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Editorial

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

I am pleased to introduce the recent 25th volume of our Oncothermia Journal (OJ). The clinical part of the present volume is especially rich in new results. The present volume of our Journal gives an insight into the diligent work of hyperthermia users showing their successes in experimental and clinical studies of the heating methods. I am especially pleased to see a controlled clinical trial for fibromyalgia syndrom with whole-body hyperthermia written by Dr. von Ardenne. The treatments of relapsed glioblastoma multiforme with oncothermia are convincing about the feasiblity of the method for this almost incurable stage of brain gliomas, as shown by Prof. G. Fiorentini and his group in two subsequent articles. The special five-years survival data with good quality of life for very advanced, metastic patients in glioblastoma, non-small-cell-lung carcionoma, pancreas tumors, breast cancer, colorectal cancer, ovary tumors or soft-tissue sarcomas are excellent proofs of the usefulness of the personalized approach of integrative medicine combined with oncothermia, written by Dr. G. Parmar. The article of Matasamoto et al. about radiotherapy combination and resensitizing of the tumor is also one of the options of the method, while Dr. Y-W. Tsang and his coauthors showed the synergy of oncothermia with liposomal drug intake. An interesting hypothesis is published by Dr. Gy. Szigeti and coworkers about the explanation of meridians by networking processes, which are essential factors in the oncothermia too. In another paper Dr. O. Szasz explains some important aspects of biolectromagnetism applied for oncothermia. The last two chapters deal with the protocols of oncothermia in various complementary applications.
The present volume offers again the high level of scientific and medical articles to the readers, representing the best values of the hyperthermia community and well shows the great development possibilities as well as the bright future of the method.
I hope, this volume serves your benefits and you will read it with enjoyments.

Sincerely yours,
Prof. Dr. Andras Szasz

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

es ist mir eine große Ehre, Ihnen den 25. Band unseres Oncothermia Journals zu präsentieren. Der klinische Teil des Journals beinhaltet besonders viele neue Ergebnisse. Darüber hinaus gibt der vorliegende Band unseres Journals einen Einblick in die intensive Arbeit der Hyperthermie Anwender. Dies geschieht anhand ihrer erfolgreichen experimentellen und klinischen Studien im Bereich der Wärmetherapien. Ich freue mich besonders über die kontrollierte klinische Studie von Dr. von Ardenne, über die Behandlung von Fibromyalgiesyndrom mit Ganzkörperhyperthermie. Prof. G. Fiorentini stellt in seinen zwei Publikationen die Behandlungen von rezidivierten Glioblastoma multiforme mit Oncothermie dar und überzeugt mit der Realisierbarkeit der Methode in diesem fast unheilbarem Stadium der Gehirngliome. Die 5-Jahres-Überlebensdaten von sehr fortgeschrittenen, metastatischen Patienten mit Glioblastom, nicht-kleinzelligem Lungenkarzinom, Pankreastumoren, Brustkrebs, Darmkrebs, Eierstockkarzinomen oder Weichteilsarkomen zeugen von hoher Lebensqualität und sind hervorragende Beweise, die für einen personalisierten Ansatz der integrativen Medizin in Kombination mit der Oncothermie sprechen. Die Publikation hierzu wurde von Dr. G. Parmar verfasst. Die Veröffentlichung von Matasamoto et al. über die Kombination von Radiotherapie und die Resensibilisierung des Tumors führt auch eine Anwendungsmöglichkeit der Methode auf. Darüber hinaus schreiben Dr. Y-W. Tsang und seine Mitautoren über die Synergie der Oncothermie mit der Einnahme von liposomalen Medikamenten. Eine interessante Hypothese wurde zudem von Dr. Gy Szigeti und seinen Mitarbeitern, über „explanation of meridians by networking processes" veröffentlicht. In einer weiteren Publikation erläutert Dr. O. Szasz einige wichtige Aspekte des Bioelektromagnetismus, die bei der Oncothermie angewendet werden. Die beiden letzten Kapitel behandeln Protokolle über Oncothermie im Rahmen verschiedener komplementärer Anwendungen.
Der vorliegende Band bietet den Lesern wieder ein sehr hohes Niveau an wissenschaftlichen und medizinischen Publikationen, welche die Werte der Hyperthermie-Gemeinschaft repräsentieren und die großen Entwicklungsmöglichkeiten sowie die vielversprechende Zukunft der Methode aufzeigen.
Ich wünsche Ihnen viel Freude beim Lesen und hoffe, dass die Informationen aus dem Journal für Sie hilfreich sind!

Mit freundlichen Grüßen,
Prof. Dr. Andras Szasz

Imprint

Rules for 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 MEHT 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 MEHT 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 erleichten, haben wir die folgenden Richtlinien für die Texterstellung entworfen.

1. Aims and Scope
The MEHT 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 MEHT Journal has an open-minded character, 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 Oncotherm community. Advertisement connected to the topic is also welcome.

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

1. Selbstverständnis und Ziele
Das MEHT Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das MEHT Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncotherm-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 elektrisches Feld, 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, Meinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen.

2. Submission of Manuscripts
All submissions should be made online via email: MEHT-Journal@oncotherm.org.

2. Manuskripte einreichen
Manuskripte können online eingereicht werden: MEHT-journal@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 submittedin a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also besubmitted 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 belisted, whose email address and full contact information has to 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 jpg-file (300dpi for photos).
- References. MEHT Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3], [1-3]. The full references should be listed numerically in order of appearance, and presented following the text of the manuscript.

3. 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 Längen haben, müssen aber die folgenden Punkte enthalten:

- Titelseite. Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte. Es muss mindestens ein Autor ausgewiesen sein, dessen Email-Adresse und Kontaktdetails angegeben werden.
- Abstracts. Abstracts müssen enthalten: Zielsetzung, Material und Methoden, Ergebnisse, Fazit.
- 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 verwendet werden (300 dpi).
- Zitate. Das MEHT Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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

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Author(s) will have the opportunity to download the materials in electronic form and use it for theirown purposes. Offprints or reprints ofthe MEHT Journal are not available.

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

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

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

8. Legal responsibility
Authors of any publications in the MEHT Journal are fully responsible for the material which is published. The MEHT 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.

8. Haftung
Die Autoren aller im MEHT Journal veröffentlichten Artikel sind in vollem Umfang für ihre Texte verantwortlich. Das MEHT Journal übernimmt keinerlei Haftung für die Artikel der Autoren. Der redaktionelle Beirat hat das Recht, Artikel abzulehnen.

9. Reviewing
The MEHT 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 topicsof the journal could be rejected without reviewing.

9. Bewertung
Die Texte für das MEHT Journal werden vom redaktionellen Beirat 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.

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Contents

Clinical studies of Loco-Regional Hyperthermia in a Naturopathic Treatment Approach to various malignancies

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Abstract

A multimodal treatment approach in integrative cancer therapies has resulted in improved overall survival and in improved markers of quality of life. This is supported by a substantial amount of evidence, predominantly from outside of North America. The primary purpose of this five-year retrospective study is to determine how loco-regional hyperthermia (LRHT), in an integrated cancer care setting, effects five-year overall survival when compared to statistics from the Surveillance, Epidemiology, and End Results Program (SEER) on seven cancer types treated at the Integrated Health Clinic (IHC), Canada. Secondary objectives included examining population baseline characteristics for those who utilize LRHT and reporting on the safety profile of this therapy. The results from the study's overall 372 patients indicate improved five-year survival rates for all seven cancer types investigated. Low numbers of adverse effects related to the treatment under consideration were reported, suggesting that LRHT is safe as a stand-alone therapy, or when used in conjunction with standard of care. The importance of these findings should be placed within the larger context of integrative cancer treatment. While the incidence of treatment related side effects during LRHT were low, and survival rates increased, the direct causes of these trends cannot be attributed solely to the intervention under study, as there are other variables to consider. In spite of these limitations, the promising results from this study highlight the need for further investigation into the addition of integrated therapies including LRHT to the standard of care in these seven cancer types studied.

Keywords: Integrative oncology; naturopathic oncology; loco-regional hyperthermia (LRHT); retrospective, cohort study; overall survival; safety

Introduction

LRHT uses local heat ranging from 40-43°C over a tumour burdened area of the body. Studies on cell cultures in the 1970s showed promising results on the justification and application of hyperthermia. Now the benefit of hyperthermia as an integrated cancer therapy is well established in many parts of the world [1], [2], [3]. LRHT is increasingly used as a stand-alone palliative treatment for solid tumours, as well as an adjunctive treatment. Hyperthermia's mechanisms of action include direct cytotoxic effects [4], chemo-sensitization [5], radio-sensitization [6], and immune induction [7], [8].

Hyperthermia is often used alongside the administration of chemotherapy, as a means to augment and improve the effects of cytotoxic agents. Hyperthermia has been shown to accelerate the primary mode of action of various chemotherapy drugs including: alkylating action, inducing protein damage and DNA strand breaks, and production of oxygen radicals [3, 4, 7, 8, 9, 10, 11, 12, 13, 14]. Chemotherapeutic agents shown to improve with hyperthermia include: melphalan, cyclophosphamide, nitrogen mustards, anthracyclines, nitrosoureas, bleomycin and mitomycin [15, 16].

In addition to its chemosensitzation effects, hyperthermia is considered a potent radiosensitizer [9]. The complementary effects between radiotherapy and hyperthermia include [5, 17, 18, 19, 20, 21, 22, 23, 24]cells in S-phase are relatively resistant to radiotherapy, but most sensitive to hyperthermia,

hypoxic cells are three times more resistant to radiotherapy than aerobic cells, whereas there is no difference in thermal sensitivity between aerobic and hypoxic cells. The potential benefits of hyperthermia as an adjunct to standard of care are promising. This combined with the knowledge that the therapy appears to be safe and does not contribute to additional treatment related toxicity [25] lends itself to a potential treatment option in cancer care.

Aside from its benefit as an adjunctive therapy there is preclinical and *in vitro* evidence for hyperthermia as a monotherapy for palliative care through its selectivity towards tumour cells [4, 26]. The physiological and molecular framework of tumour cells differs from healthy cells leaving malignant cells more sensitive to the damaging effects of higher temperatures when compared to healthy tissue [27]. Tumour architecture and vasculature supply is more chaotic than in healthy tissue. Malignant cells vigorously build indiscriminate vascular networks creating an immature and structurally unsound micro-vascular system that is less resilient to variations in perfusion [26, 27, 28]. These changes create adverse tumour micro-environmental conditions, including hypoxia, acidosis, and energy depletion [29]. These variations appear to result in LRHT's selectivity towards malignant cells. In addition, cancer cells exhibit differences in their cell morphology, membrane fluidity, and gene expression [4]. Heat increases membrane fluidity and instability of cancer cells leading to cell death directly or indirectly through increased delivery of cytostatic chemotherapy agents [4]. Furthermore, heat shock induces expression of p53, a tumor suppressor transcription factor that is often mutated or decreased in cancer cells [4, 30]. Hyperthermia thus has

direct cytotoxic effects that can lead to reduction in tumour size as a stand-alone treatment in palliative care.

In addition to its chemosensitizing effects, radiosensitizing effects, and direct cytotoxic effects, in vivo studies on LRHT report a favourable shift in the immune response towards detection and destruction of malignant cells. Hyperthermia up-regulates tumour antigen expression and increases the activity of antigen presenting cells thus leading to increased activity of T cell mediated immunity towards cancer cells [29]. Hyperthermia also triggers release of heat shock proteins (HSP)[31] which present tumour antigens to APCs increasing tumour recognition [32]. Heat induces secretion of chemokines and cytokines within tumour micro-environments [29, 33]. These chemicals draw APCs into tumour burdened areas and increase macrophage activity and tumour regression [33]. Increased tumour antigen and HSP expression coupled with enhanced activity and infiltration of APCs into tumour sites, may heighten tumour recognition through activating many branches of the immune system.

Cytotoxic T lymphocytes play an integral role in the recognition and destruction of tumour cells through the recognition of major histocompatibility complexes (MHC I) bound to tumour antigens. Tumours cells have the unique capability of downregulating MHC I, thus leading to less susceptibility for T cell mediated destruction [29]. Because natural killer (NK) cells target MHC deficient cells they are essential in countering this evasive strategy [29, 30]. Hyperthermia increases NK cell activity and thus enhances protective anti-tumour cell surveillance [29, 31, 32]. Given the direct and indirect actions that hyperthermia

appears to have on malignant cells, its use in cancer care warrants further research.

Since 2010, naturopathic doctors at the Integrated Health Clinic (IHC) in British Columbia, Canada have been documenting the potential benefits of their integrated approach to cancer care. The use of LRHT in particular has been a central part of this approach. Since the IHC began implementing LRHT in 2010, improved overall survival rates have been observed. In response to the positive trends, investigators began documenting the characteristics and disease course, including survival rates, of all patients undergoing hyperthermia as a part of their integrative care. The goal of documentation was to assess these trends using a method that illustrates the positive correlation between the use of LRHT and the overall survival rates of patients. As the nature of integrative treatment does not lend itself to single intervention research models, this paper is examining a 'whole systems' approach to treatment. A whole systems approach is a broader, more holistic framework that considers a range of variables and their interactions[34, 35], and thus offers unique insights given the integrated and interactive nature of variables within this retrospective cohort study. However, within the whole systems approach, the use of LRHT is the main variable under exploration.

With this in mind, this paper highlights the potential benefit of *a naturopathic integrative approach to cancer treatment that specifically highlights the use of LRHT*, including an evaluation of this treatment's safety. Until recently, the use of LRHT was mostly experience-based, with practitioners offering observational and anecdotal evidence, and/or their personal insights into its

effectiveness [12]. This is now rapidly changing. However, in spite of the growing evidence base that hyperthermia can indeed destroy tumor cells, and that it enhances the role of radiotherapy and chemotherapy, much more rigorous research is needed [36]. Given the opportunity for continual evaluation and the need for further documentation to increase the empirical evidence base, this retrospective analysis was undertaken. The analysis spans 5 years at a single clinic (IHC), and treatment included a number of other integrated treatments such as intravenous therapies, targeted supplementation, dietary and lifestyle changes, and fever range whole body hyperthermia.

Objectives

This research had three main objectives. The primary objective was to assess 5-year survival patterns for the seven most commonly treated cancer types at IHC, based on an integrated treatment approach to cancer treatment that included LRHT as a primary therapy. Secondary objectives included analyzing baseline patient characteristics of those using LRHT, as well as the evaluation of the safety profile of LRHT. With these objectives in mind, the following methodology and research design was employed.

Methods

Study design

This is a retrospective cohort study looking at historical data for a group of cancer patients receiving an integrative cancer care protocol. The study includes 689 patients of IHC who received integrative cancer care, including LRHT, either as an adjunctive treatment, or as a palliative treatment, from June 2010-June 2015. Initially all patients who had undergone LRHT at IHC were

included in the study. Patients sought treatment at IHC, which is a private cancer care center, of their own accord, and all patients included in the study were recommended a comprehensive integrative cancer protocol that included LRHT but was not limited to LRHT. The majority of study patients were recommended a concurrent complementary protocol that consisted of one or more of the following: Intravenous therapies, dietary and lifestyle recommendations, fever-range whole body hyperthermia, botanicals and nutritional supplements (ie Omega-3 oils, curcumin etc.).

This study received approval from the Research Ethics Board of The Canadian College of Naturopathic Medicine. On the basis of its 'minimal risk' status, this study qualified for delegated review by the REB Chair and was officially cleared to be reported June 22nd, 2015. Patient charts that were used for this review and any subsequent analysis were kept fully confidential and were anonymized according to standard ethical procedures.

Inclusion and exclusion criteria

Eligibility for the study included: a cancer diagnosis; an assessment of a disease state that could be treated with LRHT; and the ability to travel to IHC for treatment. To be included in the final cohort of this study, patients must have completed a minimum of 6 LRHT treatments. Those who received less than 6 treatments were excluded from the dataset.

Treatment protocol

LRHT and integrative therapies were administered either concurrently with chemotherapy and/or radiation, or alone as palliative therapy for solid

tumours. When LRHT was administered as an adjunctive treatment, the hyperthermia protocol was timed with the chemotherapy infusion cycles. For example, if a patient was given chemotherapy on day one and eight of a 21-day cycle, LRHT was typically administered days one, three, eight, and ten of that cycle (See Table 1).

Chemotherapy schedule	Loco-regional Hyperthermia schedule
Weekly; Day 1 of 7-day cycle	Weekly the day of or day after chemo infused
Day 1 of 14-day cycle	Day 1 and 3 of 14-day cycle
Day 1 and 8 of 21-day cycle	Day 1, 3, 8, 10 of 21-day cycle
Day 1-3 of 21-day cycle	Day 1, 3, 5 of 21-day cycle

Table 1. Treatment schedule

In the cases where LRHT was administered concurrently with radiation, the schedule was typically two to three times per week for the duration of radiation. When LRHT was administered as a stand-alone therapy for the palliation of solid tumours, the most common prescription was three times per week for four weeks.

Variables

The exploratory variable of focus was the use of LRHT as part of an integrative oncology treatment protocol. Additional candidate variables included fever

range whole body hyperthermia, intravenous therapy, dietary changes, lifestyle changes, nutritional supplementation, and repurposed pharmacological agents.

The majority of patients were recommended concurrent IV therapies during the application of LHRT. Dietary and lifestyle recommendations were also suggested as part of their comprehensive integrative treatment plan, as were botanicals and specific indicated nutritional supplements (i.e. Omega 3 oils, curcumin, etc.). At the end of these treatment courses, patients were advised to wait for three to four weeks to allow for the clearance of cellular and inflammatory debris before obtaining follow-up imaging or blood work where appropriate.

Hyperthermia technique

The Oncotherm EHY-2000+ is a form of non-ionizing therapy that elevates the temperature of the tumour macro & micro-environments, in a controlled manner, to a therapeutic range of 40 – 43^{0}C [37, 38, 39]. The device employs modulated electro-hyperthermia (mEHT) to achieve the controlled heating of a target anatomy. [40, 41]The device is a capacitive coupled impedance matching solid state electrical system that incorporates two electric capacitive plates (electrodes). One electrode is situated under the patient and is built into the treatment table, running the full length and width of the table platform. The second is a mobile electrode positioned over the patient's target anatomical area, as directed by the prescribing physician. The electrodes are coupled to the patient with electrically conductive temperature-controlled water bolus to conduct and distribute electric current into tissue, as well as

help cool the skin's surface. The capacitive system generates a 40-150-Watt radiofrequency (RF) carrier signal at 13.56 MHz, which is further modulated (amplitude modulation) for absorption by the tumour. [40, 41, 42, 43]

The significantly elevated metabolic process (cellular respiration by aerobic glycolysis) in malignant cells (Warburg effect) creates a distinguishable difference between the malignant and healthy cell microenvironments. [44, 45] The glucose consumption produces high concentrations of extracellular electrolytes enriched by metabolites and lactates in the tumour microenvironment, enhancing the ionic concentration in the extra-cellular matrix (ECM). The applied RF preferentially flows in areas where there is increased ionic concentrations (based on the conductive component of tissue impedance). [46] This energy absorption creates localized heating and a resulting temperature gradient across the malignant cell membranes. This temperature gradient stimulates several cross-membrane processes that ultimately leads to increased cell membrane permeability and resulting cell membrane destabilization. [47, 48, 49, 50, 51]

The mEHT is administered according to a patient's conventional protocol to maximize the synergistic benefits. In a palliative setting, the treatment is typically administered 2-3-times per week for a total of 12-18 treatments. Each treatment is 1- hour in duration and is administered under the supervision of the prescribing physician.

The EHY-2000 Plus is produced in the European Union as a medical device and has received market approval according to the European Medical Device Directive (CE-MDD). The EHY-2000 Plus is produced under ISO9001:2008,

ISO13485:2003, and ISO 13485:2012 standards, and is certified by TUV Product Service, Munich, Germany, and TUV SUD America. The EHY-2000 Plus carries a Health Canada Class III Medical Device License.

Statistical methods

Patient's socio-demographic and clinical characteristics were summarized using frequencies for categorical variables and mean, median, standard deviation and inter-quartile range for continuous variables. Cross-tabulation has been generated to examine the distribution of patients with different cancer types using LRHT. The stage of cancer at the time of original diagnosis, and the stage when the patients came to the clinic, were tabulated by cancer type.

Our main analysis was to estimate the overall survival rate and rates stratified by cancer types. Patients were followed until death or the end of study that was May 31, 2015. Kaplan-Meier non-parametric survival estimate was calculated and plotted for all patients in the qualified cohort and for each type of cancer sub-group. These graphs were composed of the survival rates from our clinic's patients, compared to the corresponding SEER population-based survival rates for the same type and stage of cancer. The analysis was conducted using SAS software version 9.3 (SAS Institute Inc, Cary, NC).

Results

Baseline patient characteristics

As of June 2015, the IHC had treated 652 patients using LRHT. Of these patients, 58% (n=490) met all the preliminary criteria to be included in our dataset (See table 2.). The average patient age was 58 years. Of the 490 participants eligible, 47% were male, 53% were female; 55% undertook chemotherapy concurrently with hyperthermia, and 9% used hyperthermia during radiation. In addition, 51% of patients reported having previously used chemotherapy, 28% had used radiotherapy prior to hyperthermia, and 49% had previously undergone surgery. 50% of these patients were deceased as of May 31st 2015. Of the 490 eligible patients, 64% (n= 315) of the patients had a diagnosis that fell into the seven most common cancer types treated at the IHC using LRHT (See table 4). A total of 9808 LRHT treatments were administered between June 2010 and June 2015. Patient characteristics are noted in Table 2 below.

Hyperthermia Patient Characteristics	
Characteristics	**Participants N=490**
Mean age (years)	58 ± 14
Male sex (%)	47
Concurrent Chemotherapy (%)	55
Concurrent Radiation (%)	9
Chemotherapy prior to NP$^{\Phi}$ (%)	51
Radiation prior to NP (%)	28
Surgery prior to NP (%)	49
Deceased (%)	50

$^{\Phi}$ New Patient

Table 2. Patient characteristics

Hyperthermia schedules were determined during chemotherapy or radiation to optimize chemo- and radio-sensitization, taking into account chemotherapy half-life, and radio-sensitization of tumour tissues.

The vast majority of patients treated in this study had metastatic disease (88.6% at the time of their NP Consult at IHC- See table #3). As such, these were patients receiving what is generally termed "palliative treatment" (no curative intent) and were seeking complementary means to improve their survival time and quality of life. Given these conditions, these patients were well suited to receive LRHT, since LRHT is an appropriate palliative treatment that can be safely added to other palliative treatments such as chemotherapy, radiation therapy, and other targeted therapies (See Table 3) .

	Stage at Diagnosis		Stage at New Patient consult	
	Frequency	Percent	Frequency	Percent
Localized	97	19.8	56	11.4
Regional	152	31	90	18.4
Distant	240	49	344	70.2
Unknown	1	0.2	0	0

Table 3. Stages

Cancer Type and Frequency

Over 25 different cancer types have been treated with hyperthermia at IHC; the 10 most common (See Table 4.) in order of numbers seen in our clinic were: colorectal cancer, breast cancer, lung cancer, prostate cancer, brain cancer, ovarian cancer, pancreatic cancer, rectal cancer, soft tissue sarcoma, melanoma, and uterine cancer. The total N for the 10 most commonly treated cancers receiving 6 or more LRHT was 372. The percentage distribution of all the 10 most common types is outlined in table #4 below with colorectal (18.20%) breast (16.16%) and lung and bronchus (9.82%) cases representing the largest portion (over 40%) of the cancers seen at the clinic.

Ten Most Common Cancer Types treated using LRHT		
Cancer Type	**Frequency**	**Percent**
Brain*	32	6.54
Colorectal*	89	18.20
Pancreas*	25	5.11
Lung & Bronchus*	48	9.82
Soft Tissue*	15	3.07
Melanoma	12	2.45
Breast*	79	16.16
Ovary*	27	5.52
Uterus	10	2.04
Prostate	35	7.16

Table 4. Ten Most Common Cancer Types treated using LRHT

* **Indicates cancer types where KM plots were created**

Results

Five-year survival trends

The 5-year survival data for the patients with the seven most commonly treated cancer types and stages was plotted on a Kaplan-Meier curve. This data

was then compared to survival data for standard of care using the Surveillance, Epidemiology and End Results (SEER) database as a control for the evaluation of an integrative approach where LRHT was the primary variable being explored. The graphs consist of survival probability on the vertical axis and Time from Diagnosis (in years) on the horizontal axis. The graphs are for the cancer types denoted with an asterisk in Table 4. In order to accurately compare with SEER data, only patients with stage IV cancers at diagnosis were included in the KM analysis. SEER KM plots are reflective of stage IV patients at diagnosis and do not include any other stages. We chose to exclude prostate cancer from the KM plot analysis because although a total of 35 patients with prostate cancer were treated with LRHT, only 6 of these patients had stage IV disease upon diagnosis. The KM plots are as followed (See metastatic breast cancer (IV) Fig. 1., metastatic colorectal cancer (IV) Fig. 2., glioblastoma multiforme Fig. 3., metastatic lung cancer (IV) Fig 4., stage IV ovarian cancer Fig. 5., soft-tissue cancer Fig 6., and non-resectable pancreatic adenocarcinoma Fig. 7.).

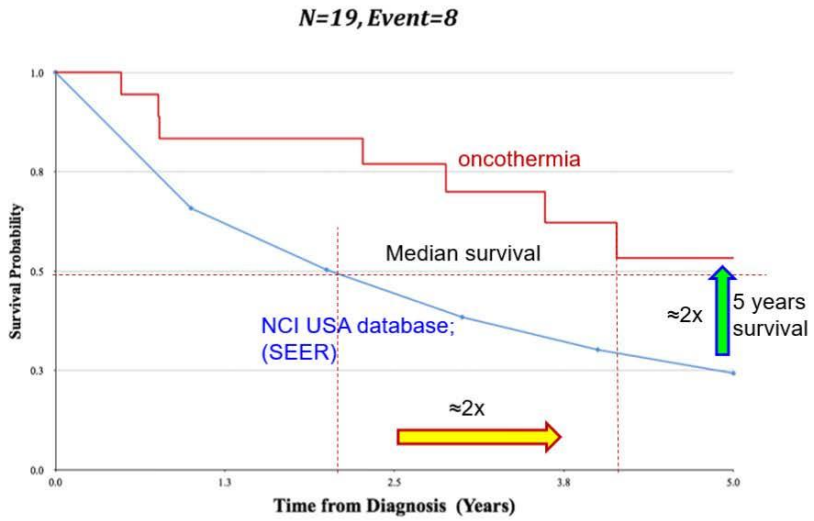

Fig.1. Metastatic breast (IV) cancer Kaplan Meier survival probability curve

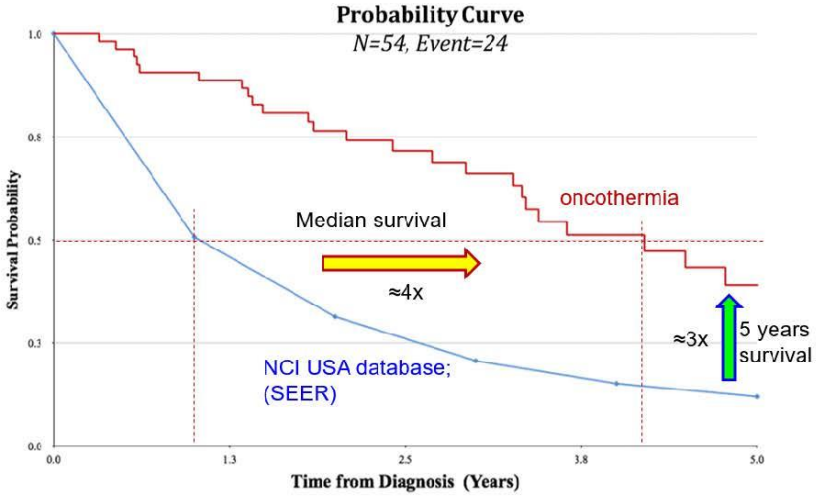

Fig. 2. Metastatic colorectal (IV) cancer Kaplan Meier survival probability curve

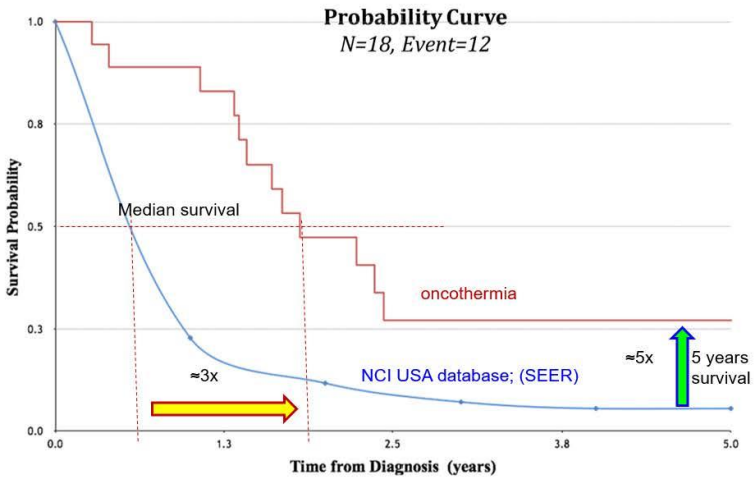

Fig 3 Glioblastoma multiforme Kaplan Meier survival probability curve

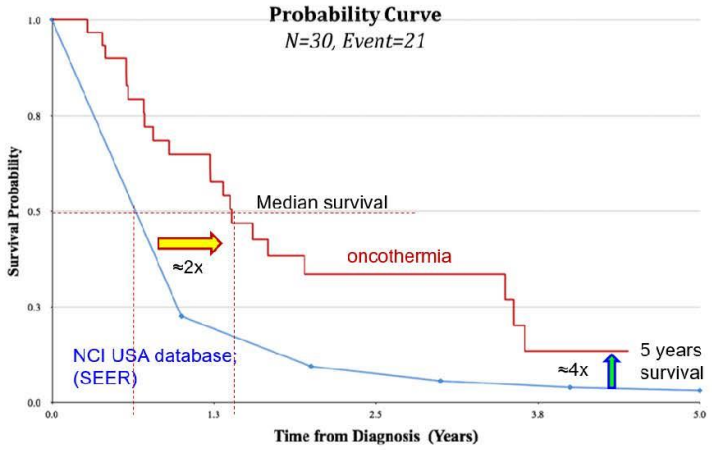

Fig 4. Metastatic lung (IV) cancer Kaplan Meier survival probability curve

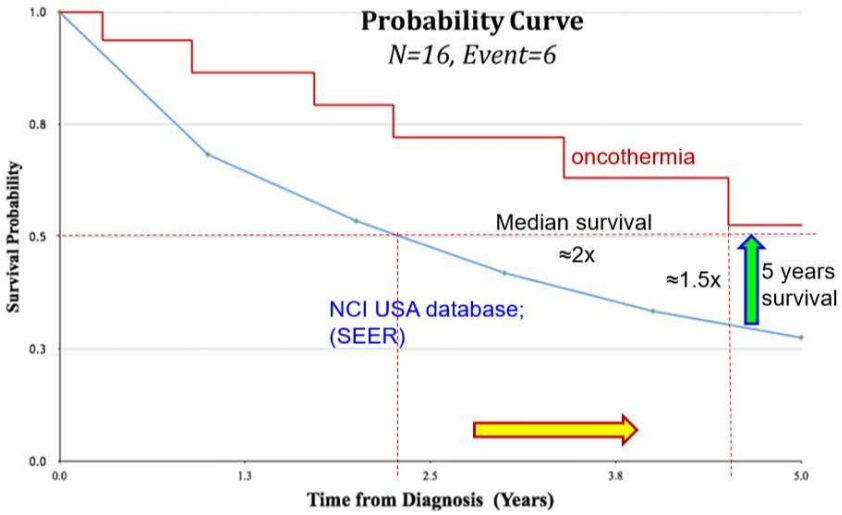

Fig. 5. Stage IV ovarian cancer Kaplan Meier survival probability curve

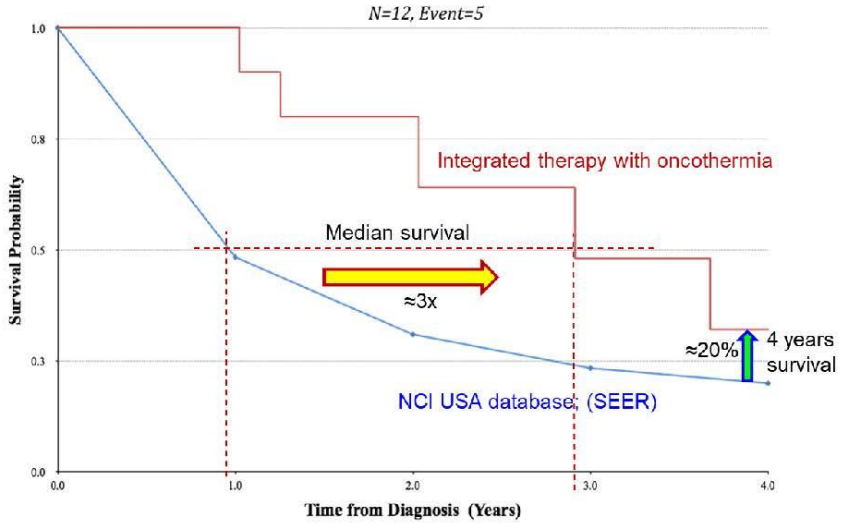

Fig. 6. Soft tissue cancer (IV) Kaplan Meier survival probability curve

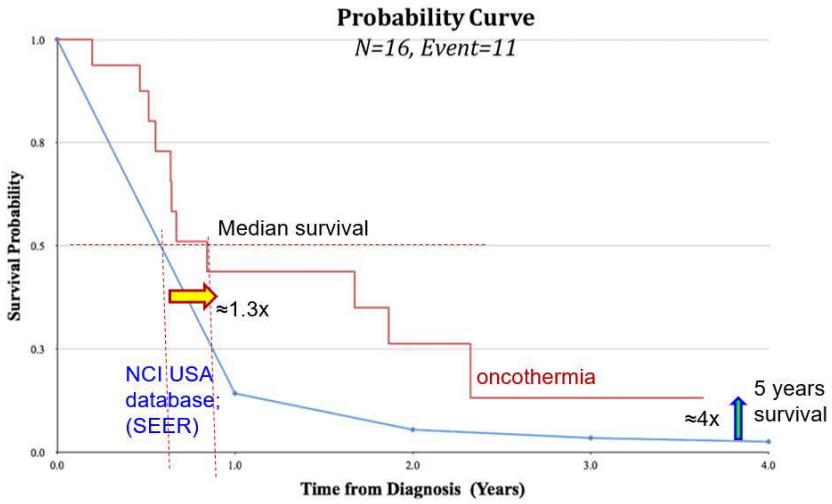

Fig. 7. Non-resectable pancreatic adenocarcinoma Kaplan Meier survival probability curve

Safety of LHRT

In accordance with the second objective of the study, the safety of hyperthermia administration was also monitored. A number of studies contend that the low levels of usage and the period of decreasing use of hyperthermia in clinical practice was primarily due to the fact that there was not adequate technology to safely heat and monitor temperature in cancerous and non-cancerous tissues [9] or that the technology was used incorrectly, failed to produce desired outcomes and thus fell short in its acceptance as an effective treatment option [52]. However, recent technological advances in both hardware and monitoring software make the use of hyperthermia easier to manage, more effective and safer [9, 37]. The findings from this study echo the claims in the literature regarding hyperthermia's safety profile.

