Microwave Treatments for Prostate Disease

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***Abstract*—This paper describes three novel microwave techniques that show promise for being useful in treating diseases of the prostate. They are: microwave urethroplasty for providing immediate symptomatic relief of urinary obstructions caused by benign prostatic hyperthrophy—this technique uses microwave balloon catheters for producing biological stems in the urethra. Initial results obtained in an Federal Drug Administration approved Phase I clinical trial are highly encouraging, hyperthermia produced in the prostate by dual microwave balloon catheters—when combined with external beam radiation or implanted radioactive seeds, this technique has the potential of improving local recurrence rates of prostate cancer over the rates that are obtained when only radiation treatments are given, and microwave poration therapy—a therapy that, when combined with either systemic or locally administered chemotherapy, has been shown to be effective in shrinking implanted prostatic tumors in rats. The potential clinical advantages of microwave poration/chemotherapy over electrochemotherapy using dc pulses for treating cancers are discussed.**

***Index Terms*—Benign prostatic hyperthrophy, hyperthermia, poration, prostate cancer.**

I. Introduction

THE prostate is a chestnut-shaped gland that surrounds the urethra of males immediately below the bladder. Diseases of the prostate include benign prostatic hypertrophy (BPH), which is an increase in the volume of the gland, and cancer. The prevalence of both BPH and prostate cancer increases with age, although cancer lags by 15–20 years. BPH is a very common disorder, affecting approximately 50% of men between the ages of 51–60 years. By the age of 80, 80% of men have this disorder, making BPH one of the most common medical disorders of older man. During an 80-year lifespan, there is a 10% probability that an American man will develop prostate cancer. BPH is the most common cause of bladder outflow obstruction in the male. Prostate cancer is the most commonly diagnosed cancer in American men and is the second leading cause of cancer mortality in these men.

In this paper, we describe three new microwave techniques that show promise for being useful in treating diseases of the prostate, which are : 1) microwave urethroplasty for providing immediate symptomatic relief of urinary obstructions caused by BPH; 2) hyperthermia produced in the prostate by dual microwave balloon catheters, which, when combined with external beam radiation or implanted radioactive seeds, has the potential of improving local recurrence rates of prostate cancer over the rates that are obtained when only radiation treatments are given; and 3) microwave poration therapy, a therapy that, when combined with either systemic or locally administered chemotherapy, has been shown to be effective in shrinking implanted prostatic tumors in rats. Work on these three techniques was supported by the National Cancer Institute, Bethesda, MD.

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II. Microwave Urethroplasty

The goal of microwave urethroplasty is to enlarge the lumen of the urethra at the site of a narrowing produced by an enlarged prostate gland (i.e., BPH). The procedure consists of heating the prostate via the urethra with microwave power and simultaneously dilating the part of the urethra that surrounds the prostate with an expansion balloon [1], [2]. The catheter that is used to perform this procedure is referred to as a transurethral microwave balloon catheter. Fig. 1 is a schematic drawing of such a catheter. The catheter consists of a plastic tubing with a lumen for inserting a miniature coaxial cable that is terminated by a microwave antenna and lumens for inflating a compression balloon with circulating cooled deionized water. Heating is with 915-MHz microwaves that are fed into the coaxial cable and broadcast into the prostate gland by the microwave antenna. An anchoring balloon is usually added to keep the catheter securely in place during the procedure.

A. In Vitro Vessel Dilation Experiment

We performed a series of *in vitro* experiments using excised bovine veins to study the effectiveness of simultaneous balloon dilation and microwave heating. An uninflated 36 French (12-mm-diameter) balloon catheter with a coaxial gap antenna in the central lumen was pushed through a length of excised bovine vessel such that the vessel extended over the full balloon length. A miniature thermocouple and a fiber-optic temperature probe were fastened to the outer surface of the balloon. The balloon was fully inflated, and the assembly was placed in a saline bath that was heated to 37 °C to simulate normal body temperature. Microwave power was then applied to the input to the antenna until the local temperatures as measured by the thermocouple and the fiber-optic probe rose by about 10 °C, which took about 150 s. This microwave heating caused only negligible increases in the temperature of the saline bath.

