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Oncological Hyperthermia: Where to Go from Here?

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Abstract

Oncological hyperthermia is one of the most versatile forms of oncotherapy. It can complement every conventional treatment method and be applied to any tumorous cancer, irrespective of its stages and localization. Numerous technical realizations are conventionally compared by their thermal effect, measured by temperature. However, nonthermal (mainly electric) excitation effects are more recognized nowadays. The technical variants alter the synergy between thermal and nonthermal energy components. Nonthermal energy absorption-induced molecular mechanisms include essential behaviors like selectivity and immunogenicity. The nonthermal electromagnetic effects excite molecular changes, intracellular signals, gene expressions, and many other chemical reactions. Their synergy with thermal conditions is based on the Arrhenius law, which describes the rapid growth of chemical reactions with temperature. A unique technical realization of hyperthermia, modulated electrohyperthermia (mEHT) tries to optimize the thermal and nonthermal effects. The results look very perspective, containing the high accuracy of targeting the tumor cells, the immunogenic cell death, and the activation of tumor-specific immune reactions restoring the healthy immune surveillance to destroy the cancer.

Keywords

Thermal, Nonthermal, Modulated Electrohyperthermia, Selection of Tumor Cells, Tumor-Specific Immune Activity, Abscopal Effect

1. Introduction

Hyperthermia (HT), a diverse field with multiple approaches in oncology, is poised to revolutionize cancer treatment. The potential to leverage the therapeutic benefits of heat offers inspiration for improved outcomes for cancer patients,

whether as a standalone treatment or in combination with other therapies. The historical origin of hyperthermia, a field traced back to ancient Greek medicine when energy delivery to the body was limited, is a testament to its evolution. The discovery of electromagnetic energy transfers a couple of hundred years ago changed hyperthermia applications. This led to the development of numerous electromagnetic energy transports, including electric and magnetic fields, electromagnetic radiation: direct current, alternating current, radiofrequency (RF), microwave, and visible light. Non-electromagnetic applications such as focused ultrasound and hyperthermic perfusions were also developed. Diverse concepts supported these developments, all with the same goal: to selectively and homogeneously heat up the tumor at higher temperatures than the homeostatic control.

All electromagnetic interactions deliver energy to the biomaterials. The energy could be realized by heat and, consequently, temperature and electron excitation, making chemical reactions. These effects are naturally together because the bioelectromagnetic interactions partly modify compounds' chemical bonds and structure with electromagnetic forces. One part of the energy absorption heats the target, and the other makes the nonthermal interactions. The two energy components are used in two kinds of hyperthermic therapies in oncology. One direction was Arsene D'Arsonval (1851-1940), a French physician who successfully used nonthermally the electric and magnetic fields for oncotherapy [1]. The direct and alternating currents, mostly nonthermal, are applied with a combination of chemotherapy (electrochemotherapy) [2] in modern medicine. At the same time, the Danish physician Kristian Overgaard (1899-1976) focused on the thermal effect alone [3]. The temperature approach was more straightforward and accessible to control and understand, and so became the mainstream of hyperthermia applications as a return to the ancient wishes with modern technologies. Due to the lack of a complete understanding of bioelectromagnetic processes, controversies were developing around it. Some measurements are misinterpreted, most claims have no data or only some subjective reports, and some results are shown only in individual cases. The wide variety of individual case reports makes it impossible to statistically evaluate those effects, which depends on the treated individuals. However, the debate about the divisive electromagnetic therapies is not useless. It provokes research and points out the physiological importance of electric currents, deriving many modern principles, including the control of the cellular effects [4] and modern neuroscience [5]. Even a general hypothesis of "biologically closed electric circuits" (BCEC) was formed based on the existence of intrinsic electric currents in the body, [6] [7], which idea is used in the treatment of malignant diseases [8] [9]. The pathological disorders [10] and wounds induce currents [11]. The spontaneous biological charge transfers caused by the tissue-repair process, [12] [13], and can be used as a noninvasive indicator of wound healing [14]. The biological effects of low-level, non-stationary magnetic fields have been observed [15] and adopted [16]. Among these effects, we may find some resonance character [17], demonstrating much experimental evidence from the field of ionic

cyclotron resonance [18]. Several theoretical explanations of the ion cyclotron resonance have been developed [19]-[24]. The resonance effects are dominantly nonthermal and focus on the molecular excitations and structural changes, inducing desired signal pathways.

