

Conference Paper

Essentials of Oncothermia

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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, which is clear in the different pathological patterns of the malignancy from their healthy counterparts. This last is described by fractal pattern evaluation technique, in 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.

1. 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 recently been 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 thermoradiation therapy [4]. The method was further developed in three various branches: the interstitial hyperthermia, including the galvanic heat stimulation, 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 LeVein et al. [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 [9–13].

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 microparticles [15] and ferrite rods [16], are usually injected into the targeted area [17]. Other inductive heatings are typically achieved without inclusion of extra magnetic material into the tumor; it uses only induction of Eddy currents [18–20]. The emerging applications of magnetic treatments were started by the nanoparticle 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 [27–30].

This rapidly emerging period was shadowed by skeptic opponents, which emphasized the increased dissemination of the malignant cells and so supported metastases by hyperthermia [31–33]. 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], and 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 to the neighboring volumes independently of how precise the focus of the energy is. The problem is the misleading aim getting uncontrollable temperature as dose and ignoring the physiological reactions of the patients. The published temperature patterns of the heating show well the problem: 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 was 4.2°C after 57 min, with as high power application as 1300 W [41]. The overall heating is obviously showing 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 ~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), and the necrosis in the tumor was 36 mL. The volume ratio of the body’s cross-section and the bolus shows that the bolus has 157% more cross-sectional area than the body. The applied frequency was 100 MHz in average. Its penetration depth is max. 5 cm, depending on the kind of the tissue. When the thickness of the bolus is in order of a few cm, the absorption of the incident energy remains in the bolus, and its cooling eliminates it. Other publications show the same problem of the heating [30, 42, 43]. Comparison of the clinical responses also clearly shows the problem of the bolus heating. The cases of nonresponders have higher bolus temperature, and the tumor is not heated [44, 45].

The same problems arise by typical capacitive coupling hyperthermia solutions. It pumps enormous energy also (1200 W) into the target, and rise of temperature was 4.8°C after 45 min. The selection by temperature between the malignant target and the nontargeted healthy tissue was approximately 1°C [46]. This large volume temperature rise was observed in other capacitive applications too [47].

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 [48]. 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 [49]. There are multiple other points that modify the temperature distribution in the body.

- (i) Not only do the temperature equalizing process but also the natural, technically nonfollowable movements of the patients (i.e., due to the breathing) modify the focus.
- (ii) The heat flow to the surroundings can damage the healthy neighborhood.
- (iii) The enlargement of the sphere having certain temperature gradients increases 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 uncontrolled. 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, and dissemination of the cells. The unwanted hot spots are created by the electromagnetic interferences and are uncontrollable with the dynamic changing of physiological parameters. These could be

TABLE 1: Collection of the studies (phase II) made by oncothermia in combination with various conventional oncotherapies. (Data are weighted averages of the study results.)

Study	Number of studies	Number of patients (<i>n</i>)	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of nonresponding 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	90.90		
Liver metastasis	7	267	86.00	18.06	80.00		
Colorectal	7	447			63.18	109.80	23.20
Gynecology (pelvic)	5	100	93.22	33.25	44.82	89.36	21.70
Breast	1	103	97.10	52.10	45.00	274.80	10.90
Esophagus	2	19	41.70	55.64	35.00	29.40	8.50
Stomach study	1	68	58.90	14.40			
Kidney cancer	1	39	84.60	35.90	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	38.80	72.00	53.40	7.60
SUM	54	2796			51.63		

TABLE 2: Collection of the miscellaneous studies made by oncothermia in combination with various other therapies.

Miscellaneous study	Number of patients (<i>n</i>)
Borreliosis	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

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, decreasing 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 supporting 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 [50]; 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 "autosuggestion" 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 the correct heating and control of the hyperthermia process. For this we have to precisely select the malignant cells and 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 is that it does not stimulate the blood-flow as physiologic feedback, consequently no contra-action starts to compensate the applied nanoscopic effect. Furthermore, the membrane excitation could excite special cellular signal-transduction pathways, which are connected with the natural

TABLE 3: Summary of the studies made by oncothermia treatment (end points are survival connected).

Study	Number of patients	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of nonresponding patients (m)	Reference
Brain gliomas	27	86.2	23.6	43	66.2	18.2	[51, 52]
Brain lioma study, phase II	140	71.7					
Astrocytoma	40		25.8	80	40.2	20.2	[53, 54]
Glioblastoma	92		16	73	21.*9	13.1	
Diffuse astrocytoma	8		52.9				
Glioma (WHO IV) study, phase II, prospective, two arms	45		15				
Passive arm	36	40	11				[55, 56]
Active arm	9	65	14.5	43	66.2	18.2	
Recurrent glioblastoma study, phase II	19	68.0	21.8	59	32.6	12.4	[57]
Glioma study, phase II	36	60.0					
Astrocytoma	9		106				[58]
Glioblastoma	27		20				
Glioma study, phase II	179						
Astrocytoma	53	100	103				[59]
Glioblastoma	126	76	16				
Advanced, relapsed brain gliomas, phase II	12		10	25			[60]
Advanced, relapsed brain gliomas, phase II	24	55	12	25			[61]
Brain glioma WHO III-IV, phase I, safety prospective	24						[62–65]
Metastatic brain tumors study, phase II	15	90.0	46.2	73	48.2	16.1	[60]
Head and neck study, phase II	64	92.2	26.1				[55, 66]
Bone-metastases, monotherapy, phase II	6	100	40.1				[55, 66]
Refractory bone-metastases study, phase II	11			90.9			[67]
Kidney cancer study, phase II	39	84.6	35.9	48	78.4	33.7	[55, 66]
Urinary bladder cancer study, phase II	18	85.0	36.5	73	42.0	22.6	[55]
Nonsmall cell lung cancer meta-analysis	311						
Passive arm	53	26.5	14				
Active arm	258	67.0	15.8	21	53.4	18.1	[68]
Nonadvanced (WHO < III)	77		11	17			
Advanced (WHO ≥ III)	140		14.7	88			
Small-cell lung cancer	28						
Passive arm	9	29					[69]
Active arm	19	58					

TABLE 3: Continued.