The IHC administered 9808 LRHT between June 2010 and June 2015 and found that the total number of adverse events was very low (n=8). The most common adverse effect was first-degree burn, occurring in a total of seven treatments and one occurrence of transient subcutaneous fibrosis affecting the fat pad over the pubic bone. However, no participants dropped out of the study due to adverse events or side effects. See Table 5 below for this distribution of adverse events.

Hyperthermia Adverse Events*

Adverse Events	**Number of Patients Affected**
LRHT 1st degree burn	7
LRHT subcutaneous fibrosis	1

*Adverse events did not delay or interfere with future treatments

Table 5. Hyperthermia Adverse Events

Discussion

Key results

The primary objective of this paper was to investigate the role of LHRT in the overall five-year survival rates. The vast majority of patients treated in this study had metastatic disease (88.6% at the time of their NP Consult at IHC. As such, these were patients receiving palliative treatment and seeking complementary means to improve their overall survival time. The application of treatment was not meant to have a curative intent and thus the risk of life altering negative interaction was low in all patients.

Moroz et al (2001) identify the lack of randomized control groups and the

confounding effect of other treatments as the two main problems confronting hyperthermia research [36]. Admittedly, this study does not avoid either of these limitations. Although the direct correlation of LRHT interventions to specific patient outcomes cannot be measured given the research design employed, the overall trends in improved patient outcomes noted in the graphs above, coupled with the very high safety profile, demonstrate that these integrative, LRHT treatments warrant further investigation.

As the graphs above show, trends with LRHT as the treatment variable displayed consistently positive outcomes in the relationship between survival probability and overall five-year survival rates. While the samples for each particular type of cancer are small (r= 12-54) all graphs show increased survival times compared to the SEER control data. A few results in particular deserve attention. The LRHT treatment group in Metastatic Breast (graph 1) and Metastatic Colorectal (graph 2) show increases in both survival probability and survival time (dropping from 1.0 to 0.5 and 1.0 to 0.4 respectively) compared to the SEER data set (dropping from 1.0 to below 0.3 and from 1.0 to 0.15 respectively). Preliminary results also show promising survival trajectories for glioblastoma multiforme and non-resectable pancreatic adenocarcinoma when hyperthermia is used as an adjunct to standard of care. The differences between five-year survival endpoints in glioblastoma multiforme show positive trends, with the LRHT group dropping from 1.0 to just over 0.5 at the two-year marker compared the SEER data set which shows a drastic drop from 1.0 to 0.2 at the two-year marker. Even greater differences are apparent in the non-resectable pancreatic adenocarcinoma with the LRHT group dropping from 1.0 to 0.3 over a *two-year* period compared with SEER data showing a drop from

1.0 to 0.2 in the first year alone.

The results from this retrospective study show promise for the utilization of locoregional hyperthermia in an integrated cancer care setting. To our knowledge this is the first study that examines its potential impact on 5-year overall survival rates. There are studies however that have found benefit for the utilization of LRHT in cancer treatment. Van der Zee et al. noted an extended duration of local control of locally advanced bladder, cervical and rectal cancer when hyperthermia was combined with radiotherapy (55% complete response rates) versus radiotherapy alone (39% complete response rates) [5]. Results were most promising for cervical cancer where combination treatment led to a complete response rate of 83% compared to 57% with radiotherapy alone. Furthermore, this study also noted an improvement in 3-year overall survival rates from 27% to 51% in the radiotherapy versus the combination therapy [5]. In a 2016 meta-analysis, the combination of hyperthermia and radiation in locoregional recurrent breast cancers enhanced the complete response rates by 22% when compared to radiation alone. In these studies, toxicity related effects did not significantly differ between either group.

Studies examining the effects of the combination of chemotherapy and LRHT have also demonstrated positive results. Patients with esophageal squamous cell carcinoma treated with bleomycin and cisplatin with or without hyperthermia noted a histological benefit in each group of 58.3% and 14.3% respectively [53]. Side effect profiles were similar in both arms of the study. Maluta et al. noted an improvement in median overall survival rate from 11 to 15 months for the treatment of locally advanced pancreatic cancer with

chemoradiation and regional hyperthermia compared to chemoradiation alone [54]. There was no noted increase in toxicity with the addition of hyperthermia. An in vitro study demonstrated the effect of hyperthermia combined with gemcitabine on apoptotic cell death in cultured human pancreatic cancer cell lines [55]. The outcome showed that hyperthermia enhanced the cytotoxicity of gemcitabine. This mechanism may be responsible for the positive results reported in Maluta's study on advanced pancreatic cancer [54]. Similarly, Vujaskovich Z. et al (2010) followed locally advanced breast cancer patients - they demonstrated enhanced therapeutic efficacy with liposomal doxorubicin combined with hyperthermia [56]. Dewey (1984) looked at the interaction of hyperthermia with radiation and chemotherapy. He found that the effectiveness of both radiation and chemotherapy may be greatly enhanced by applying hyperthermia as a combined therapy [57]. Gillette (1984) concluded the same [58]. These results suggest that selective heating of the tumor relative to the surrounding normal tissue should prove a therapeutic gain when heat is combined with radiation and chemotherapy.

Although the results from this study are overall favourable for the use of LRHT in cancer treatment, it is important to note that patients were not separated into those that underwent hyperthermia as an adjunctive treatment versus those that used it as a stand-alone therapy for palliation. The authors acknowledge that this distinction may have shifted the outcomes. Further, some patients used hyperthermia throughout their disease course for a total of many treatments and others used it for only a specific time during treatment, and then not again. These distinctions also may have an impact on individual disease progression and thus survival outcomes.

The importance of the findings of this retrospective analysis needs to be placed within the larger context of integrative cancer therapy. There was very low incidence of treatment side effects during hyperthermia administration (see table 6), as well as general trends in increased survivorship when compared with the control SEER data (Graphs 1-7). While the direct causes of the trends cannot be attributed to one intervention alone- in this case, the use of local and regional hyperthermia, results do suggest that further study is warranted into the addition of integrated therapies for patients undergoing cancer treatment.

Additional study limitations and directions for future research

Due to the nature of this assessment, there are a number of biases that deserve to be mentioned. The patients followed by IHC self-selected to undergo treatment at the facility. The patients would also have self-funded their treatment, and therefore it could be assumed that they were generally of higher socioeconomic status. Furthermore, patients were required to travel to the IHC facility for treatment, therefore those individuals not well enough to travel would have been excluded, due to their inability to access treatment.

The many variables applied in treatment and the large variation in the use of integrative treatments between patients makes any direct correlation between outcomes and specific interventions challenging. The small patient numbers per cancer type (r= 12-54) and generally late disease stage (see table #3) also limits interpretation of data. Larger numbers of patients followed for a longer period of time would strengthen claims regarding the trends noted here. Based on these identified limitations, a prospective study is now underway at the IHC to assess the effectiveness of LRHT on overall survival, progression free

survival combined with ongoing quality of life assessments.

Conclusion

This paper highlights the results of a five-year, retrospective analysis assessing the role of LRHT on five-year cancer survival rates at the Integrative Health Clinic in British Columbia, Canada. While this study acknowledges a number of significant limitations, general trends outlined in this work do offer promising outcomes in both safety and efficacy of the device and treatment in question. Results in survival rates differed significantly from the SEER dataset used for comparison. With regards to the safety and efficacy of the device, documented adverse events and risk factors appeared to be low (n=8) of the 490 total participants included in the study sample. These positive findings indicate that further research involving more rigorous treatment controls and a larger sample size is both timely and relevant to advance understandings of the role of LRHT as part of an integrated strategy towards cancer care.

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Fluctuations Hypothesize the New Explanation of Meridians in Living Systems

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Fluctuations Hypothesize the New Explanation of Meridians in Living Systems

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Abstract

Biosystems are complex. Their physiology is well-controlled with various negative feedback signals and processes, it describes by opposite interfering effects which are characterized in the Eastern philosophy by Yin-Yang (Y-Y) pairs. Y-Y pairs could be described by the promoter-suppressor pairs in a wide range of physiologic signals creating the homeostasis of the complex system. This type of control appears as fluctuations from the average (mean) value of the signal. The mean carries an ineluctable fluctuation (called pink-noise or $1/f$ noise). All signals in homeostasis have equal entropy (S_E = 1.8), which is the character of the complex equilibrium. The various controlling opposite signals (Y-Y) have different time-scales which change by aging. The processes with smaller time-scale are degraded by aging, but the pink-noise ensures that the deviations of the signals of the healthy homeostatic system remain constant. Meridians are connected to the general transport systems that combined the material and the information transport with the considerable transport networks, like blood, lymph, nerve, cell-junctions, mesenchymal "ground substance" cytoskeletons. The meridians in this meaning only virtual line averaged from multiple realized paths to connect two acupuncture points by the material, energy and information transport processes. The meridian network is designed by various coupling points (acupoints), which could be perturbed by actuating stimulus. Our objective is to describe the meridian system from complexity point of view.

Keywords

Pink-Noise, Complexity, Living System, Meridians, Acupoints, Homeostasis

1. Introduction

There are numerous questions related to Traditional Chinese Medicine (TCM),

especially to acupuncture and the existence of meridians [1]. Is it an ancient cure or modern therapy? Is it art (psychology) or a treatment (physiology)? Is it a natural philosophy or an experimental medical practice? Answers are not formed yet [2].

When the importance of the dissipative processes was recognized, and the general system theory was established [3], we started to examine living systems differently from before [4]. It was discovered how environmental impact affected living systems and we started to examine the complexity of life. We understood the problem of complexity in physiologic processes and had more and more complications to explain the interference of the signals while studying the complete system as one. We face difficult challenges to examine individual physiologic changes in isolation from the body; but discovered specific general mechanisms (universalities) which do not depend on the details of the system with the same scales through few orders of magnitudes in spatiotemporal descriptions. The hallmarks of complexity give us new insights into the description and understanding of the general integrity of living objects. Non-stationarity (time-dynamics), non-linearity (cross-talks of signals, complicated interactions), multiscale organization (spatiotemporal fractal behavior), time irreversibility (non-equilibrium dynamics and fluctuations) are all giving surprising news when studying living objects. Non-equilibrium thermodynamics started to be connected to explanations and the equilibrium became a dynamic fluctuation with unique noises.

The dialectic dynamics of life had connections to philosophy (from Lao-Zi through Heraclitus of Ephesus to Hegel GWF), understanding the strict negative feedback connections by the thesis ↔ antithesis ↔ synthesis triad.

The ancient knowledge was based on long-term and much extended observations and experimental trials which of course were mixed with the ancient beliefs, philosophy and explanation of the environmental structures. In this paper, we would like to show some consequences of the complex physiology, some hypothesized effects which could explain the existence of acupoints and meridians without using any formulation or philosophical points from the ancient explanations.

2. Method

Multiple solutions were developed for the calculation of entropy of the data-row with finite length (like a representative sampling of physiological signals). These solutions are coherent with Shannon's entropy formulation. The Richman-Moorman entropy [5] was applied to the analysis of multiscale entropy (MSE) of physiological signals [6].

Following the calculation of [6], let us denote a time-series containing N samples by $\{X_l\} = \{X_1, \cdots, X_l, \cdots, X_N\}$. Choose from this vector with m-dimension:

$$u_m(i) = \{x_i, x_{i+1}, \cdots, x_{i+m-1}\}, \quad 1 \le i \le N - m + 1 \tag{1}$$

We use the maximum of the absolute deviation of components to characterize

the distances between the vectors, so

$$d\left[u_m(i),u_m(j)\right]=\max\left[\left|x(i+k)-x(j+k)\right|\right],\quad 0\le k\le m-1 \tag{2}$$

The $u_m(i)$ and $u_m(j)$ vectors are r-neighbors when their distance is less than r. The negative logarithm of that conditional probability when the vectors remain r-neighbors is when an additional sampling is given to the time-series increasing, the length of the vectors too. Consequently, by applying this definition, Richman-Moorman-entropy is:

$$S_E=-\ln P\left(\left|x_i-x_j\right|\le r,\left|x_{i-1}-x_{j-1}\right|\le r\right) \tag{3}$$

where S_E is the Richman-Moorman-entropy. Denote $n_i^m(r)$, the number of $u_m(j)$ $(i\neq j)$ vectors which have a distance from the vector $u_m(i)$ is smaller than r. The probability that the vector $u_m(j)$ is located in the distance of r-radius from a vector $u_m(i)$ is:

$$P_i^m(r)=\frac{n_i^m(r)}{N-m+1} \tag{4}$$

where the $P_i^m(r)$ is the probability of the distance of $u_m(j)$ form $u_m(i)$ is smaller than r; while the probability that the vector $u_{m+1}(j)$ is found in the r-radius neighborhood of $u_{m+1}(i)$ is:

$$P_i^{m+1}(r)=\frac{n_i^{m+1}(r)}{N-m+2} \tag{5}$$

The conditional probability from these would be:

$$\frac{P_i^m(r)}{P_i^{m+1}(r)}\cong\frac{n_i^m(r)}{n_i^{m+1}(r)} \tag{6}$$

with these notations the Richman-Moorman-entropy could be interpreted in this form:

$$S_E=-\ln\frac{P_i^m(r)}{P_i^{m+1}(r)}\cong-\ln\frac{n_i^m(r)}{n_i^{m+1}(r)} \tag{7}$$

The $n_i^m(r)$ and $n_i^{m+1}(r)$ values could be determined to know the probability density function. We may suppose that Gaussian pink noise [6] is allowed by the central limit theorem in physiological signals [7]. To characterize the multidimensional Gaussian distribution, the covariance matrix must be given too. The power-spectrum defines the covariance matrix, and from that the entropy could be derived.

The definition of the covariance matrix containing N-number of random variables:

$$\bar{\bar{C}}\left(X_i,X_j\right):=E\left[\left(X_i-\bar{X}_i\right)\left(X_j-\bar{X}_j\right)\right] \tag{8}$$

The diagonal of the covariance matrix represents the deviations of the individual random variables. Due to the symmetry and real-elements of the hermitic matrix it could be transformed to the principal axis. The eigenvalues for this transformation:

$$\bar{\bar{C}}\bar{U}_i = \lambda_i \bar{U}_i \tag{9}$$

Therefore:

$$\bar{U}_j \bar{\bar{C}} \bar{U}_i = \lambda_i \bar{U}_j \bar{U}_i = \lambda_i \delta_{ij} \tag{10}$$

Consequently, when we form a $\bar{U}$ matrix from the eigenvectors like its columns, then:

$$\bar{\bar{U}}^{\mathrm{T}} \bar{\bar{C}} \bar{\bar{U}} = diag\left(\lambda_1, \cdots, \lambda_i, \cdots, \lambda_N\right) = \bar{\bar{\Lambda}} \tag{11}$$

is a diagonal matrix. The covariance matrix transformed random variable is:

$$\bar{Y} = \bar{\bar{U}}^{\mathrm{T}} \bar{X} \tag{12}$$

because

$$\begin{aligned} \bar{\bar{U}}^{\mathrm{T}} \bar{\bar{C}} \bar{\bar{U}} &= \bar{\bar{U}}^{\mathrm{T}} E\left[\left(\bar{X} - \bar{\bar{X}}\right)\left(\bar{X} - \bar{\bar{X}}\right)^{\mathrm{T}}\right] \bar{\bar{U}} \\ &= E\left[\bar{\bar{U}}^{\mathrm{T}}\left(\bar{X} - \bar{\bar{X}}\right)\left(\bar{X} - \bar{\bar{X}}\right)^{\mathrm{T}} \bar{\bar{U}}\right] \\ &= E\left[\left(\bar{\bar{U}}^{\mathrm{T}} \bar{X} - \bar{\bar{U}}^{\mathrm{T}} \bar{\bar{X}}\right)\left(\bar{X}^{\mathrm{T}} \bar{\bar{U}} - \bar{\bar{X}}^{\mathrm{T}} \bar{\bar{U}}\right)\right] \\ &= E\left[\left(\bar{\bar{U}}^{\mathrm{T}} \bar{X} - \bar{\bar{U}}^{\mathrm{T}} \bar{\bar{X}}\right)\left(\bar{\bar{U}}^{\mathrm{T}} \bar{X} - \bar{\bar{U}}^{\mathrm{T}} \bar{\bar{X}}\right)^{\mathrm{T}}\right] \\ &= E\left[\left(\bar{Y} - \bar{\bar{Y}}\right)\left(\bar{Y} - \bar{\bar{Y}}\right)^{\mathrm{T}}\right] \end{aligned} \tag{13}$$

Consequently, the deviation of the transformed random variable Y_j is:

$$\sigma_j' = \sqrt{\lambda_j} \tag{14}$$

On the other hand, the probability density function of an N-dimensional Gaussian noise is:

$$p\left(\bar{X}\right) = \frac{1}{\sqrt{(2\pi)^N \det \bar{\bar{C}}}} e^{\left[-\frac{1}{2}\left(\bar{X} - \bar{\bar{X}}\right)\bar{\bar{C}}^{-1}\left(\bar{X} - \bar{\bar{X}}\right)\right]} \tag{15}$$

Moreover, from this the distribution function of the transformed random variable is:

$$\begin{aligned} p\left(\bar{Y}\right) &= \frac{1}{\sqrt{(2\pi)^N \det \bar{\bar{\Lambda}}}} e\left[-\frac{1}{2}\left(\bar{Y} - \bar{\bar{Y}}\right)\bar{\bar{\Lambda}}^{-1}\left(\bar{Y} - \bar{\bar{Y}}\right)\right] \\ &= \prod_{i=1}^{N} \frac{1}{\sqrt{2\pi\lambda_i}} e^{-\frac{\left(\bar{Y}_i - \bar{\bar{Y}}_i\right)^2}{2\lambda_i}} = \prod_{i=1}^{N} p\left(Y_i\right) \\ p\left(Y_i\right) &= \frac{1}{\sqrt{2\pi\lambda_i}} e^{-\frac{\left(\bar{Y}_i - \bar{\bar{Y}}_i\right)^2}{2\lambda_i}} \end{aligned} \tag{16}$$

To calculate the covariance matrix starting from the power-density of the pink-noise:

$$S(\omega) = \begin{cases} \dfrac{K}{\omega}, & \omega_1 \le \omega \le \omega_2 \\ 0, & \text{otherwise} \end{cases} \tag{17}$$

The autocorrelation function could be determined from this by the Wiener-Khinchin-theorem [8]:

$$\Phi(\tau)=\frac{K}{2\pi}\int_{\omega_1}^{\omega_2}\frac{\cos\omega\tau}{|\omega|}\mathrm{d}\omega=\frac{K}{2\pi}\left[Ci(\omega_2\tau)-Ci(\omega_1\tau)\right],$$
$$Ci(\tau)=\gamma+\ln(\tau)+\sum_{k=1}^{\infty}\frac{(-1)^k\tau^{2k}}{(2k)!2k} \tag{18}$$

where $Ci(\tau)$ is the function of integral-cosine, and $\gamma=0.5772$ is the Euler's constant. Consequently:

$$\Phi(\tau)=\frac{K}{2\pi}\left\{\ln\frac{\omega_2\tau}{\omega_1\tau}+\sum_{k=1}^{\infty}\frac{(-1)^k}{(2k)!2k}\left[(\omega_2\tau)^{2k}-(\omega_1\tau)^{2k}\right]\right\} \tag{19}$$

3. Results

The connection of the autocorrelation function and covariance matrix for such ergodic processes like the pink-noise is 6:

$$\overline{\overline{C}}=\begin{bmatrix}\Phi(0) & \Phi(\tau) & \Phi(2\tau) & \cdots & \Phi(N\tau)\\ \Phi(\tau) & \Phi(0) & \Phi(\tau) & \cdots & \Phi((N-1)\tau)\\ \Phi(2\tau) & \Phi(\tau) & \Phi(0) & \cdots & \Phi((N-2)\tau)\\ \vdots & \vdots & \vdots & \ddots & \vdots\\ \Phi(N\tau) & \Phi((N-1)\tau) & \Phi((N-2)\tau) & \cdots & \Phi(0)\end{bmatrix} \tag{20}$$

with these conditions the MSE entropy of pink-noise [6]:

$$S_E=1.8 \tag{21}$$

To determine the homeostatic equilibrium, we make a multi-scale entropy analysis, where the $\{x_1,\cdots,x_j,\cdots,x_N\}$ is a one-dimensional discrete time-series. From this, a consecutive coarse-grained $\left\{y_r^{(\tau)}\right\}$ time-series can be constructed with τ scale-factor, as shown in Figure 1.

According to Figure 1, the members of the τ scale series are:

$$y_j^{(\tau)}=\frac{1}{\tau}\sum_{i=(j-1)\tau+1}^{j\tau}x_i,\quad 1\le j\le N/\tau \tag{22}$$

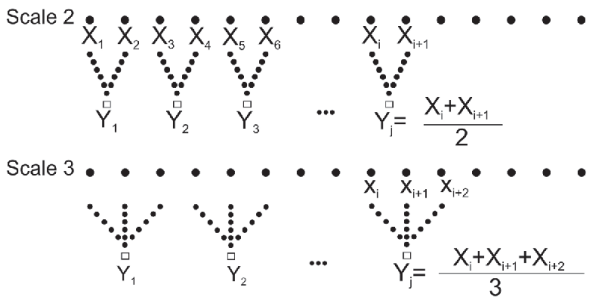


Figure 1. Illustration of the coarse-graining process in the 2nd and 3rd scale (after [9]).

MSE method is used to calculate the entropy of all the coarse-grained time-series. This was made for pink and white noises 6, and the results are shown in Figure 2. (The scale-factor is the number of terms in the average.) The $1/f$ noise does not change by the smoothing (cutting of high frequencies) of the function, and the Rich-man-Moorman entropy of pink-noise is scale-independent in a definite interval, it is constant and could characterize the homeostasis. The results are in perfect harmony with the others obtained by the other methods [10] [11], and applied to living systems [12].

The correlation of the white noise is small, so the entropy of the white noise decreases by series of higher time-factors, while in case of the pink noise the complex internal structure remains constant on the large time-scales due to its long correlation length. The short correlation length of the white noise causes high entropy on the small scales (<4), while the weaker correlation for long-scale ensures the constant entropy for pink noise in the wide range of scales.

4. Discussion

From a physical point of view, the scaling of discrete time series is a filtering process of some of the high-frequency components of the noise. We may construct a series of scales by bandwidths. The highest bandwidth is at the 1st scale, and by averaging more and more high-frequency components, higher scales have gradually narrower band-gaps. The highest frequency in the signal is well approximated by Shannon's sampling theorem [13], declaring that the highest frequency in the sampled noise is the half of the sampled frequency. Consequently, in the scale of the 2nd factor, the upper frequency is half of the half of sampled frequency, in the nth the nth-part of the bandwidth, and a similar one is valid on the low-frequency limit as well. The length of the data-series characterizes the time-length of the registering of the noise; when the sampling time is ΔT, and N is the size of the data-series then the length of the registration is $N\Delta T$. The reciprocal value of $N\Delta T$ is the smallest frequency in the sampled signal, so is the low limit of the bandwidth. Due to the decreasing length of the data series the low-frequency limit of the bandwidth grows. The scaling of the power-function $S(\omega)$ is shown in Figure 3.

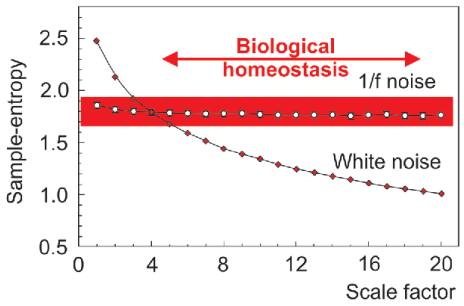


Figure 2. The result of MSE analysis of pink and white noises [6].

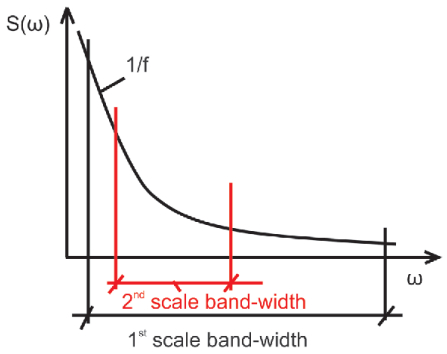


Figure 3. The shortening of bandwidth in the scaling, using the Shannon's sampling theorem. The upper limit is cutting the half of the maximal sampling frequency, while the lower limit is the double of the minimal sampling frequency. This process is continued to the 3rd, 4th, etc. scaling steps, using the n-th bandwidth determining the $(n + 1)$-th by the same procedure.

In this meaning, the Richman-Moorman-entropy of time-series shows some kind of a holographic behavior of the pink-noise, namely the entropy does not change by the truncating of the registering of the pink-noise.

The Richman-Moorman-entropy has a natural physical meaning too, (like the Shannon entropy also [14]), from its multiplication with Boltzmann constant ($kB \approx 1.38 \times 10^{-23}$ [$m^2 \cdot kgs^{-2} \cdot K^{-1}$]) we get the physical entropy of the sample. We know from thermodynamics that the entropy is a function of the state of a system, so it is a function of the state-variables, like the internal decisional energy. The internal energy in our case is the sum of the energy content of the Fourier components. Consequently, the physical entropy of the signals from pink-noise does not change by decreasing its energy, similarly to the thermodynamical entropy that has extremum in the function of energy. This allows energy exchange between the sub-systems in the thermodynamic equilibrium in the form of fluctuations without its entropy changing.

A similar attribute could exist in case of stochastic processes when a system emits pink-noise. Subsystems could change energy without changing their entropy in this fluctuation analogy. However, in this case, the entropy is not extensive. The energy is an additive magnitude but the entropy, which is constant in the homeostasis, is not an additive parameter. Consequently, on the grounds of experience, the entropy is intensive in systems of homeostasis.

In the realization of homeostasis of a living system the "ground substance", which is a considerable part of the whole weight of the system, [15], has a central role. This ground state is a gel-like mesenchymal tissue, a soft connection material. The basic information transport goes through this connective tissue, which structure contains a large amount of the extracellular matrix too. The mesenchyme ensures the alimentation and excretion of cells, it is a transmitter and filter between the capillaries and cells containing highly polymerized carbo-

hydrates glucosaminoglycans, protein associated ologasacharid chains, proteoglycans and structural glycoproteins, glycolipids in the ordered set, networked with dendrites and extracellular matrix of glycocalyx. The mesenchyme is active in three communication levels on the regulation of the system: cellular, humoral and nervous. The cellular level ensures the chemical equilibrium of the connective tissue with the system of reticuloendothelial cells. It locally controls the capillary transported materials, like oxygen, metabolites and enzymes cell-life signals. Through the humoral transports, it communicates over a long distance with subsystems by electrolyte transports (lymph, blood-stream). The nervous network functionally connects the distant parts of the system. The humoral level of systemic transport processes is slow, while the nervous communications are transported fast. All the controls have negative feedback regulating the equilibrium with action signal-pairs promoting or suppressing the actual process. We could note the balancing signal pairs as Y-Y pairs taking the notation from Ying-Yang introduced by Traditional Chinese Medicine (TCM). This feedback mechanism is the smart solution to fixing the actual expected values. A simple example for the negative feedback control in non-living systems is the weight hanging on a spring. Gravitation attracts the weight in the direction of the Earth-center, while the spring suppresses the gravitation, always works against it with the same force as gravitation acts and forms equilibrium position somewhere. During any external perturbation, the opposite effects compensate the deviations, and the weight is in its equilibrium place in the time-average. In the physiological signals, a large number of controlling pairs form the average value (equilibrium value) of the physiological signal. All the three action levels are connected in the mesenchyme; which gives "stage" to form an equilibrium.

The controlled parameters of the regulation system of homeostasis (like the actual value of a physiological signal) are realized with dialectic determination. This means that the controlled value of the physiological process is formed by the dynamical equilibrium of a large number of interfering controlling signal pairs (Y-Y). Let us study the proliferation homeostasis to elucidate this process. The essence of proliferation homeostasis is the exchange of the old or damaged to new ones, fixing the size of the organs and parts of the system. The two acting opposite regulation signals (Y-Y) generate the annihilation (Yin) and creation (Yang). Programmed cell death (apoptosis) is on the Yin side while cellular division generated by the growth-factors has a leading role on the Yang side. The healthy arrangement is a dynamic equilibrium turning to disease when it comes apart. When the Yin is dominant, apoptosis overrides the situation and an autoimmune disease is formed. In case the Yang is the dominant, creation has a central role; tumorous diseases are shaped by switching-off of the programmed cell death. The complete accommodation of the system is better when it has more Y-Y pairs which interact and form subsystems too. The homeostatic equilibrium stabilizes the energy-intake of the subsystem and the whole system as well which is described by the allometry of the living systems [16].

