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Physical principles of local heat therapy for cancer

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Abstract

Local hyperthermia therapy for cancer can produce selective heating of solid tumors on the basis of known physical laws. If energy is deposited in the general region of the tumor, temperature tends to develop in the tumor higher than that in surrounding normal tissues. The goal of therapy is to achieve cytotoxic temperature elevations in the tumor for an adequate period of time, without damaging nearby normal tissues. Several modalities exist for local heat treatment, of which radiofrequency and ultrasound offer the most promise for controlled, localized heating at depth. A paucity of blood flow in the tumor compared to that in adjacent normal tissues can enhance selective tumor heating considerably. The tumor types that have reduced flow in their central regions are especially vulnerable to heat therapy, both because they can be heated more efficiently and because hypoxic and acidotic tumor tissues are more susceptible to damage by heat. This effect is more pronounced in larger tumors, which have smaller surface-to-volume ratios and so lose heat less rapidly by thermal diffusion. Selective heat treatment of larger tumor masses with low blood perfusion, therefore, is physically practical and rational therapy. Vigorous research efforts are now underway at many centers to optimize this approach.

Key words: cancer, diathermy; heat therapy; radiofrequency, temperature distribution, thermal conductivity; tumor blood flow, ultrasound therapy

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Introduction

Throughout this century there have been scattered reports of the tumoricidal effects of hyperthermia in a wide variety of animal models and in human patients. In the past 5 years the interest in hyperthermia therapy has accelerated rapidly. Clinical reports from several institutions suggest that a significant number of patients who have failed conventional radiation or chemotherapy show dramatic tumor responses to heat, either alone (Crile 1962; LeVeen et al.. 1976: Storm et al. 1979: LeVeen et al. 1980) or in combination with radiation (Homback et al.. 1977; Hahn and Kim 1980, U et al. 1981).

The precise mechanisms for the antitumor effects of heat are not firmly established. Cell culture studies suggest that malignant cells may be slightly more heat sensitive than normal cells (Mondovi et al. 1969; Cavaliere et al. 1967; Giovanella et al. 1973). In addition, solid tumor masses in vivo seem even more heat sensitive than cells from the same tumor line grown in vitro (Song 1981; Kang et al. 1981; Song et al. 1981). Dickson and Calderwood (1980) and Henle and Dethlefsen (1980) have reviewed the requirements for thermal death of tumor tissue following in a single heat treatment. Their surveys of many animal and human studies can be summarized for typical tumors as a strength-duration curve relating the temperature rise required for thermal death to the treatment time. We have found a convenient expression for this strength-duration relationship between the temperature T (^{o}C) and the treatment time t (hours) required for tumor necrosis to be

$$T = 42 + \frac{2.5}{\sqrt{t}},$$

or, rearranging this expression in a more useful form, if one is able to raise tumor temperature T to a steady level above 42 °C, the lethal treatment time t in hours is

$$t = \left(\frac{2.5}{T - 42} \right)^2 .$$

For example, if the tumor can be heated to 44.5 °C, a treatment time of 1 hour is likely to produce tumor necrosis. If the tumor can be heated to 47 °C, only 0.25 hour of treatment is required. Stated simply, the goal of heat therapy is to maintain an elevated temperature T in the tumor for the required treatment time t , while keeping the temperature in adjacent normal tissue less than 42 ^{o}C. This paper will demonstrate how it is possible to raise temperature within a tumor to higher levels than the temperature in adjacent normal tissues, in order to produce selective cell killing in the tumor.

Physics of Heat 1ransfer

The balance of heat flow into and out of a given parcel of tissue determines its temperature. In the situation of local hyperthermia therapy, heat is deposited in the tissue by the tissue's own metabolism and to a much greater extent by the external energy source in the hands of the therapist. Such energy sources include electromagnetic waves (microwaves or radiofrequency) and therapeutic intensity ultrasound. Heat leaves the tissue as a result of thermal diffusion (conduction) and as a result of tissue perfusion with arterial blood, which can be maintained approximately at core body temperature. Classically, this heat balance in tissue is described by the bio-heat transfer equation (Cravalho et al. 1980; Chen and Holmes 1980; Jain 1980).

The Bio-Heat Equation

Consider a small volume of tissue that is being heated by an external energy source, such as absorbed electromagnetic energy. This control volume is small enough so that the thermal properties within it are uniform. The conservation of energy requirement on the control volume may be written as

$$k\nabla^2 T + \omega c_b (T_a - T) + q_m + P = \rho c \frac{dT}{dt},$$

where

k = the local tissue thermal conductivity (W/cm-°C),
T = tissue temperature (°C),
ω = blood perfusion (g/sec-cm^3).
c_b = blood specific heat (J/g-°C),
T_a =arterial temperature (°C).
q_m = metabolic heat generation (W/cm^3),
P = the absorbed power density (W/cm^3),
ρ = tissue density (g/cm^3), and
c = tissue specific heat (J/g-°C).

