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The Capacitive Coupling Modalities for Oncological Hyperthermia

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Abstract

The local-regional oncological hyperthermia has various electromagnetic methods for energy-transfer. The differences involve conceptual considerations and technical solutions. The most frequently applied energy transfer is capacitive coupling, concentrating the electric field to be the active heating component. The realization of the capacitive coupling set-up is divided into two different categories based on their goals for heating: 1) the homogeneous (conventional) heating, using isothermal conditions for dosing, and 2) the selective heterogeneous heating, using cellularly absorbed energy for dosing. The homogeneous heating utilizes plane-wave matching, absorbing the wave for energy transfer. The heterogenic heating uses impedance matching, selecting the malignant cells by their electromagnetic specialties, like their heterogenic impedance, higher membrane-raft density, and different spatio-temporal (pathologic pattern) arrangements. This article's objective is to compare and discuss the details of the two kinds of capacitive coupling techniques.

Keywords

Plane-Wave Matching, Impedance Matching, Apoptosis, DAMP, ICD, Selective Heating, Electromagnetic Heterogeneity, Membrane Raft

1. Introduction

1.1. Strategy in the Fight against Cancer

Life is based on energetically open systems, where environmental conditions determine their equilibrium. The general system's theory [1] was one of the early efforts to show the complexity of open living systems focusing on the deep embedment of its processes in the environmental interactions. Due to the environmental actions, the physical laws work well to explain the evolutionary processes

[2]. The energetically open living system intensively interacts with its environment, exchanging molecules and various thermodynamic and electromagnetic parameters. Simply speaking: our focus differs from living motility to the energy-transfer. A. Szent-Gyorgyi described the life-energy relationship using the analogy that it is not important that the monkey goes through the jungle, what is important is how the jungle goes through the monkey, in the form of nutrition, water, and oxygen, keeping the monkey alive using the environmental energy-sources [3]. The living system is complexly controlled, to maintain homeostasis. Diseases, especially cancers, break the relative equilibrium and risk the system's relative instability. The human body tries to re-establish homeostasis in many ways by enhancing the negative feedback controls. Multiple actions of human physiology try to compensate and correct the damage caused by cancer.

Healthy homeostasis struggles to control the malignancy. The first few attempts block the proliferation and start intracellularly controlling the DNA replication. It fails for various reasons, including genetic aberration [4], mitochondrial dysfunction [5], or other intracellular [6], and additionally extracellular [7] hallmarks of malignancy.

The malignancy in this general meaning is a distortion of the healthy cellular network, the rules of a multicellular organization being broken. The breaking of cellular networks is a general behavior of all tumors independent of their locations within the body. In this sense, cancer is an organizing (networking) disease, where the cells unleashed from their networks abandon the living advantages of collectivism, and individualism prevails [8]. Cancerous and bacterial proliferations have a lot in common [9]. The tumor itself has atavism qualities [10], in the sense that the malignant cells act like self-ruled unicellular organisms. The atavism-like process is general, not only with the loss of cellular connections but also with the altered intracellular genetic structures. The unicellular individualism develops the great potential for adaptability to environmental changes, making these cells more vigorous than those in the multicellular network. The modified genetic activity at the active boundary between unicellular and multicellular areas, causes disorganization of the multicellular structure, promoting primitive transcriptional programs [11]. However, the similarity with atavism is only formal. The atavistic development is supported by the environment which is rich in energy-resources needed for the proliferation. Still, the active use decreases the valuable matter around the bacteria, and only some physical processes (like diffusion, flows in aqueous solution, etc.) may passively replace the missing materials. In cancer conditions, the proliferating cell actively changes its environment, forcing the healthy host to supply the needed materials [12]. The cancer is afforded a friendly environment by the host, which tries to "heal" the abnormality by strengthening angiogenesis, injury current, and numerous other supportive mechanisms. There are telling arguments for the likening of the cancerous process to wound repair [13]. The bio-system falsely recognizes the tumor—as a wound and stimulates its environment to heal the irregularity (meaning to produce cells to heal) [14].

We are in a war against this disease [15]. The end of this war seems to be far away [16]. This war's strategic decision may be borrowed from the military: attack the enemy's weakest point, and avert to direct fight with its strongest forces. The most vital force of the malignancy is its uncontrolled proliferation, while the weakest side is the autonomy of the proliferated cells, and their isolation from the regular cellular network. The cooperation of the healthy cells regulates, controls, and supplies the members of the network. The malignant cells are "individual fighters" competing against all healthy and malignant cells for the energy sources to proliferate. This "loneliness" behavior makes the malignant cells vulnerable. They miss the complex support from the network. The missing network otherwise helps the proliferative development due to the easy motility and forming micro and macro metastases. Following this strategy, the final aim of cancer treatments is to eliminate the cancer cells throughout the body.

1.2. Some Tactical "Weapons"

To follow the strategic goal to attack the malignant cells' individualism, we have multiple "tactical" possibilities to choose from. The lack of coherence and support it in the network modifies the cells and their microenvironment. This modification could be used to select and kill the cells. The most characteristic changes are a result of the cells' autonomy:

- The individual cells are more vulnerable than the cells connected via the network. Healthy cells may share their extra absorbed energy with the neighbors, while the autonomous cells are at risk of being overloaded by the absorbed energy can be overloaded.
- The autonomy means that the cell's microenvironment is like an ocean around it, only with a few, if any, connections. The molecular "bridges" that made the bonds in the network are broken, and numerous transmembrane proteins remain unconnected and free to move along the membrane and form clusters.
- A large part of the homeostatic control is missing due to the autonomy, and the cells live unregulated. This allows the use of metabolic mechanisms which are rare in networked systems. The mitochondrial symbiosis with the cell has less importance and becomes mostly dysfunctional.
- The autonomy promotes cellular motility that uses the transport systems (lymph and blood), and once separated from the group, these cells more vulnerable.
- Consequently, the energy-demand massively increases in malignant cells as the cells require the extra energy to produce the daughter cells and to support the entire division process.
- The basic chemical reactions are out of systemic harmony. The long-range, and broadly scaled fluctuation and constant multiscale entropy is broken by autonomy, producing easily distinguishable fluctuations (noises) in measurable electromagnetic signals.

The above points are interconnected, and the "tactical actions" could affect many of them simultaneously. Some of the popularly applied treatments are as follows:

- Change the conditions by special, strict diets (like Gerson's diet), constraining the body back to the previously working equilibrium. However, in many cases, it works against the natural homeostasis; the constrained action induces new negative feedbacks from the living object. The living organism starts to fight against our constraints together with the fight against the disease itself, which unnecessarily overloads the controlling system and could lead to its collapse, causing serious side effects.
- An interesting tactic is to put out the fire with fire. This method increases the already significant metabolic rate of the malignant cells without allowing an increased delivery of the supplies. This was the original idea of hyperthermia: to locally heat the malignant tissue, and force the cells' metabolism, without allowing the replacement of the energy. This method is against the general physiological control, which is governed the blood-flow. The higher local temperature increases the blood-flow to cool-down the targeted volume. The extra blood delivers nutrients, and oxygen, so the method could easily turn in the opposite direction.
- Some proposed treatments favor fasting or supplying the body with only one kind of nutrient, like blocking carbohydrates' consumption and expecting that the limited supply will starve the malignant cells.

The above treatments do not work, mainly because the living complexity does not isolate one of the other's dynamic characters, so the action easily turns to the opposite. The general problem with these is proposed methods is that the complexity is not accounted for in the applied principles, the principles involve oversimplified mechanisms, due to the lack of complex knowledge. This problem is well formulated by a playwriter Berthold Brecht: "The aim is not to open the door to the infinite wisdom, but to circumscribe the infinite fallacy… The main reason for the poverty in science is the conceited property." [17]. The physicist Stephan Hawking formulated the same: "The greatest enemy of knowledge is not ignorance, it is an illusion of knowledge".

The dark-side of the tactical elements is the multiple quackeries distributed by social media. This approach uses the "formal knowledge" of the complexity, declaring their method as a special secret, which drives the complex processes. This could be characterized by the statement of Frederici Di Trocchio "Swindle was used to art. Nowadays, it became a science too…" [18].

1.3. Oncological Hyperthermia

Hyperthermia in oncology appeared in ancient medicine. Today heating processes for medical purposes have become a vital "home remedy", from the sun-bathing to the hot-bathes, including the Japanese high-temperature bath and Finish sauna. Hippocrates first described the application of heat in oncology

in European medicine. The use of heat therapy to cure cancer has since emerged in various settings in the medical field. The appearance of electromagnetism in medicine renewed the heating efforts, and extended the applications for various cancers. Two main categories divide the electromagnetic-based heating applications: the local deep heating which results in local-regional hyperthermia (LRHT), and the whole-body hyperthermia (WBH). Just as the categories of chemotherapy and radiotherapy include many different modes of treatments, "hyperthermia" is also a large category with different technical aspects. Figure 1 maps the main differences between the technical solutions.

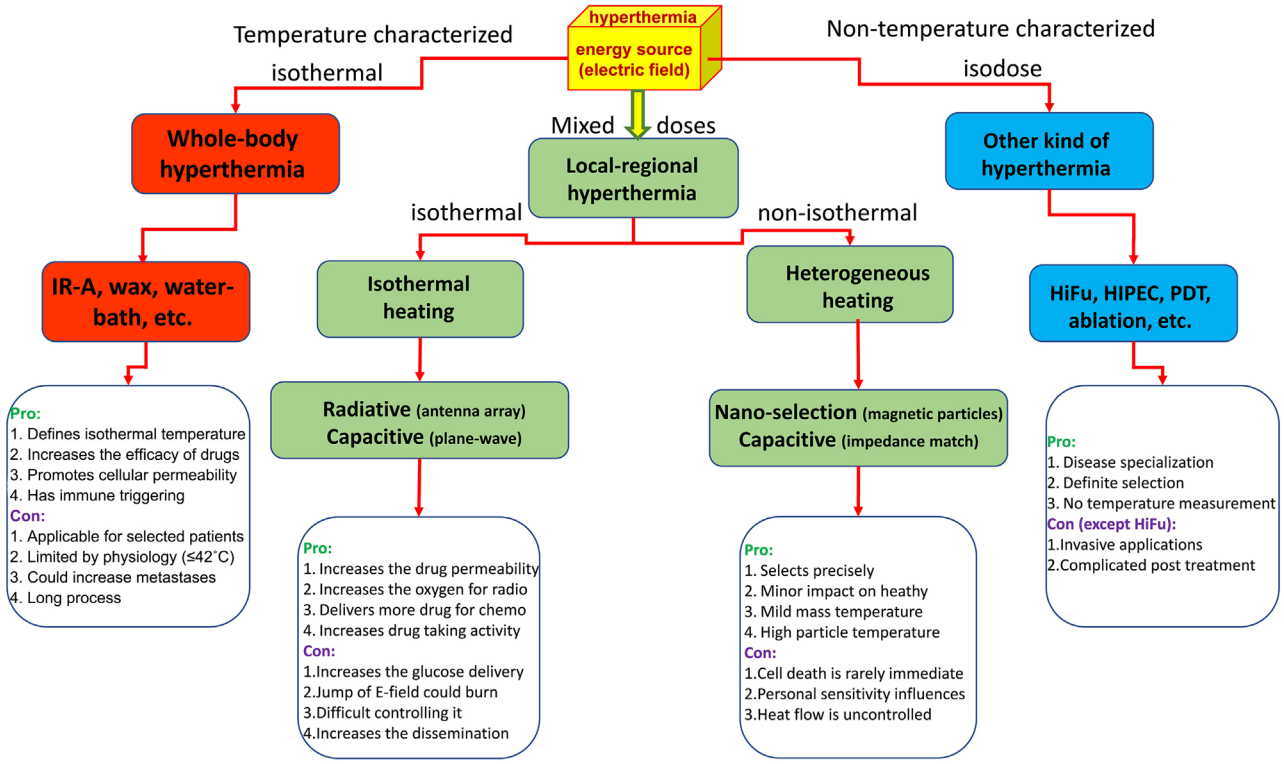

Figure 1. The major categories of hyperthermia methods.

The relatively simple physical-physiological heating concepts do not mean a simple application in humans. The complexity of human physiology, and the non-linear feedbacks of the homeostatic regulation, limits the heating possibilities. Despite the proven *in vitro* benefits of heating in cancer treatment, the clinical results have strongly demonstrated how the control of treatment is often influenced more by the human body than by the treatment intention. This complication made the development of oncologic hyperthermia non-monotonic, having both great successes and failures [19]. It was clear from the beginning of oncological applications that the real, local cell-distortion must have a high temperature, higher than the physiological limit of 42˚C. However, this limit restricts the high temperature application of WBH which has moved towards mild temperature range, promoting the reactivation of the immune system. Contrary to WBH, LRHT does not limit by the temperature in the tumor. When the high

temperature targets the healthy host tissues around the tumor, it could produce unintended necrotic burns with serious damage to the treated organ's function.

Consequently, the energy absorption during the heating process significantly depends on the technique applied. No unified protocol for the various technologically determined targets of the heat has currently been described.

The category "hyperthermia" includes various energy-absorption methods, and each individual solution requires its own protocol. It is very similar in this regard to the chemo-variants of oncological therapies. Chemotherapy, depending on the targets of the drug, has different protocols. Mixing these could cause serious adverse effects and even fatal events such as poisoning. Homogeneous targeting in most of these therapies requires very different protocols to the local or cell-sensitive selection. For example, chemotherapy is administered intravenously (i.v.), at different doses to the doses administered with chemoembolization or other types of local administration. Isodose homogeneity, as in radiotherapy, is also not used in most brachytherapies, radiation seed, or nanoparticle administration. We are sure that the hyperthermia variants also have specific differences in their dose and protocol, sharply depending on their technical solution and targeting method. Defining a general dose and protocol for all hyperthermia methods is a misleading request. The methods are not equal. Their effects are different, so the dose and protocol have to fit the specific situation.

The heating techniques determine the result of the clinical treatment. Just as the categories of chemotherapy or radiotherapy, which include many different treatments, "hyperthermia" is also a large category with different technical aspects. We have seen that exposing the tumor to 42˚C in whole-body hyperthermia has entirely different results than the same temperature in any local treatment. Characterization of the temperature alone is not enough to categorize the technical solutions.

A water bath is used in many experimental models to achieve hyperthermia, and this models homogeneous heating solutions. The various electromagnetic heating technologies also have their specialties. The bioelectromagnetic action of the technology determines the actions. Evaluating the applied technique, we consider the kind of energy delivery, the method of heat absorption, and handling the target tumor's physiological reactions, together with their inhomogeneities. The target's absorbed energy, and its temperature distribution are not the same [20], and these characteristics are largely determined by the blood-flow. The technical solutions must handle how the provided energy I transformed into the desired temperature.

1.4. The Electromagnetic Coupling Modalities

Variants of energy-transfer realize the absorption in the target. Various "antennas" (sources) couple the energy to the target (**Figure 2**). The homogeneity of the absorption defines the main character of the actual coupling. The inductive arrangements have two heating forms. One is the Eddy-current (induced current loop in the body) and the other uses magnetic materials for heating. In living

objects, both the Eddy-current and magnetic approaches are applied. Life does not have natural inherent magnetic properties. Artificial magnetic materials (like nanoparticles, seeds, rods, etc.) orient the energy for heating. Internal Eddy-current induction needs an extra high magnetic field, and the induced current has no specified orientation but is sensitive for inhomogeneities inside the body. Consequently, both induction methods heat in a heterogenic way. The conventional relative antenna solution radiates the electromagnetic energy, which is absorbed by the target. It is less sensitive to heterogenic structures, so is usually applied for homogeneous heating to use the dosing of isothermal volumes. The capacitive coupling has two major kinds of energy transfers: 1) the plane-wave antenna process, which aims to achieve similar isothermal absorption of the electromagnetic waves as the radiative applications; 2) the impedance coupling process, which uses the precise impedance-matching of the target. The isothermal kind of capacitive coupling requires high energy transferred via the plane-wave, while the impedance matching (mimics the galvanic match), uses less energy provided the heterogenic absorption processes are exploited and dominate. The galvanic coupling firmly touches the actual target. In non-living applications, this is the simple discrete resistor situation. The galvanic coupling in the case of living items applies tightly connected electrodes invasively with direct solid contact with the body's surface.

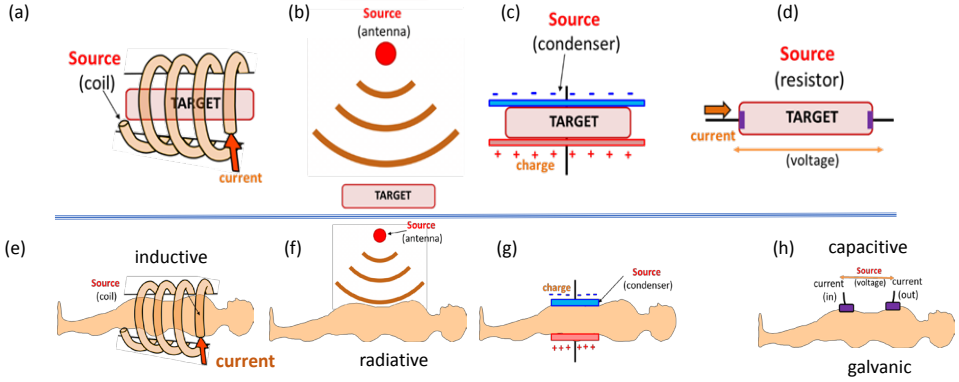

Figure 2. The major coupling methods for local-regional heating. (a)-(d) Homogeneous (non-living) targets; (e)-(h) Heterogeneous (living) target. The energy-absorption induces different effect in various couplings.

Applications using capacitive and radiative (microwave) solutions are the most popular methods used in the technical realization of the treatments; however, due to the sharp decrease of penetration depth with the increase of frequency, microwave solutions are mainly applied for surface lesions (see later). Capacitive coupling of energy delivery has become the most frequently applied technique, and the frequency of choice for the technique is the so-called "free-frequency" of 13.56 MHz, approved for industrial, scientific, and medical use (ISM frequency) [21]. Different effects in the human applications are observed, based on the coupling effects of the applied technique, **Figure 3**.

