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Thermal Dose Expression in Clinical Hyperthermia and Correlation with Tumor Response/Control¹

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Abstract

Thermal dose has been identified as one of the most important factors which influence the efficacy of hyperthermia. Adequate temperature must be delivered for an appropriate period of time to the entire tumor volume in order to achieve optimal therapeutic results. Present clinical thermometry systems provide coarse temperature readings, since only selected tumor or normal tissue temperatures are monitored. Experimental *in vitro* and *in vivo* data suggest that the minimal temperature observed in the tumor determines therapeutic effectiveness. Unfortunately, at the present time, clinical data documenting these observations are scarce. The inhomogeneity of temperature distribution throughout the tumor volume makes difficult accurate correlations with tumor response and subsequent tumor control.

Several mathematical models have been offered to express the time-temperature equivalency in relation to a reference temperature (43° equivalent). Factors such as step-down heating, fractionated hyperthermia, thermal adaptation, and combination with irradiation, in addition to physiological parameters such as blood flow, play a major role in the expression of thermal dose. In order to meaningfully express thermal dose in clinical hyperthermia, several procedures are recommended, such as static phantom studies of specific absorption rate distributions for heat delivery equipment, detailed thermal mapping in hyperthermia sessions, development of reliable predictive biomathematical models to express temperature-time equivalency, and the fostering of research in 3-dimensional noninvasive clinical thermometry.

Introduction

As demonstrated in this supplement, there are multiple factors that influence the effectiveness of hyperthermia in biological experiments and clinical cancer therapy, including biochemical (molecular), cellular, physiological, physical, and even immunological mechanisms. The factors that condition thermal dose and, hence, clinical thermal response are depicted in Table 1.

It is apparent that an adequate temperature must be delivered for an appropriate period of time to the entire tumor volume in order to achieve optimal therapeutic results. Ideally, the temperature in the tumor should rise rapidly when the treatment is begun, a homogeneous temperature should be maintained, and the temperature should return rapidly to normal after exposure has been completed.

Definition of the Problem and Clinical Experience. Even though hyperthermia has been used in the clinical management

of cancer patients for several years, there is little consistency in the way in which temperatures are expressed. Although there are definite prescriptions for temperature (generally 43°) and time (usually 60 min), variations in the temperature and the time of delivery are frequent throughout the treatment sessions (Chart 1), rendering these simple prescriptions of limited value. It is difficult to express this variation of time and temperature, and it is even more complicated to compare various treatment regimens and results.

At the present time, coarse clinical thermometry systems are available, which, at best, provide temperature readings in selected sites of the tumor or the normal tissues. However, non-homogeneous temperature distributions are seen frequently, particularly in larger masses or at greater tissue depths. Thus, the likelihood of treatment temperature measurements reflecting a representative or useful description of the treatment depends entirely on the placement of probes that measure the temperature in specific points within the treatment volume. Table 2 summarizes some of the obstacles that we currently face when we attempt to correlate hyperthermia treatment parameters with therapy outcome (tumor regression or normal tissue effects).

At the Mallinckrodt Institute of Radiology, Washington University Medical Center, superficial metastatic or recurrent tumors of various locations and histologies have been treated in a prospective nonrandomized study, utilizing combinations of irradiation and hyperthermia. Patients were treated between March 1978 and June 1983 (minimum 6-month followup). Seventy-two % of the tumors treated had received previous irradiation (from 5000 to 6500 rads at times varying from a few months to several years). In the hyperthermia study, most of the patients received doses ranging between 2000 and 4000 rads in 2 weekly fractions of 400 rads delivered every 72 hrs, followed by heat (target temperature: 42.5°, 60 min), which was usually initiated within 15 to 30 min after the radiation exposure. The desired temperature was reached in most of the patients in about 10 to 15 min, and timing was begun when the treatment volume exceeded 42°.

The fractionation every 72 hr was selected in an effort to avoid the thermotolerance described in some *in vitro* biological experiments (11). However, there is little *in vivo* evidence to support this fractionation interval. Radiation therapy was usually delivered with electrons, energies ranging from 9 to 16 MeV, depending on the size of the lesion and occasionally with cobalt-60, in which case bolus was used to diminish the skin-sparing effect. The equipment and techniques of hyperthermia have been described previously (13, 22). Most of the patients were treated with 915 MHz external microwaves, using dielectric filled waveguide applicators. A plastic bag containing deionized water was used after 1½ years into the trial to improve the coupling of the applicators to the irregular surface of the patient's body. A

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Table 1
Factors affecting "thermal dose"
Factors affecting "thermal dose"

Physical
Power deposition in target volume (modality, frequency, size of applicator)
Thermal conduction in tissue
Time
Biological
Environmental (pH, O ₂)
Time-temperature relationship
Thermal history
Intrinsic sensitivity of specific cells to heat
Tumor and host (normal tissues)
Type, size, and location of tumor
Microcirculation-blood flow (thermal convection)
Specific normal organ at risk

