

Modulated Electro-Hyperthermia in Oncology: Biophysical Selectivity, Immunogenic Cell Death and Clinical Evidence: A Narrative Review of Mechanisms and Their Translational Status

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Abstract: Loco-regional hyperthermia is one of the oldest concepts in oncology, yet its modern adoption has been constrained by two persistent problems: the inability to confine heat selectively to malignant tissue and the risk that indiscriminate warming increases tumor perfusion and promotes dissemination. Modulated electro-hyperthermia (mEHT), delivered as a capacitively coupled, amplitude-modulated 13.56 MHz radiofrequency current, was developed specifically to resolve these problems by exploiting the biophysical differences between cancer cells and their healthy hosts rather than relying on bulk temperature elevation. This narrative review organizes the available preclinical and clinical evidence around a single explanatory scaffold: a one-to-one correspondence between four fundamental, widely recognized challenges of contemporary oncotherapy and the specific mechanisms by which mEHT addresses each. The four challenges are poor tumor selectivity, the capacity of tumors to adapt and evade immune surveillance, the insufficiency of local control when survival depends on systemic disease, and the toxicity that erodes quality of life. We argue that mEHT addresses these, respectively, through biophysical self-focusing on the malignant membrane; multi-pathway apoptosis that overwhelms chaperone buffering and exposes damage-associated molecular patterns; immunogenic cell death that primes a systemic, abscopal antitumor response; and a benign adverse-event profile that preserves quality of life. We then trace the translational arc from *in silico* and *in vitro* mechanisms, through *in vivo* validation, to controlled clinical studies, including a phase III randomized trial in locally advanced cervical cancer and a meta-analysis in glioblastoma, and conclude with the limitations and the trial agenda needed to consolidate mEHT's role as an adjuvant modality. Underlying the whole account is a set of conceptual reorientations: away from attacking the tumor's strongest capability and toward its vulnerabilities; away from static hallmarks and toward biological processes; away from the tumor as target and toward the patient who bears it; away from a temperature-and-heat dogma and toward an alliance with the immune system and homeostasis; and away from temperature and toward an energy-based dose. We propose that mEHT is best understood as an expression of these reorientations, and that tumor shrinkage, while welcome, is not the goal; survival time and quality of life are.

Keywords: modulated electro-hyperthermia; oncothermia; immunogenic cell death; abscopal effect; lipid rafts; hyperthermia; radiosensitization; translational oncology

1. Introduction

Contemporary oncology integrates several rapidly advancing fields, including robotic oncosurgery, sophisticated molecular diagnostics, precision radiation techniques, targeted therapies, immunotherapies, and cellular therapies. Despite major advances in surgery, radiotherapy, chemotherapy, and immunotherapy, oncology still faces recurring translational bottlenecks. Tumors remain heterogeneous, adaptive, and capable of resisting treatment, while systemic toxicity limits dose intensity and combination strategies. Epidemiologic studies support the necessity of further efforts. The scale of the above four challenges addressed is approximately 20.6 million new cases and 9.8 million deaths in 2022 [1].

Most cytotoxic and physical therapies struggle to distinguish malignant from healthy tissue. Radiation deposits dose along its path; systemic chemotherapy distributes throughout the body; and classical hyperthermia heats whatever lies within the applied field. The therapeutic index is therefore determined by the extent of normal tissue damage that can be tolerated. Any modality that preferentially deposits its effect in malignant cells widens that index.

Tumors are not static targets. They buffer cellular stress through molecular chaperones, suppress apoptotic signaling, and actively evade immune surveillance, for example, by maintaining an immunosuppressive microenvironment and recruiting regulatory T cells. A therapy that engages only a single death pathway, or that fails to alert the immune system, invites adaptation and relapse.

Death is usually caused by systemic disease rather than failure of local control. For many solid tumors, the cause of death is not the primary lesion but micro- and macro-metastatic disease. Consequently, controlling the treated site, while necessary, is not sufficient; the clinically meaningful endpoints are disease-free and overall survival. A purely loco-regional therapy that cannot reach distant disease addresses only part of the problem.

Aggressive multimodal therapy frequently produces significant toxicity and long-term comorbidity. Even when survival improves, the burden of treatment can substantially degrade quality of life. A modality that adds benefit without adding toxicity, and that may even mitigate the side effects of concurrent therapy, is therefore especially valuable.

The challenges are usually treated as engineering problems, prompting calls for better technological solutions. One of those is hyperthermia, which has long been considered a physical adjunct, but conventional approaches have struggled with selectivity, overheating of healthy tissues, and uncertain systemic benefit.

The modulated electro-hyperthermia (mEHT), also known as oncothermia, was developed to overcome these limitations by preferentially coupling electromagnetic energy to malignant tissue and using the resulting localized biophysical stress to amplify antitumoral cytotoxic and immunologic effects [2]. The success of mEHT derives from addressing the biophysical characteristics of malignancy rather than targeting only the thermal sensitivity of malignant cells.

The translational relevance of mEHT lies not only in its ability to heat tumors, but also in its potential to convert local energy deposition into a broader biological response. The redistribution of membrane lipids and ions of tumor cells alters the membrane's capacitance, conductivity, and overall dielectric permittivity. This makes tumor cells uniquely susceptible to alternating electric fields and electromagnetic therapies, such as mEHT, that exploit these precise biophysical deviations to selectively induce stress and apoptosis in malignant tissue.

Rather than using unmodulated, continuous RF waves, a highly sophisticated approach uses amplitude-modulated or pulsed RF fields. If the modulation frequency matches the natural mechanical or chemical relaxation rates of specific membrane channel proteins, we can theoretically maximize the torque or conformational stress applied to those channels. In principle, this would allow targeted apoptosis at comparatively low total energy input, reducing the thermal load on surrounding healthy structures. This remains a hypothesis: direct experimental measurement of the proposed frequency matching at the level of individual channel proteins has not yet been reported.

The mEHT method exhibits selective targeting, sensitization of tumors to radiotherapy and chemotherapy, induction of apoptosis, and evidence of immunogenic and abscopal effects [3]. Clinical reports further suggest that mEHT can be combined with standard oncologic regimens without adding prohibitive toxicity, which is the essential requirement for any credible “bench to bed” platform [4]. The Figure 1. summarizes the main challenges in current cancer therapies.

This narrative review examines how modulated electro-hyperthermia relates to four of these challenges and evaluates the strength of the preclinical and clinical evidence available for each.

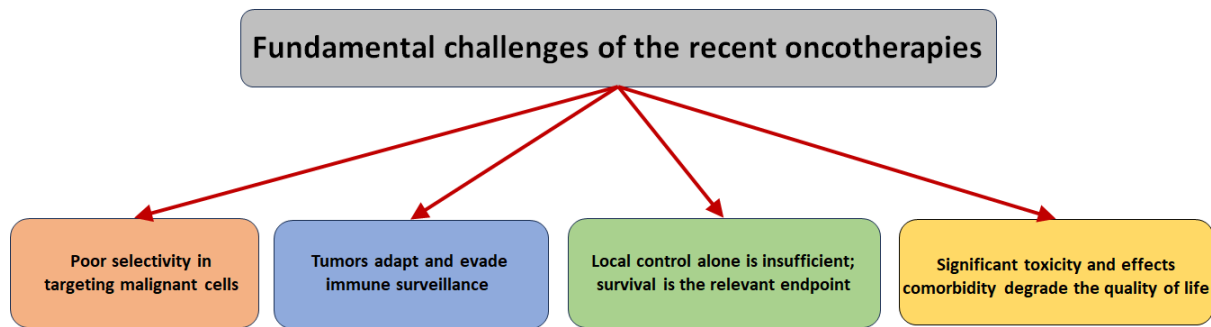


Figure 1. The central framework of this review. Four fundamental challenges of current oncotherapy.

Scope and selection of material. This is a narrative, not a systematic, review. The four challenges used to organize the article (selectivity, adaptation and immune evasion, systemic versus local control, and treatment-related toxicity) were chosen because each is routinely cited as a limiting factor in solid-tumor therapy and because each has a corresponding, separately testable mEHT mechanism. They are not an exhaustive account of the problems facing oncology: early detection, intratumoral heterogeneity, acquired molecular resistance, cachexia, and access and affordability are of comparable importance and are not addressed here. The one-to-one pairing of challenge and mechanism used below is an organizing device for the available evidence; it is not a claim that mEHT resolves these challenges completely, nor that other modalities do not address them.

Evidence base and its provenance. Material was drawn from indexed preclinical and clinical publications, as well as book chapters, conference reports, and articles in the *Oncothermia Journal*, which is published by the community of practitioners of the method and is not independently indexed. A substantial proportion of the mechanistic literature on mEHT originates from the present author's group and a small number of collaborating centers, reflecting the size of the field rather than a selection made for this review. Where evidence rests on a single group, on non-indexed sources, or on single-arm comparisons with historical controls, this is stated in the text and in the tables so that readers can weigh it accordingly. Independent replication is identified in Section 6 as the principal outstanding requirement.

2. A Change of Paradigm

Paradigm shifts do not occur solely through argument; they occur when the dominant paradigm clearly ceases to be effective, and an alternative becomes both possible and provable. Both these conditions are now present. The prevalent tumor-shrinking, proliferation-focused model has achieved real successes, but in common solid tumors, its effectiveness is declining: response rates based on shrinkage often do not lead to proportional improvements in survival, resistance develops because therapy targets the tumor's most defended capabilities, and the toxicity of increasingly aggressive treatments gradually rivals the benefits they aim to provide. These issues are not just isolated failures but part of a systematic pattern, in which repeated failures signal that the foundational assumptions, beyond tactics, require reassessment.

At the same time, the alternative has become actual rather than merely speculative. Three developments converge. First, cancer biology itself has moved from a static, gene-list picture toward a systems picture in which feedback, microenvironment, and immune surveillance are constitutive of the disease rather than incidental to it; the hallmarks have been reframed around enabling processes and immune evasion. Second, the clinical arrival of immunotherapy has demonstrated, in clinical practice and not just in principle, that recruiting the patient's own regulatory and surveillance systems can produce durable, systemic disease control, including responses at sites never directly treated. Third, on the physical side, the demonstration that an electromagnetic field can be focused selectively on the malignant membrane and dosed in energy units, with reproducible immunogenic consequences and a phase III randomized clinical trial, shows that reorientation is buildable and testable today. The change of paradigm is timely, in short, because the old model's limits and the new model's feasibility have become apparent at the same moment.

If the shifts are merely relabeled, they will be absorbed back into the old worldview and lose their force; they must be addressed as a connected set because each one removes an obstacle that would otherwise defeat the others. The common reason behind all five is that cancer is a disorder of a living, regulated, evolved system, and a therapy that ignores that systemic character will be corrected, evaded, or outlived by the system it acts upon. Each shift names one way in which the conventional approach fails to respect that character, and therefore one reason must be confronted directly rather than worked around.

2.1. Change of Targeting Paradigm

Attacking the strongest capability (proliferation) carries an intrinsic liability, because doing so applies the maximal selective pressure at exactly the point of maximal adaptive reserve, breeding resistance; targeting the weaker capabilities is an alternative worth testing, because they are where the disease has the least room to adapt. The strengths and weaknesses of malignancy are summarized in Table 1 and Figure 2.

Table 1. The strengths and weaknesses of malignancy.

Strengths	Weaknesses
Rapid proliferation	Loss of multicellular cooperation
Adaptability	Reduced networking
Genetic diversity	Loss of systemic regulation
Autonomous growth	Dependence on excessive energy consumption
Resistance	Fragile organizational complexity

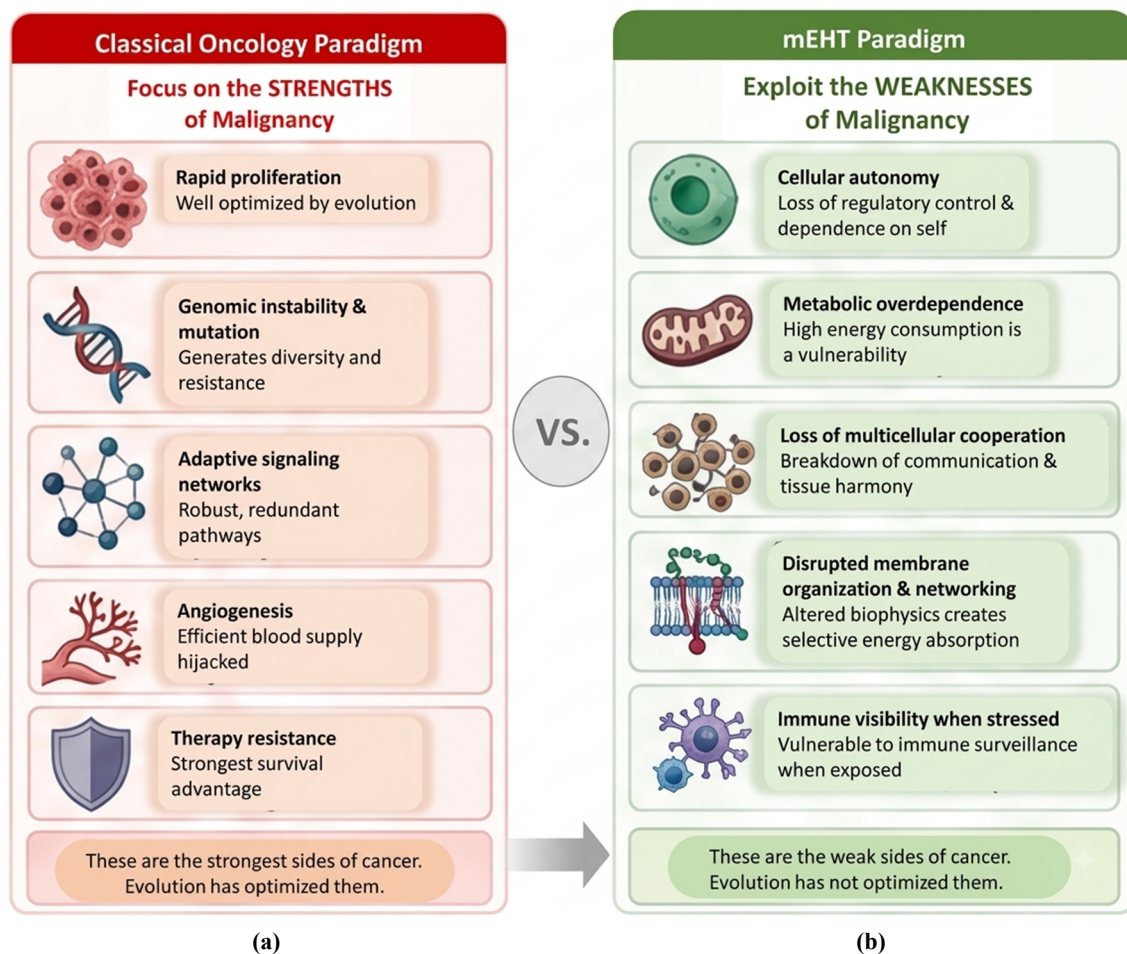


Figure 2. Target the Weaknesses, Not the Strengths. **(a)** Classical oncology. Evolution has optimized proliferation. **(b)** mEHT paradigm. Evolution has not optimized them (consequences of losing multicellular cooperation).