Bioelectromagnetic treatments are detached from hyperthermia, while the thermal and nonthermal components are applied in different shares in cancer distortion technical variants. For example, radiotherapy (RT) primarily uses nonthermal molecular breaking in DNA stands, and the thermal effects are negligible. On the contrary, hyperthermia is the opposite; it focuses on thermal energy, when the temperature is the single parameter that measures the dose, and the nonthermal energy is neglected in conventional evaluation. Such an approach to hyperthermia does not differentiate how which technique produces the heat. The exact temperature production is regarded as an identical treatment. However, it becomes increasingly evident that heat production is deeply connected to nonthermal bioelectromagnetic processes. Considering only the heat energy, the thermal homeostatic regulation, the stress reactions, the immunogenic aspects, enzymatic regulations, and many other molecular effects became one-sided, having only thermal dependence. On the other hand, the thermal calories are not equal to the same number of calories from food, inducing nonthermal chemical effects. Life is more chemical-based than thermal, so nonthermal chemistry cannot be neglected when evaluating bioelectromagnetic effects.

Energy absorption produces thermal and nonthermal processes. Thermal effects primarily involve heating tumors to temperatures typically between 39˚C to 45˚C, which may cause direct cytotoxicity, like protein denaturation. Still, it provides a general condition for optimization of the other nonthermal processes. The growing temperature increases the indispensable enzymatic reactions, but the enzymes are blocked over a thermal limit. Also, immune reactions have such thermal limitations. The nonthermal effects can significantly influence the overall efficacy and outcomes of hyperthermia treatments in oncology. The ionizing radiation like radiotherapy (RT) and the chemical interactions of drugs like chemotherapy (ChT), together with the many electromagnetic molecular effects and the immunogenic processes are nonthermal but use thermal conditions for higher efficacy (**Figure 1**). According to the Arrhenius law, thermal conditions increase sensitivity to radiation, and raising the reaction rate enhances chemotherapy efficacy. The thermal background provides optimal efficacy for the nonthermal effects of ionizing radiation (radiotherapy), chemical reactions (chemotherapy), immune processes (immunotherapy), and electrohyperthermia, which uses the electric field to modify the molecular reactions.

2. Differences between the Hyperthermia Techniques

Different hyperthermia techniques may vary in their ability to induce these nonthermal biological effects effectively. Technical differences alter the synergy between thermal and nonthermal energy components.

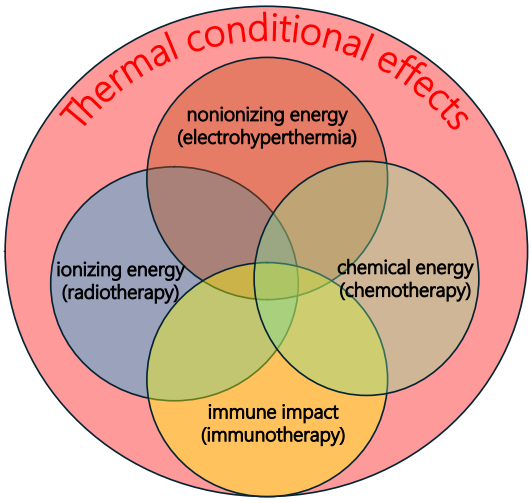

Figure 1. The thermal background (elevated temperature) provides the appropriate optimal conditions for using various nonthermal absorbed energies, including the electric field impact, ionizing and nonionizing processes, and the chemical changes by drugs.

The thermal and nonthermal processes are synergistically active in all applications, but the ratio of the two components may differ. The complex combination of the thermal and nonthermal effects can alter the physiological and biochemical properties (like blood flow, lymph transport, enzymatic processes, etc.). HT increases the microcirculation [25]-[34], and enhances the efficacy of the chemotherapies. The enhanced blood flow can improve the delivery of oxygen and ChT drugs to the tumor site [35]-[37]. Further support is that the hot drug is more reactive [38], providing excellent possibility for synergy, which is even more effective when considering accelerated drug metabolism and gained pharmacokinetic parameters. Furthermore, hyperthermia may activate the G0 phase of cell division, making these states reachable to reaction impacts. These advantages can improve the efficacy of concurrent treatments and reduce the chances of treatment resistance.

Various electromagnetic and technical parameters produce hyperthermia effects, sometimes combined with mechanical actions like ultrasound. The technical variations depend on the various chosen designs (**Figure 2**). The technical parameters use the wide variability of the electromagnetic processes including the frequency, energy delivery, acting on selected volumes, and selective molecular focusing ability, the fiend could be formed in invasive form, and depends on the energy source, the energy coupling to the target and at the end the combined (complementary) applications with other treatments concomitantly or concomitantly next to each other.