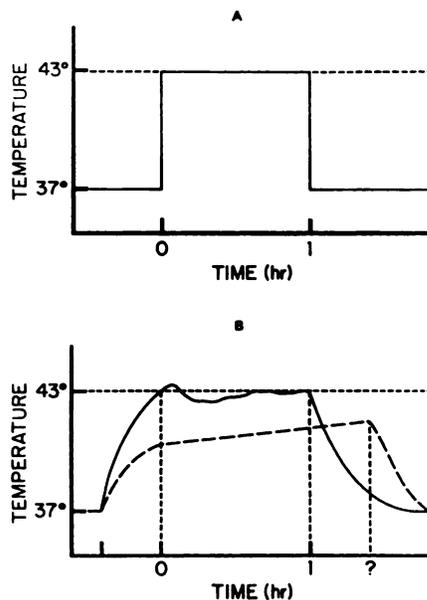


Chart 1. Continuous plot of temperature as a function of time for an idealized treatment (A) and for more realistic cases (B) which include initial build-up, plateau, and decay regions.

Table 2
Obstacles to meaningful correlation of "thermal dose" and tumor response/control
Obstacles to correlation of "thermal dose" and tumor response

Heat delivery
Nonhomogeneous power deposition and heat dissipation
Thermometry
Determination of temperature in few selected points
Variations of temperature during heating period
Biological
Variations in heat sensitivity of tumors and normal tissues
Thermotolerance
Physiological
Microcirculation, blood flow
Patient/tumor factors
Features independent from above (discomfort, geometry, etc.)

minimum of 2 thermistor probes (YSI, 524) encased in 24-gauge needles were inserted, one at the estimated maximum depth of the tumor (central axis) and one or two in the periphery. A reference thermal probe was placed at the skin surface during each treatment session. The temperature at these sites was continuously recorded on dual channel strip chart recorders. Temperatures were measured every 15 min with the power off. In general, variations of temperature of 0.5°–2° were noted with

the RF generator power on or off and appropriate corrections were made by extrapolation to obtain the actual tissue temperature. During the past 2 years, high-resistivity thermistor probes (Bowman) or gallium arsenide (Christensen) optical probes were utilized, using plastic catheters for insertion of the probes into the tissues so that temperature could be monitored continuously while RF power was on.

A group of 29 patients with 31 lesions (most of them recurrent carcinoma of the head and neck that had been treated previously with definitive radiotherapy) reported by Emami *et al.*³ were treated with a combination of interstitial brachytherapy (¹⁹²Ir) and hyperthermia. Doses of irradiation varied from 2000 to 5000 rads, delivered at the rate of 1000 rads/day. Hyperthermia treatments (43°, 60 min) were given initially, before the ¹⁹²Ir sources were inserted in afterloading plastic catheters or on the last day, after removal of the radioactive sources. Hyperthermia in most of the patients was administered with microwave antennas (915 MHz).

An attempt was made to correlate size or depth of tumors with average temperature levels reached in all treatment sessions. A correlation was also carried out between the average temperatures and complete tumor regression.

Results

A total of 130 tumors were treated with external irradiation and microwaves. Of 53 lesions treated in the head and neck, 26 (49.1%) showed a complete response, and 17 (32.1%) showed partial response (more than 50% regression in average diameter). In 9 patients with recurrent or metastatic epidermoid carcinoma infiltrating the neck, which could not be measured but was inoperable, 7 had tumor control (no regrowth) lasting several months after therapy. Of 37 patients with adenocarcinoma of breast recurrent in the chest wall, 19 (51.4%) achieved a complete regression, and 11 (29.7%) achieved a partial regression. Of 23 metastatic or recurrent melanoma nodules, many of which were located in the extremities, 16 (69.6%) exhibited a complete regression, and 6 (26.1%) exhibited partial regression. Five sarcomas treated with this combination therapy showed complete tumor regression. In the tumors that achieved a complete regression after initial therapy, 75 to 80% of the epithelial tumors and 100% of the melanomas and sarcomas had continued tumor control lasting from several months to 4 years.

Table 3 illustrates the proportion of tumors in various sizes that achieved an average temperature throughout most of the treatments. There is a trend toward higher temperatures being delivered to the smaller tumors. This observation is also reflected in tumor response. In lesions less than 4 cm in diameter, which should have been heated more efficiently with 915-MHz microwave external applicators, the complete tumor response was in the range of 60%, in contrast to only 33% in the tumors at a depth greater than 4 cm (Table 4).