Their board equilibrium governs multiple other effects. The Y-Y pairs could interfere with the same proliferation process controlling hypoxia or many other factors in the microenvironment of the cell by coupling like the humoral control. When oxygen delivery is not satisfactory (hypoxia, Yin-dominance), as it can happen at an excessive muscle activity, blood-perfusion becomes more active to compensate with increased permeability of the vessel walls, or even angiogenesis can begin (Yang-effects). In case of a further load (like regular sport activity) protocol enzymes will solute the extracellular matrix helping the mobility of the cells, and due to the effect of vascular endothelial growth factor (VEGF) they will start a higher proliferation activity and chemomechanical migration by the gradient of VEGF, building up a primitive blood-vessel network. The network is controlled by not only VEGF but the gradient of electric potential like a morphogenetic factor [17]. Potential gradient is formed by the more negative newborn daughter cells rather than by the matured neighbors (**Figure 4**).

The 4th period of angiogenesis is the maturation when the extracellular matrix is fixed; the appropriate cells are coupled and form the vessel-wall; angiopoietins complete the existing capillary network with the new one and make the vessel-system ready for proper physiological operation. Angiogenesis itself is not enough, the direction of the forming vessel is also important which is governed by the potential gradient. The final stage of angiogenesis is the optimizing stage, when the dialectic determination of Y-Y recovers its dynamic equilibrium from the alimentation point of view.

The above regulation process is rather simplified but shows a very complex adjustment of the parameters and is only one of the large number of cooperation processes forming homeostatic control. This must not be deterministic, because neither the appropriate accuracy nor the adequate stability could be ensured with quick signal-exchange. The non-deterministic process emphasizes the accidental processes determining the homeostasis on the way when the regulation is flexible and "economic", therefore it is no more accurate than it is necessary for the actual function.

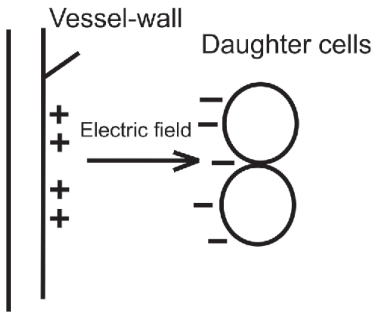


Figure 4. The forming of electric potential at angiogenesis. The electric field is an effector of the epithelial transition producing cellular joints and cytoskeletal polymerization [17].

The optimal accuracy governed by the goals of homeostasis is to provide constant environmental conditions for the living cells and their collective development. These requests are keeping the parameters within tolerance limit without the environmental conditions remaining for a longer period, assuring the mean and the deviation of a constant value. The constant mean allows fluctuations, noises when their deviation remains under the predefined limits.

We would like to show that the time-fractal fluctuation is a perfect error-signal satisfying the homeostatic requirements. We consider the mean $\left(\langle x(t)\rangle\right)$ of the n number of $x_i(t)$ signals in time t in the homeostatic controlled environment as basic signal:

$$\langle x(t)\rangle = \frac{1}{n}\sum_{i=1}^{n} x_i(t) \tag{23}$$

where the sign $\langle\ \rangle$ denotes the averaging in time. The error is the deviation from this mean, so the controlling error is the noise due to the accidental processes in the homeostatic regulation, Figure 5.

The noise $\left(z(t)\right)$ is the deviation of the actual signal $\left(x(t)\right)$ from the mean $\langle x(t)\rangle$:

$$z(t) = x(t) - \langle x(t)\rangle \tag{24}$$

Let us study the $\langle z^2(t)\rangle$ variance (square of the standard deviation) of the $x(t)$ as a function of time:

$$\langle z^2(t)\rangle = f(t) \tag{25}$$

Due to the self-similarity of the biological processes [18], the deviation of the signal must be a power function:

$$\langle z^2(t)\rangle = t^{H'} \tag{26}$$

where $H > 0$ in every case. When $H = 1$ the $\langle z^2(t)\rangle$ of the controlling error is a linear function of the time:

$$\langle z^2(t)\rangle = ct \tag{27}$$

where c is a constant. Form (26) we obtain the scaling conditions:

$$\langle z^2(rt)\rangle = r^{H'}\langle z^2(t)\rangle \tag{28}$$

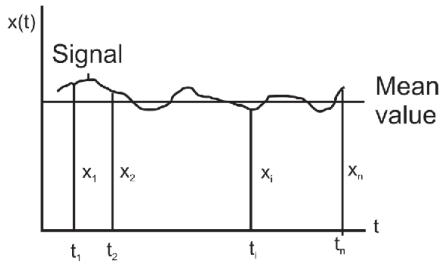


Figure 5. The noise around the mean value of a signal.

The error-signal could be characterized by its spectral power-density ($S(f)$) [19] too:

$$S(f)=F\left[G(\Delta t)\right] \tag{29}$$

where $G(\Delta t)$ is the autocorrelation function [20] of the error-signal:

$$G(\Delta t)=\left\langle z(t)z(t+\Delta t)\right\rangle-\left\langle z(t)^2\right\rangle \tag{30}$$

The power density of the noises like (28), is [21]:

$$S(f)\propto\frac{1}{f^{H'+1}} \tag{31}$$

If the error signal is a pink ($1/f$) noise, then $H'=0$. Considering (28), when the signal is pink-noise, the deviation does not depend on any r-value, so the deviation is constant in time. Consequently, there are definite limits which are never taken over by the error signal; because based on the Chebyshev inequality [22] the probability that the signal is in an interval $(\bar{x}-k\sigma,\bar{x}+k\sigma)$ is:

$$P\left(|x-\bar{x}|<k\sigma\right)>1-\frac{1}{k^2} \tag{32}$$

Therefore, when k is appropriately large for the tolerance, the signal is practically always in the requested interval.

If the power-spectrum of the error-signal is not pink-noise, its exponent is larger than [11], then according to (28), the error-signal will be increased by time and the homeostatic equilibrium will be overset. This is a failure of the balancing, it leads to a jumble of control forming irregular processes, developing the disease. The character of the noise changes, it becomes "colored noise", having $H'>0$ in (31).

The above discussion proves the fact that the physiologic signals have a pink-noise deviation from their averages keeping the limits of the homeostatic control, which in thermodynamical meaning keeps the sample entropy constant in a broad scale, $S_E=1.8$. The famous quotation formulates this dynamic request by A. Einstein: "Life is like riding a bicycle. To keep your balance, you must keep moving.", [23]. Showing it in a simple sketch, representing the instability with a double-well potential, life is somewhere at the breaking point: it has no excess energy to lose but has enough energy to not be trapped in one fixed position, so it is always fluctuating at the breaking-point, energy means the E_{breaking}, and the fluctuation is time-fractal ($1/f$ pink noise). Energy keeps the system in this point pumped from the environment, **Figure 6**.

Life is on the edge of chaos, [24], as the quote from A. Szentgyorgyi, a Nobel laureate said: "Life is nothing but an electron looking for a place to rest.", [25].

The complex properties emphasize the request for change of paradigm of physiological evaluation, [26]. The problem is that in most of the medical diagnostics organ function is examined by its own structural or functional failure, and sometimes connects with a network view. However, even networking is not enough to get the realistic picture; a complex fractal view is necessarily taking

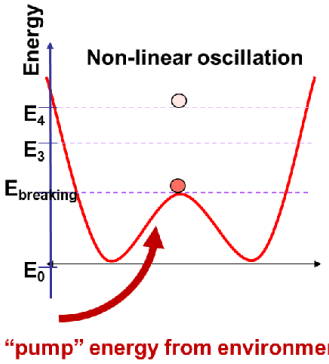


Figure 6. When the incoming energy is too high, the electron occupies a high energy level (noted by E_4 in the figure), which does not fit the homeostatic equilibrium. The electron start loosing its energy, and reaches the breaking point ($E_{breaking}$). When it looses too much energy, it will be "frozen" in one energy-well, which is again out from the homeostatic regulation. Consequently, energy keeps the electron in a "frustrated" position, at "edge of chaos" to fulfill the homeostatic equilibrium. The energy-fluctuations in this position are parts of the $1/f$-noise.

self-organized structural and dynamical (time) fractal behavior of the system into account. The mean of the physiological values does not give enough information; even its deviation could be unsatisfactory to compose a realistic diagnosis. Pink noise decides about the homeostatic equilibrium, so noise structure carries important information about the actual status of the living system.

We have to note that healthy, the healthy cell-division is also governed by fractal noise, [27]. It is shown that the relative error in the generation of the cells rapidly grows in a classical (non-fractal) model, while it remains constant (almost errorless) in case of pink-noise [28].

Aging decreases the complexity of the system, the dialectic formation of the Y-Y pairs degrades. On this way the Y-Y pairs act different time-scales, and the high frequencies gradually vanish in the noise. Consequently, aging has MSE scaling, the system develops higher scaling factors, but during the aging the entropy of physiologic signals does not change, it remains constant when the system is healthy. Thus, healthy aging is well distinguished from the disease on the level of homeostatic control, the deviation from the Y-Y determination is a character of the disease only.

The meridians are introduced by TCM to visualize the channels where the Y-Y pair acts. It is of course, a considerable simplification of the actual homeostatic balance due to the large number of active networks in the system (blood-, lymph-, nerve-networks completed with cell-junctions, cellular adherent connections, cytoskeletons, mesenchymal tissue, soft connective tissue, polymer-formations, etc.). These are interconnected and act in promoter suppressor (Y-Y) balancing as regulators. This is a controlling negative feedback loop from the initial product to the final one by interaction promoters and suppressors,

Figure 7.

The regulation network of the homeostasis is complex, having various levels of Y-Y actions, which are genuinely in interaction grouping and making new sets of actions on all levels of complexity, Figure 8.

This massive regrouping over the complete system has a well-defined regulation network based on the same negative feedback principles as the details of where this huge complexity built up, Figure 9. Life is developed as an open system, its exchange with the environment with materials, energy and other parameters essentially keep life stable. The openness is completed with energy dissipation [29], limiting the efficacy according to the entropy law of thermodynamics [30]. Of course, the inputs are noisy, as well as the outputs and all the feedback mechanisms have specific homeostatic noises as it is discussed above. The stability of this regulation is based on the constant dissipation in the open living system in a very broad scaling measured by MSE entropy ($S_E = 1.8$) keeping the entropy in the $1/f$ noise range in a very broad scaling interval.

There is a further crucial structural point of the complete organizing process. The feedback mechanisms are connected to the actual "hardcovers", so are the large networks (blood, lymph, nerve, junctions, adherents, mesenchyme, polymers, etc.). This hardware carries the "software", the regulation mechanisms, like the internet, a global network of interconnected computers, the world-wide-web (WWW), and information exchange place is based on the internet as "hardware". While WWW builds up a fractal structure, the internet does not [31]. The internet hardware has "hubs", which attract each other by the better communication possibilities guided by the economic optimizing. These systems are vulnerable due to the strong and large number of links in hubs forming strong characteristically assortative clusters. The WWW follows the user's optimization having a wide range of "weak links" meaning the connection of users outside the hub; weakens the connections to the hubs. These weak-links connect hubs with non-hubs, they make repulsion-like structures between hubs, and stabilize the system well; thus they are less vulnerable than the internet "hardware".

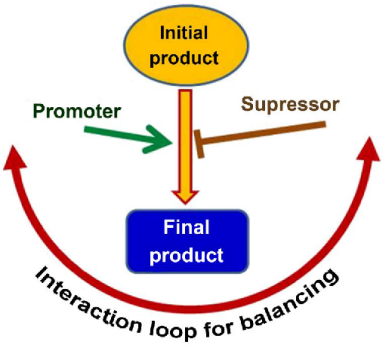


Figure 7. The balance of promoters and suppressors (Y-Y pairs) make an interaction negative feedback loop regulating each other, keeping the final product controlled.

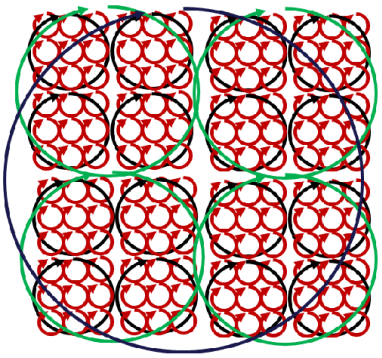


Figure 8. The regulation Y-Y loops are grouped, forming new regulation levels, and re-grouping again and so on subsequently.

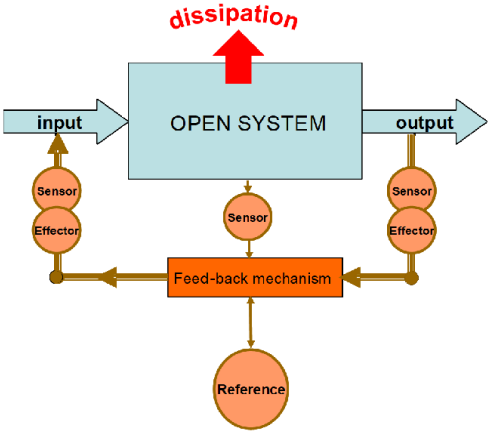


Figure 9. The complexity after all looks like one single Y-Y interaction which is regarded in TCM as the unified negative feedback Yin-Yang balance. It is a well-known negative feedback regulating principle in engineering, including dissipation due to the open system.

Living objects are built in the same way, Figure 10. The metabolic networks, the neural information exchange, the long-range correlated structures of information exchange in the living organisms work on WWW style (WS), while the large hubs as organs of the body structure are internet-like (IL). The information short-cuts (small-worlds [32]) optimize the integration of the systems as shown in the functional brain networks [33].

Meridians are probably structures that partly include large networks ("hardware", like blood, lymph, nerve), but also contain "software" components for communication between the organs ("hubs") and having intermediate points (probably the acupoints), on which we may modify the broken homeostatic equilibrium. Since the "ground substance" is the central place of the information

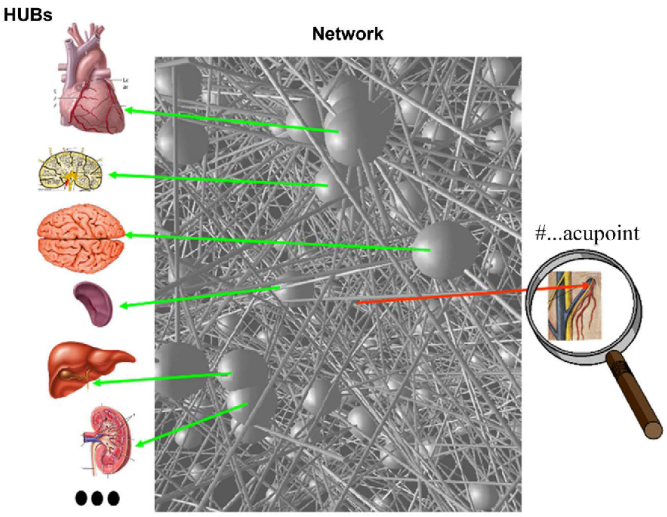


Figure 10. The schematic organizing network of the human living system. The large hubs collecting many connections and some connections are concentrated in the intermediate places (acupoints).

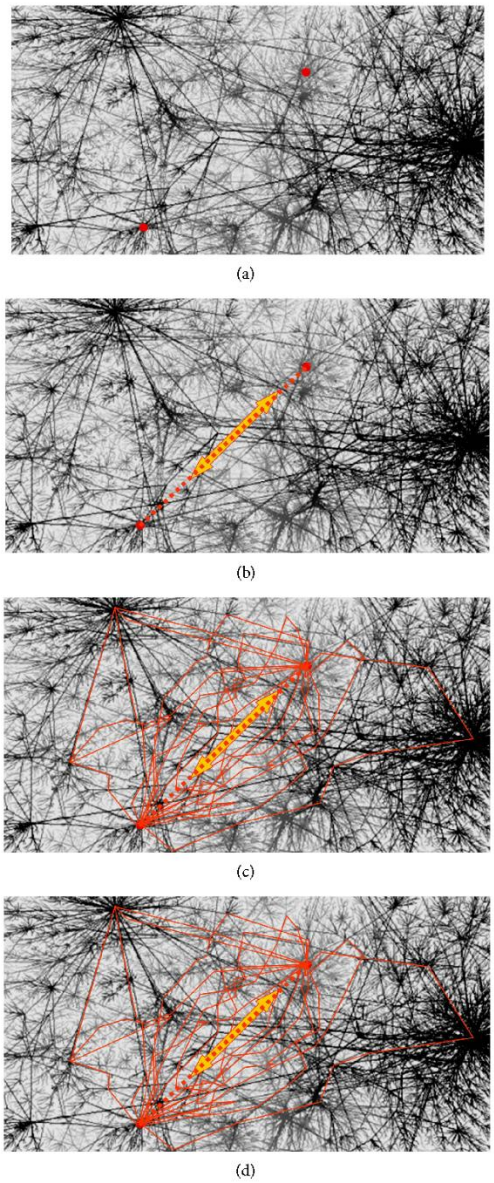
exchanges, the meridian network is probably tightly connected to the mesenchymal tissues in all over the body. However, the meridians as independent structures are not observable even by the most developed autopsy investigations. There are two reasons for this. The first is that the information exchange for homeostasis is valid only in living state. The second reason is more crucial than the first one. According to our hypothesis the meridians are information exchange lines, so they are part of the informational networks. It means that between two points (acupoints) they are not necessarily a hard connection, but the information is exchanged by the multiple connections between the points, Figure 11. The picture is similar to the traffic situation in a town. The two points could virtually be linked by a straight line (bee-line), but this line is not a real direct connection between the points. However, many routes exist, even in case we are forced to detour. The two chosen points are connected without a straight line connection between them.

The ground substance is not only a "meeting volume" of the signals but also a place for the action of interference. The links for these from the body surface are probably the acupuncture points, which connect the internal balance with the environment too. In this line, it is trivial that there is a possibility to step-in to the regulation process of homeostasis.

There are three possibilities of the effects, [34]:

1) The ground substance over-regulates. In this case, the decrease of the regulator-signal is desired;

2) The ground substance under-regulates. Toning is applied to increase the signal;



(a)

(b)

(c)

(d)

Figure 11. The forming of meridians as an information exchange virtual channel. (a) Two acupoints denoted by dots (chosen from the same meridians according to TCM); (b) The expected line of meridian according to TCM; (c) Multiple ways of information exchange connecting the two chosen points; (d) Due to the extremely large number of the possible ways for information exchange, the meridian virtually builds up. Due to the almost homogenous continue of the info-channels, the picture is very similar to the dipole forming an electric field between two opposite electric charges.

3) The deviation of the signal is too large. The error-noise is not $1/f$ pink noise. In this case, the homeostatic balance must be reconstructed by multiple acupuncture points.

5. Conclusion

We used the complexity of biosystems to study the acupuncture and meridian transports. We showed that physiology is well controlled by a complete interacting network or various negative feedback signals and processes, described by opposite interfering effects which are characterized in Traditional Chinese Medicine (TCM) by Yin-Yang (Y-Y) pairs. These regulatory pairs have a meaning in modern biology through the regulatory signals, transports, and interactions, and have a decisional role in the homeostasis of the complex system. The mean of fluctuations is used as a basis carrying a time-fractal fluctuation (called pink-noise or $1/f$ noise) of it. All signals in homeostasis have equal MSE entropy ($S_E = 1.8$). The various controlling opposite signals (Y-Y) have different time-scales and compose the pink-noise. The processes with smaller time-scale degrade by aging but pink-noise ensure that the deviations of the signals of the healthy homeostatic system remain constant by aging. The meridians are connected to the general material and information transport systems of the body completed as a meridian network by various coupling points. The coupling points which are near the skin-surface are called acupunctural points. These could be perturbed by actuating stimulus. We described the meridian system designated by the surface acupoints explaining why no structural appearance could be shown on these channels.

Acknowledgements

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia

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Research Article

Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia -

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ABSTRACT

Aim: to evaluate the efficacy and tolerability of electro-hyperthermia (ET) for the treatment of relapsed malignant glioma.

Methods: this was a retrospective observational clinical study. Patients were included in the study if they had >18 years, informed consent signed, histological diagnosis of malignant glioma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with ET.

Hyperthermia was performed with short radiofrequency waves of 13.56 MHz using a capacitive coupling technique keeping the skin surface at 26 C°. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumors was above 40 C° for more than 90% of the treatment duration (20-60 minutes gradually).

Results: 24 consecutive patients were enrolled in the study, 19 (79%) had glioblastoma multiforme (GBM) 13 were of grade 1-3 and 6 of grade 4, 5 (21%) astrocitoma.

Tumor response analysis two months after ET showed 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 astrocitoma, and 3 glioblastomas), with a response rate of 29%. The median duration of response was 16 months (range 6-120).

The median survival of whole study population was 19.5 months (range 2-156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in atrocitomas.

Conclusions: ET appears to have promising efficacy in adults with relapsed malignant glioma.

Keywords: Relapsed Malignant Glioma; Electro-Hyperthermia; Survival; Tumor Response

INTRODUCTION

The use of Hyperthermia has been known for long time, since it was found out that heat had the ability to kill cells. In the last decade, hyperthermia has been increasingly used as treatment choice for several types of cancer, because tumor cells are more sensible to heat than normal cells [1]. Several methods of hypertermia for cancer treatment are currently available, such as Magnetic Nanoparticles (mNPs) inducing intracellular hyperthermia, external Radio-Frequency (RF), hyperthermic perfusion; frequency enhancers associated to magnetic field; catheter mediated hypertermia [2-4].

Hyperthermia can be used alone or in association with chemotherapy or radiotherapy in order to improve and prolong their benefit [5-7]. The synergic effect of traditional hyperthermia (41–43°C) with chemo and radio-therapy is due to apoptosis induction, angiogenesis inhibition, chemo- and radio-sensitivity activation and high drug concentration induction inside the lesion. The heat, moreover, can induce the externalization of new antigens, thus increasing the tumor sensitivity to immunotherapy [8,9].

Gliomas represent the majority (80%) of malignant brain cancers [10]. According to the glioma grading system of the World Health Organization (WHO), the astrocytomas are classified by four grades (I, II, III, and IV); and oligodendrogliomas and oligoastrocytomas, by two grades (II and III). The most aggressive and common glioma is glioblastoma [10]. Glioblastoma Multiforme (grade IV) (GBM) represent 65% of all gliomas [11]. The prognosis is poor, especially for GBM patients, because of infiltration in surrounding brain tissues, and resistance to chemo- and radio-therapy (10). Anaplastic glioma (grade III) includes anaplastic astrocytoma, oligodendroglioma and oligoastrocytoma. It is less frequent and has a better prognosis than GBM [12]. There are only few target therapy or biological drugs available for gliomas [13]. The gold standard treatment consists of surgery followed by RT for high grade gliomas (HGG) [12,13]. When surgey is not indicated radiation and chemotherapy in association with Temozolomide (TMZ) is the most used choice for GBM [12-17].

The effectiveness of chemotherapy is not clear, but most indicated adjuvant therapy is the association of temozolomide to radiation, resulting in longer overall survival [16,17].

However, most of HGG have disease recurrence. Median overall survival of recurrent HGG is 30-33 weeks, for this reason HGG therapy is very challenging. Treatment choices for recurrent HGG are surgical resection, re-irradiation (re-RT), chemotherapy, anti-angiogenic agents, and combination therapies of hypertermia with chemo- or radio-therapy [12,13]. However there is currently no standard treatment option, and surgery is indicated only for a limited group of patients with high performance status, small lesion, and young age [18].

Radiofrequency (RF) and electro-hyperthermia can be applied intra- and extra-cranially and have efficacy of this treatment for brain-tumors [14,19-25]. As shown in randomized, controlled studies [21]. For this reason the United States Food and Drug Administration approved brain-hyperthermia for HGG.

Reports on electro-hyperthermia for MG are few [22-26]. One retrospective study shows only palliative results (22). Hager et al. (23) treated 35 patients with 13.56 MHz capacitive coupled device hyperthermia, reporting good tolerability for HGG with 11% of adverse events. He also reported improvement of survival and quality of life.

In our previous study, we treated with ET 12 patients with relapsed malignant gliomas and reported a response rate of 29% with a median duration of response of 10 months (range 4-32) [14].

The purpose of this study was to extend our previous experiences to better evaluate the activity and toxicity of ET on relapsed malignant glioma patients. This article report our experiences to the recent advancements in ET treatment of patients with gliomas, in recurrent setting.

MATERIALS AND METHODS

Patients selection

Patients were included in this study if had: > 18 years old, informed consent signed, diagnosis of HGG relapsed, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, normal hematological values and vital signs, previous temozolamide-based chemotherapy and radiotherapy. From April 2003 to January

2016, twenty four patients with relapsed HGG were enrolled in the study.

Electro-hyperthermia protocol

All patients received pre-procedural medications with a suspension of glycerol 18% and dexamethasone 12 mg before each ET session.

ET with short RF waves of 13.56 MHz was applied with capacitive coupling technique maintaining 26°C at skin contact. ET was performed with an EHY 2000 device (CE0123, Oncotherm, Traisdorf, Germany). We used a power from 40 up to 150 Watt, resulting in an average equivalent temperature of > 40°C in the tumors, for more than 90% of the treatment duration (from 20 up to 60 minutes).

The targeted area was selectively treated using an electrode system cover, excluding the eye-area from the field. ET was performed in three sessions per week, increasing the power and time each session. First treatment was always at 40 Watt for 20 minutes. Time was gradually raised from 20 to 60 minutes and power from 40 up to 150 Watt in two weeks.

Outcome measures

The tumor responses were evaluated by MR or CT scan every two months. A Complete Remission (CR) was considered the complete disappearance of the tumor. A Partial Remission (PR) was considered the reduction of at least 20% in the two greatest diameters. A Stable Disease (SD) was considered when no tumor reduction or reduction < 20% was observed. Progression was established when tumor size increased.

The ECOG performance status scale was used to evaluate the functional recovery.

Statistical analysis

Descriptive statistical analysis was performed. Continuous date were reported as median and ranges. Proportions were reported as percentages.

RESULTS

Sample characteristics

Twenty four patients were enrolled in the study. Nineteen (79%) patients had glioblastoma multiforme, 5 (21%) astrocytoma [Table 1]. Most patients 22 (92%) were pre-treated with surgery, and all patients were pre-treated with temozolomide associated to radiotherapy. Thirteen (54%) were females and 11 (46%) were males, median age was 60 [22].

Tumor response and survival

Tumor response analysis two months after ET showed 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 astrocitoma, and 3 glioblastomas), with a response rate of 29%. The median duration of response was 6 months (range 6-120). Stable disease was observed in 8 (33%) of patients and progression in 9 (38%) patiens.

Table 1: Chracteristics of the sample.

ID	Sex	Age	Type of glioma	MGMT metilated	IDH1	Response	OS (months)
01	F	41	ASTROCITOMA	YES	YES	PR	60
02	M	26	ASTROCITOMA	NO	YES	RC	60
03	M	22	ASTROCITOMA	YES	YES	RC	156
04	F	56	ASTROCITOMA III	NO	NO	SD	62
05	M	63	ASTROCITOMA/GBM	YES	NO	SD	60
06	M	58	GBM IV	NO	NO	SD	2
07	M	45	GBM IV	NO	NO	SD	14
08	F	67	GBM IV	NO	NO	PD	10
09	M	66	GBM IV	NO	NO	PD	9
10	M	54	GBM	ND	ND	PD	14
11	F	46	GBM	YES	YES	PR	24
12	M	65	GBM	ND	ND	PD	5
13	F	75	GBM	ND	ND	SD	8
14	F	76	GBM	ND	ND	PD	6
15	M	62	GBM IV	NO	NO	PD	14
16	M	74	GBM	NO	NO	SD	15
17	F	81	GBM	ND	ND	PD	8
18	M	53	GBM	ND	ND	SD	36
19	M	66	GBM	ND	ND	PR	25
20	F	66	GBM	ND	NF	SD	15
21	F	33	GBM	ND	ND	PD	32
22	F	49	GBM	ND	ND	PD	32
23	M	52	GBM IV	YES	ND	PR	24
24	F	66	ASTROCITOMA III	ND	ND	PR	63

The median survival of whole study population was 19.5 months (range 2-156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in atrocitomas.

Ten patients had an objective clinical benefit as resulting from an increase of their ECOG from 3 to 1 in 4 (16%) patients and to 0 in 2 (8%) patients.

Tolerability

ET toxicity was mostly mild (G1). We observed one (4%) head pain, one (4%) scalp burn, five (21%) epilepsy that was resolved with a medication including diazepam 10 mg in 100 ml of saline and levetiracetam in tablets without any further attack.

DISCUSSION

The first-line therapy for newly diagnosed HGG are several, including surgery, radiotherapy, chemotherapy with nitrosourea, temozolomide, bevacizumab, and irinotecan, alone or guided in combination and radiation alone or combined to temozolomide [27]. There is currently no standard treatment for relapsed HGG, and several potentially active systemic drugs are not effective because of blood brain barrier blockade [28]. Maintenance therapy and treatments for recurrent HGG widely vary according to physician, hospital and country and include surgery, re-radiation, second/third-line chemotherapies, biodegradable carmustine wafers, gene therapy and hyperthermia [28-32,19-21].

The use of Electric Capacitive Transference hypertermia increases heat of brain tumor and is harmless for surrounding brain tissue that in no case reaches a temperature > 39.2°C [20,21]. Most common side effects of hyperthermia are pain, burns or discomfort, but they are temporary and most of normal tissues are not damaged during the therapy.

Tumor cell are more sensible than normal cells to heat, and hypertermia inhibits the DNA repair system of tumor cells. For this reason classic hyperthermia (42-43°C) is often associated to chemotherapy or radiotherapy. This association is safe and well tolerated and increases the efficacy on overall survival and progression free survival [16,18].

We previously reported the results of ET treatment of 12 recurrent HGG patients [14]. We showed 1 CR and 2 PR with a response rate of 25% and a median duration of response of 10 months [14], without severe toxicity. The patient with CR is still alive with a progression free survival of 156 months.

In this paper we report our experiences in ET treatment of a larger number of 24 recurrent HGG patients. Tumor response analysis showed a similar response to that of our past paper with a response rate of 29 % two months after ET 2 (8%) complete remission (astrocytomas) and 5 (21%) partial remission (2 astrocitoma, and 3 glioblastomas). The median duration of response was longer 16 months (range 6-120) than our previous study 10 months [13]. Tumor response was coupled to an improvement of performance status in 6 (24%) patients. Moran and colleagues reported a higher response rate 66%, however they observed only SD or PR and none CR [20]. Tanaka et al. Had higher responses when treated 16 patients with brain cancers adopting hyperthermia with 13.56- MHz RF capacitive heating machine and showed a 50% of PR [19]. However the combination of hyperthermia with other methods did not allow to draw any conclusion about the efficacy of hyperthermia alone.

The median OS of whole study population was 19.5 months, 55% survival rate at 1 year, and 15 % at two years. Of particular interest we underline the presence of 3 long survivors at 156, 60, 62 months. OS was higher than that of magnetic hypertermia that resulted in survival ranging from 2.1 to 7.9 months [33].

OS was comparable to that reported by Sneed et al. 31% at the 2 years follow up [22].

Limitation of our study are the absence of an active comparator, non-randomization, and low number of patients. Further multicenter randomized studies with a larger number of patients are required to confirm our data.

CONCLUSIONS

ET hyperthermia therapy for recurrent HGG is feasible and may increase tumor response and survival. ET is a non-invasive method to treat HGG without severe toxicity.

