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Conference Paper

"Quo Vadis" Oncologic Hyperthermia?

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Hyperthermia was the very first oncotherapy in human medicine based directly on sacral and philosophical roots in ancient cultures. The discovery of electromagnetism gave new hopes a century ago; however, up to now it has been suffering from lack of wide applications. Oncological hyperthermia struggles with multiple technical and medical problems which are far from the complete solution. Technically, the deep heating, the precise focusing, the technical control, and repeatability are challenging. The missing medical explanation of the phenomenon, together with the he missing measurable dose hinders the acceptance of hyperthermia. The contra-feedback of physiology mechanisms makes this method hardly controllable. Multiple, most promising results and studies are mixed together with some negatives and controversial consequences, causing huge fluctuations of its applications. There are positive and negative "believers" of the method, but the decisional facts are missing. A new way gives shape to the development: heating in nanorange, which could solve most of the open problems in oncological hyperthermia.

1. Introduction

Hyperthermia is an ancient treatment. Hyperthermia means overheating of the living object completely (systemic) or partly (regionally or locally). "Overheating" is understood as "higher temperature than normal."

Hyperthermia is one of the most common therapies in "house" applications. It is applied according to unwritten traditions in every culture and every household. It is applied simply to prevent common cold, but it is also good for its treatment, applied for various pains (joints, muscle-spasms, etc.), applied for better overall conditions and for simply relaxing, or sometimes for spiritual reasons. The various heat therapies are commonly used complementary with natural drugs (teas, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural, and social events (ritual hot bath cultures), or with long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

The "prestige" of popular heat therapies is strongly supported by its corrective property: the person who has just received hyperthermia feels the water temperature most pleasant by hand when it is ~20°C, while the 45°C is pleasant for a hypothermic subject in the same experiment [1]. It seems that the heat therapy adjusts itself to the personal actualities; it is subjective and adaptive.

These popular treatment applications of heating are types of "kitchen medicine": the old recipes are "sure," the patient takes them and is cured when they are done according to the auricular traditional regulations. The meaning of "kitchen medicine" is, do it like in the kitchen, reading the process from the cookery-book: "heat it on the prescribed temperature for the prescribed time, and the success is guaranteed." This type of thinking has its origin from the ancient cultures, when the Sun, the fire, and the heat were somehow in the centre of the religious beliefs and philosophical focus.

This is "for sure" the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, "do it, get it." However, hyperthermia is not as simple as the traditions interpret it.

The fire and the radiation of the Sun had sacral significance in the ancient human cultures. In consequence, the heat delivery was naturally on top of the curative possibilities.

The ancient heat delivery however was ineffective and uncontrolled; deep heating was almost impossible. The method had its renaissance, when the modern electromagnetic heating techniques were applied controlling the heating process more precisely even in depth of the body. Important category of the hyperthermia was generated by electric fields [2, 3], which is even presently a hot topic in science [4, 5]. The electric conductive heating started in the late 19th century, called "galvanocautery" [6]. The method was further developed by D'Arsonval introducing the impedance (alternating current (AC), later higher frequencies, and even spark-generated currents) calling it "Arsonvalization," [7], and later a more modernized was "fulguration" [8]. The Arsonvalization method had fantastic popularity at the turn of the 19th-20th centuries, developing three different branches: the interstitial hyperthermia, including the galvanic heat-stimulation (electrochemical cancer treatment), the ablation techniques, and the capacitive coupling. The first capacitive coupled device on conductive basis was the "Universal Thermoflux." It was launched on to the market by such a giant of the electric industry in that time as Siemens, which was later further developed, and the new device by the name "Radiotherm" was launched on to the market in the early 1930s. The first start of the new capacitive-coupling technologies was in 1976 by LeVeen et al. [9] and has been widely applied since then [10–13]. Many hyperthermia devices use capacitive coupling since its application is easy and successful in clinical practices [14–17]. The other line of the hyperthermia, based on radiative heat absorption, forms antenna array [18, 19], showing many successful clinical studies too [20, 21].

From the late 1980s, the heating up of the whole body or its certain region or a definite local volume started rapid development in the modern oncotherapeutic practices. The selective energy absorption has several favorable physiological and cellular effects promoting direct and indirect tumor-destructions without notable toxicity. Its main success lies in its complementary applications. Oncological hyperthermia is an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy, and helps desensitizing the previously noneffective treatments. Hyperthermia in oncology has been debated in an increasing number of books and high-ranking clinical publications. From the standpoint of oncology, the official policy was to avoid applying hyperthermia in oncotherapies. The repulsive opinion focused on the increase of dissemination of malignant cells and so supporting the metastases [22–24]. There were also reports about the induced hepatitis by hyperthermia [25].

This is the reason, that in contrary its long history, the state of oncological hyperthermia today is similar to that of therapies at their infancy. Like many early-stage therapies, it lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

This relatively simple, physical-physiological method has a phoenix-like history with some bright success and many deep disappointments. What do we have in hand? Is it a brilliant, miraculous, nontoxic treatment, or a quackery of some charlatans?

Many of the researchers evaluating the capabilities of oncological hyperthermia share the opinion, expressed in the editorial comment of the European Journal of Cancer in 2001: the biological effects are impressive, but physically the heat delivery is problematic. The hectic results are repulsive for the medical community. The opinion, to blame the "physics" (means technical insufficiency) for inadequate treatments is general in the field of oncological hyperthermia, formulated the following statement: "The biology is with us, the physics are against us" [26]. In the latest oncological hyperthermia consensus, meeting the physics was less problematic. However, in accordance with the many complex physiological effects a modification was proposed: "The biology and the physics are with us, but the physiology is against us" [27].

The present situation apparently supports the above opinions. Probably oncological hyperthermia has the most questions in the titles of published literature. Numerous definite questions were formulated, such as the following.

(i) Is the community radiation oncologist ready for clinical hyperthermia [28]?

(ii) What happened to hyperthermia and what is its current status in cancer treatment [29]?

(iii) Where there is smoke, is there fire [30]?

(iv) Should interstitial thermometry be used for deep hyperthermia [31]?

(v) If we cannot define the quality, can we assure it [32]?

(vi) Is there a future for hyperthermia in cancer treatment [26]?

(vii) What is against the acceptance of hyperthermia [33]?

(viii) Progress in hyperthermia [34]?

(ix) Prostate cancer: hot, but hot enough [35]?

(x) Is heating the patient a promising approach [36]?

(xi) Hyperthermia: has its time come [37]?

Oncologists face multiple serious decisions when meeting a new patient. The staging and many other factors help the decision what to do: apply evidence-based protocols "A" or "B" or try something personalized. When application of hyperthermia arises, the dilemma widens: "to heat or not to heat"? Considering hyperthermia as a treatment option, new challenges occur: "How to heat? What to heat? How to control? and How to evaluate?" We would like to show where we are in the field, show a definitely new paradigm for oncological thermal treatment, and give its perspectives for the future.

2. Technical Challenges

There are various concepts to heat up the tumor locally or regionally or by heating up the whole body. The most intensive local actions are the extremely large specific absorption rate (SAR) in a small volume heating the target rapidly and intensively to the ablation (coagulation) temperatures (see Figure 1(a) [38]). In this case, the short time of action does not allow the temperature distribution in the connective tissues.