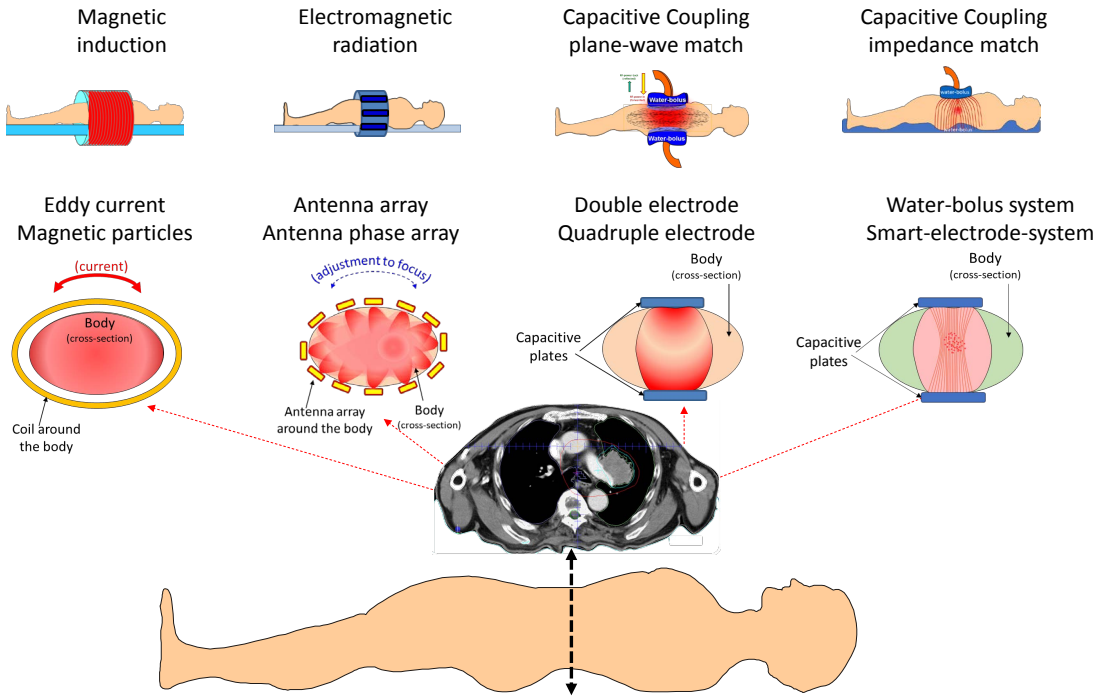

Figure 3. The local-regional treatment intends to select the cross-section of the body for energy absorption.

2. The Capacitive Coupling

Two kinds of capacitive couplings exist, depending on how the matching tunes the antenna, how the antenna structure's method and the electronical environment incorporates the tumor in the body as part of the regulated electric circuit. The concept of the complete electric circuit defines the matching method. The complete system, not only the capacitive arrangement of the electrodes, defines the coupling.

2.1. Plane-Wave Matching

The conventional solution involves plane-wave matching, in which the antenna's plane-parallel plates are tuned as per the standard antenna-tuning method. This solution does not consider the energy losses by various electric circuit elements and their interactions with the environment. In this case, the increased power (P) compensates for the lost energy. Due to the relatively high complex impedance, the voltage (V) is high, while the current (I) is low. The product of voltage and current defines the useful power, $P_{real} = V \cdot I \cdot \cos(\varphi)$, while the reactance (the power refused by the load) is $P_{react} = V \cdot I \cdot \sin(\varphi)$. The possible timing delay of the complex fit of the voltage with current is characterized by the cosine of the phase angle ($\cos(\varphi)$) of the complex values. In case of dielectric losses and/or radiations $0 < \varphi < 90^{\circ}$. Due to the losses, the impedance of the system (Z_{sys}) from the radiofrequency (RF) source to the target is large. The capacitance (C) describes the dielectric (isolating) resistivity, and the conductive part (defined by the real resistivity (R) defines the reaction time of the system (time-constant,

$\tau = R \cdot C$). The circuit for the hyperthermia plane-wave system has many various capacitances and resistivities additional to the target in the human body, and then we have to calculate the time-constant in a more complicated way (open-circuit time constant method [22]).

The time constant, in the case of plane wave solution, is relatively high, limiting the tuning's reaction time. This delay could cause a challenge when the physiological changes (breathing, heart-rate, etc.) are quicker than the reaction time. The plane wave method applies conventional antenna tuning where the antenna is fixed, so the reaction time has no relevance.

The plane-wave matching radiates RF-waves for energy-absorption, and direct heating, and necrotic cell-death (CEM 43˚C T_x dose) is expected. This matching technology aims to reach at least 43˚C temperature in the T_x effective percentages of the temperature measurement in the tumor.

The wave matching induces extensive radiation, due to the wave-transmission adding a significant factor to the energy-loss, and this could produce safety issues for operating staff. An important phenomenon of this coupling is that it could tune on the air without a patient in the active radiation zone.

2.2. Impedance Matching

The impedance matching of capacitive coupling does not use the wave concept. The system construction approaches the galvanic touch of the electrodes. The normal resistor has the maximal power in the galvanic coupling: $P_{\max} = U \cdot I$, where U is the galvanic potential (voltage), and I is the current (Amps). In the case of a patient's complex impedance (Z_{pat}) the imaginary part limits the effective power. When Z_{pat} coupled galvanically, it modifies the maximal efficient power to: $P_{Pat} = U \cdot I \cdot \cos(\varphi)$. A resonance solution of the components approaches the minimal imaginary part of the Z_{pat} impedance [23], and maximizes the power on the patient. The resonance uses a near-zero phase angle $\varphi \cong 0$ consequently $\cos(\varphi) \cong 1$ [24]. The low imaginary part decreases the voltage and increases on the same ratio the RF-current, [25] [26]; because $I_{Pat}^2 = \frac{P_{Pat}}{Z_{pat}}$, and $U_{Pat}^2 = P_{Pat} \cdot Z_{pat}$.

Approaching the proper impedance matching, the solution has negligible reflected power (order of 1 W), mimicking the skin's galvanic contact as much as possible. When the electrodes directly touch the targeted volume's surface, the galvanic situation, without any isolating materials, offers the most amount of available current. The impedance matching aims to mimic the galvanic situation as much as possible. This solution minimizes the reactive part and maximizes the real power on the load.

The main principle of impedance matching is to approach the "galvanic-like-touching" that would be the best available non-invasive electromagnetic energy-delivery. The invasive method (when electrodes are inserted into the body) is also "galvanic", but its invasivity has multiple medical complications,

such as bleeding, a high risk of infections, ulcer formation, and inflammation. One of the invasive "galvanic" methods is ablation technology, which has remarkable successes in local, small tumors [27]. With minimal energy loss, impedance matching allows the concentration of the energy on the malignant volume [28]. Due to the selection, this solution has better efficacy and offers a safer treatment because the voltage could be less than in higher resistivity isolation cases, at the same power application, while the current is increased.

The full arrangement of impedance matching minimizes the losses in the circuit ($Z_{loss} = Z_{sys} - Z_{pat} \Rightarrow min.$). The minimal loss allows optimization of the reaction time with a low time-constant. The small delay of the reaction to the physiological changes allows prompt adaptation to alterations during the treatment; even small animals in preclinical experiments have a significantly higher heartbeat and breathing frequency than humans [29].

The impedance matching needs a conductive media between the electrodes, and the RF-current flows through it. Consequently, the system cannot tune on the situation when a patient does not present in the active radiation zone. The technique therefore induces minimal radiation to the environment, and it is safe.

Due to the forced RF-current, the patient becomes an electric component of the real-time adaptive tuned electric circuit, representing active electrical impedance. In this matching, the patient is not simply an "energy absorbent" but an active electric element of the serial circuit.

2.3. Comparison of Capacitive Couplings

In general, all capacitive couplings are equal based on the formal capacitive arrangement level, however their technical details differentiate them. The variation could be so significant that it produces—either homogeneous or heterogeneous heating in the target.

Comparing the variants of capacitive couplings requires a detailed study of the electronic, structural, and material design differences of the circuits. All capacitive couplings involve a capacitor used for energy transmission to the target, emphasizing the electromagnetic interactions' electric field component, using electrodes with the target volume placed between them.

The plane wave capacitive coupling transmits the radiofrequency by the plane antenna, and some of the radiofrequency is even transmitted through the air, **Figure 4**. A popular hyperthermia technique applies a typical radiative plane-wave solution [30], but the high voltage for radiation necessitates enormous power (600 W for a mouse with tumors weighing 2 g) [31] [32]. However, the plane-wave solution could work with a lower power when the distance (space in the air) between the electrode and the body surface is small, or negligible, or the matching parameters allow high voltage and low current for the applied power.

Importantly, impedance matching of capacitive coupling does not work when isolated (*i.e.* when there is a space or air between the electrode and body surface), **Figure 5**.

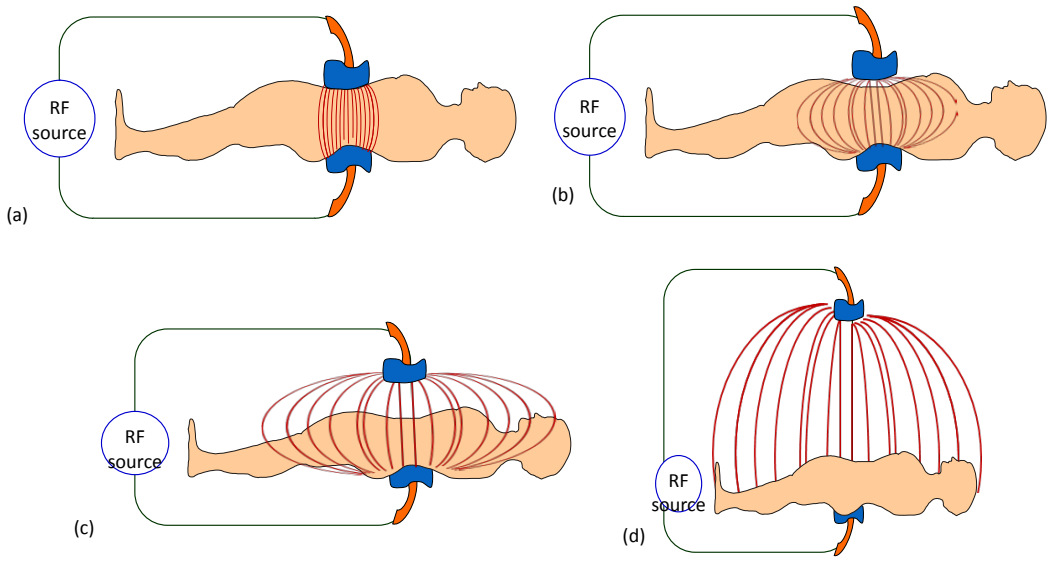

Figure 4. The plane-wave radiation works through the air, and so it is not sensitive for electrode fixing.

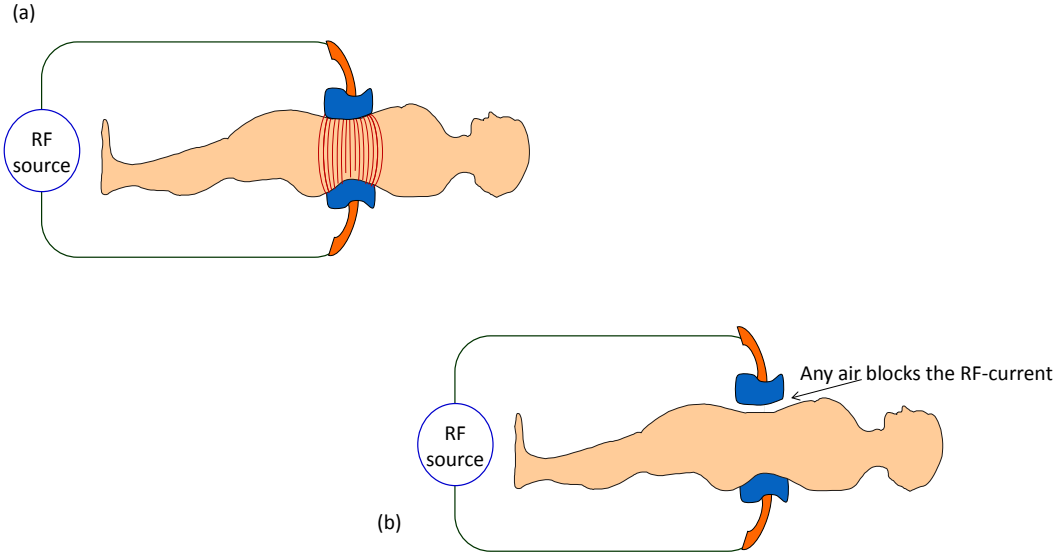

Figure 5. The impedance matching uses the RF-current-flow through the body and does not work when an air slit exists between the electrode and the body.

All capacitive couplings have an engineering control point to optimize and maximize the provided power from the RF source and, using the power-supply safely, to avoid its overheating. The measuring points fit the circuit's impedance to the source's internal resistivity, using the conventional standard 50 Ω. However, this engineering control does not take into account the medical control. The medical control or reference point refers to the point at which there is minimal loss of energy to the environment and maximal absorption in the patient while ensuring the safety of the patient and minimizing unwanted hot spots.

The optimal engineering settings do not necessarily align with the optimal requirements for the patient safety and treatment, **Figure 6**.

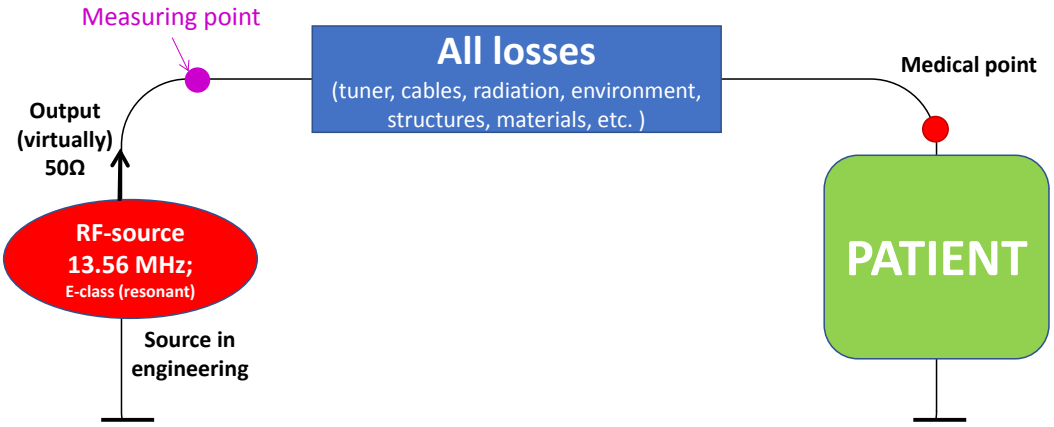

Figure 6. All losses are minimized by proper geometry, material-selection, careful design of specialized electronics, super-low imaginary (reflected) power, ($\varphi \cong 0$) etc.

There are decisional differences between the realization of capacitive coupling methods at the level of simple measuring observations. The two major categories are the plane-wave and impedance matching techniques **Figure 7**, and other solutions combine these two categories.

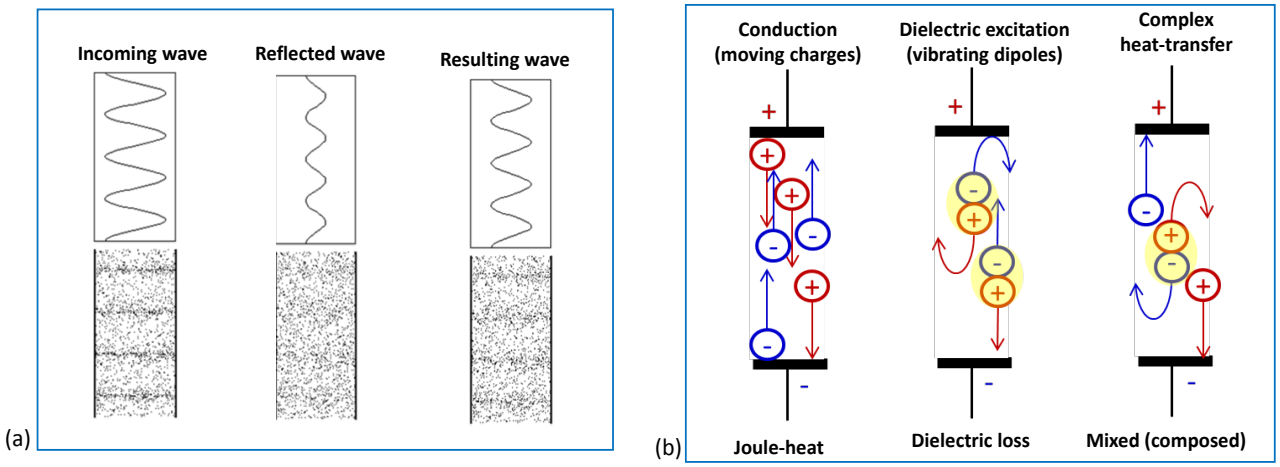

Figure 7. The matching arrangements. (a) The plane-wave matching uses a forwarded power and measures the reflected one to deduct and calculate the resulting radiative power; (b) The impedance (quasi-galvanic) matching uses the current-flow of the free charges (ionic species in aqueous electrolytes in the body) and the rotational or gradient-induced linear movements of dipoles in the tissues.

The observed differences could be technically detected by measuring the engineering reference point (optimal engineering set-up), and the medical reference-request point. The inequality between the reference points is due to the losses in the circuit, including the matching tuner, cables, radiation processes, used materials, and structures, as well as the capacitive coupling with the environmental objects (like walls, other types of equipment nearby, or the operating personnel). At this point, the engineering control and the medical control could significantly differ from each other, **Figure 8**.

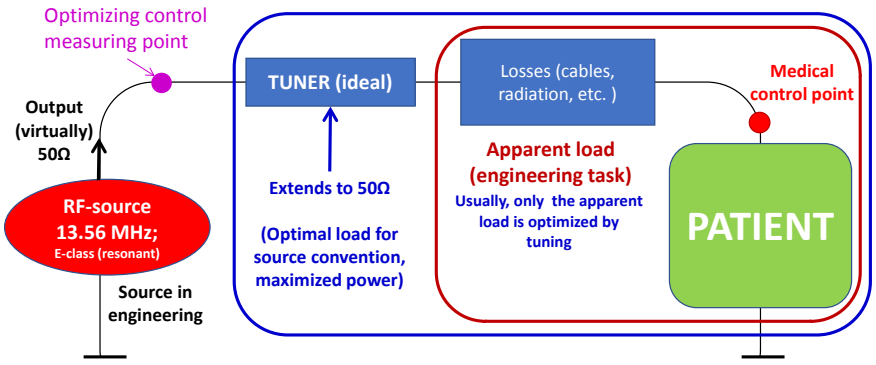

Figure 8. All losses are minimized by proper geometry, material-selection, careful design of specialized electronics, super-low imaginary (reflected) power, ($\varphi \cong 0$) etc. The matching has to accurately control the medical point shown in the figure.

The tuner electronically compensates for the overall losses, and the power-supply increases the power to replace the missing, lost energy. This type of matching procedure favors plane-waves on the patient, which uses wave-absorption, with a particular exponential decrease from the surface incident energy in the body, and is intended to create homogeneous heating in an actual depth.

The compensation of the general losses by the circuit components and environmental interactions do not optimize the patient-power from a medical point of view. After the medical point (which begins at the electrode), the initial RF-current enters the "coupling complex," including the patient's targeted volume. After this point, new unwanted losses challenge the optimization of the treatment. These include the electrode structure, electrode material, the bolus system, the patient's surface adipose tissue, the healthy impedance, etc. This extra impedance is the vital target: the impedance of the tumor. Hence the optimization of the treatment point is crucial in order to successfully heat the tumor. How this is optimised defines the type of capacitive coupling (**Figure 9**).

