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CLINICAL HYPERTHERMIA PILOT STUDIES, THOMAS JEFFERSON UNIVERSITY HOSPITAL

RESULTS OF 42.5^{o}C. ADJUVANT TO IRRADIATION

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The phase I (February 1979 - May 1980) hyperthermia experience consists of twenty-six cases, twenty of whom received x-ray therapy (electron beam) plus an average of eight hyperthermia sessions (twice weekly at 42.5 - 43.5^{o}C intralesional temperature for 40 minutes). Seventeen of the patients were heated with a 2450 microwave MHZ generator in conjunction with surface heating (circulating water bag at 45^{o}C). AGA thermograms were valuable in assessing superficial blood flow documenting heating patterns, and in predicting potential overheating which may manifest by superficial burns (blisters). Although the study is non-randomized and patient numbers small, a complete response of 50% (5 of 10) was noted amongst those patients re-treated to the chest wall for breast carcinoma recurrence following prior mastectomy and radiation therapy. The combined response (CR + PR) amongst this largest category was an encouraging 8 of 10 with follow-up averaging 5 months. The response amongst the 22 evaluable cases was mixed and variable, with 6 showing CR, 6 a PR and combined response of 55% (12/22). The results attained to date in this pilot project have been sufficiently encouraging to warrant expansion of the techniques of patient categories. The 27.12 MHZ (500 watt output) water-immersed (RCA) ridge waveguide offers considerable promise in expansion of potential eligible cases to include deep seated tumors within the pelvis, lung apex, or deep muscular (extremity) regions.

Introduction

The ability of hyperthermia to function as an adjuvant to irradiation has been unequivocably demonstrated at the laboratory level.[1,2] Under experimental conditions, a significant enhancement in radiation cell-kill has been noted[3,4] depending upon the cell system, radiation dose fraction, and timing of x-ray and heat dosage (time-duration and centigrade degrees sustained). Mechanisms of radiation-heat interpretations are not fully understood but these four mechanisms may be involved:

1. interference with repair of sublethal radiation damage (Dq on cell survival curve);

2. production of lethal cell membrane damage (perhaps independent of irradiation);

3. direct cellular lethality (especially those cells at low pH and those in the S-phase of the mitotic cycle), resulting in a change in the D_0 on cell-survival graph; and

4. "other" effects, poorly understood and not well documented.

This report will deal with the clinical hyperthermia trial at Thomas Jefferson University Hospital, attempting to utilize this modality adjuvant to irradiation for palliation of advanced, inoperable (superficial) tumor masses. In a fashion similar to that reported by D. Luk[5] and J.H. Kim,[6] radiofrequency and/or microwave heating sources were utilized. Only superficial localized or limited regional masses were considered candidates regardless of the histologic subtype or organ of origin. Ultrasonic heating techniques, as reported by Marmor et al[7] have not been developed at Jefferson but are in the planning phase.

Materials and Patients Selected

Between February, 1979 and May, 1980, twenty-six (26) patients have submitted to the clinical hyperthermia program. Criteria for selection and acceptance included the following:

1. histologically proven malignancy (each metastatic nodule/mass need not be biopsied);

2. clinical failure with all other reasonable therapeutic measures (surgery, prior radiotherapy, chemotherapy/hormones);

3. ability to heat the tumor mass with existing (RF-microwave) equipment to 42.5°C (intralesional) for 35-40 minutes for six heat sessions;

4. signing informed consent; and

5. prior radiotherapy (even to "tolerance" doses of 5000-6000 rad) is not considered a contraindication.

Since we hoped to capitalize upon the altered (hypoxic-acidic) status of tumor cells following irradiation (especially after sublethal radiation events), x-ray therapy was given first, followed by heat administration generally utilizing this protocol sequence:

Electron beam therapy, 200-250 rad to volume, 4 fractions/week	→	"Immediate" hyperthermia 42.5 - 43.5°C (intralesional) x 40 minutes twice weekly	→	Repeat cycle q. week for total of 3000-5000 rad and 6-8 heat treatments

