Henry Ford Hospital Medical Journal

Volume 29
Number 1 *Clinical Hyperthermia Today*

Article 8

3-1981

Local Hyperthermia and Radiation: A biologically-oriented clinical scheduling

G. Arcangeli

A. Cividalli

Henry Ford Hosp Med J
Vol 29, No 1, 1981

Local Hyperthermia and Radiation

A biologically-oriented clinical scheduling

G. Arcangeli MD* and A. Cividalli, D.Sc**

In a series of animal tumor studies, heat was directly delivered into the tumor mass with an interstitial applicator. After hyperthermia (44°-45°C for 45 minutes) or radiation alone (3x10 Gy), only a slight delay in tumor growth was observed, while the combined treatment, either simultaneous or sequential (i.e., heat delivered four hours after irradiation), appeared to be the most effective. The cure rate in the two combined treatment groups was 100%, in contrast to the lack of cure in the first two groups. The simultaneous use of heat and x-ray appeared to be slightly more effective than the sequential schedule; in all cases, no increase in radiation effects on normal tissue could be observed.

For clinical studies, 47 patients with a total of 101 neck node metastases from head and neck cancer have been treated in order to compare tumor response to at least two different combinations of treatment modalities in the same patient. All patients were irradiated according to a multiple daily fractionation (MDF) scheme (2+1.5+1.5 Gy/day, 4-hour intervals, 5 days/week), and hyperthermia (42°-43°C, 45 minutes) was delivered every other day immediately after the second daily radiation fraction, by means of an external applicator operating at 500 MHz. With this schedule, heat is delivered simultaneously with the second and sequentially with the first and third radiation fractions. In half the patients, misonidazole was also administered (1.2 g/m² up to a total dose of 12 g/m²). The data indicate that multimodality treatments seem to be more effective than conventional fractionation or MDF alone. In particular, the best response was obtained when MDF was combined with both misonidazole and hyperthermia. No increased radiation reactions have ever been observed in patients treated with hyperthermia also; all side effects depend mainly on misonidazole toxicity.

Biological Rationale

In the last few years basic investigations on cytotoxic and radiosensitizing mechanisms have led to a resurgence of interest in hyperthermia alone or in combination with radiotherapy as a means of treating malignant tumors.

Some measure of agreement now exists among investigators on optimum fractionation and sequence of radiation and heat. Overgaard (1) has recently demonstrated in animal tumors that a simultaneous treatment is therapeutically advantageous in situations in which tumors can be heated selectively or preferentially apart from the surrounding normal tissues, while sequential treatment has its potential in situations in which tumors and surrounding normal tissues are heated at the same temperature. This finding was confirmed by other authors (2,3) with the suggestion that under these circumstances heat should be delivered three to six hours after x-rays.

Furthermore, it is well known that above a critical temperature of about 43°C the synergistic interaction between heat and x-rays is due to an increase in the expression of lethal damage on both normal and neoplastic cells. Near 45°C hyperthermia inactivation seems to be mainly ascribed to the aspecific process of protein denaturation. Once again, temperatures above 43°C, although more effective, appear to be clinically useful only in situations in which tumors can be heated selectively or preferentially with respect to the surrounding normal tissues.

Animal Studies

By employing our interstitial applicator described elsewhere (4,5), we selectively heated small volumes of tumor tissue, as shown in Fig. 1, in mice at temperatures around 45°C. With these techniques, several multimodality treatment schedules could be tested on a relatively radio-

* Instituto Medico e di Ricerca Scientifica, Rome, Italy

** Instituto Medico e di Ricerca Scientifica and Laboratorio di Dosimetria e Biofisica, Comitato Nazionale per l'Energia Nucleare, Rome

Address reprint requests to Dr. Arcangeli, Instituto Medico e di Ricerca Scientifica, 00191 Rome, Italy

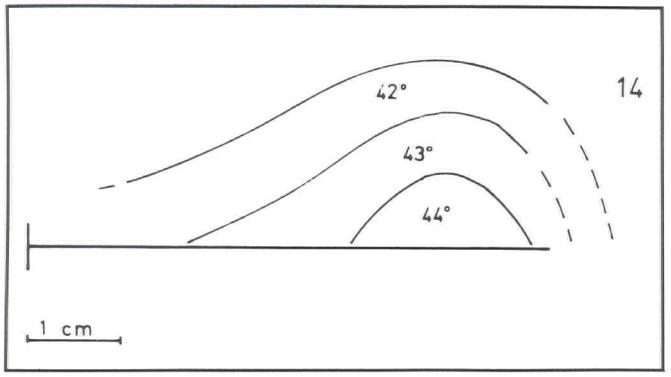

Fig. 1
In vivo temperature distribution obtained at 20 min. from the beginning of heating by an interstitial applicator operated at 500 MHz.

resistant fibrosarcoma of spontaneous origin that had been transplanted in the thighs of mice. Treatment was started eight to ten days after inoculation:

1) heat alone (44°-45°C, 45 minutes) on Monday, Thursday, and Monday;
2) radiation alone (10 Gy*) on Monday, Thursday, and Monday;
3) simultaneous radiation and heat (heat delivered immediately after irradiation according to 1) and 2));
4) sequential radiation and heat (heat delivered four hours after irradiation according to 1) and 2)).

