Essentials of Oncothermia

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Abstract

Oncothermia is a method of hyperthermia in oncology, controlling the locally applied deep-heat by selectively targeting the cellular membrane of the malignant cells. The selection of the method is based on various biophysical and biochemical achievements. There are various differences between the malignant and healthy cells, which could be used for their selection by heat targeting. The primary selection factor is a different metabolic activity which creates distinguishable environments of the malignant cells. The other factor is the clear difference of dielectric properties of the membrane and near membrane extracellular electrolytes, marking off the malignancies. There is also a structural factor also, which is clear in the different pathological patterns of the malignancy from their healthy counterparts. This last is described by fractal pattern evaluation technique, which dynamic time-fractal transformation is used for further discernment of the malignancy. My objective is to show a new heating method, which makes oncological hyperthermia controllable and effective.

Keywords: oncology, hyperthermia, heat, nanothermia, oncothermia, selectivity, cell-membrane, Warburg, Szent-Gyorgyi, fractal, radiofrequency, modulation, beta-dispersion

Introduction

Oncological hyperthermia is the overheating of the malignant tissues locally or systemically. The method is deduced from the ancient medical practices, where the heat-therapies had a central role in medicine. The local hyperthermia by the radiation of red-hot iron was the first known oncological treatment applied by Hypocrites, who described the method [1]. The main idea was originated from sacral considerations formulating the overall force of the “fire”. However, physiological consideration was also behind that together with beliefs: the local heat accelerates the metabolic activity without extra supply of this action from the unheated neighboring volumes. This physiological mechanism is accompanied by severe hypoxia and it finally kills the target by acidosis. The working idea has been recently shown, proving the impoverishment of ATP and enrichment of lactate in the locally heated tumor tissue, [2]. Due to the primitive heating techniques the ancient radiative heat is only rarely applied in real cases. The central point of the locally applied oncological hyperthermia is the selective heat-delivery into the deep-seated tumors. The discovery of the electromagnetic heating gave new perspectives for deep heating, and hyperthermia started its first “golden era” in oncology. It was among the first modern curative applications of modern techniques in oncology, [3] and was followed by a controlled clinical study involving 100 patients as early as 1912. It showed remarkable benefit of the combined thermo-radiation therapy [4]. The method was further developed in three various branches: the interstitial hyperthermia, including the galvanic heatstimulation, the ablation techniques and the capacitive coupling. The first capacitive coupled device was launched by Siemens. The skeptical opinion about oncological hyperthermia was also typical: “All of these methods impress the patient very much; they do not impress their cancer at all” [5]. After a small dormant period the phoenix life of hyperthermia in oncology started again. The first start of the new capacitive-coupling technologies was by LeVeen [6] in 1976 and has been widely applied since then [7], [8]. Its efficacy was discussed and proven in the relevant literature in its time, [9], [10], [11], [12], [13].

Treatments with coils (magnetic and inductive) are relatively rarely used due to the negligible magnetic permeability of living systems [14]. In order to improve the magnetic energy absorption within the target tissue, magnetic materials, such as micro-particles [15] and ferrite rods [16] are usually injected into the targeted area [17]. Other inductive heating is typically achieved without inclusion of extra magnetic material into the tumor, it uses only induction of Eddy-currents [18], [19], [20]. The emerging application of magnetic treatments was started by the nano-particle magnetic suspensions [21] and other magnetic liquids.

A method for electromagnetic energy delivery, that has been widely used recently is the antenna-array coupling [22]. Its subsequent developments are the annular phase array [23], the matched phase array [24], the Sigma60 [25], and Sigma-Eye [26], where the applicators use high-frequency RF (60 – 150 MHz). Nevertheless, multiple controlled clinical trials have shown the efficacy of this method [27], [28], [29], [30]. This rapidly emerging period was shadowed by skeptic opponents, they emphasized the increased
dissemination of the malignant cells which supports metastases by hyperthermia, [31], [32], [33]. Direct negative opinion was formulated about the mistakes of hyperthermia investigations [34]: “The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment.” Many researchers had been doubtful and unsettled questioning the future of hyperthermia accepting the impressive biological effects, but blaming the physical realization of the heat-delivery [35]. Annals of Surgical Oncology formulates in the actual clinical experiences of mesothelioma [36]: “The results of adjuvant intrapleural chemotherapy for mesothelioma with or without hyperthermia have been less than hoped for.” One of the flagship clinical studies of hyperthermic oncology was published about cervical cancer, with excellent results [37], the method emerged again, [38]. The control study five years later was disappointing [39].