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Radiosensitization effect of novel cancer therapy, mEHT ~Toward overcoming treatment resistance~

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Oncothermia Journal
25: 68-84
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Radiosensitization effect of novel cancer therapy, oncothermia ~Toward overcoming treatment resistance~

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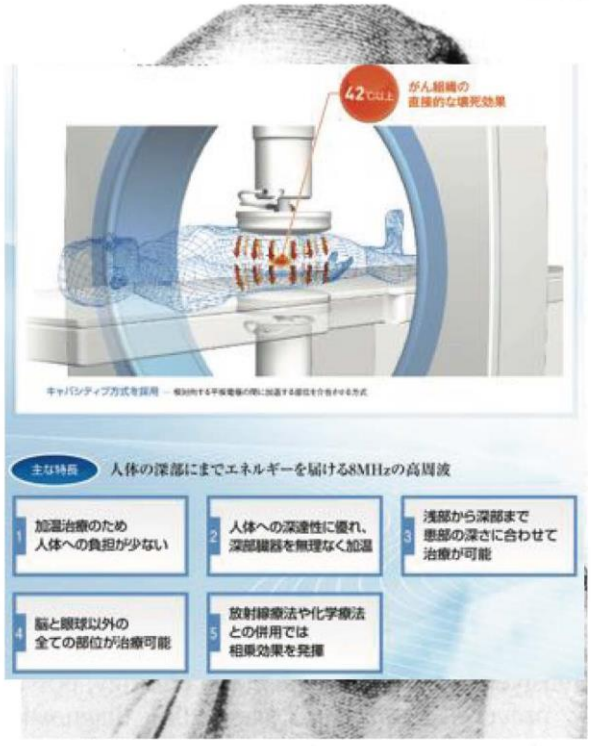
The history of hyperthermia in the cancer therapy



Hippocrates (BC 460-370)

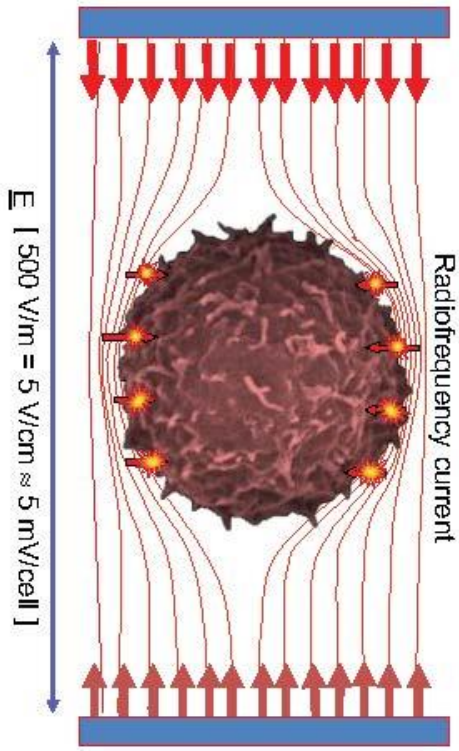
"Those who cannot be cured by medicine can be cured by surgery.
Those who cannot be cured by surgery can be cured by fire (hyperthermia).
Those who cannot be cured by fire, they are indeed incurable"

薬で治らなければ切り取ってしまえ。
それでもダメなら**火を使え。**
それでも治らないものは、決して治るものではない。（焼灼療法）

Heating by RF wave)
(Hyperthermia)

Medical treatment!

What is oncothermia?

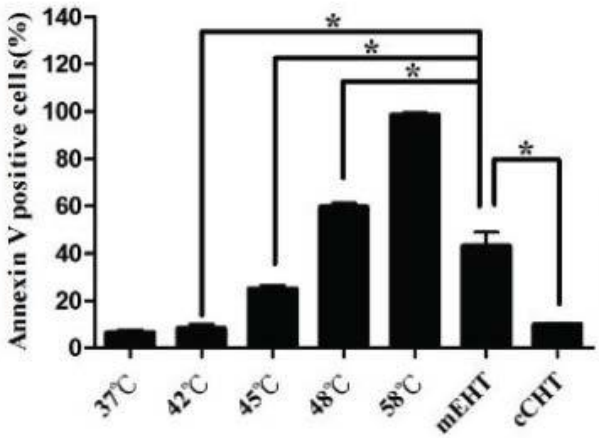


【Concepts and Features】

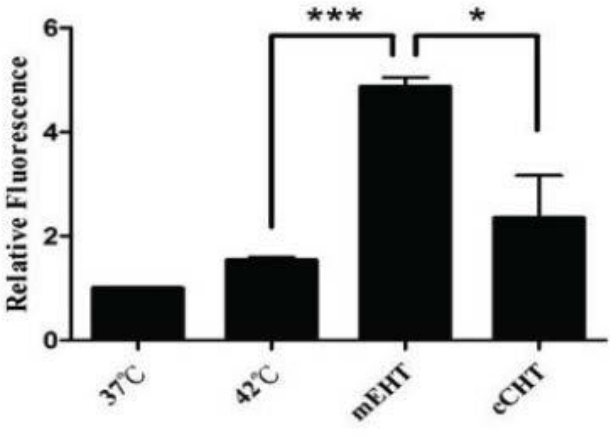
- **Attention to impedance matching**
  - ⇨ **Modulated 13.56 MHz** electromagnetic waves
  - ⇨ **Make thermal spot on the membrane of cancer cells (ununiform structure)**
- **Temperature independent factor (electromagnetic wave) is important**
- Therapeutic effects independent with high power
- **Max 150W** ⇨ Easy to control of patients
  - ⇨ Weak side effect
- Shield room is not necessary
  - ⇨ Easy to set up of machine
- **Potential of combination therapy**
  - ⇨ Immune activation affect

Biological effects by oncothermia

Induction of apoptosis



Production of ROS



Yang et al., Oncotarget 2016

Today's contents

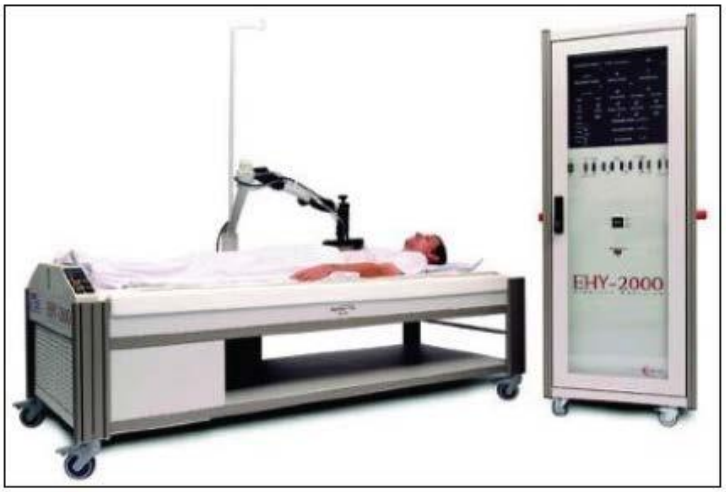
Biological effects by **combination of oncothermia and radiation**

① **Cell killing effect** and **antitumor effect** (*in vitro* & *in vivo*)

② Effect on **radioresistant cells**

⇨ **Cyclic (Intermittent) hypoxic experience cells**

Oncothermia
EHY-2000



Oncotherm HP

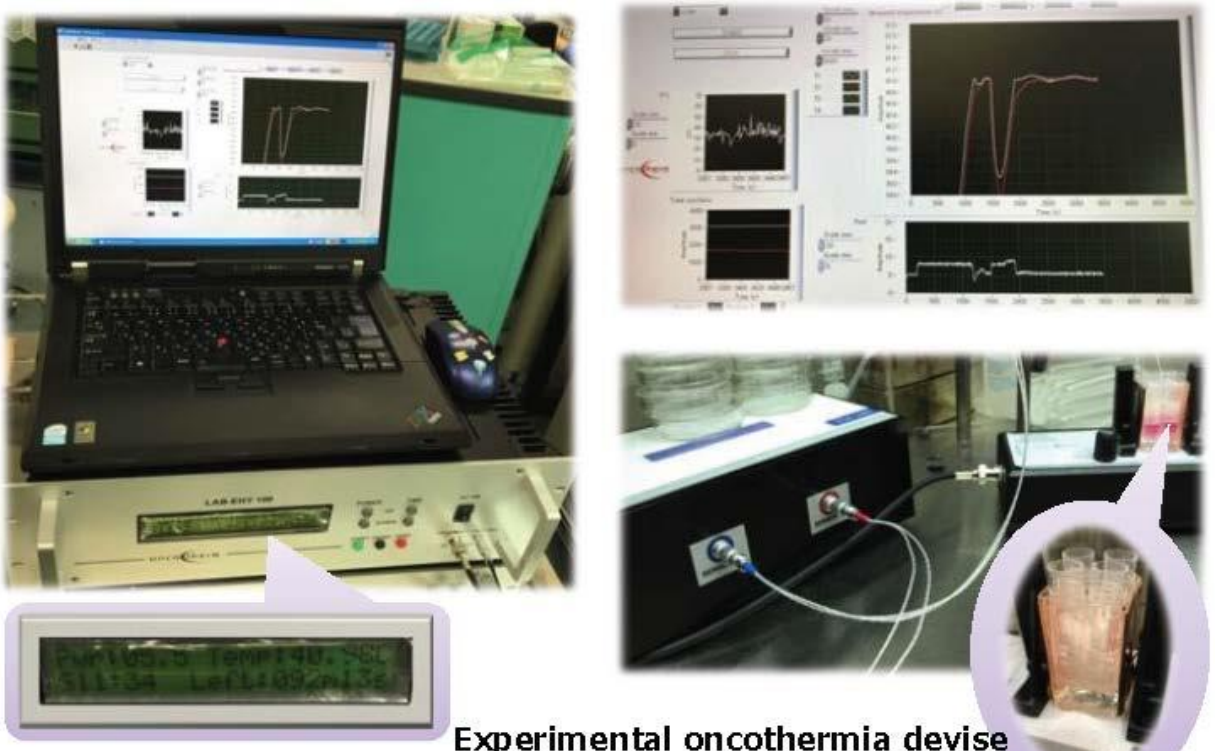
Purpose of this research

- **Comparison of the cell killing effect by Oncothermia (OT) with Water bass (WB)**
  - Time dependency
  - Temperature dependency
- **Radiosensitizing effect**
  - Cell killing effect
  - Cell death morphology
    - Apoptosis? Autophagy?
  - Cell cycle change
  - Antitumor effect (*in vivo*)

Materials and Methods *in vitro*

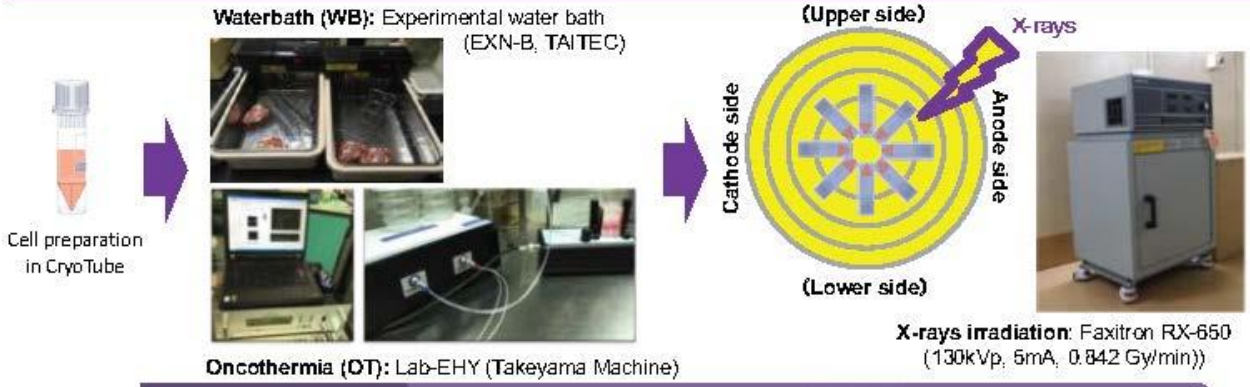
- **Cells** (frequently used in radiation research)
  - SCCVII: Chinese hamster skin squamous cell carcinoma cells
  - SAS: human oral squamous cell carcinoma cells
- **Culture condition**
  - Medium: E-MEM + 10% FBS + antibiotics
  - Incubator: 37℃, 5% CO_2
- **Treatment**
  - Water bath (WB): Experimental water bath
  - Oncothermia (OT): Lab-EHY 100 (Tateyama machine Corp.)
  - X-ray irradiation: Experimental X-ray generator (130 kV, 5mA)
- **Methods**
  - Cell death: Colony formation assay
  - Cell death morphology: Flow-cytometry technique
  - Cell cycle change: Flow-cytometry technique

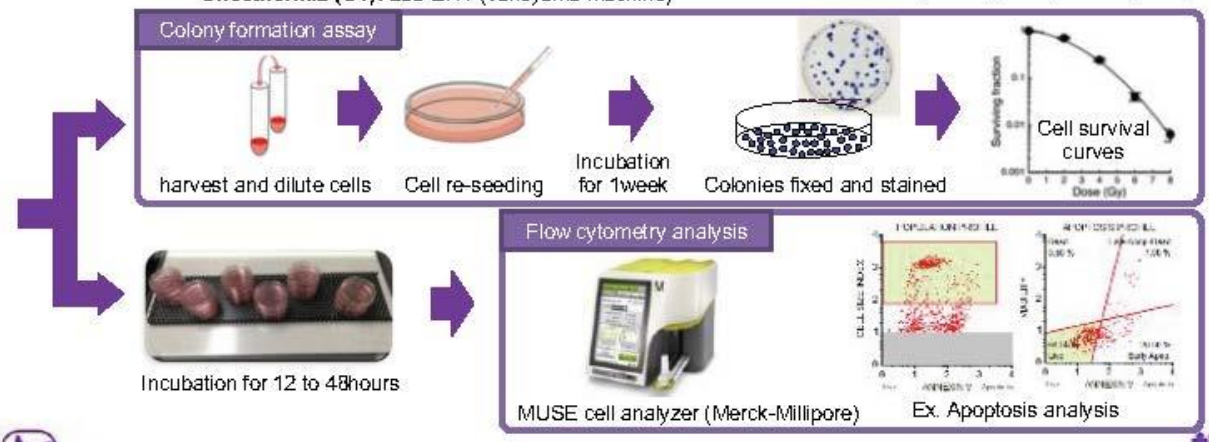
Oncothermia treatment (*in vitro*)



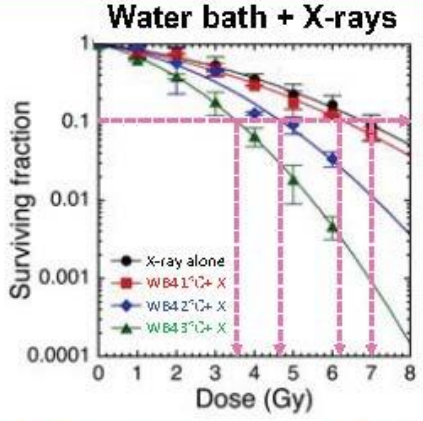
Experimental oncothermia devise
LAB-EHY 100

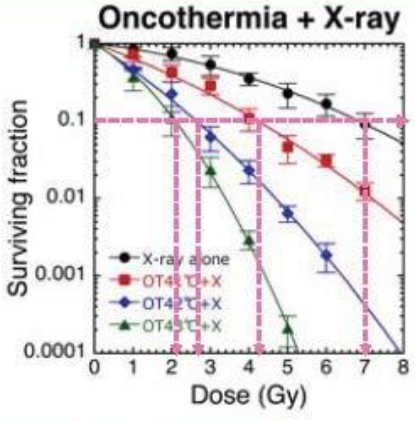
Experimental procedure (*in vitro*)





Result 2: Radiosensitizing effect of each thermal therapy





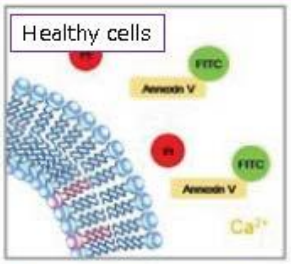
Treatment	D_{10} (Gy)*	TER**
X-ray	6.86	1.00
WB41℃+X-ray	6.35	1.08
WB42℃+X-ray	4.73	1.45
WB43℃+X-ray	3.58	1.91
OT41℃+X-ray	4.23	1.62
OT42℃+X-ray	2.64	2.59
OT43℃+X-ray	2.09	3.27

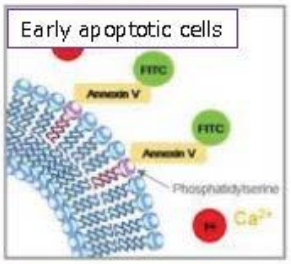
1.5倍
1.8倍
1.7倍

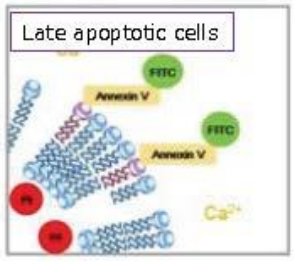
#*P*<0.01 (Student *t*-test)

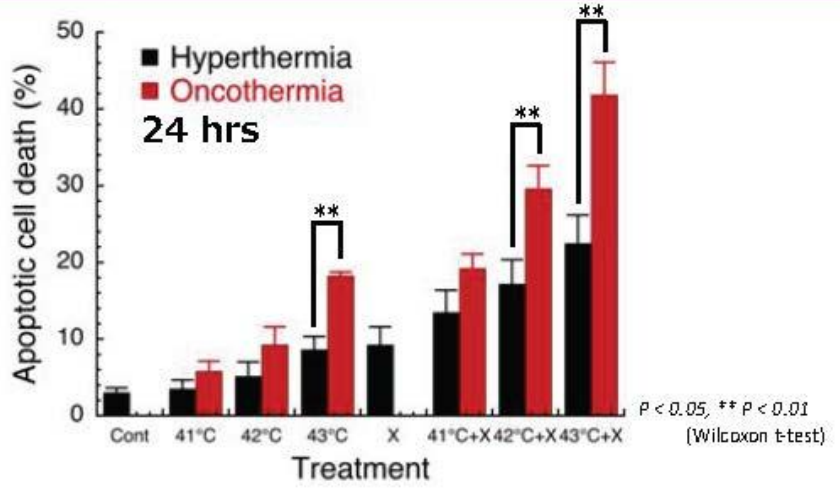
*D_{10}: biological equivalent dose introduce the 10% survival
**TER: Thermal Enhancement Ratio calculated with D_{10}(X-ray) / D_{10}(objective)

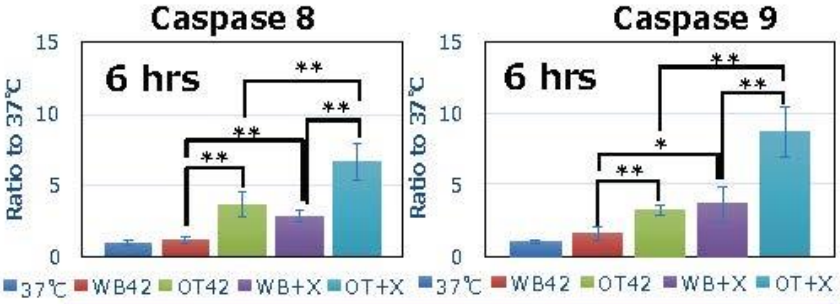
Result 3-1: Apoptosis frequency









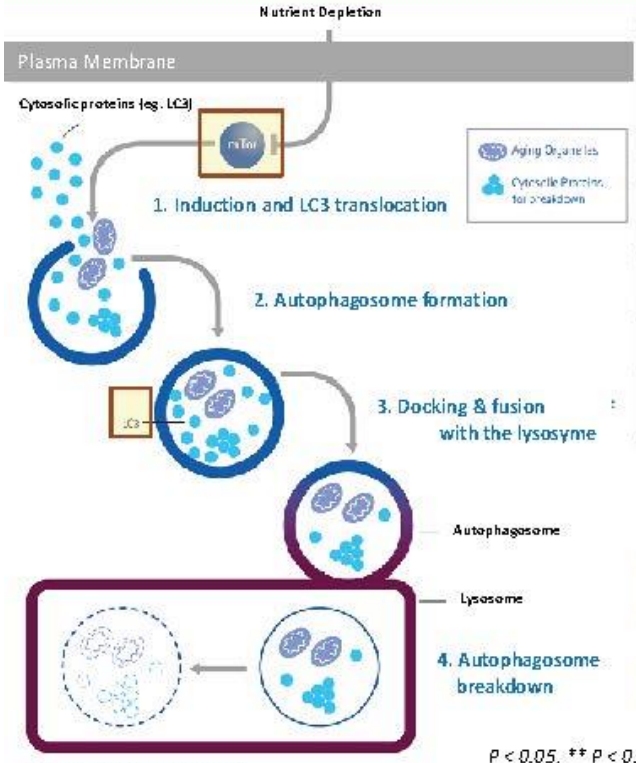


PMRC 2018/8/31

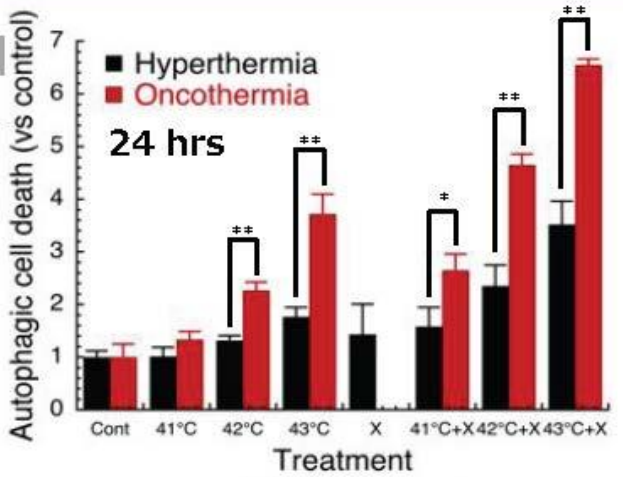
WB: Water bath 42℃, OT: Oncothermia 42℃, X-ray: 5 Gy

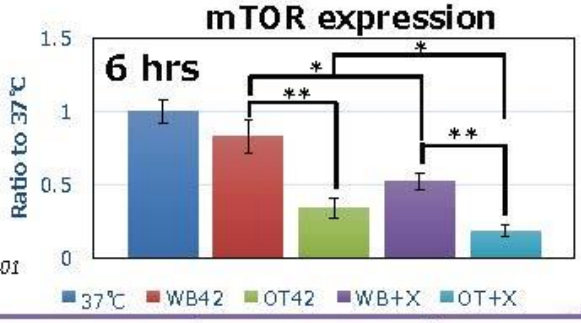
12

Result 3-2: Autophagy frequency



Merck-Millipore HPより





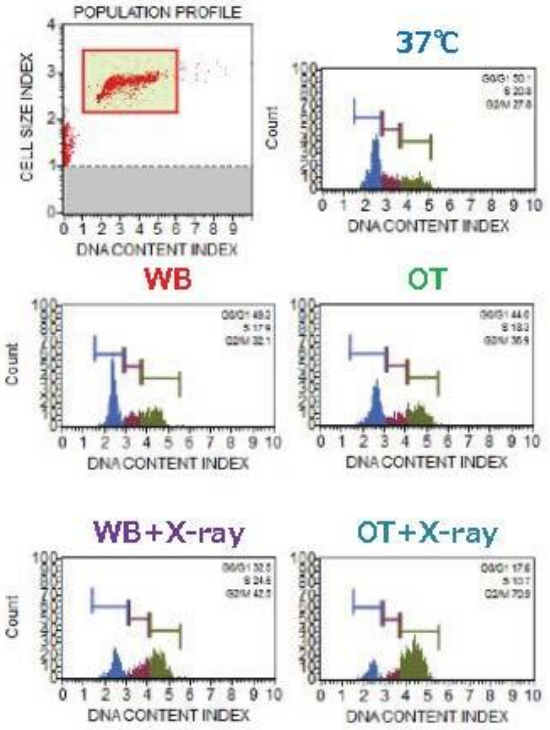
P < 0.05, ** P < 0.01
(Wilcoxon t-test)

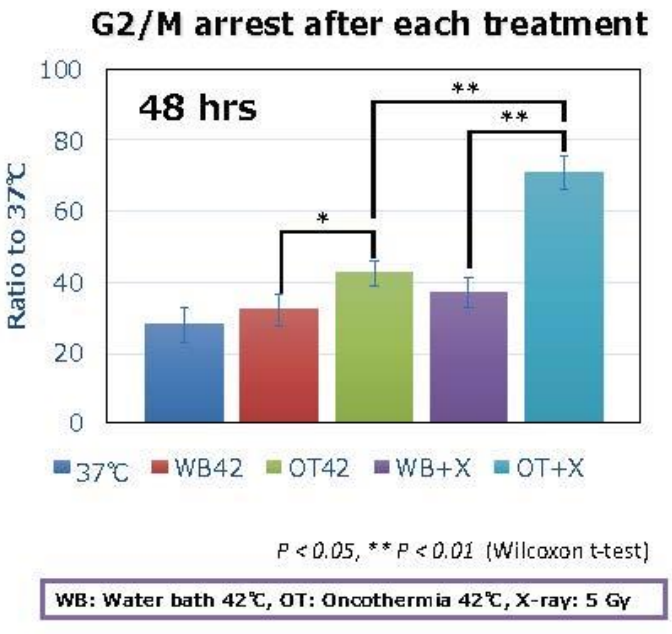
PMRC 2018/8/31

WB: Water bath 42℃, OT: Oncothermia 42℃, X-ray: 5 Gy

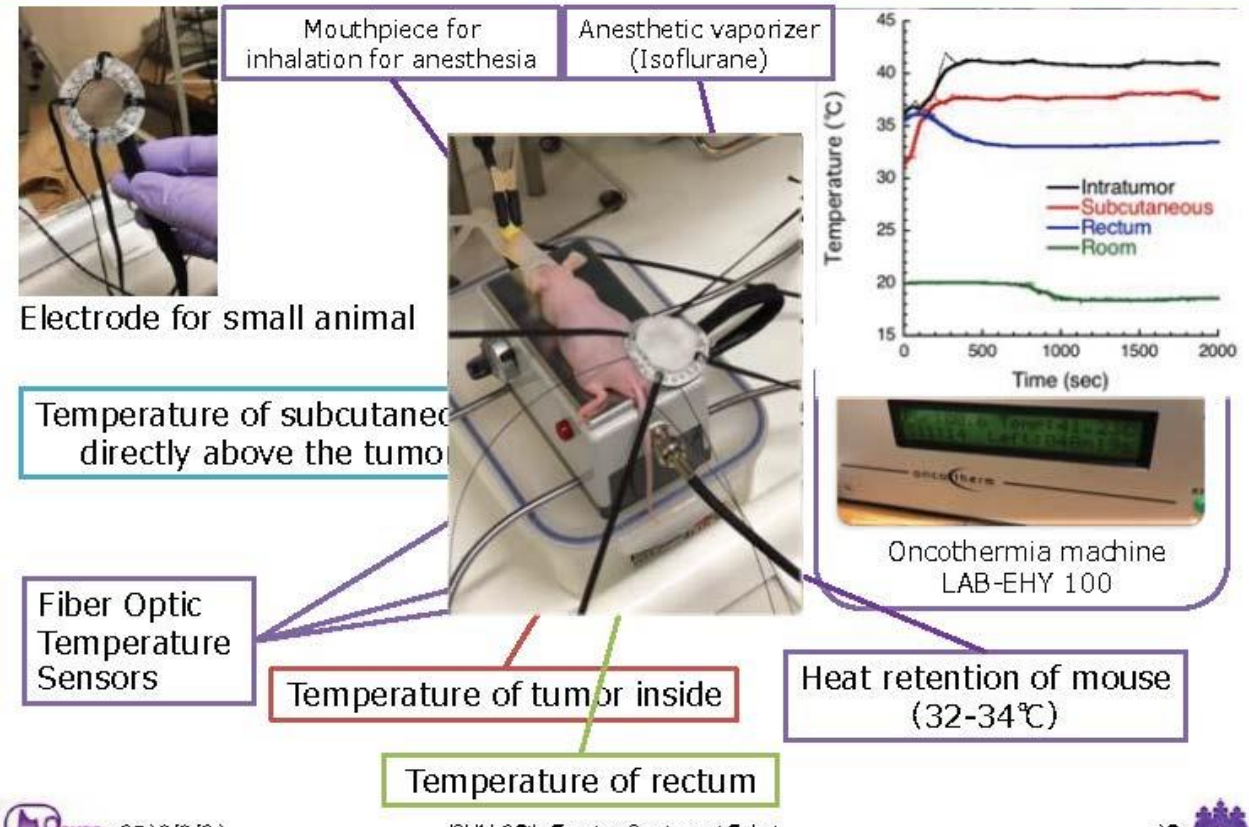
13

Result 4: Cell cycle change

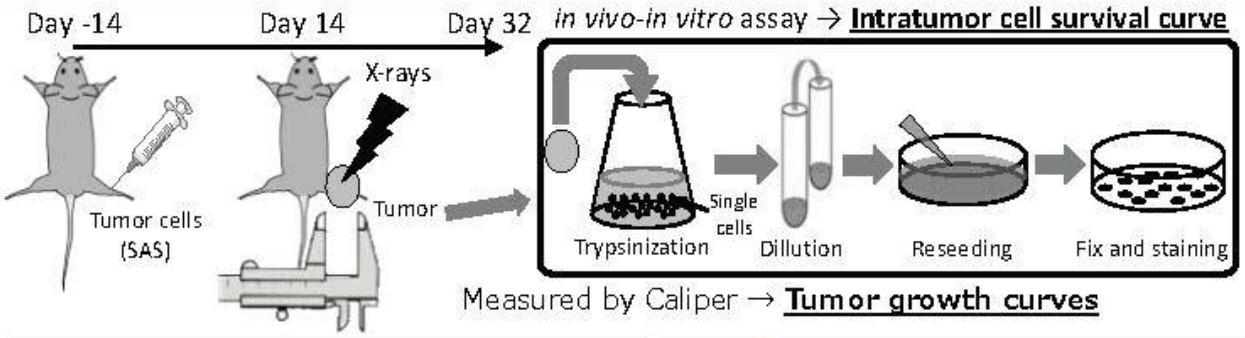


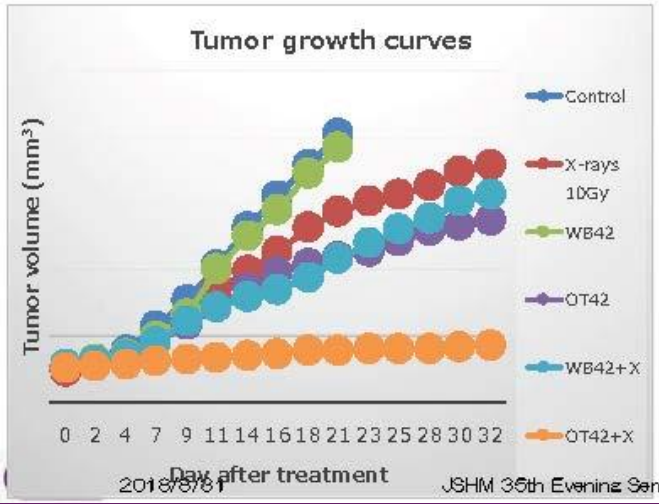


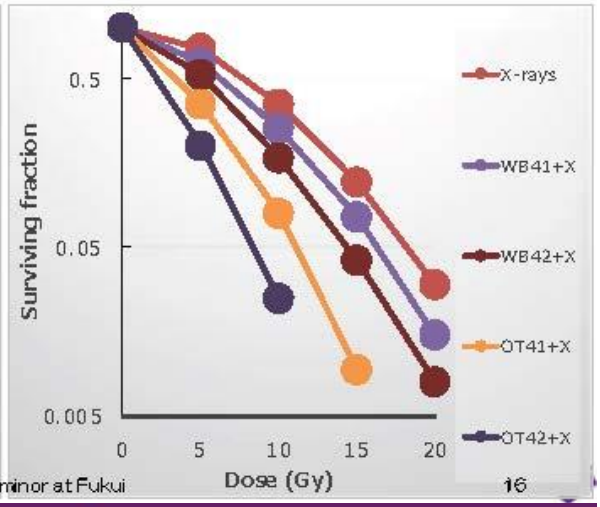
Oncothermia treatment (*in vivo*)



Result 5: Tumor growth and cell death *in vivo*







2018/8/31 JSHM 35th Evening Seminor at Fukui 16

Summary 1

<Thermal therapy alone>

- Oncothermia induced cell death depending on the heating time and temperature.
- Oncothermia showed significant cytotoxic effects (at all temperature used in this study).

