LOCAL HYPERTHERMIA FOR SUPERFICIAL AND MODERATELY DEEP TUMORS-FACTORS AFFECTING RESPONSE

HAIM I. BICHER AND RALPH S. WOLFSTEIN

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Bicher Cancer Institute, Los Angeles, California, U.S.A.

INTRODUCTION

Many reports in the peer review medical literature on the clinical application of hyperthermia over more than a decade have contributed to recognition of its safety and efficacy, with a synergistic effect in combination with radiation and/or chemotherapy. (1-36)

Mechanisms of hyperthermia effect on tumor while sparing normal tissue have been well evaluated, including interaction with ionizing radiation (37-48). Tumor cells are more sensitive to heat than normal cells. More significant however, because of physiological factors, tumor tissue is far more affected by application of heat inducing energy than is normal tissue. Tumor cells distant from capillaries undergo anaerobic metabolism and thus have lower pH. Hyperthermia impairs microcirculation in tumors, thus further increasing tumor acidity, and decreasing tumor oxygenation (37-40, 42, 46). Hyperthermia cytotoxicity is maximal in the S phase of the cell replication cycle (41, 45, 47). Since radiation and chemotherapy are least effective on cells in the S phase and induce S phase in cells undergoing sublethal injury, there is a rational basis for expecting greater tumor destruction when these modalities are combined with hyperthermia.

Most groups, including our own, have employed clinical protocols with intervals of 3 days between hyperthermia treatments, in tacit or stated deference to the well-established phenomenon of thermotolerence, which has been well described in laboratory studies that demonstrate resistance of treated cells to a second heat insult over a period of time (43, 44).

Our experience over the past four years, on which this report is based, suggests that thermotolerence may not be a definitive factor in the clinical use of hyperthermia in certain situations. In the current studies we undertook to evaluate the factors affecting response rate of superficial and deep tumors using different fractionation regimes of both irradiation and hyperthermia.

MATERIALS AND METHODS

Single air gap microwave applicators operating at 915 or 300 MHz with power up to 400 Watts* were used for hyperthermia treatment of tumors up to 5 cm from the surface. For deeper tumors two such 300 MHz were used, parallel opposed and operated in phase (POPAS) at power up to 800 watts (36,49). Thermometry was done throughout each treatment session using two triple junction copper-constantan microthermocouples (100 micron)*. Temperature readings were obtained at 4-5 minute intervals with power off, to prevent microwave interference artifact, recorded on a modified computer system that also controls the power on-off cycle. Thermocouples were placed in the tumorous and normal tissue.

Each hyperthermia treatment lasted up to one hour, with the goal of achieving minimum tumor temperature of 42 degrees C for at least 30 minutes. Hyperthermia treatments were given either twice a week over 5 weeks, as previously reported, or daily for 5 weeks. Since September of 1987 all patients have been given daily hyperthermia treatments.

All treatment was given under FDA approved protocols, and all patients accepted for treatment signed the appropriate consent form. Eligible patients had advanced primary cancer (36 patients), post treatment local recurrence (54 patients), or metastatic disease (82 patients).

For patients receiving radiation therapy, this treatment was given within 2 hours of hyperthermia, either before or after. Total radiation dose and fractionation depended on normal tissue tolerance. Patients treated with the goal of cure received the same full course of radiation therapy that would be considered appropriate if no adjunct hyperthermia were given. Patients on chemotherapy received the drug dosage schedule appropriate to their individual problem, at the discretion of the referring medical oncologist. Chemotherapy was given in conjunction with as many hyperthermia treatments as practical and as close as possible to hyperthermia, optimally by infusion continuing through the hyperthermia session.

This report analyses results of hyperthermia treatment of 299 tumors fields in 172 evaluable patients treated since September, 1984. Of these, 178 were superficial, treated with a single applicator, and 121 were treated with POPAS. Some superficial treatments (15/144) and 40% of POPAS treatments (48/121) were given with no adjunct radiation therapy; almost all of these patients did receive chemotherapy. Tumor response was evaluated by physical examination where feasible, precisely measured in 2 dimensions with estimated tumor depth, and in deeper tumors by x ray, CT or MRI. Response was graded as complete (CR) when there was no residual tumor, partial (PR) if tumor regression exceeded 50%, stable (SD) when there was less regression or no progression of tumor within two months following treatment.