What is the problem [40]? Why are conventional hyperthermia with high preciosity of focusing made by modern techniques of radiofrequency and microwave applications not able to serve the proper deep heating requests? The answer is plausible: the temperature spreads into the neighboring volumes independently of how precise the focus of the energy is. The problem is, that because of the misleading aim we get uncontrollable temperature as a dose and we ignore the physiological reactions of the patient. The published temperature patterns of the heating show the problem well: the energy is well focused, but the temperature seeking to be equalized and the focused energy-intake will heat up the tissue outside the focus as well. For example, a tumor is heated in the pelvis, and the elevation of the temperature in the tumor is 4.2 °C after 57 min, with as high power application as 1300 W [41]. The overall heating is obviously show unwanted hot-spots on the MRI pattern. The elapsed time smears the relative focused temperature. The temperature increase in the tumor was in average 4.2 °C, while in the surrounding muscle it was 3.8 °C [41]. (Note, a standard speedy electric tea kettle uses 1300 W to boil a cup of water within a couple of minutes. The increase of the temperature for the ~ 0.3 liter water is ~75 °C. In these cases we apply the same power reaching a temperature increase of ~7 °C during 60 minutes for the same volume of tumors as the cup of water in the kettle.) Analyzing the temperature pattern in details shows that the mean tumor-size was less than half a liter (419 ml), the necrosis in the tumor was 36 ml. The volume ratio of the body’s cross section and the bolus show, that the bolus has 157% more cross-sectional area than the body. The applied frequency was 100 MHz in average, which loses its 66% of the initial energy (penetration depth definition) within max. 5 cm, so the main energy-absorption was in the water of the cooled bolus. Other publications show the same problem of the heating [42]; [43]; [44]. Comparison of the clinical responses also clearly shows the problem of the bolus heating. The cases of non-responders have higher bolus temperature, the tumor is not heated [45], [46].

The same problems arise by typical capacitive coupling hyperthermia solutions. It pumps enormous energy also (1200 W) into the target and the rise of temperature was 4.8 °C after 45 min. The selection by temperature between the malignant target and the non-targeted healthy tissue was approx. 1 °C [47].

This large volume temperature rise was observed in other capacitive applications too, [48].

All of these problems are caused by the massive heating of the target, which has a physiological reaction to cool it down and to reestablish the homeostatic equilibrium. The complex physiological effects badly modify the desired effects [49]. Even when the focus is proper, the heat is distributed to the full available volume. Furthermore, the same volume heating with the identical absorbed energy will be heated to different temperatures when the blood-flow in the targeted volume is different. This is why the patterns of the specific absorption rate (SAR) of the energy and the temperature are so different in a given fixed heating process, [50]). There are multiple other points that modify the temperature distribution in the body:

- Not only the temperature equalizing process, but the natural, technically non-followable movements of the patients (i.e. due to the breathing) modify the focus.
- The heat flow to the surroundings can damage the healthy neighborhood.
- The enlargement of the sphere having certain temperature gradients increase the area of the injury current, and this supports the cell-proliferation.

Compensating these effects, the acceleration of the heating with high energy has to be applied, when the incident energy might burn the skin. In consequence, certain surface cooling is necessary. The heat-sink of the surface decreases the incident power, but its quantity has no measurable parameters. This way we lose the control of the treatment process by the incident energy, because the missing part by cooling is uncontrollable. It has serious consequences in the vigilance of the process: temperature measurement in situ is necessary to fix the dose of the energy. This measurement is mostly invasive, causing multiple complications, including inflammation, bleeding, infection, dissemination of the cells, etc. The unwanted hotspots are created by the electromagnetic interferences and are uncontrollable with the dynamic changing
of physiologic parameters. These could be controlled only by a large volume temperature pattern, which requires costly and complicated MRI measurements parallel with the hyperthermia treatments for control.

The physiological feedback of the large volume temperature equalizing is the increased blood-flow. The high blood-flow promotes the glucose influx (delivery), and supports the malignant proliferation by this supply. The increased temperature anyway gains the metabolic rate and the proliferation even by the cells in dormant (G0) phase. The higher blood-flow creates other malignant danger too: the risk of the forced disseminations and metastases, decrease the prognostic factors of survival of the patient.

The well-focused local hyperthermia treatment creates a competitive pair of effects: killing the tumor-cells by heat and support them by nutrients together with the risk of dissemination. The result of this competition is unpredictable and depends on the patient and on the applied techniques as well. The explanation of the controversial results of local hyperthermia in oncology may be simple: a reference point was missing, [51]; the temperature is not a correct reference.