<Thermal therapy + radiation>

- Oncothermia showed remarkable radiosensitization effects.

<Cell death morphology, cell cycle>

- Apoptosis, autophagy frequency and G2/M arrest was significantly increased by OT and OT+X-rays.

<Antitumor effect>

- Tumor growth was suppressed and intratumor cell death was increased significantly by the OT and/or OT+X-ray

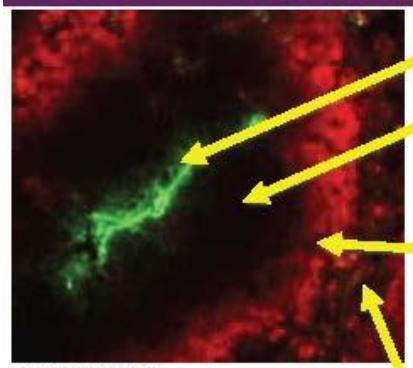
Today's contents

- Biological effects by **combination of oncothermia and radiation**
  - ① Cell killing effect and antitumor effect (*in vitro* & *in vivo*)
  - ② Effect on **radioresistant cells**
    - ⇨ **Cyclic (Intermittent) hypoxic experience cells**

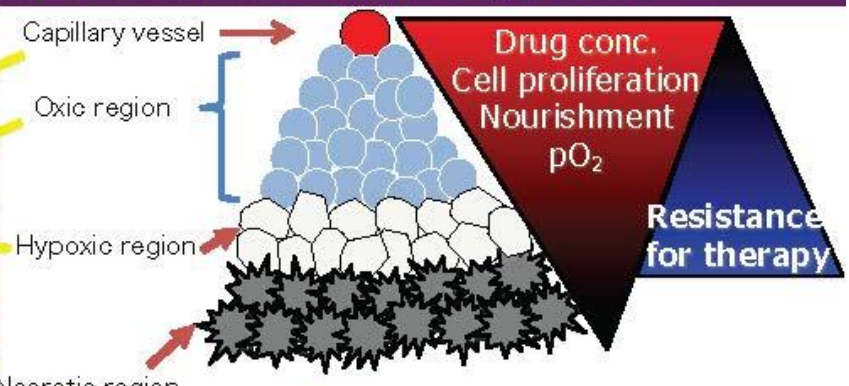
Oncothermia
EHY-2000

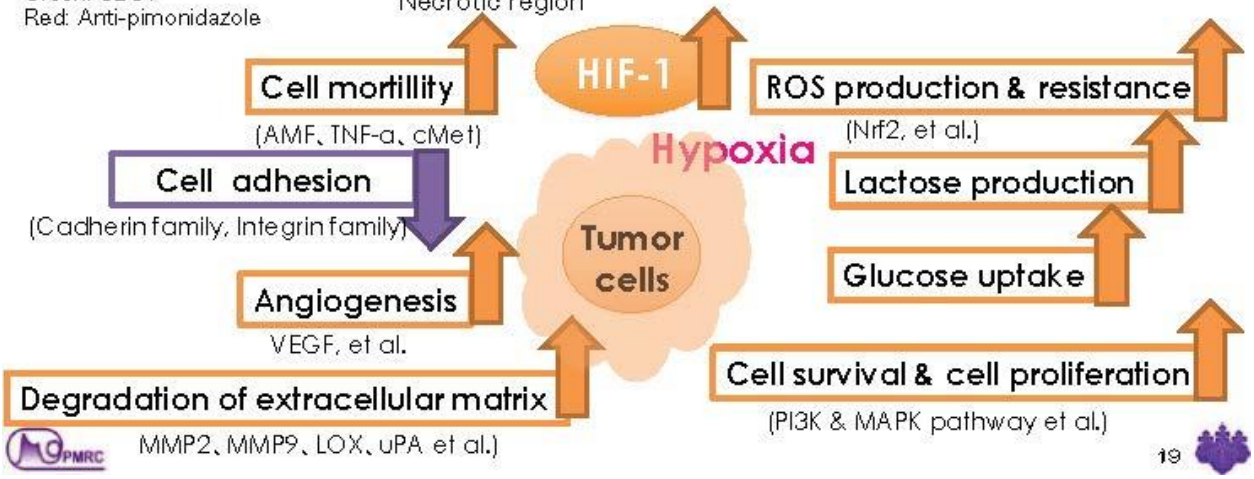
Oncotherm HP

Microenvironment in tumor: Hypoxia



Green: CD31
Red: Anti-pimonidazole



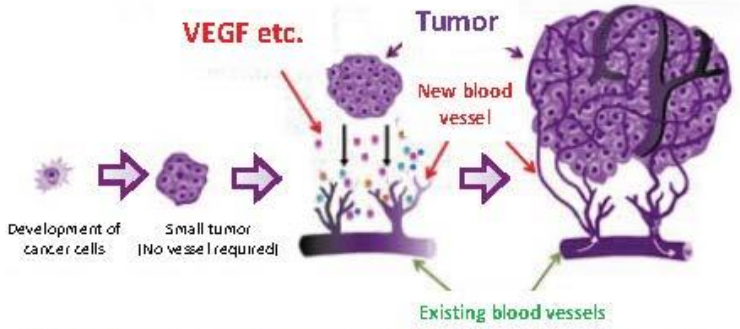


Intratumor vessel and hypoxia

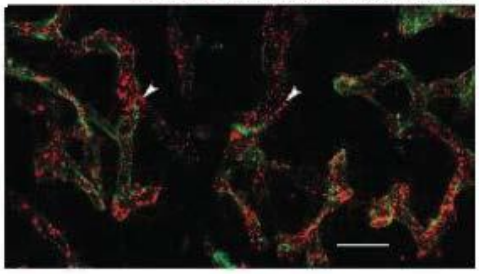
Tumors release angiogenic factors for proliferation and promote angiogenesis

Growth factors that promote angiogenesis are secreted from tumors

Tumor vessels ⇨ promote tumor growth and metastasis



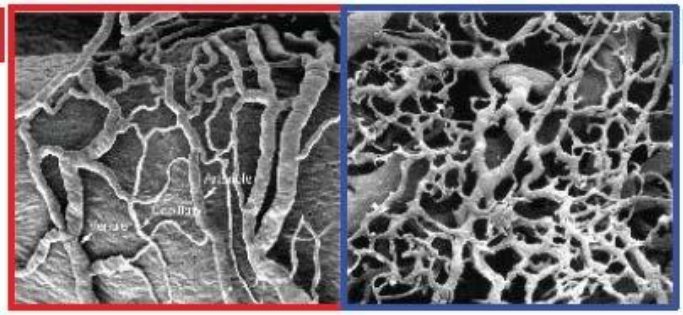
Tumor vessels (Red)
Vascular endothelial cells(Green)



D. McDonald et al., NatMed 2013

SEM images of normal and tumor vessels

Normal



Tumor

Vulnerable structure

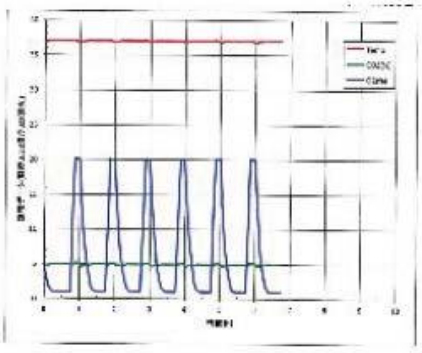
Repeated destruction and rebirth

Cyclic hypoxia

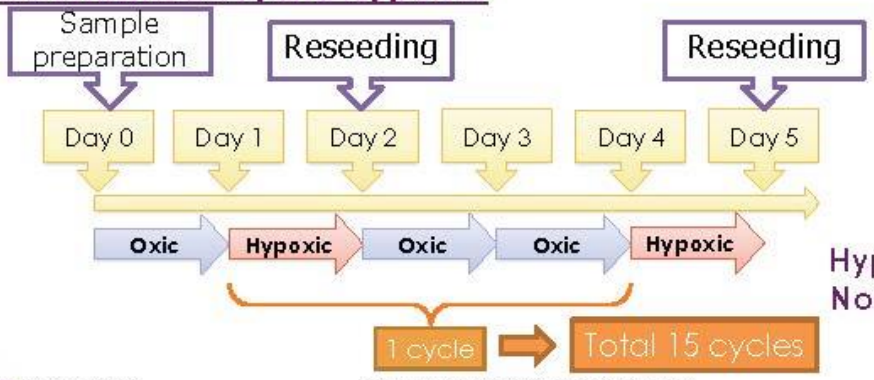
D. McDonald et al., NatMed 2013

Cyclic hypoxia treatment experiment

Cyclic hypoxia treatment

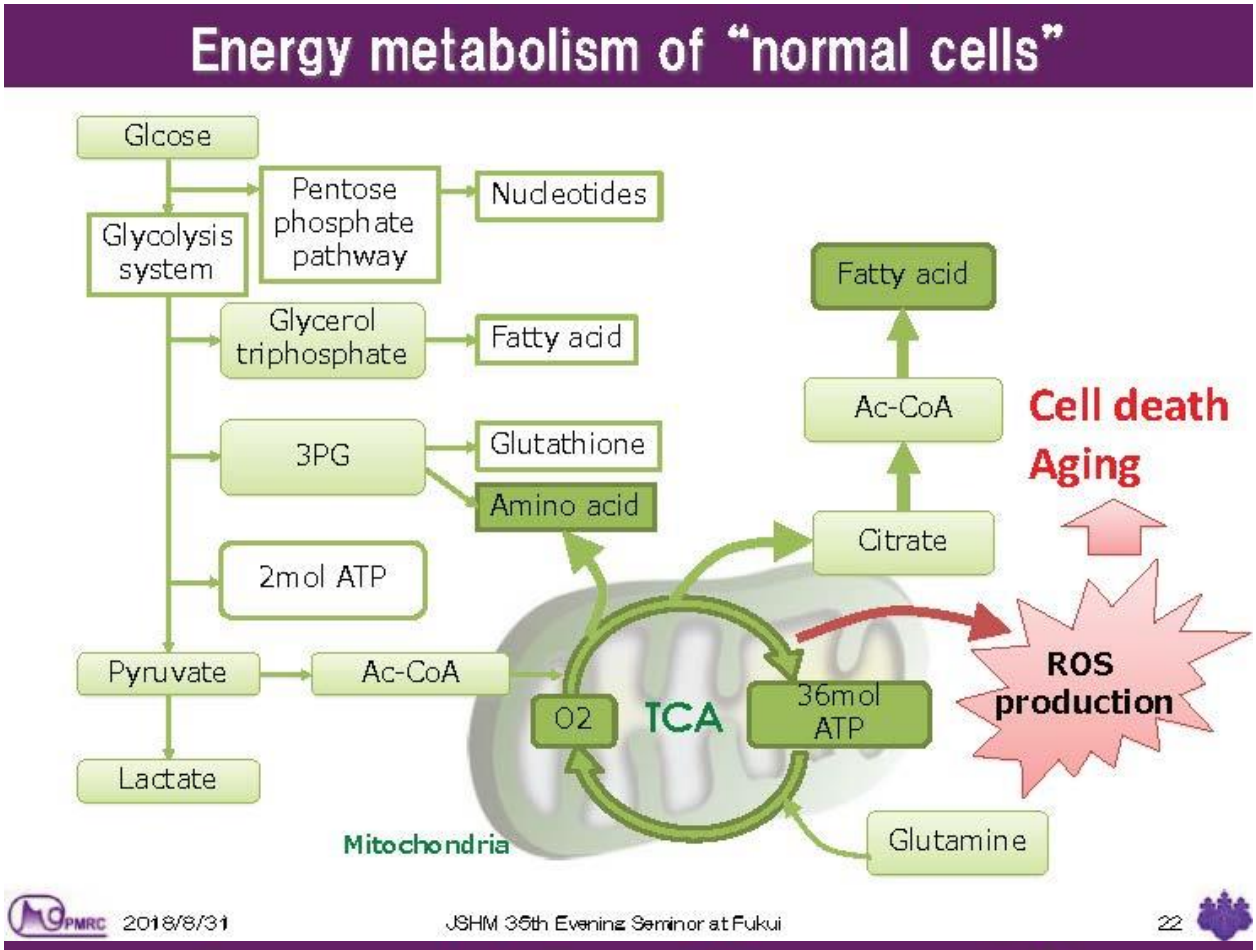


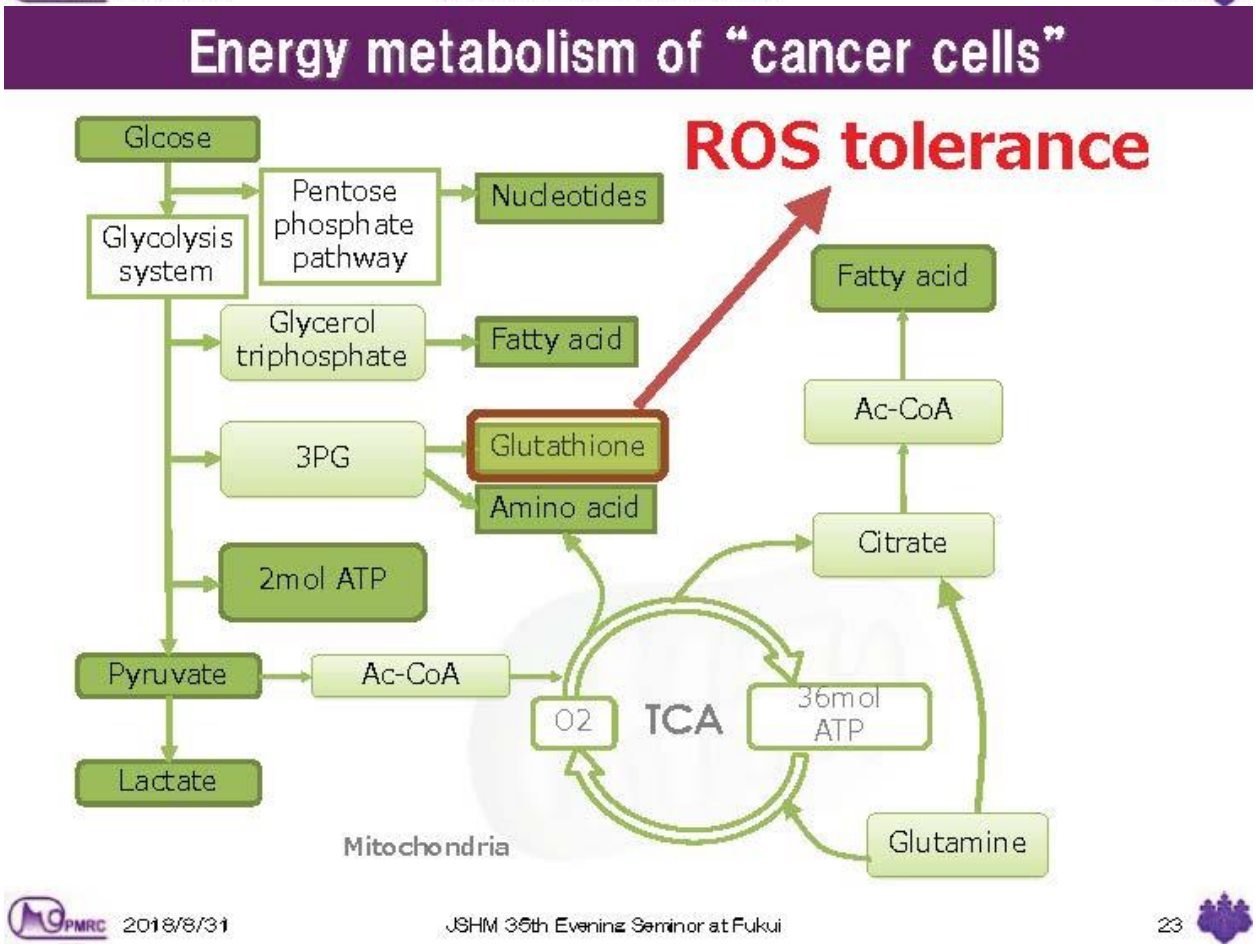
Exp. Scheme of cyclic hypoxia



Hypoxia : 0.1% O_2

Normoxia : 20.9% O_2


Energy metabolism of "normal cells"
Glcose
Pentose phosphate pathway
Nucleotides
Glycolysis system
Glycerol triphosphate
Fatty acid
3PG
Glutathione
Amino acid
2mol ATP
Pyruvate
Ac-CoA
Lactate
Fatty acid
Ac-CoA
Cell death
Aging
Citrate
ROS production
O2
TCA
36mol ATP
Glutamine
Mitochondria
2018/8/31
JSHM 35th Evening Seminor at Fukui
22


Energy metabolism of "cancer cells"
ROS tolerance
Glcose
Pentose phosphate pathway
Nucleotides
Glycolysis system
Glycerol triphosphate
Fatty acid
3PG
Glutathione
Amino acid
2mol ATP
Pyruvate
Ac-CoA
Lactate
Fatty acid
Ac-CoA
Citrate
O2
TCA
36mol ATP
Glutamine
Mitochondria
2018/8/31
JSHM 35th Evening Seminor at Fukui
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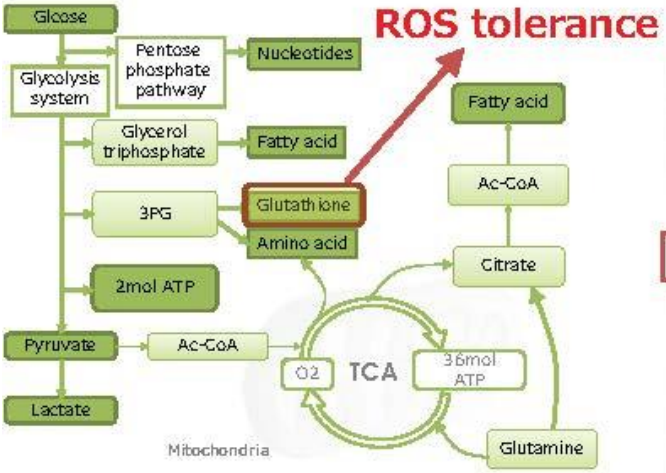
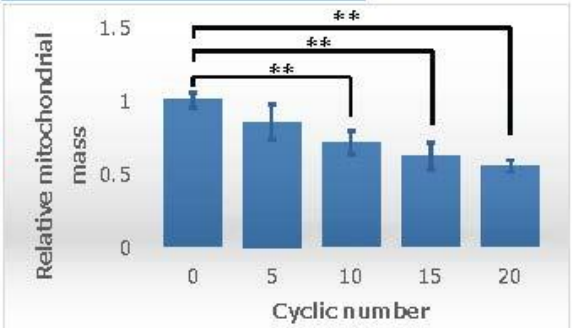
Acquisition of anaerobic glycolysis phenotype

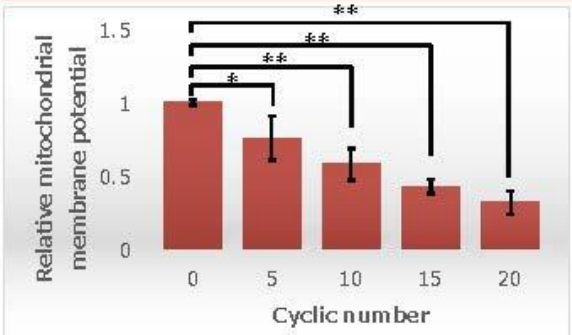
Dependency for mitochondria (TCA cycle)



Ⅰ. Mitochondrial mass

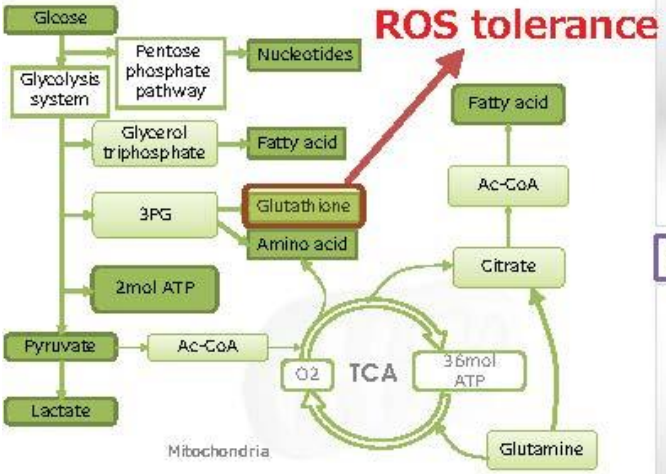


Ⅱ. Mitochondrial membrane potential

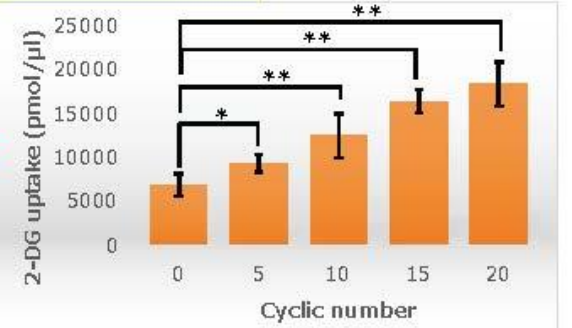


Acquisition of anaerobic glycolysis phenotype

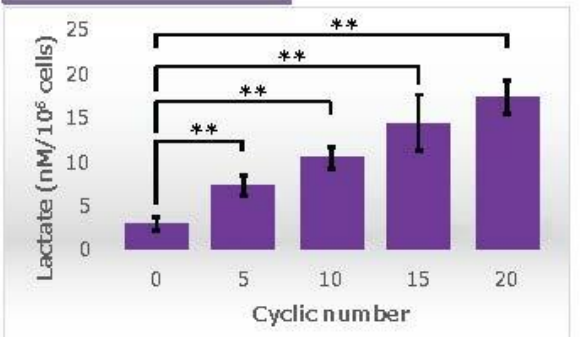
Dependency for anaerobic glycolysis system



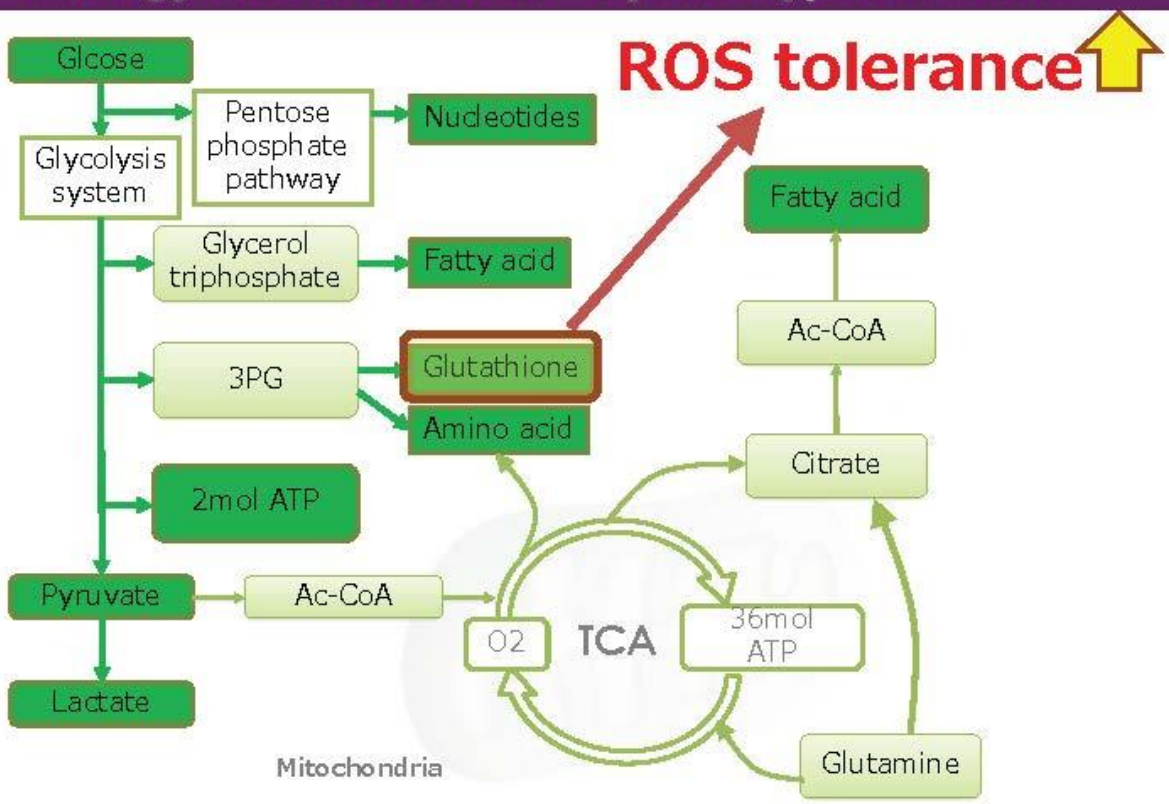
Ⅲ. Glucose uptake



Ⅳ. Lactate emission

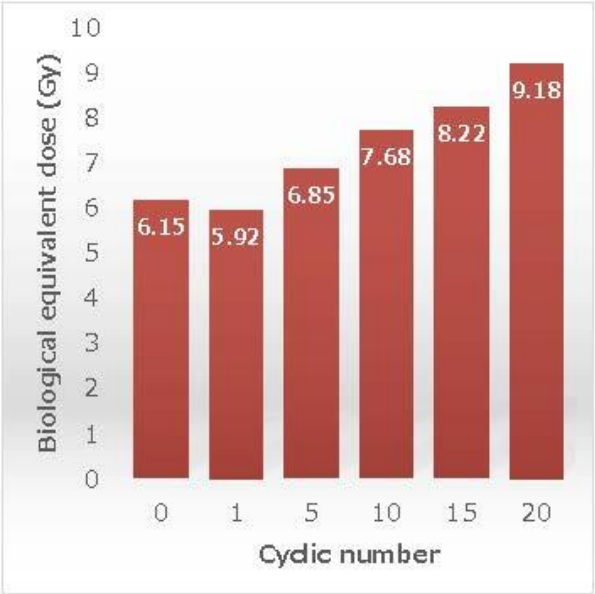


Energy metabolism of "cyclic hypoxia cells"

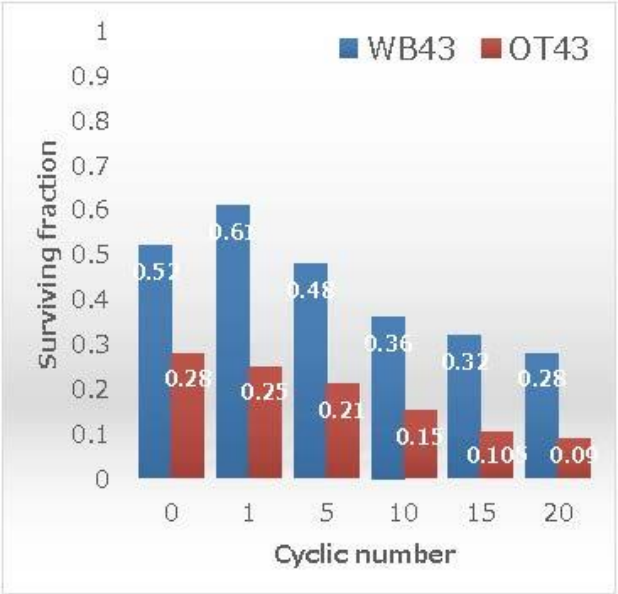


Resistance of cyclic hypoxia cells to radiation and heat

Radio-resistance



Thermal resistance



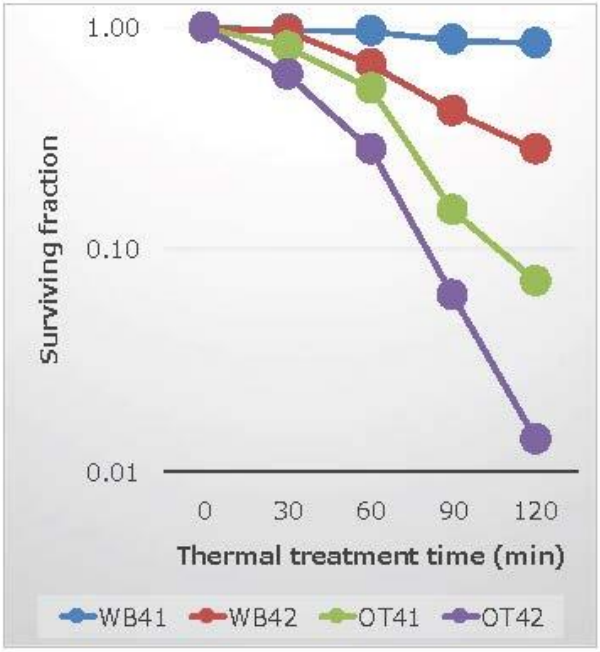
Cells: SAS (Human squamous cell carcinoma cell line)
X-ray: 130 kVp, 5 mA

Thermal therapy: 43℃-60min by WB & OT

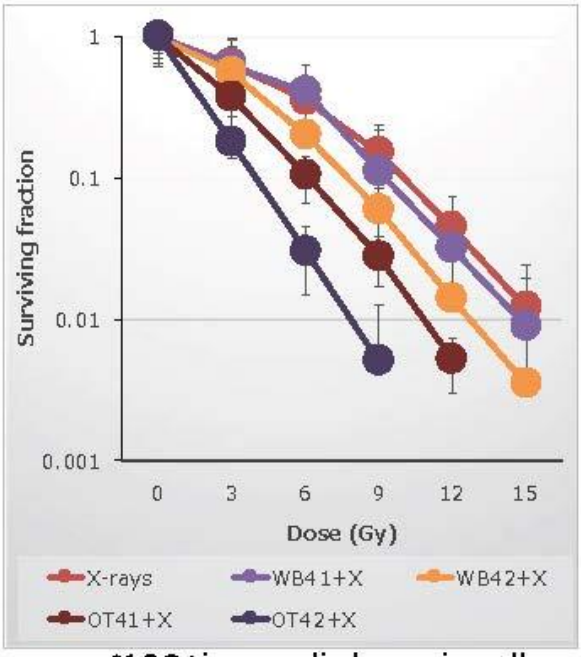
Thermal therapy is useful to radioresistant tumor cells!?

Cytotoxic effect of OT to cyclic hypoxia cells

Survival curves of cyclic hypoxia cells*1 after thermal therapy alone



Survival curves of cyclic hypoxia cells*1 after thermal and X-rays



*1 **20** time cyclic hypoxia cells
WB and **OT** treated for **60** min

Summary 2

<Cyclic hypoxia condition>

- Cyclic hypoxia enhanced the dependency to anaerobic glycolytic pathway.
- Decrease of mitochondrial mass and membrane potential.
- Increase of glucose uptake and lactose production.
- Increase of resistance to radiation but not thermal therapy.

<Biological effect of thermal to cyclic hypoxia cells>

- OT showed remarkable cytotoxic effect.
- OT showed remarkable radiosensitization effect compared with WB.

Conclusion and Future plans

- The cyototoxic effect, antitumor effect of a novel thermal therapy, **oncothermia (OT) was stronger** than water bath (WB) hyperthermia therapy.
- **OT may be effective** for cells that acquired treatment resistance by cyclic (intermittent) hypoxic environment involving recurrence etc..
- Elucidation of the **mechanism** of antitumor effect and analysis of **normal tissue response** is the most important issue in clinic. We must examine the oncothermal effect to normal tissue using in vivo model.
- It is necessary to **compare** the difference between OT and **conventional RF-hayperthermia** (ex. RF-8).