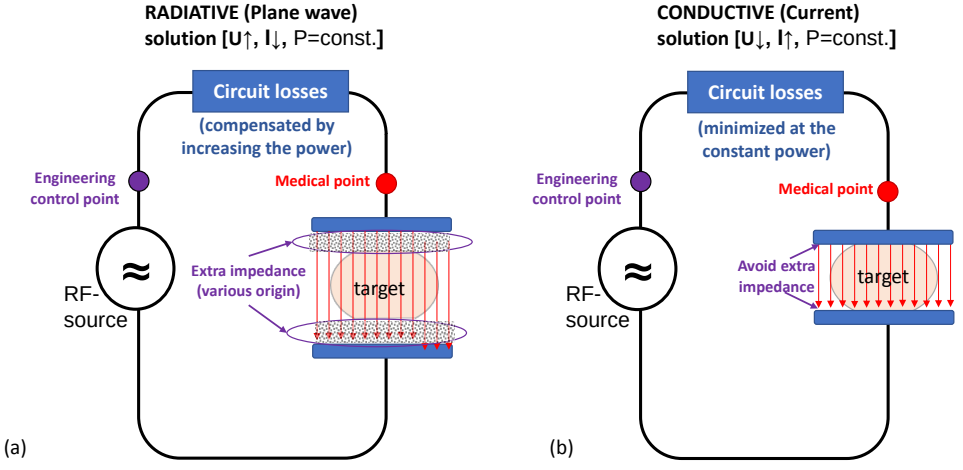

Figure 9. (a) The plane-wave matching allows a lazy connection of the electrode for various reasons; (b) The impedance (quasi-galvanic) matching does not work with improper impedance between the "medical point" and the body surface.

The impedance matching focuses on the medical control-point, minimizing the impedance of components that derail the primary target's energy, the tumor. Without taking into account the medical point, the RF-current flows through two different impedance categories: the objects' impedance, which fits the current transfer to the body, and the body impedance.

The various components of object impedance challenge the conductive approach (Figure 10).

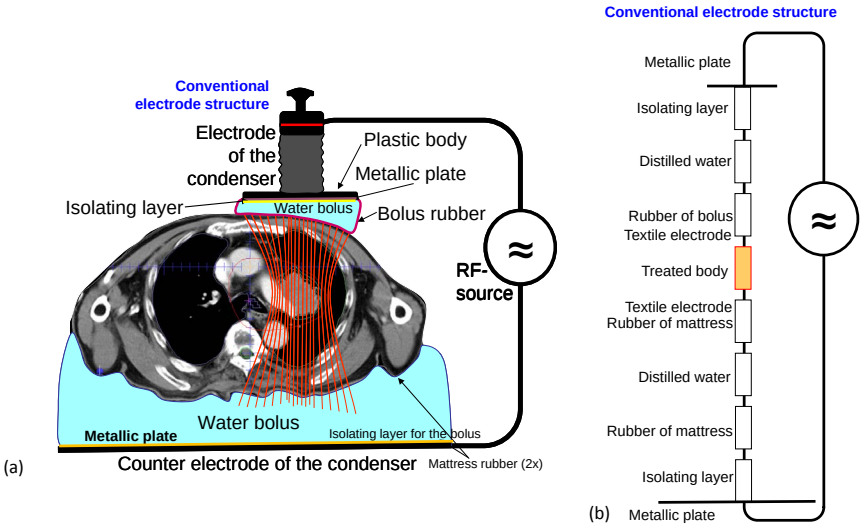

Figure 10. Numerous serial impedances modify the energy-distribution in capacitive coupling. (a) The main structure of the conventional capacitive coupling with water-bolus; (b) The draft of the impedance of the conventional electrode structure.

The best solution would be the galvanic contact of electrodes (Figure 11), which may be approached by the electrode design accompanied with the resonant compensation.

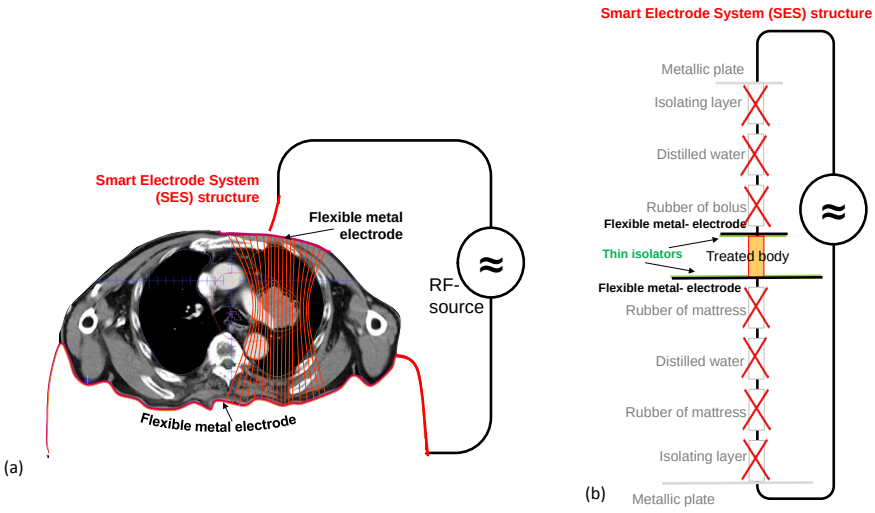

Figure 11. The draft of the design of impedance matching, which is (a) quasi-galvanic, or (b) the solution mimics the galvanic touching with a precise resonant compensation.

The body impedance contains a very heterogenic structure. Each of which represents a resistor and a serial capacitor (the inductive parts are missing) (Figure 12).

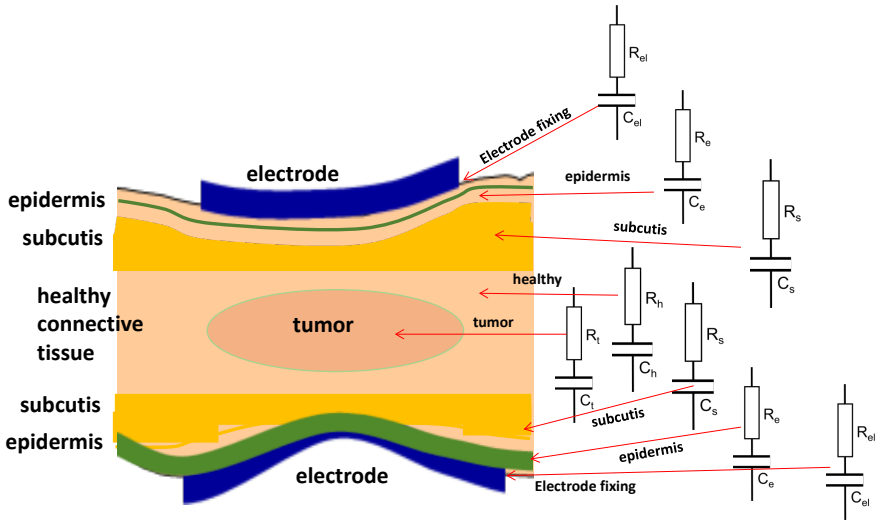

Figure 12. The major layers of the human body's targeted volume show the serial RC parts in every layer.

The compensation procedure in impedance matching minimizes the capacitive (imaginary reactance) factor, and the resistive part remains in focus. A particular category of impedance matching is the modulated electro-hyperthermia (mEHT) which selects the malignant cells in this heterogeneity, and the tumor-cells concentrate the primary energy absorption (see later text below). Consequently, the dominant resistivity part is the set of the tumor-cells in the targeted volume. On this basis, we approximate the effect of the different resistivities and the resistivity of the healthy tissues is negligible in the first attempt (Figure 13).

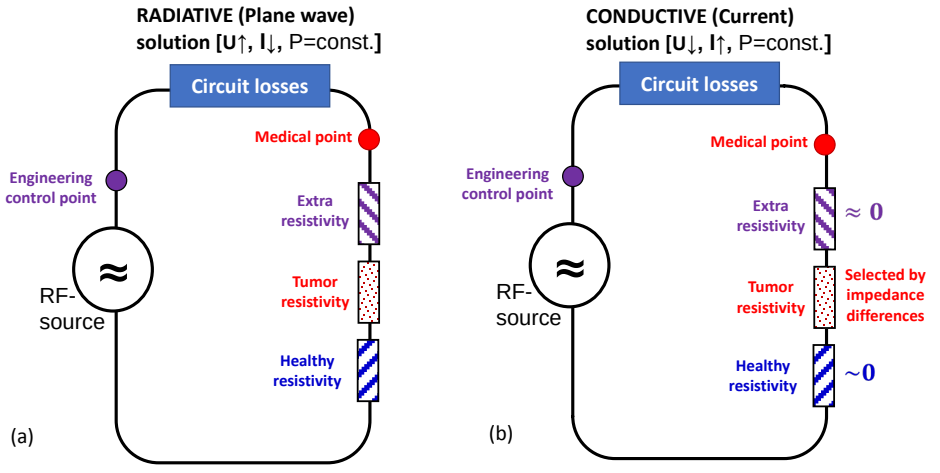

Figure 13. The voltage and current generation with the same value of power in plane-wave matching (a), and in impedance (quasi-galvanic) matching solutions (b).

All of these considerations involve a resonant matching method. AC/RF circuits imply a certain frequency determined by the values of the resistance, capacitance, and inductance of the serial circuit (Figure 14).

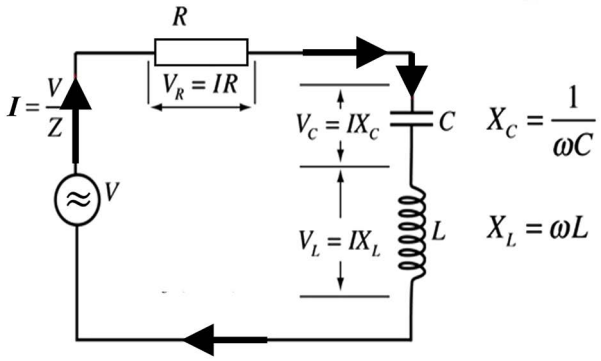

Figure 14. The discrete representation of the circuit describing the impedance matching. V_R, V_C and V_L are the voltage drop on the discrete elements. The resonant compensation produces the V_L.

The dielectric permittivity and the conductivity affect the RF-current differently, and the result is called impedance. Mathematics using complex numbers describe the two independent effects showing the conduction on the real conductor while the dielectric permittivity defines the isolators, where the conduction of the RF-current is imaginary. The patient's impedance represents the real part (R_{pat}), and the reactive part (Y_{pat}), and $Z_{pat} = R_{pat} + iY_{pat}$, where $i = \sqrt{-1}$ denotes the imaginary part. In geometrical representation, it shows a vector (Figure 15).

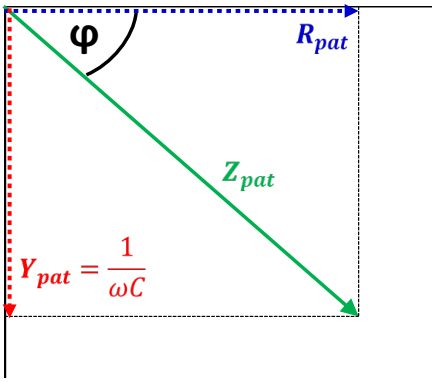

Figure 15. The vector picture of the impedance in living objects. The R_{pat} real resistance and Y_{pat} imaginary reactance produces the Z_{pat} impedance with the φ phase angle. Due to the only capacitive part (no inductive element exists in the living organisms), reactance is negative. The current appears earlier on the capacitor than the voltage. The impedance matching approaches the $\varphi \cong 0$ compensation.

The impedance minimum characterizes the serial resonance. The impedance from the imaginary parts of capacity (C), and inductivity (L) are $Y_C = \frac{1}{\omega C}$, and

$Y_L = \omega L$, respectively, and the impedance is $Z = \sqrt{R^2 + (Y_L - Y_C)^2}$. Hence, when $\omega_0 = \frac{1}{\sqrt{L \cdot C}}$ then $Y_L = Y_C$, and the resulting minimal impedance is $Z = R$ with zero phases. The selectivity of a circuit depends on the circuit's serial resistance.

The Y_{pat} depends on the applied frequency (f), while the real conductor does not depend on f. The living matter has a negligible inductive (coil-like) component in Y_{pat}. Mostly the membranes, and the other isolation layers form Y_{pat}, which act as a C capacitor, $Y_{pat} = \frac{1}{2\pi f C} = \frac{1}{\omega C}$ Where $\omega = 2\pi f$. Applying the vector representation of the impedances (Figure 15), the variation of the major layers in the target volume of a human body gives a resultant impedance $R_{pat} = \sum_{i=1}^{N} R_i$, and $Y_{pat} = \frac{1}{\omega} \sum_{i=1}^{N} \frac{1}{C_i}$. Using the resonance frequency $\omega_0 = \frac{1}{\sqrt{L \cdot C}}$, an additional inductive factor would compensate the Y_{pat} to minimize the impedance of the target. The necessary inductivity for resonance is $L = \frac{\omega_0^2}{C} = \omega_0^2 \sum_{i=1}^{N} \frac{1}{C_i}$ (Figure 16).

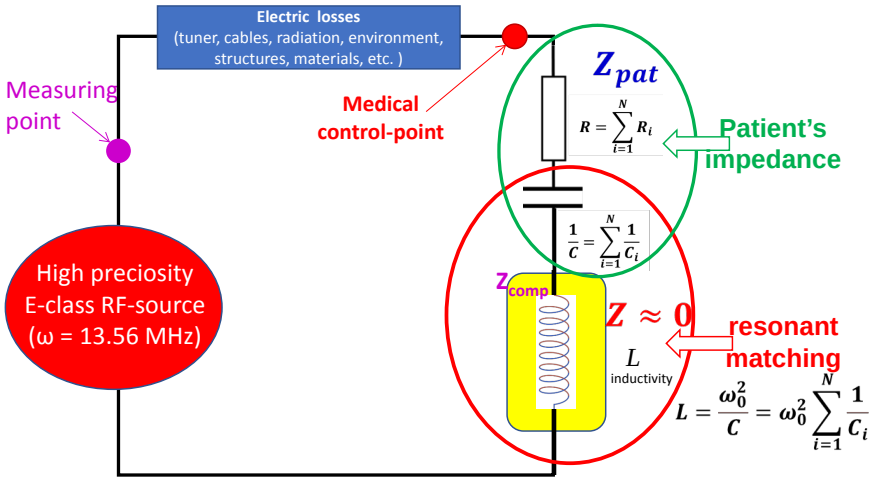

Figure 16. The patient is an electric component of a precisely tuned resonant circuit. The compensation clears the target impedance minimizing its reactance.

The compensation transforms the impedance near a real resistance value as shown in vectorial representation (Figure 17). The vectors show the complex impedances of some critical layers in the body during the RF-current flow. The horizontal axis is the real part (the real conduction), while the perpendicular one is the imaginary part, representing the isolation. All tissues have isolation also due to the various membranes. The electrode isolations are neglected, so the resulting impedance vector shows a decline, which a single inductive resonance could easily compensate for.

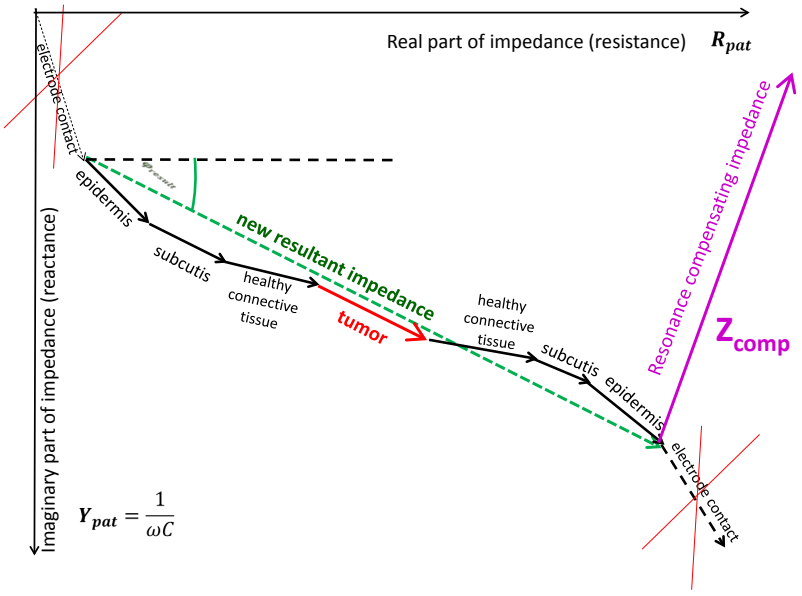

Figure 17. The vector diagram of the cross-sectional impedances in the average human body. Only the major components are shown, and for clarity, they are regarded as a discrete element.

The original current was $I_{orig} = \frac{V}{Z} = \frac{V}{\sqrt{R^2 + \left(\omega L - \frac{1}{\omega C}\right)^2}}$, the new current in resonance is higher $I_{orig} < I_{res} = \frac{V}{R}$, and in resonance depends only on the real resistivity. The current changes by resonance. The RF-current flowing through the target depends on the values of the components of the circuit. The well-selected situation filters a relatively small part of the targeted volume, the malignant cells, so their resistivity is small compared to the complete targeted volume. The small resistivity increases the peak of the current in resonance, **Figure 18**.

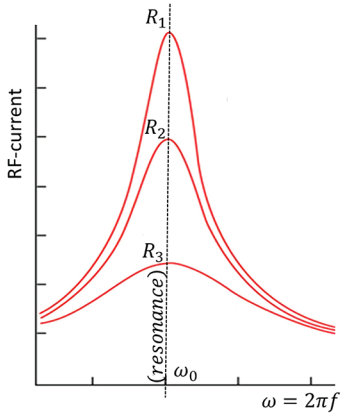

Figure 18. The RF-current distribution in the resonant conditions. The resistivity is decisional; when it is low, the peak is sharper ($R_1 < R_2 < R_3$). The $f_0 = \frac{\omega_0}{2\pi}$ is the resonant frequency.

Since this power depends on the square of the current the resonant curves appear steeper and narrower in the presence of lower resistivity. The quality factor Q is defined by $Q = \frac{\omega_0}{\Delta\omega}$ where $\Delta\omega$ is the width of the resonant power curve at half maximum (Figure 19).

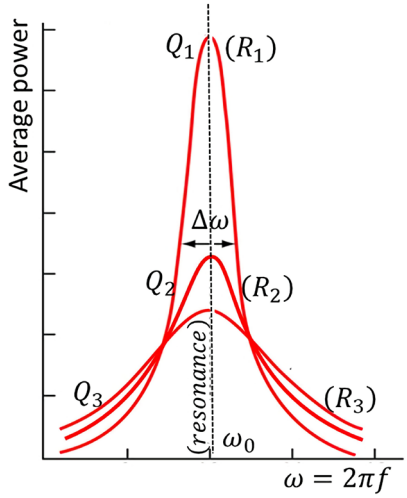

Figure 19. The resonance quality factor (Q) defines the average power in resonance. $R_1 < R_2 < R_3$, and so $Q_1 > Q_2 > Q_3$. The $f_0 = \frac{\omega_0}{2\pi}$ is the resonant frequency.

