the prostate also came from the superior rectal artery and the prostatic artery. There were very few anastomoses between the vessels from the left and right side within the prostate.

In several previous studies, the existence of a defined prostatic artery was questioned, for example, by Flocks in 1937 [177]. According to Clegg, this was probably due to misunderstandings, misinterpretations, or just differences in nomenclature. In a subsequent study by Clegg, in 1956 [178], the vascular arrangements adjacent to the prostatic capsule and the gland were more thoroughly described. Clegg divided the intrinsic prostatic arteries into the outer or capsular plexus, the intermediate zone and the urethral plexus. The main arterial supply to the gland was in this paper described as coming from arteries penetrating the capsule mainly from the lateral aspects of the prostate, from 1 to 5 o'clock and from 7 to 11 o'clock.

The first human study aiming to determine blood flow in male prostates was published in 1969 by Haffner et al. [179]. In this study, the mean blood flow in prostates with BPH was 26.7 (± 8.05) ml/min/100g, not differing from blood flow in men with prostate cancer. Inaba et al. [180] found, in a study from

1992, using positron emission tomography, that blood flow in men with normal prostates was 15.7 (± 7.5) ml/min/100g, in men with BPH 17,7 (± 5.2) ml/min/100g and in men with prostate cancer 29.4 (± 7.8) ml/min/100g. In this study, it was also evident that prostatic blood flow decreased with age, in patients with normal prostates, according to the authors, probably due to atherosclerosis.

Toma et al. [181] found blood flow in patients with BPH at a similar level as Inaba et al. [180], 22.8 (± 13.7) ml/min/100g. In that study, a significantly higher blood flow in patients with prostatitis was apparent. In 1995, Larson et al. [182] used TRUS with colour Doppler in two patients during treatment with microwaves. It was evident that the intraprostatic blood flow increased with increasing temperatures within the gland, both in the peripheral and transition zone.

Furthermore, it was discussed how blood flow acts as a heat sink, transporting heat away from the gland. Hence, the effect must be compensatorily raised to achieve adequate prostate volume reduction; that is, energy delivery must increase. Larson et al. published another study in 1995 where 15 thermosensors were put into the prostate and brought forward the notion of applying the correct thermal dose and combining it with histopathological examinations [183].

In 1998, Wagrell et al. [4] published a study showing the importance of temperature measurements during treatment. In this study, 30 patients with LUTS/BPO were included and treated with microwaves. The responder rate was 60% at the follow-up after six months, and TRUS showed that responders had less tissue left in the bladder neck area as well more pronounced volume reduction, compared to non-responders. It was also believed that energy delivery was not a helpful treatment parameter in evaluating responders. Pressure-flow studies were performed before treatment and at the six months follow-up in all patients. During treatment, TRUS with colour Doppler technique showed blood flow variations with increased blood flow as treatment commenced.

The intraprostatic blood flow differs at baseline between patients and can increase immensely with rising temperatures. In a study by Wagrell et al. [5], baseline blood flow and blood flow as a response to heat was evaluated by positron emission tomography. In that study, the intraprostatic blood flow increased during microwave treatment, and the conclusion was that temperatures must be monitored to optimise treatment. The solution to master the unpredictable blood flow was intraprostatic injections of MA via the Schelin Catheter (Figure 7). This device allows injections to be performed in the bladder neck area despite prostate size, as it is anchored with the catheter balloon. The difference between CoreTherm and the CoreTherm Concept is the addition of intraprostatic injections of MA via the Schelin Catheter.

The results from a study by Schelin [184], using the CoreTherm Concept in 15 men with LUTS/BPO showed shorter treatment time, deposition of lower amounts of energy and a lower calculated blood flow. In a study by Schelin et al., including injections with MA and evaluation of blood flow with positron emission tomography, it was evident that the addition of MA reduces or eliminates blood flow during treatment [185].

Furthermore, it was immediately apparent that the addition of MA leads to a more pronounced cell kill at follow-up with TRUS three months after treatment. The primary endpoint of 30% when using CoreTherm was therefore adjusted to 20% when using the CoreTherm Concept.

Figure 7. The Schelin Catheter. An injection device constructed as a Tiemann catheter with a ball tip and a Foley balloon to keep it in place, anchoring it at the bladder neck for precise injections via the movable injection needle. Permission from ProstaLund AB.

The concept of thermal dosage has, since microwaves were first used for patients with LUTS/BPO, been studied, discussed, tried, and in most cases, abandoned. This is because the unpredictable blood flow transports heat away from the prostate, making the calculation of an appropriate thermal dose impossible. This is changed completely when using the CoreTherm Concept, as the blood flow is abolished, or at least heavily reduced, by the injections of MA.

Treatment with the CoreTherm Concept is usually uncomplicated, with a certain amount of energy deployed in the bladder neck area and subsequent coagulative necrosis. With time, the prostate volume is reduced, and the patient is relieved of the obstruction. When using the Schelin Catheter to deploy the MA, it is possible to deploy less energy, as most of the energy stays in the adenoma and is spread in the tissue through conduction. However, it is most important to remember that the IP sensor measures temperatures in only one region of the prostate, the left upper quadrant (Figure 8).

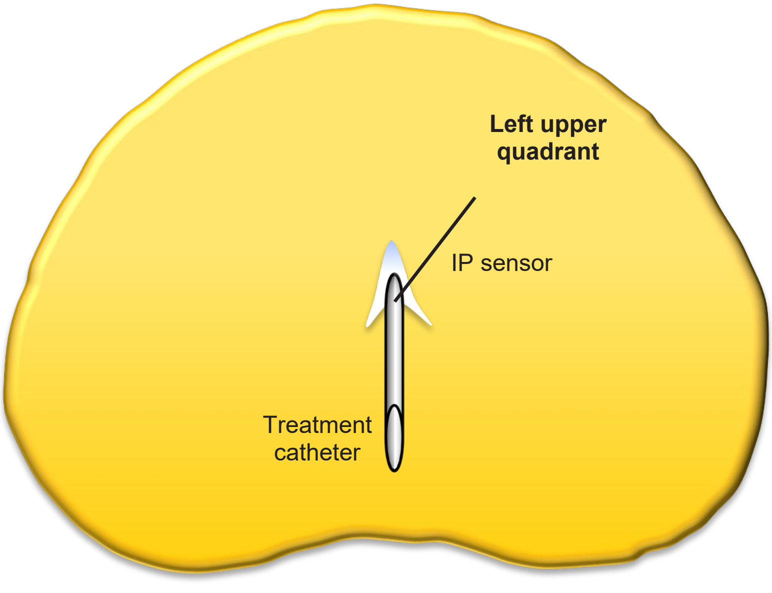

Figure 8. The prostate from an axial view, with the treatment catheter inside the prostatic urethra. Only a part of the treatment catheter is shown. The intraprostatic sensor (IP sensor) is introduced via the treatment catheter, inserted into the prostate and during treatment located in the left upper quadrant.

