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AN UPDATED ANALYSIS OF MICROWAVE HYPERTHERMIA AT 2450 MEGAHERTZ AND 915 MEGAHERTZ FREQUENCIES.

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Microwave hyperthermia at frequencies of 2450 megahertz and 915 megahertz was used to treat superficial measurable tumors of different histopathologies at various sites. Patient tolerance of temperatures up to 42.5° C. was observed. 59 courses of treatments were given to 47 patients. Hyperthermia alone at 40 to 42.5° C. was not effective to obtain tumor response. However, hyperthermia and radiation (to 2700 rads in 9 fractions over three weeks) produced complete and partial responses in three-fourths of the treatment courses. The combination of hyperthermia and chemotherapy may have great potential. Confirmation of these clinical impressions will depend on a much larger series of patient data. Participation in cooperative studies such as the Hyperthermia Study Group of Radiation Therapy Oncology Group is urged.

Key Words: Hyperthermia, microwave, radiation, chemotherapy, cancer.

INTRODUCTION

Encouraged by numerous promising reports of the tumoricidal effects of hyperthermia *in vivo* and *in vitro* (1,2,3,4), a clinical hyperthermia program was started at the Claire Zellerbach Saroni Tumor Institute of Mount Zion Hospital and Medical Center in December, 1976. This paper presents an updated analysis of results of treatment of 47 cancer patients with 2450 megahertz and 915 megahertz frequencies microwave hyperthermia.

METHODS AND MATERIALS

Instrumentations

2450 megahertz microwave was generated by a diathermy unit manufactured by Burdick Corporation (Model MW/200), and was broadcast by Burdick Type B or E applicators. Heat induction can be achieved to reach tissues about one centimeter in depth and therefore only superficial lesions can be treated by this equipment. The applicators can be either an 8 cm diameter circle or 14 x 17 cm rectangle.

A variable frequency (400 MHz - 1000 MHz) MCL Model 15122 radio-frequency generator was used to produce 915 megahertz microwave. A dielectric-filled applicator measuring 8 x 8 cm was constructed to deliver this microwave radiation and effective heating can be achieved in tissues up to 4.5 cm in depth.

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Thermometry

Tumor tissues temperature measurements were made by inserting a Yellow Springs Model 524 thermistor needle at the desired depth, with the needle positioned carefully at right angles to the electric field to minimize heating perturbance. This needle was left in situ for continuous temperature monitoring, with measurements being made at 5 minute intervals. Skin temperature was also periodically obtained.

Skin cooling was not performed for the patients included in this report, but was utilized with subsequent patient treatments.

The prescribed tumor temperature of 42.5° C. was not always achievable, due to many factors including heat conduction by local vasculature, and patient intolerance.

Treatment Schedule

Most patients were treated three times a week on Mondays, Wednesdays and Fridays for 2 or 3 weeks. Thus, these patients received either six or nine treatments of hyperthermia. Some patients were treated twice a week on a Monday-Thursday, or Tuesday-Friday schedule, however. These schedules were devised because of *in vitro* observation of the phenomenon of "thermotolerance" (5,6).

Patients who received combined hyperthermia and radiation had the hyperthermia given immediately after radiation, which was usually electron beam of the appropriate energy for the depth of the tumor at 300 rads per fraction. Chemotherapeutic drugs were given (Bleomycin intravenously for head and neck cancers) one to two hours prior to local hyperthermia for the few patients on the combined chemotherapy and hyperthermia protocol.

Patient Population

Patients accepted for this hyperthermia treatment program had observable and measurable recurrent or metastatic tumors, and had failed conventional cancer treatments. Ionizing radiation was added to hyperthermia when previous radiotherapy did not exceed normal tissue tolerance, and this usually meant the dose equivalence of about 6000 rads in 6 weeks.

Bleomycin in 5 mg bolus was given one to two hours before hyperthermia in head and neck cancers. The dosage was purposely chosen to be low so as not to mask or affect strongly any efficacy of hyperthermia.

The patients were enrolled in one of four programs: (1) Hyperthermia only, (2) Hyperthermia and radiotherapy, (3) Hyperthermia and chemotherapy, and (4) Hyperthermia plus radiotherapy and chemotherapy. To date, most patients received either hyperthermia alone, or hyperthermia and radiotherapy.

Method of Evaluation

The size of a treated lesion was measured with a caliper in at least two dimensions, and the depth of a tumor was measured whenever possible. Measurements were made before, during and after a treatment course, and at follow-up examinations of frequent intervals. Polaroid color photographs were obtained to ensure documentation, and notes were detailed to describe observations of tumor regression, normal tissue effects and patient status.

Since this group of patients had advanced cancers, survival after treatment was short. Local tumor response became the only evaluable parameter. Treatment responses were rated as complete (CR = 100% regression), partial (PR$\geq$ 50% regression) and no response (NR$\leq$ 50% regression).

