Henry Ford Hospital Medical Journal

Volume 29 | Number 4 Article 4

12-1981

Local Microwave Hyperthermia In Cancer Therapy. Preliminary Report

Carlos A. Perez

Walter Kopecky

Robert Baglan

D. Venkata Rao

Richard Johnson

LOCAL MICROWAVE HYPERTHERMIA IN CANCER THERAPY. PRELIMINARY REPORT

Carlos A. Perez, M.D., Walter Kopecky, Ph.D., Robert Baglan, M.D.
D. Venkata Rao, M.D. and Richard Johnson, M.D.*

Washington University School of Medicine, Roswell Park Memorial Institute*
and the Radiation Therapy Oncology Group

Summary

This report summarizes the preliminary experience on 26 patients treated at the Mallinckrodt Institute of Radiology with hyperthermia and irradiation. Patients were treated with 400 rad fractions given every 72 hours (twice weekly) for a total of 2400, 2800, 3200 or 4000 rad followed by hyperthermia. In addition 18 lesions were treated according to a protocol designed by the Radiation Therapy Oncology Group (RTOG) for superficial measurable tumors randomized lesions to receive three doses of 500 rad followed by hyperthermia (6 lesions), or irradiation alone (three doses of 600, 700 or 800 rad every 72 hours.

Hyperthermia was administered with 2450 MHz or 915 MHz microwave generators and appropriately designed surface applicators. Temperature used was 42.5^{o}-43^{o} C, 90 minutes, every 72 hours. Irradiation was delivered with varying energy electrons (12 to 16 Mev) as required by the size of the lesion and occasionally with Cobalt 60 in which case bolus was used to increase the surface dose.

Of the six lesions treated with 1500 rad and hyperthermia only two metastatic melanomas showed complete regression, three tumors exhibited partial regression (one metastatic epidermoid carcinoma in the abdominal wall, a melanoma and a recurrent ductal breast carcinoma of the chest wall). The two melanoma nodules with CR remained under control for 12 and 16 months after therapy. A metastatic melanoma nodule showed no significant regression. Nine of the 12 control lesions treated with radiotherapy alone, mostly melanoma or recurrent carcinoma of the breast showed complete regression after doses of irradiation alone varying from 1800 to 2400 in three fractions. The other three lesions had 50% or more regression of the tumor. Some of the patients had control of the lesions for 12 to 16 months after therapy. It was apparent that 1500 rad and hyperthermia were not as effective as higher doses of irradiation alone.

The patients treated on the intramural protocol (doses of 2400 to 4000 rad and hyperthermia) had recurrent lesions from epidermoid carcinoma of the head and neck or adenocarcinoma of the breast, most of them previously irradiated with doses ranging from 4000 to 6000 rad; other tumors included several metastatic melanoma nodules.

Four of six recurrent epidermoid carcinoma of the head and neck showed complete regression and two others 20 and 40% regression. Of three metastatic melanoma nodules treated with irradiation and hyperthermia two showed complete regression of the tumors and over 80% regression, all lasting from five to eight months.

Of eight recurrent adenocarcinoma of the breast nodules in the chest wall, two were treated with doses of 2000 rad and showed only minimal regression of the tumor and regrew within two months from treatment. This is contrasted with six other lesions, treated with eight or 10 fractions of 400 rad each; four lesions exhibiting complete regression and the other two about 80%, with a duration of about three months.

Further, three patients with rather extensive recurrent adenocarcinoma of the breast in the chest wall were treated with heat alone because of high doses of irradiation delivered previously, only minimal tumor regression was noted (less than 25%). One patient with recurrent laryngeal carcinoma in the neck treated with heat alone exhibited complete tumor regression, still present, 18 months after hyperthermia.

The doses of radiation and heat delivered have been extremely well tolerated by the normal tissues. Of the 34 sites treated, three (8%) developed blisters, three (8%) erythema only, three additional patients (8%) moist desquamation and 14 (41%) dry desquamation. There have been no instances of ulceration, necrosis or severe fibrosis in the treated areas, even in the patients surviving over one year.

In view of these preliminary observations we feel that additional clinical trials are warranted to assess the potential value of hyperthermia alone or combined with irradiation in the treatment of selected cancer patients. Intensive efforts will be immediately required to improve existing methods for delivery and measurement of heat to lesions located at more than 5 cm depth.

Introduction

Probably the first observation that heat has an effect on malignant cells was reported by Bush (1), who described the disappearance of a sarcoma following high fever in a patient with erysipela. Despite encouraging reports by Coley (2) using bacterial toxins to induce fever and Westermark (3), who used localized hyperthermia followed by two publications by Rohdenburg, 1918 (4) and Warren in 1935 (5) hyperthermia in the treatment of malignant disease has had minimal clinical application (6,7,8,9).

In the past 10 years there has been a renewed interest in this modality, with a large number of biological papers indicating that there may be significant advantages to the use of heat alone or combined with irradiation or cytotoxic drugs to enhance the killing of tumor cells (10,11,12).

The clinical use of localized or whole body heat has been severely hampered by the lack of adequate equipment to deliver effective heat in deep seated lesions and of thermometry techniques that may provide reliable information regarding the distribution of the heat in the target tissues. However, a number of institutions throughout the world have begun to utilize several modalities of heating (radiofrequency, microwave or ultrasound) in an effort to gain information relative to the tolerance of normal tissues and the optimal parameters of hyperthermia alone or combined with radiation to enhance tumor cell kill without damaging normal tissues.