When using injections of MA routinely in four locations the calculated blood flow should be abolished, or at least low. If this is not the case, the primary endpoint cannot be relied on. This is because the CK-calculation is based on the temperature input from the left upper quadrant. The fact that the injection of MA could have failed in that area means that the calculated CK is unreliable. There is a substantial risk for depositing too much energy in the other three quadrants in that situation. As for illogical temperature curves, in this situation, the possibility to use another treatment endpoint would be of immense value as there is no other safe way to finalise treatment.

In a meta-analysis by Kaye et al. [186], randomised controlled trials that compared the efficacy of different TUMT-devices versus TURP were included. The follow-up of 458 patients one year after treatment included IPSS, Q_{max}, and the PVR. They concluded that CoreTherm was the device that showed the best efficacy, with results comparable to TURP and also with a better safety profile than TURP. The randomised multicenter study of CoreTherm versus TURP included in that meta-analysis [187] showed consistent results for CoreTherm versus TURP after three [142] and five years [188]. In a Study by Gravas et al., 41 patients were treated with CoreTherm, and at follow-up, after one year after treatment, 33 men (88%) were judged as responders [189]. A study by Alivizatos et al. [190] also showed that the results after one year using CoreTherm in 38 patients were satisfactory, with improvements in IPSS, Q_{max} and PVR.

Using CoreTherm in men with CUR, being unfit for surgery, can be an excellent alternative, as indicated in a Danish study by Aagaard et al. [191], of 124 men, where 96 (77%) were relieved of their catheter at follow-up six months after treatment. The largest prostate in their study was 300 ml, and a total of 21 men had prostate volumes >103 ml. That CoreTherm may be an option in high-risk men unsuitable for surgery and catheter due to CUR has also been shown in a study by Kehinde et al. [192], although this study only included four men, the largest prostate being 150 ml. Thus, CoreTherm, and the CoreTherm Concept, seem to be a curative treatment option that can be performed on older men with LUTS/BPO and men having catheter due to CUR. Although several studies have shown size-independent efficacy, no study has focused solely on the largest prostates.

1.7.4 OTHER OPTIONS

Aquablation therapy using waterjet resection without coagulation and a robotic system is a debulking procedure named AquaBeam**.** Removal time for the obstruction is short, but sometimes additional coagulation equipment is necessary [193].

The iTind is a temporary mechanical stent that evolved from the temporary nitinol implantable device (TIND) and is to be placed in the bladder neck and prostatic urethra in order to dilate. It is removed after five days and is considered a device under development [194].

Prostatic artery embolisation is a procedure leading to ischemia with subsequent shrinkage of the glandular tissue. Access to the arterial vascular tree is accomplished via the radial or femoral artery. This can most often be performed under local anaesthesia and, after identification of the prostatic arteries during the arteriography, an embolic agent is deployed for selective occlusion. Prostatic artery embolisation can be technically challenging in patients with atherosclerosis, and the anatomy can also make access and intervention challenging [195]. The EAU recommends prostatic artery embolisation in men with moderate to severe LUTS who accept inferior results compared to TURP and prefer minimally invasive surgery. Furthermore, EAU strongly recommends that urologists are highly involved and work in a team with the interventional radiologist [6]. The American Urological Association (AUA), on the other hand, states that prostatic artery embolisation is considered an experimental treatment and should only be used in studies [7, 8]. In a study by Ray et al., prostatic artery embolisation caused prostate volume reduction of mean 29%, but was inferior to TURP in reducing IPSS and bother [196]. A study that only included prostates >80 ml, outcomes after prostatic artery embolisation also showed a men prostate volume reduction of 30% and improvements of both IPSS, QoL, Q_{max} and PVR [197]. In this latter study of only larger prostates, the outcome was better, indicating that prostatic artery embolisation could be more suitable in larger prostates.

Another treatment option uses injections of water vapour into the gland, a minimally invasive intervention named Rezūm. Median lobe treatment is a possibility in this office-based procedure. In a study of 188 men with prostates of 30-80 ml, the surgical retreatment rate was 4.4% after four years, and 30.9% had a median lobe [198]. There was no reduction of PSA, often seen after treatments that reduce prostate volume.

In smaller prostates and the presence of infravesical obstruction at the bladder neck level, there is no need for volume reduction. Instead, bilateral incisions or a unilateral posterior incision can be made in the bladder neck. This is an elegant and most often relatively simple procedure with low risks and efficacy comparable to TURP, except for higher retreatment rates [199]. Despite this, it is underused, but should be performed on selected cases. This method, transurethral incision of the prostate (TUIP), is suitable in prostates <30 ml, without a prominent middle or third lobe enlargement.

TUIP is most often performed using the resectoscope with Collings knife, but using laser is also possible [200]. The incision, or incisions, begins at a level just distal to the ureteral orifice and is continued via the bladder neck down to the verumontanum. It is possible to make a single incision straight posteriorly or two incisions angled and beginning near the ureteral orifices bilaterally. Depthwise cutting can proceed down to or through the transverse fibrous tissue at the bladder neck level. A deeper incision into the periprostatic or perivesical fat causes a slightly increased risk for complications or adhesions. One option is to make a shorter and more shallow incision or incisions only at the bladder neck level [201].

Sometimes, the line between a strict TUIP and a limited TURP is not as distinct as it might seem in theory. After a TUIP, it is often tempting to shave off any existing edges, especially if there is more tissue than expected. This can be done quickly after changing to the resection loop or performing a minimal TURP if necessary (an English Channel) [202]. Regardless of this siding, the TUIP is more than sufficient to open the restrictive and often functionally narrow bladder neck [203]. Sometimes, the condition of primary bladder neck obstruction is designated Marion’s disease after the Parisian surgeon and urologist Georges Marion, who described its anatomy and physiology, but not the surgical technique [204].

The TUIP, with diathermy, was first described in 1961 by Keitzer et al. [205] and later by Orandi [206, 207], who, after his first TUIP in 1969, continued to use it on a larger scale, presenting results in 846 patients in 1990 [208]. One advantage, compared to TURP, is a reduced risk for retrograde ejaculation, making TUIP an excellent option to TURP, especially in younger patients with limited enlargement [209]. Due to the risk profile, it can also be considered an option in older patients.

Another minimally invasive mechanical intervention, besides iTIND, is UroLift. In the LIFT study, 206 men with prostates of 30-80 ml were treated, and the 5-year follow-up showed a surgical retreatment rate of 13.6% [210]. This system lateralises the left and right lobes, which occlude the prostatic urethra. UroLift creates an anterior channel, as the permanent tissue anchors are placed to avoid the neurovascular bundles and the dorsal vein complex. There is a risk that the permanent anchors could complicate prostate evaluation with magnetic resonance imaging, and in addition, surgical retreatment rates at five years are at the high end. In guidelines from the EAU, UroLift is strongly recommended in men with prostates <70 ml without a median lobe and a need for antegrade ejaculation [6].

Another possibility to reduce prostate volume is by vaporisation. To vaporise the tissue, energy of some sort must be applied. This can be done using different kinds of energy sources, as in bipolar transurethral vaporisation of the prostate (B-TUVP) [211] or different lasers [212].

