TRANSURETHRAL MICROWAVE THERMOTHERAPY (TUMT) IN
LOCALLY ADVANCED CARCINOMA OF THE PROSTATE

M. A. LOTFI, K. EL MASLOUBY, A. HUSSEIN, M. DAW
Department of Urology, Cairo University, Cairo, Egypt

Objective Though systemic prostatic cancer disease eventually results in the patient's death, locally advanced disease may be associated with severe morbidity. The therapeutic options currently available include hormonal manipulation, radiotherapy or transurethral resection. Previous reports have suggested that local prostatic hyperthermia may have a dramatic effect on local and systemic malignant disease. This study aimed at evaluating the effect of transurethral microwave thermotherapy (TUMT) on locally advanced prostate cancer.

Patients and Methods The study included 30 patients suffering from various degrees of bladder outlet obstruction secondary to advanced hormone-refractory prostate cancer. TUMT was delivered using the Prostalund machine (Lund Science – Sweden) weekly for 6 weeks. Transurethral heating was achieved via a Foley urethral catheter provided with microwave antenna, temperature sensors and cooling channels. The rectal temperature was monitored via rectal thermosensors mounted on a specially designed rectal probe. All the patients were evaluated before and after treatment, at 1 month, at 3 months and at 1 year.

Results The mean pretreatment Boyarsky symptom score was 13.73 ± 4.15. At 1 month, 3 months and 1 year follow up the mean Boyarsky symptom score was 8.73 ± 4.14 (P<0.0001), 9.09±3.71 (P<0.0001) and 8.53 ± 3.98 (P<0.0001), respectively. The mean pretreatment peak flow rate was 7.83 ± 2.68 ml/sec. At 1 month, 3 months and 1 year follow up the mean peak flow rate was 10.1 ± 3.17 ml/sec (P=0.0045), 10.41 ± 4.35 ml/sec (P=0.011) and 7.27 ± 2.79 ml/sec (P=0.513), respectively. The mean pretreatment residual urine volume was 82.5 ml ± 65.4. At 3 months and 1 year follow up the mean residual urine volume was 58.2 ml ± 36.5 and 54.7 ml ± 51.3 (P=0.2597), respectively. The mean pre-treatment PSA value was 22 ± 16.69 ng/ml. At 1 week follow up the mean PSA value was 26.9 ± 18.63 ng/ml and at 1 year follow up the mean PSA value was 19±15.21 ng/ml (P=0.192).

Conclusion TUMT is safe and effective in alleviating obstructive symptoms in patients with advanced prostate cancer. The amelioration of symptoms was short-lived beginning to show a return to the pretreatment condition at the end of the 1-year follow-up period. The major advantages of TUMT are that it is an outpatient procedure, that it is well tolerated with minimal morbidity and that it can be offered safely for patients unfit for anaesthesia.

Key Words hyperthermia, cancer, prostate

INTRODUCTION

Prostate cancer is the most common and the most frequently diagnosed malignancy in men, apart from skin cancer. Based on autopsy studies it has been suggested that approximately 30–50% of men worldwide harbour latent prostate cancer by their 50th birthday and that over 80% of men are affected by cancer by their 80th year of life. Although latent cancer does not necessarily imply a biological potential, in the United States and other developed Western nations, prostate cancer has become the most frequently diagnosed clinical cancer1.

Approximately one third of the patients diagnosed with prostate cancer will present with advanced disease. Metastasis commonly occurs in the regional lymph nodes and/or the bony skeleton. Total androgen ablation by means of castration, anti-androgens or luteinizing hormone–releasing hormone analogues remains the standard care for the patients.
However, responses are short lived in most patients with progression to hormone refractory disease being inevitable over the course of few years.

Progressive, hormone-resistant prostate cancer presents a multitude of challenges to the patients and physicians. The appropriate delivery of palliative care requires a full assessment of the patient's physical, psychological, and social needs. Opinions from medical oncology, urologic oncology, radiation oncology, pain management and palliative care specialists are often required to devise the most appropriate treatment strategy.