The following is a report of preliminary observations accumulated at the Mallinckrodt Institute of Radiology in a selected group of patients with recurrent or metastatic superficial nodules treated over a two year period (1978-1979).

Materials and Methods

In 1978 and 1979 a total of 26 superficial tumors were treated at the Mallinckrodt Institute of Radiology with hyperthermia and irradiation.

The doses of irradiation consisted of 400 rad fractions given every 72 hours (twice weekly) for a total of 2400, 2800, 3200 or 4000 rad, in a dose seeking experiment to

assess tolerance of normal tissues and tumor response (3 to 5 patients per dose).

In addition 18 lesions were treated according to a protocol designed by the Radiation Therapy Oncology Group (RTOG) for superficial measurable tumors randomized lesions to receive three doses of 500 rad followed by hyperthermia (43^{o} C, 90 minutes, every 72 hours) or irradiation alone (three doses of 600, 700 or 800 rad every 72 hours).

Further, two recurrent nodules of head and neck epidermoid carcinoma and three extensive recurrences from carcinoma of the breast in the chest wall were treated with heat alone.

The equipment and techniques of heating as well as thermometry have been previously described (13). Microwave generators (2450 and 915 MHz) with specially designed applicators were used. Thermocouples were inserted at the depth of the tumor and over the skin surface and the temperature at these two sites was continuously recorded on a dual channel chart recorder.

Irradiation was delivered with varying energy electrons (12 to 16 Mev) as required by the size of the lesion and occasionally with Cobalt 60 in which case bolus was used to increase the surface dose.

Results

1. RTOG protocol 77-10.

Of the six lesions treated in this protocol with irradiation and hyperthermia, two metastatic melanomas showed complete regression, three tumors exhibited partial regression (one metastatic epidermoid carcinoma in the abdominal wall, a melanoma and a recurrent ductal breast carcinoma of the chest wall). The two melanoma nodules with CR remained under control for 12 and 16 months after therapy. A metastatic melanoma nodule showed no significant regression.

Some of the lesions probably did not show clinical regression because the patients were in a terminal state and died within weeks from therapy.

Nine of the 12 control lesions treated with radiotherapy alone, mostly melanoma or recurrent carcinoma of the breast showed complete regression after doses of irradiation alone varying from 1800 to 2400 in three fractions. The other three lesions had 50% or more regression of the tumor. Some of the patients had control of the lesions for 12 to 16 months after therapy.

It was apparent from this study that 1500 rad and hyperthermia were not as effective as higher doses of irradiation. On this basis, an intramural protocol was initiated which delivered higher doses of irradiation.

2. Intramural protocol.

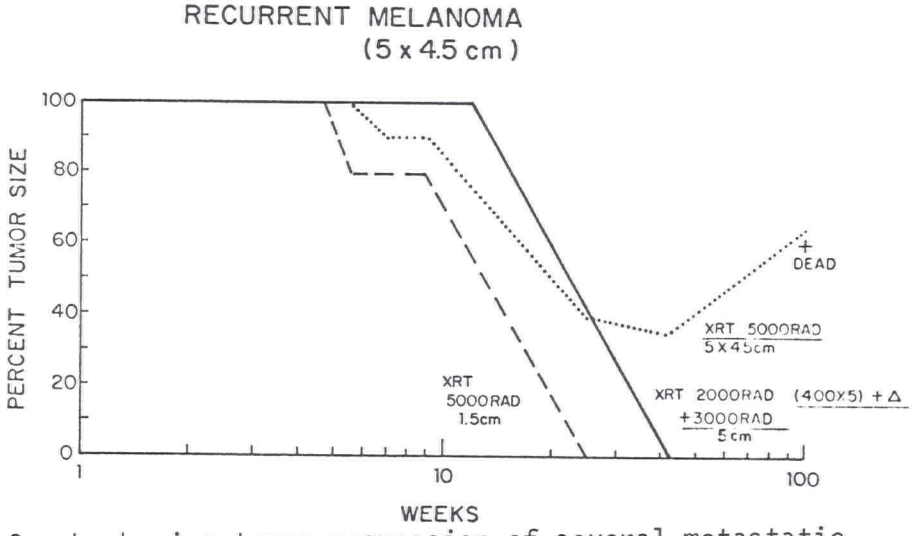
The patients treated on the Washington University intramural protocol had recurrent lesions from epidermoid carcinoma of the head and neck or adenocarcinoma of the breast most of which had been previously irradiated with doses ranging from 4000 to 6000 rad, other tumors included several metastatic melanoma nodules (Tables 1 and 2).

Four of six recurrent epidermoid carcinoma of the head and neck showed complete regression and two others 20 and 40% regression. Of three metastatic melanoma nodules treated with irradiation and hyperthermia two showed complete regression of the tumors and one 80% regression, all lasting from five to eight months.

One of the patients treated with heat alone showed complete regression of a 4 x 3 x 1 cm subcutaneous nodule with superficial ulceration of the left neck which appeared following 1½ years after delivery of 5700 rad TD to the neck with Cobalt 60 and supraglottic laryngectomy. The patient remains free of disease 15 months after therapy. Another patient, with a 7 x 3 x 5 x .5 cm recurrent epidermoid carcinoma of the scalp was treated with heat alone. Most of the tumor underwent complete regression but persistent nodule at the margin was treated with 4500 rad TD in 15 fractions, three weeks with superficial x-rays (120 KV, .3 mm cu HVL). He died eight months later with liver cirrhosis; there was no evidence of recurrent tumor (Fig. 1A, 1B).