Techniques differ in how the physiological changes can be manipulated effectively and how to improve treatment outcomes. The methods differ in activating the blood vessel permeability in tumors, which can enhance the delivery of chemotherapy drugs or oxygen to the tumor site. The nonthermal effects of various

hyperthermia techniques involve a complex interplay of molecular excitations and biological responses triggered by cellular stress responses to elevated temperatures. These responses encompass a range of molecular pathways and signaling mechanisms that influence cell survival. The hyperthermia technique also varies by modulation of the immune response, potentially enhancing immune recognition and attacking cancer cells, increasing the therapeutic outcomes in oncology.

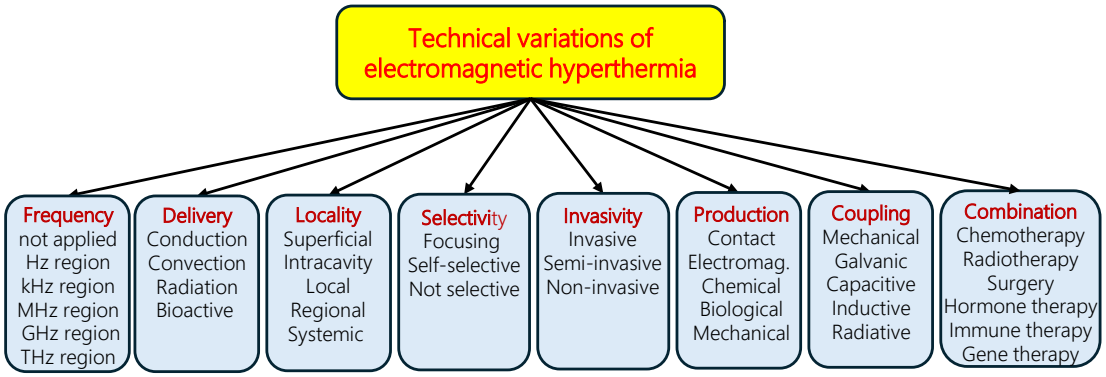

Figure 2. The possible technical parameters of electrohyperthermia methods. All shown categories have numerous subcategories and could be grouped in various technical solutions. The combination of the parameters allows hundreds of technical solutions.

The technical solution may vary the efficacy [39], modify the reaction rates measured by the Arrhenius plot [40], and develop different amounts of HSPs [41], different cell destruction [42] [43], different immune activity [44] [45], modifying the preclinical [46] and clinical results [47]. Various techniques differ in enhancing the synergistic effects of other cancer treatments, such as RT or ChT, by optimizing nonthermal mechanisms that may improve patient outcomes. The consequence of the variations appears in the essential differences between the characterization of the methods in **Figure 3**.

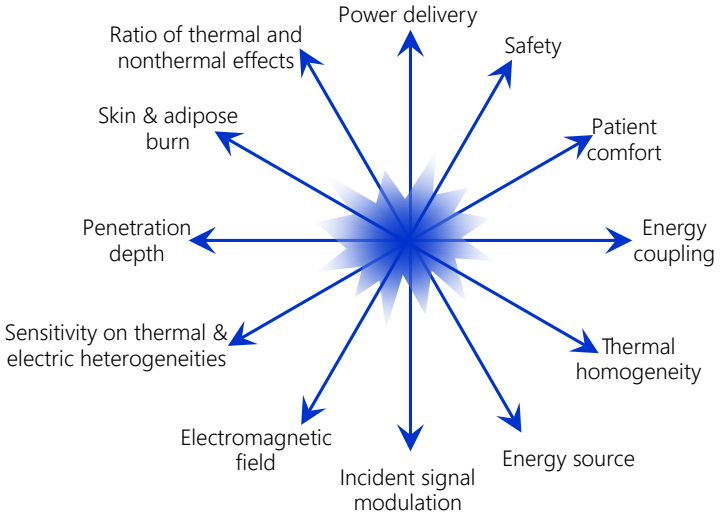

Figure 3. The primary technical and operational parameters of electromagnetic hyperthermia methods.

