ONCOTHERMIA JOURNAL

A publication of Oncotherm® ISSN 2191-6438

Special Edition - September 2020

Imprint

Editorial

Dear Readers, Dear Fellow Researchers, Dear Colleagues, Dear Friends,

the recent volume of the Oncothermia Journal is special and exclusive. We collected two articles for the practicing medical staff (physicians and trained operators of our devices), with the intention of helping their everyday work and the suffering patients. Both publications are based on the experiences of Oncothermia users, most of them have not been included in clinical trials or official research.
The first article deals with temperature measurements from the phantoms to the patients, including many preclinical measurements as well. This is an essential work that clarifies the temperature rise from the effects of mEHT showing a wide range of materials and the results of various laboratories.
The other, long-time awaited comprehensive summary includes protocols and their explanations I would like to emphasize again that the published article is based on long-time experience with the EHY-2000 and EHY-2000Plus devices, as well as three-years of experience with the EHY-2030. Most of the data are published entirely or partially, but due to their case-based level they are not included in the certification of the method. Consequently, both articles mirror the opinion of the scientists and physicians who study and use Oncothermia, but due to the lack of certification, it is not an official statement of the Oncotherm Company. The protocol[1][2][3] and guideline[4] of the Oncothermia treatment were formulated on the same basis earlier as well.
I hope this new volume gives you more benefits for your essential medical activity and helps your suffering patients.
I am thankful for your attention.

Dr. Andras Szasz
Professor, Chair, Biotechnics Department of St. Istvan University

Liebe Leserinnen und Leser, liebe Kolleginnen und Kollegen aus Forschung und Praxis,

der aktuelle Band des Oncothermia Journals ist eine besondere Ausgabe. Wir haben zwei Artikel für praktizierendes medizinisches Personal (Ärzte und geschulte Anwender unserer Geräte) gesammelt, um dieses in ihrem Arbeitsalltag zu unterstützen und leidenden Patienten zu helfen. Beide Veröffentlichungen, deren Inhalte zum Großteil noch nicht bei klinische Studien oder offizieller Forschung berücksichtigt wurden, basieren auf den Erfahrungen von Oncotherm-Anwendern.
Der erste Artikel befasst sich mit Temperaturmessungen, die zunächst an Phantomen und anschließend an Patienten vorgenommen wurden. Zudem schließt dieser viele präklinische Messungen ein. Diese grundlegende Arbeit verdeutlicht den durch mEHT hervorgerufenen Temperaturanstieg und bietet ein breites Spektrum an verschiedenen Dokumenten sowie die Ergebnisse mehrerer Laboratorien.
Die andere, lang erwartete und umfangreiche Zusammenfassung beinhaltet Protokolle und deren Erklärungen. An dieser Stelle möchte ich noch einmal darauf hinweisen, dass dieser veröffentlichte Artikel auf langjähriger Erfahrung mit den Geräten EHY-2000 und EHY-2000Plus sowie auf dreijähriger Erfahrung mit dem EHY -2030 basiert. Die meisten Daten werden ganz oder teilweise veröffentlicht, aber aufgrund ihrer fallbezogenen Ebene werden sie nicht für die Zertifizierung der Methode herangezogen. Folglich spiegeln beide Artikel lediglich die Meinung der Wissenschaftler und Ärzte wider, welche Oncothermie untersuchen und anwenden. Aufgrund der fehlenden Zertifizierung handelt es sich jedoch nicht um eine offizielle Erklärung von Oncotherm. Das Protokoll[1][2][3] und die Richtlinie[4] zur Behandlung mit Oncothermie wurden zuvor ebenfalls auf dieser Grundlage konzipiert.
Ich hoffe, dieser neue Band bietet Ihnen mehr Möglichkeiten für Ihre unerlässlichen medizinischen Tätigkeiten und hilft Ihren leidenden Patienten.

Ich bin dankbar für Ihre Aufmerksamkeit.

Dr. Andras Szasz
Professor und Vorsitzender der Fakultät für Biotechnik an der St. Istvan Universität

[1] Szasz A, Szasz O (2013) Oncothermia protocol. Oncothermia Journal 8:13-45 https://oncotherm.com/sites/oncotherm/files/2019-10/Oncothermia%20protocol.pdf

[2] Fiorentini G, Sarti D, Casadei V, et.al. (2019): Modulated electro-hyperthermia (mEHT) [oncothermia®] protocols as complementary treatment, Oncothermia Journal 25: 85-115, https://oncotherm.com/sites/oncotherm/files/2019-05/FIORENTINI2.pdf

[3] Szasz A. Marcell (2019): Conventional, „standard" chemotherapy protocols for modulated electro-hyperthermia (mEHT, trade name: oncothermia ®), Oncothermia Journal 25: 131-209, https://oncotherm.com/sites/oncotherm/files/2019-05/SZASZ%20M.pdf

[4] Szasz AM, Arkosy P, Arrojo EE, et.al. (2020) Guidelines for local hyperthermia treatment in oncology, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 2, pp.32-71, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

Rules of submission

As the editorial team we are committed to a firm and coherent editorial line and the highest possible printing standards. But it is mainly you, the author, who makes sure that the Oncothermia Journal is an interesting and diversified magazine. We want to thank every one of you who supports us in exchanging professional views and experiences. To help you and to make it easier for both of us, we prepared the following rules and guidelines for abstract submission.

Als redaktionelles Team vertreten wir eine stringente Linie und versuchen, unserer Publikation den höchst möglichen Standard zu verleihen. Es sind aber hauptsächlich Sie als Autor, der dafür Sorge trägt, dass das Oncothermia Journal zu einem interessanten und abwechslungsreichen Magazin wird. Wir möchten allen danken, die uns im Austausch professioneller Betrachtungen und Erfahrungen unterstützen. Um beiden Seiten die Arbeit zu erleichtern, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope

The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to supporting those who would like to publish their results for general use. Additionally, it provides a collection of different publications and results. The Oncothermia Journal is open towards new and different contents but it should particularly contain complete study-papers, case-reports, reviews, hypotheses, opinions and all the informative materials which could be helpful for the international Oncothermia community. Advertisement connected to the topic is also welcome.

- Clinical studies: regional or local or multilocal Oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities and treatment optimization
- Biological studies: mechanisms of Oncothermia, thermal- or non-temperature dependent effects, response to electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- Techniques of Oncothermia: technical development, new technical solutions, proposals
- Hypotheses, suggestions and opinions to improve Oncothermia and electro-cancer-therapy methods, intending the development of the treatments

Further information about the journal, including links to the online sample copies and content pages can be found on the website of the journal: www.oncothermia-journal.com

Umfang und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncothermie-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- Klinische Studien: regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen
- Biologische Studien: Mechanismen der Oncothermie, thermale oder temperaturunabhängige Effekte, Ansprechen auf ein elektrischesFeld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
- Oncothermie-Techniken: technische Entwicklungen, neue technische Lösungen
- Hypothesen undMeinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen

Weitere Informationen zum Journal sowie Links zu Online-Beispielen und Inhaltsbeschreibung sind auf der Website zu finden: www.oncothermia-journal.com

2. Submission of Manuscripts

All submissions should be made online via email: info@oncotherm.org

Manuskripte einreichen

Manuskripte können online eingereicht werden: info@oncotherm.org

3. Preparation of Manuscripts

Manuscripts must be written in English, but other languages can be accepted for special reasons, if an English abstract is provided.

Texts should be submitted in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be submitted in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be provided in JPG format.

Manuscripts may be any length, but must include:

- Title Page: title of the paper, authors and their affiliations, 1-5 keywords, at least one corresponding author should be listed, email address and full contact information must be provided
- Abstracts: Abstracts should include the purpose, materials, methods, results and conclusions.
- Test: unlimited volume
- Tables and Figures: Tables and figures should be referred to in the text (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without a reference to the text. Figure files will ideally be submitted as a jpg-file (300dpi for photos).
- References: Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3]. The full references should be listed numerically in order of appearance and presented following the text of the manuscript.

Manuskripte vorbereiten

Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.
Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.
Manuskripte können jede Länge haben, müssen aber die folgenden Punkte erfüllen:

- Titelseite: Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte, mindestens ein Autor muss genannt werden, E-Mail-Adresse und Kontaktdetails des Autors
- Abstracts: Abstracts müssen Zielsetzung, Material und Methoden, Ergebnisse und Fazit enthalten.
- Text: beliebige Länge
- Abbildungen und Tabellen: Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg eingereicht werden (300 dpi).
- Zitate: Das Oncothermia Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

4. Copyright

It is a condition of publication that authors assign copyright or license the publication rights in their articles, including abstracts, to the publisher. The transmitted rights are not exclusive, the author(s) can use the submitted material without limitations, but the Oncothermia Journal also has the right to use it.

Copyright

Es ist eine Publikationsvoraussetzung, dass die Autoren die Erlaubnis zur Publikation ihres eingereichten Artikels und des dazugehörigen Abstracts unterschreiben. Die überschriebenen Rechte sind nicht exklusiv, der Autor kann das eingereichte Material ohne Limitation nutzen.

5. Electronic Proofs

When the proofs are ready, the corresponding authors will receive an e-mail notification. Hard copies of proofs will not be mailed. To avoid delays in the publication, corrections to proofs must be returned within 48 hours, by electronic transmittal or fax.

Elektronische Korrekturfahne

Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per E-Mail informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhindern, müssen die korrigierten Texte innerhalb von 48 Stunden per E-Mail oder Fax zurückgesandt werden.

6. Offprints and Reprints

Author(s) will have the opportunity to download the materials in electronic form and use it for their own purposes. Offprints or reprints of the Oncothermia Journal are not available.

Sonderdrucke und Nachdrucke

Die Autoren haben die Möglichkeit, das Material in elektronischer Form herunterzuladen, Sonderdrucke und Nachdrucke des Oncothermia Journals sind nicht erhältlich.

7. **Advertisement**

The Oncothermia Journal accepts advertising in any language but prefers advertisements in English or at least partially in English. The advertising must have a connection to the topics in the Oncothermia Journal and must be legally correct, having checked that all information is true.

Werbung

Das Oncothermia Journal akzeptiert Werbeanzeigen in allen Sprachen, bevorzugt, aber die zumindest teilweise Gestaltung in englischer Sprache. Die Werbung muss eine Beziehung zu den Themen des Oncothermia Journals haben und der Wahrheit entsprechende Inhalte aufweisen.

8. **Legal responsibility**

Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any publications. The editorial board has the right to reject any publication if its validity has not been verified enough or the board is not convinced by the authors.

Haftung

Die Autoren aller im Oncothermia Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das Oncothermia Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Die Redaktion hat das Recht Artikel abzulehnen.

9. **Reviewing**

The Oncothermia Journal has a special peer-reviewing process, represented by the editorial board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of the reviewer will not be released and her/his name will be handled confidentially. Papers which are not connected to the topics of the journal could be rejected without reviewing.

Bewertung

Die Texte für das Oncothermia Journal werden durch die Redaktion kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden.

Contents

Oncothermia is a kind of oncological hyperthermia – a review

Szigeti GYP, Szasz AM, Szasz O

Innovation Center, Semmelweis University, Hungary (szigeti.gyula@med.semmelweis-univ.hu)
Cancer Centre, Semmelweis University, Budapest, Hungary
(szasz.attila_marcell@med.semmelweis-univ.hu)
Department of Biotechnics, St. Istvan University, Godollo, Hungary
(biotech@gek.szie.hu)

Cite this article as:
Szigeti GYP et al. (2020): Oncothermia is a kind of oncological hyperthermia – a review
Oncothermia Journal Special Edition, 2020 September: 8-48
http://www.oncotherm.com/sites/oncotherm/files/2020-09/specialedition01_2.pdf

Abstract

Oncothermia is a personalized type of hyperthermia, which selectively heats malignant cells, thermally targeting the nano-sized parts of their membranes (rafts). It raises the temperature of these clusters of transmembrane proteins by more than 3 ºC relative to their environment. The heated cells mostly die by apoptosis. The thermal damage starts to produce damage-associated molecular patterns (DAMPs), including the expression of HSP70 and HSP90 on the cellular membrane, the expression of the TRAIL DR5 death receptor and the release of HMGB1 and massive amounts of HSP70 into the extracellular matrix, producing vast numbers of apoptotic bodies. Together with this thermally induced complex process, the overall temperature rises due to heating of the selected parts. This temperature increase under in vitro conditions could be as high as to denature the proteins in a meat phantom, but under physiological conditions, it is at least 3–4 ºC, as indicated by invasive measures, both in animal and human studies. Our objective is to concentrate on the definite thermal behaviour of the oncothermia method, reviewing the resulting thermal effects, which ignite all the biomolecular changes mentioned above.

Keywords

Oncothermia, modulated electro-hyperthermia, temperature, in silico, in vitro, in vivo, preclinical, human

Introduction

The definition of hyperthermia varies by source. Commonly, "hyperthermia is the use of therapeutic heat to treat various cancers on and inside the body" [1]. Medicine.net defines the process of hyperthermia as overheating of the body [2], which is the method of whole-body hyperthermia. The various definitions differ by the target in the case of local hyperthermia. The National Cancer Institute (USA) defines the target as the cancer tissue:

"Hyperthermia (also called thermal therapy or thermotherapy) is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F)" [3]. This definition (with a tissue target but defining the cellular aim) is used by Wikipedia as well: **"**Hyperthermia therapy is a type of medical treatment in which body tissue is exposed to slightly higher temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anti-cancer drugs" [4].

The American Cancer Society (USA) defines the target as cells: "When cells in the body are exposed to higher than normal temperatures, changes take place inside the cells. These changes can make the cells more likely to be affected by other treatments such as radiation therapy or chemotherapy" [5]. The Medical Dictionary defines no target; only the temperature rise: "a much higher than normal body temperature induced therapeutically or iatrogenically" [6].

Despite the evidence of nano-range heating at the membrane [20], [31], [35] and the large-scale successes [29], [30], as well as publications [66], [65], practitioners of hyperthermia demand to see thermal effects and temperature developments. OncoTherm has taken a great interest in this project and has shown the requested temperature elevations under physiological conditions in animals and human studies, which will be published soon. Due to the frequent demands for data, we are presently showing some model experiments, as well as animal and human measurements of temperature rise in oncothermia.

Oncothermia defines hyperthermia more provisionally, emphasizing targeting of malignant cells: Oncothermia is a kind of hyperthermia, which selectively heats malignant cells to a higher temperature than that of their environment [7]. The discussion is not centered on the higher

temperature, (which is always the basic condition), but the definitions differ only in the target of heating.

The main difference is, of course, in the homogeneity of heating (temperature). The most homogeneous heating occurs in whole-body hyperthermia. It has extreme (over 40 °C) and mild (under 40 °C) versions. The local heating is, of course, non-homogenous, because only a part of the body is heated, while the blood (which also circulates over the tumour) remains at body temperature. Hyperthermia attempts to mimic the whole-body version, requiring homogeneous heating in the target as much as possible (this is the CEM [cumulative equivalent minutes] concept). Of course, by the time local (regional) treatment approaches whole-body heating, because local heating also heats up the environment. The source of the heat is the heated tumour.

Targeted therapies are a new trend in oncology. Many conventional oncologic therapies have been combined with targeted liposomal [8] or nano-particle [9] supportive therapies or radiotherapeutic interventional nano-radiation [10]. Personalization has also become a new target [11], considering the biocomplexity [12] and considering the new goals of pharmaceutical products [13]. Immune stimulation and modulation have become one of the hottest research fields [14]. These trends are focused on safe and effective treatment using the latest biomedical and biotechnical knowledge.

The original idea for local hyperthermic cancer treatment was based on real thermal targeting, focusing on the local tumour. So, targeting is not a new concept in hyperthermia. Considering precise targeting, there are many hyperthermia methods not using homogenic heating. The best example of inhomogeneity is thermal ablation. Targeting with thermal-sensitive liposomes [15] and nano-particles is a long-term goal [16]. Finally, nanoparticles are the heat absorbers: these are heating targets, and the complete tumour is heated non-homogeneously. The sources of heat to raise the temperature of the complete tumour is a dispersed set of nano-particles placed in the tumorous lesion. Hot nanoparticles heat up their environment – the tumour itself.

Change of paradigm: oncothermia

Oncothermia follows the trend of selectively targeting heterogeneous malignant tissue, heating existing natural nanoparticles (as in the case of dispersed nano-suspensions). However, the nanoparticles targeted by oncothermia are naturally presented, clusters of transmembrane proteins (membrane rafts). This explains the "nanothermia" name, which started to be used for this inhomogeneous heating.

Oncothermia uses various biophysical effects to select and heat up tumours, the malignant cells inside them and their membrane rafts. Macro-selection to find the tumour (self-focusing) is based on the Warburg effect. The high glucose metabolism of the tumour (which is also the basis of positron emission tomography (PET) diagnosis) provides a high ionic concentration in the tumour. Consequently, the tumour has high electric conduction, so the applied radiofrequency (RF) current flows automatically through the tumour. This emphasizes that macro-selection efficacy is highly correlated with diagnostic PET signals.

Selection is performed inside the tumour on a micro-scale to find the malignant cells. The dominant biophysical character of the malignant cells is that these cells are mostly autonomic. These have no connection with their neighbours (broken adherent bonds and broken junctions), whereas their healthy counterparts are part of a network. This means that the extracellular electrolytes around

the malignant cells differ greatly from the matrix around their healthy counterparts. This could also be recognized by a well-chosen electric field.

The third selection factor is nanoscopic and represents the energy-absorption itself. Clusters of transmembrane proteins (membrane rafts) have entirely different radiofrequency absorption than the surrounding membrane. This makes it possible to distinguish them and forces them to absorb most of the energy in the rafts (nanothermia) [17].

Together with the above topological selection, oncothermia applies dynamic selection. This refers to modulation, which selects by the modified dynamic properties of malignant cells compared with their healthy counterparts. The action of modulation is a definitive part of the subject of fractal physiology and mainly based on stochastic resonance.

The points of action of modulation, in short, are as follows:

- The topology of the biological tissues shows characters of the tissue and its possible diseases (topic of pathology). The tissue patterns that the pathologist evaluates by her/his expertise can be itemized and evaluated mathematically by fractals. This topologically characterized method is the part of the fractal physiology.
- The geometry of the pattern definitively determines the interactions (dynamics) of the cells involved in the structure, described by spatio-temporal dependence of the fractals. This is, of course, opposite in nature: the dynamics determines the pattern. Due to the diagnostic reality, which starts with pattern evaluation, we face the inverse problem: start with the structural results.
- The spectral density (dynamics) of homeostatic (healthy) patterns always shows exponential dependence of the f frequency, with exponent (-1), so the dependence is reciprocal, 1/f. Consequently, the dependence of the logarithm of spectral density on the logarithm of f shows a straight line with a slope of (-1). This is the fingerprint of the complexity (self-organizing behaviour). When complexity is "normal", the dynamics are healthy. When complexity is broken (deviation from 1/f dynamics), the interactions of the cells are out of homeostatic control.
- The pattern differences between healthy and malignant tissues make it possible to distinguish them. The forced healthy dynamics (1/f modulation) are an easy fit to healthy tissues, but are in disharmony with malignant ones. The effect could be pressing the precancerous (not malignant yet, but going to be malignant) cells to find their correct dynamic connections (social signals in the tissue through the re-established cadherins and junctions), or the disharmony could be so huge that it cannot be done.
- When the malignant cells are not able to find their way back to homeostasis, they absorb a finite amount of energy from the external constrains of the 1/f modulated field, which is concentrated on the clusters of transmembrane proteins (rafts), which initialize signal pathways for DAMPs, ICD and consequently, APC and T-cells (CD4+ and CD8+), (abscopal effects). These are strongly connected to immune effects, which are also intensively investigated worldwide [18].

The main point of targeting is to select where the energy must be absorbed. This is by far not a simple task in the technical reality, due to the inhomogeneity of the target. A large target is very non-homogenous in its composition and mainly in its thermal properties. Heat conduction and heat convection depend on blood perfusion and the development stage of the tumour, so equal energy absorption does not produce equal temperature. Furthermore, the inhomogeneity changes over time: homeostatic control starts to cool down the overheated volume, causing an even greater

thermal discrepancy in the tumour. This selective specific absorption rate (SAR) is the basis of the focus and the long-term challenge facing technical realization. Unfortunately, any very accurate energy deposition in the target does not mean that the temperature is also accurately fixed in that point. Despite the focused energy, the temperature varies over time in a natural way, heating up the non-targeted tissues by thermal conduction and thermal convection. The main heat-delivering process is governed by blood flow, which is anyway "responsible" for equalization of the temperature in a homeostatic manner.

Oncothermia is a kind of hyperthermia. Following the modern trend of oncology, it is personalized [19]. Oncothermia is devoted to targeting the nano-parts of the malignant lesion and selecting the malignant cells [20], targeting them by thermal energy in the nanoscale region [21], inducing natural apoptosis [22] in cancer cells and boosting immune protection mechanisms [23] accompanied by an abscopal effect [24].

Oncothermia follows a special hyperthermia concept, trying to avoid the problems of conventional hyperthermia. The conventional methods induce physiological feedback (increased blood flow), which is a technically intensive heat exchanger and could cause huge biological challenges. The two main problems are connected to the definite delivery by intensified blood perfusion, which supports tumour growth, and the intensive blood flow could increase the risk of malignant invasion and dissemination starting a competition between the lethal thermal effect and the supporting blood supply [25]. This is the main disadvantage of conventional hyperthermia. This disadvantage, of course, does not exist in vitro. The results of massive research activity conducted in vitro are misleading due to the missing physiological feedback.

To avoid these problems, hyperthermia should be applied only as a complementary therapy: its application as a monotherapy (diathermia) is contraindicated. The conventional treatment is combined with drastic radio- or chemotherapies, causing numerous side effects as we well know. With oncothermia therapy, Natural approaches are very effective in oncothermia therapy. Due to the minimized negative feedback from blood flow makes monotherapy applications of oncothermia possible [26].

This suppressed negative feedback from blood flow does not mean that oncothermia is non-thermal. Oncothermia is a kind of hyperthermia when we concentrate our heating on the cellular membrane. This heating is very intensive but very local [27], and so the physiological feedback caused by the intensification of blood flow is less effective. The oncothermia solution concentrates on the selection of malignant cells and heating up their cell membranes instead of the complete tumour mass [21]. The main problems of the complementary applications of hyperthermia in oncology is solved in this way [31]. This heating method has numerous advantages: the overall temperature could be low (while the nano-range heating is high), and the thermal cytotoxity is effective [28].

Thermal damage starts to produce damage-associated molecular patterns (DAMPs), including the expression of HSP70 and HSP90 on the cellular membrane, the expression of the TRAIL DR5 death receptor and the release of HMGB1 and a massive amount of HSP70 into the extracellular matrix, producing a vast number of apoptotic bodies. Together with this thermally induced complex process, the overall temperature rises from the heated sources of the selected parts.

These effects were followed from the basic laboratory to clinical applications [29], [30], [31]; they fit completely with the modern trends of oncotherapies. The theoretical background of oncothermia uses the complexity of homeostatic equilibrium [32] (fractal physiology [33]), but its technical solution is not simple [34], [35].

Despite its differences with hyperthermia [36], oncothermia is based on thermal effects, but the temperature distribution is far from equilibrium [37], [38]. The temperature effects of oncothermia

were reviewed previously [39], [40], but our current objective is to show a summary adding new results and reviewing the real-time temperature growth in actual studies of various conditions.

The membrane-associated nano-temperature on membrane rafts was calculated in silico [44] and was measured and will be shown by direct indication [77] and by conventional flow cytometry methods [78]. Extended preclinical temperature measurement was shown on a living pig when its liver is targeted by oncothermia [92]. The fact that oncothermia is a kind of hyperthermia is proven.

Oncothermia creates nano-heating so that the complete effect is centred on the electromagnetic selection of the membrane rafts of malignant cells. This special targeting causes the average temperature to increase over time. Fig. 1.

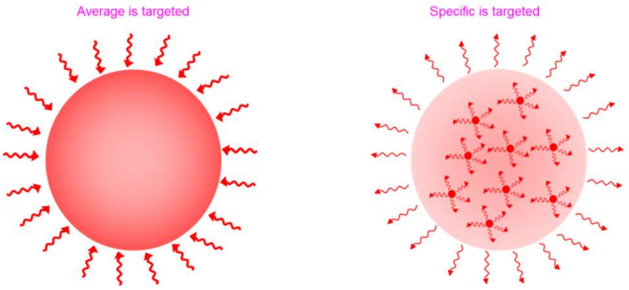


Fig. 1. The nano-scaled targets are heated, and those will heat up the complete volume

The precise focused energy does not mean the focus of the temperature, because it is naturally spread out. After a defined period, the temperature is almost equalized, and the special selection is lost.

Fig. 2.

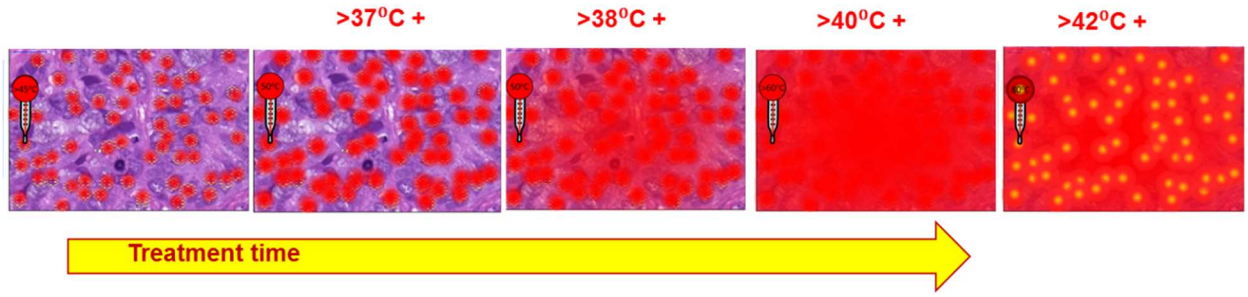


Fig. 2. The selected nano-parts heat up their complete volume, and the selection weakens over time.

The model system of heating is the extreme heat on rafts, which heats up the cell and the tumour at the end. The tumour heating is usually in the range of mild hyperthermia. Fig. 3.

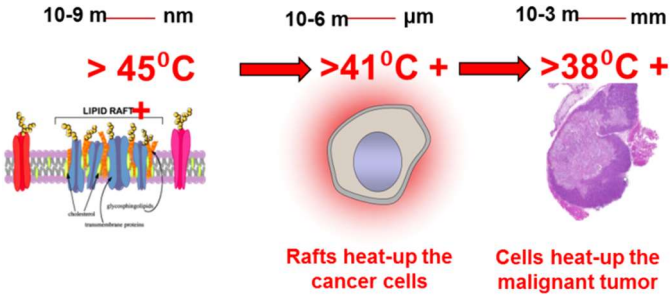


Fig. 3. Sequential heating makes the temperature on rafts extra high and that on the complete tumour mild.

The critical membrane state could cause special signals of instability. Indeed, the transition temperatures and critical fluctuations in giant plasma membrane vesicles (GPMVs) were well measured in vitro [41].

Oncothermia research is a complex process, which begins with ideas and follows with theoretical elaboration, in silico research, in vitro experiments, in vivo model-research, preclinical studies and finally, clinical applications. However, this line is multi-directional, having various feedback mechanisms modifying all steps of the processes, Fig. 4.

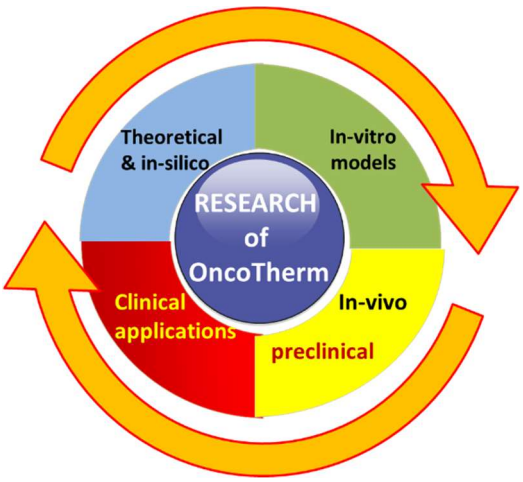


Fig. 4. The complexity and interdependence of various levels of the research

We concentrate on the heating effect of oncothermia determining the appropriate dose for the process. The goal is to show the special thermal effects of oncothermia method, showing its connection with the conventional hyperthermia therapies.

Methods

The general demand for experimental proof of the thermal effects and the temperature developments of oncothermia remain high among professionals. Oncotherm has taken a keen interest in this project and has shown the requested temperature increases in silico, in vitro, in vivo and under physiological conditions, providing preclinical (animal) and human studies.

The early in silico models were generated by MathCad programs and were later performed by computer simulation technology (CST) software, [42], developed for such hyperthermia treatments [43]. The finite integration technique (FIT) was used to solve the appropriate Maxwell equations with a low-frequency domain solver (EQS) module. Open boundary conditions were fixed at 13.56 MHz. Tetrahedral mesh (adaptive division) was for numerical calculation with an accuracy of 10^{-6} [44], [45]. The cell model used a 10–15-μm cell diameter, a 0.2-μm raft diameter, a 20-nm raft thickness and a 5-nm membrane thickness.

The phantom models were made with realistic materials: high-protein-content eggs and mixed meats, as well as liver, which showed the higher temperature clearly by changing its colour. Temperature measurements were also made by fluoro-optical sensors (Luxtron), and the application of mixed, chopped meat/fat phantom mimicking the thickness of the fatty human body (for measuring energy penetration) made possible the most realistic target in the topic.

In vitro and in vivo systems are used for measurement by various laboratories, and sample temperature is well controllable everywhere with a few Watts of power and using fluoro-optical temperature measurement (Luxtron). We show here only the results of our own measurements.

Animal measurements were made on the tumours of dogs, and experimental temperature measurements were also made on pig livers, making sure that the physiologic feedback compensation effect did not wash out the temperature elevation.

Human temperature measurements were made on sarcomas, ovary, breast and abdominal cavity. The highly specialized sterile temperature sensors were based on thermocouple platinum-iridium-rhodium materials.

Results

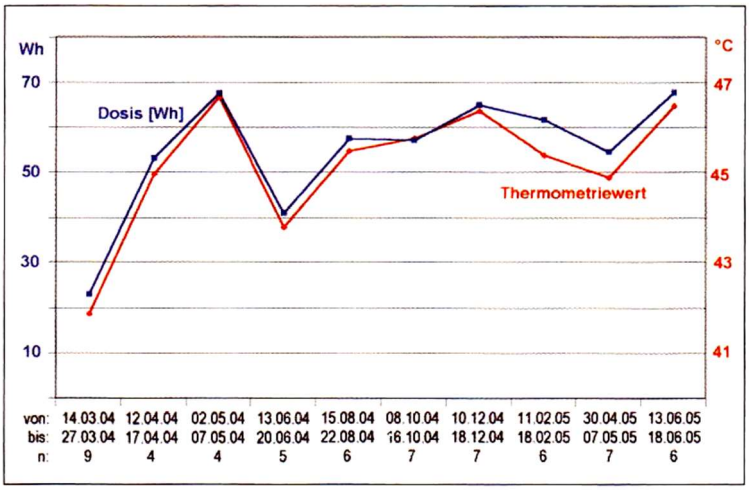
Studying the thermal actions of oncothermia, we published a couple of papers on the dosing of oncothermia [46], [47], and a generalized theory has been formulated [48]. We have shown the importance of the Arrhenius law in oncothermia as the definite fingerprint of thermal effects.

In silico we have made a model to show how the electrical field from the electrode is transferred to the target area. The main results are:

- Automatic focusing of the electrical field on tumorous areas [49], [50],
- Concentration of the electrical field in the lipid rafts on a nanoscopic scale [51],
- Calculation of temperature increase due to RF field used by OncoTherm [52], [53], [54], [55], [56],
- Deep heating with small power is possible [57], [58],
- Auto focusing of electrical field to components with higher conductivity [59], egg + liver [60].

Phantom models

The first method of approval was the conduction of measurements on various phantom models made in the beginning era of device checking. Temperature development was, on average, in the centre of the measurement, as seen in the figure below. The correlation is strong and so the calibration of the equivalent temperature is controlled and proven [61]. Fig. 5.



Mittelwerte von eingebrachter Energiedosis und Thermometriewerten

Fig. 5. The correlation of the calculated equivalent temperature in tumour-phantom and the applied dose

Numerous thermo-camera pictures were made of specialized impedance phantoms as shown below. Fig. 6.

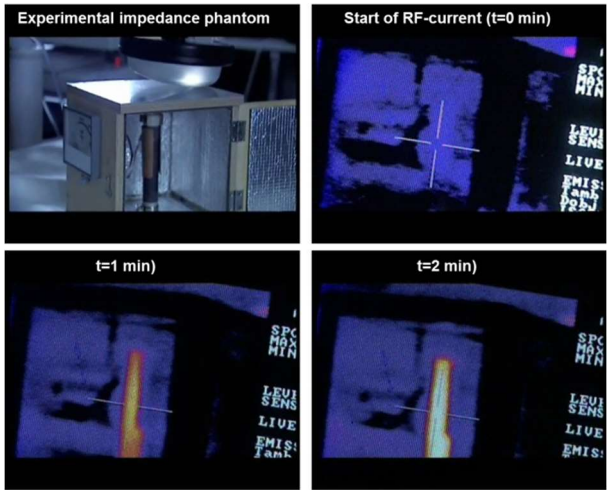


Fig. 6.

Carbon impedance in a thermally isolated box, measuring the calibration of the power of the device. The intensive temperature increase is due to the isolation, concentration of heat on the target, lack of heat conduction and convection of radiation loss to the environment.

The fruit treatment shows the temperature increase as well, Fig. 7.

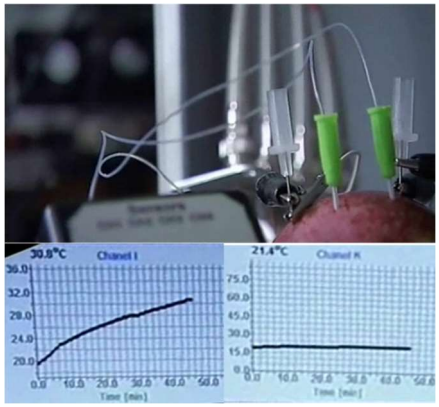


Fig. 7. A simple apple experiment showing well the heating of the apple measured inside of the fruit.

More realistic phantoms could be "constructed" out of protein structures such as eggs.

It was demonstrated in real time experiments at conferences how we can easily reach 60 ºC in the middle of the tumour model (egg white) without heating up the surrounding materials [62]. We have shown the selective and very intensive heat effect at the ICHS conference in real life: we heated up the egg white until it coagulated in water. Our colleagues were participating and could see with their eyes that the water was not heated up, but the egg-white became "hard", which meant that its temperature was over 60 °C. This is a selection on its own, because the overall temperature (water + egg) was not too high: it increased by only a few degrees. Therefore intensive mass cooling cannot stop the nano-heating on the membrane, and we have higher cytotoxicity at a lower average temperature compared with conventional hyperthermia at a higher average temperature. Fig. 8.

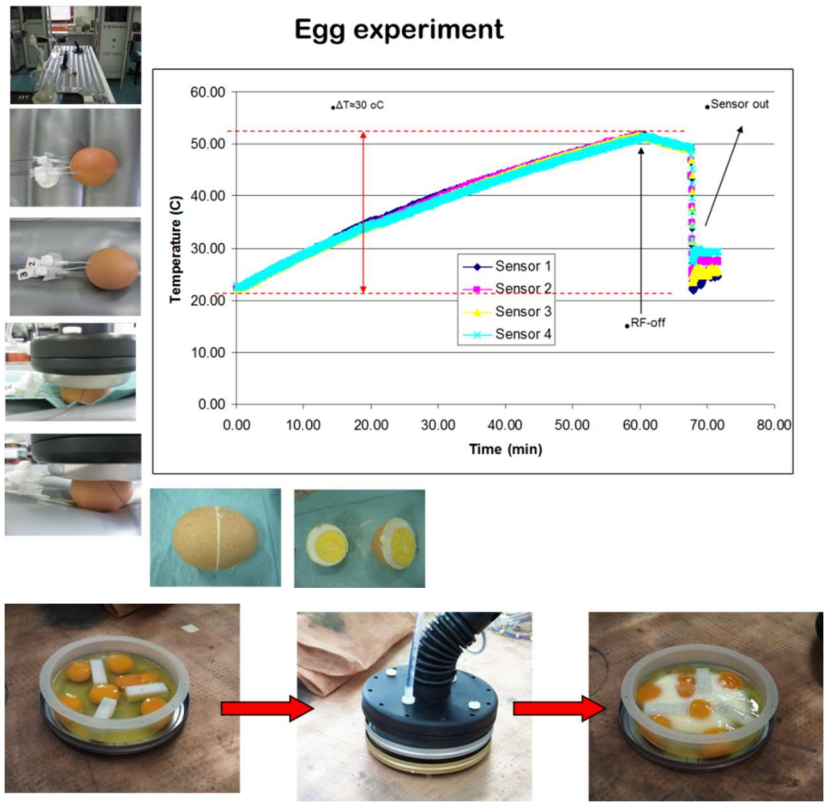


Fig. 8.

Extreme high temperature is trivially demonstrated by "cooking" or "frying" the egg with simple RF current at 150 W. The temperature increase is so great that it causes coagulation of the protein (>50 ºC).

It is more peculiar when the egg white is in a water tank. The water is not heated, but the egg white coagulates (starting from inside!), clearly showing the selection mechanism. Fig. 9.

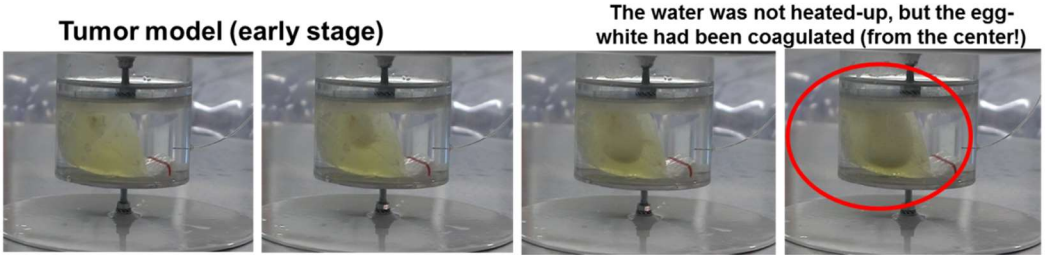


Fig. 9. The water temperature only increased slightly, but the egg white temperature inside was greater than 50 ºC, starting protein coagulation in the middle of the specimen. Thus, targeting is proven.

The same was also shown clearly when the liver was "cooked" inside, while outside, it did not show any changes. Fig. 10.

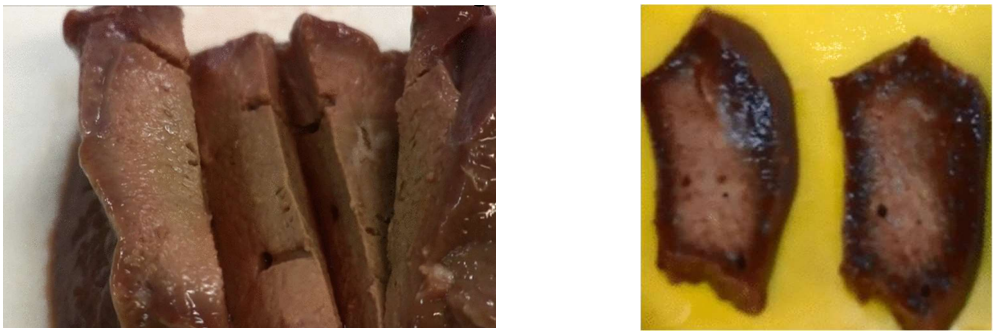


Fig. 10. The liver is "cooked" inside, while the outside is "fresh". This again shows the selection capability of the RF-current induced by EHY2000 device.

Models (mimicking the cancer region) showed the validity of this focusing [63]. Fig. 11.

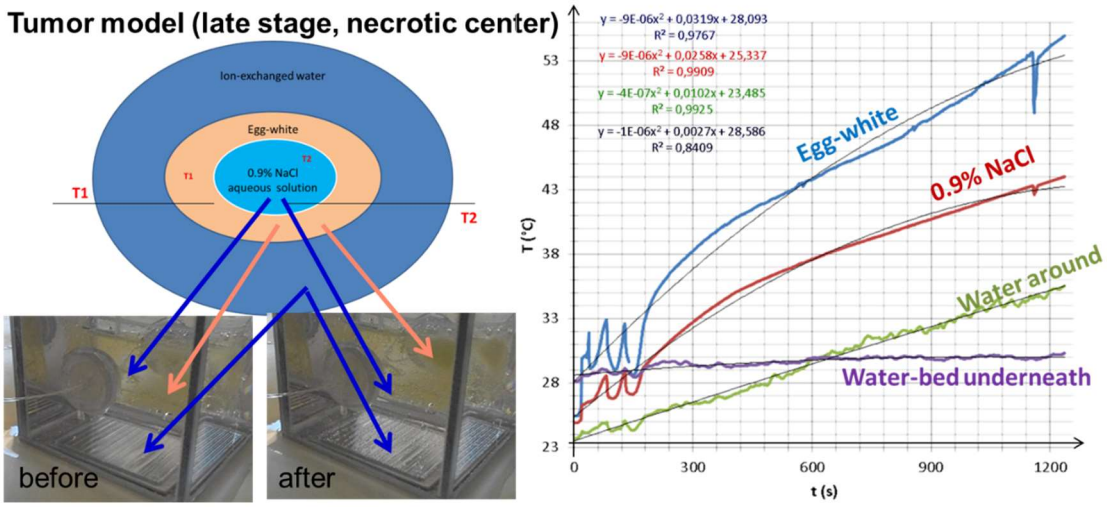


Fig. 11. Experimental results on a model of heterogenic heating

The simple meat (pork) treatment, mimicking the skin by polyethylene packing, was employed earlier on when the first TÜV approval was granted. The increase in temperature reached 5 °C in the bottom of the model (7 cm depth). It was important that we could focus the heat in the lower middle region where the gain was more than 6–9 °C [64]. In multiple replicate experiments, the results were convincing. Fig. 12.

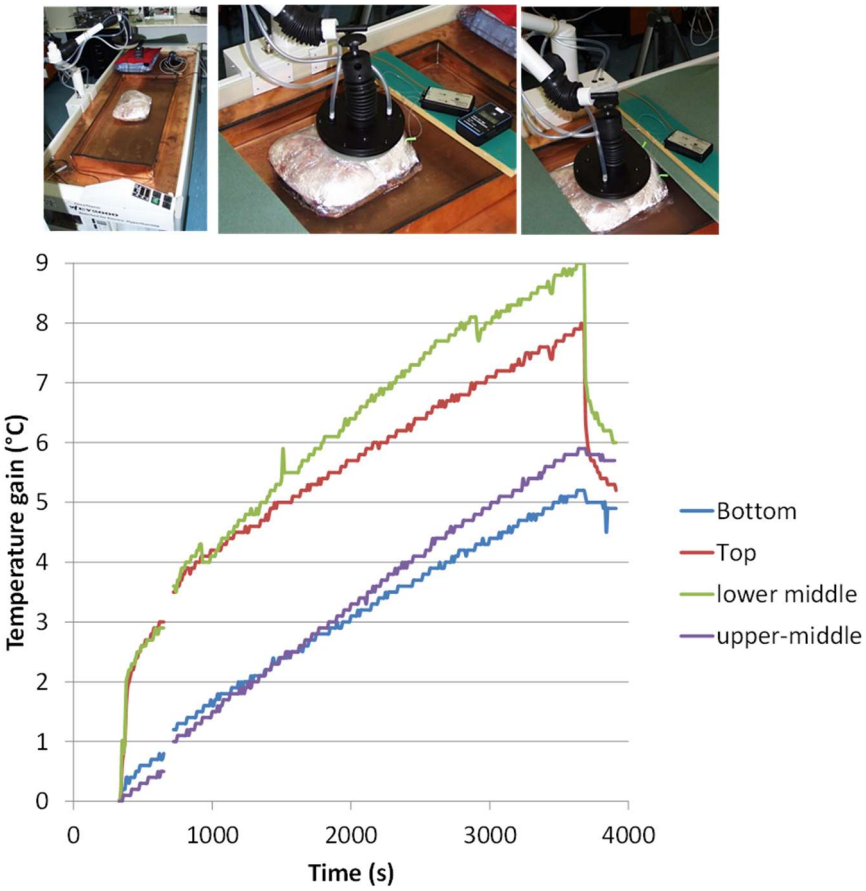


Fig. 12. A large piece (5.1 kg) pork meat phantom, wrapped in foil.

In multiple replicate experiments, similar results were obtained. Fig. 13.

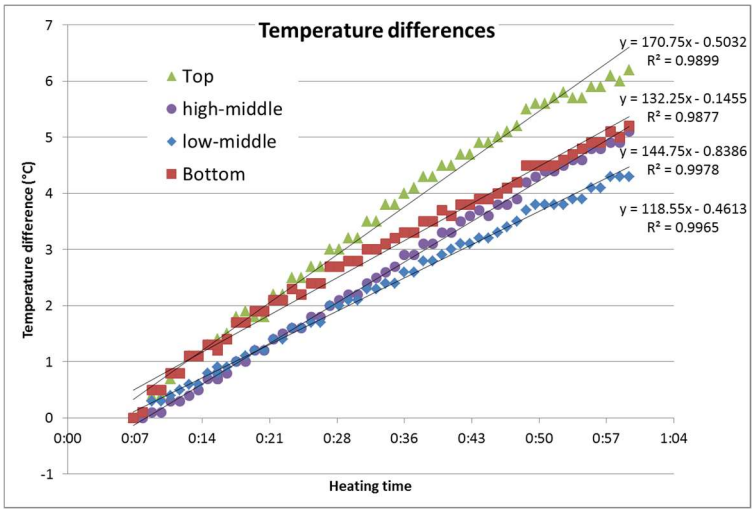


Fig. 13. Repetition of the previous (Fig. 12.) measurement.

A special meat phantom model was constructed to study the energy absorption in depth [65]. This deep temperature measurement of a meat phantom modeled the complete cross-section of a human body. The measurement shows well that, at a depth of 24 cm, the temperature increases by 19 ºC during 35 min by 100 W RF energy flow. Fig. 14.

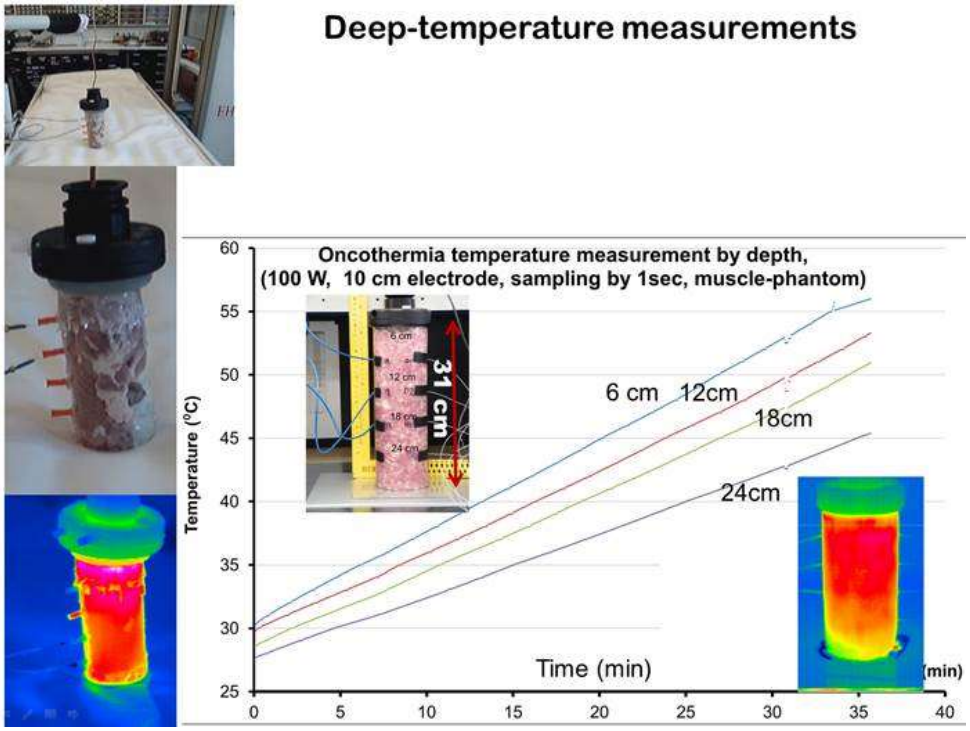


Fig. 14.

Meat phantom experiment for penetration measurement [65]

Layered meat phantom approaches the reality of the liver treatment measured by Prof. Herzog [66]. It is all well shown in the phantom: Fig. 15.

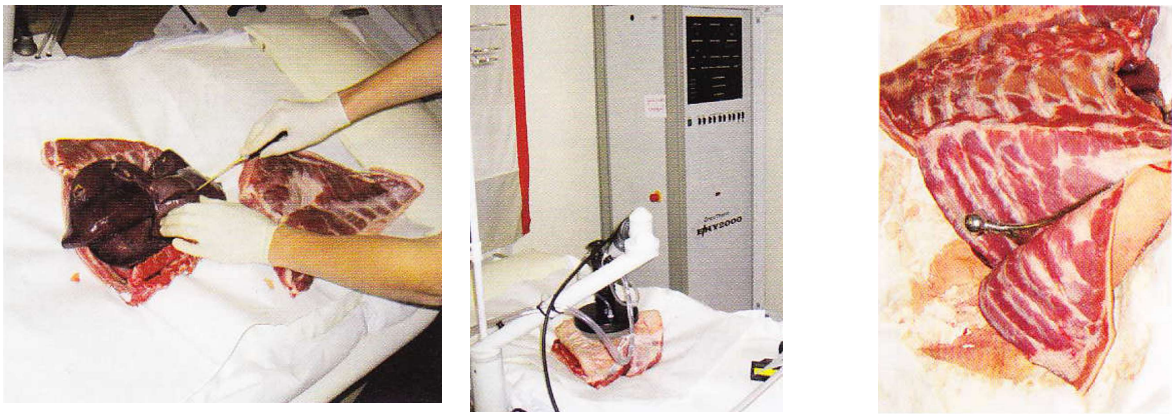


Fig. 15. Layered meat-phantom model: liver in piglet ribs and a limb prothesis

Modelling primary and metastatic tumours with a heterogeneous meat phantom [66]

The applied model shows well the temperature increase in the liver through the skin and ribs, even with a large metallic implant. Fig. 16. and Fig. 17.

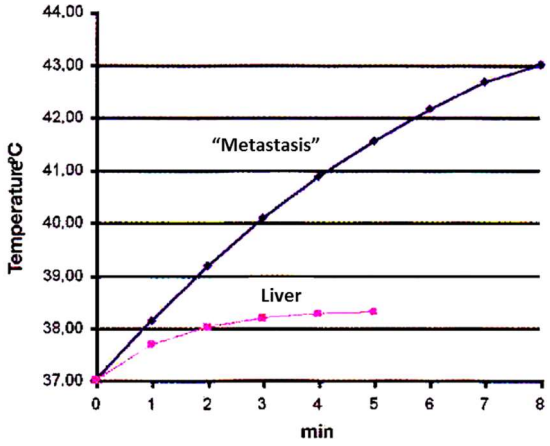


Fig. 16. Model of metastasis (◆) and liver heating when the arteria-hepatica delivers 0.32 l/min/kg blood through the liver (■). The applied power is 100 W.

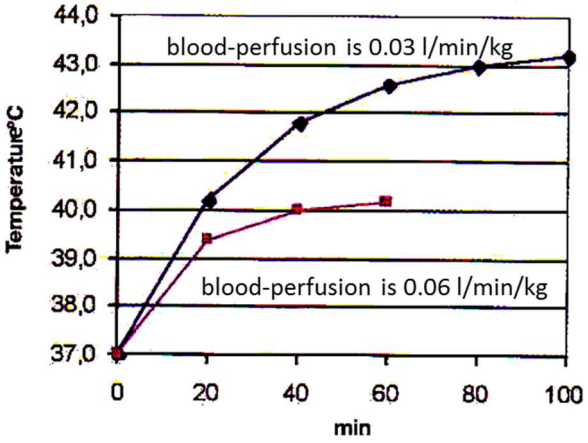


Fig. 17. Hypoxic model (◆, blood-perfusion is 0.03 l/min/kg) and normal perfusion (■, blood-perfusion is 0.06 l/min/kg)

The temperature increase is shown in the tables.

Measurement results after 15 minutes			
Measurement point		Temperature rise °C	
			(from - to)
△T	Skin	5.4	2.6 - 7.1
△T	Liver surface	4.1	2.6 - 5
△T	Liver inside	2.4	2.4 - 3.9

Hyperthermia measurement value on 100W after 26 minutes, and the temperature of a metal hip replacement which is between the skin and the ribs			
Measurement point		Temperature rise °C (from - to)	
△T	Skin	16.6	17.3
△T	Ribs	9.5	14.3
△T	Liver surface	7.9	8.5
△T	Liver inside	6.2	6.6
△T	Hip replacement	9.5*	
*Temperature is the same as the neighbouring rib tissue's temperature			

Graphical illustration is shown below in 3D. Fig. 18. and Fig. 19.

