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CLINICAL THERMORADIOTHERAPY

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A. INTRODUCTION

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 showed that restriction of blood circulation, limiting oxygen supply, rendered human skin radioresistant. Due to heterogeneous structure of tumors, in general, there are regions containing closely packed cells, remote from blood vessels and, therefore, are in hypoxic state (38). Even a very small fraction of hypoxic cells can result in failure of radiotherapy to control the tumor. In order to overcome this problem of hypoxic cells a number of different approaches have been tried. One of the early solutions was to give the total radiation dose in several fractions.

During the course of fractionated treatments the resistant hypoxic cells become sensitive oxygenated cells. This is at least true for the later doses of the multi-fraction treatment schedule. However, it is possible that some tumors do not reoxygenate completely such that some hypoxic cell still survive the treatment and are responsible for the recurrence. Even a modest number of hypoxic cells would constitute a serious problem. A significant effort has been made to compensate for this limitation. One solution is to use high linear transfer (LET) radiation instead of ordinary x- and γ -rays, such that the tumor response is independent of the presence or absence of molecular oxygen. The ideal radiation which will have oxygen enhancement (OER) of unity, such as 2MeV α - particles is incapable of penetrating sufficient tissue thickness to be of any use. The best that can be achieved is to use neutrons, pions or high-energy heavy ions. These options tend to be very expensive and limited clinical trials are still on going.

Another approach has been to place the patient in an environment of pure oxygen at a pressure of 2 to 3 atmospheres prior to radiotherapy in an attempt to increase the availability of oxygen to tumors. This technique has failed to produce any significant improvement in tumor control although a few centers around the world are still conducting clinical trials.

In recent years there has been an increasing interest in use of hyperthermia, either used alone or in combination with radiation in the treatment of cancer. Although reports on the use of hyperthermia date as far back as 1866 (5), the research in the use of hyperthermia as a possible, clinically important, anti-tumor treatment modality either used alone or in combination with radiation therapy has been stimulated in the past two decades as a result of several interesting findings in thermoradiobiological studies. The rationale for using hyperthermia is discussed next.

B. Rationale

Recent extensive radiobiological and limited clinical studies show that hyperthermia combined with radiation has a synergistic cell killing effect. Both in-vitro (21,31,32, 40) and in-vivo (12,13,15,29,39) studies show that the 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 (10,38). From a clinical point of view the most important observation is that the hypoxic cells may be equally or more sensitive to hyperthermia than aerobic cells (9,21,29,35). 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 by hyperthermia at these temperatures. Another interesting aspect is that mild hyperthermia (40 to 42°C) introduces a significant change in tumor blood flow. It has been shown both in mouse tumor and clinically (4) that hyperthermia in 40 - 42°C range increases the blood flow with a concomitant increase in oxygenation. This will effectively sensitize the otherwise radioresistant hypoxic cells in the tumor. Dramatic changes in cell survival during hyperthermia also have been observed when pH of cells is only slightly altered (11). Although there is no in-vitro data indicating 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 (8,16,27,28) indicate that 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 with normal tissue sparing. Other studies (2,24) indicate that some tumors have sluggish blood flow as compared to normal tissue. This suggests that under similar heating conditions, tumors are not able to dissipate heat as efficiently as the normal tissue resulting in differential tumor heating. These findings about the different microenvironments in tumors and normal tissue regarding pH, blood flow and nutritional state probably led the earlier investigators (6,14,-23,34), to conclude that tumor cells are selectively killed by hyperthermia.

Based on above in-vitro and in-vivo radiobiological findings several groups of investigators (2,4,19,20,23,26) are engaged in clinical studies employing a combination of hyperthermia and ionizing radiation. The clinical goals, methodology and results of some of these studies are discussed in the following section.

C. Clinical Thermoradiotherapy.

Clinical applications of combined hyperthermia and radiation treatment modality date back to the earlier part of the century. The early reports are anecdotal in nature. Most of them reported only an attempt to treat human tumors. The temperatures to which tumors and surrounding normal tissues were heated were not documented. This along with lack of radiation alone controls make it very difficult to draw any quantitative conclusions. In some cases it is difficult to establish that tumor temperature was raised at all since no temperature measurements were made.