The product view is incomplete on its own, because static targets describe a moving system inaccurately, so interventions aimed at a snapshot are outrun by the dynamics; a process-oriented view is therefore proposed here, on the argument that only by engaging feedback and surveillance can a therapy keep pace with a disease that changes. A tumor-only endpoint is an incomplete measure of benefit, because the lesion is often not what kills the patient; disseminated disease and the failure of the host are, so a measure confined to the lesion measures the wrong thing; patient-level endpoints are therefore preferable, because survival and quality of life are properties of the patient, and they are what treatment is for. A strictly temperature-defined framework is limited, in that it is energetically inefficient and provokes the very homeostatic defenses that neutralize the effect; an approach that works with immune and homeostatic regulation is argued for here, because the organism's billion-year-old regulatory processes are more powerful than any external agent and are better made partners than adversaries. And

temperature is not a satisfactory dose descriptor, because an intensive parameter cannot quantify what was delivered, leaving the field unable to study dose–response or reproduce results; an energy-based, mass-referenced dose is proposed instead, since dose–response relations cannot otherwise be established. These five reorientations are advanced as a working framework rather than as established conclusions; the sections that follow present the evidence bearing on each. Addressed together, the five shifts are mutually reinforcing; addressed singly or cosmetically, each is liable to be undone by the assumptions left standing around it.

Conventional cytotoxic therapy targets proliferation, DNA replication, and mutation—the very capabilities the malignant cell is built to defend and the ones selected for through tumor evolution. In contrast, mEHT targets weak points: cellular autonomy, metabolic dependence, loss of cooperation, disrupted communication, and immune visibility.

Attacking the strongest side invites resistance. The alternative is to target the malignant cell’s vulnerabilities: its cellular autonomy and the loss of the cooperative networking that binds healthy tissue, and its heightened, almost desperate competition for energy intake. mEHT acts precisely at these weak points. Its membrane-level field effect disrupts the autonomous cell’s control of its boundary and ion balance, and the malignant metabolic shift that drives the fight for energy (the Warburg phenotype) is precisely the property that makes the tumor electrically conspicuous and therefore selectable. In other words, the features that make a cell malignant are turned into the features that make it a target.

2.2. Change of Treatment Paradigm

Much of oncology treats the tumor as a set of static hallmarks, a list of fixed properties to be neutralized one by one. This product-oriented view captures a snapshot but misses the living system. A process-oriented view instead engages the dynamics: the feedback mechanisms that regulate the tissue, the immune surveillance that polices it, and the biological complexity through which all of these interact. mEHT is process-oriented in this sense (Figure 3).

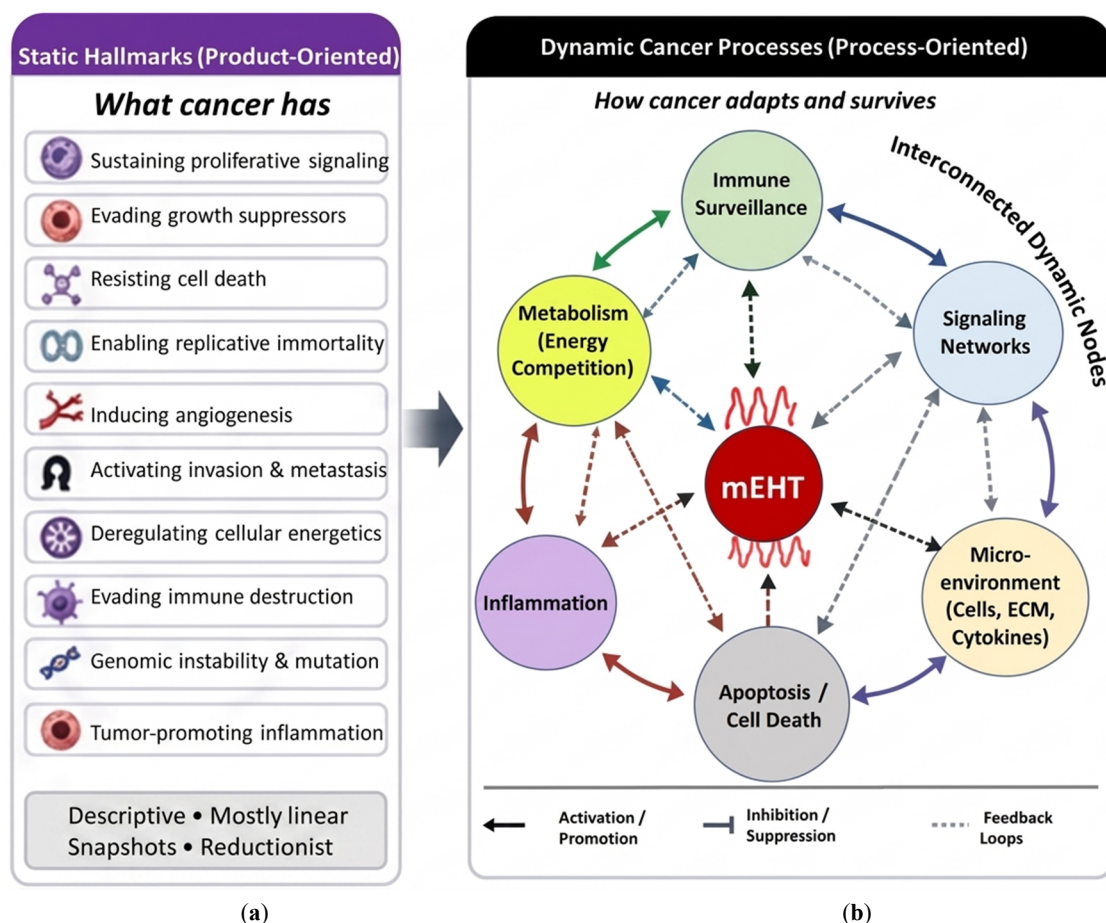


Figure 3. Static hallmarks versus dynamic cancer processes. (a) Main traditional hallmarks of cancer. (b) Dynamic networks: immune surveillance, metabolism, signaling, apoptosis, inflammation, microenvironment. mEHT is located at the center, thereby modifying network interactions.

Its main significance lies not in abating a specific amount of tumor tissue, but in initiating a process: immunogenic cell death, damage signaling, antigen presentation, and T-cell activation, which engage the body’s

innate regulatory and surveillance systems. The treatment acts as a trigger, and the body provides the response (Figure 4). A key question is what the true target is: the tumor or the patient? The patient should be the focus, considering comorbidities, overall health, social and personal factors, and quality of life. Clinically, the goal is not merely tumor reduction, imaging improvements, or biomarker normalization. Instead, it is to achieve longer survival, maintain quality of life, and restore function, regardless of tumor size.

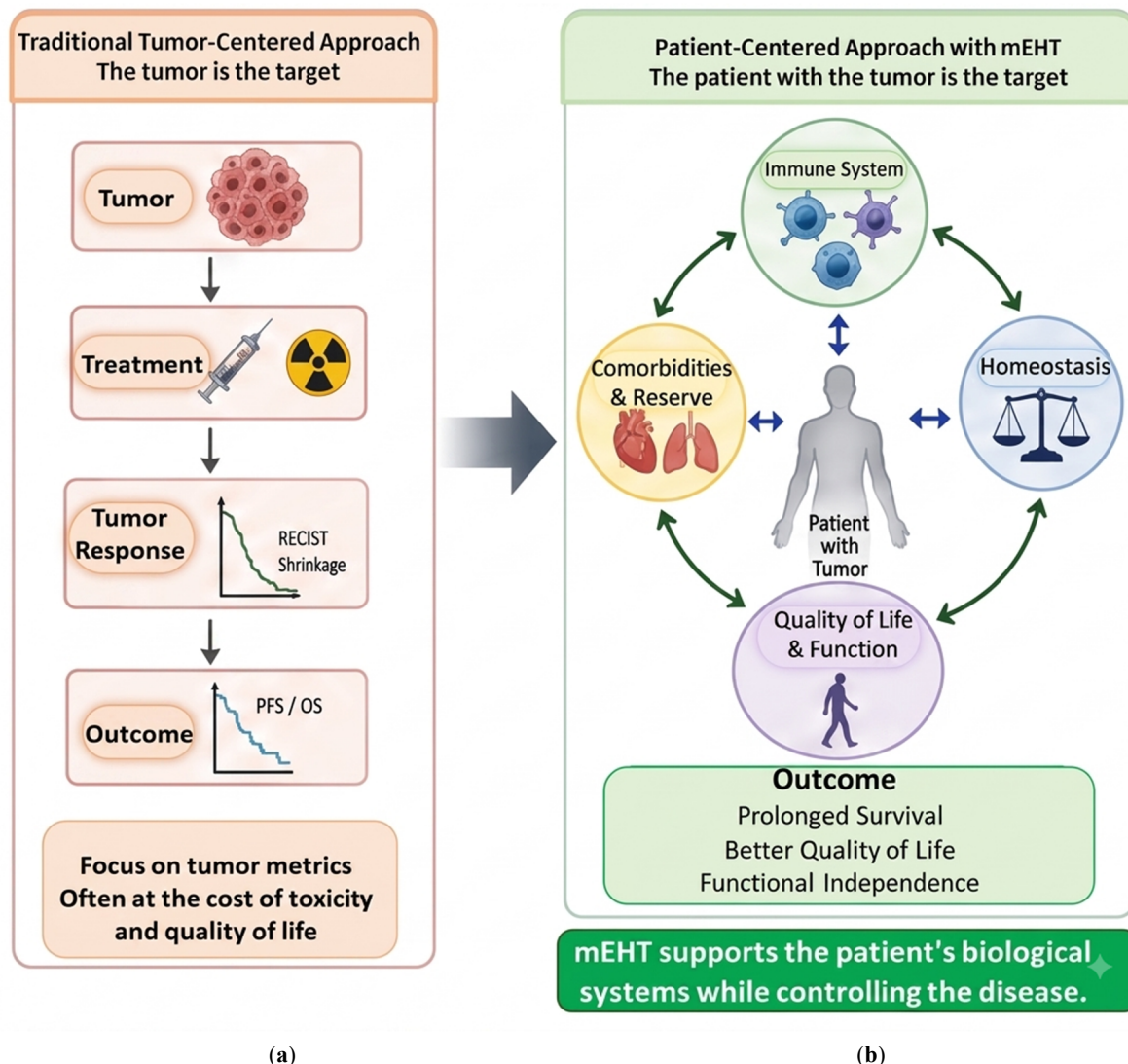


Figure 4. The shift from tumor-centered to patient-centered oncology traditional approach. (a) Tumor-centered conventional approach. (b) Patient-centered, immune-supported approach.

The focus in clinical care should be on the patient as a whole, not just the tumor, since the disease affects the entire organism. A tumor-centered approach considers treatment success to be merely reducing the lesion; however, a patient-centered approach evaluates whether the patient is living longer and better. These questions can lead to different outcomes, as aggressive local treatments may cause toxicity and impair function, potentially shortening or reducing quality of life. The clinical success of mEHT is best understood from a patient-oriented perspective because its unique benefits, such as maintained quality of life, systemic (abscopal) responses, and improved survival at acceptable costs, reflect the patient's overall condition, not solely the tumor.

2.3. Change the Hyperthermia Paradigm

Classical hyperthermia rests on a dogma: that temperature and its thermal effects are the whole story, and that the clinician's task is to impose a target temperature on the tissue [5]. In our opinion, this wastes energy and provokes the organism's defenses; a massively heated tumor volume triggers physiological corrections (increased perfusion, metabolic and homeostatic responses) that work against the intended effect. The paradigm shift is to stop fighting the living system and to enlist it. The immune system and homeostasis are treated as allies rather than

obstacles; the body's billion-year-old, evolutionarily refined processes are trusted as partners rather than overridden. mEHT is engineered around this humility: it delivers its energy as an electric field that homeostatic control cannot simply compensate for, targets malignant cells individually at the nanoscale rather than homogeneously heating a volume, and chooses mechanisms that initiate the body's own malignant-cell-killing responses. The premise is that we are not smarter than evolution and should not pretend to be (Figure 5).

Historically, hyperthermia has been characterized by temperature elevation, thermal dose, and thermal damage. This framework emerged from physics in daily life, with primary experiences from cooking in the kitchen. However, living systems are not passive materials. They are adaptive, self-organizing, nonlinearly responding evolutionary systems. The problem is that the temperature itself is not therapeutic; it is merely a condition. The therapeutic effect originates from biochemical reactions, signaling cascades, immune activation, and homeostatic responses, including immune surveillance. The living organism performs a part of the therapeutic work. Homeostatic dynamic control and the immune system have evolved over millions of years to optimize complex living processes. The therapy should work in harmony with these mechanisms, not replace them, not compete with them. The mEHT functions as a trigger, a catalyst, and a guide, supporting and allowing natural biological processes to complete the treatment.

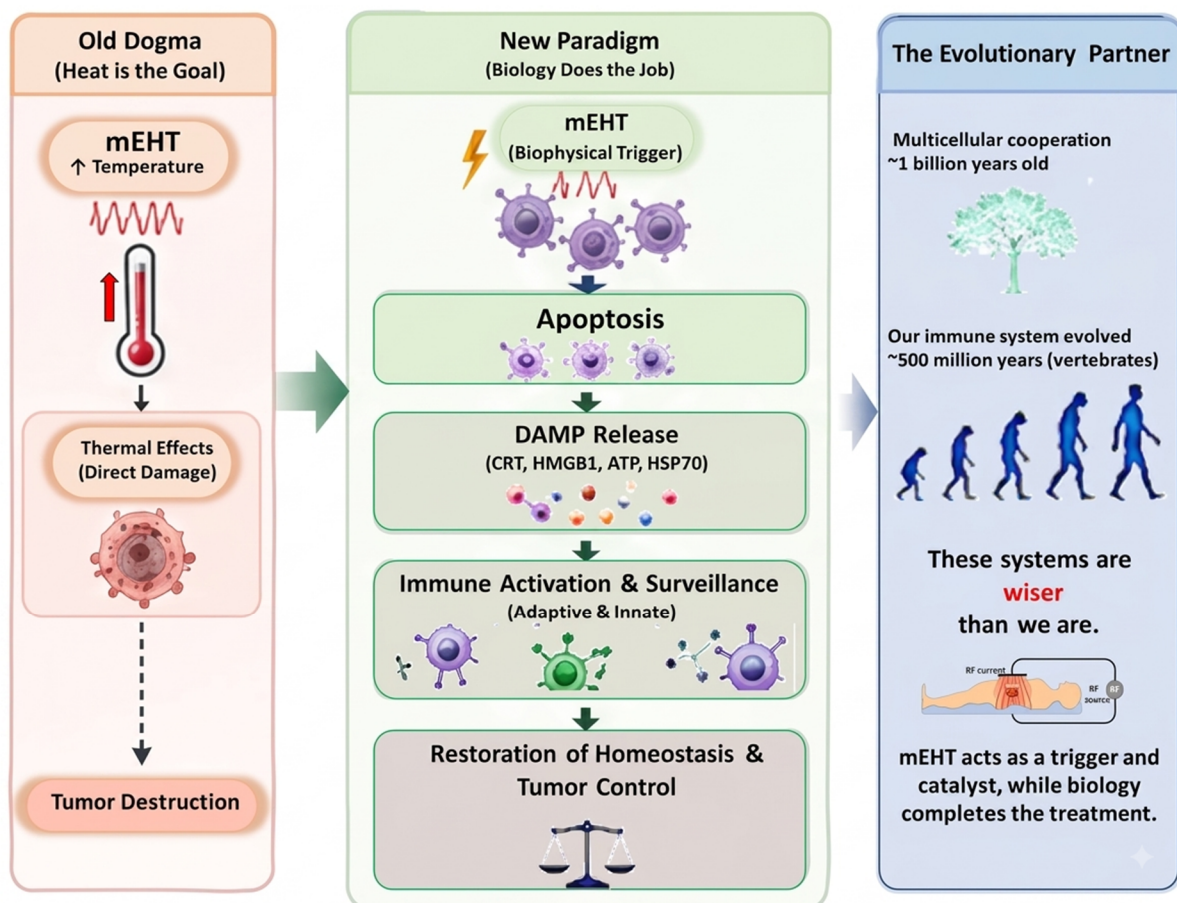


Figure 5. The treatment initiates the process; biology completes it.