Understanding how thermal and nonthermal effects interact allows us to optimize basic treatment parameters such as temperature, duration of treatment, and integration with other therapies. Technical optimization maximizes therapeutic efficacy while minimizing adverse effects on healthy tissues. The optimum of the multivariant process is a complicated task, which is the primary intention for all hyperthermic designs. The optimum is a Nash equilibrium [48]. In this state, no further change of the technical parameters produces higher efficacy, and the contradictory interactions compensate each other in a balance. The equilibrium could be lost by changes in the conditions (different individuals, tumor stage and change, increasing temperature, etc.), which needs to repeat the optimizing process.

The differences in results between hyperthermia techniques can arise due to several other factors:

1) Different techniques may heat tumors to the same average temperature, but the distribution of heat within the tumor and penetration depth can vary. Some methods may be better at uniformly heating the tumor throughout its volume, a factor that can significantly influence treatment outcomes.

2) Variations in how well different techniques achieve and maintain the target temperature can affect treatment efficacy and safety.

3) The way heat is transferred to tissues can vary between techniques. Factors such as tissue perfusion (blood flow) and the thermal properties of tissues can impact how effectively the desired temperature is reached and maintained within the tumor.

4) Hyperthermia is often used in combination with other cancer treatments. The synergy between hyperthermia and these treatments may differ depending on the specific technique, influencing overall treatment outcomes.

5) Variability in patient anatomy and tumor characteristics can also interact differently with various hyperthermia techniques, affecting individual treatment responses.

The pivotal difference between the applied techniques is the ratio of thermal and nonthermal effects. The default effect is thermal. The nonthermal impact is a complementary additive to the thermal one. The nonthermal effects are induced nonionizing in the tumor microenvironment (TME) by the electric field. The complementary synergy of these effects works like the synergic addition of nonthermal ionizing radiation (radiotherapy) to the thermal impact alone, which is a well-proven combination [49]-[51]. The thermal effect and chemotherapy combination are similar to thermal and nonthermal amalgamation. The ChT focuses on chemical reactions, which are nonthermal, but the thermal conditions may accelerate the reaction rate and the transport of the chemical drugs [52]-[54].

The nonthermal effects are a larger category than hyperthermia. Ionizing radiation, nonionizing radiation, electromagnetic fields, and drug-induced chemo changes are all nonthermal (**Figure 4**). The thermal effects promote nonthermal processes, which could change the molecular bonds and make signal excitations

by nonionizing energy as HT does. It does not have enough energy to ionize atoms or break chemical bonds. When the energy is as high as in the ionizing range, like in radiotherapy (RT), it breaks the molecular bonds. The synergy of these nonthermal effects works in thermo-radio-chemotherapy complementary applications. Thermally-induced nonthermal effects can stimulate anti-tumor immune responses by promoting antigen presentation, activating dendritic cells, and enhancing T-cell function. Changes in the TME, including increased infiltration of immune cells and modulation of immune checkpoints, can contribute to improved anti-tumor immunity.

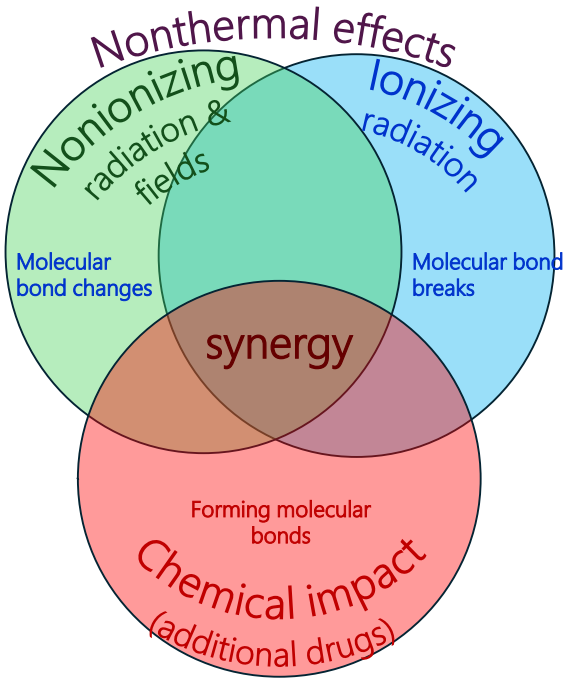

Figure 4. The ionizing and nonionizing processes have immense nonthermal effects on modifying molecular structures. Additional drugs make chemical impacts and form new molecules. Their synergy provides the basis for combining nonthermal HT effects with RT and ChT.