Pre-treatment evaluation includes assessment of tumor volume using modern techniques of ultrasound, CT scanning, and appropriate radiographic studies. An AGA thermographic camera assessed the superficial vascularity in each treated area prior to and following heat sessions, hoping to predict areas which might heat readily or overheat (large ischemic tumor masses tend to act as heat "sinks"). Temperature measurements during heat therapy were obtained every five minutes with the RF or microwave source off for 15-30 seconds utilizing Bailey thermocouple equipment. Since metal objects cannot be left within RF or microwave fields, an 18G plastic intracath is inserted under local anesthesia directly within the tumor mass, placed at different depths on each heating session (0.5 cm, 1.0 cm, 1.5 cm). Surface temperature readings are also monitored underneath a thin plastic bag of circulating hot water kept at 45°C under thermostatic control. The available fibre-optic equipment (Ramal) was found to be unreliable and was, in effect, discarded.

Circulating cold (ice) water was added to the skin surface when inadvertent overheating caused a second degree burn (blister) or when post-treatment AGA thermograms showed an area of skin heating exceeding 45°C.

Results

Table 1 summarizes the treatment parameters among twenty-six patients entered and treated with hyperthermia by May 20, 1980. Five patients could not receive additional heat therapy and received heat alone (cases 1, 7, 8, 11, and 13). The additional 21 cases received combined therapy (XRT plus immediate heat). Chest wall recurrences (failure of surgery, radiotherapy and chemotherapy) accounted for one-half of these 21 cases. Five of these ten (50%) achieved complete response (disappearance of all tumor by vision and palpation) while an additional three patients experienced a partial response (> 50% tumor shrinkage), while only two failures (< 50% response of tumor) were noted. The average radiation dosage was 2750 rad in combination with 7 heat sessions (average), two per week for one month.

The second largest group submitting to hyperthermia consisted of patients with superficial metastatic (skin) nodules or lymph nodes secondary to squamous carcinoma arising in the head and neck (3 cases) or lung (6 cases) regions. Forty-four percent of these (four) have shown a CR, while no response (< 50% shrinkage) was observed among another identical group (four). Miscellaneous patients receiving treatment included primaries in the colon, ovary, skin (melanoma) and lymph nodes (histologic lymphoma), or soft tissues (liposarcoma). The clinical results amongst the 22 evaluable patients are summarized in Table 2.

The first five patients were heated with RF techniques (18-25 MHZ), with applicators placed directly over the skin surface insulated from the skin by plastic materials. Unfortunately, these "capacitor-RF" techniques led to skin blisters in every case in spite of attempts to prevent skin burning. The remaining 20 cases were heated using <u>external</u> heat applicators, raised 2-5 cm from the skin surface. A 2450 microwave generator (100 watt max. output) was used in 17 of these 20 patients, 27.12 MHZ in the remaining 3 cases. No significant skin complication, no late effects, and no enhancement of the radiation reaction was observed among the later patients.

We will soon be expanding the program to include candidates with inoperable, recurrent and previously treated tumor located wthin the lower pelvis (prostate, bladder, rectum, cervix) in a phase I-II trial of the 27.12 MHZ ridge waveguide (RCA) applicator.

Representative case reports will be presented during the hyperthermia symposium, treatment techniques further degined, and pictoral representative of AGA thermograms demonstrated. A hand-held 2450 waveguide applicator is capable of producing intralesional temperatures of 43.0^{o}C ± 0.5^{o}C while keeping the surface at 40.0 - 41.0^{o}C, by rotating the unit to avoid uneven heating.

