Conference Paper

Burden of Oncothermia: Why Is It Special?

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There are many contradictory opinions about conventional hyperthermia in oncology. The main points are the physical and technical imperfection of classical heating, as well as the limits of the natural physiological feedback of the organism. We would like to present the definitive differences between oncothermia and conventional hyperthermia, explaining the new line of problem solving in this important field of oncology.

1. Problem

The general opinion among specialists is that the physics limits the deep heating [1]. The limit is formed by the heat conduction and other thermodynamic factors. The imperfect thermal conditions are combined with insufficient electrodynamic facilities to concentrate the energy focused in depth. This inadequacy appears in the unwanted hot spots and the overheated surface when the actually necessary energy is pumped through.

Some experts evaluated the situation a bit differently, blaming the biophysical, physiological factors having technical inefficiencies. According to this position, the physiological negative feedback seeking to reestablish the thermal homeostasis block its proper job, [2].

Certainly, both the physical and physiological deficiencies are involved in the hindrance of the success and probably it is accompanied with a factor of improper references too. In case of comparison of various heating methods, the only factor measured as relevant is the temperature in the targeted volume. However, this reference has various complex shortages and could lead to misleading consequences. The high temperature ablation in a small volume for short time cannot be compared with a longer time local or regional heating or it is even less comparable with the whole body

heating on the same temperature. When the local or regional heating reaches 41.5°C homogeneously in the target that could be a therapeutic indicator of success. However, in case of whole body hyperthermia the same homogeneous temperature could be reached, but no more curative effect is observed, it does not give the final solution of heat-therapy. Moreover, the results are completely different from the expectations of a therapist trained in local heating methods. The temperature alone is not a reference point [3], because the physiological conditions modify the actual state even when the temperature is equal. Typical example is the difference of the blood heating approaches and tissue heating ones. In blood heating cases (e.g., limb perfusion, subcutane radiative heating), the hot blood heats up the tumor. In case of the tissue, heating the blood remains cold (stays on body temperature). This difference makes huge deviations in the thermal and physiological actions: in the first case, the heat flows from the blood to the target, while in the second case it is completely the opposite. In the first case the static thermal equilibrium can be reached after a definite time, while in the second case the thermal equilibrium always remains dynamic; the heat-flow is always active from the heated volume to the other body parts by the blood flow. In this second case, the heated volume (tumor) is a hot heat source to heat the body up.

Measurement of the intensive thermodynamic parameters (like temperature) supposes at least local equilibrium, which could never be realized due to the intensive contra regulatory effects. (This concept however became the main request of the classical hyperthermia approach in its guidelines).

The forced equilibrium increases the heat flow to the blood stream, which is an effective cooling media trying to block the static concept. Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead of its elimination. (These processes are like intracellular HSP development, forced delivery of metabolic species (oxygen and nutrition), systemic cooling control, and various stress reactions, etc.) Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy).

When the temperature is not enough, the standardly used and absorbed energy (specific absorption rate; SAR) could be the solution. However, this is again problematic. Due to the variability of the blood-flow of the parts of the body, the same SAR could heat up the same volume to completely diverse temperatures. The actual blood flow cools down the target and takes the energy to an indefinite level away, because the blood flow is nonlinearly controlled by the physiologic feedback system.

In consequence, the simple temperature characterization of the therapy has numerous problems, like the following.

- (i) Temperature heats up the vicinity of the tumor; it can not be kept locally focused.
- (ii) Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.).
- (iii) Temperature requests the increase of the safety-cooling on the skin.
- (iv) The increased surface cooling blocks the temperature sensing in the skin.
- (v) The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely.
- (vi) Temperature increases the blood-flow in the region and in consequence increases the dissemination.
- (vii) In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks all the effect of radiotherapy.
- (viii) In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks all the chemopenetration into the tumor (vaso-contraction or blood-vessel blockage in the tumor).

(ix) In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues too, which is further modified with the increased vasodilatation in the healthy tissues.

(x) The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient.