Study	Number of patients	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of nonresponding patients (m)	Reference
Lung carcinoma study, phase II	61	67.2	16.4				[55, 70]
Breast cancers	103	97.1	52.1	45	274.8	10.9	[55, 66]
Soft tissue sarcoma study, phase II	16	100	35.9	31	115.3	31.3	[55]
Esophagus study, phase II	12	41.7	28.5	35	29.4	8.5	[55, 71]
Esophagus study, phase II	7		6.8	100			[72]
Liver metastases from various origin, phase II	25		20.5				[73]
Liver metastases from various origin, comparative study, phase II	28						[67]
With radiotherapy	16			81			
With chemotherapy	8			38			
Monotherapy	4			25			
Liver metastasis form colorectal origin, phase II	80	86.0	24.1				
Passive arm		53	11				
Active arm	80	91	24.1				[74]
With chemotherapy	30	80	21.5				
Monotherapy	50	92	24.4				
Liver metastasis form colorectal origin, phase II	15		23	80			[75]
Liver metastasis form colorectal origin, phase II	22		28				[76]
Liver metastasis	29			86			
Liver metastasis form colorectal origin, phase II	30		22				[77]
Pancreas tumor study, phase II	26	46.2	11.6				[78]
Pancreas tumor study, phase II	107						
Passive arm	34		6.5				[70]
Active arm	73	52.1	9.93	58	25.5	8.4	
Pancreas tumor study, phase II	30	31.0		41	34.4	5.6	[79, 80]
Pancreas tumor study, phase II	42	52.4	12.3				[81]
Pancreas tumor study, phase II	13	40.0	11.9				[82]
Stomach cancer study, phase II	68	58.9	14.4				[55]

TABLE 3: Continued.

Study	Number of patients	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of nonresponding patients (m)	Reference
Colorectal cancer ()	218	84.9	28.5				
Sigma	12			34.1			[55, 66]
Rectum	92			57.1	58	21	
Colon	114			44.2	109.8	23.2	
Colon cancer study, phase II, prospective, three arms, randomized	154						[83, 84]
Clifford TCM	53			75			
Monotherapy	50			81			
Combined therapy	51			91			
Rectum cancer study, Inoperable → operable, phase II	7			71			[72]
Rectal cancer, nonoperable, phase II	65			96			[85]
Pelvic gynecological cancer studies, phase II	74						[86]
Cervix	38	86.8	27.6	25	63.5	20.9	
Ovary	27	100	37.8	67	132.7	19.4	
Uterus	9	100	61.5	62	68.5	32.0	
Ovary, advanced, relapsed	26						[87]
Heavily pretreated	13		14.3				
Not heavily pretreated	13		27				
Prostate cancer study, phase II	18	88.9	38.8	72	53.4	7.6	[71]

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 to 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 (nonhomogeneities) are the driving forces of the dynamic processes in case of microscopic (nonhomogeneous) heating. The average temperature does not inform us about the distribution of the real energy absorption (see Figure 1).

Smaller targets with precise selection could get propositionally higher temperature keeping the average constant. The nanorange heating is the basic of oncothermia, allowing extreme heating at the membranes of the malignant cells while the average temperature does not increase as high as the physiological feedback starts to support the malignancy by higher blood flow reactions.

2. 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 following.

- (i) The absorbed energy by the tissues transfers 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 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 that not only a 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 a 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