Table 5 shows a correlation of the size of the tumors according to various histologies and the percentage of complete tumor regression according to the average temperature delivered. In the tumors less than 4 cm in diameter, approximately 60 to 70% of those achieving temperatures above 41° had a complete

³ B. Emami, J. E. Marks, C. A. Perez, G. H. Nussbaum, L. Leybovich, and D. Von Gerichten. Interstitial thermoradiotherapy in the treatment of recurrent/residual malignant tumors. Presented at 66th Annual Meeting of the American Radium Society, Coronado, CA, March 1984.

Table 3
Irradiation and hyperthermia: Correlation of average temperature and depth of tumor

Type of cancer	No. of tumors at the following size and av. temperature:								
	≤2 cm			2.1–4 cm			>4 cm		
	≤41°	41–42°	≥42.5°	≤41°	41–42°	≥42.5°	≤41°	41–42°	≥42.5°
Head and neck (epidermoid carcinoma)	3	3	13	4	7	12	3	3	5
Chest wall (adenocarcinoma)	1	4	14		5	4	2	2	5
Melanoma, sarcoma	2	5	7	1	2	7		2	2
Total	6 (11.4%)	12 (22.8%)	34 (64.6%)	5 (12%)	14 (33%)	23 (55%)	5 (21%)	7 (29%)	12 (50%)

Table 4
Irradiation and hyperthermia: complete tumor response and depth of tumor

Type of cancer	Complete responses/tumors at the following tumor size:		
	≤2 cm (%)	2.1–4 cm (%)	>4 cm (%)
Epidermoid carcinoma	12/19 (63.2)	13/23 (56.5)	1/11 (9.1)
Adenocarcinoma	8/19 (42.1) ^a	6/9 (66.7)	5/9 (55.6)
Melanoma	9/13 (69.2)	5/6 (83.3)	2/4 (50)
Sarcoma	1/1 (100)	3/4 (75)	
Total	30/52 (57.7)	27/42 (64)	8/24 (33)

^a If large area (>75 sq cm) chest wall recurrences (with poor thermal distributions) are excluded, complete response is 63%.

tumor response. Even at 41° or less, a significant number of the tumors regressed. However, in lesions larger than 4 cm, only 41.6% of those achieving a temperature higher than 42° had a complete response, and 42.8% of those receiving 41–42° achieved a complete response. No tumor responses were noted with temperatures below 41°.

In the 31 tumors treated with thermoradiotherapy, Emami *et al.*² reported similar correlations, with the tumors less than 4 cm in average diameter exhibiting 80% complete regression, a significantly higher proportion than in larger lesions (Table 6). Furthermore, 69% of 26 tumors achieving “adequate” temperatures (42° or higher for 40 min) had a complete tumor regression, in contrast to 0 of 5 treated to unsatisfactory temperatures.

Discussion

For hyperthermia to be effective in cancer therapy, as it has been demonstrated to be in animal tumors, it is imperative that the temperature within the tumor be uniform. As reported by Hill and Denekamp (12), in mice with small tumors that were heated using a water bath, wide variations in temperature were noted. Moreover, Hill and Denekamp (12) have shown different thermal enhancement ratio values for tumors heated in several anatomical sites of the mouse.

It is obvious that, ideally, a 3-dimensional representation of the temperature throughout the entire heated volume should always be obtained. However, at the present time, this is technically not possible, and the best that can be accomplished is the measurement of temperatures at a few points within the tumor.

During a hyperthermia session, 3 general temperature patterns are observed: (a) buildup, from the time the power is applied to the time when the prescribed temperature, is reached; (b) therapeutic temperature, which represents the time at which a more or less constant temperature, is delivered at the prescribed level; and (c) a cool-down or washout period, after the power is turned

off and the temperatures in the tumor and the tissues decay to normal body temperature.

Integration of all of these components is essential to determine some sort of standard or comparable dose estimate for the actual treatment given. Sapareto and Dewey (25) have proposed a system, using 43° as the reference temperature. They point out the practical application of this concept since, in cases in which the temperature is below that prescribed, the exposure time should be prolonged and, in those in which the measured temperature exceeds the prescribed temperature, the treatment time should be shortened to correct for the extra biological effect induced by the higher temperature.

The initial approach used in these studies has been to calculate the accumulated exposure (t_1) from the relationship described by Dewey *et al.* (2):

$$t_1 = t_2 R^{(T_1 - T_2)} \tag{A}$$

where t is time and T is temperature and R can be calculated as a function of the activation energy (μ) and absolute temperature (°K) from an Arrhenius plot by:

$$R = e^{-\mu/2T(T + 1)} \tag{B}$$

For sufficiently small Δt , Equation A may be described by a numerical integration as:

$$t_{43} = \sum_{t=0}^{t=final} \{R(43 - \bar{T})_{\Delta t}\} \tag{C}$$

where t_{43} is the equivalent time at 43°, \bar{T} is the average temperature during time Δt , and $R = 0.5$ above 43° and 0.25 below 43°. The relationship described above (Equation C) provides a useful method to calculate the accumulated dose at a reference temperature under a variety of heating profiles, including those temperature histories that cannot be easily described mathematically. Obviously, it has evolved primarily from studies using single uniform doses of heat. This situation is not likely to be observed in the clinic, and complicating factors which occur during treatment fractionation must be considered.