Patients who become refractory to hormonal management, particularly those with symptomatic locoregional disease such as obstructive urinary flow and pelvic pain, have limited effective treatment options. Transurethral resection or placement of a stent may have a good palliative value in carefully selected patients.

Regional hyperthermia has been under investigation and may be used alone or in combination with pelvic irradiation in patients who become refractory to the standard treatment. Its use in locally advanced prostate cancer has shown a long-lasting and good palliative effect.

PATIENTS AND METHODS

This study included 30 male patients with advanced prostate cancer treated with transurethral thermotherapy. The patients' age ranged from 58 to 80 years (mean 67.9 years). All patients had moderate to severe symptoms and signs of urinary outflow obstruction. All patients had a histological diagnosis of prostate cancer. They all had stage D (M1) disease. All the patients had received hormonal treatment for at least one year prior to inclusion in this study. Hormonal treatment failed, however, to alleviate the symptoms of obstruction. The patients were given the choice of having transurethral resection of the prostate or transurethral microwave thermotherapy (TUMT) to relieve their obstructive symptoms.

All the patients underwent certain tests. A detailed urological history was taken. Physical examination was done including digital rectal
examination (DRE). Transrectal ultrasound (TRUS) was used to measure the prostatic volume and to measure the anterior rectal wall thickness. Patients with a peak flow rate (Qmax) of less than 12 ml/sec were selected for inclusion in this study. The post-void residual urine was measured by transabdominal suprapubic ultrasound and urethral catheterization. The Boyarsky² symptom score was done. A symptom score greater than 5 was necessary for inclusion. A plain X-ray of the urinary tract (KUB) was done to exclude the presence of pelvic metallic implants and to observe the distribution of bone metastases. Laboratory studies included urinalysis and culture for the presence of urinary tract infection, blood urea nitrogen, serum creatinine, and prostate specific antigen (PSA). Radioisotope bone scan was utilized to diagnose skeletal metastases. Contraindications to transurethral therapy are bladder calculi, bladder tumors, a known neurogenic bladder, urethral strictures, an anterior rectal wall thickness of less than 5 mm, uncontrolled cardiac arrhythmias or the presence of a cardiac pacemaker, the presence of total hip replacement or pelvic metallic implants (for possible microwave interference) and the presence of active urinary tract infection. Patients with urinary tract infection were treated with appropriate antibiotics. Repeated urinalysis and culture were done to document clearance of the infection.

All patients were treated on an outpatient basis using the Prostalund machine (Lund Science, Sweden) using a microwave frequency of 915 MHz and a power output reaching a maximum of 200 watts. At the beginning, the patients were asked to micturate in order to empty the bladder prior to the session as the microwave urethral catheter does not possess a channel for bladder drainage. After instillation of 20 ml lubricating gel into the urethra the special Foley-type urethral antenna, with its in-built urethral thermoelectrodes, was inserted. The correct position of the antenna within the prostatic urethra was confirmed by abdominal (suprapubic) sonography. Localization of the balloon at the bladder neck with the patient in the supine position assures the corresponding correct position of the microwave antenna at the desired location. Then the rectal probe with its built-in three rectal thermoelectrodes was inserted into the patient's rectum while he was placed in the lateral decubitus position. The patient was then repositioned to the supine position, informed and reassured that he would feel perineal warmth which is quite tolerable, an urge to urinate and occasional bladder spasms with possible voiding around the catheter during treatment. This reduces the patient's anxiety and increases his cooperation. Generator emission was delayed for 5 minutes to give time for the cooling unit to reduce the temperature of the urethral mucosa. The flow and the desired temperature of the coolant fluid were adjusted by the operator. The desired maximum temperature inside the adenoma was selected by the operator, and the maximum rectal temperature to be reached was set at 42.5°C. The software program has the ability of conducting and adjusting microwave emission at the corresponding power output (in watts) needed to reach the desired temperature inside the prostate adenoma. Treatment can also be conducted entirely by