The combined heating and dilation resulted in increases in the diameters of the vessel that ranged from 27% to 34%. Additional tests showed that the balloon pressure caused the larger portion of the increase, but the addition of microwave heating contributed significantly to the observed increases in diameters. Fig. 2 shows the before and after photographs of one of the test samples.

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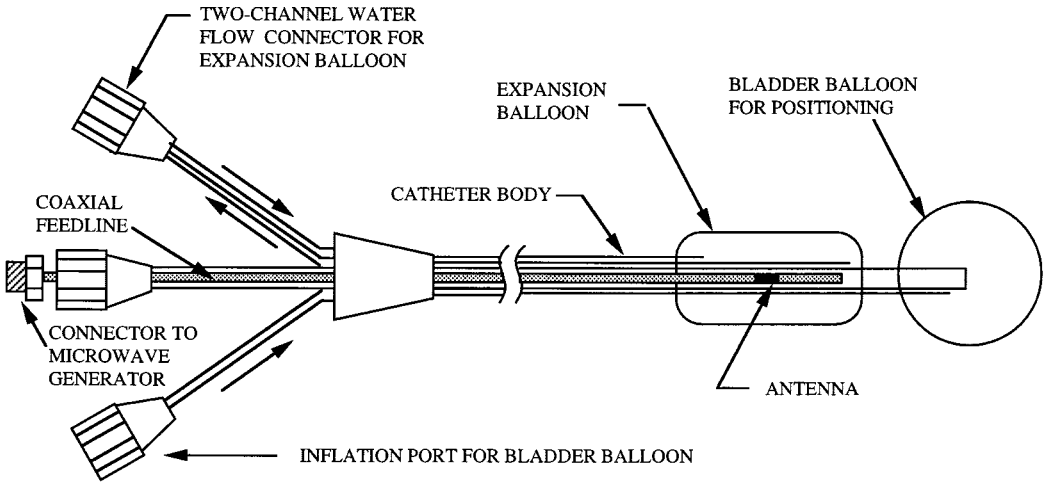
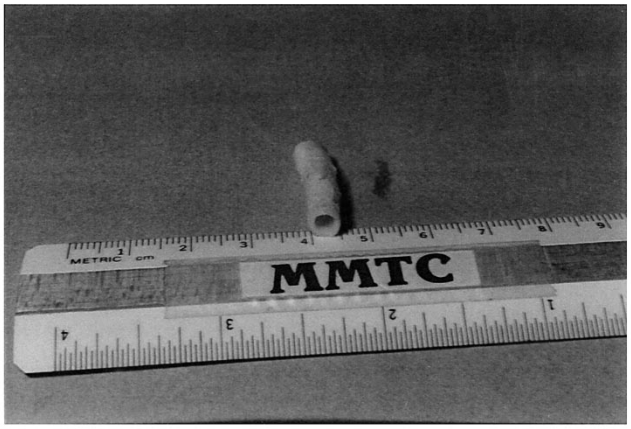
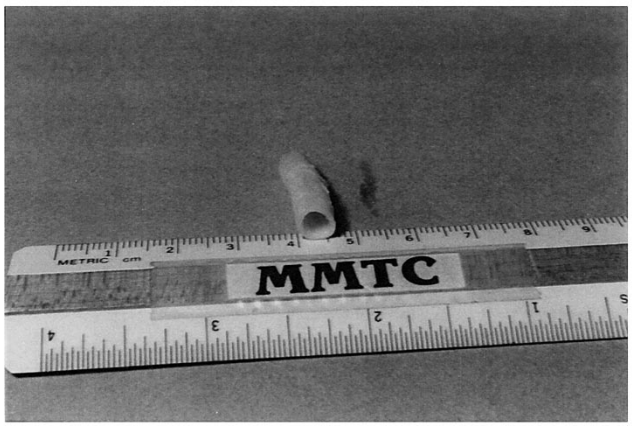


Fig. 1. Schematic diagram of transurethral microwave balloon catheter.