The earliest report of combining hyperthermia and ionizing radiation is that of Schmidt (33). He proposed the use of diathermy for localized heating of tissue to treat malignancies in combination with ionizing radiation. Arons and Sokoloff (3) used radiofrequency (RF) currents for hyperthermic treatments of intrathoracic and intra-abdominal tumors. It is difficult to establish whether they were able to raise the tissue temperature to therapeutic range since no temperature measurements were made. Woeber (42) used ultrasound with simultaneous x-irradiation to treat 20 patients with cutaneous malignancies. He reported a 40% reduction in radiation dose required for tumor control accompanied by a reduction in normal tissue reaction. Crockett et al. (7), following some experimental work on normal dog bladder treated 7 elderly patients with incurable advanced bladder carcinomas with a combination of local hyperthermia and regional radiotherapy. The radiation dose varied from 4500 to 5500 rads. These authors reported striking reduction in tumor size with no serious adverse effects. The authors suggested that the tumor response was enhanced by hyperthermia. The authors, however, did not make any attempt to determine heat distribution within the

bladder. Recently Hall (17) also reported regression of bladder papillomatosis without any complications. He heated the bladder by irrigation with water heated to 42 - 45°C. The patients were heated for 3 hours for 5 to 14 sessions.

Hartman and Crile (18) reported treatment of osteogenic sarcoma with microwave heating and various doses of radiation. Five children were treated with this combination. Two of five, one 7 year old girl with osteogenic sarcoma in the right mid-tibia, and a 16 year old boy with an osteoblastic and osteolytic lesion of the metaphysis of the distal part of the left radius, were alive five years later. The other three survived 6 to 17 months and died of metastatic disease. The two patients who had long term survival also retained function of the limb.

Stehlin (37) reported a 67% five-year survival for 32 patients he treated using heated blood for perfusion of the extremities. These hyperthermia treatments were followed by x-irradiation several weeks later. It was found that tissue temperatures of 40°C using his technique were tolerated very well for several hours. However, perfusion of extremities with blood heated to 46°C resulted in complications.

In the past few years several prospective clinical trials have been stated. The results of the Henry Ford Hospital trial are reported here.

Materials and Methods

In this study a fractionation scheme combining hyperthermia and radiation was designed with a curative intent. The protocol is summarized in Table I.

This protocol has been designed to take advantage of known effects of hyperthermia either alone or in combination with radiation. Skin cooling was implemented to prevent normal tissue damage. The number of fractions and duration of each treatment was arbitrarily chosen, taking into account factors such as patient compliance, patient comfort and possible biological factors such as thermotolerance, vascular response and repair. In addition, the total dose of radiation employed is sufficiently low to allow retreatment of previously irradiated areas.

Localized hyperthermia was induced in all patients by microwave radiation employing direct contact applicators (30). The tumor size, location and depth determine the exact applicator type and size as well as the microwave frequency (915 or 300 MHz) that are employed.* Heat is initially applied to the tumor in four fractions of 1½ hour duration at intervals of 72 hours. The temperature is monitored with either conventional (Bailey) or ultramicro thermocouples (Medtra Inc.) to maintain the tumor temperature at 45°C ± 0.5°C while the overlying, normal skin is simultaneously maintained with air cooling at or below 36°C. Following these 4 fractions the patient rests for one week. Finally, four more fractions of hyperthermia are given; this time in combination with radiation. Each of these 4 treatments consists of dose of 400 rad to the tumor immediately followed (<20 min.) by hyperthermia to a temperature of 42.0 ± 0.5°C.

These fractions are again separated by 72 hours; as before, skin cooling is used when necessary to maintain a temperature of 36°C or lower at the surface. The microwave hyperthermia was induced using direct contact applicators. These applicators are essentially square or rectangular cross-section waveguides. Two types of microwave applicators were employed in this study. One type is square or rectangular cross-section waveguide completely loaded with a low-loss dielectric material and excited in TE₁₀ mode (30). The other type of applicator employed is partially filled rectangular waveguide excited in the

* All equipment by Medtra Inc., Detroit

TABLE I

Proposed "curative" fractionation:
Hyperthermia + Radiation Therapy

1. Hyperthermia only - 4 Treatments
45°C - 90 Minutes, (skin 36°C or below)
treat every 72 hours.
2. Rest 1 Week
evaluate response to heat alone.
3. Radiation Therapy and Hyperthermia - 4 treatments -
42°C - 90 minutes
Heat follows radiation (20 minute interval)
RT: 400 rad fractions - Each treatment

Total - 8 Hyperthermia treatments
+ 1600 rads/2 weeks/4 fractions

TEM mode. This particular design results in a better heating distribution as compared to that of TE₁₀ mode applicator.* Thermometry was accomplished using ultramicrothermocouples,* one or two of these inserted in the tumor tissue depending upon the size and location.