Sapareto and Dewey (25) have offered a FORTRAN computer program, developed on a PDP11/23 system (Digital Equipment Corporation, Maynard, MA) to calculate the equivalent-minute dose (t_{43}) from treatment data. A similar program written in BASIC for the IBM personal computer (IBM Corporation, Boca Raton, FL) is provided in the “Appendix.”

The relationship described above should be of great clinical value because it seems to be valid for virtually all of the *in vitro* and *in vivo* systems which have been studied (9). Field and Morris (5) have reviewed the available literature (Table 7) and, although the absolute dose required in each study to achieve

Table 5
Irradiation and hyperthermia: correlation of average temperature and complete tumor response as a function of depth of tumor

Site of tumor	Complete responses/tumors at the following size and av. temperature:								
	≤2 cm			2.1–4 cm			>4 cm		
	≤41° (%)	41–42° (%)	≥42.5° (%)	≤41° (%)	41–42° (%)	≥42.5° (%)	≤41° (%)	41–42° (%)	≥42.5° (%)
Head and neck (epidermoid carcinoma)	1/3 (33.3)	2/3 (66.7)	9/13 (69.2)	2/4 (50)	5/7 (71.4)	6/12 (50)	0/3	0/3	1/5 (20)
Chest wall (adenocarcinoma)	0/1	1/4 (25)	7/14 (50)		3/5 (60)	3/4 (75)	0/2	2/2 (100)	3/5 (60)
Melanoma, sarcoma	1/2 (50)	3/5 (60)	6/7 (85.7)	1/1 (100)	2/2 (100)	5/7 (71.4)		1/2 (50)	1/2 (50)
Total	2/6 (33)	6/12 (50)	22/34 (64.7)	3/5 (60)	10/14 (71)	14/23 (60)	0/5 (0)	3/7 (42.8)	5/12 (41.6)

Table 6
Interstitial thermoradiotherapy: tumor response versus quality of heating

Heating	No. of responses				Total
	CR ^a	PR	NR	Not evaluable	
Satisfactory	18 (69%)	5	3		26
Not satisfactory		1	2	2	5
Total	18	6	5	2	31

^a CR, complete response; PR, partial response; NR, no response.

the end point measured showed large variation, the time-temperature relationship to achieve that end point demonstrated remarkable consistency.

Dewhirst *et al.* (4) reported on observations made on 130 dogs and cats with various malignant tumors randomized to be treated with either irradiation alone or combined with hyperthermia (prescribed dose $44^\circ \pm 2^\circ$, 30 min once a week) (460 rads twice weekly for 8 fractions). A more detailed description of their technique is included in this issue (3).

With a method described by Sapareto (24), utilizing the Arrhenius relationship for biological isoeffect between different time-temperature combinations a dose (termed equivalent-min) equivalent to a time at 43° was derived. Multivariate analysis was used to determine the most important factor to prognosticate the complete response of tumors. Not surprisingly, these studies indicated that the thermal dose in the coolest part of the tumor was the best predictor of long-term response. In addition, the equivalent-min dose calculated was the best prognostic indicator of long-term response. When the equivalent-min dose for all treatments in one animal were averaged, only a slight correlation with long-term response was seen. However, when only the first treatment was used, a much better correlation with response was observed. This higher correlation of response with first heat dose suggests that thermotolerance may reduce the effectiveness of the later treatments in multiple dose therapy, despite the separation of heat treatments by 7 days in this study, and stresses the need for better understanding of the effect of thermotolerance *in vivo*.

Oleson *et al.* (20) reported on 137 patients treated with various techniques of hyperthermia combined with moderate doses of irradiation (2400 rads delivered in 2 weekly fractions, 400 rads tumor dose) within 15 min after hyperthermia (42° for 30 min). They also observed a negative correlation between the tumor volume and response to therapy (smaller tumors exhibited better response than larger ones). Furthermore, the minimal average tumor temperature was well correlated with the probability of complete tumor response.

Evidence suggests that tumors are likely to show large differences in their sensitivity to heat because of variations in blood

flow and pH. This possibility should not limit the usefulness of thermal dose calculation models, for 2 reasons: (a) a parameter of primary importance in hyperthermic treatments is the normal tissue tolerance, which is dose limiting, as it is in radiation therapy; and (b) the purpose of any thermal dose unit is not to account for variation in sensitivity of any specific tissue, whether normal or malignant; a general thermal dose should be used to quantitate these differences so that they may be studied and compared. An analogous situation in radiation dosimetry would be the oxygen effect, in which different tumors exhibit different radiation sensitivities, presumably due to differences in tumor hypoxia. Describing this effect in terms of a radiation dose has yielded the concept of the oxygen enhancement ratio.