Finally, using temperature as a measure in hyperthermia treatment is misleading because temperature is an intensive property; it doesn't depend on the amount of tissue. Heat energy, on the other hand, is extensive and depends on mass or volume. Temperature only indicates how hot a point is, not how much energy was delivered. Ionizing radiation already uses the correct measure of energy absorbed per unit mass, the gray (1 Gy = 1 J/kg). mEHT aligns with this standard by dosing in J/kg (equivalent to Gy) and personalizing treatment through step-up heating that accounts for each patient's washout time and sensations (Figure 6). The key point is that the therapeutic effect results from the energy delivered, not from heating itself. The actual work involves chemical and molecular changes in living tissue, with heat merely creating the optimal environment, as described by Arrhenius kinetics. Ultimately, energy, not temperature, is the true currency of the treatment.

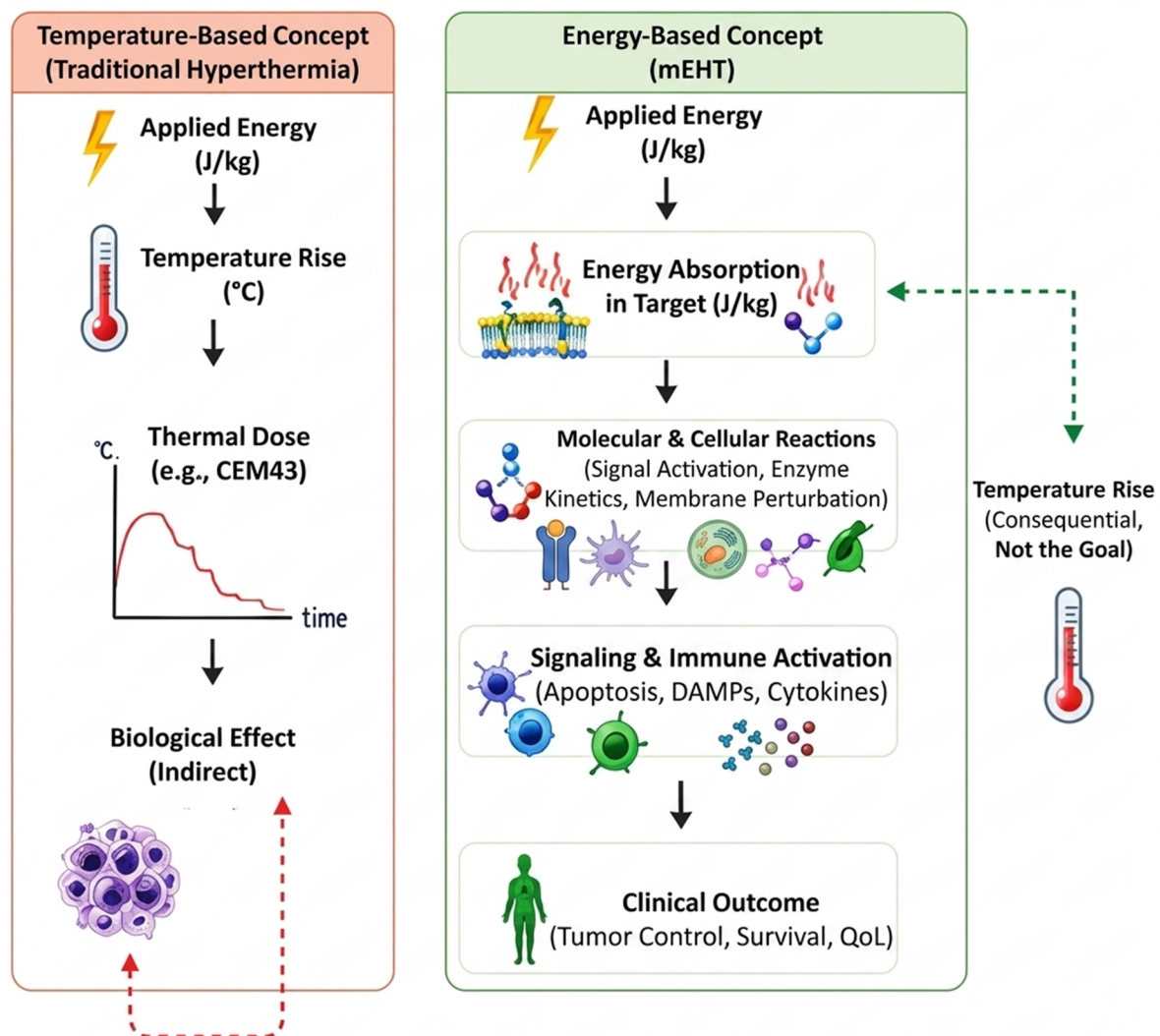


Figure 6. Energy-Based versus Temperature-Based Treatment Concepts.

The temperature model assumes that the provided energy increases the temperature, whereas the mEHT model focuses on using the energy for molecular reactions, signaling initiation, and immune activation, with temperature appearing only as a conditional side branch.

Taken together, these shifts redefine what counts as success. The oncology community often evaluates RECIST response, objective response rate, and local control. Tumor shrinkage is a welcome sign but not sufficient. Yet patients seek a longer and better life. The goals of treatment are survival time and good quality of life, patient outcomes achieved by attacking the disease's weaknesses through its own regulatory processes, with a dose measured in the natural units of delivered energy. The mechanistic and clinical sections that follow should be read in this light (Figure 7). The main clinically relevant endpoints include overall survival (OS), disease-free survival (DFS), progression-free survival (PFS), quality-adjusted survival, and the prevention of deterioration in quality of life (QoL). The secondary local response and tumor shrinkage calm the patient, consistent with the previous primary endpoints.

The paradigm shift is fundamental to the mEHT approach; it represents a completely different worldview (Figure 8). The strongest clinical argument for mEHT may not be dramatic tumor regression. The treatment model has to directly reflect patient benefits, such as prolonged survival, reduced toxicity, systemic immune effects, and improved quality of life.

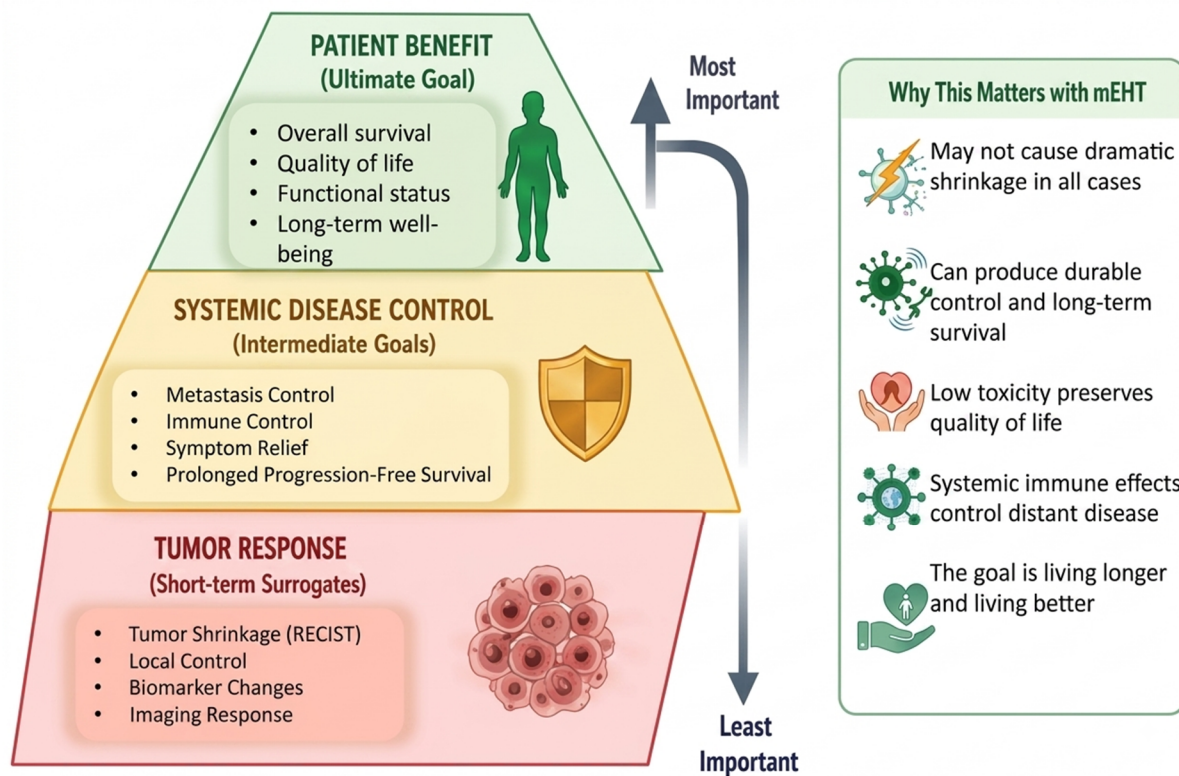


Figure 7. Hierarchy of therapeutic endpoints.

Prevailing paradigm		mEHT paradigm shift
1. Attack the strongest side Target proliferation, the capability the tumour is built to defend. Maximal effort against rapid cell division.	→	Attack the weak sides Exploit cellular autonomy, lost networking, and the fight for energy intake — the vulnerabilities, not the strengths.
2. Product-oriented Treat static hallmarks as fixed targets. A snapshot of what the tumour currently is.	→	Process-oriented Engage feedback mechanisms, immune surveillance and biological complexity — the dynamics, not the snapshot.
3. Tumour-oriented The tumour is the target. Success is measured by what happens to the lesion.	→	Patient-oriented Treat the patient who has the tumour. The target is the tumorous patient — survival and quality of life are the goals.
4. Hyperthermia dogma Temperature and thermal effects alone. The clinician overrides physiology; heat is the whole story.	→	Living complexity as ally Recruit the immune system and homeostasis as partners; trust billion-year-old evolutionary processes rather than override them.
5. Temperature as dose Characterize treatment by °C reached. But temperature is intensive — it does not scale with mass or volume.	→	Natural energy dose (J/kg) Dose in J/kg = Gy, as ionising therapy does. Energy does the job; the job is chemical — heat only raises reaction rates (Arrhenius).

Figure 8. Five paradigm shifts underlying the mEHT approach. In each row, the prevailing assumption (left) is replaced by the reorientation embodied by mEHT (right). Together, they move the goal of treatment from shrinking the tumor to prolonging survival with good quality of life.

3. Principles of Modulated Electro-Hyperthermia

The therapeutic use of heat in medicine reaches back to antiquity; the Greek physicians already associated febrile states with recovery and reasoned that controlled heating might mobilize the body's own healing responses. In modern oncology, moderate hyperthermia refers to heating a tumor to a temperature of roughly 39–42.5 °C to sensitize it to radiation and drugs. Despite a long and biologically plausible rationale, classical hyperthermia never achieved broad clinical acceptance. The reasons are instructive and motivate this review: conventional techniques heat tissue largely by raising bulk temperature, which is intrinsically non-selective; the resulting rise in blood flow could increase nutrient delivery to the tumor and, theoretically, raise the risk of metastatic spread; and the heterogeneous, hard-to-control temperature distributions produced inconsistent trial results.

Modulated electro-hyperthermia (mEHT) was conceived as a direct response to address these shortcomings. It is based on a biophysical rather than solely thermal approach. mEHT differs from classical hyperthermia in both dose concept and biological intent. Classical hyperthermia generally focuses on uniform temperature elevation, whereas mEHT emphasizes selective energy deposition and biological response within moderate temperature ranges. The literature repeatedly frames this as a shift from a simple thermal dose to a bioelectromagnetic treatment model, in which energy absorption, membrane interactions, stress signaling, and immune activation are all part of the therapeutic chain.

Instead of isothermally heating the target volume indiscriminately, mEHT uses an electric current flowing through the body in between the electrode applicators [6]. The treated volume forms part of the resonant output circuit, and the generator's matching network continuously adjusts to the patient's changing load impedance, maintaining efficient power transfer as tissue conditions change during treatment [7]. The malignant phenotype exhibits different electrical and thermal properties compared to healthy tissue. This is due to a metabolic shift toward aerobic glycolysis (the Warburg effect), increased extracellular ion levels that support rapid proliferation, waste buildup, primarily as lactic acid, a changed electrolyte order in the microenvironment, and an enrichment of energy-absorbing membrane microdomains, such as clusters of transmembrane proteins. These characteristic changes in the tumor microenvironment (TME) manifest as alterations in the tumor's electrical and thermal properties. The conductivity and electric permittivity increase, allowing the tumor to be distinguished from the healthy environment. These values differ significantly between malignant and benign tumors, as measured across 70 patients [8]. Conductivity of 0.44 S/m in tumor-bearing tissue versus 0.26 S/m in healthy pancreas, a low-frequency human measurement, which is the frequency range nearest the modulation band of mEHT [9]. The optimal frequency of the RF current is in the range of overlap of β and δ frequency dispersion [10,11]. The authoritative independent review of tissue permittivity and conductivity, including a dedicated section on malignant tissue and on α -, β - and γ -dispersion, supports both our dispersion argument and the general conductivity/permittivity contrast [12].

Within this range, 13.56 MHz is the frequency used in practice, being internationally allocated for industrial, scientific and medical (ISM) applications; the allocation, rather than a demonstrated physical optimum, is the primary reason for this choice [13]. The malignant cells disrupt their intercellular network, resulting in a remarkable change in their membrane organization compared with that of healthy network members, expressing an increased density of membrane-associated nanodomains (lipid rafts) [14], the dynamic microdomains, which serve as highly organized platforms for cell signaling. This enrichment of cholesterol and sphingolipids in malignant membranes is a novel therapeutic target in many pathologies [15]. Raft levels are enriched in cancer stem cells compared with ordinary cancer cells, which may explain why the effect might reach the resistant subpopulation [16]. Because tumor cells often exhibit significantly higher lipid raft expression and altered membrane cholesterol content than healthy differentiated cells, the Maxwell-Wagner interfacial polarization effect is inherently enhanced in malignant tissue. Current independent reviews of raft biology and its role in cancer cell survival support raft enrichment and signaling-platform functions; thus, rafts have become targets for various therapies, including oncology [17]. This allows for a purely biophysical method to trigger apoptosis in diseased cells while normal cells, with lower raft densities and different relaxation frequencies (τ), are correspondingly less strongly affected at the same radiofrequency (RF) current parameters. Selectivity here is a ratio of deposited energy rather than an all-or-none distinction.

