Techniques for Uniform and Replicable Microwave Hyperthermia of a Model Mouse Carcinoma

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Abstract—**Two techniques for localized 2450-MHz hyperthermia of experimental mouse cancers are described. In the far-field approach, superficial tumors are encapsulated in 5-cm mold-formed spheres of semi-solid phantom material, then placed in an anechoic chamber on an equipower surface. In the applicator approach, tissues are immersed in a temperature-controlled tissue-equivalent liquid bolus, and are irradiated by time-multiplexed parallel-opposed beams. Both techniques feature microwave bolusing for improved coupling and tumor heating uniformity.**

I. Introduction

IT HAS BEEN KNOWN for centuries that heat may be used therapeutically in treating cancer [1]. However, careful scientific documentation of hyperthermia as a treatment modality has a much shorter history, and the subject is being pursued actively today [2]. It is known that exposure of malignant cells to temperatures between 42 and 45°C may retard or totally inhibit their growth [3]. In combination with ionizing radiation [4], or chemotherapeutic agents [5], hyperthermia will act as a cell sensitizer, synergistically reducing dosage requirements to effect a particular response to treatment.

The production and control of thermal fields is one of the problems which must be solved before hyperthermal patient treatment regimens can be placed on a sound scientific basis. In addressing this problem, we have been involved in a preclinical research program to develop heating methods for studies with laboratory animals, our ultimate objective being to treat human cancer patients. We have appreciable treatment data for superficial normal and tumor tissues in the mouse. These tissues could be heated locally by immersion in a temperature-controlled water bath. Local treatment of deeper lying tissues, however, requires the development of alternative heating approaches.

Microwaves are a logical choice for heating of these deeper tissues, since energy may be deposited at depth, and since treatment may be localized when appropriate microwave applicators or whole-body shielding techniques are employed. In our laboratories, two techniques of microwave heating have been developed: an applicator technique and a free-field technique. In both programs, our immediate objective has been the treatment of a superficial 1-cm model tumor implanted on the flank of the C3H mouse. The following criteria were to be met. At treatment temperatures between 42 and 45°C, hyperthermia was to be administered locally to the tumor, with the rest of the mouse protected from whole-body irradiation. Within the treatment volume, heating was to be uniform to within 0.25°C overall, and temperatures were to be held constant for intervals of up to one hour. The times required to reach treatment temperature, and to cool down subsequently, were to be short compared with the treatment interval. Tumor heating was to be replicable for the variety of tumor configurations which occur within the experimental populations. Due to edema, some tumors increase in size during treatment. Heating was to be unaffected by these edematous changes.

II. Free-Field Heating

An enclosed and fully shielded microwave heating chamber ($8 \times 8 \times 10$ ft) has been constructed for the free-field microwave experiments. It is fully lined with an anechoic absorbing material (Eccosorb VHP-12), reducing reflections in the quiet zone by -45 dB at 2450 MHz. Infrared lamps located in the ceiling are used to preheat the chamber and to maintain a baseline temperature during treatment. The lamps are operated under feedback temperature control. A 3 kW 2450-MHz PM microwave source (Gerling–Moore #4003) is waveguide fed to a standard-gain horn located in the chamber ceiling. Preparations to be heated are supported down range by a styrofoam platform above the chamber floor (Fig. 1). To avoid artifact, temperatures are measured with the source off, by the insertion of a hypodermic-type thermistor probe (YSI #514). The probe is supported in an all-plastic manipulator assembly, and is oriented orthogonally to the far-field TEM plane. During irradiation, it is retracted into the shadow region below the tumor. In order to establish the treatment protocol, tumor temperatures are sampled periodically to establish and maintain steady-state heating, and are extrapolated from post-ir-

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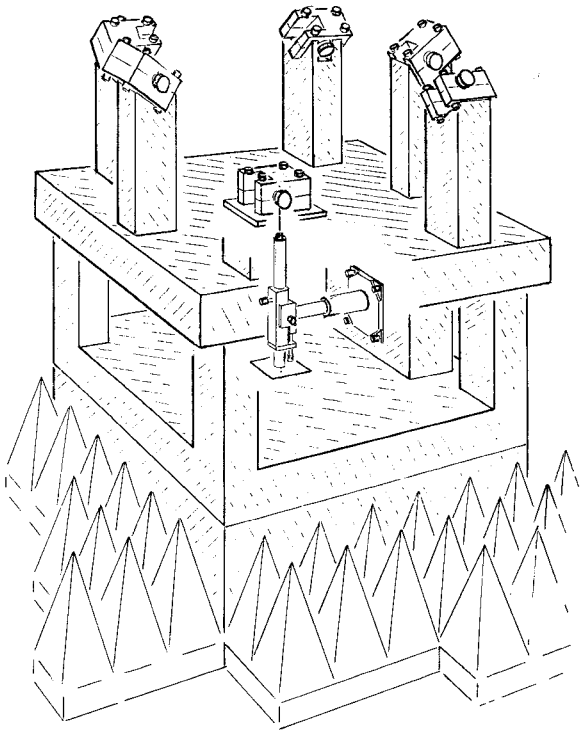

Fig. 1. Free-field mass-irradiation assembly for heating six mice simultaneously at 2450 MHz. The illustration is cut away to show the all-plastic probe drive below the styrofoam platform. Styrofoam columns are used to place mold assemblies containing the experimental tumors on a far-field equipower surface.