The essential biological differences between the electromagnetic hyperthermia techniques include numerous molecular and physiological changes (**Figure 5**). The consequence of the technical differences is the massive variation of the effects achieved with the applied method.

2.1. Thermal-Nonthermal Balance

Hyperthermia can induce various biological responses within cells and tissues beyond heating them. The optimal parameters are technique-dependent and determined by the interaction of thermal and nonthermal processes. They may enhance the overall effectiveness of HT as a treatment modality in oncology. The thermal effects induce a counter-reaction by thermal homeostasis, which tries to restore

the equilibrium thermal conditions. The nonthermal effects modify the molecular bonds and may also have counter-reactions by natural compensations, like chaperone proteins. HT's thermal and nonthermal effects interact through various biological mechanisms, often synergizing to enhance treatment outcomes and interact complexly. The potential of hyperthermia to enhance treatment outcomes is significant, offering hope for improved patient outcomes. The thermal conditions provide the optimal situation for the nonthermal contribution to vasodilation and vasocontraction, altering tumor blood flow. While heat directly damages cancer cells (thermal effect), it also releases HSPs into the tumor microenvironment (nonthermal effect) that can further sensitize cells to radiation or chemotherapy. Combining thermal and nonthermal effects can lead to complex biological responses within tumors. These responses may involve a balance between cytotoxicity (thermal) and immune activation (nonthermal), ultimately influencing tumor regression and clinical outcomes.

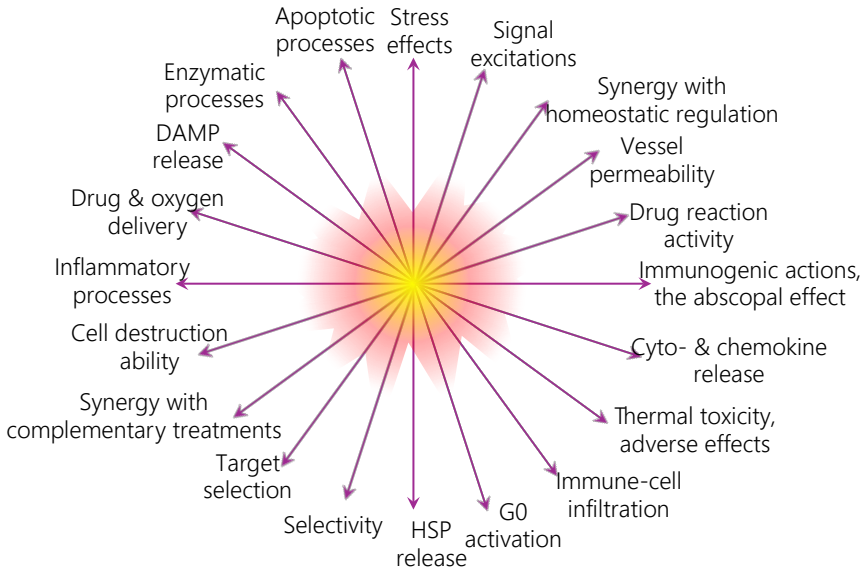

Figure 5. The important processes of mEHT.

The thermo-chemotherapy results in a better therapeutic effect, increasing the target specificity and reducing the systemic side effects [55] [56]. In some cases, low-dose chemotherapy could be used [57] [58] with hyperthermia promotion; it is also applied in low-dose metronomic chemo-regulation [59]. Some key molecular excitations and processes involved in thermal and nonthermal effects are shown in **Figure 6**.

2.2. The Modulated Electrohyperthermia

The modulated electrohyperthermia (mEHT) tries to solve the optimal equilibrium of the thermal and nonthermal effects of the absorbed energy. There are numerous optimized parameters chosen from the electromagnetic possibilities (**Figure 7**).