RESULTS

Overall results are shown in Table 1. Side effects were minimal, noted in less than 10% of patients. Superficial and POPAS treatments were equally well tolerated (Table 2). Patients did perspire quite freely during POPAS treatments, kept comfortable with damp cloths and drinks. Core temperature did not rise significantly less than 2 degrees C even after consecutive treatment of two fields given over more than 2 hours. Radiation induced skin reaction was never more than anticipated for the same dose given without hyperthermia. No patients discontinued hyperthermia treatment because of toxicity of subjective intolerance.

TABLE 1 SUMMARY RESULTS 227 PATIENTS, 172 EVALUABLE, 299 FIELDS

	Response	
CR (complete)	113	(38%)
PR (50% or more)	123	(41%)
SD (No growth at 2 months)	29	(10%)
NR (No response)	34	(11%)

Complications	
Thermal Burns	16 (Healed fully)
Ulceration	3 (Healed fully)
Pneumothorax	2 (Hospitalized 1 day)
Ileus	1 (Hospitalized 3 days)

TABLE 2 SUMMARY RESULTS

Response	Superficial	POPAS
	(N=178)	(N=121)
CR (%)	89 (50)	24 (20)
PR (%)	66 (37)	57 (47)
SD (%)	10 (6)	19 (16)
NR (%)	13 (7)	21 (17)

Abbreviations: CR, complete; PR, partial; SD, stable disease; NR, no response

Patients with objective tumor regression less than 50% but no progression at 2 months following treatment were considered to have stable disease (SD), as also suggested by others (35). Most with SD had palliation and improved clinical status. The category of SD was established because many patients, 16% of those treated with POPAS, obviously benefited from treatment but without significant objective decrease in tumor size.

TABLE 3 RESULTS BY RADIATION DOSE

	Superficial			POPAS		
	30Gy(+)	20Gy(-)	0	30Gy(+)	20Gy(-)	0
	(N=83)	(N=67)	(N=28)	(N=35)	(N=38)	(N=48)
CR (%)	45 (54)	37 (55)	7 (25)	16 (46)	3 (8)	5 (10)
PR (%)	32 (39)	20 (30)	14 (50)	14 (40)	18 (47)	25 (52)
NR +SD%	6 (7)	10 (15)	7 (25)	5 (14)	17 (45)	18 (38)

Abbreviation: (+), or more; (-), or less; CR, complete response: PR, partial response; NR, no response; SD, stable response

TABLE 4 RESULTS BY HYPERTHERMIA DOSE

A.		Superficial				POPAS	
	(N=78)		(N=76)		(N=31)		(N=29)
CR (%)	43 (55)		31 (41)		4 (13)		5 (17)
PR (%)	30 (38)		28 (37)		19 (61)		9 (31)
NR +SD (%)	5 (7)		17 (22)		8 (26)		15 (52)
B.	Subsequent results using POPAS, 25 Heat (N=61)						
CR (%)					15 (24)		
PR (%)					29 (48)		
NR +SD (%)					17 (28)		

Abbreviations: CR, complete response; PR, partial response; NR, no response; SD, stable disease

Tumor response was improved when hyperthermia was combined with higher dose of radiotherapy, as in our previous series (31). The SD-NR rate was 2-3 times greater for tumors receiving 20Gy or less compared to those treated with 30Gy or more (Table 3). Tumor response was also found to be related to the number of hyperthermia fractions (Table 4A) The NR rate was reduced by over half with more hyperthermia treatments. Because of the results of this comparison we now routinely give daily hyperthermia treatments, and results have remained essentially the same (Table 4B).

Unexpected but gratifying was the finding that POPAS treated lesions given low dose radiation versus no radiation had equivalent tumor response rates. (Table 3). Since nearly all patients receiving no radiation were on a chemotherapy regimen designed for optimal combination with hyperthermia, based on published research (29, 30, 32, 33, 34, 50, 51) one would like to ascribe the results in POPAS patients treated without radiation to the adjunct effect of chemotherapy on hyperthermia. However, in superficial tumors treated without radiation were relatively poor, little better than published reports of tumor response to hyperthermia alone (8, 9, 17, 19, 21).

