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INTERSTITIAL THERMAL THERAPY IN PATIENTS WITH LOCALIZED PROSTATE CANCER: HISTOLOGIC ANALYSIS

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ABSTRACT

Objectives. To examine, by way of histologic examination, the destruction of excised prostate glands treated with thermal ablation. Thermal ablation treatment with permanently implanted temperature self-regulating rods is being used in the treatment of localized prostate cancer.

Methods. Four patients with biopsy-proven prostate cancer, who had been scheduled for routine radical prostatectomy with a gland size of less than 70 g, Gleason sum of 7 or less, and prostate-specific antigen values less than 10.0 ng/mL, were implanted with 70°C rods under ultrasound and fluoroscopic control. The patients were then given multiple thermal treatments. Glands were removed and histologically analyzed to access the thermal destruction.

Results. Histologic examination revealed confluent thermal destruction within the rod array when the rods were placed end-to-end and no farther than 1 cm apart. Little necrosis was seen outside the array. To ensure the necessary destruction, the rods must be placed at the capsule, including posteriorly near the rectum. The results indicated that energy levels greater than 40 W-min/g of tissue should be used. This can be achieved by implanting 1.5 rods/g of prostate and treating the patient for 60 minutes. In 3 of the 4 patients, no residual cancer was found in the gland after thermal treatment.

Conclusions. Histologic examination has aided in determining the implant density and treatment time and, therefore, the necessary energy, for adequate necrosis. The technique demonstrates the ability to destroy the prostate adequately, including tissue at the capsule. This new procedure appears promising in the treatment of localized prostate cancer.

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Although radical prostatectomy, external beam radiation, and brachytherapy for the treatment of localized prostate cancer have demonstrated good long-term survival rates, their post-treatment complications continue to be a concern. In part, patient concern about complications has fueled the development of alternative treatments such as nerve-sparing surgery and high intensity focused ultrasonography.

We have developed a new system that may address the problems of complications and retreatment in cases of local failure. The technique is thermal ablation of the prostate by permanently implanted biocompatible rods. An array of rods is placed percutaneously into the prostate under transrectal ultrasound and fluoroscopic guidance in a procedure similar to the implantation of brachytherapy seeds. The patient is then placed in a coil system that heats the array of rods by an extracorporeal, alternating magnetic field. The produced heat causes necrosis of the normal glandular tissue, as well as the cancer, within the array of rods.

The rods are a ferromagnetic alloy (7% cobalt and 93% palladium by weight) and, like all magnetic materials, heat in a radiofrequency alternating magnetic field; this is termed induction heating. As the rods heat inductively, they achieve a temperature at which they become paramagnetic or nonmagnetic, at which point they stop heating. This transition is termed the Curie temperature and makes the rods temperature self-regulating (ie, the rods remain at the Curie temperature while the

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TABLE I. *Treatment variables and histologic results*

Pt. No.	Prostate Size (g)	Rods Per Gram of Tissue	Total Treatment Time (min)	Energy (W-min/g)	Gland Necrosis (%)	Location for Cancer After RP
1	47	1.82	62	50.8	85	0
2	28	2.15	20	19.4	25	Extracapsular
3	53	1.96	45	39.6	75	2 foci (mid and base), capsule and margins involved
4	72	1.20	33	17.8	70	0

KEY: Pt. No. = patient number; RP = radical prostatectomy.

field is energized). The regulation temperature can be set at manufacture to approximately ±1.5°C of any desired hyperthermia or thermal ablation value from 42° to 100°C. Each rod produces a maximum of approximately 0.45 W of power.[1] Additional technological details can be found elsewhere.[2]

The system has been tested in vitro and in vivo in a canine model and in initial clinical dosing trials.[3,4] These studies examined different rod regulation temperatures and treatment times. The studies demonstrated that rods with a Curie temperature of 70°C when placed in arrays produce consistent necrosis. Furthermore, the temperature drops quickly at the edge of the array and, therefore, rods placed at the capsule have little effect on tissue outside the prostate. The urethral mucosa can be spared by either using a cooling catheter or placing the rods 5 to 10 mm from the urethra.