A thermal dose model which accurately predicts response for normal tissue would provide a method for determining whether tumor tissue is more or less sensitive to heat under various protocols. This would be useful in predicting therapeutic gain. For example, if a particular fractionation scheme is known to produce more tumor effect than a "standard" scheme and yet thermal dose calculation based on normal tissue response predicts the same effect for this scheme as for the "standard" scheme, a therapeutic gain would occur using the new scheme. Obviously, this use of a thermal dose will require a great deal of further study.

Factors Affecting Thermal Dose

Step-down Heating. An initial exposure of cells to temperature above 43° causes a modification of the time-temperature relationship below 43° . If cells are briefly exposed above 43° and then immediately treated below 43° , the break in the Arrhenius plot seen at 43° is eliminated; thus, an *R* value of 0.5 is valid over the whole hyperthermic temperature range (7, 15). Both Sapareto *et al.* (26) and Li *et al.* (16) have suggested that the development of thermotolerance causes the break in the Arrhenius plot. Exposure to temperatures above 43° inhibits or delays the development of thermotolerance, thus allowing more rapid killing when the cells are subsequently exposed to hyperthermic temperatures below 43° . This phenomenon, of course, would affect the calculation of an accumulated dose as described below 43° . Further studies are necessary to quantitate the amount of hyperthermic temperature exposure above 43° necessary to eliminate the break in the Arrhenius relationship below 43° .

Fractionated Hyperthermia. A simple calculation of equivalent time at 43° cannot be accomplished for multiple heat doses due to the development of thermotolerance either between treatments or during protracted exposures at hyperthermic temperatures below 43° (26). As has been demonstrated clearly for a variety of cells, whether normal or malignant, previous exposure

Table 7
Summary of *R* values from *in vivo* data^a

Experimental system	Temperature range of observation	Transition temperature	<i>R</i> value for 1° above below transition	Time required at 43° for end point (min)
Mouse testis, percentage of wt loss	39.5–43.75°		0.45	4
Rat tumor 9L, heated <i>in vivo</i> , assayed <i>in vitro</i>	42.5–45.0°		0.56	32
Mouse jejunum, LD ₅₀ ^b	43.0–46.0°		0.50	37
Mouse jejunum, 50% loss of crypts	42.0–44.5°	42.3	0.45 (0.13)	40
Mouse tumor sarcoma 180, majority cure	41.0–47.0°		0.48	66
Baby rat tail skin, 50% necrosis	42.0–46.0°		0.48	73
Mouse ear skin, 50% necrosis	41.5–45.5°	42.1	0.50 (0.17)	74
Rat skin, epilation	42.0–46.0°		0.56	75
Baby rat tail skin, 5% stunting (half tail)	42.0–46.0°		0.50	80
Baby rat tail skin, 50% necrosis (whole tail)	41.8–46.0°	42.8	0.56 (0.17)	80
Mouse tumor C ₃ H/Tif, mammary carcinoma regrowth	41.5–44.5°	42.5	0.48 (0.17)	90
Mouse tumor F(Sal) fibrosarcoma, TCD ₅₀	41.5–45.5°	42.0	0.48 (0.17)	125
Mouse foot skin, epilation	42.0–45.5°		0.40	135
Mouse skin, feet and legs	43.5–45.0°		0.53	210
Mouse tumor C ₃ H, mammary carcinoma in flank, TCD ₅₀	43.0–45.0°		(0.34)	230
Pig and human skin, necrosis and cutaneous burns	44.0–55.0°		0.45	850

^a Data are from Ref. 5.

^b LD₅₀, 50% lethal dose (dose lethal to 50% of cells); TCD₅₀, mean tissue culture dose.

to elevated temperature produces resistance to further thermal damage, for periods of up to 6 days (6, 21, 23). The effect of the development of thermotolerance on the Arrhenius relationship is to cause both a shift in the break to higher temperatures and a displacement of the linear relationship toward slower rates of killing (*i.e.*, higher D_0 values) (1, 14). However, most importantly, the slope of the Arrhenius plot and, thus, the time-temperature relationship does not appear to change.

