Microwave thermal therapy in the treatment of benign prostatic hyperplasia and prostatic cancer

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Abstract

For many years, transurethral resection of the prostate (TURP) has been the definitive treatment for benign prostatic hyperplasia (BPH). However, TURP is considered rather invasive because about 20% of the patients develop significant complications within 10 years. With the development of microwave technology, minimally invasive procedures have been introduced in an attempt to decrease the morbidity experienced with TURP. Various studies reviewed in this article indicate that the outcome of microwave heat therapy for BPH and prostatic cancer is encouraging although further research is required to evaluate the long-term effectiveness and safety of this therapy. The authors conclude that, as microwave technologies improve in the near future, increased clinical utilization of this exciting method is expected.

Key words: microwave, thermotherapy, hyperthermia, prostatic hyperplasia, prostatic cancer

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Introduction

Benign prostatic hyperplasia (BPH) refers to stromal and glandular epithelial hyperplasia that occurs in the zone of the prostate that surrounds the urethra. BPH causes urinary frequency and urgency, a sensation of incomplete bladder emptying, a weak and interrupted urinary stream, straining to initiate urination, and nocturia. These symptoms are collectively called “lower urinary tract symptoms” or “LUTS” and can significantly reduce quality of life (QOL). Medical therapy is mainly used for the treatment of patients suffering from mild to moderate LUTS, and the specific treatments include alpha-1-selective adrenergic receptor antagonists, 5-alpha-reductase inhibitors, or a combination therapy with one drug from each of these classes 1)-4).

On the other hand, surgical therapy is an option for patients who have severe LUTS secondary to BPH or for whom medical therapy is not efficacious. Of the traditional surgical therapies, transurethral resection of the prostate (TURP) has been the gold-standard treatment for alleviating urinary symptoms and improving urinary flow in men with symptomatic BPH. However, the large number of retrospective reviews demonstrated that the rate of intraoperative and postoperative complications was about 20% within 10 years, and the complications included hematuria, reoperation, urethral strictures, sexual dysfunction, urinary incontinence, urinary retention, dilutional hyponatremia (water intoxication), and blood loss requiring transfusion 5)-8).

With the development of the new microwave technology, minimally invasive surgical procedures have been introduced in an attempt to decrease the morbidity experienced with standard TURP. For BPH therapy, many recent reviews and studies have suggested similar results with transurethral microwave therapy (TUMT) devices compared to TURP surgery, but with fewer serious complications when using TUMT 9)-27). In addition, microwave technology has been utilized for the treatment of prostatic cancer as a palliative therapy or an alternative to prostatectomy in high-risk patients who are not surgical candidates 13)-16). In this article, we review the safety, efficacy, and feasibility of microwave heat therapy for BPH and prostatic cancer.

Methods

Data for this review were identified on MEDLINE using the search terms including “prostatic hyperplasia,” “prostatic cancer,” “transurethral resection,” “microwave thermotherapy,” “microwave hyperthermia,” and “microwave.” From the references obtained, selection was made based on the clinical relevance and importance of the article. Both the experimental studies and the preliminary clinical reports were included in this article.

Experimental studies and preclinical trials

The first paper dealing with the effect of microwave exposure to animal prostates was presented by Petrowicz and associates in 1979 17). They performed transrectal microwave radiation of the prostate using a specially-designed applicator (433.9 MHz), and the temperature of the rectum, of the urethra, and of the prostate were measured and recorded using a thermistor probe. These authors indicated that local heating of the prostate was possible and that the induced damage of the prostate and the surrounding tissue was not severe enough to be intolerable confirmed by the histological examination. In 1980, Magin and coworkers also reported the interesting experimental study on the use of microwave heating 18). Eight canine prostates were exposed to localized intense microwave radiation (2,450 MHz) following urinary diversion by bilateral cutaneous ureterostomy. A temperature at or above 60°C for 15 minutes was maintained throughout the canine prostate whereas the temperature of the rectal lumen did not exceed 38°C because structures adjacent to the prostate were shielded using microwave reflectors. This treatment produced thermal necrosis of the prostate at 1 week without the rectal damage. Prostate tissue was totally reabsorbed at 6 months leaving only a small fibrous scar at the site of the previous prostate location.

In general, microwave therapy techniques include hyperthermia (heating prostate tissue to 42-44°C), thermotherapy (45-60°C), and thermoablation (60-75°C). In 1983, Yerushalmi et al. performed experiments using 64 rabbits in order to determine the response of normal tissues of the rectal cavity and the prostate to localized 2,450 MHz microwave hyperthermia 19).
Heat was applied by means of a coaxial probe in the rectal cavity for 30 minutes once or twice at an interval of 2 days. The temperature was maintained at 42.9-43.2°C in the rectal mucosa, and 42.6-42.8°C in the prostate. Histological examination up to 3 months after treatment revealed that in almost all of the treated rabbits no tissue or organ injury resulted from localized, deep hyperthermia at 43°C.