(a)



(b)

Fig. 2. Excised bovine vein: (a) before and (b) after exposure to dilation and microwave heating.

B. In Vivo Dog Dilation Experiments

Dilation experiments using approved protocols were performed on several anesthetized dogs. Fig. 3 is a typical plot of the temperature profiles measured during microwave urethroplasty. Note that temperature of the rectum, which can be seriously damaged by overheating, remained at safe levels during the entire treatment. In one experiment, a thermocouple was positioned near the external sphincter. This temperature also remained at safe levels, which is of critical importance because damage to the sphincter can lead to permanent incontinence.

The increase in the size of the lumen of the prostatic urethra after microwave urethroplasty was demonstrated by removing and dissecting the prostate from a euthanized dog after the procedure. Fig. 4 is a photograph of the cross section of the prostate of this dog after a single microwave urethroplasty treatment. The figure clearly shows a significant dilation, which can be considered as the production of a biological stent.

C. Clinical Trials

In a Phase-I clinical trial approved by the Federal Drug Administration (FDA), Rockville, MD, and funded by the Celsion Corporation, Columbia, MD, 20 patients were treated with microwave urethroplasty. With the patient recumbent on an examining table, a 20 French (6.7-mm-diameter) microwave balloon catheter was inserted without anesthesia into the urethra. A thermocouple was placed in the rectum to monitor the temperature of the rectal wall. Heating was for 45–60 min using about 45 W of 915 MHz. The treatments were very well tolerated. Patients who presented with obstructive urinary symptoms were usually able to urinate freely after one treatment. Based on these results, the FDA recently gave approval for Phase II clinical trials.

III. Hyperthermia Treatment of Localized Prostate Cancer

For localized prostate cancer, radical surgery and radiation are the only potentially curative therapies currently available. A significant fraction of prostate cancer patients are not candidates for surgery for a variety of reasons, ranging from poor surgical risks to refusal of surgery, and these patients are, therefore, candidates for radiation therapy. Local control of cancers treated with radiation therapy range from 83% to 95% over a five-year period (These rates are for stages A2 and B, which are cancers that are believed to be confined to the prostate gland. For an

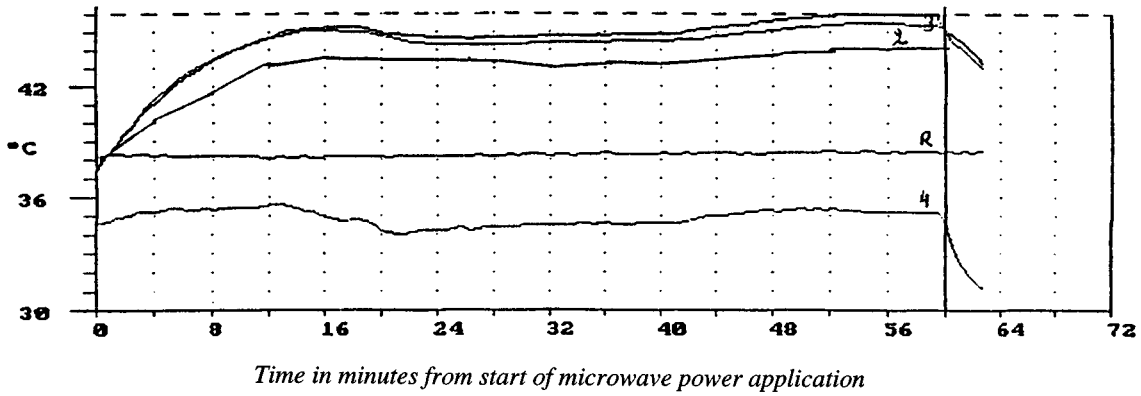


Fig. 3. Typical plot of temperature versus time from thermocouples mounted at various locations in the prostate and rectum of an anesthetized dog during microwave urethroplasty. Thermocouples 1– 3 were inserted into the prostate, thermocouple 4 was adjacent to the cooled urethra, and thermocouple R was in the rectum.

