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Clinical Hyperthermia and Irradiation: Pilot studies

John Fazekas

Ted Nerlinger

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Clinical Hyperthermia and Irradiation

Pilot studies

John Fazekas, MD* and Ted Nerlinger, BS*

Phase I (February 1979-May 1980) of our hyperthermia pilot study involved 26 carcinoma patients who participated in two treatment protocols: 20 patients received electron beam x-ray therapy plus an average of eight hyperthermia sessions (twice weekly at 42.5°-43.5°C intralesional temperatures for 40 minutes); 17 patients were heated with a 3450 microwave MHz generator in conjunction with surface heating (circulating water bag at 45°C). AGA thermograms assessed superficial blood flow to document heating patterns and forewarned of potential overheating as manifested by superficial burns (blisters).

Although our study is nonrandomized and our patient numbers are small, we noted a complete response (CR) of 50% (6 of 11) among those patients who were being retreated at the chest wall for a recurrence of breast carcinoma following mastectomy and radiation therapy. Among this largest group, the combined response (CR and PR) was an ecouraging 8 of 11, with an average follow-up time of five months. Among the 22 cases that could be evaluated, the response varied; six had a complete response, five a partial response, and 11 a combined response (50%). The results of this pilot study are sufficiently encouraging to consider expanding potential eligible cases to include deep-seated tumors within the pelvis, lung apex, or deep muscular (extremity) regions.

It has been unequivocally demonstrated that hyperthermia can be an adjuvant to irradiation in the laboratory (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). Although it is not fully understood how hyperthermia enhances the effect of irradiation, four mechanisms may be involved: 1) interference with repair of sublethal radiation damage; 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); and 4) "other" effects, which are poorly understood and not well documented.

Our report describes the clinical hyperthermia trial at Thomas Jefferson University Hospital, which used hyperthermia as an adjuvant to irradiation to treat superficial, advanced, inoperable tumor masses. With a method similar to that of Luk (5) and Kim, et al (6), we used radiofrequency (RF) and/or microwave heating sources. Only superficial localized or limited regional tumor masses were considered for treatment, regardless of the histologic subtype or organ of origin. Ultrasonic heating techniques, as reported by Marmor, et al (7), have not been developed at our institution, but they are in the planning stage.

Materials and Patients Selected

Between February 1979 and May 1980, 26 patients participated in the clinical hyperthermia program. Criteria for selection and acceptance included: 1) histologically proven malignancy (a biopsy was not performed on every metastatic nodule/mass); 2) clinical failure with all other reasonable therapeutic measures (surgery, prior radiotherapy, chemotherapy/hormones); 3) capability of heating the tumor mass with existing equipment (RF-microwave) to 42.5°C (intralesional) for 35-40 minutes for six heat sessions. Previous radiotherapy treatment (even to "tolerance" doses of 5000-6000 rad) was not considered a contraindication.

Pretreatment evaluation included assessment of tumor volume with ultrasound techniques, CT scanning, and appropriate radiographic studies. An AGA thermographic camera photographed the superficial vascularity in each treated

* Department of Radiation Therapy and Nuclear Medicine, Thomas Jefferson University Hospital, Philadelphia, PA

Address reprint requests to Dr. Fazekas, Department of Radiation Therapy, Thomas Jefferson University Hospital, 1025 Walnut St, Philadelphia, PA 19107

area before and after the heat sessions, so that we might predict areas that would heat readily or overheat (large ischemic tumor masses tend to act as heat "sinks").

Since we hoped to capitalize on the altered (hypoxic-acidic) status of tumor cells after irradiation (especially after sublethal radiation events), we administered x-ray therapy first, followed by heat, generally according to this protocol sequence:

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

Using Bailey thermocouple equipment, we measured temperatures during heat therapy every five minutes with the RF or microwave source off for 15-30 seconds. While the patient was under local anesthesia, an 18G plastic intracatheter was inserted directly within the tumor mass, placed at different depths with each heating session (0.5 cm, 1.0 cm, 1.5 cm). We also monitored surface temperature readings beneath a thin plastic bag of circulating hot water maintained at 45°C. 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 that exceeded 45°C.

Results

Table I summarizes the treatment parameters for 26 patients treated with hyperthermia by May 20, 1980. Five patients who could not receive additional radiation therapy were treated with heat alone (cases 1, 7, 8, 11, and 13).

Of the 22 cases that were available for evaluation by the end of our pilot study, six experienced a complete response (disappearance of all tumor on sight and palpation), and five had a partial response (>50% tumor shrinkage). Eleven of the 22 had no response, as measured by <50% tumor shrinkage.

Chest wall recurrences (failure of surgery, radiotherapy, and chemotherapy) accounted for 11 of the 22 cases. Six of these patients had a complete response, while three additional patients experienced a partial response. Only two failures were noted in this group. The average radiation dosage was 2750 rad combined with an average of seven heat sessions, two per week for one month.

The second largest group submitting to hyperthermia (nine patients) consisted of those with superficial, metastatic skin nodules of lymph nodes secondary to squamous carcinoma arising in the head and neck (three cases) or in the lung (six). Of these, three had a partial response, while no response was observed in six cases. A third group of six patients had tumors at various sites, which included primary carcinomas in the colon, ovary, skin (melanoma) and lymph nodes (histologic lymphoma), or soft tissues (liposarcoma).