In Fig. 2, the effect of heat alone, radiation alone, and combined treatment is compared with the control growth curve. After hyperthermia or irradiation alone, tumor growth was only slightly delayed. Heat combined with radiation appears to be the most effective treatment schedule, as a 100% cure rate was observed in contrast to the absence of cure in the first two groups. Also, the simultaneous use of heat and x-rays appears to be more effective than the sequential schedule, even though in both groups the effect can surely be defined as supra-additive.

These results clearly favor the use of hyperthermia and radiation simultaneously when heat can be properly delivered to the tumor mass. When care is exercised in the heat treatment, the simultaneous use of hyperthermia and radiation does not produce any increased radiation effects on normal tissues.

* Gy = Gray; 1 Gy = 100 rad

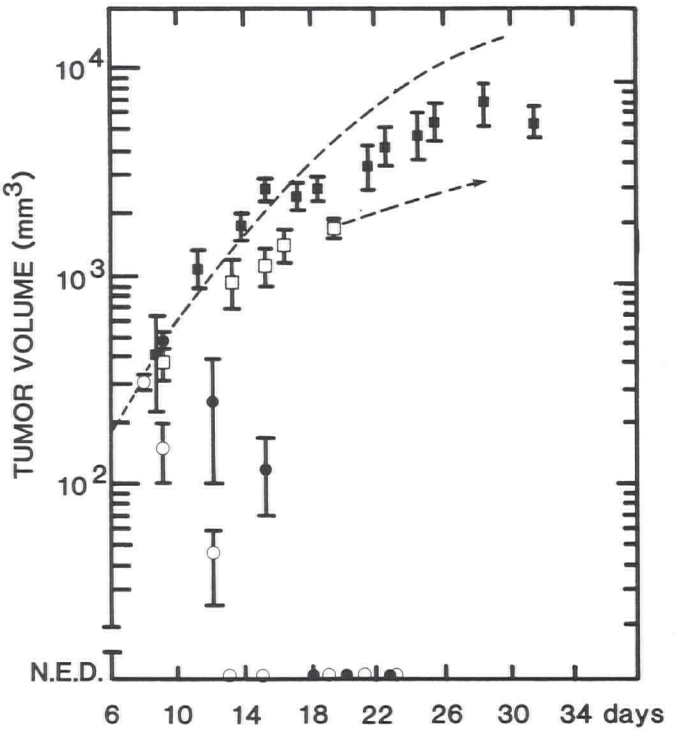

Fig. 2
The effect of several treatment modalities on a fibrosarcoma of spontaneous origin, transplanted in the thigh of mice.—Control growth curve; ■ = Heat alone; □ = Radiation alone; • = Sequential radiation and heat; ○ = Simultaneous radiation and heat.

Clinical Studies

In our treatment schedules, hyperthermia is delivered immediately after the second fraction of a thrice daily fractionation course of radiotherapy. Heat is delivered simultaneously with the second, and sequentially with the first and the third radiation fractions. This treatment schedule represents a compromise between the nondifferential, radiosensitizing effect of simultaneous treatment on both neoplastic and normal tissue and the more selective cytotoxic effect of a sequential treatment on tumors.

The aim of our study was to treat comparable lesions in the same patients with at least two different combinations of treatment modalities. For this purpose, we selected 47 patients with a total of 101 neck node metastases (N_2- N_3) from head and neck cancer.

Irradiation

All patients were irradiated with a 5.7 MeV photon beam, through an anterior field that covered the whole neck or through two cross-firing portals when concomitant treatment of the primary tumor was required. Patients were irradiated according to a multiple daily fractionation (MDF)

scheme, as described elsewhere (6). It consisted of 2+1.5+1.5 Gy/day, four-hour intervals between fractions, five days/week, up to a total dose of 40-70 Gy.

Hyperthermia

Hyperthermia (HT) was induced in patients by our TUETT 500 apparatus with an external applicator operated at 500 MHz (7). Temperature was monitored every 10 minutes at the tumor center by means of thermocouples inserted through teflon cannulae previously positioned into the node. Heat was delivered on Monday, Wednesday, and Friday of each week, immediately after the second daily fraction, at a temperature of about 42°-43°C.

