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# On the Thermal Distribution in Oncological Hyperthermia Treatments

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## Abstract

The temperature is one of the principal controlling parameters of oncological hyperthermia. However, local heating forms a complicated thermal distribution in space and has developed over time, too. The decisional factors are the heterogeneity of the targeted volume, the electrolyte perfusions controlled by thermal homeostasis, and the spreading of the heat energy with time. A further complication is that the energy absorption sharply changes by depth, so the spatiotemporal development of the temperature distribution requires specialized methods to control. Most of the temperature imaging facilities (thermography, radiometry, electric impedance tomography, etc.) are less precise than the medical practice needs. In contrast, precise point sensing (like thermocouples, thermistors, and fluoroptical methods) is invasive and measures only a discrete point in the robustly changing thermal map. The two most precise thermal imaging methods, computer tomography, and magnetic resonance are expensive and have numerous technical complications. Our objective is to show the complexity of the temperature distribution inside the human body, and offer a relatively simple and cheap method to visualize its spatiotemporal development. A novel emerging technology, the application of ultrasound microbubble contrast agents is a promising method for solving complicated tasks of thermal distribution deep inside the living body. Noteworthy, the temperature distribution does not determine the full hyperthermia process, nonthermal effects make considerable impact, too. Additionally to the difficulties to measure the thermal heterogeneity during hyperthermia in oncology, numerous nonthermal processes, molecular and structural changes are triggered by the incoming electromagnetic energy, which presently has no spatiotemporal visualization technique. Microbubble imaging has a suitable spatiotemporal thermal resolution, and also it is sensitive to nonthermal effects. Its application for characterization of the modulated electrohyperthermia (mEHT) may open a new theranostic facility, using the synergy of the thermal and nonthermal effects of the radiofrequency

delivered energy. This complex approach gives facility to follow the mEHT processes, and the proposed microbubble ultrasound imaging has a particularly promising advantage sensing and acting also nonthermally, having potential to characterize the thermally conditioned nonthermal electromagnetic effects in oncologic hyperthermia. The mEHT combined with microbubble ultrasound images could be a robust theranostic method against cancer.

## Keywords

Microbubbles, Thermal Heterogeneity, Electric Heterogeneity, Bloodstream, Thermal and Nonthermal Synergy, Temperature Distribution, Temperature Measurements

## 1. Introduction

The medical processes using heat were the first curing approach, remaining a vital "household remedy" even nowadays. The heat from the sunlight is also a well-accepted universal support of health in our modern era, and the biological effects of the Sun (natural, organic vegetation, vitamin support for humans, etc.) are essential for our healthy daily life. Ancient hyperthermia included artificial fever as a common wish of doctors. Their wish was clear: "Give me the power to produce fever, and I will cure all diseases" [1]. The dream of ancient medical geniuses Hippocrates and Rufus of Ephesus about the ability to induce artificial fever to cure cancer [2] seems to be valid, observing promising results. Hypocrites successfully applied local radiative heating to treat breast cancer [3]. Hypocrites had no extended knowledge about the complex regulation of the human body in thermal homeostasis, which is primarily performed by blood perfusion to the heated volume. The temperature approximation by local heating was deduced from the daily practice in households and applied to nonliving systems (cooking, hot water production, etc.) Later, we understood more about the enormous complexity of the human being and its complex interactions with the environment, which defines thermal homeostasis and complicates the treatment with heat. Controlled and homogeneous (isothermal) heating is difficult, and due to physiological activity, it cannot be fixed for a longer time than physiologic relaxation.

The whole body heating is one of the dream-realizing oncological methods of old Greek physicians. It has almost complete thermal homogeneity of the entire body like fever does. Seemingly, whole-body hyperthermia (WBH) offers the best heating possibility because of its easy control (measurements in body lumens) and the complete isothermal load on all malignant cells and tissues. However, the WBH does not provide the expected good results despite the complete isothermal load. Furthermore, this heating has a serious limitation: the physiologic temperature limit <42˚C). The overall survival was better when the chemotherapy was administered alone than in combination with WBH [4], and

the toxicity was also higher in the combined treatment [5]. Contrary to the 10+ times higher dose of WBH (measured with standard dose), a fourfold development of metastases was measured in canine sarcomas combined with radiotherapy compared to local heating [6]. The optimal local cell distortion needs higher temperature than the systemic physiological limit of 42˚C. The demand for higher temperatures for direct cellular degradation challenges such applications and favors the local heating applications. Contrary to WBH, the local heating does not load the patient's cardiovascular system, and negligible electrolyte loss happens, making it possible to include more patients with comorbidities to malignancy.

The local heating is a game-changer (**Figure 1**). The local temperature depends on the local absorption and the local heat convection and conduction. Among such conditions, the apparently simple role of the thermal methods does not describe the processes with sufficient preciosity. The thermal effects are inhomogeneous, reflecting the heterogeneity of the target tissues, so the isothermal explanation, which was appropriate in WBH, is not applicable to the local processes. The actual temperature depends on the local parameters in microregions formed by the differences in electrolyte constituents, and the nonthermal effects on the molecular reaction and structures. The nonthermal effect involves the fact that when "under the influence of a field, the system changes its properties in a way that cannot be achieved by heating" [7].