The unique physical properties of rafts make them good energy absorbers, acting as localized energetic “sinks” or “antennas” when exposed to an external alternating electric field. In this way, the mEHT selectively deposits energy into tumor cells and their cell membrane. These differences allow the field to focus on the tumor, concentrating energy at the cell membrane while keeping the macroscopic temperature within the mild range [18]. Mild hyperthermia's effect on distant metastasis versus ablation's local effect, supports the mild-temperature

argument on independent grounds [19]. This heterogeneity in heating is essential for precise energy targeting of tumor cells while maintaining the activity of temperature-sensitive immune cells in the TME.

The absorbed energy excites membrane channels and transmembrane proteins included in the raft clusters [20]. The localized energy absorbed by the raft does not simply dissipate as random heat; instead, it targets the high concentration of transmembrane signaling proteins and ion channels anchored within these domains. This localized thermodynamic stress triggers apoptosis via two primary pathways: activation of voltage-gated and mechano-sensitive channels, and clustering and activation of death receptors (extrinsic pathway) [21]. The intense local gradient $|E_{raft}|$ alters the transmembrane potential ($\Delta\phi_m$) specifically across the raft domain. This localized depolarization or electro-mechanical torque (via Maxwell stress tensor forces acting on the rigid raft) forces a conformational change in raft-associated ion channels, such as voltage-gated calcium channels (VGCCs) or transient receptor potential (TRP) channels [22]. This induces a massive, sudden influx of extracellular Ca^{2+} ions directly through the raft. The localized hyper-concentration of intracellular Ca^{2+} overloads the nearby mitochondria, disrupting their membrane potential ($\Delta\psi_m$), inducing the opening of the mitochondrial permeability transition pore (mPTP), and releasing Cytochrome c into the cytosol to activate the cas9/cas3 intrinsic apoptotic pathway.

Localized RF energy absorption alters the lateral-line tension at the interface between the raft and non-raft domains. The dynamic change in this boundary energy overcomes the thermodynamic barrier that prevents receptor mixing. The high-frequency micro-vibrations and localized phase-boundary changes drive the mechanical aggregation (clustering) of these death receptors, even in the absence of their natural ligands. The forced trimerization of Fas/TNFR1 within the energized raft recruits the Fas-associated death domain (FADD) and procaspase-8, thereby assembling the death-inducing signaling complex directly at the inner leaflet of the raft and initiating the extrinsic apoptotic cascade.

To orient the intracellular signal cascade, a low-frequency (α frequency dispersion), a time-fractal amplitude modulation, or pulsed fields are applied to the RF high-frequency carrier [23,24]. The working hypothesis is that the modulation spectrum overlaps the relaxation rates of raft-bound channel proteins, which would permit apoptosis to be triggered with comparatively low total energy input and a limited thermal load on surrounding healthy structures. The modulated RF, together with triggering the extrinsic apoptotic pathway through Caspase8 (Cas8), ignites the mitochondrial-based intrinsic pathway (through Cas9) and a caspase-independent pathway (through AIF), leading to immunogenic cell death (ICD) with damage-associated molecular patterns (DAMPs) [25,26].

The mEHT treatment functions are therefore better described as a field effect with a thermal component rather than as heating tissue. Over the past two decades, *in silico* modeling, *in vitro* experiments, and *in vivo* tumor models have progressively revealed how this selective energy deposition translates into tumor cell death, damage signaling, and immune activation; in parallel, clinical studies across a broad range of tumors have reported on feasibility, safety, local control, survival, and quality of life. What has been missing is not data but a unifying frame. This review supplies one. We take the four fundamental challenges of current oncotherapy that practicing oncologists encounter daily and, for each, present the corresponding mEHT mechanism along with the preclinical and clinical evidence supporting it. The structure mirrors a clinical thought process: name the problem, then show the solution and its evidence base.

The setting of mEHT is an asymmetric capacitive electrode arrangement. The asymmetry is applied in the applicator's geometries (the down electrode is much larger than the movable upper one), and the field production is also asymmetric (the large applicator is grounded) [27] (Figure 9). The device operates at low incident power, typically not exceeding 150 W, and controls the microscopic (raft-located) target temperature at $\sim 42^\circ\text{C}$, generally $<43^\circ\text{C}$, while the macroscopic tumor temperature remains in the mild fever range ($<40^\circ\text{C}$). The skin temperature is controlled by the applicator's positioning, keeping it $<38^\circ\text{C}$. The provided energy is usually $<12\text{ kJ/min}$. The treatment guidelines are developed by an international team of professionals [28].

The treatment goals differ significantly between mEHT and classical hyperthermia: mEHT heats at a microscopic level, focusing energy directly on malignant cells and creating a heterogeneous temperature distribution. In contrast, classical hyperthermia aims for macroscopic heating, seeking a homogeneous, isothermal temperature across the entire tumor mass (Figure 10a), in contrast, mEHT heats self-focused, heterogeneous microscopic targets of the malignant cells (Figure 10b). The heterogeneous energy deposition also characterizes radiotherapy, with a focus on DNA strand breaks and minimal thermal effects (Figure 10c), while the mEHT triggers the apoptotic signals by energy absorption in the rafts. Both effects achieve apoptosis.

Two activity features of mEHT processes distinguish it from classical capacitive or radiative hyperthermia. First, mEHT uses the electric and thermal contrast between tumor and host tissue to concentrate current in malignant tissue, producing a self-focusing effect. Second, the carrier in mEHT is amplitude-modulated with a time-fractal (1/f-type) pattern, which enhances field focusing on cellular and subcellular structures and triggers intracellular signaling pathways that induce ICD and DAMP production

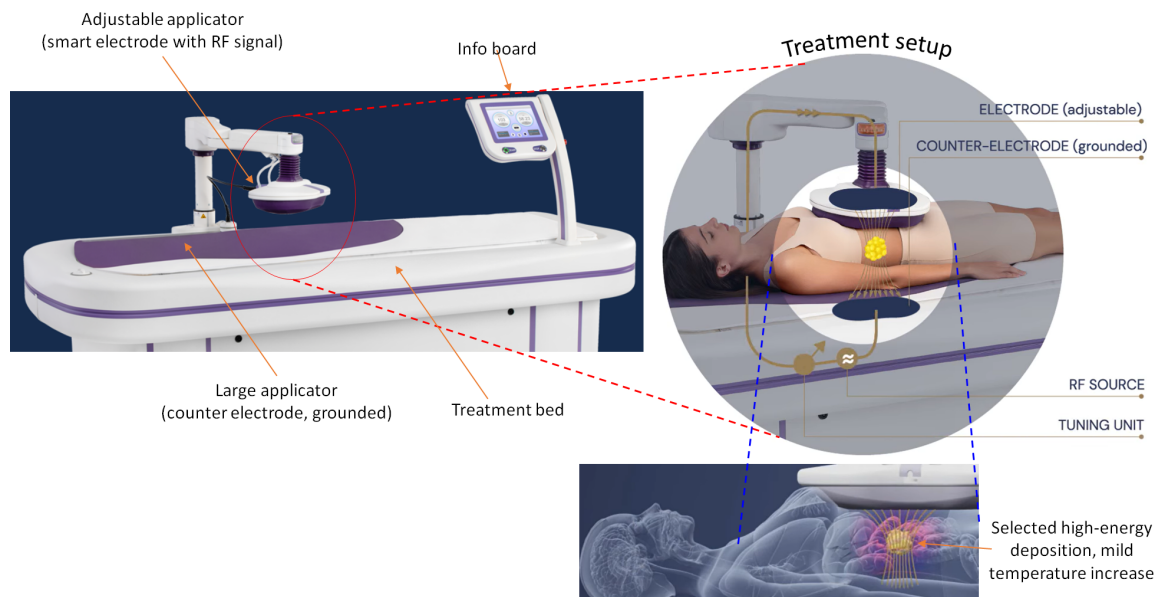


Figure 9. The mEHT system (EHY-2030).

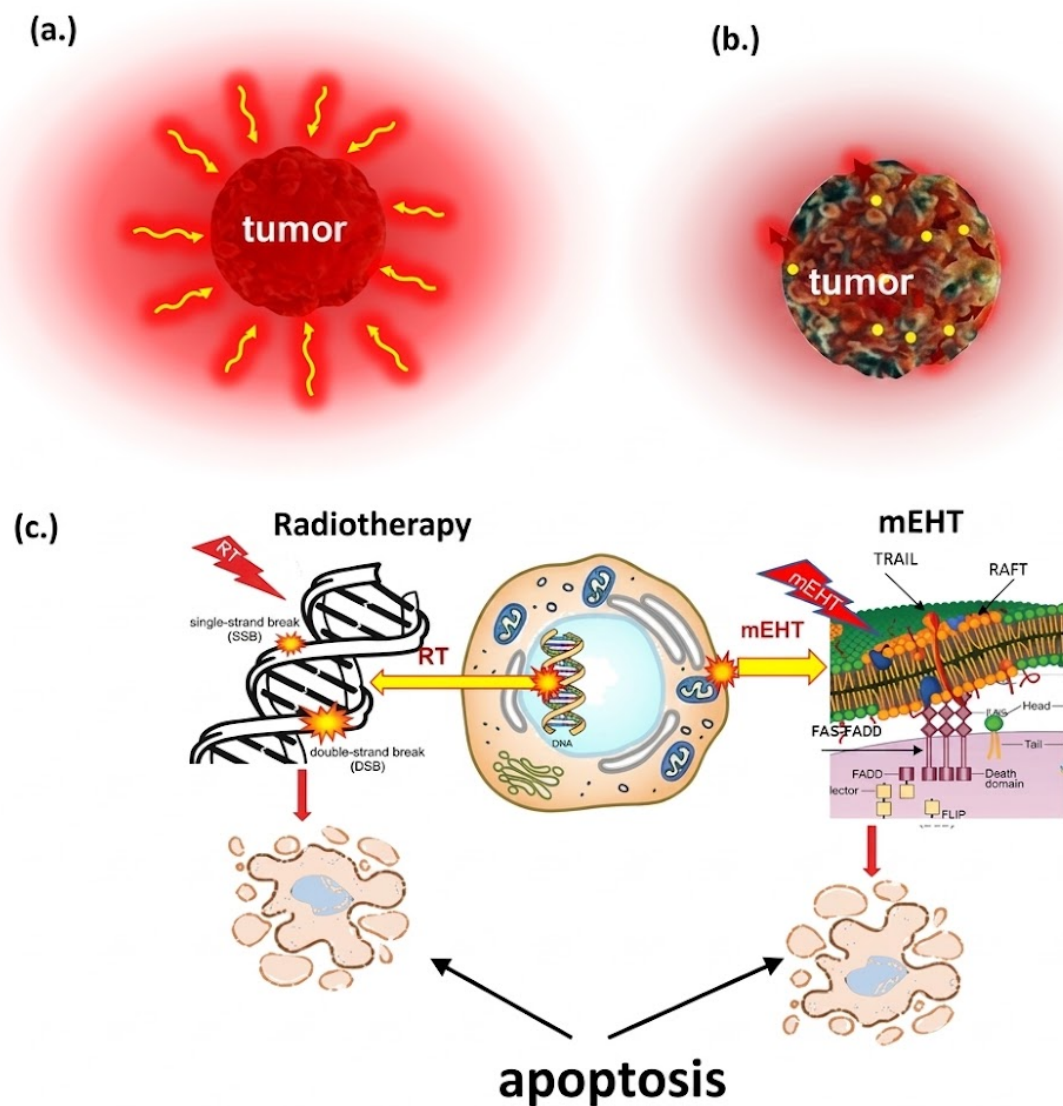


Figure 10. The homogeneous and heterogeneous energy absorption processes. (a) Homogeneous (conventional hyperthermia) focuses on the tumor mass, intending to heat it isothermally. (b) mEHT uses self-focused

heterogeneous energy absorption, achieving more accurate temperature concentration in the tumor while keeping its temperature mild, whereas the targeted rafts' temperature is ~ 3 °C higher. (c) Radiotherapy and mEHT share the same principle: heterogeneous energy absorption to induce apoptosis.

The treatment process also varies: in mEHT, focusing is automatic via real-time electric impedance matching; in contrast, the classical capacitive method focuses mechanically on the tumor by varying electrode sizes, while the radiative antenna array adjusts focus by varying the radiation intensities from different directions

The consequence is that energy is preferentially deposited on the plasma membrane and, in particular, on its cholesterol- and protein-rich microdomains, the lipid rafts, where local heating occurs at the nanoscale even though the bulk temperature remains mild. This distinction between nanoscale membrane heating and macroscopic temperature is central to understanding why mEHT can produce cell-level damage without the bulk thermal injury and perfusion effects that troubled classical hyperthermia.

Usually, the tumor is well protected, with poor T-cell infiltration, few dendritic cells (DCs) in the mass, but high protumoral T_{regs} and MDSCs, immunosuppressive cytokines (IL-10, TGF- β) and high expression of PD-L1. It is a remarkable feature of mEHT treatment that it converts the cold tumor into a hot one, with infiltration of CD8+ T-cells (CTLs), activated DCs, reduced T_{regs} and MDSCs, having pro-inflammatory cytokines (IL-12, IFN- γ) and has enhanced antigen presentation (Figure 11). Independent review shows precisely how these claims transform, including ICD induction and the immunosuppressive-to-immunogenic shift [29].

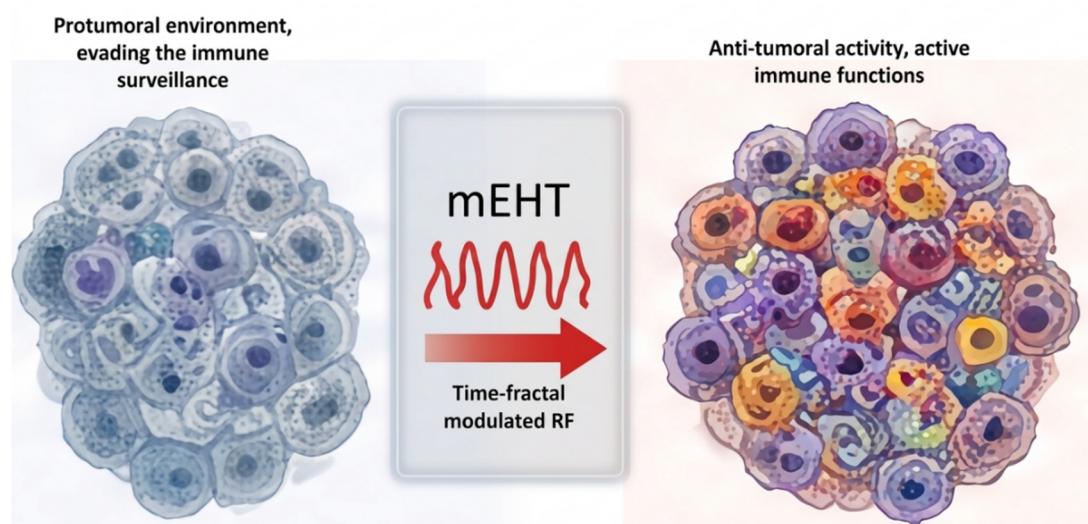


Figure 11. mEHT transforms cold tumors into hot ones.

Importantly, other oncotherapies (tumor-treating fields, TTFields [30]) extensively use selective electromagnetic effects to kill cancer cells. Independent demonstrations show that non-ionizing electric fields produce membrane-potential disruption, calcium-channel effects, and immune activation, the same mechanistic family mEHT invokes [31], including immune activation by applied fields [32].