The present main-stream thinking of oncological hyperthermia is a typical loss of aims by illusions, believing the overall control of temperature. The temperature however is only a condition for the treatment and not its aim. The question “Tool or goal?” has become relevant to study the temperature alone. Take a simple example of mixing the tool and the goal in our everyday life: the graduation is a tool for our professional life, however when somebody regards the certificate of studies as a goal, its application, the aim of the study is lost. Mixing the tool with the action creates false goal in hyperthermia application: increase the temperature alone. This “auto-suggestion” creates such a situation in which magnetic resonant imaging (MRI) is applied to control the temperature during the treatment instead of using this capable imaginary method to see what is happening in the tumor indeed.

Our tasks are finding the correct heating and control the hyperthermia process. For this we have to precisely select the malignant cells and we must not heat up all the materials in the targeted tumor, only the membrane of the cancerous cells. This selected nanoscope energy-absorption liberates not as much heat energy which heats up all the mass equally, so its efficacy could be significantly higher. The main advantage however is its independent action from? the physiologic feedbacks, no contra-action starts to compensate its effect.

Furthermore, the membrane excitation could excite special cellular signal-transduction pathways, which are connected with the natural apoptotic cell-death, and so the negative feedback loop of the complex living system is supported. (The conventional hyperthermia by its overall heating excites negative feedback mechanisms act against the temperature growth, so the system starts “fighting” against the healing process.) The temperature as the average of kinetic energy in the system has a double role in the control of the heat-absorption.

It characterizes the heat-absorption, when the heating is homogeneous (see before), and its gradients (non-homogeneities) are the driving forces of the dynamic processes in case of microscopic (non-homogeneous) heating. The average temperature does not inform us about the distribution of the real energy-absorption (see Figure 1.).

![Figure 1.](image)

**Figure 1.** The average temperature is not able to characterize the thermodynamic situation. The internal temperature differences could serve as driving forces of various processes on the same average temperature of the system

**Method**

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:

- The absorbed energy by the tissues transfers the effect to the deep-seated tumor.
- The heat-exchange by the blood-flow.
- 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 uncontrolled. The real effect, which is used for the intended treatment is less than the losses, and the efficacy is usually less than 25%, which is very low. The problem of this is not only that the large part of energy is wasted, but also the useless energy part could be dangerous by overheating the healthy tissues as well as increasing the metabolic rate and also having physiology reaction to this effect which tries to break the homeostasis. 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 losses in the surrounding and avoiding the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increase the efficacy:

- Apply the electric field as carrier of the energy, and that field cannot be compensated by homeostatic control.
- Apply a correct microscopic targeting, using the cell-by-cell energy-absorption efficiently.
- Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- Apply a mechanism, which carries info that disseminated cells have to be blocked.

Oncothermia changes the paradigm of local hyperthermia in oncology to solve the above problems [52]. This hyperthermia technology heats non-equally; concentrating the absorbed energy to the extracellular electrolytes [53]. This method creates inhomogeneous heating, microscopic temperature differences are far liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis. The synergy of electric field with the thermal effects effectively and selectively does the job [54]. Oncothermia uses nano-heating technology to select and heats effectively the membrane of the malignant cells. The heating is concentrated mostly on the cellmembranes, so the nano-range energy-liberation could be precisely controlled without considerable wasted energy and without having disadvantages by the heating of the tumor-environment in average.

The general idea of microscopic heating is simple: the heating energy is not liberated in a sudden single step, but regulated and multiple small energy liberation does the same job, Figure 2. In our case, the forwarded energy selectively targets the most influential areas. Instead of the high, general energy pumping into the lesion, the energy is liberated at the membranes of the malignant cells.

Figure 2. The difference of macro- and micro-liberation of energy. The efficacy of the last one is much better

The precisely targeted power and its efficacy are usually not connected. The microscopic effects, instead of the large energy liberation, is one of the most update thinking in energy source developments. The relatively low efficacy combusting engines are intended to be replaced by the fuel-cell energy-sources and electric motors, which are based on the membrane regulated microscopic reactions of gases. (Mostly hydrogen and oxygen gases are in use.)

Good examples are the standard incandescent bulb and the energy saving fluorescent ones, using a fraction of the power for the same light. The incandescent bulb creates light by high-temperature filament, which heats up the environment, having only 10% efficacy, while the fluorescent has more than 40%. It could be developed further by the higher nanoscopic energy-liberation, when not the molecules but the electrons are directly involved in the light-production. These are the LED bulbs, having more than 90% efficacy in producing light.

Oncothermia [55] is a kind of hyperthermia with nanoscopic heating processes. Instead of the undistinguished cells by the classical overall heating of hyperthermia, oncothermia nanoscopically selects and attacks the malignant cells. It has a simple setup. The modulated radiofrequency current (RF) flows through the targeted lesion, see Figure 3.
The radiofrequency current (RF-current) flows through the body and delivers energy to the malignant cells. The frequency is low (13.56 MHz) chosen to satisfy multiple requests:

- It is a free-frequency for medical applications in hospitals and clinics, as well as in general use of for example RF-identification.
- It is in the range of the beta-dispersion which is one of the selection factor of oncothermia.
- It is low enough to have long wavelength for near-field use with high penetration into the body when the impedance matching [56] is fixed.
- It is high enough to be modulated by time-fractal fluctuations.