Of the three metastatic melanoma nodules, treated with irradiation and hyperthermia two showed complete regression of the tumors, which lasted from five to 10 months. One of the patients had two lesions (Fig. 2A, 2B); one was treated with irradiation (5000 rad) and hyperthermia, with practically complete regression, which lasted for eight months. The patient died with widespread metastases. The second lesion was treated with irradiation alone (as control site); a regression of 75% was noted, with regrowth within six months of therapy (Fig. 3).

Figure 3



Graph showing tumor regression of several metastatic melanoma nodules.

Of eight recurrent adenocarcinoma of the breast lesions in the chest wall, two were treated with doses of 2000 rad and they showed only minimal regression of the tumor and regrew within two months from treatment. This is contrasted with six other lesions, treated with eight or 10 fractions of 400 rad each, four lesions exhibiting 100% regression and the other two 80% response, with a duraction of about three months.

In the three patients with rather extensive recurrent adenocarcinoma of the breast and the chest wall treated with heat alone because of high doses of irradiation delivered previously, only minimal regression was noted (less than 25%).

Normal tissue reactions

The doses of radiation and heat have been extremely well tolerated by the normal tissues. Of the 34 sites treated, three (8%) developed blisters, three (8%) erythema only, three additional patients (8%) moist desquamation and 14 (41%) dry desquamation.

This is in contrast to the patients treated with irradiation alone, three of whom developed moist desquamation with doses of 2100 and 2400 rad in three fractions (5%).

There have been no instances of ulceration, necrosis or severe fibrosis in the treated areas, even in the patients surviving over one year.

The degree of fibrosis existing at the time of the irradiation and hyperthermia, due to previous radiotherapy has not been aggravated by the additional hyperthermia and irradiation treatment.

Discussion

In vitro and *in vivo* biological experiments suggest that heat may be more damaging to tumor than to normal cells because of a variety of reasons, which include 1) reduced blood supply in the tumor, 2) possible inherent increased sensitivity of hypoxic cells to heat and 3) metabolically deprived tumor cells with reduced pH. In addition, heat affects cells in "S" phase, which are known to be resistant to irradiation (10,11,14).

The sensitivity of hypoxic cells to heat is complicated by the possible association of low oxygen tension with nutrient deficiency or reduced pH. As pointed out by Dewey (11) this response of the tumor may be complicated by physiological changes associated with lowering in blood flow and oxygen tension produced by the hyperthermia.

Heat causes a greater degree of mitotic delay than irradiation, and this factor may affect the distribution of cells in the cell cycle after heat or x-rays (15,16).

Experiments are being conducted at the present time to separate the thermal from the nonthermal effects produced by some of the heating modalities used, such as ultrasound and radiofrequency hyperthermia.

It is important to gather information concerning the effects of heat alone or combined with irradiation or cytotoxic agents on human tumors. Also, of equal significance are the observations concerning the effects of this modality on the normal tissues. Since qualitatively the reactions may be similar it is critical to quantitate as much as possible both tumor regression and normal tissue injury.

In regard to normal tissue response, Moritz and Henriques (17) demonstrated that skin in contact with hot water would suffer severe damage once a critical temperature had been reached. Similar observations have been noted in the tails of baby rats immersed in hot water. The authors calculated that an increase of only 20% in heating time or less than $.5^{o}$ C at the critical temperature would enhance the probability of tissue necrosis from zero to 100%. This underlines the importance of the need for accurately measuring the temperature and to deliver uniform temperature in the volume treated in clinical applications.

The reduction in dose of irradiation combined with heat to produce the same biological

effect has been defined as thermal enhancement ratio (TER). If there is greater TER in tumor than normal tissues the differences is defined as therapeutic gain factor (TGF).

Unfortunately, before an optimal clinical use of heat can be accomplished there are a number of technological problems related to heating sources, clinical thermometry and definition of a variety of treatment factors which may influence the effects of this modality alone or combined with irradiation which will require a great deal of effort in development and well designed clinical trials.

The currently existing hyperthermia modalities, microwave, radiofrequency and ultrasound have inherent advantages and disadvantages which have been summarized by other authors (18). At the present time a major obstacle to clinical application of heat is the inability to deliver adequate and homogeneous temperatures to deep seated tumors (3 cm penetration of 915 MHz and 4 cm for 433 MHz microwave). Lower frequencies (27 MHz) may provide better depth temperature but heat deposition is diffuse and cannot be localized to small volumes.

Also, invasive thermometry must be used with each application, which represents some discomfort to the patient. In addition, hyperthermia with ultrasound cannot be carried out with deep seated tumors unless they are near a natural hollow viscera, such as the esophagus, bladder, rectum etc. Furthermore, only a few points of temperature can be measured. This is unsatisfactory, since we know that in steady state phantoms the thermal distribution is not homogeneous. In addition, there is a decreased temperature in the depth of the tissues, due to absorption and dissipation (18). Also, the intricacies of the relationship between microcirculation, blood flow and temperature distribution have just begun to be explored (19).