Since that width turns out to be $\Delta\omega = \frac{R}{L}$, the value of Q can also be expressed as $Q = \frac{\omega_0 L}{R}$. The Q is a commonly used parameter in electronics, with values are usually in the range of $Q = 10$ to $Q = 100$ for circuit applications. The smaller the resistance, the higher the "Q" for given values of L and C. The power, of course, depends on the product of actual current and voltage. When the current increases due to the resonance, the voltage decreases, while maintaining the same power.

The resonant approach uses the minimizing of the reactance (imaginary part) of impedance. Physiological regulation also has a vital role in the process. One of the reasons for using the plane-wave capacitive coupling is the surface adipose tissue challenge, forming an isolator-like layer at the skin. In a plane-wave situation, the voltage is increased to surmount the gap by the isolator of the adipose layer. However, this way, the energy-absorption in this layer is extremely large, so the risk of burn increases. In order to avoid this risk, the plane-wave method uses intensive cooling of the skin by using the bolus system, Figure 20.

However, this cooling has unexpected positive feedback reactions from the physiological control of the body homeostasis: the cooled skin lowers the blood-flow in the subcutis, which increases the layer's isolation towards RF-current. This induces a higher voltage request, which increases the risk of burn, so a further increase of the cooling is necessary. It further increases the isolation, and so

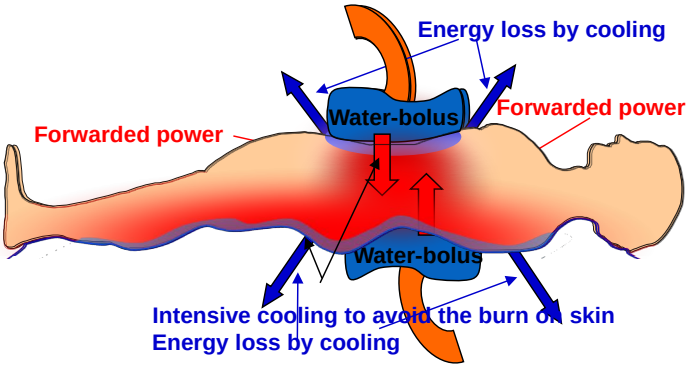

Figure 20. The cooling of the bolus produces uncontrolled energy-loss and induces a positive-feedback physiological regulation. (see the text)

on, the situation would be hard to control. Furthermore, the intensive cooling absorbs a large part of unmeasured energy, which makes the therapy dosing with incident energy impossible, as is similar in the case of ionizing radiation. Consequently, the impedance matching takes attention to the cooling process and keeps the homeostatic control stable in the subcutis layer under the electrodes.

In summary, the strategy of impedance matching concentrates on increasing the current as much as possible. The major factors to maximize the current are:

- the resonance approach,
- the design, structure, materials of the electrode system,
- the grounding optimization to lower the radiation, and coupling to environmental objects,
- the regulation of the homeostatic status of the skin blood-flow (which regulates the imaginary part of the skin-structure of the patient),
- eliminating the losses in an electric circuit as much as possible,
- the high current value (in the unchanged power conditions) makes a more effective selection,
- the high current accompanied with low voltage at the constant power, increasing the safety of the treatment.

3. The Modulated Electrohyperthermia (mEHT)

3.1. The Challenge of Homogeneous Heating

The classical heating concept applies a mass-heating of the entire tumor. The mass heating tries to be homogeneous in temperature (isotherm), and uses the temperature as the only control parameter.

The control of homogeneous (conventional) heating is problematic because

1) the local blood-flow is enhanced, which increases the risk of dissemination and metastases,

2) colossal power is necessary to ensure quasi homogeneity, which again involves many safety issues,

3) due to the heterogeneity of the target, the control of homogeneity is very complicated, in most cases it could not be achieved,

4) the homogeneous hyperthermia thermally kills the cells and occasionally triggers immunogenic effects in the area,

5) the challenge of measuring temperatures at has not been solved; MRI thermometry is promising but still has challenges,

6) the only homogenous (and large CEM43T100) solution is the whole body treatment (WBH), which does not show the expected success.

The invasive measurement of the tumor's temperature has multiple problems, as a result the temperature is typically measured in the nearby lumina or cavities of the body. So the mass heating must be regional, having comparable temperature in the nearby lumen (like oesophagus, bronchus, colon, vagina). The same isotherm heating appears in the plane-wave concept of capacitive coupling. The modulated electro-hyperthermia (mEHT) method uses impedance matching of capacitive coupling with some unique features, which have been developed over the past 32 years, and documented and patented. The mEHT method harnesses the impedance matching shown above with additional elements, improving its efficacy.

The present technical challenges are:

1) The energy selection ensures the local place of energy absorption. It has major complications due to the normal physiological movements caused by breathing; and the technical solution has limitations when attempting to heat deep-seated tumors without considerable heating of other tissues.

2) The dose determination, which controls the medical application, is a mandatory parameter, but the heating techniques determine the clinical results. We have seen that exposing the tumor isothermally to 42˚C in whole-body hyperthermia, has entirely different results than the same temperature in any local treatment. The technical solutions based on the temperature alone do not characterize the applied method.

3) The role and measurement of temperature in the treatment efficacy are challenging. The value of the temperature in the target supposes an isothermal mass-heating, which never happens in LRHT. The temperature measurement approximates the tumor's value, checking the temperature in the nearby lumen (like esophagus, bronchus, colon, vagina). This method assumes that the heating does not focus on the tumor-mass, but equally heats its healthy environment.

Due to the above challenges, temperature measurement is mandatory to approximate the absorbed energy, which differs from the technically provided value. The high energy losses (like various electric losses, losses from cooling water, etc.), and the need to control safety (avoid burns) are fundamental reasons to measure the temperature.

3.2. Heterogeneous Heating

The mEHT chooses a new paradigm, it heats the cancer-cells selectively in the tumor, using the malignant cells' unique thermal and electromagnetic characteristics. The structural change of the local heat-capacities, heat-conduction differences, heat transfer by blood, and lymph electrolytes cause the thermal hete-

rogeneity. Significant differences in the electric behavior of micro-states of living matter determine the electromagnetic heterogeneity. The variation of electric conductivity and dielectric permittivity by the living processes and the differences of lipid-protein structures in the cell-membranes and the cells' cooperative differences appear to be the most influential factors for electric heterogeneity. Further differences between the malignant cells and their healthy counterparts develop as a result of the heat-resistance, motility of the cells, and cellular and extracellular mechanical properties.

Some other significant differences are present at a molecular level, but these are less effective in distinguishing the malignant cells from their healthy counterparts. Using heterogeneity offers a valuable tool to select the malignant cells in the heterogenic tissue. The RF-current presents a possible tool for clear recognizing of the heterogeneities. The current-flow changes based on the electric heterogeneities and its heating effects connect the current to the thermal properties. An essential component of tissue heterogeneity involves molecular reactions, which differ depending on the tissue and cells. For example, the apoptotic control, a well-known regulation in healthy tissues, is almost entirely missing in malignant tissue, as described in the hallmarks of apoptosis could happen through multiple molecular mechanisms, which do not work in cancer.

3.3. Considering the Homeostatic Regulation

From the beginning of human medicine, physicians recognized the equilibrium of the living organisms, which defines the healthy state, and has multiple dynamic components which are finely balanced. This was the first recognition of homeostasis, which has definite lower and upper limits of the interactions and conditions. The body homeostasis is stable within a certain interval of the parameters; the level of any interactions is determined and measured by the harm caused at the extreme limits. However, the harm is a relative notion: the safety and the harmless categories are not identical. The "no action" treatment can be safe but harmful because the uncontrolled disease harms, which we can stop by action. The acceptable changes in medical actions attempt to reestablish the normal, healthy homeostasis; or if it is not possible anymore, then it attempts to approach it as close as possible. The Hippocrates-phrase, "Nil nocere" also has to be understood in this way. Otherwise, the meaning is "Do nothing".

The internal transports, like the blood-stream, have a central role in keeping homeostasis. The blood circulation regulates multiple vital processes, including the heat exchange, to ensure the body's proper functional conditions. The blood-stream tries to compensate for the overheating by intensive perfusion and regulation of the vessels' flow-capacity. However, the regulation process of the blood-stream is non-linear. The quantitative analysis [33] shows the non-linear changes of the blood-flow in characteristic tissues varying by the temperature. The deviation (selection) of the tumor blood-flow starts just above 38˚C, **Figure 21**.

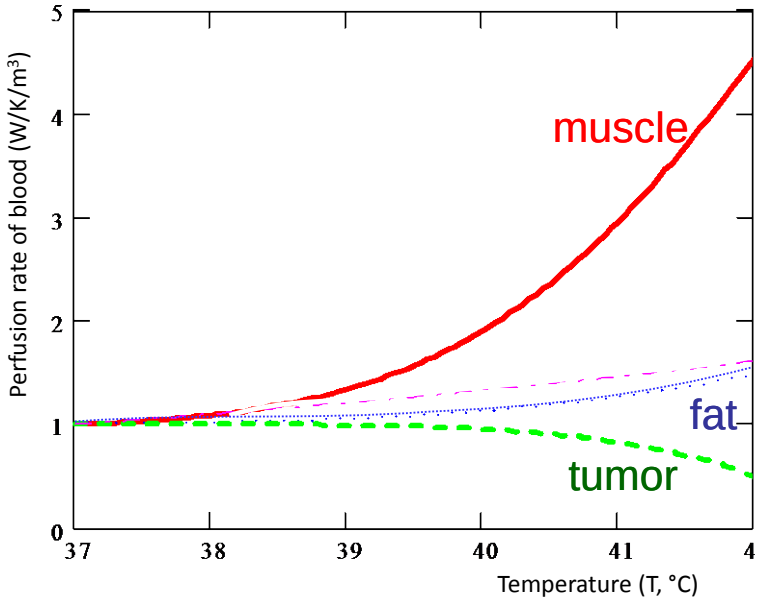

Figure 21. Relative quantitative changes of the blood-flow by a temperature increase in muscle, adipose tissue, and tumor lesion.

Due to the variation of the blood-flow, the necessary energy in a mass unit (specific absorption rate; SAR [W/kg]) non-linearly changes in the range between 39˚C - 42.5˚C [34] by the actual temperature, **Figure 22**.

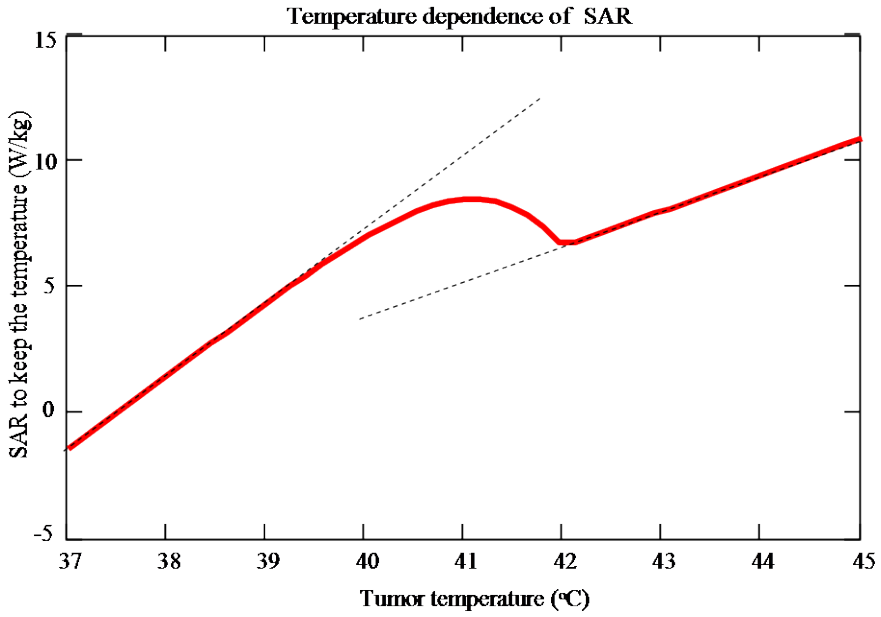

Figure 22. Variation of the requested specific absorption rate (SAR) to keep the given temperature in the tissue.

The non-linear regulation is general, using physiologic control by negative feedbacks. The promoter-suppressor action realizes the contraction of the feedbacks, which has a broad response-time for intervention.

3.3.1. The Selection Mode

The classical heating concept applies mass-heating of the entire tumor. The mass heating tries to be homogeneous in temperature (isotherm) and uses the temperature as the only control parameter. As previously discussed the temperature is usually measured in the nearby lumina or cavity and the same temperature must therefore be achieved in the lumina/cavity. The mEHT method uses a different paradigm, its heats the cancer-cells selectively in the tumor (**Figure 23**), using the malignant cells' unique thermal and electromagnetic characteristics.

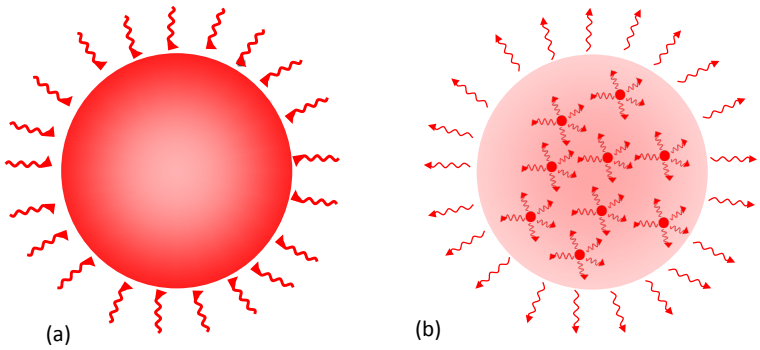

Figure 23. The differences between the heating paradigms: (a) Plane wave matching homogeneous heating causes energy-absorption in the complete target, while (b) impedance matching could be selective, heats only selected parts in a heterogenic manner, heating up the surrounded tissue by heat conduction (mEHT principle).

The selection uses the natural heterogeneity. The RF-current recognizes the electrical heterogeneity, and its heat effect results in thermal heterogeneity, resulting in the complex synergy of electric, and thermal processes [35], induces molecular changes driven by mEHT. The malignant differences make it possible to distinguish malignant cells from healthy cell structures [36]. The amount and composition of the extracellular aqueous electrolyte in the micro-environment of tumor cells massively differs from healthy tissues.

The malignant cells need a significantly higher energy amount than the healthy cells due to the intensive metabolism required to supply their proliferation [37]. The metabolic rate in most of the tumors is higher than their healthy counterpart (at least 15%, [38]), which selectively increases their temperature. The process has positive feedback because the higher temperature decreases the tissue's impedance [39]. Their metabolism requests a robust amount of nutrients which in the simplest way demands glucose. Due to the high level of necessary ATP production, the tumor cells predominantly perform simple anaerobic glycolysis instead of mitochondrial phosphorylation. The positron emission tomography (PET [40] [41]) identifies the extreme glucose intake in cancer cells. The rapid, intense fermentative process produces lactate, increasing the electrolyte's ionic conductivity in the cellular microenvironment, jointly with the higher in- and outflux transport of other ionic species. The increased ionic concentration means higher conductivity [42] of the microenvironment of tumor-cells, so it lowers the whole tumor's resistivity. This can be used to distinguish between

healthy and malignant situations [43]. The RF-current selectively flows through the low resistance (highly conductive) tumor rather than the more resistive healthy environment.

Malignant cells are autonomic, independently fighting for the energy against all other cells irrespective of healthy or fellow cancer-cells. For autonomy, they break their networking bonds and stop direct intercellular communications. The bonds formed by adherent proteins and junctions mostly vanish. Due to the missing cellular network, the extracellular matrix of malignant cells has high dielectric permittivity, which can be used for selection [43]. The structure of the microenvironment rearranges due to the missing bonds [44]. The altered structure allows the recognition of the malignant cells by their dielectric properties, which modifies the applied RF current [45] [46]. A well-developed diagnostic method uses this phenomenon [47], and it is applied in mammography [48].

The permittivity and the conduction modify the complete impedance in the microenvironment of the malignant cells [5], allowing their selection in an automatic way, while the RF-current flows in the direction of low electric impedance. The RF-current-density (specially chosen frequency and modulation) self-selectively flows toward the malignant cells, which is measurable by MRI current density imaging, [49] [50] [51]. This effect is completely automatic, it follows all movements of the cells in real-time, actually solving the challenge of focusing. The direct MRI electrical impedance tomography confirms the feasibility of using the impedance differences for selection [52].

The broken bonds between the cells leave the transmembrane proteins unconnected. These transmembrane proteins group by lipid-protein interaction in the membrane. The concentration of lipid rafts on malignant cells' membranes is significantly higher than on the membrane of non-malignant cells. The impedance-selected malignant cells' dense lipid rafts become an easy target of energy absorption. The rafts' clusters absorb the energy from the RF-current selectively [53] because the rafts have significantly lower electric impedance than the surrounding isolating lipid membrane. The selective energy-absorption promoted by a characteristic frequency dispersion in the applied 13.56 MHz frequency range (β/δ dispersion [54]), and the Schwan effect [55]), targets the lipid-protein interactions and selects water-bound states [56] at the membrane, effectively focusing the energy on the target [57]. This way, the natural electric heterogeneities drive the selection for energy absorption automatically, constructing an "autofocusing" process.

Further selection could be realized by the structural differences of the malignant tissue from their healthy counterpart. Usually, the pathological investigation of biopsies utilizes these differences by image pattern recognition in the samples. The pathological pattern naturally affects the RF-current in-situ, allowing additional selection of cancer tissue in the body. The alterations of the pattern modify the cells' spatiotemporal interactions, which dynamically act via intercellular interactions. The well-chosen noise could transduce free energy for the cellular reactions [58]. The dynamic relations produce a noise of homeostatic

equilibrium, which is measured as a peculiar signal [59] [60]. This noise differs in malignancy versus healthy tissue and is measurable by the RF current [61]. The noise difference is the basis for the applied modulation on the RF carrier in the mEHT method [62]. The modulation is an information delivery to the malignant lesion. The applied time-fractal has such autocorrelation time-lags that well fit the apoptotic excitation processes and may also act in enzymatic catalysis [58]. The spectrum of the reaction-times and rates appears in the modulation frequencies. The mEHT method applies such modulation, which is in harmony with the homeostatic collective network.

The collective excitations comprise the non-local waves and activate the energy-flow in the homeostatic networks. These excitations are mostly in a low-frequency range, and the expected frequency spectrum follows the natural 1/f fluctuations. Simply speaking, the modulation acts in harmony with the natural collective processes, promoting them, like keeping the swing in motion using harmonic push. Both the multicellular networked and the unicellular autonomic states of cells maintain a balance which is probably realized by an electromagnetic route [63]. The FDA-approved TTF also uses this kind of interaction to arrest malignant cell-division [64]. The method of mEHT uses an electrical field to modify the polymerization processes in the mitotic phase of the cellular division [65] with fractal noise modulation for a complex effect.

Furthermore, the applied noise is an active harmonizing factor [66], which has an emerging physiological application [67]. The fluctuations of electrical properties have unique information related to cell-membrane processes [68]. The monitoring of the noise as fluctuations in the complex system could be a factor in its surveillance [69]. Forcing harmony reconstructs the broken E-cadherin-beta-catenin cellular connections [70], which as was effectively and repeatedly demonstrated in an independent study [71]. The malignant cells' membrane is more rigid [72], while the cells themselves are softer than their neighboring healthy cells. The adherent connections and junctions could be formed only when the reactive ligands are close to each other.