The discussion of all these behaviors is seen below.

The current which flows through the chosen part of the body starts from one electrode and ends on the other one, periodically changing its direction according to the carrier frequency. The current is directed by the impedances inside the targeted volume, the current automatically flows to the “easiest” direction, where the conductance and dielectric conditions are optimal. Oncothermia uses three factors to direct the current to select malignant cells, i.e. those current paths which include malignant cells are favored. Certainly, the biophysical behaviors have to be studied to fix the optimum. The first selection factor is the well-known metabolic differences between the malignant and healthy cells. Due to the high energy demand of the malignant proliferation, the malignant cells metabolize more to supply their needs. Furthermore, the process to produce ATP differs in malignant cells from the normal ones. While the dominance of the mitochondrial ATP production characterizes the healthy tissue, when 36 ATP is produced from one glucose molecule during the complete cycle, the fermentative ATP production dominates the metabolism of malignant cells, only two ATPs are produced from one glucose molecule [57]. Consequences of this huge difference are enormous: the requested glucose influx of malignant cells is considerably higher, which is standardly measured by Positron Emission Tomography (PET). The considerable glucose consumption certainly produces high concentration of adducts, the extracellular electrolytes enriched by metabolites and lactates in the vicinity of the malignant cells, robustly enhances the ionic concentration in the connected electrolytes. The applied RF-current naturally flows with higher density in the areas where dense ionic conditions allow the easy flow, Figure 4. This could be measured by current density images with MRI [58], by simple impedance measurements in vitro [59] and in vivo too [60].
This gives us a possibility to distinguish the malignant cells automatically and individually, see Figure 5. This automatic focusing makes it possible for the current density to follow any movements (breathing, heart-beats, muscle-movements) in the target tissue.

**Figure 5.** The microscopic heating of the extracellular electrolyte around the malignant cells excite the membrane and makes temperature gradient in a few nanometer distance

The above selection is based on the conductive component of tissue impedance. The permittivity component is also selective. Malignant cells differ from their healthy counterpart not only by their metabolic processes, but their collective behavior sharply identifies them. The malignant cells are autonomic, they are individual "fighters", having no collective driving of their activity, while the healthy cells have social signals [61]. These connections commonly regulate and control their life. These cells are specialized for work-division in the organism, and their life-cycle is determined by the collective “decisions”. This requests definite order in the connective electrolytes. Indeed, the order was proven, [62], [63], [64], [65]. Contrary, the malignant cells which have no such order in their immediate extracellular connections, Figure 6. The disorder increases the electric permeability of the electrolyte near the malignant cells, [66]. The higher permittivity is also a selection factor, which is used to distinguish the malignancy by Szent-Gyorgyi’s cellular categories alpha- and beta-states, [67], [68].

**Figure 6.** The difference of the healthy and malignant tissue is well observable by their organization structure

This dielectric differences are well completed by the specialties of the cell-membrane of the malignant cells.

- The efficacy of the ATP production in cancerous cell is low. The large ATP demand for the proliferative energy-consumption allows less ATP for active membrane stabilization by K+ & Na+ transport, so the membrane potentiating weakens [69].
- The cellular membrane of cancerous cells differ electrochemically also from the normal, its charge-distribution also deviates [70].
- The membrane of the cancerous cell differs in its lipid and sterol content from their healthy counterpart [71].

The membrane-permeability is changed by the above differences. In consequence of these the efflux of the K+, Mg++ and Ca++ ions increases, while the efflux of Na+ decreases together with the watertransport from the cell. Consequently, the cell swallows, its membrane potential decreases further [72]. (The efflux of K+ regulates the pH of the cell, takes the protons out from the cytosol.) The concentration of Na+ increases in the cytosol, and parallel to this the negative ion-concentration also grows on the glycocalyx shell, decreasing the membrane potential and the tumor will be negatively polarized on average, [73]. This fact was well used for direct current treatment (electro-
chemical cancer therapy (ECT)) by Nordenstrom [74], [75], and others [76], [77], [78]. There is a further selection based on complex impedance, the $\beta$-dispersion [79] (Maxwell-Wagner effect). The bound water to the membrane has the upper part of the $\beta$-dispersion, (denoted by $\delta$, [81]), which has a further selection role in oncothermia. The treatments have to be chosen in the frequency-range of $\beta$-dispersion, promoting it with amplitude modulated pink-noise, expecting most of the changes in the complex system [82]. The carrier frequency and its modulation are selected by the membrane properties difference between the malignant and healthy cells [83], [84], [85].