In 1985, a preliminary study was performed by Harada et al. on the use of a transurethral probe for prostate thermal coagulation using 20 mongrel male dogs. The prostates of the dogs were radiated with microwave energy of 50 watts or 100 watts for 30 seconds. This study revealed that blood circulation in the prostate tissue, measured by the hydrogen gas clearance method, significantly decreased after the microwave exposure in all cases. Histological examination revealed that an extensive necrotic region with hemorrhage inside the prostate was noted immediately after the procedure. Moreover, at 14 days following the procedure, a large cavity was obtained inside the prostate and fibrous tissue was apparent around the cavity.

Devonec and associates performed transurethral microwave heating of the prostate in 7 patients under general anesthesia prior to TUR and investigated a thermo kinetic analysis in 1991. Fiberoptic temperature probes were inserted within the prostate (2 fibers) at a distance of 5 to 20 mm from the microwave antenna. The urethral and rectal temperatures were automatically recorded by means of fiberoptics positioned along the urethra and in the rectum. From these trials, they demonstrated that the intraprostatic temperature could be raised to therapeutic level (above 45°C) within 15 to 20 minutes of microwave radiation (35 watts). Also, the urethral and rectal temperatures were constantly monitored and maintained below 45°C and 42.5°C during the treatment. The macroscopic examination of the tissue showed that the treatment area was symmetrical with necrosis on both sides of the median line that expanded to a distance of 5 to 17 mm from the urethral lumen. The urethral mucosa and the periurethral tissue were preserved to a depth of 2 to 5 mm from the urethral lumen. The peripheral zone of the prostate and the capsule were both preserved.

In 1995, Bostwick and Larson evaluated the effect of microwave thermotherapy in 13 dogs receiving 48-79 minutes of focused irradiation (16-45 watts, intraprostatic temperature>45°C) delivered by a specially-designed transducer with an operator-controlled directional antenna. In the acute phase (5-13 days), the prostate showed periurethral coagulative necrosis with hemorrhage. In the subacute phase (17 days), the hemorrhagic necrosis was resolving, often with cystically dilated urethra due to sloughed necrotic tissue. By the chronic phase at 24-38 days, there was further resolution, with patchy residual inflammation at the periphery. In all cases, the prostatic capsule was intact. These pathologic findings in the canine prostate after microwave hyperthermia appeared to be similar to those in the human prostate.

These experimental studies and preclinical trials mentioned above and other multiple studies confirmed that transurethral microwave therapy could be safely administered, and a tissue effect was clearly shown by histological examination.

Clinical trials in benign prostatic hyperplasia

In 1985, Yerushalmi et al. reported transrectal microwave hyperthermia to treat patients with BPH who were poor operative candidates. Twenty nine patients were treated twice weekly, for 1 hour, without sedation on an outpatient basis. All patients tolerated treatment well without secondary effects. These authors suggested that localized deep microwave hyperthermia was safe and effective in the treatment of BPH. The earliest major trial involving transurethral microwave hyperthermia was reported by Devonec et al. in 1991. In a trial of 37 patients, a therapeutic temperature range of 45-55°C was achieved. They showed a mean decrease in symptom score of 33%, an increase in peak flow rate of 2.4 mL/sec, and a mean decrease in residual urine volume of 59 mL.

In contrast, the first report dealing with the use of transurethral microwave coagulation (thermal ablation) followed immediately by TURP was published by Harada et al. in 1987. These authors performed a comparative study on 35 patients with symptomatic BPH. The patients were assigned randomly to 2 groups: 16 patients underwent transurethral microwave prostatic coagulation followed by immediate...
TURP (combined group) and 19 patients underwent conventional TURP alone (TURP group). The employed microwave probe consisted of a rigid coaxial cable with a 24F (8 mm) outside diameter and had a moderate curve at its distal portion. To avoid inadvertent dislocation of the probe, suprapubic trocar cystoscopy was performed as a means of monitoring the conditions during the coagulation procedure. The prostate was exposed to microwave radiation (2,450 MHz) with the output of 100 watts for 30 seconds. As a result, although there was no difference in the mean resection weight of the prostate between the 2 groups, the mean resection rate (g/min) in the combined group was higher than that of the TURP group. Blood loss of the combined group was significantly lower than that of the TURP group, and blood transfusion was required in 4 patients in the TURP group while no patients required transfusion in the combined group.