Among the biologically related events that have significant impact in clinical application of heat are the following:

1. Temperature and time of heat exposure.

In vitro and in vivo experiments have demonstrated that there is a greater degree of cell kill with increasing temperatures, particularly above 42^{o} C. The time of exposure to heat and the temperature are closely interrelated. According to Henriques (20) over 43.5^{o} C the effect of increased temperature of 1^{o} C is equivalent to a decrease in heating time by a factor of two (and vice versa).

2. Fractionation and thermal tolerance or resistance.

Henle and Leeper (21) have demonstrated in vitro that fractionated hyperthermia may result in thermal tolerance, which can be represented as an increase in the Do of a subsequent hyperthermia survival curve which has been distinguished from the repair of sublethal heat damage reflected as a return of the shoulder (21,22). The time for development of maximal thermal tolerance and the level of this phenomenon depend upon the degree of damage induced by the first heat treatment (23,24). Thermal tolerance has been observed in most cultured mammalian cells and in all normal tissues evaluated. Thermal tolerant cells may be more resistant to irradiation (21,25,26), which makes this even a more important problem when both modalities are combined.

As noted by Field and Bleehen (12) low heating times at moderate temperatures may induce thermal resistance, which could have a profound clinical affect.

3. Sequential administration of heat and irradiation.

Overgaard and Overgaard (27) observed in a mouse mammary carcinoma treated with 27 MHz microwave that the central portion of the tumor was more severely damaged than the periphery. This would support the use of combined irradiation and heat, hyperthermia being especially effective against centrally located hypoxic cells system to irradiation and irradiation eliminating the tumor cells in the periphery of the tumor, where heat would be less effective.

Dewey et al. (10) and Sapareto (28) have shown that cells at low pH are less efficient in repairing sublethal heat damage which can interact with sublethal radiation damage. These authors have shown in cells in vitro that when heat and irradiation are administered together there is a greater cell kill than when heat is delivered more than 30 minutes before or after administration of the irradiation. When the two modalities are combined the increased cell killing follows the pattern of direct heat injury not that of irradiation, thus the effect of the radioresistant S phase cells is greater than on the more radiosensitive cells in other portions of the cell cycle (late G1 or G2 interface).

Dewey (11) has hypothesized that if heat is delivered three hours prior to irradiation, cells with a low pH will have minimal ability to repair heat damage and therefore may be greatly sensitized to the affects of subsequent irradiation. In vivo data reported by Overgaard (27) and Stewart and Denekamp (14) in animals suggests that when the irradiation is delivered before the heat skin behaves like cells with normal pH and tumor cells as those having low pH. However, when the heating preceeds irradiation the data for the skin parallels that of in vitro experiments, but for tumors it is not reproducible.

Several preliminary reports on the clinical application of hyperthermia have been published recently.

Hornback et al. (7) reported on 70 patients with advanced malignant tumors of various histological types treated with microwave radiation (433 MHz) and ionizing radiation (doses ranging from 1100 in two weeks to 6000 rad in six weeks). Twenty-one patients completed the planning course of treatment and were followed for a minimum of nine months. Ninety percent experienced complete relief of symptoms and 80% exhibited complete tumor regression. Nine of the complete responders remained free of tumor from nine to 14 months after therapy. The combined treatment was well tolerated, without significant skin or subcutaneous tissue injury.

LeVeen et al. (29) described the results in 21 patients with different malignant neoplasias treated with radiofrequency (13.56 MHz). The authors describe tumor regression or destruction without residual tumor at autopsy, but it is difficult to ascertain from their publication exactly how many patients had complete or partial tumor regression and how many have survived for extended periods of time after therapy.

Kim and Hahn (30) reported partial and transitory tumor regressions in 10 of 19 patients treated with 27.2 MHz radiofrequency inductive heating (30 minutes, 42^{o} C). In contrast, the same authors observed partial or complete tumor regression in 42 of 54 patients receiving a combination of heat immediately before irradiation (1000 to 2000 rad). These authors reported enhanced skin reactions after this combined therapy only in patients treated to areas including skin grafts or extensive fibrosis from previous surgical procedures.

Marmor et al. (31) reported results in 26 evaluable courses of hyperthermia in 21 patients with superficial metastatic or recurrent malignant tumors treated with a minimum of 43° C for 30 minutes given three times weekly. Tumor response was analyzed after six treatments. Of the lesions treated three had complete response (12%) and 11 a partial response (42%). Squamous cell carcinoma lesions of the head and neck showed several regressions (one complete only). There were five patients who developed small superficial cutaneous burns that healed in seven to 10 days. There were four instances of extensive central tumor necrosis. Ten of the 26 courses of treatment resulted in significant pain during the ultrasound irradiation, usually subsiding after completion of the treatment. There was no significant correlation between the temperature in the center of the tumor and the injury to the normal tissues, except that four cases of central necrosis were observed with temperatures above 44° C. Previous irradiation of the treated area did not decrease the tolerance of the normal tissues to ultrasound.

A subsequent report by Marmor and Hahn (9) describe their experience on 16 patients receiving 18 courses of irradiation with ultrasound for recurrent tumors after doses of irradiation ranging from 4400 to 11,000 rad. Eleven of the 18 courses of ultrasound resulted in objective tumor response (only two complete). In addition, five previously irradiated patients were given six courses of heat plus low dose irradiation (1200 to 2400 rad). Three patients showed complete tumor response and two partial tumor regression, suggesting that the combination of heat and irradiation was more effective than ultrasound alone.