4. mEHT Devoted to Resolving the Challenges

4.1. Challenge I: Selectivity: The Biophysical Basis

The mEHT leverages cancer vulnerabilities by focusing on changes in conductivity, membrane structure, metabolic activity, and intercellular communication. The malignant phenotype, at the level of bioelectricity, is a different material from that of healthy tissue. The shift toward elevated aerobic glycolysis and the massive demand for nutrients during aggressive proliferation increase the concentrations of mobile ions and metabolic intermediates, thereby increasing electrical conductivity [33]. Human lung tumor dielectric values are approximately twice those of non-neoplastic parenchyma, a directly measured, histology-confirmed contrast [34]. The altered membrane composition and the high density of membrane raft microdomains [35] raise permittivity and polarizability. The higher conductivity and electrical permeability guide the RF current to the TME, concentrating the energy delivered there. Cancerous tissues also differ in cell density, pH, and water content. Each of these differences increases the tendency of an applied radiofrequency field to deposit energy in the tumor. Because the wavelength at 13.56 MHz is far larger than the treated volume, the tissue behaves as a quasi-static dielectric, and the field redistributes itself to favor the more conductive, higher-permittivity malignant regions (Figure 12a).

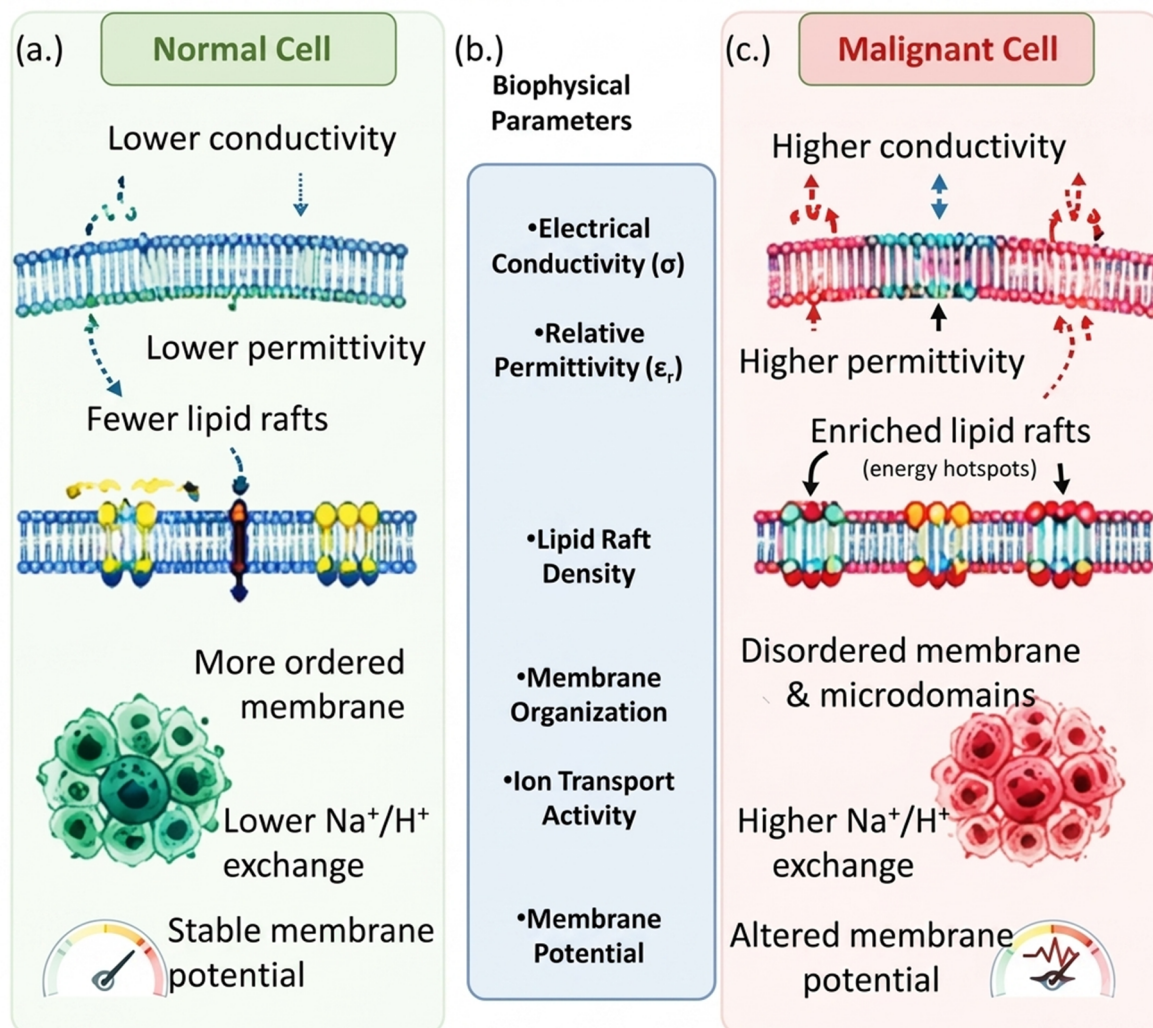


Figure 12. Biophysical basis of selectivity. mEHT preferentially couples with malignant cells due to their biophysical parameters. **(a)** In normal tissue, the cells' comparatively low conductivity and permittivity allow the field to pass through without deviating from its direction, resulting in the standard field distribution. **(b)** The biophysical parameters play a role in the selection. **(c)** In malignant cells, the exceptionally high metabolism-driven rise in conductivity and permittivity is accompanied by energy-absorbing membrane lipid rafts. It concentrates the amplitude-modulated field, thereby disrupting membrane potential and ion flux and initiating apoptotic signaling, while the macroscopic temperature remains within the mild range.

Modeling of energy absorption at the membrane indicates that the lipid rafts act as preferential sinks for the applied field [36]. The membrane mass is composed largely of protein and lipid, and most membrane proteins reside within raft microdomains; their dielectric properties and geometry concentrate the field, thereby heating the raft locally. This nanoscale heating, rather than bulk temperature elevation, is proposed as the proximate physical cause of the downstream biological effects. The same selective deposition disrupts the transmembrane potential and perturbs ion permeability, thereby interfering with intracellular signal transduction and favoring the initiation of programmed cell death (Figure 12b).

The importance of this mechanism lies not merely in its ability to preferentially heat the tumor. Because the field focuses on the membrane and its rafts, mEHT directly engages membrane-proximal death-receptor machinery and stress responses [37]. Selectivity is thus the entry point to the cellular and immunological cascade developed in the next sections: it determines that the damage signal originates in the tumor cell, in a form that the immune system can subsequently read. In addition, because the effect does not depend on driving bulk temperature high, the perfusion-mediated dissemination risk that limited classical hyperthermia is largely avoided (Figure 12b).

4.2. Challenge II: Defeating Adaptation: Multi-Pathway Apoptosis

A central reason tumor resist therapy is their ability to buffer stress and to suppress any single death pathway. mEHT counters this by engaging several programmed death mechanisms in parallel, so that the cumulative insult

exceeds the cell's adaptive capacity. Detailed molecular studies in colorectal and other models have mapped this response with unusual clarity.

In colorectal allograft and xenograft models, mEHT produces the morphological hallmarks of apoptosis, nuclear shrinkage, apoptotic bodies, and DNA fragmentation, confirmed by the TUNEL assay [38]. At the molecular level, both arms of caspase-dependent programmed cell death are activated. The extrinsic arm is marked by up-regulation of cleaved, activated caspase-8 downstream of death-receptor and FAS–FADD signaling [25]. The intrinsic mitochondrial arm is marked by the translocation of the pro-apoptotic protein Bax to mitochondria and the release of cytochrome c, culminating in the activation of Cas3 as the executioner. *In vitro* studies in melanoma cell-line further show that within hours of treatment the anti-apoptotic proteins XIAP, BCL-2 and BCL-XL fall [39], while the pro-apoptotic BAX and PUMA rise, and that by 24 h there is nuclear accumulation of phosphorylated p53 (Ser15) together with reduced phosphorylated Akt (Ser473), driving a caspase-3-mediated death response alongside p21-mediated cell-cycle arrest [40]. Caspase-independent death via the apoptosis-inducing factor (AIF) and reactive oxygen species, together with DNA double-strand breaks, adds further parallel routes to the same end [41] (Figure 13a).

Tumor cells respond to stress by up-regulating heat-shock proteins, which normally act as chaperones that protect against death. mEHT induces a broad and rapid heat-shock response; in human colorectal xenografts, messenger RNA for HSP70 family members and their co-chaperones peaks around four hours after treatment, with upregulation across the HSP70, HSP90, and HSP60 families. Crucially, HSP70 has a dual role: an intracellular, anti-apoptotic chaperone function and an extracellular, pro-immunogenic function. The interpretation supported by the data is that massive apoptosis proceeds despite the increased chaperoning, indicating that the parallel death signals overwhelm the protective response [42], and that the released, extracellular HSP70 is simultaneously recruited as an info signal [43]. In this way, the tumor's own adaptive machinery is turned against itself (Figure 13b).

The same stress that causes cell death also triggers the externalization and release of molecules known as damage-associated molecular patterns (DAMPs) [44]: calreticulin (CRT) exposure on the cell surface acts as an “eat-me” signal, extracellular ATP functions as a “find-me” signal, HMGB1 translocates from the nucleus to the cytoplasm and then outside the cell acting as a “danger signal”, and HSP70 is released as an “info signal” [45]. Immunofluorescence studies show calreticulin accumulation at the membrane (co-localizing with membrane markers), increased levels of HSP70 in the TME and membrane, and HMGB1 release after treatment, all significantly above sham controls (Figure 13c). These DAMPs serve as a bridge to the immune responses, providing precise information about the cell's malignant nature through a specific spatiotemporal sequence. This promotes tumor-specific immunogenicity, restores immune surveillance, and prevents malignant cells from evading the immune system [46]. In addition to extracellular HSP70 release, the malignant cell under mEHT stress expresses membrane-bound HSP70, which rapidly activates innate immunity by attracting NK cells to destroy the affected cell [39].

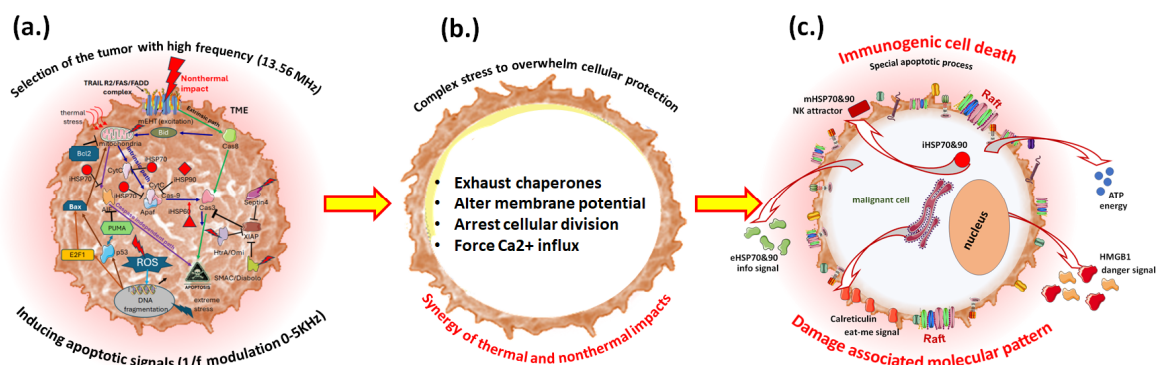


Figure 13. Schematic of the mEHT mechanism of action, from selective energy deposition to systemic antitumor immunity. **(a)** Selective targeting and apoptotic initiation. The 13.56 MHz modulated field, combined with 1/f modulation (0–5 kHz), selectively addresses malignant cells and triggers both extrinsic (TRAIL-R2/FAS/FADD → Cas8 → Bid) and intrinsic (mitochondrial, Bcl2/Bax, CytC/Apaf/Cas-9) apoptotic pathways, alongside caspase-independent (AIF) signaling, p53/PUMA activation, ROS generation, and DNA fragmentation. **(b)** Synergy of thermal and nonthermal effects. The combined thermal and field-specific (nonthermal) impacts exhaust molecular chaperones, alter membrane potential, arrest cell division, and force Ca²⁺ influx. **(c)** Immunogenic cell death. The resulting special apoptotic process exposes and releases damage-associated molecular patterns (DAMPs), surface calreticulin (“eat-me” signal), membrane and extracellular HSP70/90 (“info”-signal), released HMGB1 (“danger” signal), and ATP, concentrated at lipid rafts.

4.3. Challenge III: Beyond Local Control: Immunogenic and Abscopal Effects

Because survival depends on systemic disease, the most consequential property of mEHT is its ability to convert loco-regional treatment into systemic treatment. The mechanism is immunogenic cell death (ICD): tumor cells dying under mEHT do so in a manner that alerts and instructs the immune system, producing tumor-specific cytotoxic T lymphocytes (CD8⁺ CTLs), which circulate in the bloodstream and effectively perform an *in situ* tumor vaccination (Figure 14a).

In colorectal allografts, the release of HSP70, calreticulin, and HMGB1 after mEHT is accompanied by significant tumor infiltration of S100-positive antigen-presenting dendritic cells and CD3-positive T cells, with only scant FoxP3-positive regulatory T-cells, a configuration that favors an effective antitumor response rather than tolerance [47]. The released DAMPs provide both the ‘danger’ context and the antigen cargo: calreticulin acts as an ‘eat-me’ signal promoting phagocytosis of dying cells, while extracellular HSP70 and HMGB1 promote dendritic-cell maturation and antigen cross-presentation. DAMP release drives dendritic cell activation and maturation, enhancing antigen presentation (↑MHC I/II, co-stimulation). Matured dendritic cells migrating to the draining lymph node prime and expand tumor-specific cytotoxic CD8⁺, helper CD4⁺, and $\gamma\delta$ T-cells, CD8⁺ T-cell [48]. (Figure 14b).

The decisive preclinical observation is systemic: when mEHT applied to one tumor is combined with a T-cell-promoting agent, significant cell death occurs not only in the treated tumor but also in the untreated contralateral tumor, demonstrating a genuine systemic antitumor effect [48]. Complementary work shows that intratumoral injection of dendritic cells can amplify the local mEHT effect into a systemic one, and that in a melanoma xenograft mEHT promotes accumulation of natural-killer cells at the treated, but not the untreated, nodules [39]. Together, these results establish that mEHT-induced ICD can prime circulating effector cells capable of acting at a distance [49] (Figure 14c). In this way, systemic antitumor immunity is proposed to govern both local and distant (abscopal) tumor control.

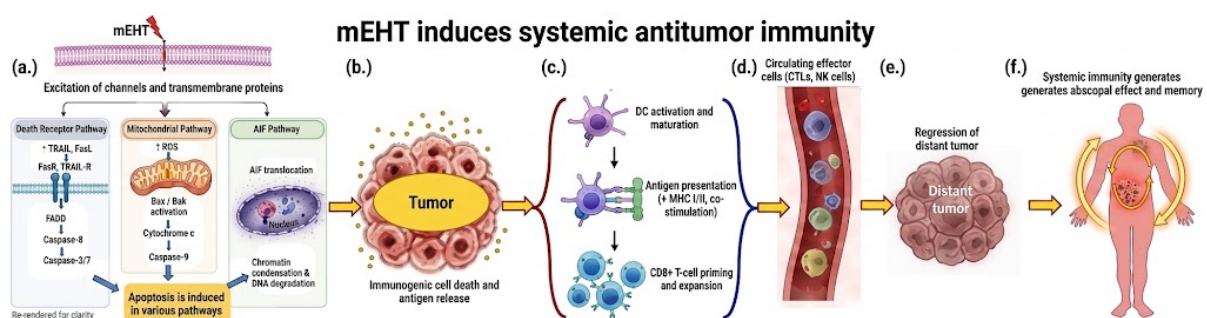


Figure 14. From local treatment to systemic immunity. (a) mEHT triggers multi-pathway, immunogenic cell death (b) The treated tumor releases the DAMPs CTR, HMGB1, ATP, and HSP70, thereby exposing tumor antigens. (c) These signals drive maturation of antigen-presenting dendritic cells. (d) Immune cells migrate to the draining lymph node and cross-present tumor antigen, priming CD8⁺ cytotoxic, CD4⁺ helper and $\gamma\delta$ T cells while regulatory T-cell activity is suppressed. (e) The resulting tumor-specific effector T cells circulate. (f) The circulating CTLs and NKs attack distant, untreated metastases. (f) The process produces an abscopal effect and enables tumor vaccination.