Local hyperthermia in oncology has numerous technical challenges that must be solved to develop this excellent method further. Heating with mechanical waves (ultrasound) or electromagnetic methods has serious technical difficulties regarding the selective focusing of the energy absorption to the target deep in the body. There is a massive development in oncology in all its conventional and non-conventional therapy modalities. Modern oncological hyperthermia is a competitive method [8], but has not had enough attention in the medical community. One of the major factors of the lack of acceptance in the professional medical community and a narrow range of applications is the conception that

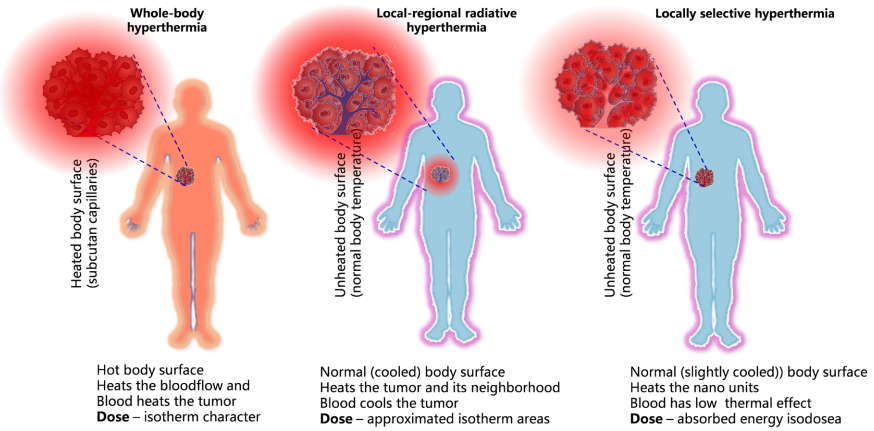



**Figure 1.** The main categories of hyperthermia in human cancer treatment.

hyperthermia is a simple heating method. Most physicians think about this method as a "kitchen" process, considering the devices as the heat-providing oven, where the tumors are targeted and "cooked" ("Too hot for cancer" [9]). Indeed, the application of hyperthermia looks (but only looks!) very simple, so various "household" or technically underdeveloped solutions are applied widely, which tends to appear as charlatanism and has a danger of a completely negative opinion from the medical experts. The general thinking about controlling the hyperthermia process is also kitchen-like, *i.e.*, at what temperature and for how long is it applied, just like when we bake a biscuit at home. The terms "heat", "temperature", and "thermal", are falsely used as equivalent meanings, making it difficult to understand the technical challenges.

Temperature is always a critical issue in the hyperthermia treatment in oncology. There are intensive discussions about its role in heat treatment. The debate became intensive when modulated electrohyperthermia (mEHT) was invented, introducing nonthermal components to thermal activities [10]. The expectations from hyperthermia are high and varied by application. In oncology, selective tumor destruction is the principal goal, but not by ablation alone. It is expected to be more gently and well controlled, with a low rate of adverse effects. There are numerous challenges to fulfilling the expectations. The challenges are multifaceted:

a) Heating the tumor in the depth of the body delivers energy through the healthy host which could cause its damage. The heat-induced toxicity is more frequent in the skin and the adipose tissue layer [11].

b) Avoid surface thermal toxicity; intensive cooling is applied in most heating techniques. The cooling causes vasocontraction in the area, and the decreased blood flow increases the risk of surface burn again. It is a positive feedback loop.

c) The cooling sinks a large part of the incoming energy. The energy loss by cooling does not allow the incoming power to be used as a dose.

d) Due to the complicated focusing techniques and problematic matching solutions, a vast amount of energy is applied (>500 W) to reach the heating goals. This energy mostly does not reach the target; the process has low efficacy [12]. For example, an extremely low efficacy (<0.1%) is reached when a <2 g tumor is heated to 45 °C in a 10 min treatment period, with 600 W power [13].

e) The dose must be based on the absorbed power in the target. However, due to the lack of knowledge about the real absorbed energy, the temperature measurement becomes mandatory to be oriented about the absorbed energy, assuming that the tumor is isothermally heated, which is far from reality.

f) The precise focus does not follow the patient's movements (e.g., breathing, internal physiological movements, skeletal muscle activity), so the heating focus is larger than the tumor.

g) The local heating of the tumor makes vasodilation at the most proliferative boundary of the tumor. The increased blood perfusion could increase the risk of cell dissemination and metastases.

h) Possible interference from the heating electromagnetic waves could create hot spots outside the target, causing uncontrolled safety problems.

## 2. Temperature Development in Living Objects

Contrary to its apparent simplicity, it is an extremely complicated technical task to heat selected body parts. The in-depth heating of the target faces serious physiological and technical challenges. The primary obstacle is the heterogeneity of the target, which has various electrolytes enveloped by membranes and other structures, and between them, it has lymph and blood transport. The local active biological processes in the focused tissues and systematically regulated non-linear physiological feedback by thermal homeostasis make the phenomena non-homogeneous and complicated, and the technical solution must fit these conditions.

Hyperthermia in oncology is at the crossroads of the development of heating methods. Hyperthermia includes a broad group of energy-absorption methods. The heating techniques determine the result of the clinical treatment, and the individual technical solutions require an appropriate protocol. The technical solution may influence the heating speed, which may change the bloodflow, and the chosen frequency with the same instrumental solution may change the survival time [14]. The technical optimization could increase the temperature with reduced power [15]. The power does not linearly control the temperature [16] at inhomogeneities of the regional target and may cause frequent patient complaints [17]. The contrary results of the cervix trial for the uterus cervix ([18] and disadvantages [19]) or the different observations of hyperthermia timing with RT combination ([20] and [21]) probably at least partly were the consequence of the different techniques.