2 AIMS

Lead me, follow me, or get out of my way.
George S. Patton

The aims of this thesis, and the underlying studies, were to disclose some aspects of implemented methodological alterations regarding TUMT with feedback technique, evaluate the efficacy of TUMT with feedback technique, and the CoreTherm Concept in large prostates, and investigate the effect of intraprostatic injections of MA during TURP.

P**aper I** elucidated the impact on cell kill when using intraprostatic injections of MA via the Schelin Catheter before TUMT with feedback technique and assess clinical response three months after treatment.

Paper II assessed the scientific basis for using thermal dosage as an alternative treatment endpoint, based on prostate volume and age when using the CoreTherm Concept.

Paper III evaluated the short- and long-term efficacy of CoreTherm and the CoreTherm Concept in patients with prostate volumes ≥80 ml.

Paper IV studied if intraprostatic injections of MA before TURP reduce total peroperative bleeding and blood loss.

3 PATIENTS AND METHODS

Only those who are asleep make no mistakes.
Ingvar Kamprad

The papers included in this thesis are based on three patient cohorts, where **Papers I-II** partially encompass a subgroup of patients also included in **Paper III** (Figure 9). In the first two retrospective studies (**Papers I-II**), 278 consecutive patients treated in 2003-2007 at an outpatient clinic were included. The third study (**Paper III**), also retrospective with partially prospectively collected data, covers year 1999-2015. This study includes treatments from a hospital clinic and an outpatient clinic, a total of 570 men, limited to large prostates. **Paper IV**, a prospective multicenter study, included 100 patients from three hospital clinics in Sweden.

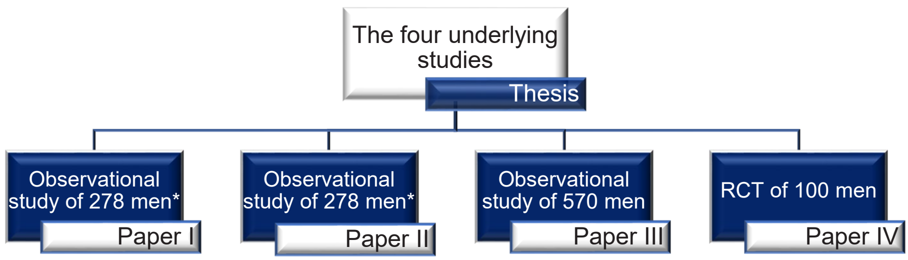

Figure 9. Overview of studies included in this thesis (*same patient cohort).

3.1 ETHICS

After applications, the regional ethical committee at the University of Linköping granted ethical approvals for all studies. **Paper I-II** dnr 2010/394-31, **Paper III** dnr 2010/394-31 and dnr 2015/471-32 and **Paper IV** dnr M238-08. Patients treated 1999-2009 were included in the primary application (dnr 2010/394-31). The described overall objectives in the ethical application were focused on treatment outcomes, retreatment rates, adverse events, prostate volume reduction after treatment and energy deposition.

To increase the number of patients treated, we also included patients treated 2010-2015 in **Paper III** (dnr 2015/471-32). For **Papers I-III,** data were collected from medical journals and presented at group level, making identification of specific patients impossible. No intervention or additional tests were performed regarding the studies.

Paper IV was a prospective and randomised study (dnr M238-08). All patients received oral and written information, and they thereafter signed the informed consent. The intraprostatic injections were judged to cause no additional pain as the patients were to be anaesthetised. Systemic severe effects of the adrenaline injection were deemed unlikely as the patients were to be carefully monitored in the operating theatre. It was presumed that those who received an adrenaline injection during the procedure could have the operation performed with less perioperative bleeding and blood loss.

3.2 STUDY POPULATION

Papers I-II included 278 patients treated according to the CoreTherm Concept during 2003-2007 at an outpatient clinic in Kalmar, Sweden. They all sought care due to LUTS or had CUR and, after evaluation, were deemed that BPO was the underlying cause. Treatment according to the CoreTherm Concept was the method of choice for all patients. This cohort was evaluated before treatment according to the usual routine and at follow-up three months after treatment. TRUS was routinely performed.

In **Paper III**, we included all patients with LUTS/BPO having a prostate volume ≥80 ml treated with CoreTherm or the CoreTherm Concept from the same outpatient clinic and the only hospital clinic at Kalmar County Hospital 1999-2015.

In **Paper IV**, a prospective and randomised multicenter study conducted at Kalmar County Hospital, Ljungby County Hospital and Växjö County Hospital. A total of 100 patients with LUTS/BPO were included and randomised 1:1.

3.3 STATISTICS

Statistica version 10 (Statistica; StatSoft, Tulsa, OK, USA) was used for all statistics in **Paper I**. Pretreatment data such as patient age at the time of treatment, pretreatment prostate volume, symptom score, QoL, and peak urinary flow measurement were extracted from the medical journals. Treatment data as treatment time and energy delivery were available from the time of the treatment from the computer software. Follow-up data consisted of symptom score, QoL and peak urinary flow measurement and post-treatment prostate volume. Descriptive statistics for pretreatment data such as age at the time of treatment, pretreatment prostate volume, treatment time and energy delivery were presented as mean and median values, including standard deviation and range.

Calculated CK and measured prostate volume reduction were normally distributed and analysed using repeated-measures analysis of variance (ANOVA) with the prostate volume dichotomised into two groups. All patients with a QoL of 0-1 or having a reduction of symptom score ≥50% and those who were catheter dependent and were able to void spontaneously after treatment were judged as responders. Responder rate was defined as the number of patients judged as responders divided by the total number of patients in the study.

In **Paper II,** Statistica version 12 (Statistica; StatSoft, Tulsa, OK, USA) was used for all calculations. Descriptive statistics for the skewed distributed data as age, prostate volume, treatment time, energy consumption and cell kill were presented with the median value, range and interquartile range. In the context of this study, it was considered appropriate to define an optimal treatment meeting all these criteria: logical temperature curves, a calculated blood flow ≤20 ml/min and a cell kill indicating a fulfilled treatment without premature termination. In the multiple regression analysis, age and prostate volume were the independent variables and energy delivery the dependent variable. The level of significance was decided to be $p<0.05$.

Statistica version 13 (TIBCO Software, Inc, Palo Alto, CA, USA) was used for all **Paper III** statistics. Descriptive pretreatment data were analysed, mean and median, including standard deviation and range, was calculated. When analysing retreatment data, patients were divided into two groups, hereafter evaluating differences using Kruskal-Wallis ANOVA followed by Mann-Whitney's U-test, in case of significance.

The survival analyses were conducted according to the Kaplan-Meier model, including categorisation into groups according to age, LUTS/BPO versus CUR and prostate volume. Censoring occurred if diagnosed with prostate cancer.

In **Paper IV**, Statistica version 13 (TIBCO Software, Inc, Palo Alto, CA, USA) was used. The main aim was to evaluate bleeding in the two treatment groups using the volume of peroperative bleeding divided by the resected weight of prostatic tissue. This was the primary outcome variable, measured in ml bleeding/g resected tissue. The null hypothesis was tested at the 5% significance level. Baseline and treatment data were presented as mean (SD) and median (range) in all patients and separately for the control and interventional groups. The Mann-Whitney's U-test was used for continuous data and Fisher's exact test for non-continuous data.