Considering the terms from left to right, the first represents the net heat transfer out of the control volume by the process of thermal diffusion, described by Fourier's law. Thermal diffusion is the transport of heat within a material by random molecular motion. The term, k, is the coefficient of thermal conductivity, an inherent thermophysical property of the tissue. The value due to blood perfusion represents the heat gain by convective transport (bulk flow) of arterial blood at temperature T_a into the control volume. It is assumed that blood entering the smaller arterial vessels at temperature T_a comes into thermal equilibrium with surrounding tissues at temperature T. This assumption is based upon the anatomic and physiologic realities that (a) the vascular tree is highly branched, so that the number of capillaries in tissue is large, providing essentially uniform percolation of blood through the tissue, (b) the blood flow velocity in capillaries is much slower than in large arteries, which carry arterial blood to the tissue at essentially core body

temperature T_a , and (c) the mass of the tissue is much greater than the mass of the blood within it.

Chen and Holmes (1980) have scrutinized this assumption and found it to be essentially valid for tissues that are not close to very large blood vessels. Assuming percolation and thermal equilibration of capillary blood with tissue, the heat transfer due to blood perfusion is the product of blood flow rate per unit volume ω, specific heat of blood c_b, and the temperature difference between incoming arterial blood and the tissue ($T_a - T$). In the particular application of local heat therapy for cancer, the tissue will be warmer than arterial blood and hence this value will be negative, representing heat loss from the control volume. The third and fourth terms represent heat gains due to exothermic metabolism q_m, and power input from an external source P. In the local heat therapy of tumors, P is much greater than q_m .

Finally, the right-hand term of the bio-heat equation represents the rate of change in internal energy per unit volume of the tissue due to its temperature change. Under steady-state conditions in which temperature is constant ($dT/dt = 0$), this last term is zero, so that the heat loss from conduction and blood perfusion exactly balances the heat gain from metabolic and external sources. If the heat gain exceeds heat loss, the tissue temperature will increase with time.

The simplest, clinically realistic solution of the bio-heat equation, which has been studied by Cravalho and coworkers, is for a spherical tumor surrounded by a single type of normal tissue (Fig. l). The bio-heat equation for this one-dimensional spherical system has the form

$$\frac{1}{r^2}\frac{d}{dr}\left[r^2\frac{dT}{dr}\right]+\omega(r)\frac{c_b}{k}\left(T_a-T\right)+\frac{P(r)}{k}=0$$

for steady-state conditions and uniform thermal conductivity. Blood perfusion $\omega(r)$ and external power input P(r) are specified functions of the variable r, the radial distance from the center of the tumor. The metabolic heat generation q_m may be considered to be either negligible or included into the term P(r).

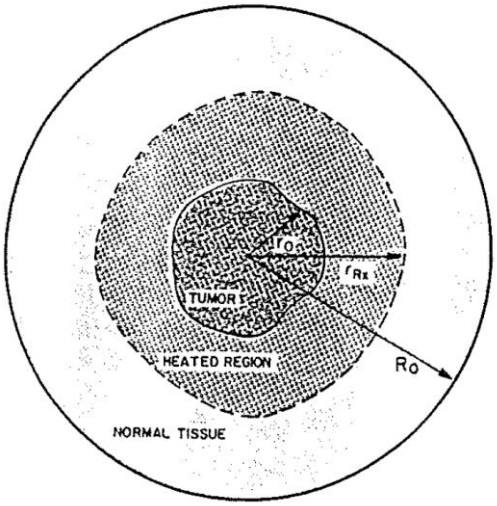

Fig. 1. Model of a spherical tumor of radius r_0, embedded in normal tissue. Heat is deposited in a region concentric with the tumor and extending to radius r_{Rx}.

Let us assume that a spherical tumor of radius r_0 is treated by local heat therapy. Power is deposited from an external source to a radial distance r_{Rx}. A large shell of unheated, normally perfused tissue, $r > r_{Rx}$ surrounds the heated region, $r < r_{Rx}$. In actual computations the radius of the unheated shell may be only 2 or 3 times that of r_{Rx}, beyond which the tissue is thermally undisturbed. The two appropriate boundary conditions for this second-order differential equation are zero temperature gradients at the center ($r = 0$) and at the outer boundary ($r \rightarrow \infty$) to satisfy coordinate symmetry and adiabatic conditions respectively. Necessarily, as r approaches infinity, the temperature of the undisturbed tissue approaches the arterial temperature T_a.

To illustrate the physics of selective tumor heating, we solved the bio-heat equation for this geometry, using a finite-difference routine with a mesh size of 200 nodes, according to standard computational techniques (Incropera and DeWitt 1981). The values $\omega(r)$ and $P(r)$ were represented by 25 discrete levels.