Misonidazole (MIS)

In about half the patients, a hypoxic cell sensitizer (misonidazole, provided by courtesy of the Prodotti Roche, Milan, Italy) was also employed. The drug was orally administered in a 1.2 g/m² dose two hours before the first daily fraction of radiation, for 10 treatment days, up to a total dose of 12 g/m².

Response evaluation and treatment protocols

The volume of the lesions under treatment was weekly estimated by measuring in three planes. Complete response was defined as reduction of tumors to less than palpable size. Patients were assigned to one of the two basic treatment groups (MDF alone and MDF + MIS), and heat was delivered to one of the nodes in each patient, so that all lesions were treated according to the following treatment protocols:

1) MDF	Alone	32 nodes
	HT	27 nodes
2) MDF + MIS	Alone	22 nodes
	HT	27 nodes

Results

The results at 12 months' follow-up, obtained with different treatment protocols, are shown in Table I and are also compared with those obtained in our historical series of patients treated with conventional fractionation of 2 Gy/day. With respect to this control group, all data in other protocols indicate an increase of local response, especially in the groups treated also with hyperthermia. When the percent of successes in surviving patients is plotted against the period of observation (Fig. 3), local control rate in the two basic categories (MDF and MDF + MIS) appears to be better than that in the control group of conventional fractionation, although a statistically significant difference ($0.05>p>0.01$) could be demonstrated only in the second category of patients treated with MDF + MIS, and only at the end of treatment. Naturally, no statistical difference could be calculated between the two basic treatment groups. When hyperthermia was delivered also (Fig. 4), the local control rate was even better and seemed to remain at the same level through the follow-up period, suggesting that recurrence is rarely a cause of death in these latter groups. At the end of treatment, the results obtained in patients treated with hyperthermia were also statistically different not only from the historical series ($0.05>p>0.01$) but also from the group treated with MDF alone ($p<0.05$). Unfortunately, because many of these patients died, it was not possible to calculate a statistical difference at 12 months between the group treated with MDF alone and those treated with heat also, although in the latter a statistically significant difference ($p<0.05$) could be seen when compared to the historical series treated with conventional fractionation.

No increased radiation reactions have ever been observed in patients treated with hyperthermia. In two patients, some skin burns, which rapidly healed, were observed at the beginning of this study, due to the use of an improper applicator. Other side effects have been observed only in patients treated with MIS as well. These consisted of mild nausea (75%), which was easily controlled by methoclopramide, generalized skin papillary rashes (two patients removed from protocol), and mild peripheral neuropathy (10%). Furthermore, in the misonidazole group all four patients irradiated through two cross-firing portals experienced oropharyngeal mucositis that occurred earlier, longer, and stronger than in the patients treated through the same portals with MDF alone.

TABLE I

Results of Different Treatment Protocols

Complete Response at 12 Months	MDF alone	MDF + HT	MDF + MIS alone	MDF + MIS + HT	Conventional Fractionation
Crude	7/32 (.22)	11/27 (.41)	7/22 (.32)	8/20 (.40)	6/46 (.13)
Actuarial	7/16 (.44)	11/15 (.73)	7/12 (.58)	8/10 (.80)	6/28 (.21)

MDF = multiple daily fractionation
HT = hyperthermia
MIS = misonidazole

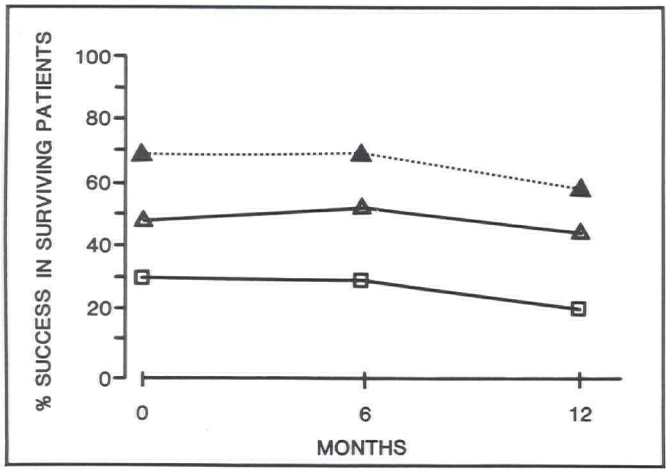

Fig. 3

Local control rate in patients of the two basic treatment categories (MDF and MDF + MIS), surviving at the time of observation. ⊡——⊡ = Radiation alone (conventional fractionation; historical series); △——△ = Radiation alone (MDF: 2 + 1.5 + 1.5 Gy/day, 4 h intervals, 5 days/week); ▲·····▲ = Radiation (MDF) + Misonidazole (MIS: 1.2 g/m² daily, for 10 treatment days).