Results

At this time 62 patients have been treated with a total of 82 fields. Tables II and III summarize the results. A total response is observed in 49 treatment fields and a partial response in 27. No response was observed in only 6 fields. These included 1 squamous cell carcinoma, 1 adenocarcinoma and 1 sarcoma. The only complications that were directly attributable to treatment were 2 skin burns as a result of inadequate surface cooling and 2 tongue and pharynx burns. All of these healed completely. One patient with a history of epilepsy experienced a grand mal seizure during treatment of a neck tumor. Three marginal recurrences and 5 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 feasible to obtain actual thermometry for every treatment of every field with minimum patient discomfort.

Table III summarizes results by histology. It indicates that malignant lymphoma is most responsive to this combination treatment. It should be pointed out that tumor regression following completion of treatment is very slow and requires approximately two months before the total effect is observed. Another interesting observation made during these treatments is that the microwave power required to maintain the desired treatment temperatures declines following the first or second treatment of a given field. These two phenomena are probably related to heat induced physiological changes within the tumor which are involved in the ultimate destruction of the tumor. Further physiological studies are currently in progress.

Another interesting outcome of this study is to speculate on the possible meaning of the three marginal recurrences; they may indicate that this combined modality is effective in the treatment of microscopic disease. More time for follow-up and the input of more patients is required before a true evaluation of the clinical efficacy of this protocol can be made.

Discussion

Recent studies (2,4,19,20,23,25,41) involving a combination of hyperthermia and x-irradiation have made a serious effort to measure and document the hyperthermia treatments more accurately. In most cases a comparison with radiation alone controls is made. Kim et al. (23) have treated 50 patients with a variety of cutaneous tumors. Improved results are reported 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 of these modalities used alone. These authors report complete disappearance of multiple recurrent melanoma nodules without unusual normal skin reactions. However, combination therapy did produce enhanced skin reactions in patients whose treated areas included either a skin graft or heavily scarred skin from extensive surgery.

In their study the above authors report 78% overall tumor control rate after combined therapy as compared with 26% after radiation alone. These investigators utilized two heating methods. Some patients with tumors on extremities were heated by immersion in waterbath. The rest of the patients were treated using RF (27.12 MHz) inductive heating.

* All equipment by Medtra Inc., Detroit

TABLE II

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

TABLE III

<u>HISTOLOGY</u>	<u>NO. OF FIELDS</u>	<u>RESPONSE</u>	<u>FOLLOW-UP (Months)</u>
Malignant Melanoma	17	8 Total 6 Partial 3 No Response	2 months - 1 year
Malignant lymphoma	8	8 Total	2 - 7 months
Squamous cell carcinoma	19	7 Total 11 Partial 1 No Response	2 - 6 months
Adenocarcinoma	33	24 Total 8 Partial 1 No Response	2 - 7 months
Other (transitional cell, basal cell, glioma, sarcoma)	5	2 Total 3 Partial	2 - 9 months
Summary	82	49 Total 27 Partial 6 No Response	2 months - 1 year

Total Response: No tumor at 2 months follow-up and thereafter.

Partial Response: Tumor decreased in size to half or less at 2-months follow-up.

It should be pointed out that there is a great deal of variation in both the radiation dose and the hyperthermia treatment duration as well as in the number of fractions. The radiation doses employed varied from 800 rad in two fractions for melanoma to 2400 rad in 8 fractions for Kaposi sarcoma. Similarly hyperthermia (43.5°C) treatments vary from 2 fractions of 30 min. for melanoma to 5 fractions of 60 min. for mycosis fungoides. The hyperthermia treatments followed immediately the radiation treatments in all cases. This data does not suggest any particular treatment schedule for a particular tumor. The study does, however, demonstrate the improved effectiveness of combined thermoradiotherapy as compared hyperthermia or radiation alone.