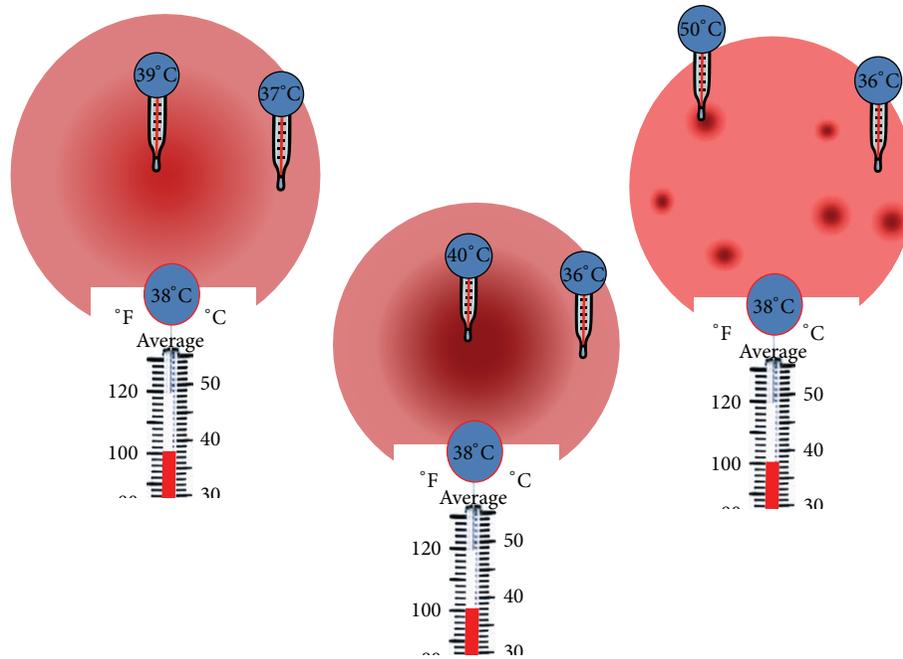


FIGURE 1: The average temperature is not able to characterize the thermodynamic situation. The internal temperature differences could serve as driving forces of various processes on the same average temperature of the system.

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 a correct microscopic targeting, using the cell-by-cell energy absorption efficiently.
- (iii) Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- (iv) Apply a mechanism, which carries the information that disseminated cells are to be blocked.

Oncothermia changes the paradigm of local hyperthermia in oncology to solve the above problems [88]. This hyperthermia technology heats nonequally, concentrating the absorbed energy to the extracellular electrolytes [89]. This method creates inhomogeneous heating, and microscopic temperature differences are far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes and ignites signal pathways for naturally programmed cell death, avoiding the toxic effects of the simple necrosis. The synergy of electric field with the thermal effects successfully and selectively does the job [90]. Oncothermia uses nanoheating technology to select and heat the membrane of the malignant cells effectively. The heating is concentrated mostly on the cell membranes, so the nanorange energy liberation could be precisely controlled without considerable wasted energy and without having disadvantages by the heating of the tumor environment on 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.

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 more 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 [91] 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 (RF) current flows through the targeted lesion; see Figure 3.

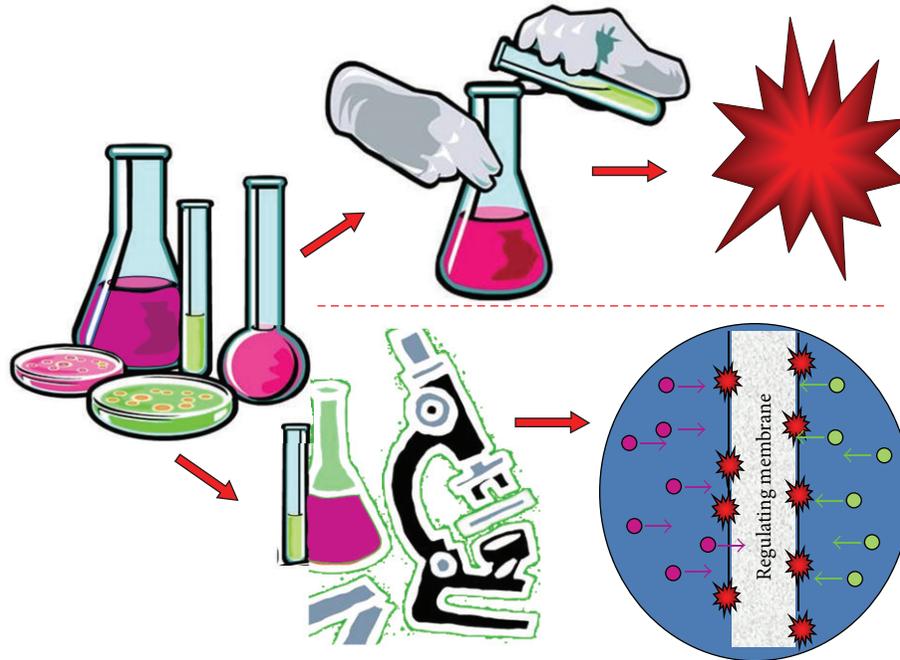


FIGURE 2: The difference of macro- and micro-liberation of energy. The efficacy of the last one is much better.

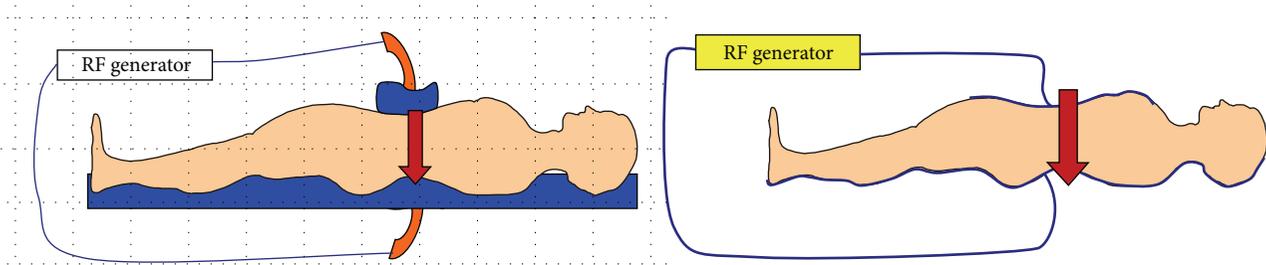


FIGURE 3: Oncothermia setup. The cell culture/animal/human is a part of the electric circuit. Energy is carried by 13.56 MHz RF current (fractal modulated): (a) EHY2000 local/regional treatment, (b) EHY3000 multilocal treatment.