The first five patients treated (Table I) were heated with RF techniques (18-25 MHz), with applicators placed directly over the skin surface and insulated from the skin by plastic materials. Unfortunately, these "capacitor-RF" techniques led to skin blisters in every case despite attempts to prevent skin burning. The remaining patients were heated by external heat applicators raised 2-5 cm from the skin surface. A 2450 microwave generator (maximum output of 100 W) was used for these patients, while a 27.12 MHz ridge waveguide (RCA) applicator was used in the remaining three cases (cases 6, 8, 11). Among this larger group of 21 patients, we did not observe any significant skin complications, late effects, or enhanced reaction from radiation.

Summary

We will soon expand our program to include candidates with inoperable, recurrent, and previously treated tumors located within the lower pelvis (prostate, bladder, rectum, cervix) in a phase I-II trial of the 27.12 MHz ridge waveguide applicator. With the hand-held 2450 waveguide applicator, we can achieve intralesional temperatures of 43.0°C ± 0.5°C while keeping the surface at 40.0°-41.0°C by rotating the unit to avoid uneven heating.

TABLE I

Case # Age/Sex	Date Rx	Primary Site	Area Treated	Method (Δ)	No. of (Δ) Tx	Radiation Therapy	Results
1. 49 F	2/79	oropharynx	6 x 9 x 35 cm	RF alone	4	None	response <50% died of Ca
2. 69 F	2/79	adenoca, breast	35 x 35 cm chest wall	RF + XRT	9	875/4	blister, NR
3. 35 M	4/79	tongue, squamous	large cerv. nodes	RF + XRT	5	400/4	response <50%, blister, died 3 mo
4. 59 F	5/79	adenoca, breast	mult. nodules chest wall	XRT + RF	10	1100/4	regression of nodules
				(Re-treat)	2	400/2	>50%, died 1 yr
5. 65 F	5/79	adenoca, breast	4 cm mass chest wall	XRT + RF	10	500/5	NR
6. 64 F	7/79	sarcoma	>10 x 15 cm buttocks	XRT + 27 MHz	9	2750/11	softer, but NR
7. 66 F	10/79	adenoca, breast	1.5 x 1 cm chest wall	45°C H_2O + 2450 MHz	8	None	CR, alive and well at 7 mo
8. 72 F	9/79	adenoca, colon	10 x 10 cm	27 MHz	7	None	bleeding and size unchanged
9. 58 F	12/79	adenoca, breast	1.0 x 1.4 cm chest wall	XRT + 45°C H_2O + 2450 MHz	10	5000/20	response >50%, alive and well at 5 mo
10. 58 M	1/80	oropharynx, squamous	>10 cm skin (cerv) mass	XRT + 2450 MHz	8	3750/17	response >50%
				(Re-treat)	4	1600/4	alive at 5 mo
11. 50 M	7/79	melanoma, skin	4 cm lymph nodes	XRT +Δ	2	4400/22	died of dissem. Ca
12. 53 F	12/79	adenoca, breast	chest wall (mult. nod.)	XRT + 45°C H_2O + 2450 MHz	7	4400/22	CR, NED 5 mo
13. 73 M	1/80	lung	5 x 8 cm supraclav. mass	45°C H_2O + 2450 MHz	10	None	NR, died 4/80
14. 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 and well, 4 mo
15. 66 M	1/80	lung, squamous	supraclav. recurrent, squamous	XRT + 45°C H_2O + ice H_2O + 2450	8	3600/18	>50%, alive and well, 4 mo
16. 63 F	1/80	adenoca, breast	chest wall	XRT + 45°C H_2O + 2450	6	4035/17	CR, alive and well, 5 mo
17. 42 F	2/80	lung, squamous	6 cm post. cerv. mass	XRT + 45°C H_2O + 2450	8	4250/17	>50% response, pain gone
18. 62 F	3/80	adenoca, breast	mult. chest wall	XRT + 45°C H_2O + 2450	8	3000/10	CR at 1 mo
19. 65 F	4/80	adenoca, breast	4 cm sternal mass	XRT + 45°C H_2O + 2450	7	3000/12	CR, alive and well at 3 mo
20. 48 M	4/80	lung, squamous	6 x 5 cm mass left neck	XRT + 45°C H_2O + 2450	5	2599/10	NR, pt. died during Rx
21. 55 F	4/80	ovary	10 cm cut-aneous mass	XRT + 45°C H_2O + 2450	1	300/1	NP, pt. admitted
22. 70 M	5/80	adenoca, lung	10 cm post. chest wall mass	XRT + 45°C H_2O + 2450	6	2800/14	response <50%
23. 71 M	5/80	adenoca, lung	8 x 6 cm supraclav.	XRT + 45°C H_2O + 2450	6	2750/11	response <50%
24. 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. 54 F	5/80	skin, melanoma	4 x 3 cm subcutaneous masses	XRT + 45°C H_2O + 2450	3	1200/3*	---
26. 50 F	5/80	adenoca, breast	15 x 12 cm chest wall ulcer	XRT + 45°C H_2O + 2450	1	200/1*	---

Δ = heat
RF = radiofrequency
XRT = x-irradiation
CR = complete response, disappearance of tumor
PR = partial response, >50% tumor shrinkage
NR = no response, <50% tumor shrinkage
* Patients currently under therapy

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