Determinants of Selective Tumor Heating

In any particular numerical solution of this spherical bio-heat equation, one must, of course, specify the size (radius) of the tumor, the blood flow in the tumor and in the surrounding normal tissue, the pattern of transition in blood flow between tumor and normal tissue, and the radius of the treated region. In these computations we adjusted the value of power input--as one would hope to do in practice--to maintain the normal tissue at the edge of the tumor at a "safe" temperature, which we took to be 42 °C.

Let us choose as a starting point the following specific conditions: Tissue thermal conductivity: 0.6 W/m-°C, that of water. Blood and tissue specific heat: 4179 J/kg-°C, that of water. Blood and tissue densities: 1 g/ml. Effective arterial blood temperature: 37 $_{o}$C. Tumor radii: 5, 10, 20, or 40 mm. Power deposition: uniformly distributed and extending from the center of the tumor to twice the radius of the tumor. Blood flow: 15 ml/min/100 g in both tumor and normal tissue. By varying the parameters in the bio-heat equation from these base values, it will be easy to demonstrate the influence of the important physical factors in local heat therapy, as they have been described in the published literature.

Power Input

The most straightforward means of producing selective tumor heating is to focus the external input power directly on the tumor. Fig. 2 presents data for a 20-mm-radius tumor model with uniform input power (W/ml) focused within different concentric treatment regions 2.0 to 0.8 times the tumor radius. In Fig. 2, as in the remaining temperature distributions, the power was adjusted to maintain the edge of the tumor at 42 °C. Improved focusing of power on or, even better, within the tumor causes the tumor to become progressively warmer than surrounding tissues. Focusing energy within the border of the tumor itself is an especially effective way to produce selective heating. The ability to focus power within the tumor, however, depends not only upon accurate knowledge of the extent of the tumor but also upon the specific technology used for heating.

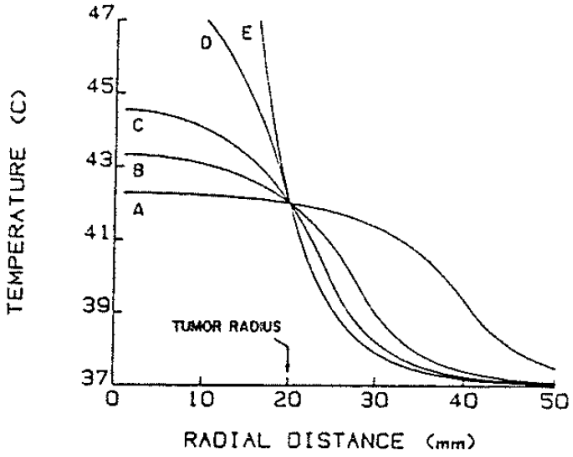

Fig. 2. Effects of progressive focusing of uniform input power on the temperature distribution in and around a spherical tumor. Radial distance 0 indicates center of the tumor. The tumor radius is 20 mm. Perfusion is constant at 15 ml/min/1 00 g. A, power 0.05692 W/ml to 40 mm; B, power 0.07462 W/ml to 28 mm; C, power 0.09527 W/ml to24mm; D, power 0.15803 W/ml to 20 mm, the tumor radius; E, power 0.38118 W/ml to 16 mm, 80% of the tumor radius. Power adjusted to maintain edge of the tumor at 42 ^{o}C.

Let us consider briefly the alternative modes for delivering input power. Microwave energy may be coupled into the tissue by a radiator (usually a hemisphere or corner reflector) placed several centimeters above the skin. The heating across the surface of the skin is not uniform and the superficial tissues are heated most. Microwaves are relatively difficult to focus, especially on deeper lesions (Hunt 1981). These physical limitations notwithstanding, Hornback and associates and Raymond U and coworkers have achieved promising results with microwave hyperthermia, especially in combination with radiotherapy.

Radiofrequency (RF) current is more effective than microwave energy in producing deep heating of tissue (Scott 1953; Scott 1957). In clinical units, RF current at 13.56 or 27.12 MHz can be applied with completely insulated, parallel plate electrodes placed several centimeters from the tissue to be heated. The electrodes can be either placed on the skin or separated from the skin by an air gap. The diameter of the electrodes determines to a first approximation the diameter of the treatment field, if the separation of the electrodes is approximately equal to their diameter. In this configuration the tissue forms part of the dielectric in the capacitor formed by the two electrodes. If the electrodes are close to the skin, the tissue heating is nonuniform, with subcutaneous tissues heated the most. However, if they are located a few centimeters from the skin, the RF field is much more uniform and the heat is more uniformly distributed (Scott 1957). Capacitive RF heating is the approach originally reported by LeVeen and coworkers (1976) and with which he continues to achieve good clinical results (LeVeen et al. 1980). His latest apparatus incorporates arrays of electrode pairs to achieve a focusing effect.