Based on these observations, the fundamental method of calculating equivalent-min is still valid for thermotolerant cells. However, the dose calculated must be reduced to account for the degree of thermotolerance present. A measure of this degree of thermotolerance has been proposed by Henle and Dethlefsen (8) as a ratio of D_0 values from survival curves for Chinese hamster ovary cells, with or without thermotolerance, and is termed the thermotolerance ratio. Thus, it may be possible to describe this phenomenon as a dose-modifying factor similar to that for the oxygen effect (oxygen enhancement ratio) seen with cell killing by ionizing radiation. The thermotolerance ratio which can be induced with acute heating treatments ranges from approximately 2.4 to 4.5 (1, 8, 10). Note this is not the same as the ratio of survival levels which can reach factors of greater than 1000 (11). Law (14) also has shown a ratio of approximately 3 between doses in the presence and absence of thermotolerance for the same normal tissue damage *in vivo*. Further investigations of these dose-modifying concepts are necessary to determine the feasibility of this approach.

An additional complication of thermotolerance is the development of tolerance during the warm-up period of the heat treatment or during protracted (4 hr) exposure below 43°. While the *R* value of 0.25 below 43° does partially account for some of this tolerance, this technique does not completely correct for this phenomenon and requires further study.

Thermal Adaptation. Another factor, probably closely related

to thermotolerance, is the ability of cells to modify their heat sensitivity based on the normal temperature to which they have become adapted (17). It may be that the break in the Arrhenius plot at 43° is not an absolute temperature but is, in fact, a relative temperature which becomes lower as the cells become adapted to lower normal environmental temperatures.

Hyperthermia Combined with Radiation

While the time-temperature relationship for combined hyperthermia and radiation interaction has not been well established and the literature contains conflicting information, evidence does suggest that this relationship is different from that for heat alone. Chart 2, from Sapareto *et al.* (27), shows the survival of mammalian cells *in vitro* for heat doses at various temperatures with durations adjusted to achieve the same heat alone killing combined with an X-ray dose of 500 rads. Although the heat-alone response is flat, the combined response shows a minimum at about 42.5°, whether radiation was given either during or after heating. This result demonstrates clearly that the time-temperature relationship for heat alone does not apply to the interaction between heat and radiation, for, if it were valid, the combined treatment response would also have been flat. This phenomenon may be due in part to variation in sensitivity to heat during different parts of the cell cycle. Heat-alone survival is predominantly determined by the G₁ cell response, while the combined response in Chart 2 is predominantly due to the response of late S-phase cells, since the radiation dose caused most of the killing. The time-temperature relationship for S-phase cells has not yet been determined.

While this response (Chart 2) agrees with the *in vitro* results of Loshek *et al.* (18), the opposite effect was seen by Law *et al.* (15) *in vivo*. The results of Law *et al.* suggest that, the higher the temperature, the greater the interaction between modalities.

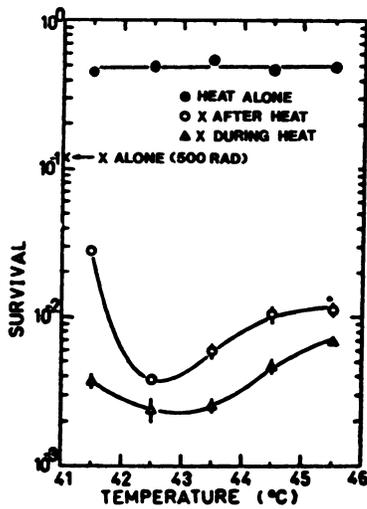


Chart 2. Survival of Chinese hamster ovary cells exposed to heat alone (●) or to heat combined with radiation is shown as a function of temperature. Cells were given heat treatments at each temperature, with times adjusted to achieve the same heat-alone killing. Radiation (5 Gy) was given either immediately after (○) or simultaneously with (△) heating. Reproduced from Ref. 27 with permission from Pergamon Press, Ltd.

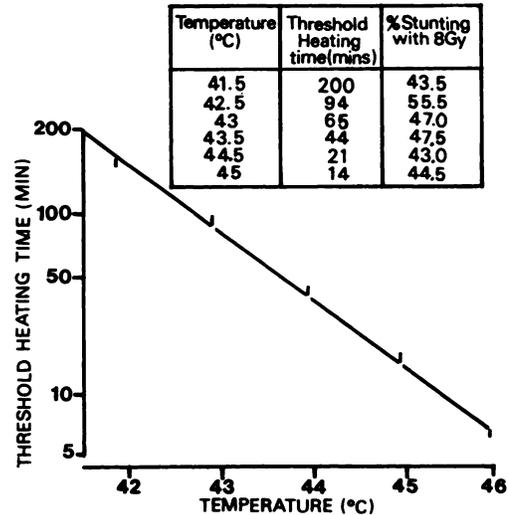


Chart 3. Thermal stunting threshold time plotted against temperature in rats. The inset shows the interpolated heating times for the experimental temperature used and the corresponding stunting obtained when these treatments are combined with 8 Gy of X-rays. The line was fitted by regression analysis. Reproduced from Ref. 19 with permission.