As a result, the cellular connections have a geometric requirement to be re-established. The fermentative way of metabolism of malignant cells develops a strongly negative glycocalyx shell, which works against the proper geometric order, blocking bonding between the appropriate ligands. However, the extremely high fluctuating cataphoretic forces from the pink-noise modulation compensate the repulsion, and make the adherent connections possible.

The modulated carrier signal targets the selected malignant cells, and the cells rectify (demodulate) the received signal. The demodulation process uses two factors:

normal rectification by the highly polarized cell-membrane, [73] [74] [75].

stochastic resonance that makes the rectification, [76]

The non-temperature dependent rectification (non-linearity) was a question-mark for a long time because only linear attenuation was measured through the living object. The double membrane effect causes this apparent linearity. The

challenge is to measure the rectification in a tissue in which every cell with its opposite positions of the entry and exit points on the cell membrane acts like two diodes connected oppositely. So no rectification could be detected by measuring the tissue alone, Figure 24.

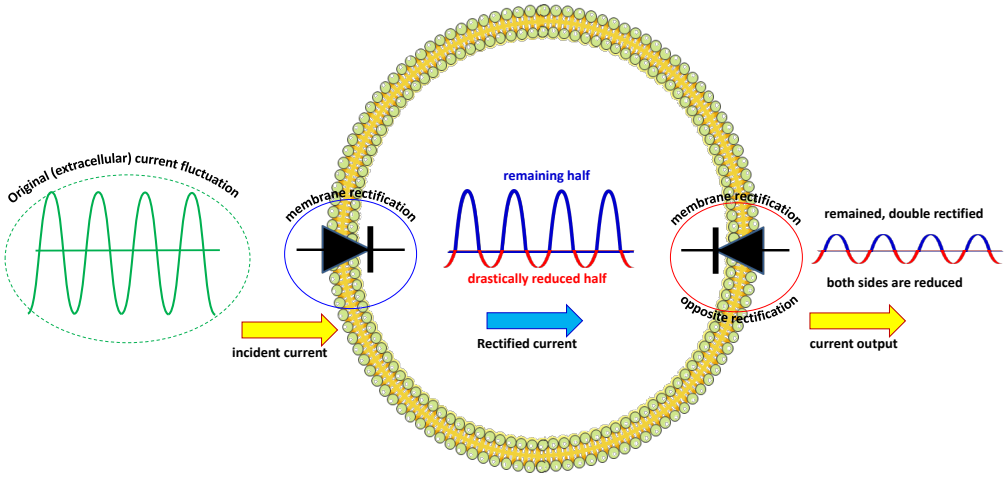

Figure 24. The symmetric but opposite rectification of the cell-membrane when the current goes through the cell makes the measured material linear, the rectification is not visible.

The mEHT impedance-matched capacitive coupling has four interconnected mechanisms for selection: the heterogeneities in conductivity and dielectric permittivity select the tumor, and its independent, while the membrane rafts absorb the energy in selected cells (the hyperthermia step), and the spatiotemporally distinguishable tumor-pattern provides an additional factor for selectivity, and isolation of the malignant cells, Figure 25.

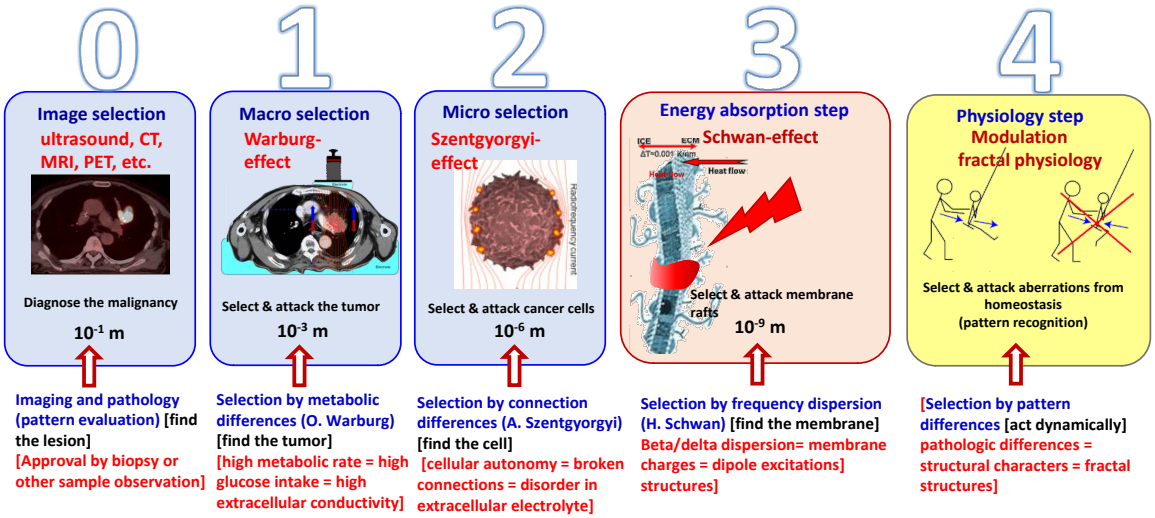

Figure 25. The steps of the mEHT action. (0) The conventional imaging supports the diagnosis; (1) The macro selection by conductive heterogeneities; (2) The micro-selection by the permittivity heterogeneities; (3) The energy absorption (the hyperthermia step) on the nano-range membrane raft; (4) A broad time-fractal spectrum recognizes and corrects the spatiotemporal pattern irregularities in the body.

Contrary to the above complex focusing (selection) mechanisms of mEHT, the plane-wave capacitive coupling methods regulate their approximate focussing of the energy by the size of the electrodes. The appropriately chosen electrode size is their focusing mechanism and their homogeneous mass-heating does not select on the cellular level.

The homogeneous heating has to balance the higher temperature and the increased blood-flow, induced by the intensive heating. The bloodstreams are a promising sensitizer of chemo- and radiotherapies, but are also a potential promoter of metastases resulting from the massive transport possibility of the cancer-cells. This process risks increase the metastases by forming circulating tumor cells (CTC). The CTCs could produce micrometastases throughout the entire body, which are not observable by the present imaging techniques. Heterogenic heating with microscopic (cellular) selection does not have such a challenge: the targeted particles can be supposed to have equal absorbed energy-doses, so the absorbed energy is the measured parameter. While the homogeneous heating method heats all parts of the target from outside, the heterogenic heating heats only the selected particles, and those heat the tumor where they are located. The selected particles are heated up intensively to have a higher temperature than their environment. The RF current at the <15 MHz frequency predominantly flows in the extracellular electrolyte. Its energy-absorption creates an active temperature gradient through the membrane [77], converting the electric heterogeneity to a thermal one. The mEHT heating does not make a massive general temperature increase of the targeted volume, macroscopically it presents a moderate temperature increase, but microscopically mEHT could produce extreme hyperthermia [78] [79]. The gradient causes the complete target's heating to the level of mild hyperthermia [80], which complements the applied chemo- and radiotherapies [81], but reduces the risk of metastases by CTCs. Notably, the pharmacokinetics of drugs are promoted by mEHT selective heating [82] [83].

The mEHT limits the increase of the SAR, which forces the development of the temperature. At a high temperature, the microscopic selection disappears, and an average temperature characterizes the target, like in plane-wave energy absorption **Figure 26**. For mEHT, the limited energy-absorption is mandatory.

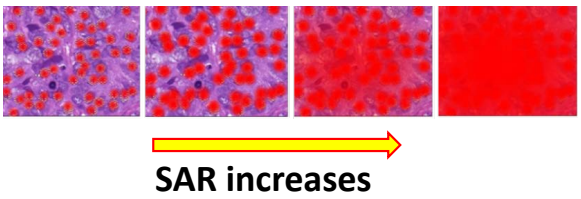

Figure 26. When the energy is too high, then everything is heated up, no selection could be seen. The selection factors became negligible. The selectivity has been lost, like the difference between the medicament and poison.

The electromagnetic selection mechanisms are general, and valid to all electromagnetic absorption methods treating cancer. However, the careful design

with focus on the precise selection emphasizes the anyway small effect. The emphasis of the selection over the thermal averaging needs the above factors, which consistently exceed the selection effects over the massive trend to homogeneous temperature averaging. On average, the relatively small SAR is high in the rafts, similar to the nanoparticle selective heating. However, the nanoparticles in mEHT are molecular clusters, which are sensitive to overheating. When the absorbed energy destroys the rafts by overheating them then the mEHT loses its largest advantage: the excitation of signal-transports for apoptosis and immunogenic cell-death.

A natural question arises: without the modulation is the effect of mEHT the same as other capacitive plane wave techniques applied at a lower power? The answer is yes, if their technical solutions fit the low energy, then they could form such complex situations as the modulation and the low-energy selection does.

However, it is not enough to have low energy alone; it must be that the energy is there where we need it, inside. For this, absolute fine-tuning (resonance to kill all imaginary part of the impedance), in order to promote the high current instead of the high voltage at the coupling, and the well-controlled radiation losses. An example for this fine tuning is how: the same Otto engine works in the high and low category cars. However, the same petrol makes different values for dynamism, the fuel consumption of the cars or the same electromotor principle gives different "output" efficiency in the electric car.

In summary, the specialization operates with precise electromagnetic impedance selection [84], using the heat on membrane rafts [53], and makes harmony by applying thermal [85], and non-thermal effects [86] [87]. The applied modulation well supports the precise selection of the malignant cells [85]. The mEHT breaks the paradigm that the physical conditions do not allow the proper biological effects, as researchers show from Charite University [88]. The electric concept in sequential magnification summarizes the main principle, **Figure 27**.

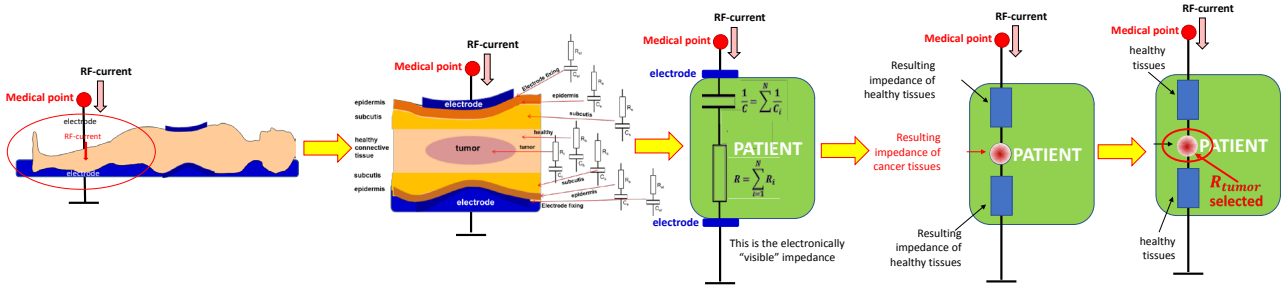

Figure 27. The series of the action of mEHT shows how it matches the focus on the tumor.

3.3.2. Penetration Depth

The penetration depth in the case of wave-absorption is the radiative penetration depth defined by the planar-wave absorption [89] [90], which is a loss of the absorbed specific energy or field in the body. The definition of the penetration depth of energy-absorption is the distance in the body when the initial 100% of

energy from the surface decreases by 1/e (remains only 37% of the energy). This does not mean blocking the beam deeper. It is an exponential function. We have practical knowledge about the X-ray diagnosis, which sees the deep lesions in the body. However, these X-rays have less penetration depth than 10 cm, Figure 28 [91].

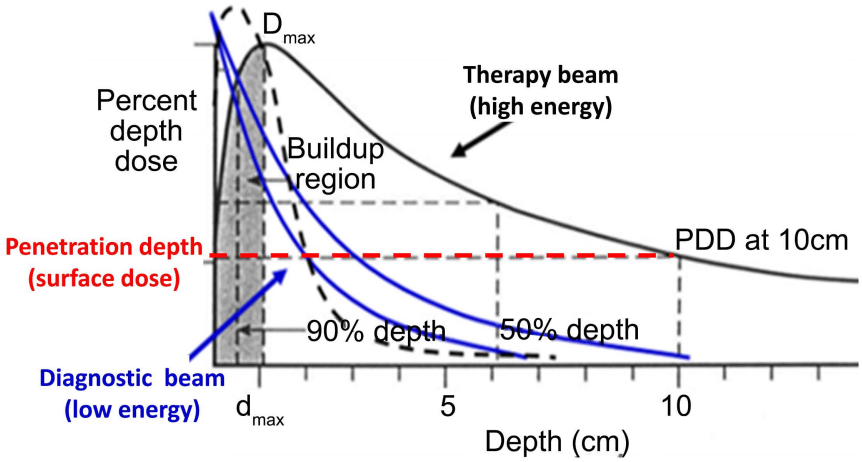

Figure 28. Diagnostic and therapeutical photon beams in X-ray radio diagnosis and therapy. Typical dose curves by photon (X-ray, γ-ray) radiation with typical penetration into dense tissues.

The beam continues its way in the body with 37% intensity, reaching the doubling of the penetration depth with 13.7% intensity, and so on, Figure 29.

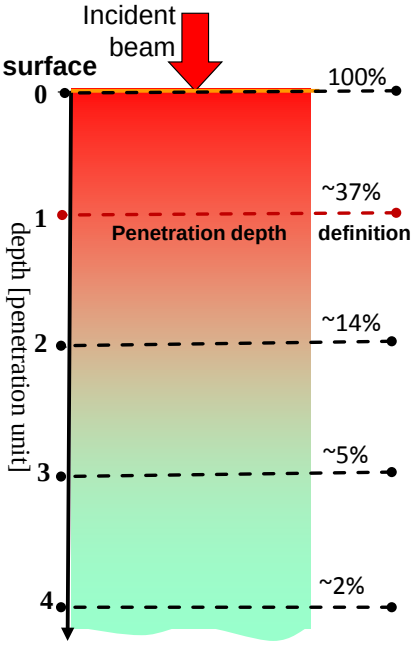

Figure 29. The principle of the definition of penetration depth: when the energy loss is 63% (remains 37%). Four times of penetration-depth, about 2% of the energy of the incident beam remains. This is the basis of X-ray diagnostic detection.

Assuming a patient with 20 cm thickness, the X-ray detection has less than 2% of the initial 100% beam intensity, but this is enough to construct an image, Figure 30 [92].

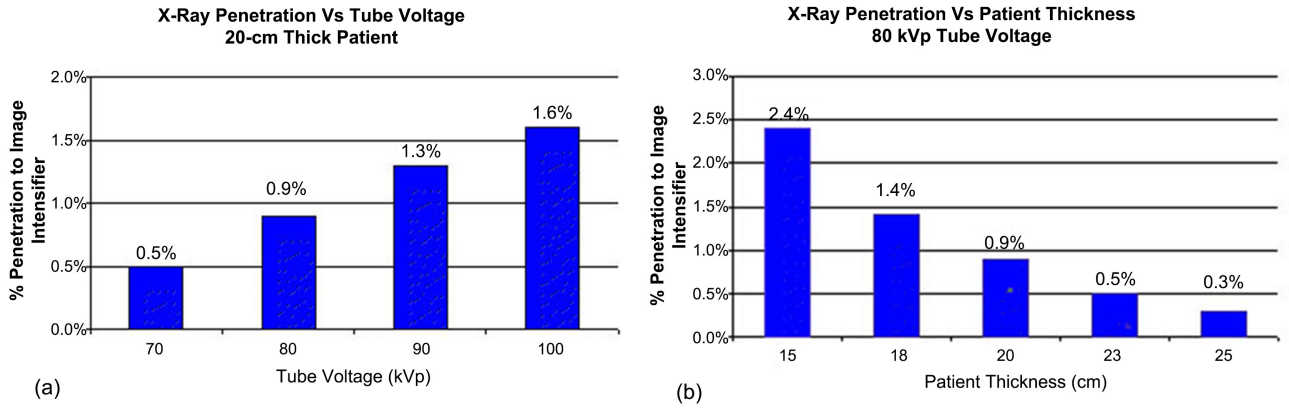

Figure 30. Typical intensities (percentage of the incident 100% beam) can be detected for X-ray images through the patient. In this case, and this tube voltage, the 20 cm patient thickness is approx. four times larger than the penetration depth. (a) Dependence of the voltage of the tube; (b) Dependence of the thickness of the patient at 80 kVp tube voltage.

In the case of electron-beam, the exponential loss is sharper, decreasing quickly, Figure 31 [93].

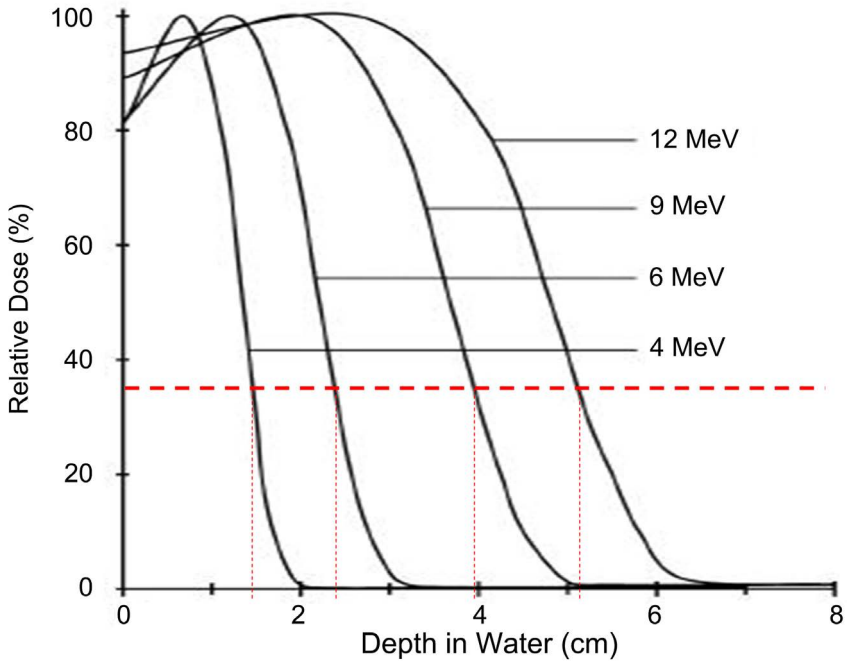

Figure 31. Penetration of electron-beam has a sharper decrease by depth. The definitive penetration depth is a few cm, shown with a dashed line.

In the case of non-ionizing radiation, the penetration is longer depending on the applied frequency (Figure 32) [94] and conductivity of the tissue (Figure 33) [94].

