

Clinical Thermoradiotherapy

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A clinical trial is currently in progress to determine the efficacy of combined fractions of hyperthermia and radiation. The protocol consists of two parts. First, four fractions of microwave-induced hyperthermia ($45.0^{\circ} \pm 0.5^{\circ}\text{C}$) are applied for 1½ hours to the volume encompassing the tumor, each separated by 72 hours. After a one-week rest, a second series of four fractions is administered again at 72-hour intervals. Each fraction consists of a 400 rad dose of radiation followed within 20 minutes by hyperthermia ($42.5 \pm 0.5^{\circ}\text{C}$) for 1½ hours.

The failure of conventional radiotherapy to control a significant number of tumors without any extensive adverse effects on the surrounding normal tissue is mainly attributed to the presence of a viable hypoxic fraction of cells in these tumors. As far back as 1909 Schwarz (1) showed that if blood circulation was restricted by limiting oxygen supply, human skin become radioresistant. Because of the heterogeneous structure of tumors in general, there are regions containing closely packed cells, remote from blood vessels, that are hypoxic (2). If even a very small fraction of hypoxic cells exists, radiotherapy will not be able to control the tumor.

To overcome this problem, many different approaches have been tried. One early solution was to give the total radiation doses in several fractions. During the course of fractionated treatments, the resistant hypoxic cells become oxygen sensitive, at least during later doses. However, it is possible that some tumors do not reoxygenate completely so that some hypoxic cells still survive and cause a recur-

Currently, we have treated 62 patients with 82 fields with a mean follow-up time of six months to date. Total regression was observed in 60% of all cases, and partial regression in 33%; no response was seen in only 6% of all those treated. Five local and three marginal recurrences have been observed. This paper discusses details of response based on site, histology, and classification.

rence. Even a few hypoxic cells would constitute a serious problem. To compensate for this limitation, one solution has been to use high linear energy transfer (LET) radiation instead of ordinary x- and γ -rays, so that the tumor response does not depend on the presence or absence of molecular oxygen. The ideal radiation that will have oxygen enhancement (OER) of unity, such as 2MeV α particles, is incapable of penetrating tissue deeply enough to be useful. The best that can be achieved is through the use of neutrons, pions, or high-energy heavy ions. These options tend to be very expensive, and limited clinical trials are still going on.

In another approach, the patient is placed in an environment of pure oxygen at a pressure of 2 to 3 atmospheres before radiotherapy begins in an attempt to increase the availability of oxygen to tumors. This technique has not produced any significant improvement in tumor control, although a few centers around the world are still conducting clinical trials.

In recent years there has been increasing interest in hyperthermia to treat cancer, used either alone or in combination with radiation. Although reports on its use date back to 1866 (3), research on hyperthermia has been stimulated in the past two decades by several interesting findings in thermoradiobiological studies.

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Rationale

Recent, extensive radiobiological and limited clinical studies show that hyperthermia combined with radiation has a synergistic cell-killing effect. Both *in vitro* (3-6) and *in vivo* (7-11) studies show that thermal enhancement depends not only on the sequence of the two treatments, but also on cell cycle effects. The synergistic effect is most pronounced for radioresistant S-phase cells (12,2). Clinically, the most important observation is that the hypoxic cells may be equally or more sensitive to hyperthermia than aerobic cells (3,10,13,14). The rationale for using hyperthermia above 43°C in combination with ionizing radiation is that the viable hypoxic tumor cells, which are radioresistant, will be destroyed at these temperatures. Mild hyperthermia (40°-42°) also introduces a significant change in tumor blood flow. It has been shown both in mouse tumor studies and in clinical trials (15) that hyperthermia in the 40°-42°C range increases the blood flow with a concomitant increase in oxygenation. It will effectively sensitize the otherwise radioresistant hypoxic cells in the tumor. Dramatic changes in cell survival during hyperthermia have also been observed when the pH of cells is only slightly altered (16). Although there are no *in vitro* data to indicate differential response or sensitization of tumor cells as opposed to normal tissue cells, the cellular environment in the two cases is expected to be quite different *in vivo*. For example, several studies (17-20) indicate that the pH of fluid in human and rodent solid tumors is lower than the normal pH of 7.4. This will result in differential tumor cell killing that spares normal tissue. Other studies (21,22) show that some tumors have a sluggish blood flow as compared to normal tissue. This finding suggests that under similar heating conditions tumors are not able to dissipate heat as efficiently as the normal tissue. These findings about the different microenvironments in tumors and normal tissue regarding pH, blood flow, and nutritional state probably led earlier investigators (23-26) to conclude that hyperthermia selectively killed the tumor cells.

