Biological Effect of 27.12-MHz Short-Wave Diathermic Heating in Experimental Tumors

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Abstract—**Twelve isologous experimental mouse tumors of different origin, degree of differentiation, and histology have been treated with short-wave diathermy (27.12 MHz) in the temperature range 41–43°C. All heated tumors react clinically in a similar way with shrinkage and hardened consistency of the palpable tumor. Local control was normally obtained after a certain minimum threshold heat dose, but the curability varied in different tumors from 9 to 25 percent. By lower heat doses usually no control was obtained, but a slight variation in heat sensitivity exists. Higher heat doses did normally not improve the curative results but deviations under special conditions were observed. A mutual variability of temperature and heating time without alteration in biological effect was observed.**

Histologic examination of heated tumors showed local destruction of the tumor core in all cases. However, in some of the tumors unaffected tumor cells were observed in the periphery of the treatment field and resulted in regrowth of tumor. Therefore, the quantitative curative results were varying for the different tumors after identical hyperthermic treatments. This may be explained by a technical insufficiency of the local diathermy. Such treatment will, at tumors characterized by a high peripheral blood flow and intense infiltrative growth, often be insufficient due to a heterogenous heating of these peripheral cells. A correlation between the degree of peripheral infiltrative growth and cure rate was found. No other relationship was established between the curative effect of hyperthermia and tumor characteristic parameters.

I. Introduction

SEVERAL techniques have been proposed in order to utilize the destructive effect of moderate hyperthermia on malignant tumors [1], [4], [5], [8], [10], [11], [13], [15], [21].

Among these, short-wave diathermy seems to have a number of features which may make it useful in human tumor therapy. These include 1) a good heat penetration of tissue if the electrodes are placed properly; 2) less interaction at tissue interfaces at low frequencies than in the microwave area; and 3) the possibility of using interstitial electrodes (implant needles, rectal, or bladder electrode, etc.) [2], [3], [8], [9], [14], [21].

On this background a study of the effect of 27.12-MHz diathermy was performed in a number of experimental solid tumors. The purpose of the study was to evaluate the biological effect and technical problems related to such therapy.

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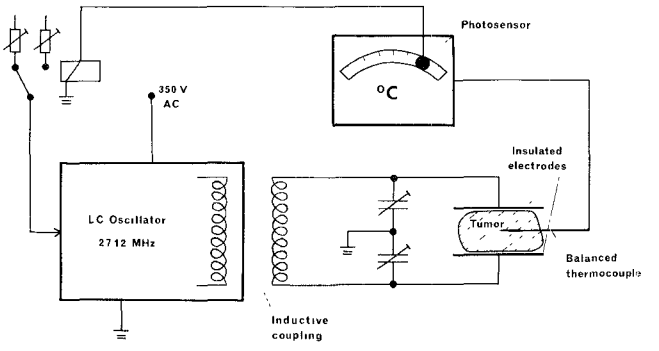

Fig. 1. Diagram of the heating unit. A 27.12-MHz *LC* oscillator is connected via an induction coil to a resonator circuit in which the tumor acts as a semiconductor. The tumor is placed between two insulated electrodes (capacitor plates) (2–4 cm^2). A balanced thermocouple is placed in the tumor tissue parallel to the electrodes, regulating automatically by an electrical thermometer the output of the heating unit between two levels in order to maintain a stable tumor temperature. Maximal output of the system is about 6 W measured by calorimetry with water in an insulated 8-cm^3 container.

II. Materials and Methods

A. Heating Technique

A model generator with a 27.12-MHz *LC* oscillator was used. The tumors inoculated into the flank or inguen were placed between insulated electrodes (Fig. 1). This technique allowed heating of the tumors to a temperature between 41–43°C within 2–4 min corresponding to a specific absorption rate (SAR) about 300 W/kg [9] (Fig. 2). The temperature was maintained by automatic regulation and variations were within about 0.1°C.