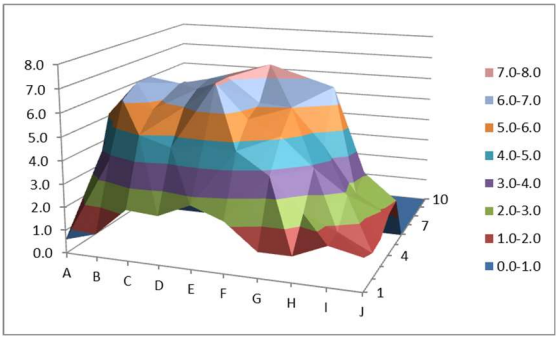


Fig. 18. The skin tissue by 20 cm electrode, 100 W; 15 min

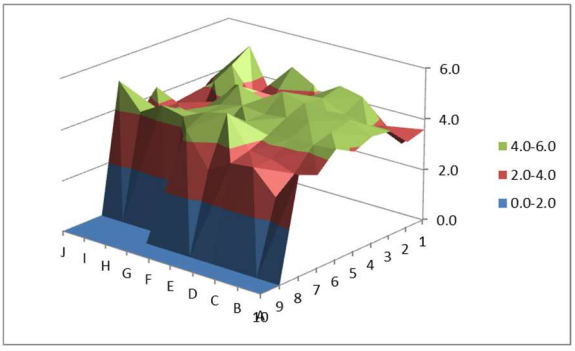


Fig. 19. Deep-seated liver, electrode 20 cm diameter, 100 W; 15 min

Piglet (without its harslet) is measured reaching a 12 ºC temperature increase with 100 W for 18 min. The piglet was packed in kitchen polyethylene foil to avoid further bleeding and to mimic more isolation of "fat skin" on its body surface. Fig. 20.

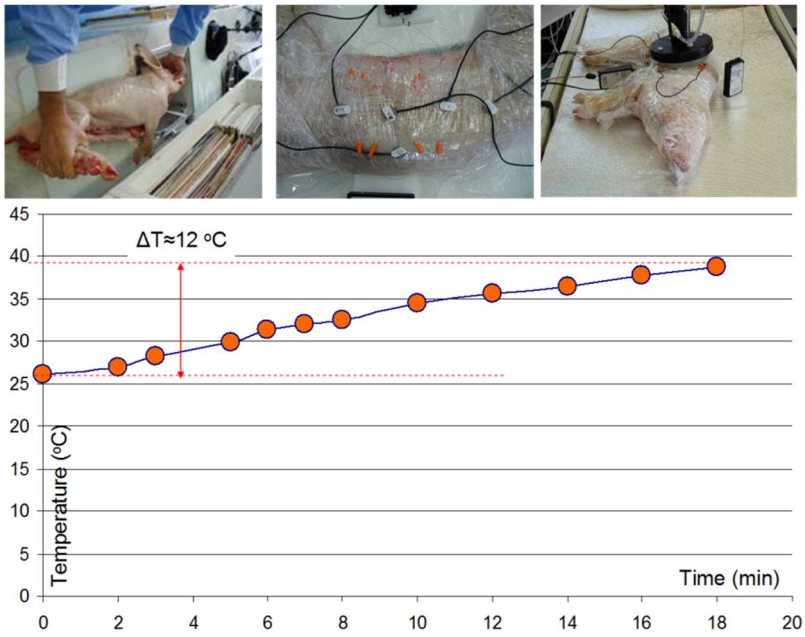


Fig. 20. Piglet measurement ex-vivo. (Wrapped in foil.)

In silico models

The early in silico models showed clear selection by the inhomogeneity of the tissue materials. Tumour tissue has higher conductivity [67] and a higher dielectric constant [68], which we used for electromagnetic selection. The in-silico calculation was made with MathCad. The strong selection (energy targeting) is theoretically proven by this calculation. Fig. 21.

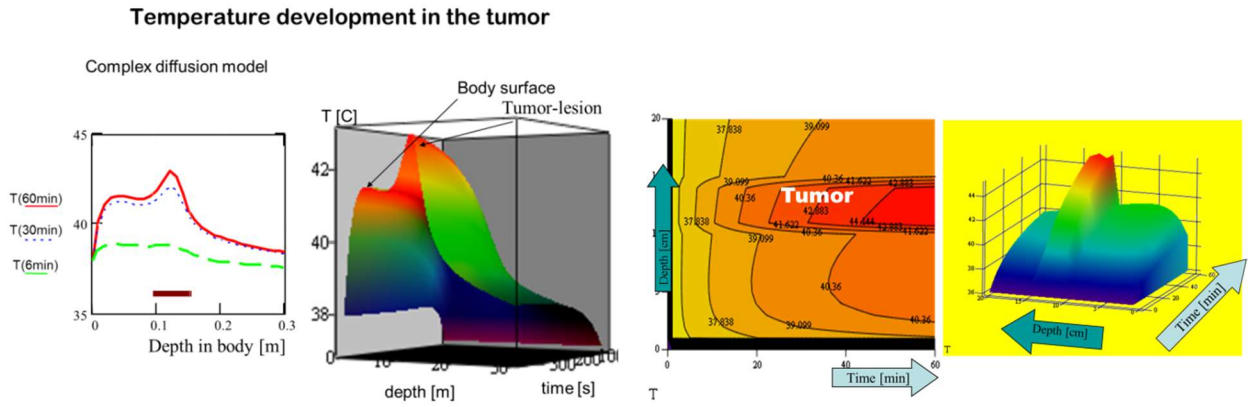


Fig. 21. The temperature increase is calculated by the impedance specialties of tumour tissue

Other in silico models were developed for micro-range differences in the tumour. The cell membrane contains clusters of transmembrane proteins (rafts), and those are targeted by oncothermia. The in-silico model calculated a layer of the rafts fitting its thickness into the membrane phospholipid bilayer (single-layer model) and more realistically, when it is thicker, making complex interactions with the electrolytes in their vicinity look like a layered system in the membrane (sandwich model). Fig. 22.. Fig. 23.

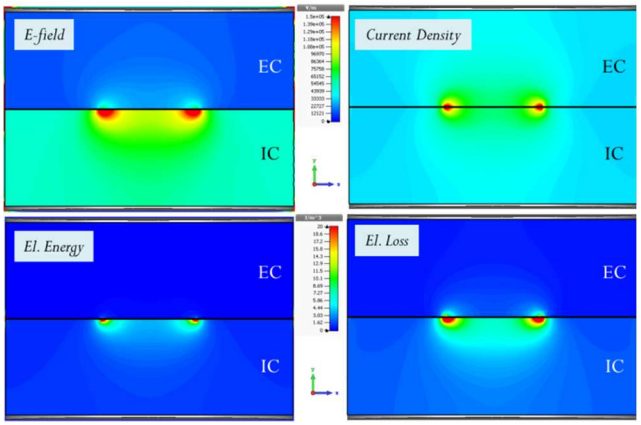


Fig. 22. Simple (single-layer) model

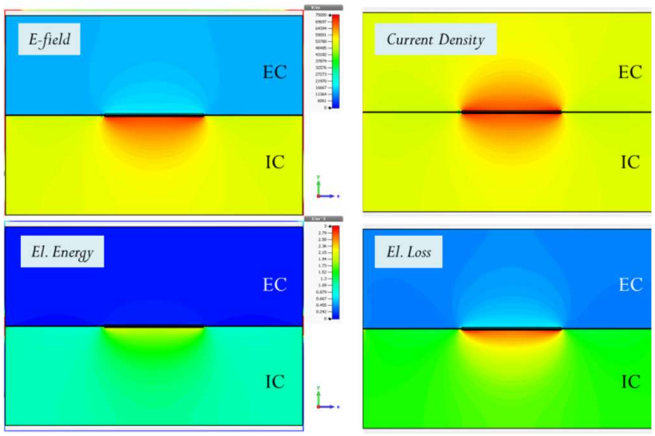


Fig. 23. Complex (sandwich) model

The calculation shows how targeting is effective at high temperatures in the nanoscopic range. The energy loss on the raft is significant. Fig. 24.

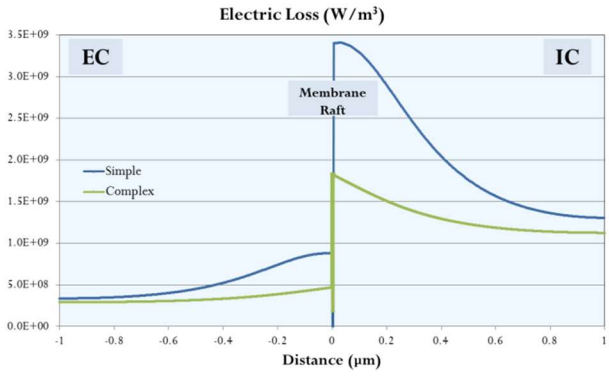


Fig. 24. Energy loss on the membrane rafts in the two models

The micro-domains have an even higher temperature gain when the contact between the cells amplifies the current density, causing energy absorption at these points. Fig. 25.

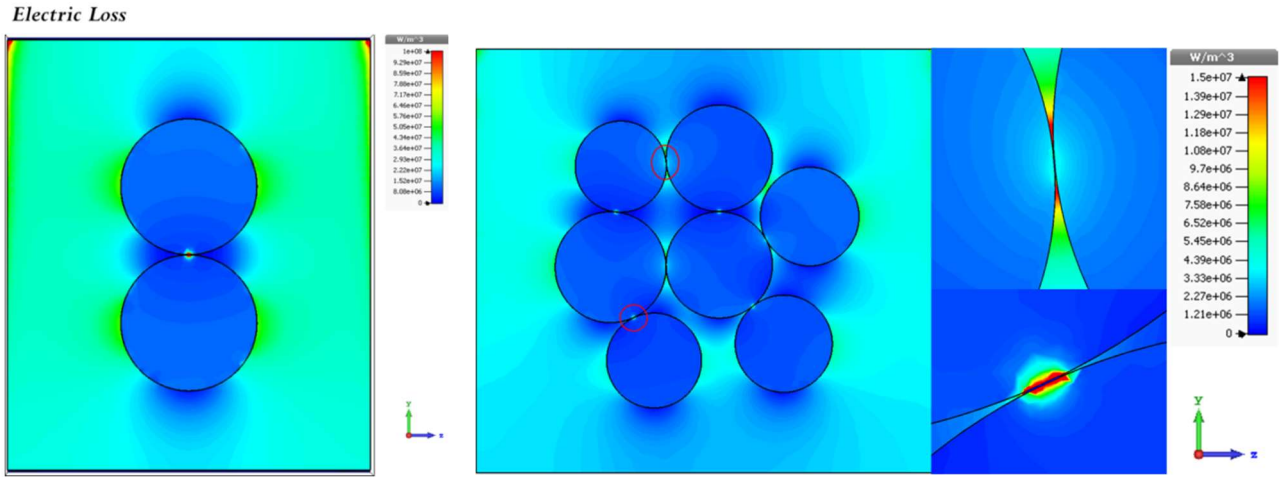


Fig. 25. Electric loss at the micro-domain connections

When the phantom and in silico models were summarized, two main parameters were shown. The first was the focusing of energy on the targeted area, which could also be proven in vitro by the co-culture experiments, showing that the in-silico model represents the in vitro model correctly.

Secondly, the energy placed in lipid rafts was shown in the in-silico model [69] , which correlated with the increased temperature in the cell membrane. In vivo models show that the cell membrane temperature in lipid rafts is about 3–6 °C higher [7], which means that more heat reaches those nanoparts.

In vitro models

We can show hyperthermia and the additional effects of the OncoTherm treatments on in vitro models. The following main issues are considered:

- Heating up cell lines to 42 °C is possible [70], [71],
- Positive effects of conventional hyperthermia and additional effects of the OncoTherm type of hyperthermia [72],
- Selective focusing on tumour cells without harming healthy cells [73],
- Calibration curve for the temperature vs killing rate of conventional hyperthermia and OncoTherm type of hyperthermia shows a 4-5-fold increase in effectiveness at the same temperature or the same effectiveness at a 3-centigrade lower temperature [74],
- Cell membrane temperature is on average 3-6 °C higher than average temperature [74], [75].

Many laboratories are working in vitro with oncothermia, conducting specialized research on the mechanism of cytotoxicity and probing the limits of its application [76], [77]. Typical temperature curves are linear applying a few watts of power in average. Fig. 26.

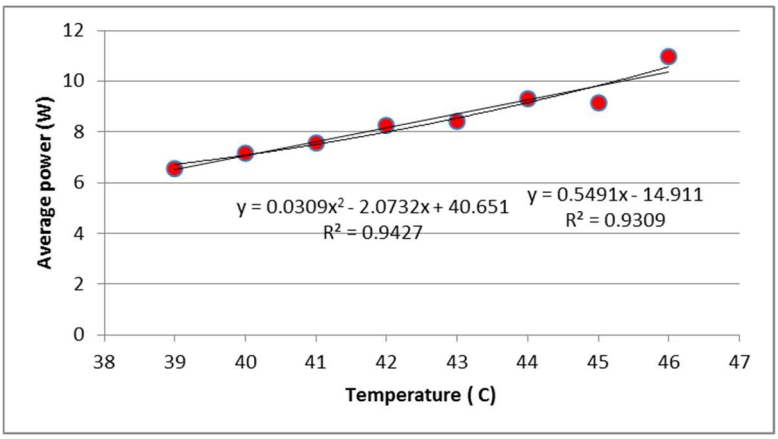


Fig. 26. Typical temperature curves shown for in vitro systems

In the early studies of molecular biology of oncothermia, the in vitro systems showed interesting results for E-cadherin, beta-catenin and other protein changes [29]. The newer results show the targeting specialty of oncothermia in vitro [78], [79]. Fig. 27.

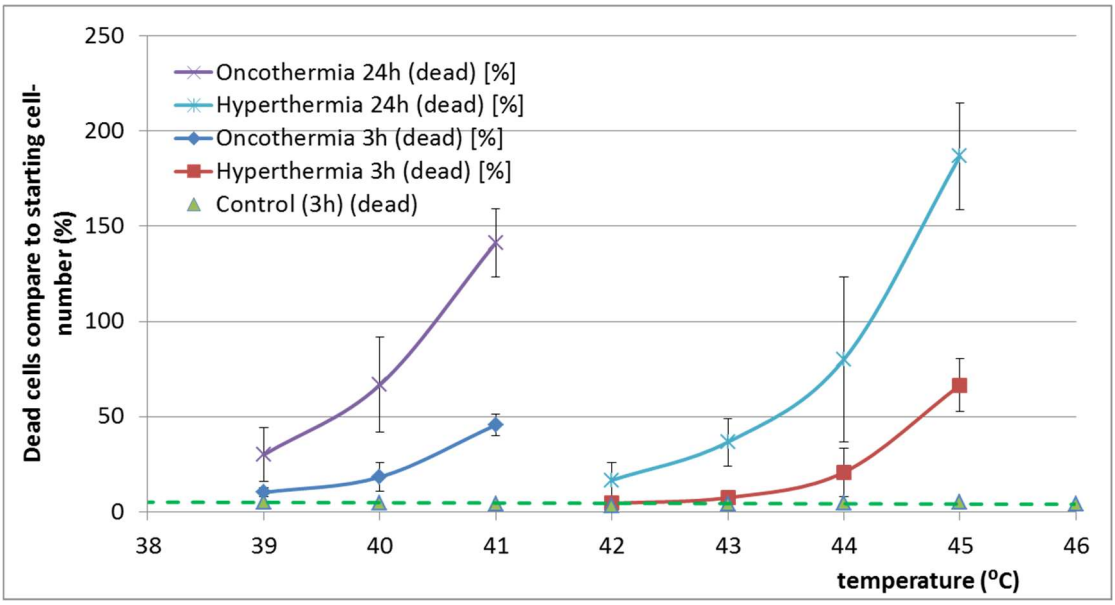


Fig. 27. The thermal effect of oncothermia acts much earlier than that of conventional hyperthermia [78], [79]. The error bars represent standard deviations.

The temperature dependence of cell death (U937, human histiocytic lymphoma cell line) is shown clearly. Conventional hyperthermia can be used to calibrate the temperature. According to this calibration, oncothermia produces a temperature at least 3 ºC higher in nano-targets than in the average electrolyte. This in vitro result corresponds well with the earlier measured in vivo results. Fig. 28.

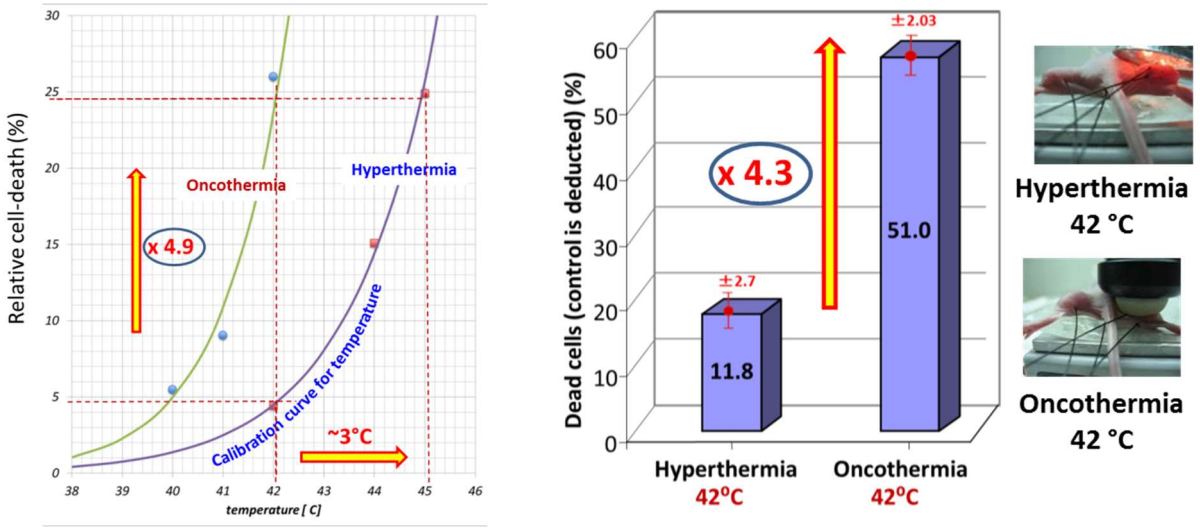


Fig. 28. Experiments show 4.9 and 4.3 times larger cell-distortion at 42°C than its conventional hyperthermia counterpart in vitro and in vivo, respectively

The in vitro and in vivo temperature results show about the same 3 ºC overheating of the nano-range targets compared with the average

This nano-targeting could be measured by the calcium influx by oncothermia. Fig. 29.

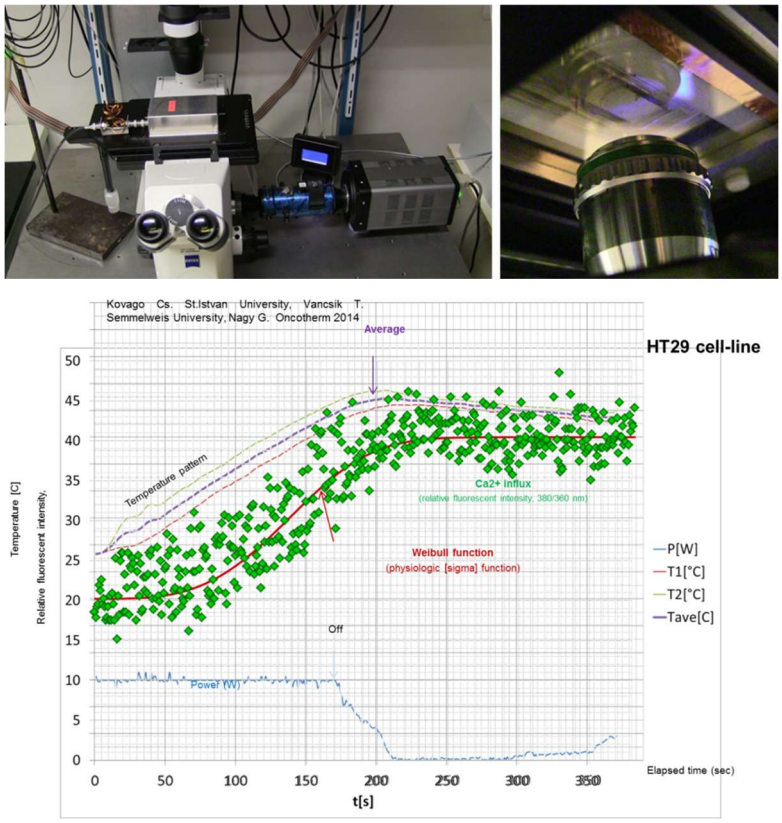


Fig. 29. The calcium influx follows the temperature well and is a good fit to the physiological Weibull curve in vitro in the HT29 cell-line

The change in calcium influx shows well the same shift that was measured in other experiments. Nano-heating is in action. Fig. 30.

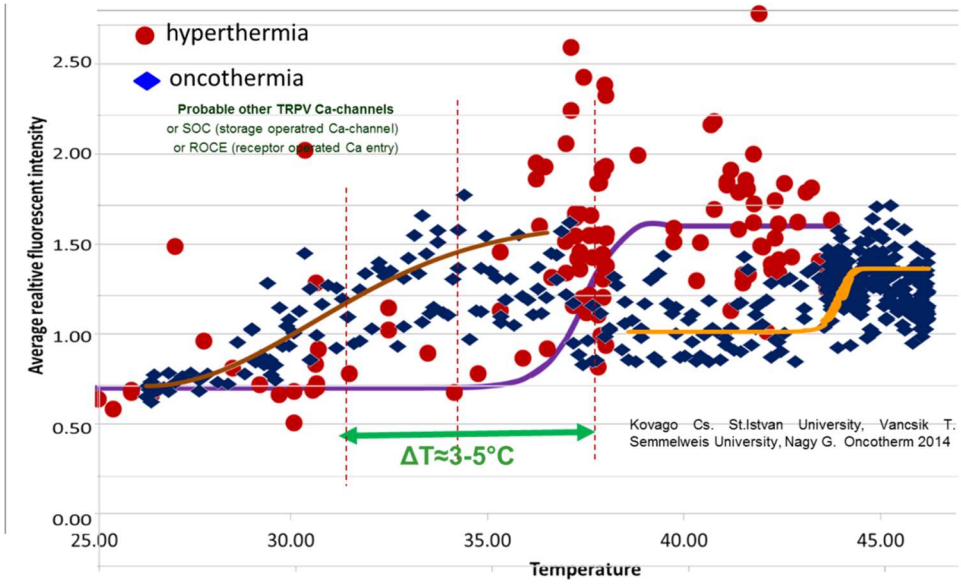


Fig. 30. The calcium influx in the case of the A431 cell line in conventional hyperthermia (♦) and in oncothermia (●) cases

Summarizing the in vitro measurements, the calibration of the cancer killing rate between conventional hyperthermia and the OncoTherm type of hyperthermia gives about the same percentage increase. This correlates with the theory that the temperature in the cell membrane is higher than the average cell temperature. Furthermore, the in vitro measurements provide a fairer assessment, showing biomolecular and immunohistochemical results, which lead us to the immune and abscopal effects in vivo.

In vivo models

- Heating up the target area to 42+ °C [80],
- Heating up the tumour in vivo to 42 °C is possible [81],
- Positive effects of conventional hyperthermia and additional effects of the OncoTherm type of hyperthermia [72],
- Selective focusing on tumour cells without harming healthy cells [82],
- Calibration curve of the temperature-killing rate of conventional hyperthermia and OncoTherm type of hyperthermia shows a 4–5-fold increase in effectiveness at the same temperature or the same effectiveness at a 3 °C lower temperature [71]

Numerous in vivo models were made and published during the era of research on oncothermia from the beginning of its applications [23], [22], [24], [38], [83], [84], [85], [86]. Some typical ones are shown below for nude and SCID mice. Fig. 31.

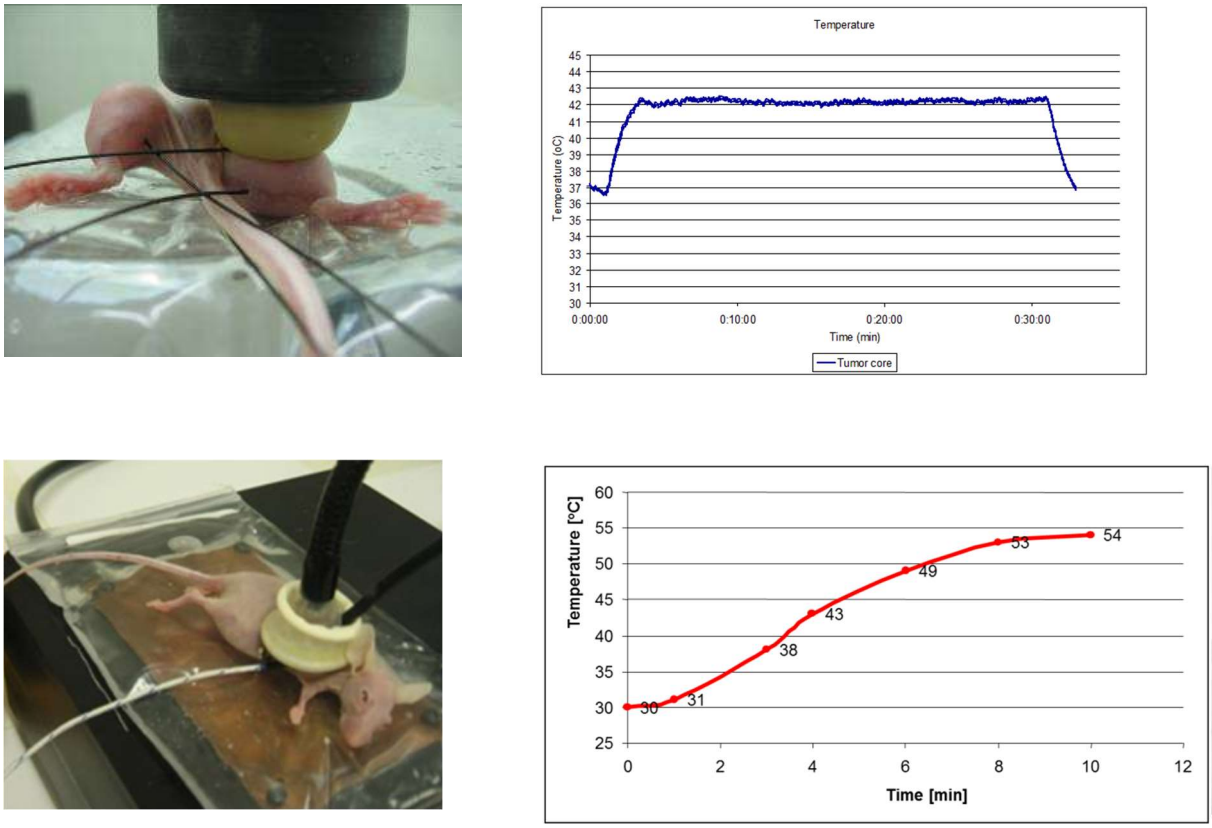


Fig. 31. Typical in vitro heating curve for nude mice allowing the temperature to be kept stable at 42 ºC. Test animal: HT-29 (human colon adenocarcinoma) cell line tumour bearing nude mice (Balb/C Nu/Nu); power: 8 W/6.4 W (SWR:1.5); Energy: 4.8 kJ/3.8 kJ

Experimental study with human medulloblastoma shows also definite temperature increase in the tumour Fig. 32.

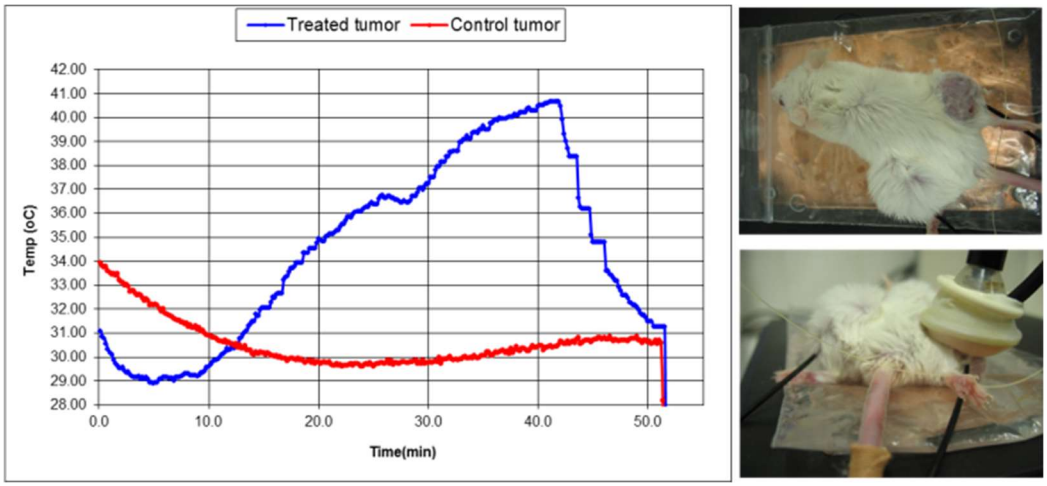


Fig. 32. Experimental animal: SCID mouse with human medulloblastoma tumour; Location of the tumour: femoral region, both sides; Radiopharmaceutical: 99 mTc labelled liposome (experimental product of the OSSKI); Injected dose: 35 MBq/0.1 mL 13 W/5 W (SWR = 2.1); 5 min (3.9 kJ)

The experimental animal model show temperature increase in the liver, Fig. 33.

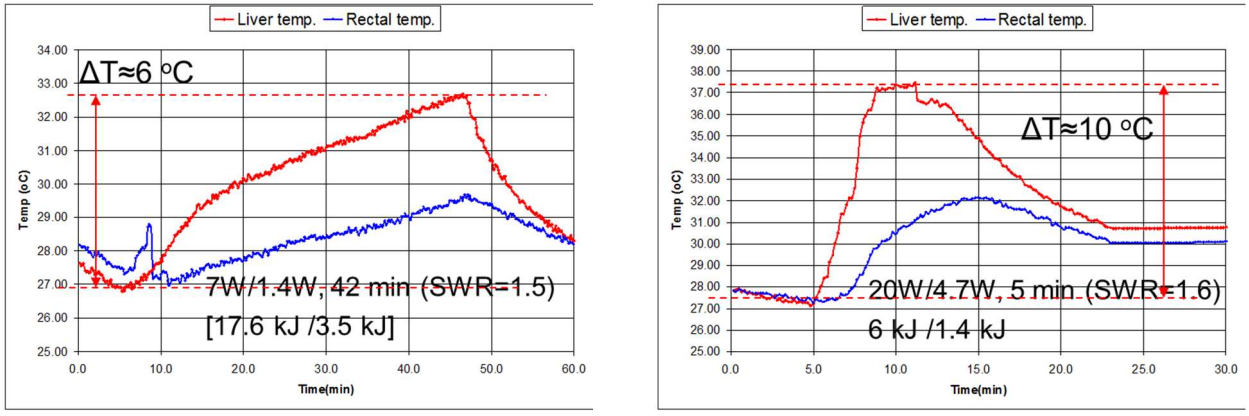


Fig. 33. Liver temperature of the mice. The gain in temperature is obvious.

Different electrodes were also tried for the best treatment performance. The bolus electrode and the flexible one are shown below. Fig. 34.

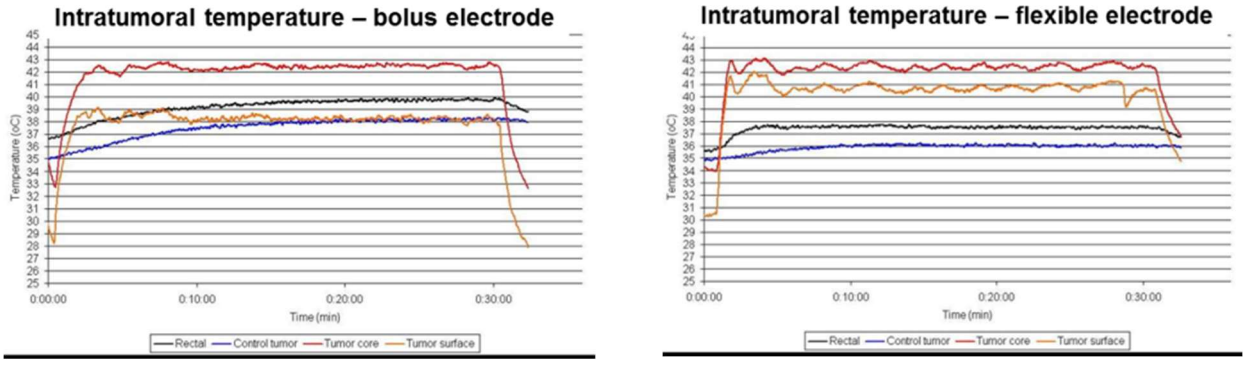


Fig. 34. Electrode comparison. The temperature is well controllable in both cases.

An important study was published [28], in which the macro-temperature was cooled down while the micro-heating (selective targeting) was active. In this way, oncothermia showed its superior efficacy under low macro-temperature conditions. Fig. 35.

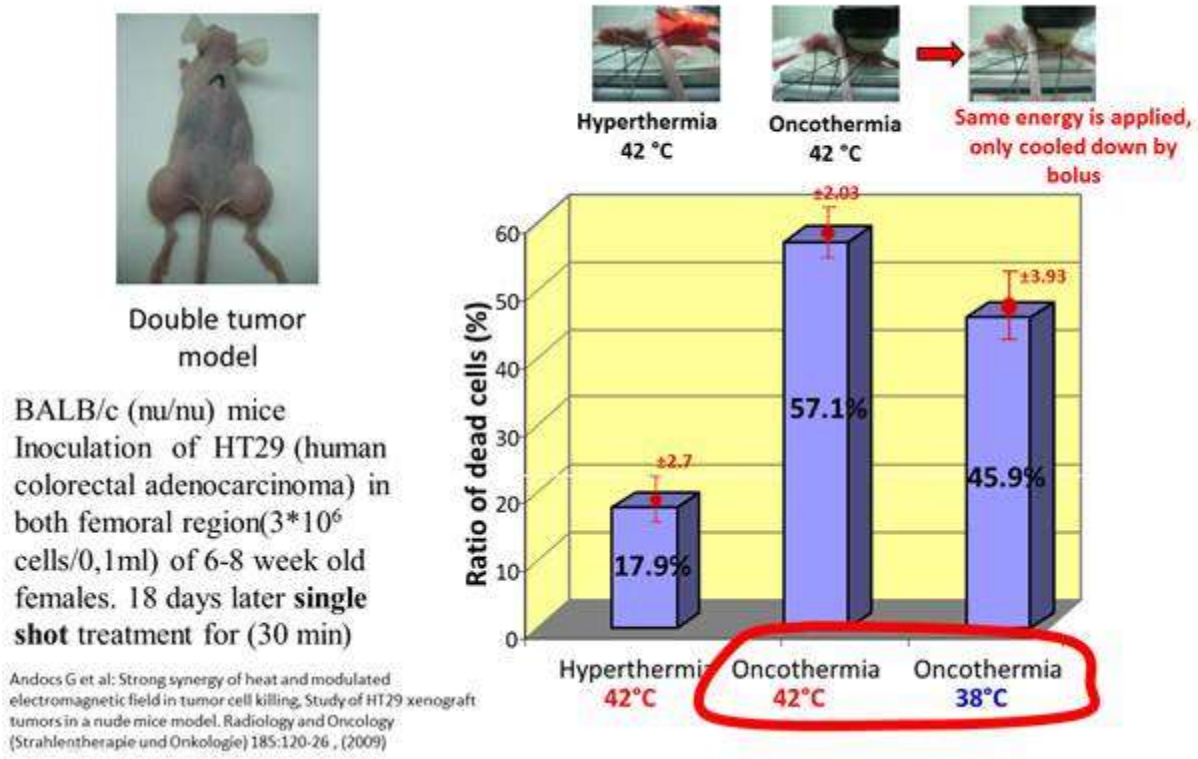


Fig. 35. Macro cooling only slightly affects cytotoxicity when micro-targeting is held constant.

This nano-technology uses natural (instead of artificial) nanoparticles on the membrane. The membrane effects have been shown in numerous molecular biology investigations over time [22], [23], [36], [38], [83], [84]. The effects on the membrane were measured with ultramodern immunohistochemistry and widely published: Fig. 36.

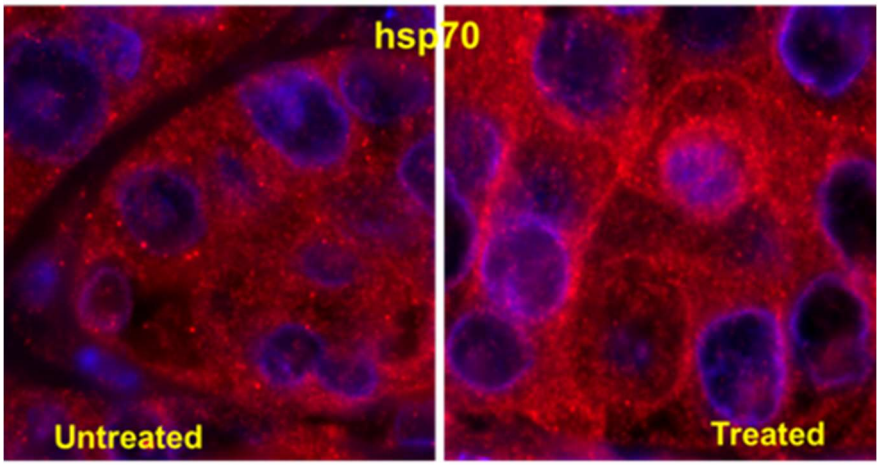


Fig. 36. HSP70 membrane expression [83]

An intensive membrane excitation special apoptotic process is induced, causing a massive "natural" programmed cell death. Fig. 37.

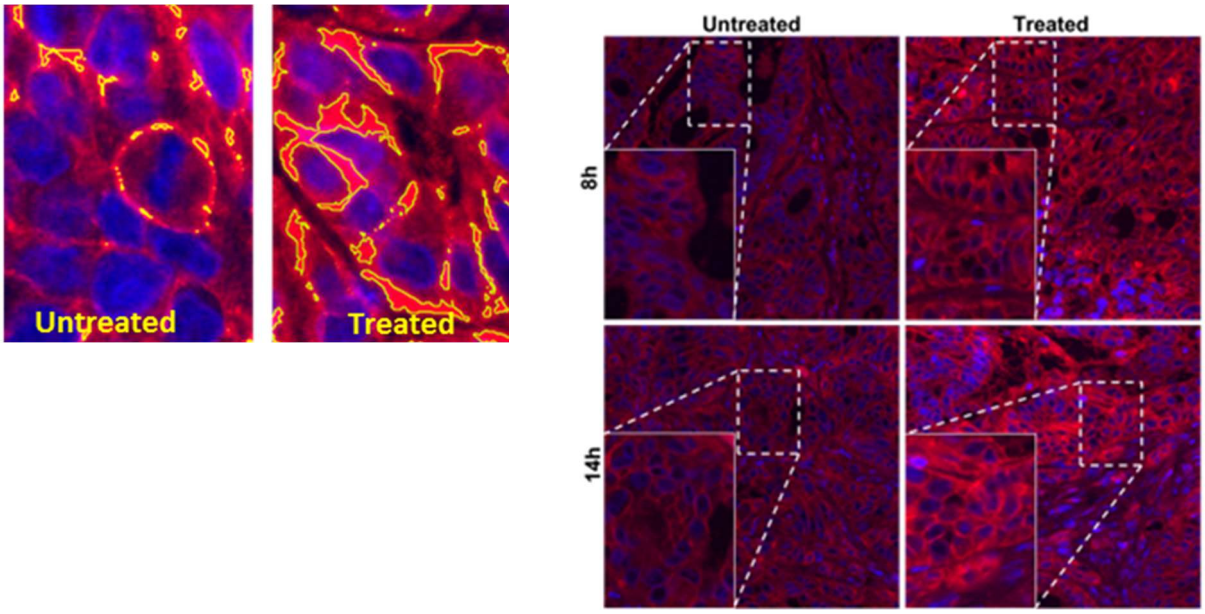


Fig. 37. TRAIL R2 (DR5) death receptor membrane expression [83]

The mitochondrial membrane pore forming and release of cytochrome C (the point of no return to apoptosis) is measured in the treated mice, Fig. 38.

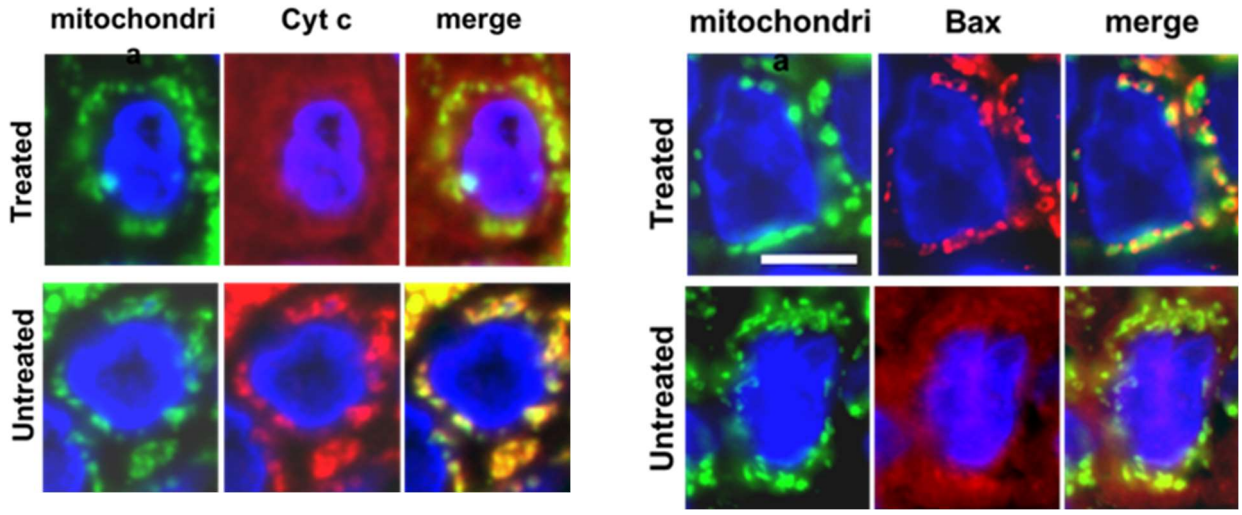


Fig. 38. Bax and Cytochrome C expression on the mitochondrial membrane

The upregulation of calreticulin was typical in the experiments, Fig. 39.

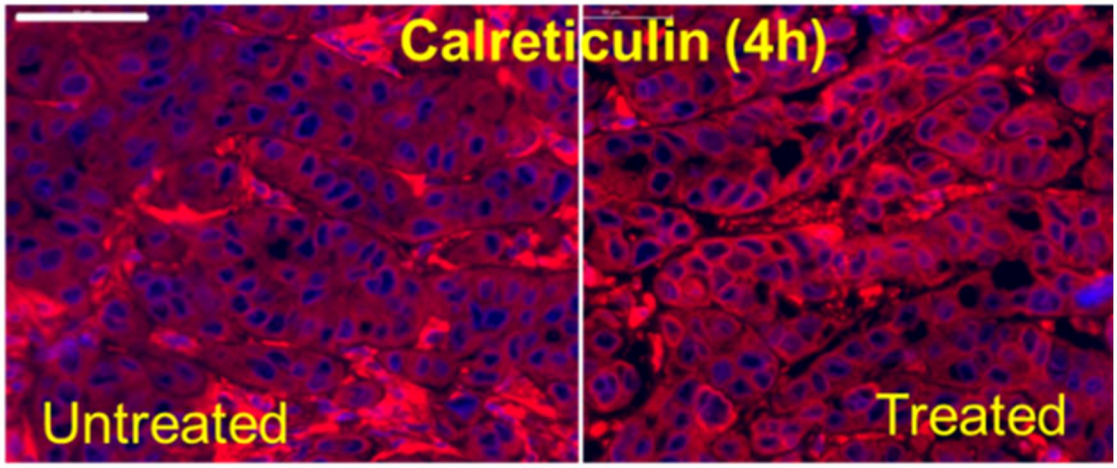


Fig. 39. Calreticulin upregulation at the membrane [83]

Furthermore, many membrane-associated proteins were measured by immunohistochemistry (like FADD, FAS), reporting the energy excitation on the selected membranes.

Because of the massive production of apoptotic bodies, a damage- associated molecular pattern (DAMP) forms, and possible immunogenic cell death ensues. The special molecular interactions allow a bystander effect and possible abscopal effect and probably could lead us to "tumour vaccination" by oncothermia. [89]. These are important for the natural approach to treatment.

Summarizing the in vivo experimental models (immunocompetent and immune-deficient murine models), we used inoculated tumours and metastases in animals. The veterinary cases showed the same effects on naturally developed tumours in animal (preclinical) measurements. Furthermore, the deep penetration and the temperature development are also shown clearly in the animal models.

Veterinary applications

The veterinary applications are real preclinical works, containing naturally developed solid tumours instead of the artificially injected ones in small laboratory animal models (mainly murine models). The results of veterinary cases (treatments are performed in veterinary clinics in Hungary and in Japan), have been presented at various conferences worldwide.

- Published results show the possibility of heating up larger animals (pigs) with 100-150 W in the targeted area [81], [87],
- Cases showing special effects on various tumours, spectacularly improving the quality of life (QoL) of companion animals [87]

Extended preclinical (veterinary) studies were conducted for oncothermia approval, [88], [89], [90], where the temperature was measured in vivo for preclinical use. The first measurements were performed on healthy beagle research animals. Fig. 40.

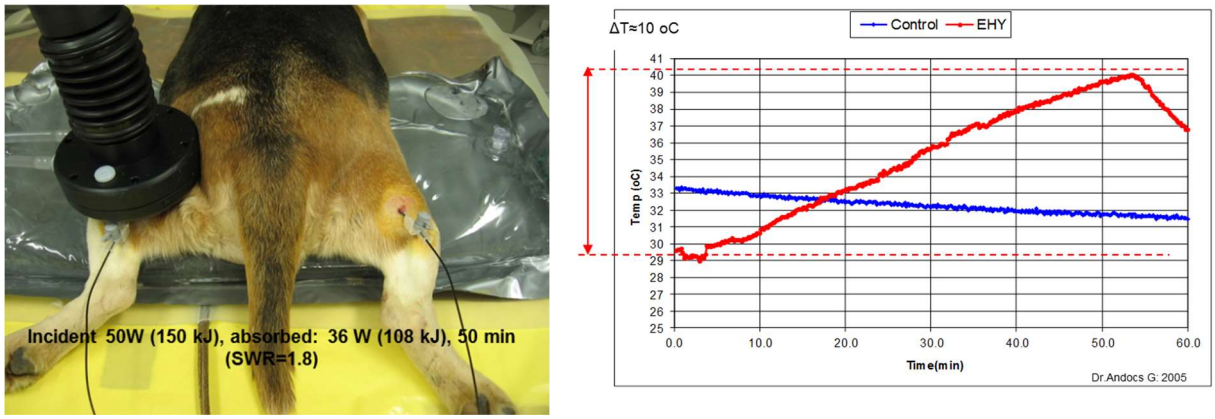


Fig. 40. A beagle dog shows a 10 ºC temperature increase by oncothermia (50 W, 50 min)

The flexible electrodes were well applicable on the curvatures of the animal forms, Fig. 41.

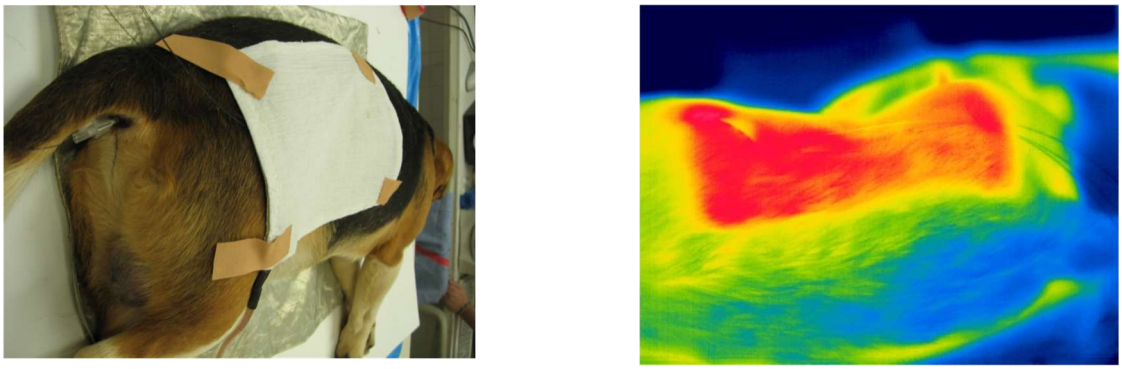


Fig. 41. The thermo-camera spot shows well the definite heating possibility. The electrode was rectangular to show that its shape conforms with the heating.

Later, real tumorous dog patients were measured. Treatment of a 10-year-old male dog with very aggressive proliferative, possible metastases in the regional lymph nodes and fibrosarcoma in the mandibula (left side) was performed [90]. The case is a relapse after surgery and gamma irradiation, Fig. 42.

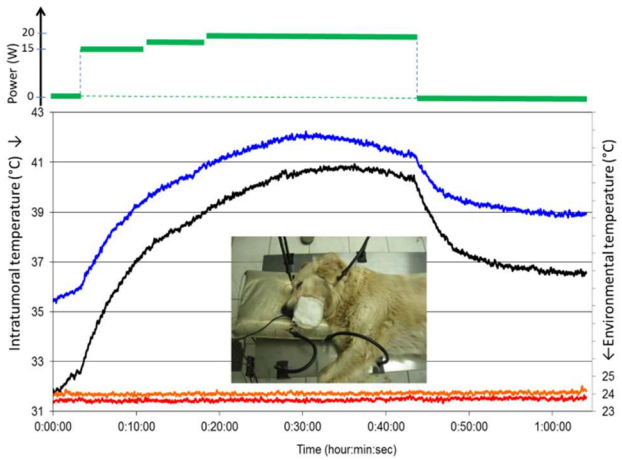


Fig. 42. The temperature rises to 41–42 ºC in the tumour when up to 20 W of power is applied. The treatment had a duration of 45 min.

A 12-year-old old bull terrier shows more than 42 ºC in its tumour [91]. Fig. 43.

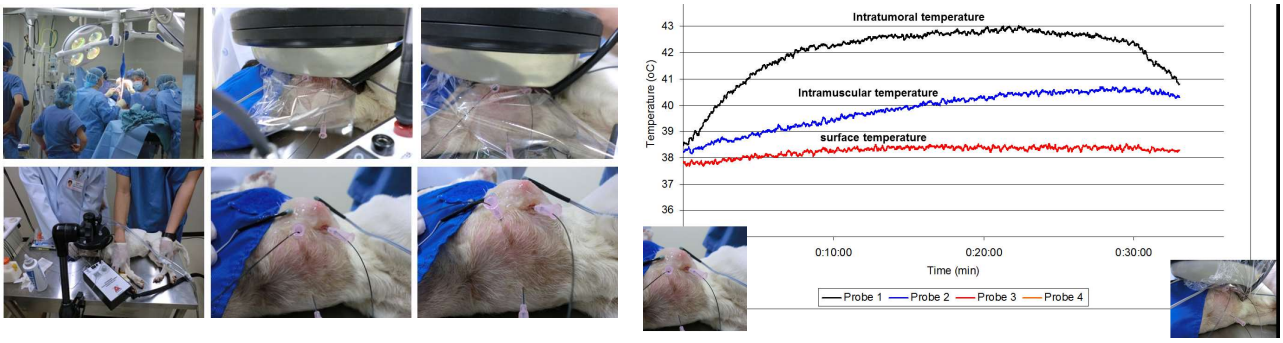


Fig. 43. The intratumoral sensor shows a high temperature in the tumour

Special, high precision temperature measurement was performed recently in the livers of healthy pigs [92]. Fig. 44.

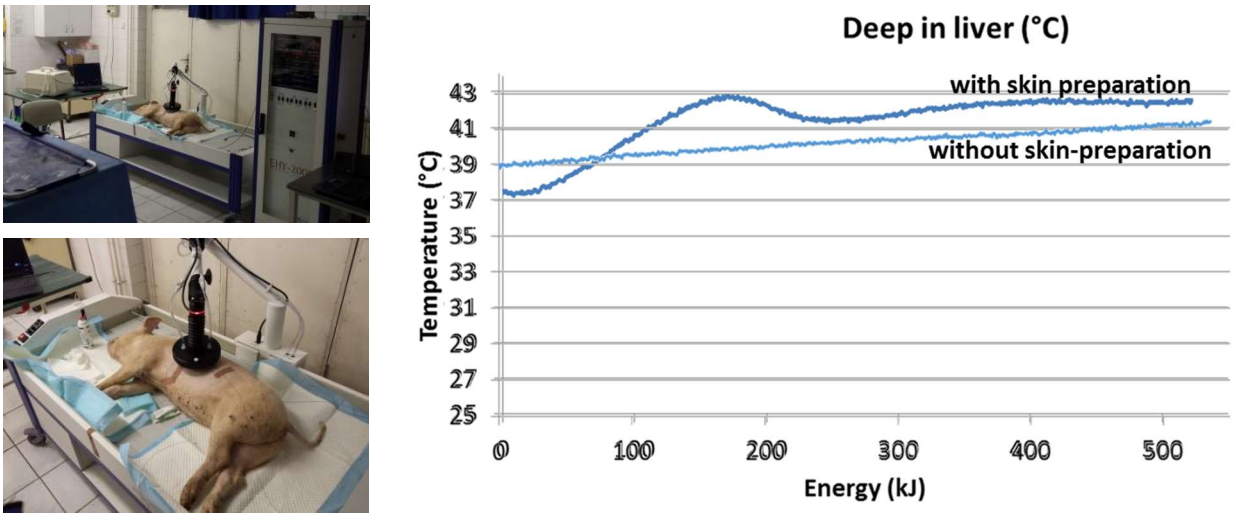


Fig. 44. 150 W, 60 min. (the power was one time down-regulated when the surface was over 41°C) [92]

The veterinary (companion animals and livestock) studies show well the large-body heating facility and the well-functioning bolus system, and the results demonstrate well the animals' increased QoL. These results are intensively used in human studies.