Recently, Bicher et al. (32) described the preliminary results of treatment with microwaves (frequencies of 2450, 915 and 300 MHz) for 90 minutes. The skin was cooled by an air jet. Tissue temperature was kept at 45° C when hyperthermia alone was used and at 42° C in combination with radiation. Patients were treated twice a week with 72 hour intervals between treatments. The regime consisted of four treatments of hyperthermia alone followed by a week of rest. Thereafter each hyperthermia treatment was preceeed by a 400 rad fraction or x-irradiation delivered in four combined treatments to a total of 1600 rad. Twenty-three patients encompassing 37 treatment fields have been entered into the protocol. Most tumors responded to treatment, 62% of these with total disappearance; skin, brain, breast and spinal cord are among the treated areas. Melanomas and lymphomas are the most sensitive tumors, sarcomas the most resistant; adeno and squamous cell carcinoma intermediate. No toxicity induced by this combination has been detected, even in areas previously irradiated to high doses.

Arcangeli et al. (33) reported on a group of 15 patients with N2 and N3 multiple cervical lymph nodes for head and neck cancer treated with multiple daily fractionation radiotherapy (total doses of 4000-7000 rad) and local hyperthermia (2450 or 915 MHz). Seventeen of 20 lymph nodes (85%) treated with this combination achieved complete regression compared with six of 13 (46%) treated with multiple fractionation irradiation alone and 14 of 46 (30%) with lymph nodes treated with conservative fractionation radiotherapy (historical controls). The authors did not observe enhanced normal tissue reactions.

From preliminary studies it is apparent that heat alone, or optimally combined with irradiation has the ability to destroy tumor cells and has potential clinical application in cancer management. However, an intensive effort must be devoted to the development of adequate equipment that can deliver heat to deep seated tumors, located in the thorax, abdomen or pelvis. Even though ultrasound has definite advantages over radiofrequency of

microwave in terms of depth of penetration, a major obstacle faced by this modality is the reduction and absence of penetrability induced by air tissue or tissue bone interfaces.

Furthermore, dosimetric observations have documented the lack of uniformity in heat distribution with some modalities and applicators as well as the non-uniform distribution of heat in most tumors. Stringent quality control programs in hyperthermia, like the irradiation must be designed to enhance the accuracy of determination of heat absorption in tissues and to monitor the temperature at various sites throughout the administration of hyperthermia. The Radiation Therapy Oncology Group is developing a collaborative hyperthermia physics reference center to provide the standards for dosimetry in clinical trials conducted by this group. In addition, major efforts and funds should be devoted to the design and development of invasive and non-invasive clinical thermometry technology. Since it is extremely difficult to do in situ measurements at multiple sites in deep seated tumors, non-invasive thermometry techniques must be developed in appropriate models, so that only a few reference points, such as in the surface and the center of the tumor, when clinically feasible, should be carried out with every treatment. As the advances in technology evolve it will be important to continue clinical trials to determine the optimal schemas for administration of heat and irradiation or drugs to achieve the maximum therapeutic gain.

TABLE 1

HYPERTHERMIA STUDY

PATHOLOGICAL DIAGNOSIS - RTOG 77-10

Initials	Tumor Site	Histology	Initial Size-mm	Treatment		Maximum Skin Subcutaneous Reaction	% Maximum Tumor Regression	Response Duration (months)
				XRT Dose	Hyperthermia			
KMR	R Axilla	Epidermoid	14 x 14	700 x 3	None	None	50%	Expired 6 wks Post
KMR	R Breast	Epidermoid	22 x 28	800 x 3	None	None	50%	"
OC	L Upper Thigh	Melanoma	25 x 25	600 x 3	None	None	100%	12
OC	L Upper Thigh	Melanoma	10 x 10	600 x 3	None	None	100%	12
OC	L Lower Thigh	Melanoma	5 x 5	700 x 3	None	--	100%	12
EO	R Chest Wall	Ductal	15 x 15	700 x 3	None	--	100%	3
EO	R Scapula	Ductal	25 x 25	800 x 3	None	--	100%	3
EH	L Thigh	Melanoma	10 x 10	700 x 3	None	Moist Desq	100%	16
EH	L Inguinal Area	Melanoma	20 x 35	800 x 3	None	Moist Desq	100%	16
EH	L Inguinal Area	Melanoma	25 x 40	800 x 3	None	Moist Desq	100%	16
OC	Abdominal Wall	Melanoma	15 x 15	800 x 3	None	None	100%	6
OC	L Groin	Melanoma	20 x 16	800 x 3	None	None	70%	6
KMR	Ant Abd Wall	Epidermoid	26 x 22	500 x 3	2450 MHZ	Blister at Margin	50%	Expired 8 weeks Post Tx
OC	Left Mid Thigh	Melanoma	50 x 50	500 x 3	2450 MHZ	Blister	100%	12
OC	Left Mid Thigh	Melanoma	7 x 7	500 x 3	2450 MHZ	Blister	60%	4
EO	R Chest Wall	Ductal	30 x 30	500 x 3	2450 MHZ	Moist Desq and Blister	25%	3
EH	Left Thigh		10 x 10	500 x 3	2450 MHZ	Moist Desq	100%	16
OC	Left Knee	Melanoma	10 x 10	500 x 3	915 MHZ	None	0%	--

TABLE 2

PHASE I-II HYPERTHERMIA STUDY

(915 MHZ - 42.5 - 43°C - 90 MINUTES)