In analyzing results by tumor site, we found that CR rate in superficial tumors was nearly threefold better than in POPAS treated lesions, while SD-NR rate was correspondingly less (Table 2). Much of this difference is accounted for by results in treatment of breast adenocarcinoma (primary and recurrent), a category that included over half of all superficial lesions and had by far the best results (Table 5). Indeed, at least 50% response rate (CR&PR) was as good in tumors of pelvis, chest and pancreas (Table 6) as in superficial lesions exclusive of breast (Table 5).

TABLE 5 SUPERFICIAL HYPERTHERMIA RESULTS

Site	#	CR	(CR +PR%)	PR	SD	NR
Breast	91	60	(95)	25	3	2
Head + Neck	39	15	(71)	15	1	8
Other	48	14	(81)	25	6	3
Total	178	89	(87)	66	10	13

Toxicity: 10 Skinburns, 3 Ulcerations

Abbreviation: CR, complete response; PR, partial response
NR, no response; SD, stable disease

The group of patients treated for potential cure is of particular interest. This group comprises only 22 patients with advanced primary or local postoperative recurrence, excluding those with pancreas adenocarcinoma (Table 7). Ten had breast cancer, 7 with untreated primary tumors including 5 measuring 10 cm. or more 3 with palpable axillary or supraclavicular adenopathy and 3 with untreated post mastectomy chest wall recurrence. Except for 2 with postoperative recurrent cervical nodes, all patients required at least two hyperthermia treatment fields to cover their extensive disease. Seventeen of the 22 (77%) had CR. Twelve are alive, 10 at least 1 year, all but one free of local recurrence. Of 20 patients evaluable, for at least 1 year, 8 (40%) have no evidence of disease. Only 1 patient of 17 with CR has had recurrence within the treatment field following definitive combined treatment.

For 150 patients, 87% of the total evaluable, the treatment goal could only be palliation, local tumor control and possible prolongation of life. In such cases treatment failed in 18 (12%), who did not have at least stable disease with palliation. Of the 117 patients for whom significant tumor regression was achieved (CR&PR), 90 are evaluable for at least 6 months.

Of 31 patients with CR 20 (65%) lived at least 6 months with no local recurrence; and 12 (39%) are alive 6 to 38 months after treatment (Table 8) including 3 with no evidence of disease. Of 60 patients with PR 17 (28%) lived 6 months or more without regrowth of treated disease; and 10 (17%) remain alive 6 to 48 months following treatment (Table 9).

When regrowth occurs, manifested by change in size on examination or x-ray, recurrent symptoms, and/or increase in tumor markers such as CEA, the tumor is retreated. For example: A 46 year old male with 60 pound weight loss over one year and progressive intractable abdominal pain finally developed obstructive jaundice and underwent by-pass surgery for unresectable pancreatic carcinoma with liver invasion and regional adenopathy. It was recommended that he have no treatment. After further deterioration over 2 months, he was too weak to walk when hyperthermia was started in combination with 5-fluorouracil. Palliation and improvement in his general condition during 5 weeks of daily hyperthermia treatment allowed him to return to work. CT scan showed 75% regression of the primary mass, normal liver and complete regression of adenopathy. He continued to function well for over a year during which time two additional courses of hyperthermia combined with 5-FU were required. His last course of hyperthermia, this time given along with 45 Gy was less effective clinically; however, CT scan 6 minutes later showed no tumor. Serial retreatment with hyperthermia has not resulted in toxicity, except probably in a 72 year old male with liver metastasis and mesentric adenopathy secondary to colon adenocarcinoma, who twice developed ileus.

TABLE 6 HYPERTHERMIA RESULTS WITH POPAS

Site	#	CR	(CR+PR%)	PR	SD	NR
Pancreas	14	1	(71)	9	2	2
Liver	28	3	(46)	10	6	9
Other Abdomen	8	1	(50)	3	2	2
Pelvis	32	9	(78)	16	5	2
Lung	14	6	(79)	5	2	1
Other Chest	25	4	(72)	14	2	5
Total	121	24	(67)	57	19	2