This report presents data on the histologic features of prostate tissue after the use of thermal rods with a regulation temperature of 70°C rods in 4 patients with Stage T1-T2 prostate cancer.

MATERIAL AND METHODS

Patients with biopsy-proven prostate cancer (Stage T1-T2, prostate-specific antigen less than 10 ng/mL, Gleason sum of 7 or less, and prostate size less than 70 g by ultrasonography), who were scheduled for radical prostatectomy, were offered enrollment in the study. Four patients were enrolled. The patients ranged in age from 52 to 71 years, and the prostate-specific antigen values varied from 5.0 to 8.0 ng/mL, prostate volumes ranged from 28 to 69 g, and Gleason sums varied from 6 to 7. Patients were treated at the University of Chile in Santiago under an institutional review board-approved protocol with informed consent.

Thermal rods (ThermoRod, ATI Medical, San Diego, Calif) with a regulation temperature of 70°C were implanted under spinal anesthesia using ultrasonography and fluoroscopy. The rods (1 mm in diameter and 14 mm long) were implanted with a 17-gauge, thin wall needle and obturator. The rods were implanted end-to-end in the needle tracks with two to three rods per tract, depending on prostate length, and the tracks were separated by no more than 10 mm. Rods were placed at the capsule, except near the rectum, where they were placed approximately 5 mm from the capsule; rods were also placed 5 to 10 mm from the urethra. Implantation was accomplished in less than 1 hour and led to a minimum of 1.20 rods/g of tissue and a maximum of 2.15 rods/g (Table I).

Patients were treated in a coil system that produced an alternating magnetic field (50 G root mean square at 50 kHz) at the level of the patient's prostate. Thermal treatments were initiated the day after rod implantation; four treatments were given with each session, separated by 24 hours. Earlier studies with only one quarter to one half of the prostate treated with arrays of 70°C rods produced little patient discomfort during the 1-hour treatments[4]; therefore, 60-minute treatments were planned. Because no urethral or rectal temperature monitoring was performed during the treatments presented in this study, we thought it unwise to use analgesia or anesthesia for pain and allowed the patients to limit the time of their four treatments on the basis of personal comfort.

Radical prostatectomies were performed 9 to 31 days after the last thermal treatment. During this period, patients did not receive antibiotics and did not require catheterization. After radical prostatectomy, the specimens were fixed for at least 72 hours in 10% neutral buffered formalin. The surfaces were inked to ensure that the anatomic orientation could be identified on tissue sections, cut perpendicular to the urethra into 3- to 5-mm slices, with the rods in place (Pathology Associates, Frederick, Md). The rod pieces were then removed and the slices embedded in paraffin. The paraffin blocks were cut by standard microtome technique, and the whole mount sections stained with hematoxylin-eosin. A single pathologist (C.E.P.) performed the histologic evaluation. Each level was evaluated histologically for the percentage of necrosis, presence of necrosis at the gland resection margin, percentage of the gland occupied by viable tumor, presence of viable tumor at the margin, Gleason grades, and presence or absence of capsular and perineural involvement.

RESULTS

The total treatment time ranged from 20 to 62 minutes, in approximately four equal sessions; the total time for each patient is given in Table I.

The variation in total treatment time led to a substantial difference in the amount of energy that each patient had delivered to his gland. As each rod produces approximately 0.45 W of power (P), the amount of energy (E) delivered to each gram of prostate during the treatment time (T) is calculated by $E = P \times \text{rods/g} \times T$. This value varied from 17.8 to 50.8 W-min/g; the values for each patient are given in Table I.