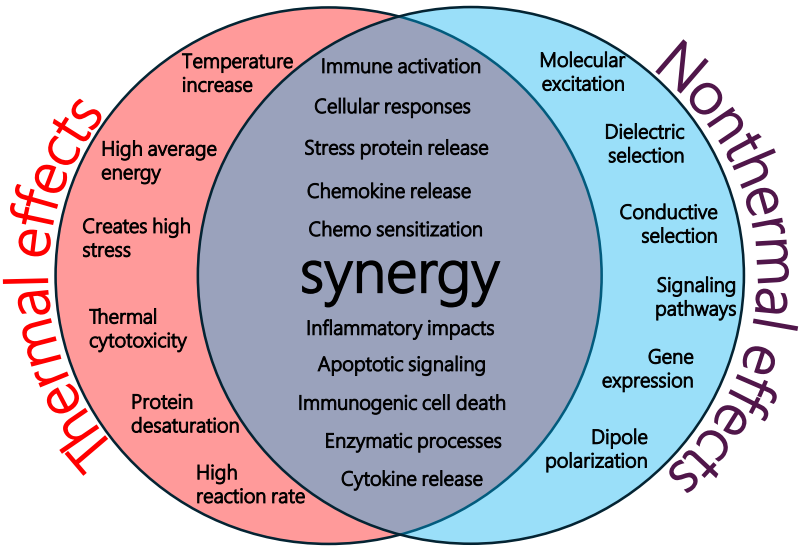

Figure 6. Differences and similarities interact in a synergy of energy absorption's thermal and nonthermal components.

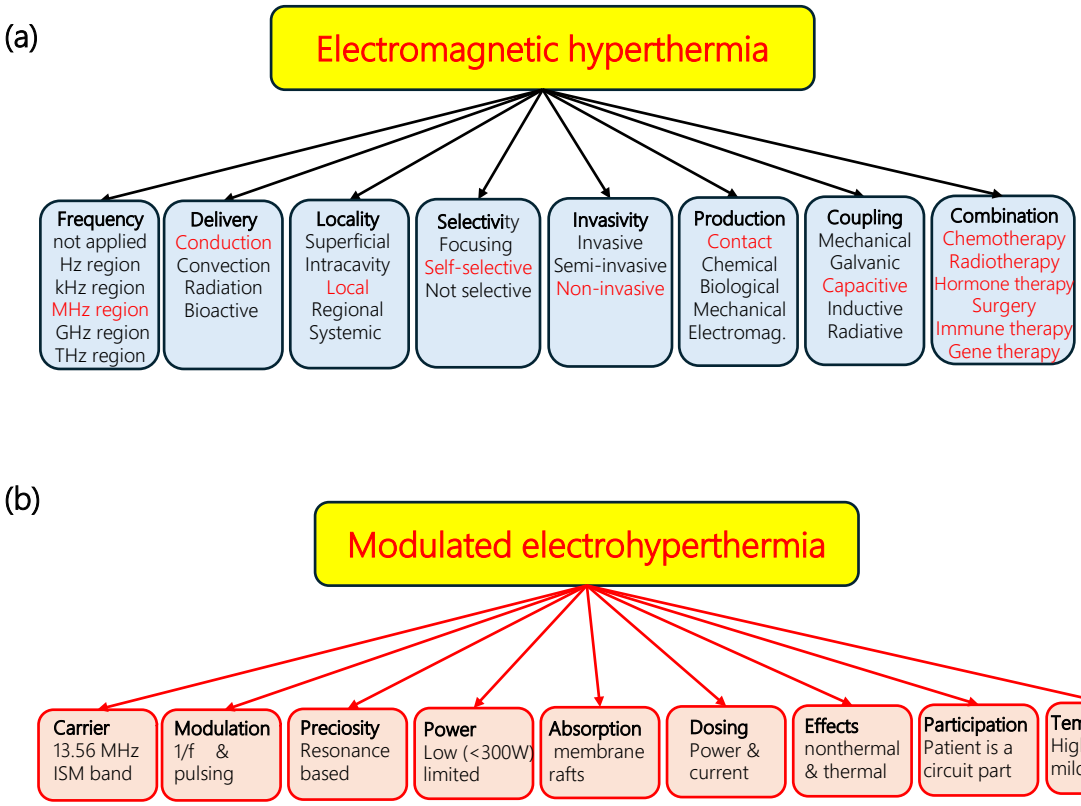

Figure 7. The selected parameters for mEHT. (a) Selection from the possibilities of electromagnetic hyperthermia (emphases with red letters); (b) The most important parameters of mEHT.

The chosen parameters of mEHT contribute to the synergy of thermal and nonthermal effects and harmony with natural homeostatic control. In details:

1) The carrier frequency is 13.56 MHz, which is in the β/δ frequency dispersion

range. The β-dispersion is interfacial polarization [60], targeting the cancer region [61]. This frequency is optimal for selecting malignant tumors based on their extra electric conductivity [62], driving the radiofrequency (RF) current to this region. This behavior can also be used for diagnostics [63]. The cancer cells in the tumor behave autonomically and break the healthy network connections with other cells, which increases their dielectric constant (permittivity) [64]-[66], which allows their recognition [67] [68]. The 13.56 MHz is an ISM standard for hospitals, so it does not require extra shielding for operation. The high conductivity and dielectric behavior concentrate the energy absorption on the cell membrane [69]. The tumor microenvironment (TME) differs from the general extracellular matrix (ECM) [70], which helps the selection process.