Toxicity: 6 Skin burns, 2 Pneumothorax, 1 Ileus

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; NR, no response

TABLE 7 PATIENTS COMPLETING DEFINITIVE TREATMENT

Patient	Tumor site/stage/type	Treatment Gy	Heat	Resp.	Status
10 63 F	O Ph T3N1 Squ	70	2/W	C	10m rec
HC 70 F	Neck Rec An	60	2/W	N	1.5m rec
IB 56 F	Br T4N? Ade	50	2/W	C	44m NED
AC 58 F	PI T3No Squ	70	2/W	C	46m NED
BS 48 F	Br T3N? Inf	50	2/W	P	?
MC 56 F	Lung T4No OC	40	2/W	C	4m met
JS 32 M	O Ph T2no AC	60	2/W	C	38n NED
DL 50 F	Br T4No Ade	50	2/W	P	?
LD 41 F	Br Rec Ade	64	2/W	P	?
CM 64 M	Neck Rec Squ	72	2/W	C	22m NED
LF 54 F	Br Rec Inf	60	5/W	C	26m NED
WM 61 F	Br Rec Ade	50	5/W	C	23m NED
DJ 49 F	Br T4N1 Inf	70	5/W	C	7m NED
JT 74 F	N Ph T3N1 Squ	50I	5/W	C	13m NED
FA 61 F	Br T4N2 Ade	66	5/W	C	17m NED
RE 60 F	Lung T2N2 Ade	66	5/W	C	13m NED
JF 73 M	Lung T1N2 OC	55	5/W	C	3m met
JR 58 F	Br T4N1 Ade	60	5/W	C	14m met
LW 79 F	Br T4No Ade	50	5/W	P	12m rec
SL 52 M	Ton T3N1 Sq	70	5/W	C	8m met
NS 66 M	Pros T2N? Ade	40+33I	5/W	C	9m NED
GH 62 M	Esop T2ND Squ	60	5/W	C	4m met

Abbreviations: O Ph, oral pharynx; Br, breast; PI, piriform sinus: N Ph, nasal pharynx; Ton, tongue; Pros, prostate: Esop, esophagus; I, implant; W, Week; Rec, reccurence; NED, no evidence of disease, Met, metastasis; Squ, squamous cell; Ana, anaplastic; Inf, inflammatory OC, oat cell; AC, adenocystic; Ade, adeno.

TABLE 8 PATIENTS TREATED WITH LIMITED GOAL COMPLETE RESPONSE DURATION

Status	Total	25 Heat	10 Heat	30Gy (+)	20Gy (-)
	(N=31)	(N=18)	(N=13)	(N=17)	(N=14)
No rec min 6m (%)	20 (65)	3 (72)	7 (54)	8 (47)	12 (86)
Alive min 6m (%)	12 (39)	10 (56)	2 (15)	5 (29)	7 (50)

Abbreviations: (+), or more; (-), or less; m, months: rec, recurrence; min, minimum

TABLE 9 PATIENTS TREATED WITH LIMITED GOAL PARTIAL RESPONSE DURATION

Status	Total	25 heat	10 heat	30 Gy (+)	20 Gy (-)
	(N=60)	(N=41)	(N=19)	(N=27)	(N=33)
No rec min 6m (%)	17 (28)	13 (32)	4 (21)	5 (19)	12 (36)
Alive min 6m (%)	10 (17)	9 (27)	1 (5)	2 (7)	8 (24)

Abbreviation: (+), or more; (-), or less; m, months; rec, recurrence; min, minimum

DISCUSSION

We have herein reported results obtained in 172 patients treated by one group, employing various techniques of external microwave hyperthermia. Best results have been obtained in the group of patients, previously discussed, that we were able to treat definitively (Table 7), as reported by other groups (15, 27).

Treatment results in superficial lesions appear to have been much better than in deep lesions using POPAS (Table 2). Analysis of results by radiation dose, however, shows no significant difference in those tumors receiving 30 Gy or more (Table 3). More superficial than deep tumors received a higher dose of irradiation, respectively 47% (83/138) vs. 29% (35/121). Response in deep tumors improved with higher radiation dose (Table 3). Independent of radiation dose tumor response was significantly better when more hyperthermia treatments were given (Table 4), which calls into question the applicability of thermotolerance in clinical practice.

The phenomenon of thermotolerance has been well established in the laboratory by in vitro and in vivo experiments (43, 44). Both normal and cancer cells and tissue have been found to resist a second heat insult for over a month following initial heating. It is far from clear, however, what effect thermotolerance has along with the many other factors that affect tumor response to hyperthermia in clinical practice. Most clinics, including our own until recently (3, 4, 31), have empirically given hyperthermia treatment on a twice a week basis. Even with weekly treatment only the first hyperthermia session should be fully effective if thermotolerance were a predominant operating factor.