Recently, transurethral microwave heat treatment, including low-energy transurethral microwave thermotherapy (LE-TUMT) and high-energy transurethral microwave thermotherapy (HE-TUMT), has been utilized for the treatment of BPH and prostatic cancer as a minimally invasive procedure. Several different types of microwave devices have been available around the world, including the Prostatron (Technomed Medical System, Lyons, France), Targis (Urologix, Inc, Minneapolis, Minnesota, USA), Microthermer (Laser Electro Optics, London, UK), Prostalund (Lund Instruments AB, Lund, Sweden), Urowave (Dornier MedTech America, Kennessaw, Georgia, USA), Prostcare (Bruker Medical, Wissembourg, France), Thermex-II (Direz, Petah tiqva, Israel), LEO Microthermer (Laser Electro Optics, London, UK), PRIMUS U + R (Tecnomatix, Monheim, Germany), and original modifications. The TUMT method using the above-mentioned devices combines the principles of microwave radiative heating and conductive cooling to destroy tissue within the prostate while preserving the other structures of the lower urinary tract.

The first-generation TUMT device has been used to demonstrate that LE-TUMT is a safe treatment, having low morbidity, good tolerability, and effective short-term outcomes. In general, LE-TUMT provides a therapeutic temperature of 45-60°C within the prostate. Many investigators have indicated that long-term follow-up in patients undergoing LE-TUMT reveals subjective symptom score improvement, although for only limited reduction in most cases. Several prospective, randomized studies (against sham therapy or TURP) have demonstrated consistent symptomatic improvement and improvement in peak urinary flow rate of 35-58% over baseline. However, long-term efficacy of LE-TUMT seems to be limited. Re-treatment rates are substantial, reportedly 57-84% by 5 years. Using the lower-energy Prostatron Prostasoft 2.0, Ohigashi et al. reported a 67% re-treatment rate within 5 years with only 11% "satisfied" with treatment.

On the other hand, HE-TUMT devices were developed in order to increase the efficacy of LE-TUMT. A therapeutic temperature within the prostate achieves more than 70°C using second-generation devices. d’Ancona et al. treated 247 patients with symptomatic BPH with HE-TUMT. Following 12 months, while the peak flow rate increased a mean 57%, the symptomatic score decreased a mean 59%. These authors indicated that independently-predictive baseline parameters for poor response included the patients’ age, the size of the prostate, and the grade of bladder outlet obstruction. Thalmann et al. treated 200 patients using the second-generation Targis thermotherapy device, and their results demonstrated that only 22% of the patients required additional treatment after a median observation time of 42 months. Moreover, in the 162 patients evaluated 6 months after treatment, the median post-void residual urine volume decreased from 170 mL before treatment to 17 mL after 6 months and remained unchanged. Similarly, recent, longer-term follow-up studies demonstrated that the new generation HE-TUMT devices provided a significant improvement in both the QOL score and in the objective parameters with acceptable medical and surgical re-treatment rates of 7% to 29%. And the authors also reported that 78% to 82% of the patients were satisfied. However, several studies have indicated that the enhanced efficacy of HE-TUMT is associated with both an increase in postoperative morbidity and with a decrease in tolerability, including irritative voiding symptoms, retrograde ejaculation, and urinary retention.
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of TUMT with TURP have clearly demonstrated striking differences and the general acceptance of TUMT as a promising therapy. Hoffman et al. evaluated 6 distinct randomized trials of TUMT with TURP in 2004. Overall, 540 participants were randomized in the 6 trials, including 322 to TUMT and 218 to TURP. TUMT was routinely used as an outpatient procedure, while TURP was an inpatient procedure with a median hospital stay of 5 days. TUMT was performed using Prostatron in 5 trials and ProstaLund in 1 trial as a microwave device. Catheterization was consistently longer after TUMT, at 7-15 days, compared with 2-4 days after TURP. TUMT was somewhat less effective than TURP in reducing LUTS. The pooled mean urinary symptom score for men undergoing TUMT decreased 65% in 12 months (from 19.4 to 6.7), compared with 77% (19.6 to 4.5) in men undergoing TURP. The pooled mean peak flow rate for men undergoing TUMT increased by 70% (7.9 to 13.5 mL/s), and by 119% (8.6 to 18.7 mL/s) in men undergoing TURP. From the viewpoint of complications, retrograde ejaculation (57.6% versus 22.2%), transfusions (5.7% versus 0%), and re-treatment for strictures were all significantly common after TURP. However, re-treatment for BPH symptoms was significantly more common after TUMT. They concluded that TUMT techniques were effective and safe short-term alternatives to TURP for treating BPH. However, TURP provided greater symptomatic and urinary flow improvements and fewer subsequent BPH treatment compared with TUMT.