Human clinical studies

- Case studies show that temperatures of 42 °C can be reached deep inside the body, even at lower power [73], [93].
- Side effects are very low with the OncoTherm type of hyperthermia [94], [95], [96].
- The OncoTherm type of hyperthermia can increase survival time and QoL in conjunction with standard therapies [97], [98].
- Even temperature-sensitive parts such as the brain can be treated with the OncoTherm type of hyperthermia [99], [100], [101], [102].

- Clinical efficacy is proven high [103], [104], [105], [106], [107], [108], [109], [110], [111], [112], [113], [114], [115], [116], [117], [118], [119], [120], [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132], [133], [134], [135], [136].

Clinically, it has been shown that the temperature increases in the complete tumour and that blood-flow increase is important for promoting drug delivery to the target. An important prospective double-arm study was conducted with Nefopam in healthy volunteers [137]. (Note: the blood-flow increase and the temperature were directly measured in cervical cancer, presented in the annual conference of Society of thermal medicine, [138].)

Oncothermia treatment is simple and easy to use. Fig. 45.

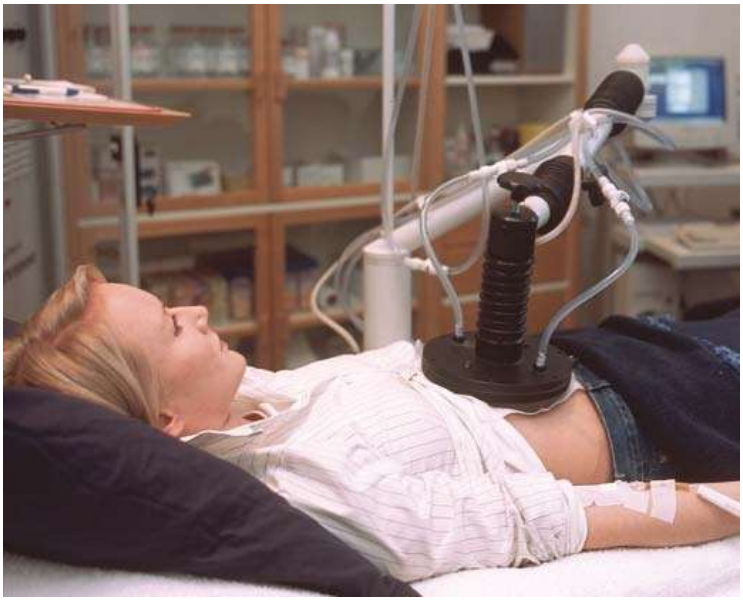


Fig. 45. Oncothermia treatment in clinical conditions

The first and most spectacular indication of the temperature is the thermocamera measurement. Fig. 46.

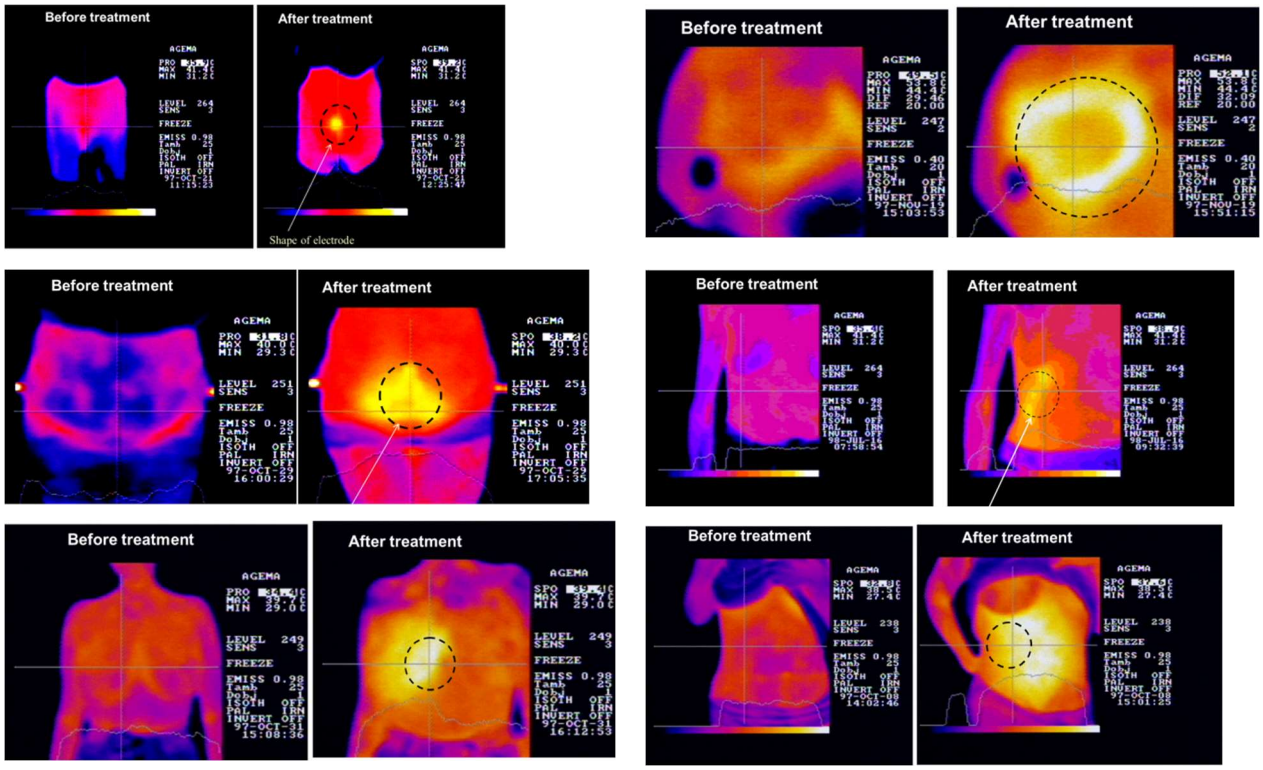


Fig. 46. Various patients before and after oncothermia measured with precise thermos-camera AGEMA-Pro

Temperature measurement of lymph node metastasis of the left side of the neck of a 50-year-old male patient (139). The primary tumour is carcinoma unknown primary (CUP). Squamous cell carcinoma G3 was slightly differentiated. Complex therapy was applied, consisting of trimodal, curative radio-chemo-thermo treatment. Intratumoral in situ temperature measurement (Luxtron fluoro-optical system) applied step-up heating from 50 to 80 W. Low power was used for chemo-induction, inducing mild hyperthermia, a 1.6 °C increase in temperature Fig. 47.

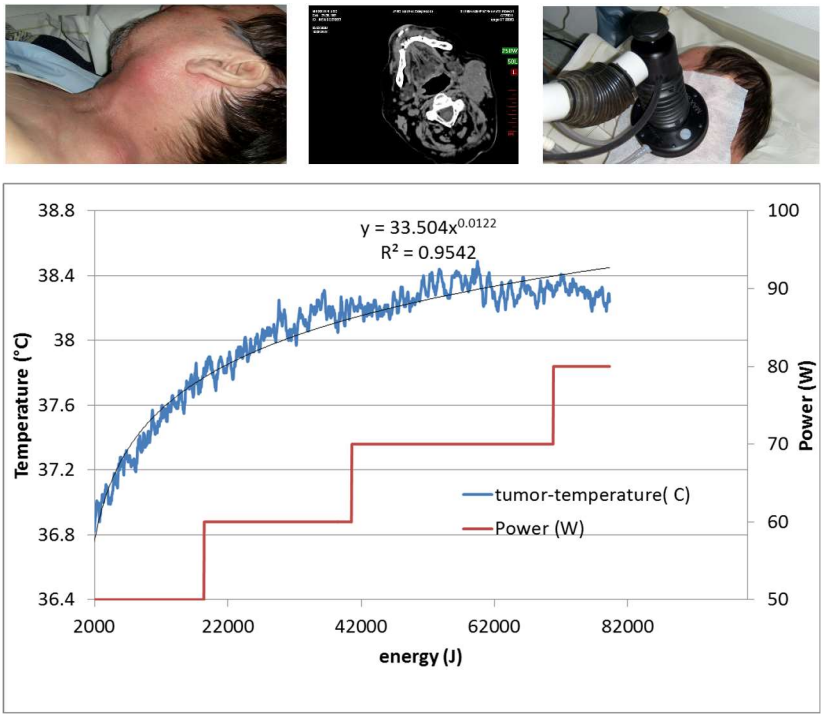


Fig. 47. Temperature development in lymph node metastasis. Low energy was used, causing mild hyperthermia.

Another male patient (87-year-old), with malignant fibrotic histiocytoma G3, was treated with curative radio-thermo therapy (double modality), and oncothermia was used to measure intratumoral temperature in situ [31], which was greater than 43 ºC in the tumour. Fig. 48.

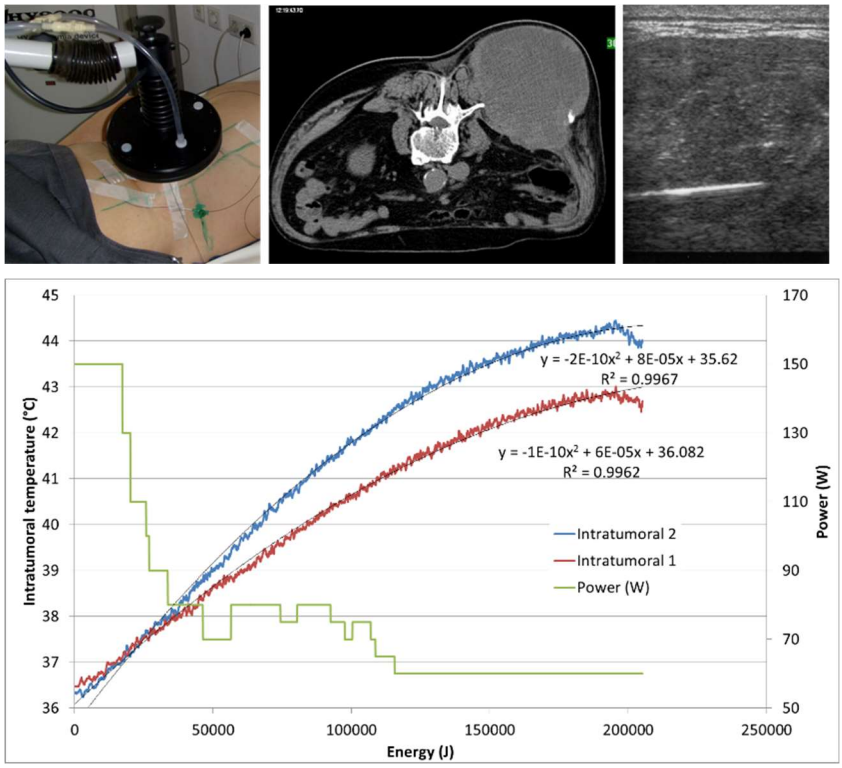


Fig. 48. Sarcoma lesion, huge tumour. The temperature could be raised high enough (>42 ºC), even by low energy application (<100 W on average).

Treatment of ovary was also registered [140]. Fig. 49.

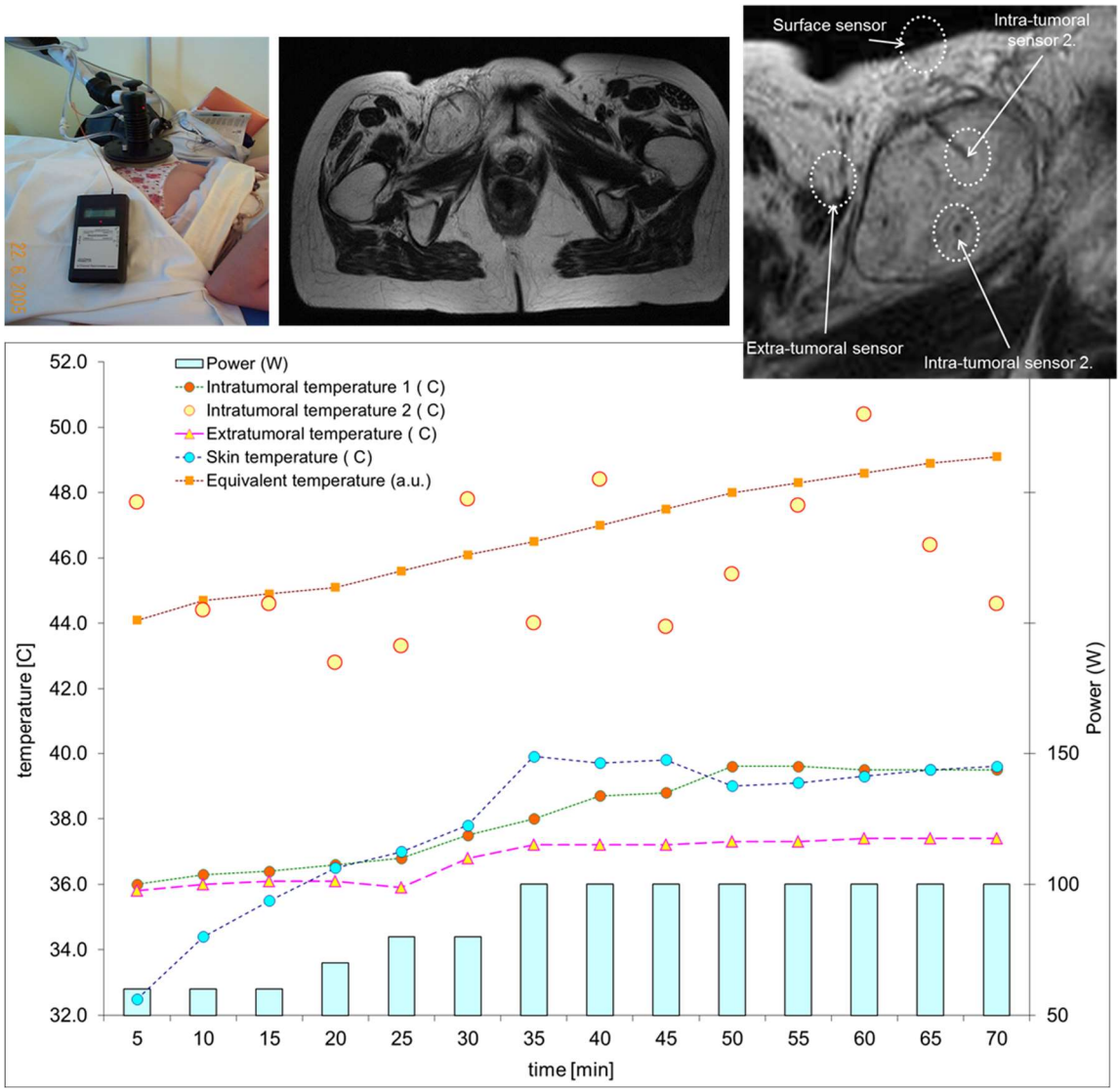


Fig. 49. Treatment of ovary. The maximal power was 100 W, while the temperature was measured very heterogeneously. One part of the tumour was heated extremely (probably it had necrotic volume where the sensor was inserted), whereas the other part had mild hyperthermia over 39 ºC.

Temperature measurement in the abdomen (12 cm in depth) was also measured by interventional radiology positioning [140]. The measured temperature was over 41 ºC, with maximal power of 140 W. Fig. 50.

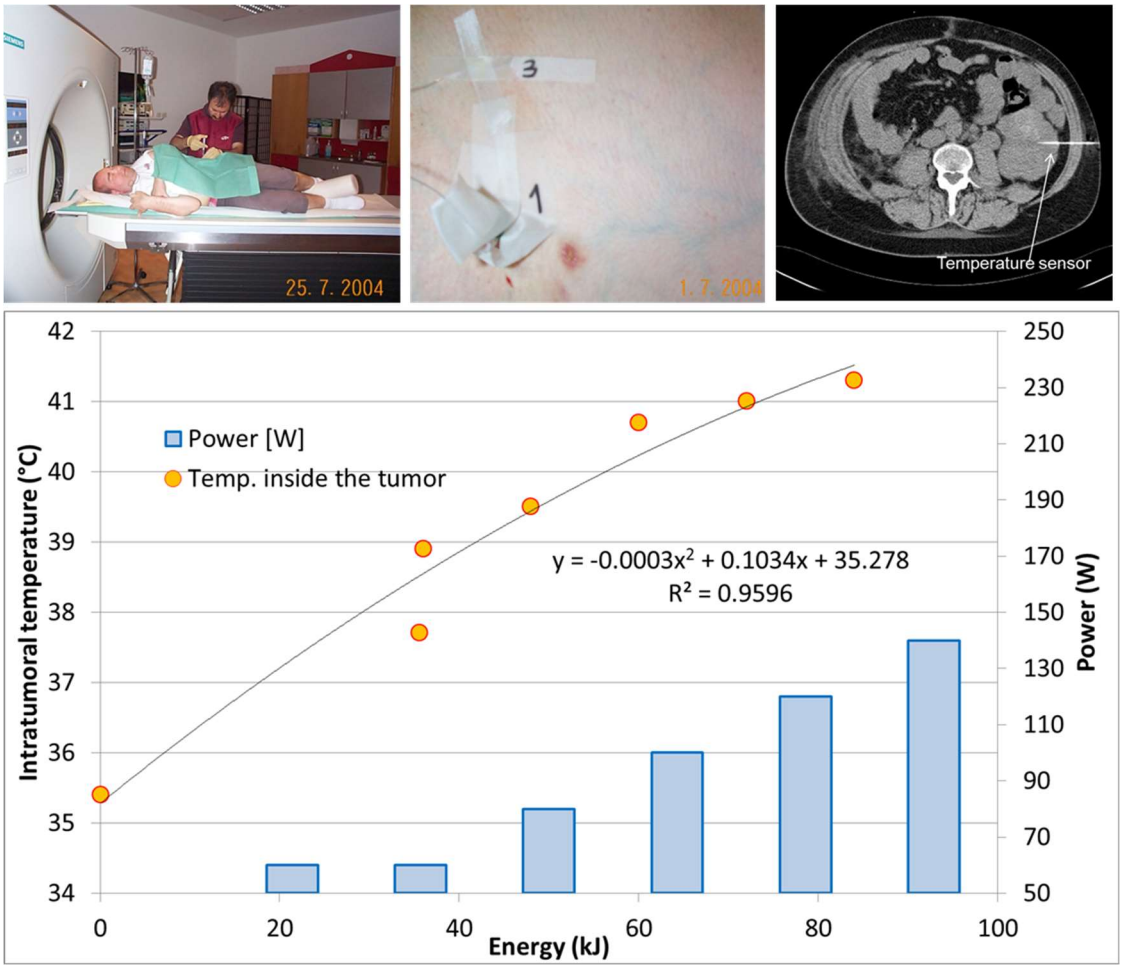


Fig. 50. Abdominal temperature measurement

Temperature measurement of mammary carcinoma shows elevation of the temperature by 140 W over 41 ºC (140). Fig. 51.

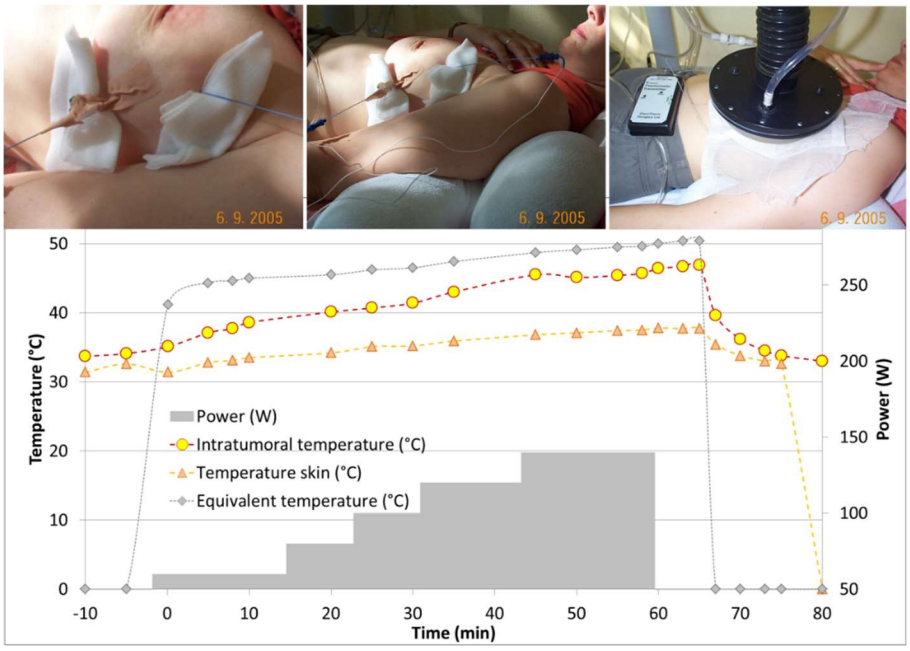


Fig. 51. The temperature of mammary carcinoma closely follows the equivalent temperature, due to the fatty tissue dominance in the breast.

Abdominal treatment with two intratumoral sensors shows high temperature at 150 W end power [140]. Fig. 52.

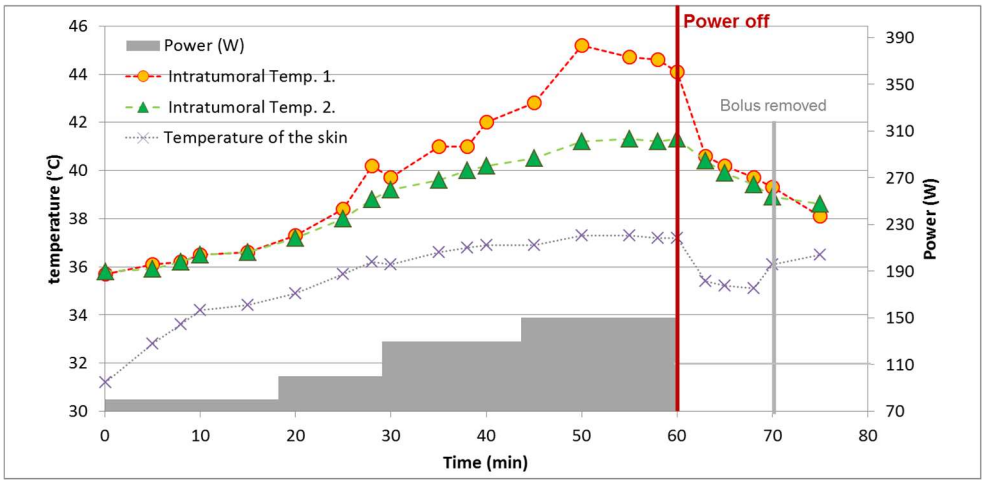


Fig. 52. Intratumoral sensors in cancer of abdomen location.

Oncothermia treatment of the abdomen also shows increase of the temperature, Fig. 53.

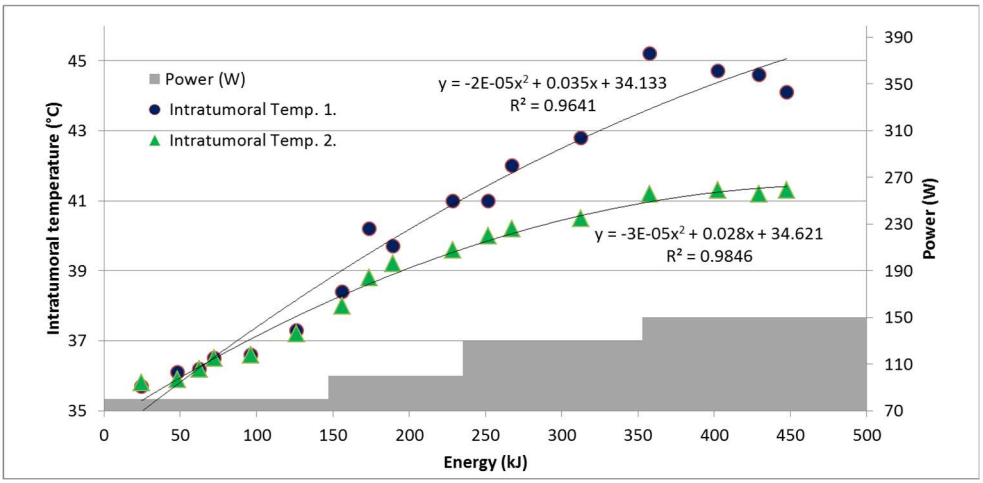


Fig. 53. Time dependence and energy dependence of the temperature development in abdominal treatment

Invasive temperature measurement in the cervix uteri shows high temperature with low power supply due to the low blood perfusion into the area [141]. Fig. 54.

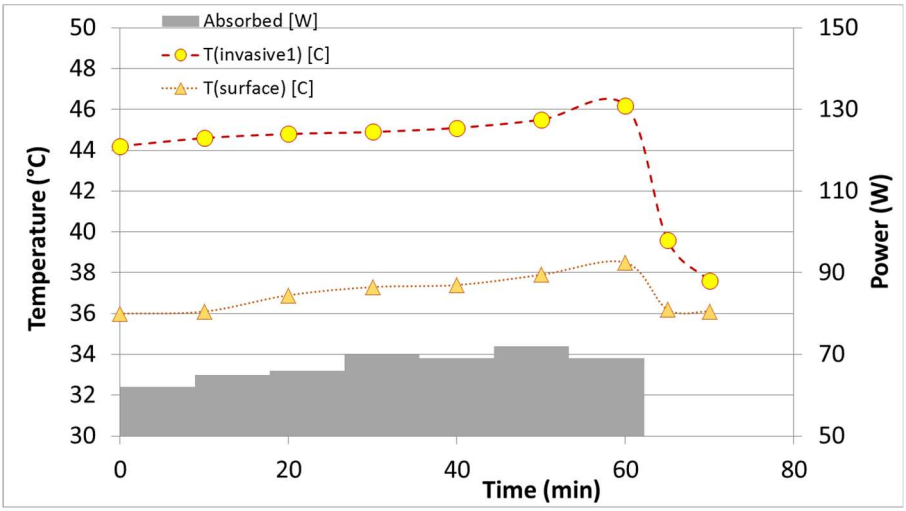


Fig. 54. Cervix temperature is shown high, while the surface temperature increases moderately

Several effects could be shown at all research levels. These consist of the basics of hyperthermia (heating) and those of the Hippocratic oath (nil nocere – do no harm). Every research level interacts with others, and their feedback and learning are effectively used under various conditions in complex oncothermia research.

This nano-targeting makes personalized, precise and controlled clinical treatments possible. The clinical success well proves the special character of this method, [142], [26], [143], [144], [145], [146], [147], [148], [149], [150], [151], [152], [153], [154], [155], [156].

Discussion

Heating

One of the basic principles of hyperthermia is that the tumour can be heated up, depending on the definition, either to normal body temperature or to another specific temperature. A temperature increase to 42 °C can be demonstrated in in silico, in vitro and in vivo models, as well as it was proven in both animal and human measurements.

OncoTherm devices are capable of heating up even larger, deep-seated tumours inside the body using the "low" power of capacitive coupled RF power.

Side effects (toxicity)

To date, the only known side effects discovered in any model when treatment protocols have been followed are first-degree burns (skin-redness, <8% of cases) and second-degree burns (blisters, <3% of cases).

Focusing

In silico and in vitro models of oncothermia have shown 100% tumour-cell specificity. At higher levels, proving the theory is more difficult, but no contradictory results have been obtained. However, we should consider that the OncoTherm type of hyperthermia can be applied to brain tumours, for which conventional hyperthermia is contraindicated. This is because heating normal cells and tissues

will generate a protective mechanism in the brain, which causes oedema. However, this type of reaction was not found with the OncoTherm type of hyperthermia.

Special patients: Non-heatable patients

In conventional hyperthermia, the "non-heatable" patient group consists of patients in whom the tumour (average) temperature cannot be heated up to more than 40–41 °C. By using the OncoTherm method (part of) this group can still be considered heatable, as the cell membrane temperature can be 3–6 °C higher than that of the cell or its surroundings. This means having a temperature of 36–39 °C, as an average temperature could already generate a temperature of 42 °C in the cell membrane, producing a hyperthermic effect (effectivity), as in conventional hyperthermia.

Future

For the immunological effects, the immune system must be prepared for the fight against cancer; the adaptive immune system must make preventive steps to demolish the tumour. This immune-effect is only possible if the immune system is not heated above 40 °C, otherwise the therapy is not only against the tumour cells but against the immune cells, too [157], [158]. Due to this it could be a big question to check the best temperature for the treatment (like by whole body hyperthermia now we known that the moderate (38-40 °C range) is better than the extreme (42-43 °C) one). Oncothermia is a mild-hyperthermia in the tumour tissue but extremely large in cancer-cells at cellular locations [159], [160].

These facts are extremely important in integrative medicine, where the immune effects are crucial. For this reason, the results of [161] were particularly encouraging. They used immune stimulators and achieved long survival times. We applied the TCM immune-stimulator (Xiao-Aiping) in laboratory animals (murine model) and obtained a fantastic abscopal effect, supporting the earlier clinical results of Gurdev et al.

Conclusion

Temperature development by the oncothermia method is shown in all research and study lines: in silico, in vitro, in vivo, preclinical (animal) and human studies. The temperature corresponds to mild hyperthermia (increasing the local target volume) temperature by more than 3 ºC, while nano-heating of membrane rafts produces local extremes of additional 3 ºC increases over the target volume average.

Oncothermia has definite clinical advantages:

- High efficacy and safety issues. Efficacy is increased by apoptosis induced by selective heating. We observed that these natural nanoparticles are transmembrane proteins, containing the most important signalling networks for apoptosis.
- We have shown that apoptosis exists and constitutes a special kind of cell death: immunogenic cell death. (These are published in high impact factor, peer-reviewed Journals [162], [163].) This induces the immune effects and causes an abscopal effect in the body. Clinically, this results in a higher QoL of the patient.
- The selected tumour cells need much less energy to heat up than the complete cancer tissue. Consequently, oncothermia needs less incident power than other conventional hyperthermia devices, which makes surface burns rare.

- Furthermore, due to the low incident power, there is a low risk of burn, despite of the moderate cooling of the skin. Due to the low cooling loss, the incident power is mainly absorbed in the target and makes setting the dose of the process according to incident energy instead of the temperature rise possible.

Acknowledgements

Authors are greatly thankful to the researchers who produced the results connected to temperature development throughout the long history of oncothermia possible. We especially thank Dr. Gabor Andocs, Dr. Lajos Balogh, Dr. Georg Brunner, Dr. Friedrich Douwes, Prof. Alexander Herzog, Prof. Harm H. Kampinga, Ms. Eva Kiss, Dr. Csaba Kovago, Dr. Tibor Krenacs, Dr. Nora Meggyeshazi, Mr. Gabor Nagy, Ms. Edina Papp, Prof. Helmut Renner, Dr. Huseyin Sahinbas and Mr. Tamas Vancsik and Dr. Gurdev Parmar. Authors are grateful for the continuous technical support of Oncotherm Kft.

This research was supported by the Hungarian National Research Development and Innovation Office KFI grant: 2019-1.1.1-PIACI-KFI-2019-00011.

References

[1] Oncology Encyclopedia (2008) http://www.answers.com/topic/hyperthermia
[2] Medical dictionary (2008) http://www.medterms.com/script/main/art.asp?articlekey=3848
[3] http://www.cancer.gov/about-cancer/treatment/types/surgery/hyperthermia-fact-sheet
[4] https://en.wikipedia.org/wiki/Hyperthermia_therapy
[5] http://www.cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/hyperthermia
[6] http://medical-dictionary.thefreedictionary.com/hyperthermia
[7] Andocs G, Rehman MU, Zhao Q-L, et. al. (2016) Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells, Cell Death Discovery, 2, 16039; doi: 10.1038/cddiscovery.2016.39
[8] Deshpande PP, Biswas S, Torchilin VP (2013) Current Trends in the Use of Liposomes for Tumor Targeting. http://www.medscape.com/viewarticle/810685
[9] Steichen SD, Caldorera-Moore M, Peppas NA (2013) A review of current nanoparticle and targeting moieties for the delivery of cancer therapeutics. European Journal of Pharmaceutical Sciences 48:416-427
[10] Maggiorella L, Barouch G, Devaux C, Pottier A, Deutsch E, Bourhis J, Borghi E, Levy L (2012) Nanoscale radiotherapy with hafnium oxide nanoparticles. Future Oncol 8(9):1167-81
[11] Fleck R, Bach D (2012) Trends in Personalized Therapies in Oncology: The (Venture) Capitalist's Perspective. J Pers Med 2(1):15-34.
[12] West JB. (2006) Where medicine went wrong. World Scientific
[13] Rosenberg SM, Queitsch C (2014) Combating evolution to fight disease. Science 343:6175. 1088-1089
[14] Chen DS, Mellmann I (2013) Oncology meets Immunology. Immunity 39:1-10
[15] Perche F, Torchilin VP (2013) Recent Trends in Multifunctional Liposomal Nanocarriers for Enhanced Tumor Targeting. Journal of Drug Delivery 2013, Article ID 705265, 32 pages
[16] Ota S, Yamazaki N, Tomitaka A, Yamada T, Takemura Y (2014) Hyperthermia using antibody-conjugated magnetic nanoparticles and its enhanced effect with cryptotanshinone. Nanomaterials 4:319-330. doi:10.3390/nano4020319
[17] Vincze Gy, Szigeti Gy, Andocs G, Szasz A. (2015) Nanoheating without Artificial Nanoparticles, Biology and Medicine 7(4):249
[18] JJ Skitzki, Repasky EA, Evans SS (2009) Hyperthermia as an immunotherapy strategy for cancer. Curr Opin Investig Drugs 10(6):550-558
[19] Szasz O, Andocs G, Meggyeshazi N (2013) Oncothermia as personalized treatment option. Hindawi Publishing Corporation, Conference Papers in Medicine 2013, Article ID 941364, 6 pages,

http://dx.doi.org/10.1155/2013/941364
[20] Szasz A (2013) Electromagnetic effects in nanoscale range, In book: Cellular Response to Physical Stress and Therapeutic Application, Shimizu T, Kondo T (eds) Nova Science Publishers, Inc.
[21] Szasz O, Szasz A. (2014) Oncothermia – Nano-heating paradigm. J Cancer Sci Ther 6(4):117-121
[22] Meggyeshazi N, Andocs G, Balogh L, et al. (2014) DNA fragmentation and caspase-independent programmed cell death by modulated electrohyperthermia. Strahlenther Onkol 190:815-822
[23] Andocs G, Meggyeshazi N, Balogh L, et al. (2015) Up-regulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modulated electrohyperthermia. Cell Stress Chaper 20(1):37-46
[24] Qin W, Akutsu Y, Andocs G, Suganami A, Hu X, Yusup G. et al. (2014) Modulated electro-hyperthermia enhances dendritic cell therapy through an abscopal effect in mice. Oncol Rep 32(6):2373-2379.
[25] Szasz A (2013) Challenges and solutions in oncological hyperthermia. Thermal Med 29(1):1-23
[26] Jeung TS, Ma SY, Lim S, Szasz A. Cases that resond to onctohermia monotherapy. Hindawi Publishing Corporation, Conference Papers in Medicine. Vol. 2013, Article ID 392480
[27] Szasz A, Vincze Gy, Szasz O, et al. (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology 22:103-15
[28] Andocs G, Renner H, Balogh L, et al. (2009) Strong synergy of heat and modulated electromagnetic field in tumor cell killing. Strahlenther Onkol 185(2):120-126
[29] Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagnetic Biology and Medicine 28:148-165
[30] Szasz A, Szasz N, Szasz O (2013) Local hyperthermia in oncology, In book: Hyperthermia, Huilgol N (ed), InTech
[31] Szasz A, Szasz N, Szasz O (2010) Oncothermia: Principles and Practices, Springer
[32] Hegyi G, Vincze Gy, Szasz A. (2012) On the dynamic equilibrium in homeostasis. Open Journal of Biophysics 2:64-71. http://dx.doi.org/104236/ojbiphy.2012.23009
[33] West BJ. (2013) Fractal Physiology and Chaos in Medicine. World Scientific-könyv b
[34] Baronzio GF, Hager ED (eds) (2006) Hyperthermia in Cancer Treatment: A Primer. Springer Verlag, Landes Bioscience
[35] Szasz A (2014) Bioelectromagnetic paradigm of cancer treatment – oncothermia, In book: Bioelectromagnetic and Subtle Energy Medicine, Rosch PJ (ed.), CRC Press, Taylor and Francis Group, pp. 323-336
[36] Hegyi G, Szigeti GyP, Szasz A (2013) Hyperthermia versus oncothermia: Cellular effects in cancer therapy, Conference Papers in Medicine, Vol. 2013, Article ID 672873, http://www.hindawi.com/journals/ecam/2013/672873/, Hindawi
[37] Szasz O, Andocs G, Szasz A (2011) Effects far from equilibrium in electromagnetic heating of tissues. Oncothermia Journal 3:61-61, http://www.oncothermia-journal.com/journal/2011/Effects_far_from_equilibrium_in_electromagnetic_heating_of_tissues.pdf
[38] Andocs G, Galfi P, Renner H, Balogh L, Fonyad L, Jakab Cs, Szasz A (2009) Thermally induced but temperature independent cell-destruction by modulated electrohypertmeia (oncothermia) in nude-mice xenograft model. Society for Thermal Medicine 2009: Expanding the Frontiers of Thermal Biology, Medicine and Physics. Tucson, USA, 2009.04.03-2009.04.07. pp. 49-49. Paper O511, http://www.oncotherm.com/web/cus/%2847%29%20Thermally%20induced%20but%20temperature%202009.pdf
[39] Szasz O (2011) Temperature measurements during oncothermia (collection of temperature measurements in loco regional hyperthermia). Oncothermia Journal 4:62-86, http://www.oncothermia-journal.com/journal/2011/Temperature_measurements_during_oncothermia.pdf
[40] Szasz O (2011) The role and measurement of temperature in oncothermia. Oncothermia Journal 4:13-14, http://www.oncothermia-journal.com/journal/2011/The_role_and_mesurement_of_temperature_in_oncothermia.pdf
[41] Veatch SL, Cicuta P, Sengupta P, Honerkamp-Smith A, Holowka D, Baird B (2008) Critical fluctuations in plasma membrane vesicles ACS Chem Biol 3:287-295
[42] Computer Simulation Technology (CST) 3D Electromagnetic Simulation Software (Darmstadt, Germany) - http://www.elektronikpraxis.vogel.de/CST-D-Computer-Simulation-Technology-AG/firma/228228/
[43] CST, Neufield, BSD-Neufeld E (2008) High resolution hyperthermia treatment planning, dissertation, ETH No. 17947

[44] Papp E, Vancsik T, Kiss E, et al. (2015) Membrane raft absorption in the modulated electro-hyperthermi (mEHT), 33rd ICHS conference, Bad Salzhausen, 10-12 July
[45] Vincze Gy, Szigeti Gy, Andocs G, et al. (2015) Nanoheating without artificial nanoparticles (Part I. Theoretical considerations), submitted to Biology and Medicine
[46] Szasz A (2007) Hyperthermia, a modality in the wings. J Cancer Research and Therapeutics 3:56-66
[47] Szasz A, Vincze Gy (2006) Dose concept of oncological hyperthermia: Heat-equation considering the cell destruction. J Cancer Research and Therapeutics 2:171-181
[48] Vincze Gy, Szasz O, Szasz A (2015) Generalization of the thermal dose of hyperthermia in oncology. submitted to Open Journal of Biophysics
[49] Vincze Gy, Szigeti Gy, Andocs G, Szasz A (2015) Nanoheating without artificial nanoparticles. Biology and Medicine 7(4):249
[50] Szasz A (2013) Electromagnetic effects in nanoscale range. In book: Cellular Response to Physical Stress and Therapeutic Applications, Tadamichi Shimizu, Takashi Kondo (eds), Ch. 4., Nova Science Publishers, Inc
[51] Papp E. (2015) Membrane raft absorption in the modulated electro-hyperthermia (mEHT); submitted to Journal of Cancer Research and Therapeutics
[52] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology 22(2):103-115
[53] Szasz O, Szasz A (2016) Heating, efficacy and dose of local hyperthermia. Open Journal of Biophysics 6:10-18
[54] Vincze Gy, Szasz O, Szasz A (2015) Generalization of the thermal dose of hyperthermia in oncology. Open Journal of Biophysics 5(4):97-114
[55] Szasz A, Vincze Gy (2006) Dose concept of oncological hyperthermia: Heat-equation considering the cell destruction. J Cancer Res Ther 2(4):171-181
[56] Szasz A (2007) Hyperthermia, a modality in the wings. J Cancer Res Ther 3(1):56-66
[57] Szasz O, Szasz A (2016) Heating, efficacy and dose of local hyperthermia. Open Journal of Biophysics 6:10-18
[58] Herzog A (2008) Messung der Temperoturverteilung om Modell der nicht perfundierten Schweineleber bei lokoler Hyperthermie mit Kurzwellen mit l3.56 MHz; Forum Medicine, pp.30-36
[59] Szasz A, Szasz O, Szasz N (2006) Physical background and technical realization of hyperthermia. In book: Locoregional Radiofrequency-Perfusional- and Wholebody- Hyperthermia in Cancer Treatment: New clinical aspects, Baronzio GF, Hager ED (eds), Ch. 3., Springer, New York, NY, pp 27–59
[60] Nagy G, Meggyeshazi N, Szasz O (2013) Deep temperature measurements in oncothermia processes. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 685264
[61] Kaltofen S (2006) Eindrücke vom 4. HOT (((.Oncotherm Anwender- und Interessententreffen, Die Natruheilkunde, Heft 1, pp. 4-6
[62] Szasz O (2012) commonly performed real-time demonstrations in 31th Annual Conference of ICHS, 12-14 October, Budapest, Hungary
[63] Meggyeshazi N, Nagy G (2012) Inhomogeneous thermal models for oncothermia, internal material
[64] Internal measurement for CE – ISO requirements
[65] Nagy G, Meggyeshazi N, Szasz O (2013) Deep Temperature Measurements in Oncothermia Processes. Conference Papers in Medicine. Volume 2013. Article ID 685264. Hindawi
[66] Herzog A (2008) Messung der Temperoturverteilung om Modell der nicht perfundierten Schweineleber bei lokoler Hyperthermie mit Kurzwellen mit l3,56 MHz; Forum Hyperthermie, Forum Medicine, 1/10, pp.30-36
[67] Scholz B, Anderson R (2000) On electrical impedance scanning – principles and simulations Electromedica Onco 68:35-44
[68] Chaudhary SS, Mishra RK, Swarup A, Thomas JM (1984) Dielectric properties of normal and malignant human breast tissues at radiowave & microwave frequencies. Indian J Biochem Biophys 21:76-79
[69] Papp E, Vancsik T, Kiss E, Szasz O. (2017) Energy absorption by the membrane rafts in the modulated electro-hyperthermia (mEHT), OJBIPHY, 7, 216-229
[70] Cha J, Jeon T-W, Lee CG, Oh ST, Yang H-B, Choi K-J, Seo D, Yun I, Baik IH, Park KR, Park YN, Lee YH (2015) Electro-hyperthermia inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis. Int Journal Hyperthermia (Epub ahead of print) 1-9
[71] Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A (2009) Strong synergy of heat and modulated

electro-magnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model. Strahlentherapie und Onkologie 185:120-126
[72] Tsang Y-W, Huang C-C, Yang K-L, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, Szasz A, Li W-T, Chi K-H (2015) Improving immunological tumor microenvironment using electro-hyperthermia followed by dendritic cell immunotherapy. BMC Cancer 15:708
[73] Szasz A, Szasz N, Szasz O (2010) Oncothermia – Principles and Practices. Springer Science, Heidelberg
[74] Andocs G, Rehman MU, Zhao QL, Papp E, Kondo T, Szasz A (2015) Nanoheating without Artificial Nanoparticles Part II. Experimental support of the nanoheating concept of the modulated electro-hyperthermia method, using U937 cell suspension model. Biology and Medicine 7(4):1-9
[75] Vancsik T, Kovago Cs, Kiss E, et al. (2017) Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts - publication is in preparation (Nidda)
[76] Tsang Y-W, Huang C-C, Yang K-L, et al. (2015) Improved immunological tumor microenvironment by combined electro-hyperthermia followed by dendritic cell immunotherapy, submitted to Cancer Immunology, Immunotherapy
[77] Vancsik T, Andocs G, Kovago Cs, et al. (2015) Electro-hyperthermia may target tumor-cell membranes, 33rd ICHS conference, Bad Salzhausen, 10-12 July
[78] Andocs G, Rehman MU, Zhao Q-L, et al. (2015) Comparative study of bioeffects by oncothermia and conventional heat treatment, 33rd ICHS conference, Bad Salzhausen, 10-12 July
[79] Andocs G, Rehman MU, Zhao Y-L, et al. (2015) Nanoheating without artificial nanoparticles (Part II. Experimental support of the nanoheating concept of the modulated electrohyperthermia method, using U937 ell suspension model), Biology and Medicine 7(4):1-9
[80] Qin W, Akutsu Y, Andocs G, Sugnami A, Hu X, Yusup G, Komatsu-Akimoto A, Hoshino I, Hanari N, Mori M, Isozaki Y, Akanuma N, Tamura Y, Matsubara H (2014) Modulated electro-hyperthermia enhances dendritic cell therapy through an abscopal effect in mice. Oncol Rep 10.3892/or.2014.3500
[81] Balogh L, Polyak A, Postenyi Z, et al. (2016) Temperature increase induced by modulated electrohyperthermia (oncothermia®) in the anesthetized pig liver, J Cancer Res and Ther, 12:1153-59
[82] Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148-165
[83] Andocs G, Meggyeshazi N, Balogh L, Spisak S, Maros ME, Balla P, Kiszner G, et al. (2014) Upregulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modulated electrohyperthermia. Cell Stress and Chaperones. DOI 10.1007/s12192-014-0523-6, 2014 June
[84] Meggyesházi N, Andocs G, and Krenacs T (2013) Programmed cell death induced by modulated electro-hyperthermia, Conference Papers in Medicine, Volume 2013, Article ID 187835, http://dx.doi.org/10.1155/2013/187835, Hindawi
[85] Kovago Cs, Meggyeshazi N, Vancsitk T, et al. (2015) Abscopal effect by modulated electro-hyperthermia, presentation at ESHO conference, 24-26 June, Zurich, Switzerland
[86] Meggyeshazi N, Kovago Cs, Vancsik T, et al. (2015) Tumor cell death induced by modulated electrohyperthermia in combination with Marsdenia tenacissima in mureine colorectal allograft tumor model, presentation at the annual 33rd ICHS Conference, 10-12 July, Bad Salzausen, Germany
[87] Andocs G, Osaki T, Tsuka T, Imagawa T, Minami S, Balogh L, Meggyeshazi N, Szasz O, Okamoto Y (2013) Oncothermia research at preclinical level. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 272467
[88] Andocs G, Osaki T, Tsuka T, et al. (2013) Oncothermia research at preclinical level. Conference Papers in Medicine, Volume 2013, Article ID 272467, http://dx.doi.org/10.1155/2013/272467, Hindawi
[89] Andocs G, Meggyeshazi N, Okamoto Y, Balogh L, Szasz O (2013) Bystander effect of oncothermia. Conference Papers in Medicine, Volume 2013, Article ID 953482
[90] Andocs G (2011) Treatment made at the Joliot Curie Institute, Budapest, Hungary
[91] Andocs G (2013) Measurement in Tottori Veterinarian University, Tottori, Japan
[92] Balogh L, Kovago Cs, Gyongy M (2015) Tumor-temperature by oncothermia in real-animal, 33rd Annual Conference of ICHS, 10-12 July, Bad Salzhausen, Germany
[93] Lee SY, Kim M-G (2015) The effect of modulated electro-hyperthermia on the pharmacokinetic properties of nefopam in healthy volunteers: A randomised, single-dose, crossover open-label study. Int J Hyp (Epub ahead of print): 1-6, http://www.ncbi.nlm.nih.gov/pubmed/26507458
[94] Jeung TS, Ma SY, Choi J, Yu J, Lee SY, Lim S (2015) Results of oncothermia combined with operation,

chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. Case Reports in Clinical Medicine 4:157-168
[95] Volovat C, Volovat SR, Scripcaru V, Miron L, Lupascu C (2014) Romanian Reports in Physics 66(1):175-181
[96] Wismeth C, Dudel C, Pascher C, Ramm P, Pietsch T, Hirschmann B, Reinert C, Proescholdt M, Rümmele P, Schuierer G, Bogdahn U, Hau P (2010) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas – Phase I clinical results. J Neurooncol 98(3):395-405
[97] Ferrari VD, De Ponti S, Valcamonico F, Amoroso V, Grisanti S, Rangoni G, Marpicati P, Vassalli L, Simoncini E, Marini G (2007) Deep electro-hyperthermia (EHY) with or without thermo-active agents in patients with advanced hepatic cell carcinoma: phase II study. J Clin Oncol 25:185, 15168
[98] Cremona F, Pignata A, Izzo F, Ruffolo F, Delrio P, Fiore F, D'Angelo R, Palaia R, Daniele B, Grazano F, Puppio B, Guidetti GM, Parisi V (2003) Tolerability of external electro-hyperthermia in the treatment of solid tumors. Tumori 89(4 Suppl):239-40
[99] Hager ED, Sahinbas H, Groenemeyer DH, Migeod F (2008) Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia. ASCO, J Clin Oncol, Annual Meeting Proceedings (Post-Meeting Edition) 26:2047
[100] Sahinbas H, Groenemeyer DHW, Boecher E, Szasz A (2007) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas. Deutsche Zeitschrift fuer Onkologie 39:154-160
[101] Douwes F, Douwes O, Migeod F, Grote C, Bogovic J (2006) Hyperthermia in combination with ACNU chemotherapy in the treatment of recurrent glioblastoma. St. Georg Klinik, Germany
[102] Hager ED, Dziambor H, App EM, Popa C, Popa O, Hertlein M (2003) The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. Proc ASCO 22:118, 47;Proc Am Soc Clin Oncol 22: 2003
[103] Mambrini A, Del Freo A, Pacetti P, Orlandi M, Torri T, Fiorentini G, Cantore M (2007) Intra-arterial and systemic chemotherapy plus external hyperthermia in unresectable biliary cancer. Clin Oncol (R coll Radiol) 19(10):808-806
[104] Hager ED, Dziambor H, Höhmann D, Gallenbeck D, Stephan M, Popa C (1999) Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Res 19(4C):3403-3408
[105] Gadaleta-Caldarola G, Infusino S, Galise I, Ranieri G, Vinciarelly G, Fazio V, Divella R, Daniele A, Filippelli G, Gadaleta CD (2014) Sorafenib and locoregional deep electro-hyperthermia in advanced hepatocellular carcinoma. A phase II study. Oncol Lett 8(4):1783-1787
[106] Fiorentini G, Giovanis P, Rossi S, Dentico P, Paola R, Turrisi G, Bernardeschi P (2006) A phase II clinical study on relapsed malignant gliomas treated with electro-hyperthermia. In Vivo 20(6A):721-724
[107] Szasz A (2014) Current status of oncothermia therapy for lung cancer. Korean J Thorac Cardiovasc Surg 47:77-93
[108] Seung-Gu Yeo (2015) Definitive radiotherapy with concurrent oncothermia for stage IIIB non-small-cell lung cancer: A case report. Experimental and Therapeutic Medicine pp. 1-4
[109] Douwes F, Bogovic J, Douwes O, Migeod F, Grote C. (2004) Whole-body hyperthermia in combination with platinum containing drugs in patients with recurrent ovarian cancer. Int J Clin Oncol 9(2):85-91
[110] Kleef R, Kekic S, Ludwig N (2012) Successful treatment of advanced ovarian cancer with thermochemotherapy and adjuvant immune therapy. Case Rep Oncol 5:212-215
[111] Bogovic J, Douwes F, Muravjov G, Istomin J (2001) Posttreatment histology and microcirculation status of osteogenic sarcoma after a neoadjuvant chemo- and radiotherapy in combination with local electromagnetic hyperthermia. Onkologie 24(1):55-58
[112] Rubovszky G, Nagy T, Godeny M, Szasz A, Lang I (2013) Successful treatment of solitary bone metastasis of non-small-cell lung cancer with combination of bevacizumab and hyperthermia. Pathol Oncol Res 19(1):119-22
[113] Schrrmacher V, Bihari A-S, Stücker W, Sprenger T (2014) Long-term remission of prostate cancer with extensive bone metastses upon immuno- and virotherapy: A case report. Oncology Letters 8:2403-2406
[114] Lee DY, Park JS, Jung HC, Byun ES, Haam SJ, Lee SS (2015) The outcome of the chemotherapy and oncothermia for far advanced adenocarcinoma of the lung: Case reports of four patients. Advances in Lung Cancer 4:1-7
[115] Lee DY, Haam SJ, Kim TH, Lim JY, Kim EJ, and Kim NY (2013) Oncothermia with chemotherapy in the

patients with Small Cell Lung Cancer. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 910363
[116] Dani A, Varkonyi A, Magyar T, Szasz A (2009) Clinical study for advanced non-small-cell lung cancer treated by oncothermia. Forum Hyperthermie; DGHT, 2009
[117] Volovat C, Volovat SR, Scripcaru V, Miron L (2014) Second-line chemotherapy with gemcitabine and oxaliplatin in combination with loco-regional hyperthermia (EHY-2000) in patients with refractory metastatic pancreatic cancer - preliminary results of a prospective trial. Romanian Reports in Physics 66(1):166-174
[118] Dani A, Varkonyi A, Magyar T, Szasz A (2008) Clinical study for advanced pancreas cancer treated by oncothermia. Forum Hyperthermie 1:13-20
[119] Douwes F, Migeod F, Grote C (2006) Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und einer Zytostase mit Mitomycin- C und 5-Fluorouracil/ Folinsäure. Onkologische Fachklinik St. Georg, Bad Aibling
[120] Douwes FR (2006) Thermochemotherapy of the advanced pancreas carcinoma. Biologische Medizin 35:126-130
[121] Douwes FR (2004) Thermo-Chemotherapie des fortgeschrittenen Pankreaskarzinoms. Ergebnisseeiner klinischen Anwendungsstudie. Onkologische Fachklinik St. Georg, Bad Aibling
[122] Hager ED, Süsse B, Popa C, Schritttwieser G, Heise A, Kleef R (1994) Complex therapy of the not in sano respectable carcinoma of the pancreas – a pilot study. J Cancer Res Clin Oncol 120:R47,P1
[123] Ballerini M, Baronzio GF, Capito G, Szasz O, Cassutti V (2013) Androtherm application for the Peyronie's Disease. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 962349
[124] Douwes FR (2011) Für und Wider des Prostata-Karzinom-Screenings. Prostata Newsletter (PNL) Ausgabe August 2011
[125] Douwes FR (2011) Neue Studie heizt Diskussion über den Wert von PSA-Tests an. Prostata Newsletter (PNL) Ausgabe August 2011
[126] Douwes FR (2008) Prostatakarzinom: Neue Aspekte für Diagnostik und Therapie. Facharzt Gynakologie/Urologie, 2:23-29
[127] Douwes FR (2008) Sanfte Hilfen für die Prostata. CO'Med, 4:1-2
[128] Douwes FR (2005) Bestrahlung der Prostata erhöht Rektum-Ca-Risiko. Klinik St. Georg
[129] Maar K (2004) Rebell gegen den Krebs. Bioogische Intersivtherapie – Neue Hoffnung für Patienten? Neomedica GmbH, Klosterneuburg
[130] Douwes FR, Lieberman S (2002) Radiofrequency Transurethral Hyperthermia and complete Androgen Blockade. A Nonsurgical Approach to Treating Prostate Cancer. Alternative & Complementary Therapies 8(3):149-156
[131] Douwes FR (2002) Diagnostik hyperthermia in early stage prostate cancer. Focus Alternat Complement Ther 6(1):77-78
[132] Douwes FR (2001) Adjuvante Radiotherapie: Welcher Patient mit Prostatakarzinom profitiert? Prostata Newsletter (PNL), Ausgabe August 2011
[133] Douwes F, Sillner L, Köhnlechner M (1999) Hoffnung bei Porstata-Beschwerden. Die neue Therapie ohne Messer. Herbig Verlagsbuchhandlung GmbH
[134] Szasz A (2003) Malignus és belignus prosztatadaganatok hyperthermiája. Magyar Urológia 15:87-88
[135] Strauss C, Kotzen J, Baeyens A, Maré I (2013) Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 293968
[136] Pesti L, Dankovics Z, Lorencz P, Csejtei A (2013) Treatment of advanced cervical cancer with complex chemoradio – hyperthermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 192435
[137] Lee SY, Kim M-G (2015) The effect of modulated electro-hyperthermia on the pharmacokinetic properties of nefopam in healthy volunteers: A randomised, single-dose, crossover open-label study, Int J Hyp (Epub ahead of print):1-6, http://www.ncbi.nlm.nih.gov/pubmed/26507458
[138] Lee SY (2016) Increase in intra-tumor blood flow and sub-tumor temperature in cervix cancer by electro-modulated hyperthermia, Int. Congress Hyperthermic Oncology, 11-15 April, 2016, New Orleans
[139] Renner H. Klinikum Nurnberg Nord (2012) temperature measurement, internal
[140] Sahinbas H. University Witten-Herdecke, Institute of Microtherapy, Bochum, Germany, temperature measurement, internal