The proper process from receiving mEHT energy to the CD8⁺ CTL is a complex sequence of events. Important that the cell-killing is “gentle” enough not to cause toxic release (various necrotic processes) and that the released proteins remain fully functioning, as well as that the temperature of the tumor mass remains under 40 °C to keep the immune cells active in time. The *in situ* process of T-cell priming and producing tumor-specific immune activity has a time sequence of DAMP release as shown in Table 2.

This mechanism has a striking human correlate. In a secondary analysis of the phase III cervical cancer trial [50], the addition of mEHT to chemoradiotherapy was associated with complete metabolic resolution of disease in extra-pelvic, out-of-field lymph nodes in some participants, that is, regression of lesions not within the treated radiation field. A response outside the treated volume is consistent with an abscopal effect. This observation arises from a secondary, non-pre-specified analysis of a trial not powered for that endpoint, and is therefore hypothesis-generating rather than confirmatory; it does, however, provide a clinical counterpart to the preclinical abscopal data [51]. Real-world abscopal benefit in 61.3% of 142 selected patients, associated with improved overall survival, represents the current best evidence on how often the phenomenon is actually seen [52]. Authoritative framing of the phenomenon and its evidentiary history shows a response outside the treated tumor volume, consistent with an abscopal effect [53].

Table 2. Reported time sequence of DAMP release, as proposed in the cited studies.

Phase	Time-Frame	Key DAMP	Spatial Action	Immune Purpose
Early (Pre-apoptotic)	Minutes to hours	ATP & Calreticulin (CRT)	TME ATP is secreted; CRT translocates from ER to the plasma membrane.	ATP acts as a “Find-me” signal for APCs; CRT provides the “Eat-me” signal
Intermediate (Apoptotic)	12–24 h	HSP70	Surface/TME HSP70 clusters in membrane rafts before being released into the ECM	Chaperones tumor antigens; provides a molecular identification for DC recognition.
Late (Secondary Necrosis)	24–48+ h	HMGB1	Extracellular: Passive release from the nucleus into the surrounding tissue.	Acts as a “danger” signal to drive DC maturation and cross-presentation.

4.4. Challenge IV: Tolerability and Quality of Life

A therapy that improves outcomes at the cost of quality of life has limited value, particularly for patients with advanced disease. mEHT’s physical principles predict a benign safety profile, and the clinical record supports this [54,55]. Because the modality uses low-intensity incident power and keeps macroscopic temperature within the mild range, it does not produce the strongly disruptive biochemical reactions associated with ablative heating. Across clinical series and the randomized cervical-cancer trial, adding mEHT to standard chemoradiotherapy did not materially alter the toxicity profile [56].

Beyond avoiding harm, mEHT has been reported to preserve, and in some analyses, improve quality of life when added to standard care, and to mitigate the burden of concurrent oncotherapy [57]. In the resource-constrained cervical-cancer setting, adding mEHT was associated with improved quality of life and, notably [56], a net cost saving over three years [58,59]. This economic feature is especially advantageous for low- and middle-income countries, where treatment costs are a key driver. The mEHT cost reduction is an unusual and welcome combination in oncology, where benefit and cost typically move together. Favorable tolerability also makes mEHT an attractive, repeatable, outpatient adjunct that can be combined with most existing modalities.

4.5. Four Challenges—Four Resolutions

The four challenges above are serious in daily oncology practice. The mEHT solutions could be a step forward to renew the oncologic therapy paradigm (Figure 15), Table 3.

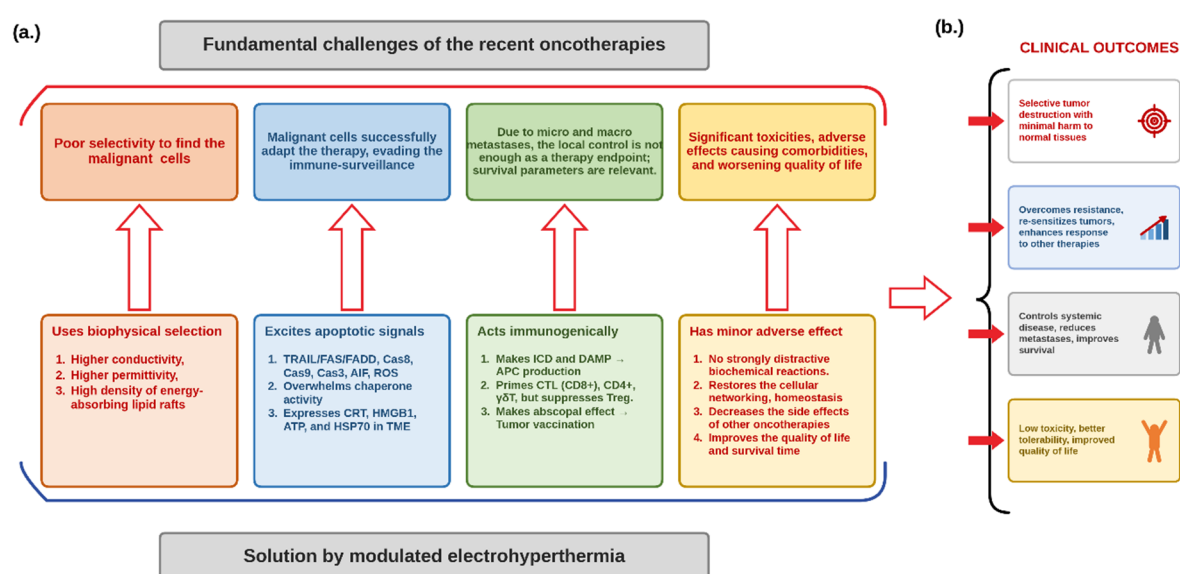


Figure 15. Solution proposal of the challenges by mEHT. (a) The MEHT answers the challenges. (b) The clinical consequences.

Table 3. Summary of the general requirements and the corresponding mEHT mechanisms.

Requirement	mEHT Mechanism
Selectivity	Biophysical targeting
Cell death	Apoptosis
Systemic effect	ICD and immunity
Tolerability	Low toxicity

5. The Translational Arc: From Bench to Bedside

The four challenges above describe mechanisms and their evidence, which can be turned into the translational sequence summarizing the pipeline, from computational and cell-based mechanisms, through *in vivo* validation, to early and then controlled clinical studies, and finally to the patient-centered endpoints that matter: local control, survival, quality of life, and cost (Figure 16).

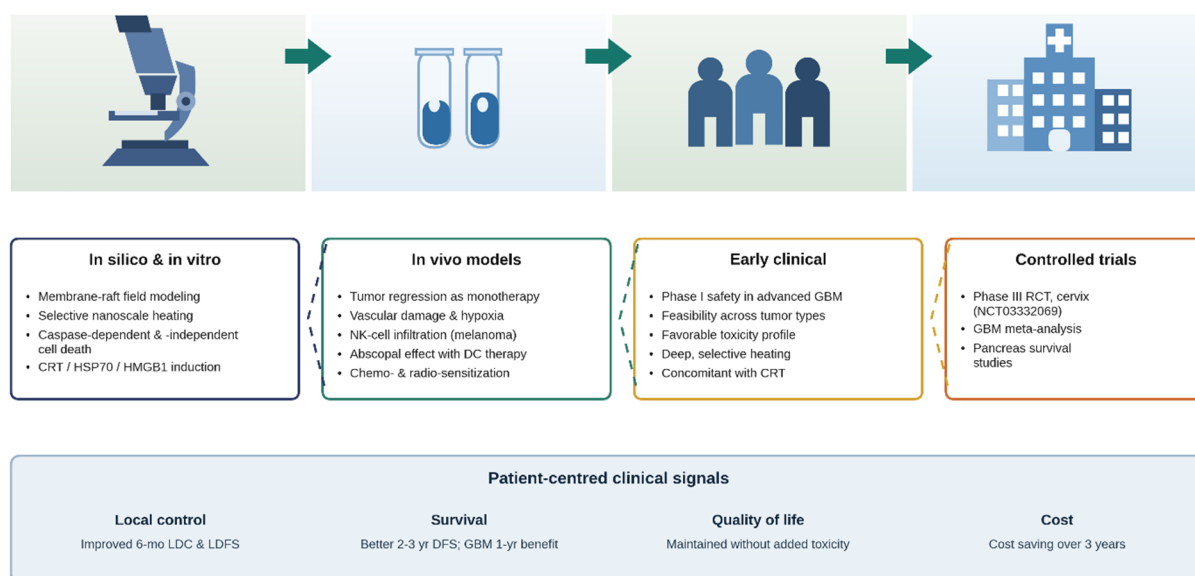


Figure 16. The translational pipeline: from discovery to standard of care, from bench to bedside. Mechanistic findings established *in silico* and *in vitro* are validated *in vivo*, then carried into early and controlled clinical studies; the convergent clinical signals are local control, survival, quality of life, and cost. Each stage maps back onto the four fundamental challenges named in Figure 1. Each pipeline stage addresses the four fundamental oncologic challenges: selectivity (biophysics), multi-path apoptosis (chaperone overload), immunogenic/abscopal effect (systemic control), minimal toxicity & preserved QoL.

The clinical outcomes are encouraging, even though mEHT is used only for advanced, mostly metastatic cases when conventional therapies fail. Due to the heavily pretreated patients with various comorbidities and treatment histories, assembling a large cohort that could be randomized into two statistically equivalent groups is only feasible when conventional therapies (such as multimodal complex methods, usually radiochemotherapy) are available as a promising curative option. Often, cases are compared using case-control (propensity score) or historical local data because conventional options are unavailable, and creating a randomized control arm is both unethical and unacceptable to patients in such situations. Most trials are intention-to-treat (ITT) based. The double-arm studies, including a few Phase II/III randomized controlled trials (RCTs), are summarized in Table 4. Notably, in such advanced cases, quality of life is frequently improved, and safety and tolerability profiles are excellent.

The single-arm trials are more frequent and show the mEHT strengths, and are summarized in Table 5. Because these are uncontrolled series, they can establish feasibility, tolerability and hypothesis-generating survival signals, but they cannot establish efficacy.

Table 4. Summary of Double-arm Phase II/III Clinical Studies of Modulated Electro-Hyperthermia (mEHT). mEHT offers a superior therapeutic index with high selectivity for immune activation, low toxicity, and a positive impact on quality of life.

Ref. Tag	First Author & Year	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Bone Metastases					
[60]	Kim et al., 2024	Bone metastases (pelvic/spinal)	61 total 3 groups: RT/mEHT/RT + mEHT	Retrospective. RT, mEHT, or RT + mEHT; pain by Brief Pain Inventory (BPI), morphine-equivalent medication (MeM), breakthrough-pain (BTP) episodes	RT + mEHT gave significantly better pain relief, lower MeM use and fewer BTP episodes than either modality alone. QoL: pain-related QoL improved with the combination; mEHT effective even in RT-resistant lesions.
Brain Gliomas					
[61]	Fiorentini et al., 2018 (Integr Cancer Ther; also Oncothermia J 2018)	Brain, relapsed GBM & astrocytoma	149 total GBM 111, AST 38 mEHT 52 (28 GBM + 24 AST) vs. BSC 97	Retrospective multicenter controlled. mEHT (40–42.5 °C, 40–150 W) ± integrative care vs. best supportive care (BSC)	3-mo tumor response, GBM 29% vs. 4%; AST 48% vs. 10% (mEHT vs. BSC). 5-year OS, AST 83% vs. 25%; GBM 3.5% vs. 1.2%. 1-/2-year OS (mEHT): AST 77.3%/40.9%, GBM 61%/29%. QoL: palliative benefit reported. No randomization (limitation).
Cervix Cancer					
[62]	Lee S-Y et al., 2017	Cervix, recurrent (post-RT)	38 total CT 20 vs. CT + mEHT 18	Chemotherapy (platinum-based) alone vs. chemotherapy + mEHT, recurrent cervical cancer after irradiation	CT + mEHT feasible and advantageous, particularly in patients with regional lymph-node metastasis (better response). Longer follow-up needed for DFS; significance for survival not reached in this small series.
[58]	Lee S-Y et al., 2023	Cervix, locally advanced (LACC)	95 total CCRT 53 vs. CCRT + mEHT 42	Observational retrospective. Concurrent chemoradiotherapy (CCRT) alone vs. CCRT + mEHT	Whole cohort: CR 53% vs. 71% ($p = 0.065$, NS); NED 68% vs. 83% ($p = 0.086$, NS). LN-metastasis subgroup: CR 45% vs. 71% ($p = 0.038$); NED 58% vs. 82% ($p = 0.032$); DFS significantly better ($p = 0.04$); OS NS ($p = 0.10$).

Table 4. Cont.

Ref. Tag	First Author & Year	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Cervix Cancer					
[50]	Minnaar et al., 2019 (PLoS ONE)	Cervix, LACC (Phase III RCT)	210 randomized; 202 evaluable: mEHT 101 vs. control 101	Phase III RCT. Chemoradiotherapy (CRT) ± mEHT (2×/week before EBRT); HIV-positive and -negative	6-mo local disease control 45% vs. 24% ($p = 0.005$); complete metabolic response 58% vs. 36% ($p = 0.003$); 6-mo LDFS OR 0.36 (95%CI 0.19–0.69, $p = 0.002$), favoring mEHT.
[59]	Minnaar et al., 2022 (Cancers)	Cervix, LACC (Phase III RCT, survival)	210 (same trial) CRT + mEHT vs. CRT	Two- and three-year survival, late toxicity, QoL and cost-effectiveness of CRT ± mEHT	Disease recurrence reduced: 2-year HR 0.67 (95%CI 0.48–0.93, $p = 0.017$); 3-year HR 0.70 (0.51–0.98, $p = 0.035$). QoL: significantly improved with mEHT; no increase in late toxicity; mEHT + CRT cost-dominant.
[56]	Minnaar et al., 2020 (Int J Hyperthermia)	Cervix, LACC (toxicity/QoL)	Same trial, HIV-positive subgroup	Analysis of treatment-related toxicity and QoL of HIV-positive cervical cancer patients receiving CRT ± mEHT	Addition of mEHT did not increase early toxicity of CRT. QoL: maintained/improved with mEHT in HIV-positive patients; mEHT well tolerated (mild adipose/surface burns in a minority).
[51]	Minnaar et al., 2020 (Front Oncol)	Cervix, LACC (abscopal effect)	Extra-pelvic nodal subgroup: 54 mEHT vs. 54 controls	Analysis of abscopal (out-of-field) responses on 18F-FDG PET/CT, CRT ± mEHT	Complete metabolic resolution of extra-pelvic disease in 24.1% (13/54) mEHT vs. 5.6% (3/54) control ($p = 0.013$), potentiation of the abscopal effect by mEHT.
[63]	Minnaar et al., 2024 (ESTRO)	Cervix, LACC (long-term)	Same Phase III cohort	Conference report (ESTRO 2024), extended/abscopal follow-up of the Phase III trial	Continued survival/abscopal benefit of adding mEHT to CRT reported. Full numerical detail not available from the abstract.
Lung Cancer					
[64]	Ou et al., 2020	NSCLC, advanced/refractory (Phase II RCT)	97 randomized: IVC + mEHT + BSC 49 vs. BSC 48	Randomized Phase II. Best supportive care (BSC) ± high-dose IV vitamin C (IVC) + mEHT	PFS 3.0 vs. 1.85 mo ($p < 0.05$); OS 9.4 vs. 5.6 mo ($p < 0.05$), favoring IVC + mEHT. QoL: improved with combination (prior study); combination safe.