RF energy can also be coupled into the tissues inductively with a helical coil placed a few centimeters from the skin. Eddy currents in the tissue cause maximum heating in the tissues having the lowest resistivity. We have found this type of inductive heating to be quite effective in producing uniform energy deposition, when two coils are arranged as shown in Fig. 3. Such coils, known as Helmholtz coils, produce a relatively uniform alternating electromagnetic field throughout most of the volume between the coils. The actual temperature profile generated depends upon the material between the coils. An insulator will not be heated at all. A uniform conductor, such as a tissue phantom made of salt-containing gel, will be heated more toward the periphery of the coil than in the center. Actual tissue, however, is heated quite uniformly, perhaps because cell walls and tissue planes break up the larger eddy currents into multiple smaller ones. We have found that Helmholtz coils can be used quite successfully to focus energy on tumors of the extremities, head, and neck in large and small animals. Recently, Storm and coworkers (1981) described a magnetic loop applicator for local hyperthermia therapy in human patients.

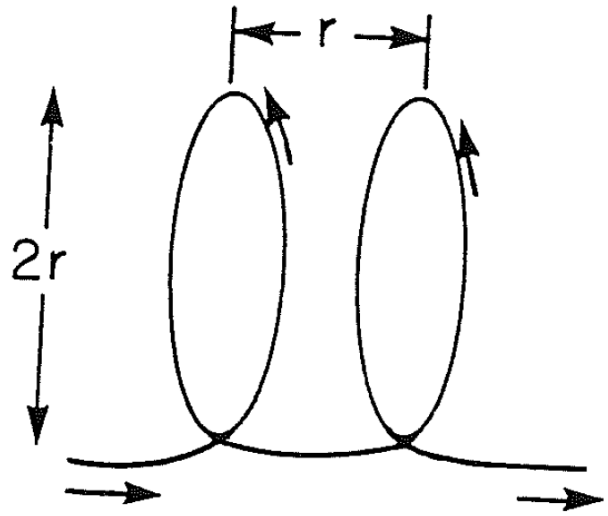

Fig. 3. Helmholtz coils spaced one coil radius, r, apart provide an approximately uniform electromagnetic field between the coils for inductive heating of tissue. Arrows indicate current flow during one half-cycle of RF current.

The most controllable means of producing focused power for tumor heating is therapeutic intensity ultrasound. Ultrasonic energy that is absorbed by the tissue during the attenuation process constitutes the absorbed power P, and causes a local temperature rise. The depth of penetration of ultrasound is a function of its frequency, and ultrasound beams can be focused to produce high intensity at depth. Focusing capability means reduced local injury to normal tissues and reduced pain and discomfort during treatment (Lele et al. 1981). Lele and coworkers at MIT have devised a computer-controlled insonation system suitable for clinical use in tumors up to 8 cm in diameter. The major limitation of therapeutic intensity ultrasound is its inability to penetrate gas-filled spaces (such as lung and bowel) and bone.

Blood Flow

During local heat therapy of larger tumors, say over 20 mm in diameter, the rate at which blood flow to the tissue carries away heat is a major determinant of the tissue temperature rise (Cravalho et al.; Voorhees and Babbs 1981). During heating, blood perfusion per gram of tissue is less in larger tumor masses than that in surrounding normal tissues (Song et al. 1980). Part of the difference in the perfusion rates seems to be due to thermally induced vasodilation in normal tissues, but not in tumor tissues. In Song's (1980) studies of local hyperthermia, for example, blood flow in normal skin and muscle markedly increased during heat treatment, thereby producing a cooling effect. However, blood flow did not increase in tumors greater than 1 ml in volume. This phenomenon is easily understood upon closer examination of tumor blood vessels. It is commonly believed that the blood supply of solid tumors is high because a large vascular

network is often found surrounding them at surgery. However, larger tumor nodules surrounded by blood vessels on the surface, arc often found to have poorly perfused, necrotic cores.

Moreover, it now appears that the vessels that do nourish solid tumors are quite abnormal in character. Compared to normal tissues, tumors seem to have an overabundance of sinusoidal capillary beds. These capillary sinusoids are broader and longer, and are separated by larger intercapillary distances than are normal capillaries (Ide et al. 1939; Vaupel 1977; Intaglietta et al. 1977; Folkman 1976). Folkman and associates (Folkman 1976; Folkman and Cotran 1976) have shown that neoplastic cells in vivo are supplied by an abnormal pattern of blood vessels that were formed in response to a chemical tumor angiogenesis factor liberated by tumor cells. The tumor angiogenesis factor appears to stimulate the growth of capillaries but not to stimulate the development of these capillary sprouts into well differentiated, larger caliber arterioles that are capable of dilating in response to heat. As a consequence of this abnormal tumor microvasculature, blood flow through tumor tissues remains more sluggish than in the normal tissues of origin (Gullino and Grantham 1961; Cataland et al. 1962; Vaupel 1977; Peterson 1979).