The main possible direction is massive heating, intending to reach the highest available temperature with the most precise focus on the targeted tumor. Contrary to the macro selective focusing the micro/nano selection could be applied **Figure 2**. The macro method makes a focus arrangement by the device operator focusing on the tumor location, according to the focus plan obtained by software calculation from the available data [22]. The micro/nano selection concentrates on the special micro/nano objects (like nanoparticles, seeds, special bonds, etc.) inoculated or readily available in the tumor. The micro/nano objects are particularly good energy absorbers from external sources, and so those automatically and selectively heat up. These hot objects heat their surroundings, and so heat the tumor if they are located there. The advantage of this method is its more precise and controlled heating because the energy absorption happens surely in the micro/macro-objects. Thermal toxicity cannot be created in the volumes where the heated particles are not present, so surface burning is also avoided. The disadvantage of the micro/nano selection method is that it needs to inoculate particles in the tumor precisely. When the particles are delivered by the bloodstream, and those equally distributed in the body, then all the body parts,

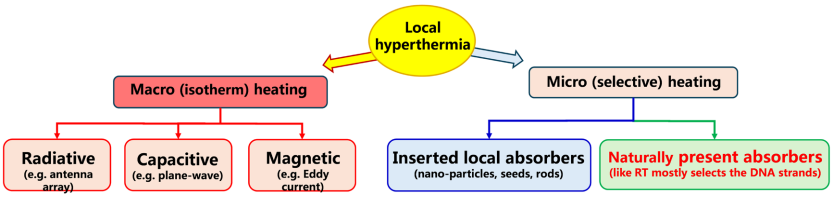



**Figure 2.** Categories of local hyperthermia.

which are under the external energy-delivery, will also be heated, including the subcutan area, and the same technical complication occurs as in the macro heating processes.

The heat-induced temperature is not isothermal in the body. Because of the natural heterogeneity, the temperature development differs by tissue region, determined by the thermal properties in the target. Heat conduction, convection, and surface radiation influence the local thermal parameters, which definitively depend on the transport (like blood and lymph) processes. Additionally, to thermal heterogeneities, the uneven distribution of energy delivery modifies the heat's spreading (**Figure 3**).

The local heating is naturally not isothermal; the temperature changes non-homogeneously [23]. The dose is, of course, lowered by the distance from the center of the heating focus. The quasi-isothermal circles (spheres) are denoted by $T_x$ which refers on the temperature in $x\%$ of the heated tumor. Consequently, $T_x$ average temperature decreases when $x$ increases, well approached with normal distribution, **Figure 4**. Note the $T_x$ may change over time because the heat spreads and changes the temperature in the target.

The standard hyperthermia dose is the cumulative equivalent minutes at 43˚C (*CEM*43˚C). It usually refers to the effect at 43˚C. where the necrotic cell destruction is observed by Arrhenius fit in vitro [25]. A phase transition happens in lipid membranes [26] [27] which causes tell disruption [28] at approximately 42.5˚C [29]. The characteristic phase transition change in the Arrhenius plot was observed clinically, too [30] [31].

The temperature difference between the center and the margin of the tumor is 4˚C (from 45˚C to 41˚C **Figure 5**. [32]), which lowers the *CEM* 43˚C. The *CEM*43˚C difference appears between the $T_{10}$, $T_{50}$, and $T_{90}$ approach, observed more than 10-times drop between the averaging volumes [33]. Knowing that the tumor margin has the most vivid proliferation, it looks that 45˚C is suboptimal to obtaining clinical results. However, we know from clinical practice the absorbed energy does the job, even much smaller central temperature of the tumor.

The $T_x$ may change over time because the heat spreads and changes the temperature in the target. The temporarily defined homogeneous volume may dynamically change by elapsed time; the situation is far from equilibrium [34], and the temperature and space distribution vary **Figure 6**. Consequently, for better characterizing the hyperthermia thermal effect, the temperature distribution has to be measured in space and time.