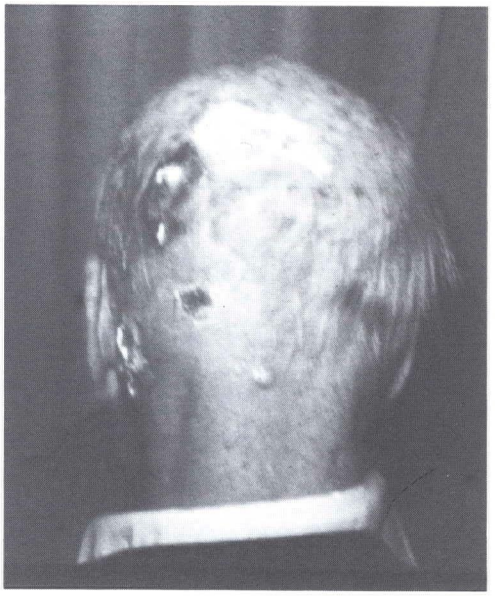
EPIDERMOID CA, HEAD AND NECK, RECURRENT

INITIALS		SITE OF TUMOR	SIZE(CM)	PERCENT REGRESSION	DURATION (MONTHS)	NORMAL TISSUE REACTION
	HEAT ALONE					
W.S.		LEFT NECK	4 x 3	100	13	DRY DESQ
W.B.		SCALP	7 x 3.5	100	8	DRY DESQ
	HEAT AND XRT					
J.V.	400 RAD x 6	FLOOR OF MOUTH	.5 x 3.5	20	2	DRY DESQ
H.B.	400 RAD x 7	LEFT NECK	4 x 3	40	1	DRY DESQ
C.H.	400 RAD x 8	RIGHT NECK	4 x 4	100	3	DRY DESQ
D.S.	400 RAD x 6	RIGHT NECK	2.5 x 2	100	2	DRY DESQ
P.L.	400 RAD x 10	LEFT NECK	- -	100	5	DRY DESQ
L.H.	400 RAD x 10	LEFT NECK	- -	100	7	DRY DESQ
		ADENOCARCINOMA				
	HEAT ALONE					
G.W.		BREAST/CHEST WALL	18 x 15	25	1	DRY DESQ
J.K.		BREAST/CHEST WALL	18 x 9	25	6	DRY DESQ
P.S.		BREAST/CHEST WALL	15 x 11	15	2	DRY DESQ
	HEAT AND XRT					
I.A.	400 RAD x 5	BREAST/RIGHT NECK	5 x 3	10	2	DRY DESQ
I.A.	400 RAD x 5	BREAST/AXILLA	3 x 2	16	2	DRY DESQ
M.W.	400 RAD x 10	BREAST/NECK NODES	5.5 x 3	100	1	DRY DESQ
M.W.	400 RAD x 10	BREAST/NECK NODES	5 x 2	100	1	DRY DESQ
M.W.	400 RAD x 10	BREAST/NECK NODES	4 x 2.5	100	1	DRY DESQ
J.H.	400 RAD x 10	BREAST/CHEST WALL	3 x 3	100	5	ERYTHEMA
B.M.	400 RAD x 8	LUNG/RIGHT NECK	1 x .5	80	3	ERYTHEMA
B.M.	400 RAD x 8	LUNG/CHEST WALL	1 x .5	80	3	ERYTHEMA

(ALL PATIENTS HAD PREVIOUS IRRADIATION TO SITE NOW TREATED)

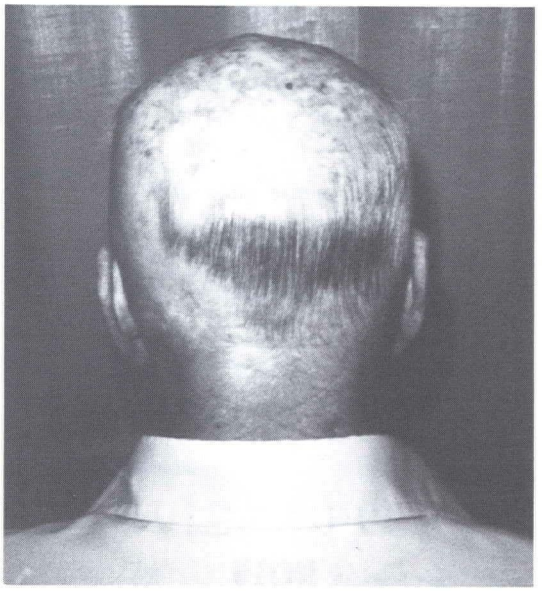
		METASTATIC MELANOMA				
	HEAT AND XRT					
R.H.	400 RAD x 8	RIGHT POST-AURICULAR	2 x 1.5	100	7	DRY DESQ
P.M.	400 RAD x 8	GROIN	8 x 3	100	5	ERYTHEMA
W.K.	400 RAD x 5 + 500 RAD x 6	RIGHT LEG	5 x 4.5	80	8	DRY DESQ
	XRT ALONE					
W.K.	400 RAD x 5 + 500 RAD x 6	RIGHT LEG	5 x 5	60 (REGROWTH)	8	DRY DESQ
		SOFT TISSUE SARCOMA				
	HEAT AND XRT					
H.R.	400 RAD x 10	LEFT FOREHEAD	3.5 x 3.5	100	7	DRY DESQ
L.R.	400 RAD x 11	RIGHT TEMPORAL	4.5 x 4	100	4	DRY DESQ
	"	"	2.5 x 2.5	"	"	DRY DESQ