In addition to the temperature as reference, we have challenges from the variation of the patient's individual behaviors. We have to calculate not only the physiology of the patient, but the psychology as well, not forgetting that the treated body part organ belongs to somebody. The personal differences are modified by the previous treatments and tolerances and by the personal tolerance limits. Most of the decisions in serious cases need medical experience; we do not apply automatically the prescribed protocols formulated for an average patient.

2. Solution

The physiology is an interdisciplinary subject; it applies numerous principles and discoveries. The electronic structure approach of solid state physics (e.g., [4]), the superconductivity (e.g., [5]), the electromagnetism (e.g., [6]), the thermodynamics (e.g., [7, 8]), and so forth are all parts of the physiology and make it really complex as the phenomena of life itself is. The living organism develops itself, rearranges, reorganizes the incoming chemicals, builds up its own structure, and consequently lowers the entropy. Various modern approaches were developed in the last decades on this complexity, like self-organization [9], fractal physiology [10], and the bioscaling [11]. These modern achievements are used as solutions for the above problems of hyperthermia in oncology.

There are special biochemical and biophysical changes caused by the above differences of the malignant cells and used for oncothermia specialties:

- (i) their extracellular matrix has different concentration of ions [12], which can be measured by positron emission tomography (PET) [13];
- (ii) they have different conductive behaviors [14] which can be measured by electroimpedance tomography (EIT) [15];
- (iii) their electromagnetic environment (how they conduct the electromagnetic currents and waves) is different, [16, 17]. This can be measured by K. S. Cole and R. H. Cole impedance measurements [18];
- (iv) the order of their electrolyte (aqueous solution) differs, [19]. The healthy tissue has ordered water states [20] in extracellular matrix [21, 22], while malignancy decreases the order of the electrolyte matrix, decreasing the cell-cell adhesion promoting the proliferation [23];

- (v) the dynamical process has special self-organization [24]. It forms special structures [25, 26], its bioscaling [27] and noise spectrum [28] certainly differs in the cancerous state. Recognizing the tissue is based on the well coded information of self-organized order of the actual pattern [29, 30].

The solution of the problems of conventional hyperthermia is the nanothermia; it targets the cell membrane of the malignant tissue and does not waste the heat (energy) to the volumes which are irrelevant in the point of view of destroying the malignant cells. This nanothermia heating (concentration of nanoscopic range of the target) is the oncothermia [31], using the distinguished points of the differences between the malignant and healthy cells. The clue to find the mechanisms, which could create the requested optimization, selection, and control of the energy intake, is based on the clear biophysical differences between healthy and cancerous cells, finding the biophysical property to focus the energy on the desired cellular membranes. The hyperthermia is macroheating; it heats a given volume of the target equally and distributes the SAR in conductive and convective ways. The result is that the heated volume will be a massive heat source to elevate the temperature of the complete neighboring tissues, unselectively.

The efficacy of the energy depletion intended to be pumped into the tumor is limited by the energy loss outside the malignant target. The main factors of the useless energy absorptions are

- (i) the absorbed energy by the tissues transferring the effect to the deep-seated tumor,
- (ii) the heat exchange by the blood flow,
- (iii) the heat exchange by the heat conduction from the tumor to the surroundings.

These heat sinks modify the overall performance of the treatment and make the full heating process for the malignancy uncontrollable. The real effect used for the intended treatment is less than the loss, and the efficacy is usually less than 25%, which is very low. The problem of this is not only that a large part of the energy is wasted, but also that the useless energy part could be dangerous by overheating the healthy tissues as well as increasing the metabolic rate and it also gives physiological reaction to this effect which tries to break the homeostasis [32]. The massively heated tumor volume intensifies the control of physiology and weakens the expected effect.

The adequate corrective actions for these challenges would be the more precise targeting, decreasing the loss in the surroundings and to avoid the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increase the efficacy.

- (i) Apply the electric field as carrier of the energy and that field cannot be compensated by homeostatic control.
- (ii) Apply correct microscopic targeting, using the energy absorption cell by cell efficiently.

- (iii) Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- (iv) Apply mechanism, which carries info for disseminated cells to be blocked.