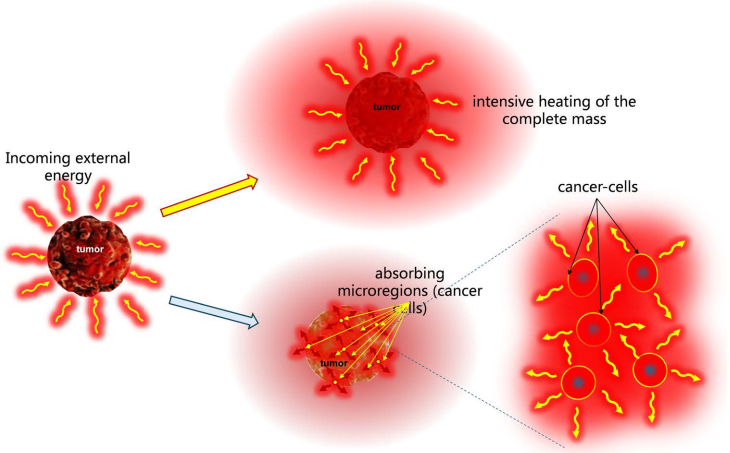
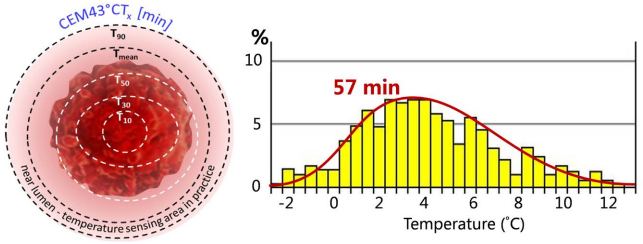
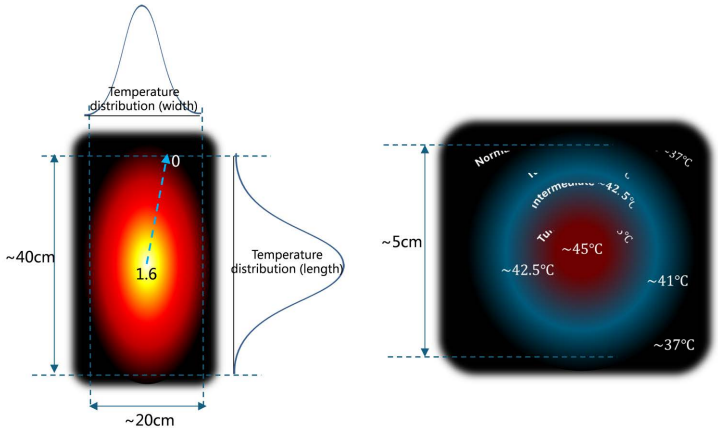



**Figure 3.** The homogeneous and heterogeneous intention of cancer heating.




(a) (b)

**Figure 4.** The heated focus rapidly spreads, and the temperature increases in a broader region. (a) The CEM43 dose depends on the isothermal areas, which differ by distance and develop by time. (b) The temperature distribution across the tumor after 57 min of treatment was measured by MRI [24]. $\Theta$ is the temperature measured by MRI. The distribution was measured in 0.5˚C intervals.




(a) (b)

**Figure 5.** Central spot of focus has a significantly higher temperature than the margin. (a) The temperature distribution with radiative phase array (800 W, 80 MHz) in the center of the applicator ~1.6 intensity compared to the normal, non-heated surrounding, which is zero [33]. The size of the radiated spot is ~40 × 20 cm. The temperature distribution is approximately Gaussian. (b) Human heating with radiative (RF phase array) has 45˚C in the center of focus, while the margin of the tumor has 41˚C. The size of the tumor is ~5 cm [32].

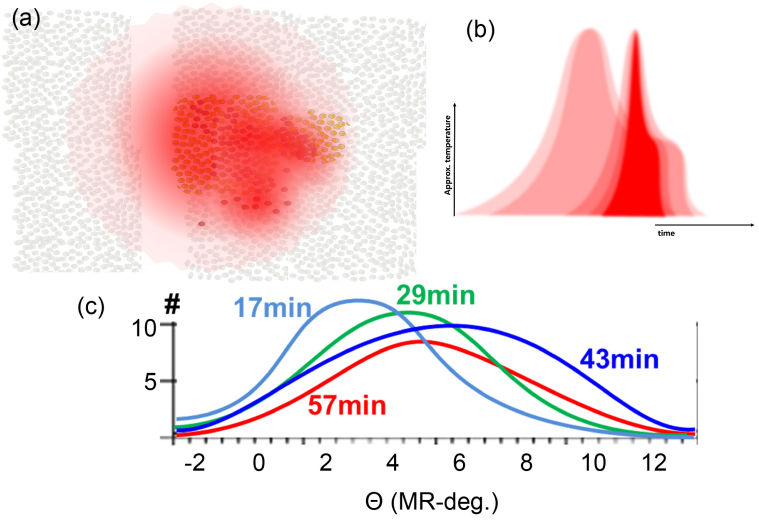



**Figure 6.** The energy absorption heterogeneously follows the tissue structures and their thermal and electric changes. (a) The heated spots dynamically overlap (b) and change over time. The complete phenomena spatial-temporarily change. The temperature maximum is assumed when the heating is in the equilibrium phase. (c) The smoothed distribution curve of $\theta$ by time development [24]. The peak shows the shift to higher temperatures and higher smearing over time.

## 3. Temperature Distribution Imaging

Thermometry is mandatory for homogeneous tumor heating when the dose CEM43˚C $T_x$ defines the isothermal volumes $x$ by $T_x$ temperature of the target. The necessity of the temperature measurement appears with other clinical demands too:

1) Due to the intended mass heating, a vast amount of energy has to be pumped into the body. The skin area at the incident signal needs intensive surface cooling, which takes out a not-controlled part of the energy. Due to the sizeable resistive bolus (saline in), a large part of the energy does not heat the target. This effect uncontrollably modifies the incident power to the target, and the absorbed energy in the target may be controlled only by the temperature. No other control of energy exists in the target.

2) Surface burns and hotspots could happen. The safety requests temperature control. Hotspots are due to the heterogeneity of the body and the interferences of the electromagnetic waves. These spots are potential dangers of thermal toxicity.

