

Effects of Microwave-induced Local Hyperthermia on Mammary Adenocarcinoma in C3H Mice¹

Jozef Mendecki,² Esther Friedenthal, and Charles Botstein

Departments of Radiotherapy [J. M., C. B.] and Pediatrics [E. F.], Montefiore Hospital and Medical Center, Albert Einstein College of Medicine, Bronx, New York 10467

SUMMARY

Microwave-induced hyperthermia was focused locally upon mammary adenocarcinoma implanted in C3H mice when the tumor reached 6 mm in diameter. In 54 treated mice, all tumors diminished in size after the first exposure (43°, 45 min) and disappeared completely following the second treatment. No other effects from heat application were apparent. All the mice in the microwave-treated group survived the whole period of observation (4 months) without any evidence of tumor, while 18 nontreated controls died within 4 weeks after inoculation.

INTRODUCTION

The search for improved modalities in cancer therapy has led to the exploration of various ways of inducing hyperthermia, especially in view of the recent encouraging results with this form of treatment reported from many centers (4, 6, 8). In the majority of cases, however, the use of systemic or regional hyperthermia was limited by the heat tolerance level of the organism, as well as by the appearance of certain local and general complications (2, 3). One of the more promising methods of localized heat treatment is the microwave irradiator, which can be applied directly over the tumor site and which affords control of heat penetration, temperature rise, and irradiated volume.

We wish to report the results of ongoing experiments involving the use of microwave irradiation in the treatment of a solid tumor.

MATERIALS AND METHODS

The tumor under study was a mammary adenocarcinoma, induced by implanting 5×10^5 cells of a tumor homogenate s.c. into the lower abdomen of inbred 1-month-old C3H mice. A 100% take was observed, and the treatment began on the 5th day postinoculation, when the tumor reached 6 mm in diameter.

The mice were anesthetized by i.p. injection of Nembutal, 50 mg/kg body weight, and were immobilized on an adjust-

able board. A thermocouple was affixed to the tumor surface, which was then covered with 2 layers of thin plastic foil in order to minimize heat loss from the irradiated area and to prevent possible skin damage. The heat was produced by a 10-watt microwave generator (constructed by RCA Laboratories, Princeton, N. J.) at a radiation frequency of 2450 MHz, connected to an applicator designed to provide heat penetration limited to a hemispherical volume of approximately 1.5 cm in diameter. This applicator does not rely on a resonance field; it is instead matched to the electrical properties of animal tissue and thereby permits the propagation of electromagnetic energy without causing a discontinuity at the applicator-tissue interface. The tumor was heated by placing the applicator on the plastic foil covering the tumor surface. A temperature of 43° was achieved within 2 to 3 min by utilizing the full power of the microwave irradiator. Thereafter, by use of an attenuator, the power was regulated to maintain a constant temperature of 43° for the entire period of the treatment. The temperature was monitored throughout the heating procedure by a telethermometer.

The experiment was performed on 6 groups, each consisting of 12 tumor-bearing mice. Three in each group were used as nonheated controls; 9 were subjected to temperatures of 43° applied to the tumor area for a 45-min period in a course of treatment given once every other day for a total of 4 treatment courses. The control animals were subjected to anesthesia only, following the same schedule.

In a separate experiment, intratumor temperature of anesthetized animals during the application of local hyperthermia was measured by thermistor probes and was found to be approximately 0.5° higher than that of the tumor surface, while the central body temperature remained in the range of 31-33° during the treatment period and did not differ from that of the anesthetized untreated controls.

The survival of the animals and the growth rate or regression of the tumor served as criteria of therapeutic results.

Microscopic studies of the implanted areas of the surviving mice were carried out 4 months after treatment.

RESULTS

In all 54 of the heat-treated mice, decrease in the size of the tumor was observed after the 1st treatment, with com-

¹ Supported partially by NIH Training Grant C.A.O. 5257-3.

² To whom requests for reprints should be addressed, at Department of Radiotherapy, Montefiore Hospital and Medical Center, 111 East 210th Street, Bronx, N. Y. 10467.

Received January 8, 1976; accepted March 18, 1976.

plete disappearance of the palpable mass after the 2nd exposure to heat therapy. The skin covering the inoculated area was basically intact, except for a slight loss of elasticity, and no epilation was observed. The mice did not suffer any general ill effects after the exposure to heat, and they remained active and healthy throughout the observation period.

Pathological examination performed on several cured animals 4 months after treatment failed to reveal any metastases. The site of the original tumor inoculation was histologically free of cancer. All 18 nontreated control animals exhibited rapid growth of their tumors, which, within 3 to 4 weeks reached a diameter of about 25 mm. Dissection of the tumors revealed a necrotic center surrounded by viable periphery. In all tumor-bearing control animals, the spleen, free of tumor, was enlarged to about 5 times its normal size. On the average, the untreated animals died 4 weeks after inoculation.

DISCUSSION

The experiment was designed primarily to test the effect of physiologically tolerated microwave heating on solid tumors. No attempt was made at elaboration of details such as optimization of dose, fractionation, timing, etc. Instead, the basic parameters of temperature, time of treatment, and intervals were chosen on the basis of biological considerations. The rationale for using a temperature of 43° stems from reports (1, 7) that lower temperatures have produced only retardation of tumor growth, while higher temperatures have resulted in considerable damage to the heated tissues. The 45-min treatment period was convenient for keeping the mice immobilized with only 1 dose of anesthesia. The intertreatment interval of 48 hr was used to allow full recuperation of the animals from the effects of the procedure.