Temperature measurements were performed by placing a balanced thermocouple [20], [21] (Fig. 3) parallel to the surface of the electrodes. The thermocouple was surrounded by an air-filled lumen in order to avoid perturbation of the field around the metallic thermocouple, which would result in the production of a heterogeneous treatment field and give an abnormally high temperature reading [2], [3], [14] (Fig. 4). Practically, due to inhomogenecity in the tissue between the capacitor plates, it was impossible to align the thermocouple totally perpendicular to the field, but as the insulated thermocouple is small compared to the wave length in the medium, the perturbation was thereby also reduced. This would not be the case if microwave heating were applied. The thermocouple was via a *LC* lowpass filter connected to an Ellab thermome-

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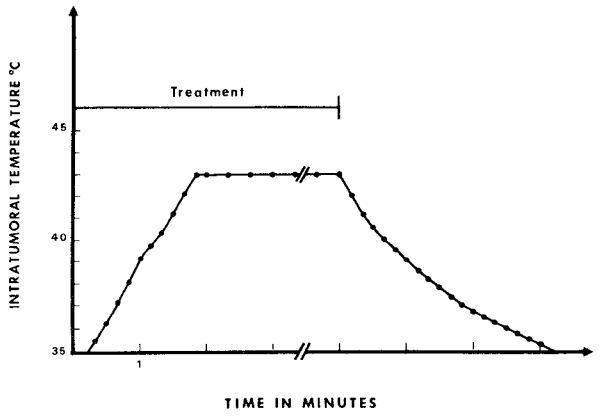

Fig. 2. Profile for the intratumoral temperature during 27.12-MHz diathermic heating. The tumor temperature reaches the actual treatment temperature (43°C) within 2 min and remains stable until treatment is stopped. Subsequent cooling to normal temperatures occurs within a few minutes. Based on the linear temperature increase the SAR is calculated to about 300 W/kg.

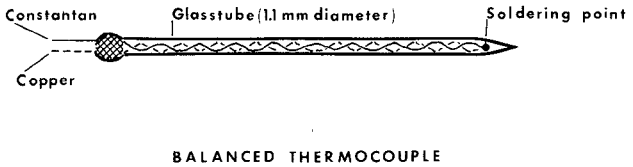

Fig. 3. High-frequency field balanced thermocouple. A thermocouple made of twisted 0.05-mm copper and constantan wire with a soldering point at the tip is placed in an air-filled glass tube with a lumen diameter of 1 mm. The thermocouple is connected to an Ellab TE 3 electrical thermometer with a light sensor which is able to regulate the output of the diathermic generator.

ter model TE3 which through a photosensor automatically regulated the output of the generator between two levels in order to maintain a stable tumor temperature. Calibration was performed in a treatment field against a quartz toluol thermometer and in a water bath against a standardized high-precision mercury thermometer.

B. Animals and Tumors

A number of different transplantable spontaneous mouse tumors were treated in this way. These tumors, which are listed in Table I, were selected with respect to variation in various parameters, such as origin, histology, growth characteristics, and radiosensitivity, in order to analyze possible factors which may influence the tumor response to hyperthermic treatment.

All tumors were propagated by serial transplantation. Minced tumor homogenate was inoculated in an amount of 5–10 μl into the flank or inguen of isologous mice. The tumors were treated at a size of 150–200 mm^3, and all treatments were performed under Nembutal anesthesia (72 mg/kg) given by intraperitoneal injection.

The results were evaluated as local tumor control (i.e., total disappearance of the tumors 120 days after treatment) or by histological examination at different times after treatment.