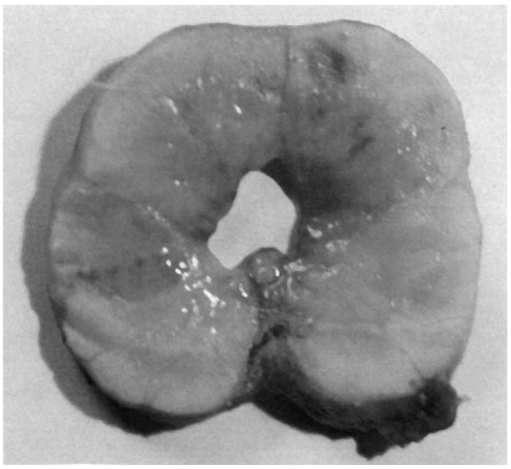


Fig. 4. Cross section of the prostate of a dog after a single microwave urethroplasty treatment showing dilation (production of a biological stent).

exact definition of these stages, see [3].) The addition of hyperthermia to the radiation treatment has the potential of improving the local control rates achieved with radiation treatments alone.

In hyperthermia treatments of cancer, malignant tissues are heated and maintained at elevated temperatures for a certain length of time. Hyperthermia treatments are usually combined with either chemotherapy or radiation treatments or, in some instances, with both treatment modalities. Numerous animal and clinical studies have demonstrated that combined radiation/hyperthermia treatments provide local control of cancer superior to that of radiation treatments alone, provided that the temperatures of all malignant tissues are raised to sufficiently high temperatures and maintained at these temperatures for sufficiently long durations [4], [5]. The safe implementation of these two seemingly simple requirements is, in practice, often very difficult because there are only narrow ranges of temperature duration that produce good therapeutic effects in malignant tissues without damaging healthy tissues. If the temperature-duration ranges of the hyperthermia treatments are too high, all exposed tissues, whether malignant or healthy, are permanently damaged. If, on the other hand, the temperature-duration ranges of the treatment are too low, both malignant as well as healthy tissues are spared. The optimum values for temperature duration for hyperthermia treatments have never been accurately established, but often used values are approximately 43 °C for about 45 min.

Studies of the response of spontaneous animal tumors to combined radiation/hyperthermia treatments (thermoradiotherapy) have shown that the response rate of these tumors depends strongly on the minimum temperature reached in any part of the tumor during the therapy: the higher the minimum temperature, the better the response rate. High minimum tumor temperatures can only be safely maintained if the tumor temperatures during the hyperthermia treatments are nearly uniform. If the tumor temperatures are highly nonuniform, it becomes impossible to reach high minimum tumor temperatures without causing unacceptable burning of the hotter part of the tumor or of the healthy tissues surrounding it.

The first clinical hyperthermia equipment for treating localized prostate cancer was developed about 20 years ago by a physician/technical team that included three of this paper's authors (i.e., Friedenthal, Mendecki, and Sterzer). In this early work, hyperthermia was produced in the part of the prostate closest to the rectum by means of coaxial rectal applicators, and the local hyperthermia was combined with external beam irradiation. The anecdotal results obtained were encouraging. Similar encouraging results were obtained with regional hyperthermia using large waveguide applicators [6]–[8].