This difference in results may be due to physiological factors or it may be cell-type dependent. Since the *in vivo* study of Law *et al.* was performed in normal tissue, it may be possible that tumor cells will react more like cells *in vitro*. This would lead to the conclusion that lower hyperthermic temperatures would give a greater therapeutic gain. Unfortunately, in almost all of the available *in vivo* studies, no attempt has been made to adjust heating time to obtain the same "heat dose" at different temperatures for tumors. Further information is essential to understand the time-temperature relationship for the interaction between heat and radiation and, like the heat-alone studies, will provide important information for clinical studies.

Myers *et al.* (19), utilizing the epithelial cartilage of the rat tail exposed to different doses of irradiation or heat (water bath), demonstrated that there is a rapid rise of the thermal enhancement ratio with increasing temperature or time or both. They noted that the combined data for both direct heat damage and thermal enhanced X-ray damage demonstrated that the heating time must be halved for every degree increase in temperature to achieve the same level of tissue damage. The inset table in Chart 3 shows the equivalency of the various temperatures when combined with 8 Gy.

Conclusions and Recommendations

It is apparent that there are many spatial and chronological variations in the temperature delivered to the tumor and normal tissues throughout a clinical hyperthermia treatment. Furthermore, it is imperative that some method be established to compare thermal doses. Many factors must be considered before any thermal dose expression can be used with confidence in the clinic. These factors include, but are not limited to, better thermal mapping and an understanding of both thermal history and the interaction of heat and radiation. Further investigation is necessary to determine the physical characteristics and thermodynamics as well as cell kinetic factors that affect the response of tissues to either heat alone or heat combined with radiation, so

that reliable predictive dose expressions can be developed. Experimental observation in pet animals and in humans has documented the importance of correlating the thermal dose achieved in the tumor volume with the response to therapy. However, more studies evaluating the usefulness of thermal dose expressions on tumor response are necessary; moreover, information on thermal dose as a predictor of normal tissue damage may be even more important.

In order to meaningfully express thermal dose in clinical hyperthermia, efforts in the following areas are recommended: (a) static phantom studies of performance characteristics of heat delivery equipment through measurement of SAR distributions; (b) *in vivo* temperature measurements throughout every hyperthermia session, using as many thermometry probes as possible (thermal mapping); (c) determination of build-up, variations of prescribed temperature-time and wash-out (decay) temperatures; (d) immediate development of reliable predictive biomathematical models to express temperature-time equivalency to a reference temperature (*i.e.*, 43°); and (e) foster research in tridimensional noninvasive clinical thermometry.