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.

- (i) It is a free frequency for medical applications in hospitals and clinics, as well as in general use, for example, RF identification.
- (ii) It is in the range of the beta dispersion which is one of the selection factors of oncothermia.
- (iii) It is low enough to have long wavelength for near-field use with high penetration into the body when the impedance matching [92] is fixed.
- (iv) It is high enough to be modulated by time-fractal fluctuations.

The discussion of all these behaviors are 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, that is, those current paths are favored which include malignant cells are favoured. 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 normal. While the dominance of the mitochondrial ATP production in the healthy tissue produces 36 ATP from one glucose molecule during the complete cycle, the fermentative ATP production, which dominates the metabolism of malignant cells, results only two ATPs

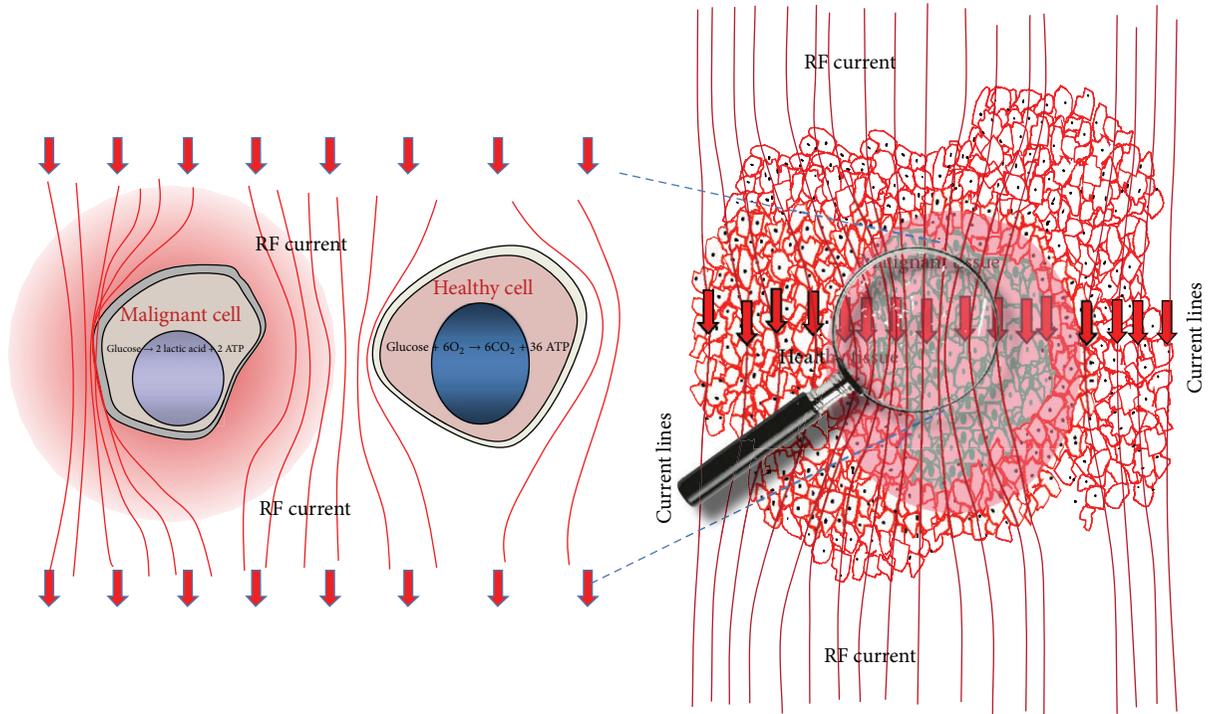


FIGURE 4: The radiofrequency current is focused on the tumor lesion and microscopically flows in the extracellular electrolytes around the malignant cells.

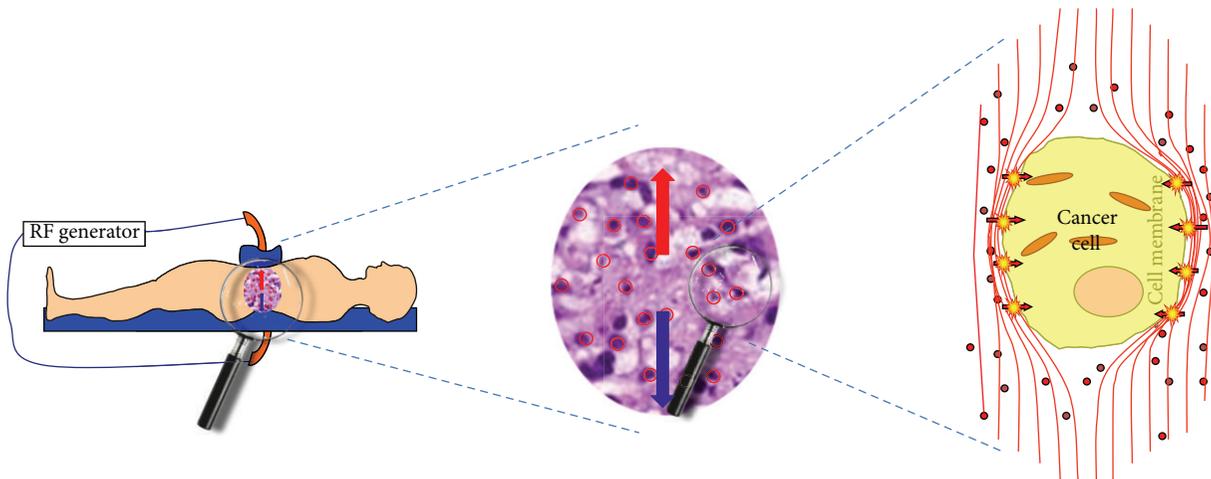


FIGURE 5: The microscopic heating of the extracellular electrolyte around the malignant cells excites the membrane and makes temperature gradient in a few nanometer distance.

from one glucose molecule [93]. 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, lactates in the vicinity of the malignant cells, and 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 [94], by simple impedance measurements *in vitro* [95] and *in vivo* too [96].