Recent results obtained by a group from Duke University, Durham, NC, using combined external beam irradiation and external regional hyperthermia to treat locally advanced prostate cancer are also encouraging [9]. To quote from the conclusion of this study: "In spite of the inability to achieve high tumor temperatures, the relapse-free survival rate in this population of patients with very advanced localized prostate cancer treated with radiation therapy plus hyperthermia compares favorably with most series using radiation therapy alone. Further studies aimed at improving the ability to deliver hyperthermia to the prostate are warranted."

A. Generation of Hyperthermic Temperatures in the Prostate with Microwave Balloon Catheters

In the approach we are currently exploring, the prostate is heated by means of two cooperating microwave balloon

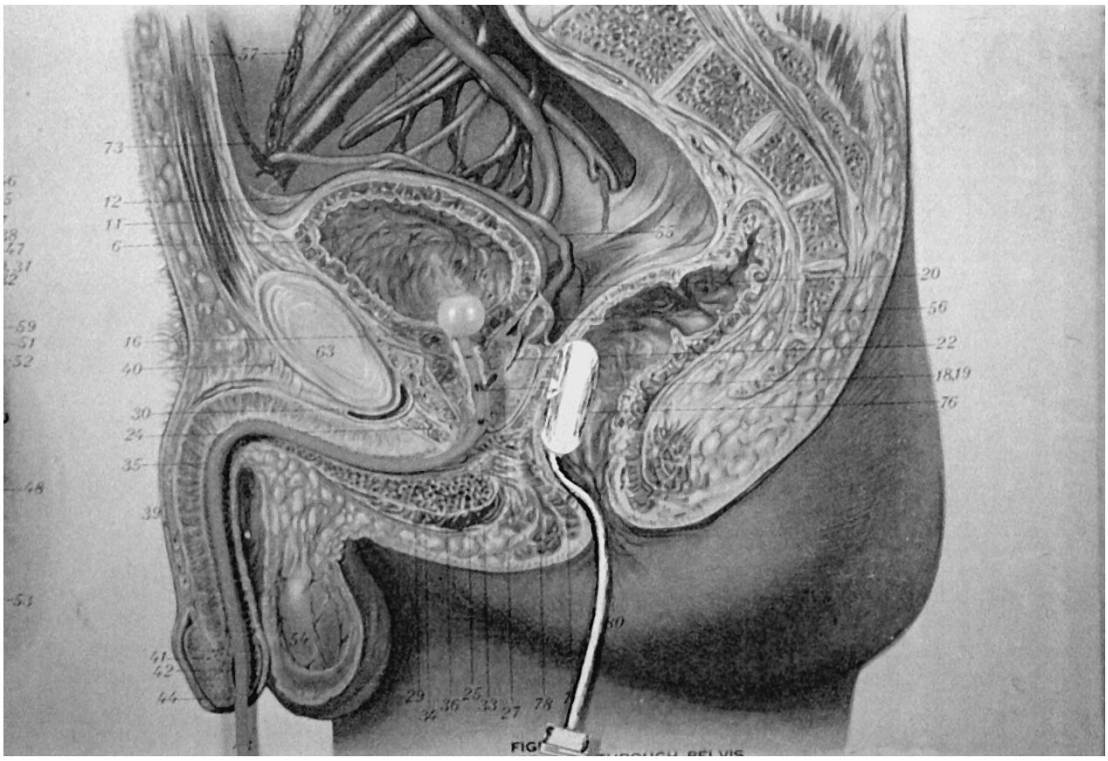


Fig. 5. Illustration of the method for uniformly heating prostate glands with cooperating transurethral and transrectal microwave balloon catheters. The antenna of the transrectal catheter is directional, broadcasting most of its energy in the direction of the prostate.