<table>
<thead>
<tr>
<th></th>
<th>Total No.</th>
<th>Successful No.</th>
<th>Successful %</th>
<th>Improved No.</th>
<th>Improved %</th>
<th>Stationary No.</th>
<th>Stationary %</th>
<th>Deteriorated No.</th>
<th>Deteriorated %</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 month</td>
<td>30</td>
<td>7</td>
<td>23.0%</td>
<td>20</td>
<td>66.6%</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>10.0%</td>
</tr>
<tr>
<td>After 3 months</td>
<td>22</td>
<td>3</td>
<td>13.6%</td>
<td>18</td>
<td>81.8%</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>4.5%</td>
</tr>
<tr>
<td>After 1 year</td>
<td>15</td>
<td>3</td>
<td>20.0%</td>
<td>11</td>
<td>73.3%</td>
<td>1</td>
<td>6.6%</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 6: Changes in the Peak Flow Rate after Thermotherapy

<table>
<thead>
<tr>
<th></th>
<th>Total No.</th>
<th>Successful</th>
<th>%</th>
<th>Improved</th>
<th>%</th>
<th>Stationary</th>
<th>%</th>
<th>Deteriorated</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 1 month</td>
<td>30</td>
<td>10</td>
<td>33.3%</td>
<td>11</td>
<td>36.7%</td>
<td>5</td>
<td>20.0%</td>
<td>3</td>
<td>10.0%</td>
</tr>
<tr>
<td>After 3 months</td>
<td>22</td>
<td>6</td>
<td>27.3%</td>
<td>10</td>
<td>45.5%</td>
<td>2</td>
<td>9.1%</td>
<td>4</td>
<td>18.2%</td>
</tr>
<tr>
<td>After 1 year</td>
<td>15</td>
<td>4</td>
<td>26.7%</td>
<td>7</td>
<td>46.7%</td>
<td>2</td>
<td>13.4%</td>
<td>2</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

Successful = Peak flow rate exceeded 12 ml/sec.
Improved = Improvement not reaching the critical level of admittance to (or exit from) the study.
Stationary = Peak flow rate was found to be the same as before the treatment.
Deteriorated = Peak flow rate has deteriorated following the treatment sessions.

the operator by setting off the auto-display and resorting to manual increase or decrease of the power output in watts directly. The desired temperature reached within the adenoma was in the range of 48-52 C° at a power setting of 60-100 watts. This technique has worked perfectly and safely with most patients without the need of terminating the procedure prematurely due to the patient’s intolerance. The software program continuously monitored the urethral and rectal temperature, and although the temperature achieved in these areas was limited (urethral temperature: 45 C° - rectal temperature: 42-5 C°) the intraprostatic temperature was easily in the range of 48-52 C° during the one-hour treatment session. However, the operator can increase or decrease urethral cooling and increase or decrease the power output.

At the end of the session the catheter and rectal probe were removed and the patient was advised to stay until he voided successfully. The patient was warned that mild haematuria was anticipated during the first 24 hours after the treatment session and that it would resolve spontaneously. The patient was not sent home except after voiding in the hospital. The patients were instructed to take a non-steroidal anti-inflammatory agent to minimize any discomfort as well as post-treatment oedema. Oral prophylactic antibiotics were prescribed to prevent subsequent infection for a period of three days.

Each patient received 6 sessions of one-hour treatment. The patients were then informed about their follow-up dates at one week, one month, three months and one year post-treatment.

For post-treatment evaluation physical examination was done including DRE and the maximum flow rate was assessed on two separate trials of voiding of at least 150 cc each. The post-void residual urine volume was estimated using suprapubic ultrasound and urethral catheterization. The Boyarsky symptom questionnaire was presented to our patients in Arabic as the majority of our patients were illiterate and needed extensive explanation as to the exact meaning of each symptom score without posing leading questions. PSA measurement was done after one week of treatment and after one year. Radiosotope scanning for bone metastasis was done one year after treatment.

RESULTS

All patients were evaluable at one month following TUMT. At three months following TUMT, 22 patients were evaluable, while at one year following TUMT only 15 patients were evaluable. The Anova test was used to compare the mean values.