The space and time heterogeneity of the tumor development needs an appropriate thermal measuring control, so the temperature in time development and in the space distribution together. The *CEM*43˚C thermal dose parametrization raises many doubts and debates [35]. In numerous cases, the calculated *CEM*43˚C fall to fit the observed tumor destruction [36]. The *CEM*43˚C dose cannot describe the real situation of the hyperthermia processes without collected real spatiotemporal information. The challenge arises from the non-uniform spatiotemporal temperature distribution, heterogenic varying the cellular destruction

in the target. The contradictory measurement results could be caused by the discrete temperature measurements in time and space locations while the effects rapidly and nonlinearly change with the temperatures.

Measuring the temperature is relatively easy in phantoms, in vitro, and in vivo experimental conditions for small body animals when thermal homogenization can be ensured. In these cases, the spatiotemporal development of the temperature could be followed by point sensors (like thermocouples, thermistors, fluoroptical sensors, etc.) taking care that the detector material does not interact with the external energy source, itself making heating heterogeneity. The usual contact temperature sensors could give realistic control only when many independent points are measured Figure 7. When the point is near the arteries of a highly vascularized area, the temperature is less than in the low vascularization part. The point sensors are invasively placed in the appropriate position. The invasive temperature sensing may induce severe safety and treatment problems: discomfort, pain, possible infections, ulcers, and even some metastasizing by releasing tumor cells into the bloodflow. Due to these complications, the intraluminal or intracavitary catheters measure the temperature near the tumor in many practical clinical solutions. However, the measurement in a lumen (esophagus, rectum, vagina, etc.) is not accurate to ensure focusing and safety (avoid hotspots) and far not enough to conduct a treatment focus on a tumor far from the lumen. A further challenge of temperature point sensing is technical. The invasive temperature sensors could behave like a receiver antenna, and its extra energy absorption heats the sensor, so the measured temperature is undoubtedly higher than that in the measurable media. Applying optical wire sensing [37] could be a solution when the dielectric optical cable absorbs no selective energy from the applied frequency.

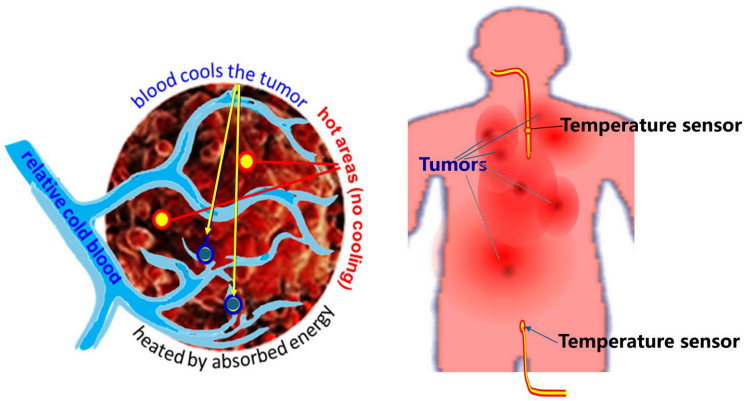
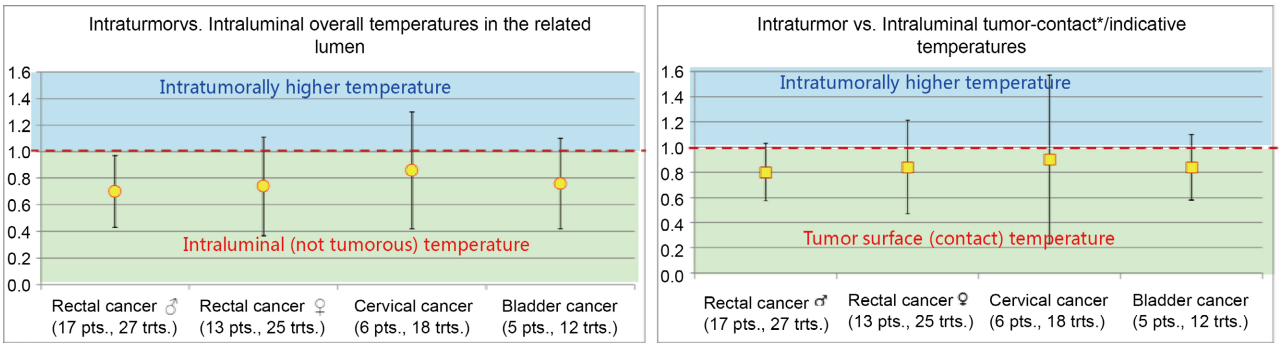



Figure 7. Challenges of temperature measurements: (a) the invasively inserted point sensors detect the very local temperature and not the average isothermal; (b) the semi-invasive temperature sensing intraluminal (esophagus, bronchus, urethra, vagina, rectum) catheters in lumens. The nearest lumen could be far from the tumor and so does not measure its temperature.

The specific absorption rate (SAR) distribution has smeared the boundary of the intended focus even in the homogeneous media [33]. Isothermal heating intention usually heats a much larger volume than the targeted tumor. The attempt of the noninvasive temperature measurement in the nearby lumen increases the heat loss in healthy volumes. The heat diffusion smears the boundary of the intended focus with elapsing time. The focus boundary does not vanish isotropically. The extension depends on the heterogeneous thermal parameters of the neighboring tissues. The cervix tumor temperature in direct vaginal contact appears lower than in the vaginal lumen [38] [39]. The MRI contactless temperature measurement in treatment focusing on the prostate shows 4.2˚C and 3.8˚C in the treated tumor and its healthy neighboring muscle tissue [24]. The temperature dispersion also differs: it was 9˚C broad range in the prostate, while it was only 4˚C in the adjacent (out of focus) muscle tissue. The measurements in other cavities also show higher temperatures than the targeted tumor in focus [40], contrary to the lower SAR outside the center of the focus [33]. All of the above challenges make the temperature measurements inaccurate the obtained results are not precise enough and sometimes contradictory **Figure 8**. [40].