Oncothermia selects by the above electromagnetic differences, and heats up the membrane of the malignant cells. The RF-current, which flows through the cancerous lesion is automatically focused by its lower complex impedance [86], it will flow mainly in the extracellular electrolyte (see Figure 7/a.), because the cells are electronically capsulated (isolated) by their membrane by more than one-million V/m fieldstrength. The membrane is a good isolating lipid (fatty) layer. The membrane disruption is one of the targeted aims [87], [88], [89], so that is why many research groups deal with the electric field action on the cellular divisions [90], [91], [92], [93]. The main advantage of the electric field application is the missing control of the organism, physiology control over this effect; no physiology feedback limits directly the electric field, only its consequences 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 °C) difference between the inner and outer temperature of the cell. This looks only a small difference, but regarding the very tiny membrane layer (5 nm), the small difference in standard conditions is high: ~200,000 °C/m! The system is far from thermal equilibrium [94]. This starts a prompt heat-flow from outside to 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 not heated up to the same temperature as outside. The not so high radiofrequency (13.56 MHz) is absorbed in all the electrolytes, but the main energy absorption is in the membrane and the extracellular electrolyte [95]. This creates an extreme SAR between the cells, which makes temperature gradient through the membrane [53]. The treated tissue will be inhomogeneously heated, the heat flows from the extracellular to the cytosol through the membrane, accompanied with definite other thermodynamical and chemical changes [53]. These definite thermal currents will be continued till the extra- and intracellular temperature reaches equilibrium, so the intracellular electrolyte is heated up to the equal level (see Figure 7/b.).

![Figure 7](image_url)

**Figure 7.** Oncothermia delivers its energy mainly into the extracellular electrolyte, creating a temperature gradient through the cellular membrane (a). The thermal gradient action due to the non-homogenous heating is active until the thermal equilibrium equalizes the temperature (b).

The cell killing needs energy, and afterwards the overall energy of the system would be decreased from a well ordered (bounded) state (which was in the case of the living cell) to a disordered chemical state with some broken chemical bonds. The transition from the ordered (chemically higher energy) state to the disordered (chemically lower state) arrangement of the well-known gap energy must be pumped. This gap-energy has different components. For hyperthermia, the heat energy gives the full energy consumption, however, in oncothermia, a significant field effect takes part in the distortion mechanism [53].

This simple method allows easier cell-destruction by oncothermia, (see Figure 8.); similar to the well-known catalytic reactions.
Oncothermia needs less thermal energy to make the same distortion as the classical hyperthermia does. The missing connections (adherent bonds, junctions) are selected not only by the dielectric properties of the cells, but they also affect the energy-absorption and the cellular protections against the energy overload. The absorbed energy by a healthy cell can easily be shared by the connections with the neighboring cells, damping the effect of the energy-overload. The malignant cells have no such possibility, the no network distribution could protect them from the energy-overload.

The large extracellular SAR makes not only thermal, but also the electric inhomogeneity in the tissue; the extracellular matrix has higher current density than the other electrolytes. The current density gradient is accompanied with 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, [96]. This effect helps to suppress the metastatic dissemination and it also promotes the intercellular signals to activate the natural cellkilling mechanisms. Not only the heating makes the effect, but also the electric field itself has a strong synergy with this [97].

An important and unique specialty of oncothermia is the modulation of the carrier frequency. This timefractal pattern carried by the basic frequency distinguishes in similar way as the pathological evaluation does. The famous Adey-window was the first proof of the special modulation effects [98], [99], published in the early 1990s. The modulation of RF-carrier frequency started to be used [100], and became an important new method for cancer therapies [101]. Numerous clinical results show its efficacy [102], [103], [104], [105],[106], [107], and oncothermia has been applying it since the beginning. Biopsy specimens are evaluated by pattern-recognition of the experienced pathologist. One of the modern pattern-description is measuring the fractal dimension of the actual pattern. The malignancy has characteristic fractal dimension differences, the cancer has its own fractal structure, [108]. The analysis of fractal structures could even indicate the stage of the disease [109]. Careful fractal analysis can make predictive information, making a significant prognostic value, [110].