Hornback et al. (19) treated 72 patients with advanced cancer using the combined therapy. Of the patients treated with hyperthermia prior to radiation therapy, 53% experienced complete remission of symptoms while in the group of patients 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 rads. Heat treatments were given using 433.92 MHz microwaves. Although the authors mention having attempted to measure tumor temperature during these treatments, there is no mention of tumor temperatures achieved in the patients.

Johnson et al (20) conducted a pilot study to evaluate normal skin and melanoma tumor thermal enhancement ratios of 41.5 to 42°C hyperthermia with radiation. The response of normal skin to the treatment was measured 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 bring to light some of the problems associated with obtaining useful clinical data. The study involved patients with multiple metastatic melanoma lesions. At least three lesions were chosen on each patient. The patients were divided into three groups and given one, 3 or 4 fractions, with a minimum 72 hours interval between each fraction. Radiation dose per fraction for different lesions on a patient varied from 500 to 900 rad. In some cases single fractions of 1000, 1100, 1200 or 1300 rad were used. On all patients one lesion was heated immediately following radiation therapy and the other two or more lesions treated with radiation alone were used for comparison. Hyperthermia treatments were administered using 915 MHz direct contact microwave applicators (30). Duration of hyperthermia treatments varied between 1 and 2 hours at 41.5-42.0°C.

Skin enhancement ratio (SER) and tumor enhancement ratio (TER) could be evaluated only for a limited number of patients because of lack of follow up data. 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 up to 4cm in diameter and 2cm depth 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. (26) reported a very limited study combining heat and radiation. Of the 40 patients treated with hyperthermia, four were treated in combination with radiation. Each had a minimum of 3 nodules. One nodule received a heat treatment of 43°C for 40 minutes using radiofrequency currents. Another nodule received radiation alone from two radium needles to a dose of 4000 rads in 100 hrs. A third lesion had the same dose plus simultaneous heat to 43°C for 40 minutes using radium needles as heating electrodes.

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

Another limited study (41) treated two groups of patients with radiotherapy alone, hyperthermia alone, and combined treatment. One group of patients received 200-600 rad fractions, 2-5 times per week to a total of 1800-4200 rad in 5-14 fractions. The other group of patients received the combined thermoradiotherapy treatments only, radiation fractions of 200-600 rad, 2-5 times a week to a total of 2000-4800 rad in 6-20 fractions. Hyperthermic treatments for both groups was 42-44°C, 2-3 times per week to a maximum of ten sessions in four weeks. Hyperthermia treatments were given using either 2450 or 915 MHz microwaves. The first group of 8 patients, six patients experienced complete regression of lesions treated with radiation plus 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 2/4 cases. No adverse side effects were observed on normal tissue from the combined treatments.

Another interesting study was reported by Arcangeli et al. (2). Fifteen patients with multiple neck node metastases from head and neck were treated with either radiation alone or in combination with hyperthermia. A total of 33 neck nodes were treated, 12 with radiation alone and the rest with the combination. Hyperthermia was induced by 500 MHz microwaves using 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, 4-5 hour interval between fractions, 5 days per week, up to a total of 4000/7000 rad. All the lesions were irradiated with the same total dose, whether or not they received hyperthermia.

The MDF schedule resulted in 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 in the treatment schedule, 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 were treated with combined treatment.

In the study reported here, an overall total response rate of 60% has been obtained. 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 in the treatment of malignant disease.

Abstract

A clinical trial is currently in progress to determine the efficiency of combined fractions of hyperthermia and radiation. The protocol consists of two parts. First, 4 fractions of microwave induced hyperthermia ($45.0 \pm 0.5^{\circ}\text{C}$) are applied for $1\frac{1}{2}$ hours to the volume encompassing the tumor, each separated by 72 hours. Allowing for a one week rest, a second series of four fractions are administered again at 72 hour intervals. Each of these fractions consists of a 400 rad dose of radiation followed within 20 minutes by hyperthermia ($42.5 \pm 0.5^{\circ}\text{C}$) for $1\frac{1}{2}$ hours.

Currently 82 fields have been treated on 62 patients with a mean follow-up time to date of 6 months. Total regression is seen in 60% of all cases, partial regression in 33% and no response is seen in only 6% of all treatments; 5 local and 3 marginal recurrences have been observed. Details of response based on site, histology and classification are discussed.

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