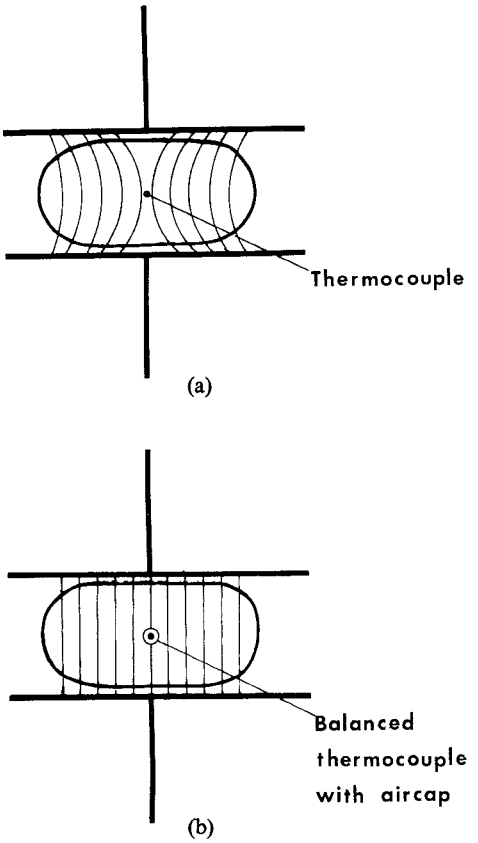

Fig. 4. Schematic representation of the interaction between the thermocouple and the heating current field. (a) A normal thermocouple is placed in the field which is concentrated around the metallic needle (field line deviation exaggerated in order to illustrate the problem). This results in a falsely high temperature reading and produces a heterogeneous treatment field with reduced heating in the tumor periphery. (b) The same situation, but with a balanced thermocouple with an air cap. This setup gives a true temperature and a more homogeneous treatment field.

III. Results

Initially, one tumor (HB) was studied at different temperatures and treatment times [21]. The clinical response is seen in Table II.

These results showed that it was possible to control an experimental tumor by local diathermy. The cures were obtained without evidence of damage to normal tissue, and the tumor destruction seems therefore to be a selective process.

It is seen from Table II that cures occur at all the temperature levels studied, but after different exposure times. It is typical that after a certain treatment time (dependent on the treatment temperature) the curative yield increases from zero or only a few percent to about 20-percent tumor control. This threshold heat dose (heat dose: combination of temperature and treatment time) giving $\geqslant$ 20-percent cures is seen in Fig. 5, where the time–temperature relationship is shown. The figure demonstrates that below about 42.5°C, the time and temperature are related in such a way that for each 0.5°C the temperature is reduced, the treatment time should be

TABLE I
CHARACTERISTICS OF THE 12 DIFFERENT TUMORS USED IN THE STUDY

Tumor	Strain of mice	Tissue of origen	Histopathology
BM	DBA	Mamma	Well-differentiated adenocarcinoma
BMA	DBA	Mamma (mutation of BM)	Anaplastic carcinoma
BP	Balb C	Primary in the axilla	Plasmocytoma
BT	C3H	Mamma	Well-differentiated adenocarcinoma
C	C3H	Mamma	Well-differentiated adenocarcinoma
CS	StB	Bone	Chondroblastosarcoma
HB	C3H	Mamma	Anaplastic Carcinoma
O	C3H	Mamma	Moderately differentiated adenocarcinoma
P	AKA	Mamma	Well-differentiated adenocarcinoma
SM	AKA	Testis	Seminoma
SS	StA	Pulmonary stroma	Fibrosarcoma
X	C3H	Mamma	Moderately differentiated adenocarcinoma

TABLE II
INFLUENCE OF TIME AND TEMPERATURE ON THE CURATIVE EFFECT IN THE HB MAMMARY CARCINOMA FOLLOWING LOCAL 27.12-MHZ DIATHERMY

Treatment temperature °C	Treatment time (min)											
	7.5	12	15	20	30	45	60	90	120	180	240	480
40.5									0/31[1] 0%			
41.0							0/33 0%		0/29 0%			2/7 28%
41.5					0/124 0%		1/45 2%		0/32 0%	1/14 7%	8/28 28%	
42.0					0/34 0%		1/31 3%	1/16 6%	4/18 22%			
42.5	0/20 0%				1/35 3%	3/34 8%	9/40 23%	8/34 24%	4/17 24%			
43.0			0/15 0%		2/18 11%	8/40 20%	16/23 25%					
43.5		0/8 0%		1/35 3%	27/142 19%	2/9 22%	41/162 25%					

[1]Number of cures/number of treated.

doubled to obtain an equivalent response. At temperatures higher than 42.5°C, the curve is less steep, and the treatment time tends to double for each 1°C decrease, but this level has not been studied in detail in the present investigation. However, such a relation was also found in other studies on the time–temperature relationship and may be due to a difference in the biological heat sensitivity of cells at temperatures below and above 42.5°C, respectively [7], [12], [18], [19].