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  - Dr. Andocs Gabor
  - Mr. Kazuhiro MATSUI


Thank you for your attention!!
PMRC

Modulated electro-hyperthermia (mEHT) (oncothermia®) protocols as complementary treatment

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Oncothermia Journal 25: 85-115
www.oncothermia-journal.com/journal/2019/Modulated_electro_hyperthermia_protocol.pdf

Modulated electro-hyperthermia (mEHT) [oncothermia®] protocols as complementary treatment

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Abstract

The article deals with the protocols of modulated electro-hyperthermia (mEHT, tradename: oncothermia®), which changes the isothermal heating with a heterogenic one. The method is a typical theragnostic targeted therapy, focusing on the transmembrane protein clusters (rafts) on the malignant cells. It is a complementary therapy, applied in cases, when the conventional therapies have failed or simply not applicable alone. It could resensitize the previously applied chemo- or radiotherapies, or could be applied together with new therapies, including the drugs for palliative protocols and best supportive care. Its monotherapy application is also possible when no other solution can be counted. The mEHT treatment improves the quality of life, reduces the side effects of other therapies, and in vast cases, turns the palliative protocol to curative results.

Keywords

Modulated electro-hyperthermia, mEHT, protocol, complementary treatment, palliation, supportive care, curative intent, chemotherapies, radiotherapies, immune-effects, abscopal effect

Introduction

The method of modulated electro-hyperthermia (mEHT, tradename: oncothermia®), is an effective [1], [2], and broadly used [3], complementary therapy [4]. The mEHT differs from other hyperthermia methods [5]; its mechanism is based on a selective energy-absorption in the malignant cells [6] in a targeted way. Heterogeneity is based on the biophysical differences of the malignant cells and their healthy counterparts; and uses the bioelectromagnetic differences of the cancer cells in the

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microenvironment. The cellular selectivity of the malignant cells realizes a targeting of clusters of transmembrane proteins (rafts) on their membrane. This targeted therapy can produce a few centigrade higher temperature in the targeted spots, than in the mass of the tumor. The high temperature of the rafts produces an external excitation of the various apoptotic pathways and kills the malignant cells by the process of immunogenic cell-death by damage-associated molecular pattern [7] like it is approached as the effect on therapy-resistant cancer [8], and which could be effective together with chemotherapies [9]. The mEHT renews the paradigm of hyperthermia [10], turning it from the isothermal to the heterogenic heating.

The energy absorption form the electric field is directed to the malignant cells to excite the apoptotic signal pathways, [11]. This solution avoids high energy absorption in the average mass of the tumor, while selectively targets the malignant cells with a very high energy [12], [13]. This heterogeneity allows the control of the blood-flow of the tumor [14], providing a better transport of complementary applied drugs and oxygen but suppressing the risk of the dissemination of the malignant cells. The specialties of the blood in capillaries affected by increased temperature has been analyzed [15], and its unique feature is used, [16].

Our objective with this article is to show the protocol of modulated electro-hyperthermia, (mEHT, [oncothermia®]) method and to clarify the application in the conventional curative intention.

Method

The mEHT method does not apply the isotherm dose concept [17] to make the thermal effect destroy the malignancy. The correct dosing [18] is based on the heterogenic selection of malignant cells and on the method of heating them individually instead of the homogeneous heating of the complete tumor-mass [19]. The selection of the cells uses the biophysical differences of the malignant cells and their healthy counterparts [20]. The four characteristic differences are:

1. The high metabolic rate of malignant cells, due to their intensive energy-intake for proliferation [21]. This is the Warburg effect, [22]; which is used intensively in positron emission tomography (PET, [23]). This effect causes a high conductivity of the tumor-mass [24], due to the increased ionic concentration in its volume. The higher conductivity will drive the appropriate radiofrequency current to flow through the tumor [25], automatically selecting the target.
2. Partial or complete autonomy of malignant cells [26] differ from the normal ones. It is the broken connectivity with neighboring cells [27], and broken signal exchanges [28]. This makes a disordered structure in the extracellular matrix

of the tumor cells (a high dielectric constant is created, [29], which drives the RF-current to the malignant cells more precisely [30].

3. Due to the previous point, malignant cells have a large number of transmembrane proteins without bonding it outside. These proteins form clusters on the membrane (membrane rafts), which have a high concentration on the membrane of the malignant cells [31]. The protein-lipid interaction characterizing the membrane rafts is sensitive on the radio frequency in the range of the so-called beta/delta frequency-dispersion [32]. The energy absorption of the selected cells by previous points will be taken on the membrane rafts [33], and will be heated to a lethal thermal effect, [34].
4. Malignancy brakes the healthy structure of its environment, [35]; and stops the standard homeostatic control of the system [36]. To select the broken homeostatic dynamism, mEHT applies a time-fractal modulation [37], which attacks the deviated dynamism of the malignancy [38].

Based on these particularities, it is clear that a proper bioelectromagnetic interaction could select the malignant cells from their tumor-mass or even from the complete system [39] and could destroy them [40]. Local treatments are performed with a 13.56 MHz medical frequency as a carrier, and it is amplitude modulated. The patient is part of the resonant circuit [41], which resonance ensures the most optimal energy intake for the selected malignant cells [42].

General safety considerations

The mEHT treatment is highly personalized [43]. The technical solution [41], [44], [45], [46] is continually upgraded by up-to-date technology and enforced with a sophisticated tuning system, which automatically matches the changed position of the patients, the variation of the tumor size or the movements. The radiofrequency source is highly effective [47], (E-class source with an efficacy higher than 90%). The high efficacy and the precise, real-time feedback measurement of any changes in the target (position, structure, composition), make it possible to apply a lower overall power (much less than any of the other devices in the market) and increase the safety of the mEHT method. The high efficacy allows the measurement of the dose in the absorbed energy [48], [49], which is supported by the theoretical considerations [50], [51], [52]. Absorbed energy develops the temperature, using a specific absorption rate to characterize the changes [53].

The traditional protocols, that were applied from the start of the mEHT applications is collected elsewhere [54], therefore we show a few other protocols and solutions for some of the complicated cases. The mEHT therapy is certainly complementary, and mostly applied in those stages, when the conventional solutions alone could only

deliver unsatisfactory results [55], [56], [57], [58]. The treatment by mEHT is especially useful in the cases when the conventional curative approach has been changed to palliative, but despite the patient being in a late stage, mEHT still has curative intent. In some instances, it is part of the palliation, mainly for increasing the quality of life (QoL) and to suppress the side-effects of conventional therapies. The palliative approach may be applied in very early stages as well (early palliation, [59]), consequently, mEHT could be applied even in the first line of the treatment with an expectation of effective supporting care compensating the toxicity of the chemotherapy. The application of mEHT in early stages could also increase the efficacy of the standard treatment.

The treatment indications are any solid tumor, primer, metastatic or recurrent, in any treatable cases with any TNM and stage. The curative goal is to increase the efficacy of the applied conventional treatment, or resensitize the tumor even in the refractory state. When the goal is palliative, the pain-reduction and the increase of QoL are the most frequent endpoints. Monotherapy can only be applied when another conventional therapy is not applicable at all, (organ failure, haemato-insufficiency, refractory disease, psycho-resistance, or other reasons not considering conventional therapies).

The treatment with mEHT does not increase the adverse effects of the complementary therapies applied together with it. Even some indications show that mEHT decreases the side effects of the other therapies.

It is not recommended to use the device on:

- patients with pacemakers or built-in field sensitive devices (if not produced considering the newest standards of electromagnetic compatibility). The applicability of mEHT also depends on the distance between the place of treatment and the built-in field sensing device.
- patients unable to communicate (babies, toddlers, patients in coma, or unconscious, patient in shock, etc.),
- patients without temperature and pain perception in the treated area,
- patients with epilepsy or those who are sensitive to electromagnetic fields,
- patients under immune-suppression due to organ-transplant,
- patient unable to lie in the proper position for the treatment,
- pregnant patients,
- sedated or comatose patients.

Treatment is strictrly prohibited through any implantation by plastic surgery (like breast implants)!

Apply with special care in the following cases:

- on patients with acute systemic or localized infections or inflammatory processes,
- on elderly patients who usually experience a higher level of pain under the heavy applicator,
- on areas with a high amount of fat. These areas must be closely monitored for surface burns and subcutaneous fibrosis,
- thick hair in the treated area (hair, pubic hair, etc.) could mismatch the treatment and could cause a surface burn,
- fluids in the treated volume may affect energy distribution (e.g., urine or ascites). Ask urination before treating the pelvic area and ask the patient to not drink before treating gastric lesions. (Offering drinks after the treatment avoids dehydration.)
- with metallic implants larger than 2 cm diameter volume under the targeted area,
- Take care about the non-smooth fixation of the applicator to the skin, leaving air under the active area (like over navel or concave forms, like the anus, armpit, loins, etc.).
- The treatment efficacy could be lowered, when the applicator is not parallel with the counter electrode in the bed.
- Take special care when the applicator is over a volume with lower blood-flow (like ears and bony areas in thin patients).

Protocols

The treatment protocols of mEHT have some common rules, [60]:

1. Firstly, apply the "gold standards" and use mEHT when others fail alone. (refractory, relapsing, inoperable, psycho-resistance, no result expected by conventional therapies alone, etc.).
2. The therapy of mEHT is complimentary. Apply it only in combination with conventional treatments (except if conventional treatments are not applicable).
3. Treatment time shall be between 45 and 90 minutes (average: 60 minutes)
4. Treatment frequency shall be 2 to 3 times a week, or in some cases, low-doses shall be applied every day for radio-sensitizing.
5. The number of treatments in a cycle shall be between 4 and 12 (average: 5.8)

6. The number of cycles shall follow the complementary protocols (average: 2.3)
7. In the cases of treatments of sensitive organs (like the brain), more time is needed to adapt the modulation.
8. Relaxed conditions must be formed around the patient

General recommendations for applying mEHT combined with intravenous (i.v.) administration of any drugs (chemotherapy, immune therapy, supportive therapy, etc.):

1. According to our researches, the most effective way of treatment is the concomitantly applied mEHT with i.v. administration. This helps the chemo-drug selection, contributes to targeting and attacking the malignancy, and helps drug-permeability through the vessel walls by activating the chemical reactions on- site.
    a. Even when the i.v. is shorter in time than the prescribed mEHT dose/session, mEHT shall be continued until its prescribed dose.
    b. When the mEHT is shorter in time than the i.v. process, you may proceed with the mEHT until the end of the i.v; however, maximally for 100 minutes. Longer therapy sessions are ineffective.
    c. In case of chrono-chemotherapy (12-24h i.v. administration) mEHT can be applied in any time during the chrono-chemotherapy, but the bet is at the start of the treatment.
2. When the i.v. administration is repeated weekly or monthly; mEHT must be applied continuously 1-3 times a week, (on the highest frequency every other day).
3. When the mEHT is concomitant with any i.v. therapy, use step-up heating. In any other cases (when the patient tolerates it) step-down heating can also be applied.
4. When various i.v. administration is made every day, mEHT can be applied every day concomitantly as well, but only with the $^3/_4$ of the dose.

To optimize the treatment efficacy and reduce the influence of the personal variability on the results, a protocol is fixed for the heating process. Step-up heating is necessary for combined therapies (the rate of the tempreture increase depends on the tolerance of the patients). The gradually increased power keeps the homeostatic control active and exercises the adaptability of 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 it is moderate in cancer-cells [61]. Consequently, the protection against the increasing temperature is higher in healthy cells. In other words: the 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. This way, it 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 develops high blood-perfusion to the subcutaneous tissue, which helps to optimize the treatment and increases its efficacy (62). The thermal homeostasis makes the vasodilatation more effective which increases the risk of dissemination of malignant cells forming micro and macrometastases. This is the reason for only applying mEHT together with other cell-killing methods. It 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 the method to make a complementary treatment with other therapy modalities (conventionally chemotherapy or radiotherapy) more effective. The basic steps of step-up heating are shown in Figure 1.

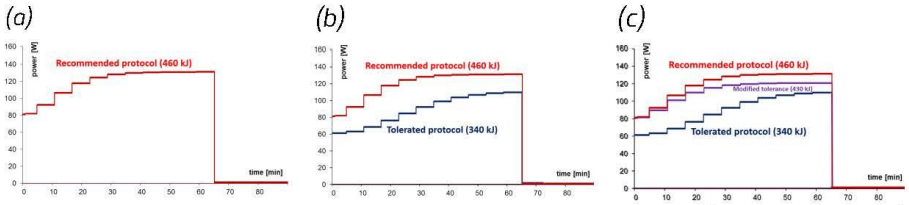


Fig. 1. The step-up heating method creates a gradual (quasi-stationary) temperature increase, making sure that the average time of the reconstruct the homeostatic equilibrium is 6 min. (a) the example of a recommended protocol, (b) example of the tolerance of the patient, which depends on the personal feelings, (c) the repeated treatments modify the tolerance level in most of the cases.

The recommended protocols of the most frequent malignancies are listed in Table 1. These values are only guiding proposals, and its application strongly depends on the actual situation and the patient's individual reaction.

Localizations	min. W	max. W	duration (min)	saturation at time (min)	Energy [kJ] /session	sessions/ cycle	Energy [kJ] /cycle
Medium (20cm diameter)) electrode							
Brain	30	120	40	30	136	6	816
Face, sinus	40	110	40	25	166	6	996
Head-neck	50	130	60	25	390	7	2730
Shoulder	60	150	60	15	503	8	4024
Thorax	80	150	60	8	542	7	3794
Armpit	40	120	60	30	331	7	2317
Arm	50	140	60	30	464	8	3712
Breast (mamma)	60	140	60	15	473	8	3784
Lung	80	150	90	15	734	9	6606
Spleen	60	120	60	20	397	8	3176
Liver, bile	60	150	60	25	454	9	4086
Stomach, deudeum	60	150	60	14	507	8	4056
Pancreas	60	150	60	14	507	8	4056
Intenstine	60	150	60	25	455	8	3640
Colon, sigma,rectum	60	150	60	20	470	9	4230
Vulva, vagina	40	100	50	30	217	6	1302
Cervix	60	150	60	30	430	7	3010
Ovary	60	150	90	30	655	9	5895
Penis	40	100	40	30	149	3	447
Prostate	60	150	90	15	719	8	5752
Kidney	60	150	60	20	471	8	3768
Urinary bladder	60	150	60	10	521	7	3647
Leg, limb	60	150	60	4	553	8	4424
Inguinal region	50	120	60	35	248	6	1488
Buttock	60	150	60	15	503	8	4024
Superficial tumors	60	150	60	4	553	8	4424
Large (30cm diameter) electrode							
Lung	60	150	90	3	784	12	9408
Liver	60	150	90	5	773	10	7730
Peritonium	70	150	90	10	753	10	7530
Pelvis, ovary	60	150	90	20	693	10	6930
Pancreas-liver	60	150	90	15	719	10	7190
Abdoman	60	150	90	10	746	10	7460
Thorax	60	150	90	5	773	10	7730
Small (10cm diameter) electrode							
Brain	40	60	40	30	112	5	560
Neck lesions	40	80	60	30	243	6	1458
Face, sinus	30	60	50	40	128	5	640
Eye	20	40	15	20	22	2	44
Superficial tumors	40	80	60	10	296	6	1776

Table 1. The list of the recommended protocol of some frequently occurred malignancies. Recommended energy is not a must, it is only a guideline, and everything depend on the tolerance of the patient.

When the recommended protocol is not achieved, the elongation of the treatment could be helpful (Figure 2.), however it shall not be longer than 90 min. When treatment time is for example longer than 1.5 hour, stopping the treatment is unreasonable. The number of sessions in the cycle could be increased to fit the requested overall energy.

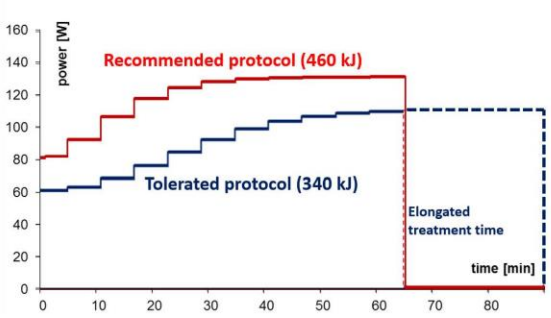


Fig. 2. The elongated treatment-time could correct the missing dose from the recommended protocol due to the actual limit of toleration.

The results can be measured by the change of the available tumor-markers during the treatment. A tumor-marker is not feasible for diagnostics, because it depends on multiple factors, not only on the malignant processes. However, its change which correlates with the applied treatment is a reasonable sign to evaluate the progress of the treatment. Figure 3. [63], [64].

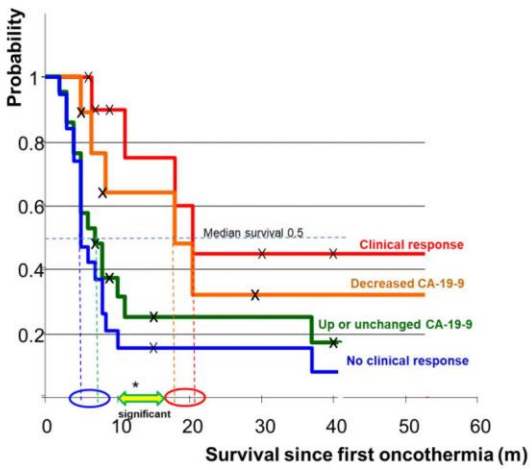


Fig. 3. Clinical study of the tumor-marker in pancreas-carcinoma cases. The measured clinical response by imaging shows good correspondence with the tumor-marker changes, and the difference shown by the tumor-marker CA-19-9 is significant.

In some cases, patients adapt to the treatment dose in a gradually increasing level, Figure 4. The operator may slightly, delicately try increasing 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 an extended experience from the operator. It is not suggested for unexperienced staff.

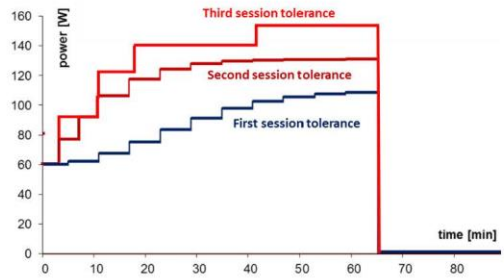


Fig. 4. Patients could gradually develop a higher adaptability of the treatment than the initial one.

However, in the case of monotherapy, the situation is different, and the step-down heating is more convenient for optimizing when no other possibility is available. Contrary to the step-up heating which seeks the equilibrium, the step-down heating creates hypoxia and non-equilibrium processes, so it is applicable in the monotherapy cases. The step-down heating starts with a maximal power, and the rate of energy-decrease must be decided by the tolerance of the patient. From the patient's side, the step-up heating is based on the adaptability, while the step-down is based on the tolerance of the patient, Figure 5. The forced non-equilibrium heating in the step-down process creates vasocontraction in the cancerous tissue (65), and the goal in this monotherapy mode is to make vasocontraction with a high inner temperature, blocking the blood-supply as much as possible and so utilizing the available metabolic energy without remarkable replacements quickly.

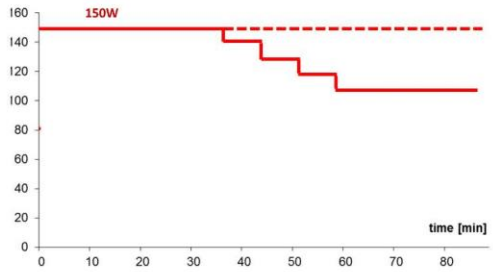


Fig. 5. In case of the step-down treatment protocol, the treatment runs on the maximal tolerated power through the whole treatment time. The dashed line is the overall maximum; and the solid line shows an example on how to reduce the power by the patient's tolerance, communicated verbally.

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 (66), where lipid phase-transition happen (67), and the new compound has lower energy barrier for the reaction (68).

However, we expect less effective treatment in step-down protocol than in the complementary step-up cases. The heterogenic tumor has an "onion" structure: the most vivid parts are on the tumor -surface and the main heat absorption is inside, heating up the inner volume of the solid tumor quickly [69]. The increased blood flow in the healthy neighborhood increases the risk of dissemination, and the vasocontraction in the inner tumor will be irrelevant in the development of metastases by the blood-transport. In these special conditions, when mEHT is applied as monotherapy [70] the number of cycles can increase drastically [71].

We did not find any negative cross-effects with any kind of applied complementary therapies. Also, there is no indication that mEHT reduces the success of complementary applied conventional therapies. We have never been informed about cases, when the treatment was responsible for the worsening of the initial state of the patient during the 30 years application of mEHT.

Protocols of complementary applications of mEHT are not automatisms, they must be harmonized with the conventional therapy. The general protocol, requesting the application of mEHT together with chemotherapy, however there are examples of not giving chemo on the same day. When a trimodal (radio-chemo-thermo) therapy is applied, we must consider that some chemo-drugs are radiosensitizers (like cisplatin). In this case the mEHT can be applied on another day.. Another reason not applying the chemotherapy and mEHT on the same day is when a clinical trial requests a large standardizing of the patient cohort, but the repeated drug administration is not tolerable for all the participants. When we expect such problems, it is better to administer the mEHT independently from the chemotherapy in order to keep the homogeneity of the cohort as much as possible.

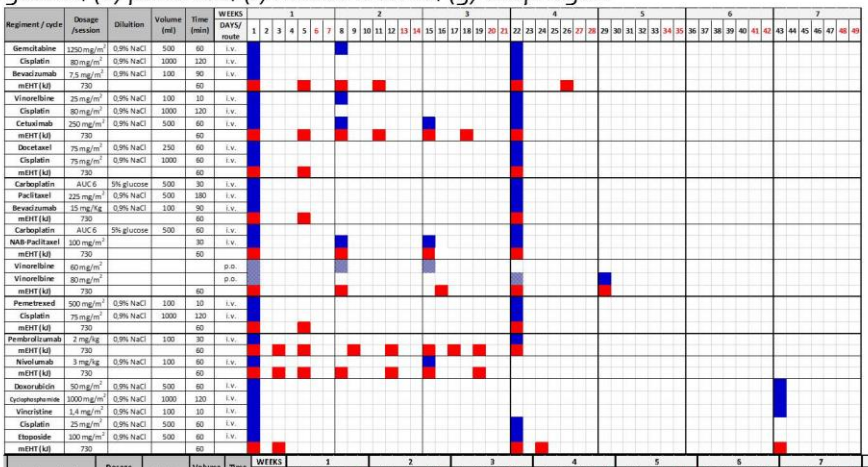
The guiding principle must be centered on the patient's needs and must optimize the whole protocol according to personalized way. The bio-variability, and the stochastic processes break the strict determination.

Guiding examples

The most common chemotherapy protocols in combination with mEHT taken from the practice of Department of Oncology and Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord Pesaro, Italy are listed in Table 2.

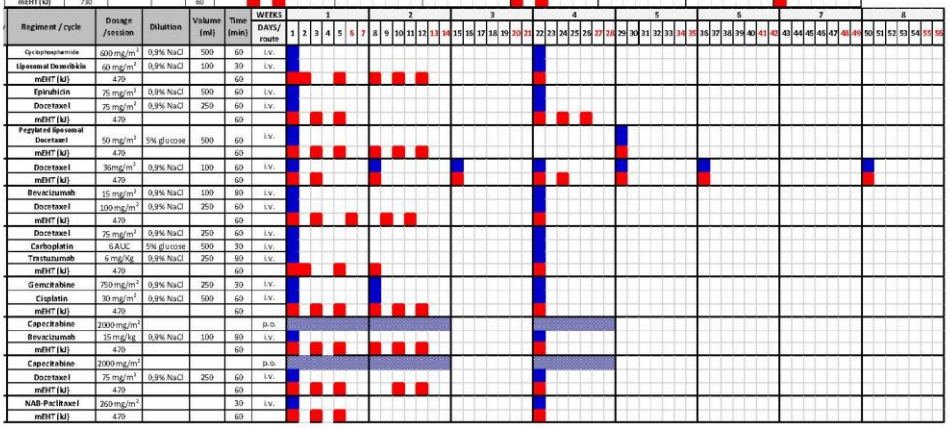
Table 2. The protocols of mEHT (mEHT) with various, common, standard chemotherapy regiments in various malignant diseases. The blue fields are the administrations of the drug, and the reds are mEHT therapies. The blue with the pattern is oral administration. (These protocols are collected from the applications in Department of Oncology and Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord Pesaro, Italy) (a) non-small cell lung carcinoma; (b) breast cancer; (c) gastrointestinal (colorectal & intestines); (d) gastric; (e) pancreas; (f) mesothelioma; (g) esophagus.

a



Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	WEEKS DAYS/ route
Gemcitabine	1250 mg/m²	0,9% NaCl	500	60	i.v.
Cisplatin	80 mg/m²	0,9% NaCl	1000	120	i.v.
Bevacizumab	7,5 mg/m²	0,9% NaCl	100	90	i.v.
mEHT (kl)	730			60	
Vinorelbine	25 mg/m²	0,9% NaCl	100	10	i.v.
Cisplatin	80 mg/m²	0,9% NaCl	1000	120	i.v.
Cetuximab	250 mg/m²	0,9% NaCl	500	60	i.v.
mEHT (kl)	730			60	
Docetaxel	75 mg/m²	0,9% NaCl	250	60	i.v.
Cisplatin	75 mg/m²	0,9% NaCl	1000	60	i.v.
mEHT (kl)	730			60	
Carboplatin	AUC 6	5% glucose	500	30	i.v.
Paclitaxel	225 mg/m²	0,9% NaCl	500	180	i.v.
Bevacizumab	15 mg/Kg	0,9% NaCl	100	90	i.v.
mEHT (kl)	730			60	
Carboplatin	AUC 6	5% glucose	500	60	i.v.
NAB-Paclitaxel	100 mg/m²			30	i.v.
mEHT (kl)	730			60	
Vinorelbine	60 mg/m²				p.o.
Vinorelbine	80 mg/m²				p.o.
mEHT (kl)	730			60	
Pemetrexed	500 mg/m²	0,9% NaCl	100	10	i.v.
Cisplatin	75 mg/m²	0,9% NaCl	1000	120	i.v.
mEHT (kl)	730			60	
Pembrolizumab	2 mg/kg	0,9% NaCl	100	30	i.v.
mEHT (kl)	730			60	
Nivolumab	3 mg/kg	0,9% NaCl	100	60	i.v.
mEHT (kl)	730			60	
Doxorubicin	50 mg/m²	0,9% NaCl	500	60	i.v.
Cyclophosphamide	1000 mg/m²	0,9% NaCl	1000	120	i.v.
Vincristine	1,4 mg/m²	0,9% NaCl	100	10	i.v.
Cisplatin	25 mg/m²	0,9% NaCl	500	60	i.v.
Etoposide	100 mg/m²	0,9% NaCl	500	60	i.v.
mEHT (kl)	730			60	

b



Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	WEEKS DAYS/ route
Cyclophosphamide	600 mg/m²	0,9% NaCl	500	60	i.v.
Liposomal Doxorubicin	60 mg/m²	0,9% NaCl	100	30	i.v.
mEHT (kl)	479			60	
Epirubicin	75 mg/m²	0,9% NaCl	500	60	i.v.
Docetaxel	75 mg/m²	0,9% NaCl	250	60	i.v.
mEHT (kl)	479			60	
Pegylated liposomal Doxetaxel	50 mg/m²	5% glucose	500	60	i.v.
mEHT (kl)	479			60	
Docetaxel	36mg/m²	0,9% NaCl	100	60	i.v.
mEHT (kl)	479			60	
Bevacizumab	15 mg/m²	0,9% NaCl	100	90	i.v.
Docetaxel	100 mg/m²	0,9% NaCl	250	60	i.v.
mEHT (kl)	479			60	
Docetaxel	75 mg/m²	0,9% NaCl	250	60	i.v.
Carboplatin	6 AUC	5% glucose	500	30	i.v.
Trastuzumab	6 mg/Kg	0,9% NaCl	250	90	i.v.
mEHT (kl)	479			60	
Gemcitabine	750 mg/m²	0,9% NaCl	250	30	i.v.
Cisplatin	30 mg/m²	0,9% NaCl	500	60	i.v.
mEHT (kl)	479			60	
Capecitabine	2000 mg/m²				p.o.
Bevacizumab	15 mg/kg	0,9% NaCl	100	90	i.v.
mEHT (kl)	479			60	
Capecitabine	2000 mg/m²				p.o.
Docetaxel	75 mg/m²	0,9% NaCl	250	60	i.v.
mEHT (kl)	479			60	
NAB-Paclitaxel	260 mg/m²			30	i.v.
mEHT (kl)	479			60	

c

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	DAYS/ route
Oxaliplatin	85 mg/m²	5% glucose	500	120	i.v.
Irinotecan	125 mg/m²	0,9% NaCl	500	30	i.v.
mEHT (kl)	500			60	
Oxaliplatin	85 mg/m²	5% glucose	500	120	i.v.
Calcium folinate	200 mg/m²	0,9% NaCl	250	120	i.v.
5-Fluorouracil	2600 mg/m²	0,9% NaCl	1000	24 hours	i.v.
mEHT (kl)	500			60	
Gemcitabine	1000 mg/m²	0,9% NaCl	250	30	i.v.
mEHT (kl)	500			60	
Nab-Paclitaxel	125 mg/m²			30	i.v.
Gemcitabine	1000 mg/m²	0,9% NaCl	250	30	i.v.
mEHT (kl)	500			60	
Cisplatin	80 mg/m²	0,9% NaCl	1000	120	i.v.
Gemcitabine	1000 mg/m²	0,9% NaCl	250	30	i.v.
mEHT (kl)	500			60	
Oxaliplatin	85 mg/m²	5% glucose	500	120	i.v.
Calcium folinate	200 mg/m²	0,9% NaCl	250	120	i.v.
5-Fluorouracil	2600 mg/m²	0,9% NaCl	1000	24 hours	i.v.
mEHT (kl)	500			60	

d

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	DAYS/ route
Epirubicin	50 mg/m²	0,9% NaCl	250	30	i.v.
Oxaliplatin	130 mg/m²	5% glucose	500	120	i.v.
Capecitabine	1250 mg/m²				p.o.
mEHT (kl)	510			60	
Docetaxel	75 mg/m²	0,9% NaCl	250	60	i.v.
mEHT (kl)	510			60	
Oxaliplatin	85 mg/m²	5% glucose	500	120	i.v.
Calcium folinate	200 mg/m²	0,9% NaCl	250	120	i.v.
5-Fluorouracil	2600 mg/m²	0,9% NaCl	1000	24 hours	i.v.
Docetaxel	50 mg/m²	0,9% NaCl	250	60	i.v.
mEHT (kl)	510			60	

e

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	DAYS/ route
Gemcitabine	1000 mg/m²	0,9% NaCl	250	30	i.v.
Capecitabine	1660 mg/m²				p.o.
mEHT (kl)	510			60	
Gemcitabine	1000 mg/m²	0,9% NaCl	250	30	i.v.
mEHT (kl)	510			60	
Pegylated liposomal Irinotecan	80 mg/m²	0,9% NaCl	500	90	i.v.
Calcium folinate	400 mg/m²	0,9% NaCl	250	120	i.v.
5-Fluorouracil	2400 mg/m²	0,9% NaCl	500	46 hours	i.v.
mEHT (kl)	510			60	

f

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	DAYS/ route
Pemetrexed	500 mg/m²	0,9% NaCl	100	10	i.v.
Cisplatin	75 mg/m²	0,9% NaCl	500	60	i.v.
mEHT (kl)	780			60	

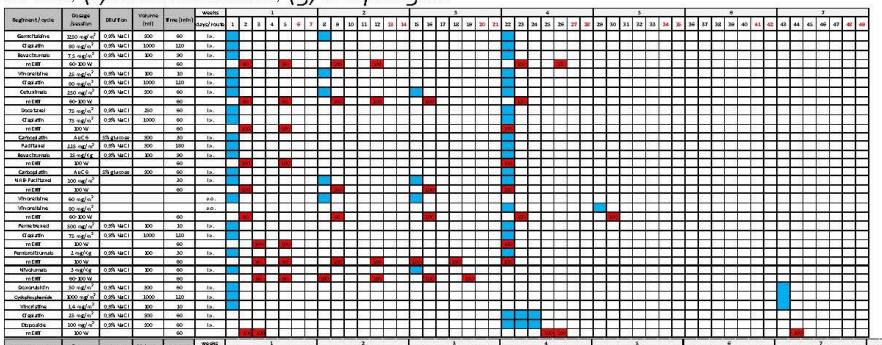
g

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	DAYS/ route
5-Fluorouracil	1000 mg/m²	0,9% NaCl	1000	24 hours	i.v.
Cisplatin	100 mg/m²	0,9% NaCl	500	120	i.v.
mEHT (kl)	450			60	

The other, individual protocols are used in the same indications as above. These are applied when the patient has reduced tolerance in palliative intent, Table 3. The most remarkable difference is the shift of mEHT treatment from the same day of chemotherapy to the next one. This is usually due to the expectation that the most active pharmacokinetic period of the drug is expected on the next day. In these cases, they do not calculate the active dose, they used the power as a dose, due to the immediate heating (step-down) regarding this approach as monotherapy on that day.