Due to the control complications of the temperature, some clinical trials divide the patients into the "heatable" and "not-heatable" groups [41] [42]. This selection of the inclusion criteria is based on the possibility of a temperature increase in the patient's selected area. However, the temperature in one spacetime point alone does not decide the development of the temperature in the entire treatment. This selection puts the patients in incorrect categories when complications of the real temperature measurement are evaded in an incorrect way. The selection could exclude many patients who could have benefited from the treatment. Moreover, the "cherry picking" selection method of patients is statistically incorrect and does not fit the medical approach.

Control of electric impedance could also be a temperature-measuring method. The growing temperature decreases the electric impedance [43], and the correlation




(a) (b)

**Figure 8.** Measurement of the intratumoral temperature in radiative heating. (a) The intratumoral temperature is lower than the temperature of the surrounding lumen. (b) The intratumoral temperature is lower than the temperature of the tumor-surface (constant temperature).

makes the temperature non-invasively measurable [44]. The great advantage is that it is not invasive, but on the other hand, the information about the position of the heated volume is lost. The impedance changes offer a calibration possibility, but its application for humans is questionable due to the considerable electric inhomogeneities of the body under the sensing electrodes.

Infrared thermography (thermocamera measurement) is widely applied for measuring the surface temperature [45]. It gives a detailed and spectacular temperature mapping in two dimensions. It could be used in diagnostics and screening, too [46]. But its sensing depth is very shallow (~100 μm). Moisture in the surface could block the measurement, which otherwise depends very much on the form of environmental conditions (environmental temperature, air movements, radiations, etc.) [47]. However, due to the murine model's thermal conduction and convection, the surface measurement gives information in depth [48]. The method can be used to follow the thermal homeostatic physiology [49].

In the early 90$^{th}$ in last century thermal microwave radiometry was intensively studied in hyperthermia [50] [51]. This promising method directly measured the thermal effects because it measured the thermal radiation. Twenty years later, the mode-developed microwave techniques in the GHz region allowed a renewal of the method [52] [53]. Using an isothermal phantom (pork muscle), the measured temperature with radiometry agreed significantly with the point-sensing thermocouple [54]. The method allowed us to produce an internal thermal map of the internal organs and tissues, so the thermoradiometry research was accelerated a few years ago [55]. A multi-frequency volumetric thermoradiometry was applied to measure the local heat source inside the human chest with satisfactory accuracy [56]. However, the method is not yet completely prepared for hyperthermia practice.

Thermometry can be provided with computed tomography (CT). An image obtained by a CT scan shows pixels with information about the X-ray attenuation in the tissue elements of corresponding voxels. CT thermometry has a good spatiotemporal resolution in experiments: 1.2 mm spatial resolution with an acquisition time of 500 ms [57]; however, its temperature resolution of 3 - 5˚C is not enough for hyperthermic application. The newest CT thermometry article [58] shows a strong correlation between CT-measured thermal volumetric expansion physical density and temperature changes. Still, its significance is shown in higher temperatures as hyperthermia in humans.

Magnetic resonance imaging (MRI) is one of the advanced inside spatiotemporal temperature measurements. The MRI combination with a radiative hyperthermia system could provide a temperature map [24] instead of point sensing only. Detailed research in an application has shown the feasibility of the method in some special clinical applications [59] [60] [61]. The MRI refers to the chemical or structural fingerprints of the temperature. Its accuracy depends on the phantom calibrating the actual temperature measurement. The calibration will be insufficient if the phantom has no adequate materials containing physiologi-

cal and chemical similarities to living. Most of the pitfalls of MRI thermometry occur due to the electromagnetic (electric permittivity, magnetic permeability, electric conductivity) and chemical (chemical shift) [62]. The image artifacts from the additional frequencies of the radiation heating are also common and need electric engineering correction with appropriate RF filters [63]. Using frequency variation requires a variation of the filters too. The developed MR thermal map of the temperature distributions with annular phased array radiative treatments shows limitations and requests control possibilities for various tumor sites [60]. Individual limitations of radiative HT include anatomical, biological, and clinical factors causing complications in controlling the SAR distribution [64]. The water calibration [65] validates the temperature change in the MRI thermal map. The temperature in the body changes with many other parameters, essentially modifying the MRI signal. Cellular disruption is the final goal of hyperthermia. It modifies the MRI signal. The MRI measurement, in addition to the temperature, strongly depends on the structure of the measured volume. However, the calibration does not consider the final task: no structural change happens in the reference phantom; however, the main expected change is the cellular destruction by the hyperthermia treatment. The false calibration may result in inaccurate temperature measurements. In humans, the temperature measured by MRI ($\Theta$ value, MRI-temperature) slightly correlates with the normal temperature [24]. The clinical hyperthermia treatment changes the proton resonance frequency shift, which is measured by MRI, which could cause inaccuracy. This could be partially corrected with oil reference [66].