Fig. 4 illustrates the influence of reduced tumor blood flow during local heating, as described by Song and coworkers (1980). In this illustration, focusing was assumed to be poor, with uniform energy deposition extending to twice the radius of the tumor. As before, power input was adjusted to maintain the tumor edge at 42 ^{o}C. When tumor perfusion is equal to normal tissue perfusion, there is virtually no selective heating of the tumor. When tumor perfusion is less than normal tissue perfusion, tumor heating is improved. Clearly, tumors with relatively poor blood flow are more easily heated than tumors with blood flow equal to that in surrounding normal tissues.

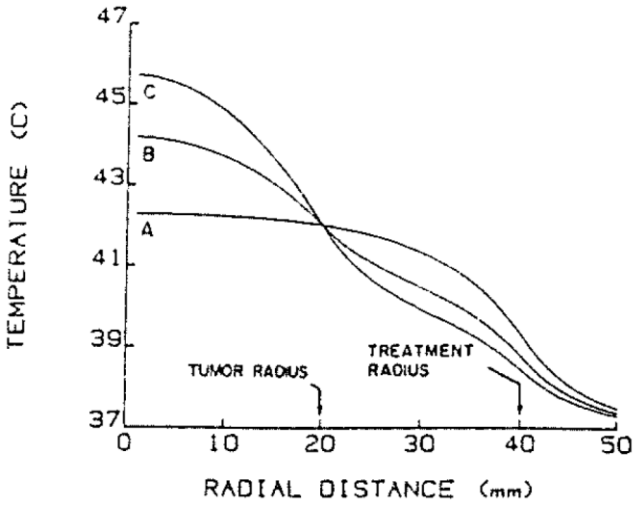

Fig. 4. Effects of progressive reduction of blood flow on the temperature distribution in and around a spherical tumor. The tumor radius is 20 mm. Tumor edge 42 ^{o}C. The treatment radius is constant at 40 mm. The normal tissue perfusion is constant at 15 ml/min/100 g. A, tumor perfusion (equal to normal tissue perfusion) 15 ml/min/100 g, power 0.05692 W/ml; B, tumor perfusion 5 ml/min/100 g, power 0.04252 W/ml; C, tumor perfusion 0 ml/ ml/100 g, power 0.03359 W/ml.

Reduced blood flow in tumors during heat therapy has important biochemical as well as thermal effects. Hypoxia and the resultant anaerobic metabolism and local acidosis make the tumor tissue in the heated region more vulnerable to thermal injury. This phenomenon has been shown quite clearly both in vitro and in vivo (Gerweck and Rottinger 1976; Dewey and Freeman 1980; Song 1981). Thus, there are two reasons why tumor types that have abnormally low blood flow are likely to be good candidates for local heat treatment: they are easier to heat selectively and they are especially heat sensitive.

Distribution of Blood Flow

In Fig. 4 we assumed a uniform value for blood flow in the tumor tissue, changing abruptly to a uniform value for blood flow in the surrounding normal tissue. In actuality, of course, the distribution of perfusion is more complex. A number of authors have described radial distributions of tumor blood flow in which a poorly perfused core is surrounded by a hyperperfused outer shell. For example, closer examination of the local blood flow of BA 1112 sarcoma implants in rats by Gross (1979) and Endrich and coworkers (1979) revealed five concentric zones of perfusion, as illustrated in Fig. 5. This general pattern of tumor vascularity (a well-perfused outer shell, an underperfused mantle layer, and a necrotic core) has been observed in a variety of systems, including rat myelosarcoma (Habighorst 1977), transplanted Brown-Pearce rabbit epithelioma (Ide, 1939), and hamster malignant neurilemoma (Eddy and Casarett 1973).

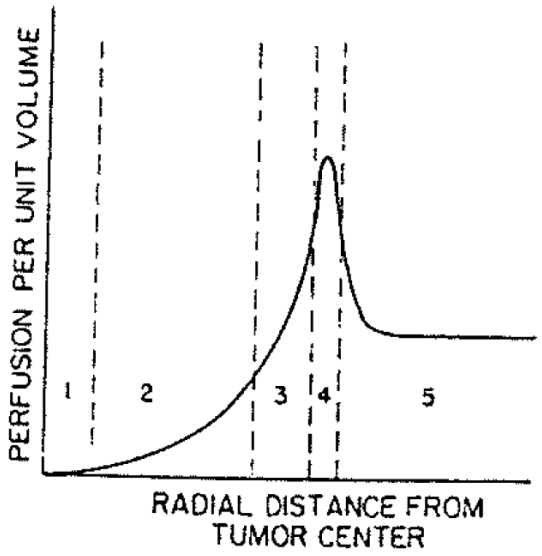

Figure 5. Radial distribution of tumor blood flow as hypothesized by Endrich and coworkers (1979). Zone 1: necrotic area in center. Zone 2: semi-necrotic area containing capillaries that extend for long distances without branching, and no larger vessels. Zones 3 and 4: the growing shell with larger venules and few arterioles. Zone 5: healthy normal tissue.