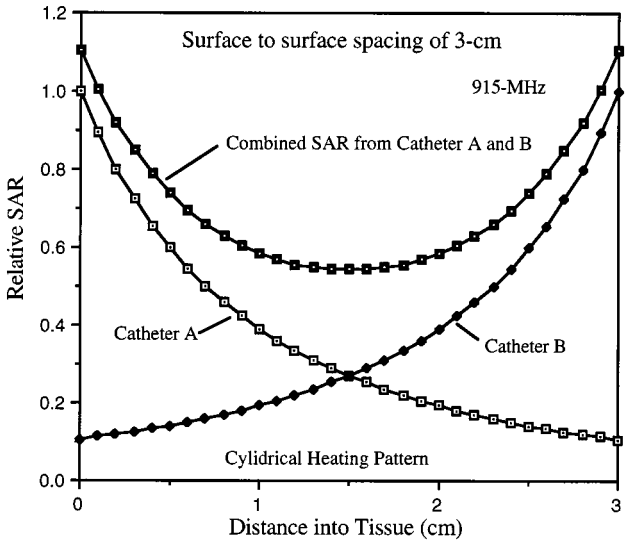


Fig. 6. Calculated SARs for two microwave balloon catheters facing each other.

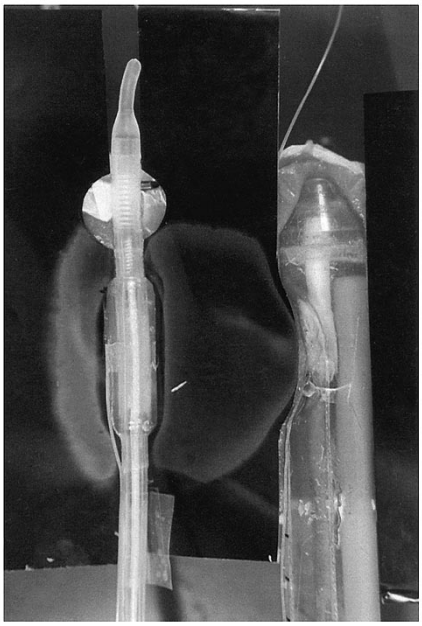


Fig. 7. Heating patterns in tissue-equivalent phantom with two applicators placed 4.5 cm apart.

catheters—one catheter with its balloon located in the prostatic urethra and the other with its balloon in the rectum opposite the prostate gland [2]. This approach, which is illustrated in Fig. 5, was chosen because prostatic tumors develop primarily within the posterior lobe located between the rectum and urethra. The amount of microwave power deposited by each individual catheter decreases with distance from the surface of their respective balloons. However, calculations show that the combined specific absorption rate (SAR) of the two balloon catheters facing each other tends to be much more nearly uniform (see Fig. 6).

The concepts illustrated by Figs. 5 and 6 were tested in tissue equivalent phantoms. The microwave power from a 915-MHz generator was timeshared between a transurethral and transrectal applicator. The measured heating pattern when