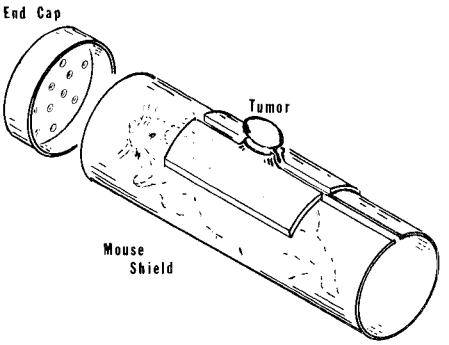

Fig. 2. Aluminum sleeve used to shield the mouse from whole-body free-field irradiation. The tumor is pulled away from the mouse flank, with mouse connecting tissue drawn through a longitudinal slot. It is then placed on styrofoam spacers to extend it away from the sleeve surface.

radiation temperature recordings on a strip chart. In addition, an equivalent volume of tissue-equivalent phantom material is continuously monitored during treatment. The extrapolation technique is most successful with larger volumes of heated tissues and tissue-like materials. In this case, cooling rates are slow with respect to probing times.

Shielding is accomplished by placing the unanaesthetized mouse within a cylindrical metal sleeve, with perforated end caps (Fig. 2). The flank tumor is drawn away from the body, with the intervening tissue bridge pulled through a longitudinal slot on the sleeve's surface. The tumor is slid to the midpoint of the cylinder, where it is taped in place. A metallic tape is used above the open sleeve aperture. In later experiments, a 6-mm spacer of dense styrofoam has been used to extend the tumor outward from the shield surface into the heating field.

At first, bare 1-cm tumors were placed on the microwave free-field axis [6]. Since coupling was poor, high source power was needed to heat these tumors from room temperature (25°C) to the hyperthermal region above 40°C, even though they were placed in the near field. Tumors heated up slowly and exhibited excessive temperature nonuniformity in the hyperthermal steady-state ($\pm 1°$ at 40°C). Uniformity was only marginally improved ($\pm 0.5°$ at 40°C) when the ambient temperature was increased from 25 to 32°C.

More recently [7], 1-cm tumors have been encapsulated within a 5-cm spherical mass of tissue-equivalent phantom material, such as that developed by Guy [8]. The tumor is imbedded in the material at a central region where energy deposition is peaked and where temperature gradients are minimum [9]. This procedure markedly improves steady-state tumor temperature uniformity ($\pm 0.1°$ at 44°C) as shown in Figs. 3 and 4, in which plots of temperature versus probe position are illustrated. In Fig. 3, the probe traverse is upward through the center of the tumor from the shadow region below the mold, and is along the axis of the field. In Fig. 4, the mold has been turned on its side after heating, and the probe traverse is parallel to the electric vector. At 2450 MHz, the larger diameter of the tumor phantom complex improves coupling to the extent that the far field may be used for heating, with the encapsulated tumors approximately 2 m from the antenna. Heat up to the treatment temperature now takes place at the rate of nearly 1°C per minute when heated at a source power of 1.8 kW. Thereafter, hyperthermal treatment may be sustained with much lower source power. Since heating in the tumor is governed by the larger encapsulation geometry, it is nearly independent of the initial shape or subsequent edema in 1-cm tumors. This use of tissue-equivalent phantom material is analogous to a method of tissue "bolusing" widely used by radiation therapists, from whom we have adopted the term "microwave bolus" for the encapsulation technique.