This gives us a possibility to distinguish the malignant cells automatically and individually (Figure 5). This automatic focusing makes it possible to follow any movements (breathing, heart beats, and muscle movements) in the target tissue, and the current density follows it.

The above selection is based on the conductive component of tissue impedance. The permittivity component is also

selective. Malignant cells not only differ from their healthy counterpart by their metabolic processes, but also 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 [97]. 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 [98–101]. On the contrary, the malignant cells have no such order in their immediate extracellular connections (Figure 6). The disorder increases the electric permeability of the electrolyte near the malignant cells [102]. 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, [103, 104].

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

- (i) 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^+ and Na^+ transport, so the membrane potentiating weakens [105].
- (ii) The cellular membrane of cancerous cells differs electrochemically also from the normal, and its charge distribution also deviates [106].
- (iii) The membrane of the cancerous cell differs in its lipid and sterol content from its healthy counterpart [107].

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 water transport from the cell. Consequently, the cell swallows, and its membrane potential decreases further [119]. (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 in average [120]. This fact was well used for direct current treatment (electrochemical cancer therapy (ECT)) by Nordenstrom [121, 122] and others [123–125].

There is further selection based on complex impedance, the β -dispersion [126] (Maxwell-Wagner effect) [127]. The bound water to the membrane has the upper part of the β -dispersion (denoted by δ [128]), which has further selection role in oncothermia. The treatments have to be chosen in the frequency range of β -dispersion, promoting it with amplitude modulated pink noise, expecting most of the changes in the complex system [129]. The carrier frequency and its modulation are selected by the membrane properties difference between the malignant and healthy cells [130–132].

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 [133],

and 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 field strength. (The membrane is a good isolating lipid (fatty) layer). The membrane disruption is one of the targeted aims [134–136], as well as many research groups are dealing with the electric field action on the cellular divisions [137–140]. 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, and 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 ($1/1000^\circ C$) difference between the inner and outer temperatures 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: $\sim 200,000^\circ C/m!$ The system is far from thermal equilibrium [141]. 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 [142]. This creates an extreme SAR between the cells, which makes temperature gradient through the membrane [89]. The treated tissue will be inhomogeneously heated; heat flows from extracellular to cytosol through the membrane, accompanied with definite other thermodynamical and chemical changes [89]. These definite thermal currents will be continued till the extra- and intracellular temperatures reach equilibrium, so the intracellular electrolyte is heated up to the equal level (see Figure 7(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 [89]. This simple method allows easier cell destruction by oncothermia (see Figure 8), similar to the well-known catalytic reactions.

The missing connections (adherent bonds, junctions) not only are selected by the dielectric properties of the cells but 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

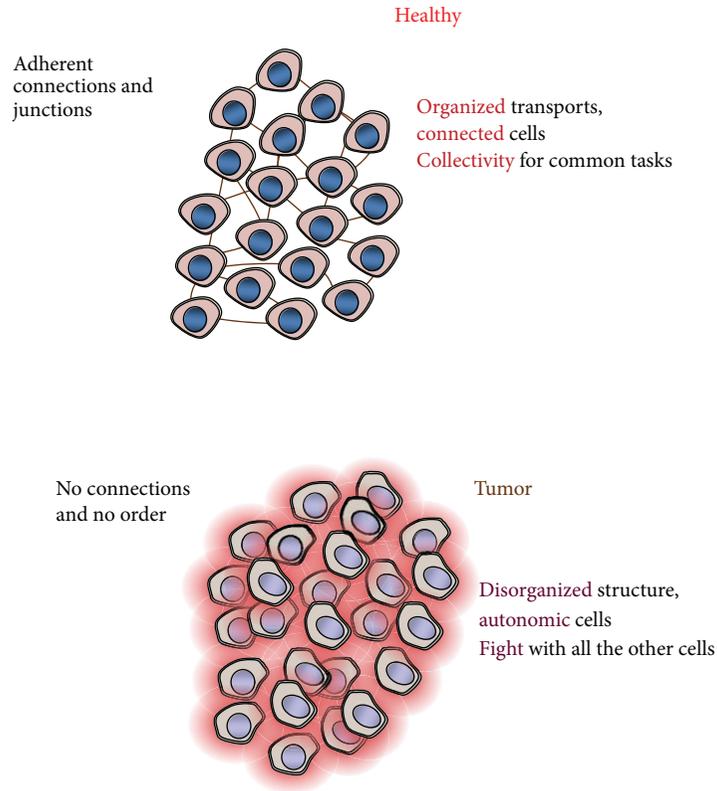


FIGURE 6: The difference of the healthy and malignant tissues is well observable by their organization structure.