Appendix

```

10 'Program Tequiv
20 'Copyright—S. Sapareto 8/13/83 Version 1.00
30 'This program is designed to take sequential temperature
40 'values and calculate the accumulated equivalent time and
50 'degree*minutes converted back to time at a reference
60 'temperature.
70 DEFINT I-O
80 DIM TEMP(2000),TIME(2000)
90 'To modify default parameters change these data statements
100 'before compiling
110 NPRINT=0 : TREF=43 : TBREAK=43 : RABOVE=.5 : RBE-
LOW=.25 : TSTRT=41 : OUTPT=2
120 CLS : KEY OFF
130 OPEN "LPT1:" FOR OUTPUT AS #2 : OPEN "SCRN:" FOR OUT-
PUT AS #3
    
```

```

140 INPUT "Do you want the output to go to the Screen or Printer?
(S/P)",OUTPT$
150 IF OUTPT$="S" OR OUTPT$="s" THEN OUTPT=3
160 INPUT "Do you wish to have the data file printed out? (Y/N)
",QUERY$
170 IF QUERY$="Y" OR QUERY$="y" THEN NPRINT=1
180 'Set reference and break temperatures
190 PRINT "Enter reference temperature (Default=";TREF;"): ";
200 LINE INPUT "", TREF$
210 IF TREF$="" THEN TREF=VAL(TREF$)
220 PRINT "Enter break temperature (Default=";TBREAK;"): ";
230 LINE INPUT "",TBREAK$
240 IF TBREAK$="" THEN TBREAK=VAL(TBREAK$)
250 'Read in data
260 GOSUB 770 'Subroutine datrd(temp,time,ilen,ident)
270 IF OUTPT=3 THEN CLS
280 'Calculate doses
290 GOSUB 600 'Calculate sumrf(temp,time,ilen)
300 T43 = SUMRF
310 GOSUB 690 'Calculate dgmin(temp,time,ilen)
320 TDM43 = DGMIN / (TREF-TSTRT)
330 'Print data file
340 IF NPRINT=0 THEN 400
350 FOR I=1 TO ILEN
360 PRINT#OUTPT, USING "(###.###)";TIME(I);
370 PRINT#OUTPT, USING "##.##";TEMP(I);
380 IF I=ILEN OR I MOD 5 = 0 THEN PRINT#OUTPT,
390 NEXT
400 'Output results
410 PRINT#OUTPT, : PRINT#OUTPT, IDENT$
420 PRINT#OUTPT, USING "R=###.### FOR TEMP)";RABOVE;
430 PRINT#OUTPT, USING "###.##";TBREAK
440 PRINT#OUTPT, USING "R=###.### FOR TEMP(<";RBELOW;
450 PRINT#OUTPT, USING "###.##";TBREAK
460 PRINT#OUTPT, STRING$(70,"-")
470 ITREF = INT(TREF)
480 PRINT#OUTPT, "|";SPC(6);"DATA | TOTAL | t";SPC(10);"|
t";SPC(4);"(ABOVE ";
490 PRINT#OUTPT, USING "##.##) |";TSTRT
500 PRINT#OUTPT, "|";SPC(5);"POINTS | TIME |";ITREF;SPC(7);
510 PRINT#OUTPT, "| dm";ITREF;SPC(12);"| "
520 PRINT#OUTPT, STRING$(70,"-")
530 PRINT#OUTPT, USING "| ###.## |";ILEN;
540 PRINT#OUTPT, USING "##.## MIN |";TIME(ILEN);
550 PRINT#OUTPT, USING "###.### MIN |";T43;
560 PRINT#OUTPT, USING "###.## MIN |";TDM43
570 PRINT#OUTPT, STRING$(70,"-");
580 IF OUTPT=2 THEN PRINT#OUTPT, CHR$(12) ELSE
PRINT#OUTPT,
590 END

600 'Function Sumrf(temp,time,ilen)
610 TSUM=0!
620 FOR J=1 TO ILEN-1 : R=RABOVE :
TAVE=ABS((TEMP(J)+TEMP(J+1))/2!): DELTAT=ABS(TIME(J+1)-
TIME(J))
630 IF TAVE<=TBREAK THEN R=RBELOW
640 TSUM=TSUM+DELTAT*R^(TBREAK-TAVE): NEXT
650 'Convert equivalent time at break temperature to reference tem-
perature
660 R=RABOVE
670 IF TREF<TBREAK THEN R=RBELOW
680 SUMRF=TSUM*R^(TREF-TBREAK): RETURN
690 'Function Ogmin(temp,time,ilen)
700 'Calculate accumulated degrees*time above tstrt
710 OGMIN=0!
720 FOR J=1 TO ILEN-1 : TAVE=ABS((TEMP(J)+TEMP(J+1))/2!)

```

```

730 DELTAT=ABS(TIME(J+1)-TIME(J))
740 IF TAVE>TSTRT THEN DGMIN=DGMIN+DELTAT*(TAVE-TSTRT)
750 NEXT
760 RETURN
770 'Subroutine datrd(temp,time,ilen,ident$)
780 ON ERROR GOTO 990
790 LINE INPUT "Enter file name: ";FILNAM$
800 OPEN FILNAM$ FOR INPUT AS #1
810 LINE INPUT#1,IDENT$
820 DELTAT=0!
830 'Determine the time increment between points from positions 10-
13 of ident.
840 IDELT = VAL(MID$(IDENT$,10,4))
850 DELTAT=IDELT/60!
860 PRINT "Enter time increment (seconds) (default=";DELTAT+
60!;"): ";
870 LINE INPUT "",RESP$
880 IF RESP$("<") AND VAL(RESP$)>0 THEN DELTAT=VAL(RESP$)/
60!
890 'Read the temperature values from the file
900 ILEN=1
910 WHILE NOT EOF(1)
920 INPUT#1,TEMP(ILEN)
930 ILEN=ILEN+1
940 WEND
950 ILEN=ILEN-1
960 FOR I=1 TO ILEN : TIME(I)=DELTAT*(I-1) : NEXT
970 CLOSE #1
980 RETURN
990 'We go here if the aforementioned file is non-existent, i.e.,
995 IF ERR=53 THEN 1000 ELSE STOP
1000 'we enter the data by hand via the keyboard.
1010 '
1020 'Read the first line identifying the file
1030 PRINT "Enter identifier (one line): "
1040 LINE INPUT";";IDENT$ : PRINT
1050 'Read the time and temperature values
1060 PRINT "Enter time(min), temperature values, (return):"
1070 PRINT " ((return) to end data)"
1080 ILEN=1
1090 LINE INPUT";" :TEMPSTR$ : PRINT
1100 IF TEMPSTR$="" THEN TIME 1130
1110 P=INSTR(TEMPSTR$,".") : TIME(ILEN)=VAL(TEMPSTR$) :
TEMP(ILEN) = VAL(RIGHT$(TEMPSTR$,LEN(TEMPSTR$)-P))
1120 ILEN=ILEN+1 : GOTO 1090
1130 ILEN=ILEN-1 : RETURN

```

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