3.4 METHODOLOGY

During 2003-2008, data from 283 treatments were meticulously documented, including TRUS in the follow-up. Thus, this specific group was judged suitable for the assessment of prostate volume reduction. One experienced urologist performed TRUS with the same equipment before and after treatment, considered a major strength of this study. Furthermore, 278 treatments were included, which was judged to be a sufficiently large number of treatments. The achieved cell kill at treatment is a software-based calculation, which is not affected by study design.

The evaluation of responders in **Paper I** must be interpreted with some caution, as some follow-up data were missing and since two symptom scores were used, in combination with the evaluation of QoL after the intervention (Table 1). Incomplete emptying, intermittency, weak stream, straining and hesitancy were classified as voiding symptoms, and frequency, urgency, nocturia and dribbling (post-micturition) as storage symptoms when using the modified Madsen-Iversen score (mMIS).

	IPSS	MIS	mMIS
Incomplete emptying	0-5	0-4	0-2
Frequency	0-5	0-3	0-2
Intermittency	0-5	0/3	0-2
Urgency	0-5	0-3	0-2
Weak Stream	0-5	0-4	0-2
Straining	0-5	0/2	0-2
Nocturia	0-5	0-3	0-2
Hesitancy	-	0/3	0-2
Dribbling	-	0/2	0-2
QoL	0-6	-	0-6

Table 1. Point system for the International Prostate Symptom Score (IPSS), the Madsen-Iversen Score (MIS) and the modified MIS (mMIS). Dribbling is, by definition, post-micturition dribbling.

After treatment, evaluating the responder rate was done using a modification of the system of outcome variables used by de Wildt [213]. After collecting all available data and before the statistical analysis, it was evident that it was impossible to strictly use these criteria for evaluating responders. Therefore, it was decided to use available data for as correct an estimation of responder rate as possible. Before treatment, all patients had a QoL of ≥2 points, and it was decided that a QoL of 0-1 after treatment had to be reached, or a reduction of the symptom score ≥50%, or if the patient was relieved of his catheter at follow-up. This resulted in 87% responders, and this evaluation is more of an indication that treatments worked sufficiently well. Adverse events were few, and no serious adverse events were found in the clinical records.

Paper-II was an observational study, including the same patients as in **Paper I**. As the intent was to evaluate if energy consumption could be used as an alternative endpoint, it was judged rational only to include treatments that were likely to have been performed with no significant shortcomings. Therefore, it was decided that three parameters had to be sufficiently accomplished during treatment. These were logical temperature curves, a low calculated blood flow and a fulfilled primary treatment endpoint. It is possible that the inclusion of all treatments would have had an impact on the regression analysis, as correct energy delivery is dependent on correct temperature input and a low blood flow. The calculated CK was in some cases at the low end, but the intent was to include, rather than to exclude, as many treatments as possible.

Paper III focused on retreatment rates when using CoreTherm or the CoreTherm Concept on large prostate glands. All patients registered in the southern part of Kalmar County primarily treated with CoreTherm, or the CoreTherm Concept were included. Although these methods share many similarities, dividing all patients into two treatment groups would probably have shown lower retreatment rates for the CoreTherm Concept. Only the outpatient clinic had consistently documented injections, and the treatments with CoreTherm were a fraction of the total number of treatments. We, therefore, decided to evaluate CoreTherm and the CoreTherm Concept together. Complications such as bleeding, strictures and incontinence are extremely uncommon after treatment with microwaves but were not included in the study since the primary objective was the need to undergo retreatment, and complications would have been harder to evaluate retrospectively.

Paper IV was designed as an open, prospective, controlled, randomised multicenter study. The starting point for **Paper IV** was a study performed by Schelin [214], constituting the pilot study on which the power analysis was based. The primary outcome measure was blood loss (ml) per resection weight (g), with secondary outcome variables as resection weight, transfusion and complication rate. A power calculation, based on the mean effect of the primary outcome variable and variance of the pilot study, was performed when the study design was defined, and before treatments were initiated. It was decided that a significance level of 5% and a power of 80% was desirable.

The power analysis thereby determined that a sample size of a total of 84 patients would be sufficient to achieve statistical significance. We included a total of 100 patients, randomised 1:1 into an interventional and a control group. As intraprostatic injections of adrenaline lead to vasoconstriction and the consequent whitening of the prostatic tissue, blinding the surgeon was not judged possible. Blinding the patient was not judged relevant with regards to the outcome variables. We also used concealed allocation, where 100 envelopes were used, prepared before the study started. Inclusion criteria were prostate enlargement >30 ml, IPSS >12 points, Q_{max} <13 ml/s and a signed informed consent. Exclusion criteria were known intolerance of mepivacaine or adrenaline or inability to tolerate a TURP operation.

4 RESULTS

Say what you mean and mean what you say.
George S. Patton

The addition of intraprostatic injections with MA via the Schelin Catheter when treating the patient with the CoreTherm Concept leads to an underestimation of cell kill. This is shown in **Paper I** of this thesis, illustrated in Figure 10. This is a key finding, as the recommended calculated cell kill of 20% (primary treatment endpoint) is inaccurate, and a prostate volume reduction that exceeds the calculation is most evident. It was possible to evaluate 265 men (95%) regarding actual prostate volume reduction. Prostate volume data were dichotomised into prostate volumes <100 ml and ≥100 ml, respectively. The calculated cell kill was 21%, with no differences between the groups (p=0.7431).

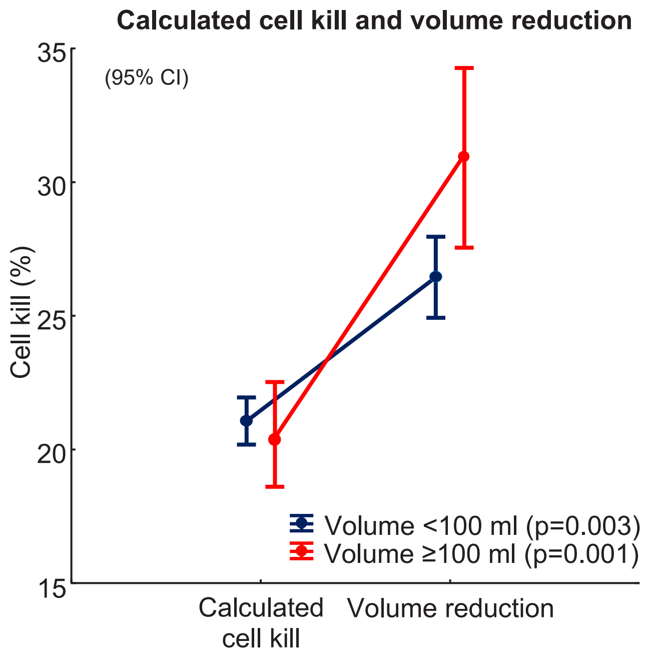

Figure 10. The cell kill (CK) calculated by the software during treatment and the measured volume reduction at follow-up three months after treatment. Displayed is mean values and 95% CI. The difference between calculated CK and prostate volume reduction is calculated for the two groups, with p=0.003 for prostate volumes <100 ml and p=0.001 for prostate volumes ≥100 ml.