On the basis of reports found in the literature (5, 9) with regard to C3H mammary adenocarcinoma treated with other heating methods, we expected a regression or temporary arrest of the growth. Instead, we found complete eradication of tumors in the treated mice and a 100% long-term survival. In experiments performed by Thrall (9), who induced hyperthermia by immersion of the tumor-bearing limb in a bath at 44.5°, no tumor cures were observed. Overgaard (5), using local diathermy on the same tumor, obtained selective destruction of the tumor without damage to normal tissue in only 25% of the experimental animals. We suggest that the complete eradication of the tumors obtained in our experiments can be related to the well-concentrated local heat. Microwaves are particularly well suited to induce highly localized effective hyperthermia. Their penetration into living tissue can be regulated by the frequency used. Power levels required to raise the tumor environment to the desired temperature can be easily adjusted, and the heated volume can be controlled by the

design of the applicator. Furthermore, by the use of a matched applicator, "hot-spot" effects resulting from standing wave phenomena can be avoided and uniform heating can be assured.

Heating by microwaves takes place not by conduction from the outside but by exciting the tissue molecules in the path of the electromagnetic signal. While the skin loses some of the induced heat by radiation, the inside of the tumor does not, and it is thus maintained at a somewhat higher temperature, despite circulatory cooling effects.

The encouraging results of our initial experiments suggest related investigations to optimize doses and fractions of hyperthermia treatments. In addition, it would be important to explore hyperthermia in conjunction with radio and chemotherapy, and to investigate such areas as synchronization of the hyperthermic treatment with cell mitotic cycle, and the possible enhancement of the immune response mechanism as a result of localized heating.

On a more fundamental level, the study of underlying molecular and biochemical processes would allow a better understanding of the events leading to the thermal cell damage.

ACKNOWLEDGMENTS

The experiment could not have been initiated without the generous aid of RCA Laboratories, whose enthusiasm and support is gratefully acknowledged. In particular, the authors wish to thank Robert Paglione, for designing and constructing the apparatus, and Mark Nowogrodzki, for his help in defining the experiment.

The mammary adenocarcinoma was obtained through the courtesy of Eli Seifter, Departments of Biochemistry and Surgery, Albert Einstein College of Medicine, Bronx, N. Y.

REFERENCES

1. Ben-Hur, E., Bronk, B. V., and Elkind, M. M. Thermally Enhanced Radio-response of Cultured Chinese Hamster Cells: Inhibition of Repair of Sublethal Damage and Enhancement of Lethal Damage. *Radiation Res.*, 58: 38-51, 1974.
2. Dickson, J. A., and Ellis, H. A. Stimulation of Tumor Cell Dissemination by Raised Temperature (42°C) in Rats with Transplanted Yoshida Tumors. *Nature New Biol.*, 248: 354-358, 1974.
3. Dickson, J. A., and Muckle, D. S. Total Body Hyperthermia versus Primary Tumor Hyperthermia in the Treatment of Rabbit VX-2 Carcinoma. *Cancer Res.*, 32: 1916-1923, 1972.
4. Hall, R. R., Schade, R., and Swinney, J. Effects of Hyperthermia on Bladder Cancer. *Brit. Med. J.*, 2: 593-594, 1974.
5. Overgaard, J., and Overgaard, K. Investigation of the Possibility of a Thermic Tumor Therapy—Shortwave Treatment of a Transplanted Isologous Mouse Mammary Carcinoma. *European J. Cancer*, 8: 65-78, 1972.
6. Pettigrew, R. T. The Effect of Whole Body Hyperthermia in Advanced Cancer. *Brit. J. Cancer*, 30: 179, 1974.
7. Robinson, J. E., and Wizenberg, M. J. Thermal Sensitivity and the Effect of Elevated Temperatures on the Radiation Sensitivity of Chinese Hamster Cells. *Acta Radiol. Therap. Phys. Biol.*, 13: 241-248, 1974.
8. Stehlin, J. S., Giovannella, B. G., di Ipolya, P., Muenz, L. R., and Anderson, R. F. Results of Hyperthermic Perfusion for Melanoma of the Extremities. *Surg. Gynecol. Obstet.*, 140: 338-348, 1975.
9. Thrall, D. E., Gillette, E. L., and Bauman C. L. Effect of Heat on the C3H Mouse Mammary Adenocarcinoma Evaluated in Terms of Tumor Growth. *European J. Cancer*, 9: 871-875, 1973.

Cancer Research

The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

Effects of Microwave-induced Local Hyperthermia on Mammary Adenocarcinoma in C3H Mice

Jozef Mendecki, Esther Friedenthal and Charles Botstein

Cancer Res 1976;36:2113-2114.

Updated version Access the most recent version of this article at:
<http://cancerres.aacrjournals.org/content/36/6/2113>

- E-mail alerts** [Sign up to receive free email-alerts](#) related to this article or journal.
- Reprints and Subscriptions** To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
- Permissions** To request permission to re-use all or part of this article, use this link <http://cancerres.aacrjournals.org/content/36/6/2113>. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.