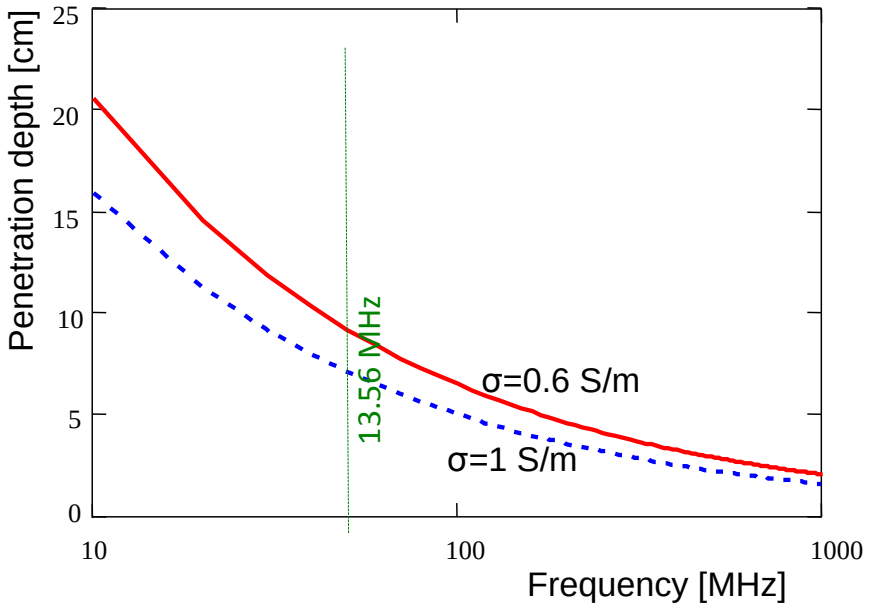

Figure 32. The penetration depth (37%) depends on the conductivity of the tissue. The average conductivity of muscle is approximately 0.5 S/m, so the penetration depth at 13.56 MHz frequency is about 17 cm. (at 8 MHz, it is approx. 20 cm.)

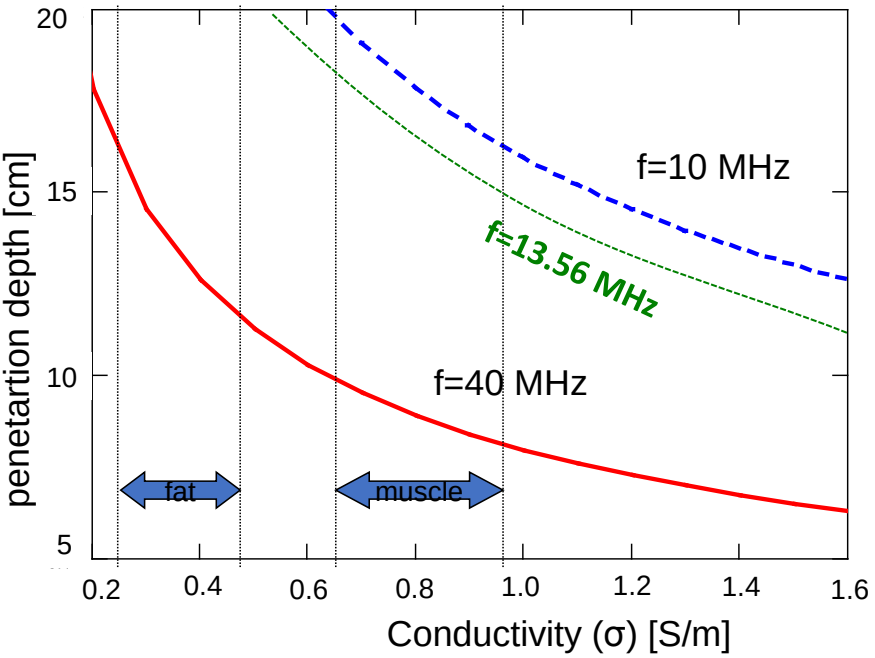

Figure 33. While the penetration depth is high in the fat, that absorbs a high energy value, leading to adipose burn. The apparent contradiction is the constrained increased voltage of the electrode required to push through the fatty tissue.

The jump of the electric field vector on the surface layer causes energy-absorption.

Measurements of the frequency dependence of the penetration depth in ex-vivo tissues show the correctness of the above considerations, Figure 34 [95].

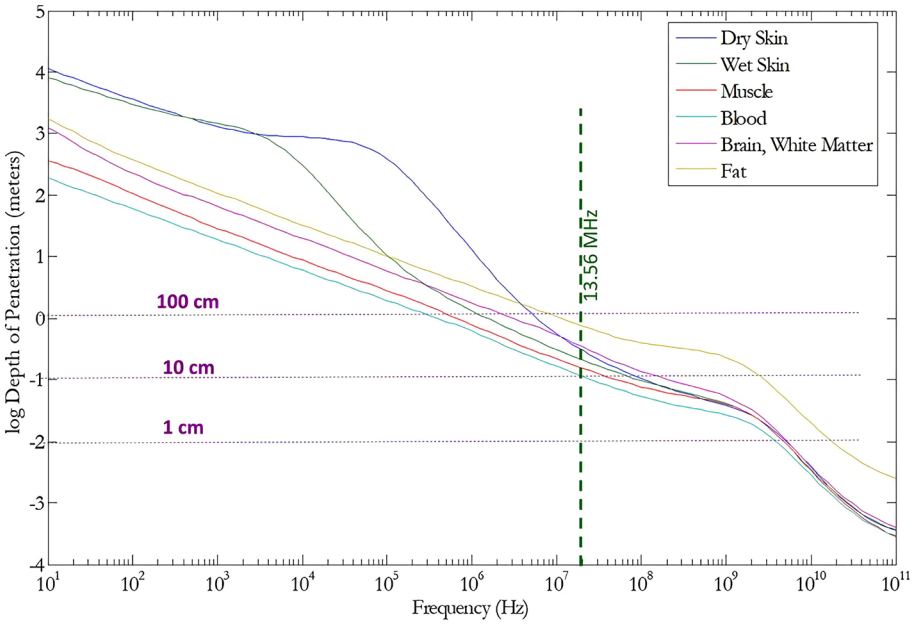

Figure 34. The penetration depth in various tissues vs. applied frequency. The 13.56 MHz is over 10 cm in all of the cases (the lowest is for blood, which is very good for selection). The penetration is rapidly decreasing by increasing frequency.

It is clear that the same forwarded energy exposition with identical energy-flow [W/m^2] can cause different energy-absorptions depending on the given conditions [96] [97], the actual organ [98], and the actual frequency [99]. The penetration depends on the electromagnetic parameters but does not depend on the patients' thickness. The impedance matching increases the penetration depth in homogeneous media by an additional 38%. (Note that the measurements and calculations assume homogeneous media.) The impedance matching selection focuses on the tumor-cells. The mEHT maximizes the RF-current, and only the focusing and the original energy deposit has importance [28]. The selection means that the real penetration is much more, and crosses the entire body.

3.3.3. Action Depth

Plane-wave capacitive coupling and all the homogeneous heating methods use only the heat to destroy the cancer-cells. The mEHT in its selective (heterogenic) heating combines the heat effect with the excitation of cellular signals. This fact modifies the induced processes' action depth as mEHT does not need such a massive energy-absorption as homogeneous heating needs in order to heat for the entire tumor-mass. We know very well that the real depth where the action is effective is an interval. For example, the effects of X-ray for apoptosis do not follow the decreasing energy-curve at the penetration. Even oppositely, it increases when the energy drops below a specific level, **Figure 35** [100]. This is because the smaller energy can generate bystander effects and so it can trigger apoptotic signals. This makes a complete interval for the apoptosis, which does not correlate with the penetration depth.

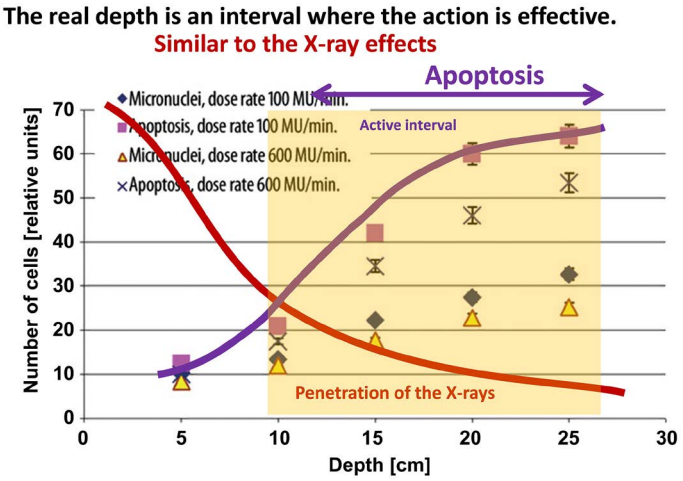

Figure 35. The number of cells with micronuclei, apoptosis as a medium depth function for 100 MU/min, and 600 MU/min dose rates, $p < 0.05$. Each point represents the mean value of three experiments; MU—Monitor Units (arbitrary).

The mEHT method also kills the malignant cells with apoptosis [101]. The apoptotic signal needs much less energy (and field) than the necrotic process [102], shown in the strict synergy of the heat and field effects [35]. The selection and initialization of the process are essential for this, which could happen by a few watts in-depth only. This is even more trivial when we see the immune effects, which are generated, act at distant sites [103], and have no real boundary with the observed abscopal effect [104]. In this meaning, instead of the penetration depth, we have to use the "depth of action," which defines the depth when the mEHT is active, even when the energy is less than the 37% of the incident beam, Figure 36.

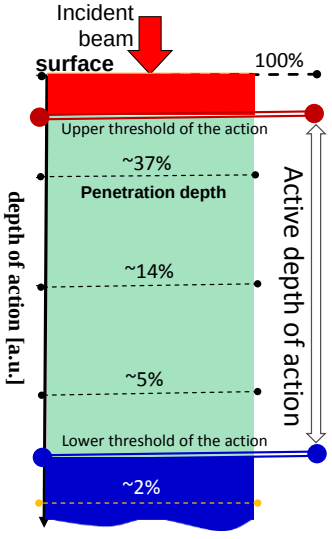

Figure 36. The active depth of mEHT is deeper than the average penetration depth because even 5 W could cause lethal apoptotic signals in selected cells. When the incident beam has 100 W energy, the depth when the mEHT is active could be three times the definitive (37 W) penetration depth.

The increased drug penetration and intensified pharmacokinetics by mEHT [82] [83] promote further elongation of the action depth.

In summary, the action depth for mEHT is deeper than the thickness of the patient's treated cross-sectional distance up to 60 cm (~200 cm circumflex of the cross-section).

3.3.4. The Dosing

Oncological hyperthermia presently faces multiple problems [19], where the most challenging is the lack of a clearly defined and measurable dose for clinical and research applications. The correct dose-definition of hyperthermia therapy is a critical issue in research and is crucial to the future of hyperthermia in oncology [105].

In a homogeneous heating approach, the dose considerations concentrate on the volume percentage, which could be considered having isothermal status. Complete homogeneity of heating of living objects could be achieved only in the WBH process, as LRHT has huge anatomical, physiological, bio-electromagnetic, and thermal heterogeneities, limiting the isodose-type approach. In the WBH process, the temperature was easily measurable and could be used for dosing the therapy. The proposed dose at present is the cumulative equivalent minutes referring to 43˚C: $CEM43\,T_x$ (measured in minutes) [106] [107] [108]; referring to necrotic cell killing at 43˚C. Due to the natural inhomogeneities, this dose contains the percentage of the target which has an approximately isothermal condition, denoted by T_x at the end of the practical applications [107]. For example, when the measured temperature is actually T_{90} in 90% of the monitored sites (referred to as the thermal isoeffect dose in 90% of the area).

In LRHT, the absorbed energy creates heat, but due to the non-linear feedback by transport properties (intensified blood and lymph flow), the situation is far from a state of equilibrium [109]. The blood-flow increases more in the healthy host tissues, causing a certain gradient of the flow intensity to heat the tumor's boundary. The most vivid, mostly proliferative layer of the tumor is near its border, so the cells which need the most heat-treatment remain at a lower temperature than the internal part of the tumor lesion, so the basic homogenous requirement is less realizable in the vivid tumor part than inside of its volume, which is often necrotic, without transport activity. The temperature dosing is problematic not only by the missing the isotherm condition but also because of its very complicated measurement.

Moreover, $CEM43\,T_x$ is controversial, it failed to show the local control characterization of clinical results in soft tissue sarcomas, [110], but was correlated with clinical results for superficial tumors [111]. When administering a dose of $CEM43\,T_{90}$ for local hyperthermia, it did not show a correlation between dose and clinical outcomes (like local remissions, local disease-free survival, and overall survival) [112]. It is calibrated by *in vitro* experiments [110], which are far from the reality of human medicine. Its necrotic reference at 43˚C makes this

dose unrealistic because in most human hyperthermia treatments, such a temperature is not reachable in the whole tumor. While the high temperature is realized in the ablation-like locality, the dosing by $CEM43\,T_x$ was false [113]. The inapplicability of this in-vitro calibrated dose is echoed in the whole-body hyperthermia (WBH) application, in which $CEM43\,T_{100}$ is very high (T_{100} means the complete isothermal heating of the tumor by the whole-body heating), but the results are very different from the same dose provided by local hyperthermia of the tumor lesion [114].

However, the challenge is that due to the considerable energy-loss in homogeneous heating processes, the temperature measurement is mandatory because otherwise there is no idea about the actual absorbed power in the target. In the method of mEHT, the measurement is not necessary in order to determine the absorbed power. The technique is able to accurately measure the absorbed energy by the incident beam [84]. Due to the high efficiency of current matching [115], the dosing of the treatment is simply calculable by the absorbed energy [64] [116] instead of by the complicated, inaccurate, and mostly invasive measurement of local temperature.

3.3.5. Heating Process

The homeostatic concept allows adaptation time for the physiological regulations to stabilize the actual homeostatic status. This complex approach requests a non-constant power during the treatment [117]. The simplest realization of the complex process involves step-up heating. The step-up heating is crucial. It has multiple additions to the success of mEHT:

- At electromagnetic heating, the stress is considerably focused on the cells which develop stress-proteins (HSPs) (chaperons to defend their status). The healthy cells rapidly develop 10-times more protective intracellular HSPs than the base level, while the stressful malignant cells only develop a maximum of 30% - 50% more of these intracellular proteins. This makes the healthy cells more protected compared to their malignant counterparts.
- The gradually increased HSP chaperones in malignant cells have time to go to the membrane and be liberated from the cell when the rafts are excited and the signals force their release (such selection does not occur in healthy cells). This liberation process is one of the factors of immunogenic cell death.
- The step-up heating supports the heating periods and upregulates the power when it starts to be saturated, which is optimal for the mEHT selection system.
- The step-up fits the homeostatic equilibrium, and so mEHT remains within the well-controllable quasi-linear physiological reactions.
- The sudden heating causes non-linear, non-controllable conditions, and the power shoots over the burning limit, and in most of the cases causes blisters (as is frequently reported by radiate heating methods). So the step-up method allows the control of homeostasis and helps the patient adapt to the ac-

tual energy-increase (I quote a famous experiment when a frog is in the water, which is slowly but gradually heated-up, the animal remains in hot water, even to its death, however, when you try to put a frog in hot water directly, it immediately tries to escape).

When the mEHT is applied strictly as a monotherapy, then step-down heating is necessary to block the neoangiogenic vessels. Due to the missing radio- or chemotherapy effect, the serious cases' metastatic spread has a higher probability, so blocking the vessels' immediately is crucial. But of course, the operating control in these cases has to be more strict.

Even in the step-up approach, the longer heating time tends to the homogenic temperature distribution due to the thermal equalization processes. To keep the non-homogeneous selection, periodic heating is also applicable, but it was only shown in preclinical applications [118].

3.4. Molecular Differences between the Effects of Impedance, and Plane-Wave Matching

The high energy absorption excites the rafts to trigger a signal transmission [78] [79]. The extrinsic signal transfer ignites apoptosis [101] [119] [120], **Figure 37**.

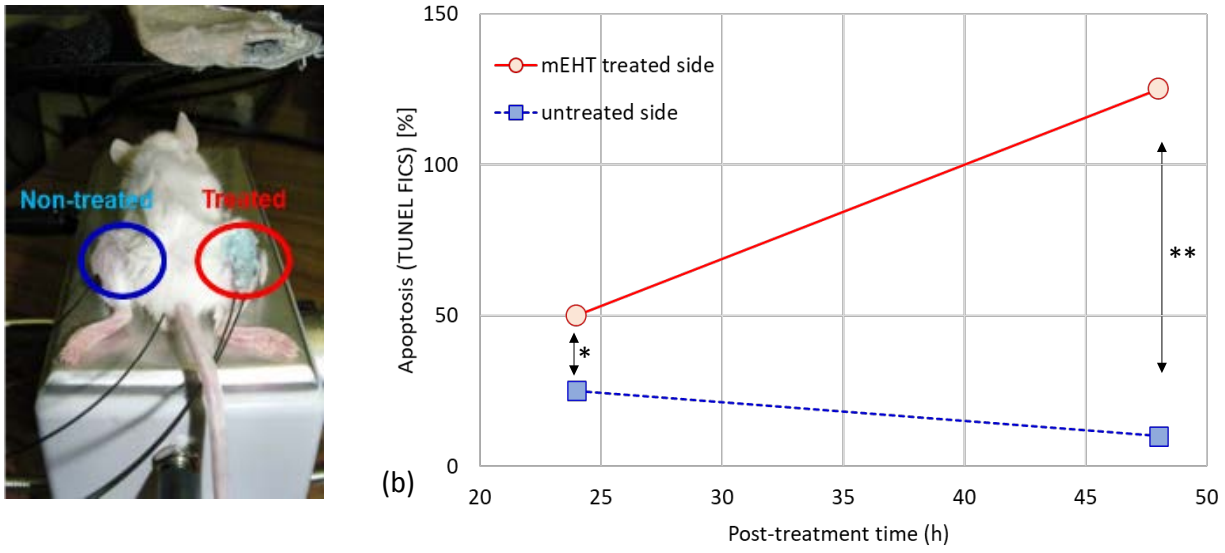

Figure 37. Late apoptosis measurement with TUNEL FICT method (Annexin V positive cells %) in HT29 cells (*in vivo*) 42˚C 30 min treatment parameters, two tumor animal models (a), results show a significant increase of apoptosis in the treated side.

The difference between the molecular effect of the two matching methods of capacitive coupling techniques has been effectively demonstrated *in vitro* [71]. The plane-wave capacitive hyperthermia (PWCHT) gives the same results as the naturally homogeneous water-bath hyperthermia (WBHT), as seen by the apoptotic processes including the reactive oxygen species (ROS) and calreticulin (**Figure 38**) [121].

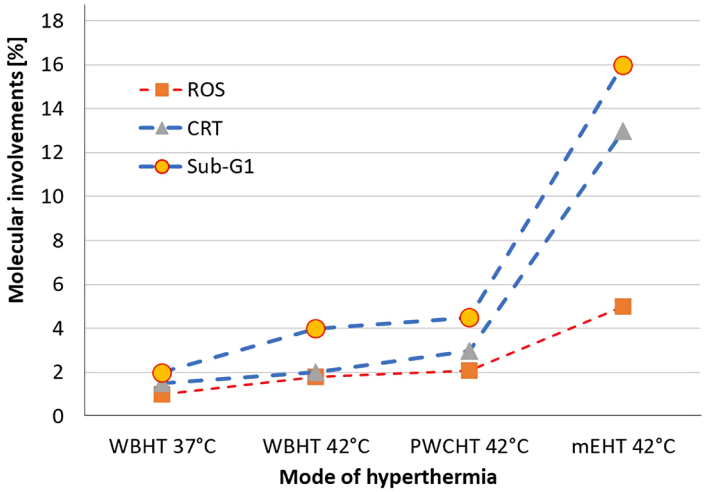

Figure 38. Molecular changes in Hepatoma (HepG2) cell-line *in vitro*. Apoptosis final state TUNEL (Annexin V positive cells %). WBHT—water bath hyperthermia (homogeneous heating reference at 37˚C and 42˚C); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C.