In 2 patients, no cancer was found in any section. In patient 2, extracapsular foci of tumor were found in one level on the right but not at the resection margin. In patient 3, two small focal lesions were found on the left in two levels: both involving

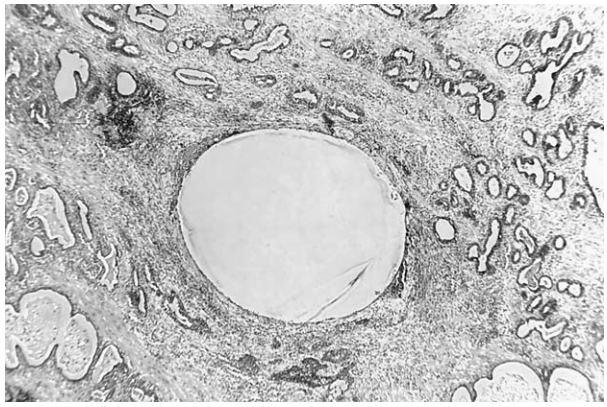

FIGURE 1. *Site of isolated rod with minimal necrosis and surrounding tissue response. Original magnification ×4.*

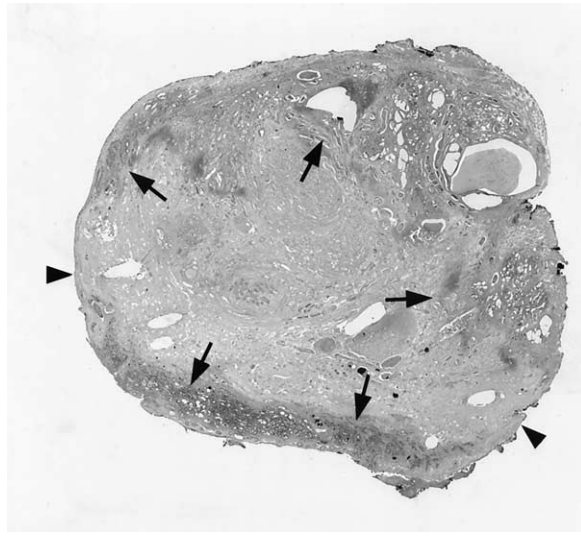

FIGURE 2. *Whole mount section of prostate with confluent necrosis centrally (arrows) with focal extension through capsule (arrowheads).*

the capsule and the resection margin. Table I summarizes the histologic results.[3] Correlating the amount of necrosis with the energy used to ablate the gland found that patient 1 had 85% necrosis with 50.8 W-min/g, patient 2 had 25% necrosis with 19.4 W-min/g, patient 3 had 75% necrosis with 39.6 W-min/g, and patient 4 had 72% necrosis with 17.8 W-min/g.

Necrosis was generally centered on the rod sites. Isolated rods had only 1 to 2 mm of surrounding necrosis (Fig. 1). In those areas in which the necrosis was not confluent, surrounding reactive changes included vascularization and prominent glandular squamous metaplasia. Rods properly implanted into arrays led to confluent extensive areas of necrosis within the array (Fig. 2). This was most prominent in gland 4, in which nearly the entire gland was necrotic. However, necrosis at the edge of the rod array extended only 1 to 2 mm from the outer rods (Fig. 3).

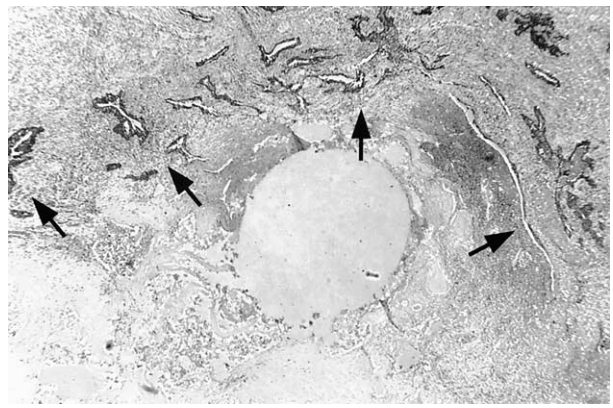

FIGURE 3. *Necrotic tissue (arrows) surrounding an outer rod at the array edge. Note that the necrosis extends only 1 mm beyond the rod, although it is confluent centrally where other rods were place, beyond the edge of the photograph. Original magnification ×4.*

COMMENT

Although several groups have investigated the induction heating of Curie point, temperature self-regulating rods for the treatment of tumors,[5–7] technical problems such as nonbiocompatible alloys[8] and difficulty in manufacturing rods with a specific regulation temperature[9] have limited the technology's clinical usefulness. The present palladium-cobalt rods have overcome earlier problems and can be used for the thermal destruction of tissue (70°C rods) or for hyperthermia treatments (55°C rods) in conjunction with radiation.[10] Although comprised of mostly palladium, the cost of the rods per procedure is similar to that of brachytherapy seeds.