Contrary perhaps to intuition, the presence of a hyperperfused outer shell may actually improve the ability to selectively heat the tumor core. Fig. 6 presents perfusion and temperature profiles for a 20-mm- radius tumor model with two transition patterns between tumor and normal tissue blood flow. Provided power input is adjusted to maintain the tumor edge at42 °C the effect of the distributed perfusion is to create a larger temperature gradient between the center and the edge of the tumor. Greater perfusion in the tumor shell does not necessarily prevent selective tumor heating. Indeed, moderately increased flow in the tumor shell permits greater power input to the tumor core and higher overall tumor temperatures, when the tumor edge is maintained at 42 ^{o}C. Of course, if the entire tumor is hyperperfused selective heating would be very difficult to achieve.

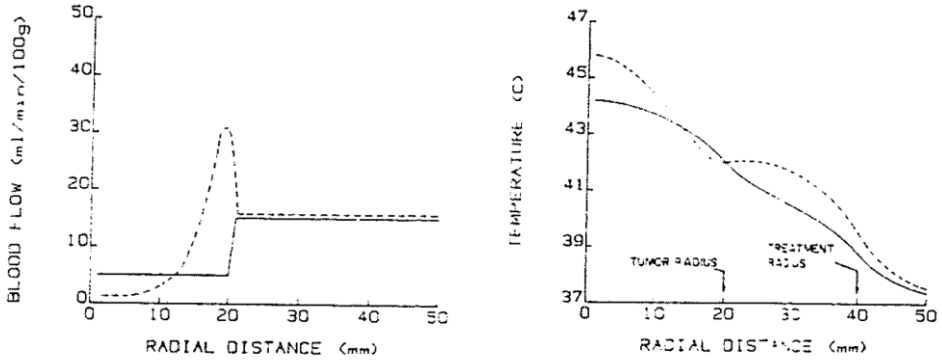

Fig. 6. Influence of a hyperperfused outer shell on the radial temperature distribution. The treatment radius is constant at 40 mm. Tumor edge: 42 ^{o}C. Solid line: perfusion and temperature profiles in tumor model without a hyperperfused outer shell, power 0.04252 W/ml. Dashed line: presence of higher perfusion in the tumor shell than in the tumor core, power 0.06272 W/ml. Left: blood flow distributions. Right: temperature distributions.

Thermal Diffusion

In the presence of a significantly reduced perfusion in the tumor compared to surrounding normal tissues, the effectiveness of local tumor heating is greater for larger tumors than for smaller ones. This result is a consequence of thermal diffusion. The effect of tumor size on the temperature distribution can be illustrated by solution of the bio-heat equation. Figs. 7 and 8 show the calculated temperature distributions in and around tumors with different radii, assuming uniform power deposition throughout a volume twice the tumor radius (i.e., $r_{Rx} = 2r_0$). With uniform blood flows in the tumor and in the surrounding normal tissues a minimal effect of tumor size upon tumor temperature rise is evident (Fig. 7). If, however, one assumes that blood flow throughout the tumor is one-third that in the normal tissue, then the central tumor temperature increases as a function of the tumor size (Fig. 8).

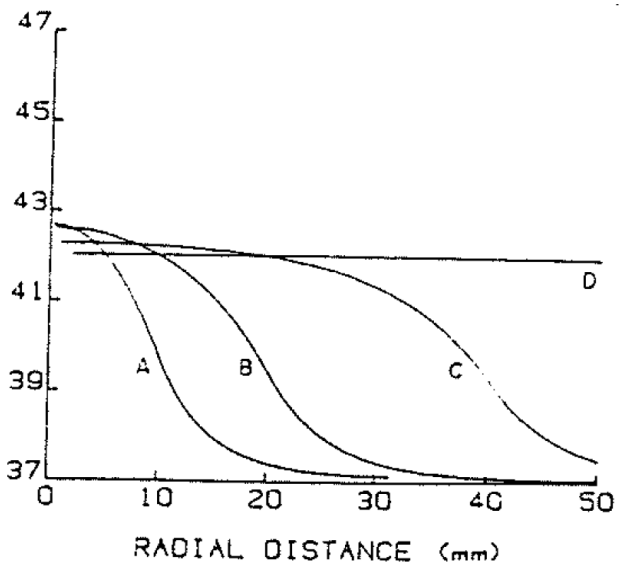

Fig. 7. Influence of tumor size on radial temperature distribution with uniform blood flow (15 ml/min/100 g) throughout the tumor and surrounding normal tissues. A, power 0.15415; B, power 0.07891; C, power0.05692; D, power 0.05251. A 5 cm tumor, B 10 cm tumor, C 20 cm tumor, D 40 cm tumor.