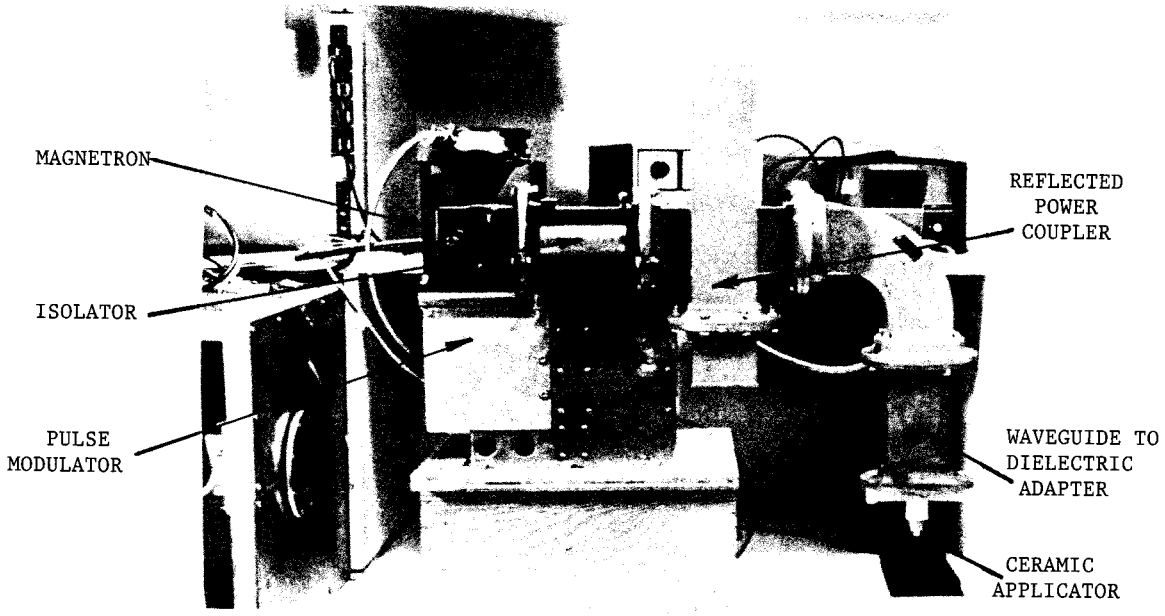


Fig. 8. Experimental setup. The power generated by a magnetron oscillator passes through a waveguide to a ceramic applicator that serves to concentrate the microwave power into tissues.

the two applicators were placed 4.5 cm apart is shown in Fig. 7. Note the overlap of the heating patterns produced by the individual applicators. On the basis of these encouraging results, we plan to proceed to testing the dual microwave balloon catheter concept in an animal model.

IV. Microwave Poration Therapy

The success of chemotherapy in treating malignant tumors depends on the ability of drugs to access and accumulate in sufficient quantity in the cells of the tumors. In many cases, the natural resistance of the malignant cell membranes to penetration by foreign molecules prevents the necessary access, and the ability of malignant cells to pump out foreign molecules limits the accumulation of those that did manage to penetrate into the cells.

The resistance of malignant cells to penetration by foreign molecules and their ability to pump out foreign molecules can be countered by creating temporary pores in the membranes of the malignant cells. While the cells are porated, large molecules including genes, large chemotherapeutic molecules, etc. can enter into the cells. Once the pores reseal themselves, these molecules are trapped inside the cells.

Cells can be temporarily porated with short dc pulses that generate electric fields of several kilovolts/centimeter [10]. Poration using dc pulsing combined with low-dose systemic chemotherapy or chemotherapy directly injected into tumors, a procedure referred to as electrochemotherapy, is now clinically in use to treat a variety of cutaneous tumors, including head and neck tumors, melanomas, superficial breast cancer lesions, etc. [11]–[13]. To generate the required electric fields in the tumors, electrodes are placed across the tumors that are being treated. Electrodes for treating small cutaneous tumors can be placed on the skins of the patients. Treatment of large cutaneous lesions or deep-seated tumors requires invasive needle-type arrays.

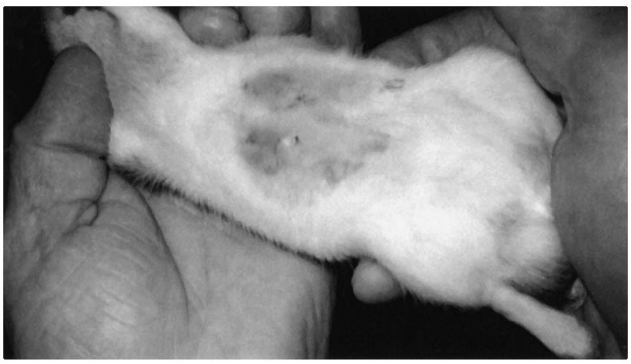


Fig. 9. Rat with four implanted tumors five days after microwave poration and systemic injection of Taxol.

