ProstaLund®

CoreTherm®

The making of a new machine

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Foreword

This booklet provides a summary of published pivotal clinical trials and other principal studies of CoreTherm for treating BPH. Many more scientific papers have been published about CoreTherm but, due to space limitations, we have included only the foremost papers that tell the core story – how CoreTherm came to be, the theory behind it and the clinical evidence. If you would like to have offprints of the papers referred to and cannot find them in your library, please send us a note to info@prostalund.com and we will be happy to send them to you.

CoreTherm, often cited in the literature as PLFT (ProstaLund Feedback Treatment), is a state-of-the-art device to treat BPH that uses high-energy focused microwaves to shrink the prostate and relieve the obstruction and associated symptoms. The treatment begins with a transurethral injection of Mepivacaine, which is administered with the Schelin catheter. The CoreTherm treatment catheter (shown on the cover) is then inserted, the power turned on and the prostate heated to 55°C for 10 minutes. CoreTherm displays the true intraprostatic temperature and tissue shrinkage in real-time to steer treatment. No other device can do that. Precise treatment. No guessing.

Ten minutes. That is all it takes to perform this remarkably fast and effective treatment.

The patient is then released but will need an indwelling catheter for about a week, sometimes a little less or more, depending on the preconditions. After about a month, the patient will notice significant improvements, which will amplify over the weeks to come. After three months, the clinical outcome is on par with traditional surgery but with considerably less risk and adverse events.

CoreTherm is a truly transformational treatment for BPH. Here is what it is not: It is not an in-patient procedure. It does not occupy hospital beds for several days. It does not require anesthesiology support and surgical facilities. It does not exclude frail and weak patients. It is not the TUMT of yesterday. It is simply a 10-minute outpatient treatment that is astonishingly good.

Interested? The science behind CoreTherm is presented in this booklet. We hope you will enjoy reading it.

THE MAKING OF A NEW MACHINE

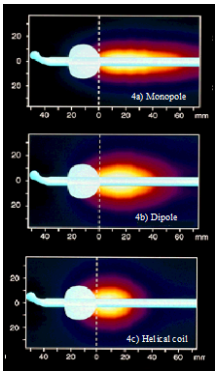
The story of CoreTherm began 20 years ago. The grand idea to abandon surgery and treat enlarged prostates with heat instead had emerged a decade earlier. At that time, it had led to many different devices of various kinds and brands; some had very low power output, some had very high, some used a cooled treatment catheter and some did not. Some even heated through the rectum, although that path did not last long. Heating via the transurethral pathway soon became the standard and the TUMT – transurethral microwave thermotherapy – concept was born.

Companies experimented with design and function but most people had little understanding of the action of microwaves in tissue and the underlying core physics. The clinical outcomes of the early machines were random and inconsistent; some patients did very well, others did not. But there was great optimism about the technology because everybody saw the enormous potential of replacing surgery that patients did not want with minimally invasive treatment. As always, when a technology is new and pristine, there was a lot of experimentation on optimal treatment time, microwave power, temperature and things like that. It was the golden age of myth and speculation. Some argued that microwaves had a spooky action on alfa-receptors because patients usually reported improvements in symptoms. Some argued that the catheter needed to be cooled to protect the prostatic urethra from the heat. Other reasoned that it was a bogus claim because it was not preserved during TURP, so why did it matter now?

The real reason a cooled catheter came to be was that the market leader at the time used a catheter made of a certain plastic material. That material absorbed microwaves and would melt if not cooled. The marketing department put a clever spin on this and created the *"cool to preserve the prostatic urethra"* myth. To this day, no science has ever shown that protecting the prostatic urethra was of any appreciable value but the myth still lives on 20 years later. However, as high energy microwave machines were developed in later years to come, cooling the catheter became necessary for purely technical reasons.

1996

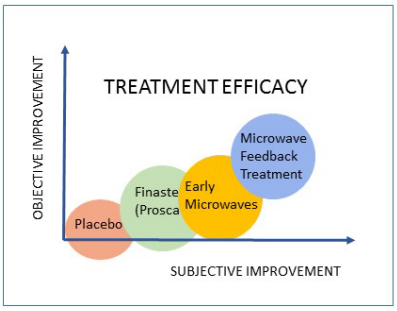
ProstaLund had launched its first machine a few years earlier and was now onto the job of designing the next-generation machine, codenamed "Eagle." It was brought to life a few years later as "ProstaLund Compact" and the treatment as "ProstaLund Feedback Treatment – PLFT" but the marketing people quickly decided to rebrand it all to "CoreTherm" when the device was released in the US market a few years later. The design team behind "Eagle" was asked to create a new device that delivered consistent and superb treatment outcomes. To do that, science had to be done to answer fundamental questions.