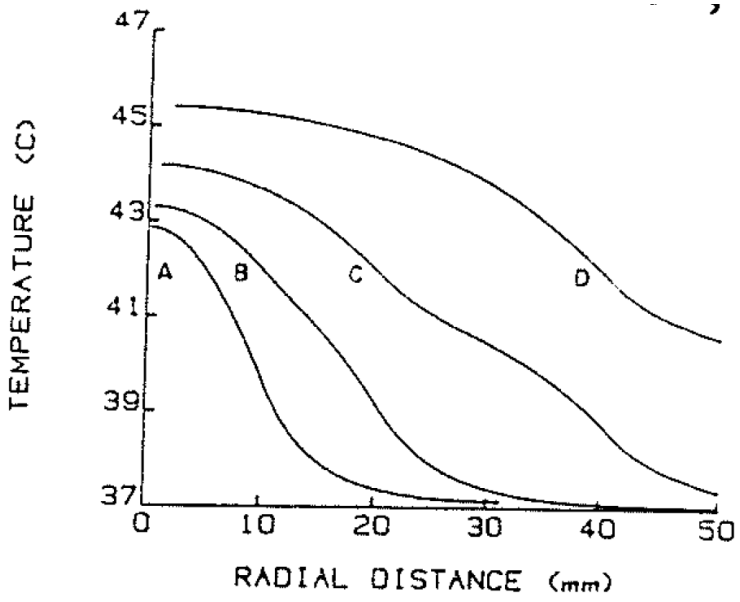

Fig. 8. Influence of tumor size on radial temperature distribution with blood flow in tumor = 5 ml/min/100 g and blood flow in surrounding normal tissues = 15 ml/min/100 g. A, power 0.14514; B, power 0.06786; C, power 0.04252; D, power 0.03414. A 5 cm tumor, B 10 cm tumor, C 20 cm tumor, D 40 cm tumor.

These interesting results are easily understood. Heat is deposited uniformly in the tumor and adjacent tissues, and in the presence of reduced tumor blood flow it would be expected that temperature within the tumor would become greater than in the surrounding tissue. It follows that heat flow from the tumor by thermal diffusion will become significant, and in the limit of zero perfusion will be the only mode of heat transfer out of the tumor.

To appreciate the influence of tumor size, therefore, one only need recognize that the heat loss by thermal diffusion will be related to the product of tumor surface area, $4\pi r_0^2$, and the temperature gradient at r_0, while the heat gain from the absorbed power will be proportional to the tumor volume, $(4/3)\pi r_0^3$. As the radius of the tumor increases, its volume increases as the cube of the radius, while its surface area increases only as the square of the radius. In order for heat loss by thermal diffusion to keep pace with heat gain in larger tumors, a greater temperature gradient at the edge of the tumor and in turn a higher center temperature will be established. It also follows that the effect of tumor surface-to-volume ratio is more pronounced when tumor blood flow is low, in which case thermal diffusion becomes the primary means of heat loss from the tumor.

Fig. 9 presents the limiting case in which tumor blood flow is assumed to be zero. By comparison of Figs. 7, 8, and 9, it is apparent that larger tumors with reduced blood flow can be selectively heated quite easily, even in the absence of focused input power.

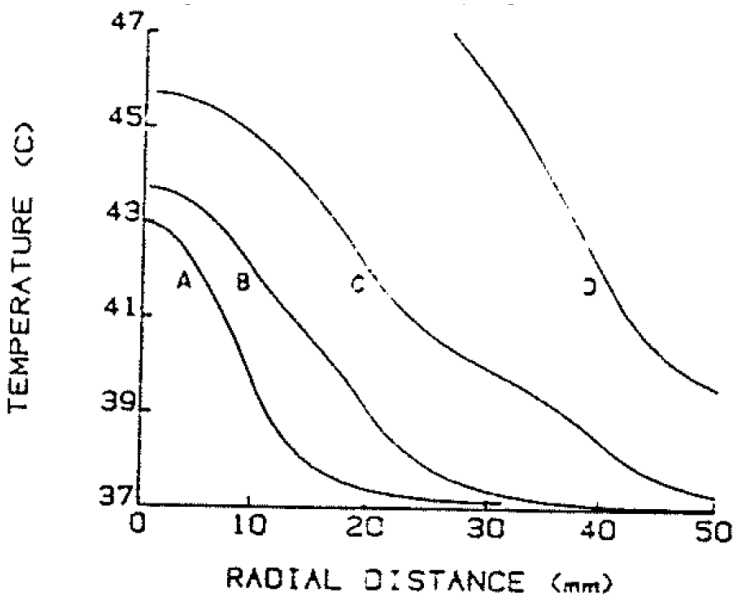

Fig. 9. Influence of tumor size on radial temperature distribution with blood flow in tumor = 0 and blood flow in surrounding normal tissues = 15 ml/min/100 g. A, power 0.14054; B, power 0.06190; C, power 0.03359; D, power 0.01999. A 5 cm tumor, B 10 cm tumor, C 20 cm tumor, D 40 cm tumor.

