RESPONSE OF A MODEL MOUSE CANCER TO FREE-FIELD MICROWAVE HYPERTHERMIA

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ABSTRACT

274 mouse tumors, in batches of up to seven mice, were given free-field hyperthermal treatment at 2450 MHz. Regrowth studies show greater thermal sensitivity than with water bath heating, suggesting temperature heterogenities, microwave effects, or physiological factors.

I. INTRODUCTION

A program for free-field microwave heating is being developed in our laboratories for hyperthermal treatment of a model mouse carcinoma. The far-field approach was chosen for study because it offers the possibility of simultaneous treatment of multiple tumors when placed on an equipower surface in the far field of an antenna . Technical objectives included devising a means for heating the tumors uniformly (within 0.2°C overall), limiting treatment to the tumor region, and shielding the mouse from local heating fields.

The model tumor system is a third-generation mammary carcinoma, transplanted on the mouse flank.[6] and is treated at a volume slightly less than 0.5 cm^3. During treatment, the tumor is drawn through a slot in a cylindrical aluminum mouse shield, exposing the tumor while protecting the animal.[4] The tumor is held away from the protective sleeve by polystyrene spacers. As shown in Figure 1, a 5 cm sphere of tissue-simulating phantom material is used as a "microwave bolus". The bolus improves tumor coupling to local heating fields and distributes temperature gradients over the larger bolus volume (reducing local gradients within the tumor).[1]

Tumor placement within bolus, replication of bolus geometry, and positioning in the heating field are facilitated by using molds of dense polystyrene, shown in Figure 1.

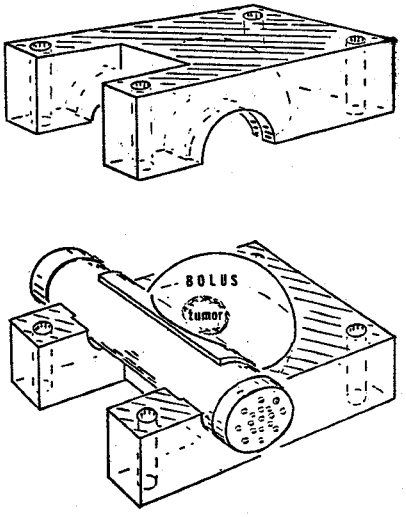

Figure 1. Sleeve, bolus, and mold assembly.

Previous temperature probings of the bolused tumors had indicated "front-to-back" temperature differences not exceeding 0.2°C overall.[5] However, we recognized the limited spatial resolution of the hypodermic thermistor probes that were used and the impossibility of achieving a complete thermal mapping of the tumor without producing unacceptable trauma. Accordingly, we concluded that the actual heating experience of malignant cells within the tumor would best be elucidated by a regrowth tumor study.[6] The strategy was to compare regrowth data from tumors heated in the free-field with those from the same tumor system heated in water baths. Our previous studies had shown that water bath immersion produced highly uniform tumor temperatures.[3] Discrepancy in regrowth following nominally similar treatments (time and temperature) would indicate possible temperature discrepancies or different microwave heating bioeffects.

II. METHODS

A microwave chamber, anechoically treated for 2450 MHz, was constructed for the study.[5] An equipower surface was mapped with an isotropic electric field probe, intercepting the central field axis 200 cm below a standard-gain ceiling-mounted antenna. 2450 MHz microwave heating was provided by a waveguide feed from a high-power source. Six molds containing tumors were placed concentric to the field axis for simultaneous heating, as shown in Figure 2, with a seventh animal on axis. Molds were spaced at least 25 cm apart to reduce field interactions.[2] Mold assembly positions were further refined experimentally by temperature measurements in bolus since interactions between irradiation fixtures, including protective sleeves and molds, could affect heating at each candidate mold position. The on-axis mold was monitored during heating at the steady state. The source was then shut off and the temperature of each off-axis mold assembly was measured. Care was taken to ensure that the probe measurement position was replicated. The plastic thermistor probe drive is shown in Figure 2.

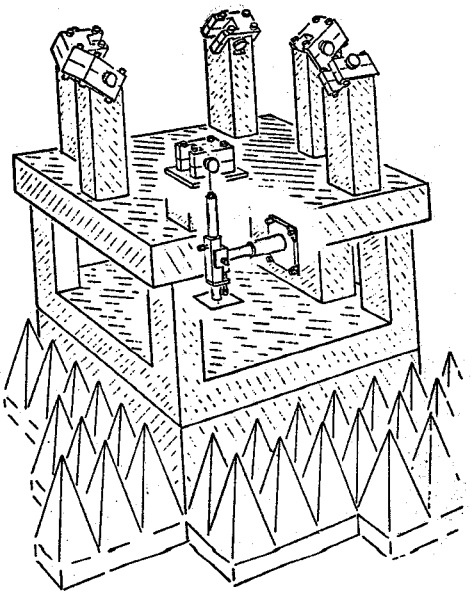

Figure 2. Free-field irradiation assembly.