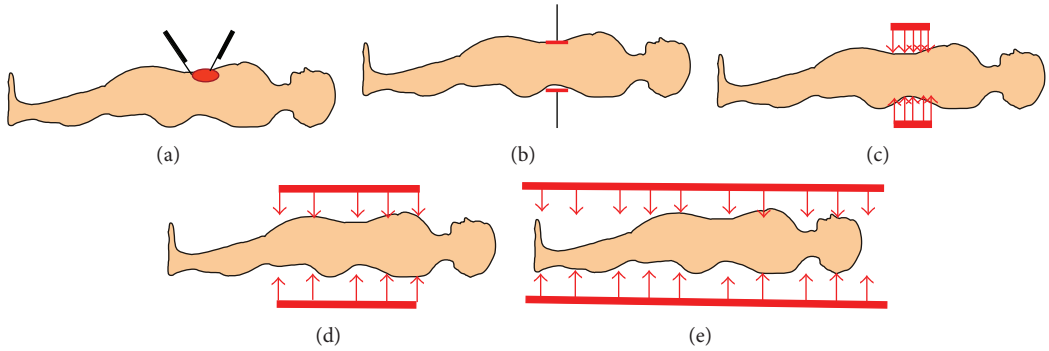


Figure 1: The main heating variations according to the targeted volume. The ablation (a) targets small volume with high SAR, while the local solutions ((b) and (c)) focus the electromagnetic energy from outside, and their SAR density is much lower, not making any coagulative processes; the part-body (d) and the whole-body (e) treatments are nonfocused techniques for temperature increase of a large targeted volume or the complete system.

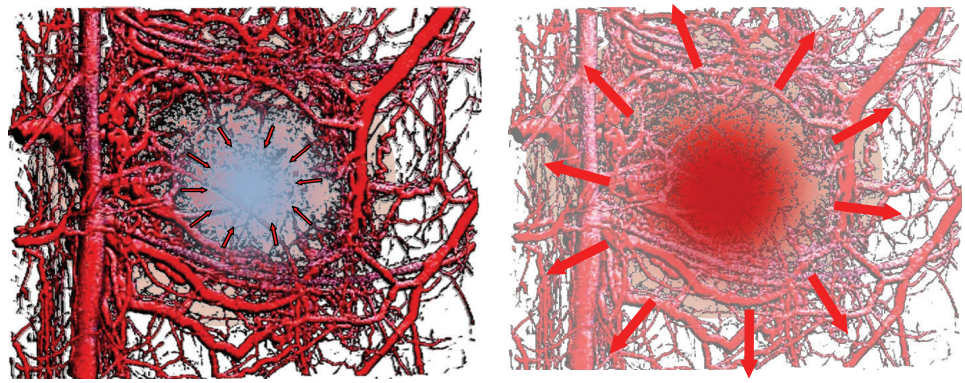


Figure 2: Opposite thermodynamic mechanisms of whole-body, systemic (a), and local (b) heating methods. The blood-heated tumor in whole-body treatment reaches thermal equilibrium after a certain time, while the local treatment is always in nonequilibrium state because the body temperature is lower than the heated tissue, creating intensive heat flow from the target to the neighborhood.

These ablation techniques due to their large and localized request of SAR are mostly invasive, only the superficial lesions can be ablated noninvasively.

The local hyperthermia is mostly a noninvasive focused deep heating, having longer time to reach the heat effects due to the time-limited SAR administration in deep regions (see Figures 1(b) and 1(c)). Heating a part of the body (regional or part-body heating [39]) targets a larger volume with the aim to eliminate the regional dissemination and metastases (see Figure 1(d)), while there is a whole body treatment to heat up the complete body systemically (see Figure 1(e)).

Thermodynamically, the systemic and local/regional treatments differ in their energy intake. The whole-body treatment is based on the blood heating (mostly heats up the subcutaneous capillary bed or heats the mainstream of the blood directly with extracorporeal heater), while the local hyperthermia is definitely a tissue heating approach. This difference drastically divides the two methods from thermal point of view. In whole-body treatment, the blood is a heating medium; it delivers the heat to the tumor and heats it up; while in local treatment, while the blood remains on body temperature during the local heating, so the blood here is a cooling medium (heat sink) for the locally heated tumor (see Figure 2).

The whole-body heating could be solved by various ways, like steam, water, or radiation heating. There are other possibilities as well (e.g., wax heating, hot-air heating, etc.) but the limited possible heat flux and the poor technical realizations hinder these solutions. These are based on the blood heating in the subcutaneous capillary bed, and the physiological reactions (vasodilatation and sweating) work well against the huge heat flux into the body. The long heating time is also challenging (over an hour) to move the body away from the healthy homeostasis. The heat flux is limited through the skin by the heat injuries (~0.5 W/cm^2 is the limit), so the contact heating with steam and water has definite problems. The radiation heating could be solved by special infrared wave (Infrared A) which penetrates deeper

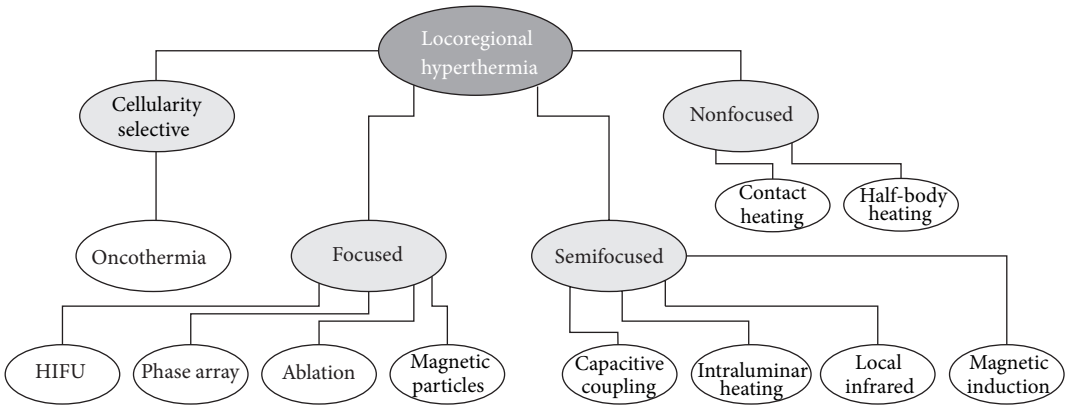


Figure 3: Various methods of the localregional hyperthermia with electromagnetic and ultrasound (HiFu) heating.