FIGURE 1A



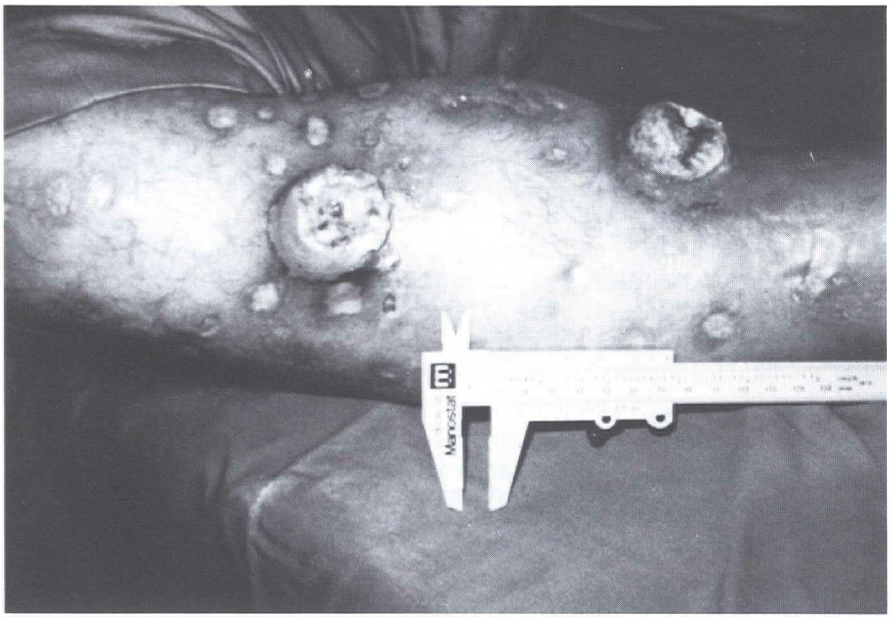
Recurrent epidermoid carcinoma of the scalp treated with heat alone. Most of the tumor underwent complete regression but persistent nodule at the margin was treated with 4500 rad TD in 15 fractions, three weeks with superficial x-rays (120 KV, .3 mm cu HVL).

FIGURE 1B



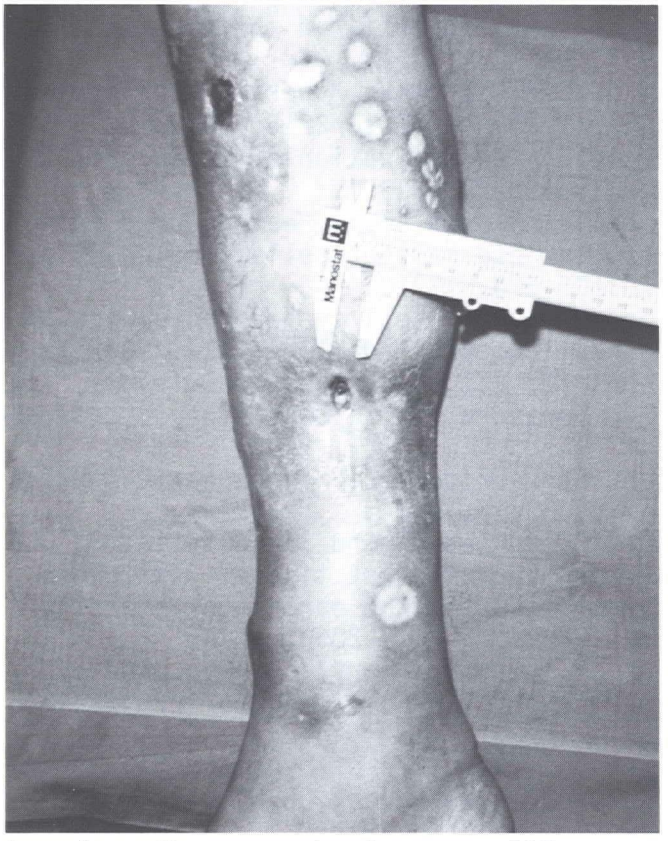
Photograph seven months after treatment showing complete regression of tumor.

FIGURE 2A



Pretreatment photograph of two large ulcerated metastatic nodules (4 cm in diameter) in the leg. The upper lesion was treated with a combination of irradiation (5000 rad in 11 fractions) and hyperthermia. The lower lesion was treated with the same dose of irradiation but without heat.

FIGURE 2B



Photograph six months after therapy, showing over 90% regression of the tumors. The lower lesion, treated with irradiation alone recurred shortly thereafter.