Table 2. The protocols of mEHT (mEHT) with various, common, standard chemotherapy regimens in various malignant diseases. The blue fields are the administrations of the drug, and the reds are mEHT. The blue with the pattern is oral administration. (These protocols are collected from the applications in Department of Oncology and Hematology, Azienda Ospedaliera Ospedali Riuniti Marche Nord Pesaro, Italy) (a) non-small cell lung carcinoma; (b) breast cancer; (c) gastrointestinal (colorectal & intestines); (d) gastric; (e) pancreas; (f) mesothelioma; (g) esophagus.

a



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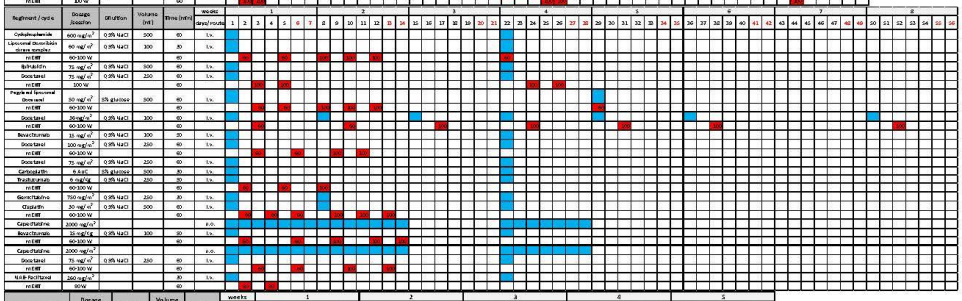

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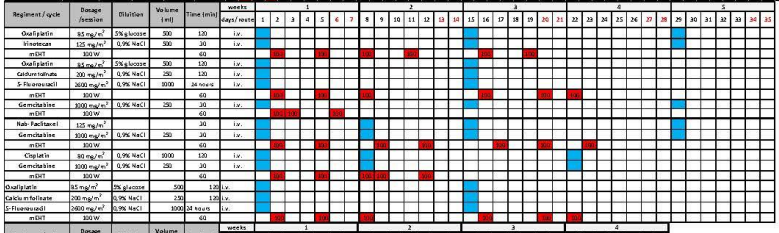

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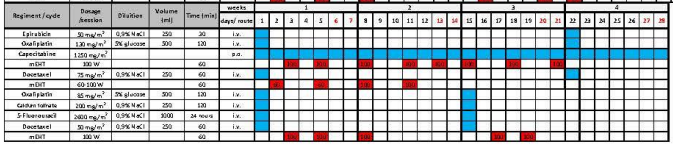


e

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	weeks / days / route
Gemcitabine	1000 mg/m²	0.9% NaCl	250	30	i.v.
Capecitabine	1660 mg/m²				p.o.
mEHT	100 W			60	
Gemcitabine	1000 mg/m²	0.9% NaCl	250	30	i.v.
mEHT	100 W			60	
Pegylated liposomal doxorubicin	30 mg/m²	0.9% NaCl	500	90	i.v.
Calcium folinate	400 mg/m²	0.9% NaCl	250	120	i.v.
5-fluorouracil	2800 mg/m²	0.9% NaCl	500	46 hours	i.v.
mEHT	100 W			60	

f

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	weeks / days / route
Pemetrexed	500 mg/m²	0.9% NaCl	100	10	i.v.
Cisplatin	75 mg/m²	0.9% NaCl	500	60	i.v.
mEHT	100 W			60	

g

Regiment / cycle	Dosage /session	Dilution	Volume (ml)	Time (min)	weeks / days / route
5-fluorouracil	1000 mg/m²	0.9% NaCl	1000	24 hours	i.v.
Cisplatin	100 mg/m²	0.9% NaCl	500	120	i.v.
mEHT	100 W			60	

The protocols show the minimal cycle of the treatment, which may be repeated in consideration of the remission of the lesion and the tolerance of the patient. Also, sometimes chemotherapy management is not concomitant with the mEHT but given on another day. It is usually provided, when chemotherapy has been active for a long time, and it forms its most active pharmacokinetic effect after the i.v. administration is taken.

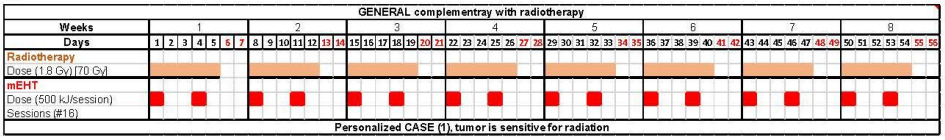
The single driving idea of the protocols are that the patients who are treated with mEHT, had been treated earlier by conventional therapies unsuccessfully. Due to the high variety of the reasons of conventional therapies' failure, the newly started treatment must be strongly personalized [72]. The method could be well tailored to the patient's stage, pretreatments, quality of life, and curative possibilities [43]. The task for optimizing the protocol of mEHT has some specialized possibilities:

1. Starting the mEHT as a resensitizer of the earlier failed therapy, apply it together with the conventional protocols or, if the risk of toxicity is high, with reduced doses for curative intent.
2. Starting mEHT as a new therapy, using immune-effects (immune actions like check-point inhibitors, CAR-T therapy, abscopal-inducing radiotherapy, etc.) with curative intent.
3. Applying mEHT as monotherapy together with supportive care, improving the quality of life of the patients with palliative intent, which can turn to curative in some personalized cases.

The protocols with chemotherapy shown above are the combinations of the standard, evidence-based regimens of drugs for a few of the most frequent malignant solid tumors. The number of applied cycles of mEHT fits the cycles of the standard chemotherapy. It is shown, that a lower than advised number of mEHT sessions could drastically decrease the survival probability in advanced gynecological applications [73], where the 24 sessions (3 cycles) had shown optimal results. These could be further combined with any conventional modern therapies, like surgery, radiotherapy, gene-therapy, immune-therapy, check-point inhibitors, etc. If the patient is unfit for chemotherapy, but other therapies are applicable, those combinations are also

Table 5. Sample solutions of complementary application of ionizing radiation to mEHT (a) two mEHT sessions or (b) three sessions in a week.

a.



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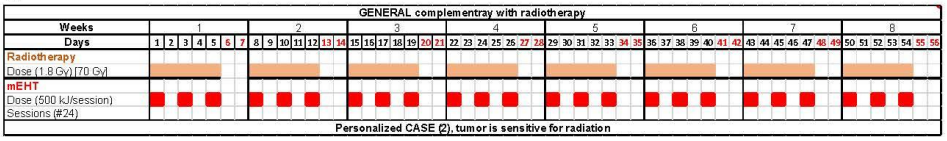
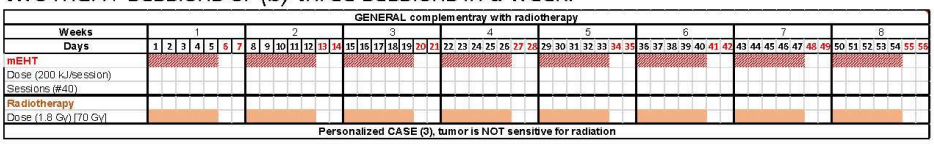


If the tumor is not sensitive to the ionizing radiation, mEHT has to be applied first to deliver blood into the lesion, providing a follow-up support for the radiotherapy. In this case, the normal dose of mEHT must be halved and must be applied so that no longer than 30 minutes elapses between mEHT and the ionizing radiation, see Table 6.

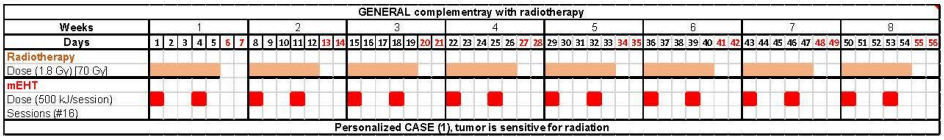
Table 6. Sample solutions of sensitizing application of ionizing radiation to mEHT (a) two mEHT sessions or (b) three sessions in a week.



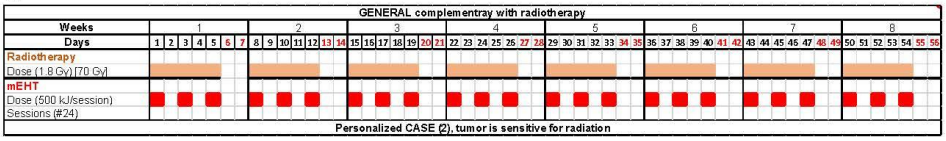
In some cases, the sensitizing of the ionization radiation is not enough. For higher efficacy, a complete mEHT treatment is applied after the radiation too, Table 7.

Table 5. Sample solutions of complementary application of ionizing radiation to mEHT (a) two mEHT sessions or (b) three sessions in a week.

a.

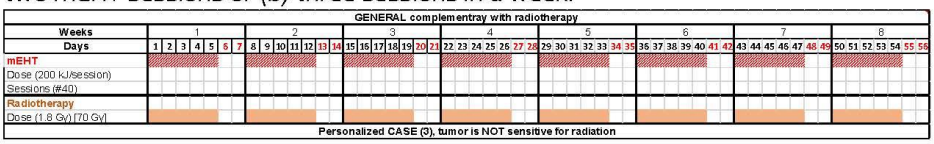


b.



If the tumor is not sensitive to the ionizing radiation, mEHT has to be applied first to deliver blood into the lesion, providing a follow-up support for the radiotherapy. In this case, the normal dose of mEHT must be halved and must be applied so that no longer than 30 minutes elapses between mEHT and the ionizing radiation, see Table 6.

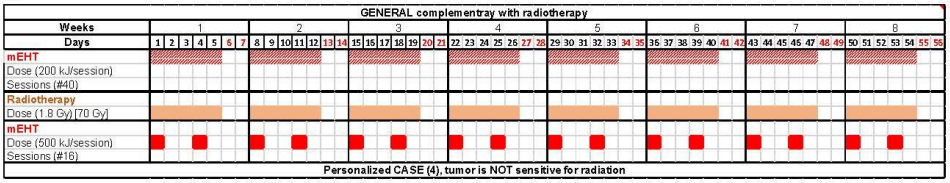
Table 6. Sample solutions of sensitizing application of ionizing radiation to mEHT (a) two mEHT sessions or (b) three sessions in a week.



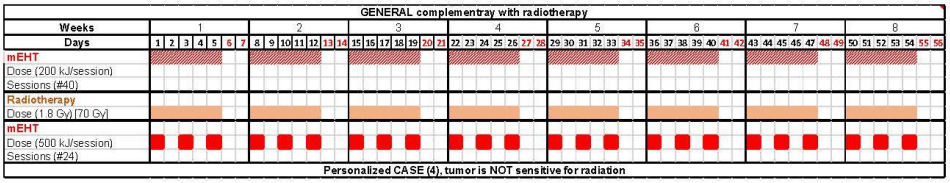
In some cases, the sensitizing of the ionization radiation is not enough. For higher efficacy, a complete mEHT treatment is applied after the radiation too, Table 7.

Table 7. Sample solutions to complete synergy application of ionizing radiation to mEHT (a) two mEHT sessions or (b) three sessions in a week.

a.



b.



The following case examples are rare: leiomyosarcoma of uterus Table 8., [74]; and breast, Table 9., [75] treated by palliative intent, but the result is definitely curative. Complete remission is achieved.

Table 8. Leiomyosarcoma of uterus, trimodal therapy

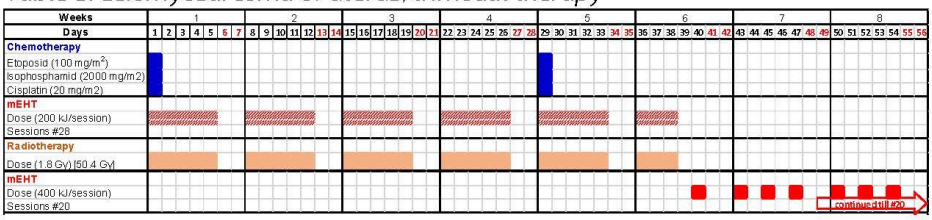
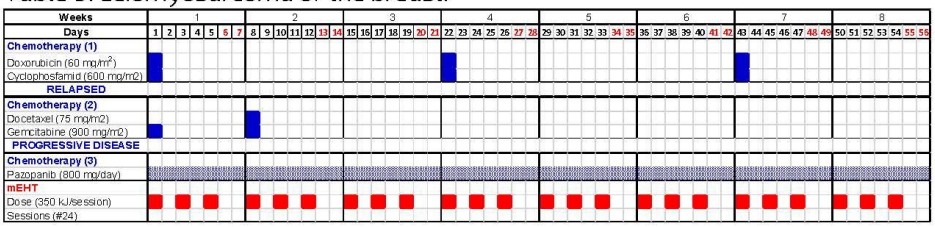
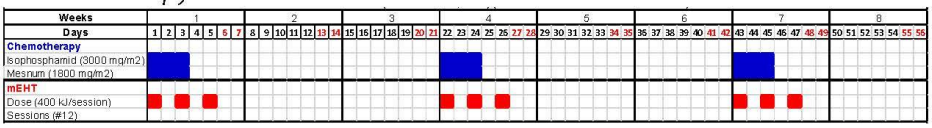


Table 9. Leiomyosarcoma of the breast.



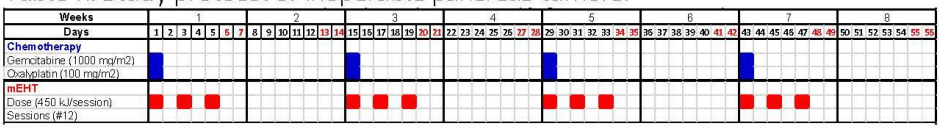
The clinical trial for soft-tissue sarcoma (Phase II, n=24) after a recurrence of first-line treatment with Doxorubicin) Table 10., [76], shows a good, progression-free survival (4.7 m).

Table 10.Prospective clinical study for soft-tissue sarcoma (n=24), after failing the first line therapy with Doxorubicin.



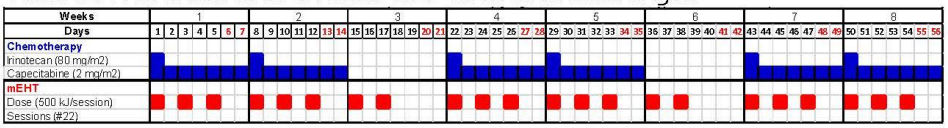
The malignancies of the pancreas are one of the less successful areas of oncology. A study (n=26) of inoperable pancreas tumors treatment after the progression in the first line with gemcitabine shows 8.9 months overall survival, Table 11. [77].

Table 11. Study protocol of inoperable pancreas tumors.



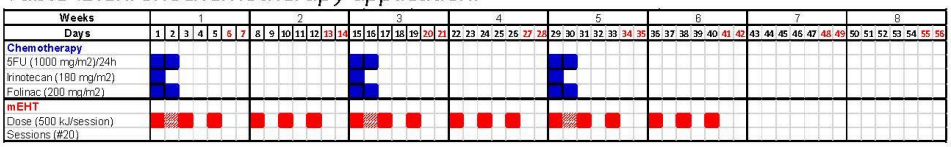
Colorectal cancer frequently makes prompt metastases in the liver. A study of the treatment of the liver (n=15) after the R0 surgery of primary colorectal cancer and showing progression of the tumor after first line treatment with oxaliplatin, folic acid and 5FU is shown in Table 12. [78]. Interesting observation: the first line (without mEHT) showed 51% response, while the second therapy (complementary with mEHT) had an 80% response rate.

Table 12. Treatment of liver metastasis form colorectal origin.



The chrono-chemotherapy (usually called after the inventor "De Gramont protocol") is a curative intent for C1800-1890 and C19-20 tumors, Table 13., [79].

Table 13.Chronochemotherapy application.



The advanced esophagus tumor has a bad prognosis, however the personalization with mEHT improves the expectations, in the cases Table 14. [80]; and Table 15. [81] the complete remission was 12 and 39 months after finishing the therapy.

Table 14. Advanced metastatic esophagus treatment with trimodal therapy, inoperable (cT2 cN1 M1a G3 R2).

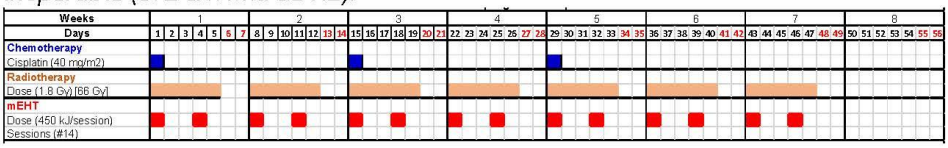
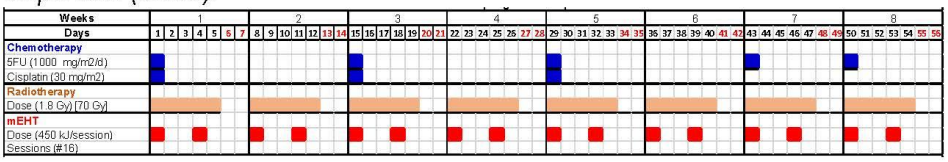


Table 15. Advanced metastatic esophagus treatment with trimodal therapy, inoperable (G3 R2).



Colorectal cancer is a very common malignancy. Curative intent protocols for stage III/IV lesions (n=10) and (n=6) are shown in Table 16. and Table 17. [73].

Table 16.Curative protocol (FOLFOX+mEHT) for colorectal cancer stage III/IV.

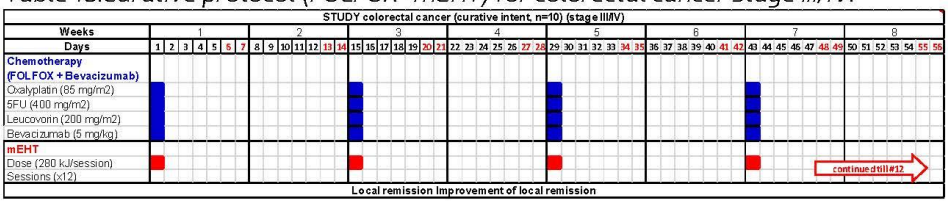
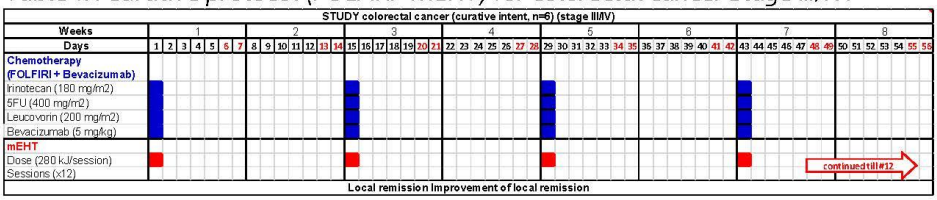


Table 17. Curative protocol (FOLFIRI+mEHT) for colorectal cancer stage III/IV.



A small number of cases were studied for ovarian and breast cancer, [73]. The applied protocols are shown in Table 18. and Table 19., respectively.

Table 18. Ovarian cancer treatment protocol in a small study (n=5) .

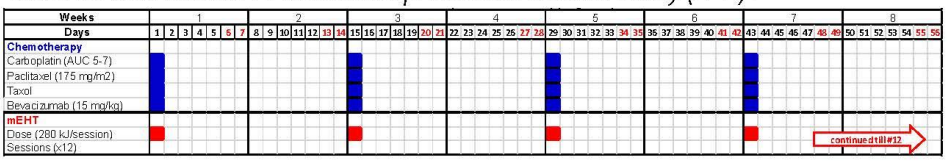
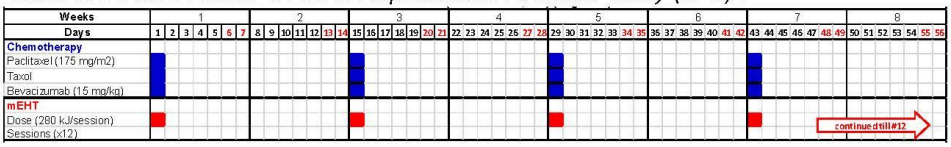
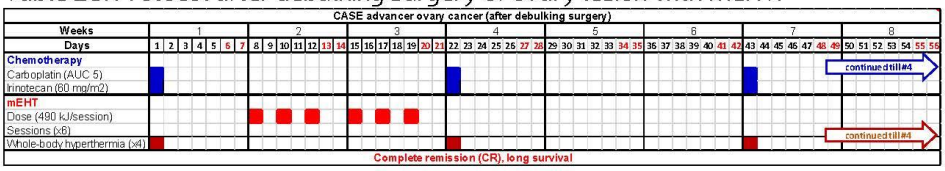


Table 19. Breast cancer treatment protocol in a small study (n=5) .



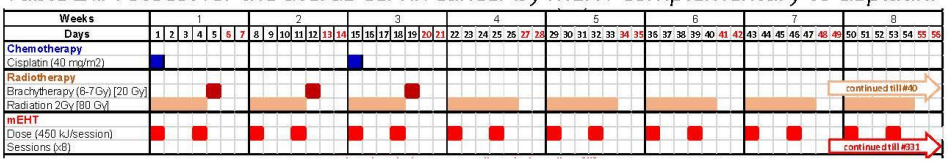
Another protocol for advanced ovary case after debulking surgery is shown in Table 20. [82].

Table 20. Protocol after debulking surgery of ovary lesion with mEHT.



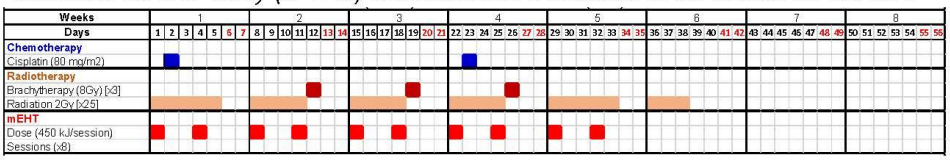
The protocol of the phase II study for uterus cervix cancer (n=72) is shown in the Table 21. [83]. The quality of life, the remission rate and the overall survival time were all improved by the therapy.

Table 21.Protocol for the uterus cervix cancer by mEHT complementary to cisplatin.



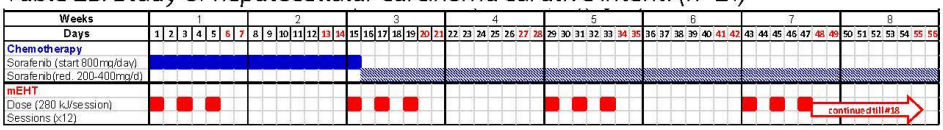
A complex phase III study (n=236) is in progress for trimodally treatment of uterus cervix. The applied protocol is shown in Table 22. [84].

Table 22.Phase III study (n=236) with trimodal treatment of uterus cervix tumors.



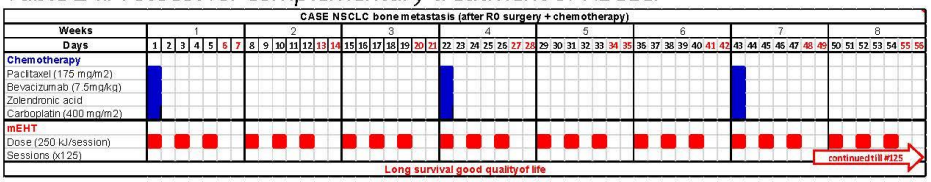
Hepatocellular carcinoma also has a poor prognosis. The protocol is successfully applied in a study (n=21) with Sorafenib+mEHT for stage III/IV diseases, Table 23. [85]. The overall survival median was 315 days while the progression-free survival is 160 days.

Table 23. Study of hepatocellular carcinoma curative intent. (n=21)



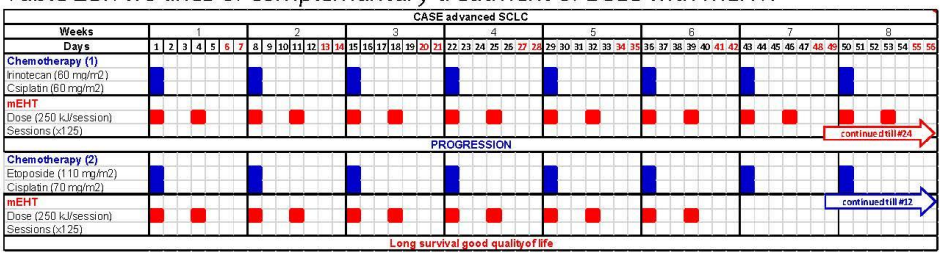
The non-small-cell-lung carcinoma (NSCLC) is one of the most frequent malignancies worldwide. A case protocol with complementary mEHT is shown in Table 24. [86]. The patient has shown a good quality of life with long overall survival.

Table 24.Protocol for complementary treatment of NSCLC.



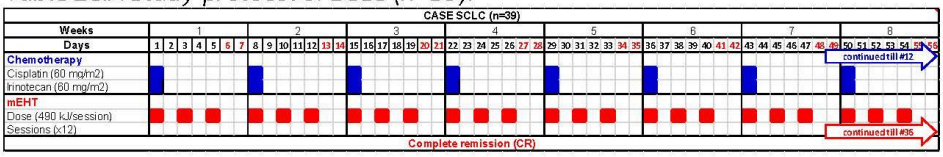
The small-cell-lung cancer (SCLC) is not as frequent as NSCLC, but it is more aggressive, its prognosis is much worse than for NSCLC. A protocol in this case has two mEHT treatment lines as it is shown on Table 25. [87].

Table 25.Two lines of complemantary treatment of SCLC with mEHT.



The protocol of a phase II study (n=39) from SCLC with improved response rate is shown in Table 26. [88].

Table 26.A study-protocol of SCLC (n=39).



Some case reports of the protocols are collected in Table 27. The complementary applications of these are following the general rules of the protocol conventions shown above.

Table 27. Some case-reports with mEHT complementary treatment in cases when the conventional treatment fail or inapplicable.

Principal investigator	Case	stage	patient		pretreatment				treatment with mEHT				Result	
			sex	age	surgery	chemo therapy	radio therapy [Gy]	complication	chemotherapy	radio therapy [Gy]	#mEHT sessions	Remark		
Herzog A.	Mammary carcinoma		F	60	inop.			ulcerous, bleeding	Vinorelbine, MitomycinC	no			complete remission	89
Chi K-W.	Mammary carcinoma		F	n.d.	inop.			ulcerous, bleeding	no	2 (x25)	7		complete remission	90
Ranieri G.	Breast cancer with lung metastasis		F	55					bevacizumab (x12)		24		partial remission	73
Jeung T.	Hepatocellular carcinoma		M	61	no	TACE	no	hepatitis B, chirrosis	no	no	24	monotherapy	complete remission	71
Chi K-W.	Hepatocellular carcinoma								Lipodox 20mg (x3)	2 (x23)	5		complete remission	91
Chi K-W.	Advanced hepatoma								Keytruda, Lipodox	2 (x23)	15		partial remission	92
Chi K-W.	Cholangiocarcinoma								Avastin,Gemzar, 5FU, Keytruda	2 (x15)	10		partial remission	93
Kirchner H.	Liver metastasis from colon (transversum)		M	61	Hemi-coectomy				Erbitrux, carnpo		12		partial remission	78
Chi K-W.	recurrent nasopharyngeal carcinoma								nivolumab	2 (x30)	6		complete remission	94
Herzog A.	tonsils carcinoma lymph+pulmonary metastases		F	55	inop.				MitomycinC, 5FU &Cisplatin, 5FU	no	6		complete remission	95
Herzog A.	Metastatic tonque carcinoma		F	41	R0 (x3)			relapses	Cisplatin, 5FU	no	6		complete remission	96
Sahinbas H.	Sinus metastasis from colon		M	46	inop.	local chemoperfusion					12	monotherapy	complete remission	97
Renner H.	Squamous epithelium carcinoma, sinus sphenoidalis	n.d.	M	67	inop.			opthalmoplegy	no	1.8 (x30)	6		complete remove of opthalmoplegy	98
Herzog A.	Non-Hodgkin lymphoma	WHO IV	F	38	inop.			block vision	bendamustin	no	8		complete remission	99
Herzog A.	Non-Hodgkin lymphoma		F	65							6	monotherapy	partial remission, no symptoms	100
Renner H.	Rectum carcinoma	rcT4cN0M0 G4 R2	F	36	inop.			progression	Cisplatin	1.8 (x25)	14		partial remission	101
You S-H.	Rectum carcinoma		M	60						1.8 (x28)	10		complete remission	102
Herzog A.	Rectum carcinoma		M	68				intenstine obstruction	FOLFOX	no	8		partial remission, pain-free	103
Ranieri G.	Colorectal cancer with liver metastasis		M	71					bevacizumab (x12)		10		partial remission	73
Fiorentini G.	Relapsed astrocytoma	G3	F	24	no					no			complete remission (13y)	104
Hager D.	Anaplastic astrocytoma	G3				PCV (x5)	1.8 (x30)	progression	no	no	>50	monotherapy	partial remission (6y)	105
Fiorentini G.	Relapsed astrocytoma	G3	F	32							>30		partial remission (4y)	104
Akasheh M.	Brain metastais from breast	(terminal)	F	53							10	monotherapy	partial remission	106
Fiorentini G.	Glioblastoma multiform	G3									16		partial remission	104
Sahinbas H.	Glioblastoma multiform	G4							Temozolamid		>20		partial remission (1.5y)	107
Herzog A.	Recurrent astrocytoma	G3	F	32	R0	BCNU (x2)	no	Progression	Temozolamid		16		complete remission	108
Sahinbas H.	Ependymoma	G3	M	10	R0	yes	yes	Karnofsky <30%			22	monotherapy	partial remission	105
Sahinbas H.	Anaplastic astrocytoma	G4	F	26			seed implant 50Gy	progression	Temozolamid		10		partial remission	110
Sahinbas H.	Esphagus cancer		M	46	op.	multiple	1.8 (x28)	complete obstruction			12	monotherapy	remove the obstruction, partial remission	111
Renner H.	Esphagus cancer metastasis in mediastinum and celiac ganglia	cT2cN1M1a G3 R2	M	50	inop.				cisplatin	1.8 (x35)	14		complete remission (1y)	80
Renner H.	Esphagus cancer metastasis in multilocal lymphnodes	G3	M	51	inop.				cisplatin, 5FU	1.8 (x40)	16		complete remission (2.5y)	81
Chi K-W.	Urothelial-cell carcinoma of renal pelvis with abdomen and liver metastases								no	2 (x20)	6		complete remission	112
Pang CLK.	Ovary cancer		F	60	oophorohy sterectomy	intraperitoneal Carboplatin +others		Karnofsky <60%					Karnoffsky 100%, complete remission	73
Ranieri G.	Ovarian cancer with liver and spleen metastases		F	56					bevacizuumab (x12)		24		partial remission	113
Chi K-W.	uterine sarcoma with peritoneal seedings							refractory	nivolumab, ipilimumab	1.5 (x30)	6		complete remission	114
Renner H.	Cervix carcinoma	cT4cN0M0 G3	F	61						1.8 (x28)	6		pathologically complete remission ypT0ypN0	71
Jeung T.	Stomach carcinoma	WHO IV	F	54							36	monotherapy	partial remission	71
Jeung T.	Bladder (+brain) metastasis from pancreas		M	49		yes	3 (x10) (on brain)				12	monotherapy	complete remission	71
Jeung T.	Pancreas cancer and liver metastasis		M	58	inop.	yes		progression			42	monotherapy	complete remission in both lesions	115
Renner H.	NSCLC	cT3cN0M0 G2 R2	F	79	inop.				Cisplatin	1.8 (x30)	9		partial remission	116
Lee C-G.	NSCLC	cT4N3M0	M	51					paclitaxel cisplatin	2.2 (x30)	10		partial remission	116
Lee C-G.	NSCLC	cT3N3M0	M	45					docetacel, cisplatin	1.8 (x28)	10		complete remission	116
Lee C-G.	NSCLC	cT4N1M0	M	74					Paclitaxel, carboplatin	1.8 (x35)	12		partial remission	116
Lee C-G.	NSCLC	cT3N3M0	M	60					docetacel, cisplatin	1.8 (x28)	10		complete remission	117
Brockmann W-P.	SCLC		M	69					yes		8		partial remission	

Any supportive care can be applied as well, that is allowed by the primary conventional regiment. Supportive therapies complete the mEHT action well and have a positive effect on the quality of life. It can be Traditional Chinese Medicine (TCM) [118], [119], [120], [121], [122], high-dose vitamins [123], or other proven remedies (like pain-killers, immune-supporters, electrolyte regulators, etc.).