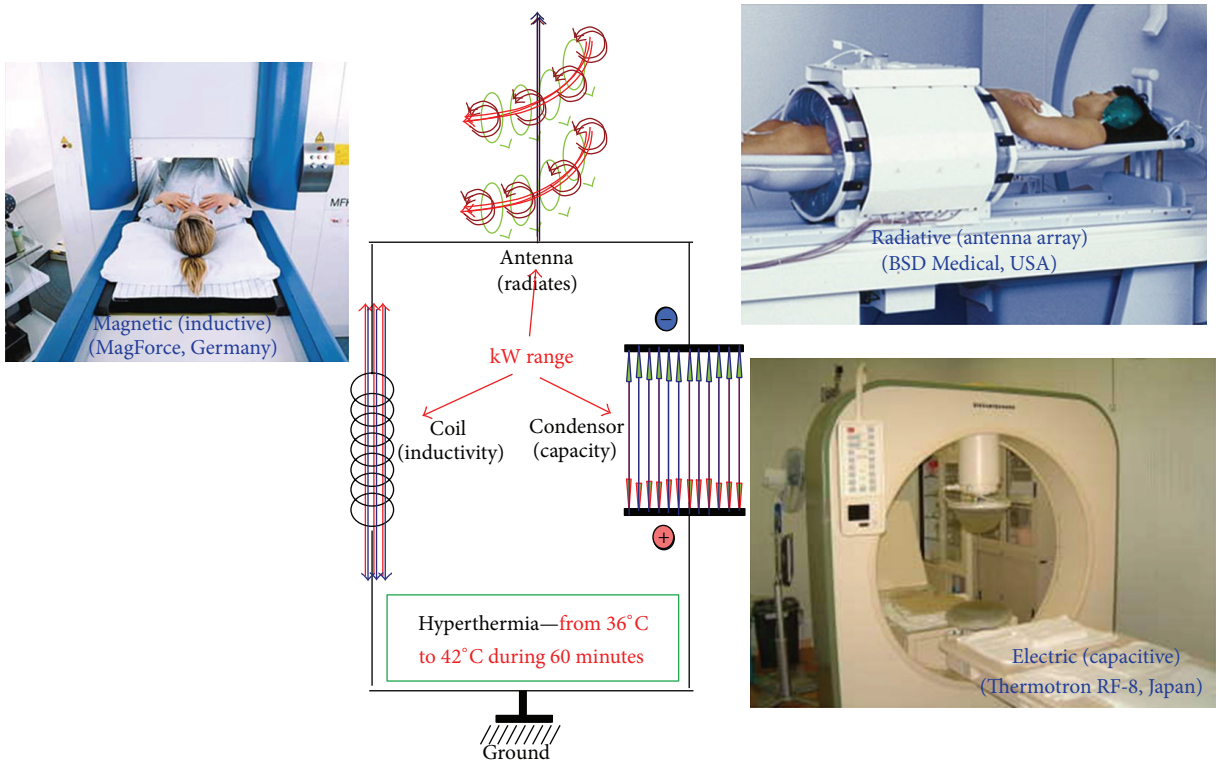


Figure 4: Electromagnetic fields are used in contemporary hyperthermia devices to heat up the body locally or regionally. All of these solutions are in range of kW energies because the intensive physiological feedback tries to cool down the heated lesion.

(~1-2 mm) into the subcutaneous layer and could manage higher energy flux without burn injuries. The method has many early descriptions [40–43], but the dominant systemic hyperthermia method is based on the infrared radiation by multireflecting filtering [44, 45] or by water filtering [46–49]. In the following, we are going to concentrate on the local and regional heating techniques, which are mostly used in hyperthermia practices in oncology. Their various categories are roughly shown in Figure 3.

The local/regional solutions are basically based on the electromagnetic effects, simple radiation (antenna effect) magnetic field application (coil effect), or electric field application (condenser effect); see Figure 4. These methods have high-energy applications (kW range) to ensure the quick heating and the supply of the energy, which is gradually lost by the intensive cooling of the neighborhood of the target.

The race for the high power density in the focused area increases the risk of burns and the risk of misfocusing the fields resulting in hot spots in the healthy volumes. The most part of the forwarded energy; however, is wasted due to the natural equalization of the temperature by the connected tissues to the target and by the intensive and steadily growing heat-exchanging mechanism of the blood flow.

There are numerous electromagnetic hyperthermia methods applied. These are distinguished by the kind of the fields, frequencies, heated volume, conjunction with other

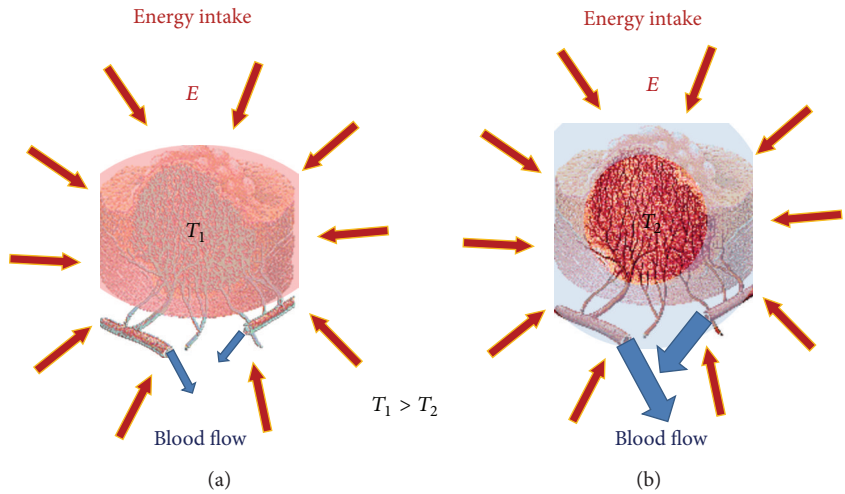


Figure 5: The same energy (E) is given to the same volume with different blood flows. When the blood flow is weak (a) and strong (b), the reached temperature is high or low, respectively.

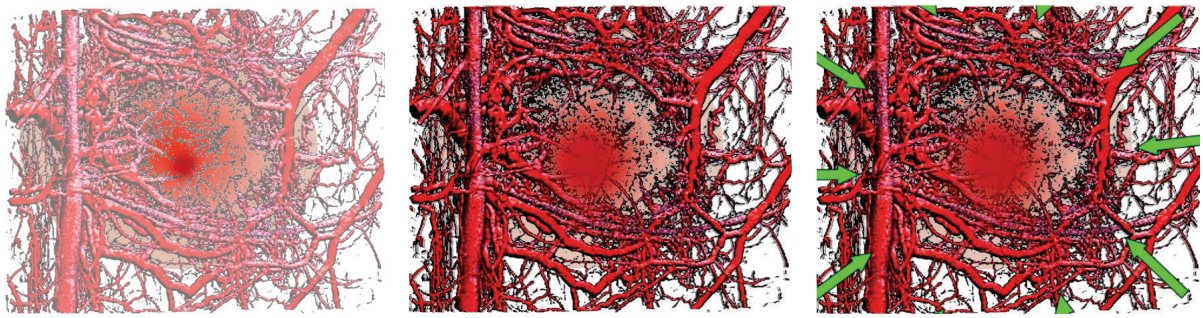


Figure 6: The focused local heating situation. (a) The local energy absorption impoverishes the ATP of the tumor, and it is destroyed. (b) The pumped energy has time to be distributed and heats up the surroundings. (c) The heated tissues deliver more glucose to supply the tumor and increase the risk of dissemination by increased blood flow.

methods, and so forth. In order to eliminate a part of the above challenges, we try to go over the limits by technical tricks: cooling the surface to limit the surface load, focusing the energy on the lesion, controlling the hot spots by imaging methods, and so forth. The main problems with the technical tricks include the loss of the basic control over the processes, requesting growing sophisticated methods to keep the pocess under control. This happen in the situation when we study the temperature which can be reached by any actual SAR energy. The blood perfusion modifies the temperature, and even when the same energy is absorbed by the same volume, their temperature could be significantly different due to the different blood flow through the target; see Figure 5.

3. Biological Challenges

The original idea of the local hyperthermia was to force the tumor metabolism by heat. When the surrounding tissue is intact, it does not deliver more glucose for the forced metabolism (Figure 6(a)). The tumor very quickly deflates from nutrients, empties all its energies, suffers, and burns away [50]; the rapid increase of the lactate concentration [50] supports the cell destruction mechanism in the targeted volume as well.