It is very promising that a good temperature measurement was achieved in high-intensity focused ultrasound (HIFU) [67]. The speed of sound monitoring gives precise spatiotemporal temperature information with ±0.2˚C resolution, providing stable and accurate hyperthermia control for an extended treatment time, too. This result encourages us to think about the ultrasound temperature measurement in electromagnetically energized hyperthermia methods, too.

## 4. Discussion

The role of temperature is a permanent question of hyperthermia applications in oncology. There are discussions and debates about its importance and problems of how to measure its rising inside the human body. There are intensive discussions about the controlling parameters and dose of the treatment. The doubts about temperature as a goal of hyperthermia have multiple origins with sharply differing arguments. The debate concentrates on the difference between temperature and the absorbed energy. In a homogeneous, nonliving matter, the absorbed energy and the temperature growth are linearly changing; both parameters equally describe the thermal state of the matter when we know the mass and the specific heat of the absorbed material. The realistic assumption in this case is that the total absorbed energy is devoted to raising the temperature homogeneously in the entire target. This assumption is entirely baseless in living objects.

The living object is heterogeneous and reacts to absorbed energy with various molecular and physiological responses. There is no direct linear connection between the temperature and the absorbed energy [68].

The temperature impacts the body's homeostatic control, which monitors thermal conditions and regulates the body's temperature and its parts compared to a set point in the hypothalamus [69]. The feedback tries to restore the baseline condition of the unheated target. Feedback regulation non-linearly increases the blood flow [70] [71], as an effective heat exchanger, and the regulation intensifies other physiological mechanisms to forcefully control conditions [72]. The thermally regulated blood flow delivers more oxygen for complementary radiotherapy and increases the drug concentration from chemotherapies. On the other hand, the higher nutrition support and increased metabolic rate of the tumor by growing blood perfusion, as well as the higher risk of malignant dissemination by intensive blood circulation, contradicts the general goal of the treatment to destroy the malignancy. The absorbed energy and the temperature have no direct connection in the heating of living objects; they are connected by the peculiarities of the living target [73] The contradictory balance of the temperature development (**Figure 9**) has multiple uncertainties. It delivers good local control of tumors with complementary treatments but does not increase the survival times due to the metastatic risks. An early phase III clinical study faced this problem; the clear local advances of HT+RT compared to RT alone did not appear in the survival time in breast tumors [74]. Another study obtained the same controversy: local remission success and the opposite in the overall survival [75]. The development of distant metastases was also observed [76]. The same reason led to a debate about local hyperthermia results for the cervix, showing both advantages [18] and disadvantages [19] in survival. A further study of cervix carcinomas supports the survival benefit [77], but again a critic has questioned this result [78] [79]. Another phase III trial of cervical carcinomas with HT plus brachytherapy involving 224 patients noticed the same controversies between survival time and local control [80]. The controversy was observed in a study of locally advanced non-small-cell lung cancer (NSCLC) having a significant response rate improvement, although there was no change in overall survival [81]. A multicenter phase III trial for NSCLC also showed no improvements in overall survival in the hyperthermia cohort [82]. The cause was directly shown: distant metastases appeared five times higher (10/2; $p = 0.07$) in the HT+RT group than in the RT cohort [82]. The study of the surface tumors had the same contradiction between the local control and survival rate [83]. The thermally assisted dissemination of malignant cells creates micro- and macro-metastases that cause contradictory results. We must learn from the contradictions and follow the admonishment of Dr. Storm, a recognized specialist in hyperthermia: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment" [84].

The solution to get out of the trap is using thermal-independent effects. The

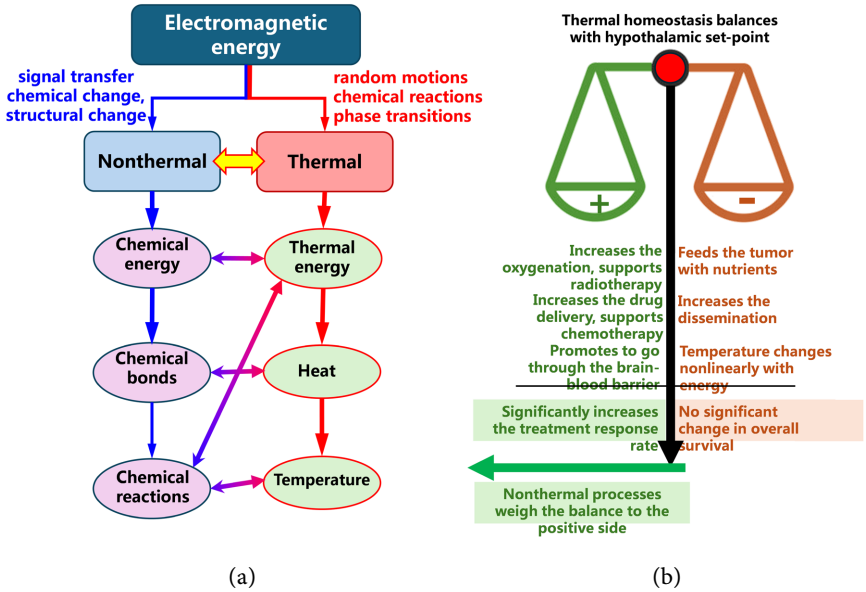



**Figure 9.** The balances of dynamic control of hyperthermia applications. (a) The division of the electrodynamic energy to thermal and nonthermal components, and its complex cooperation. (b) The thermal homeostasis balances, and fluctuates between the complex variants. The nonthermal processes force the advantageous effects.