The data in Table II also demonstrate another typical observation in the effect of local diathermic heating of solid tumors. Even though the heat dose is increased beyond the threshold dose by a factor of up to four, this does not improve the curative results. The dose-response

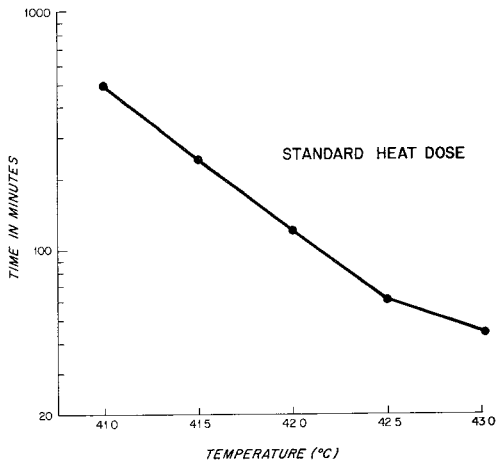

Fig. 5. Time–temperature relationship to obtain equal response ($\geq$ 20-percent local control, see Table II) in the HB mammary carcinoma. The curve is a modified Arrhenius curve which, between 41 and 42.5°C, has an inactivation energy of 270 kcal/mole corresponding to a doubling of the treatment time for each 0.5°C decrease in temperature. At higher temperatures ($\geq$ 42.5°C) the slope becomes less steep with a doubling time for each 1°C decrease.

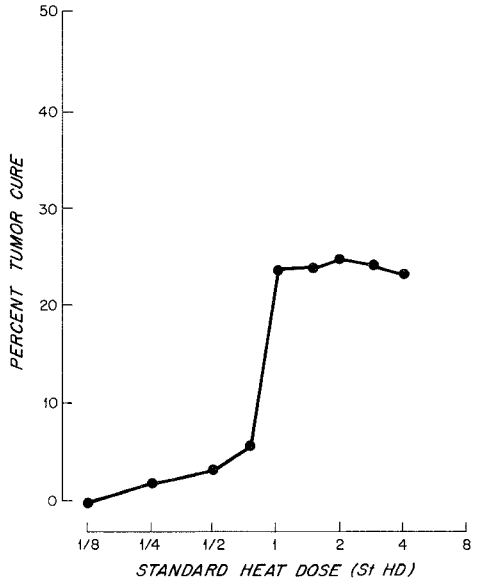

Fig. 6. Dose-response curve for local tumor control of the HB mammary carcinoma treated with diathermy. A marked increase to about 20-percent tumor control is seen at 1 StHD, but further treatment does not improve the curative effect.

curve showed a plateau at a level of about 20-percent cures (Fig. 6). This is in contrast to what is found after a probably more homogeneous heating (e.g., water bath), where the dose response is from 0 to 100 percent [6], [18], [19]. Therefore, it seems that about 80 percent of the HB tumors failed to be controlled, even though they were given a dose which biologically may be sufficient to destroy all tumor cells.

The initial clinical response was the same in all tumors treated with a "curative heat dose." The tumor shrank, became increasingly firm, and gradually disappeared, but in about 80 percent, recurrent growth appears within one to two weeks. This recurrence was always found in the periphery of the treated tumors.

Histopathological examination of such tumors demonstrated that in many cases a small marginal spot of viable tumor cells causing the regrowth could be observed. This was especially found as small tumor islands situated in the surrounding fatty or connective tissue. It was apparent that this area was more resistant to hyperthermia, or that it had been exposed to the smaller heat dose, either because of peripheral vascular cooling or a heterogeneous heat distribution in the tissue.

In order to analyze the impact of such peripheral recurrences and consequently the possibilities of obtaining cure in different tumors, a number of other tumors were studied. As previously mentioned, these were selected so as to represent a wide range of tumors with different characteristics.