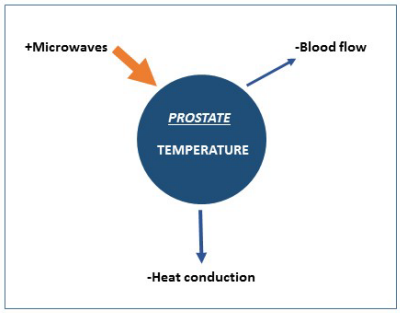
In an attempt to bring order to the morass of myth and speculation, the scientific paper *"The heat is on - but how?"* was published in the British Journal of Urology by Bolmsjö et al. [1]. It described the underlying physics of TUMT, its action in the body and why some technical designs were better at focusing microwave heat into the prostate than others. It became the starting point for a quest by research teams to find the common denominator for the perfect microwave treatment.

Early clinical work

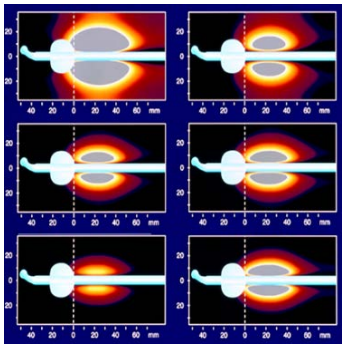
Next, in a paper by Wagrell et al., "*Intraprostatic Temperature Monitoring during Transurethral Microwave Thermotherapy for the Treatment of Benign Prostatic Hyperplasia"* published in the Journal of Urology in 1998, Wagrell showed that intraprostatic temperature was the most important factor for achieving outstanding clinical outcomes [2]. At too low a temperature, the treatment would fail. The paper also launched the idea that blood flow had to be taken into account because it counteracted the heat due to its cooling effect. Wagrell used color Doppler ultrasound imaging to visualize the prostate during treatment and had observed a huge rise in blood flow during the treatment. The paper established that temperature was the key factor for treatment outcome.



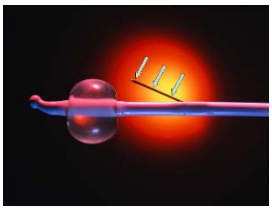
That discovery led to a subsequent paper, *"Optimizing transurethral microwave thermotherapy: a model for studying power, blood flow, temperature variations and tissue destruction,"* published in the British Journal of Urology in 1998 by Bolmsjö et al. [3]. The paper made headlines at the time and was on the cover of the journal. Wagrell's study established that tissue temperature was the key factor and had to be controlled. The paper by Bolmsjö teaches that tissue temperature is determined by three processes: generation of heat though absorption of the microwaves, dispersion of heat by conduction in the tissue and loss of heat or cooling through the blood flow. The paper also discusses the finding in the previous paper that blood flow is not constant, but changes during the course of treatment as the blood circulation reacts to heat. The conclusion was obvious: the intraprostatic temperatures had to be monitored during treatment or the treatment would be unpredictable. Patients with inherent high intraprostatic blood perfusion would be undertreated, while patients with low perfusion were at risk of being overtreated.



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

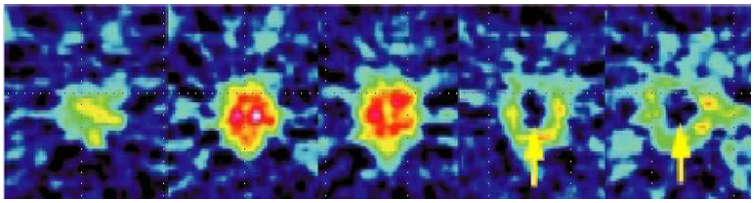


This was an important finding because higher-energy devices were about to be brought to the market at the time. From then on, the CoreTherm treatment catheter had an integrated thin monitoring probe, with multiple temperature sensors, that protrudes from the catheter into the prostate and monitors temperature throughout treatment.