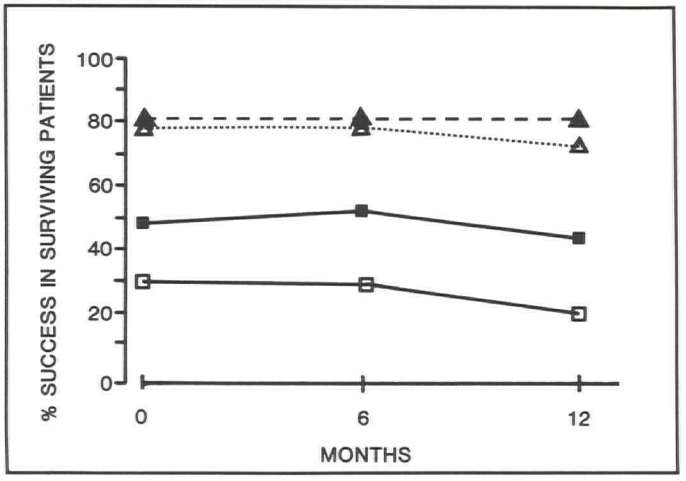

Fig. 4

Local control rate in patients treated with hyperthermia also, surviving at the time of observation. ⊡——⊡ = Radiation alone (conventional fractionation; historical series) ■——■ = Radiation alone (MDF); △·····△ = MDF + Heat (HT: 42°-43°C, 45 min, immediately after the second daily fraction of radiation, on days 1, 3, and 5 of each week); ▲— — —▲ = MDF + HT + MIS.

Discussion

Our experimental and clinical results clearly show the increased effect of ionizing radiation on tumors by means of hyperthermia. Whether heat delivered sequentially (e.g., four hours later) with respect to radiation is therapeutically more advantageous than heat administered simultaneously with radiation is still to be proved, especially when late effects to normal tissue are considered. However, our results on mouse tumors heated with an interstitial applicator indicate that the use of hyperthermia and radiation simultaneously is therapeutically superior when heat can be preferentially delivered to the tumor mass.

Although our treatment schedule of combined hyperthermia and radiation can be considered a compromise between simultaneous and sequential heat delivery, the most important observation of our study is that this treatment modality causes very little toxicity in patients. The absence of increased normal epithelial tissue reaction is encouraging, even though more precise experimental and clinical studies of the heat sequence and duration are still necessary, especially in regard to nonreversible late injury to normal tissues.

Local tumor control also appears to be improved when hyperthermia was also applied to the two basic categories of treatment (MDF and MDF + MIS), thus confirming that hyperthermia can be a useful tool for enhancing radiation response in human tumors.

References

1. Overgaard J. Effect of fractionated hyperthermia and radiation on an experimental tumor and its surrounding skin. In: Proc, 1st Meeting of European Group of Hyperthermia in Radiation Oncology. Arcangeli G, Mauro F, eds. Milan: Masson Italia, 1980:241-45.

2. Field SB, Lunec J, Morris CC, Myers R. Optimal treatment with hyperthermia and ionizing radiation. In: Proc, 1st Meeting of European Group of Hyperthermia in Radiation Oncology. Arcangeli G, Mauro F, eds. Milan: Masson Italia, 1980:223-29.

3. Stewart FA, Denekamp J. The therapeutic advantage of combined heat and x-rays on a mouse fibrosarcoma. Br J Radiol 1978;51:307-16.

4. Arcangeli G, Cividalli A, Lovisolo G, et al. A needle-like microwave applicator for interstitial hyperthermia: Thermodosimetry in phantom and in vivo. 3rd Int Symposium on Cancer Therapy by Hyperthermia, Drugs and Radiation. Ft. Collins, Colorado: 1980:22-26 (Abst Te 1).

5. Arcangeli G, Barni E, Cividalli A, et al. Microwave interstitial hyperthermia by a (multiple) needle applicator. 2nd Meeting of European Group of Hyperthermia in Radiation Oncology. Rome, September 19-20, 1980 (Abst 1/8).

6. Arcangeli G, Mauro F, Morelli D, et al. Multiple daily fractionation in radiotheraphy: Biological rationale and preliminary clinical experiences. Europ J Cancer 1979;15:1077-83.

7. Arcangeli G, Barni E, Cividalli A, et al. Effectiveness of microwave hyperthermia combined with ionizing radiation: Clinical results of neck node metastases. Int J Radiat Oncol Biol Phys 1980;6:143-48.