The mean pre-treatment Boyarsky symptom score was 13.73±4.15. At one month follow up the mean Boyarsky symptom score dropped to 8.73±4.14 which was statistically highly significant (P<0.0001). At three months follow up it remained 8.09±3.71 (P<0.0001). At one year follow up the mean Boyarsky symptom score was still 8.53±3.98 (P<0.0001) (Table 1).

The mean pre-treatment peak flow rate was 7.83±2.68 ml/sec. At one month follow up it increased to 10.1±3.17 ml/sec (P=0.0045). At
Table 7: Changes of the Residual Urine Volume after Thermotherapy

<table>
<thead>
<tr>
<th></th>
<th>Total No.</th>
<th>Successful No.</th>
<th>%</th>
<th>Improved No.</th>
<th>%</th>
<th>Stationary No.</th>
<th>%</th>
<th>Deteriorated No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 3 months</td>
<td>22</td>
<td>3</td>
<td>13.6%</td>
<td>11</td>
<td>50.0%</td>
<td>6</td>
<td>27.3%</td>
<td>2</td>
<td>9.1%</td>
</tr>
<tr>
<td>After 1 year</td>
<td>15</td>
<td>4</td>
<td>26.7%</td>
<td>5</td>
<td>33.3%</td>
<td>5</td>
<td>33.3%</td>
<td>1</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

Successful = Post-void residual urine decreased by greater than 75% of the pre-treatment value.
Improved = Improvement not reaching the critical level of admittance to (or exit from) the study.
Stationary = Post-void residual urine was found to be the same as before treatment.
Deteriorated = Post-void residual urine has deteriorated following the treatment sessions.

three months follow up the mean peak flow rate was 10.41±4.35 ml/sec. This was statistically significant (P=0.011). At one year follow up the mean peak flow rate returned to the pre-treatment level of 7.27±2.79 ml/sec (P=0.513) (Table 2).

The mean pre-treatment residual urine volume was 82.5±65.4 ml. At three months follow up the mean residual urine volume dropped to 58.2±36.5 ml. At one year follow up the mean residual urine volume was still 54.7±51.3 ml. The decrement in the residual urine volume did not mount to a statistical significance (P=0.2597) (Table 3).

The mean pre-treatment PSA value was 22±16.69 ng/ml. At one week follow up the mean PSA value was 26.9±18.63 ng/ml. At one year follow up the mean PSA value was 19±5.21 ng/ml. The variation in the PSA mean was not statistically significant (P=0.192) (Table 4).

Another parameter, that the patients reported while the study was still in progress, is the subjective amelioration of pelvic and perineal pain which retrospectively was present in almost all of our patient population at the start of the study. At one month follow up 25 out of 30 patients reported an amelioration of the pelvic pain (83.33%). At three months follow up 16 out of 22 patients reported a significant pain reduction (72.73%). At one year follow up 11 out of 15 patients reported a maintained improvement (73.33%).

Pre- and post-treatment bone scan showed no change in the status of osseous metastases in the 15 patients who completed the study.

Complications of TUMT were few as all patients tolerated the procedure and there was no need to interrupt or to end any treatment session.

Bladder spasms with passage of urine around the urethral catheter were a very common event. During the first 48 hours following the treatment, haematuria was very common; 28 cases (93.3%) experienced mild haematuria that necessitated no special treatment. Heavy pyuria following the treatment was uncommon (the routine anti-infective treatment usually was sufficient to guard against urinary tract infection). In the three cases reporting a severe infection (10%), urine culture and sensitivity followed by the appropriate antibiotics succeeded in controlling the infection. One patient (3.3%) experienced incontinence that lasted 5 months and was controlled with anticholinergic therapy.

The subjective measures for assessment (Table 5) were estimated by the Boyarsky symptom score questionnaire, while the objective measures for assessment (Tables 6, 7) included the peak flow rate and the amount of post-void residual urine.