With this paradox in mind we have tried giving hyperthermia treatment daily 5 days per week and have found significantly better tumor response using daily treatment. The number of superficial and deep tumors that failed to regress by at least 50% (NR+SD) was 32/105 (31%) with biweekly treatments as compared to 13/109 (12%) following daily hyperthermia treatment (Table 4). These results provide further demonstration that thermotolerance is much less important in clinical hyperthermia practice than other factors as yet poorly defined. Tumor heating is never homogeneous, and it is likely that the inhomogeneities vary from one hyperthermia treatment to another; thus inhomogeneous heating may actually be advantageous, by heating cells that have not developed thermotolerance. Since the development of thermotolerance has been shown to be partially inhibited at low pH (53), and tumors have low pH further reduced by hyperthermia, thermal response of tumor relative to normal tissue may be enhanced by daily heat treatment.

partially inhibited at low pH (53), and tumors have low pH

Other groups have used daily hyperthermia treatment successfully. Moffat et al {30} and Falk et al (54) reported on thermochemotherapy in 178 patients with unresectable hepatic neoplasm given "1 to 25 treatment courses (median 6 courses) --- of 1-5 consecutive daily sessions of 75-120 min. thermotherany---". Hornback et al (55) treated stage IIIB cancer of the cervix with irradiation given 150-200 cGy per day to 40gy and "each patient was exposed to 40 to 45 minutes of heat after each external radiation treatment". Corry et al (24) gave one to three courses of hyperthermia for superficial tumors, that "consisted of one hour treatment on three successive days of each week". Falk et al (39) treated pancreatic cancer with "two to three consecutive daily sessions every 2 weeks" along with chemotherapy. Hornbeck et al (6) treated a hemangiosarcoma of the scalp with "3000 rad at 200 rad/day, each treatment followed immediately by 20 minutes of heat". Earlier they (5) reported on 21 patients given 3-6000 rads at 100-200 rads/day with "20 minutes of microwave radiation to the local tumor area immediately prior to the prescribed dose of ionizing radiation".

Marmor and Hahn (22) compared tumor response between matched tumors in the same patient with multiple superficial lesions given 2-6000 rads in 200-400 rad fractions. "One of the matched nodules was given hyperthermia (43ºC) for 15 minutes before and 30 minutes after each radiation fraction". While the number and frequency of neither hyperthermia nor radiation treatments were otherwise specified, at least some patients must have been treated daily." Seven of 15 patients had an improved response in the tumor that received hyperthermia", and the difference was more apparent in those given low-dose radiation (2-4000 rad).

Streffer et al (56) found that the development of thermotolerance was suppressed in human melanoma cells given fractionated heat combined with ionizing radiation: "thermotolerance is apparently not a significant factor after combined treatment schedules which are used in clinical tumor therapy". Arcangeli and Nervi (23) gave weekly or twice weekly hyperthermia to separate tumors in the same patient for 5 weeks. "When comparing equal RT fractionation schedules (i.e. daily fractions of 2Gy) tumor TER increased from 1.83 to 2.2 when the number of equal HT treatments (i.e. 43.5 degrees Celsius for 45 minutes) was doubled from 5 to 10. The skin TER, in contrast, appeared to decrease with increasing number of fractions. "They (23) concluded that:" Our data does not seem to evidentiate any thermotolerance induction in human tumors, at least by using clinical treatment schedules like those employed in this study, although the problem can only be clarified with more clinical data". Our data supports these conclusions.

Analysis of response duration in our current series (Tables 8, 9) raises serious questions regarding the use of radiation therapy. When response (CR or PR) was achieved with 20Gy or less, including patients given no radiation, duration of response was more prolonged than with a higher radiation dose. The numbers of patients surviving at least 6 months with no local recurrence were, respectively, 24/47(51%) vs. 13/44 (30%). Comparable figures for 25 vs. 10 hyperthermia treatments were, respectively 26/59 (44%) and 11/32 (34%). For those patients still alive at the time of this writing (minimum 6 months) with or without local recurrence the figures are even more striking: less vs. more radiation, 15/47 (32%) vs. 7/44 (16%); more vs. fewer hyperthermia treatments, 19/59 (32%) vs. 3/32 (9%). We know of no other study that has analyzed results in this way. Does palliative irradiation impair immune response so much as to adversely affect survival? Does hyperthermia enhance immune response so much that more treatments improve survival? These questions remain unanswered and require further investigation.

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