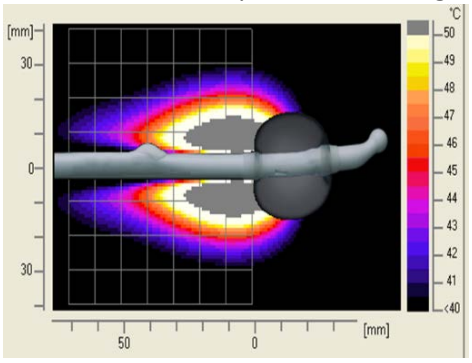
Breakthrough

Subsequently, in an absolutely brilliant paper by Wagrell, *"Intraprostatic Blood-Flow Changes during ProstaLund Feedback Treatment Measured by Positron Emission Tomography,"* first presented in his PhD dissertation in 1999 and later published in the Journal of Endourology [4], he used positron emission tomography to map the intraprostatic blood flow at treatment start and after 6, 21, 35 and 55 minutes. Wagrell convincingly demonstrated that there is a dramatic increase in prostatic blood flow during the first phase of treatment when the gland tries to cool away the heat from the microwaves and the subsequent dramatic event when the intraprostatic blood flow collapses some way into the treatment as the microwave heating becomes so intense that the defense mechanism gives up. At that point, the temperature spikes and coagulation necrosis occurs within minutes, if not seconds. When this happens, treatment must end. The paper concluded that all treatments should be individualized and intraprostatic temperature must be monitored. Without it, the physician does not know when the temperature breakthrough occurs and when to end the treatment. The paper laid the foundations for understanding treatment dynamics.



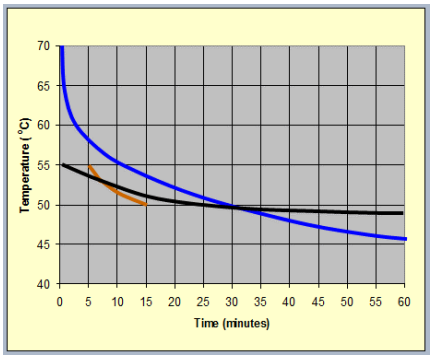
The cell-kill concept

It was now known that the quality of TUMT treatment was determined by what temperatures were achieved. This in turn was determined by the amount of microwave power administered minus the unknown blood flow. But how could all of this be quantified to make the treatment predictable and understandable? The next paper, *"Cell-Kill Modeling of Microwave Thermotherapy for Treatment of Benign Prostatic Hyperplasia,"* by Bolmsjo et al. [5] published in the Journal of Endourology in 2000 gave the answer: by correlating the intraprostatic temperature to the amount of prostate shrinkage. The paper states that the main purpose of heat treatment is to shrink the prostate in a similar way to surgery. And so the "cell-kill" concept and algorithms were born and subsequently integrated into the CoreTherm device to steer treatment. The paper gave the theoretical framework for how to calculate cell-kill during treatment based on microwave power and measured intraprostatic temperatures. But one important riddle remained to be solved: what was the human prostate cell sensitivity to heat? That is, at what thermal dose will the cell be destroyed?

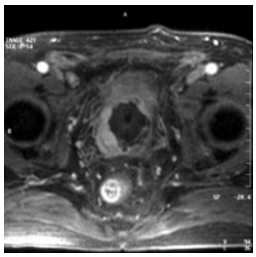


Thermal dose

The answer came in “In vitro assessment of the efficacy of thermal therapy in human benign prostatic hyperplasia” by Bhowmick et al., published in the International Journal of Hyperthermia [6]. The study was performed at the University of Minneapolis and was initiated and sponsored by ProstaLund. It is a cornerstone for understanding the action of heat treatment. It teaches that the time it takes to create tissue necrosis in a human prostate falls exponentially with increased temperature: it takes 1 hour to create tissue necrosis at 45°C, but only 5 minutes at 55°C and 1 minute at 70°C.



In a subsequent paper, “Evaluation of Microwave Thermotherapy with Histopathology, Magnetic Resonance Imaging and Temperature Mapping” by Huidobro et al., published in The Journal of Urology, 2004, it was shown that CoreTherm’s cell-kill calculation was accurate and corresponded to the cell death and shrinkage found by histopathology and MRI [7]. Many other studies followed with the same results: the cell-kill calculation works and is a valuable tool to steer treatment.



All the fundamental discoveries for how to use microwave treatment had now been made and it was time to transfer all this knowledge to something useful. Although CoreTherm around that time was a highly effective and safe treatment with features like real intraprostatic temperature monitoring and automatic cell-kill calculation, it was still a 45 to 60-minute-long treatment, not always comfortable, and it was thought that the treatment needed further refinement.