Oncothermia uses these new approaches to fit it in the best curative performance. This new approach (the fractal physiology) is applied in oncothermia. The carrier electric field delivers the time fractal structure to the tissues, enhancing considerably the selection between the connected healthy cellular community and the individual autonomy of the malignant proliferation.

In this application, there is no considerably heat flow to the blood stream, no gain of the feedback of electrolyte balancing loop. Oncothermia uses tumor killing approach, which is well fitted into the dynamism of the living system, it does not constrain for false defense. Thermal gradients make dynamism in a very local area of the cell membrane of malignant cells. The applied selection focuses on this thermal nonequilibrium.

The applied fractal modulation [33] makes the selecting and supporting of the natural processes possible to activate the natural healing mechanisms and reestablish the healthy "social signal" between the isolated cells, promoting the antimalignancy collectivity. The carrier frequency delivers the information (modulation frequencies), for which the cancer cells are much less "transparent" than their healthy counterparts are. Malignant cells are heated up by the selectively absorbed energy. What makes the difference in the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special "social" signals [34] commonly regulating and controlling their life. They are specialized for work division in the organism, and their life cycle is determined by the collective "decisions." The cancerous cells behave noncollectively; they are autonomic. They are "individual fighters," having no common control over them; only the available nutrients regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version; the cellular communications disappear [35].

By modulation, the cellular connections (adherent connections, gap junctions) of malignant cells are reestablished to avoid the further dissemination. Selection is solved on cellular level, and it suppresses the dissemination of the malignant cells. The method is similar to the process when the light goes through the window glass. When the glass is transparent to that specific set of colors (visible light, definite interval of frequencies), its absorption is almost zero; all the energy goes through it. However, when it has any bubbles, grains, precipitations, and so forth, those irregularities will absorb more from the energy, their transparency is locally low, their energy absorption is high and they are heated up locally. It is a self-selection depending on the material and the frequency (color) we apply in the given example. Cell membrane permeability is increased by the nanothermia process, expressing the HSP on the outer membrane signaling the cell malignancy for the systemic immune actions. Cell membrane is excited to ignite various communication pathways in the cells.

The relatively slow “step-up” heating keeps the nonequilibrium conditions stable for long time for action. The advantage of the step-up heating protocol is that it does not create considerable physiological contra-actions; the slow heating makes the healthy tissue adapted to the growing temperature and does not generate high stress and following stress reactions. Oncothermia is mainly regulated by the patient’s tolerance. Its control is based on thermal sensing of the patients, for safety and for efficacy reasons. Safety means avoiding burning the tissue of the subcutaneous layers, and the efficacy means applying such energy, which does not overload the patient’s natural defending/protective system.

Oncothermia heats the target as the fuel cells liberate the energy. The selection of malignant cells is made by their metabolic activity according to Warburg [36], a nobel-laureate in physiology. Warburg recognized the metabolic difference between the malignant and healthy cells: the malignant cells have much higher flux of glucose than their healthy counterparts do. The higher glucose metabolism needs larger ionic fluxes in the vicinity of the individual tumor cells.

The RF current, which flows through the cancerous lesion, automatically focused by its lower impedance, will flow mainly in the extracellular electrolyte, because the cells are electronically capsulated (isolated) by their membrane by more than one-million V/m field strength. (The membrane is a good isolating lipid (fatty) layer). The membrane disruption is one of the targeted aims [37–39], and many research groups are dealing with the electric field action on the cellular divisions [40–43]. The main advantage of the electric field application is the missing control of the organism; there is no physiologic sensor and control of this effect. No physiologic feedback limits the electric field directly; only the consequences of its action could be regulated. The process made by oncothermia has its main energy delivery into the extracellular liquid, heating it up, and creating a little ($1/1000^{\circ}\text{C}$) difference between the inner and outer temperature of the cell. This is only a small difference, but regarding the very tiny membrane layer (5 nm), the small difference in standard conditions is high: $\sim 200,000^{\circ}\text{C}/\text{m}$! The system is far from the thermal equilibrium [44]. This starts a prompt heat flow from the outside of the cell through the membrane and permanently acts till the temperature difference exists. Despite the quick heat flow through this tiny membrane, the heat-current is long-lasting, till the full cellular interior is heated up to the same temperature as outside.

