RESPONDERS AND NONRESPONDERS TO TRANSURETHRAL MICROWAVE THERMOTHERAPY: A MULTICENTER RETROSPECTIVE ANALYSIS


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ABSTRACT

Purpose: We attempted to identify any parameter that could possibly lead to a successful treatment outcome after transurethral microwave thermotherapy.

Materials and Methods: Clinical parameters and treatment profiles of 292 patients were analyzed in a retrospective multicenter manner. Responder and nonresponder groups were identified according to a given definition.

Results: No statistically significant differences in baseline characteristics were found. Responders showed a 76% symptomatic improvement rate compared to 27% in nonresponders, and an 82% improvement rate in peak flow compared to a 5% decrease in nonresponders. Responders also showed a significantly greater increase in posttreatment PSA level and a significantly greater amount of energy released during treatment.

Conclusions: No baseline clinical parameter is capable of predicting treatment outcome.

Key Words: prostatic hypertrophy; microwaves; hyperthermia, induced

Microwave heating of the prostate is a fascinating approach to the treatment of voiding disturbances in patients with benign prostatic hyperplasia (BPH).

Thermotherapy applies high power microwave energy deep within the lateral prostatic lobes. The results of transurethral microwave thermotherapy are promising. It is presumed that clinical benefit is achieved by a small decrease in adenoma volume and the destruction of certain specific cell types that have some role in the development of bladder outlet obstruction. The clinical improvement has been shown not to be due to a placebo effect or the result of the associated instrumentation in randomized trials of transurethral microwave thermotherapy versus a sham procedure.

However, the criteria currently used for inclusion do not prevent a high variability in terms of clinical response to transurethral microwave thermotherapy and treatment outcome. Digital records of the microwave treatments from a large series of patients undergoing microwave therapy at 17 different prostate centers worldwide constitute the material for the study.

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SCREENING consisted of a patient history with the Madsen-Iversen symptom score, physical examination with digital rectal examination of the prostate, hematology and blood chemistry studies, including prostate specific antigen (PSA) measurements, electrocardiography, chest x-ray, kidney and bladder ultrasound imaging or excretory urography, transrectal ultrasound of the prostate and uroflowmetry (twice) with measurements of post-void residual volume using ultrasound. All patients studied were candidates for transurethral resection of the prostate and had a Madsen-Iversen symptom score of 8 or more, maximum flow rate 15 ml. per second or less and post-void residual volume 250 ml. or less. Patients were excluded from the trial because of an obstructive prostatic middle lobe, complications of BPH, suspicion of prostate cancer, presence of any condition that could interfere with bladder dynamics and patient compliance to the protocol.

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

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

RESULTS

Of 292 patients evaluable for analysis 136 were responders and 156 were nonresponders. Analysis of patient parameters at screening showed no significant difference between the 2 groups (table 1). Changes in Madsen-Iversen symptom score, maximum flow rate and post-void residual volume are presented in figure 2. Responders showed an average improvement of 76% for Madsen-Iversen symptom score and an increase in maximum flow rate of 82%, with a decrease of 37% in post-void residual volume (table 2). Nonresponders had an average decrease of 27% for symptom score, an actual decrease in flow rate of 5% and only a decrease of 14% in post-void residual volume.

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

Different parameters derived from digital records of the microwave treatments were analyzed (fig. 4). The amount of energy released during treatment, measured as total energy dose, average dose and maximum power output, was significantly different in the 2 groups. The higher amount of energy released in the responder group resulted in a higher temperature at the level of the urethra. The number of urethral alarms was greater in responders versus nonresponders but the difference was not significant (fig. 5). Notwithstanding a higher energy release in responders, temperatures recorded at the level of the rectal wall were comparable in the 2 groups. Nevertheless, fewer rectal alarms were observed in responders compared to nonresponders.

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics</th>
<th>Mean ± SD</th>
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<tr>
<td><strong>Responders</strong></td>
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<tr>
<td>Age (yrs.)</td>
<td>66.8 ± 7.9</td>
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<tr>
<td>Prostate vol. (ml.)</td>
<td>45.0 ± 18.0</td>
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<tr>
<td>Madsen score</td>
<td>13.7 ± 4.0</td>
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<tr>
<td>Maximum flow rate (ml/sec.)</td>
<td>8.8 ± 3.7</td>
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<tr>
<td>Post-void residual vol. (ml.)</td>
<td>96.0 ± 158.0</td>
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<td>PSA (ng/ml.)</td>
<td>4.1 ± 4.3</td>
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</table>
The outcome of thermotherapy has been shown previously to be variable between different sites.\textsuperscript{3,5,7,8,12} To identify selection criteria that could possibly predict successful treatment outcome, a large series of patients was evaluated according to the response to treatment. Responder and nonresponder characteristics at screening were not statistically different, which further supports a previous supposition from our group that currently only baseline urodynamic parameters can predict clinical outcome from microwave treatment.\textsuperscript{9} Provided the 2 groups of patients were comparable at baseline, a different microwave treatment profile could have been responsible for the different outcome in the 2 populations. The treatment profile reflects the energy delivered to the prostate, and depends on the number of the rectal and urethral alarms (fig. 1). The alarms result in a safe treatment but they may limit the emission of microwave energy. In view of the results achieved with higher energy levels, we believe that the safety of treatment obviously interferes with efficacy. One cannot have high temperatures within the prostate using low power levels.\textsuperscript{10} We know that the amount of heat produced within the prostate is correlated with objective clinical outcome but such parameters are not available in this series. Nevertheless, we still have an indirect measure of intraprostatic temperatures, which is given by the elevation of PSA on the days following transurethral microwave thermotherapy. We do not know whether epithelial cell damage is
of any importance in the clinical response to microwave therapy but it is certainly 1 of the 3 major cellular components of BPH. Interestingly, the variation of the PSA level within 1 week after treatment was significantly different in the 2 groups. Variation among the individual patients is high and reflects the different response of the individual prostate to microwave treatment, which we observed in previous studies. The kinetics of the PSA increase are outside the objectives of our study but they certainly deserve attention in the future. The concept was confirmed in a recently conducted placebo controlled study.3

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

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

What happened to this greater amount of energy released into the prostate of patients who did well? A higher energy dose produced a higher urethral temperature, which is not evident when examining the peak urethral temperature achieved during treatment but it was clear if we note the maximum urethral temperature sustained for at least 3 minutes. A higher urethral temperature has, of course, triggered a greater number of urethral alarms, although the difference between the 2 groups was not significant because of the high variability of this parameter in different treatments (0 to 150). Transient interruption of microwave emission seems not to be detrimental to treatment outcome or the total energy dose. Therefore, where is all this energy going? The flux of energy emitted by the microwave antenna passes through the prostate from the urethra to the rectum. As the irradiative energy is absorbed by tissue it is transformed into heat energy and the temperature increases. When temperatures increase vasodilatation occurs creating a heat sink, which may carry away significant amounts of heat. If irradiative energy is largely absorbed by prostatic tissues then rectal temperature cannot increase (by lack of energy) and, consequently, we expect fewer rectal alarms. Interestingly, this is what happened in the responder group. Lower temperatures were measured in the rectal wall of these patients and fewer alarms were recorded.

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

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

Vincent Cabane assisted with the study.

REFERENCES