When the heat delivery is intensive and short enough, the local energy absorption heats up the target and ablation happens. If the energy is not enough for the coagulation, longer time is necessary for heating. In this case, the locally absorbed energy heats up not only the chosen target but the surrounding tissue, and even the whole body is heated up by the heat-exchanging mechanisms mainly by the blood flow in the target (Figure 6(b)). The higher blood flow delivers more glucose and nutrients to the tumor, causing opposite effect than the expected. In this way, a competition starts: which one is quicker, the distortion or the supply; there is no control on the process (Figure 6(c)). Furthermore, the higher blood flow is a real risk of the enhanced dissemination of the malignant cells (see Figure 6(c)). This contradictory effect really blocks the controlling facilities of the processes, and so the result is incalculable and unpredictable. The real physical rule is that the energy can be focused precisely, but the temperature is not

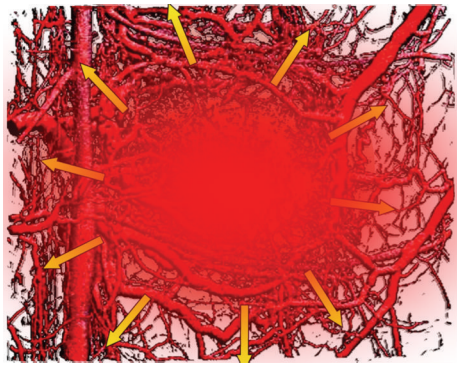


Figure 7: The locally heated volume heats up its neighborhood intensively. The energy is focused, but the temperature is not. The distribution of the temperature is forced by the physiological feedback trying to reestablish the homeostatic equilibrium.

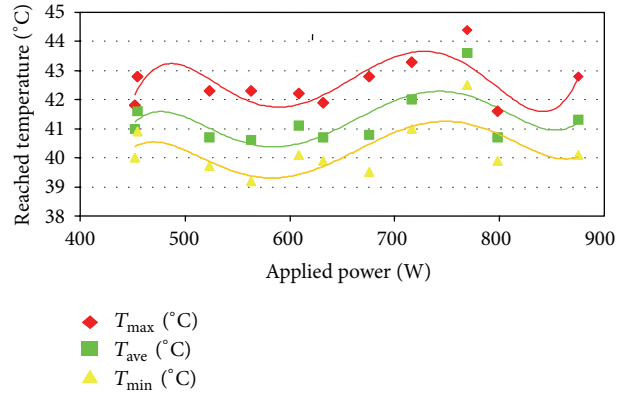


Figure 8: The homeostatic control keeps the temperature in a range, independent of the absorbed power.

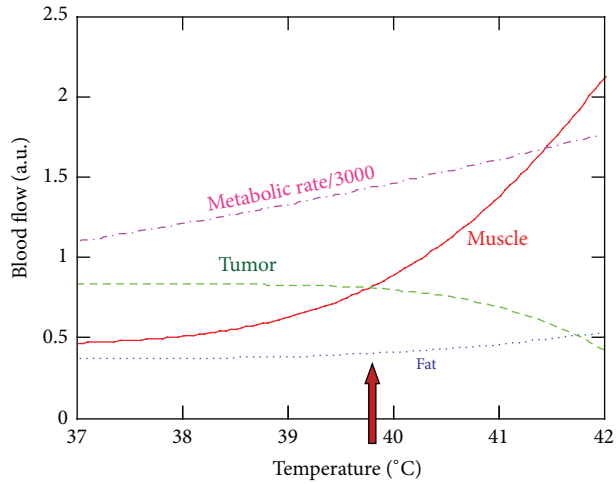


Figure 9: The blood flow rapidly grows by the local temperature in the muscle tissue while the metabolic rate has linear increase only in the given temperature interval. The threshold (see text) is noted by an arrow.

focusable, that is naturally distributed in the available volume trying to reach equilibrium (see Figure 7).

Complementary chemo-or radiotherapy naturally helps controlling the process due to the higher chemoactivity [51]. The promoted, optimized chemointake helps to overcome the fail of chemotherapies by the patient's intolerance (when it is not allowed to take big doses of drugs, e.g., at renal or liver insufficiency, insufficient blood-composition, etc.). In these cases, the same results may be achieved by the combination of decreased chemodose and heat therapy [52]. Hyperthermia supports the radioefficacy [53, 54] together with the applied heat. Hyperthermia has also been found to have pronounced advantages for surgical interventions. Through the hyperthermia-induced inhibition of angiogenesis and heat entrapment, the outline of the tumor often becomes pronounced and the size of the tumor often shrinks making previously dangerous operations possible [55]. The feasibility of the preoperative application for locally advanced rectal cancer is well shown in a Phase II clinical trial [56]. Postoperative application of hyperthermia has also been thought to prevent relapses and metastatic processes [57]. Intraoperative radiofrequency ablation [58] and local hyperthermia [59] have also been used to improve surgical outcomes.

However, the complementary actions of other therapies in many cases could not compensate the blood flow support of the tumor in a controlled way. Due to the physiological factors, the heat treatment effects depend on the dynamism of the heat delivery [60]. The quick heating acts differently on the local reactions and on the general thermoregulations from the slow one, because the physiological reaction time is relatively long. The highly nonequilibrium conditions in local-regional heating could not be stabilized; the stationer process is strongly influenced by the temperature regulation of the body. The measurements in humans evidently show the huge adaptability of the thermoregulation [61] (see Figure 8).

The temperature equalizing process naturally depends on the heat exchange and heat conduction facilities, which are drastically enhanced by the growing temperature (see Figure 9 [62]).

When the energy transfer starts to heat up the whole body through the blood heating of the target volume, new controlling processes (like sweating cutaneous vasodilatation, etc.) become active. The proper solution of hyperthermia would be when not increasing the complex feedback mechanisms against the heating action; having no unwanted gain of the blood flow in the target. We have to act in the feedback loop mechanisms to reach the optimal situation, and not to excite the contra-(negative feedback) actions (see Figure 10(b)). The physiology acts against the local heating, which causes rapid heat exchange of the target tissue with its connective tissues, and forces the body to make extra activity against local hyperthermia too. The reason for the enhanced heat conduction in the heated volume is simply physiological: the complex organism tries to reestablish the homeostatic equilibrium [63]; it compensates the growing temperature with the higher cooling blood flow (see Figure 10(a)). The absolute blood flow values of the tumor and its connective neighborhood develops oppositely and turns over at threshold temperature

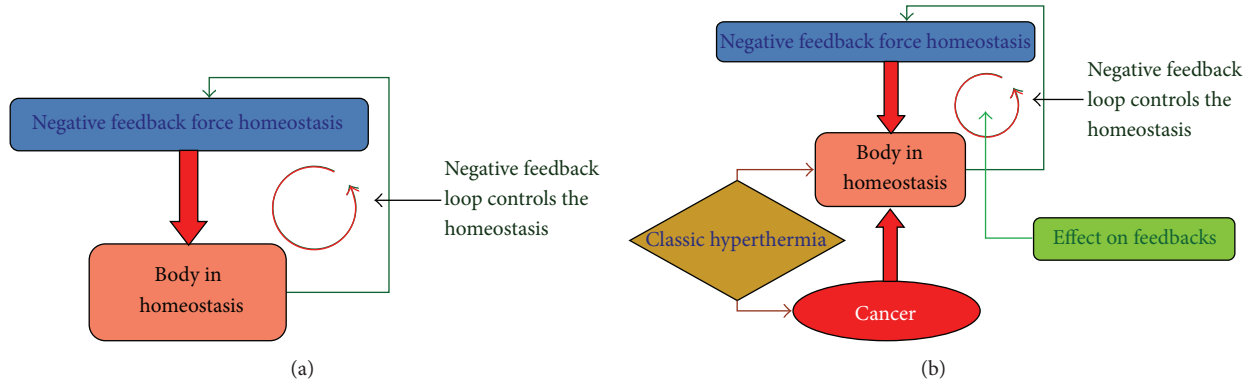


FIGURE 10: The feedback mechanisms of the complex living objects. (a) A definite set of negative feedback mechanisms keeps the homeostatic equilibrium of the system. (b) The classic hyperthermia forces the system to protect and act oppositely. The optimal action would be to act on the feedback mechanisms.