Based on the above *in vitro* and *in vivo* radiobiological findings, several groups of investigators (15,21,25,27-29) are using a combination of hyperthermia and ionizing radiation in clinical studies. The clinical goals, methodology, and results of some of these studies are discussed in the following section.

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Clinical applications of combined hyperthermia and radiation treatment date back to the beginning of the century, but early reports are anecdotal. Most reported only an attempt to treat human tumors and did not document the

temperatures to which tumors and surrounding normal tissues were heated. This imprecision, along with the lack of radiation controls alone, makes it very difficult to draw any quantitative conclusions or even to establish that tumor temperature was raised at all.

The earliest reported combination of hyperthermia and ionizing radiation is that of Schmidt (30) in 1909. He proposed to treat malignancies by using diathermy for localized heating of tissue in combination with ionizing radiation. Some years later, Arons and Sokoloff (31) used radiofrequency (RF) currents for hyperthermic treatments of intrathoracic and intra-abdominal tumors. However, since they made no temperature measurements, it is difficult to establish whether they were able to raise the tissue temperature to a therapeutic range. Woeber (32) used ultrasound with simultaneous x-irradiation to treat 20 patients with cutaneous malignancies. He reported that tumors could be controlled with a 40% reduction in radiation dose and that reactions of normal tissues were also diminished. Crockett, et al (33), following some experimental work on normal dog bladders, treated seven elderly patients who had incurable advanced bladder carcinomas with a combination of local hyperthermia and regional radiotherapy. The radiation dose varied from 4500 to 5500 rad. These authors reported that the treatment produced a striking reduction in tumor size without any serious adverse effects. Although they suggested that hyperthermia enhanced the tumor response, they did not attempt to determine heat distribution within the bladder. Recently, Hall (34) also reported regression of bladder papillomatosis without any complications. Each patient's bladder was irrigated for three hours at a time with water heated to 42°-45°C for 5-14 sessions.

Hartman and Crile (35) treated osteogenic sarcoma in five children with microwave heating and various doses of radiation. Two of the five were alive five years later and were still able to use their limbs. One was a seven-year-old girl with osteogenic sarcoma in the right mid-tibia, and the other was a 16-year-old with osteoblastic and osteolytic lesions of the metaphysis of the distal part of the left radius. The other three children survived six to 17 months and died of metastatic disease.

Stehlin (36) reported a 67% five-year survival rate for 32 patients he treated by using heated blood to perfuse the extremities, followed by x-irradiation several weeks later. He found that at tissue temperatures of 40°C patients tolerated the treatment very well for several hours, but when the extremities were perfused with blood heated to 46°C, complications resulted.

In the past few years several prospective clinical trials have been started. We are reporting the results of the Henry Ford Hospital trial.

Materials and Methods

In this study we designed a fractionation scheme that combined hyperthermia and radiation with a curative intent. The protocol is summarized below.

1. Hyperthermia only: 4 treatments at 45°C for 90 minutes (skin 36°C or below), at 72-hour intervals;
2. Rest one week; response to heat alone evaluated;
3. Radiation therapy and hyperthermia: 4 treatments at 42°C for 90 minutes; heat follows radiation (20-minute intervals); RT: 400 rad fractions for each treatment;

Total: 8 hyperthermia treatments + 1600 rad/2 weeks/4 fractions.

This protocol has been designed to take advantage of the known effects of hyperthermia either alone or combined with radiation. Skin cooling was implemented to prevent normal tissue damage. We chose the number of fractions and duration of each treatment at random, taking into account such factors as the patient's compliance and comfort and possible biological factors such as thermotolerance, vascular response, and repair. In addition, the total dose of radiation was low enough to allow previously irradiated areas to be treated more than once.

Localized hyperthermia was induced in all patients by microwave radiation that used direct contact applicators (37). The tumor size, location, and depth determine the exact type and size of applicator to be used as well as the microwave frequency (915 or 300 MHz).^{*} Heat is initially applied to the tumor in four fractions of 1½ hours each at 72-hour intervals. The temperature is monitored with conventional (Bailey) or ultramicrothermocouples (Medtra Inc) to maintain the tumor temperature at 45°C ± 0.5°C, while the overlying, normal skin is simultaneously air cooled at or below 36°C. After these four fractions have been applied, the patient rests for one week and then receives four more fractions of hyperthermia, this time in combination with radiation. Each of these four treatments consists of doses of 400 rad to the tumor followed immediately (20 minutes) by hyperthermia at a temperature of 42.0° ± 0.5°C, again at 72-hour intervals. As before, skin cooling is used to maintain a temperature of 36°C or lower at the surface.