It was evident that microwave bolusing might be used to treat multiple animals simultaneously. Two requirements would have to be met: a means to standardize bolus shape and the tumor encapsulation site within molds of low-loss material, and an appropriate surface of far-field equipower density. The equipower surface area would have to be large enough so that animals could be placed where interactions between their shields would be small. Accordingly, isotropic field probes have been used to map surfaces intercepting the field axis at 200 and 215 cm. If animal spacing is 25 cm ($2\lambda_0$), up to 13 mice may be accommodated within a 1-m^2 region on this surface, with acceptably small interactions [10]. However, only six animals are being heated simultaneously at the present time. The animals are located on the heating surface via styrofoam columns extending from the support platform

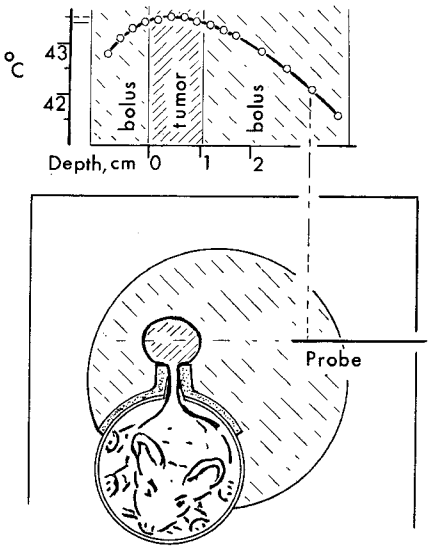

Fig. 3. Temperature profile through the center of a 1-cm tumor, shown above the cross-sectional diagram of the bolused tumor. Incident free-field microwaves propagate from the left, parallel to the probing axis. An outline of the surrounding mold assembly is also shown.

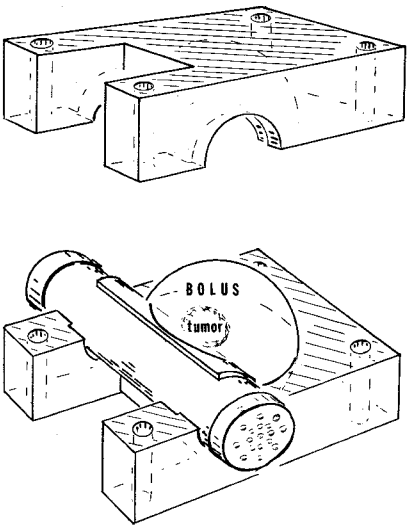

Fig. 5. Two-piece styrofoam mold assembly used to replicate free-field bolus geometry and tumor placement. The assembly has been separated to expose the mouse shield and adjacent bolus. Upon assembly, mold halves are secured together with four nylon screws inserted through the alignment holes in each mold section.

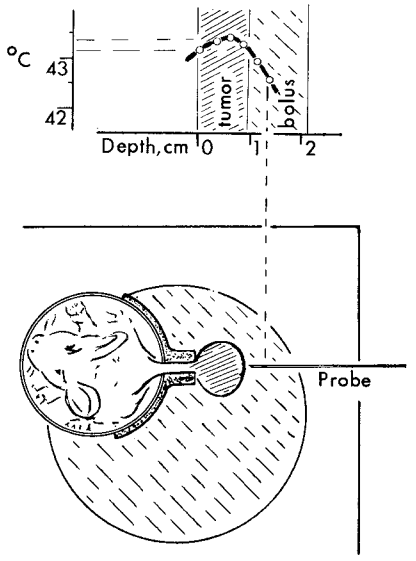

Fig. 4. Temperature profile through the tumor of Fig. 3, perpendicular to the direction of incident microwaves.

(Fig. 1). Mouse shields are oriented normal to the electric vector. The center mold contains no tumor, but is instrumental with a thermistor probe to monitor heating at the tumor encapsulation site.

A mold technique based on the method of Guy [8] is used to replicate bolus shape and tumor placement (Fig. 5). Molds from dense styrofoam are machined to form the 5-cm bolus sphere, and to clamp the shielded mouse such that tumor is located in the bolus peaking region. A thin film polyethylene sheet (Saran Wrap), is interposed between the bolus material and the mold surfaces. This prevents impregnation of the porous mold material as well as reducing moisture loss. So treated, bolus material does not dry out even if given prolonged heat exposure (2 hours at 45°C). The molds are then assembled together with nylon screws. After assembly of the molds, the animals are placed in the range for treatment.

As currently developed, the free-field microwave technique may be used to administer local hyperthermia to a model 1-cm tumor system situated on the mouse flank. Encapsulation within a tissue-equivalent bolus yields excellent temperature uniformity within the tumor and a stable coupling geometry which may be replicated for batch treatment of tumors in the far field.

III. Applicator Heating

A small animal hyperthermia treatment system using parallel-opposed microwave applicators has been in use since 1976. Operating at 2450 MHz, it employs simulated TEM waveguide applicators, time multiplexed so that tumor heating occurs from two opposite sides [11]. The tumor of an unanaesthetized mouse is encapsulated in bolus material (either liquid or solid) located between opposed beams. In Fig. 6, the block diagram shows the dual beam tumor treatment system for a temperature-controlled liquid bolus.

The energy deposition profile of Fig. 7 indicates that heating uniformity in bolus is improved with two opposed beams and that energy deposition at depth increases with the number of multiple opposed beams. With the two-beam system, hypodermic-type thermistor (YSI-500 series) probe scans indicate thermal nonuniformity of less than 0.1°C in a 1-cm bolus region orthogonal to the electric field and parallel to the top bolus surface.

