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A 5.8 GHz OPHTHALMIC MICROWAVE APPLICATOR FOR TREATMENT OF CHOROIDAL MELANOMA

by

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Summary

We report on the use of a 5.8 GHz microwave applicator to treat choroidal melanoma (Greene) in rabbits. The physical requirements needed to treat these intraocular tumors are quite different from those encountered elsewhere in the body. From a trans-scleral approach the penetration needed is minimal (5-10 mm.). The fibrous sclera is the only structure between the heat source and the tumor. The sclera has a relatively low water content when compared to tumor. This fact in addition to the frequency dependent interactions of tissue and electromagnetic radiation, results in an advantage to the use of the 5.8 GHz microwave device in treating intraocular malignancies.

Introduction

Choroidal melanoma is the most common ocular malignancy in adults. The mortality rate associated with these tumors when they are larger than 200 cu. mm. is approximately 50% at 5 years.[1] A controversy exists as to whether enucleation (surgical removal of the eye) inhibits or promotes metastasis.[2,3] In certain clinical situations total removal of the eye is the treatment of choice, but in most cases it is possible to spare the affected eye while effectively treating the intraocular malignancy.

The goals of local treatment of choroidal melanoma are sterilization of tumor tissue, retention of the globe, and preservation of sight. With this in mind the ophthalmic community has recently accepted radiation therapy as an alternative to enucleation.

Low energy sources of ionizing radiation (i.e. iodine-125) have been shown to be the most effective form of radiation therapy of choroidal melanoma.[4,5] Iodine-125 seeds are placed in an array within a saucer-like gold scleral plaque. Metals with high atomic number, such as gold, effectively attenuate radiation. The plaque is sutured onto bare sclera over the base of the intraocular tumor. In this way a unidirectional radiation source most efficiently sterilizes tumor tissue, with sparing of normal ocular and extraocular structures.

Hyperthermia and radiation act synergistically in the treatment of neoplastic disease. In addition to its primary cytocidal effects, relatively small elevations in tumor temperature produce radiation sensitiziation of malignant tissues.[6-8] The radiation dose previously required to sterilize an intraocular tumor might be lower. Certainly the number of cancer cells killed would be increased thereby reducing the possibility of spread or recurrence. It is reasonable to expect that by adding hyperthermia current radiotherapy of choroidal melanoma would be significantly improved.

Hyperthermia has augmented chemotherapy in regional perfusion of cutaneous melanomas.[9] The use of local hyperthermia to increase the uptake of chemotherapeutic drugs, or the possibility of liberating such agents from heat sensitive liposomes is in the offing.[10,11]

Contact conduction and electromagnetic heat induction are best suited to plaque technique.[12,13] A simple etched element heater* that delivers heat by conduction was used to establish the thermal tolerance of scleral tissue in vivo. Adverse intraocular effects of episcleral application of contact heating led us to the conclusion that this method was not acceptable for treatment of intraocular tumors. All but one treatment regimen ($50^{\circ}C$ x 1 hr. x 1 day), which had questionable therapeutic potential, caused extensive damage to both the sclera and intraocular structures. Therefore, we felt a more efficient form of heating was required.

This report concerns the use of a 5.8 GHz ophthalmic microwave applicator to treat choroidal melanoma. Our studies involve the use of white New Zealand rabbits. Due to the inherent characteristics of high frequency electromagnetic heat induction, this microwave device is shown to elevate intraocular temperature to within therapeutic range without damage to sclera or other normal ocular structures.

Microwave Applicator

The microwave applicator, shown in Fig. 1, is constructed using a short length of UT-34** semi-rigid coaxial cable that is a shorted spiral transmission line printed on a bowl-shaped 5880 RT/Duroid*** substrate. The semi-rigid cable is 0.86 mm. in diameter, the Duroid substrate is 10 mm. in diameter, and the spiral transmission line is 6 mm. in diameter.

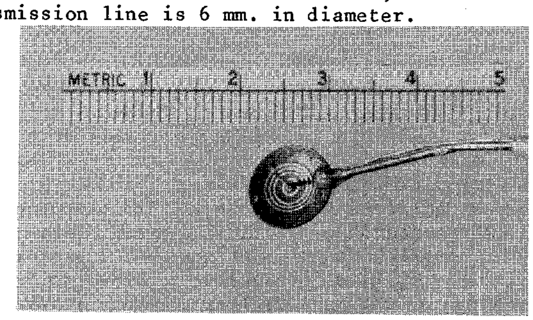

Fig. 1 5.8 GHz Ophthalmic Microwave Applicator
Three thermocouples in heat shrink tubing at 90° with the face of the plaque.