The underestimation of cell kill was more pronounced in prostates ≥100 ml than prostates <100 ml. For prostates <100 ml, the mean prostate volume reduction was 26% ($p=0.003$), and for prostates ≥100 ml the mean prostate volume reduction was 31% ($p<0.001$).

The responder evaluation demanded a QoL of 0-1, a symptom score reduction of ≥50% or catheter freedom, resulting in a responder rate of 87%. A total of 191 patients (69%) had a QoL of 0-1, corresponding to delighted or pleased, another 36 patients (13%) had a reduction of symptom score of ≥50%, and 16 patients (6%) became catheter free after treatment. These results correspond to a responder rate of 88% (227 men) in patients with LUTS/BPO, and 84% (16 men) in patients with catheter due to CUR.

Treatment was completed without the addition of sedatives in 273 men (98%), and in 276 men (99%), local anaesthesia was the only analgesic used. Two men (1%) received an analgetic drug intravenously on demand. Minor adverse events, such as urinary tract infections and urge discomfort after treatment, were commonly noted in the medical records. However, no serious adverse events or hospital admissions were recorded.

In **Paper II**, we concluded that the thermal dose correlated to prostate volume and age. In the instructions for use (IFU, ProstaLund AB, Lund, Sweden), a concept of energy points based on prostate volume is used. We could, in this study, confirm that this approach is judged appropriate. A total of 199 treatments showed logical treatment curves and a relatively low calculated blood flow, indicating fitting MA injections and also that the alternative treatment endpoint was achieved, presented in Table 2.

Assessment of treatments *(n=278)*	Yes	No
Logical temperature curves	238	40
Calculated blood flow ≤20ml/min/100g	215	63
Primary endpoint achieved (cell kill)	234	44
Optimal treatment	199	79

Table 2. The number of patients with logical temperature curves, a calculated blood flow ≤20ml/min/100g and a calculated cell kill of ≥15% for prostates <100 ml and ≥12% for prostates ≥100 ml. The number of optimal treatments is also presented.

The multiple linear regression analysis showed that both prostate volume before treatment and age were independent predictors of energy deposition, Equation 2.

$$\text{Thermal dose (kJ)} = 27 + 0.19 \times \text{prostate volume (ml)} - 0.16 \times \text{age (yrs)}$$

Equation 2. The equation for the multiple linear regression analysis. The thermal dose is dependent on prostate volume and age.

Thus, the thermal dose increases with increasing prostate volume ($p<0.001$) and decreases with increasing age ($p<0.01$). The appropriate thermal dose can be calculated from the equation. The correlation between prostate volume and energy delivery is shown in Figure 11, and the correlation between age and energy delivery is displayed in Figure 12.

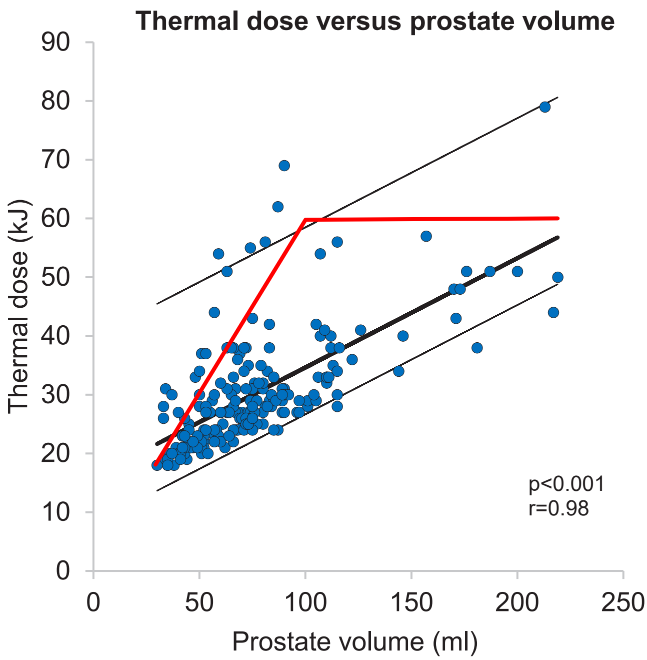

Figure 11. The broad, solid middle line represents the regression line, and the thin solid lines represent the upper and lower 95% CI. A blue dot represents each case. The broad red line represents the calculated energy deposition used as an alternative treatment endpoint (energy points) in the instructions for use by ProstaLund AB.

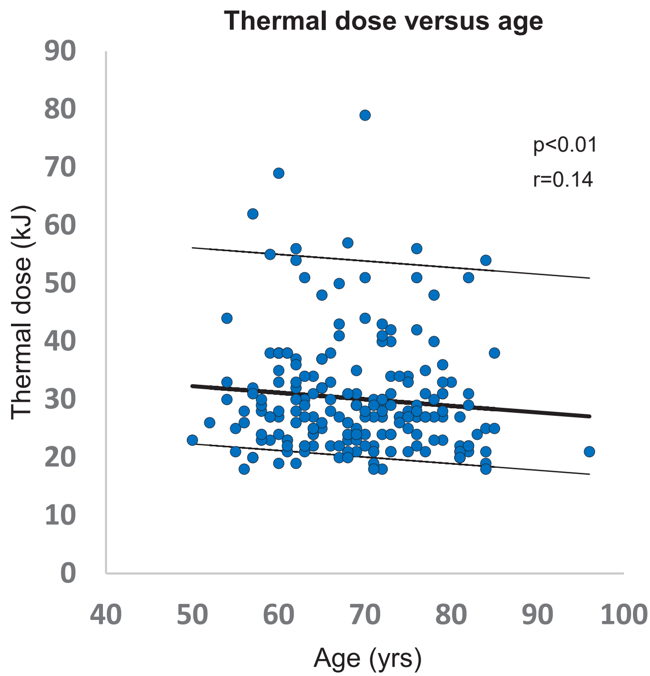

Figure 12. The broad, solid middle line represents the regression line, and the thin solid lines represent the upper and lower 95% CI. A blue dot represents each case.

Treatment with CoreTherm, and later the CoreTherm Concept, has been performed in our settings at two clinics regardless of prostate volume for over two decades. In **Paper III**, we primarily aimed at evaluating efficacy in all treatments with the CoreTherm Concept or CoreTherm in prostates ≥80 ml during 1999-2015. We focused on male residents in a defined catchment area in Kalmar County at the end of the study in 2019. We identified a total of 570 men that were treated during this period.

The mean age was 73.1 years, and a total of 126 men (22.1%) were older than 80 years. The mean prostate volume, measured by TRUS, was 114.1 ml, and the largest prostate was 366 ml. The mean IPSS was 19.7 points, corresponding to severe LUTS, and in those patients where the MIS was used, voiding symptoms were dominating. The QoL mean value was 4.1, corresponding to mostly dissatisfied.