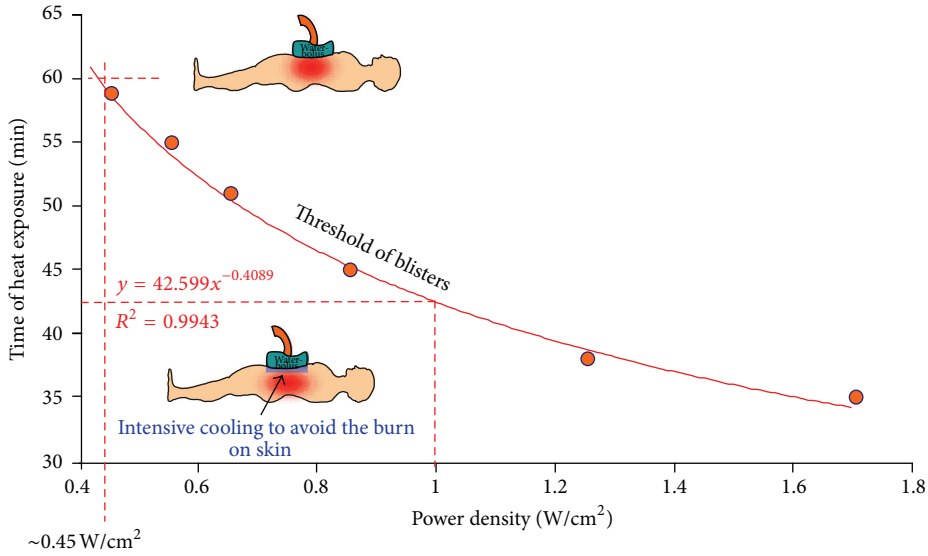


FIGURE 11: The blistering limit of the heating through the skin.

value, allowing a drastic exponential increase of the blood-flow in the healthy tissue [64, 65].

Hyperthermia in oncology has similar status to other medicaments; the difference between the medicine and poison is only the dose. There are certain energy flows necessary for the deep heating, but of course the energy passing through the subcutaneous layers is limited by the toxicity, the burning. The blistering limit depends on the density of energy (W/cm^2) and the duration time of its application see Figure 11 [66].

To find the optimal path, it is necessary to fix the limits of the dosage. The lower limit is of course determined by the minimal effect by heating and the upper limit is determined mainly by the safety issues, like it is usual for overdoses. We have to consider that the modern hyperthermia is always complementary, so the other methods have to be considered at hyperthermia applications. The lower limit of the hyperthermia dose is probably the normothermia, where nothing else has action only the complementary treatment alone. With slight heating locally or systemically, it probably has no effect directly on the tumor, but it helps to increase the immune effects and enhances the complementary effects by the increased blood flow and by the exponential temperature dependence of the chemical reactions (Arrhenius law). For the upper limit, however, there are very definite technical and physiological parameters: the surface power density of the signal is limited by the blistering shown above to 0.5 W/cm^2 (60 min basis), the internal hot spots could hurt the healthy tissue, and in the systemic application the physiology anyway limits it at 42°C. To avoid the overheating of the surface intensive surface, cooling is applied in most of the electromagnetic hyperthermia techniques. In this case, the physiology has negative feedback control again. In hot environment, the subcutaneous layers have vasodilatation; high blood flow helps the heat exchange with the environment, it radiates out the excess body heat (Figure 12(a)). In cold environment, the blood flow is limited; the surface layer isolates the body Figure 12(b). Both cases change the heat- and electric

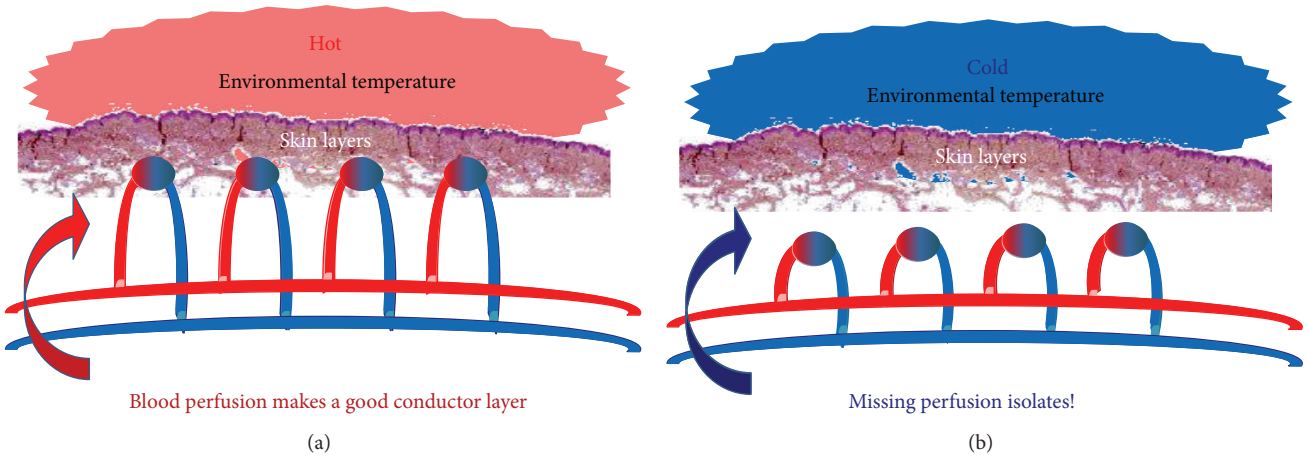


Figure 12: The environmental temperature significantly modifies the subcutaneous blood-perfusion. The hot environment (a) stimulates vasodilatation to cool down the body, while the cold environment works oppositely (b); definite vasocontraction helps isolate the body and avoids the loss of the body temperature.

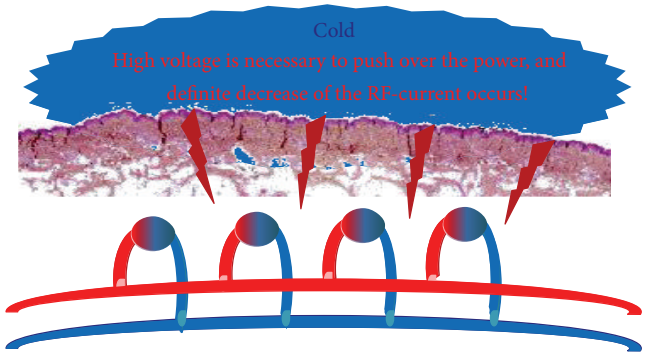


Figure 13: The constrained power produces high voltage on the skin layer. This finds narrow channels to go through, causing high risk of electric bum.

conductivity, as well as the dielectric properties of the skin layers. When the constrained forwarded power is applied, the voltage drops on the isolating (cooled) layer. High voltage is necessary to pump through the requested constrain power through this isolation barrier. The relative high voltage lowers the current and less RF current reaches the targeted deep volumes.