* Minco Prod., Inc., Minn., MN 51432
** Uniform Tubes, Inc., Collegeville, PA 19426
*** Rogers Corporation, Chandler, AZ 85224

The surface temperatures and temperatures at depth produced by this applicator on a muscle-equivalent phantom+ are shown in Fig. 2 (b) and (c). The surface heating is fairly uniform over an 8 mm. diameter surface area with the hottest spots occurring at the center of the applicator and near the coax-to-microstrip transition.

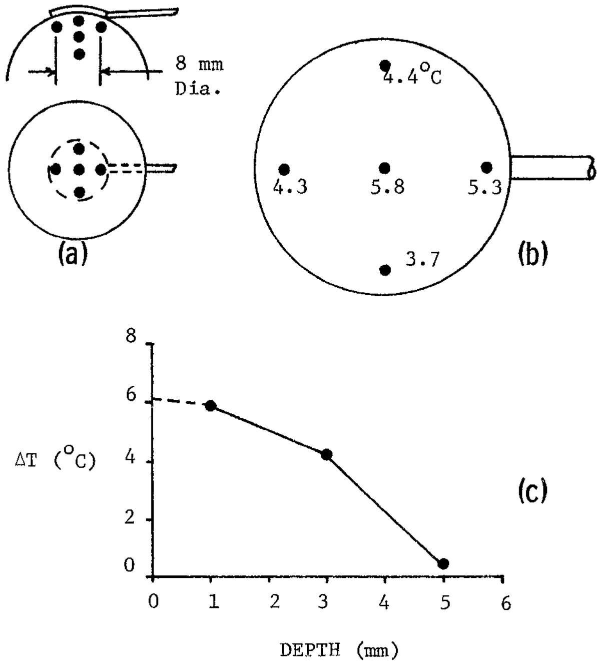

Fig. 2 (a) position of 0.08 thermocouples in phantom material. (b) Temperature rise measured 1 mm from applicator. (c) Temperature rise in center of applicator at 1, 3 and 5 mm depths.

The measured depth of penetration (the depth at which the temperature rise is one-half of the temperature rise on the surface) for this applicator operating at 5.8 GHz is 3.5 mm. The power used for these measurements was 1.5 watts for 30 seconds.

The relative heating in a fat-muscle tissue model due to plane-wave radiation can be calculated (see reference 14) using the data found in reference 15. The calculation for 5.8 GHz is shown in Fig. 3, the 1 mm. fat layer simulates the sclera and the muscle layer simulates the tumor. This shows that there should be very little heating of the sclera. The effect of blood flow is neglected in this calculation.

Intraocular Thermometry

Three copper-constantan thermocouple thermometers were used to measure temperatures at 1, 3, and 5 mm. from the surface of the 5.8 GHz ophthalmic microwave applicator. These thermocouples were made from TW-40 wire.**** Heat shrink Teflon tubing was first used to incorprate these thermometers in a semi-firm casing. This allowed for penetration of the sclera. The thermocouples stand at 90° to the face of the microwave plaque (Fig. 1). Two thermocouples enter the eye to a distance of 3 and 5 mm., while the 1 mm. thermocouple served to monitor the temperature at the base (sclera). However, we found that the Teflon thermister casing frequently bent off axis. Therefore we changed to a more rigid Lucite housing.++

+ 69% H_2O, 30% gelatin, 1% NaCl (see ref. 16)
++ Prod. J. Gatz, J. Ryan, Brookhaven Natl. Lab., Upton, NY 11973

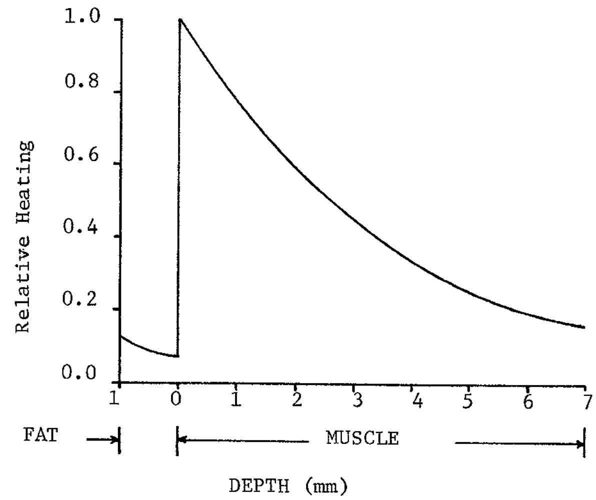

Fig. 3 Relative heating in a fat-muscle tissue model (f_o = 5.8 GHz, ϵ_f = 5.05, ϵ_m = 43.3, σ_f = 0.0034, σ_m = 0.047, ρ_{fm} = 0.5 $\underline{/176^o}$)