RESULTS

Fifty-seven patients received hyperthermia, but ten patients were not evaluable due to early deaths, inadequate measurable lesion, premature surgical excision, and lost to follow-up. The distribution of the different types of tumors treated by hyperthermia was not representative of the cases treated with radiation therapy in our department. Most of the patients treated with 2450 megahertz microwave had chest wall recurrence of breast cancer after mastectomy, radiotherapy and chemotherapy or hormonal therapy. On the other hand, many patients treated with 915 megahertz microwave had nodal recurrences in the neck or the groin in previously irradiated areas.

TABLE I

2450 MHz		915 MHz	
No. of patients	Histopathology	No. of patients	Histopathology
26	Breast carcinoma	2	Renal carcinoma
1	Breast sarcoma	1	Nasopharyngeal carcinoma
1	Chondrosarcoma	2	Colonic carcinoma
1	Histiocytic lymphoma	1	Rectal carcinoma
1	Rectal carcinoma	2	Breast carcinoma
		1	Vaginal carcinoma
		1	Floor-of-Mouth carcinoma
		3	Laryngeal carcinoma
		1	Melanoma
TOTAL = 31		TOTAL = 16	

Histopathology of lesions treated by 2450 megahertz and 915 megahertz microwave hyperthermia.

Some patients were treated with hyperthermia to more than one site. A few sites received two series of treatments of hyperthermia with an interval of time between two treatment courses. Altogether there were 40 courses given with 2450 megahertz and 19 courses with 915 megahertz microwave.

Hyperthermia Alone vs. Hyperthermia and Radiation

At the temperature range of 40 - 42.5° C., hyperthermia alone did not seem to be effective in inducing tumor regression. When hyperthermia was given after low dose radiation (mostly 1800 rads/6 fractions to 2700 rads/ 9 fractions), a higher response rate was observed. A comparison of treatment response rate is made between hyperthermia alone and hyperthermia plus radiotherapy in Table 2. Since most of these patients died within a few months after hyperthermia, a study of the duration of treatment responses would not be meaningful.

TABLE II

Primary Site	Hyperthermia alone			Hyperthermia + Radiation		
	CR	PR	NR	CR	PR	NR
Adenocarcinoma						
Breast		1	5	10	13	5
Rectum		1			1	1
Colon				2		
Ovary	1					
Kidney						3
Squamous cell carcinoma						
Head and Neck			2	2	1	1
Lung					1	
Vagina			1			
Sarcoma						
Extremity					1	
Breast						1
Melanoma						
Extremity					1	
Lymphoma						
Lymphatics				1		
TOTAL	1	2	8	15	18	11

Local tumor response to treatment with hyperthermia alone and hyperthermia plus radiation. CR = complete response, PR = partial response, NR = no response.

Renal cell carcinoma and sarcoma seemed to have a lower tumor response rate. The one case of melanoma achieved near complete regression after hyperthermia and radiation, but there was residual induration on clinical palpation.

Hyperthermia and Chemotherapy

There were only four cases of combined treatments of hyperthermia and chemotherapy. As mentioned previously, the chemotherapy consisted of Bleomycin 5 mg intravenously one to two hours prior to hyperthermia. In fact, three of the four patients also received 2700 rads in 9 fractions with electron beam. All four cases were squamous cell carcinoma

recurrent in the neck from nasopharyngeal and laryngeal primary tumors. One patient who received hyperthermia and bleomycin experienced a complete response for two months, but failed at the edge of the treatment area. Two patients who received hyperthermia, bleomycin and radiation probably had complete control of disease. One died accidentally at 12 months post treatment, and one continued to be in remission also at 12 months. The fourth patient had a partial response and at the present time was only three months post treatment.

DISCUSSION

To date we have found that microwave hyperthermia delivered in the manner described has been generally well tolerated by patients. Unfortunately, hyperthermia alone to a temperature of 42.5° C. has not been successful in producing tumor responses. Higher temperatures may be more effective, but they may also be associated with higher rates of morbidity.

We found that hyperthermia (42.5° C.) combined with low-dose radiation has produced significant tumor responses. Our patients mostly had received previous radiotherapy and out of consideration of those patients' safety, the dose of radiation with hyperthermia was necessarily lowered. It may be possible to achieve improved local control of bulky tumors by utilizing hyperthermia and moderate doses of radiation. This concept is appealing to radiation oncologists since local control of bulky, hypoxic tumors remain a real challenge indeed.

Similarly, the possibility of improved local control with hyperthermia and chemotherapy is an exciting one. Dramatic results were reported *in vivo* and *in vitro* (7,8,9). Our experience in this regard has been anecdotal. A larger series of patients will be required in order to draw a conclusion.

There are marked limitations in clinical applications of our present treatment system. The problems of accomplishing satisfactory thermal dosimetry in conformance with clinical requirements has been addressed (10). We will need to make headway in equipment research and development for better heat delivery and thermometry. Certainly, there is plenty of room for innovative designs and treatment techniques to approach different anatomical locations of cancerous tumors.

At our present status of knowledge of hyperthermia, the importance of sharing information and cooperative studies cannot be stressed enough. Much human and material resources can be saved by a well-planned, concerted scientific effort. Participation in the Hyperthermia Study Group of the Radiation Oncology Group (RTOG) is therefore worthwhile.

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