Combined Effects

Having examined the determinants of selective tumor heating separately, let us consider a realistic combination of circumstances in which heat therapy is likely to be effective. Consider a relatively large solid tumor nodule of 20 mm radius which has inherently low blood flow (5 ml/min/100 g compared to 15 ml/min/100 g in surrounding tissue) and upon which it is possible to focus input power in a field 1.4 times the tumor radius. The solid curve in Fig. 10 represents the temperature profile predicted from the bio-heat equation for this situation. If a temperature in excess of 44.5 ^{o}C were maintained in the core of the tumor for 1 hour, thermal death of tumor tissues would likely occur.

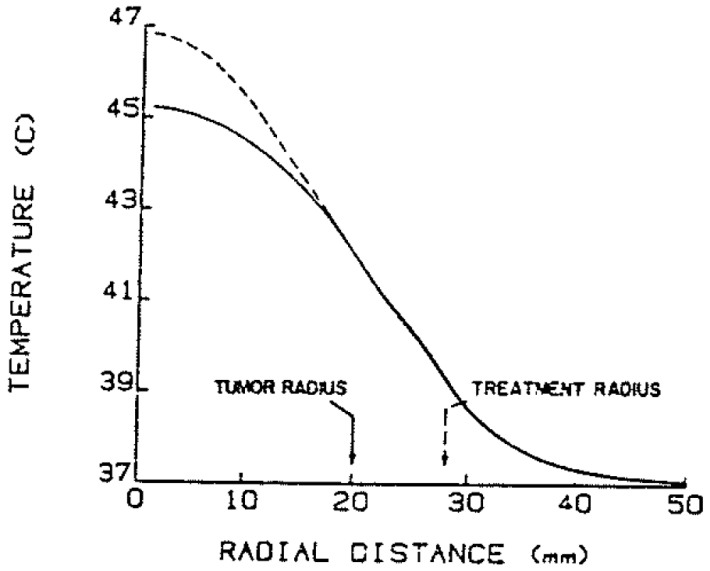

Fig. 10. Expected temperature profiles in clinically realizable hyperthermia therapy. The radius of the tumors is 20 mm. The treatment radius extends to 28 mm, 1.4 times that of the tumor. Perfusion is 5 ml/min/100 g; perfusion in surrounding normal tissues is 15 ml/min/100 g. The power input is 0.05458 W/ml. Broken line: the tumor perfusion is reduced to zero from the center of the tumor to a distance of 24 mm, as might occur after microvascular thrombosis. Perfusion in surrounding normal tissues remains 15 ml/ min/100 g. The power input is reduced to 0.05162 W/ml in order to maintain the tumor edge at 42 ^{o}C.

In this regard, Eddy's description of microvascular pathology after heat treatment of tumor implants is most interesting (Eddy et al.. 1981). He showed elegant microscopic evidence of microvascular thrombosis after heat treatment of tumor implants, presumably due to endothelial damage of the tumor capillaries by heat. Sludging of red blood cells and clotting inside the tumor capillaries most likely reduce local blood flow to near zero, an effect also detected by Kang and coworkers for periods of 1 to 24 hours after heating. If such stasis of flow is a general response

of tumor vessels to heat, then follow-up heat treatment 1 to 24 hours after initial focused heat treatment may be especially effective, since tumor blood flow will then be greatly reduced. Higher temperatures would be predicted for the 20-mm-radius tumor, if blood flow in the central region of the tumor were reduced to zero because of microvascular damage incurred in a preceding treatment. Such follow-up treatment could provide an opportunity for destruction of viable cells in the tumor shell. Associated cellular hypoxia and acidosis might easily permit thermal killing of the majority of the tumor mass.

Residual viable cells near the tumor edge can in principle be dealt with in several ways: (1) deliberate over-treatment to destroy these cells as well as a thin shell of normal tissue surrounding the tumor, (2) follow-up radiation or chemotherapy that may be preferentially effective upon tissues near the tumor edge which have been sensitized by heat, or (3) subsequent heat treatments as necessary at a much later date. In regard to the latter, it seems unlikely that surviving tumor cells would develop resistance to heat therapy, since their survival is due largely to geometric location (i.e. they happened to be located at the edge of the tumor) rather than to intrinsic heat resistance.

Future Progress

The factors that permit selective elevation of tumor temperature to lethal levels are few in number and easily characterized. Indeed, Chato (1980) and Bowman (1981) have proposed use of a single needle-like probe that measures thermal conductivity, thermally significant blood flow, and prevailing tissue temperature in rapid succession. Use of such research tools in conjunction with solutions of the bio-heat equation for non-spherical geometries is likely to provide more detailed understanding of the physics of tumor heating. Certainly the clinical results of hyperthermia therapy will improve as characteristics of tumor types most susceptible to heat are identified. Further progress is almost certain as we gain improved understanding of the physiology of tumor blood flow and the technology of energy delivery. Practical techniques of local heat therapy will soon reflect improved monitoring of tissue temperatures and more sophisticated treatment schemes based upon the principles just set forth. Within a decade, we believe, heat therapy for cancer will become commonplace and successful--as accepted in medical practice as radiotherapy is today.

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