DISCUSSION

Microwave energy refers to an electromagnetic field within a frequency range lying between the broadcast band (radio frequencies) at the lower end and the infrared spectrum at the upper end. The frequencies often used for microwave heating are 915 ± 25 MHz or 2450 ± 50 MHz as assigned by the Federal Communications Commission. These frequencies correspond to wavelengths of
0.328 and 0.122 meters, respectively. The wavelength dictates the construction characteristics of the energy emitting source, which in most prostatic applicators is a coaxial antenna. Another characteristic of the microwave wavelength is that as the wavelength increases so does the depth of tissue penetration.

In this study transurethral microwave thermotherapy (TUMT), using the Prostalund machine (Lund Science, Sweden), was used for the treatment of local symptoms due to prostate cancer that were unrelieved by conventional systemic therapy on a group of 30 hormone-refractory prostate cancer patients with obstructive symptoms and chronic pelvic pain.

Yerushalmi et al. first reported the clinical use of transrectal prostatic hyperthermia in combination with radiotherapy or endocrine therapy for advanced prostate cancer patients. The procedure was safe and effective. When combined with radiotherapy it was possible to decrease the total dose of radiation, thus decreasing related complications and at the same time achieving results at least comparable to those obtained with radiotherapy alone.

Servadio and Leib reported on the use of heat for local palliation of 27 cases with localized diseases. Nineteen received heat in addition to endocrine therapy, and 8 received heat in addition to radiotherapy. The authors reported a marked relief in the obstructive symptoms and removal of the permanent catheter in 12 of 27 cases with retention. Considerable improvement in urine flow and reduction in residual urine was observed in another 11 cases. Relief of severe pelvic pain was obtained in 9 of 15 cases.

Stawarz et al. used hyperthermia as a palliative treatment for advanced adenocarcinoma of the prostate. Fifteen patients with progressive adenocarcinoma of the prostate were treated: 8 patients (53%) had severe and 7 (47%) had moderately severe symptoms and signs of urinary outflow obstruction and/or pelvic pain caused by the presence of locoregional disease. All sessions in the 15 studied patients were well tolerated. Therapeutic temperature (43.5°C) was obtained in all treatments. There was no local or referred pain during or following the sessions. A change in quality of life measured by a decrease in symptoms and signs caused by the presence of prostate cancer was recorded in 11 patients (73%), while in 4 patients (27%) there was no change noted. The decrease in signs and symptoms was marked in 5 (33%), moderate in 3 (20%) and minimal in 3 (20%) patients.

Our series showed a highly statistically significant improvement in the mean Boyarsky score assessed preoperatively, one month, three months and one year after treatment. Similarly, a highly statistically significant and significant improvement was found in the mean peak flow rates measured preoperatively, one month and three months postoperatively. The mean flow rate returned to near base line at one year follow up. However, the drop in the mean residual urine volume three months and one year after treatment was not statistically significant.

Khair et al. analyzed the pathological changes occurring after microwave thermotherapy in whole mount radical prostatectomy specimens from patients with cancer. Nine patients scheduled for radical prostatectomy for clinically localized prostate cancer were treated with transurethral microwave thermotherapy. The prostates from patients who underwent radical prostatectomy within 4 to 90 hours of thermotherapy showed haemorrhagic necrosis and tissue devitalization without a significant inflammation. Necrosis involved contiguous areas of benign epithelium, stroma and cancer without skip areas. The mean volume of necrosis was 8.8 cc (range 1.4 - 17.8 cc), and the mean percentage of the prostate involved by necrosis was 22% (range 3% - 39%). The necrosis was symmetric around the urethra in 6 of 7 cases. Urethral dilatation was observed in three patients, and the mean maximum radial distance of necrotic tissue was 1.4 cm (range 0.6 - 1.8 cm). The prostates from the two patients who underwent radical prostatectomy 12 months after thermotherapy showed periurethral fibrosis, non-specific chronic inflammation and squamous metaplasia of the urothelium. The mean volume of necrosis remaining was 0.2 cc. The mean percentage of the prostate involved by necrosis one year after thermotherapy was less than 1%. There was some reabsorption of dead tissue. The mean maximum radial distance of the necrotic tissue was 0.4 cm (0.2 and 0.7cm respectively). The prostatic urethra had viable and partially denuded urothelium in all cases. This proves that the effect of TUMT wanes off by the end of the first year following treatment.
We conclude that prostatic heat treatment has a role in the treatment of local obstructive symptoms, pain and discomfort induced by prostatic cancer and unrelieved by systemic therapy.