Even with this approach, we were unable to determine off-axis positions and assembly orientations which would exactly replicate on-axis heating. It became clear that the heating experience of each mold was a function not only of its initial temperature, but also of its heatup rate, and of any additional excess gain or loss of heat in the presumed steady state as a result of free-field range position and local field interactions. Although range ambient temperature, and consequent initial bolus temperature were controlled to within 0.2°C prior to treatment, temperature variations between 0.5 and 1.0°C were observed off axis when the central assembly reached target temperature. Temperatures were most nearly uniform when the cylindrical mouse shields were aligned perpendicularly to the far-field electric vector and staggered for minimum end-to-end interaction. When power was adjusted to maintain constant temperature of the central assembly, the off-axis assemblies might increase or decrease as much as 0.5°C during treatment.

To characterize the temperature experience of tumors exposed to the microwave field in each of the range positions tumor temperature measurements were made at three different times: (1) immediately after the central assembly had reached target temperature; (2) at mid-treatment time; and (3) immediately after treatment. Cooling rates were slow (time constant greater than 60 minutes) with minimal cooling during source-off measurements. This facilitated graphic extrapolation of tumor temperature to values during microwave irradiation.

III. RESULTS

274 mouse tumors were treated in the study. Following treatment, the tumors were measured thrice weekly to determine the time post-irradiation to regrow to double the initial volume, defined as regrowth time. Tumors which did not regrow by 50 days post-treatment were classified as "cures", and were not included in regrowth results. In Figure 3, regrowth times in days are plotted as a function of hyperthermal treatment time in minutes. Tumors with temperatures between 40.75°C and 41.75°C were grouped and handled as a nominal 41.25°C data set; tumors with temperatures up to 45.75°C were grouped similarly (42.25--45.25°C). Sham-irradiated controls were treated at 37°C.

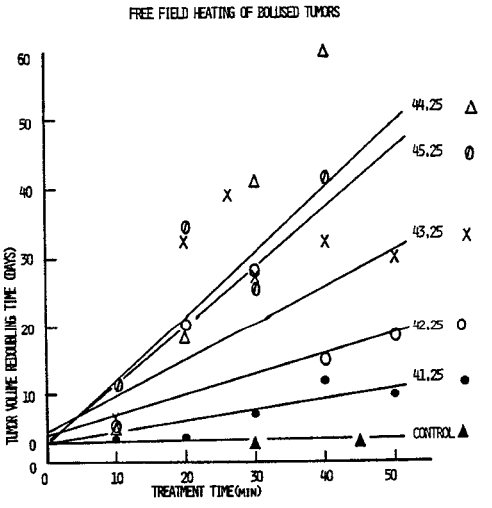

Figure 3. Effect of free-field microwave heating on tumor volume redoubling time.

Each data point represents the mean regrowth time for multiple animals (typically 6 or more), except for the two longest treatment times in the 45.25 degree group. However, the regrowth slopes were calculated by entering individual regrowth times, rather than grouped means. Regrowth response within the same treatment group varied considerably from tumor to tumor, as illustrated by the scatter of data points in the plot. Although the slopes of the other temperature groups are well-separated, there is no significant difference between slopes for 44.25 degree and 45.25 degree data sets.

Slopes calculated in this way have been used to characterize thermal sensitivity of this same tumor system with other modes of heating[6] Furthermore, plots of thermal sensitivity on a log scale vs treatment temperature are usually linear over at least a limited temperature range (a quasi Arrhenius plot). The free-field microwave data are shown in Figure 4. This figure also includes similar data from a previous study of the same tumor system, in which water-bath heating was used.[6] The response lines are best fit lines to both microwave and water bath data based on a common mean slope, but excluding the free-field 45.25 degree slope, which appeared inconsistent with the other free-field data. The two response lines are displaced by an amount equivalent to a temperature difference of 1.2°C, indicating either a greater thermal sensitivity of the microwave-heated tumors or an equivalent uncertainty in temperature characterization. Extrapolation of the water-bath response curve to 40°C (nominal threshold for thermal damage) yields tumor redoubling time of approximately three days at normal body temperatures near 38°C, consistent with that for non-irradiated controls. The response line for the microwave-irradiated tumors extrapolates to a regrowth value approximately double that for the controls.

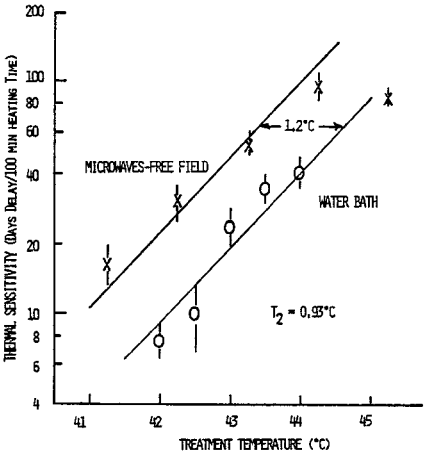

Figure 4. Comparative response of tumors to free-field microwave and water bath induced hyperthermia.

CONCLUSIONS

Our previous water-bath studies, in which heating was highly uniform, have shown that the tumor regrowth curves are approximately linear, as shown in Figure 3. Furthermore, as shown in Figure 4, extrapolation of the best-fit quasi-Arrhenius plot for the water bath data the threshold for thermal injury (40°C) predicts the growth rate of the untreated tumors.

The water bath data suggest that the malignant cell population evidently responds homogeneously to uniform non-specific heating. The discrepancy in the microwave-heated tumor response may be the result of one or more of the following factors: a) temperature heterogeniety within the free-field-heated tumor; b) differential biological response of the tumor system to microwave irradiation; or c) possible physiological effects of tumor encapsulation and/or support

during free-field irradiation.

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