The fractals in patterns are accompanied by fractal dynamics. This new discipline is the “Fractal Physiology”, ([111], [112], [113], [114]), which has a fundamental role in the structure of the healthy organism and is a basis of the self-similarity in biology, which is well-recognizable in the scaling behavior of the living objects, [115], [116], [117].The time fractal which characterizes the healthy tissue is the 1/f fractal-fluctuation. This is the modulation which we apply in the tumor-cure. The effect is simple: the system, which easily emits a frequency fluctuation can easily absorb it as well. So the applied modulation helps to localize the tumor-boarder, helps to “clear” the contours, and (most importantly) helps to select (self-focus) the energy-intake. Simply speaking, it works like the hammer on the drill, when you would like to make a hole in the concrete wall: it makes the action more effective. You may also switch off this modulation. Why? Because, you must not use the modulation in the sensitive organs (like the brain) from the very beginning. It causes head-ache and severe pain. In these cases from the third treatment the doctor starts the modulation in subsequently increased time, reaching the permanent modulation regime at the 8th treatment (if the patient has not complained). I propose to use the modulation in all the “usual” cases, but be careful when treating brain, spinal-cord, and head-and-neck cases. In non-tumorous applications the modulation has no role at all.

The fractal modulation, which is applied by oncothermia selects and re-establishes the apoptotic pathway functions. A day after oncothermia a definite difference can be detected between the anyway identical oncothermia treatments which are different only in the application of the modulation. Both
Results

Using the modern achievements of the physiology, oncothermia answers positively on the doubts about the conventional hyperthermia. The experimental and preclinical results are described in other articles presented in this conference [119], [120], [121], [122], [123], [124], [125], [126], so I summarize the clinical results only. Remarkable amount of retrospective and prospective clinical studies are available to indicate the oncothermia effect in humans [127], [128]. 62 studies were performed with altogether 3790 patients, from six countries (Hungary, Germany, Korea, China, Italy, Austria). The collection outlook is shown in Table 1, 2.

| Study          | Number of studies | 1st year survival (%) | Median overall survival (m) | Responding patients/ratio (%) | Median overall survival of responding patients (m) | Median overall survival of non-responding patients (m) |
|----------------|-------------------|-----------------------|----------------------------|-------------------------------|-----------------------------------------------|-----------------------------------------------|
| Brain studies  | 10                | 521                   | 73.99                      | 22.19                         | 44.09                                         | 51.31                                         | 15.88                                         |
| Pancreas studies | 6              | 184                   | 47.04                      | 11.02                         | 53.05                                         | 28.09                                         | 7.58                                          |
| Lung studies   | 5                 | 636                   | 64.76                      | 15.79                         | 25.73                                         |                                               |                                               |
| Bone           | 3                 | 79                    | 40.10                      | 90.60                         |                                               |                                               |                                               |
| Liver metastasis | 7              | 267                   | 86.00                      | 18.06                         | 80.00                                         |                                               |                                               |
| Colon/rectal   | 7                 | 447                   | 63.18                      | 109.80                        | 23.20                                         |                                               |                                               |
| Gynecology (pelvic) | 5         | 100                   | 93.22                      | 33.25                         | 44.82                                         | 80.36                                         | 21.70                                         |
| Breast         | 1                 | 103                   | 91.17                      | 52.10                         | 45.00                                         | 274.80                                        | 10.90                                         |
| Esophagus      | 2                 | 19                    | 41.70                      | 55.64                         | 35.00                                         | 29.40                                         | 5.50                                          |
| Somach study   | 1                 | 68                    | 55.90                      | 14.40                         |                                               |                                               |                                               |
| Kidney cancer  | 1                 | 30                    | 84.60                      | 35.00                         | 48.00                                         | 78.40                                         | 33.70                                         |
| Urinary bladder cancer | 1 | 18 | 85.00 | 36.50 | 73.00 | 42.00 | 22.60 |
| Head and neck  | 1                 | 64                    | 92.20                      | 26.10                         |                                               |                                               |                                               |
| Soft tissue sarcoma | 1 | 16 | 100.00 | 35.90 | 31.00 | 115.30 | 31.30 |
| Prostate       | 3                 | 135                   | 88.90                      | 38.60                         | 72.00                                         | 53.40                                         | 7.60                                          |
| SUM            | 54                | 2706                  | 51.03                      |                               |                                               |                                               |                                               |

Table 1. Collection of the studies (Phase II) made by oncothermia in combinations with various conventional oncotherapies. (Data are weighted averages of the study-results)

| Miscellaneous Study          | Number of patients (n) |
|------------------------------|------------------------|
| Borrellosis                   | 12                     |
| General oncology             | 277                    |
| TCM general oncology         | 306                    |
| Abdominal effusion           | 49                     |
| Peyronie’s disease           | 25                     |
| Chronic pelvic inflammation  | 283                    |
| Asthma                       | 7                      |
| Chronic bronchitis           | 35                     |
| SUM patients                 | 994                    |