Thermotherapy is considered a minimally invasive procedure. It is given without anaesthesia with its potential hazards and risks, thus it is very convenient for high-risk patients who are considered unfit for anaesthesia. It is given on an outpatient basis. No mortality has been recorded from the procedure and its morbidity was extremely low. The improvement in the peak flow rate was short-lived and returned to pre-treatment levels by the end of one year follow up.

The possible application of prostatic hyperthermia as a first-line treatment for prostate cancer, either alone or in combination with new therapeutic procedures, such as immunotherapy, or other accepted forms of treatment such as chemotherapy or radiotherapy, requires further extensive studies.

REFERENCES


RESUME

La Thérométhrapie Transurétrale par Micro-Ondes dans le Cancer Localement Avancé de la Prostate

Objectif Bien que le cancer de la prostate métastasié aboutit éventuellement à la mort du patient, le cancer localement avancé peut être associé à une sévère morbidité. Les options thérapeutiques actuellement disponibles incluent les manipulations hormonales, la radiothérapie ou la résection transurétrale. Des études antérieures ont rapporté que l'hyperthermie locale de la prostate peut avoir un effet sur la maladie cancéruse localisée ou avancée. Cette étude avait pour but d'évaluer les effets de la thermothérapie transurétrale par micro-ondes dans le cancer localement avancé de la prostate.

Matériel et Méthodes Cette étude incluait 30 patients souffrant d'obstruction cervico-urétrale de degrés divers secondaire à un cancer de la prostate avancé en échappement hormonal. La TUMT a été réalisée avec l'appareil Prostiald (Lund Science –Sweden), à raison d'une séance par semaine pendant 6 semaines. Le réchauffement transurétral a été obtenu à travers une sonde de Foley délivrée avec une antenne micro-onde, capteurs de température et un canal de refroidissement. La température rectale a été surveillée via des capteurs thermiques rectaux montés sur une sonde rectale spéciale. Tous les patients ont été évalués avant le traitement, à un mois, 3 mois et un an.
après la procédure. **Résultats** Le score de Boyarsky moyen avant le traitement était de 13,73±4,15. A 1 mois, 3 mois et 1 an de suivi, le score de Boyarsky moyen était respectivement de 8,73±4,14 (p<0,0001), 9,09±3,71 (p<0,0001) et 8,53±3,98 (p<0,0001). Le débit maximal moyen avant le traitement était de 7,83±2,68 ml/sec. A 1 mois, 3 mois et 1 an de suivi, il était respectivement de 10,1±3,17 ml/sec (p=0,0045), 10,41±4,35 ml/sec (p=0,011) and 7,27±2,79 ml/sec (p=0,513). Le résidu post-mictionnel moyen avant le traitement était de 82,5 ml±65,4. A 1 mois, 3 mois et 1 an de suivi il était devenu respectivement à 58,2 ml±36,5 and 54,7 ml±51,3 (p=0,2597). Le taux moyen de PSA avant le traitement était de 22±16,69 ng/ml. Une semaine après le traitement il était de 26,9±18,63 ng/ml et à un an 19±15,21 ng/ml (p=0,192). **Conclusion** TUMT est sûre et efficace pour soulager les symptômes obstructifs du cancer avancé de la prostate. L’amélioration des symptômes a été de courte durée revenant à la situation d’avant le traitement après un an de suivi. Les avantages majeurs de la TUMT sont qu’il s’agit d’une procédure ambulatoire, bien tolérée avec un morbidité minime qui peut être proposée à des patients qui ne peuvent subir une anesthésie.

All correspondence to be sent to:

Mohamed Amr Lotfi, M.D.
11, Talaat Harb Street
Caire
Egypt

Ph: ++20-2-3932778
Fax: ++20-2-5085021

malotfi@menanet.net