The microwave hyperthermia was induced with direct contact applicators, which are essentially square or rectangular cross-section waveguides.^{*} We used two types of microwave applicators: 1) a square or rectangular cross-section waveguide completely loaded with a low-loss dielectric material and excited in TE₁₀ mode (37); 2) a

partially filled rectangular waveguide excited in the TEM mode. The second applicator distributes heat better than the first one. Thermometry was accomplished by inserting one or two ultramicrothermocouples^{*} in the tumor tissue, depending upon the size and location.

Results

To date, 62 patients have been treated with 82 fields (Tables I and II). A total response was observed in 49 treatment fields, a partial response in 27, and no response in only 6 fields. These included one each of squamous cell carcinoma, adenocarcinoma, and sarcoma. The only complications that could be directly attributed to treatment

TABLE I
Treatment Results

82 Fields Treated	62 patients
Total Response	49 (60%)
Partial Response	27 (33%)
No Response	6 (7%)
<i>Recurrence</i>	
Local:	5
Marginal:	3
<i>Complications</i>	
Skin burns:	2 (completely healed)
Tongue and pharynx burns:	2 (completely healed)
Grand seizure:	1 (epileptic patient)

TABLE II

Histology	No. of Fields	Response	Follow-up
Malignant melanoma	17	8 Total 6 Partial 3 No response	2 mo-1 yr
Malignant lymphoma	8	8 Total	2-7 mo
Squamous cell carcinoma	19	7 Total 11 Partial 1 No response	2-6 mo
Adenocarcinoma	33	24 Total 8 Partial 1 No response	2-7 mo
Other (transitional cell, basal cell, glioma, sarcoma)	5	2 Total 3 Partial	2-9 mo
Summary	82	49 Total 27 Partial 6 No response	2 mo-1 yr

Total Response: No tumor at two months' follow-up and thereafter.

Partial Response: Tumor decreased in size to half or less at two months' follow-up.

^{*} All equipment by Medtra Inc, Detroit, MI

were two skin burns caused by inadequate surface cooling and two tongue and pharynx burns; all healed completely. One patient with a history of epilepsy experienced a grand mal seizure when being treated for a neck tumor. Three marginal recurrences and five local recurrences have been noted. Although it should be emphasized that great care is needed during the initial planning and set-up for the patient, it is possible to obtain actual thermometry for every treatment of every field with minimal patient discomfort.

Table II summarizes histological results. Among our patients, malignant lymphoma was most responsive to this combination treatment. It should be pointed out that tumor regression after treatment ends is very slow and requires approximately two months before the total effect is observed. We also discovered during these treatments that the microwave power required to maintain the desired treatment temperatures declines after the first or second treatment of a given field. These two phenomena are probably related to heat-induced physiological changes within the tumor that affect its ultimate destruction. Further physiological studies are currently in progress.

Another interesting outcome of this study concerns the possible significance of the three marginal recurrences; they may indicate that this combined modality effectively treats microscopic disease. More time is needed for follow-up, and more patients must be treated before the clinical efficacy of this protocol can be fully evaluated.

Discussion

Recent studies (15,21,25,27,28,38,39) involving a combination of hyperthermia and x-irradiation have attempted to measure and document hyperthermia treatments more accurately. In most cases, these studies compared their treatment methods with radiation controls alone. Kim, et al (25) treated 50 patients who had a variety of cutaneous tumors. They reported improved results for both the radiosensitive (i.e., mycosis fungoides) and radioresistant (i.e., melanoma) tumors with the combined hyperthermia and radiation treatment as compared to either modality used alone. Their overall tumor control rate was 78% after combined therapy as compared with 26% after radiation alone. Multiple recurrent melanoma nodules completely disappeared without unusual normal skin reactions. However, combination therapy did intensify skin reactions in patients whose treated areas included either a skin graft or heavily scarred skin from extensive surgery.

These investigators used two heating methods. Some patients with tumors on extremities were heated by immersion in waterbath, while the rest of the patients were treated with RF (27.12 MHz) inductive heating. In their study, there

was a great variation in both the radiation dose and the length of hyperthermia treatment as well as in the number of fractions. The radiation doses varied from 800 rad in two fractions for melanoma to 2400 rad in eight fractions for Kaposi sarcoma. Similarly, hyperthermia (43.5°C) treatments varied from two fractions of 30 minutes for melanoma to 5 fractions of 60 minutes for mycosis fungoides. The hyperthermia treatments immediately followed the radiation treatments in all cases. While these data do not suggest any particular treatment schedule for a particular tumor, they do demonstrate the greater effectiveness of combined thermoradiotherapy as compared to hyperthermia or radiation alone.