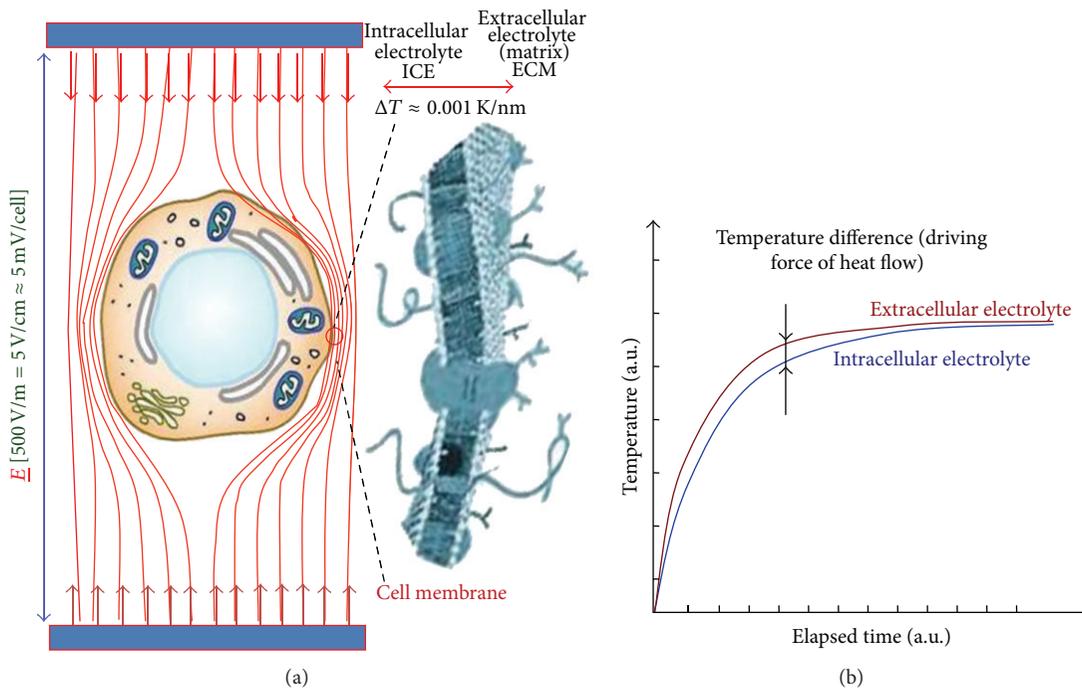


FIGURE 7: Oncothermia delivers its energy mainly into the extracellular electrolyte, creating a temperature gradient through the cellular membrane (a). The thermal gradient action due to the nonhomogenous heating is active until the thermal equilibrium equalizes the temperature (b).

TABLE 4: Summary of the studies made by oncothermia treatment. (end points are response connected.)

Study	Number of patients	Complete remission (CR) [%]	Partial remission (PR) [%]	No change (NC), stable disease (SD) [%]	Overall response rate (CR + PR + SD) [%]	Reference
Colorectal inoperable, liver metastasis	60					
CDDP	28	0	3.57	3.57	7.14	[108]
OXALI	32	0	15.63	15.63	31.25	
Ovary (relapsed, advanced epithelial)	26					[87]
Heavily pretreated	13	0.00	23.08	38.46	61.54	
Not heavily pretreated	13	30.77	23.08	38.46	92.31	
General oncology	277		21.50	37.00	58.50	[109]
TCM general oncology	306					
Oncothermia + TCM	75	6.67	57.33	26.67	90.67	[110]
Oncothermia + TCM + i.v.CTx	65					
Passive arm	51	7.84	60.78	15.69	84.31	[110]
Active arm	14	14.29	64.28	21.43	100.00	
Oncothermia + TCM + abdominal perfusion	87				0.00	
Passive arm	45	2.22	40	24.44	66.66	[110]
Active arm	42	7.14	54.76	26.19	88.09	
Oncothermia + TCM + bladder perfusion	37					
Passive arm	24	0	50	12.5	62.50	[110]
Active arm	13	7.69	53.85	30.77	92.31	
Oncothermia + TCM + RTx	42					
Passive arm	30	3.33	50	16.67	70.00	[110]
Active arm	12	8.33	66.67	16.67	91.67	
Abdominal effusion + oncothermia	49	4.08	53.06	16.38	73.52	[110]
Chronic pelvic inflammation	283					[111]
Passive arm	143					
Active arm	140	46.10	29.40	19.60	95.10	
Chronic bronchitis, TCM + oncothermia	35	30.00	24.30	25.70	80.00	[111]
Colon cancer study, phase II, prospective, three arms, randomized	154					[110]
Clifford TCM	53	5.7	28.3	18.9	52.90	
Monotherapy	50	10	26	26	62.00	
Combined therapy	51	13.7	45.1	23.5	82.30	
Colon operability	7	71			71.00	[112]
Prostatitis	72					[111]
Passive arm	36	16.70	27.80	19.40	63.90	
Active arm	36	41.70	36.10	22.20	100.00	
Prostate study	184	49.5	15.2	15.8	80.50	[113]
Prostate cancer (Kleef) (Gleason Score 2–6)	16					[114]
Oncothermia + hormone therapy	8				50	
Oncothermia monotherapy	8				37.5	

TABLE 4: Continued.