Table 4. Cont.

Ref. Tag	First Author & Year	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Peritoneal Carcinomatosis					
[65]	Pang (C.L.K.) et al., 2017	Peritoneal carcinomatosis + malignant ascites (Phase II RCT)	260 total mEHT + TCM 130 vs. IPCI 130	Randomized Phase II (1:1, ITT). Local mEHT + TCM ('Shi Pi') vs. intraperitoneal chemoinfusion (IPCI)	mEHT + TCM gave better ascites/disease control than IPCI with markedly less toxicity (non-toxic regimen). KPS improvement 54.5% vs. 47.8%. QoL: better tolerability/quality of life favored mEHT + TCM.
Pancreas Carcinoma					
[66]	Fiorentini et al., 2019	Pancreas, stage III–IV	106 total mEHT 39 vs. no-mEHT 67	Retrospective observational. mEHT (±CHT/RT) vs. no-mEHT (CHT/RT)	Median OS 18.0 mo (mEHT) vs. 10.9 mo (no-mEHT). Higher partial-response/lower progression with mEHT at 3 mo. QoL: palliative benefit reported; mEHT well tolerated.
[67]	Fiorentini et al., 2021	Pancreas, stage III–IV	158 total CHT + mEHT 58 vs. CHT 100	Observational. Chemotherapy + mEHT vs. chemotherapy alone (gemcitabine-based)	OS 19.5 vs. 11.02 mo ($p < 0.001$); PFS 12 vs. 3 mo ($p < 0.001$), favoring CHT + mEHT, with comparable toxicity.
[68]	Fiorentini et al., 2023	Pancreas, advanced (stage III–IV)	217 total CHT + mEHT 89 vs CHT 128	Multicenter retrospective comparative (case-control). Chemotherapy + mEHT vs. chemotherapy alone	OS 20 vs. 9 mo ($p < 0.001$); PFS 7 vs. 5 mo ($p < 0.05$); partial response 45% vs. 24% ($p = 0.0018$); progression 4% vs. 31% ($p < 0.001$). Adverse events in only 2.6% of mEHT sessions (no added toxicity).

AST astrocytoma, BSC, best supportive care; BTP, breakthrough pain; CCRT/CRT, concurrent chemoradiotherapy; CHT/CT, chemotherapy; CR, complete remission; CI confidence interval, DFS, disease-free survival; EBRT, external beam radiotherapy; GBM glioblastoma multiforme, HR hazard ratio, IPCI, intraperitoneal chemo infusion; ITT intention to treat patients, IVC, intravenous vitamin C; KPS Karnofsky performance score, LACC, locally advanced cervical cancer; LDFS, local disease-free survival; LN, lymph node; MeM, morphine-equivalent medication; NED, no evidence of disease; NS, not significant; NSCLC non-small-cell lung carcinoma, OR overall response rate, OS, overall survival; PFS, progression-free survival; Pts. Patients, RT, radiotherapy, RCT, randomized clinical trial, QoL, quality of life, TCM, traditional Chinese medicine.

Table 5. Single-arm clinical studies of mEHT method.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Bone				
Arrajo et al. [69]	Bone metastases (painful)	Single-arm series	mEHT in monotherapy for painful bone metastases	Observational monotherapy report, mEHT alone produced pain palliation in metastatic bone disease. No comparator arm; significance not tested. QoL : pain relief reported as the main benefit.
Brain				
Roussakow [70]	Recurrent glioblastoma	Two-centre cohort (comparative, effect-to-treatment)	mEHT concurrent to dose-dense temozolomide 21/28 regimen	Retrospective two-centre German cohort with systematic comparison/effect-to-treatment analysis, mEHT + dose-dense TMZ associated with improved survival and favorable cost-effectiveness vs. comparator data.
Van Gool et al. [71]	Glioblastoma (GBM)	Case series	ICD therapy (NDV + mEHT) during maintenance chemo + multimodal immunotherapy	Demonstrated induction of immunogenic cell death (ICD) during maintenance TMZ; mEHT one of the ICD components. Descriptive case material.
Schirmacher et al. [72]	GBM/mixed (single institution)	Institutional series	Individualized multimodal immunotherapy (IMI): DC vaccine + NDV + mEHT	Scientific rationale + clinical experience for IMI (mEHT as ICD inducer). Single-institution experience; outcomes vs. historical references.
Van Gool et al. [73]	IDH1 wild-type GBM	50 patients (single institute; 28 unmeth + 22 meth)	IMI (NDV + mEHT ICD; DC vaccine; modulatory immunotherapy) + standard care	Single-institute IMI experience extending the synergy data to MGMT-methylated and -unmethylated GBM; survival benefit suggested vs. historical Stupp outcomes. No randomized control.
Van Gool et al. [74]	IDH1 wt, MGMT-unmeth GBM	Group-1 (no TMZ) 7 vs. Group-2 (TMZ+IMI)	Maintenance TMZ + IMI (NDV + mEHT ICD; DC vaccine) vs. IMI without TMZ	Median OS 18 mo (TMZ+IMI) vs. 11 mo (IMI, no TMZ); 2-year OS 17% vs. 0% (log-rank $p = 0.027$), significant synergy between maintenance TMZ and IMI.
Van Gool et al. [75],	GBM (methodology)	Methodological analysis	Commentary on RCT design for GBM immunotherapy	Argues RCTs for GBM immunotherapy are ‘challenged’ by individualized, multimodal designs. Not an outcome trial; no arms/significance.
Van Gool et al. [76]	DIPG (children)	Single-institution series	Multimodal immunotherapy (incl. mEHT) added to combination treatment	Addition of multimodal immunotherapy to standard care for paediatric DIPG; feasibility and survival experience reported without a control arm.
Van Gool et al. [77]	GBM	Review/series	Personalised medicine in GBM (IMI incl. mEHT)	Book-chapter overview of the personalized IMI approach; consolidates the institutional experience rather than presenting a new controlled dataset.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Brain				
Van Gool et al. [78]	GBM	Series (Oncothermia J)	Hyperthermia (mEHT) as part of multimodal immunotherapy	Describes mEHT's role within multimodal GBM immunotherapy; observational, no internal comparator.
Douwes et al. [79]	Recurrent glioblastoma	Single-arm	Hyperthermia + ACNU chemotherapy	Combination thermochemotherapy series in recurrent GBM; response/survival reported without a control group.
Hager et al. [80]	High-grade malignant glioma	Single-arm (ASCO)	RF-hyperthermia	ASCO abstract; feasibility of RF-hyperthermia in high-grade glioma. Quantitative comparison not available from the abstract.
Hager et al. [81]	Glioblastoma grade IV	Case/small series	Regional deep hyperthermia + thalidomide + high-dose ascorbic acid + complementary therapy	Integrative multimodal case material; descriptive outcomes only (German-language report).
Roussakow [82]	Brain glioma & lung	Meta-analysis (Level II)	Systematic review + meta-analysis of mEHT trials	Pooled/meta-analytic Level-II evidence indicating survival benefit of mEHT in glioma and lung cancer, with economic evaluation. Synthesis of multiple cohorts rather than a single trial.
Wismeth et al. [54]	Relapsed high-grade glioma	Phase I, single-arm	Transcranial electro-hyperthermia + alkylating chemotherapy	Phase I, established feasibility/safety of transcranial EHT with chemotherapy; dose-finding, not a comparative efficacy trial.
Sallabanda et al. [83]	Recurrent high-grade glioma	Manuscript	Reirradiation ± mEHT for high-grade gliomas	Reirradiation series; patient numbers, comparative results and significance not yet available (pre-publication document).
Breast				
Szasz AM. et al. [84]	Breast cancer (advanced; 11 IDC)	n = 11 evaluable (13 enrolled, 2 excluded. All patients have advanced metastases) Single-arm series	mEHT (EHY-2000/2030) + chemo, (book chapter)	Median treatment 11.2 weeks (range 2.4–23.2), after treatment OS ≈ 2 months. Most durable responses in skin/bone mets; shorter with liver/lung. Favorable prognostic factors: lower stage, ≤2 metastatic sites; younger age and ≥3-organ metastases were poor prognostic factors. Subgroup KM curves by IHC subtype (LumA/LumB/TNBC/TNBC-HER2-BRCA+) shown but underpowered. No control arm.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Breast				
Parmar et al. [85]	Breast (stage IV)	n = 72 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 5.0 year and mean 8.2 years, clearly above the SEER stage-IV breast control (mEHT survival ~50% at 5 years vs. SEER <30%). Single-arm vs. SEER; mEHT safe (<0.1% AE over 16,752 sessions), QoL maintained.
Cervix				
Pesti et al. [86]	Cervix (LACC)	n = 34, (single-arm)	Complex chemo-radio-mEHT	Response rate measurement. CR + PR = 73.5%, SD = 14.7%, PD = 11.8%,
Lee S-Y. et al. [87]	Cervix (LACC)	n = 20 (single-arm, not curative)	mEHT (temperature measurement)	1.8 °C temperature increased from 36.7 °C baseline (4.91%). Δ RI = -0.21 (-51.84%), Δ S/D = -0.43(-25.09%)
Cholangiocarcinoma				
Parmar et al. [85]	Cholangio-carcinoma (stage IV)	n = 9 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Subgroup survival values are not reproduced here. The source reports identical figures (median 4.0 year and mean 4.1 years) for several of its smallest subgroups (cholangiocarcinoma, head and neck, lymphoma, uterus, rectum); since these cannot all be subgroup-specific, the values are withheld pending clarification from the original authors. Single-arm vs. SEER; mEHT safe (<0.1% AE over 16,752 sessions), QoL maintained.
Kleef et al. [88]	Cholangiocellular (CCC)	5 CCC pts (IMT); IMT vs. conventional	Integrative immunomodulatory treatment (incl. mEHT, IL-2, low-dose ICI)	CCC subgroup: median survival ~10 months after IMT initiation. Across the GI cohort, mEHT had the strongest individual OS effect (HR 0.3055, $p = 0.026$).
Colorectal				
Migeod [89],	Colorectal	Series	Combined thermochemotherapy with oncothermia	German-language thermochemotherapy series; descriptive outcomes, no internal control reported.
You et al. [90]	Locally advanced rectal	60 patients (single-arm phase 2)	Preoperative mEHT + chemoradiotherapy	Early phase-2: pathologic complete response ~15% (T)/76.7% (N); total/near-total regression 33.3%; low thermotoxicity. Single-arm; comparable outcomes at reduced radiation dose.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Colorectal				
Kleef et al. [88]	Colorectal (CRC)	n = 21 CRC pts; IMT vs. conventional CT	Integrative immunomodulatory treatment (incl. mEHT)	CRC subgroup: median survival ~20 months after IMT. mEHT was the IMT component with the most positive OS effect (HR 0.3055, $p = 0.026$) across the GI cohort.
Ranieri et al. [91]	Metastatic colon	Pilot, single-arm, n = 40	Bevacizumab + FOLFOX-4 + deep electro-hyperthermia (1st-line)	Pilot study, combination feasible and active as first-line metastatic colon therapy. Disease control PR ~6%, SD ~18% Longer treatment: CR ~2%, PR ~7%, SD ~18%. medianPFS = 12.1 m, Median OS = 21.4 m
Parmar et al. [85]	Colon/rectum (stage IV)	colon n = 79; rectum n = 23 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Colon: median OS 4.0 year and mean 4.5 years, vs. SEER (mEHT survival ~40% at 5 years vs. SEER ~15%). Rectum: subgroup survival not reproduced here (the source reports the same values for several small subgroups; see cholangiocarcinoma row). Single-arm vs. SEER; mEHT safe, QoL maintained.
Izadi-Najafabadi et al. [92]	Colorectal (integrative)	Manuscript	Integrative naturopathic care + mEHT	Colorectal integrative manuscript; patient numbers, comparison and significance not yet available (pre-publication).
Standish et al. [93]	Advanced cancers (incl. CRC)	Manuscript	Naturopathic oncology + mEHT (survival analysis)	Survival-focused naturopathic oncology manuscript; data not yet available for tabulation.
Esophageal				
Akutsu [94]	Esophageal (immune)	Basic + clinical (conference)	mEHT (immune-reaction study)	Explored whether mEHT elicits an immune reaction (basic + clinical data, Matsubara group). Conference report; no controlled outcome comparison.
Kleef [88]	Esophageal (EC)	n = 4 EC pts (IMT)	Integrative immunomodulatory treatment (incl. mEHT)	EC subgroup: median survival ~20 months after IMT initiation. mEHT strongest individual OS contributor across the GI cohort (HR 0.3055, $p = 0.026$).
Head & Neck				
Parmar [85]	Head & neck (stage IV)	n = 13 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Subgroup survival not reproduced here (the source reports the same values for several small subgroups; see cholangiocarcinoma row). Single-arm vs. SEER; mEHT safe, QoL maintained.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Liver				
Gadaleta-Caldarola [95]	Hepatocellular carcinoma (advanced)	21 patients (single-arm phase II)	Sorafenib + locoregional deep electro-hyperthermia	Phase II: stable disease 50%, partial response 5%, progression 45%; median time-to-progression 5.2 mo; median OS 10.4 mo (95%CI 10–11). Single-arm; well tolerated.
Chi KH [96]	Liver/mixed (immuno-RT)	Series (Oncothermia J)	Tumor-directed immunotherapy: radiotherapy + oncothermia (mEHT)	Reports combined RT + mEHT as <i>in-situ</i> tumor-directed immunotherapy with abscopal signals; observational clinical results, no randomized comparator.
Lung				
Fiorentini et al. [97]	Lung (abscopal)	Perspective/cases	mEHT (abscopal-effect perspectives)	Conceptual report with case material on abscopal responses during mEHT in lung cancer. No controlled outcome data.
Yoon et al. [98]	Metastatic NSCLC (abscopal)	Case report	mEHT (with systemic therapy)	Single case documenting an abscopal effect in metastatic NSCLC treated with mEHT.
Parmar et al. [85]	NSCLC (stage IV)	n = 54 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 1.5 year and mean 1.9 years, survival curve above the SEER stage-IV NSCLC control. Single-arm vs. SEER; mEHT safe (<0.1% AE), QoL maintained.
Lee DY et al. [99]	Small-cell lung cancer	Series	Oncothermia (mEHT) + chemotherapy	mEHT added to chemotherapy in SCLC (conference paper); feasibility and response reported, no control arm.
Iyikesici et al. [100]	Metastatic NSCLC	Feasibility, single-arm	Metabolically-supported chemotherapy + ketogenic diet + hyperthermia + HBOT	Feasibility of the metabolically-supported multimodal protocol (incl. mEHT) in metastatic NSCLC; encouraging response/survival without a comparator.
Ou et al. [57]	Stage III–IV NSCLC	Phase I safety, single-arm	High-dose IV ascorbic acid + mEHT	Safety/pharmacokinetic phase I, IVC + mEHT safe in stage III–IV NSCLC (basis for the later RCT). QoL: improved. No efficacy comparator in this study.
Lymphomas				
Parmar et al. [85]	Lymphoma, Hodgkin & non-Hodgkin (stage IV)	n = 12 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Subgroup survival not reproduced here (the source reports the same values for several small subgroups; see cholangiocarcinoma row). Single-arm vs. SEER; mEHT safe, QoL maintained.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Multi-Cohort/Mixed				
Garay et al. [101]	Gastrointestinal (single centre)	34 enrolled, 33 analysed (23 panc, 7 CRC, 3 hepatobiliary, etc.)	mEHT 2–3×/week + various chemotherapy (gemcitabine, FOLFIRINOX, etc.)	All inoperable/metastatic. Single-arm pilot; Kaplan–Meier shown for pancreas and CRC subgroups (no numeric medians tabulated in the chapter). Mean time on treatment 32.8 week; well tolerated (transient breaks for fever/pain in 17). No internal control.
Chi M-S et al. [102]	Mixed (abscopal)	3 patients (case series)	Radiotherapy + mEHT	Three documented putative abscopal responses to combined RT + mEHT. Hypothesis-generating case series.
Kleef et al. [103]	Stage IV mixed (23 histologies)	131 patients (single-arm)	Loco-regional + whole-body HT + IL-2 + low-dose ipilimumab/nivolumab	Heavily pre-treated stage IV cohort: OS 66.5% at 12 mo and 36.6% at 24 mo; immune-related adverse events mostly grade 1–2. Single-arm exploratory case series.
Chi K-H et al. [96]	Mixed (17 cancer types; immuno-RT)	60 patients (27 localized + 33 metastatic)	Radiotherapy (median 50.4 Gy) + weekly mEHT ± systemic therapy	In-field objective response 60.7% overall (localized 77.8%, metastatic 60.6%); large tumors > 500 mL responded better (CR/PR 91.7% vs. 62.5%, $p = 0.049$). Abscopal: 3/33 metastatic (9.1%) with >90% out-of-field shrinkage, all with autoimmune reactions. Mean OS 16.0 mo; CR/PR 18.3 vs. SD/PD 9.4 mo ($p < 0.001$). 95% free of significant toxicity. Single-institution, level IV.
Ranieri et al. [104]	Metastatic mixed	Pilot (~23 pts), single-arm	Bevacizumab-based chemo + regional deep capacitive hyperthermia	Pilot in mixed metastatic cancers, combination feasible/active; response and survival reported without a randomized control. CR = 33%, PR = 11%, SD = 28%, mean OS = 16.5 m, time to progr. = 11.3 m
Pang LKC et al. [105]	Colon carcinoma (integrative)	Series	Oncothermia (mEHT) + Clifford TCM immune booster	Integrative colon-carcinoma series with mEHT + TCM; disease-control/symptom benefit reported, no formal comparator arm.
Ovary				
Ranieri et al. [104]	Ovarian (within mixed cohort)	Pilot subset, single-arm n = 5	Bevacizumab-based chemo + regional deep capacitive hyperthermia	Ovarian patients within the mixed-metastatic pilot; combination feasible/active. Very small number of patients
Kim et al. [55]	Ovarian/fallopia n/peritoneal (recurrent)	12 evaluable: paclitaxel + mEHT 6 vs. cisplatin + mEHT 6	Randomized Phase I safety, weekly paclitaxel + mEHT vs. cisplatin + mEHT (KGOG 3030)	No dose-limiting toxicity in either arm (safe). Median PFS 3.0 vs. 6.8 mo; median OS 11.5 mo vs. not reached. Hypothesis-generating; not powered for efficacy.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Ovary				
Yoo et al. [106]	Recurrent/progressive ovarian	Phase I/II, single-arm (MTD)	mEHT dose-escalation monotherapy (2nd-line)	mEHT feasible and complication-free; maximal tolerated dose up to 150 W for 1 h/day. QoL : assessed with FACT-O scale. No comparator arm.
Van Gool et al. [107]	Ovarian	Series (Oncothermia J)	Multimodal immunotherapy (incl. mEHT) for ovarian cancer	Describes multimodal immunotherapy with mEHT in ovarian cancer; observational, no internal control. (Listed twice in the source.)
Parmar et al. [85]	Ovary (stage IV)	n = 33 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 3.5 year and mean 4.2 years, survival above the SEER stage-IV ovarian control. Single-arm vs. SEER; mEHT safe (<0.1% AE), QoL maintained.
Pancreas				
Petenyi et al. [108]	Inoperable PDAC	78 total mEHT 39 vs. matched control 39	mEHT + chemotherapy vs. matched chemotherapy (case-control)	Trend toward improved OS with mEHT ($p = 0.142$, NS) in matched pairs; mEHT associated with better survival overall, though metastatic mEHT patients fared worse (HR 2.17, $p = 0.030$).
Dobos et al. [109]	Advanced pancreatic	Retrospective (biomarker analysis)	mEHT + chemotherapy (immune-marker/CRP dynamics)	Analysed immune-marker and C-reactive-protein dynamics under mEHT and their prognostic value; supports an immune-modulatory mechanism rather than reporting an arm-vs-arm survival comparison.
Parmar et al. [85]	Pancreas (stage IV)	n = 27 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 1.1 year and mean 1.7 years, at 2 years the mEHT curve sits ~30% vs. SEER ~20% reached within the first year. Single-arm vs. SEER; mEHT safe, QoL maintained.
Volovat et al. [110]	Refractory metastatic pancreas	Prospective, single-arm	Gemcitabine + oxaliplatin + loco-regional hyperthermia (2nd-line)	Preliminary prospective results, combination feasible with disease-control signals in refractory metastatic pancreatic cancer. No control arm.
Kleef et al. [88]	Pancreatic (PC)	14 PC pts; IMT vs. conventional CT	Integrative immunomodulatory treatment (incl. mEHT)	PC subgroup: median survival ~20 months after IMT initiation. mEHT the strongest individual OS contributor across the GI cohort (HR 0.3055, $p = 0.026$).
Iyikesici et al. [111]	Metastatic pancreatic	Single-arm	Metabolically-supported chemo + ketogenic diet + hyperthermia + HBOT	Long-term survival outcomes of the metabolically-supported multimodal protocol (incl. mEHT); favorable OS reported without a comparator group.