2) The applied amplitude modulation is chosen from the low-frequency α-dispersion range, providing the appropriate extrinsic signaling for apoptosis and immunogenic cell death, forcing healthy homeostatic control [71].

3) The complete selection is resonance-based [72], accurately ensuring the optimum of the processes. Resonance is stochastic and fits the impedance matching and also the modulation [73].

4) Due to the molecular selection, the energy is not used to heat the entire tumor mass, which allows much lower incident power than in conventional hyperthermia applications [74]. This makes the method safer and causes fewer adverse effects, avoiding thermal toxicity (burns).

5) The overlapping δ-dispersion [75] helps to select the water-bonded lipid-protein complexes in the glycoprotein lipid microdomains (rafts) [76]. The membrane rafts are enveloped in a nonconductive lipid membrane environment, so their relatively high conduction achieves their precise heating by increasing the mEHT treatment's heating preciosity [77]. Raft excitation is highly likely in these conditions and may trigger intracellular signals [78].

6) Due to the high preciosity and proper selection, the dosing does not need temperature control or enough energy (power, RF current) control in the treatment.

7) The thermal and nonthermal effects are synergistically optimized [74], giving the suitable condition for the signal transfers to develop a molecular pattern in an appropriate space-time form, releasing damage-associated molecular pattern (DAMP) in an immunogenic cell death (ICD) process [79].

8) The unique real-time tuning, which matches the patient's impedance to the treatment, increases the treatment accuracy [80]. The patient is an organic part of the RF resonant conditions, acting like one of the discrete elements of the electric circuit [81].

9) The mEHT is a kind of hyperthermia but a heterogeneous heating solution [82]. The selectively heated microdomains work like nanoparticle heating. The domains absorb high energy, having higher temperatures than their environment. They start to heat by conducting their vicinity, which produces a mild temperature level on average in the tumor.

The mEHT method has numerous publications discussing the above phenomena. The most comprehensive material could be found in two books, and some chapters of others dealing with this method [83]-[88].

3. Perspectives of Modulated Electrohyperthermia (mEHT)

The mEHT fits the latest trends in oncotherapy development [89] [90]. It is selective, safe and immunogenic.

3.1. Selective Application Using the Cancer's Electric and Thermal Differences (Biophysical Characters)

The main selectivity characters of mEHT [91]:

- Choses the tumor by high conductivity;
- Choses the tumor cells in the tumor mass by their autonomy;
- Choses the transmembrane proteins by their easy excitation;
- Absorbs the energy by homeostatic harmony.

The mEHT selectively attacks the malignant cells and mostly naturally kills them. It is essential because it allows for more effective and targeted treatment strategies, which can lead to better outcomes for cancer patients. When mEHT selectively targets the cancer cells, it can minimize damage to surrounding healthy tissues and organs, reducing the severity of side effects experienced by the patient. Selective targeting allows mEHT to focus more effectively on eliminating cancerous cells. This can enhance the overall efficacy of treatment by increasing the likelihood of killing cancer cells while sparing healthy ones. Cancer cells can develop resistance to treatments over time, making them harder to eliminate. The mEHT targets specific vulnerabilities of malignant cells and may reduce the likelihood of resistance developing, potentially improving long-term treatment outcomes. The selectivity of mEHT towards specific types of cancer cells can lead to more personalized treatment approaches. This could involve tailoring therapies based on the patient's cancer cells' genetic profile or other characteristics, potentially optimizing treatment effectiveness. The selectivity of mEHT can contribute to better patient outcomes by maximizing the therapeutic effect on cancer cells while minimizing harm to healthy tissues. This balance is crucial for improving cancer patients' survival rates and quality of life.

3.2. The Nonionizing Nonthermal Electric Field Application

The RF application of mEHT is nonionizing. It represents an innovative approach that offers significant advantages in terms of efficacy, safety, and patient-centered care compared to traditional ionizing radiation or chemotherapy. Continued research and technological advancements in this field hold promise for further improving outcomes and expanding treatment options for cancer patients.The mEHT offers several advantages that make it valuable in clinical practice. The main nonionizing nonthermal processes used by mEHT:

- Changes chemical processes without extra toxicity by using only natural

processes;

- Guides the processes in harmony with homeostasis (note that it is applicable not only for oncology);
- Helps to reduce the side effects of conventional therapies by targeting the tumor;
- Improves the efficacy of chemo reactions and radio effects (note that it is applicable not only for oncology).