A total of 333 men (58.4%) had LUTS/BPO, and 237 (41.6%) used a catheter, of which 225 (94.9%) used a permanent indwelling catheter (cathéter à demeure, CAD), and 12 (5.1%) clean intermittent catheterisation. Within the first year after treatment a total of 26 retreatments were performed (4.6%), TAE in three men (11.5%), TURP in 12 men (46.2%), and 11 men (42.3%) retreated with microwaves. In those 26 men that were retreated, ten (38.5%) had LUTS/BPO, and 11 (42.3%) used catheter due to CUR, lacking data regarding the use of a catheter in five men (19.2%).

Furthermore, at the three months follow-up, a total of 32 men used CAD and eight used clean intermittent catheterisation. Among the 32 men that used CAD five did not use a catheter before treatment, and among those eight men using clean intermittent catheterisation all men used a catheter before treatment. Thus, according to the defined primary endpoint, a total of 61 men (10.7%) were early failures, leading to an early success rate within the first year of 89.3%, by that definition. Compared to those retreated later or not retreated, a significant difference was found regarding IPSS ($p<0.001$), mMIS voiding score ($p=0.017$) and QoL ($p=0.003$).

An additional 56 patients (10.3%) had to undergo surgery due to LUTS, indicating late failure at one year or later. TAE was performed on 14 men (2.6%) and TURP in 42 men (7.7%). Another 50 men (9.2%) were retreated with the CoreTherm Concept or CoreTherm. The long-term retreatment free survival during the follow-up, ranging up to 20 years, was 76.8%. Thus, a total of 438 men were only treated once, and 132 men (23.2%) had some retreatment, the surgical retreatment rate being 12.5% (71 patients). There was a significantly lower retreatment rate in older versus younger men ($p=0.04$), but no difference regarding retreatment in those with LUTS/BPO versus catheter ($p=0.93$) or those with prostate volume ≤100 ml or >100 ml ($p=0.97$). An overview of retreatment modalities, retreatments and retreatment rates is presented in Table 3.

Retreatment	<1 year	≥1 year	Total
TAE	3 (11.5)	14 (13.2)	17 (3.0%)
TURP	12 (46.2%)	42 (39.6)	54 (9.5%)
TUMT	11 (42.3%)	50 (47.2)	61 (10.7%)
Total	26	106	132 (23,2%)

Table 3. An overview of retreatments.

The retreatment data in **Paper III** represents all primary retreatments, but some patients also had a second treatment (12 men, 2.1%), a third treatment (3 men, 0.5%), or a fourth treatment (1 man, 0.2%) during follow-up. Also, it was evident that early retreatments were more common in patients primarily treated during the first years of the study period than the later years: year 2000: 2 patients; 2001: 4; 2002: 4; 2003: 5; 2004: 2; 2005: 3; 2006: 2; 2008-2009 and 2012-2013: 1. This leads to 17 early retreatments during 1999-2004, seven early retreatments 2005-2009 and two early retreatments 2010-2015.

In **Paper IV,** a total of 81 patients were eligible for evaluation, randomised to the control or the experimental group. The patients in the experimental group were as a mean four years older (p=0.041), no other significant difference was found between the groups. The mean prostate volume was 55,7 ml, mean IPSS 20.1 points, and mean QoL 3.7 points.

We found that the addition of intraprostatic injections with MA brought significantly higher resection weight in the experimental group (p=0.026), mean 26 grams versus 22 grams in the control group. There were no other significant differences in the outcome variables, but a tendency in the direction of reduced blood loss (mean 130.7 ml versus 156.2 ml) and blood loss per resection weight (mean 4.8 ml/g versus 6.6 ml/g) in the experimental group. No patients required blood transfusion in the perioperative period.

Complications occurred in five men (6.2%): one man had transient hypertension and bradycardia during surgery, two men resorbed minor volumes of irrigation fluid, one man had a postoperative urinary tract infection requiring antibiotics intravenously, and one man developed pancreatitis, as well as having prolonged bladder irrigation after surgery (<48 hours). According to the Clavien-Dindo classification [215-217], three of these men had grade I, and two men had grade II, adverse events.

5 DISCUSSION

The saddest aspect of life right now is that science gathers knowledge faster than society gathers wisdom.

Isaac Asimov

The papers in this thesis target the CoreTherm Concept and the TURP. Although these methods are different, they share some similarities. They both reduce symptoms in patients with LUTS or CUR due to BPO. They both lead to volume reduction, where the primary purpose of treatment is to reduce urinary flow resistance. The methods were both introduced several decades ago, but TURP is older and considered the gold standard for prostates with a volume of 30-80 ml. Most importantly, none of the methods oppose each other. They could both have their prominent place in the treatment armamentarium, and as their respective pros and cons differ, they could be seen as complementary.

In **Paper I**, treatment with the CoreTherm Concept and the CK-calculation was the main focus. The Schelin Catheter was the core tool that made the transition from the regular CoreTherm treatment to the CoreTherm Concept possible. This catheter makes intraprostatic injections with MA feasible, and it was introduced and approved for use in 2002. The first studies with microwaves were carried out without injections during the 1990s and often aimed at a cell kill of 30%, which was based on empirical data. It was established and shown in several studies that the calculated CK without MA corresponded to the actual volume reduction [2, 174, 175, 218].

Besides published data, it was also evident in routine follow-ups of everyday patients that the prostate volume reduction after treatment corresponded to volume reduction, measured by TRUS. However, when the Schelin Catheter came on the market it was immediately apparent that treatment was faster and most often pain-free. This led to the instant use of the catheter, and at follow-up with TRUS volume reduction turned out to be more pronounced.

During the following years the treatment goal was set at a lower level, reduced from 30% to 20%. The primary objective in **Paper I** was to evaluate cell kill using MA during CoreTherm. After the Schelin Catheter's approval, patients treated 2003-2008 were meticulously evaluated at an outpatient clinic after treatment, including TRUS.

It was therefore decided that evaluating these patients regarding volume reduction would be appropriate. In all cases, the same equipment for evaluation before and after treatment was used, as well as the same equipment for the microwave treatment. The evaluation by the same urologist before and after treatment was, apart from using the very same equipment, an evident strength of the study. The apparent weakness of this study is the evaluation of responders. Different approaches to evaluating responders to curative treatment in patients with bother due to LUTS/BPO or CUR are often used. In patients using catheter due to CUR a responder or a non-responder is perhaps, somewhat easier to define (*id est* catheter freedom).

These criteria, used to define responders, are often referred to as the de Wildt criteria. In a study by Sagen et al. [219], modified criteria proposed by de Wildt were used to define responders after TURP (188). One out of four criteria regarding IPSS, Q_{max}, PVR, and bother, had to be fulfilled in that study. This approach is similar to what was used in **Paper I**, where a responder had to show a symptom score reduction of ≥50% or a QoL of 0-1 or being catheter free after being catheter dependent. Thus, Q_{max} and PVR were excluded from the definition of responders. The sole use of QoL in assessing outcome after treatment for LUTS/BPO has been evaluated and suggested by O'Leary [220].