On the other hand, the high surface voltage will find the special conductive channels (blood vessels, lymph passes, swelling paths, nerve sensors, etc.) and like "sparking" passes through the isolating layer, causing electric bum despite the intensive cooling; see Figure 13.

The intensive cooling of the surface creates a further problem: the forwarded energy as parameter is not suitable when the cooling on the surface is intensive because there is no idea about the energy lost by cooling. When we apply forwarded energy over one kW and the cooling has similar energy taken off, the control becomes very complex.

The other problem could be when the energy heats mostly the bolus liquid as the most energy-loaded surface layer and deeper seated body itself are not directly heated up. Again, the forwarded power does not give information about the real energy load of the tumor.

Hyperthermia struggles with the technical problems above, and sometimes it hinders the biological factors. The uncontrolled absorbed energy situation requests local control; the energy intake which would be the natural dose measurement like in radiotherapy or like the chemical doses of medicine, cannot be applied here. Local, in situ measurement is necessary to dose the treatment, and that only could be the temperature. The presently applied dose concept (CEM) is physically incorrect (temperature is not a dose), and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in an extreme case reaches 42°C (even 43°C is applied sometimes in special conditions; CEM100%), but the expected distortion of the tumor does not happen. The high energy of the local heating The high energy of the local heating (which is in most of the cases more than 1 kW) makes vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40°C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppressor of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood perfusion, which definitely modifies all the electromagnetic applications through it.

The ultimate challenge is to develop heat resistance, which could make the hyperthermia ineffective; the disease could become refractory for heating.

4. Medical Challenges

Both the technical and biological challenges robustly appear in medical applications. However, some additional problems arise in medical considerations. The main point is connected to the inherent behavior of the malignancy. The malignant tumor looks local but it is systemic; the main dangers of it are the dissemination of the malignant cells and the formation of

distant, far away metastases. The survival prognosis is drastically worsened when the tumor is disseminated and metastasized. Considering this problem, we have three-front fights.

(1) Primary solid tumor, which proliferates and there is no natural block because the apoptosis is missing.

(2) Dissemination transforms the local lesion to systemic disease. The dissemination occurs mostly by missing adherent connections and missing cell-cell adhesions. When no dissemination happens, the tumor is benign.

(3) The formation of the distant metastases is the consequence of many various factors and one major is the missing immune reaction.

The dosing and control of the treatment is not only a technical and biological challenge. It is a hard problem of the medical application of hyperthermia. Without definite protocols, it is a weak approach and has no possibility for comparison of the results and does not give reliable possibility for the patients. However, the dose itself has numerous questions anywhere. The problem is mainly connected with the biovariability which makes humans also individual. The dose has to be personalized, but then many points of the fixed protocol could not be fulfilled, and the collection of the cohorts for studies became complicated as well.

The dose in radiotherapy, measured in Gy (J/kg), is a good quantitative parameter. However, its efficacy depends on many physiological and technical parameters (like the oxygenation of the tissue, the focusing arrangement of the devices, the fractionating possibilities, etc.). There are some surface burns representing the direct toxicity, which also can limit the application. Anyway the efficacy is measured by off situ diagnosis (comparison of the before and after states), and the safety is fixed by the dose escalation studies, where the severe toxicity blocks the further increase.

The chemotherapy is definitely based on the toxicity limit. All the patients have the same dose depending on their surfaces. The dose is calculated by mg/m^2, irrespective of the size of the tumor, or any other personal specialties. We assume that the drug which is solved by blood is equally delivered to all of the body volumes, and it is supposed that the tumor has been infiltrated by the drug in the same way as the other tissues do. The safety is again measured by dose escalation studies. The concept is to apply the largest tolerable dose ("tolerable" means controllable side effects) and measure the efficacy off situ later, in the same way (mainly by imaging) as the radiotherapy does.

In case of hyperthermia, the highest tolerable temperature is defined, while the safety limit is also defined by the temperatures (hot spots). Due to the long treatment time, the patient roughly senses the toxic dose (burning), so in hyperthermia the actual immediate correction of the dose could be done.

Another medical challenge of hyperthermia is its locality. The treatment is local, considering the tumor local too. But the malignancy is not local. Particularly, it is not local when high-line treatment is applied after the failure of some earlier treatments, and the case is advanced, metastatic. At this point, the local treatment alone is dubious even when the focusing is absolutely perfect, and the action is concentrated completely on the desired target only.

5. Possible Answers to the Challenges

There is a new method emerging: oncothermia [67]. It is devoted to "pick up the gloves." It is a precise impedance (resistivity) matched system (Figure 14). This impedance fit is mainly based on RF current and not on the voltage (potential) which is represented by a capacitor. Of course, this is also a capacitive coupling, but the electrodes of the capacitors are better conductors and promoting conductive behaviors than capacitors. While the capacitive coupling is based on dielectric loss of the material, the impedance matching is mainly Joule heat, concentrating on the conductive part of the dielectric constant.

The capacitive coupling has two possible solutions: dominating the field (voltage) between the electrodes or dominating the current (ampere) from one electrode to the other. Oncothermia is this second type, using the current source instead of the voltage source. It is a special capacitive solution, using impedance matching for treatment. This heating is sensitive for the electrode direct touching, when they are not well connected to the body, the process stops, while the usual capacitive coupling acts when the certain high isolation (i.e., lifted electrode) is involved. The current forcing solution forces the current through the target (starting from one electrode and finishing on the opposite, changing the situation by every period of the source). The two solutions have a lot in common, but the main difference is the current fixing. The same power has different effects because the multiplication of the actual amperes and voltages defines the constant power.

In conductive oncothermia, the RF current flows through the whole volume between the applied electrodes. In the oncothermia case, the area of the cross-section that the RF-current flows through changes by depth, and it decreases the current density (current through a unit area). The energy deposition of the current in a unit volume, however, depends on the current density, which makes the energy absorption nonuniform in relation to depth.

The better impedance coupling is supported by a technical trick, the asymmetric electrodes (see Figure 15). The specific absorption rate (SAR) is much better in asymmetric solution starting on the surface, and the symmetric exceeds it in depth of 22 cm. Deeper than 22 cm the symmetric becomes better, which is for humans the full cross-thickness of a laying person.

Oncothermia impedance coupling has special electrode construction to avoid any capacitive radiation, which could make noncontrolled losses of unwanted shortage of penetration depth. It works by 13.56 MHz carrier frequency, applying definite, patented [68] time-fractal modulation with special template of its construction.