REFERENCES

1. Busch W: Uber den Einfluss welchen heftigere Erysipelen zuweilen auf Organisierte Neubildungen ausuben. Verhandlungen des Naturh. Preuss Rheinl: 23:28-30, 1866.
2. Coley WB: The treatment of malignant tumors by repeated innoculations of erysipelas - with a report of 10 original cases. Amer J Med Sci: 105:487-511, 1893.
3. Westermark F: Uber die Behandlung des Ulcerirended Cerixcarcinoms. Mittle Konstanter Wärme. Zbl Gynak: 1335-1339, 1898.
4. Rohdenburg GL: Flunctuations in the growth of malignant tumors in man, with special reference to spontaneous recession. J Cancer Res: 3:193-225, 1918.
5. Warren SL: Preliminary study of the effect of artificial fever upon hopeless tumor cases. Am J Roentgen: 33:75-87, 1935.
6. Pettigrew RT, Galt JM, Ludgate CM and Smith AN: Clinical effects of whole-body hyperthermia in advanced malignancy. Brit Med J: 4:679-682, 1974.
7. Hornback, NB, Shupe RE, Shidnia H, Joe BT, Sayoc E and Marshall C: Preliminary clinical results of combined 433 megahertz microwave therapy and on patients with advanced cancer. Cancer: 40:2854-2863, 1977.
8. Holt, JAG: The use of V. H. F. radiowaves in cancer therapy. Australas Radiol: 19:1975.
9. Marmor JB and Hahn GM: Ultrasound heating in previously irradiated sites. Int J Radiat Oncol Biol Phys: 4:1029-1032, 1978.
10. Dewey, WC, Highfield DP, Freeman ML, Coss RA, Wong RSL and Barrau MD: Cell Biology of Hyperthermia and Radiation. 6th Int Congr Radiat Res (Tokyo), ed S Okada, p. 832-840, 1979.
11. Dewey WC, Hopwood LE, Sapareto, SA and Gerweck LE: Cellular Responses to Combinations of Hyperthermia and Radiation. Radiology: 123:463-474, 1977.
12. Field SB and Bleehen NM: Hyperthermia in the treatment of cancer. Cancer Treatment Reviews: 6:63-94, 1979.
13. Kopecky WJ and Perez CA: A Microwave Hyperthermia Treatment and Thermometry System. Int J Radiat Oncol Biol Phys: 5:2213-2215, 1979.
14. Stewart FA and Denekamp J: Sensitization of mouse skin to X-irradiation by moderate heating. Radiology: 123:195-200, 1977.
15. Dewey WC, Westra A, Miller HH, et al.: Heat-induced lethality and chromosomal damage in synchronized Chinese hamster cells treated with 5-bromodeoxyuridine. Int J Radiat Biol: 20:505-520, 1971.
16. Kal HB, Hatfield M and Hahn GM: Cell cycle progression of murine sarcoma cells after irradiation or heat shock. Radiology: 117:215-217, 1975.
17. Moritz AR and Henriques FC: Studies of thermal injury. II. The relative importance of time and surface temperature in the causation of cutaneous burns. Am J Path: 23:695-720, 1947.
18. Guy AR, Lehmann JF and Stonebridge JB: Therapeutic Applications of Electromagnetic Power. Proc IEEE: 62(1):55-75, 1974.
19. Endrich B, Zweifach BW, Reinhold HS and Intaglietta M: Quantitative studies of microcirculatory function in malignant tissue: Influence of temperature on microvascular hemodynamics during the early growth of the BA 1112 rat sarcoma. Int J Radiat Oncol Biol Phys: 5:2021-2030, 1979.
20. Henriques FC: Studies of thermal injury. V. The predictability and the significance of thermally induced rate processes leading to irreversible epidermal injury. Arch Path: 43:489-502, 1947.
21. Henle KJ and Leeper DB: Interaction of hyperthermia and radiation in CHO cells: Recovery kinetics. Radiation Research: 66:505-518, 1976.

22. Gerner EW and Schneider MJ: Induced thermal resistance in HeLa cells. Nature: 256:500-502, 1975.
23. Law MP, Coultas PG and Field SB: Induced thermal resistance in the mouse ear. Brit J Radiol: 52:308-314, 1979.
24. Henle KJ, Bitner AF and Dethelfsen LA: Induction of thermotolerance by multiple heat fractions in Chinese hamster ovary cells. Cancer Research: 39:2486-2491, 1979.
25. Nielsen OS and Overgaard J: Hyperthermic radiosensitization of thermotolerant tumor cells in vitro. Int J Radiat Biol: 35:171-176, 1979.
26. Law, MP, Ahier RG and Field SB: The response of the mouse ear to heat applied alone or combined with X rays. Brit J Radiol: 51:132-138, 1978.
27. Overgaard K and Overgaard J: Investigations on the possibility of a thermic tumor therapy - I. Short-wave treatment of a transplanted isologous mouse mammary carcinoma. Eur J Cancer: 8:65-78, 1972.
28. Sapareto SA, Raaphorst GP and Dewey WC: Cell killing and the sequencing of hyperthermia and radiation. Int J Radiat Oncol Biol Phys: 5:343-347, 1979.
29. LeVeen HH, Wapnick S, Piccone V, Falk G and Ahmed N: Tumor eradication by radiofrequency therapy. Response in 21 patients. JAMA: 235:2198-2200, 1976.
30. Kim JH and Hahn EW: Clinical and Biological Studies of Localized Hyperthermia. Cancer Research: 39:2258-2261, 1979.
31. Marmor JB, Pounds D, Postic TB and Hahn GM: Treatment of superficial human neoplasms by local hyperthermia induced by ultrasound. Cancer: 43:188-197, 1979.
32. Bicher HI, Sandhu TS and Hetzel FW: Hyperthermia and radiation in combination: A clinical fractionation regime. Int J Radiat Oncol Biol Phys: (In press).
33. Arcangeli G, Barni E, Cividalli A, Mauro F, Morelli D, Nervi C, Spano M and Tabocchini A: Effectiveness of microwave hyperthermia combined with ionizing radiation: Clinical results on neck node metastases. Int J Radiat Oncol Biol Phys: 6:143-148, 1980.