[141] Douwes F (1999) temperature measurement, internal
[142] Szasz A (2014) Current status of oncothermira therapy for lung cancer, Korean J Thorac Cardiovasc Surg 47(2):77-93
[143] Rubovszky G, Nagy T, Godeny M, et al. (2013) Successful treatment of solitary bone metastasis of non-small cell lung cancer with bevacizumab and hyperthermia. Pathol Oncol Res 19:119-122
[144] Lee JS, Yoon SM (2012) Case of abscopal effect with metastatic non-small-cell lung cancer. Oncothermia Journal 5:53-57
[145] Lee DY, Park SJ, Jung HC, et al. (2015) The outcome of the chemotherapy and oncothermia for far advanced adenocarcinoma of the lung: Case reports of four patients. Advances in Lung Cancer 4:1-7
[146] Jeung TS, Ma SY, Choi J, et al. (2015) Results of oncothermia combined with operation, chemothermapy and radiation therapy for primary, recurrent and metastatic sarcoma, Case Reports in Clinical Medicine 4:157-168
[147] Gadaleta-Caldarola G, Infusino S, Galise I, Ranieri G, et al. (2014) Soraenib and locoregional deep electro-hyperthermia in advanced hepatocellular carcinoma: A phase II study, Oncology Letters 8:1783-1787
[148] Sahinbas H, Gronemeyer DHW, Bocher E, Szasz A (2007) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas, Deutsche Zeitschrift fur Onkologie 39:154-160
[149] Lee Y (2013) Oncothermia application for various malignant diseases, Conference Papers in Medicine, Volume 2013, Article ID 245156, http://dx.doi.org/10.1155/2013/245156, Hindawi
[150] Pang CLK (2012) Research progress of hyperthermia integrate with TCM in treating cancer, presentation at the annual ICHS Conference, 12-14 October, Budapest, Hungary
[151] Pang CLK (2015) Hyperthermia in Oncology, CRC Press
[152] Pesti L, Dankovics Zs, Lorencz P, and Csejtei A (2013) Treatment of advanced cervical cancer with complex chemoradio – hyperthermia, Conference Papers in Medicine, Volume 2013, Article ID 192435, http://dx.doi.org/10.1155/2013/192435, Hindawi
[153] Lee DY, Haam SJ, Kim TH, et al. (2013) Oncothermia with chemotherapy in the patients with small cell lung cancer, Conference Papers in Medicine, Volume 2013, Article ID 910363, http://dx.doi.org/10.1155/2013/910363, Hindawi
[154] Fiorentini G, Yoon SM, Okamoto Y, Andocs G, Baronzio G, et al. (2013) Abscopal effect: new perspectives in Oncothermia, Oncothermia Journal 7:297-281
[155] Yimin L, Pang CLK, Zhang T, et al. (2031) Deep Regional Hyperthermia combined with traditional Chinese medicine in treating benign diseases in Clifford Hospital, Oncothermia Journal 7:157-165
[156] Pang CLK (2013) Progress of research of hyperthermia integration with TCM in the treatment of cancer. Oncothermia Journal 7:36-42
[157] Repasky E, Issels R. (2002) Physiological consequences of hyperthermia: heat, heat shock proteins and the immune response, Int. J. Hyp. 18(6), 486-489
[158] Shen R-N, Lu L, Young P, Shidinia H, et.al. (1994) Influence of elevated temperature on natural killer cell activity, lymphokine-actiated killer cell activity and lectin-dependent cytotoxicity of human umbilical cord blood and adult blood cells, Int. J. Radiat. Oncol. Biol. Phys. 29(4), 821-826
[159] Andocs G, Rehman MU, Zhao QL, Papp E, Kondo T, Szasz A. (2015) Nanoheating without Artificial Nanoparticles Part II. Experimental support of the nanoheating concept of the modulated electro-hyperthermia method, using U937 cell suspension model, Biology and Medicine 7(4):1-9
[160] Andocs G, Rehman MU, Zhao Q-L, Tabuchi Y, et al. (2016) Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells, Cell Death Discovery (Nature publication), 2, 16039, 1-10
[161] Baronzio G, Parmar G, Ballerini M, Szasz A, Baronzio M, Cassutti V (2014) A brief overview of hyperthermia in cancer treatment. Journal of Integrative Oncology, 3:1
[162] Meggyeshazi N, Andocs G, Balogh L, Balla P, Kiszner G, Teleki I, Jeney A, Krenacs T (2014) DNA fragmentation and caspase-independent programmed cell death by modulated electrohyperthermia. Strahlenther Onkol 190:815-822
[163] Andocs G, Meggyeshazi N, Balogh L, Spisak S, Maros ME, Balla P, Kiszner G, Teleki I, Kovago Cs, Krenacs T (2014) Upregulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modualted electrohyperthermia. Cell Stress and Chaperones 20(1):37-46

Summary and update of the method modulated electro-hyperthermia

Minnaar CA, Szasz AM, Arrojo E, Lee S-Y, Fiorentini G, Borbenyi E, Pang CLK, Dank M

Division of Radiobiology, Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa
Division of Oncology, Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary
University Hospital Marqués de Valdecilla, Santander, Spain
Department of Radiation Oncology, Chonbuk National University Hospital-Chonbuk National University Medical School, Jeonju, Jeonbuk, Republic of Korea
Clinical Hyperthermia Unit, Ravenna 33 Clinic, Ravenna, Italy
Cancer Center, Clifford Hospital, Guangzhou University of Chinese Medicine, P.R. China

Cite this article as:
Minnaar CA et al. (2020): Summary and update of the method modulated electro-hyperthermia
Oncothermia Journal Special Edition, 2020 September, 49-130
www.oncotherm.com/sites/oncotherm/files/2020-09/specialedition02.pdf

Abstract

Our objective is to describe the technical principles, protocols, and clinical practice of modulated electro-hyperthermia (mEHT, oncothermia®), with special attention to the newest model (EHY-2030). Modulated electro-hyperthermia changes the hyperthermia paradigm in oncology and therefore requires a specialized and unique protocol-description. The major difference is that the mEHT heating technology breaks the concept of the homogeneous (isothermal), heating standard. The technology takes into account the obvious heterogeneity of the tissues, the natural structure of the tumor, and the microscopic biophysical differences between the tissues which determine the energy absorption. The cellular selection targets the malignant cells and induces apoptotic molecular changes with the goal of destroying the malignant cells and triggering a remote effect to target distant malignances (abscopal effect). These special technical qualities require a new treatment protocol, a new dose concept, and new recommendations for complementary combinations in order to optimize the treatment of malignant diseases. In order to understand the protocol updates, including the change in dosing, a detailed understanding of the technical qualities of the device and the effects on cells is necessary. The authors have undertaken a complete evaluation of the new EHY-2030 device, including the history, the theory, and a technical and clinical assessment, which we present in this report.

Keywords

Modulated electro-hyperthermia, mEHT, EHY-2000+, EHY-2030, abscopal, immune, safety, temperature, dose, hyperthermia

Introduction

Hyperthermia might appear to be a very new, modern therapy in oncology. However, it is in fact the oldest identified tool to be used against cancer, [1]. The application of heat-therapy for malignancies dates back over a thousand years and has shown extensive results, supporting the application of energy-absorption in tumors to eliminate the tumors.

Hyperthermia in oncology is at crossroads, [2]. One of the main factors which has contributed to the current situation is the challenge associated with the classically applied homogeneous local heating of the tumor. The problem arises from the enormous heterogeneity of the tumor and its environment, as well as and the physiological mechanisms regulating thermal homeostasis. Homogeneous (isothermal), heating does not consider the heterogenic mixed structures in the body. Another factor is the difference in the behavior of the vascular systems between malignant tissues and healthy tissues. The forced general increase of the temperature results in feedback which induces strong homeostatic thermal-control measures, primarily involving the blood flow, [3]. The healthy tissues undergo intense vasodilatation, while the tumorous arteries dilate at mild temperatures, [4], [5], but after a tumor-specific threshold is reached, vasocontraction dominates in the tumor, [6], [7]. The increased blood flow intends to cool down the heated volume, while the vasoconstriction works like a heat-trap, [8]. The proposed solution to these challenges is the application of heterogenic heating, which selectively targets the cancer cells using energy-dissipation.

The objective of our present article is to summarize the knowledge on a novel paradigm of hyperthermia which applies heterogenic energy absorption. The developed method for this change in the paradigm is modulated electro-hyperthermia (mEHT, oncothermia®), [9], which is applied worldwide. This work intends to condense the knowledge which led to the development of the

newest model in the mEHT technology; the EHY-2030. To this end, the authors have undertaken a complete evaluation of the new EHY-2030 device, including the history, the theory, and a technical and clinical assessment, which we present in this report.

Historical notes

Heating is an old medical therapy that was extensively used in ancient cultures. The practice of hyperthermia has sacral roots (heat originated from the Sun), and ancient users observed curative results for a broad variety of diseases, including cancer. The strong belief and respect for heat as a healing modality led to the use of extreme measures to induce fevers.

The practice of inducing a fever began with the malaria parasite, which was used to treat syphilis, and for this a Nobel Prize was awarded to Wagner-Jauregg, [10] in Austria. During the same period another pyrogen (liposaccharide toxin), was used by Cowley in the USA for the treatment of cancer, [11], with some success. Despite the success, his method was overshadowed by the development of radiation therapies at the time, and the method was forgotten. Such periods of success followed, by a decline in popularity, have been repeated throughout the history of hyperthermia and there is a risk of a repeat of the situation today. The rough structure of oncological hyperthermia shows the many different techniques to treat cancer in modern time, Fig. 1.

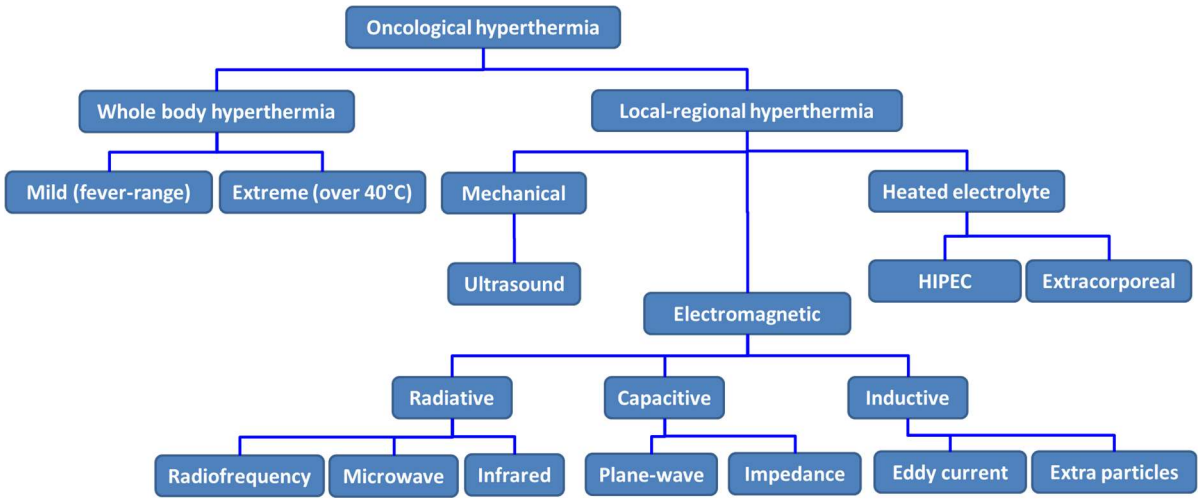


Figure 1. Oncological hyperthermia methods (some categories may overlap each other).

Definitions

Hyperthermia is a promising oncological treatment modality, [12], [13]. Despite the definitive difference, the process of actively overheating (hyperthermia), and the raised body-temperature (fever), are frequently misunderstood to be part of the same modality. The heat (which is the energetic origin of hyperthermia), and the temperature (which is connected to fever which has a measurable parameter), are basically different categories. The heat (energy), depends on the mass (volume), while the temperature does not. Temperature is an average of the heat all over the target. Increasing the temperature (e.g. [°C]), requires energy (e.g. Joule, [J]).

When the mass (volume), increases, it requires an increase in heat (energy), in order to reach the same temperature. Not only does the temperature increase use the incoming energy, but any

structural or chemical changes also absorb the energy in order to perform the change or transition. As such, the chemical reactions are a result of the energy input, and the temperature is an outcome. The temperature is the result of the excess energy that is not absorbed by the chemical or structural modifications. Applying this logic, temperature should not be the goal of the treatment, rather the energy absorption should be the goal, and the rise in the temperature is a consequence.

When conducting a search for "hyperthermia" in medical databases, "malignant hyperthermia", and not "hyperthermia the treatment modality", is the most common result, [14]. It is possible that the chosen name for hyperthermia the "treatment modality" may contribute to the misunderstanding by suggesting that the homogeneous (isothermal), temperature is the primary character. A further challenge is the variety of descriptions of hyperthermia available.

- Hyperthermia is the overheating of the body (Medicine.Net, [15]), "much higher than normal body temperature, induced therapeutically or iatrogenically".
- Medical Dictionary, [16]: This definition focuses on the body heating but does not mention the local possibility. It is too broad, and it includes any external accidental causes (such as weather).
- Similarly, the Free Dictionary describes hyperthermia as, [17] "an abnormally high fever, sometimes induced as treatment for disease".
- The National Cancer Institute (USA), proposes a more sophisticated definition: "Hyperthermia is a type of cancer treatment in which body tissue is exposed to high temperatures (up to 113°F)", [18]. This definition emphasizes temperature as the characterizing parameter.
- The Kadota Fund International Forum Consensus declares hyperthermia is a "modest elevation of temperature in the range of 39–45°C", [19].
- The Medical Encyclopedia of Rochester University says, [20]: "Hyperthermia is heat therapy. Heat has been used for hundreds of years as cancer therapy".
- Medline Plus describes hyperthermia as the use of heat to damage and kill cancer cells without harming normal cells, [21]. This definition speaks about the heat without mentioning the temperature, which is correct.
- The popular "Wikipedia" states that hyperthermia is a type medical treatment involving the exposure of body tissue to higher temperatures in an effort to treat cancer, [22].
- The American Cancer Society defines hyperthermia as the "carefully controlled use of heat for medical purposes" and discusses the changes that take place inside the cells in response to high temperatures, [23].
- A more recent guideline for hyperthermia, which concentrates on the application of modulated hyperthermia, states that, [24] "Oncological hyperthermia is a method for killing malignant cells by controlled thermal effects and has the potential to sensitize complementary therapies while avoiding the destruction of healthy cells."

Most of the above definitions have common errors: the use of the terms "temperature" and "heat" is incorrect; the complementary application (which is the most frequent application of hyperthermia as its almost always used combined with other therapies), is rarely mentioned; a broad temperature development is described (from slightly higher, modest, to much higher); and the target could be the body as the whole, the tumor, the tissue, or the cell. The correct definition should include some vital points: that the goals are to destroy the malignancy, to keep the healthy cells intact, and to support the complementary therapies, as illustrated in Fig. 2. The latter comes from the convincing experience gained over time demonstrating that malignancy is a complex disease, requiring a complex combination of multiple therapies to cure it.

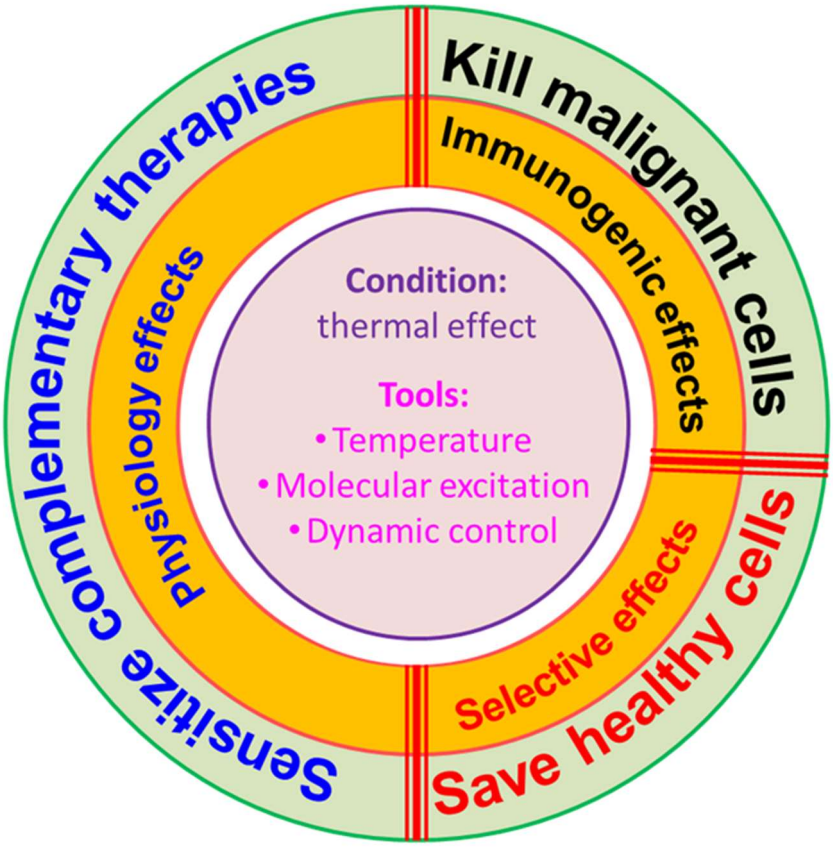


Figure 2. "Hallmarks" of a successful therapy. The outer circle shows the basic requirements, while the inner one collects the possible gentle methods (these are described in this article below), and the center summarizes the condition and tools which are needed for the gentle but effective oncologic hyperthermia actions.

Life is not static, it is in a state of permanent development, permanent change and energy intake. Temperature is a conditional factor. In hyperthermia, temperature is a tool, which ignites changes in the delicate living balance, and the changes are chemical, structural and physiological. Nobel-laureate, A. Szent-Gyorgyi, remarked that in the life-energy, it is not important that the monkey goes through the jungle, but that the jungle goes through the monkey, in the form of nutrition, water, and oxygen, [25]. The jungle, in this story, is the conditional factor, the conditional environment for the monkey, it is only one of the tools of survival for the monkey. The temperature in hyperthermia is also only a tool, a condition which promotes the desired action, which is the distortion of the malignant disease in the system.

As such, considering the temperature as conditional tool, the authors support the last definition from the those listed above. It clearly formulates the goal (killing of the malignant cells), the condition (thermal effects), and the possible complementary applications. As the inner circle shows in Fig. 2., the approach, which is the method described in this article, is the immunogenic cell death, the selective effects, and the use of physiology to support the complementary conventional therapies.

Our approach is the selective cell-killing with immunomodulation in a mild local temperature condition which supports the cell-killing effects of the complementary therapies. The method which has been developed in order to achieve this, and which we describe in detail in this manuscript, is modulated electro-hyperthermia (mEHT, oncothermia ®).

Similarities and differences in hyperthermia treatment concepts

Whole-body hyperthermia (WBH), has an obvious measurable characteristic: the body temperature. In this systemic treatment the blood delivers the heat to the tumor from the heated subcutaneous periphery of the body. Depending on the level of heating, WBH can be subdivided into mild (fever

like), hyperthermia and extreme (limited by the physiological threshold of 42°C), hyperthermia. The two approaches cover different expected therapeutic results: the fever range WBH, [26] focuses on the immune effects, [27], [28], [29], and through these effects, targets the malignancy throughout the body, [30]. The extreme heating aims for the direct killing of the malignant cells throughout the body, [31]. Super extreme heating (>43.5º), has also been proposed, [32]. The eligible patients for all extreme heating processes need to be carefully selected due to the extremely taxing conditions associated with prolonged exposure to high temperatures.

This manuscript focuses on local hyperthermia in oncology. Both the macroscopic and microscopic conditions of local heating differ substantially from WBH, Fig. 3. While in WBH the blood is heated and heats the whole body up, including the tumor, in local heating the blood has the opposite action: it aims to cool down the heated mass back to body temperature.

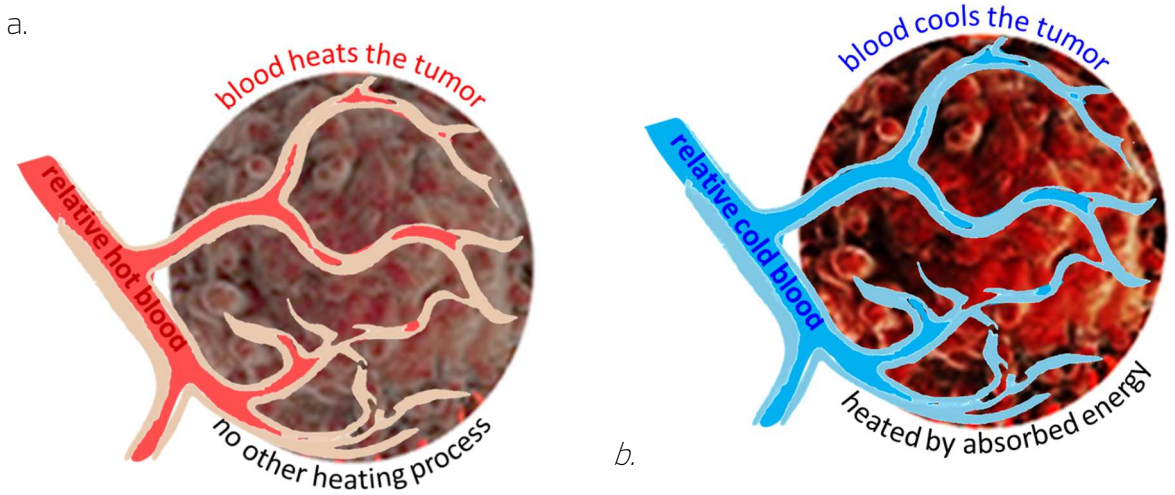


Figure 3. Difference between the heating modes (a), the WBH method when the heated blood heats up the unheated tumor, (b), the local approach occurs when the blood remains at body temperature while the tumor is heated locally. In this case the blood is a cooling medium.

During the heating-up period, in both the systemic and loco-regional cases, the initial state before heating is in equilibrium, however as the treatment progress, the system works towards achieving a state of "dynamic equilibrium" (steady-state resulting from saturation, a "plateau"). In both heating methods, the absorbed energy in the dynamic but steady state, replaces the energy lost as a result of the natural cooling processes. In WBH, the cooling mechanisms are the natural heat loss from the body surface, and the cooling effect of breathing. In local heating, the energy spreads to other parts of the body from the local site via the blood flow. In this case the cooling effect of the body increases as the treatment continues. During WBH, a plateau is reached at which point there is equilibrium between the heat loss and the energy input. However, during local heating there is a constant and dynamic balance between the two opposing energy-flows. The challenge in this case is that the energy balance is not constant, because the amount of the cooling medium (the blood flow), has a non-linear dependence on the temperature, while the balancing energy supply is linear. In the local case, a permanent microscopic temperature gradient exists which results in a heterogenic temperature pattern which follows the heterogenic vasculature, [33]. Unlike WBH which reaches a stable, homogeneous state by time, local heating does not reach a state of stable and homogenous heating, Fig. 4.

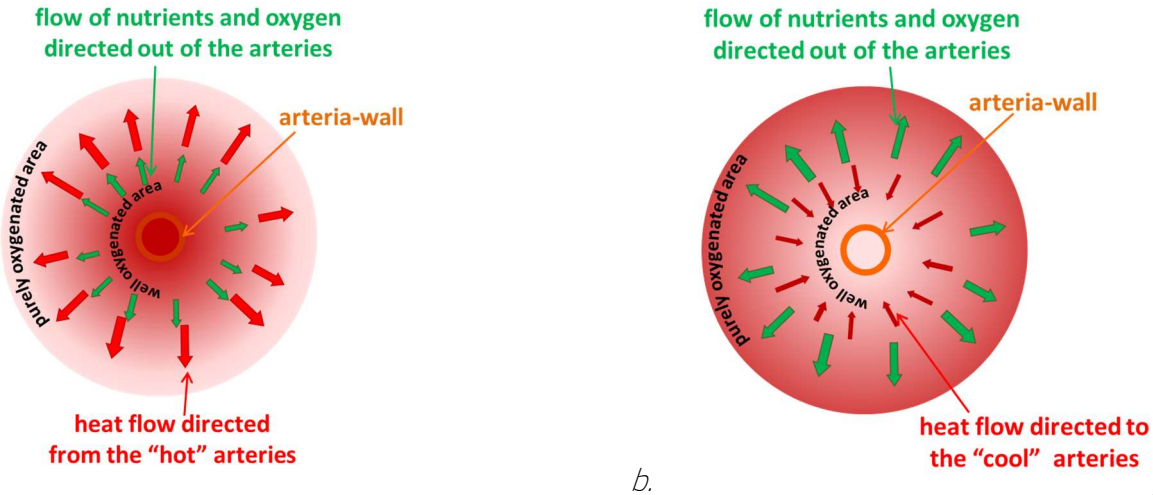


Figure 4. The situation around the arteries differs between WBH and local hyperthermia. (a), In WBH the blood heats the body, so the arteries carry the heated blood to the tumors, along with the nutrients and the oxygen. (b), In local hyperthermia the blood cools the tumor and the gradient of nutrients has the same direction as in the WBH. However, while the WBH achieves a complete thermal equilibrium when the volume reaches the same temperature as the blood; in local treatment the inequality of the temperature does not vanish, making this situation unstable.

Local – regional hyperthermia

We describe two categories in local-regional heating: homogeneous (isothermal), and non-homogeneous or heterogeneous (selective), heating. The two categories are divided based on how the applied energy is utilized, which is a result of the how the energy-source is coupled to the target, Fig. 5. Each division has further sub-variants, which differ in their technical solution within the framework of the same concept. The basic conceptual categories (homogeneous and the heterogeneous), which are a result of the energy-absorption, apply radiative, capacitive, or inductive methods. Galvanic coupling is also applied; however, it is not depicted in Fig. 5 as it is used for surface lesions or invasive applications.

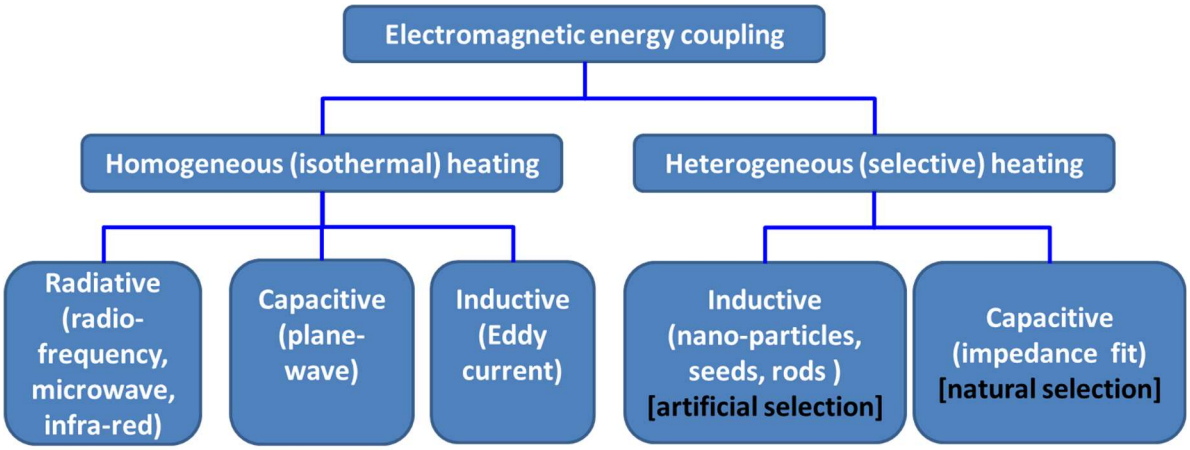


Figure 5. The electromagnetic energy-coupling structure of categories of local hyperthermia. The "impedance fit" in the selective (heterogeneous), category is the unique modulated electro-hyperthermia (mEHT).

The isothermal concept in local heating originated from the fever, which is isothermal all over the body. According to this idea the local treatment has to be as similar as possible to the whole-body temperature gain, only in a local volume. This concept was originally described by Hippocrates, who treated breast cancer using the heat radiating from a red hot iron, and thought about the heat as a local fever, [1]. At that time, it was not possible to measure the temperature, and there was no knowledge of the physiological feedback controls and the blood flow regulation in the body. As technical developments enabled the measurement of temperatures, homogeneous heating became a quantifiable condition, and the understanding of physiology as regulator of thermal homeostasis improved. The concept was primarily applied to superficial targets, but investigations into methods of heating deeper tumors continued. However, applying isothermal principles for deep heating has the following challenges:

- The transfer of energy into a target volume deep in the body without overheating the surface as the incident energy penetrates into the body;
- The measurement of temperature in a heterogenic volume without multiple invasive/in-situ measurements;
- The compensation for the non-linear feedback of the homeostatic control, especially the blood flow.

The solutions, according to the classical heating paradigm:

- Radiate energy to the volume and cool down the overheated surfaces in order to avoid the risk of burn.
- Heat as homogeneously as possible. Measure the temperature in as many points as possible and use a dose which has been verified on homogeneous models (like *in silico* or *in vitro* homogeneity). Characterize the isothermal volumes in the complete target by its percentage. These principles led to the development of the cumulative equivalent minutes (CEM), [34], [35], which is based on the necrosis of Chinese hamster ovary cells *in vitro* at $\mathbf{43°C}$, [36].
- Add the x percentage of the homogeneity of the T temperature to the comparison ($\boldsymbol{CEM43°CT_x}$), [37]. Introducing the $\boldsymbol{T_x}$ percentage of homogeneity explains the heterogenic heating at a macro-level, [38]. While in the *in vitro* treatments, this measurement has no relevance as the cell-culture is, [39].
- The classical heating concept disregards the change in the use of the absorbed energy, namely: the changes in the blood flow quickly stabilize a static state of heating, when the temperature does not change. This phase of heating compensates only for the energy loss which is caused by blood flow and not for other losses, [40].

Unfortunately, the above solutions, including the CEM solution, resulted in further challenges:

- In principle, the sensors must be inserted into the tumor and, due to its heterogeneity, multiple sensors have to be inserted during each treatment session. The invasive temperature measurement process is not safe and could cause further dissemination of the malignant cells as well as infection.
- The intensive proliferation of the tumor needs an increased supply of nutrients. The induced high blood flow supports the tumor with the necessary metabolite components, potentially supporting the increased proliferation.
- The majority of the disseminated malignant cells are transported by the blood flow. The elevation of its stream increases the risk of invasion and dissemination of the malignant cells.
- Technically, due to basic electromagnetic reasons, the focusing preciosity increases as the frequency tends towards the radiative range, where the wavelength is smaller than the

distance of the source from the target, [41]. Contrary to this, the penetration depth of the energy decreases based on the frequency, [42] of the electromagnetic radiation, so the increased accuracy of the focus decreases the effective depth of the energy-absorption.

Modulated electro-hyperthermia (mEHT, oncothermia®), attempts to change the paradigm and overcome the above challenges, [9]. Our present discussions detail the technical method and the amended clinical protocols.

Brief comparison of the devices providing local – regional hyperthermia

It is important to emphasize that all the heating treatments fall into the category of hyperthermia, irrespective of which concept is used. However, the distribution of the temperature as well as the tools, goals, synthesis of heat, and bio-effects differ.

1. The fever method of heating, which has been applied as far back as Hippocrates' time, supports isothermal heating in that the goal is the temperature. Various tools have been developed to obtain the desired outcome. Applying isothermal heating in a fever-like state, the goal, or outcome is the body temperature and the temperature can therefore be used as a measure of treatment efficiency, or dose, [43].
2. In the non-isothermal paradigm, the temperature is a tool, forming a condition of the distortion of malignancy. The destruction of the malignant cells is the goal of this paradigm and the temperature is a local condition resulting from the treatment, [44].

Conventional hyperthermia is achieved using a variety of techniques such as mechanical (ultrasound), high frequency (microwave), ultra-high frequency (infra-red), and contact solutions (like hyperthermic intraperitoneal chemotherapy, HIPEC). Our focus is on the application of local radiofrequency (RF), electromagnetic treatment, which is limited to two basic methods: radiative and capacitive coupling of the energy between the source and the target, [45].

Radiative techniques

The radiative technique relies on the focused antenna array, [46], [47]. In this method, the tumor can be located deep within the body and the antenna array is electronically controlled to focus the energy on the target volume (antenna phase array, [48]). The focusing requires a high frequency (around 100 MHz), which has a small penetrating depth. As such the incoming energy decreases by 68% within less than 5cm from the surface. Due to the large energy-loss, a high forwarded power is necessary in order to reach the desired homogeneous temperature at the required depth. The high incident power necessitates the intensive cooling of the surface in order to avoid surface burns. The cooling is achieved using a water bolus, which also absorbs a large portion of the energy. It is therefore difficult to determine the amount of useful energy (energy absorbed in the target volume), and the energy lost during the treatment. Without knowing the dose of the useful energy, temperature must be used as a measure of treatment efficiency and safety. A high power is required in order to achieve the desired temperatures in classical hyperthermia models. These high temperatures may result in vasoconstriction within the tumor, which causes a heat trap and further increases the intratumoral temperature. In this manner, high temperatures may be reached, and necrosis of the tumor tissue may develop as a result. With vasoconstriction however comes a decrease in perfusion and the sensitizing effects to chemotherapy and radiotherapy are lost.

Capacitive techniques

The other popular conventional coupling method is the capacitive arrangement, [49], [50]. The patient is placed in between plan-parallel electrodes representing a condenser, where the patient is a part of the dielectric material. Due to the large isolation layers (sometimes air between the electrode and the skin), the plane wave travels through the patient and can therefore reach the depth of body. The orientation or focusing of the waves is the primary technical challenge in this coupling. Capacitive coupling does not have electromagnetic focusing potential and still attempts to heat as homogeneously as possible, [51], [52]. Despite the high power applied (800-1300W), the maximum temperature achieved is still only $\approx$ 42°C, [53]. In a laboratory device developed for the experimental treatment of small rodent tumor models, a power output as high as 200 W was required, [54]. In the capacitive coupling method, the sizes and the distances of the electrodes determine the approximate focus, [55], however the position of the electrodes also modifies the focus, [56]. The goal of the plane-wave is conventional isothermal heating. In order to reduce pain and improve the applied power, impedance matching using a "subtrap" method has been applied, [57]. This involves forming a parallel resonant circuit, maximizing the impedance of the target. The addition of saline solution to the bolus, [58], [59] tries to lower the impedance further, but due to its relative high conductivity, the saline is heated up by the electric field, which is a further (sometimes vast), energy loss. This additional energy loss must be compensated by increasing the forwarded energy from the RF supply. The amount of the energetic losses emphasizes the necessity of the temperature measurement to approximate the absorbed energy in the target volume, for the same reasons as with the radiative technologies.

In most of the conventional hyperthermia solutions, the targeted tumor of the patient is independent from the source, and the changes in the target (increasing blood flow, mechanical movements, changes in the tumor, etc.), do not change the source and its tuning. There is no auto-feedback facility for the target modifications. The source provides the fixed electric parameters (such as the power), and the operator can change the parameters when an increase in the reflected power, or changes in the other measured parameters (like the temperature due to defocusing), are observed. The treatment adaptation depends on the experience of the operator and the observability (measurability), of the changes.

Modulated electro-hyperthermia

During mEHT, the treated patient is involved in a resonant electric circuit, [60], so any change appears immediately in the electric control of the treatment. This provides automatic feedback that reacts in cases when the change is not visible to the operator. This auto-feedback allows for the personal adaptation of the treatment to the patient for the optimal energy-absorption, [61], [62].

Modulated electro-hyperthermia (mEHT, oncothermia®), represents a new paradigm, [63], [64]. The coupling used is impedance matching, which is a specialized capacitive solution, [42]. In this technology the isolating layers are compensated with resonant (serial circuit), coupling and the applicators (specialized electrodes), behave like a metal layer touching the skin. This technical solution does not pose a risk of electric shock, because the isolating layer is compensated electronically. For the compensation the applicator system has a careful technical design, ensuring minimal energy losses. The most advanced version is the smart electrode system (SES), in the EHY-2030 device. Furthermore, the impedance coupling allows the electric selection of the malignant cells in order to solve the challenges and advance the change in the paradigm. Due to the minimal energy losses, [65], the absorbed energy can be directly measured. The absorbed energy produces the change in temperature, and in this situation the dose of the treatment is not connected to the temperature. The well-tuned and controlled energy intake allows the measurement of the absorbed

energy, which is regarded as the dose of the treatment, [42], [66]. The absorption occurs dominantly on the transmembrane proteins of the malignant cells, and despite the moderate energy input, these molecules can be heated to high temperatures due to their nanoscopic sizes, [67].

The natural movements of the body (such as breathing), pose another challenge to the conventional heating methods. These movements could result in a displacement of up to a few centimeters. Conventional hyperthermia applies two solutions for this situation:

- To avoid this problem a narrow focusing is be applied, which concentrates on the part of the target volume which remains within the concentrated energy flow, despite the movements;
- A larger target volume is selected in order to keep the entire tumor in the treatment field despite the movements.

In both of the above solutions, two conventional principles are ignored: the homogeneous heating, and the selective focus on the tumor. In mEHT the situation is different because the RF-current, which represents the effective energy, will flow automatically through regions with lower impedance, selecting the malignant tissues and cells, irrespective of their movements.

Change of paradigm using modulated electro-hyperthermia (mEHT)

Challenges

In order to change the paradigm, we must move away from focusing on the tumor alone and work towards eliminating the systemic disease, [68], [69]. The patient is a complex system requiring a complex approach to treatment, considering the patient as a whole (including living conditions, well-being, personal networking, and comorbidities), [70]. If the intention is to work towards a treatment which supports the patient, then the patient's homeostatic system must cooperate with, and not work against, the applied therapy, [71], [72], (Fig. 6). The tumor-oriented approach works against the homeostatic actions: it forces the elimination of the tumor, irrespective of its embedded complexity in the host tissue and in the entire system. When the temperature rises drastically, the body tries to re-establish the thermal homeostasis. On the other hand, when the treatment is patient-oriented, the process carefully works to support the homeostasis. In the case of mEHT, the selective energy absorption at the cell membranes has been shown to produce programmed cell-death (apoptosis), and actively supports the immune surveillance (mainly the innate and adaptive immune system), which is a part of homeostatic control.

Fig. 7 shows the goal of patient-oriented treatments compared to the tumor-focused treatments, as described by the manufacturer. Fig. 8. summarizes the technical differences between tumor and patient oriented treatment.

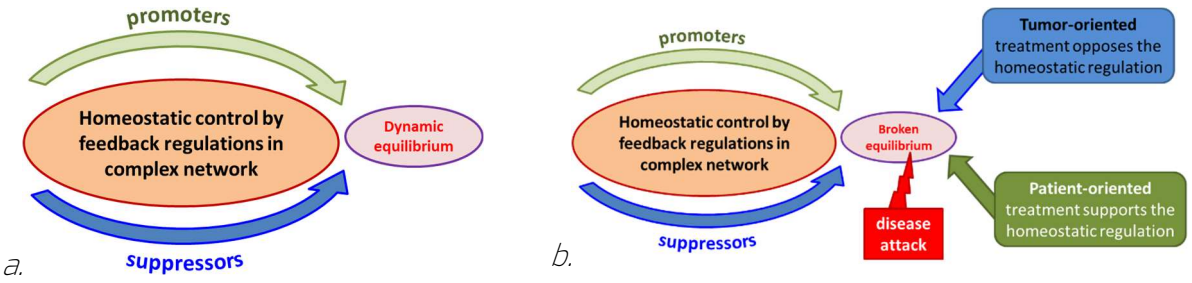
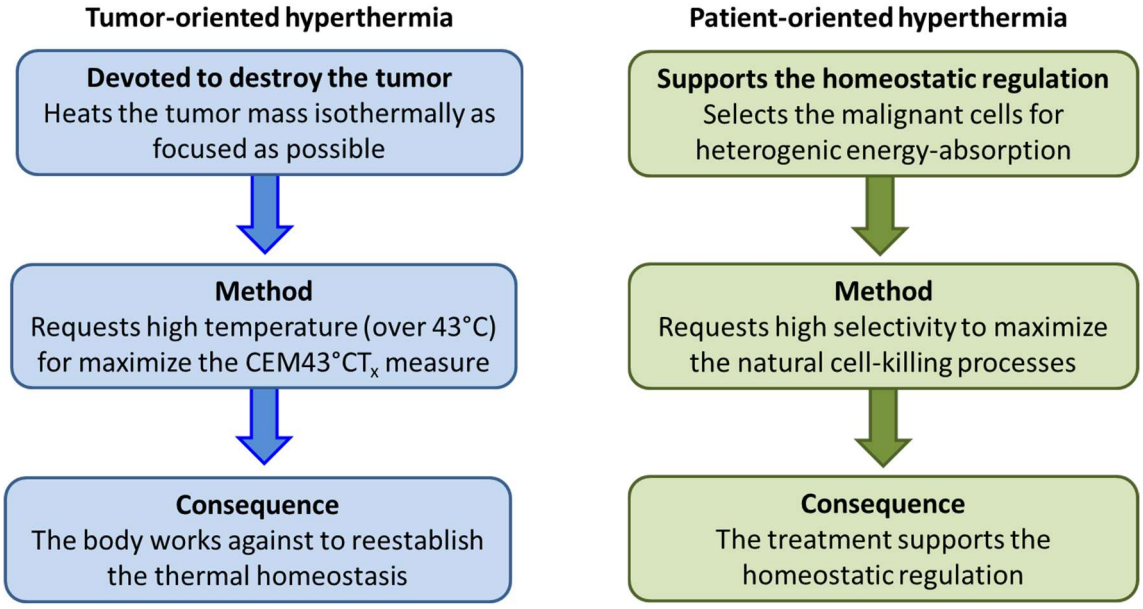
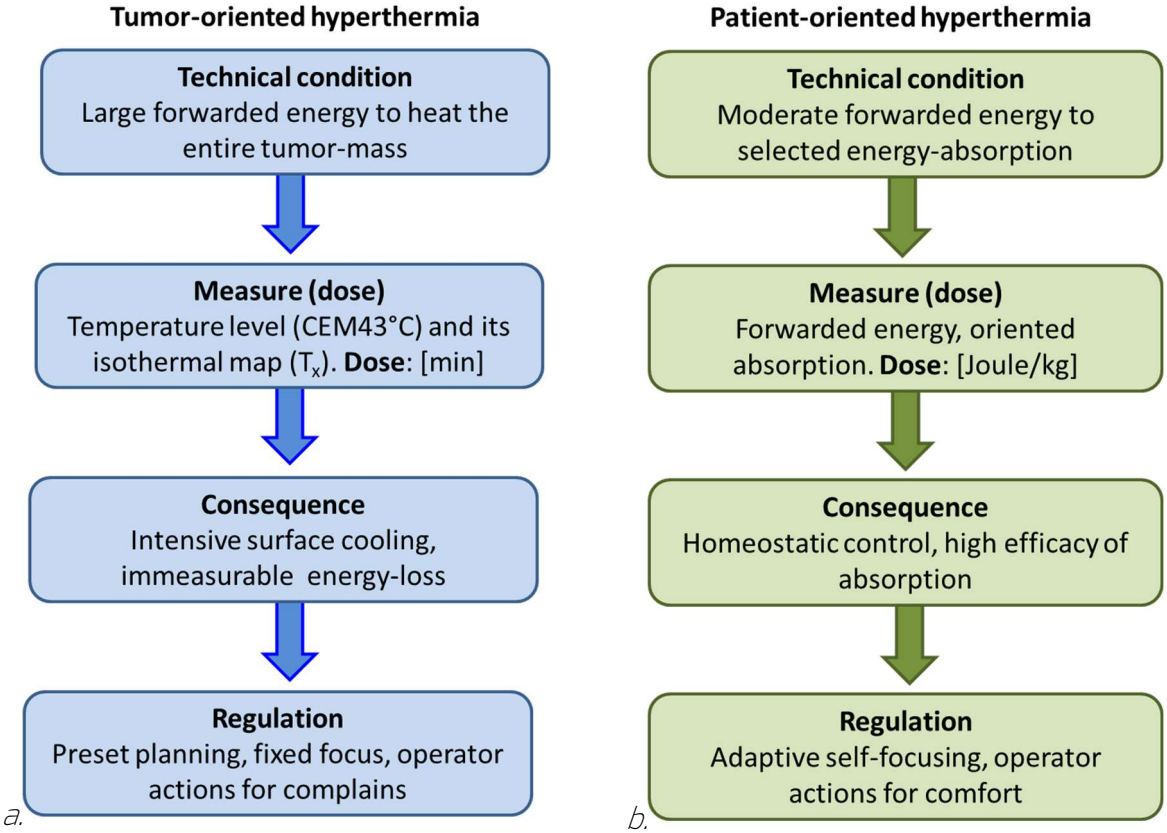


Figure 6. Effect of the homeostasis (a), The dynamic equilibrium set by a complex network of feedback regulations in the promoter ↔ suppressor interactions. (b), The disease (cancer), breaks the balance. Two types of treatments act differently.



a. *b.*

Figure 7. Comparison of the concepts (a), tumor-oriented (b), patient-oriented.



a. *b.*

Figure 8. The technical differences of the concepts (a), tumor-oriented, (b), patient-oriented solution.

Depending on the heating method and the tumor location or type, the tumor may require a pre-evaluation in order to determine the "heat-ability" of the tumor before commencing hyperthermia

treatment, [73]. However, what is overlooked is the likelihood that although the absorbed energy did not cause an increase in temperature sufficient to meet the technical requirements of the treatment, the absorbed energy may still effect a change.

The mEHT method uses the certain biophysical differences between the malignant cells and their healthy counterpart to achieve direct and selective effects on malignant cells, destroying them in harmony with the homeostatic control, and extending the local effect to systemic.

Technical Solutions

The change in the paradigm has the potential to solve the historical challenges associated with conventional hyperthermia, and to improve the tumor-killing ability of the treatment. In order to change the paradigm, a shift in thinking from using temperature as a tool, to using temperature as a desired result, must occur. In order to achieve this, the following modifications to the principles are necessary:

1. Apply heterogenic heating instead of isothermal heating. The heterogeneity has to follow the natural structure of the target, with selection of the malignant cell to be destroyed.
2. The precise selection of the malignant cells is required in order to concentrate the incident energy on the cellular effects within the tumor.
3. The characteristics of the energy delivery are chosen based on the ability to trigger the desired intracellular signals in the cancer cells, and to provide a driving force to promote the collective behavior of the cells, instead of the autonomic behavior of malignant cells.
4. The dose is the applied energy.
5. The dose is chosen carefully: it should not be so high as to heat up the complete tumor-mass, only the selected cells should be targeted.
6. The forwarded energy is not constant during the treatment and it is periodically modified according to the protocol for the tumor type, location and the applied complementary treatment.
7. The patient is actively involved in the treatment dose by providing feedback on the tolerance of the incident energy (sensation at the point of contact).
8. The efficacy of the actual treatment is measured by the outcomes and not by the achieved temperature.
9. The overall survival time (OS), and the quality of life (QoL), are used as measures of the success of the treatment, and not only the local control.

These points are achieved with the synergistic action of the electromagnetic energy and the temperature in the mEHT method, [74], [75]. The temperature is responsible for the thermal effect described by the Arrhenius law, [76], Fig. 9/a. This law approximates the reaction rate by a probability determined by the negative exponent of the ratio of the activation energy (the energy barrier for the reaction), and the temperature represented energy ($\boldsymbol{R \cdot T}$), {where $\boldsymbol{R}$ is the gas-constant and $\boldsymbol{T}$ is the temperature}. The biological changes however are not as simple as the gas or solid-state reactions, with the presence of enzymes to assist in surmounting the energy barrier, Fig. 9/b. The enzymatic reaction is not so simple and it forms complex transient states at the top of the barrier Fig. 9/c., which in turn promotes the suppression of the barrier. The mEHT method has a similar effect to the action of enzymes, but instead of the chemical process, electromagnetic interactions form the transition state, in the same manner as the chemical complexes.

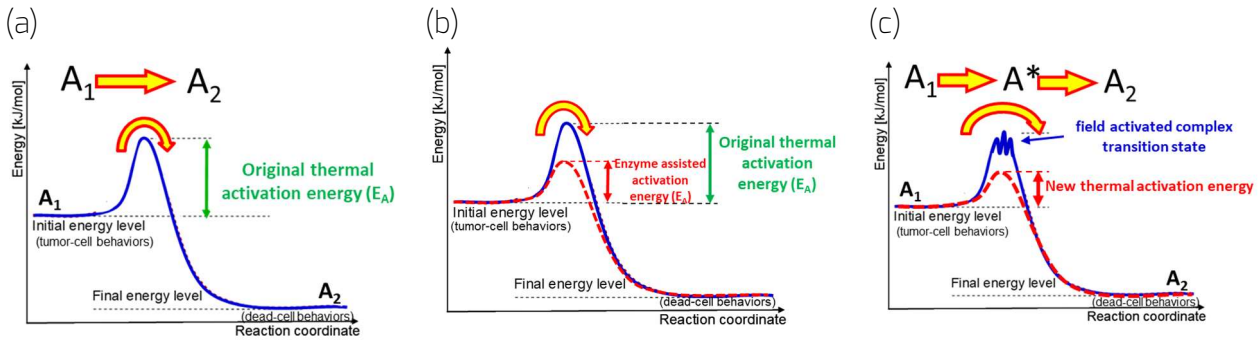


Figure 9. The thermal reactions. (a), simple Arrhenius law, (b), the enzymatic assisted jump lowers the energy barrier, accelerates the reaction rate, as the biological processes do it, (c), the enzymatic transition state could be constructed by the electromagnetic field.

The intermediate transition state depends on the field-strength, while the square of the field produces the heating energy, Fig. 10. The mEHT treatment becomes complex due to the two pathways which are involved in the two basic activities: the heat causes cellular and physiological modifications, while the field is responsible for molecular and immunological changes. All homeostatic actions are complex, having supportive and suppressive actions to keep a dynamic balance.