The complex modulated signal works effectively on the selection of malignant cells and promotes the heat dispersion of the membrane-bounded water states. Together with the state-of-the art fractal physiological considerations

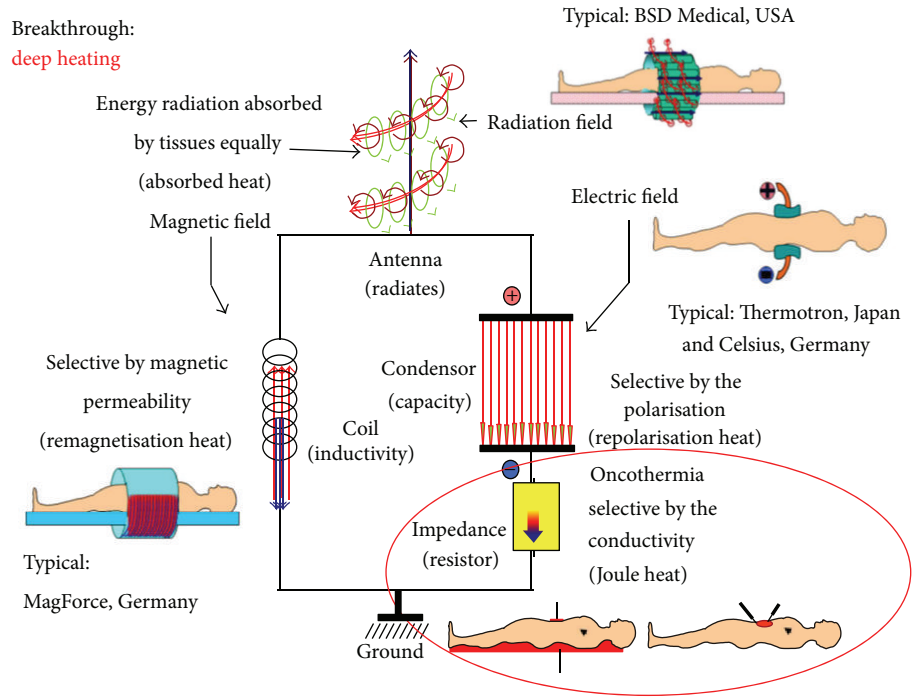


Figure 14: Impedance matching is the main factor of oncothermia.

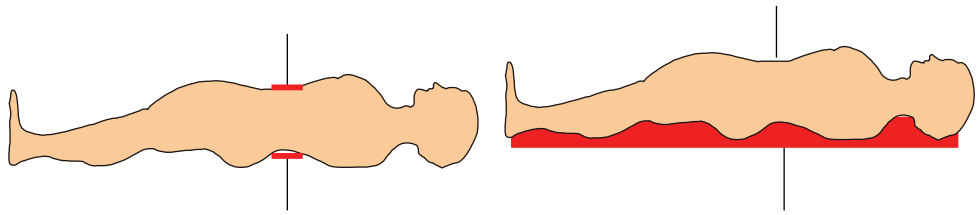


Figure 15: The symmetric (a) and asymmetric (b) electrode arrangement. The asymmetric arrangement has higher RF current at same power.

the concept is based on Warburg's principle of fermentative ATP production and on Szent-Gyorgyi's principle of permittivity changes of malignant membranes [69]. There are numerous clinically proven advantages of oncothermia recognized [67]. Oncothermia uses the well-established gold-standard to optimize the dose, which is the same as used in radiotherapies. The selection can heat up the malignant cells extremely high, without the same heating in the other parts of the tissue (Figure 16(a)). However, by higher temperature the selection would be less emphasized, while the average is growing; see Figures 16(b) and 16(c).

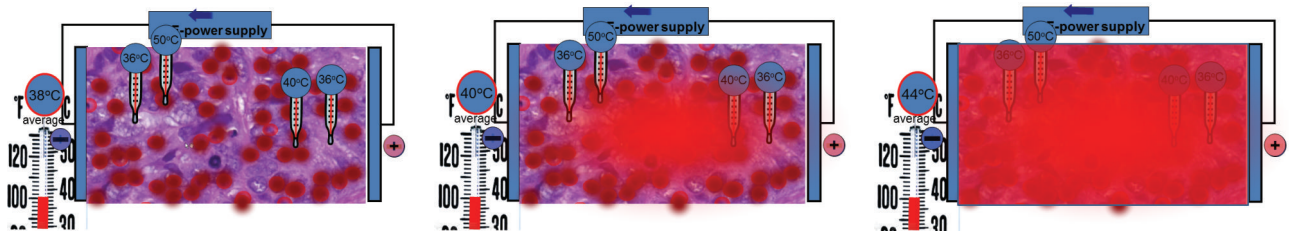
The RF current flows dominantly in the extracellular electrolyte; the cell membrane is enough for the energy-absorption in it and in its surrounding thin electrolyte layers (see Figure 17).

The selection mechanisms [69] concentrate various effects on the membrane of the malignant cell, [70] (Figure 18). The most important consequence of this excitation is the apoptosis which is formed in majority of the selective cell killing [71].

An important observation shows the result of selection in oncothermia. While in conventional hyperthermia the relative cell distortion is 17.9% at 42°C; for oncothermia it is 57.1% in identical temperature [72] (Figure 19). Measurements were made by cooling the tumor intensively down to near body temperature (38°C). In this measurement, we take care of the same forwarded power as it was in the previous 42°C process. It was interesting to observe the cell distortion rate, which remained much higher than the conventional hyperthermia reaches in 42°C.

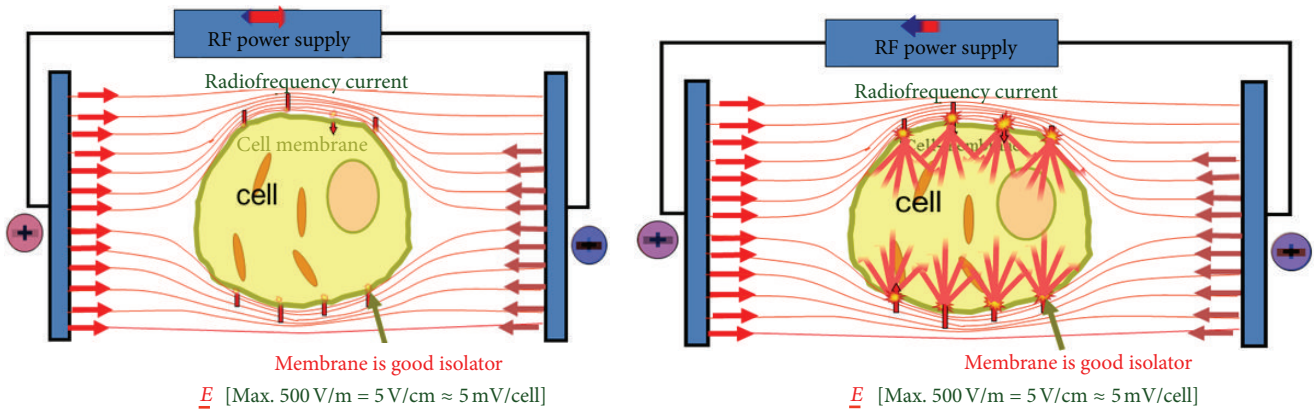
The careful, patented control of physiology of the skin at the treated volume [73] makes it possible to pump the highest available energy through the epidermis without toxicity. This lets us use the precisely matched and measured energy as control parameter; the cooling does not modify the energy intake.

The new technology allows using as much overall energy as necessary for the cellular heating, having no energy loss by the heated noncancerous volumes. The energy is selectively absorbed in the nanorange of the membrane of malignant



(a) (b) (c)

Figure 16: Heating with high selectivity in nanoheating process while the average temperature is kept low (a), when increasing the average temperature, the selectivity lowers (b) and fixes the tissue in equilibrium, where no selectivity exists ever more (c).