Table 1

Case # Age/Sex	Date Rx	Primary Site	Area Treated	Method (Δ)	No. of (Δ) Tx	Rad. Therapy	Results
1. DV 49 F	2/79	oropharynx	6x9x35 cm	RF alone	4	None	resp <50% expired of Ca
2. KS 69 F	2/79	adenoca, breast	35 x 35 cm chest wall	RF + XRT	9	875/4	blister, NR
3. HR 35 M	4/79	tongue, squamous	large cerv. nodes	RF + XRT	5	400/4	resp <50%, blister, died 3 mo
4. LS 59 F	5/79	adenoca, breast	mult. nodules chest wall	XRT + RF	10	1100/4	regression of nodules >50%, died 1 yr
				(retreat)	2	400/2	
5. LB 65 F	5/79	adenoca, breast	4 cm mass chest wall	XRT + RF	10	500/5	NR
6. MD 64	7/79	sarcoma	>10 x 15 cm buttocks	XRT + 27 MHZ	9	2750/11	softer, but NR
7. DM 66 F	10/79	adenoca, breast	1.5 x 1 cm chest wall	45^oC H_20 + 2450 MHZ	8	None	CR, alive & well at 7 mo
8. MS 72 F	9/79	adenoca, colon	10 x 10 cm	27 MHZ	7	None	bleeding and size unchanged
9. HM 58 F	12/79	adenoca, breast	1.0 x 1.4 cm chest wall	XRT + 45^oC H_20 + 2450 MHZ	10	5000/20	resp >50%, alive & well at 5 mo
10. AM 58 M	1/80	orpharynx, squamous	>10 cm skin (cerv) mass	XRT + 2450 MHZ	8	3750/17	resp >50%
				(Retreat)	4	1600/4	alive at 5 mo
11. CH 50 M	7/79	melanoma, skin	4 cm lymph nodes	XRT + Δ	2	4400/22	died of dissem Ca
12. WS 53 F	12/79	adenoca, breast	chest wall (mult. nod.)	XRT + 45^oC H_20 + 2450	7	4400/22	CR, NED 5 mo
13. JH 73 M	1/80	lung	5 x 8 cm supraclav. mass	45^oC H_20 + 2450 MHZ	10	None	NR, died 4/80

Table 1 (continued)

Case # Age/Sex	Date Rx	Primary Site	Area Treated	Method (Δ)	No. of (Δ) Tx	Rad. Therapy	Results
14. JB 55 F	1/80	adenoca, breast	2.6 x 1.5 cm chest wall nodules	XRT + 45°C H_2O + 2450 MHZ	8	5400/27	CR, alive & well, 4 mo
15. JJ 66 M	1/80	lung, squamous	supraclav. recurrent, squamous	XRT + 45°C H_2O + ice H_2O + 2450	8	3600/18	>50%, alive & well, 4 mo
16. RM 63 F	1/80	adenoca, breast	chest wall	XRT + 45°C H_2O + 2450	6	4035/17	CR, alive & well, 5 mo
17. JS 42 F	2/80	lung, squamous	6 cm post. cerv. mass	XRT + 45°C H_2O + 2450	8	4250/17	>50% resp. pain gone
18. JS 62 F	3/80	adenoca, breast	mult. chest wall	XRT + 45°C H_2O + 2450	8	3000/10	CR at 1 mo
19. EF 65 F	4/80	adenoca, breast	4 cm sternal mass	XRT + 45°C H_2O + 2450	7	3000/12	CR, alive & well at 3 mo.
20. RD 48 M	4/80	lung, squamous	6 x 5 cm mass left neck	XRT + 45°C H_2O + 2450	5	2599/10	NR, pt. expired during Rx
21. AB 55 F	4/80	ovary	10 cm cutaneous mass	XRT + 45°C H_2O + 2450	1	300/1	NP, pt. admitted
22. CZ 70 M	5/80	adenoca, lung	10 cm post. chest wall mass	XRT + 45°C H_2O + 2450	6	2800/14	resp <50%
23. JE 71 M	5/80	adenoca, lung	8 x 6 cm supraclav.	XRT + 45°C H_2O + 2450	6	2750/11	resp <50%
24. MH 76 F	5/80	histiocytic lymphoma	2.5 x 2.5 cm nasal cavity mass	XRT + 45°C H_2O + 2450	3	1200/6*	---
25. JS 54 F	5/80	skin, melanoma	4 x 3 cm subcutan. masses	XRT + 45°C H_2O + 2450	3	1200/3*	---
26. AM 50 F	5/80	adenoca, breast	15 x 12 cm chest wall ulcer	XRT + 45°C H_2O = 2450	1	200/1*	---

* Patients currently under therapy

Table 2

Summary of Hyperthermia Experience
(February 1979 - May 1980)

Number of patients treated		26
Response categories		
22 evaluable	NR - (<50% shrinkage)	10/22
	PR - (>50 tumor shrinkage)	6/22
	CR - (disappearance of tumor)	12/22
Histologic Types (Primary)		
	Breast adenocarcinoma	11
	Lung - squamous or adenoca	6
	Head and neck primaries	3
	Miscellaneous sites	6

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