Treatment with the CoreTherm Concept and CoreTherm is, in most cases, uncomplicated for both the urologist and the patient. Microwaves are applied to the prostate, and usually, the treatment progresses relatively fast, and the treatment can be terminated when reaching the primary treatment endpoint. If using CoreTherm, treatment can last up to one hour, depending on achieved temperatures, primarily dependent on blood flow. Treatment with the CoreTherm Concept is usually faster, most often <15 minutes. There is nowadays no apparent reason for using CoreTherm instead of the CoreTherm Concept. The main prerequisite for a correct cell CK-calculation is logical temperature curves, but also a treatment without interruptions is vital for a correct calculation. When the temperature curves are logical, the position of the IP sensor in relation to the catheter is correct, and the catheter is correctly placed. It is impossible to rely on the temperature input if there is a rotational fault with the catheter and the IP sensor. This can, in turn, lead to under- or overestimation of cell kill. This means that there is a need to replace the catheter and the IP sensor, implying that the treatment is temporarily paused. In these situations it would be beneficial to use another treatment endpoint, as the CK-calculation may be inaccurate. It would also be beneficial for the patient if the treatment catheter could stay in place without interruptions.

In **Paper II**, we found that prostate volume and age were predictors of energy consumption. These parameters can thereby be used to calculate appropriate energy delivery. Thus, appropriate energy deposition in each case can be calculated beforehand. Hence, in those situations where the temperature curves are illogical there is no need to replace the treatment catheter and IP sensor. Treatment can instead commence, and as an alternative to using the primary treatment endpoint of 20% the alternative endpoint based on energy delivery can be used. There is one other situation where energy calculation before treatment is of value in everyday clinical work. The first phase using the CoreTherm Concept includes the deposition of MA in four quadrants of the prostate. As the IP sensor is inserted and located in the left upper quadrant, this is the only area that feeds the software with temperature data.

The CK-calculation is based on this temperature input, and as the IP sensor is located in one quadrant, it reflects the temperature in this area. This also means that the primary treatment endpoint of a 20% cell kill is solely based on data from a limited part of the prostate. If the injection of MA fails in the left upper quadrant, but is successful in the other three quadrants, there is an obvious risk of depositing too much energy in the prostate. Thus, when having too highly calculated blood flow, the alternative treatment endpoint suggested in **Paper II** must be used, and the primary treatment endpoint disregarded. Besides these developmental issues regarding the CoreTherm Concept and CoreTherm these treatments have been used in prostates >80 ml, but no studies have been published exclusively on the subject. Therefore, it seemed appropriate to evaluate the short- and long-term efficacy of the CoreTherm Concept and CoreTherm in men with large prostates, as this could be an excellent outpatient alternative.

In **Paper III**, we concluded that only 12.5% had to be retreated with surgery, and 3.5% with an open approach. As mentioned, some studies with CoreTherm have included large prostates, although not evaluated separately. In the study by Aagaard et al. [191], prostate volumes reached up to 300 ml. Most patients in their study were also judged unfit for surgery with a median age of 80 years. There is no clear definition regarding retreatment rates in patients with LUTS/BPO. Instead, retreatment is often defined in the study design and can differ considerably between studies, hence making comparisons difficult.

It was also found that a substantial amount of the TURPs performed included a median lobe resection, as described in the operative report. Because intravesical prostatic protrusion was not recorded before treatment, but only prostate volume measured by TRUS, it was judged that no further evaluation was possible in this respect. Also, an evaluation of an operative report must be interpreted with some caution. Nevertheless, the presence of a median lobe was mentioned quite frequently. Thus, it is plausible that early failure of the CoreTherm Concept is correlated to the presence of a median lobe or a high-grade intravesical prostatic protrusion. Although no intervention can be expected to cure every patient, interestingly, the prevalence of median lobes of 10-15% seems to correspond to the 12.5% of patients that were surgically retreated in **Paper III**.

It must also be pointed out that the patients with large prostates treated in **Paper III** were not routinely evaluated preoperatively with cystoscopy. An evaluation of the bladder neck was undertaken using cystoscopy only in men where a median lobe was suspected on TRUS, and despite this, in some cases treated with the CoreTherm Concept. The fact that it is possible to treat some men with median lobes with microwaves must also be addressed and discussed. When suspecting a median lobe on TRUS in the clinical setting a cystoscopy must be undertaken to evaluate the bladder neck area. With the instrument in the prostatic urethra, the configuration can be assessed. If there is a vertical opening it is possible to treat the patient with the CoreTherm Concept, but if there is only an opening, which can be compared to convexity pointing ventrally, a sad mouth appearance, treatment is futile.

In patients with comorbidity demanding some kind of antithrombotic treatment it is advantageous if the treatment can be continued without changes in this medication. Although such drugs can be temporarily discontinued it complicates the procedure and increases the risk for errors. The risk for bleeding with continued medication should not, in an ideal situation, increase morbidity. Some surgical laser interventions can be performed despite continued anticoagulative or antiplatelet treatment, as HoLEP [130] and vaporisation with greenlight laser [221]. Regarding the CoreTherm Concept it is not recommended, and not necessary, to make adjustments to any of the antithrombotic medications. Although none of the studies in this thesis explicitly targets this area, 27 patients in **Paper III** did not discontinue warfarin despite treatment, according to clinical routine. That treatment with microwaves can be safely performed despite ongoing antithrombotics is coherent with data from previous studies on TUMT and antithrombotic treatment. In a study of 105 men by Saitz et al. a total of 86% did not discontinue anticoagulatives, while only two (1.9%) experienced haematuria that necessitated admission, and no patients were transfused [222].

Men with enlargement of the central zone pose a specific problem when it comes to LUTS/BPO. Enlargement of the transition zone leads to lateral lobe enlargement, with possible subsequent obstruction of the prostatic urethra. On the other hand, enlargement of the central zone leads to a median lobe that can obstruct the outlet from the bladder and distally, functioning as a partially adherent ball valve. In surgery, this usually constitutes a minor problem, the median lobe must be removed together with the rest of the adenomatous tissue. As for the methods in this thesis, this median lobe dilemma is only valid for the CoreTherm Concept, as it is no problem in a TURP.

In the Olmsted County study, 322 men were evaluated with TRUS, and by definition 10% had a trilobal enlargement [223], that is, lateral lobe enlargement and enlargement of the central zone. The intravesical prostatic protrusion by the median lobe also roughly corresponds to the results in a study by Park et al., where 15% of the 134 patients had a protrusion of the central zone of a similar degree [224]. Intravesical prostatic protrusion has also been shown to correlate with the severity of BPO on pressure-flow studies [225].

Based on the findings obtained herein the CoreTherm Concept may well be used in patients with a median lobe but, most likely the retreatment frequency is higher in this subgroup of patients. Many men with large glands are often subjected to TAE or other open surgical interventions just because of the size of the gland. This means that procedures are performed under general anaesthesia, with occasional high risks for bleeding and morbidity, and in many cases time consuming and expensive surgery. In **Paper III,** we show that the CoreTherm Concept is an alternative to TAE, especially suitable for older men. In addition, as the prostate volume is reduced, many men can have a TURP instead of a TAE if retreatment is deemed necessary.