(a) (b)

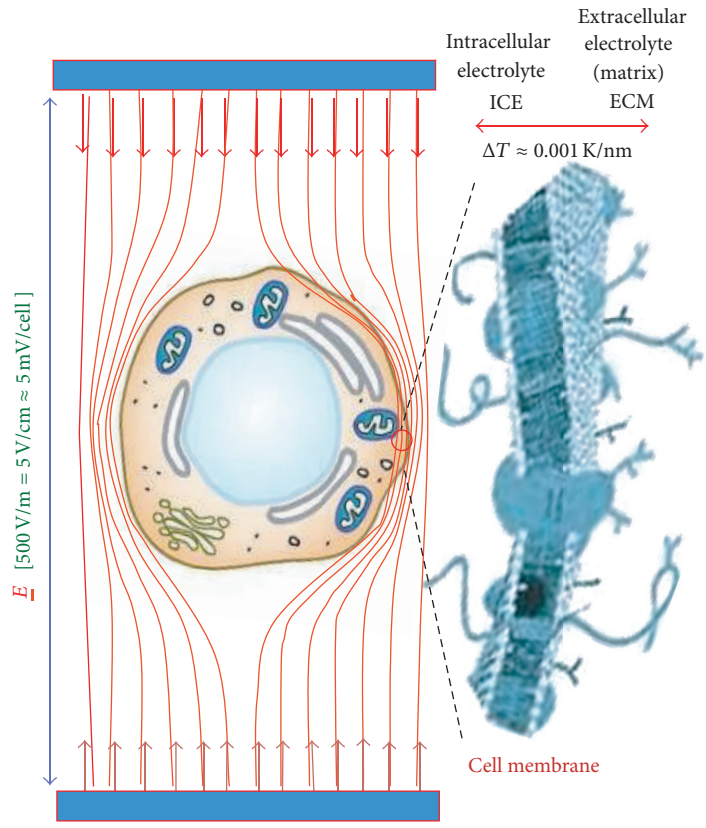
Figure 17: The RF current penetrates into the cytoplasm only slightly; the majority of the energy is absorbed in the membrane and in its immediate vicinity (a). The temperature gradient excites the membrane (b).

cells. The 1/10th of the usually applied energy in similar devices is eligible to reach high-quality results in preclinical and clinical uses, mainly in survival time and quality of life. The main medical advantages of the method together with the effective selection and distortion of the malignant cells are the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. More details about this method were presented in this conference [69].

The dose is an important factor of efficacy safety and reproducibility in oncothermia. Conventional hyperthermia overemphasizes the temperature as a dose, which anyway is necessary for safety reasons, because the forwarded power and SAR do not correlate. The temperature is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic, average of the individual energies of the small units in the system. In chemotherapy the cytotoxic remedies could cease very serious side effects; their safety has an emphasized role in their applications. The chemodoses are determined by the safety (toxicity) limits, independent of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then, the chemodose could be modified or a complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.

When the medication definitely has no side effects (or the side effects are manageable), then the dose by their safety role has no upper limit. Anyway, when the dose is prescribed by fixed patient-independent protocol, it is not realistically applied. When the prescribed energy is too high for the actual patient (high biovariability), the actually applied dose has to be lowered, trying to fit it for the actual patient.

Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) senses and notes the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much, actually it has to be modified on personal requests. On the other hand, when the preset energy dose is too small (the patients can actually tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible because the surface of the skin has the highest thermal load, and the heat sensing is also there. This personalized dose regulation is the main factor of the safety, and together with this, for the efficacy too.



$T_o + \Delta T$, $\Delta T \approx 0{,}01^{\circ}\mathrm{C}/10\,\mathrm{nm} \approx 10^{6\circ}\mathrm{C/m}$, temperature-gradient-driven processes

$j_q = \alpha \Delta T \quad \alpha = 1{,}4 \cdot 10^2 \left(\frac{\mathrm{W}}{\mathrm{Km}^2}\right) \quad \Delta T = \frac{j_q}{\alpha} \approx 10^{-2}(\mathrm{K})$

$\frac{\Delta T}{\xi} = \frac{10^{-2}\mathrm{K}}{10^{-8}\mathrm{m}} = 10^6\left(\frac{\mathrm{K}}{\mathrm{m}}\right)$

Heat flow ≈ 1.5 (pW/μm^2) at 1 (K/s), metabolic heat flow ≈ 0.002 (pW/μm^2), destroys the ordered membrane

Thermoelectrical current ≈ 150 (pA/μm^2) (Na^+influx) normal ≈ 12 (pA/μm^2) (Na^+efflux), drastically decreases the membrane potential, and destabilizes the membrane

Thermomechanical pressure ≈ 1320 kPa, (electro-osmotic effect, rigid tumor-cell membrane), water pressure

Rectifying effect leads a positive feedback to gain the temperature and the pressure in the membrane

Specific absorption rate of water is high in the membrane (10 MHz)

Synthesis of HSP-s additional extracellular and membrane HSP70 appears through the more permeable membrane

Membrane-associated apoptotic pathways are activated (E-cadherin, beta-catenin, and p53 expression)

Figure 18: Various effects at the malignant cell are forced by the RF field. The main effect is, however, to excite the pathways for apoptosis.

6. Future Tasks

There are numerous exciting tasks for the future of hyperthermia in oncology. Here is a list of them below without detailed description.

(1) It is desired to extend to local treatment to whole-body effect, but affecting selectively only the malignant cells (irrespective of where they are in the body). This has numerous preliminary results by the bystander (abscopal) effect, which is definitely dose dependent and connected to the immune activation processes [74].

(2) Oncothermia is completed by the preliminary results to solve the memory (vaccination) effect in situ personalized for the cancer patients. The memory effect was shown and used [75, 76], through T-cell activation.

(3) More precise and specialized personalized effects have to be used by proper dose adjustment and modulation template [77].

(4) More complementary applications have to be worked out. Conventional gold standard therapies have to be widely applied in high-line treatments too, working out the resensitizing processes for the previously refactory treatment. New therapies (dendritic cell [78], stem cell [79], etc.) have to be involved in the combinative complementary processes.

(5) There are multiple cases presented in this conference too [80, 81], showing the possibility to form the fatal cancer disease chronic, applying it for a long time (like dialysis), and making the patient's survival much elongated with good quality of life.

7. Conclusion

Nanoheating technology offers a renewing of the conventional hyperthermia. It is a synergy of the bioelectromagnetism with the fractal physiology. Oncothermia approach opens possibilities of stable controlled treatment without

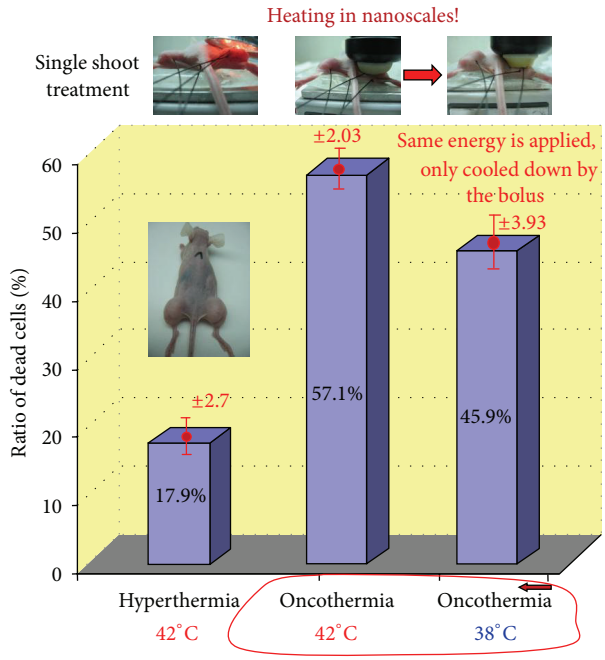


Figure 19: Oncothermia is more effective than conventional hyperthermia on the same temperature, and remains effective in case of lower average temperatures too.

controversial challenges. It is a vivid way to solve the old-problems in hyperthermic oncology; it is a controlled, reproducible and reliable, treatment.

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