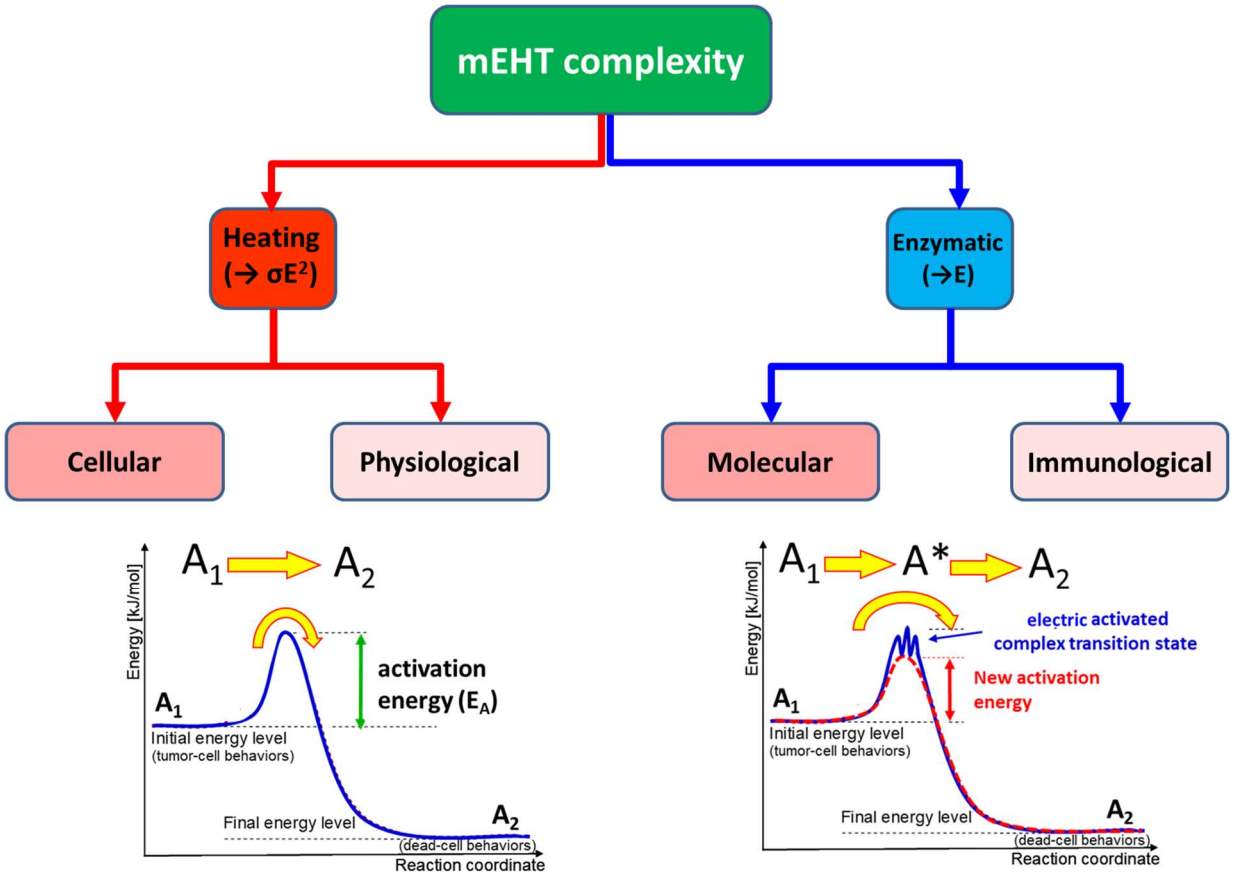


Figure 10. The actions of the electric field (a), heating, depends on the square of the field multiplied by the conduction of the media, (b), linearly depends on the field, and dominantly acts on the dipoles (polarization, dielectric permittivity).

The cell destruction is supported by heat, [77], as the heat causes an increase in intracellular pressure, [140], promotes membrane damage, [77], [78], improves selection by increasing cellular sensitivity, [79], and can trigger necrotic cell-destruction, [80]. However the effects of heat could also oppose the initial treatment goals by necrotic changes (toxicity, inflammation), [81], by increasing the risk of developing stress resistance, [82], by promoting anaerobic metabolism, [83], and by promoting cellular autonomy with breaking the cadherin connections, [84].

The physiological effects of heat promote: the vascular, [85] and drug permeability through the blood vessels, [86], and cellular membranes, [9], [140], and even through the blood-brain-barrier, [87]; and the drug transport to the tumor, [88]. The increased relative blood perfusion, [6], [89], delivers more oxygen, which is required for radiotherapy, and the reaction rate of the drug, [90]. Together with these supportive actions there are certain negative influences from the enhanced blood-flow in the heated volumes. The blood delivers nutrients supporting the tumor and increases the dissemination risk via the bloodstream, potentially supporting the formation of metastases, [91], [92], [93].

The field effects, and the resulting energy absorption, are no less important than the heating effects. On a molecular level the effects include: selection of the membrane rafts, [94]; excitation of the intracellular signals with extrinsic effects, [95]; stimulation of apoptosis and autophagy, [96]; and promoting the reconnection of the lost intercellular bonds, [97], [98]. Importantly, however, the field triggers immuno-oncological and systemic effects: damage associated molecular pattern (DAMP) formation, [99]; triggering of immunogenic cell-death, [100]; antibody presenting cell (APC) formation, [101]; and the development of tumor-specific immunity which may stimulate the abscopal effect and potentially in-situ tumor-vaccination, [102]. There are however also some negatives associated with the field treatment: the E-field jumps between layered boundaries which can cause burns, [103], [45]; it is difficult to control the field-effect, [45]; the personal sensitivity of the patient influences the reactions, [104]; and cell-death is rarely immediate so the results of the treatment occur over a longer period of time, [105]. Additionally, a long adaptive time is needed for immune actions, and when the temperature is high (over 40°C), the immune activity is suppressed, [106], [107].

Brief history of mEHT

The mEHT technology has a history that goes back more than 20 years, [108], [109]. The scientific background was developed at the Surface Physics Laboratory in the Eötvös Science University, Budapest. In 1988 a spin-off company was started, with the goal of realizing the synergy of bio-electromagnetic and surface physics. Starting with invasive galvanic therapy, the electromagnetic elimination of the tumor was the initial focus. However, the medical problems associated with the invasiveness of the technique, meant that developing a non-invasive method became crucial (1990). After four years of research, the first commercial device received the GS-sign (Geprüfte Sicherheit, meaning "Tested Safety"), issued by TÜV, the largest Notified Body in Germany and later in the EU. After an additional four years, in 1998, TÜV certified the ISO approval of the company, and gave the CE certification for the EHY-2000 device. Since the certification, the device has been continuously developed, improved, and approved by TÜV. A complete renewal of the electronic solution took place in 2004, with the development of the EHY-2000 plus (EHY-2000+). The company, Oncotherm Kft., has also developed other medical devices, although the EHY-2000 series remained the most popular:

- for electric cancer therapy ECT-2000 continued the invasive treatment,
- for prostate tumors the transurethral solution (PCT-2000),
- for whole-body treatment (WBH-2000)
- for interstitial (ablation), hyperthermia (ICT-2000),

- for veterinarian use (EHY-500 or VetEHY).

The company pursued the development of the popular technology, launching the compact EHY-2010), and a device which has a novel electrode system that can be tailored to different size electrodes, large enough to cover the entire body (multi-local treatment, EHY-3000).

The design of the EHY-2030 began eight years ago and the device received CE approval in 2019. The EHY-2030 integrates the knowledge collected during the last 20 years of applications to improve patient and clinician experience.

The main events of the history of the method are shown in Fig. 11.

Figure 11. The short summary of the historical steps of the development of mEHT in research and market. ©Oncotherm GmbH/Kft.

Technology of mEHT

The technology harnesses the synergy between the electromagnetic and thermal effects of the method on the malignant cells, [110], [111].

The electronic technology

All of the activities (chemical reactions), of life take place in aqueous solutions containing electrolytes. These electrolyte rich solutions are found in both the intra- and extracellular environment. Lipid membranes, which separate the compartments, contain a bilayer of phospholipids with various molecules, including glycoproteins. Ionic exchanges occur between the compartments via passive or active transport across the membrane. The maintenance of the acid-base balance is a part of the complex homeostatic control, which also includes fluid balance, temperature, glucose availability, and a huge number of other stabilizing factors, which are tightly interconnected to ensure a dynamic steady-state of equilibrium in the system.

Cancer disrupts the healthy equilibrium, initially only on a microscopic and local level, but eventually the disruption becomes macroscopic and systemic. This disruption begins with renegade cells, [112], which develop in opposition to the networked healthy host tissue. The opposing reactions relate to the intensive proliferation of the malignant cells, which, due to its space-requiring progression, increases the mechanical pressure in the developing tumor, [113]. This stage of the cellular development is referred to as the α-state, while the networking cells form the β-state, [114]. Cell division in healthy tissue ensures the replacement of cells which have undergone cell death, usually via apoptosis, or supports the growth of healthy tissue. In malignant tissue, cell division continues despite the reduction or absence of apoptosis and cell death, [115], [116]. One of the goals of the mEHT method is the induction of apoptosis in malignant tissue.

One of the weaknesses of cancers is that the aggressive proliferation breaks the networking bonds of the cells, forming autonomous units in competition for the available nutrients, forcing the host to develop a supportive environment to meet the cellular demands. The actual delivery of ionic solutes increases in the microenvironment of malignant cells, as nutrients are brought in at increased rates and the waste must be removed, resulting in an increased exchange of ionic solutes across the membranes. The higher ionic concentration has an effect on the electric characteristic of the tissues: the conductivity carried by ions increases in the malignant structure. The resulting lowered resistivity channels the applied RF electric current to the malignant cells, creating a process of self-selection. The next step is to develop a mechanism that is able to control the balance between the β-and α-states in the disrupted system. To achieve this, the electromagnetic behavior of the electrolytes in the living systems is manipulated, [117]. The cooperative cells mostly run on oxidative metabolism, and their division is controlled by the cells in their neighborhood. However malignant cells in opposition can be targeted by modifying the microenvironment and the membranes, triggering not only the apoptotic processes, but also the repair of the lost networking connections. These mechanisms are described in the following pages.

The electromagnetic effects of mEHT are a result of the external source of the field. The absorbed energy can be measured by the forwarded power P_{fwr}, calculating the impedance loss which is measurable by the reflected power P_{refl} or more preciously (due to the impedance matching), with the phase angle (P_{refl} , phase shift), between the applied voltage U and the RF current I. The useful power P_{use} in this would be

$$P_{use} = P_{fwr} - P_{refl} = U \cdot I \cdot cos(\varphi)\ [W] \qquad (1)$$

The goal of the mEHT technique is to have $P_{refl} \approx 0$, or in the impedance formulation $\varphi \cong 0$, when the electric circuit is in resonance; while applying a precise and constant frequency of $13.65\ MHz$. Furthermore, the current must be maximized as the energy-absorption depends directly on the current. When the P_{use} is constant, and the current is at its maximum, the voltage will be at its minimum, which increases the safety of the treatment, optimizing the efficacy.

The development of malignancy changes not only the conductivity, but by disrupting the intercellular network, dielectric differences are created as a result of disorder in the tissue. The microenvironment of these disconnected cells will be structurally different from normal tissue, lacking the networking connections, such as the cadherins and junctions. The disorder makes the cancer cells distinguishable from healthy tissue and this change in the dielectric permittivity, and in the conductive and dielectric properties, results in the different electromagnetic impedance of the microenvironment of cancer cells, compared to that of healthy cells. This provides additional guidance for the RF current flow, allowing the automatic selection of the malignant cells by mEHT. In a sense, mEHT has a "theranostic" action in that it can select and treat the malignancy simultaneously.

The thermal technology

After recognizing the malignant cells, the energy-absorption creates the hyperthermia step. Due to the un-bonded transmembrane proteins, the concentration of highly dynamic and heterogeneous glycolipoprotein microdomains on the membrane surface (also known as membrane rafts), significantly increases. A well-chosen frequency (acting in the range of β/δ dispersion), directly targets the lipid-protein bonds and heats up the membrane rafts to a conditional temperature. This step is equivalent to the conventional hyperthermia method, only instead of a macro-absorption, mEHT selectively applies micro- (nano), heating.

The energy absorbed in the system is used to trigger reactions, and transitions. In some instances, the result is the release of heat, and in other instances the increased heat triggers the transition. A simple example involves boiling water: where the temperature ($100℃$ in normal pressure), is a conditional necessity to form steam from the liquid, but during the process only the structure changes (from liquid to gas), the temperature remains constant, until the phase transition is finished. In the mEHT technology similar conditions have to be realized: a definite temperature required by the micro-environment must be reached, and the subsequent energy, which is absorbed by the molecular clusters (rafts), will cause changes in the structure and excite the molecules. It appears that this is one of the steps involved in initializing apoptotic signals in the various pathways in the cell.

It is important to tune the conditional temperature to the optimal range, otherwise the requested molecular changes cannot be controlled. When the temperature is low, then the energy absorbed by the membrane raft is also low, and the molecular modifications do not happen. When the temperature is too high, the molecules are destroyed, necrosis occurs, which contradicts with the goal of synchrony between mEHT and the homeostatic control. When the energy dose is too high, not only do the mechanisms become less controllable, the selection of cells diminish as the rapidly rising temperatures results in the spread of the absorbed energy into the wider environment. This process starts to heat up the mass of tumor instead of the cells alone, so the selectivity, which was established by the electric tuning, is lost.

To avoid losing the electric selection by the thermal spread, a step-up heating process is applied. In the heating process the temperature and the absorbed energy correlate; the temperature grows linearly with the absorbed energy. The linear growth in a unit of time characterizes the absorbed power, which is specific in a unit mass, and measured by the Specific Absorption Rate, (SAR, $[W/kg]$). When the temperature starts to equalize with the environment, the SAR spreads, and becomes saturated only at the point at which the homeostatic-regulated blood-flow is able to re-establish balance in the system. In this case the temperature does not change as the blood flow compensates for the absorbed energy, and the SAR replenishes the energy, which is taken away by the blood flow, (washout mechanism). In order to avoid this situation, the temperature needs to be continuously adjusted, by increasing the applied power. In this method the power is gradually increased, considering the optimal energy-absorption, using the SAR to completely heat the selected malignant cells.

Due to the selection and heating technique applied in mEHT, which targets nanoscopic regions on the cell membrane, the macroscopic temperature increases only moderately. The clinical consequences of the moderate increase in temperature are important:

1. The mEHT treatment induces less adverse effects, decreasing the delivery of supporting nutrients, and lowering the risk of invasion and dissemination.
2. Despite the lower overall temperature, the increase of blood flow is sufficient to promote the effects of chemotherapy by
    a. increasing the concentration of the drug in the tumor,
    b. increasing the reaction rate of the drugs.

3. Additional to the moderately increased blood flow, the electric field increases the penetration of the drug through the membranes of the malignant cells in the high-pressure space-occupying tumor by promoting the permeability of the cell membrane to the drug.
4. In combination with radiation therapy, the overall increase in blood-flow increases the oxygen perfusion and the oxygen in turn is able to attach at the point of DNA breaks, blocking the activity of reparation enzymes. The additional oxygen also increases the formation of reactive oxygen species which play an important role in further DNA damage.
5. The macroscopic temperature increase remains under the vasocontraction limit, so the enhancement of the chemotherapies and radiotherapies and other blood-delivered therapies (like immune, enzyme, gene), are not limited.

Synergy of electric and thermal actions – the physiologic "technology"

The automatic selective steps and the hyperthermia related energy absorption depends on the applied RF technology. This requires the specialized permanent control of the impedance tuning, as well as the careful development of the optimal thermal conditions in the hyperthermic step. The "theranostic-like" action results in the selection of specific molecules in the selected cells in selected tissues. The effects of cancer are however broader than only the cellular effects. There is a disruption in the collective behavior that characterizes the complexity of the multicellular organism. The unicellular behavior of the autonomic cancer cells only benefits their condition temporarily as they are better able to survive, proliferate and adapt, but the lack in collectivity will eventually result in their destruction.

The disorder in cancer cells appears in the structural pattern of the specimens as evaluated by pathologist, making the disease recognizable and providing prognostic information from the development of the disorder in the structure, compared to the natural healthy samples. The structural pattern provides an extra selection factor for electromagnetic interactions. The macroscopic disorder increases the macroscopic permittivity, which is observed microscopically. Consequently, macro-selection occurs due to the structure. However, the situation is more complex. The collectivity of healthy cells, accompanied by the synchrony of the various chemical changes in healthy cells, results in measurable fluctuation signals in the system, characterizing the homeostatic equilibrium. One example of such a fluctuation is the heart-rate variation (HRV), which has emerging applications in diagnostics and in the improvement of physical well-being and health. Other reactions (for example nervous signals, or even the extra- and intracellular signals transmitted via definite pathways), also produce definite and repetitive distributions of the fluctuations. These variations group the systemically regulated and controlled chemical reactions in space and time, which has a defined order and an interdependence in the healthy complex system. When the ordered complexity (homeostasis), is derailed, the spectrum of the fluctuations also changes, which can be used as tool for the early recognition of diseases. The mEHT method utilizes these complex fluctuations to further select between the healthy and the disordered malignant tissue. To achieve this, mEHT applies a modulation of the carrier frequency, which forces the correct homeostatic fluctuation (synchrony), of the interaction. The modulated signal aims to promote the complex regulations, suppressing the malignant disorder. One of the consequences is to promote the reconnection of the cells, limiting the autonomy of the malignant processes, [169]. The theory is that the applied fluctuation as modulation collectively vibrates the transmembrane proteins to reorganize and recreate intercellular bonds, as this represents the state of minimal energy expenditure. The re-bonded connections promote the overall control, attaching the cells to neighboring tissues, and blocking the invasion into the vessels and the subsequent dissemination of malignant cells.

The absorbed energy also triggers extrinsic apoptotic signals, which could excite variants of the apoptotic processes:

1. The apoptosis produces apoptotic bodies, exosomes and other small vehicles.
2. A DAMP formation, which when appearing appropriately at the correct time and location, can complete the apoptosis via immunogenic cell-death (ICD).
3. In the ICD process, the freed special DAMP molecules like the 70 kDa heat-shock proteins (HSP70), calreticulin, HGMB1 and ATP, provide "information signals", "eat me signals", "danger signals", and "find me signals", respectively; providing tumor-specific information for immune actions.
4. The DAMP induced ICD forms APCs by maturation of the dendritic (DC), or other APC forming (macrophages), cells.
5. The APC helps to produce tumor specific immune actions by forming killer (CD8+), and helper (CD4+), T-cells, directly carrying the tumor-specific information.
6. The immune action promotes the abscopal effect, targeting the distant metastases by the naturally prepared T-cells.
    a. This may result in a positive change in the metastases (eliminate it completely or partially, or at least stop their growth) providing essential benefit for OS and QoL of the patient.
    b. The immune-process may function as a "tumor-vaccination" when the re-challenging of the same malignancy does not cause cancer.
    c. The production of active tumor-specific T-cells does not require outside laboratory work in this case, as these are prepared in-situ and in real-time.

The HSP proteins have various functions in the living organisms; they are present in all cells from unicellular to multicellular systems. The HSPs have a chaperon-like role in the cells, are involved in protein folding, in apoptosis, in autophagy, and in immunity. Simply put, HSPs are protectors of the status of the system, internally providing support for the survival of that cell, while extracellularly they promote the healthy organizing actions, helping to eliminate the cells which are out of the expected order. Their Janus face character plays a role in the development of therapy resistance, but also has an extended role in the immune surveillance. Their role in the protection of the cancer cells among the massive environmental challenges during the proliferation is essential, aiding the adaptation of the cancer cells to the extreme conditions. On the other hand, when re-localized and expressed on the cancer cell membrane and released into the extracellular matrix, they supply information about their host which is essential to the APC forming tumor specific immune action. The differences between HSP concentrations in malignant and healthy cells is measurable, as cancer cells have significantly more stress, resulting in as much as a ten-fold increase in the intracellular HSP, in order to defend the cells against apoptosis or autophagy. However, when a general external additional stress, such as a temperature increase, activates the cellular protection in the healthy cells, the HSP expression increases drastically (up to ten-fold), while in the cancer cells where the original HSP concentration was extremely high, the newly expressed HSPs less than double the HSP concentration. This could be one of the factors causing the higher heat-sensitivity of cancer cells, which are unable to survive the heat-stress exposure as long as the healthy counterparts are able to.

The vulnerability of cancer cells to heat also partly depends on their autonomy. The energy which targets them remains in the cell, as the cell is unable to share the energy with neighboring cells, through the intercellular network.

Other technical considerations

Surface Cooling

In order to ensure the optimal efficacy, the technique reduces the risk of burning and increases the general safety of the treatment. Generally applied surface cooling in hyperthermia technologies avoids the burning of the skin. While mEHT applies surface cooling methods, the methods are less intensive that those applied in conventional hyperthermia solutions. The temperature is adapted to the patient's actual needs during mEHT, recognizing the limits of overcooling the surface by the mEHT technology by the active physiological feedback of the body. When the cooling is too intensive, the blood-flow is reduced by the thermal control of the body, and the surface layers lose their natural cooling capacity, and increase their isolating properties. These changes in an overcooled surface cause further (secondary), burns, as increased voltage is required in order to penetrate the increased isolating layers.

The applied RF frequency

The chosen carrier radiofrequency (RF), for mEHT is 13.56 MHz. The reasons why this frequency was chosen are:

a. It is a free standard frequency available for medical use, so it avoids interferences with other devices.
b. It is in the optimal range of the modification possibility of lipid-protein interaction, (β/δ dispersion). The lower frequencies lose the range of the δ dispersion, and so lose some of the important lipid reactions.
c. Its penetration depth (where its initial 100% energy decreases to 36%), is 18-cm, which is more than the half-thickness of most humans.
d. The electric impedance of the lipid membranes of the cell are not negligible at this frequency. The higher frequency selection tends to neglect the differences and results in the homogenous energy absorption.
e. The combination of this carrier with modulation is optimal. The carrier frequency has a deep penetration, carrying the information of the modulation, similarly to the radiobroadcasts.

The applied modulation

The RF signal in mEHT also acts as a carrier of information. The information is coded in the amplitude modulation in mEHT, [60]. The modulation frequency is broad spectrum (carrying information in a similar manner to the way radiobroadcasts carry the information of music or speech), [118]. It is chosen based on the natural homeostatic fluctuations, promoting the selected cells and their microenvironments to find their natural state of harmony and in doing so, to rearrange their lost connections and form a network again. In this manner, it has potential to force the system into a state of homeostasis.

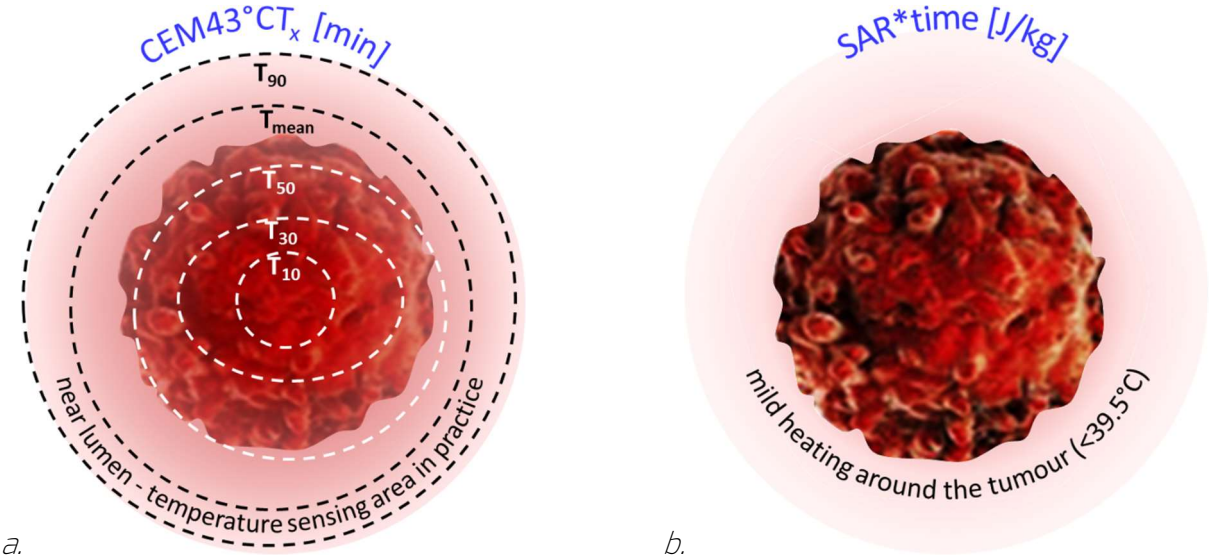
The homeostatic regulated living structure is self-organized and self-similar, which has a fractal structure in space and time. This fractal noise has the ability to synchronize various important signals by the process of autocorrelation. The width of the frequency spectrum is restricted only by the regulation of the standards.

The modulation depth is optimized by the cellular selection of the active carrier. When the modulation depth is too high, selection function lowers. The modulation depth has to be higher than the rectification preciosity of the targeted membranes, and the signal gain by the process and may contribute to the triggering of the apoptotic pathways in the cell.

Dose and treatment control in mEHT treatments

The preciosity, which also involves the tuning and the complete renewal of the electronics of EHY-2030 with the latest technology, allows for a more precise dosing of during mEHT treatments. The principle of the dose paradigm has not changed, and the absorbed energy is still considered as the dose. Several clinical studies have demonstrated improved outcomes and efficacy, [241], [235], [202], [203], [193], while using this dosing concept instead of the traditional dose measurements such as the $CEM43°CT_x$ method. Where intratumoral temperatures are not available (mostly due to safety reason), conventional hyperthermia may measure temperatures in a nearby lumen and the intraluminal temperature is often assumed to represent the tumoral temperature, however this is not accurate and there is a risk that this measurement provides misleading information about the treatment.

The energy absorption measurement is controllable, and even more precise in the EHY-2030. Fig. 12. shows a comparison of the conceptional difference between the doses CEM43 and mEHT doses. The essential difference between the homogeneous (contours of $CEM43°CT_x$), and heterogenic (selective energy absorption provides large contrast between the heated and unheated parts), heating.



a. *b.*

Figure 12. Comparison of the doses. (a), the $CEM43°CT_x$ contours (measured in minutes), (T_x contours show the approx., areas where the T temperature could be regarded as homogeneous. x is the percentage of the area where the T temperature characterizes the isotherm.) Due to safety reasons the temperature is typically measured in a nearby lumen. (b), the selective energy absorption ($SAR \cdot time$), (measured in J/kg, [Gy]).

The patient characteristics and sensitivity to the treatment is an important factor of the dose. In conventional hyperthermia, the patient information, such as tolerance and sensitivity, changes the preplanned treatment and the temperature is reduced to the tolerable level. As a consequence, the $CEM43°CT_x$ dose differs from patient to patient. This situation is similar during mEHT treatments where the feedback from the patient is a vital factor in the choice of power output. As in conventional hyperthermia, the energy dose may also differ based on the patient's individual tolerance, however

due to the significantly lower incident power (in average 8 times lower), the patient will still tolerate a higher dose than in conventional heating.

Doses in protocols

The dosing of the mEHT treatment measures the effective interaction of RF-field with the tissues during the treatment, it gives information which is used for the active control of the therapy. Two doses need the attention of the physician:

1. The treatment dose of the running session. This dose has an upper limit determined by the available maximum power from the device and the time of the session, which is fixed in the protocols.
   This dose is defined in the protocols for various cancer types, however, there may be variations based on the patient's state, comfort and complaints. The planned dose is therefore only a proposal based on statistical evaluation of gathered data and allows for real-time modifications based on the situation. The protocol of the treatment is flexible due to the personalization of the process.
2. The overall therapy dose that the patient receives altogether in the therapy period. This dose is usually a simple, mechanically formed sum of the actual doses in the individual treatment sessions, forming an overall dose of the therapy cycle.
   This dose is however not automatic, and it also requires extra attention to fit flexibly to the results of the cycle. The physician has to consider:
   a. What frequency, periodicity, of the treatment sessions will be applied in the cycle;
   b. What breaks were introduced between the individual treatments influencing the planned periodicity;
   c. The dose of the repeated cycles has to be considered and added to calculation.

   The protocols for cancer variants provide guidelines on how to manage this dose (e.g. how many sessions are proposed in a cycle for the given cancer), however this is mainly defined by the status of the patients and requires personalization based on the development of the patient's cancer-state.

In summary both dose types (the treatment and the therapy doses), have to be handled flexibly depending on the patient and on the progress of the therapy. These considerations are tailored to the patient-oriented cancer therapy and adapted to the complex personalized treatment.

Dose units

The dose unit requires well-defined properties:

1. It must be measurable and reproducible.
2. It must be an extensive parameter. This means that it depends on the size (mass), of the target, not the shape. The energy absorption has to be selective, regardless of the staging and comorbidities, and has to be able to be applied in combination with other therapies.
3. It must include a safety concept and risk/benefit considerations (approved by dose-escalation) and include the safety limit.
4. It has to correlate with the efficacy (measure in clinical practice).

Dose in conventional hyperthermia

Presently conventional hyperthermia uses the cumulative equivalent minutes, which refers to the necrosis which occurs in the Chinese hamster ovarian carcinoma cell-line when heated to $43°C$ *in*

vitro. This dose measurement has numerous challenges according to the basic requirements for dose concept:

1. It is hard to measure in a living human
    a. The most accurate temperature sensing method is a point sensor, which has to be inserted invasively into the body and must remain in place throughout the duration of the hyperthermia treatment.
    b. The point sensor does not present an accurate picture of the entire tumor, due to the heterogeneity of the mass. The sensor reports only the temperature at the location of the sensor. One of the factors which contributes to the heterogeneity of temperature within the tumor is the variation in temperatures at the site of the arteries. The tissue in the immediate vicinity of the artery are cooled by the blood flow. These tissues are therefore likely to have a lower temperature. Multiple sensors would therefore need to be inserted in order to obtain an accurate picture of the temperature distribution within the tumor.
    c. The invasive process has to be repeated during each treatment session in order to measure the actual dose. The invasiveness is associated with some serious risks, such as infection and dissemination of the disease, and this destroys the risk/benefit balance of the treatment.
    d. The non-invasive temperature monitoring using magnetic resonance imaging (MRI), detects the time-shifts, which are not only temperature dependent. The reference for that measurement is a homogeneous phantom without dynamic chemical changes, which are characteristic to the life and to the effect of hyperthermia in action. The temperature is representative of the changing in the target after the absorption of energy and the alterations are detected by the MRI. Unfortunately, the modification of the structural or chemical changes in the target cannot be separated from the signal which is considered to be the temperature. When the modification occurs at a low temperature, the measurement on the MRI suggests a high temperature due to the time-shift change.
2. The temperature is an average parameter, it does not change by the mass. An isothermal mass has the same temperature in all the parts. The mass is connected to the heating energy, which is proportional.
3. The CEM reference is necrotic. In the majority of cases, conventional hyperthermia does not cause necrosis in the complete tumor mass, so it is not comparable to the *in vitro* experimental situation.
4. The CEM reference is on a cell-line measurement, which is homogeneous, unlike tumors.
5. The kink on the Arrhenius plot, which is the theoretical basis of the complete CEM construction, has not yet been fully explained.
6. The CEM definition does not have a correct SI unit, and it cannot be correctly defined in its present form.

It is well-known, that the temperature alone is not enough to ensure the appropriate distortion of the malignant cells. With WBH methods, the whole body may be heated to extremely high temperatures (up to the physiological limit of $\mathbf{42°C}$); and provide more CEM in one session than during any local treatment. However, the tumor-cells are not eliminated from the body. Most local hyperthermia techniques are able to achieve the planned $\mathbf{42°C}$, in only 10% of the target volume ($\boldsymbol{CEM43°CT_{90}}$ is calculated). Consequently, the overall CEM dose is smaller, and the basic average temperature is lower, than the temperature in the hottest 10% of the mass. This undermines the feasibility of the $\boldsymbol{CEM43°CT_x}$ dose.

Dose in mEHT treatment

The new paradigm changes the dose to one which better characterizes the treatment and is proportional with the mass as is naturally required. This dose is the absorbed energy (E_{abs}), measured in J/kg units, which is the same principle as the dose in the ionizing electromagnetic radiation. In radiotherapy it is the Gray ($Gy = J/kg$). The dose provided in a second is measured by the specific absorption rate (SAR), in (W/kg), units, which is limited by the highest available power from the mEHT equipment. The maximum power is determined by the safe penetration of the energy by the skin, which is $\approx 0.5\ W/cm^2$. The dose during one session is the sum of SAR multiplied by the time when it is actually active from t_{start} to t_{end}, so the dose:

$$E_{abs} = \int_{t_{start}}^{t_{end}} SAR(t)dt \ \left[\frac{J}{kg}\right] \quad (2)$$

Notes on dose concept of mEHT

The application of this type of dose requires numerous technical and conditional details.

1. The energy absorption is directed to the targets, which are the malignant cells. The energy develops the expected and planned molecular and structural changes, which are proportional to the applied energy-dose.
2. The basis of the dose is that due to the impedance matching by the resonance, the energy-loss by coupling is small and regulated. We can therefore be sure, that the forwarded and controlled energy is accurately absorbed in the target.
3. The coupling conditions are repeatable, so reproduction of the same coupling is precise.
4. The surface cooling draws only a small part of the forwarded energy.
5. The applicators and their boluses absorb only a low level of energy.
6. The radiation of the RF circuit is negligible.
7. This dose is independent from the measurable temperature, so it is safer and more precise.
8. Due to the electromagnetic selection, the treatment adapts to the movement of the patient (shifting of the position), as well as the natural physiological movements of the system (breathing, heartbeat, peristaltic movements, etc.). The treatment effectively adapts to the physiological changes (like the non-linear change of blood flow), due to the impedance of the target, as it follows these variations. These processes make the dose personalized, so the mEHT reliably adapts its focus to the designated target volume.
9. The energy-absorption is active in the presently undetectable micro-clusters as well, irrespective of the accuracy of the present imaging techniques.
10. The built-in limit of the incident power density of mEHT ($\approx 0.5\ W/cm^2$), guarantees the safety of the treatment, avoiding dangerous overdosing.

The dose prescription has to be personalized in all therapeutic modalities. The personalization in mEHT means that when the patient cannot be treated with the prescribed dose during the specified time in one session, then the session time and/or the number of sessions per cycle can be increased.

The dose for the actual treatment and the dose in the complete therapy consider different concepts. While the patient's feedback regarding the sensation during the treatment modifies the actual treatment, the full therapy is defined by the efficacy of the treatments. The treatment sessions are maximized for the absorbed power, limited by the patient's tolerance. However, the complete therapy (number of treatments) does not have a tolerance limit, and can be continued up to the time that the desired result has been achieved

The most effective way to assess local control is using imaging (CT, MRI, PET, etc.), studies. These should be administered after treatment cycles in order to determine the benefit and toxicity of the treatments. The long-term control of local disease can shift the mEHT protocols towards long term, chronic protocols.

However, the efficacy of the treatment is determined by more than the local control. The local control of the tumor does not mean that the patient is cured. Micro and macro-metastases could be active at distant sites, which limits, the survival of the patients, as well as the quality of life. Due to these reasons, the measure of the efficacy of the therapy has to include the prolongation of the survival and the improvement in the quality of life.

Step forward with the mEHT technology: the EHY-2030

The concept of the mEHT treatment focuses on the interest of patients. The manufacturer summarizes these points in the proposed 3E+3S concept, which has been their core concept for over a decade, Fig. 13.

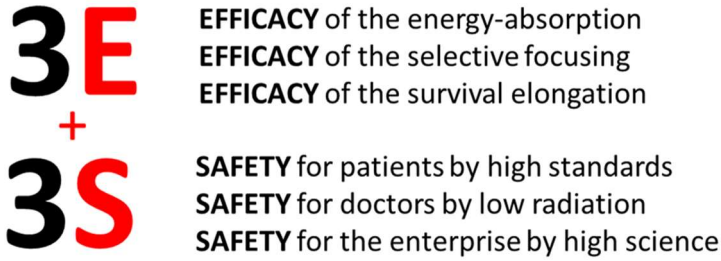


Figure 13. The strict 3E+3S concept of development of EHY-2030.

The continuous development of the mEHT technology is based on the research conducted primarily using the laboratory devices (LabEHY-100 and LabEHY-200). The laboratory works are combined with the theoretical and model calculations, developing various measurements which can be extrapolated from the lab setting to the clinical setting. Previously the clinical research has focused on the EHY-2000 and EHY-2000+ models. Based on the new research and the clinical experiences with the devices, a completely new model was developed (EHY-2030), and lunched. In this section we discuss the technical developments that have culminated in the launch of the EHY-2030, and the subsequent need for the modification of the protocols, [4], [119].

The concept of the two devices, the EHY-2000 series and the EHY-2030, is the same: the cellular selection, molecular excitation and immunogenic effects, form the backbones of these applications. The difference between the devices is in the drastically improved user experience, including modern electronics, user-friendly automatization. The EHY-2030 has more precise impedance matching which results in higher treatment efficiency, more reliable treatments, and better control of the parameters, increasing the expected success of the treatment. The ergonomic design, the modern outfit, simplified operations, amongst other qualities, make the EHY-2030 attractive for patients and for the medical staff. Based on these improvements and advantages, and on the increased demands of the Medical Device Regulation (MDR), (previously the Medical Device Directive (MDD)), in the European Union (EU), the EHY-2030 replaces the older versions, providing a higher standard of mEHT.

The theoretical work on mEHT is based on the concept modelled *in silico*. The next step was the experimental part with the LabEHY system, a device developed to mimic the human treatments on

murine and other animal models, providing feedback on the theoretical considerations, and supporting the further development of the human treatments.

All of the research and development steps are interconnected and have a feedback loop which continuously drives the development forwards. The EHY-2000+ and the EHY-3000 have provided case-reports, studies, and trials which have supported the development of the new EHY-2030 system.

The new (completely flexible), patented, [120], electrode has been studied in selected clinics around the world.

Initial evaluations on the performance of the EHY-2030 have been conducted in Semmelweis University Budapest, Hungary; the Marques de Valdecilla University, Santander, Spain; and the Charité (Humboldt University), Berlin, Germany. The Oncology Center of the Semmelweis University provided data and practical information during the entire development process in the frame of the Hungarian Competitiveness and Excellence Program grant (NVKP_16-1-2016-0042), 2016 to 2019.

The Oncotherm EHY-2030 (Fig. 14.) was developed to meet the high-level requirements of a modern medical practice. The equipment is isolated from the common power-network for safety purposes and is supported by a specially developed control and data management software.

Figure 14. The EHY-2030 device.

This device combines the best clinical features from the EHY-2000+ and EHY-3010. The combined optimization is completed with the newest modern electronics, the updated knowledge of hyperthermia in general, and the state-of-the-art bioelectric triggering of molecular reactions, producing immunogenic effects to target the disease, systemically.

Main parts

It is recommended that the operators learn the names of the device parts (Fig. 15.) so that in the event that technical assistance is required, the problem can easily be reported to the Oncotherm technical team.

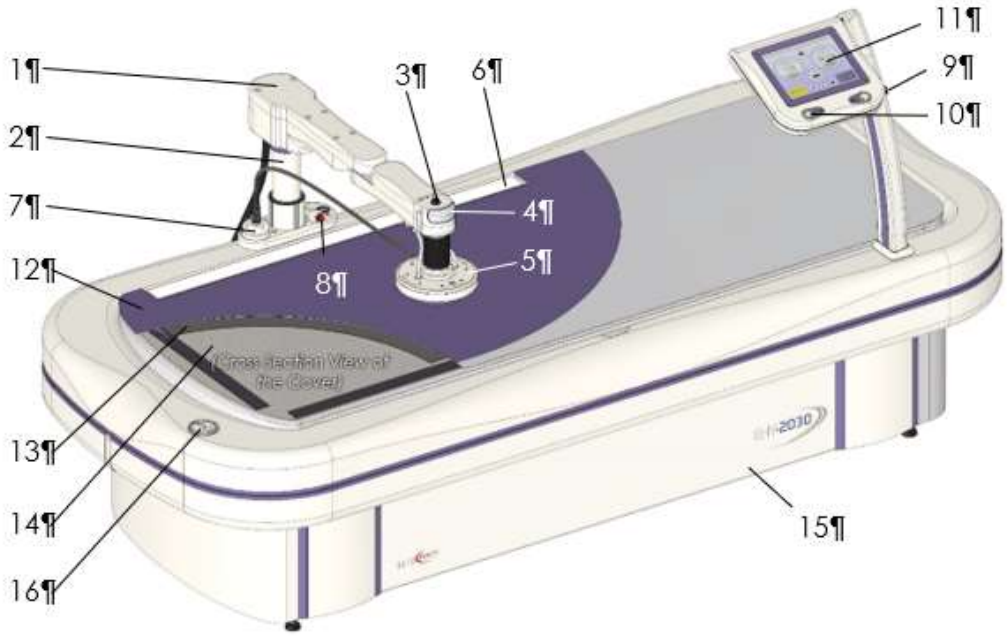


Figure 15. Parts of the EHY-2030. 1. Motorized electrode arm, 2. Linear actuator, 3. Smart electrode remove button, 4. Positioning guidance LED bar, 5. Smart electrode, 6. Grounding bar, 7. Magnetic grounding disc, 8. Patient stop button, 9. Emergency stop button, 10. Display interface buttons, 11. Touch screen display, 12. Synthetic leather cover, 13. Conductive fabric layer, 14. Mattress, 15. Front cover, 16. Coolant indicator/Fill-hole

One of the main changes of the treatment bed is the replacement of the water-mattress with a soft, foam one. The change is not only formal, but also has an important electronic reason: the water mattress formed a part of the resonant circuit tuned by the device. In the EHY-2030 the electrode is near to the skin of the patient, increasing the energy-concentration on the tumor and the selected malignant cells. The new solution was initially applied in the EHY-3000 devices and the clinical publications proved the efficacy of this development, [121], [122], [123], [124], [125], [126], [127], [128], [129], [130], [131], [132].

Smart electrode system (SES)

The second electrode of the circuit, the upper applicator, has also undergone a drastic change. The construction of the SES avoids the technical impedance loads and concentrates on the patient's impedance. In the new construction the RF-current does not flow through the water-bolus, and the active electrode is nearer to the skin of the patient than in the standard EHY-2000 electrode. Despite the close proximity of the electrode to the surface, the applicator remains flexible, and smooth enough to fit on the patient's skin with appropriate contact between the patient and the full active surface of the electrode. The SES developments were also tested on the EHY-3000. The changes made to the electrode pair (the bed and the applicator), are a great step towards a higher concentration of the power on the patient's malignancy, [133]. The solution increases the personalization because the resonant system is more sensitive to the impedances in the body, increasing the preciosity of the "theranostic-like" effects of the mEHT method.

Other notable changes include the electronic adjustment, and the robotic positioning of the applicator instead of the manual fit used in the EHY-2000+ model. This solution makes it possible to ensure

the best available electric connection for the RF-current, so that together with the electrode changes, further reductions in the impedances in the resonant circuit are made.

Coupling and tuning optimizing

The smart applicator concept senses the precise fit of the electrode on the body-surface and provides visible signal feedback to the medical operator regarding the quality of the positioning for the improvement of the tuning.

The device is sensitive to, and reacts to, the changes in the impedances, which involves the patient's characteristics, the process of the treatment effects, and the movements of the patients including the normal internal movements such as breathing. The automatic selection of malignant cells by the electromagnetic method helps to focus the energy-absorption in the chosen cells, and this is further optimized by the tuning.

Software

The software is designed to be easy-to-use. The EHY-2030 system incorporates a Patient Management System (PMS), offering the possibility of data-collection and handling. In this module, recording and reviewing personal patient information and treatment data, designing treatments, treatment initialization, termination or monitoring, are available through a personal computer.

Technical details of EHY-2030

The equipment is a high-tech, high-quality unit, incorporating the latest available techniques from Oncotherm. The output power is stable enough for dosing, which requires the calculation of the forwarded energy. The technical data are as follows:

Mains supply:	100-230V (50/60Hz)
Max power consumption:	800 W
Max output power by RF generator:	800 W_{pp}
Rated RF output power:	350 W_{eff}
Adjustable RF range:	25-350W (5W resolution)
Nominal electrical load:	50 Ω
Output carrier frequency:	13.56 MHz
Output modulating frequency:	0-10 000 Hz
	(Time-fractal, experimentally optimized)
Adjustable treatment duration:	1-90 min (1 min resolution)
Dimension (L*W*H):	2500 mm x 1150mm x 1350 mm
Total weight:	200 Kg
Electrical safety classification:	Class I, Type BF (IEC 60601-1),

Degree of protection:	IP2X
Max. weight of the patient:	150 kg
Operating conditions:	
Temperature:	+15°C ..... +30°C
Relative humidity:	20% 60%
Air pressure:	800 hPa ..... 1060 hPa
Electrode type:	flexible tissue with metallic layers
Bolus type:	temperature-controlled bolus
Coolant medium:	distilled water
Electrode variants:	D200: 200 mm diameter max 150 W
	D300: 300 mm diameter max 250 W
Graphical user interface:	LCD touchscreen, 800*600 pixel
Viewing angle (vertical):	110º
Expected Useful Life:	7 years

Tuning: The auto-matching unit (auto-tuner), always tunes for a calibrated value, a standard 50 Ω (fits the impedance), so that the delivered output power is calibrated.

Electrical safety classification:	Class I
Type BF:	IEC 60601-1
Type of certificate:	CE_{0123} (MDD),

Certifications for compliance to the standards

The technical safety of the mEHT devices is certified by the German TÜV, the largest Notified Body in Europe. The products have CE certification according to the Medical Device Directive (MDD), and the production is approved by ISO13485 standard, ensuring the highest quality and reproducibility of the products. All products have a certificate of conformity. The device safety includes the Electromagnetic Conformity (EMC), which guarantees the satisfaction of the radiation standards representing no risks for the patient or medical staff. The newest EHY-2030 has also completed all of the certificates in the EU and has entire market approval for EU utilization and for export.

Evidence of the mEHT method

Over the years, numerous case-reports, studies and clinical trials with the EHY-2000+ and EHY-3000 devices have provided a solid basis for development of the EHY-2030. It takes a long time to move from the research and development phase to the clinical phase [134], and the process requires rigorous testing and feedback at each stage of the development. There are various challenges associated with hyperthermia [135], however the modern developments in mEHT technology are showing great strides in overcoming these challenges. This section highlights the preclinical and

clinical work on mEHT providing insight into the direction that we can expect mEHT to move into over the next few years [111].

Theoretical and *in silico* studies

The theoretical models behind mEHT have been discussed extensively in the literature with a vast amount of available publications which explain the method, [136] as described in the previous sections. The fundamental concepts of mEHT, as described previously, are the self-selection abilities, [76], [137], the importance of the homeostatic equilibrium, [138], the interdependence of the energy absorption, the temperature, [139], and change in the dosing concept enabling the energy to form the dose instead of the temperature, [42]. The change of the microenvironment of the selected malignant cells by the absorbed energy, [140] and the charge redistribution in this microenvironment, [141] are also discussed in the framework of the mEHT method. Several publications have demonstrated the synergistic relationship between the field and the thermal effects, [142],[143]. The complex characteristics of the technology are also discussed in detail in the literature, [144].

The theoretical considerations of the noise fluctuations in the microenvironment of the cells describe the potential of the frequency to excite the membrane states of transmembrane proteins [145] by fractal noises, [146]. In a similar way to the modification of water-states in biomaterials [147] and the action of the electric field in a noisy environment due to the vector potential [148].

The feasibility of electromagnetism in cancer treatment has been discussed, [144] and a physical analysis of the amplitude modulation of the powerful carrier frequency has been conducted in order to better understand the effects of the modulation [149], [150].

The effects of the basic selection mechanism of mEHT, considering the microenvironment of the cells, and applying the Warburg and Szent-Gyorgyi effects, are discussed in detail [151]. The membrane effects are discussed in the frame of the excitation of transmembrane proteins, involving the transient receptor potential vanilloid (TRPV) channel, [152]. In this study, mEHT was shown to be similar to nanoparticle heating, but instead of the injection of artificial nanoparticles, mEHT harnesses naturally found nano-units in the malignant cells: the membrane rafts. The nanoscopic treatment is discussed fully in connection with the therapeutic applications, [153]. Electromagnetic model calculations numerically demonstrate the nano-heating resulting from energy absorption at the membrane raft of malignant cells, [154].

The intracellular impacts of the chosen RF current on the cytoskeleton has also been studied, [155], [156]. When exposed to the same temperature, the effects on *in vitro* cell lines are superior of mEHT with modulation are superior to other heating methods, [65].

An essentially new theoretical approach had been published for the evaluation of single arm studies in a series of papers, [157], [158], [159]. The patients in terminal stage of disease do not have any further curative options as all other treatments have failed. A conventional palliation protocol starts at this time-point. The evaluation loses the possibility to form a satisfactory number of patients in the cohort for the control group, because of the highly variable history including multi-line therapies, as well as the personal differences between the patients. As there are not further options for treatment, enrolling a control group and administering treatment would be unethical. The best comparison would be to administer “best supportive care” protocols. In most of the cases mEHT administered at the end stages of disease faces the challenge of the control group and in most studies involving end-stage patients, the treatment is studies in a single arm trial with a prospectively or retrospectively controlled cohort. The single arm clinical trials are regarded as weak as there is

no “blinding”, no randomization, no control of the variables etc. This proposed approach applies the basic organization of the homeostasis as a reference, understanding that the tumor is out of this healthy structure. The survival measures, according to this model, could increase the level of evidence of studies on end-stage patients, [159].

A clear trend in the desired outcome is the local treatment with systemic effects, likely through immunogenic abscopal mechanisms, [160], [161], [162].

The theoretical considerations and model calculations were verified in measurements, on non-living phantoms, preclinical *in vitro* and *in vivo* experiments, and of course by clinical studies; which are summarized in the following part below.

Phantom measurements

The phantom measurements indicate the heating process in a stable system without physiological control. The phantom model is heterogeneous, and partly mimics the real conditions in the body. The material was chopped pork-meat, including muscle and fat in the approximate ratio of the real patient without cachexia, [163]. The results show the temperature development in the chopped meat phantom without malignant tissue. To demonstrate the selective action, a phantom of egg-white in distilled water was used and coagulation of the egg white was observed while the surrounding water was unheated, [164]. The liver, or balls of caviar, immersed in water were also used as a phantom and demonstrated selective heating [164]. The sophistically layered egg white phantom model experiment demonstrates the complex selection process of mEHT, [164]. A meat and liver layered phantom with a malignant liver tumor was also measured, [164], and the selection was shown. These experiments were presented at numerous conferences and attracted the interest of the participants. The selective heating characteristics of mEHT were independently simulated and successfully evaluated experimentally, [165].

The phantom comparison in real human devices was also measured and showed the advantages of the flexible electrode. Here the tuning loss was technically equalized. In these measurements (Fig. 16.), the efficacy is 20% better in EHY-2030 and the heating profile is much more unified in depth.

These phantom experiments presented on the EHY-2000+ formed part of the driving factors in the development, construction, and optimization of the EHY-2030, [166].

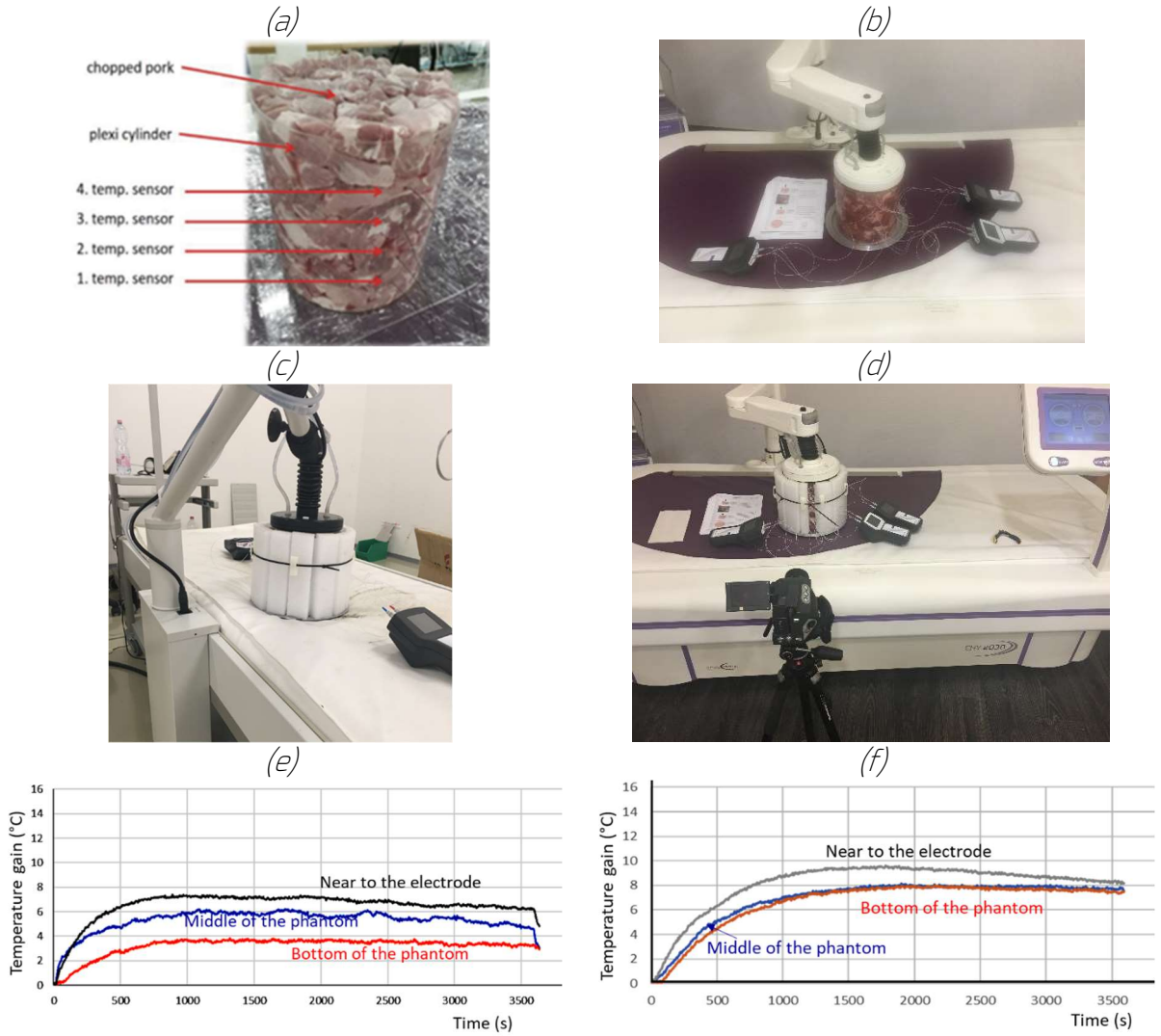


Figure 16. The comparison of the EHY-2000+ and EHY-2030 phantoms. (electrode 20 cm diameter, power 100W), (a), the setup of the meat-phantom, (b), the set-up of the phantom on the bed, (c), the setup for EHY-2000+ measurement, (d), the setup for EHY-2030 measurement, (e), the results for EHY-2000+, (f), results for EHY-2030.