In order to standardize the effect of the heat treatment, it was necessary to introduce the concept of a "standard heat dose" (StHD) [22], [23]. This was defined as the dose required to produce $\geq$ 20-percent cures in the HB tumor (e.g., 42.5°C for 60 min or 42°C for 120 min). The relationship between time and temperature and thereby the treatment time required to obtain a StHD at a given temperature appear from the curve in Fig. 5. This StHD is valid only in the temperature range between 41 and 42.5°C.

Table III shows the relationship between tumor cures and heat doses in 12 different tumors.

These data indicate that a general threshold dose seems to be required to obtain a curative effect in the tumors, but this may show some variation from tumor to tumor (i.e., the thermal sensitivity is not the same in all tumors). The concept of the standard heat dose is, however, valid in the sense that the correlation between time and temperature was the same in all tumors studied (Table IV). The curative yield following the actual threshold dose was not the same in all the tumors, but showed variations from a few to about 25 percent. It can, therefore, be concluded that it is possible to obtain local control in a number of different solid tumors following diathermic heating, but that the heat sensitivity of the tumors and also the level of tumor cures showed variations.

The question was, therefore, "What factors influenced the curative yield in these tumors treated with local diathermia?"

The variations in the curative yield were not explained by different sensitivities to hyperthermia, as the tumors showed dose-response curves from 0- to 100-percent cures when treated with a water bath technique ensuring a more homogeneous tumor heating [18, (unpublished observations)].

All recurrences were of the same peripheral type as described for the HB carcinoma. A careful analysis of the tumor characteristics and histological appearance was

TABLE III
CURATIVE RESPONSE BY VARIATIONS IN THE SIZE OF HEAT DOSE

		Multiples of standard heat dose							
Tumors	Controls	1/4	1/2	1	1 1/2	2	3	4	8
BM	0/190			11/81[3] 14%		3/21 14%	3/16 18%	2/21 10%	
BMA	0/195			1/46 2%					
BP	0/130			0/42 0%		0/30 0%	0/13 0%	0/37 0%	0/36 0%
BT	0/149	0/17		1/19 5%		3/64 5%			
C	0/158		0/13	8/55 14%		3/21 14%	6/13[1] 46%		
CS	0/173		0/6	6/33 18%		7/43 16.3%			
HB	0/200	2/129 1.5%	2/65 3%	25/109 23%	8/34 24%	20/80 25%	2/9 22%	41/162 25%	
O	0/200	0/14	3/13[2] 23%	6/30 20%					
P	0/205			1/47 2%					
SM	0/145	2/36 5%		1/31 3%					
SS	0/286	0/15	1/33 3%	9/37 24%					
X	0/234		0/14	22/162 14%		2/16 13%	3/12[1] 25%		

[1]Significant increase in cure rate as compared with tumors treated with 1 or 2 standard heat doses ($P < 0.005$).

[2]No significant decrease in tumor cures as compared with the cure rate obtained with 1 standard heat dose.

[3]Number of cures/number of treated.

TABLE IV
CURATIVE RESPONSE IN SOME TUMORS TREATED BY BIOLOGICAL EQUIVALENT VARIATIONS OF TEMPERATURE AND TIME ACCORDING TO THE STHD CONCEPT

	1 Standard heat dose				
Tumor	41°/480'	41.5°/240'	42°/120'	42.5°/60'	43°/30'
BM				9/45[2] 20%	2/36 5.5%[1]
C		4/34 11.7%		6/44 13.6%	
CS				4/21 19%	2/12 16.6%
HB	2/7 28.5%	8/28 28.5%	4/18 22.2%	9/40 22.5%	2/18 11%[1]
SS			3/14 21.4%	6/23 26%	
X		4/25 16%	9/62 14.5%	9/75 12%	

[1]Significantly fewer tumor cures as compared with tumors treated with 1 StHD given in the form of combinations of longer exposure times and lower temperatures ($P < 0.005$).

[2]Number of cures/number of treated.