Hornback, et al (27) used the combined therapy to treat 72 patients who had advanced cancer. Of those treated with hyperthermia before radiation therapy, 53% experienced complete remission of symptoms, while of those treated with heat following radiotherapy, 92% showed complete remission. Again, there was no set protocol and the radiation doses varied from 50 to 600 rad per day, with total doses from 3000 to 6500 rad. Heat treatments used 433.92 MHz microwaves. Although the authors mention that they attempted to measure tumor temperature during these treatments, tumor temperatures in the patients are not given.

Johnson, et al (28) conducted a pilot study to evaluate normal skin and melanoma tumor thermal enhancement ratios of 41.5°-42°C hyperthermia with radiation. They measured the response of normal skin to treatment by evaluating the degree of erythema according to a numerical scoring system. Tumor response was assessed by measuring tumor diameter. Although the study was not conclusive about the thermal enhancement ratio, it did highlight some of the problems in obtaining useful clinical data.

The study involved patients with multiple metastatic melanoma lesions. At least three lesions were chosen on each patient, all of whom were divided into three groups and given one, three, or four fractions, with a minimum 72-hour interval between each fraction. Radiation dose per fraction for different lesions varied from 500 to 900 rad. In some cases, they used single fractions of 1000, 1100, 1200, or 1300 rad. In all patients one lesion was heated immediately after radiation therapy, and was then used for comparison with other lesions treated with radiation alone. Hyperthermia treatments, which varied between 1 and 2 hours at 41.5°-42°C, were administered with 915 MHz direct contact microwave applicators (37).

Because of the lack of follow-up data, skin enhancement ratio (SER) and tumor enhancement ratio (TER) could be evaluated for only a few patients. SER values varied from

1.2 to 1.7, while TER values in most cases were 1.3. This study demonstrated, however, that superficial tumors of up to 4 cm wide and 2 cm deep could be heated with an accuracy of $\pm 0.5^{\circ}\text{C}$ either during or after radiation with 915 MHz microwaves.

Manning, et al (29) reported on a very limited study that combined heat and radiation. Of 40 patients treated with hyperthermia, four were treated in combination with radiation. Each had a minimum of three nodules. One nodule received a heat treatment of 43°C for 40 minutes with radio-frequency currents. Another nodule received radiation alone from two radium needles to a dose of 4000 rad in 100 hours. A third lesion received the same dose in addition to heat to 43°C for 40 minutes simultaneously, with radium needles used as heating electrodes.

The response rate for the heat-radiation combination was 80-90% compared with a 50% response rate for heat alone and radiation alone. These authors suggest a beneficial therapeutic ratio and minimal side effects from the combined treatment.

Another limited study (39) treated two groups of patients either with radiotherapy alone, hyperthermia alone, or combined treatment. One group received 200-600 rad fractions, 2-5 times per week for a total of 1800-4200 rad in 5-14 fractions. The other group received combined thermoradiotherapy treatments only, radiation fractions of 200-600 rad, 2-5 times a week, for a total of 2000-4800 rad in 6-20 fractions. Both groups received hyperthermic treatments ($42-44^{\circ}\text{C}$) 2-3 times per week to a maximum of 10 sessions in 4 weeks. Either 2450 or 915 MHz microwaves were used for the treatments. In the first group of eight patients, lesions in six patients regressed completely after they were treated with radiation and hyperthermia within one month of therapy. None of the tumors treated with hyperthermia alone regressed completely. In the second group of patients, 73% showed tumor regression. Melanoma regressed completely in two of four cases. No adverse side effects on normal tissue were observed from the combined treatments.

Arcangeli, et al (21) reported that 15 patients with multiple neck node metastases from head and neck were treated either with radiation alone or radiation combined with hyperthermia. A total of 33 neck nodes were treated, 12 with radiation alone, and 21 with the combination. Hyperthermia was induced by 500 MHz microwaves with a non-contact applicator.

These investigators used a very interesting fractional scheme. Described as a multiple daily fractional (MDF) scheme, it consists of $200 + 150 + 150$ rad/day, with 4-5 hour intervals between fractions, for 5 days per week, and

up to a total of 4000/7000 rad. All lesions were irradiated with the same total dose, whether or not they received hyperthermia.

The MDF schedule resulted in a 46% complete response, which was enhanced to 85% complete response when combined with hyperthermia; the remaining 15% showed partial response. It should be noted that when MDF was combined with hyperthermia, heat was applied immediately after the second daily fraction. The authors did not observe any abnormal reactions in areas that received the combined treatment.

In the study reported here, we have obtained an overall total response rate of 60%. Although further study and follow-up are necessary and other protocols must be examined, it is clear from these results that regardless of anatomical location and tumor histology, hyperthermia appears to be an effective modality to treat malignant disease.

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