It is important to note that the purely homogeneous heating resulting from the water-bath hyperthermia (WBHT) produces comparable results to the plane-wave matching, indicating that plane-wave matching techniques also favour homogeneous heating, while mEHT differs significantly in the effects and outcomes. The apoptotic process involves a change in the potential of the mitochondria's membrane and the Ca^{2+} influx into the cell, **Figure 39** [122].

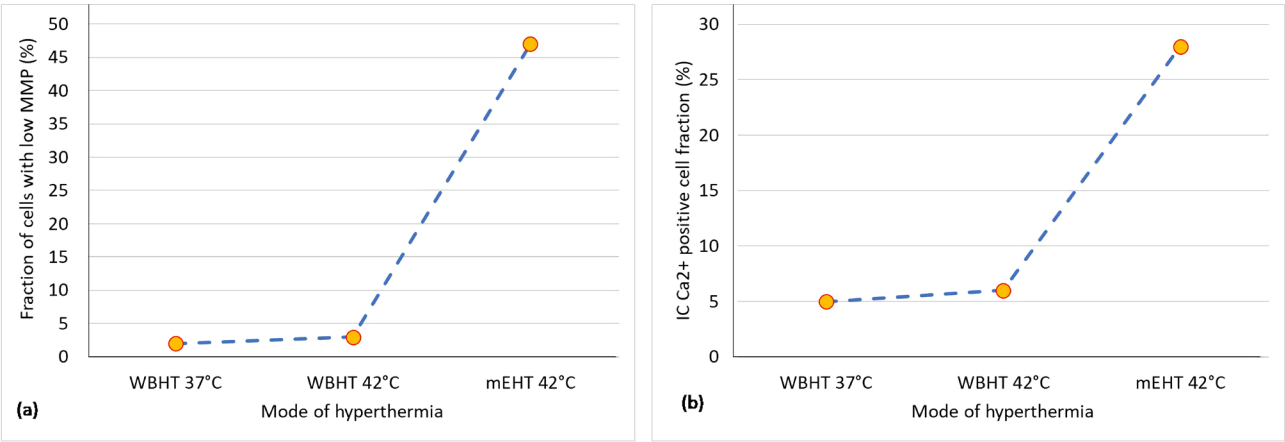

Figure 39. Comparison of heterogeneous heating caused by mEHT with homogeneous heating. (a) Fraction of cells with lowered mitochondrial membrane potential; (b) The calcium influx and intracellular ionic concentration (homogeneous (WBHT) heating reference at 37˚C and 42˚C, mEHT at 42˚C). Abb: WBHT—water bath hyperthermia, mEHT: modulated electro-hyperthermia.

The caspase developments' variants during the apoptosis require the extrinsic and intrinsic pathways (involving Caspases 8 and 9 **Figure 40**), and the caspase-independent signal routs [101]. Additionally, Septin4 blocks the XIAP, which makes free the extrinsic pathway from this suppressor [123]. All of these factors combined ensure apoptosis is the final result.

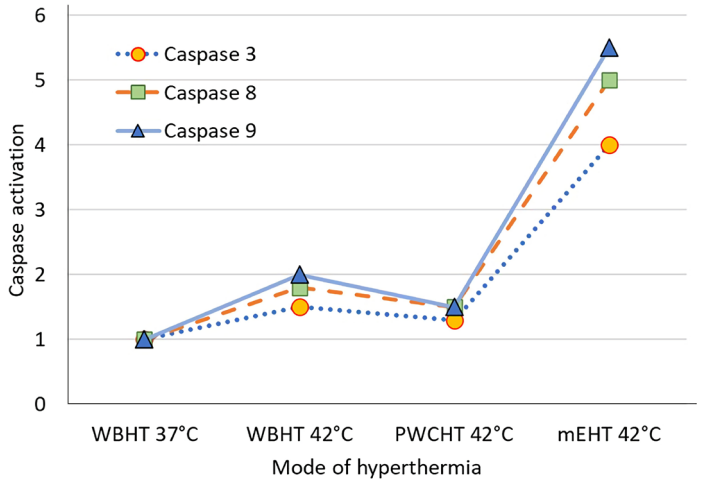

Figure 40. Caspase activation shows Caspase 8 and Caspase 9 for extrinsic and intrinsic pathways, respectively. WBHT—water bath hyperthermia (homogeneous heating reference at 37˚C and 42˚C); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT—modulated electro-hyperthermia at 42˚C.

The homogeneous heating results in energy-absorption in the tumor-mass, in an attempt to realize an isothermal situation. However, mEHT focuses the energy absorption on membrane rafts (nanoscopic size). The excess energy makes the extrinsic excitation of the apoptotic pathways (TRAIL-FAS-FADD complex), and makes the gradients through the cell-membrane, producing various thermal effects [79]. It increases the extracellular and the raft temperature to a level much higher than their environment. In consequence the calibration curves by measuring the apoptotic intensity significantly differ, **Figure 41** [35] [79]. It is clear that mEHT produces the same 25% relative cell-death as homogeneous heating in ≈3˚C lower temperature, which is an approximate difference between the local nano-temperature (at the membrane rafts) and the tumor-average temperature.

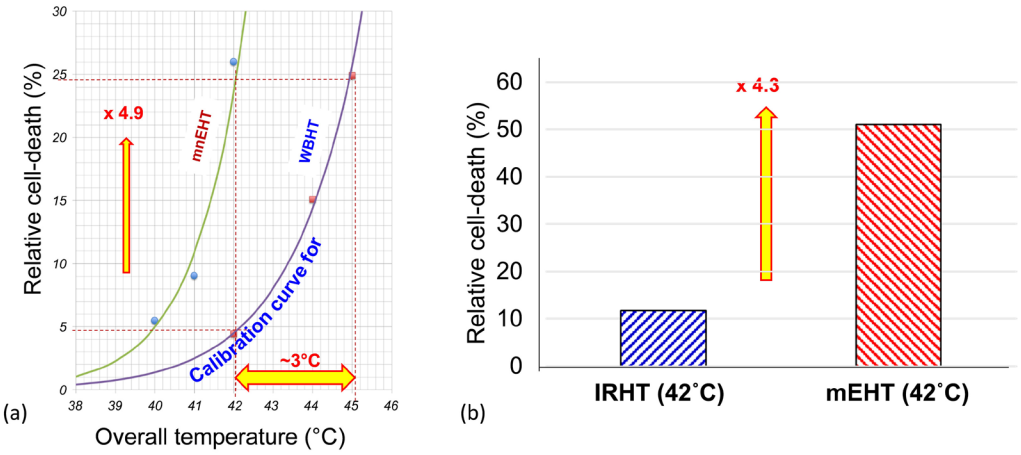

Figure 41. The relative cell-death (%) (a) *in vitro* [U937 cell-line] and (b) *in vivo* [HT-29 cell-line, xenograft]. The mEHT heterogeneous heating is >4 times more effective than the homogeneous technique at the 42˚C reference temperature. (IRHT—infrared, homogeneous heating technics).

In another experiment, a rough calibration comparison between mEHT and water-bath homogeneous heating shows even higher differences between the nano-scale and macro-average temperature, Figure 42.

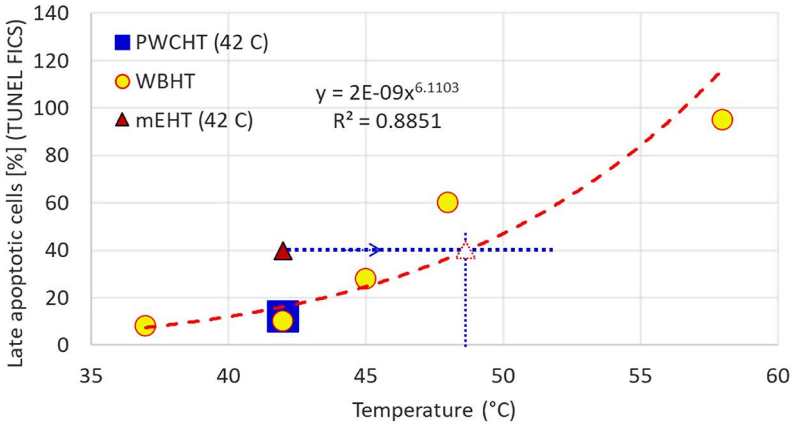

Figure 42. The temperature dependence of the apoptosis. The mEHT at 42˚C produces such apoptotic level, like homogeneopus heating does at >45˚C (WBHT—water bath hyperthermia (homogeneous heating reference); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C). (Apoptosis final state TUNEL (Annexin V positive cells %))

A direct temperature measurement of membrane rafts also shows a significant difference in a pilot experiment, Figure 43 [124].

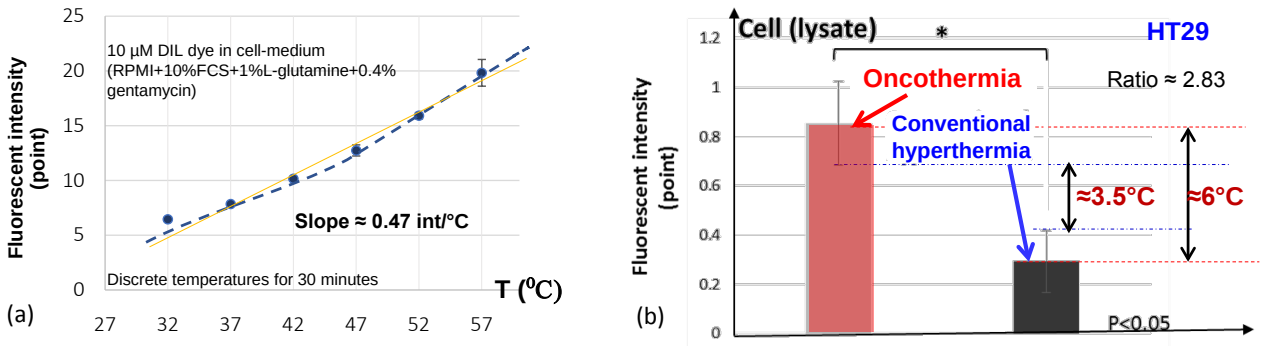

Figure 43. Membrane temperature measurement *in vivo* (mice, HT29 cells) 42˚C, 30 min. (a) *DIL* (Dilatometry)temperature calibration; (b) Fluorescent measurement, show the much higher temperature on the membrane of mEHT treated sample than on the membrane of the homogeneously (WBHT) heated one.

The heating certainly causes stress, producing chaperone proteins. The most characteristic protein family of chaperons is the heat shock protein 70 (HSP70). This protein has a double edge sword reaction: intracellularly it tries to avoid the cell's apoptosis, extracellularly it acts oppositely: it promotes the cellular apoptosis. Any kind of hyperthermia results in the expression of HSP70, but at different levels. Due to the large electromagnetic load that accompanies the heating processes, mEHT trigger the expression of more HSP70 than homogeneous heating, Figure 44. This difference is most significant 48 hours after treatment.

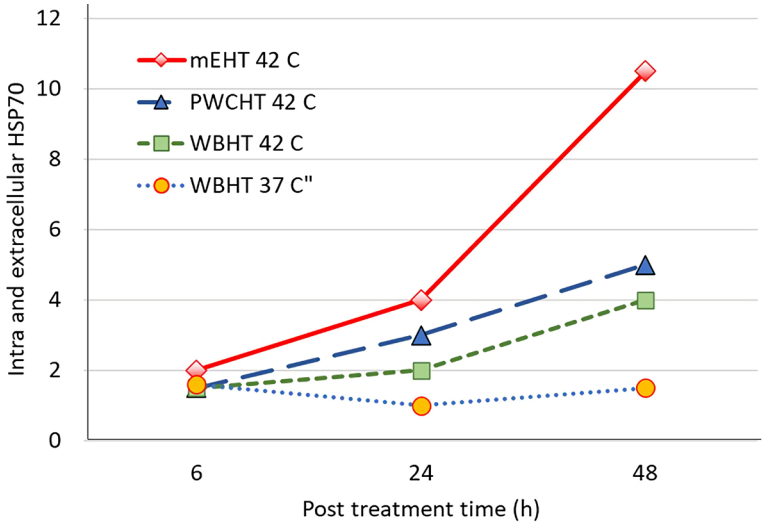

Figure 44. Comparison of the cleaved Caspase CD3+ expression. (WBHT—water bath hyperthermia (homogeneous heating reference); PWCHT—plane-wave capacitive hyperthermia at 42˚C, mEHT at 42˚C).

However, the location of the measured HSP70 is different. After 48 hours the concentration of the intracellular HSP70 returns to the level it was before the heating, but the extracellular levels increase, **Figure 45** [125].

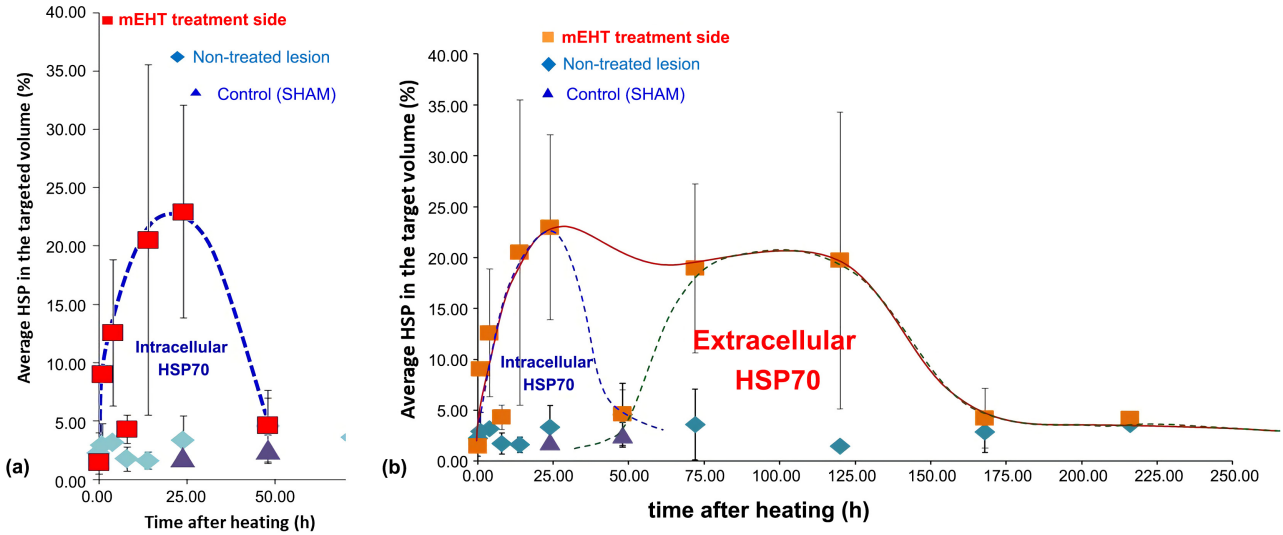

Figure 45. Development of HSP70 after mEHT treatment of *in vivo* xenograft mouse model (HT29 cell-line, at 42˚C, 30 min). (a) The level of HSP70 returned to the baseline level at 48 h post-treatment; (b) The development of the extracellular HSP70 only returns to the baseline level after a week.

A detailed review of cancer models describes the molecular mechanisms of mEHT [126].

3.4.1. Immunogenic Cell-Death

The apoptosic process caused by mEHT causes special immunogenic type of changes, allowing the genetic information to form antigen-presenting cell (APC)

by the maturation of the dendritic cells (DCs) or the macrophages. The excitation of the actual membrane rafts initiates immunogenic cell death (ICD). This process starts by producing a particular damage-associated molecular pattern (DAMP) (**Figure 46**) [127].

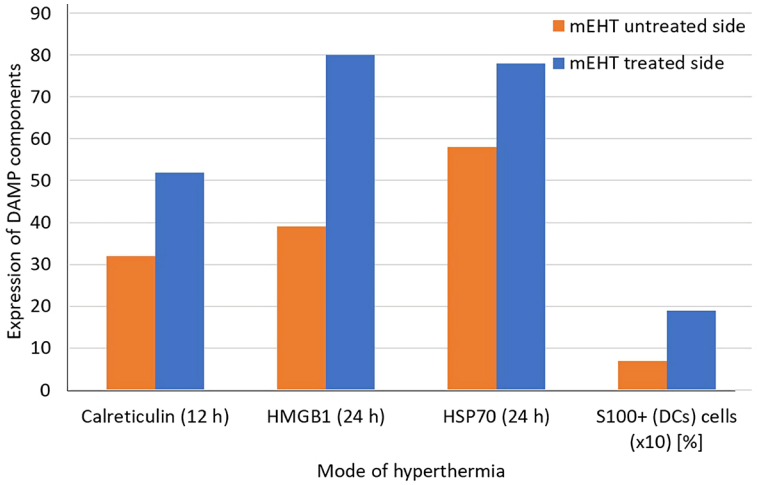

Figure 46. The DAMP development *in vivo* in an allograft mouse model (CT26 cells).

The proper signal transfer, and DAMP production could be limited or blocked by too much energy absorption on the rafts, which destroys it instead of exciting the transmembrane proteins, and receptors. The high energy-absorption may ignite phase transition mechanisms. For example, the kink in the Arrhenius plot at ~42.5˚C is probably a lipid-associated phase transition [128] [129] [130], which could lower the activation energy needed to facilitate the desired changes [131]. The change in the kink is expected to be influenced by the blood flow [33]. Among such conditions, the immunogenic cell-death is seldom, and also the APC and the immune actions will not be produced, because the temperature is high, and the membrane phase-transition makes hard producing apoptotic bodies. Well-defined sequences and spatio-temporal actions are necessary for the DAMP, which high energy technologies are not able to do. The possible small amount of proper DAMP production by high energy technologies would be disrupted, resulting in a mixture of effects, as is often observed many hyperthermia studies. This causes inconsistent results as there is no control of the processes in the complex dynamical network seen at a nanoscopic level.

3.4.2. Tumor-Specific Immune Effect

The main effect of mEHT is the energy absorption, like in all hyperthermia treatments, but it is further enhanced by the selection mechanisms, which makes it heterogenic, targeting, and energy-focused. The bio-electromagnetic and structural differences of malignancies appear in their spatial and temporal self-organized fractal structure, harnessed by the modulation effect. The DAMP-ICD associated tumor-specific immune effect is active in the entire body and therefore acts as vaccination. The re-challenge of the body with the same

malignancy therefore be expected to be unsuccessful [121]. It is an excellent advantage that without any invasive sampling and extra laboratory preparation, the immune effect is in situ and real-time.