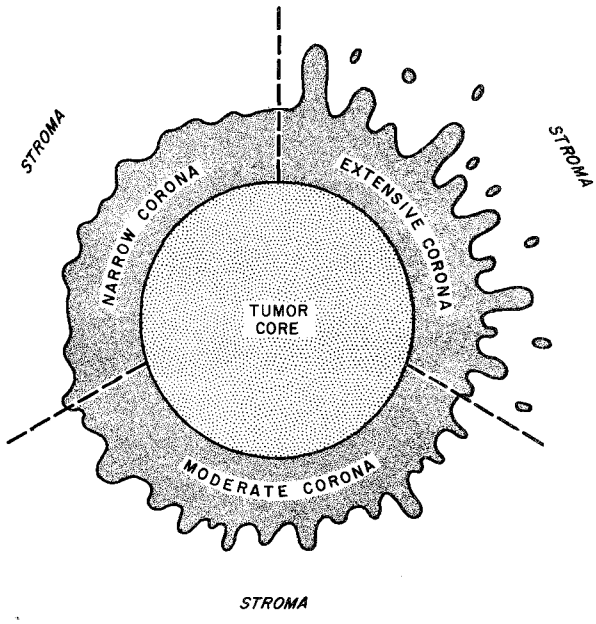

Fig. 7. Diagram showing the variations in peripheral infiltration of different tumors. The tumors can be divided into those with 1) a narrow corona (< 150-μm tumor spread outside the bulk), 2) an extensive corona (diffuse infiltration without definable external limits), and 3) a moderate corona (scattered tumor elements observed > 150 μm outside the bulk, but without diffuse infiltration).

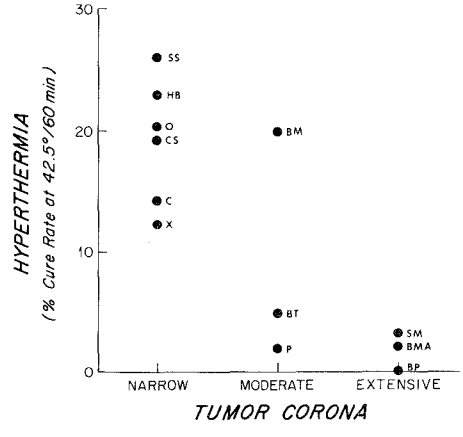

Fig. 8. Relationship between the tumor cure rates at 1 StHD (42.5° for 60 min) and peripheral extension of the tumors (for definition, see text to Fig. 7). There is a positive correlation between the cure rates and the limitations of peripheral tumor infiltration.

therefore performed. This showed that only one parameter revealed a positive correlation with the cure rate. The degree of peripheral infiltration by the tumor cells into the surrounding tissue was assessed histologically. The tumors could be classified in three different groups according to the degree of peripheral infiltration as seen from Fig. 7. When compared with the curative response following hyperthermia, it was found that a correlation between the degree of peripheral infiltration and the cure rate was present in such a way that tumors with a narrow corona have a higher number of cures than tumors with more infiltrative growth (Fig. 8). The latter showed a marked tendency to recurrence consequent to peripheral failure.

More indirect evidence of the same phenomenon is found in Table V. This shows that when tumors treated with a threshold heat dose are given an additional dose of radiation which may be sufficient to control the peripheral well-oxygenated tumor cells, there is a marked increase in the cure rate of the tumors which have a low control rate when treated by heat alone. In contrast, tumors which gave a better local control following hyperthermia alone

TABLE V
ENHANCEMENT OF TUMOR CURE FOLLOWING COMBINED HYPERTHERMIA AND RADIATION TREATMENT VERSUS HEAT TREATMENT ALONE

Tumor	Radiation (2000 rads)	Hyperthermia (42.5°C - 60 min)	Hyperthermia + radiation (42.5°C - 60 min + 2000 rads)	Enhancement[2] factor
BM	0/55[3] 0%	9/46 19%	14/56 25%	1.3
BMA	-	1/46 2%	3/10 30%	15.0
C	0/33[1] 0%	6/45 13%	18/30[1] 60%	4.6
CS	1/22 5%	5/22 22%	3/10 30%	1.4
HB	0/55 0%	9/40 23%	15/20 75%	3.2
P	1/15 7%	1/47 2%	5/14 35%	17.5
SS	2/23 9%	7/24 29%	5/14 35%	1.2
X	0/17 0%	9/75 12%	6/24 25%	2.0

[1]Radiation dose 1500 rads.
[2]Enhancement factor:

$$\frac{\text{Cure rate by combined hyperthermia-radiation}}{\text{Cure rate by hyperthermia}}.$$

[3]Number of cures/number of treated.

showed only a two to three times increase. In other words, the additional radiation treatment prevented recurrence of a larger number of tumors when they had a wide peripheral growth.