Study	Number of patients	Complete remission (CR) [%]	Partial remission (PR) [%]	No change (NC), stable disease (SD) [%]	Overall response rate (CR + PR + SD) [%]	Reference
Prostate cancer (Kleef) (Gleason Score 7–9)	17					[114]
Oncothermia + hormone therapy	11				81.82	
Oncothermia monotherapy	6				33.33	
Peyronie’s disease	25				100	
Pancreas	42		23.8	31	54.80	[81]
Pancreas	30	3.3	33.3	40	76.60	[79, 80]
Esophagus		8	50	42	100.00	[72]
CRC liver	22	5		23	28	[76]
CRC liver	15		20	60	80.00	[75]
CRC liver oxalplatin	12				8.3	[77]
CRC liver cisplatin	18				27.8	
Advancer liver	28					[67]
Oncothermia + RTx	16		31	50	81	
Oncothermia + CTx	8		13	25	38	
Oncothermia monotherapy	4			25	25	
Brain	19		11	32	43	[57]
Asthma	7		75	10	85	[115]
Small-cell lung cancer (SCLC)	38		44.7	15.8	60.5	[116]
Benign tumors oncothermia + TCM	35	54.3	25.7		80.00	[111]

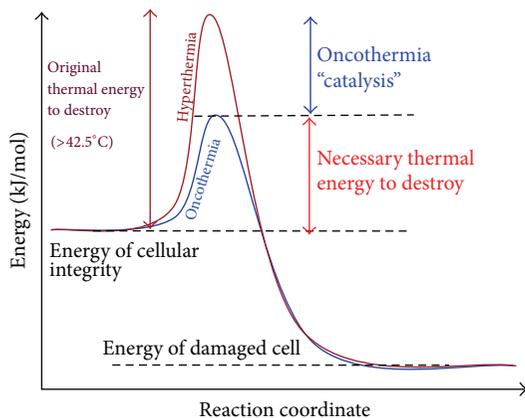


FIGURE 8: Oncothermia needs less thermal energy to make the same distortion than the classical hyperthermia does.

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 [143]. This effect helps suppress the metastatic dissemination

as well as promote the intercellular signals to activate the natural cell-killing mechanisms. Not only the heating makes the effect, but also the electric field itself has a strong synergy with this [144].

An important and unique specialty of oncothermia is the modulation of the carrier frequency. This time-fractal pattern carried by the basic frequency distinguishes on similar way as the pathological evaluation does. The famous Adey window was the first proof of the special modulation effects [145, 146], published in the early 1990s. The modulation of RF-carrier frequency started to be used [147] and became an important new method for cancer therapies [148]. Numerous clinical results show its efficacy [149–154], and oncothermia applied it from its very beginning. Biopsy specimens are evaluated by pattern recognition of the experienced pathologist. One of the modern pattern descriptions is measuring the fractal dimension of the actual pattern. The malignancy has characteristic fractal dimension differences, and the cancer has its own fractal structure [155]. The analysis of fractal structures could even indicate the stage of the disease [156]. Careful fractal analysis can make predictive information, making a significant prognostic value [157].

The fractals in patterns are accompanied by fractal dynamics. This new discipline is the “Fractal Physiology,” ([158–161]), which has a fundamental role in the structure of the healthy organism and is a basic of the self-similarity in biology, which is well recognizable in the scaling behavior of

TABLE 5: Summary of the studies made by oncothermia treatment. (end points are quality of life 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	[108]
OXALI	32	46.88	7.86	100.00	
Borreliosis	12		100.00	100.00	[117]
Abdominal effusion + oncothermia	49	88.88	73.91	85.70	[110]
Colon cancer study, phase II, prospective, three arms, randomized	154				[110]
Clifford TCM	53	37.7	13.73	58.49	
Monotherapy	50	36	23.53	60	
Combined therapy	51	58.8	62.75	86.28	
Prostate study	184				[113]
Prostate study	115		76.2	94.1	[118]
Colon operability	7		86	43	[112]
CRC liver	15				[75]
CRC liver oxaliplatin	12	66.7		83.3	[77]
CRC liver cisplatin	18	11.1		27.8	

TABLE 6: Summary of the studies made by oncothermia treatment. (end points are tumor-marker connected.)

Study	Number of patients	Tumor-marker decrease [%]	References
Colorectal inoperable, liver metastasis	60		[108]
CDDP	28	14.29	
OXALI	32	37.50	
CRC liver oxaliplatin	12	58.30	[77]
CRC liver cisplatin	18	5.60	

the living objects [162–164]. 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 that easily absorbs it as well. So the applied modulation helps localize the tumor boarder, helps “clear” the contours, and (most importantly) helps 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 switch off this modulation also. Why? Because you must not use the modulation in the sensitive organs (like the brain) from the very beginning. It makes 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 take very much care in brain, spinal cord, and head and neck cases. In nontumorous applications the modulation has no role at all.

The fractal modulation which is applied by oncothermia selects and reestablishes 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 treatments cause the same effect immediately after the application; however a day later definite differences appear. The treated lesion by nonmodulated signal started regrowth; the ratio of dead volume in the tumor decreases. At the same time the modulated treatment caused the opposite: the dead volume increases, and in two days the complete tumor was almost destroyed after a single shot treatment reaching 42°C in average in both the modulated and nonmodulated cases.

Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat flow on the membrane supported by the electric field effects). It is natural, it is not against the homeostasis, and physiology does not work against the action [165]. The main task is to direct the physiology in the standard way and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium, have to be stopped.

3. 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 papers presented in this conference [166–173], so I summarize the clinical results only. Remarkable amounts of retrospective and prospective clinical studies are available to indicate the oncothermic effect in humans [174, 175].

62 studies were performed with altogether 3790 patients, from six countries (Hungary, Germany, Korea, China, Italy, and Austria) [176]. The collection outlook is shown in Tables 1, 2, and 3.

The survival time connected data, response rate connected data, the quality of life connected data, and tumor-marker connected data are collected in Tables 4, 5, and 6, respectively.

Further clinical trials are in progress on advanced ovary, esophagus, breast, and pancreas tumors.

4. Conclusion

Oncothermia is the cellular selective, highly effective nanoscopic heating of malignant cells. It is a feasible treatment for oncology in all the phases of malignant diseases. This nanothermic 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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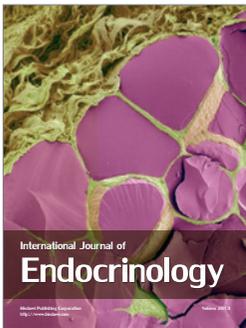
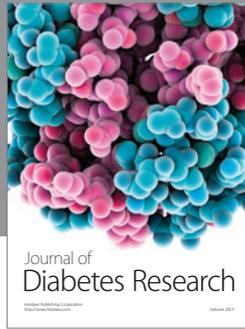
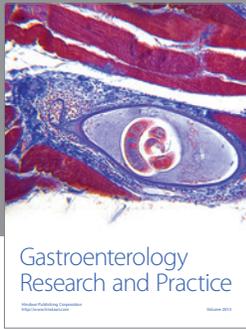
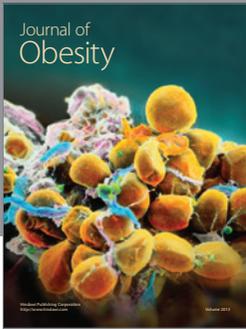
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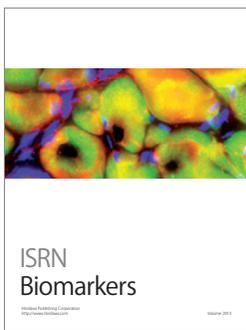
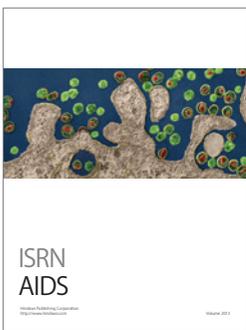
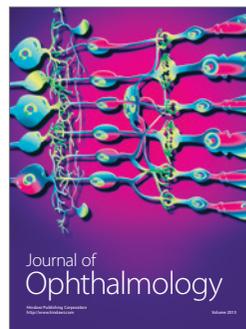
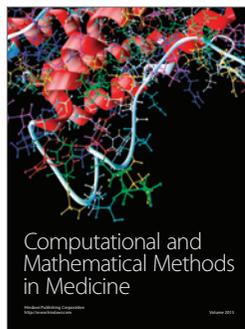
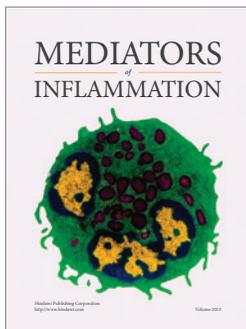
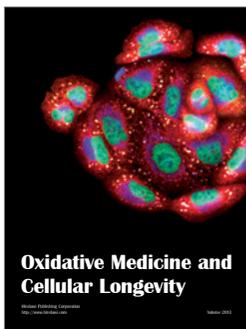
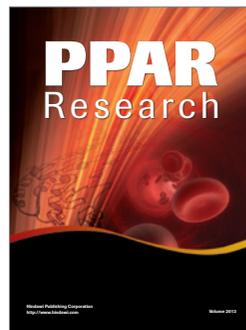
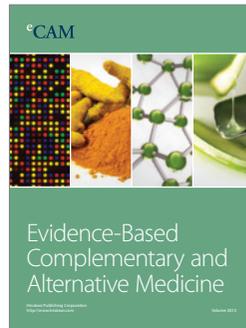
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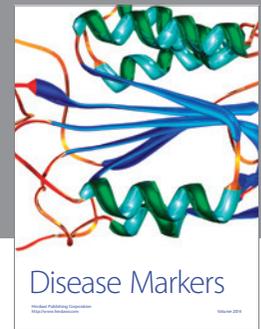
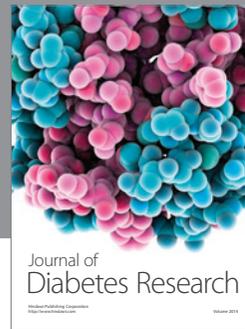
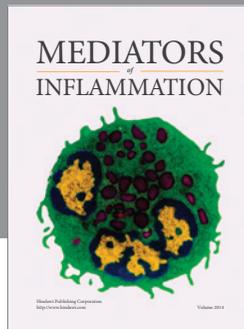
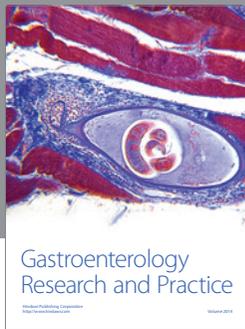
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