Table 2. Collection of the miscellaneous studies made by oncothermia in combinations with various other therapies.
The survival time connected data, response rate connected data, the quality of life connected data, and tumor-maker connected data are collected in Tables 3, 4, 5 and 6., respectively.

| Study                                | Number of patients | 1st year survival (%) | 2 year survival (%) | 3 year survival (%) | Median overall survival (m) | Median overall survival of responding patients (m) | Reference |
|--------------------------------------|--------------------|------------------------|---------------------|---------------------|-----------------------------|---------------------------------------------------|-----------|
| Brain gliomas                        | 27                 | 66.2                   | 23.6                | 43                  | 66.2                        | 18.2                                              | [129],    |
| Brain-glioma study Phase II,         | 140                | 71.7                   |                     |                     |                             |                                                   | [130]     |
| Astrocytoma                          | 40                 | 25.8                   | 80                  | 40                  | 20.2                        |                                                   | [131],    |
| Glioblastoma                         | 92                 | 16                     | 73                  | 21.9                | 13.1                        |                                                   | [132]     |
| Diffuse astrocytoma                  | 8                  | 52.9                   |                     |                     |                             |                                                   | [133]     |
| Glioma (WHO IV) Study, Phase II,     | 45                 | 15                     |                     |                     |                             |                                                   | [134]     |
| Recurrent glioblastoma study, Phase II | 19              | 68.0                   | 21.8                | 59                  | 32.5                        | 12.4                                              | [135]     |
| Glioma study, Phase II              | 36                 | 60.0                   |                     |                     |                             |                                                   | [136]     |
| Astrocytoma                          | 9                  | 108                    |                     |                     |                             |                                                   | [137]     |
| Glioblastoma                         | 27                 | 20                     |                     |                     |                             |                                                   | [138]     |
| Glioma study, Phase II              | 179                | 100                    | 103                 |                     |                             |                                                   | [139]     |
| Astrocytoma                          | 53                 | 100                    |                     |                     |                             |                                                   | [140]     |
| Glioblastoma                         | 126                | 76                     | 16                  |                     |                             |                                                   | [141]     |
| Advanced, relapsed brain gliomas, Phase II | 12            | 10                     | 25                  |                     |                             |                                                   | [142]     |
| Advanced, relapsed brain gliomas, Phase II | 24            | 55                     | 12                  | 25                  |                             |                                                   | [143]     |
| Brain glioma WHO III-IV, Phase I, safety prospective | 24 | 90.0 | 50.2 | 39 | 48.2 | 16.1 | [138] |
| Metastatic brain tumors study, Phase II | 15 | 99 | 46.2 | 73 | 48.2 | 16.1 | [139] |
| Head and neck study, Phase II | 64 | 92.2 | 26.1 | | | | [140] |
| Bone-metastases, monotherapy, Phase II | 6 | 100 | 47.1 | | | | [141] |
| Refractory bone-metastases study, Phase II | 11 | 90.9 | | | | | [142] |
| Kidney cancer study, Phase II | 11 | 84.8 | 35.0 | 48 | 78.4 | 33.7 | [143] |
| Urinary bladder cancer study, Phase II | 18 | 85.0 | 36.5 | 73 | 42.0 | 22.6 | [144] |
| Non-small cell lung cancer meta-analysis | 311 | 53.5 | 14.0 | | | | [145] |
| Passive arm                          | 258                | 67.0                   | 15.8                | 21                  | 53.4                        | 18.1                                              | [146]     |
| Active arm                           | 77                 | 17.9                   |                     |                     |                             |                                                   | [147]     |
| Advanced (WHO III)                   | 140                | 14.7                   |                     |                     |                             |                                                   | [148]     |
| Small cell lung cancer               | 28                 | 17.9                   |                     |                     |                             |                                                   | [149]     |
| Lung carcinoma study, Phase II       | 61                 | 87.2                   | 16.4                |                     |                             |                                                   | [150]     |
| Breast cancers                       | 103                | 97.1                   | 52.1                | 45                  | 274.8                       | 10.9                                              | [151]     |
| Soft tissue sarcoma study, Phase II  | 16                 | 100                    | 35.0                | 31                  | 115.3                       | 31.3                                              | [152]     |
| Esophagus study, Phase II            | 12                 | 41.7                   | 26.5                | 35                  | 29.4                        | 8.5                                               | [153]     |
| Esophageal study, Phase II           | 25                 | 8.8                    | 100                 |                     |                             |                                                   | [154]     |
| Liver metastases from various origin, Comparative study, Phase II | 25 | 26.5 | | | | | [155] |
| Liver metastases from various origin, Comparative study, Phase II | 25 | 26.5 | | | | | [156] |
| With radiotherapy                    | 15                 | 51                     |                     |                     |                             |                                                   | [157]     |
| With chemotherapy                    | 16                 | 81                     |                     |                     |                             |                                                   | [158]     |
| Monotherapy                          | 4                  | 25                     |                     |                     |                             |                                                   | [159]     |
| Liver metastases from colorectal origin, Phase II | 80 | 86.0 | 24.1 | | | | [160] |
| Passive arm                          | 53                 | 11                     |                     |                     |                             |                                                   | [161]     |
| Active arm                           | 89                 | 91                     | 24.1                |                     |                             |                                                   | [162]     |
| With chemotherapy                    | 59                 | 80                     | 21.5                |                     |                             |                                                   | [163]     |
| Monotherapy                          | 59                 | 92                     | 24.4                |                     |                             |                                                   | [164]     |
| Liver metastases from colorectal origin, Phase II | 5 | 25 | 80 | | | | [165] |
| Liver metastases from colorectal origin, Phase II | 15 | 25 | 80 | | | | [166] |
| Liver metastases from colorectal origin, Phase II | 22 | 28 | | | | | [167] |
Table 3. Summary of the studies made by oncothermia treatment (End-points are survival connected)