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Prostate				
Douwes [112]	Prostate cancer	Series (Oncothermia J)	Hyperthermia for prostate cancer	Overview/series on hyperthermia as a treatment option for prostate cancer; descriptive outcomes, no control.
Parmar [85]	Prostate (stage IV)	n = 25 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 8.3 year and mean 9.1 years, the most favorable site in the cohort, well above the SEER stage-IV prostate control. Single-arm vs. SEER; mEHT safe, QoL maintained.
Sarcoma				
Jeung [113]	Sarcoma (primary/recurrent/metastatic)	Case series	Oncothermia (mEHT) + surgery + chemotherapy + radiotherapy	Multimodal series in sarcoma with mEHT; response/survival in selected cases, no control arm.
Parmar [85]	Soft-tissue sarcoma (stage IV)	n = 16 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 3.1 year and mean 2.7 years, survival above the SEER stage-IV soft-tissue sarcoma control. Single-arm vs. SEER; mEHT safe (<0.1% AE), QoL maintained.
Volovat [114]	Advanced soft-tissue sarcoma	Single-arm	Ifosfamide + loco-regional hyperthermia (post first-line relapse)	Combination in relapsed advanced abdominal soft-tissue sarcoma; disease-control signals reported without a comparator.
Melanoma				
Parmar [85]	Melanoma (stage IV)	n = 12 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Median OS 2.6 year and mean 2.7 years, survival above the SEER stage-IV melanoma control. Single-arm vs. SEER; mEHT safe, QoL maintained.
Gastric				
Iyikesici [115]	Advanced gastric	Single-arm	Metabolically-supported chemo + ketogenic diet + hyperthermia + HBOT	Survival outcomes of the metabolically-supported multimodal protocol (incl. mEHT) in advanced gastric cancer; favorable OS without a comparator group.
Kleef [88]	Gastric (GC)	5 GC pts (IMT)	Integrative immunomodulatory treatment (incl. mEHT)	GC subgroup: median survival ~10 months after IMT initiation. mEHT strongest individual OS contributor across the GI cohort (HR 0.3055, $p = 0.026$).

Table 5. Cont.

Reference	Tumor Site	No. Pts. (Arms)	Treatment Used	Primary Results/Clinical Outcomes (Comparison, Significance, QoL)
Uterus				
Parmar [85]	Uterus (stage IV)	n = 11 (single-arm vs. SEER)	Integrative naturopathic care + mEHT (8-year study; SEER historical control)	Subgroup survival not reproduced here (the source reports the same values for several small subgroups; see cholangiocarcinoma row). Single-arm vs. SEER; mEHT safe, QoL maintained.

CCC, cholangiocellular carcinoma; CRC, colorectal cancer; CT/CHT, chemotherapy; DC, dendritic cell; EC, esophageal cancer; EHY, electro-hyperthermia; GBM, glioblastoma multiforme; GC, gastric cancer; HBOT, hyperbaric oxygen therapy; HR, hazard ratio; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; IMI/IMT, individualized multimodal immunotherapy/immunomodulatory treatment; IVC, intravenous vitamin C; mEHT, modulated electro-hyperthermia; MTD, maximal tolerated dose; NDV, Newcastle disease virus; NS, not significant; NSCLC, non-small-cell lung cancer; OS, overall survival; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; QoL, quality of life; RT, radiotherapy; SCLC, small-cell lung cancer; TMZ, temozolomide.

6. Limitations and Open Questions

A balanced appraisal must be explicit about what the evidence does not yet establish.

- Evidence level. Outside cervical cancer, much of the clinical literature is observational or retrospective and is therefore vulnerable to selection and reporting biases. Despite unified guidelines and protocols, survival estimates derived from meta-analyses of various design studies, as in glioblastoma, should be interpreted with appropriate caution.
- Attribution. Because mEHT is almost always added to chemoradiotherapy, isolating its specific contribution from that of concurrent treatment is difficult; randomized comparisons such as the cervical-cancer trial are the only reliable way to do so, and they remain few.
- Dosimetry. Although the energy-based dose ($\text{J/kg} = \text{Gy}$) provides the correct conceptual unit, a fully standardized, validated protocol for measuring and reporting delivered dose at the relevant scale is not yet uniform across devices and centers, complicating cross-study comparison. Phantom-based and computational dosimetry are advancing but need consensus.
- Mechanism-to-clinic gap. The abscopal mechanism is mechanistically compelling and supported by model data and a randomized out-of-field signal, but controlled clinical confirmation across tumor types is still limited.
- Heterogeneity. Protocols vary in fractionation, sequencing relative to radiation, and total energy delivered, which contributes to between-study variability.
- Historical-control comparisons. Several single-arm series in Table 5 compare treated patients with stage-matched survival from the SEER registry. Registry populations differ systematically from patients who present at specialized centers in performance status, comorbidity, treatment history, socioeconomic position and completeness of staging; SEER survival is also aggregated over calendar periods during which standard therapy changed. Differences observed against such controls are therefore not attributable to mEHT and should be read as descriptive rather than as estimates of treatment effect.
- Provenance of the evidence. A significant portion of the mechanistic and clinical literature cited here originates with the author's group and collaborating centers, and some appears in the *Oncothermia Journal*, edited volumes, or conference reports rather than in independently indexed journals. Independent replication by groups with no ties to the method's development is the single most important requirement for the field and is stated first in the research agenda below. Evidence that field-based modalities can reach pivotal randomized endpoints serves as a useful benchmark for the research agenda [116].
- Mechanism-to-clinic gap. Acknowledging and further developing the evidentiary standard of field allocation suggests a methodological standard for what counts as demonstrated ICD [117].

7. A Proposed Agenda for Confirmatory Research

- (1) Replicate the cervical cancer phase III result in independent, multicenter randomized trials, with overall survival as a primary endpoint and pre-specified analysis of out-of-field (abscopal) responses.
- (2) Standardize energy dosimetry: adopt the J/kg (Gy -equivalent) energy dose as the reported standard, with personalized step-up protocols, so that treatments are comparable across devices and centers and dose-response can be studied as it is in radiotherapy.
- (3) Test rational combinations suggested by mechanism, for example, with PARP inhibitors (exploiting mEHT-induced DNA double-strand breaks), with agents that block hypoxia-driven angiogenic recovery after mEHT-induced vascular damage, and combination with immune-checkpoint inhibitors to amplify the ICD-primed response [118].
- (4) Characterize the immune response directly in patients (circulating tumor-specific T cells, DAMP markers) to convert the abscopal mechanism from inference to measurement.
- (5) Define the patients and settings most likely to benefit, building on the observation that early introduction in newly diagnosed disease produced the largest glioblastoma benefit.

8. Conclusions

Modulated electro-hyperthermia is best understood not as a refinement of heating but as a field-driven, membrane-targeted modality whose selectivity opens a coherent biological cascade. That cascade maps cleanly onto the four fundamental challenges of oncotherapy: biophysical selectivity addresses the targeting problem; multi-pathway apoptosis that overwhelms chaperone buffering counters tumor adaptation; immunogenic cell death and the abscopal effect extend control from the local site to systemic disease; and a benign safety profile preserves quality of life and, in at least one randomized setting, lowers cost.

The novelty of mEHT may lie in the formulation of a unified translational oncology framework. It simultaneously addresses the four major unresolved problems of modern cancer therapy—selectivity, resistance, metastatic disease, and toxicity—through a single biophysically driven mechanism that evolves from local nanoscale interactions into systemic, immune-mediated effects.

The translational arc from *in silico* mechanism to a phase III randomized trial is now substantial enough to take mEHT seriously as an adjuvant modality, while remaining honest that confirmatory, standardized, multi-center evidence is the necessary next step. The framework presented here is intended to make both the promise and the gaps legible to the laboratory scientist, to the trialist, and to the practicing oncologist at the bedside. Above all, it asks for a change of paradigm: to attack the disease through its weaknesses rather than its strengths, to treat processes rather than products, to treat the patient rather than the lesion, to enlist the immune system and homeostasis as billion-year-old allies rather than override them, and to dose in the natural units of delivered energy rather than in temperature. Seen this way, tumor shrinkage is a means and not the end. The end, the only end that matters to the person, is to live longer and to live well.

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Conflicts of Interest

The author is one of the originators of modulated electro-hyperthermia and of the oncothermia concept, is named on patents relating to the method, and is affiliated with XAX Consulting LLC (Lincoln, MA, USA), which provides consultancy in this field. The author has had a long-standing professional and commercial association with the development of the technology reviewed here, and is an editor of the Oncothermia Journal and of edited volumes cited in this article. These interests are declared so that readers may weigh the interpretation offered here accordingly. No sponsor had any role in the selection of the material, the analysis, or the decision to submit.

Use of AI and AI-Assisted Technologies

AI tools were used to control the spelling, grammar, and style of the article.

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