Schelin catheter

The final step to perfecting the treatment came with an ingenious invention, the Schelin catheter. This is a transurethral catheter with a built-in flexible cannula to inject drugs directly into the prostate just before the CoreTherm treatment. In an instant, it became easy to administer local anesthetics, such as lidocaine, into the prostate prior to the treatment. By adding epinephrine to the cocktail, the intraprostatic blood flow could be effectively shut off for the 10 minutes or so that it takes the body to wash out epinephrine. The absence of the cooling blood flow in the prostate then made it administering CoreTherm treatment easy and very fast. In *“Mediating Transurethral Microwave Thermotherapy by Intraprostatic and Periprostatic Injections of Mepivacaine Epinephrine: Effects on Treatment Time, Energy Consumption, and Patient Comfort”* [8], Schelin reports the use of this device and the dramatic effect it had on CoreTherm treatment time and patient comfort.

In a subsequent study, *"Effects of Intraprostatic and Periprostatic Injections of Mepivacaine Epinephrine on Intraprostatic Blood Flow during Transurethral Microwave Thermotherapy: Correlation with [^{15}0]$H_2$0-PET"* by Schelin et al., the authors demonstrated how injection of Mepivacaine effectively curbed blood flow during treatment [9].

In the aftermath, no other invention has had greater impact on CoreTherm treatments than the Schelin catheter. It has transformed CoreTherm treatments from a 45 to 60-minute-long procedure into the current 10-minutes procedure under local anesthesia.

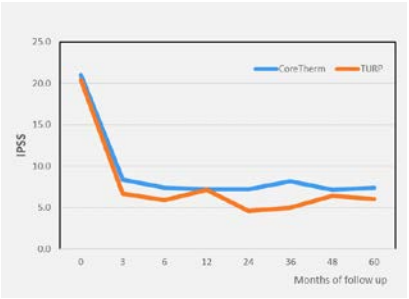
THE CLINICAL EVIDENCE

ProstaLund now felt the new machine was technically far ahead of all its competitors. The knowledge acquired in the previously described science was incorporated in the new device and it had all the "must-have" features like intraprostatic temperature monitoring and cell-kill control. The company then made the strategic decision to sponsor a large FDA-controlled randomized multicenter clinical trial in which CoreTherm was compared with the gold standard of the time - TURP. The study design involved 10 hospitals in the US, Denmark and Sweden, including the Mayo Clinic in Scottsdale and the largest urology center in the Nordic countries, Herlev Hospital in Copenhagen. A total of 154 patients were randomized to either CoreTherm or TURP (ratio 2:1). Patients were followed up at 3, 12, 36 and 60 months [10, 11, 12]. An extract of the 5-year data follows.

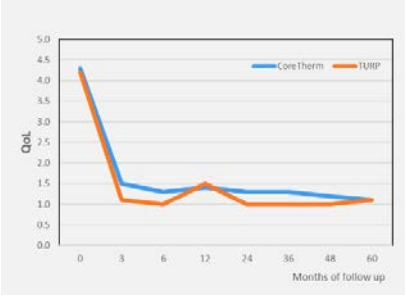
FDA-controlled randomized multicenter study: CoreTherm vs TURP

Introduction and Objective: A prospective randomized multicenter study of the safety and efficacy of ProstaLund CoreTherm® microwave treatments (PLFT®) for BPH was compared to TURP, 5 years post treatment. Efficacy variables were IPSS, bother score, Qmax, prostate volume, residual urine volume and adverse events.

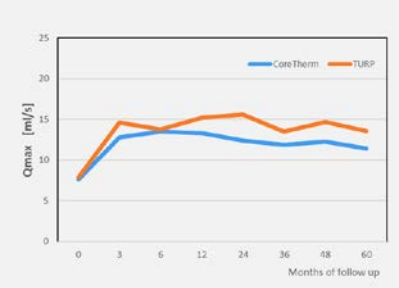
Methods: The study was conducted at 10 centers in the US and Scandinavia. A total of 154 patients with BPH were randomized to CoreTherm or TURP at a 2:1 ratio. The CoreTherm treatments were carried out with intraprostatic temperature monitoring and by adjusting the microwave power for each patient in order to obtain desired tissue necrosis (≈30% of prostate volume at baseline). The TURP procedures were carried out using the standard protocols at each center.