In vitro preclinical evidence

Intensive preclinical studies connect the theoretical and phantom experiments with the clinical applications. This step of the development proves the concepts in living objects and shows the direct molecular changes when the system homogeneously contains only malignant cells are demonstrated *in vitro*. The *in vitro* experiments focus on the cellular mechanisms and the results provide valuable information about the electromagnetic effects on the malignant growth and cellular reactions to the electromagnetic stresses.

As with the phantom experiments, the preclinical measurements also provide important pieces of information to verify, validate, and calibrate the mEHT processes. However, the *in vivo* experiments differ from *in vitro* experiments in multiple crucial conditional points:

- the inherent heterogeneity of the tumor,
- the heterogeneity of the healthy host and their common boundary,
- the non-linear thermal homeostatic control which regulates the blood flow,
- the immune control of the animal,

- the possibility of the follow-up observation.

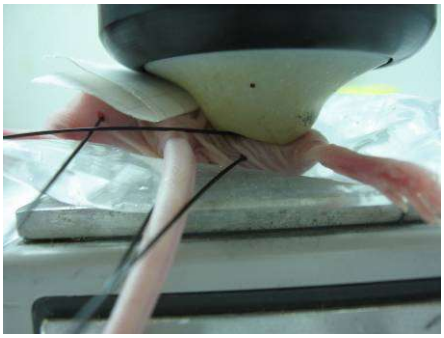
A part of *in vitro* experiments studied the selection of the nano-sized membrane rafts of malignant cells verifying the previously formulated ideas, [167]. The important conclusion is that the nano-effects fit the Arrhenius plot, confirming the thermal behavior of the process. However, it is shown that the effect is improved with the addition of the electric field effects. Apoptotic processes begin at a temperature approximately 3°C lower with the electric field effects, compared to conventional homogeneous heating. The analysis of mRNA levels using Gene-Chip analysis, showed significantly different signal pathways in the apoptotic processes between the applied methods. When compared to homogenous water bath heating, mEHT also performed better, [168]. Other experiments showed additional effects of mEHT compared not only to water-bath, but to other capacitive coupling methods as well, observing significant differences supporting the mEHT method, [169]. Importantly, the energy dosing method proposed by mEHT has been demonstrated, supporting the replacement of temperature with energy control, [170].

One study showed the growth of malignant cells was inhibited by apoptosis induced by mEHT in a glioblastoma cell-line, [171]. Such cellular effects inducing apoptosis are extensively investigated *in vivo* (see below).

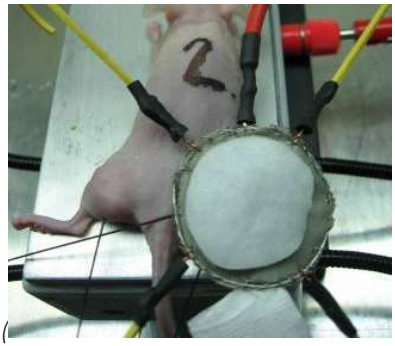
Some studies have focused on the complementary applications of mEHT. The combination with radiotherapy to treat lung cancer cell-lines shows the synergistic effect of mEHT with the ionizing radiation, [172], even in megavoltage applications, [173]. The combination with chemotherapy was investigated using doxorubicin alone, [88], and with liposomal envelops, [174], again showing synergistic effects.

In vivo preclinical evidence

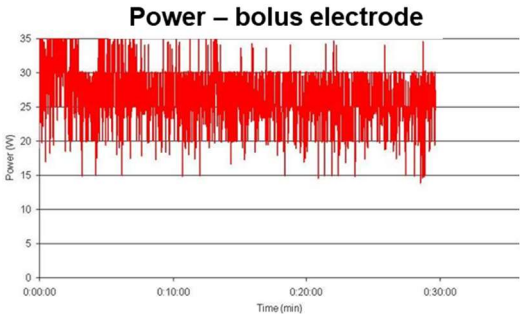
The first technical step was the comparison between the bolus and new flexible electrode, in order to confirm improved efficacy, Fig. 17. The difference in the power output is high, but it was not possible to apply the same tuning solution in the LabEHY as in the human device. For the energy dose, the technical loss was calculated by software specific to the LabEHY and was considered as a modification of the energy. The efficacy of the flexible electrode is about 20% better than the bolus in the preclinical studies. The technical difficulties with the bolus in the LabEHY did not modify the results as with the preclinical *in vivo* experiments, it was possible to measure the temperature in order to determine absorbed energy, which provided the decisional parameter for the dose. In the human devices such technical discrepancies were not observed as the electronics with larger tuners in the human devices restricted the energy losses in tuning process. In the LabEHY the small size of the device prohibited the use of this technical solution for the bolus, where the isolating layers of the bolus have to be compensated. Such compensation was however not necessary for the flexible electrode as there was no need for an isolation rubber or additional layers.



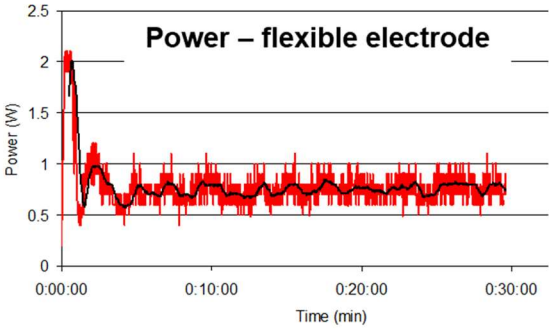
(a)



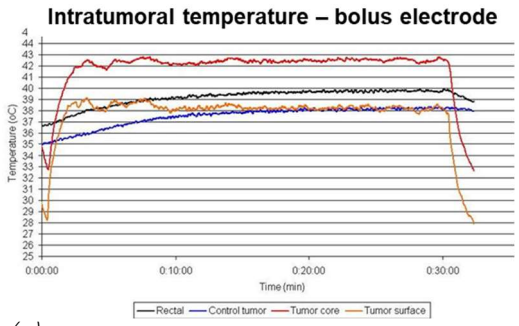
(b)



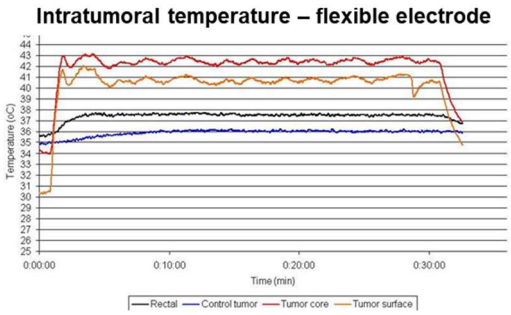
(c)



(d)



(e)



(f)

Figure 17. The comparison of the efficacy of the bolus and flexible electrode. (a), the bolus arrangement, (b), the flexible electrode arrangement, (c), the power to achieve 42 ºC in bolus system, (d), the power to achieve 42 ºC in flexible electrode system, (e), the temperature control for bolus system, (f), the temperature control of the flexible electrode system.

While the *in vivo* murine studies can approach the human clinical results, there is still as significant variation expected due to a number of fundamental differences, such as:

- the different complete homeostatic control and the high heartbeat rate,
- the different immune reactions,
- the artificially developed tumors and metastases,
- the naturally shorter lifespan and the associated complications with the follow-up period.

One of the first *in vivo* results showed a strong synergy between heat-energy and the modulated electric field in tumor cell killing observed in xenograft tumor model, [110]. This examination verified the hypotheses regarding the synergy of the thermal and electromagnetic factors in mEHT processes. The next step was to compare the efficacy of the electrode systems of the bolus-based EHY-2000+ and the flexible electrode applied in EHY-2030. The comparison proved the assumption of the higher efficacy, the with the same effect reached, with less power, as shown in Fig. 15. This important result has a direct impact on the human clinical applications in that it is likely that less power will be tolerated by the patients during the EHY-2030 treatments than during the EHY-2000+

treatments. However, the improved efficiency of the treatment means that the effect will be similar, despite the lower power and this will still fit with the patient's personal feedback.

Verification of the improved performance of the EHY-2030 system, most of the *in vivo* preclinical treatments now use the flexible electrode system, providing further information about the complex effects.

Another preclinical study reported early changes in mRNA levels a significant change in protein expression including the expression HSP, in xenografted human colorectal cell lines treated with mEHT, [175]. Preclinical in vivo studies have also shown the effect of the modulation compared to conventional heat, [176]. Injecting additional gold-nanoparticles (gNPs), into preclinical animal models (murine) demonstrated the selective nano-heating capacity of mEHT. In the study, when the gNPs were injected and the tumor was subsequently treated with mEHT, a reduced rate of apoptosis was observed compared to mEHT alone, despite the temperature in the combined treatment reaching the same as the temperature would without the gNPs. In this case it appears that the gNPs compete for the energy, and less effect is therefore expected on the membrane rafts, [177].

The thermal dose absorption follows the expected selection, [178]; and this has also been visualized after the combination of mEHT with radiotherapy, [179], [180]. The thermal effect was measured invasively in the liver of anesthetized pig, [181], and in combination with radiotherapy in murine models, [182].

Due to the theoretical assumptions, a large amount of information has collected on the cell-death of the targeted malignant cells. It has subsequently been clearly demonstrated that mEHT is a strong inducer of apoptosis [95], promoting a more gentle method which fits in with the natural balance and order, to induce cell-killing rather than causing direct destruction to the tissue. The apoptotic cell-distortion differs from necrosis in that it is not forced, and it does not trigger the same homeostatic feedback reaction to clear up the damage at the necrotic site. It has also been shown that the apoptosis following mEHT corresponds to the energy-dose concept of mEHT, [183]. One study even measured the potential of mEHT-induced apoptosis in ovarian and cervical cancers of tumor-bearing mice, in combination with macrophage-inhibitor, [184].

Saupe *et al* showed reported that mEHT treatments resulted in the breaking up of the clustered rouleaux's formation of erythrocytes in human cases, which may increase the surface area of the erythrocytes, potentially allowing for enhanced oxygen uptake, [185].

The mEHT produces a DAMP induced by an apoptotic process, [99]. The DAMP plays an important role in the immunogenic actions and therefore may contribute to the effect seen in distant metastases after mEHT treatments, [186]. However, in some cases the stress induced p53-mediated growth inhibition has been observed without major immunogenic effects, [187]. The combination of mEHT and dendritic cell (DC), injection has also shown a tendency towards triggering an abscopal effect, [101], throughout the maturation (forming antigen presenting cell, APC), of the injected DC. The mature DC produces CD4+ and CD8+ "helping" and "killer" T-cells, which could trigger a tumor-specific action, all over the body. This APC produced immunity could be strong enough to protect against a recurrence, as was noted after the re-challenge of the same tumor in murine models was rejected after the treated the initial tumor with the mEHT and DC combination, [188]. This shows the possibility of the "tumor vaccination", [102], which induces tumor-specific immunity against the relapsing of developing tumor again.

Clinical evidence

The clinical evidence validates the above theoretical considerations and measurements. First, the clinical applications need to demonstrate the thermal component of the mEHT therapy. The complementary application requires improved blood perfusion. A temperature increases sufficient to improve perfusion in cervical tumors has been demonstrated clinically, [189]. The improved pharmacokinetic action as a result of mEHT has also been demonstrated, [190], [191] and the safety has been demonstrated, with acceptable thermal toxicity, [192], even in high risk (obese, radiosensitive) populations, [244].

Recently, a comprehensive review on the clinical results of mEHT was published, [193]; providing the general feasibility of the method in clinical oncology. Retrospective clinical reports have even demonstrated significant increases in the overall survival rates in various advanced, late stage cancers treated with naturopathic therapies [194]. New clinical trials are in progress [195].

The management of brain tumors with mEHT is one of the most impressive applications as the technique allows for the transcranial, non-invasive, safe treatment of the central nervous system. Modulated electro-hyperthermia has been used for the management of a variety of brain tumors, including glioblastoma multiforme (GBM), in their primary, relapsed, and advanced stages [196]. Safety has been demonstrated when mEHT was combined with chemotherapy (ACNU), for the treatment of brain tumors, [197], and phase II studies subsequently reported improved outcomes without any adverse events [198], [199], [200]. Similar results were reported at different clinical sites [201], [202]; with improved survival and disease control when compared to best standard of care for relapsed and recurrent tumors [203], [204]. A retrospective evaluation of 140 patients with different stages of disease demonstrated similar results with improved survival rates when treated with mEHT, [205]. Recent reports indicate the induction of immunogenic cell death (ICD) during maintenance chemotherapy and subsequent multimodal immunotherapy for GBM, [206], [207]. Finally a meta-analysis of the research on mEHT used to treat GBM, which also included an economic evaluation, showed that mEHT significantly enhances the efficacy of dose-dense temozolomide regimens with significantly less toxicity, and that the addition of mEHT was cost-effective, [208].

A range of organs from the gastrointestinal (GI) tract have been treated with improved outcomes with mEHT, [209]. The most frequently treated malignancy of the GI tract is colorectal cancer and liver metastases from colorectal cancer, where the results show significant improvement in overall survival [210], [211]. One case report has even demonstrated the complete response of a stage III colorectal tumor in an 81 year old patient not eligible for surgery, following treatment with Oxaliplatin, 5-florouracil (5-FU) and calcium folinate (FOLFOX6), concomitant to RT and local mEHT, [212]. The preoperative, neoadjuvant application of mEHT has also shown promising results, [213]. The second most frequently treated GI tract malignancy is advanced gastric cancer, [123].

A phase II study reported that the treatment of advanced hepatocellular carcinoma treatment with mEHT combined with sorafenib was safe, feasible and showed promise for improved survival outcomes, [214]. Heavily pretreated hepatocellular carcinoma patients responded with improved well-being and stable disease after treatment with mEHT with/without Oxaliplatin, [215]. One case of successful treatment of cholangial carcinoma has also been reported, [216].

Pancreatic cancer is associated with a poor prognosis, with limited treatment options available showing improved long-term survival. The use of mEHT has shown to be of benefit in advanced, pancreatic tumors which have failed previous treatments and for which there are no further options. In these cases, mEHT applied as a monotherapy, resulted in improved well-being, prolonged survival and increased rates of disease stabilization, [217]. In combination with conventional chemotherapy regimens, mEHT and supportive treatments showed improved survival rates when applied as a first-line treatment, [121]. These results were repeated with other complex treatment combinations in a

larger number of patients, [218], [219], [220]. The benefit of mEHT in second-line treatment protocols has been shown, [221], [222]. A pilot study showed potential for mEHT to be used for the treatment of partially resected (R1) pancreas tumors, [223].

Lung cancer is the leading cancer globally with the highest number of cancer related deaths reported worldwide, [224]. The application of mEHT in advanced non-small-cell lung cancer (NSCLC) cases shows feasibility and improved survival, [225], [226], and a report on four cases of advanced adenocarcinoma of the lung treated with chemotherapy and mEHT showed survival rates beyond two years, [227]. The combination of mEHT with chemotherapy and supportive therapies demonstrated feasibility, [124], and a case report combining mEHT with radiotherapy for the management of NSCLC in an 83 year old patient resulted in complete response and the patient was alive and disease free at 18 months post treatment, [228].The rarer, but more aggressive, small-cell-lung cancer (SCLC) has also responded well to mEHT treatment, [229]. Interesting research on intravenously administered high-dose vitamin C therapy with mEHT for heavily pretreated, advanced, refractory NSCLC showed that the combination was safe, [230] and had better outcomes compared to patients treated only with best supportive care, [231].

The gynecological applications of mEHT include cervix, ovary, and breast tumors. Breast cancer is the most common cancer in women globally, and in developing countries cervical cancer has the highest mortality rate of all cancers in women, [224]. These are therefore important fields in mEHT research and applications, [232], [233]. Case studies, [234], and clinical trials confirm the efficacy of mEHT for the treatment primary, [41], or residual / recurrent, [235], cervical tumors. The research on mEHT and other hyperthermia methods used to treat cervical cancer is extensive, allowing the comparison between mEHT and other conventional hyperthermia methods used to treat cervical cancer. Modulated electro-hyperthermia has shown similar, [236], [237], or better [238], [53], results compared to other techniques in randomized clinical trials. An extended Phase III randomized, controlled clinical trial for locally advanced cervical tumors has been conducted in South Africa on HIV positive and negative patients, including an evaluation of the viral status of the participants, [239]. Local control was evaluated by 18F-FDG PET/CT imaging studies at six months, [240], [241], and survival updates have been made available, [242], [243]. The study has been extended to include a five-year post-treatment survival evaluation. Quality of life was independently evaluated demonstrating improved QoL and mEHT was not associated with additional chemotherapy and radiotherapy related adverse events. The safety of mEHT was demonstrated, with low rates of adipose burns, even in obese patients, when compared to other methods of heating, [244]. The six-month post treatment evaluation also suggested the presence of an abscopal effect triggered by mEHT, and this was evaluated and reported separately, [245].

Ovarian cancer is a dangerous malignancy due to the risk of early and extensive metastatic disease in the peritoneum. Low dose check-point inhibitors in combination with complex therapies, including mEHT, has shown potential to improve outcomes [246]. Safety in relapsed, refractory, heavily pretreated ovarian cancer patients treated with mEHT has been proven, [247] Modulated electro-hyperthermia combined with traditional Chinese medicine has also been compared to HIPEC and showed less toxicity and improved results, [248].

The complex treatment of breast cancer with mEHT has shown some benefits as well, [249]. Long-term survival of a breast cancer patient with extensive liver metastases treated with mEHT, immunotherapy and virotherapy resulted in a five-year disease-free survival, [250].

Sarcomas have shown a good response to hyperthermia treatment and are especially helpful in limb sparing treatment protocols and for inoperable tumors. Results of various sarcomas treated with mEHT showed the potential for mEHT to be used to treat this malignancy, [251]. The treatment of case of primary leiomyosarcoma of the breast with mEHT as a complementary treatment to

chemotherapy was also successful, [252]. Clinical trial of the management of advanced abdominal soft-tissue sarcoma after relapse treated with mEHT also shows benefit, [253].

Multiple other localizations have been studied, [254], [255], [256], and the abscopal effect has been observed in combination with check-point inhibitors, [257]. Interesting research on mEHT applied as a monotherapy, when no other possibilities were available, for a variety of tumor is promising, [203], [202], [258].

The most important development in the clinical field of mEHT is the immune application, which has the potential to extend the treatments to beyond the local disease and to target systemic disease as well, [259]. The systemic extension has a pivotal role in extending the survival of patients by reducing the risk of distant metastases and possibly aiding in the elimination of distant metastases. In the latter case, mEHT could prove useful in treating palliative patients with curative intent. The immune-stimuli *in vivo* also showed the distant effects of mEHT after local treatments, [186], [101], [188], which is in line with observations in humans, [245], [257]. The combination of mEHT with low dose radiation and using low-dose Granulocyte-macrophage colony-stimulating factor as an immune stimulant, [260] in NSCLC, further alludes to the immunogenic effects of mEHT. The effect of immune stimulation by mEHT has even been intensively used in combination with traditional Chinese medicine, [261].

Last, but certainly not least as there is surely more to come in the near future, is the research on mEHT combined with Newcastle virus, [262], [263], as an immune stimulant, [206], [264], for tumors including advanced metastatic breast cancer, [250], and bone-metastatic prostate cancer, [265].

Protocols

The detailed data above and the everyday practice with 500+ devices worldwide has allowed the development of recommendations for protocols and treatment implementation. Years of use have shown that the all solid tumors, irrespective their TNM and stage, could be treated with mEHT. The important factor is that the target volume differs from the healthy tissue, based on the characteristics describe in Section 4. Primary, metastatic and recurrent tumors are eligible for treatment with mEHT. Experience with the three devices have been combined and summarized in order to develop the most optimal use of the newest model, the EHY-2030. The following guidelines assume the knowledge and understanding of the earlier published guideline, [4] and protocol, [266], for the EHY-2000, as well as an understanding of the basic knowledge of the mEHT method, [9]. The traditional, conventional chemotherapy protocols which have been applied for decades in combination with mEHT are collected elsewhere, [267].

General safety

Modulated electro-hyperthermia is not a substitute for conventional therapies, but rather it is a supportive treatment.

The operator has to follow the instructions mentioned in the following paragraphs, otherwise burning or overheating of the tissue may occur. The temperature calculation (displayed temperature), is only a calculation. Take into consideration that the temperature of some points of the heated local area can be considerably higher than the average. This effect is called “hot spots” in the literature. This inaccuracy can cause overheating of the healthy tissue. The calculation is based

on the so-called "equivalent temperature" concept. This means that mEHT heats up the tissue according to a dynamic, gradient.

The efficacy of the energy absorption, calculated using the difference between the forwarded and reflected power, is checked during the start of each treatment but will not be checked continuously during the treatment. Factors such as shifting in the patient's position, movement of the electrode, or local interferences may result in an increase in the reflected power during the treatment, which could risk overheating of the tissue. The smart electrode system on the EHY-2030 has automatic positioning to find the optimal electrode position and the device should only report a small reflected power during a well-tuned treatment. Despite this, the reflected power must still be checked during the treatment by the operator. In the event that the reflected power increases, adjustments to the patient, electrode and surroundings need to be made to reduce the reflected power. Should this fail, pausing the treatment, repositioning, and restarting the treatment may be required.

We the authors have not noted any negative cross-effects between mEHT and applied complementary therapies and we have not reported a reduction in the efficacy of therapies with the addition of mEHT. The manufacturer has confirmed that they have also not been notified of any of the above from any of their many users around the world.

The new electrode system on the EHY-2030, using more precise tuning of the resonance combined with state-of-the-art electronic support, increases the available current density at the same power. The higher current density in the EHY-2030, compared to the EHY-2000, increases the treatment efficiency at the same power output. The risk of a treatment-related burn is therefore higher in the EHY-2030 than in the EHY-2000+, at the same power output. However, the higher power output on the EHY-2030 allows for the use of a larger electrode, as is used in the EHY-3000. The device recognizes the electrode size and limits the power to a $0.5\ W/cm^2$ incident density. The risk is that when the electrode placement is not correct, and the entire electrode surface is not in contact with the skin, a higher incident power density may develop on the reduced surface area of the portion of the electrode which is in contact with the skin. To reduce this risk as much as possible, there is an additional electronic sensing of the electrode position built in, with an LED-light row on the electrode, signaling the correct contact.

The safe distances during the treatment are shown in Fig. 18. Unlike conventional hyperthermia installations, no shielding is needed in the treatment room. The average room-size is $30\ m^2$ and this includes space for the patient's companions to accompany him or her, and space for the operator. A distance of 1.5m should be maintained around the device during treatments, which is slightly different to the recommended 1m for the EHY-2000+.

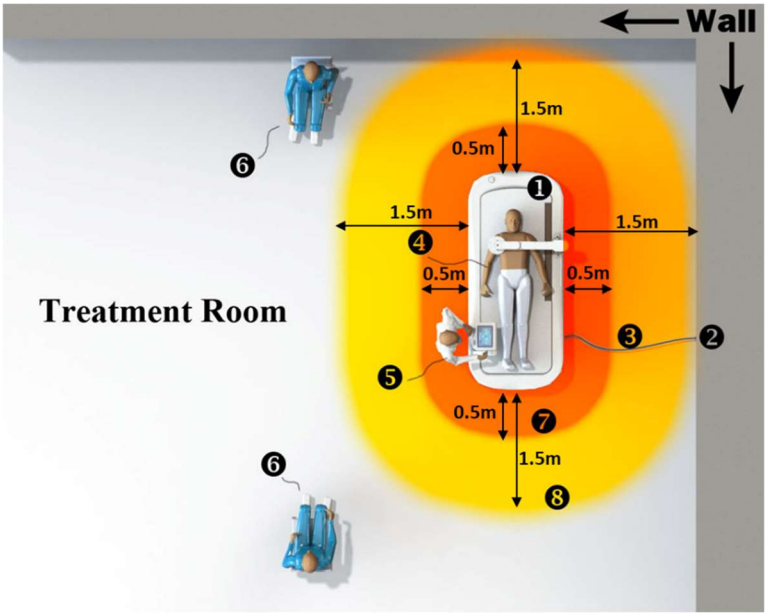


Figure 18. (1), EHY-2030 device, (2), Mains, (3), Power cable cord, (4)Patient, (5), Operator, (6), Patient's companions, (7), Forbidden area; aside from the operator and the nurses, nobody else is allowed to remain there during the treatment. (distance = 0.5 meter), (Orange area), (8), Free Area; The minimum distance from the device is 1.5 meter. (Yellow Area)

Safety conditions

- The importance of the condition warrants repeating: mEHT does not substitute conventional therapies, it only supports the treatments.
- Before each treatment, all metallic and magnetic objects (necklaces, rings, watches, piercings and other jewels, pipes, coins, phones, hairpins, pens, etc.), should be removed from the patient's body and placed at least 1.5m away from the bed.
- All electronic equipment must be removed from the patient, including hearing-aids, headphones, cellphones, music devices and "wire-connected" instruments.
- Do not treat near the eyes of the patient. The direct RF-radiation can cause temporary or permanent blindness. The treatment of the head requires special training at one of the Oncotherm reference clinics.
- Special care is necessary when the treatment area contains hair, (e.g. pubic hair, facial hair, the hair on the scalp or hair on the chest), as burning and mistreatment are a likely result. To prevent burning, the area should be shaved, or at the very least, the treatment should be conducted with extra care, paying close attention to the region, applying a lower power for a longer period if necessary. Alternatively, ultrasound/ECG gel can be applied to the treatment region to improve the contact over the hair. Stop the treatment immediately if the patient notes any discomfort or redness or reports any other adverse events.
- Operating the device is not suggested for staff during pregnancy.
- When rearranging and/or repositioning the applicator, please pause the treatment.
- In case of any necessary medical assistance during the treatment (injection, infusion, etc.), please pause/stop the treatment while in contact with the patient and administering the medical care.

- Stop the treatment immediately if anything unusual happens (e.g. erythema, burning, etc.), and ask for the help of a trained doctor if it is needed.

Contraindications

Prohibited treatment conditions

The device cannot be used when the patient is under **deep sedation** or **anesthesia** and the application of analgesics in the treated area is prohibited. This is because the patient's feedback of the thermal sensitivity is a vital safety parameter.

For the same reason as above, do not use the device on patients with a reduced ability to sense pain.

The device cannot be used when the patient is **unconscious**.

The device cannot be used on patients with a reduced ability to communicate.

Do not use the device on patients with an open wound, hemorrhagic syndrome, ulcerating tumor, or unhealed postoperative suture on the head or neck. The risk of inducing bleeding near vital structures and vessels as a result of the treatment could be life-threatening.

Do not use the device on pregnant patients.

Do not use the device on patients with a Karnofsky performance index less than 30%.

Treatments should not be administered to patients with breast prosthesis in the treatment field, as rupture and leakage of the prosthesis may occur.

Contraindications with conditional possibilities

Some clinical practices have experience and results in the following otherwise contraindicated situations. In order to treat under the following circumstances, experience and specialized conditions and preparation are required:

When the patient has an implanted active medical device in any anatomical location, even if it is outside the treatment field (e.g. cardiac pacemaker, deep brain stimulator, implanted hearing aids, implanted erectile function stimulator, etc.), treatment with mEHT is generally prohibited. However, when the conditions are prepared for any unexpected problems, it might be possible. Such preparations include the immediate availability of emergency medical aid should any adverse event occur as a result of RF interference with the built-in device. Treatments in these cases are the sole responsibility of the physician in charge and must be supervised by the prescribing physician. Special written consent from the patient is also required with an explanation of the risk versus benefits.

These restrictions are especially valid when the patient is treated in the head and neck area and has any implanted medical device or any non-removable object in the neck or head (e.g. implanted deep brain stimulator, implanted hearing aids, etc.).

Extreme care must be taken when treating with any of the following in the treatment field:

- Metallic implants
- Plastic prosthesis
- Stents

- Urinary Catheter
- Stoma
- Drains e.g. cranial/post op
- Staples or clips due to prior surgeries

In the event of any uncertainty regarding items within the treatment field, please contact the manufacturer for guidance prior to commencing and planning treatments.

Cautions

The user of this device must be a physician and/or a trained clinical staff member. Oncotherm issues certificates for authorized/trained operation personnel.

The treatment must be continuously monitored by the trained and certified staff member.

Smart Electrode placement: Check the position of the smart electrode to keep it as parallel to the bed surface as possible (try to avoid placing the smart electrode at an angle to the bed). The applicator (smart electrode), has a flexible water-bolus to enable the best fit with the patient. Please note that the inclined positioning of the smart electrode must be carefully controlled because some temperature increase can occur at the skin's surface. This will not be an immediate effect and can be managed appropriately with patient feedback during the treatment. In addition, users are advised to place medical hygienic paper between the smart electrode and the patient to avoid direct skin contact. When positioning the smart electrode, avoid direct patient contact with the white plastic enclosure of the smart electrode during the treatment to reduce the potential for burning.

Do not use the equipment for any purpose or in any manner other that the manner for which it is intended, doing so can be dangerous. Always refer to the User's manual for guidance.

Check the patient and ask for feedback regarding the sensations and any potential discomfort.

Check that the water-cooling mechanism of the smart electrode is working before positioning it.

The use of any additional tool during the treatment, such as a temperature measurement device, that has not been authorized or manufactured by Oncotherm for control, is prohibited. External metallic devices could function as an antenna. Do not use any system-independent electric device during the treatment. It can cause an electric shock due to the broken safety isolation.

Magnetically sensitive products are to be kept far away from the device in order to prevent the loss of information on data carriers.

Do not clean the smart electrodes while the equipment is on! Do not use wet textiles that can result in the release of water into the equipment.

The optimal placement of the applicator is the horizontal position (parallel with the counter electrode). Such an arrangement provides the most effective power. Note, that in many cases a low power is required for the treatment (for example when treating a brain tumor), and this can be affected by the output power control or by placing the smart electrodes in a non-parallel arrangement. The patient must be between the smart electrode and counter electrode.

Do not wrap the small electrode in any textile material for the treatment. Reduce the thickness of any textile material to the minimum between the smart electrode and the skin of the patient (i.e. remove clothing on both sides of the treatment area). Textile quality influences the tuning, which can lead to a system error in tuning under the given circumstances. Ideally, isolate the patient's skin from the smart electrode surface using medical hygienic paper-toweling (see detailed description in Accessories and Appendix 6 for datasheet in the user's manual). Any other material may impact the tuning of the device.

Radio-frequency treatment influences the surroundings. Therefore, some attention should be paid to the set up and furnishings in the room in which treatments will take place. Do not install the machine in the vicinity of any sensitive equipment (ECG, EEG, intensive-care control-monitor, ultra-sound, video rectoscopy and other sensitive imaging systems, etc.), without shielding. Shielding is also required to protect the device if it is in the vicinity of large electro-magnetic sources and high-power machines (power transformer, X-ray units, NMR, CT, etc.). It should be noted that microwaves could influence the Oncotherm device in the treatment room as well, and vice-versa. Make sure that these machines are sufficiently shielded.

The personnel responsible for the treatment/equipment should check the cables before each treatment. At any doubt about the integrity of the isolation, stop the treatment and call for an immediate service check-up.

Clean the smart electrodes before each treatment. Follow the procedure described in "disinfecting the accessories" in the user's manual. 70% IPA (Isopropyl Alcohol), based solution (or its substitute), must be used for disinfecting.

Before beginning the treatment, any sharp objects (knives, scissors, needles, pens, pencils, glasses, etc.), must be removed and kept far away from the **mattress**.

All metallic and magnetic items, including clothes, jewelry, watches, cell phones and bank cards with magnetic strips should be removed from the patient's body and placed safely away from the device during the treatment.

Accessory equipment connected to the analogue and digital interfaces must be certified according to the respective IEC standards. If in doubt, consult the technical service department or your local representative.

Inherent risks of the treatment

- When the patient has acute inflammation, locally or systemically.
- When the patient is too weak to tolerate the pressure of the applicator.
- When the patient has thick adipose tissue at the treated area.
- When the patient intensively sweats under the electrode.
- When the patient is thin, and the applicator is over a volume with lower blood-flow (like ears and bony areas in thin patients).
- When the patient has hair on the treated area.
- When the patient has plastic, saline or metallic implants in the treated volume. Treatment through the breast implants is prohibited.
- When the patient has ascites in the treated volume.
- Avoid having natural liquid (like urine, liquid in the stomach, etc.), in the treated area.
- Isolate the umbilicus from direct power when it is under the electrode.

Developing hotspots

The safety of mEHT treatments performs better than conventional hyperthermia processes. The selective heating does not necessitate high incident energy, as only a small part of the targeted tumor represents the malignant cells. The maximum power density on the electrode is $0.5\ W/cm^2$, which is safe. The usual problem involving the formation of hot-spots in conventional hyperthermia is not of significant concern during mEHT on the EHY-2030 as the energy focus is in depth and the highest temperature outside the focus would be at the surface, where the power starts to penetrate the body. This skin surface is kept cool, so overheating is unlikely. From the surface the energy absorption exponentially decreases (the penetration depth is defined in the depth where the starting surface power drops to 36% of its original power, which is approximately 18 cm deep in the average human body). The autofocusing successfully modifies this exponential decay and further lowers the risk of unwanted overheating of any tissues involved.

The crucial sensing method is the patient and the patient feedback. The patient must report any discomfort during the treatment, avoiding any overheating of the skin due to an incorrectly fitted electrode on the body surface. When only a part of the electrode is in contact with the patient, the entire power goes through the area in contact, increasing the power density to above the critical $0.5\ W/cm^2$.

Written consent for the treatment

In such countries, where it is necessary or mandatory, a written consent has to be signed by the patient before the start of the first treatment. This consent has to contain the following points:

- Clear capacity (or ability), to make the decision.
- The medical provider must disclose information on the treatment, test, or procedure in questions, including the expected benefits and risks, and the likelihood (or probability), that the benefits and risks will occur.
- The patient must comprehend the relevant information.
- The patient must voluntarily grant consent, without coercion or duress.

Doctors must provide the patient with sufficient information about a particular treatment or test so that the patient can decide whether or not they wish to undergo such a treatment or test. This process of understanding the risks and benefits of treatment is known as informed consent. It is based on the moral and legal premise of patient autonomy: Patients have the right to make decisions about their own health and medical conditions.

The patient must give their voluntary, informed consent for the treatment as is the case for most medical tests and procedures. The legal term for failing to obtain informed consent before performing a test or procedure on a patient is called battery (a form of assault).

For many types of interactions (for example, a physical examination with the doctor), the implied consent is assumed.

For more invasive tests or for those tests or treatments with significant risks or alternatives, the patient must be asked to give explicit (written), consent.

Under certain circumstances, there are exceptions to the informed consent rule. The most common exceptions are these:

I. An emergency in which medical care is needed immediately to prevent serious or irreversible harm.

II. Legal incompetence in which someone is unable to give permission (or to refuse permission), for testing or treatment.

Protocol-consensus

The presented protocols are conditional pieces of information, formulated from *in silico*, *in vitro* and *in vivo* preclinical research, as well as from the available practical clinical experience. As mEHT treatments are personalized for the patients, the protocols can be considered as guidelines and are not absolute. The adaptation of the treatment parameters to the actual patient, to the conditions of the tumor, to the patient physiology, including the immune and general status, and to the additional non-mEHT treatments, is essential.

In general, the recommendations are to administer mEHT on the same day as chemotherapy. However, there are examples of cases where chemotherapy was not administered on the same day. When a trimodal (radio-chemo-thermo), therapy is applied, we must consider that some chemotherapeutic agents are also radiosensitizers (such as cisplatin). In this case the mEHT can be applied on non-chemotherapy days. Another reason for not applying chemotherapy and mEHT on the same day is when a clinical trial requests the standardization of the patient cohort, but the repeated drug administration is not tolerable for all the participants. In such a case, mEHT may be administered independently from chemotherapy in order to standardize the variables as much as possible.

The protocol for each patient must focus on the specific requirements of the patient allowing some variability of the guidelines in order to optimize the protocol for the patient.

Complementary applications

Modulated electro-hyperthermia is primarily a complementary therapy, most commonly applied in cases where conventional solutions alone delivered unsatisfactory results. The mEHT treatments are especially useful in the cases where the conventional curative approach has been changed to palliative protocols as a result of failure of the curative treatment. The intent may therefore be curative, or palliative, and mEHT may be applied in first the first line of treatment or later. When the goal is palliative, pain-reduction and the improvement of QoL are the most common endpoints. The complimentary application of mEHT may also be of benefit in early stages of disease, for example in instances where patients are unable to tolerate the required curative dose of the conventional treatment. Tumor indications include any solid tumors, primary, metastatic or recurrent, in any treatable cases, without limitation according to the TNM stages.

The combined application of mEHT with conventional treatments serves two main purposes:

- Increase the efficacy of the conventional oncotherapy, sometimes in combination with more than one (like chemoradiotherapy),
- Re-sensitization of the refractive tumor for re-treatment with the conventional therapy.

The basic principle of the mEHT protocols is to always adjust the mEHT protocol according to the conventional protocols. However, all of the treatment protocols of mEHT have some common points, [268], which are applicable for all types of mEHT devices:

1. Firstly, the "gold standards" of treatment for the specific tumor must always be applied. Modulated electro-hyperthermia should be applied in combination with conventional treatments when the conventional treatments alone have failed (for example in refractory

disease, relapsed disease, or inoperable tumors), or when the conventional treatment alone is not expected to result in the desired outcome.

2. The application of mEHT as a complementary treatment to a first-line conventional therapy is justified when the expectations of the results of the standard therapy alone are sub-optimal. The following situations are examples of such instances:
    a. The treatment of tumors with known radioresistance (for example hypoxic, large, or bulky tumors), with ionizing radiation.
    b. When there is a risk that the chemotherapy is not able to actively (optimally), penetrate the tumor, for example due to the tumor's high internal pressure,
    c. When immediate and complete absorption of the applied treatment is required, for example after the injection of laboratory prepared active cells such as CAR-T,
    d. When the natural enzyme processes or the drug itself requires a higher temperature to increase the reaction-rate,
    e. Combined with the use of liposomal or other heat-sensitive vehicles delivering the drug to the tumor.

The conditions of the treatment should fulfill the following points:

1. Treatment time shall be between 45 and 90 minutes (average: 60 minutes).
    a. The shorter time could be applied with special intermittent protocols (see later).
    b. Increasing treatment times beyond 90 minutes is associated with a risk of the development of thermo-resistance, which decreases the efficacy of the cellular distortion.
2. Treatment frequency
    a. shall be two to three times a week, with at least 48 hours between the treatments. This time between treatments allows the tumor to recover from the heat-resistant state of chaperone proteins (HSPs).
    b. in some cases, low-doses can be applied every day for a radio-sensitizing effect. In this case the low intensity of heating develops less HSPs, and the radiotherapy surmounts this blockage. This protocol requires that irradiation is completed within 30 minutes of the completion of the mEHT treatment.
3. The number of treatments in a cycle are between 4 and 12 (average: 5.8). This again must follow the conventional treatment and be optimized to the protocols of the conventional treatment.
4. The number of cycles shall follow the complementary protocols
    a. Applied according to the number of cycles of the conventional therapy (average: 2.3),
    b. when the conventional therapy has chronic, long-term periodicities, then mEHT could be continued in between the treatment periods.

Ensuring a relaxed environment and promoting a relaxed state in the patient improves the patient experience, but importantly also improves patient tolerance, which could be impaired by anxiety and stress. The physio-feedbacks activated in response to stress (raised blood-pressure, blood flow, nerve activation, sweating, etc.), impair patient tolerance could reduce treatment efficiency. A relaxed condition may also reduce the development of stress-proteins.

Notes:

a. in cases of the treatment of sensitive organs (such as the brain), different protocols have to be applied, adapting the heating conditions and the modulation effects,
b. the averages in brackets are based on clinical experience and published reports and are only a guideline. The patient stage, tolerability and the development of the curative process, will ultimately determine the required number of treatments.

Complementary to drug administration

Recommendations for applying mEHT combined with intravenous (i.v.), or oral drug administration (chemotherapy, immune therapy, supportive therapy, etc.):

Usually, the most effective protocol is the concomitant application of mEHT with the drug administration.

1. This aids in:
    a. The selection of the local tumor, due to the local mEHT action,
    b. The targeting of the tumor cells by the drug due to the selective heating of the microenvironment,
    c. The promotion of blood vessel-permeability to improve the delivery of the drug to the target,
    d. Increasing the permeability of the cellular membrane for the action of the drug,
    e. Increasing the local pharmacokinetic activity and the chemical reaction rate of the drug at the target, based on the Arrhenius law.
2. Combining mEHT with the i.v. or oral administration of drugs:
    a. When applied simultaneously, if the i.v. administration time is shorter than the prescribed mEHT dose/session, mEHT shall be continued until its prescribed dose.
    b. When applied simultaneously, if the mEHT treatment time is shorter than the i.v. drug administration time, the mEHT treatment should still not exceed a time of 90 minutes.
    c. In the case of chrono-chemotherapy (12-24h i.v. administration), mEHT can be applied at any time during the chrono-chemotherapy, although the ideal timing is as close to the start of the drug administration as possible,
    d. When the i.v. drug is repeated weekly or monthly, mEHT should be applied weekly (one to three times per week), with a step down-protocol on the days on which no other therapy is administered, and a step–up protocol on the days that mEHT is administered simultaneously with the i.v. medication.
    e. When different i.v. or oral treatments are administered each day, mEHT can be applied every day concomitantly, but only at a maximum of half of the usual energy dose.
    f. When mEHT is combined with the daily oral administration of a drug, then mEHT should be administered one to three times per week, using a step-up protocol.

Complementary to ionizing radiation

When considering the effects of the stand-alone radiotherapy or stand-alone hyperthermia on cellular destruction, both treatments may induce necrosis, which in itself has positive feedback. Based on this, necrosis would occur independent of the order of the treatments. In order to determine the order of the treatments and the protocols for mEHT, an understanding of the additional effects of mEHT on radiotherapy sensitization is essential.

The cell-killing effects of radiotherapy are primarily a result of double strand breaks in the DNA, and the addition of hyperthermia inhibits the repair of DNA double strand breaks. However, the most important boost in the cell-killing effects of radiotherapy is a result of the physiological reaction to the heat. As such, the heat-producing effect of the energy-absorption during mEHT plays the leading role when combined with radiotherapy.

The physiological effects of hyperthermia include an increase in the electrolyte transport systems like the blood-flow and lymphatic movement. This in turn increases the oxygen perfusion in the target volume. The presence of oxygen at the time of irradiation causes radiation sensitivity, [269], enhancing the cell-killing effects of radiotherapy. However, there could also be an inhibitory effect when HT induces hypoxic conditions, which may happen at temperatures higher than $43°C$, which

stimulate vasoconstriction. The timing and the sequencing of the radiotherapy and mEHT is determined based on a complex set of physiological interactions:

1. The first point is to consider the blood-perfusion in the targeted tumor:
    a. When the tumor is hypoxic, it is becoming more resistant to radiotherapy, because the broken DNA strands have quicker reparation. Ionizing radiation causes DNA damage by producing a free radical. Oxygen has a high affinity to electrons and therefore quickly reacts with the radical, resulting in creation of reactive oxygen species, which in turn causes irreversible damage to the tumor cell DNA, [33]. To increase the oxygenation in the target, mEHT should be applied first, at a low (less than half), dose, with the sole purpose of increasing the blood flow, and subsequently boosting the effects of the following irradiation. In this case, the time between mEHT and radiotherapy has to be reduced to as short as possible, with a maximum of 30 minutes between the completion of mEHT and the completion of radiotherapy. Any longer and the tumor begins to cool, and the oxygen perfusion returns to normal.
    b. Depending on the tissue, the effects of ionizing radiation and the formed radicals in the tissue may last two to six hours beyond the completion of irradiation. It is therefore also possible to apply mEHT as a radiosensitizer after the administration of radiotherapy. In this instance a higher dose of mEHT should also be applied in order to trigger all the additional benefits of mEHT, other than simply the improved perfusion at mild temperatures. When the tumor is well oxygenated, it is already sensitive to radiotherapy, then ionization radiation must always be applied first, with mEHT afterwards, at the highest dose possible. When mEHT is applied after radiotherapy, the timing between radiotherapy and mEHT should be as short as possible, with a maximum benefit noted when the mEHT is started within two hours of completing radiotherapy. The maximum recommended time between completion of mEHT and radiotherapy is four hours.
2. Mild temperature increases are sufficient to enhance perfusion, [270] and to enhance the formation of numerous reactive oxygen species (ROS), such as hydrogen peroxide, superoxide anions, nitric oxide, hydroxyl radical, etc. Superoxide dismutase (SOD), forms an essential component in the defense against ROS. Another benefit to the heating the tumor is that heat-stress could result in a decrease in SOD levels, which also leads to cell death, [271].
3. There is a risk that the heating protocol described could support the repair of DNA when heating is applied after radiotherapy. The first thirty minutes of "warming up" period could be considered as preheating. This preheating could increase the activity of reparation enzymes, [272], although the risk is reduced once the thermal and field effects begin to take effect in the tumor. As such the field effects of mEHT are important when mEHT is applied after radiotherapy. In order to block the enzyme activity, a threshold temperature must be exceeded. So the protocol when mEHT is applied after radiotherapy should apply a maximum power (using a quick step-up protocol), for no more than six minutes, after which the power may be reduced to the original protocols, and based on the patient's tolerance. This blocks the enzymatic activity early on in the treatment. Intermittent, and short increases in power for no longer than six minutes can be repeated through throughout the treatment.

The other important interaction to consider is the blocking of DNA repair mechanisms in the presence of heat. Two mechanisms are possible:

1. The increased presence of oxygen inhibits DNA repair. Oxygen has a high electron affinity and therefore it readily reacts with the free radical found at the lesion produced by ionizing radiation on the DNA strand. In doing so, oxygen cements the damage to the lesion, inhibiting further repair. In the absence of oxygen, the damage caused by the free radicals is more easily restored by hydrogen donation from non-protein sulfhydryls in the cells, [269].

a. In severely hypoxic tumors, there may be no oxygen available to block the repairs and improving the blood flow improves the oxygen perfusion in the target volume.
b. The blood flow however must be not too intensive, because it could promote the tumor-growth and risk the dissemination of tumor-cells.
c. The heat stress must be limited, because the radiotherapy induces extra stress proteins and together with the intensive heating, resistance to the treatment may develop.
d. When the temperature is too high, causing vasoconstriction, again increasing the hypoxic conditions, the heat treatment could have a negative, or inhibitory effect on the ionizing radiation.

2. Deactivation of the repair enzymes is a complex task.
    a. The hyperthermia induced HSP70 and HSP27 are involved in regulating the base excision repair enzymes in response to radiotherapy stress, [273]. This is initially a supportive mechanism of reparation, but this only lasts until the heat-shock load is too much, resulting in the deactivation of the enzymes. The stress caused by radiotherapy also produces HSPs, but different types and amounts.
    b. The heat-stress independently affects enzyme activities, such as a variety of irreparable DNA mismatches, heat-activated methylation, hydrolysis, mono- or di-adduct damages, etc.

Monotherapy applications

Modulated electro-hyperthermia as a monotherapy (stand-alone treatment), can only be applied in cases when there are no further conventional options for treatment. Examples of such instances include organ failure, haemato-insufficiency, immune-deficiency, refractory disease, or psycho-resistance. Modulated electro-hyperthermia has also been applied as a chronic treatment to reduce the risk of relapse or to induce a state of stable disease.

Clinical practice

Step-up-heating

To optimize the treatment efficacy, a step-up protocol is proposed for the heating process. The protocol exploits the concept of quasi-adiabatic energy-absorption during the heating period. This principle allows for the excitation and subsequent heating of the membrane rafts by the absorbed energy; however, the heating time is short enough to prevent the spread of the heat to the areas outside of the target volume. The time required for the heat to start spreading, based on the physiology, is approx. $\approx 6\,min$, and occurs when the blood flow regulation starts to cool down the heated area to control the thermal homeostasis. Once the spreading of the heat is underway, an increase in the power will step-up the energy-absorption, and the targeted heating begins again, in a quasi-adiabatic way, while the physiological control again follows the change.

The timing of the step-up heating depends on the personal condition of the patient, including the actual blood pressure, stress, and heartbeat. The personal variability could influence the results, so it has to be considered as an important factor when deciding on the applied protocol. The rate of the temperature increase depends on the tolerance of the patients. In general, when the patient has unusual stress towards the treatment, the heat tolerance is much lower and prolonging the step-up time allows for a more comfortable experience. However, as the patient becomes more comfortable, heat tolerance during the subsequent treatments may improve. The step-up process does not only apply to the individual treatments, but also to the treatments in a cycle of therapy. In other words, the maximum power output of the first treatment is lower and is increased further at

each subsequent treatment. Patients adapt to the treatment dose in a gradually increasing manner, with subsequently repeating sessions, Fig. 19. The operator may slightly, delicately try to increase the power until it is tolerated while the patient's feedback is continually and closely monitored. This could optimize the applied power due to the acclimatization of the patient. This practice requires extended experience from the operator and is not suggested for unexperienced staff.

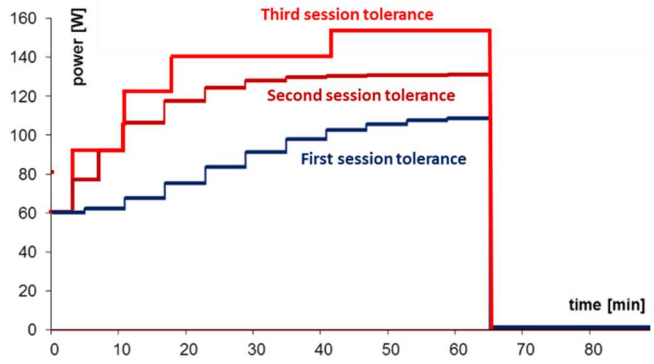


Figure 19. Patients could gradually develop a higher adaptability of the treatment than the initial one.

Step-up heating is necessary for combined therapies. The gradually increased power keeps the homeostatic control active and exercises the adaptability of the patient. This process becomes a selection possibility due to the stress adaptability of the healthy tissue to the heat control and the developing resistance is significantly higher in the healthy tissue than in the tumor, where the cells are under continuous stress. The stabilized healthy host develops stress-resistive chaperone proteins, which may be useful for the resistance of the drug or radiotherapy stresses in the healthy tissue as it prepares the healthy tissue to become selectively desensitized to the complementary conventional therapy. In this way, mEHT may assist in decreasing the adverse effects of concomitantly applied conventional therapies.

In some cases, when the patient has a low tolerance, intermittent heating increases the efficacy. This heating is an alternative on-off process when the maximum available power is used for a short time (less than the half of the physiological reaction), after which the power is turned off for a period as long as it was on maximum. After this the treatment power is returned to the same level as before applying the on-off surge. This process could be repeated several times during the treatment in order to increase the dose to the tumor. The operator can apply as many of these on-off surges, with as high a power as is tolerated by the patient.

In most of the cases, mEHT is applied using a step-up heating protocol. The principle of this heating method considers the huge jump of heat-shock protein development in healthy cells while the jump in cancer-cells is only moderate, [79]. Consequently, the protection against the increasing temperature is higher in healthy cells. In other words: cancer cells are more sensitive to heat. The gradually increased temperature (step-up heating), helps to adapt healthy cells to the heat, which is not the case for malignant cells. In this way, the treatment develops a selective protection for non-malignant cells.

Furthermore, the step-up heating allows the homeostatic thermal feedback to stabilize the homeostasis, which creates the appropriate blood flow for the drug delivery; but keeps it controlled by the moderate mass-heating. The step-up heating promotes increased blood-perfusion to the subcutaneous tissue, which helps to optimize the treatment and increases its efficacy, [103]. The thermal homeostasis makes the vasodilatation more effective which increases the risk of dissemination of malignant cells forming micro and macro-metastases. For this reason, mEHT is only applied together with other cell-killing methods in a step-up heating protocol. Modulated electro-hyperthermia complements their effects for the best available destruction of the tumor

without risking the dissemination of the vivid malignant cells. Vasodilatation is based on the adaptability of the patient, and it is also required to complement other therapy modalities (conventionally chemotherapy or radiotherapy), making them more effective. The basic steps of step-up heating are shown in Fig. 20.