A. Poration Using Microwaves

We have demonstrated in an animal model that high-power microwave pulses, just like multikilovolt/centimeter dc pulses, can enhance the uptake of large chemotherapeutic molecules by malignant tumors, and can thereby enhance the anticancer activity of chemotherapy [14]. The animal model we used in our experiments were Copenhagen rats with transplanted AT2 prostatic tumors. The tumor model was obtained from the Johns Hopkins Medical Center, Baltimore, MD.

The high-power microwave pulses were generated using a pulsed magnetron oscillator that was lent to us by the Army Research Laboratory, Adelphi, MD. The electrical characteristics of magnetron oscillator were as follows:

frequency	2.82 GHz;
peak power	166 kW;
pulsewidth	0.25 μs;
duty cycle	0.0005%.

Fig. 8 shows a photograph of the experimental setup.

In the experiments, a thermocouple was inserted into the tumor that was exposed to pulsing. The average power from the magnetron was adjusted to keep tumor temperatures below 39 °C. The rats were injected with fluorescin isothiocyanate Dextran molecular weight 10 000 and the tumors were exposed for 30 min to microwave pulsing. There was almost no uptake of Dextran by tumors that were not pulsed. On the other hand, there was significant uptake of Dextran by tumors pulsed with microwaves.

There was *no* significant uptake of Dextran by pulsed healthy muscle tissues of rats. This may be because the membranes of malignant cells are weaker than those of healthy cells [15]. Also, microwave pulses tend to generate higher local electric fields in the membranes of malignant cells than in those of healthy cells. This is because malignant cells tend to have more irregular shapes with sharp protrusions than do normal cells. This causes local field enhancement, a phenomenon well known to microwave tube engineers [16].

Fig. 9 shows a rat with four implanted tumors five days after microwave poration and systemic injection of Taxol. The head-end nonpulsed tumors increased in size, while the two tail-end tumors have shrunk and are barely palpable. In an ongoing program sponsored by the National Cancer Institute, Bethesda, MD, we plan to optimize treatment protocols in rats with implanted prostate tumors using both systemic and intratumor chemotherapy, and investigate immunological responses of distant metastases.

V. Conclusion

The three new microwave modalities that have been described in this paper have the potential to make significant contributions to the treatment of diseases of the prostate. Microwave urethroplasty, unlike transurethral thermal ablation, shows promise of providing patients with immediate symptomatic relief from urinary obstructions without the need for temporary indwelling urinary catheters. Heating of prostate tumors with multiple balloon catheters shows promise of being able to achieve the nearly uniform hyperthermic temperatures required for optimum local control with radiation/hyperthermic therapy. Microwave poration therapy, the most immature of the three modalities, shows promise of being effective against prostate cancer when combined with chemotherapeutic agents that by themselves show little activity against prostate cancer. The difference in uptake of chemotherapeutic agents between normal and malignant cells due to microwave pulsing is intriguing because it might be possible to exploit this effect to lessen the harm to normal cells by chemotherapy.

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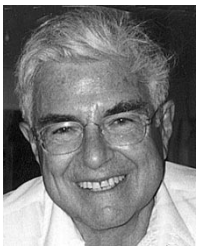

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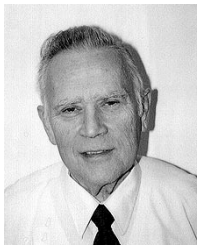

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He served in the U.S. Army with assignments at the Signal Corps Engineering Laboratories and the Naval Research Laboratory prior to earning his degrees. He has worked on numerous microwave component and system projects at RCA, Harrison, NJ, including development of low-noise amplifiers for aircraft weather radars and modules for the Lunar Module landing radar. In 1975, he was transferred to the David Sarnoff Research Laboratory, Princeton, NJ, where he continued to work on microwave subsystems for commercial and military applications. Since 1988, he has been a Member of the Technical Staff at MMTC Inc., Princeton, NY, where he has been engaged in research and development of industrial and medical microwave sensors and other microwave subsystems. He has authored or co-authored several technical papers on subjects involving microwave subsystems and applications. He holds 28 U.S. patents.

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