Studies with DC, **Figure 47** [121]; and Marsdenia Tenacissima (MTE), **Figure 48** [127] as an immune-support suggest that when the patient's immune system is weak, due to tumor-development and the side effects of the previous treatments, additional immune support could help for complete action.

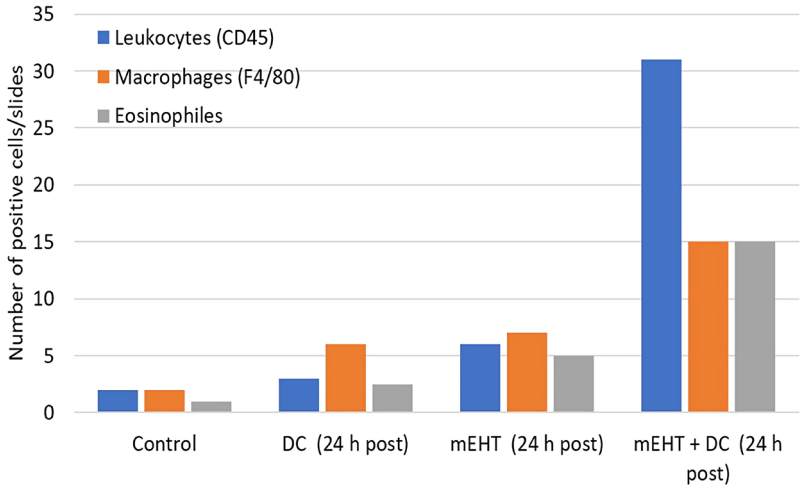

Figure 47. Immune invasion at the tumor 24 h post-treatment (DC—dendritic cell injection).

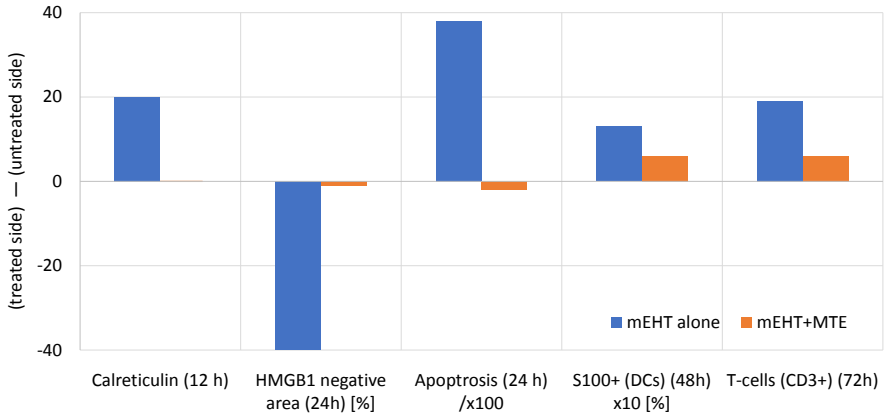

Figure 48. Effect of the immune-support Marsdenia Tenacissima (MTE).

This way, mEHT can create a favorable tumor microenvironment for an immunological chain reaction, improving the success rate of intratumoral dendritic cell immunotherapy [104] [121]. The applied paradigm's strategic point is that our task is to help the body recognize and destroy the malignancy. Targeting a product (such as weak points of tumor growth or simple destruction of the cell by thermal necrosis) could not repair the complex system. The entire process has to be targeted in order to re-establish the healthy state [132]. Developing a tumor-specific immune reaction directly drives the immune system to reparation.

The mEHT method recognizes the tumor by its biophysical, mainly electric impedance parameters, which at the same time has diagnostic value, Figure 49 [104] [133] [134].

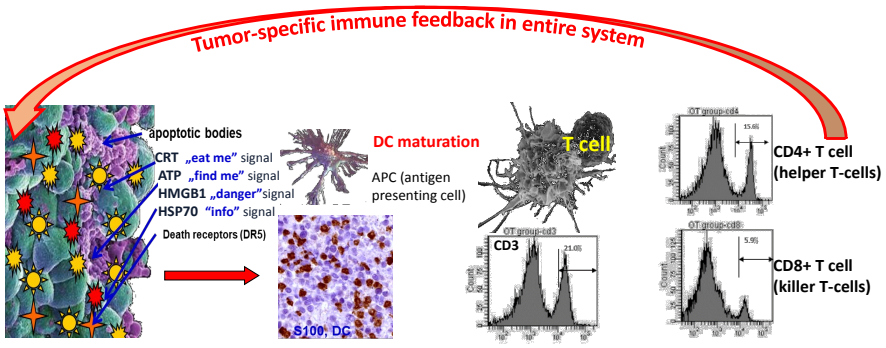

Figure 49. Producing the tumor-specific immune reaction. The gentle apoptosis produces DAMP and ICD presenting genetic information to antigen-presenting cells (APCs) which produces killer T-cells which are active in the entire body. (Works like a tumor-vaccination.)

The mEHT in this combination is a typical theranostic [135] therapy, which could be applied in combination with other standard tumor therapies like chemotherapies [136] [137], radiotherapies [138] [139], or check-point inhibitors [140]. A promising immunological approach is the combination of mEHT with viral therapies [141] [142].

3.5. Clinical Applications

A review of the clinical pieces of evidence of mEHT summarized essential clinical evidence [143]. The clinical trials are summarized in Table 1.

Table 1. Clinical trials that used mEHT in combination with other treatments.

No.	Tumor site	Number of patients	Treatment used	Results	Reference
1	Relapsed high-grade gliomas	15	mEHT + alkylating chemotherapy	Tolerable and safe for patients with relapses by high escalation of the dose too.	Wismeth, *et al.* 2010 [144]
2	Advanced gliomas	12	Chemotherapy, radiotherapy + mEHT	CR = 1, PR = 2, RR = 25%. Median duration of response = 10 m. Median survival = 9 m, 25% survival rate at 1 year.	Fiorentini, Giovanis, *et al.* 2006 [145]
3	Relapsed malignant gliomas	24	mEHT	Median survival = 19.5 months, 55% survival rate at 1 year, 15% at 2 years.	Fiorentini, Sarti, *et al.* 2018 [146]
4	Advanced glioblastoma	60	mEHT + immunotherapy	No added toxicity by immunotherapy. Median progression-free survival (PFS) = 13 m. Median follow up 17 m, median OS was not reached. Estimated OS at 30 m was 58%.	Van Gool, *et al.* 2018 [142]
5	Various brain-gliomas	140	Chemotherapy + radiotherapy + mEHT	OS = 20.4 m. mEHT was safe and well tolerated.	Sahinbas, *et al.* 2007 [147]
6	High-grade gliomas	179	mEHT + radiotherapy + chemotherapy	Longstanding complete and partial remissions after recurrence in both groups.	Hager, Groenemeyer, *et al.* 2008 [148]

Continued

7	Glioblastoma & Astrocytoma	149	mEHT + radiotherapy + chemotherapy (BSC, palliative range)	5y-OS = 83% (AST) in mEHT vs. 5y-OS = 25% by BSC. 5y-OS = 3.5% in mEHT vs. 5y-OS = 1.2% by BSC for GBM. Median OS = 14 m of mEHT for GBM and OS = 16.5 m for AST.	Fiorentini, Sarti, *et al.* 2019b [149]
8	Advanced hepatocell. carcinoma	21	Chemotherapy + mEHT	PR = 1, CR = 0, SD = 11. Combined therapy was effective, and no major complications were observed.	Gadaleta-Caldarola, *et al.* 2014 [150],
9	Refractory hepatocell. carcinoma	22	mEHT + thermo-active agents (TAA) or mEHT without TAA	CR = 1, PR = 0. Median OS = 20.5 weeks. 50% showed evidence of increasing QoL and minimal toxicity.	Ferrari, Ponti *et al.* 2007 [151]
10	Small-cell lung cancer (SCLC)	22	Chemotherapy + mEHT	mEHT enhanced destroying the cancer cells. Improved the OS of patients too.	Lee, Haam *et al.* 2013 [152]
11	Advanced cervical cancer	236	Random. Phase III (chemoradiation alone (CHR) and mEHT group (mEHT + CHR) [preliminary data]	Preliminary data for first 100 participants. A positive trend in survival and local disease control by mEHT. No significant differences in acute adverse events or quality of life between the groups.	Minnaar, Baeyens *et al.* 2016 [153]
12	Advanced cervical cancer	38	Chemotherapy + /− mEHT	The overall response (CR + PR + SD vs. PD) to was significantly greater with mEHT. No complications or extra adverse effect by mEHT.	Lee, Lee *et al.* 2017 [136]
13	Advanced cervical cancer	72	Radiotherapy + chemotherapy + mEHT	CR + PR = 73.5%; SD = 14.7%. The addition of mEHT increased the QoL and OS.	Pesti, *et al.* 2013 [139]
14	Advanced cervical carcinoma	20	mEHT + radiotherapy + chemotherapy	mEHT increases the peri-tumour temperature and blood flow in human cervical tumours, promoting the radiotherapy + chemotherapy.	Lee, Kim, *et al.* 2018 [154]
15	Advanced cervical carcinoma	108	mEHT + chemoradiotherapy	The metabolicly complete remnission (CMR) of disease outside the radiation field at 6 m post-treatment shows abscopal effect, significantly associated with the addition of mEHT.	Minnaar, Kotzen, *et al.* 2020b [155]
16	Advanced cervical carcinoma	206	Random. Phase III (chemoradiation alone (CHR) and mEHT group (mEHT + CHR) [preliminary data]	Compliance to mEHT treatment was high (97% completed ≥8 treatments) with no significant differences in CRT-related toxicity between treatment groups or between HIV-positive and -negative participants.	Minnaar, Kotzen, *et al.* 2020a [156]
17	Advanced cervical carinoma	202	mEHT + chemoradiotherapy	Six month local disease-free survival (LDFS) = 38.6% for mEHT and LDFS = 19.8% without mEHT ($p = 0.003$). Local disease control (LDC) = 45.5% with mEHT LDC = 24.1% without mEHT; ($p = 0.003$).	Minnaar, Kotzen, *et al.* 2019 [157]
18	Stage III-IV NSCLC	15	Ascorbic acid (AA) infusion + mEHT	AA safely synergies with mEHT and well tolerated, no major adverse effects	Ou, Zhu, *et al.* 2017 [158],
19	Advanced NSCLC	97	mEHT + radiotherapy + chemotherapy	Median OS = 9.4 m with mEHT OS = 5.6 m without mEHT; ($p < 0.0001$). Median PFS = 3 m for mEHT and PFS = 1.85 m without mEHT; $p < 0.0001$.	Ou, Zhu, *et al.* 2020 [159]
20	Advanced NSCLC	311 (61 + 197 + 53)	Radiotherapy + chemotherapy + mEHT	Two centres PFY ($n = 61$), HTT ($n = 197$) control ($n = 53$). 80% (PFY), 80% (HTT) had distant metastases, conventional therapies failed. Median OS = 16.4 m (PFY), 15.6 m (HTT), 14 m (control); 1st y survival 67.2% (PFY), 64% (HTT), 26.5% (control).	Dani, Varkonyi, *et al.* 2011 + Szasz, 2014b [160]

Continued

21	Advanced NSCLC	44	Chemotherapy + ketogenic diet + hyperbaric oxygen + mEHT	Mean OS = 42.9 m, PFS = 41 m. No problems were encountered due to fasting, hypoglycemia, ketogenic diet, mEHT or hyperbaric oxygen therapy.	Iyikesici, 2019 [161],
22	Peritoneal carcinomatosis with malignant ascites	260	mEHT + traditional Chinese medicine (TCM) compared to intraperitoneal chemoinfusion (ICI)	The Objective response rate (OPR) = 77.7% in study group (mEHT + TCM) vs. OPR = 63.8% in the ICI group. The QoL = 49.2% vs. 32.3% in the active and control group. Adverse effect rate (AER) = 2.3% vs. 12.3%.	Pang, Zhang, *et al.* 2017 [162]
23	Advanced rectal cancer	76	mEHT + radiotherapy + chemotherapy	Downstaging + tumor regression, ypT0, and ypN0 was better with mEHT than without. No statistical significance.	You *et al.* 2020 [163]
24	Liver metastasis from colorectal cancer	80	Chemotherapy + mEHT	Median OS = 24.5 m, and expected (historical) OS = 11 m.	Hager, *et al.* 1999 [164]
25	Various types of sarcoma	13	Radiotherapy + chemotherapy + mEHT	Primary, recurrent, and metastatic sarcomas responded to mEHT, the masses regressed.	Jeung, *et al.* 2015 [165]
26	Soft-tissue sarcoma	24	Chemotherapy + mEHT	Pathological response rate (pRR) = 42% in neoadjuvant chemo-hyperthermia treatment median OS = 31 m.	Volovat, Volovat *et al.* 2014a [166]
27	Advanced pancreas carcinoma	25	mEHT + chemotherapy + ketogenic diet + oxygen therapy	Mean follow-up = 25.4 m, median OS = 15.8 m, median PFS = 15.8 m.	Iyikesici, 2020a [167]
28	Advanced pancreas carcinoma	26	Chemotherapy + mEHT	SD = 9 (48%), PR = 4 (21%) PD = 6 (31%)	Volovat, Volovat *et al.* 2014b [168]
29	Advanced pancreas	106	mEHT + radiotherapy + chemotherapy	After 3 m, PR = 22 (64.7%), SD = 10 (29.4%), PD = 2 (8.3%) with mEHT after 3 m of the therapy. In group without mEHT in the same time: PR = 3 (8.3%), SD = 10 (27.8%), PD = 23 (34.3%). The median OS = 18 m with mEHT and OS = 10.9 m without mEHT.	Fiorentini, Sarti, *et al.* 2019[a] [169],
30	Advanced pancreas carcinoma	20	Enzyme-therapy + immunolo-modulation + hormone therapy + mEHT	Median OS > 10 m. Most patients experienced partially excellent improvement of QoL.	Hager, Süsse, *et al.* 1994 [170]
31	Advanced pancreas carcinoma	133 (26 + 73 + 34)	Radiotherapy + chemotherapy + mEHT	Two centres PFY ($n = 26$), HTT ($n = 73$) control ($n = 34$). 59% (PFY), 88% (HTT) had distant metastases, conventional therapies failed. Median OS = 12.0 m (PFY), 12.7 m (HTT), 6.5 m (control); 1st y survival 46.2% (PFY), 52.1% (HTT), 26.5% (control) QoL was improved.	Dani, Varkonyi, *et al.* 2008 [171]
32	Ovarian cancer	19	mEHT with dose escalation	The mEHT treatment was feasible in patients with recurrent or progressive ovarian cancer without any complication.	Yoo *et al.* 2019 [163],
33	Metastatic cancers (colorectal, ovarian, breast)	23	mEHT + radio-therapy + chemotherapy	OS and time to progression (TTP) were influenced by the number of chemotherapy cycles ($p < 0.001$) and mEHT sessions ($p < 0.001$). Bevacizumab-based chemotherapy with mEHT has a favorable tumor response, is feasible and well tolerated for metastatic cancer patients.	Ranieri, *et al.* 2017 [172]

Continued

34	Different types of metastatic/recurrent cancers	33	mEHT + radiotherapy	CR = 2 (6.1%), Very good PR = 5 (15.2%), PR = 13 (39.4%), SD = 9 (27.3%), PD = 4 (12.1%). Three patients (9.1%) developed autoimmune toxicities. All these three ptients had long-lasting abscopal responses outside the irradiated area.	Chi, Mehta, *et al.* 2020 [173]
35	Advanced gastric cancer	24	mEHT + chemotherapy + ketogenic diet + oxygen therapy	CR = 22 (88%) Mean follow-up = 23.9 m, mean OS = 39.5 m, mean PFS = 36.5 m,	Iyikesici, 2020b [174],
36	Various		mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Fiorentini 2020 [175]
37	GBM		mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Van Gool 2021 [176]
38	Rectal cancer	120	mEHT + radiotherapy + surgery	In mEHT group, 80.7% showed down-staging compared with 67.2% in non-mEHT group.	Kim 2021 [177],
39	Gliomas	164	mEHT + chemotherapy + radiotherapy	CR + PR is 41.4% for mEHT and 33.4% for conventional therapies.	Fiorentini 2020 [178]
40	Gastrointestinal cancer	34	mEHT + chemotherapy	The feasibility and success of oncothermia is proven.	Garay 2020 [179]
41	Ovarian, cervical cancer		mEHT + chemotherapy + radiotherapy	The feasibility and success of oncothermia is proven.	Wookyeom 2018 [180],
42	Breast cancer	13	mEHT + chemotherapy + surgery	The feasibility and success of oncothermia is proven.	Szasz AM 2020 [181]
43	Cervical cancer	38	mEHT + chemotherapy	Cox-regression for CTx + mEHT study-group, (Rs-variable time-ratio of start of mEHT compared to OS (overall survival) Coefficient = 6.1, CI (95%) = 7.96; StErr = 4.06, $p = 0.13$, Hazard = 449.	Lee 2020 [81]
44	Various sites	277	mEHT + chemotherapy	52% of the entire group was subjected to result analysis. 48% was not traceable. The result of the 52% was 21.5% PR, 36% SD, 28.9% PD, and 12.6% exitus. So 58.5% of the patients showed either stable disease or partial remission.	Lee 2013 [182]
45	Various sites	784	mEHT + chemotherapy + radiotherapy + surgery	Preliminary results show promising survival trajectories. mEHT is a safe treatment with very few adverse events or side effects, allowing patients to maintain a higher quality of life.	Parmar 2020 [183]
46	Various sites		mEHT + chemotherapy + radiotherapy	Planned trial	Arrojo 2020 [184]
47	Various sites		mEHT + chemotherapy + radiotherapy	The feasibility and success of oncothermia is proven.	Szasz AM 2019 [143]
48	Brain tumor	54	mEHT + chemotherapy	mEHT strongly and significantly enhances the efficacy of the ddTMZ 21/28 d regimen ($p = 0.011$), with a maximum attainable MST of 10.10 months (95%CI 9.10 to 11.10).	Roussakow 2017 [185]

4. Conclusions

The two variants of capacitive coupling, the plane-wave, and impedance matching, make different treatment applications in preclinical experiments and human

medical applications. Technically the difference between these capacitive methods is the design for homogeneous or heterogeneous heating. The homogeneous heating needs to measure the target's temperature, obtaining information about the amount of absorbed energy, while the impedance matching gets direct information about the energy-absorption. This results in a difference in the dosing method because, in the homogeneous approach, the temperature is the mandatory part of the heating dose, while in the heterogeneous case, the absorbed energy characterizes the process. The heterogeneous heating without artificial nanoparticles is realized in the mEHT method. This method has special qualities which improve the conventional hyperthermia results:

1) Excites apoptotic signals by extrinsic pathways.

2) Though the selected membrane rafts, mEHT excites the TRAIL DR5 death-receptor (with FADD and FAS complex), and this extrinsic excitation triggers the ICD.

3) The raft excitation triggers the DAMP and ICD, crucial for the immunogenic (abscopal) effect. This turns the local treatment into a systemic treatment, shown in the elongation of the survival time, without being limited to local control.

4) The immunogenic effect is vital for the cases with far advanced, relapsed, metastatic disease, and not only locally advanced cases.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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