Results: Subjective improvement, IPSS, was similar in both treatment groups. At 3-months follow-up, there was a marked decrease in mean IPSS from 21 to 8 in the CoreTherm group and from 20 to 7 in the TURP group, sustained over the 5 years with no statistical difference between the two groups. The same pattern was also seen for bother score with no statistical difference between the two groups. Qmax appeared to be somewhat better with TURP (difference vs CoreTherm was 2 ml/s), however there was no statistically significant difference between the two groups.



Over the complete 5-year study, the frequency of severe adverse events reported as related to the treatment was 5% in the CoreTherm group and 17% in the TURP group. Severe adverse events in the CoreTherm group were hematuria, urine retention and bladder calculus. In the TURP group the events were hematuria, UTI, urosepsis, TURP syndrome and clot retention.



Conclusions: 5-year follow-up shows comparable efficacy in both treatment groups. Long term follow-up of adverse events during the post-treatment period up to 5 years reveals no major safety concerns for CoreTherm. Hence, CoreTherm may be one of the best minimally invasive procedures that can be performed in an outpatient setting, challenging TURP as the preferred first-line treatment of patients.

Patients in urinary retention

Soon after CoreTherm was launched, reports started to appear of its use on patients with chronic urinary retention. In one of the early papers on the subject [13], 24 patients in urinary retention and with an indwelling catheter were treated. Of these, 19 (80%) were successfully relieved of their indwelling catheter. This was the era before the Schelin catheter, so treatment duration in that study was still about an hour and the corresponding total microwave energy was 211 kJoule. That early study sparked renewed interest in offering treatment to frail and weak patients who were not candidates for surgery and were often on indwelling catheters. Could the CoreTherm treatment be used for them?

Randomized multicenter study on CoreTherm vs surgery for patients in persistent urinary retention

A prospective study protocol was subsequently designed to investigate CoreTherm on this patient category: the study was a randomized multicenter study comparing CoreTherm with TURP and prostate enucleation in patients with BPH and persistent urinary retention [14]. The study involved 120 patients and 17 hospitals in Sweden, Denmark and Norway. The result confirmed earlier studies: 79% of the patients receiving CoreTherm were relieved of their indwelling catheter vs 88% in the surgery group. CoreTherm again confirmed its favorable safety profile: one serious adverse event occurred in the CoreTherm group (hematuria) compared with five cases in the surgery group (hematuria, urinary tract infection, hemorrhage, stroke and bladder neck sclerosis). The Schelin catheter had not yet been launched, so treatment time was still on the high side (47 minutes) and the microwave energy administered was 152 kJoule. Twelve of the patients treated with CoreTherm had a prostate size greater than 100 grams before treatment – the largest was 176 grams. Earlier, there was often a notion that microwaves should not be used for prostates larger than 100 grams. This study clearly showed that large size was not a matter of concern.

Danish study on chronic urinary retention confirms efficacy

In a recent study at one of the largest Danish urology centers, Faurholt Aagaard et al. used CoreTherm on patients in chronic urinary retention and unsuitable for surgery [15]. In all, 124 patients were treated with CoreTherm: 77% were relieved of their indwelling catheters, which is consistent with previous results. The authors conclude that CoreTherm is an effective treatment for patients who are not candidates for surgery: "The risks associated with TUMT are substantially lower than those associated with surgery, making it an important complementary alternative in the treatment of BPH for these high-risk patients." Notably, the Schelin catheter was used in the majority of cases, which in this study cut the treatment time from 60 minutes to 15 minutes. A consequence of the positive results of this study is that CoreTherm is now routinely offered to this patient category in many places in Denmark.

Using the Schelin catheter

As described in the previous section, no other invention has had greater positive impact on CoreTherm treatment than the Schelin catheter. It is used to inject local anesthetics directly into the prostate prior to treatment. It has transformed CoreTherm treatment from a procedure that took about 45-60 minutes into the 10-minute treatment of today. In addition, considerably less microwave energy is used to heat the prostate than before. Does that matter? Yes, it does. Being able to use less energy means lower risk of heating adjacent tissue, such as the external sphincter.

In one of the first clinical papers on the use of Mepivacaine, patient comfort was significantly enhanced, treatment duration was halved from 60 minutes to 30 minutes and total microwave energy used decreased from 172 kJoule to 65 kJoule without impairing clinical efficacy [8].