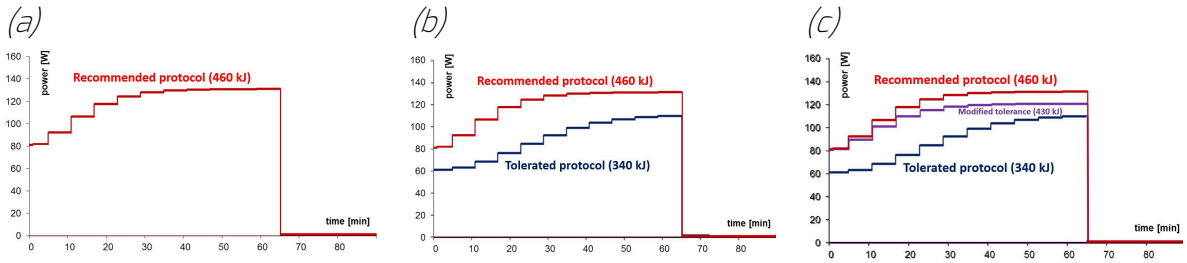


Figure 20. The step-up heating method creates a gradual (quasi-stationary), temperature increase, making sure that the average time of the reconstruct the homeostatic equilibrium is 6 min. (a), the example of a recommended protocol, (b), example of the tolerance of the patient, which depends on the personal feelings, (c), the repeated treatments modify the tolerance level in most of the cases.

Step-down heating

When applied as a stand-alone treatment, the situation is different, and a step-down heating protocol is more appropriate for optimizing the treatment. When applied with other treatments, mEHT supports the actions and boosts the effects of the conventional treatments, and the immunogenic actions of mEHT are secondary, and in some cases may even be suppressed by the applied drug or ionizing radiation. Contrary to the step-up heating, which seeks to achieve equilibrium, the step-down heating creates a non-equilibrium situation which is constantly maintained during the treatment. In this approach the heating of the membrane rafts, the production of immunogenic cells death by appropriate DAMP, and development of the (systemic), tumor-specific immune action are the most important effects. In addition to the bio-electromagnetic selection, the increasing hypoxic conditions within the tumor at increased temperatures also contribute to the selection process in step-down heating. The step-down heating starts with a maximum power, and the rate of energy-decrease is determined by the tolerance of the patient. If the patient tolerates the power, the power can be left on the maximum output. However, as the patient experiences discomfort, the power output should be decreased accordingly. From the patient's perspective, the step-up heating is based on the adaptability, while the step-down is based on the tolerance of the patient, Fig. 21. The forced non-equilibrium heating in the step-down process could create vasocontraction in the cancerous tissue, [4], which further increases the temperature within the target, promoting the characteristic selection of the temperature development. The inner temperature blocks the blood-supply as much as possible and so quickly utilizes the available metabolic energy in the absence of replacements which would otherwise have been brought by the fresh blood-flow.

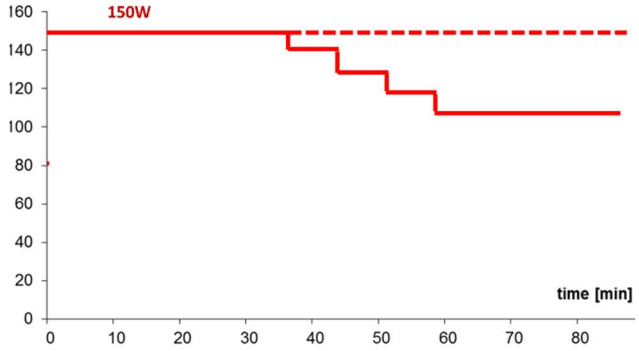


Figure. 21. In case of the step-down treatment protocol, the treatment runs on the maximal tolerated power throughout the duration of the treatment. The dashed line is the overall maximum; and the solid line shows an example on)f how to reduce the power according to the patient's tolerance, which is communicated verbally.

The step-down heating can lower the activation energy of the leading lipid chemical reactions of the cells when the starting temperature is higher than $43°C$, [274]. At this temperature lipid phase-transition occurs, [275], and the new compound has a lower energy barrier for the reaction, [276].

However, we expect less effective treatment in a step-down protocol than in the complementary step-up cases with conventional hyperthermia, if the temperature rises too much, over $40°C$. At high temperatures the step-down heating also has a Janus-face characteristic. Too high a temperature suppresses the activity of the immune cells and at the end blocks the immunogenic activity, blocking the systemic effect against the distant micro- and macro-metastases. The high temperature in the step-down heating is mostly good for the local response but could negatively affect the overall survival.

The higher dissemination rate is followed by a decrease in the survival. The heterogenic tumor has an "onion" structure: the most vivid parts are on the tumor-surface and the main heat absorption is inside rapidly heating up the inner volume of the solid tumor, [277]. This thermal contrast of the "onion" heterogeneity is connected to physiological changes. The healthy neighborhood develops rapid, non-linear vasodilatation, increasing the blood flow and promoting dissemination of the rapidly proliferative outside cells of the tumor. This external "layer" therefore represents a "danger zone". In this process the vasocontraction in the inner tumor will be irrelevant in the development of metastases via the blood-transport, but its high temperature improves the interfacial gradient and the contra-action of the treatment goals. Fortunately, the macroscopic temperature in mEHT increases only moderately.

In these special conditions, when mEHT is applied as monotherapy, [278] the number of cycles could be drastically increased, [279], and may have the potential to convert the disease into a chronic condition, when the macroscopic temperature (not the nanoscopic temperature estimate as displayed on the device), in every treatment in the session is limited to under $40°C$, as occurs during mEHT treatments.

Positioning

The correct position of the electrode and the patient is important for the success of the treatment. The electrode must cover the diagnosed tumor and should be as parallel with the mattress on treatment bed as possible, Fig. 22.

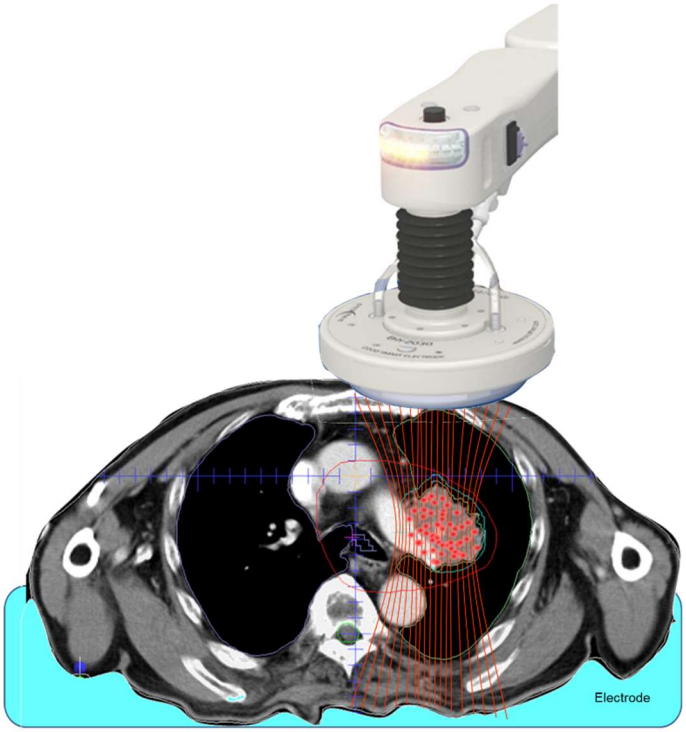


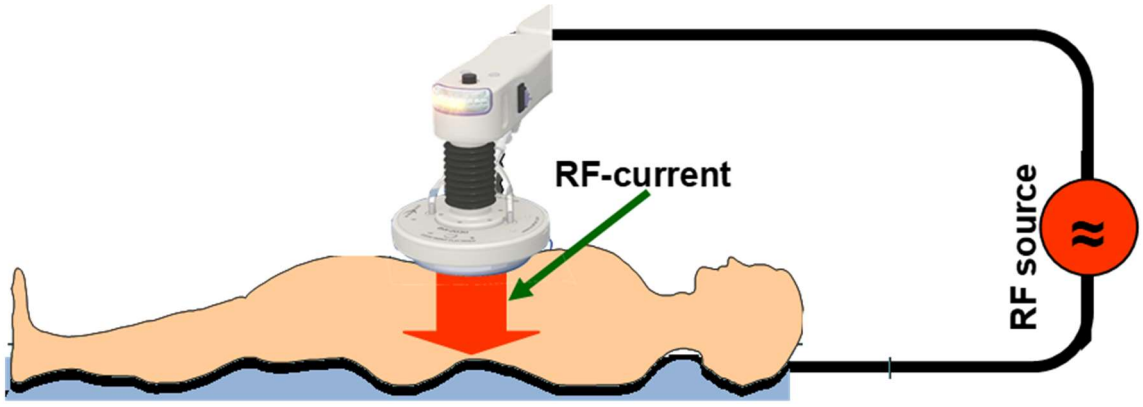
Figure 22. The position of the electrode covers the diagnosed tumor

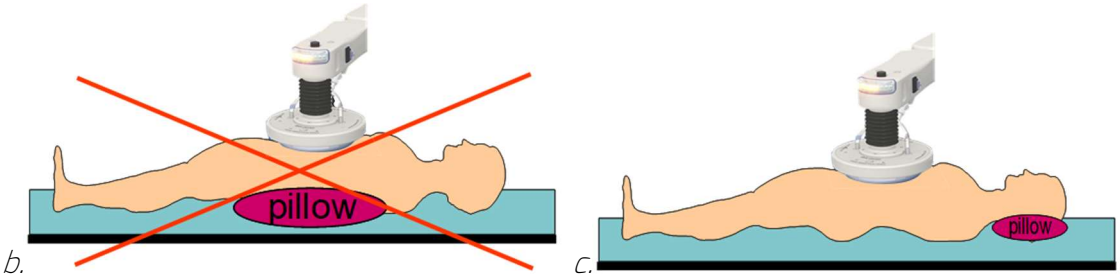
The self-selective, self-focusing process will be activated, and the absorbed energy will be concentrated on the membrane rafts of the tumor-cells, resulting in the heterogenic heating of the tumor volume.

Pillows and props may be used to ensure the correct position of the patient, however it is imperative that the pillows or props are not in the treatment field and do not block the direct path of the RF-current from the upper electrode down to the mattress electrode, Fig. 23. The placement of blankets, textile tissues, or other items which may block the flow of the RF-current is also not permitted. The only exception is the placement of hygienic, medical paper-toweling between the electrode and the skin of the patient.

The supine, prone, and lateral recumbent treatment positions of the body are shown on Fig. 24., [280].The abbreviations for the names of the positions are listed in Fig. 25.

a.





b. c.

Figure 23. The unobstructed path for RF-current (a), the current flow, (b), example of an incorrect pillow position, (c), correct pillow position.

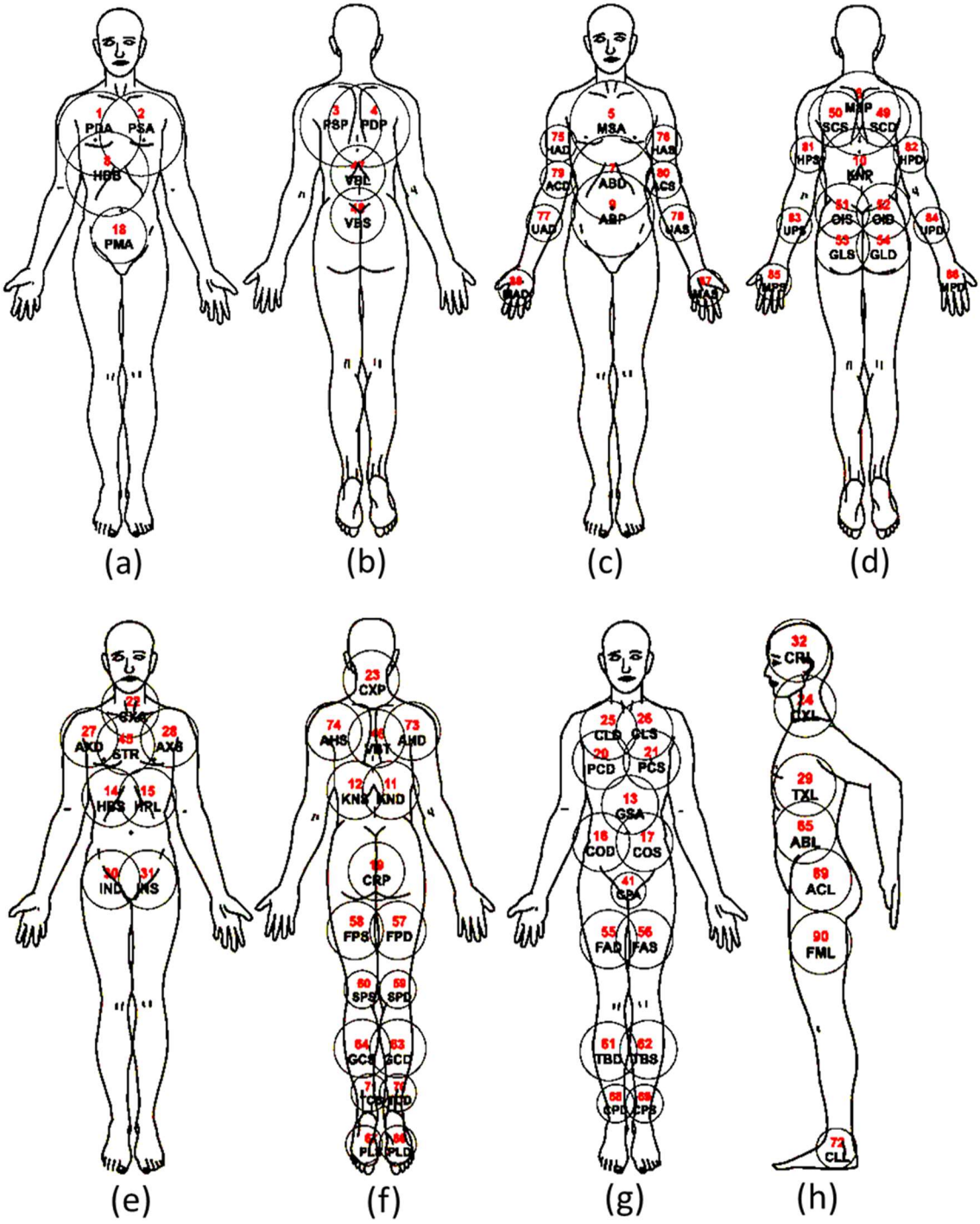


Figure 24. Positions of the electrode on the various body-parts.

1	PDA	Right Pulmonary Front	24	CXL	Lateral Neck	47	VBL	Lumbar	70	TCD	Right Achilles
2	PSA	Left Pulmonary Front	25	CLD	Clavicular Right	48	VBS	Sacral	71	TCS	Left Achilles
3	PSP	Right Pulmonary Rear	26	CLS	Clavicular Left	49	SCD	Scapular Right	72	CLL	Lateral Condylar
4	PDP	Left Pulmonary Kear	27	AXD	Right Axillary	50	SCS	Scapular Left	73	AHD	Rigt Shoulder
5	MSA	Mediastimal Front	28	AXS	Left Axillary	51	OIS	Left Iliac	74	AHS	Left Shoulder
6	MSP	Mediastimal Rear	29	TXL	Lateral thoracic	52	OID	Right Iliac	75	HAD	Front Right Humeral
7	ABD	Abdominal	30	IND	Right inguinal	53	GLS	Left Gluteal	76	HAS	Front Left Humeral
8	HBB	Hepato-Biliary Large	31	INS	Left inguinal	54	GLD	Right Gluteal	77	UAD	Front Right Forearm
9	ABP	Abdominal-Pelvic	32	CRL	Lateral Cranial	55	FAD	Front Right Femoral	78	UAS	Front Left Forearm
10	KNP	Renal	33	TLX	Thyroid-Laryngeal	56	FAS	Front Left Femoral	79	ACD	Right Ulnar
11	KND	Renal Right	34	CRF	Front Cranial	57	FPD	Rear Right Femoral	80	ACS	Left Ulnar
12	KNS	Renal Left	35	CRT	Cranio Temporal	58	FPS	Rear Left Femoral	81	HPS	Rear Left Hunmeral
13	GSA	Gastric	36	CRO	Cranio Occipital	59	SPD	Right Popliteal	82	HPD	Rear Right Humeral
14	HBS	Hepato-Biliary Small	37	MXL	Maxillary	60	SPS	Left Popliteal	83	UPS	Rear Right Humeral
15	HPL	Hepato-Pancrio-Splenic	38	OPL	Oropharyngeal	61	TBD	Right Tibia	84	UPD	Rear Right Forearm
16	COD	Colono-Ovarian Right	39	ORD	Right Orbital	62	TBS	Left Tibia	85	MPS	Rear Left Forearm
17	COS	Colono-Ovarian Left	40	ORS	Left Orbital	63	GCD	Right Calf	86	MPD	Rear Right Palm
18	PMA	Small Pelvis	41	GPA	Genito-Perineal	64	GCS	Left Calf	87	MAS	Front Left Palm
19	CRP	Colorectal	42	OLA	Oral-Labial	65	ABL	Lateral Abdominal	88	MAD	Front Right Palm
20	PCD	Pectoral Right	43	FRA	Frontal Anterior	66	PLD	Right Plantar	89	ACL	Coxofemoral
21	PCS	Pectoral Left	44	POL	Parotid	67	PLS	Left Plantar	90	FML	Lateral Femoral
22	CXA	Front Neck	45	STR	Sternal	68	CPD	Right Ankle			
23	CXP	Rear Neck	46	VBT	Thoracic spine	69	CPS	Left Ankle			

Figure 25. List of abbreviations of positions.

Dosing

The recommended protocols for the most frequently treated malignancies are listed in Fig. 26. Note that these are guidelines and the final protocol depends on the actual situation and the patient's individual reaction. These doses are averages from reports as well as the anecdotal experiences of the doctors. The real dose must be adjusted to the patient's tolerance. In case of lung cancer, the length of the treatment may be longer than 60 minutes but should not exceed 90 minutes.

The sensitivity of the patient for the applied power can highly increase when the perspiration or any wet layer appear on the treated skin under the electrode. When the patient complains, please wipe the skin and the electrode surface dry. You may apply a thin layer of antiperspirant spray or use talcum powder to avoid the intensive development of sweat on the surface. In serious cases, antiperspirant medication can be applied.

Abr.	Name	View	Electrode Diameter [cm]	Start power [W]	End power [W]	duration (min)	DOSE (kJ)
PDA	Right Pulmonary Front	Supine	30	80	116	65	478
PSA	Left Pulmonary Front	Supine	30	80	116	65	478
PSP	Right Pulmonary Rear	Prone	30	80	120	70	523
PDP	Left Pulmonary Kear	Prone	30	80	120	70	523
MSA	Mediastimal Front	Supine	30	80	115	78	539
MSP	Mediastimal Rear	Prone	30	80	111	70	481
ABD	Abdominal	Supine	30	80	120	75	547
HBB	Hepato-Biliary Large	Supine	30	80	123	70	537
ABP	Abdominal-Pelvic	Supine	30	80	119	68	508
KNP	Renal	Prone	30	80	115	60	453
KND	Renal Right	Prone	20	60	108	65	459
KNS	Renal Left	Prone	20	60	108	64	456
GSA	Gastric	Supine	20	60	102	60	413
HBS	Hepato-Biliary Small	Supine	20	60	107	71	476
HPL	Hepato-Pancrio-Splenic	Supine	20	60	107	71	476
COD	Colono-Ovarian Right	Supine	20	60	103	66	437
COS	Colono-Ovarian Left	Supine	20	60	104	70	456
PMA	Small Pelvis	Supine	20	60	100	60	403
CRP	Colorectal	Prone	20	60	103	72	459
PCD	Pectoral Right	Supine	20	60	98	65	410
PCS	Pectoral Left	Supine	20	60	98	65	410
CXA	Front Neck	Supine	20	60	97	60	388
CXP	Rear Neck	Prone	20	60	99	60	399
CXL	Lateral Neck	Lateral	20	60	95	60	382
CLD	Clavicular Right	Supine	20	60	102	65	431
CLS	Clavicular Left	Supine	20	60	102	65	431
AXD	Right Axillary	Supine	20	60	99	60	399
AXS	Left Axillary	Supine	20	60	99	60	399
TXL	Lateral thoracic	Lateral	20	60	102	65	431
IND	Right inguinal	Supine	20	60	97	60	388
INS	Left inguinal	Supine	20	60	97	60	388
CRL	Lateral Cranial	Lateral	20	60	90	60	356

Abr.	Name	View	Electrode Diameter [cm]	Start power [W]	End power [W]	duration (min)	DOSE (kJ)
STR	Sternal	Supine	20	60	102	73	457
VBT	Thoracic spine	Prone	20	60	99	60	399
VBL	Lumbar	Prone	20	60	99	60	399
VBS	Sacral	Prone	20	60	99	60	399
SCD	Scapular Right	Prone	20	60	101	68	436
SCS	Scapular Left	Prone	20	60	101	68	436
OIS	Left Iliac	Prone	20	60	104	66	445
OID	Right Iliac	Prone	20	60	104	66	445
GLS	Left Gluteal	Prone	20	60	96	60	384
GLD	Right Gluteal	Prone	20	60	96	60	384
FAD	Front Right Femoral	Supine	20	60	99	60	399
FAS	Front Left Femoral	Supine	20	60	99	60	399
FPD	Rear Right Femoral	Prone	20	60	96	60	384
FPS	Rear Left Femoral	Prone	20	60	96	60	384
TBD	Right Tibia	Supine	20	60	96	60	384
TBS	Left Tibia	Supine	20	60	96	60	384
GCD	Right Calf	Prone	20	60	99	60	399
GCS	Left Calf	Prone	20	60	99	60	399
ABL	Lateral Abdominal	Lateral	20	60	105	70	463
AHD	Rigt Shoulder	Prone	20	60	90	60	356
AHS	Left Shoulder	Prone	20	60	90	60	356
ACL	Coxofemoral	Lateral	20	60	93	60	370
FML	Lateral Femoral	Lateral	20	60	93	60	370
ATT	Anterior Thorax Trans	Supine	45	90	158	70	695
ATL	Anterior Thorax Long	Supine	45	90	158	70	695
AAT	Anterior Abdomen Trans	Supine	45	90	164	68	715
AAL	Anterior Abdomen Long	Supine	45	90	164	68	715
APT	Anterior Pelvic Trans	Supine	45	90	178	68	774
APL	Anterior Pelvic Long	Supine	45	90	178	68	774
PTT	Posterior Thorax Trans	Prone	45	80	155	60	639
PTL	Posterior Thorax Long	Prone	45	80	155	60	639
PAT	Posterior Abdomen Trans	Prone	45	80	160	60	662
PAL	Posterior Abdomen Long	Prone	45	80	160	60	662
PPT	Posterior Pelvic Trans	Prone	45	80	154	60	634

Figure 26. List of proposed doses in different positions.

One of the key principles of mEHT is the restoration of the natural state of homeostasis. To this end, mEHT aims to avoid applying too much pressure on the system which could in turn tip the homeostatic mechanisms further from the imbalance that already exists as a result of the malignant tissue. By alerting the immune system to the presence of the malignant cells (via mechanisms such as triggering the release of extracellular HSP70 and triggering apoptosis which releases genetic material used to identify the malignant cells), the tumor becomes recognizable and in this way mEHT can support the homeostatic actions involved in destroying the unwanted malignant cells.

Patient adaptation for the dose

The concept that the difference between the medicine and the poison is the dose, is also applied to the prescription of mEHT. The dose of mEHT is determined by the energy required to support the

movement towards homeostasis in the body. When the dose of mEHT is too low, then the efficacy fails, when it is too high, then "poisoning" can occur in the sense that the natural processes are disrupted beyond repair. For example, applying the maximum power possible can result in discomfort and adverse effects in the patient, and the power should always be adjusted to the patient's tolerance in order to support the treatment of the patient. The dose principle in mEHT therefore has its own limitations:

1. The optimal dose is patient dependent, so the patient-oriented focus is essential.
2. A specific value or dose can therefore not be determined for a cycle of treatment, even in the same patient. The dose has an interval where the optimum range could be defined (it follows fuzzy logic).
3. The timing of administration and the overall sum of dose are also decisional factors for the optimal treatment.

The supportive effects of mEHT include:

1. Slight increase in the temperature (under the threshold of $40°C$), creating a normal homeostatic reaction (local fever-like, or inflammatory condition),
2. Triggering various apoptotic pathways (to promote natural programmed cell-death), in the selected malignant cells

The dose of mEHT which supports the homeostasis:

1. The optimal dose of mEHT treatment is ensured by the patient feedback during the process, avoiding erythema or burns in the skin or adipose tissue.
2. Monitoring the patient's response to treatment in order to ensure an adequate number of treatments to achieve the desired clinical outcome.
3. The timing of administration has three factors:
    a. The duration of the treatment is limited by two factors: the maximum time limit (less than 90 min), to protect against thermo-resistance, and the tolerance limit of the patient in the given treatment. When the recommended dose in KJ is not achieved, increasing the duration of the treatment could be helpful (Fig. 27.), provided the treatment time does not exceed 90 min. In cases where prolonging the treatment time still does not achieve the desired dose, then the number of sessions in the cycle could be increased to fit the requested overall energy.
    b. Determining how long to continue a treatment cycle for is based on the tumor's response to the treatment. Evaluating the tumor response can be achieved using imaging studies or hematological investigations where possible, such as the use of tumor markers Fig. 28, [281], [282].
    c. The complete dose is calculated after all cycles, once the patient reaches a follow-up period, without treatments. This dose depends on the patient's status, which has to be measured by imaging techniques together with the disappearance of the symptoms. The dose is the sum of all doses divided by the number of treatments.

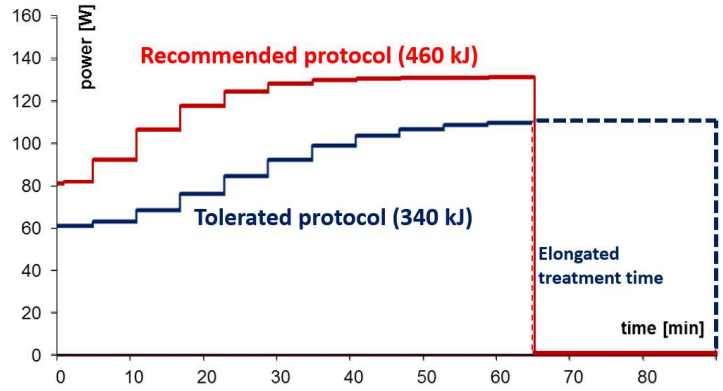


Figure 27. The elongated treatment-time could correct the missing dose from the recommended protocol due to the actual limit of toleration.

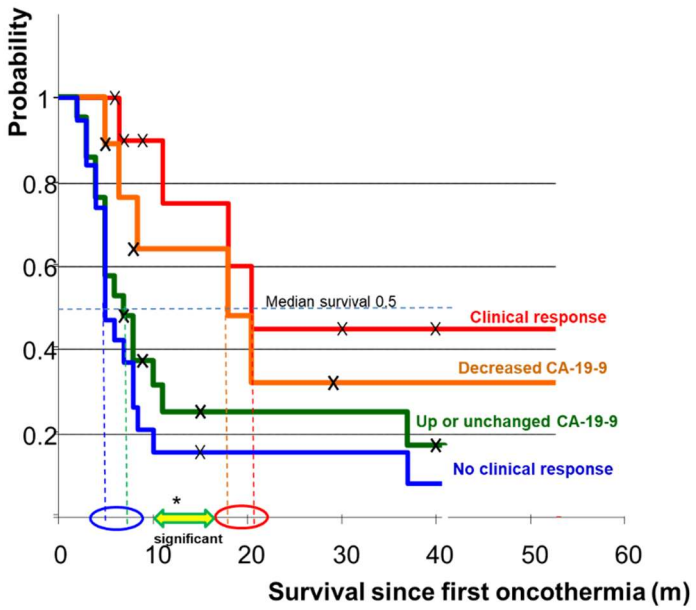


Figure 28. Clinical study of the tumor-marker in pancreas-carcinoma cases. The measured clinical response by imaging shows good correspondence with the tumor-marker changes, and the difference shown by the tumor-marker CA-19-9 is significant.

One of the main differences between the newer EHY-2030 and the EHY-2000 series technology is the higher efficacy of the EHY-2030 treatments. As such, the recommended doses with the EHT-2030 are 15% less than what is applied with the EHY-2000+. However, the dose calculation must account for the surface energy-load (measured in W/m^2), when the electrode size is larger than those recommended (and available), for EHY-2000+. In this case, dose has to be increased proportionately to the increase in the surface areas.

Brain treatment

The only meta-analysis comparing mEHT to other hyperthermia techniques was conducted on brain tumors. The results were significant and demonstrated significantly improved outcomes and economic benefits when mEHT was applied for the management of brain tumors, compared to treatment without hyperthermia, [208]. For this reason, mEHT is indicated in the management of patients with glioblastoma multiforme tumors. Treating the brain requires special care and therefore a special mention in this review.

It is important to carefully monitor and control side-effects of the patient which could be a result of the brain tumor, the conventional treatment, or the mEHT treatment (headache, dizziness, epilepsy, etc.), and ask before each treatment how the patient felt after the last treatment. In case of adverse effects, do not increase the dose, until the adverse effects resolve.

Please, position the electrode carefully, it must be as far as possible from the eye, Fig. 29.

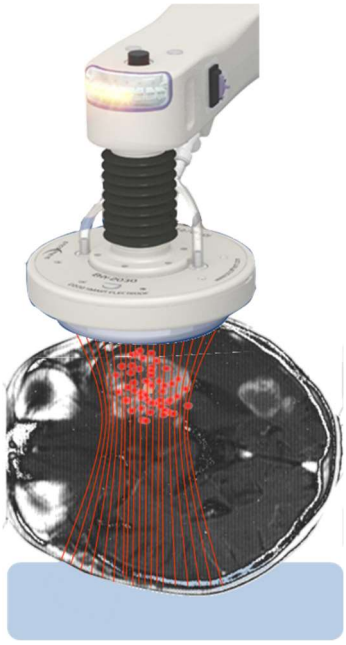


Figure 29. The electrode positioning for brain tumor treatment.

The patient must lay down on the bed. When placing any normal pillow under his/her head, the air in the pillow will prevent the RF-current to flow, and all the current will flow through the neck and shoulder to the counter electrode, Fig. 30.

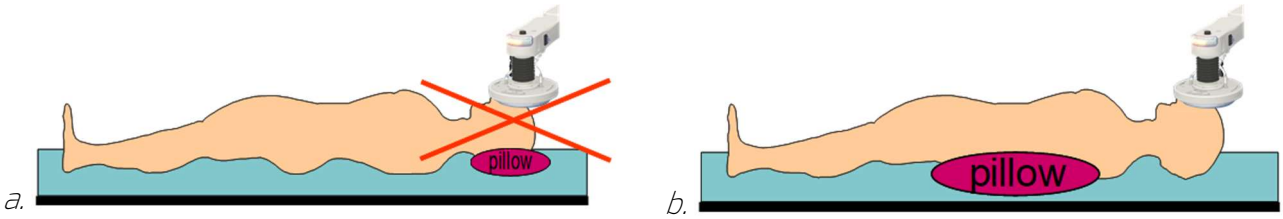


Figure 30. a) incorrect placement of the pillow. b) correct placement of the pillow

If a pillow is required for proper positioning, use the optionally provided special electrode pillow, supplied by the manufacturer, under the head of the patient, Fig. 31., or as a temporary solution a distilled water-filled pillow can be used.

Figure 31. Position correction by water-pillow or other provided (specially coated), pillow

The patient must be in a relaxed position and the body should be stabilized and supported with additional pillows or blankets to ensure comfort during the treatment The possible positions are shown in Fig. 32., [280].

At the initial treatment, apply 30-40 W for 30 minutes without modulation.

At the second treatment, increase the power from 40 W to 60 W gradually over 40 minutes.

From the third treatment onwards, apply modulation and increase the power from 40 W to 80 W gradually for 60 minutes. The protocol is shown in Fig. 33.

Please repeat the protocol two to three times a week, with at least one-day between the treatment sessions.

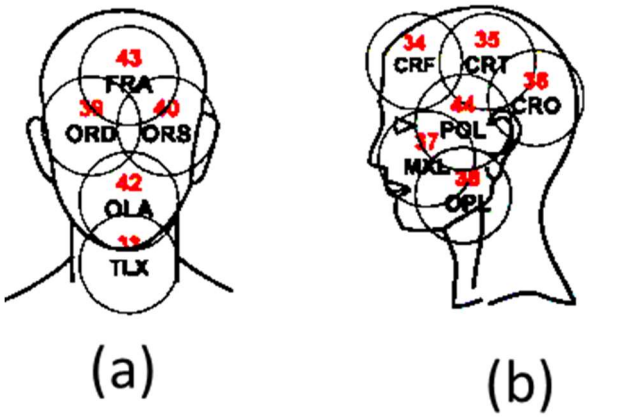


Figure 32. Possible electrode positions for brain treatment with mEHT.

1. Session		2. Session		3. Session		4. Session		5. Session		6. Session			Further	
min	Watt	min	Watt	min	Watt	min	Watt	min	Watt	min	Watt		min	Watt
10	30	20	40	20	40	20	60	20	60	20	60		20	60
20	40	20	60	20	60	20	80	10	80	10	80		10	80
				20	80	20	100	20	100	10	100	...	10	100
								10	120	10	120		10	120
										10	140		10	140
20		40		60		60		60		60			60	

Figure 33. The protocol for brain treatment with EHY-2030. This is an optimized version of the protocol of EHY2000 shown in a safety clinical trial, [196]. The modification is based on the higher performance of the EHY-2030. Please be careful however, because it is extremely patient dependent, so monitor the patient frequently, and reduce the dose when necessary.

Summary

The concept

1. The new paradigm has essential consequences in the practice of hyperthermia. The process of providing energy during the treatment has been modified. Instead of continuously pumping the energy into the system during the mEHT treatment, step-up heating is required. This heating method gradually increases the power (and consequently the absorbed energy), depending on the actual patient and tumor conditions.
    a. The actual conditions are partially defined by the blood-flow of the target. The temperature at the given continuous incident energy first increases linearly (quasi-adiabatic condition), and then in time it starts to deviate from the starting slope, showing that the energy is spread by natural heat conduction mechanisms as well as by the temperature induced (non-linear), blood flow. Over time the temperature in the region reaches a stable point and does not change, provided the power is constant. However, the active period of energy-absorption in the selected target occurs when the energy does not spread and is not removed via the various transport systems (blood, lymph). So, keeping the optimal energy-absorption, when the slope of temperature development begins to deviate from the initial linear slope, the power is again increased, again creating a linear slope for the optimal use of the energy.
    b. In the case, where the energy is applied as a monotherapy (in the absence of any other complementary treatments), the step-up heating is not optimal, due to adaption of the blood flow to the situation. In these cases, the maximum available power should be continuously applied, reduced only when the patient reports discomfort. When the patient complains, the power is decreased gradually until the discomfort is resolved.
2. The most important factor of the treatment practice is the patient's ability to sense and report back to the operator.
    a. The treating process has to react to any distress during the treatment, which is not only a safety issue, but an important physiological factor as well. The patient under distress has numerous physiological reactions (such as sweating, changing the blood pressure, changing the homeostatic regulation by the nervous system and developing stress proteins against the treatment).
    b. The patient is the main safety sensor. The individual sensing of the heat allows the personalization of the treatment and limits the risk factors.
    c. The temperature sensing is individually tuned by transient receptor potential channels (TRP), of the cells, representing the cellular temperature sensor on the membrane. When one patient is more sensitive to the rising temperature than another patient, it means that the membrane effects, - which are the goal of the treatment, - require less energy absorption initially. In this case, do not force a higher energy dose, as the lower dose could have the same effects on a nanoscopic level in the patient, compared to the patient with a higher dose.
    d. The patient as a sensor is partly "built-in" to the electric regulation, because any changes in the target, modifies the tuning and the device optimizes the treatment.
3. The patients' personal involvement in the treatment control does not only involve the sensing, but also the adaption to the changing conditions. These adaptive mechanisms could be short term (during the actual treatment), or long term (during the cycle involving numerous treatment sessions). Each adaptation changes the temperature sensing and modifies the therapy conditions. Consequently, all treatments are individual, and there is no possibility for an automated treatment protocol.

The treatment processes

The following points contain the steps of a typical treatment. It is suggested to keep a copy of this page near the device.

1. Choose the proper electrode and disinfect it.
2. Fix the electrode to the holding arm and connect the water tubes.
3. Connect the electrode ground magnet disc to the ground bar.
4. Lay the patient on the bed and place the electrode as smoothly as possible on the patient in the identified treatment area.
5. Turn on the device using the switch on the right side of the display.
6. Let the self-test run. The self-test takes less than a minute.
7. Set the treatment parameters using the display.
8. Start the treatment with the Start button (or soft button on the display).
9. Let the treatment run until the set time runs out. The device signals the end of the treatment with an audio signal. After pushing the Stop button the device runs a self-test automatically.
10. Remove the patient from the bed.
11. Once the self-test is completed, you can begin the next treatment.

Possible adverse effects

Like all medical treatments mEHT can also have adverse effects. It is important to mention that these are rare and are often connected to comorbidities and the extreme sensitivity of the patient.

Possible short-term side-effects

- ☐ Moderate local pain during the procedure
- ☐ Nausea
- ☐ Vomiting
- ☐ Diarrhea
- ☐ Confusion
- ☐ Slowed psychomotor functions
- ☐ Dizziness
- ☐ Somnolence
- ☐ Hemiparesis
- ☐ Cranial nerve dysfunction
- ☐ Aphasia
- ☐ Seizures
- ☐ Hydrocephalus
- ☐ Thirstiness
- ☐ Facial flushing

- Skin effects, typically the local skin erythema in the area of exposure
- Fatigue, short-term asthenia
- Headache (mainly in brain applications)
- Short-term euphoria
- Sub-febrile temperature for several days after treatment

Possible long-term side-effects

- Burns of the skin
- Burns of subcutaneous tissue
- Subcutaneous fat-burn
- Subcutaneous fatty fibrosis

Conclusion

The mEHT treatment is safe and has demonstrated efficacy for local control as well as for overall survival with improved quality of life. The efficacy of mEHT can also be seen in cases when the conventional therapies have failed. The future of mEHT tends towards the field of immuno-oncology, with the potential to induce abscopal effects to target distant lesions as well as the local disease. The new EHY-2030 device is a highly improved system, integrating the long history of scientific, practical, and clinical experience of the mEHT applications worldwide.

Acknowledgement

Authors AM Szasz, E Borbenyi and M Dank are thankful for the support of the Hungarian Competitiveness and Excellence Programme grant (NVKP_16-1-2016-0042).

The authors thank the manufacturer, Oncotherm Kft., for their support of the review, providing vital information regarding the history of the company and the technical specifications of the EHY-2030, and in so doing the manufacturer has enabled a comprehensive review of the technology.

References

[1] Seegenschmiedt MH, Vernon CC (1995), A Historical Perspective on Hyperthermia in Oncology. In: Seegenschmiedt MH, Fessenden P, Vernon CC (eds), (1995), Thermoradiotherapy and Thermochemotherapy Vol. 2: Clinical Applications, Springer Verlag, Berlin, pp. 3-46

[2] Roussakow S (2013), The History Of Hyperthermia Rise And Decline. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 428027, http://www.hindawi.com/archive/2013/428027/

[3] Hahn, G.M.: Blood-flow. In: Field, S.B., Franconi, C. (eds.), Physics and Technology of hyperthermia, No. 127, pp 441-446. NATO ASI Series, Series E: Applied Sciences, Martinus Nijhoff Publishers, Dordrecht, Bosto, Lanchester (1987)
[4] Dudar TE, Jain RK (1984), Differential response of normal and tumor microcirculation to hyperthermia. Cancer Res 44(2):605-612
[5] Song CW (1984), Effect of Local hyperthermia on blood-flow and microenvironment: a review. Cancer Res 44(10 Suppl):4721s-4730s
[6] Song CW, Park H, Griffin RJ (2001), Theoretical and Experimental Basis of Hyperthermia. In: Kosaka M, Sugahara T, Schmidt KL, et al (eds), Thermotherapy for Neoplasia, Inflammation, and Pain, Springer Verlag Tokyo, pp 394-407
[7] Song, C.W., Choi, I.B., Nah, B.S., et. al.: Microvasculature and perfusion in Normal tissues and tumors. In: Seegenschmiedt, M.H., Fessenden, P., Vernon, C.C. (eds.), Thermo-radiotherapy and Thermo-chemotherapy, vol. 1, pp. 139-156. Biology, physiology and physics, Springer Verlag, Berlin Heidelberg (1996)
[8] Guy, A.W., Chou, C.K.: Physical aspects of localized heating by radio-waves and microwaves. In: Storm, K.F. (ed.), Hyperthermia in cancer therapy, GK Hall Medical Publishers, Boston (1983)
[9] Szasz A, Szasz N, Szasz O (2010), Oncothermia – Principles and practices. Springer Science, Heidelberg, http://www.springer.com/gp/book/9789048194971
[10] Whitrow M. (1993), Julius Wagner-Jauregg (1857–1940). London: Smith-Gordon, 1993.
[11] Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas with a report of ten original cases. Am J Med Sci 1893;105:487-511
[12] Nielsen OS, Horsman M, Overgard J (2001), A future for hyperthermia in cancer treatment? European Journal of Cancer 37(13):1587-1589
[13] van der Zee J (2002), Heating the patient: a promising approach? Annals of Oncology 13:1173-1184
[14] Pubmed, https://pubmed.ncbi.nlm.nih.gov/?term=hyperthermia Cited 19 July 2020
[15] Medicine.net, https://www.medicinenet.com/script/main/art.asp?articlekey=3848, last accessed on 19 June, 2019
[16] Medical dictionary (2008), http://www.medterms.com/script/main/art.asp?articlekey=3848
[17] The free dictionary (2008), http://www.thefreedictionary.com/hyperthermia Cited 19th July 2020.
[18] National Cancer Institute, https://www.cancer.gov/about-cancer/treatment/types/surgery/hyperthermia-fact-sheet, last accessed on 19 June, 2020
[19] van der Zee J, Vujaskovic Z, Kindo M, Sugahara T. The Kadota Fund International Forum 2004 – clinical group consensus. Int J Hyperthermia 2008;24:111–2
[20] Medline Encylcopedia https://www.encyclopedia.com/medicine/drugs/pharmacology/hyperthermia (accessed Jun.21, 2020)
[21] Medline Plus https://medlineplus.gov/ency/patientinstructions/000904.htm CIted 19th July 2020
[22] Wikipedia, https://en.wikipedia.org/wiki/Hyperthermia_therapy, last accessed on 19 July, 2020
[23] The American Cancer Society, https://www.cancer.org/treatment/treatments-and-side-effects/treatment-types/hyperthermia.html, last accessed on 19 June, 2020
[24] Szasz AM, Arkosy p, Arrojo EE, et.al. (2020), Guidelines for local hyperthermia treatment in oncology, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 2, pp.32-71, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[25] Szentgyorgyi A (1978), The living state and cancer. Marcel Dekker Inc, New York
[26] Ostberg JR, Repasky EA (2000), Use of mild, whole body hyperthermia in cancer therapy. Immunol Invest 29(2):139-142
[27] Appenheimer MM, Qing C, Gipard RA et al (2005), Impact of Fever-Range Thermal Stress on Lymphocyte-Endothelial Adhesion and Lymphocyte Trafficking. Immunological Inestigations 34(3):295-323

[28] Shah A, Unger E, Bain MD et al (2002), Cytokine and adhesion molecule expression in primary human endothelial cells stimulated with fever-range hyperthermia. Int J Hyperthermia 18(6):534-551
[29] Burd R, Dziedzic TS, Xu Y et al (1998), Tumor Cell Apoptosis, Lymphocyte Recruitment and Tumor Vascular Changes Are Induced by Low Temperature, Long Duration (Fever-Like), Whole Body Hyperthermia. J Cell Physiol, 177(1):137-147
[30] Toyota N, Strebel FR, Stephens LC et al (1997), Long Duration - Mild Whole Body Hyperthermia with Cisplatin: Tumor Response and Kinetics of Apoptosis and Necrosis in a Metastatic at Mammary Adenocarcinoma. Int J Hyperthermia 13(5):497-506
[31] von Ardenne A, Wehner H. (2006), Extreme Whole-Body Hyperthermia with Water-Filtered Infrared-A Radiation, In book: Hyperthermia in Cancer Treatment: A Primer, Baronzio GF, Hager ED, (Eds.), Springer, Ch.19. pp.237-247
[32] Suvernev AV, Ivanov GV, Efremov AV, Tchervov R. (2000), Whole Body Hyperthermia at 43.5-44°C: Dreams or Reality? In book: Hyperthermia in Cancer Treatment: A Primer, Baronzio GF, Hager ED, (Eds.), Springer, Ch.18. pp.227-237
[33] Graham, K. and Unger, E. (2018), Overcoming tumor hypoxia as a barrier to radiotherapy, chemotherapy and immunotherapy in cancer treatment, *International Journal of Nanomedicine*,Vol.13,pp.6049–6058
[34] Perez CA and Sapareto SA: Thermal dose expression in clinical hyperthermia and correlation with tumor response/control. Cancer Research, 44,4818-4825, 1984
[35] Dewey WC: Arrhenius relationships from the molecule and cell to the clinic. Int J Hyperthermia, 10(4),457-483, 1994
[36] Sapareto SA and Dewey WC: Thermal dose determination in cancer therapy. Int J Radiat Oncol Biol Phys, 10(6), ,787-800, 1984
[37] Dewhirst MW, Viglianti BL, Lora-Michiels M. Hanson M and Hoopes PJ: Basic principles of thermal dosimetry and thermal thresholds for tissue damage from hyperthermia. Int J Hyperthermia, 19:267-294, 2003
[38] Fatehi D, van der Zee J, Notenboom A, et.al. (2007), Comparison of intratumor and intraluminal temperatures during locoregional deep hyperthermia of pelvic tumors, Strahlentherapie und Onkologie, 183:479-86
[39] Mouratidis PXE, Rivens I, Civale J, et.al. (2019), 'Relationship between thermal dose and cell death for "rapid" ablative and "slow" hyperthermic heating', Int J Hyperthermia, 36:1, 228-242
[40] Wust P. (2005), Thermoregulation in humans, Experiences from thermotherapy, Stuttgart, 21 November 2005
[41] Vorst AV, Rosen A, Kotsuka Y. (2006), RF/Microwave interaction with biological tissues, John Wiley & Sons, Hoboken, NJ, USA
[42] Szasz O, Szigeti GyP, Vancsik T, Szasz A. (2018), Hyperthermia dosing and depth of effect, Open Journal of Biophysics, 2018, 8, 31-48, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=81896
[43] Szasz A. (2020), Challenges and solutions of oncological hyperthermia, , Cambridge Scholars Publishing, ISBN-13: 978-5275-4817-6, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[44] Szasz A, Iluri N, Szasz O (2013), Local hyperthermia in Oncology – To Choose or not to Choose? A chapter in book: Hyperthermia, Ed: Huilgol N, ISBN 980-953-307-019-8, InTech, Ch.1. pp.1-82; http://www.intechopen.com/books/hyperthermia/local-hyperthermia-in-oncology-to-choose-or-not-to-choose-
[45] Szasz A, Szasz O, Szasz N (2006), Physical background and technical realization of hyperthermia. In: Baronzio GF, Hager ED (eds), Hyperthermia in Cancer Treatment: A primer, Ch. 3., Springer, New York, NY, pp 27–59
[46] Wust P, Hildebrandt B, Sreenivasa G et al (2002), Hyperthermia in combined treatment of cancer. Lancet Oncol 3(8):487-497

[47] Turner PF (1984), Regional hyperthermia with an annular phase array. IEEE Trans Biomed Eng BME-31:106-111
[48] Wust, P., Fahling, H., Wlodarczyk, W.: Antenna arrays in the sigma-eye applicator: Interactions and transforming networks. Med. Phys 28, 1793-1805 (2001)
[49] LeVeen HH, Wapnick S, Piccone V et al (1976), Tumor eradication by radiofrequency therapy. JAMA 235(20):2198-2200
[50] Abe M, Hiraoka M, Takahashi M et al (1986), Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (thermotron RF-8), in combination with radiation for cancer therapy. Cancer 58:1589-1595
[51] Song, C.W., Rhee, J.G., Lee, C.K., et. al.: Capacitive heating of phantom and human tumors with an 8 MHz radiofrequency applicator (Thermotron RF-8*). Int. J. Radiation Oncology Biol Phys. 12(3), 365-372 (1986)
[52] Juang T, Neuman D, Schlorff J, et.al. (2004), Construction of a conformal water bolus vest applicator for hyperthermia treatment of superficial skin cancer, Proceedings of the 26th Annual International Conference of the IEEE EMBS, San Francisco, CA, USA, September 1-5, 2004
[53] Harima Y, Nagata K, Harima K, et.al. (2001), A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIB cervical carcinoma, Int. J. Hyperthermia, 17(2):97-105
[54] Sakagami T, Ohno T, Furuya T, Matsumaoto M, Kobayashi T, Takada F, Sawada Y, Shiomi M, Hosomi M, Tanida N, Satomi M, Shimoyama T, Sasaki T, Matsuda T. (1993), Development of Thermotron RF I.V (a mini device for 8 MHz radiofrequency capacitive heating), and the effect of its application on implanted tumour in rats, In book: Matsuda T (ed), Cancer treatment by hyperthermia, radiation and drugs, Taylor&Francis, London-Washington DC, Ch.12, pp 127-138
[55] Kok HP, Navarro F, Strigari L, et.al. (2018), Locoregional hyperthermia of deep-seated tumours applied with capacitive and radiative systems: a simulation study, Int. J. Hyperthermia, 34:6, 7141-730
[56] Seong JS, Chu SS, Kim GE, et.al. (1989), Unusial angular arrangement of electrodes in capacitive heating device, J Korean Soc Ther Radiol, 7(2):313-320
[57] Murata T, Akagi K, Ostapenko VV, et.al. (1998), Relevance of a new impedance matching or subtrap method for the reduction of pain during hyperthermia, Acta Oncologica, 37(5), 485-488
[58] Brezovich IA, Lilly MB, Durant JR, et.al. (1981), A practical system for clinical radiofrequency hyperthermia. Int J Radiat Oncol Biol Phys 7:423–430 44.
[59] Reddy NMS, Shanta V, Krishnamurthi S (1986), On minimization of toxicity to skin during capacitive radiofrequency hyperthermia. Br J Radiol 59:1129–1131
[60] Ferenczy GL, Szasz A. (2020), Technical challenges and proposals in oncological hyperthermia, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 3, pp.72-90, Cambridge Scholars,https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[61] Szasz O (2013), Renewing Oncological Hyperthermia-Oncothermia. Open Journal of Biophysics, 3:245-252, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=38154
[62] Szasz O (2013), Essentials of oncothermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 159570, http://www.hindawi.com/archive/2013/159570/
[63] Szasz A, Szasz O, Szasz N (2001), Electro-hyperthermia: a new paradigm in cancer therapy. Deutsche Zeitschrift fur Onkologie 33:91–99, http://real.mtak.hu/6593/
[64] Hegyi G, Szasz O, Szasz A (2013), Oncothermia: A new paradigm and promising method in cancer therapies. Acupuncture and Electro-Therapeutics Res. Int. J. 38:161-197, http://www.ncbi.nlm.nih.gov/pubmed/24494322
[65] Szasz O, Szasz A (2016), Heating, efficacy and dose of local hyperthermia. Open Journal of Biophysics, 6:10-18, http://www.scirp.org/journal/PaperInformation.aspx?paperID=62874
[66] Lee S-Y, Szigeti GP, Szasz AM (2019), Oncological hyperthermia: The correct dosing in clinical applications, Int. J. Oncology, 54: 627-643, https://www.ncbi.nlm.nih.gov/pubmed/30483754
[67] Szasz O, Szasz A.M. Minnaar C, Szasz A (2017), Heating preciosity - trends in modern oncological

hyperthermia. Open Journal of Biophysics 7:116-144, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=77458

[68] Alfred J. Barich, Lazaros Daniilidis, Michael Marangos (2018): Oncothermia and the paradigm shift in integrative oncology; Oncothermia Journal 24:373-404 , https://oncotherm.com/sites/oncotherm/files/2018-10/Oncothermia_and_the_paradigm_shift.pdf

[69] Douwes FR (2012), Is an Integrative Cancer Therapy Concept (ICTC), the answer to improve the present situation in cancer care? Oncothermia Journal 6:27-32, https://oncotherm.com/sites/oncotherm/files/2017-07/Is_an_integrative_cancer_therapy_concept_%28ICTC%29_the_answer.pdf

[70] Szasz A. (2018), Local oncothermia treatment fights against systemic malignancy; Oncothermia Journal 22: 58-84, https://oncotherm.com/sites/oncotherm/files/2018-03/Local_oncothermia_treatment.pdf

[71] Szasz A (2013), "Quo vadis" oncologic hyperthermia? Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 201671, http://www.hindawi.com/archive/2013/201671/

[72] Szasz A (2016), Quo vadis oncological Hyperthermia Update 2016. Oncothermia Journal 18:12-41, https://oncotherm.com/sites/oncotherm/files/2017-07/Quo_vadis_oncological_Hyperthermia_Update_2016.pdf

[73] Jones, E., Dewhirst, M., Vujaskovic, Z.: Hyperthermia improves the complete response rate for superficial tumors treated with radiation: results of a prospective randomized trial testing the thermal dose parameter CEM 43°T90. Int. J. Rad. Oncol. Biol. Phys. 57, S253-S254 (2003)

[74] Szasz A. (2018): Basic principle and new results of Oncothermia; Oncothermia Journal 22:178-205, https://oncotherm.com/sites/oncotherm/files/2018-03/Basic_principle_and_new_results_of_Oncothermi.pdf

[75] Szasz A (2013), Challenges and Solutions in Oncological Hyperthermia. Thermal Med 29(1):1-23, https://www.jstage.jst.go.jp/article/thermalmed/29/1/29_1/_article