The rod regulation temperature, spacing, and treatment time were previously studied in patients undergoing thermal treatments followed by radical prostatectomy.[4] The number of patients presented in this report was small; however, the data do add additional important characteristics for the successful thermal destruction of tissue. Other investigators have determined that thermal rods need approximately 200 mW/cm to overcome the cooling effects of blood flow.[8] This suggests that our rods needed a minimum of about 280 mW of output power (1.4 cm × 200 mW/cm = 280 mW). The rod power output varies with the angle (Φ) between the rod's longitudinal axis and the magnetic field as approximately $\cos^2 \Phi$; therefore, if the rod is not parallel to the field, the power will be reduced.[11] Because perfect alignment is not possible during implantation and patient movement can cause further variations, we chose a minimal out-

put of 450 mW (ie, approximately 60% more than required). This added power allows the rod to be at an angle of 30° with the field and still put out more than 280 mW ($P = 450 \times \cos^2 30° > 325$ mW).

The power delivered to the tissue does not completely account for the histologic results. The extent of necrosis also depends on the amount of time the power is applied (ie, the energy applied to the tissue, in watt-minutes per gram; Table I). Previous studies have demonstrated that 60-minute treatments caused confluent necrosis within the 70°C rod array[4]; however, only patient 1 had a total treatment time of 60 minutes. Patients 1 and 3 had the highest applied energy, 50.8 and 39.6 W-min/g, and had the most extensive tissue destruction, 85% and 75%. Patients 2 and 4 had the lowest applied energies, less than 20 W-min/g, yet had great variation in the amount of necrosis, 25% and 70%, respectively. The large variation in these 2 patients was most likely caused by the difference in treatment times. Patient 2 was treated for 20 minutes in four sessions, an average of only 5 minutes per treatment. As steady state thermal equilibrium is not reached instantaneously but requires several minutes, the period that the gland was treated was only 2 or 3 minutes per treatment. The results of treatment with this patient demonstrate that shortened treatment times limit the amount of tissue destruction.

To achieve greater than approximately 75% destruction of prostatic tissue it appears that energy levels greater than 40 W-min/g must be used. Given the rods per gram of prostate implanted, patients 1, 2, and 3 would have had energies greater than 50 W-min/g if a single treatment time of 60 minutes had been used. A longer treatment time will necessitate anesthesia or analgesia during the treatments and may necessitate temperature measurement in the urethra and rectum. Patient 4 would have had only 32.4 W-min/g even with a 60-minute treatment; this patient needed to have 1.5 rods/g implanted to achieve the energy criteria.

Even a high power of 39.6 W-min/g and 70% gland necrosis (patient 3) did not ensure the complete destruction of the cancer. Probably more important clinically is where viable tissue was present after treatment. Rods were not placed at the capsule near the rectum but were placed about 5 mm from the capsule. This posterior region is where most of the viable tissue was left in patients 2, 3, and 4, and this is the area in which the residual cancer in patient 3 was found in two histologic sections. Therefore, to ensure tissue destruction at the edge of the gland, rods must be placed at the capsule, even at the rectal grove. Histologic sections from this study, as well as previous data from phantom,[4] animal,[3] and human[4] studies demonstrated that the temperature and tissue necrosis drops off sharply outside the rod array (ie, 1 to 2 mm); thus, rods may be safely placed at the capsule near the rectum. This is in contrast to the drop off within the rod array, where power from adjoining rods is additive and creates necrosis 5 mm from each rod. However, for safety, future studies will need to monitor rectal temperatures during treatment.

CONCLUSIONS

Histologic evaluation demonstrated confluent necrosis within an array of rods when the rods were placed end-to-end and no more than 1 cm apart. Little necrosis was seen outside the array, and to ensure that the entire gland is treated, rods must be placed at the capsule. Adequate necrosis can be achieved by placing 1.5 rods/g of prostate and using a 60-minute treatment time. The results appear promising for this technology in the treatment of localized prostate cancer.

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