In general, surgery is a procedure that can lead to bleeding, which is most evident in one of the true kingpins of urology. That is in TURP, the gold standard in patients with LUTS/BPO and a prostate volume of >30 ml and <80-100 ml. That this surgical intervention can lead to quite bothersome bleeding is well known, and it has been so since man began to remove prostatic tissue. Bleeding can occur during surgery, in the direct postoperative period and also several weeks after the intervention. Different approaches have been tried to reduce bleeding in the perioperative phase, and the first was, of course, when monopolar electrosurgery was introduced, and then some decades later, when the bipolar technique was introduced.

In **Paper IV** we made an effort to improve the TURP with regards to bleeding during resection. In some way, this study can be regarded as a cross-fertilisation from the CoreTherm Concept. That our primary general focus aimed to reduce bleeding was a natural step, whereby reduced blood flow is accomplished using the CoreTherm Concept. We did not reject the null hypothesis, probably due to underpowering of the study and a type II error. This was perhaps caused by patients lost to follow-up from one of the hospitals in the study or a power calculation that underestimated the number of patients needed. In **Paper IV** bleeding in the control group was 7.1 ml/g, and in the interventional group, 5.0 ml/g, compared to 15.4 ml/g and 4.8 ml/g in the study by Schelin [214], and 12.9 ml/g and 9.1 ml/g in the study by Lira-Dale [226], respectively. Adverse events were scarce, and no serious adverse events occurred during the surgery or the first 30 days after the intervention.

The Swedish Agency for Health Technology Assessment and Assessment of Social Services (in Swedish abbreviated SBU) published a comprehensive literature review regarding LUTS/BPO in 2011 [227]. They established that TUMT leads to symptom reduction, reduces bother and increases urinary flow, but with inferior results compared to TURP. SBU also concluded that TUMT should not be recommended in prostates <30 ml and that retreatment rates <3 years were higher than for TURP. In the latest guidelines from the EAU, TUMT is not mentioned or evaluated as a treatment option [6], despite recommendations in previous guidelines. The AUA considers TUMT an option but, according to their guidelines, patients must be informed that retreatment rates are higher than for TURP [7, 8].

6 CONCLUSIONS

The journey of a thousand miles begins with one step.
Lao Tzu

In **Paper I**, we found that the addition of MA via the Schelin Catheter leads to an underestimation of cell kill during treatment with CoreTherm. This is of clinical importance, and pinpoints a vital difference between CoreTherm and the CoreTherm Concept, meaning that different primary treatment endpoints should be used, as the final prostate volume reduction after treatment is underestimated using MA.

The use of energy calculation based on prostate volume and age before treatment is possible using the CoreTherm Concept. This is shown in **Paper II** and strengthens the recommendation to use this as a complementary treatment endpoint.

This critical finding makes the treatment safer and, in some cases, probably more accurate. In those cases where the temperature curves are unreliable, or the blood flow calculations show a significant blood flow despite MA injections, this contributes to the treatment concept.

An age and prostate volume-independent outpatient option in men with LUTS/BPO would be beneficial. In **Paper III**, we evaluated the short- and long-term efficacy of the CoreTherm Concept in prostates ≥80 ml. We found that surgical retreatment was low, only 12.5%, with a mean and median follow-up of 10 years. The CoreTherm Concept should thereby be considered an excellent alternative to TAE, especially in fragile patients.

TURP is one of the mainstays in urological surgery. In **Paper IV**, a randomised multicenter study, we injected MA into the prostate before and during surgery. We found that that this lead to a significantly increased resection weight and a tendency towards less bleeding.

7 FUTURE PERSPECTIVES

Be not the first by whom the new are tried, nor yet the last to lay the old aside.
Alexander Pope

There seems to be a never-ending flow of new techniques with the intent to cure patients with LUTS or CUR due to BPO. Perhaps this is, to some extent, driven by the conviction that a single method can be the solution in all patients and become the gold standard. This method must, of course, be prostate size- and age-independent and, most importantly, suit all patients regarding efficacy, tolerability and safety. The CoreTherm Concept does, in many ways, tick those boxes, and is an outpatient option to surgical intervention. Despite that the CoreTherm Concept, in many ways, is a one-size-fits-all solution, it does not fit all men, but it fills the enormous gap between conservative treatment and surgery. In addition to filling a gap, it can also replace medical treatment for those men who wish to be cured instead of being doomed to lifelong medication or replace surgery for those wanting a less invasive procedure. The number of curative treatments in Swedish men with LUTS/BPO has declined about 50% since the peak in the 1980s, and, in the last few years about 5000 men yearly had some intervention for their enlarged prostate [228].

Outpatient procedures, such as TUMT, are relatively common, but many more patients could benefit from this treatment modality. Parallel to the decrease in curative treatments, an increase in medical treatment is evident in Sweden, with now more than 200 000 men using medication for their LUTS to reduce bothersome symptoms [229]. Furthermore, with an increasing number of older men >80 years [230], the need for curative options suitable for men with comorbidity and larger prostates will most likely increase. Offering a cure for these older men, sometimes having permanent indwelling catheters due to CUR, must be prioritised, both from a societal and an individual perspective.

Predicting what the future holds is tricky in any area and encumbered with the risk of incorrectness. Nevertheless, it is possible to argue that when it comes to treatment in patients with LUTS or CUR due to BPO, predicting the future is relatively easy, because the future is already here, but it is not evenly distributed. By introducing the CoreTherm Concept, we can supplement the treatment armamentarium with a method available to all men who want to avoid medication or surgery.

It is thereby possible to just welcome the future. The door must, however, be opened by those who have the keys in their hands, as elegant as it is simple. There is at present no need for nanotechnology or new treatment modalities that most often resemble the short lives of mayflies. The addition of the CoreTherm Concept to TUIP, TURP and TAE fills a gap, and together they constitute a full treatment armamentarium for most men with LUTS/BPO.

There is no doubt that there is more to explore regarding microwave treatment. In men with LUTS/BPO. In **Paper III** of this thesis, we evaluated the short- and long-term efficacy of the CoreTherm Concept in large prostates. We found that many patients retreated with surgery did have a prominent third lobe. A prospective study including men with LUTS/BPO and prostates with a median lobe enlargement, evaluated in detail before intervention with TRUS and cystoscopy, would be an important research area. Evaluation of responders and retreatments for these particular patients would add new essential knowledge, probably of value for future patients. The evaluation with cystoscopy should include the presence and appearance of a vertical opening, which would require a new and standardised classification system. The evaluation with TRUS should include an evaluation of the intravesical prostatic protrusion.

In **Paper IV**, we used MA via the Schelin Catheter to evaluate bleeding parameters during and after TURP. The apparent next phase would include an additional power analysis, with an increased number of patients in a similarly designed study, to investigate if a statistically significant difference exists. However, the possible use of the Schelin Catheter in a completely different context, using other pharmacological agents, or use this catheter in men having other problems than an obstructing adenoma, would perhaps be of more value for future patients.

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