IV. DISCUSSION AND CONCLUSION

Treatment of different experimental solid tumors showed that heating with local short-wave diathermy is able to control such tumors without causing appreciable damage to normal tissue.

The curative effect is obtained at different treatment temperatures, and a characteristic relation between treatment time and temperature exists. A similar relation has been observed in other *in vivo* and *in vitro* systems treated with hyperthermia by different techniques and may indicate a general nature of the hyperthermic inactivation of tumor cells [6], [7], [12], [18], [19], [23].

The observed time–temperature relation allowed the introduction of a StHD concept which can be used in comparing the responses of treatment at different temperatures and in different tumors. The validity of the StHD, however, can be limited to a temperature range between 41 and 42.5°C as other factors may influence the hyperthermic reaction at higher temperatures [7], [18].

The thermal sensitivity shows some variation between the tumors investigated, which may be due to differences in their biological heat sensitivity, as has also been shown for tumor cells *in vitro* [7], [16], [24].

Tumors heated locally with 27.12-MHz diathermy showed a large number of recurrences. The recurrence frequency was correlated with the degree of peripheral infiltration by the tumor cells and may be due either to insufficient or heterogeneous heating or to decreased biological sensitivity of these peripheral cells.

It has been established that peripheral tumor cells which are in a more physiological environment are more resistant to heat than cells which are under the influence of hypoxia, insufficient nutrition, or increased acidity—all factors characteristic for the environment in the tumor core [7], [16], [18]. Peripheral cells may, therefore, be less sensitive to hyperthermia and thus give rise to regrowth. However, if the tumors are exposed to a more homogeneous heating, as by the water bath technique, a high cure rate can be obtained at the same temperature and treatment time. Furthermore, an increase in the diathermic heating up to eight times the threshold dose does not improve the curative yield, which might be expected in case of a variation in biological sensitivity.

Vascular cooling is not likely to be the cause of the regrowth as this occurs only in a single peripheral area, whereas many other areas in the periphery which have identical vascularization show destroyed tumor cells [23].

Therefore, it seems that a heterogeneous and insufficient physical destruction by the heat applied by the present diathermia technique is the most likely explanation. This would be expected as a consequence of variations in the electric capacity between the tumor and the fatty or connective tissue, which predominates in the tumor periphery.

The usefulness of low-frequency diathermy in tumor control is, therefore, limited by the application technique and by the tissue heterogenicity, and such conditions should be borne in mind when applying this technique in human treatment. However, it is possible that another electrode design with a conic field may be more useful as such a technique has proved to give a higher amount of controls in other tumor systems heated by a 13.65-MHz radio-frequency heating technique [15].

On the other hand, combination of heat and ionizing radiation increases the frequencies of tumor control. A moderate dose of radiation is able to control a large amount of the peripheral tumor cells which may be insufficiently heated. Secondly, hyperthermia may sensitize the tumor to the effect of ionizing radiation and thereby enhance the general tumor cell response [7], [8], [18], [22], [24]. Furthermore, one of the greatest advantages of the effect of hyperthermia is the ability of heat to destroy preferentially tumor cells situated in an hypoxic and acidic environment [7], [16]–[18], [23]. Such cells are difficult to control by radiation therapy or chemotherapy and may be the source of regrowth of tumors following treatment with such modalities. A combined hyperthermia and radiation treatment will, therefore, even though the peripheral heat response is uncertain, be of great benefit in the overall local tumor control due to the destruction of radio-resistant cells, and the problems related to peripheral hyperthermic control seem of less importance in practical clinical use when the treatment is given as such a combined modality [17], [18].

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