[76] Szasz O, Szigeti GyP, Szasz A. (2017), On the self-similarity in biologyical processes, OJBIPHY, 7(4):183-196, http://file.scirp.org/pdf/OJBIPHY_2017090715550515.pdf

[77] Yatvin MB, Dennis WH (1978), Membrane lipid composition and sensitivity to killing by hyperthermia, Procaine and Radiation. In: Streffer C, vanBeuningen D, Dietzel F et al (eds), Cancer Therapy by Hyperthermia and Radiation, Urban & Schwarzenberg, Baltimore, Munich, pp 157-159

[78] Nishida T, Akagi K, Tanaka Y (1997), Correlation between cell killing effect and cell-membrane potential after heat treatment: analysis using fluorescent dye and flow cytometry. Int J Hyperthermia 13(2):227-234

[79] Watanabe M, Suzuki K, Kodama S et al (1995), Normal human cells at confluence get heat resistance by efficient accumulation of hsp72 in nucleus. Carcinogenesis 16(10):2373-2380

[80] Bowler, K., Duncan, C.J., Gladwell, R.T., et. al.: Cellular heat injury. Comp. Biochem. Physiol. 45A, 441-450 (1973)

[81] Kabakov AE, Gabai VL (1997), Heat Shock Proteins and cytoprotection: ATP-deprived mammalian cells. (Series: Molecular Biology Intelligence Unit), Springer Verlag, New York, Berlin, Heidelberg

[82] Huot J, Roy G, Lambert H, Landry J (1992), Co-induction of HSP27 Phosphorylation and Drug Resistance in Chinese Hamster Cells. Inter J Oncology 1:31-36

[83] Semenza GL (2008), Tumor metabolism: cancer cells give and take lactate. The Journal of Clinical Investigation 118(12):3835-3837

[84] Friedl J, Turner E, Alexander HR Jr (2003), Augmentation of endothelial cell monolayer permeability by hyperthermia but not tumor necrosis factor: evidence for disruption of vascular integrity via VE-cadherin down-regulation. Int J Oncol;23:611-616

[85] Lefor AT, Makohon S, Ackerman NB. (1985), The effects of hyperthermia on vascular permeability in experimental liver metastasis, J.Surg. Oncol. 28:297-300

[86] Nilsen NO (1984), Endothelial changes and microvascular leakage due to hyperthermia in chick embryos, Virchows Archiv B; 46:165–174

[87] Zhang S-F, Xu C-L, Liu C-M. (2015), Drug delivery strategies to enhance the permeability of the blood–brain barrier for treatment of glioma, Drug Design, Development and Therapy, 9:2089-2100

[88] Vancsik T, Forika G, Balogh A, et.al. (2019), Modulated electro-hyperthermia induced p53 driven apoptosis and cell cycle arrest additively support doxorubicin chemotherapy of colorectal cancer *in vitro*, Cancer Medicine, doi: 10.1002/cam4.2330,https://www.ncbi.nlm.nih.gov/pubmed/31183995

[89] Song CW, Choi IB, Nah BS et al (1995), Microvasculature and Persfusion in Normal Tissues and Tumors. In: Seegenschmiedt MH, Fessenden P, Vernon CC (eds), Thermoradiometry and Thermochemotherapy, Vol. 1. pp. 139-156

[90] Urano M (1994), Thermochemotherapy: from *in vitro* and *in vivo* experiments to potential clinical application. In: Urano M, Douple E (eds), Hyperthermia and Oncology, VSP Utrecht, Tokyo, 4:169-204

[91] Oliveira-Filho RS, Bevilacqua RG, Chammas R, (1997), Hyperthermia increases the metastatic potential of murine melanoma, Brazilian Journal of Medical and Biological Research, 30:941-945

[92] Shah SA, Jain RK, Finney PL (1983), Enhanced metastasis formation by combined hyperthermia and hyperglycemia in rats bearing Walker 256 carcinosarcoma. Cancer Lett. 19(3):317-23

[93] Nathanson SD, Nelson L, Anaya P, Havstad S, Hetzel FW (1991), Development of lymph node and pulmonary metastases after local irradiation and hyperthermia of footpad melanomas, Clinical and Experimental Metastasis 9:377-392

[94] Papp E, Vancsik T, Kiss E, Szasz O. (2017), Energy absorption by the membrane rafts in the modulated electro-hyperthermia (mEHT), Open Journal of Biophysics, 7, 216-229, https://file.scirp.org/pdf/OJBIPHY_2017102715065328.pdf

[95] Meggyeshazi N, Andocs G, Balogh L et al. (2014), DNA fragmentation and caspase-independent programmed cell death by modulated electro-hyperthermia. Strahlenther Onkol 190:815-822, http://www.ncbi.nlm.nih.gov/pubmed/24562547

[96] Airi Ota (2017), Anti-tumor effects of a new low-energy thermal therapy, Oncothermia; Tsukuba University, Japan; Presented on conferences of Japan Hyperthermia Association and International Association for the Sensitization of Cancer Treatment

[97] Andocs G, Szasz O, Szasz A (2009), Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165, http://www.ncbi.nlm.nih.gov/pubmed/19811397

[98] Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et.al. (2016), *In vitro* comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, doi: 10.18632/oncotarget.11444, http://www.ncbi.nlm.nih.gov/pubmed/27556507

[99] Andocs G, Meggyeshazi N, Balogh L et al. (2014), Upregulation of heat shock proteins and the promotion of damage-associated molecular pattern signals in a colorectal cancer model by modulated electro-hyperthermia. Cell Stress and Chaperones 20(1):37-46, http://www.ncbi.nlm.nih.gov/pubmed/24973890

[100] Andocs G, Meggyeshazi N, Okamoto Y, Balogh L, Kovago Cs, Szasz O (2013), Oncothermia treatment induced immunogenic cancer cell death. Oncothermia Journal 9:28-37, https://oncotherm.com/sites/oncotherm/files/2017-07/Oncothermia_treatment_induced_immunogenic_cancer_cell_death.pdf

[101] Qin W, Akutsu Y, Andocs G et al. (2014), Modulated electro-hyperthermia enhances dendritic cell therapy through an abscopal effect in mice. Oncol Rep 32(6):2373-2379, http://www.ncbi.nlm.nih.gov/pubmed/25242303

[102] Andocs G, Szasz A, Iluri N. (2014), Tumor vaccination, Patent Nr.: EP2703001A1, https://patentimages.storage.googleapis.com/18/c9/33/863f7c44264668/EP2703001A1.pdf , USA patent Nr. US2015/0217099A1 (2015), https://patentimages.storage.googleapis.com/e1/7c/63/686955ae68f159/US20150217099A1.pdf

[103] Szasz O, Szasz A (2016), Considering skin physiology in capacitive-coupled hyperthermia. Journal of

Advances in Physics 11(9):3966-3972; https://cirworld.com/index.php/jap/article/view/206
[104] Vincze Gy, Szasz A (2016), Notes on psychophysics. Journal of Advances in Biology 9(1):1756-1760; https://doi.org/10.24297/jab.v9i1.4400
[105] Meggyeshazi N, Andocs G, Krenacs T (2013), Programmed cell death induced by modulated electro-hyperthermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 187835, http://www.hindawi.com/archive/2013/187835/
[106] Beachy SH, Repasky EA. 2011. Toward establishment of temperature thresholds for immunological impact of heat exposure in humans. Int J Hyperthermia 27:344–352.
[107] Skitzki JJ. Repasky EA. Evans SS. (2009), Hyperthermia as an immunotherapy strategy for cancer, Current Opinion in Investigational Drugs 10:550-558
[108] Szasz A, Szasz N, Szasz O (2003), Hyperthermie in der Onkologie mit einem historischen Überblick. Deutche zeitschrift für onkologie 35: 140-154, https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2003-43178
[109] Szasz O (2013), Past, Present and Future of Oncothermia. Oncothermia Journal 9:55-69 https://oncotherm.com/sites/oncotherm/files/2017-07/Past%2C_Present_and_Future_of_Oncothermia.pdf
[110] Andocs G, Renner H, Balogh L, Fonyad L, Jakab C, Szasz A (2009), Strong synergy of heat and modulated electro- magnetic field in tumor cell killing, Study of HT29 xenograft tumors in a nude mice model. Strahlentherapie und Onkologie 185:120–126, http://www.ncbi.nlm.nih.gov/pubmed/19240999
[111] Szasz A. (2020), Preface, for the book Challenges and solutions of oncological hyperthermia, ed. Szasz A., pp. viii-Xiii, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[112] Weinberg RA (1998), One renegade cell. Basic Books, A Member of the Perseus Books Group, New York
[113] Wu M, Frieboes HB, McDougall SR, et.al. (2013), The effect of interstitial pressure on tumor growth: coupling with the blood and lymphatic vascular systems, J Theor Biol. 320:131-151
[114] Szentgyorgyi A (1978), The living state and cancer. Marcel Dekker Inc, New York
[115] Hannahan D, Weinberg RA. (2000), The hallmarks of cancer, Cell, 100:57-70
[116] Hannahan D, Weinberg RA. (2011), Hallmarks of cancer: The next generation, Cell, 144:646-674
[117] Szentgyorgyi A (1998), Electronic Biology and Cancer. Marcel Dekkerm New York
[118] Andras Szasz, Oliver Szasz (2018): Time-fractal modulation of modulated electro-hyperthermia (mEHT), Oncothermia Journal 24:318-332, www.oncothermia-journal.com/journal/2018/Time_fractal_modulation.pdf
[119] Fiorentini G, Sarti D, Casadei V, et.al. (2019): Modulated electro-hyperthermia (mEHT), [oncothermia®] protocols as complementary treatment, Oncothermia Journal 25: 85-115, https://oncotherm.com/sites/oncotherm/files/2019-05/FIORENTINI2.pdf
[120] Szasz A, Szasz O, Iluri N. (2010) Flexible and porous large-area electrode for heating, patent Nr. EP2237833B1, https://patentimages.storage.googleapis.com/89/02/9a/ad6d257852ba72/EP2237833B1.pdf
[121] Iyikesici MS. (2020), Long-term survival outcomes of metabolically supported chemotherapy with Gemcitabine-based or FOLFIRINOX regimen combined with Ketogenic diet, hyperthermia, and hyperbaric oxygen therapy in metastatic pancreatic cancer, Complement Med Res, 27(1):31-39, https://www.ncbi.nlm.nih.gov/pubmed/31527373
[122] Iyikesici MS, Slocum A, Turkmen E, et al. (2016), Complete response of locally advanced (stage III), rectal cancer to metabolically supported chemoradiotherapy with hyperthermia, Int J Cancer Res Mech, 2(1): doi http://dx.doi.org/10.16966/2381-3318.120,
[123] Iyikesici MS. (2020), Survival outcomes of metabolically supported chemotherapy combined with Ketogenic diet, hyperthermia, and hyperbaric oxygen therapy in advanced gastric cancer, Nigerian Journal of Clinical Practice, 23:734-40, https://www.ncbi.nlm.nih.gov/pubmed/32367884
[124] Iyikesici MS. (2019), Feasibility study of metabolically supported chemotherapy with weekly

carboplatin/paclitaxel combined with ketogenic diet, hyperthermia and hyperbaric oxygen therapy in metastatic non-small cell lung cancer, Int. J. Hyp. 36(1):445-454, https://www.ncbi.nlm.nih.gov/pubmed/30931666

[125] Lyikesici MS, Slocum AK, Slocum A, et.al. (2017), Efficacy of metabolically supported chemotherapy combined with ketogenic diet, hyperthermia, and hyperbaric oxygen therapy for stage IV triple-negative breast cancer, Cureus DOI: 10.7759/cureus.1445, 9(7): e1445, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5589510/

[126] Zais O (2013), Lyme Disease and Oncothermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 275013, http://www.hindawi.com/archive/2013/275013/

[127] Brockmann W-P. (2019-2020), Vom Abskopaleffekt zur Abskopaltherapie – Provizierte Spontanremissionen als neue Immuntherapie bei Krebs, Teil I: Abskopaleffekte in der Onkologie, Vorwort und Einführung, Die Naturheilkunde/ Forum Komplementäre Onkologie, Ausgabe 4/2019, 6-7, Teil IIa: Fallbezogene Abskopaltherapie mit provoziert radiogenem Abskopaleffekt entsprechend einer radiogenen autologin spezifischen Immuntherapie (RASI), Die Naturheilkunde/ Forum Komplementäre Onkologie, Ausgabe 5/2019, 3-5, Teil IIb: Weitere fallbezogene Darstellungen der abskopaltherapie, Die Naturheilkunde/ Forum Komplementäre Onkologie, Ausgabe 1/2020, 3-5, Teil III: Literaturvergleich und Diskussion, Die Naturheilkunde/ Forum Komplementäre Onkologie, Ausgabe 2/2020

[128] Brenner J. (2010), Large field electrodes in the treatment with local-regional hyperthermia, Oncothermia Journal, 1:23-23,

[129] Borbenyi E., Judit Desfalvi, Gyongyver Szentmartoni (2018): Breast Cancer Series Treated with Modulated ElectroHyperthermia (mEHT), a single center experience; Oncothermia Journal 24:109-121 https://oncotherm.com/sites/oncotherm/files/2018-10/Breast_cancer_serires.pdf

[130] Szasz AM, Szentmartoni Gy, Garay T, et.al. (2020), Breast cancer series treated with modulated electro-hyperthermia (mEHT), – A single centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 5, pp.105-109, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[131] Garay T, Kiss E, Szentmartoni Gy, et.al. (2020), Gastrointestinal cancer series treated with modulated electro-hyperthermia (mEHT), – A single centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 8, pp.159-162, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[132] Hyperthermia, https://chemothermia.com/therapies/hyperthermia/, last accessed: 9 July 2020

[133] Szasz O, Szigeti GyP, Vancsik T, Szasz A. (2018), Hyperthermia dosing and depth of effect, Open Journal of Biophysics, 2018, 8, 31-48, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=81896

[134] Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148–165, http://www.ncbi.nlm.nih.gov/pubmed/19811397

[135] Minnaar C. (2020) Challenges associated with hyperthermia, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 1, pp.1-31, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[136] Szasz A. (2019) Thermal and nonthermal effects of radiofrequency on living state and applications as an adjuvant with radiation therapy, Journal of Radiation and Cancer Research, 10:1-17, http://www.journalrcr.org/article.asp?issn=2588-9273;year=2019;volume=10;issue=1;spage=1;epage=17;aulast=Szasz

[137] Szasz O, Szigeti GP, Szasz A. (2019) The intrinsic self-time of biosystems, OJBIPHY, 9, 131-145, https://file.scirp.org/pdf/OJBIPHY_2019040815291683.pdf

[138] Hegyi G, Vincze Gy, Szasz A (2012) On the Dynamic Equilibrium in Homeostasis. Open Journal of Biophysics 2:64-71, http://file.scirp.org/pdf/OJBIPHY20120300001_81525786.pdf

[139] Szasz O, Szigeti GyP, Szasz A (2016) Connections between the specific absorption rate and the local temperature. Open Journal of Biophysics 6:53-74; http://file.scirp.org/pdf/OJBIPHY_2016063014260548.pdf

[140] Szasz A, Vincze Gy, Szasz O, Szasz N (2003) An energy analysis of extracellular hyperthermia. Magneto- and electro-biology 22(2):103–115, http://www.tandfonline.com/doi/abs/10.1081/JBC-120024620
[141] Szasz A, Vincze Gy, Szigeti Gy, Szasz O. (2017) Internal charge redistribution and currents in cancerous lesions, J Adv in Biology, 10(2):2061-2079, http://cirworld.com/index.php/jab/article/view/6328/6283
[142] Vincze Gy, Szasz A. (2018) Similarities of modulation by temperature and by electric field, OJBIPHY, 8, 95-103, https://www.scirp.org/journal/PaperInformation.aspx?PaperID=84883
[143] Szasz O, Szigeti GyP, Szasz A, Benyo Z. (2018) Role of electrical forces in angiogenesis, OJBIPHY, 8, 49-67
[144] Szasz O. (2019) Bioelectromagnetic paradigm of cancer treatment – Modulated electro-hyperthermia (mEHT), OJBIPHY, 9, 98-109, https://file.scirp.org/pdf/OJBIPHY_2019022616103729.pdf
[145] Vincze Gy, Szasz A, Szasz N (2005) On the thermal noise limit of cellular membranes. Bioelectromagnetics 26(1):28–35, http://www.ncbi.nlm.nih.gov/pubmed/15605404
[146] Szasz A. (2014) Oncothermia: Complex therapy by EM and fractal physiology, XXXIth URSI General Assembly and Scientific Symposium (URSI GASS), IEEE Xplore 20 October 2014, DOI: 10.1109/URSIGASS.2014.6930100, https://ieeexplore.ieee.org/document/6930100
[147] Andocs G, Vincze Gy, Szasz O, Szendro P, Szasz A. (2009) Effect of Curl-Free Potentials on Water. I Electromagn Biol Med 28(2):166–181, http://www.ncbi.nlm.nih.gov/pubmed/19811398
[148] Szasz A, Vincze Gy, Andocs G, Szasz O (2009) Do Field-Free Electromagnetic Potentials Play a Role in Biology?. Electromagn Biol Med 28(2):135–147, http://www.ncbi.nlm.nih.gov/pubmed/19811396
[149] Wust P, Ghadjar P, Nadobny J, et.al. (2019) Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia, Int. J. Hyp., 36(1):1246-1254, https://www.ncbi.nlm.nih.gov/pubmed/31818170
[150] Wust P, Nadobny J, Zschaeck S, Ghadjar P. (2020) Physics of hyperthermia – Is physics really against us?, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 16, pp.346-376, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[151] Szigeti GP, Szasz O, Hegyi G (2017) Connections between Warburg's and Szentgyorgyi's Approach about the Causes of Cancer. Journal of Neoplasm 1(2:8):1-13; http://neoplasm.imedpub.com/connections-between-warburgs-and-szentgyorgyis-approach-about-thecauses-of-cancer.pdf
[152] Vincze Gy, Szigeti Gy, Andocs G, Szasz A. (2015) Nanoheating without Artificial Nanoparticles, Biology and Medicine 7(4):249, http://www.omicsonline.com/open-access/nanoheating-without-artificial-nanoparticles-0974-8369-1000249.php?aid=61783
[153] Szasz A (2013) Electromagnetic effects in nanoscale range. Cellular Response to Physical Stress and Therapeutic Applications (eds. Tadamichi Shimizu, Takashi Kondo), chapter 4. Nova Science Publishers, Inc
[154] Papp E, Vancsik T, Kiss E, Szasz O. (2017) Energy absorption by the membrane rafts in the modulated electro-hyperthermia (mEHT), Open Journal of Biophysics, 7, 216-229, https://file.scirp.org/pdf/OJBIPHY_2017102715065328.pdf
[155] Vincze Gy, Sziget GyP, Szasz A (2016) Reorganization of the cytoskeleton. Journal of Advances in Biology 9(2):1872-1882; https://cirworld.com/index.php/jab/article/view/4059
[156] Vincze Gy, Szasz A. (2015) Reorganization of actin filaments and microtubules by outside electric field, Journal of Advances in Biology 8(1):1514-1518
[157] Szasz O, Szasz A. (2020), Parametrization of survival measures, Part I: Consequences of self-organizing, Int J Clinical Medicine, 11, 316-347, https://www.scirp.org/journal/paperinformation.aspx?paperid=100454
[158] Szasz A, Szigeti GyP, Szasz AM. (2020), Parametrization of survival measures, Part II: Single arm studies, Int J Clinical Medicine, 11, 348-373, https://www.scirp.org/journal/paperinformation.aspx?paperid=100456

[159] Szasz A, Szigeti GyP, Szasz AM. (2020), Parametrization of survival measures, Part III: Clinical evidences in single arm studies with endpoint of overall survival, Int J. Clinical Medicine, 11, 389-419, https://www.scirp.org/journal/paperabs.aspx?paperid=100784

[160] Andocs G, Meggyeshazi N, Okamoto Y, Balogh L, Szasz A (2013), Bystander effect of oncothermia. Oncothermia Journal 7:343-347, https://oncotherm.com/sites/oncotherm/files/2017-07/Bystander_effect_of_oncothermia_T.pdf

[161] Fiorentini G, Yoon SM, Yan O, Andocs G, Baronzio GF, Laurent S, Balogh L, Szasz A (2013), Abscopal effect: new perspectives in Oncothermia. Oncothermia Journal 7:279-281, https://oncotherm.com/sites/oncotherm/files/2017-07/Abscopal_effect_new_perspectives_in_Oncothermia_T.pdf

[162] Szasz O. (2020), Local treatment with systemic effect: Abscopal outcome, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 11, pp.192-205, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[163] Nagy G, Meggyeshazi N, Szasz O (2013), Deep temperature measurements in oncothermia processes. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 685264, http://www.hindawi.com/archive/2013/685264/

[164] Szigeti GyP, Szasz AM, Szasz O. (2020), Oncothermia is a kind of oncological hyperthermia – a review, Oncothermia Journal, Special Edition, 8-48, www.oncotherm.com/sites/oncotherm/files/2020-07/specialedition01

[165] Hossain MT, Prasad B, Park KS, et al. (2016), Simulation and experimental evaluation of selective heating characteristics of 13,56 MHz radiofrequency hyperthermia in phantom models, Int J Precision Eng and Manufacturing, 17(2):253-256, DOI: 10.1007/s12541-016-0033-9

[166] Orczy-Timko B. (2020), Phantom measurements with the EHY-2030 device, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 18, pp.416-428, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[167] Andocs G, Rehman MU, Zhao QL, Papp E, Kondo T, Szasz A. (2015), Nanoheating without Artificial Nanoparticles Part II. Experimental support of the nanoheating concept of the modulated electro-hyperthermia method, using U937 cell suspension model, Biology and Medicine 7(4):1-9, https://www.omicsonline.org/open-access/nanoheating-without-artificial-nanoparticles-part-ii-experimental-support-of-the-nanoheating-concept-of-the-modulated-electro-hyperthermiamethod-0974-8369-1000247.php?aid=60362

[168] Andocs G, Rehman MU, Zhao Q-L, Tabuchi Y, Kanamori M, Kondo T. (2016), Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cell, Cell Death Discovery (Nature Publishing Group), 2, 16039, http://www.nature.com/articles/cddiscovery201639

[169] Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et.al. (2016), *In vitro* comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, doi: 10.18632/oncotarget.11444, http://www.ncbi.nlm.nih.gov/pubmed/27556507

[170] Kao P H-J, Chen C-H, Chang Y-W, et al. (2020), Relationship between energy dosage and apoptotic cell death by modulated electro-hyperthermia, Scientific reports, 10:8936, DOI: 10.1038/s41598-020-65823-2, https://www.nature.com/articles/s41598-020-65823-2

[171] Cha, J, Jeon T-W, Lee C-G et al. (2015), Electro-hyperthermia inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis, Int. Journal Hyperthermia, 31(7):784-792, http://www.ncbi.nlm.nih.gov/pubmed/26367194

[172] Son B, Jeon J, Lee, et.al. (2019), Radiotherapy in combination with hyperthermia suppresses lung cancer progression via increased NR4A3 and KLF11 expression, Int J. Radiat Biol, 2019 Sep 9:1-36. doi: 10.1080/09553002.2019.1665213, https://www.ncbi.nlm.nih.gov/pubmed/31498019

[173] McDonald M, Jackson M, et.al. (2018), First *in vitro* evidence of modulated electro-hyperthermia

treatment performance in combination with megavoltage radiation by clonogenic assay, Sci Rep. 8(1):16608. doi: 10.1038/s41598-018-34712-0, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226525/

[174] Tsang Y-W, Chi K-H, Huang C-C, et.al. (2019), Modulated electro-hyperthermia-enhanced liposomal drug uptake by cancer cells, International Journal of Nanomedicine, 14:1269-1579, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743710/pdf/jcav09p0041.pdf

[175] Meggyeshazi N, Andocs G, Spisak S et al. (2013), Early changes in mRNA and protein expression related to cancer treatment by modulated electro-hyperthermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 249563, http://www.hindawi.com/archive/2013/249563/

[176] Szasz O, Andocs G, Meggyeshazi N (2013), Modulation effect in oncothermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 395678, http://www.hindawi.com/archive/2013/398678/

[177] Chen C-C, Chen C-L, Li J-J, et.al. (2019), The presence of gold nanoparticles in cells associated with the cell-killing effect of modulated electro-hyperthermia, ACS Applied Bio Materials, 1-44, https://doi.org/10.1021/acsabm.9b00453

[178] Prasad B, Kim S, Cho W, et.al. (2018), Effect of tumor properties on energy absorption, temperature mapping, and thermal dose in 13,56-MHz radiofrequency hyperthermia, J Thermal Biology, 74:281-289, https://www.ncbi.nlm.nih.gov/pubmed/29801639

[179] Kim J-K, Prasad B, Kim S. (2017), Temperature mapping and thermal dose calculation in combined radiation therapy and 13.56 MHz radiofrequency hyperthermia for tumor treatment. Proc. SPIE 10047, Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXVI, 1004718; http://spie.org/Publications/Proceedings/Paper/10.1117/12.2253163?origin_id=x4318

[180] Kim W, Kim MS, Kim HJ et al. (2017), Role of HIF-1α in response of tumors to a combination of hyperthermia and radiation *in vivo*. Int J Hyperthermia 28:1-8, http://www.ncbi.nlm.nih.gov/pubmed/28659004

[181] Balogh L, Polyak A, Postenyi Z et al. (2016), Temperature increase induced by modulated electro-hyperthermia (oncothermia®), in the anesthetized pig liver, Journal of Cancer Research and Therapeutics, 12(3):1153-1159, http://www.cancerjournal.net/article.asp?issn=0973-1482;year=2016;volume=12;issue=3;spage=1153;epage=1159;aulast=Balogh

[182] Prasad B, Kim S, Cho W, et.al. (2019), Quantitative estimation of the equivalent radiation dose escalation using radiofrequency hyperthermia in mouse xenograft models of human lung cancer, Scientific Reports, Nature, 9: 3942, https://www.nature.com/articles/s41598-019-40595-6

[183] Kao PH-J, Chen C-H, Tsang Y-T, et.al. (2020), Relationship between energy dosage and apoptotic cell death by modulated electro-hyperthermia, Scientific Reports, 10, 8936, https://doi.org/10.1038/s41598-020-65823-2

[184] Yang W, Han GH, Shin H-Y, et.al. (2018), Combined treatment with modulated electro-hyperthermia and an autophagy inhibitor effectively inhibit ovarian and cervical cancer growth, International Journal of Hyperthermia, 36(1):9-20, https://doi.org/10.1080/02656736.2018.1528390

[185] Saupe H, Szigeti GyP, Andocs G (2016), Why modulated electro-hyperthermia (mEHT), destroys the rouleaux formation of erythrocytes? Journal of Advances in Biology 9(3):1945-1955; http://paper.researchbib.com/view/paper/111077

[186] Vancsik T, Kovago Cs, Kiss E et al. (2018), Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts, J Cancer, 9(1): 41-53, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5743710/pdf/jcav09p0041.pdf

[187] Besztercei B, Vancsik T, Benedek A, et al. (2019), Stress-induced, p53-mediated tumor growth inhibition of melanoma by modulated electro-hyperthermia in mouse models without major immunogenic effects, Int J Molecular Science, 20(16). pii: E4019. doi: 10.3390/ijms20164019, https://www.mdpi.com/1422-

0067/20/16/4019
[188] Tsang Y-W, Huang C-C, Yang K-L, et al. (2015), Improving immunological tumor microenvironment using electro-hyperthermia followed by dendritic cell immunotherapy, BMC Cancer 15:708, http://www.ncbi.nlm.nih.gov/pubmed/26472466
[189] Lee S-Y, Kim J-H, Han Y-H, et al. (2018) The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma, Int. J. Hyperthermia, 34(7):953-960, doi: https://doi.org/10.1080/02656736.2018.1423709
[190] Lee SY, Kim M-G. (2015) The effect of modulated electro-hyperthermia on the pharmacokinetic properties of nefopam in healthy volunteers: A randomised, single-dose, crossover open-label study, Int J Hyp, 28:1-6, http://www.ncbi.nlm.nih.gov/pubmed/26507458
[191] Lee SY, Kim M-G. (2016) Effect of modulated electro-hyperthermia on the pharmacokinetics of oral transmucosal fentanyl citrate in healthy volunteers, Clinical Therapeutics, 38(12):2548-2554, https://www.ncbi.nlm.nih.gov/pubmed/27866658
[192] Cremona F, Pignata A, Izzo F et al. (2003) Tolerability of external electro-hyperthermia in the treatment of solid tumors; Tumori 2003 Jul-Aug;89(4 Suppl):239-40, Tumori 2003 Jul-Aug;89(4 Suppl):239-40, http://www.ncbi.nlm.nih.gov/pubmed/12903605
[193] Szasz AM, Minnaar CA, Szentmartoni Gy, et al. (2019) Review of the clinical evidences of modulated electro-hyperthermia (mEHT) method: an update for the practicing oncologist, Frontiers in Oncology, Vol. 9, Article 1012, pp. 1-8., https://www.frontiersin.org/articles/10.3389/fonc.2019.01012/full
[194] Parmar G, Rurak E, Elderfield M, et.al. (2020) 8-year observational study on naturopathic treatment with modulated electro-hyperthermia (mEHT): A single-centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 13, pp.227-266, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[195] Arrojo EE. (2020) The position of modulated electro-hyperthermia (oncothermia) in combination with standard chemo- and radiotherapy in clinical practice – Highlights of upcoming phase III clinical studies in hospital Universitario Marqués de Valdecilla (HUMV), in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 4, pp.91-104, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[196] Wismeth C, Dudel C, Pascher C, et al. (2010) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas – Phase I clinical results. J Neurooncol 98(3):395–405, http://www.ncbi.nlm.nih.gov/pubmed/?term=Transcranial+electro-hyperthermia+combined+with+alkylating+chemotherapy+in+patients+with+relapsed+high-grade+gliomas+%E2%80%93+Phase+I+clinical+results
[197] Douwes F, Douwes O, Migeod F et al. (2006) Hyperthermia in combination with ACNU chemotherapy in the treatment of recurrent glioblastoma. St. Georg Klinik, Germany
[198] Hager ED, Dziambor H, App EM et al. (2003) The treatment of patients with high-grade malignant gliomas with RF-hyperthermia. Proc ASCO 22:118, #47;Proc Am Soc Clin Oncol 22: 2003
[199] Hager ED, Birkenmeier J. (2006) Glioblastoma multiforme Grad IV: Regionale Tiefenhyperthermie, Antiangiogenese mit Thalidomid, Hochdosis-Ascorbinsäureinfusionen und komplementäre Therapie, Deutsche Zeitschrift für Onkologie 38(3):133-135, DOI: 10.1055/s-2006-952050, https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2006-952050
[200] Hager ED, Sahinbas H, Groenemeyer DH et al. (2008) Prospective phase II trial for recurrent high-grade malignant gliomas with capacitive coupled low radiofrequency (LRF) deep hyperthermia. ASCO, J Clin Oncol, Annual Meeting Proceedings (Post-Meeting Edition) 26:2047, https://ascopubs.org/doi/abs/10.1200/jco.2008.26.15_suppl.2047
[201] Fiorentini G, Giovanis P, Rossi S, et al. (2006) A phase II clinical study on relapsed malignant gliomas treated with electro-hyperthermia. In Vivo 20(6A):721–724, https://www.ncbi.nlm.nih.gov/pubmed/17203754

[202] Fiorentini G, Sarti D, Milandri C, et.al. (2017) Retrospective observational clinical study on relapsed malignant gliomas treated with electro-hyperthermia, Int J Neurooncol and Brain Tumors, 1(1):9-13, https://www.scireslit.com/Neurooncology/IJNBT-ID12.pdf

[203] Fiorentini G, Sarti D, Milandri C, et.al. (2018) Modulated electro-hyperthermia in integrative cancer treatment for relapsed malignant glioblastoma and astrocytoma: Retrospective multicenter controlled study, Integrative Cancer Therapies, DOI: 10.1177/1534735418812691, https://www.ncbi.nlm.nih.gov/pubmed/30580645

[204] Fiorentini G, Sarti D, Casadei V, et.al. (2020) Modulated electro-hyperthermia for the treatment of relapsed brain gliomas, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 6, pp.110-125, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[205] Sahinbas H, Groenemeyer DHW, Boecher E, Szasz A (2007) Retrospective clinical study of adjuvant electro-hyperthermia treatment for advanced brain-gliomas. Deutsche Zeitschrift fuer Onkologie 39:154–160, https://www.thieme-connect.com/products/ejournals/abstract/10.1055/s-2007-986020

[206] Van Gool SW, Makalowski J, Feyen O, Prix L, Schirrmacher V and Stuecker W. (2018) The induction of immunogenic cell death (ICD) during maintenance chemotherapy and subsequent multimodal immunotherapy for glioblastoma (GBM), Austin Oncol Case Rep, 3:1-8, https://www.austinpublishinggroup.com/oncology-case-reports/all-issues.php

[207] Stefaan W. Van Gool, Jennifer Makalowski, Wilfried Stuecker (2018): Modulated electro-hyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors; Oncothermia Journal 248: -269 https://oncotherm.com/sites/oncotherm/files/2018-10/Modulated_electohypertermia_%28mEHT%29_as_part_of.pdf

[208] Roussakow S. (2017) Clinical and economic evaluation of modulated electro-hyperthermia concurrent to dose-dense temozolomide 21/28 days regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-centre German cohort trial with systematic comparison and effect-to-treatment analysis, BMJ Open, 7:e017387.doi.1136/bmjopen-2017-017387, http://bmjopen.bmj.com/content/bmjopen/7/11/e017387.full.pdf

[209] Garay T, Kiss E, Szentmartoni Gy, et.al. (2020) Gastrointestinal cancer series treated with modulated electro-hyperthermia (mEHT) – A single centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 8, pp.159-162, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[210] Hager ED, Dziambor H, Höhmann D, et al. (1999) Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Res 19(4C):3403–3408, http://www.ncbi.nlm.nih.gov/pubmed/10629627

[211] Hager ED. (2004) Lebermetastasen bei kolorektalen Karzinomen, Deutsche Zeitschrift für Onkologie, 36:132-134

[212] Iyikesici MS, Slocum A, Turkmen E, et al. (2016) Complete response of locally advanced (stage III) rectal cancer to metabolically supported chemoradiotherapy with hyperthermia, Int J Cancer Res Mech, 2(1): doi http://dx.doi.org/10.16966/2381-3318.120, https://sciforschenonline.org/journals/cancer-research/IJCRMM-2-120.php

[213] You SH, Kim S. (2019) Feasibility of modulated electro-hyperthermia in preoperative treatment for locally-advanced rectal cancer: Early phase 2 clinical results, Neoplasma, doi: 10.4149/neo_2020_190623N538, https://www.ncbi.nlm.nih.gov/pubmed/32039629

[214] Gadaleta-Caldarola G, Infusino S, Galise I, et al. (2014) Sorafenib and locoregional deep electro-hyperthermia in advanced hepatocellular carcinoma. A phase II study. Oncol Lett, 2014 Oct,8(4):1783-1787, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4156230/

[215] Ferrari VD, De Ponti S, Valcamonico F et al. (2007) Deep electro-hyperthermia (EHY) with or without thermo-active agents in patients with advanced hepatic cell carcinoma: phase II study. J Clin Oncol 25:18S,

15168, http://ascopubs.org/doi/abs/10.1200/jco.2007.25.18_suppl.15168
[216] Reimnitz U (2010) Cholangiocellular carcinomas: survival without symptoms with hyperthermia – A case study. Oncothermia Journal 1:20-22, https://oncotherm.com/sites/oncotherm/files/2017-07/Cholangiocellular_carcinoma_-_survival_without_symptoms_with_hyperthermia_-_a_case_study.pdf
[217] Fiorentini G, Sarti D, Casadei V, et al. (2019) Modulated electro-hyperthermia as palliative treatment for pancreas cancer: A retrospective observational study on 106 patients, Integrative Cancer Therapies, Vol. 18:1-8, https://journals.sagepub.com/doi/pdf/10.1177/1534735419878505
[218] Douwes F, Migeod F, Grote C (2006) Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und einer Zytostase mit Mitomycin- C und 5-Fluorouracil/ Folinsäure. Onkologische Fachklinik St. Georg, Bad Aibling, https://www.researchgate.net/publication/237633519_Behandlung_des_fortgeschrittenen_Pankreaskarzinoms_mit_regionaler_Hyperthermie_und_einer_Zytostase_mit_Mitomycin_C_und_5FluorouracilFolinsaure
[219] Douwes FR (2006) Thermochemotherapy of the advanced pancreas carcinoma. Biologische Medizin 35:126–130, https://www.researchgate.net/publication/287861898_Thermo-chemotherapy_of_the_advanced_pancreas_carcinoma
[220] Douwes FR (2004) Thermo-Chemotherapie des fortgeschrittenen Pankreaskarzinoms. Ergebnisseeiner klinischen Anwendungsstudie. Onkologische Fachklinik St. Georg, Bad Aibling
[221] Volovat C, Volovat SR, Scripcaru V et al. (2014) Second-line chemotherapy with gemcitabine and oxaliplatin in combination with loco-regional hyperthermia (EHY-2000) in patients with refractory metastatic pancreatic cancer - preliminary results of a prospective trial. Romanian Reports in Physics 66(1):166-174, http://www.rrp.infim.ro/2014_66_1/A18.pdf
[222] Dani A, Varkonyi A, Magyar T, Szasz A (2008) Clinical study for advanced pancreas cancer treated by oncothermia. Forum Hyperthermie 1:13–20, http://www.pyatthealth.com/wp-content/uploads/2015/03/Hyperthermia-Pancreatic-Cancer.pdf
[223] Hager ED, Süsse B, Popa C et al. (1994) Complex therapy of the not in sano respectable carcinoma of the pancreas – a pilot study. J Cancer Res Clin Oncol 120:R47,P1
[224] Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R.L., Torre, L.A. and Jemal, A. (2018), Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68: 394-424. doi:10.3322/caac.21492
[225] Szasz A (2014) Current status of oncothermia therapy for lung cancer. Korean J Thorac Cardiovasc Surg 47:77-93, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4000888
[226] Dani A, Varkonyi A, Magyar T, Szasz A (2009) Clinical study for advanced non-small-cell lung-cancer treated by oncothermia. Forum Hyperthermie; DGHT, 2009
[227] Lee D-Y, Park S-J, Jung H-C et al. (2015) The Outcome of the Chemotherapy and Oncothermia for Far Advanced Adenocarcinoma of the Lung: Case reports of four patients. Advances in Lung Cancer 4:1-7, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=54620
[228] Yeo S-G. (2015) Definitive radiotherapy with concurrent oncothermia for stage IIIB non-small-cell lung cancer: A case report. Experimental and Therapeutic Medicine pp. 1-4, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4509030/
[229] Lee D-J, Haam S-J, Kim T-H et al. (2013) Oncothermia with chemotherapy in the patients with Small Cell Lung Cancer. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 910363, http://www.hindawi.com/archive/2013/910363/
[230] Ou J, Zhu X, Lu Y, et.al. (2017) The safety and pharmacokinetics of high dose intravenous ascorbic acid synergy with modulated electro-hyperthermia in Chinese patients with stage III-IV non-small cell lung cancer, European J Pharmaceutical Sciences, 109:412-418, http://www.sciencedirect.com/science/article/pii/S0928098717304554?via%3Dihub

[231] Ou J, Zhu X, Chen P, et al. (2020) A randomized phase II trial of best supportive care with or without hyperthermia and vitamin C for heavily pretreated, advanced, refractory non-small-cell lung cancer, Journal of Advanced Research, 24:175-182, https://www.ncbi.nlm.nih.gov/pubmed/32368355

[232] Garay T, Borbényi E, Szasz AM, et.al. (2020) Treatment of locally advanced triple-negative breast cancer with oncothermia, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 10, pp.187-191, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[233] Szasz AM, Szentmartoni Gy, Garay T, et.al. (2020) Breast cancer series treated with modulated electro-hyperthermia (mEHT) – A single centre experience, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 5, pp.105-109, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia

[234] Pesti L, Dankovics Zs, Lorencz P et al. (2013) Treatment of advanced cervical cancer with complex chemoradio – hyperthermia. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 192435, http://www.hindawi.com/archive/2013/192435/

[235] Lee S-Y, Lee N-R, Cho D-H, et al. (2017) Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation; Oncology Letters, DOI: 10.3892/ol.2017.6117 http://www.spandidos-publications.com/10.3892/ol.2017.6117

[236] Franckena, M., Stalpers, L. J. A., *et al.* (2008) Long-Term Improvement in Treatment Outcome After Radiotherapy and Hyperthermia in Locoregionally Advanced Cervix Cancer: An Update of the Dutch Deep Hyperthermia Trial, *International Journal of Radiation Oncology Biology Physics*,Vol.70,No.4,pp.1176–1182

[237] Franckena, M., De Wit, R., *et al.* (2007) Weekly systemic cisplatin plus locoregional hyperthermia: An effective treatment for patients with recurrent cervical carcinoma in a previously irradiated area, *International Journal of Hyperthermia*,Vol.23,No.5,pp.443–450

[238] Harima, Y., Ohguri, T., *et al.* (2016) A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer, *International Journal of Hyperthermia*,Vol.32,No.7,pp.801–808

[239] C Strauss, J Kotzen, A Baeyens et al. (2013) Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 293968, http://www.hindawi.com/archive/2013/293968/

[240] Minnaar CA, Baeyens A, Aeni OA et al. (2019) Defining characteristics of nodal disease on PET/CT scans in patients with HIV-positive and -negative locally advanced cervical cancer in South Africa, Tomography, 5(4):339-345, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6935993/

[241] Minnaar CA, Kotzen JA, Ayeni OA, et.al. (2019) The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomized controlled trial, Plos ONE 14(6): e0217894, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6584021/

[242] C Minnaar, A Baeyens, J Kotzen (2016) Update on phase III randomized clinical trial investigating the effects of the addition of electro-hyperthermia to chemoradiotherapy for cervical cancer patients in South Africa. Physica Medica 32(2):151-152; http://www.physicamedica.com/article/S1120-1797(16)30175-2/abstract

[243] Minnaar C, Baeyens A, Kotzen J, Vangu MD. (2018) Survival of cervical cancer patients with or without associated HIV infection and treated with modulated electro-hyperthermia combined with chemo-radiotherapy, 32nd Annual Meeting of the European Hyperthermia Society, OP 13, Strahlenther Onkol (2018) 194:476

[244] Minnaar CA, Kothzen JA, Naidoo T, et al. (2020) Analysis of the effects of mEHT on the treatment-related toxicity and quality of life of HIV-positive cervical cancer patients, Int J Hyperthermia, 37(1):263-272, https://www.ncbi.nlm.nih.gov/pubmed/32180481

[245] Minnaar CA, Kotzen JA, Ayeni OA, et al. (2020) Potentiation of the abscopal effect by modulated electro-hyperthermia in locally advanced cervical cancer patients, Frontiers in Oncology, 10(376):1-8, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7105641/
[246] Kleef R, Kekic S, Ludwig N. (2012) Successful treatment of advanced ovarian cancer with thermochemotherapy and adjuvant immune therapy. Case Rep Oncol 5:212-215, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3369243/
[247] Yoo HJ, Lim MC, Seo S-S, et.al. (2019) Phase I/II clinical trial of modulated electro-hyperthermia treatment in patients with relapsed, refractory or progressive heavily treated ovarian cancer, Japanese Journal of Clincal Oncology, 1-7, doi: 10.1093/jjco/hyz071, https://www.ncbi.nlm.nih.gov/pubmed/31070763
[248] Pang, C. L. K., Zhang, X., *et al.* (2017) Local modulated electro-hyperthermia in combination with traditional Chinese medicine vs . intraperitoneal chemoinfusion for the treatment of peritoneal carcinomatosis with malignant ascites : A phase II randomized trial, *Molecular and Clinical Oncology*,Vol.6,pp.723–732
[249] Lyikesici MS, Slocum AK, Slocum A, et.al. (2017), Efficacy of metabolically supported chemotherapy combined with ketogenic diet, hyperthermia, and hyperbaric oxygen therapy for stage IV triple-negative breast cancer, Cureus DOI: 10.7759/cureus.1445, 9(7): e1445, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5589510/
[250] Schirrmacher V, Stücker W, Lulei M, et.al. (2015), Long-term survival of a breast cancer patient with extensive liver metastases upon immune and virotherapy: a case report; Immunotherapy 7: 855–860, http://www.ncbi.nlm.nih.gov/pubmed/26020523
[251] Jeung T-S, Ma S-Y, Choi J et al. (2015), Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. Case Reports in Clinical Medicine 4:157-168, http://www.scirp.org/journal/PaperInformation.aspx?PaperID=56280
[252] Lee SY, Lee N-R. (2016), Positive response of a primary leiomyosarcoma of the breast following salvage hyperthermia and pazopanib, Korean J Intern Med, doi: 10.3904/kjim.2015.242, http://www.ncbi.nlm.nih.gov/pubmed/27079325
[253] Volovat C, Volovat SR, Scripcaru V et al. (2014), The results of combination of ifosfamid and locoregional hyperthermia (EHY 2000), in patients with advanced abdominal soft-tissue sarcoma after relapse of first line chemotherapy. Romanian Reports in Physics, 66(1):175-181, http://www.rrp.infim.ro/2014_66_1/A19.pdf
[254] Ranieri G, Ferrari C, Di Palo A, et al. (2017), Bevacizumab-Based Chemotherapy Combined with Regional Deep Capacitive Hyperthermia in Metastatic Cancer Patients: A Pilot Study, Int. J. Mol. Sci. 18, 1458, 1-16, https://www.ncbi.nlm.nih.gov/pubmed/28684680
[255] Youngsuk Lee (2013), Oncothermia Application for Various Malignant Diseases. Hindawi Publishing Corporation Conference Papers in Medicine, Volume 2013, Article ID 245156, http://www.hindawi.com/archive/2013/245156/
[256] Lee D, Kim S-S, Seong S, et al. (2016), Stage IV wilms tumor treated by Korean medicine, hyperthermia and thymosin-α_1: A case report. Case Rep Oncol 9:119-125, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4899649/
[257] Chi M-S, Mehta MP, Yang K-L, et al. (2020), Putative abscopal effect in three patients treated by combined radiotherapy and modulated electro-hyperthermia, frontiers in Oncology, 9:1012, 1-8, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6837995/
[258] Jeung TS, Ma SY, Yu J et al. (2013), Cases that respond to oncothermia monotherapy, Conf. Papers in Medicine, Vol. 2013, Article ID 392480, Hindawi, https://www.hindawi.com/journals/cpis/2013/392480/
[259] Chi K-H. (2020), Tumour-directed immunotherapy: Clinical results of radiotherapy with modulated electro-hyperthermia, in book Challenges and solutions of oncological hyperthermia, ed. Szasz A., Ch. 12, pp.206-226, Cambridge Scholars, https://www.cambridgescholars.com/challenges-and-solutions-of-oncological-hyperthermia
[260] Seong MY, Jung SL (2012), Case of Abscopal effect with Metastatic Non-Small-Cell Lung Cancer.

Oncothermia Journal 5:53-57, https://oncotherm.com/sites/oncotherm/files/2017-07/Case_of_abscopal_effect_with_metastatic_non-small-cell_lung_cancer.pdf
[261] Pang LKC (2012), Clinical Research on Integrative Treatment of Colon Carcinoma with Oncothermia and Clifford TCM Immune Booster. Oncothermia Journal 5:24-41, https://oncotherm.com/sites/oncotherm/files/2017-07/Clinical_research_on_integrative_treatment_of_colon_carcinoma_0.pdf
[262] Schirrmacher V, van Gool S, Stuecker W. (2019), Breaking therapy resistance: An update on oncolytic Newcastle disease virus for improvements of cancer therapy, Biomedicines, 7, 66, doi:10.3390/biomedicines7030066, https://www.ncbi.nlm.nih.gov/pubmed/31480379
[263] Schirrmacher V (2015), Oncolytic Newcastle disease virus as a prospective anti-cancer therapy. A biologic agent with potential to break therapy resistance. Expert Opic Biol Ther 15(12):1757-1771; http://www.ncbi.nlm.nih.gov/pubmed/26436571
[264] Schirrmacher V, Lorenzen D, Van Gool SW, et al. (2017), A new strategy of cancer immunotherapy combining hyperthermia/oncolytic virus pretreatment with specific autologous anti-tumor vaccination - a review. Austin Oncol Case Rep 2(1):1-8, https://www.austinpublishinggroup.com/oncology-case-reports/fulltext/aocr-v2-id1006.php
[265] Schirrmacher V, Bihari A-S, Stücker W, et al. (2014), Long-term remission of prostate cancer with extensive bone metastases upon immuno- and virotherapy: A case report. Oncology Letters 8:2403-2406, http://www.ncbi.nlm.nih.gov/pubmed/25364402
[266] Szasz A, Szasz O (2013), Oncothermia protocol. Oncothermia Journal 8:13-45 https://oncotherm.com/sites/oncotherm/files/2019-10/Oncothermia%20protocol.pdf
[267] Szasz A. Marcell (2019): Conventional, „standard" chemotherapy protocols for modulated electro-hyperthermia (mEHT, trade name: oncothermia ®), Oncothermia Journal 25: 131-209, https://oncotherm.com/sites/oncotherm/files/2019-05/SZASZ%20M.pdf
[268] Szasz A, Szasz O (2013), Oncothermia protocol. Oncothermia Journal 8:13-45,
[269] Brown, J. M. (1999), The hypoxic cell: A target for selective cancer therapy - Eighteenth Bruce F. Cain Memorial Award Lecture, Cancer Research,Vol.59,No.23,pp.5863–5870
[270] Dewhirst MW, Vujaskovic Z, Jones E, et.al. (2005), Re-setting the biologic rationale for thermal therapy, Int. J. Hyperthermia, 21(8):779-790
[271] Gaitanaki C, Mastri M, Aggeli I-KS, et.al. (2008), Differential roles of p38-MAPK and JNKs in protection or apoptosis in the hyperthermic perfused amphibian heart, J Experimental Biology, 211, 2524-2532
[272] Daniel RM, Danson MJ. (2013), Temperature and the catalytic activity of enzymes: A fresh understanding, FEBS Letters 587, 2738-2743
[273] Mendez F, Sandigursky M, Franklon WA, et.al. (2000), Heat-Shock proteins associated with base excision repair enzymes in HeLa cells, Radiation Research, 153, 186-195
[274] Guy AW, Chou CK (1983), Physical aspects of localized heating by radio waves and microwaves. In: Storm, K.F. (ed.), Hyperthermia in cancer therapy. GK Hall Medical Publishers, Boston
[275] Lindholm C-E. 1992. Hyperthermia and radiotherapy. Ph.D. Thesis, Lund University, Malmo, Sweden.
[276] Dewey WC, Hopwood LE, Sapareto SA et al. 1977. Cellular response to combination of hyperthermia and radiation. Radiology 123(2):463–474.
[277] Hafstrom L, Rudenstam CM, Blomquist E et al. 1991. Regional hyperthermic perfusion with melphalan after surgery for recurrent malignant melanoma of the extremities. J Clin Oncol 9:2091–2094
[278] Gellermann J, Wlodarczyk W, Hildebrandt B, Ganter H, Nicolau A, Rau B, Tilly W, Fähling H, Nadobny J, Felix R, Wust P; (2005), Noninvasive Magnetic Resonance Thermography of Recurrent Rectal Carcinoma in a 1.5 Tesla Hybrid System; Cancer Res. 65:5872-5880
[279] Jeung TS, Ma SY, Yu JH et al. (2013), Cases that respond to mEHT monotherapy, Conf. Papers in Medicine, Vol. 2013, Article ID 392480, Hindawi
[280] Roussakow S. (2003), the positions of the electrodes (official Russian protocol)< Galenic Institute,

Moscow, Russia
[281] Douwes F. (2008), Thermo-Chemotherapie des fortgeschrittenen Pankreaskarzinoms. Ergebnisse einer klinischen Anwendungsstudie, https://www.klinik-st-georg.de/thermo-chemotherapie-des-fortgeschrittenen-pankreaskarzinoms/
[282] Douwes F. Migeod F. Grote C. (2006) Behandlung des fortgeschrittenen Pankreaskarzinoms mit regionaler Hyperthermie und einer Zytostase mit Mitomycin- C und 5-FU, https://docplayer.org/48541273-Behandlung-des-fortgeschrittenen-pankreaskarzinoms-mit-regionaler-hyperthermie-und-einer-zytostase-mit-mitomycin-c-und-5-fluorouracil-folinsaeure.html

This work was supported by the

Hungarian National Research Development and Innovation Office KFI grant: 2019-1.1.1-PIACI-KFI-2019-00011.

EHY-2030

A revolutionary new concept

- New automatic controlled step motor tuning system for rapid impedance matching to achieve faster tuning times
- Newly developed RF generator with modified power
- Electronically controlled electrode arm to easily and accurately horizontally position the smart electrode
- User friendly touch screen display with full system control
- New shape and design to ease patient anxiety
- Changeable strechy textile electrode for the smart electrode system and bed
- Hand-held emergency stop switch fort he patients
- Integrated PMS-100 Patient Management System

oncotherm
hyperthermic oncology

MANUFACTURER

HUNGARY
Oncotherm Kft.
Gyár utca 2.
2040 Budaörs, Hungary

Phone (+36) 23-555-510
Fax (+36) 23-555-515

info@oncotherm.org
www.oncotherm.com

GERMANY
Oncotherm GmbH
Belgische Allee 9
53842 Troisdorf, Germany

Phone (+49) 2241-319920
Fax (+49) 2241-3199211

info@oncotherm.de
www.oncotherm.de

USA
Oncotherm Ltd.
LLC, 1942 Broadway Street
Suite 314C

Boulder CO 80302
United States

Phone: (406) 225-7009
www.oncotherm.com