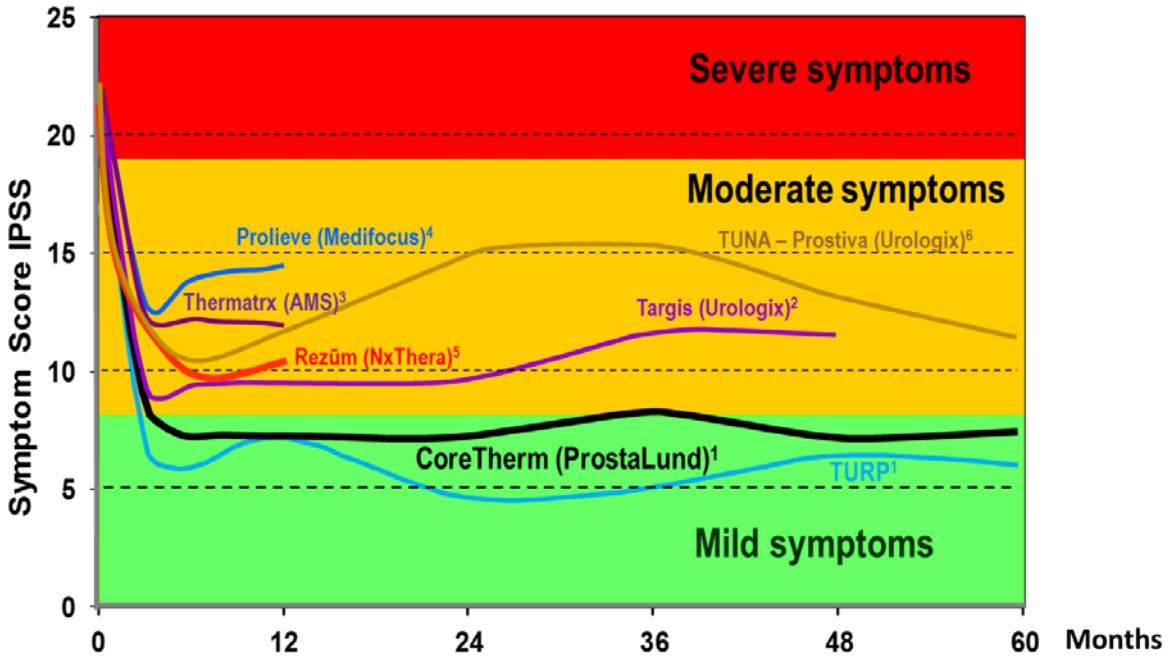
As doctors learned how to perfect the use of the Schelin catheter, patient comfort during treatment was further enhanced and treatment time shortened even more. Today, the CoreTherm treatment duration is typically 6 to 15 minutes, with an average of 10 minutes. In a retrospective analysis by Stenmark et al. [16] of 283 CoreTherm treatments between 2003 -2008, the median treatment time was 11 minutes and the median microwave energy used was 30 kJoule. In that study, prostate size varied from 28 to 219 grams.

Final word

This is the story of the making of a new machine: CoreTherm. It gives a glimpse into all the research and efforts that were undertaken by so many in order to perfect the machine. Is CoreTherm the most efficient, well-thought, advanced and well-documented minimal invasive BPH device there is on the market? We think so.

How does CoreTherm compare with other technologies?

The graph below shows the results from pivotal clinical trials for Prolieve, TUNA, Thermatrx, Targis and Rezūm (the latter is a new TUNA-derivative). Isn't it interesting that CoreTherm is the only minimal invasive device that has TURP-like outcome? Isn't it interesting that CoreTherm and TURP are the only methods where IPSS falls from severe to mild symptoms (the green area below), whereas patients still have moderate symptoms after all the others (the yellow area)?



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In a recent meta-analysis by Kaye, Smith, Badlani, Lee and Ost [17], they analyzed all published data on HE-TUMT and all randomized controlled trials that compared HE-TUMT with TURP. They concluded: "present day HE-TUMT machinery is more effective than previously used low-energy machinery. This is most evident when the CoreTherm device is used. These findings, coupled with the decreased costs and morbidity associated with HE-TUMT, support this treatment as a reasonable alternative to TURP".

CoreTherm in 10 seconds

- Fast: a treatment takes 10 minutes on average.
- Safe: intraprostatic measurement of temperature and automatic cell-kill monitoring
- Efficacy: 5 years follow up study shows same results as TURP but with considerably less side-effects
- Durable outcome
- A unique option to treat patients with:
  - Small to large prostates, even very large
  - Chronic retention patients: 4 of 5 are freed of their indwelling catheter.
  - High-risk patients unsuitable for surgery

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