The large extracellular SAR makes not only thermal, but also electric, effects in the tissue; the extracellular matrix has a higher current density than the other electrolytes. The current density gradient is accompanied by the gradient of the electric field, which could reorient the high-dielectric constant proteins in the extracellular liquid. The orientation of these protein molecules would be constrained perpendicular on the membrane surface. By this effect, the lost adherent connections could be rebuilt between the malignant cells, which were indeed shown experimentally [45]. This effect helps to suppress the metastatic dissemination as well as to promote the intercellular signals to activate the natural cell killing mechanisms.

Development of the thermotolerance, such as heat-shock protein (HSP) production [46], is one of the suppressors success of hyperthermia, [47]. From the point of view of the thermotolerance, one of the most prominent chaperone proteins is the HSP72. The concentration of this HSP is 5–10 times lower in the healthy cells than in the malignant ones, [48]. However, responding to the heat treatment, their concentration in healthy cells became 8–10 times higher, while the same heat treatment of the HSP72 multiplication creates only 1.2–1.5 times higher concentrations in malignant cells, [48].

Oncothermia is a highly personalized, energy-dose dependent, and nanoscale heating technology, which can solve all the debated problems of the conventional hyperthermia. Oncothermia uses higher thermal load on cellular membrane than any other hyperthermia can, but its physiological feedback remains low, due to the nanoscale capability of the treatment. Also the excited apoptotic pathways, reestablished adherent connections, and controlled abscopal effect makes the job.

Oncothermia is personalized; the heat delivery has numerous important physiological controls. The objectivity of the treatment definitely depends on the radiofrequency current and its gained voltage on the given impedance on the tumor. This current is well regulated by the skin conductance and by the connected physiological changes. The inconvenient feeling of RF-heating defines a pain limit, which depends on many objective and individual factors. A good approach is to regard the nerve cell sensitivity objective (the cellular processes are well unified) and regard the personal differences as influence of physiological factors. The main factor for heat sensitivity is the blood perfusion and blood flow in the subcutaneous layers where the heat sensing nerves are located. The high blood flow is an effective heat exchanger, it cools the given volume, and the nerves tolerate higher energy flow through the layer. The high blood cooling is not only the facility to have higher energy flow, but also to get more current through the volume. The higher current density excites the nerve sensing, and the feeling again is an overheating, requests downregulation. In case of low blood perfusion the current is small, so the nerves can tolerate more intensities than in any other situations. The crucial point is the surface heat regulation, which has to be carefully done by the electrode systems. When the surface temperature is kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. A detailed mathematical model has been worked out for this regulation mechanism and applied in oncothermia treatment.

The other factor is connected to the psychological interaction with the treatment process as well. In any protocols, when the temperature is described as a dose, the required temperature cannot be achieved. Then of course it is forced by the power, so the incident energy is not limited in this case. In fact, the opposite reaction has to happen: if the patients cannot tolerate the prescribed power (and required temperature), then a lower one has to be applied. The pain in the body depth is independent of the temperature sensing nerves; the pain there has other mechanisms, which are not part of the prevention of damage (like the temperature

sensing), but sensing the actual damage itself. Consequently, blocking the surface heat sensors is a high risk factor, which is never made in oncothermia therapies.

While the temperature has physiological blood flow response, the current (electric field) has no such homeostatic regulation; it has only pain response from the skin. This pain tolerance is constant (saturated) at 13.56 MHz [49]. This allows an objective pain sensing by the current, which depends on the thickness of the adipose layer. This creates negative feedback signal: when the fat is thick, the temperature grows and makes a temperature pain limit which increases the blood flow by vasodilatation by step-up heating. The current in this way grows, but when the blood conductance becomes too high, the pain from the current will limit the process again and controls the personal merit, which is pretty objective due to the saturation of the current sensing.

3. Conclusion

Oncothermia is a feasible method to treat any solid malignant tumors irrespective of its primary or secondary status and irrespective of the advanced stage of the disease. The only two parameters which are considered as useful for measuring the treatment efficacy are the survival time and the quality of life.

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