Etched Element Contact Heater*

Thermofoil heaters are thin flexible laminated assemblies composed of one or more etched-foil resistance elements bonded between layers of electrical insulation. The heating surface is 1.0 cm. in diameter and less than 1.0 mm. in thickness. The resistance element (75 ohm) is encased in Kapton insulation; a clear, amber colored polymide base film attached with thermoplastic adhesive. A 2 mm. free margin of this material was left at the periphery of the device through which 4 sutures were placed. A DC power supply is required for the induction of heat.

A copper-constantan thermocouple is positioned at the center of the hyperthermia plaque to monitor scleral temperatures. A thermal fuse can be added as part of this system. Temperatures are constantly monitored by digital readout.****

Experimental Model

Our studies required the use of 2-3 kg. New Zealand white rabbits. The average rabbit eye is 2-4 mm. smaller in diameter than a human eye. The Greene strain of amelanotic melanoma was placed in, and grown from the rabbit choroid.[17,18] The local growth characteristics and metastatic pattern of the rabbit choroidal melanoma are very similar to the human.[19] Observation of growth was achieved with indirect ophthalmoscopy. Tumor size was documented with fundus photography and ultrasonography. This allows for treatment of similarly sized tumors.

Results

A time-temperature relationship exists for hyperthermic deactivation of malignant cells.[23] These values, dependent upon physiologic and cellular parameters, have not been determined for choroidal melanoma. Therefore our initial goal was the local elevation of intraocular and intratumor temperature in a range of 41°C-47°C. These doses were delivered for periods of ½ or 1 hour on each of 1, 3, or 5 consecutive days.

**** Bailey Inst., Inc., Saddle Brook, NJ 07662

Normal and tumor bearing rabbit eyes were removed one month after treatment; at which time gross and histologic examinations were performed.

In normal eyes exposed to hyperthermic doses within the therapeutic range, no adverse effects were noted outside the local area of treatment. The sclera beneath the plaque remained intact while an abrupt attenuation or thinning of the retina often defined the local area of treatment.

Adequately treated intraocular tumors exhibited evidence of cellular damage and cessation of growth in the treated area. Histologic examination of the sclera, adjacent retina, and normal ocular structures showed no apparent adverse effects. Tumors with base diameters exceeding that of the plaque and under-treated tumors displayed less or no apparent therapeutic effect.

Conclusion

Malignant melanomas are known to be more responsive to a combination of radiation and hyperthermia than to either given alone.[6,20,21] In addition to its primary cytocidal effects, hyperthermia potentiates other anticancer modalities. These qualities make it the perfect adjunct to plaque irradiation of choroidal melanoma.

Utilizing available technology there are three methods of inducing local hyperthermia in patients: simple contact conduction, electromagnetic radiation (radiofrequency and microwaves), and ultrasound.[12] Contact heating and electromagnetic radiation are best suited to plaque technique.

An ideal dose distribution is characterized by uniform heating of the neoplasm with sparing of normal ocular structures. We feel that the 5.8 GHz ophthalmic microwave applicator best offers this potential.

Our efforts with the etched element heater showed scleral melting at low thermal doses. With this contact device, the entire hyperthermic dose was delivered to the sclera. Intraocular and intratumor temperatures were dependent upon conduction and convection.

In comparison with contact heating, high frequency electromagnetic radiation exhibits greater penetration into lossy dielectrics such as living tissue.[12,14,15] In addition, low water content should inhibit induction of heat within the fibrous sclera.[14,15]

Our preliminary observations are that the 5.8 GHz ophthalmic microwave applicator induced a localized and well quantified elevation of intraocular temperature within the therapeutic range. Utilizing the rabbit model of choroidal melanoma, adequately treated tumors exhibited histologic evidence of cellular damage and cessation of growth. On histologic examination of normal ocular structures, no adverse effects which might preclude the use of this device were noted. This study suggests that the 5.8 GHz ophthalmic microwave applicator satisfies the requirements for hyperthermic treatment of intraocular tumors.

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