However, overall heating uniformity within a bolused 1-cm tumor is very dependent on the type of bolus material employed. We have found that with semi-solid Guy-type muscle phantom [8], tumor heating nonuniformities are large. There are unavoidable temperature

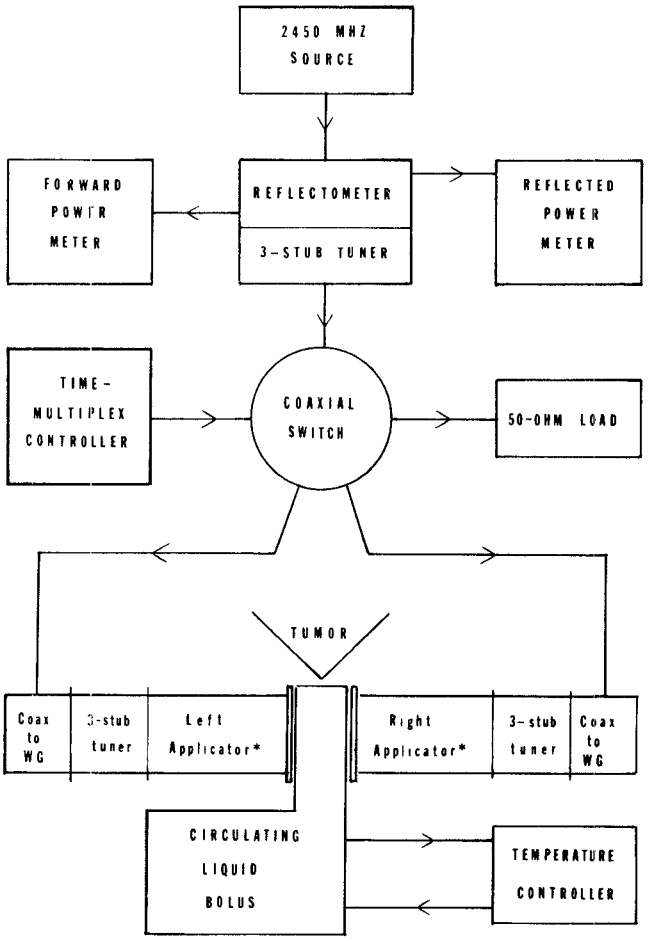

Fig. 6. Block diagram of the dual-beam tumor treatment system.

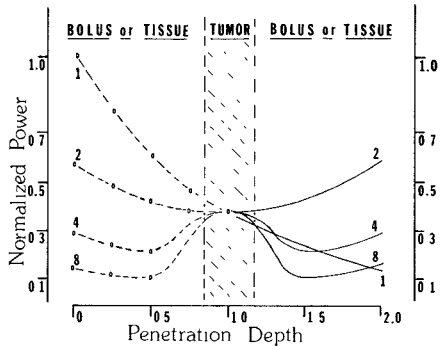

Fig. 7. Energy deposition profile for one applicator beam, and profiles for two, four, and eight coplanar, symmetrically opposed beams. Penetration depth is expressed as the distance into the material normalized by the skin depth, and is frequency independent.

gradients from surface to interior in this material. In a stirred liquid bolus, these gradients can be made trivially small. The liquid also improves thermal coupling between bolus and tumor. We are currently using a solution constituted from 80-percent (w/w) isotonic saline and 20-percent (w/w) ethanol. Electric properties of this solution closely approximate those of wet tissues at 2450 MHz. Even when unstirred, substitution of the liquid bolus has resulted in substantially improved tumor heating uniformity and a significant reduction in thermal inertia, as shown in Table I. Faster liquid heatup may be due to the realization of a more favorable bolus coupling geometry rather than to calorimetric properties of the solution, although the liquid phase promotes convective heat tranfer between tissue and phantom. With its inherent ability to be well stirred and temperature regulated outside the microwave field, we have obtained excellent heating results on flank tumors immersed in the solution.

TABLE I
TUMOR HEATING CHARACTERISTICS OF SOLID AND LIQUID BOLUS MATERIALS (PARALLEL OPPOSED APPLICATORS)

	SOLID	BOLUS
TYPICAL HEATING RATE[1]	1.1°C/min	3.5°C/min
HEATING NON-UNIFORMITY OF TUMORS[2]	0.33±0.05 °C	0.15±0.07 °C

[1]Average over the time required to heat 1-cm tumors from 37.5 to 43.0°C.
[2]Mean of temperature range for six tumors.

The 2450-MHz applicator and free-field tumor treatment systems described in this paper are currently in use in a long-term study to evaluate microwave hyperthermia as a cancer therapy modality.

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