| Study                              | Number of patients | Complete remission (CR) [%] | Partial remission (PR) [%] | No change (NC) Stable disease (SD) [%] | Overall response (CR+PR+SD) [%] | Reference |
|------------------------------------|--------------------|-----------------------------|---------------------------|---------------------------------------|--------------------------------|-----------|
| Colorectal inoperable, liver metastasis | 60                 |                             |                           |                                       |                                 |           |
| CDDP                               | 28                 | 0                           | 3.57                      | 3.57                                  | 7.14                           | [166]     |
| OXALI                              | 32                 | 0                           | 15.63                     | 15.63                                 | 31.25                          |           |
| Ovary (relapsed, advanced epithelial) | 26                 |                             |                           |                                       |                                 |           |
| Heavily pretreated                 | 13                 | 0.00                        | 23.08                     | 38.46                                 | 61.54                          | [165]     |
| Not heavily pretreated             | 13                 | 30.77                       | 23.08                     | 38.46                                 | 92.31                          |           |
| General oncology                   | 277                | 21.50                       | 37.00                     | 58.50                                 |                                 | [167]     |
| TCM general oncology               | 306                |                             |                           |                                       |                                 |           |
| Oncothermia + TCM                  | 75                 | 6.67                        | 57.33                     | 26.67                                 | 90.67                          | [168]     |
| Oncothermia+TCM+i.v.CTx            | 65                 |                             |                           |                                       |                                 |           |
| Passive arm                        | 51                 | 7.84                        | 60.78                     | 15.69                                 | 84.31                          | [168]     |
| Active arm                         | 14                 | 14.29                       | 64.28                     | 21.43                                 | 100.00                         |           |

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Table 4. Summary of the studies made by oncothermia treatment. (End-points are response connected)

| Study                                             | Number of patients | Pain-reduction [%] | Increasing performances [%] | Better overall QoL [%] | Reference |
|---------------------------------------------------|--------------------|--------------------|----------------------------|------------------------|-----------|
| Colorectal inoperable, liver metastasis           | 60                 |                    |                            |                        |           |
| CDDP                                              | 28                 | 17.86              | 39.29                      | 57.14                  | [166]     |
| OXALI                                             | 32                 | 46.88              | 7.86                       | 100.00                 |           |
| Borrellosis                                        | 12                 | 100.00             | 100.00                     | 100.00                 | [176]     |
| Abdominal effusion + oncothermia                  | 49                 | 88.88              | 73.91                      | 85.70                  | [168]     |
Table 5. Summary of the studies made by oncothermia treatment. (End-points are quality of life connected)

| Study                          | Number of patients | Tumor-marker decrease [%] | References |
|--------------------------------|--------------------|---------------------------|------------|
| Colorectal inoperable, liver metastasis | 60                 | [166]                     |            |
| CDDP                           | 28                 | 14.29                     |            |
| OXALI                          | 32                 | 37.50                     |            |
| CRC liver Oxyplatin            | 12                 | 58.30                     | [155]      |
| CRC liver cisplatin            | 18                 | 5.60                      |            |

Table 6. Summary of the studies made by oncothermia treatment. (End-points are tumor-marker connected) Further clinical trials are in progress on advanced ovary, esophagus, breast, and pancreas tumors

**Conclusion**

Oncothermia is the cellular selective, highly effective nanoscopic heating of malignant cells. It is a feasible treatment for oncology in all phases of malignant diseases. This nanothermia application solved the uncontrolled controversies of the conventional hyperthermia in oncology. Numerous new ways of research can be initialized by the presently achieved results. Further basic research and clinical studies are in progress.

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