Clinical trials in prostatic cancer

Microwave therapy for prostatic cancer includes local hyperthermia and thermotherapy (in other words, thermal ablation or coagulation). The first clinical experience of microwave hyperthermia was reported by Mendecki et al. in 1980. Two patients with inoperable prostatic cancer underwent a total of 4 or 6 microwave hyperthermia treatments with the coaxial applicator (42.5°C for 30 minutes), in combination with either radiotherapy or radiofrequency hyperthermia. These 2 patients had no significant complications related to the heating procedures. A rectal examination revealed that the prostatic tumor was markedly diminished in size in one patient although long-term follow-up was not obtained. In 1982, Yerushalmi et al. reported a study on the treatment of 15 patients with prostatic cancer using localized deep hyperthermia, either alone or in combination with radiotherapy or hormonal therapy. This preliminary report suggested that localized microwave hyperthermia seemed to be a promising and safe method of treatment for prostatic cancer. Servadio et al. treated 30 patients with advanced prostatic cancer using local microwave hyperthermia and demonstrated that marked objective and subjective improvement was noted in the majority in 24 months of follow-up.

Montorsi et al. reported the method of transrectal microwave hyperthermia for advanced prostatic cancer in 1992. Hyperthermia was applied to 46 patients (stage DI or D2) who had urinary symptoms and local pain unrelied by total androgen ablation therapy. The treatment was administered in 10, 60-minute sessions twice a week for 5 weeks. The temperature in the prostate was maintained at 43-44°C during the procedure. At 2 years, the mean residual urine volume was significantly decreased, while the mean peak flow rate was improved but not significantly. These authors concluded that prostatic hyperthermia was a safe and effective palliative procedure for bladder outlet obstruction due to advanced prostatic cancer. In contrast, Strohmaier et al. investigated the histological effects of microwave hyperthermia in 20 patients and then demonstrated that hyperthermia was not adequate as a single treatment for prostatic cancer because definite signs of tumor cell necrosis could not be seen in any of the patients 1-2 weeks after treatment.

On the other hand, microwave thermotherapy (coagulation procedure) was used for the treatment of prostatic cancer by Harada et al. in 1985. Three patients with prostatic cancer underwent transurethral coagulation of the prostate and thereafter significant destruction of prostatic tissue with relief of obstruction was observed without serious complications. In 1991, Kigure et al. performed transurethral microwave coagulation of the prostate under ultrasonic monitoring on 9 patients with prostatic cancer who had severe dysuria or urinary retention. The prostate was irradiated with microwave energy of 100 watts for 60 seconds once or twice. As the procedure progressed, the coagulated tissue around the prostatic urethra gradually appeared as a hyperechoic area as compared to the noncoagulated area. After a total of 60 sec-
onds of microwave irradiation, the prostatic urethra was widely opened, and a hyperechoic area in the prostate was extended. All of the 9 patients were able to void satisfactorily without any serious complications following the treatment. These authors concluded that intraoperative, real-time ultrasonic scanning allowed safe and more efficacious application of prostatic microwave coagulation. In 1999, Khair et al. evaluated the histological effects occurring after microwave thermotherapy which was performed on 9 patients with localized prostatic cancer who were scheduled for radical prostatectomy. Histological examination in patients who underwent radical prostatectomy within 4 to 90 hours of thermotherapy revealed that necrotic change was noted in 80% to 100% of the volume of cancer in 4 cases, 40% to 60% in 2 cases, and 5% in 1 case.

Microwave thermoablation by means of the percutaneous method also has been utilized for the treatment of prostatic cancer. Trachtenberg et al. performed percutaneous transperineal microwave thermoablation for the selective patients with failures of external-beam radiation therapy for localized prostatic cancer. Short-term follow-up data showed relatively good results that, at 12 months, 12 of the 20 patients had no biochemical or histological evidence of disease, and 11 of the 14 patients who had an initial PSA concentration of <10 ng/mL showed no evidence of disease.

Conclusions

Microwave heat therapy, including hyperthermia, thermotherapy, and coagulation therapy, is one of the several minimally-invasive procedures in the treatment of both benign prostatic hyperplasia and prostatic cancer. Transurethral microwave thermotherapy (TUMT) involves the insertion of a specially-designed urinary catheter with a microwave antenna which heats the prostate and destroys the enlarged prostate tissue. TUMT has a great advantage in that the procedure can be performed without sedation on an outpatient basis. Up to this point in time, the outcomes of TUMT for benign prostatic hyperplasia and prostatic cancer are encouraging. The authors conclude that further research is required to evaluate the long-term effectiveness and safety of this therapy.

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