Nonionizing mEHT is delivered strictly localized. This localization helps minimize systemic toxicity and adverse effects commonly associated with systemic treatments like chemotherapy. The locally enhancing reaction rate of the chemo drug increases its efficacy, and the higher blood perfusion also increases its concentration. The locally higher concentration leaves less concentration for systemic adverse effects. It can be repeated multiple times if necessary, without cumulative toxicity. This flexibility can be beneficial for managing recurrent tumors or addressing residual cancer cells after initial treatment. The nanoscopic raft heating of mEHT offers precise control over the treatment area and depth, allowing clinicians to target tumors accurately. This precision helps to concentrate the therapeutic effect on the cancerous tissue while preserving nearby critical structures. The mEHT can often be combined with other treatment modalities such as surgery, radiotherapy, chemotherapy, or immunotherapy. This multimodal approach can synergistically enhance treatment outcomes by targeting different aspects of cancer biology or overcoming treatment resistance. The mEHT has demonstrated effectiveness across a range of cancer types and stages. They can be tailored to specific tumor characteristics, making them versatile in clinical oncology practice. It typically results in less discomfort, shorter recovery times, and improved overall quality of life for cancer patients.

3.3. Immunogenic Effects, Tumor Vaccination

The immunogenic effects of mEHT therapy refer to the treatments' ability to stimulate the body's immune system to recognize and attack cancer cells. This approach offers several distinct advantages in the treatment of cancer. The immunogenic effects in cancer therapy represent a promising avenue for improving treatment outcomes, expanding treatment options, and potentially achieving long-term remission or even cures for certain types of cancer. The main immunogenic effects of mEHT [92]:

- Activates the innate and adaptive immune system by recognizing the cancer cells;
- Produces tumor antigen presentation for killer T-cells;
- Attacks the cancer cells all over the body in micro and macro metastases (abscopal effect);
- Works like tumor vaccination (patented).

The immunogenic effect of mEHT can specifically target cancer cells based on their unique molecular markers or antigens, potentially sparing healthy tissues from damage. The induced immunogenic cell death releases unharmed molecules

with information about the cancer cells, which was hidden for immune surveillance until this. This targeted approach also enhances the specificity of treatment. The mEHT immunogenic cell death (ICD) can induce a durable antitumor response. Once activated, the immune system can continue recognizing and eliminating cancer cells, providing long-term benefits. ICDs can activate immune cells throughout the body, enabling them to seek out and destroy cancer cells wherever they may be present, including micro and macro metastatic sites (abscopal effect) [93] [94]. This systemic effect enhances the treatment's ability to address widespread disease. The likelihood of developing resistance to mEHT therapy decreases over time is minimal. The mEHT can overcome these resistance mechanisms by targeting different pathways or enhancing immune surveillance. The mEHT can be combined with other treatments that can synergistically improve treatment outcomes by simultaneously targeting multiple aspects of cancer biology. The mEHT immunogenicity is automatically tailored to individual patients based on their immune profile and the specific characteristics of their cancer. This personalized approach also may improve treatment efficacy and reduce unnecessary side effects. The mEHT-induced ICD may successfully treat cancers that were previously difficult to treat with conventional therapies. The mEHT develops a tumor-specific vaccination, which can induce immunological memory. This means that the immune system retains a memory of the cancer cells, protecting against recurrence or future metastases.

4. Conclusions

The perspectives of hyperthermia, especially the modulated electrohyperthermia, have multiple possible ways for future realization.

1) Hyperthermic therapies must increase their focus on the target, avoid unwanted hot spots in healthy tissues, and limit heat spreading by natural heat conditions. The mEHT, with its molecular selectivity on the membrane rafts of malignant cells, optimizes the selectivity of energy absorption.

2) Hyperthermia must harmonize thermal and nonthermal processes to choose the best signal pathways to destroy the tumor. The mEHT optimizes the molecular actions and signals excitations with a synergy of the thermal and nonthermal processes.

3) The rapid development of immuno-oncology affects all modern oncology treatments. Hyperthermia must fit this new trend. The mEHT, which induces immunogenic cell death, induces immunogenic effects and could be well harmonized with other immunotherapies.

Conflicts of Interest

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

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