thermal effects rapidly increase the chemical rate constant, promoting the chemical (enzymatic) reactions. The nonionizing radiation causes two groups of effects: thermal processes [85] and nonthermal molecular excitations [86]. These effects are in synergy and influenced by homeostatic surveillance. The thermal energy absorption component improves the conditions of the molecular and chemical changes forced by nonthermal activity. The increasing target's temperature promotes the nonthermal "chemical machinery" [87] [88]. These effects have to be used in synergy which is realized by the well-chosen modulated radiofrequency electromagnetic effect in the mEHT technique [89]. The thermal component provides the appropriate temperature of the TME by heating the membrane rafts [90]. Another general thermal action affects the extracellular matrix (ECM) and a part of the TME. This acts mechanically and molecularly [91], accompanying the thermal absorption of transmembrane protein clusters. The nonthermal component excites the membrane receptors of the cells. The well-chosen electric current can deliver energy for molecular excitations involving various ionic and molecular interactions [68]. The process only has a subtle thermal effect and excites the molecules or structures that fit the applied resonant conditions [92].

The complex thermal and nonthermal processes must be measured for dosing the mEHT treatment. The temperature provides basic information about the chemical reaction rate, which undergoes rapid nonlinear development in the physiological range of temperature, described by the Arrhenius plot as shown above. It needs such a method, which is well sensitive to both factors and makes the imaging in space in real-time. One of the promising methods is ultrasound

imaging with microbubble contrasting agents [93], [94]. The microwave also has thermal and nonthermal effects [95], [96], which may have addition to the cell-membrane focused mEHT by increase the cell membrane permeability for $Ca^{2+}$ ions [97]. The ultrasound-exposed microbubbles have an impact on the membrane potential and so increase the $Ca^{2+}$ influx, and the activation of the $Ca^{2+}$-dependent potassium channels [98]. Noteworthy, the $Ca^{2+}$ ion exchange also has an important factor in mEHT treatment [99] [100]. Another remarkable nonthermal effect of ultrasound is enhancing the voltage-sensitivity of myocardial perfusion imaging [101], which could be a great advantage in sensing the voltage-sensitive impacts of mEHT, too. The mEHT essentially varies the membrane-driven processes, showing high voltage change even at low *SAR* [102], which can help the signal's excitation of the raft proteins [103]. The electrostatic charge of the membrane attracts the ions from the *ECM*, which is sufficient to establish a transmembrane potential [104]. Blocking the cell cycle is connected to the electric field activity and it is primarily nonthermal [105]. The electric field enters the cell, using partly the voltage-sensitive phosphatase (VSP) [106] and alters the cytoskeletal polymerization [107]. The cytoskeleton reconstruction has field-controlled phosphorous hydrolysis with a resonant-type change. The mEHT produces stochastic resonance, selectively inducing various biological enzymatic reactions and polymerization processes [92], which selection could be promoted by ultrasound processes like the electric field influences the acoustic response with a low-strength electric field on the order of 1 V/cm [108], which promotes the effect of mEHT. The ultrasound could influence the charge distribution [109], supporting mEHT to suppress cancer development [110]. The ultrasonic wave may induce an electric current [111], which may cooperate with the mEHT activity against the tumor-stimulating injury current. All of these cooperative possibilities could build up a novel, effective theranostic method, creating a successful cancer treatment.

## 5. Conclusion

The most requested parameter of hyperthermia treatments is the temperature. The local heating of humans is never homogeneous. The body heterogeneities, the developing thermal spot of energy absorption make distribution of the thermal processes in space and time. The spreading of the local focus by heat convection and conduction is mandatory information for the clinical use of the conventional radiation heating. However, measuring the temperature in the deep-seated malignant volume is not simple. Together with the heterogeneity of the SAR distribution, the structural inhomogeneities are inherent features of the living system. The various structural scales have different modifications to the temperature distribution. Numerous conditions make it difficult to determine the temperature of a living object. The temperature is very much non-homogenous site by site. The temperature does not characterize the cellular and physiological changes but does general conditions for chemical reactions. The non-

thermal processes use the conditions to accelerate the caused changes and optimize the synergy with thermal homeostasis. The only temperature as dosing works perfectly if the physiological factors (bloodflow/vascularization, metabolism, chaperone-protein production, dissemination, apoptotic action, etc.) are not involved, and the tissue can be regarded as homogeneous and semi-isolated mass from its surroundings.

Due to this inevitable heterogeneity temperature imaging in space and its development in time is requested for the proper characterization of the heating as the condition of the nonthermal molecular changes. Multiple methods are available, but all have some serious disadvantages: point sensors are accurate but measure only a point invasively, thermography is applicable only on the very surface distribution, and electric impedance and radiometry are not accurate in registering the space distribution. The expensive CT and MRI imaging are complicated methods, their combination with the heating device is complicated, and their thermal distribution measurements have a lot of pitfalls. Furthermore, the nonthermal components of the induced processes are not measurable with the above methods. A novel emerging technology, the application of ultrasound microbubble contrast agents is a promising facility for solving complicated tasks. It has good spatiotemporal resolution and is sensitive to nonthermal effects. The microbubbles could be synergized with modulated electrohyperthermia (mEHT), completing it as a strong theranostic method in the "war" against cancer.

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## Conflicts of Interest

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

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