A clear and detailed warning for patients is mandatory about categorically blocking uncontrolled and unproven ""miracle hyperthermia therapies at home". Sauna or other systemic or local heating could cause a growth in the number of circulating cancer cells, causing metastases in sensitive linked organs. Furthermore, only the surface is heated by most of the saunas, where no remarkable increase of the body temperature could be achieved. In the surface heating the intensive high blood-flow enriches the drugs in the surface area of the patients increasing the adverse effects all over the body.

In some extreme cases, the mEHT treatment could be continued for years, controlling the fatal disease with chronic care [124].

Conclusion

We had shown, that mEHT is applicable curatively even in cases when conventionally only palliative care can be provided. It is feasible for broad range of solid tumors; is easy to use and may be combined with any well proven onco-therapies.

Acknowledgment

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Technique of Whole-Body Hyperthermia and the Fibromyalgia Syndrome–first Controlled Clinical Trials

Alexander von Ardenne

Von Ardenne Institute of Applied Medical Research GmbH

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Oncothermia Journal 25: 116-130
www.oncothermia-journal.com/journal/2019/Technique_of_whole_body_hyperthermia.pdf

Von Ardenne Institute
of Applied Medical Research
GmbH

non-oncological Hyperthermia

Technique of Whole-Body Hyperthermia and the Fibromyalgia Syndrome

– first Controlled Clinical Trials

Alexander von Ardenne

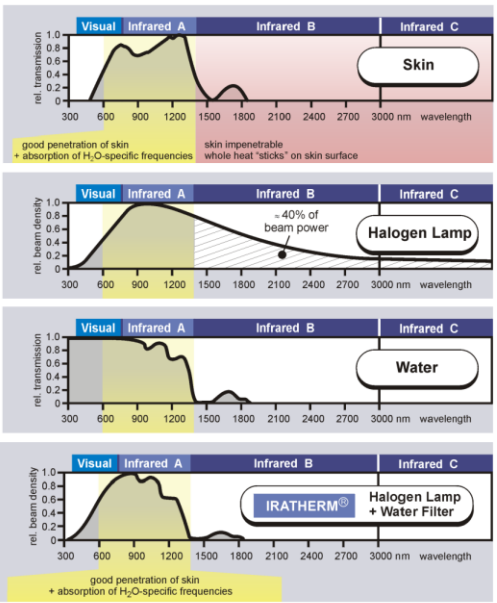
Why Water-Filtered Infrared-A Radiation for Whole-Body Hyperthermia ?

The spectral transmission of skin starts at a long wave visual light of about 600 nm wavelength (see "Visual") and passes the whole infrared-A until its upper long wave limit of about 1,400 nm wavelength. In contrast to that, the skin is nearly impenetrable to heat radiation from the spectral regions of infrared-B and infrared-C. Therefore one can speak of "deep-acting heat" in the case of infrared-A heat radiation, whereas with infrared-B and infrared–C radiation we speak only of "surface heat".

Red light lamps or halogen lamps are well-known and powerful heat radiators. The latter mostly operates on higher power. The following presentation of spectral distribution of a halogen lamp shows that its heat radiation contains 40% of the unwanted, skin–straining infrared-B and infrared–C radiation.

Water is the appropriate choice of filter to eliminate infrared-B and infrared-C radiation because water, similar to skin, has a selective transmission of infrared radiation. This property results from the fact that the skin of an adult consists to 75% of water. Just like skin, water is a good transmitter of infrared-A radiation. While infrared-B and infrared-C are nearly completely absorbed, only small absorption bands (near 950 nm and 1,150 nm) are given in the spectral region of infrared-A.

By placing a water filter in front of a halogen lamp, the result is a heat radiation, with a spectral distribution nearly equal to the spectral transmission of the skin.

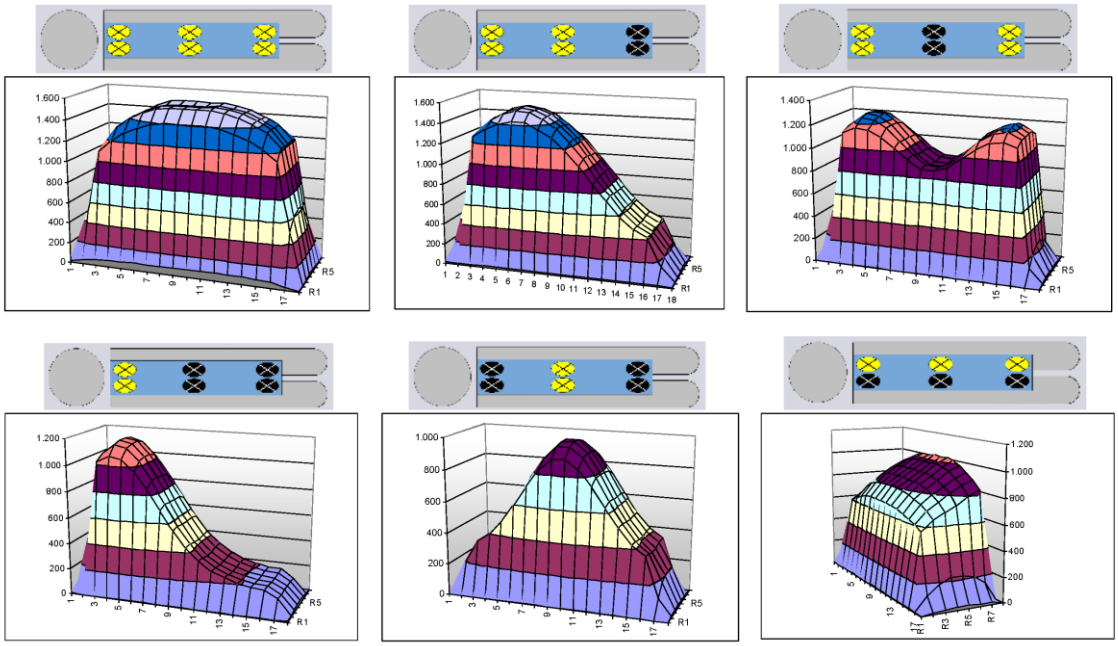


Using water-filtered infrared-A radiation the IRATHERM® allows a much higher irradiation level than that of commercial infrared or halogen lamps at same skin tolerance (Δ = factor 2.6). Water-filtered infrared-A is heat radiation similar to natural sun radiation because natural sun radiation is formed with the help of the humid atmosphere of the earth.

Whole-Body Hyperthermia Equipment „IRATHERM®1000“

with water-filtered infrared-A radiation for body-core temperature untol 40.5 °C and higher

Variation of Irradiance in Level of Patient Net (6 single controllable radiators)



The Three Levels of Whole-Body Hyperthermia (WBH)

	Mild WBH		Moderate WBH		Extreme WBH
Target Temperature body-core, T(rectal)	< 38,5 °C		38,5 °C - 40,5 °C		> 40,5 °C
Duration of Application in the given temp. region	≤ 30 min	> 30 min	≤ 180 min	> 180 min	usually ≥ 60 min
Load of Patient	sweating, no thermoregulatory stress	sweating, no thermoregulatory stress	thermoregulatory stress, unsedeted / lightly sedeted	thermoregulatory stress, lightly / strongly sedeted	thermoregulatory stress, deep intravenous anesthesia or general anesthesia
Supervision of Patient	without care	care by nurse T(axill) or T(rectal) or T(sublingual) or T(tympanal)	care by nurse with medical supervision contineously T(rectal) ± T(axill / tymp) + HF/SpO2 ± ECG sporadic ± NIBP („±" means optional)	care by nurse with medical supervision contineously T(rectal) + T(axill) + HF/SpO2 + ECG/RESP sporadic + NIBP	medically guided treatment intensive monitoring
Range of Indications (selection)	relaxation, wellness	rehabilitation, physiotherapy, rheumatology, orthopaedics	rheumatol., dermatol., oncology, psychiatry, immunology, environmental medicine	oncology chronical infection	oncology, chronical infection

heckel-medizintechnik and Von Ardenne Institute 01/2018

Possible Indications of Moderate Hyperthermia

- arterial hypertension
- overstraining of musculature, especially deep-lying muscles of lumbar region
  (adjuvant to massage treatment)
- chronic back pain
  (after detailed establishing a diagnose)
- fibromyalgia syndrome
- therapy-resistant neuralgias
- migraine
- sub-acute, chronic inflammation
- rheumatic diseases
  (degenerative and sub-acute inflammatory)
- ankylosing spondylitis
- systemic scleroderma
- allergic rhinitis
- bronchial asthma
- neurodermatitis
- depression / SAD
- cancerous diseases
  (an adjuvant measure to standard therapies and immune modulation)
- regeneration or rehabilitation in sports medicine

acc. to K.L. Schmidt: Hyperthermie und Fieber,
M. Heckel: Ganzkörper-Hyperthermie und Fiebertherapie a.o. 06/01

Fibromyalgia Syndrome (FMS)

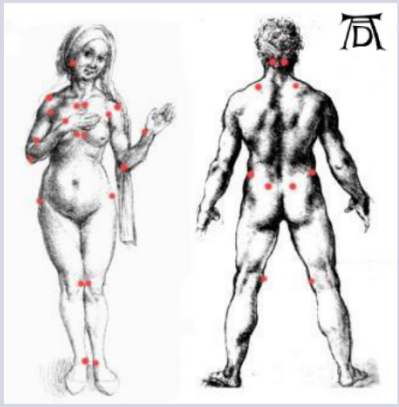
Necessity of interdisciplinary **S3-Guideline**: *„Because of the incidence of FMS, the controversies about its classification and treatment as well as its inappropriate health care“*

- **Definition**

  Core symptoms of FMS are
  chronical pains in several body regions
  among other symptoms like
  sleep disturbances, none-relaxing sleep
  and fatigue (physically and/or spiritually).

- **Prevalence**

  In western industial nations in general adult population
  the prevalence is 0.7 – 3.3%.
  Women are more frequent affected than males.
  Women in (D) between 35 and 74 years: 5.5%.



from S3-Guideline 2012

Fibromyalgia Syndrome (FMS)

S3-G.: Genesis of this disease is still unexplained.
Present state of studies doesn‘t allow a categorical statement about the etiology of FMS.

Risk indicators, Etiology and Pathophysiology (choice)

- Inflammatory-rheumatic diseases, Gene polymorphisms, lack of physical activity, sexual abuse, stress at workplace, ...
- Lack of vitamin D, Infection diseases, changed central pain processing, dysfunction of hypothalamus-hypophysis-adrenocortical axis, ...

Wolfe 2011, Weir 2006, Häuser 2011, Kivimäki 2004, McBeth 2010, Petzke 2010, McBeth 2007, Holliday 2010,

from S3-Guideline 2012

Effect of a Serial Whole-Body Hyperthermia with Water-Filtered Infrared-A Radiation on Fibromyalgia Pain

[Schleenbecker HG, Schmidt KL. Phys Rehab Kur Med 1998;8:113-117]

Pilot Study

Patients

11 female patients (53 ± 5 years)
fibromyalgia (established acc. to Wolfe 1990, Müller 1990, Yunns 1981), known for several month to 12 years

Method

serial mild infrared-A-hyperthermia, 3 x / week, over 3 weeks,
each 30 min duration with rise in T_{tymp} of 1.3 °C

- measurement of tenderness threshold on 24 tenderpoints with dolorimeter
- measurement of subjective pain intensity with pain score for 11 sections of the body
- measurement of subjective pain intensity with visual pain analog scala

Result

Treatment →	Before 1.	After 1.	Before Last	Significance
tenderness threshold	**2.0** ± 0.3	2.3 ± 0.5	**2.2** ± 0.4	n.S.
pain score	**2.5** ± 0.9	1.3 ± 0.6	**1.7** ± 0.5	S.
pain analog scala	**68** ± 7	31 ± 5	**37** ± 16	S.

A mild whole-body hyperthermia with water-filtered infrared-A radiation „*has a significant analgesic effect in fibromyalgia, especially under repeated application*".

Clin J Pain 2007; 1: 67-75

A Randomized Controlled Trial on the Effectiveness of Mild Water-filtered Near Infrared Whole-body Hyperthermia as an Adjunct to a Standard Multimodal Rehabilitation in the Treatment of Fibromyalgia

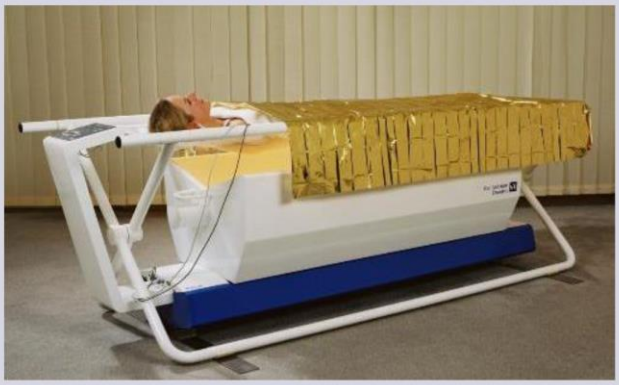
Thomas Brockow MD, Andreas Wagner MD, Annegret Franke PhD, Martin Offenbächer MD MPH and Karl L. Resch MD PhD

Efficacy of a serial Whole-Body Hyperthermia by wIRA (NI-WBH) as an Adjunct to a Standard Rehabilitation (MR) in the Treatment of Fibromyalgia

[Brockow T, Wagner A, Franke A, Offenbaecher M, Resch KL. The Clinical Journal of Pain 2007;1:67-75]

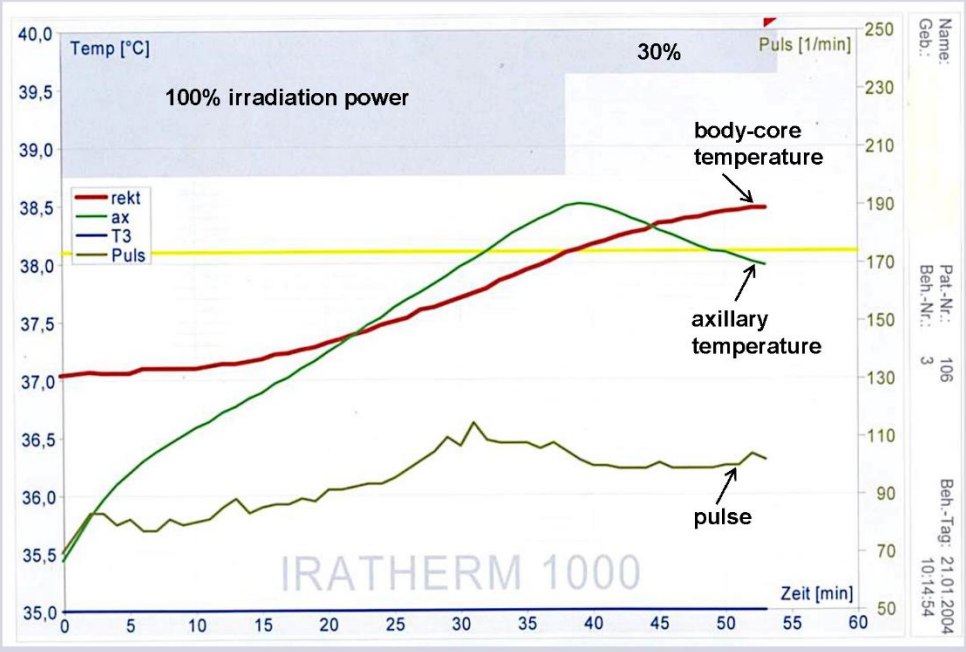
- Inclusion of 139 patients:
  - fulfillment of ACR 1990 criteria for fibromyalgia[1)]
  - pain intensity of last week ≥ 40 mm on 100 mm pain intensity VAS
  - physical-functioning subscale FIQ-G [x)] ≥ 1.2 [2)]
  - age 18 … 70 years

- Device: IRATHERM®1000, using exclusively water-filtered infrared-A heat-radiation



[1)] Wolfe et al. 1990,
[2)] Offenbächer et al. 2000
[x)] German Version of„Fibromyalgia Impact Questionnaire“

WBH Treatment with Water-Filtered Infrared-A Radiation



Efficacy of a serial W
Adjunct to a Standar
[Brockow T, Wagner A, Frank

a
75]

Multimodal Rehabilitation (**MR**)

5 x 60' pain management (relaxation techniques...)
6 x 30' muscular cardiorespiratory and endurance training
6 x 30' water-based exercises (34°C water temperature)
6 x 30' flexibility training
6 x 30' ergometer training (Pulse = 180-age)
6 x ↕Δt occupational therapy (group therapy)
3 x 90' health education (self exercise programs ...)
1 x 90' nutritional consulting
Additive: indication related treatment of concomitant diseases

- Patients got **randomised**:

either a **standard multimodal rehabilitation (MR)**
+ a **mild water filtered infrared-A Whole-Body Hyperthermia (WBH)**
(body-core target temperature 38.1°C; 6 sessions/3 weeks)

study group — NI-WBH + MR

or **exclusively**
a **standard multimodal rehabilitation**

control group — MR

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[Brockow T, Wagner A, Franke A, Offenbaecher M, Resch KL. The Clinical Journal of Pain 2007;1:67-75]

- **Primary Objective Parameter**

  - affective pain (McGill Pain Questionaire,
  - sensory pain German version)

  Secundary Objective Parameter

  - pain intensity (pain scale of FIQ)
  - FM-related quality of life (FIQ2000, German version)

- **Clinical Instruments**

  - total number tender points
  - mean tender point threshold
  - total tender point pain intensity

- **Measuring Points in Time**

  - before and after intervention,
    3 and 6 month after end of intervention

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[Brockow T, Wagner A, Franke A, Offenbaecher M, Resch KL. The Clinical Journal of Pain 2007;1:67-75]

Results

NI-WBH + MR / MR	baseline	end of therapy	3 mon after	6 mon after	significance
affective pain	35,5 / 37,1	-11,4 / -6,2	- 8,2 / -3,1	- 6,2 / -2,1	P < 0,0005
sensory pain	22,3 / 22,0	- 3,9 / -1,4	- 3,7 / +0,4	- 2,5 / +0,9	P = 0,001
pain intensity	6,4 / 6,2	- 2,4 / -0,9	- 1,6 / +0,1	- 1,2 / +0,2	P < 0,0005
QOL	43,3 / 45,6	-17,5 / -11,6	-13,6 / -2,5	- 9,5 / -0,4	P < 0,0005
pain intensity (TP's)	1036 / 1017	-139 / -32			P < 0,001

„NI-WBH + MR is superior to MR only in relation to pain control and amelioration of FM-specific QOL. These findings are remarkable because effectiveness of NI-WBH has been evaluated in addition to a multimodal rehabilitation program. ... all side effects were disappearing within 30 min after NI-WBH."

NI-WBH = **N**ear-**I**nfrared **W**hole-**B**ody **H**yperthermia
MR = **M**ultimodal **R**ehabilitation

Efficacy of a serial Whole-Body Hyperthermia by wIRA (NI-WBH) as an Adjunct to a Standard Rehabilitation (MR) in the Treatment of Fibromyalgia

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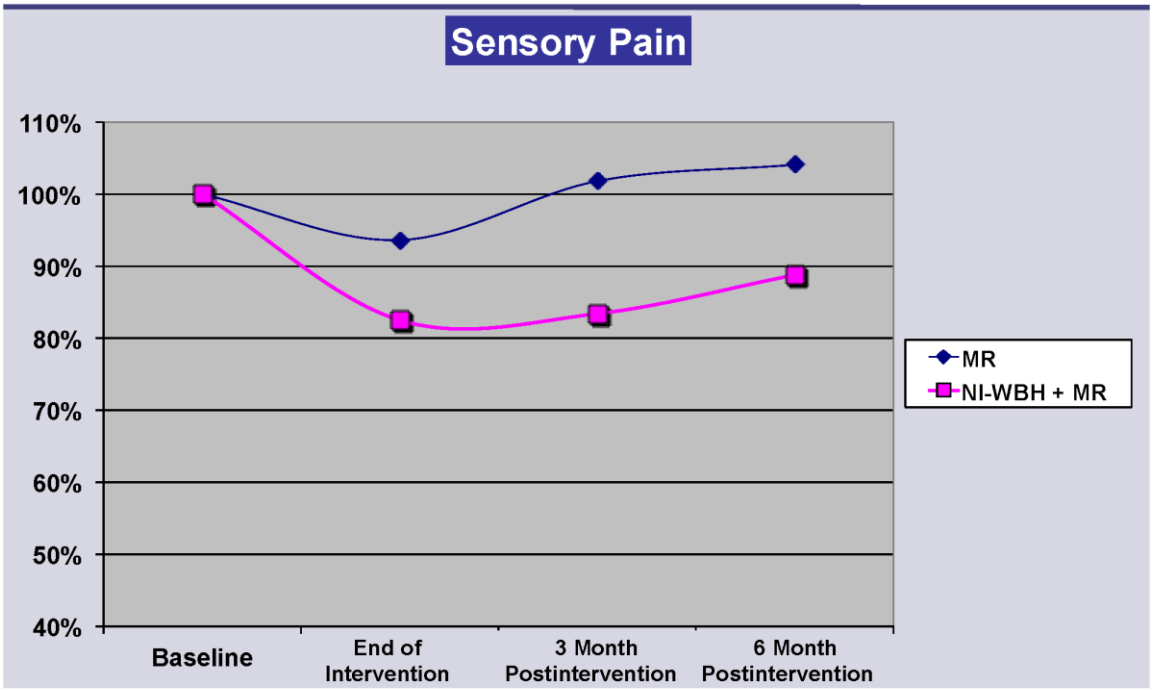

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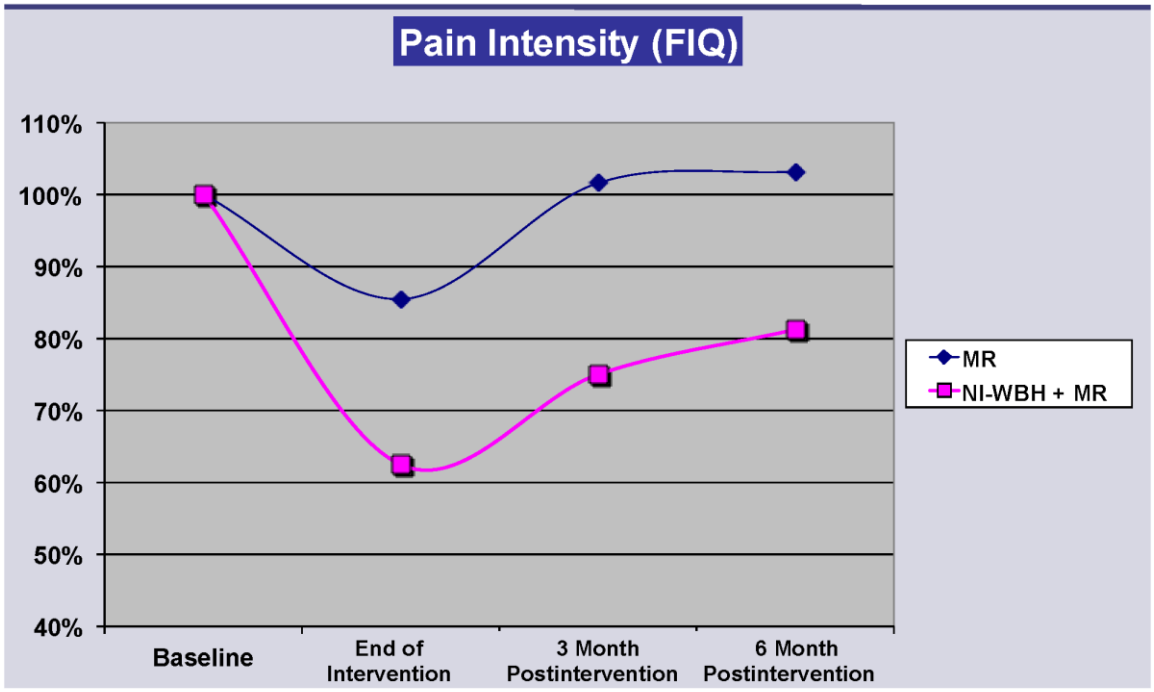

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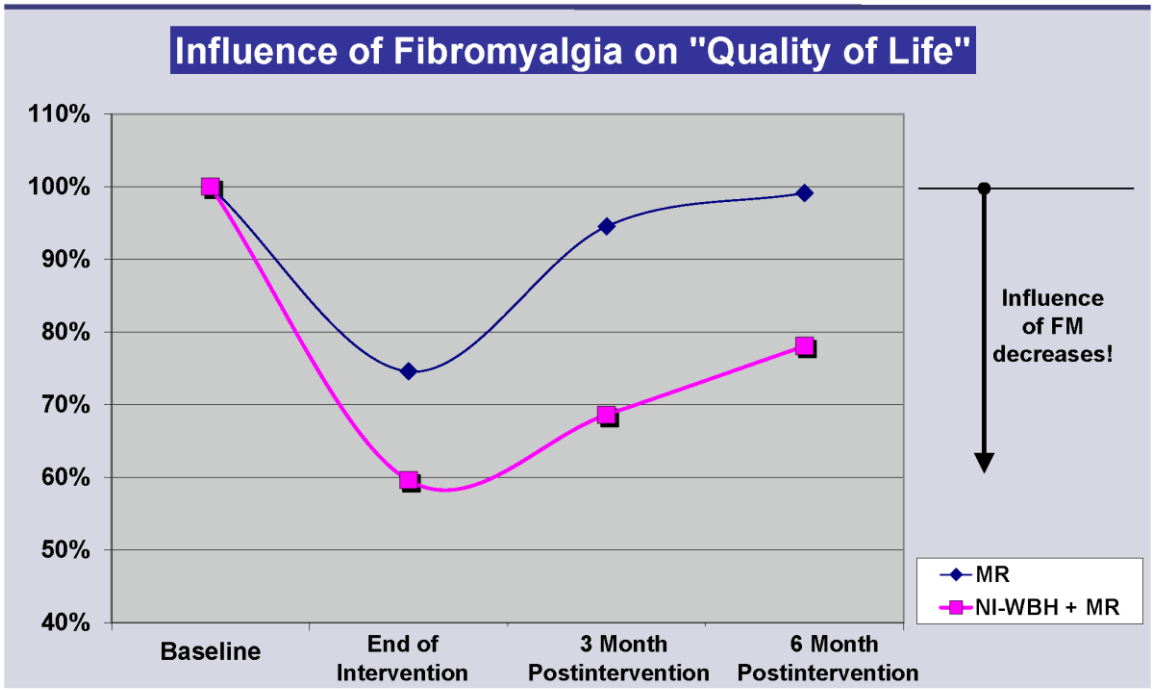

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Effect Sizes (95% Confidence Interval)	End of Therapy	3 Month after End of Therapy	6 Month after End of Therapy
affective pain	**0.60** (0.26-0.94)	**0.54** (0.20-0.88)	**0.44** (0.10-0.78)
sensory pain	**0.42** (0.08-0.76)	**0.62** (0.29-0.96)	**0.46** (0.12-0.80)
pain intensity	**0.60** (0.25-0.94)	**0.59** (0.25-0.94)	**0.51** (0.16-0.85)
FIQ-G-shortened	**0.41** (0.07-0.75)	**0.72** (0.37-1,08)	**0.60** (0.25-0.95)
FIQ-G		**0.75** (0.40-1,10)	**0.59** (0.25-0.93)
mean tender point threshold	**0.53** (0.19-0.87)		
total tender point pain intensity	**0.66** (0.31-1,00)		
total number tender points	**0.44** (0.10-0.78)		

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Summary

Study group (NI-WBH + MR) showed:

- significant treatment effects for all study parameters
- superior pain reduction versus standard therapy alone
- clinically relevant mean effect sizes
- sustainability until 6-month-follow-up
- side effects in 20% of study patients (especially blood pressure dysregulations), short-lived and disappearing in < 30 min after NI-WBH

„The German Fibromyalgia Consumer Report“ 2012, in which 1.661 Affected People Evaluated the Effect of Therapies

[Häuser W, Jung E, Möller B, Gesmann M, Langhorst J, Weiss T, Thoma R. Schmerz 2012;26:150-159]

TOP TEN
of Patients
most beneficially perceived Therapies
in Fibromyalgia

- whole-body heat therapy
- thermal bathes
- fibromyalgia education
- laying down and resting
- local heat therapy
- lymphatic drainage
- functional training
- bathes
- osteopathy
- dance therapy

Efficacy of a serial Whole-Body Hyperthermia by wIRA (NI-WBH) as an Adjunct to a Standard Rehabilitation (MR) in the Treatment of Fibromyalgia

[Walz J, Hinzmann J, Haase I, Witte T. Der Schmerz 2013;1:38-45]

Controlled Clinical Trial with 6 Month Follow-Up

Patients

Fibromyalgia (in acc. to ACR1990 criteria for FM, age18...70 years)
67 pat., **MR**-group 21 Pat. (50 ± 11y) ↔ **NI-WBH1** + **MR**-group 20 pat. (54 ± 8y) **1** x / week over 3 weeks
↔ **NI-WBH2** + **MR**-group 26 pat. (57 ± 9y) **2** x / week over 3 weeks

Therapy

standard rehabilitation (**MR**) ± serial mild infrared-A hyperthermia (**NI-WBH1** and **NI-WBH2**)
increase of body-core temperature within 40 min until T_{rect} = 38.0 °C plus 18 min plateau phase

Prim.Outcome:	measuring of pain intensity	by 11 stepped numerical rating-scale (NRS)
Sec. Outcome:	measuring of affective pain	by 14 stepped items (emotional)
	measuring of sensory pain	by 10 stepped items (body related)
	measuring of FMS related quality of life	by German version FIQ-G (QOL)
	measuring of depression	by subscale out of the Brief Symptom Inventory

Result

NI-WBH1 / NI-WBH2 / MR	baseline	end of therapy	6 mon post	significance
pain intensity (NRS)	**7.2 / 7.4** / 6.9	**-2.9 / -2.7** / -0.9	**-3.0 / -1.8** / -0.5	P < 0.001
affective pain	**37.2 / 41.3** / 36.8	**-7.5 / -9.5** / -2.7	**-9.0 / -3.8** / -0.9	P = 0.005
sensory pain	**20.4 / 24.5** / 24.3	**-0.7 / -2.5** / -1.6	**-2.4 / -0.7** / -2.0	P = 0.462
QOL	**54.6 / 53.4** / 47.3	**-21.2 / -17.9** / -7.1	**-14.7 / -8.1** / -3.1	P = 0.014
depression	**2.5 / 2.4** / 2.3	**-0.9 / -0.6** / -0.5	**-0.6 / -0.3** / -0.2	P = 0.451

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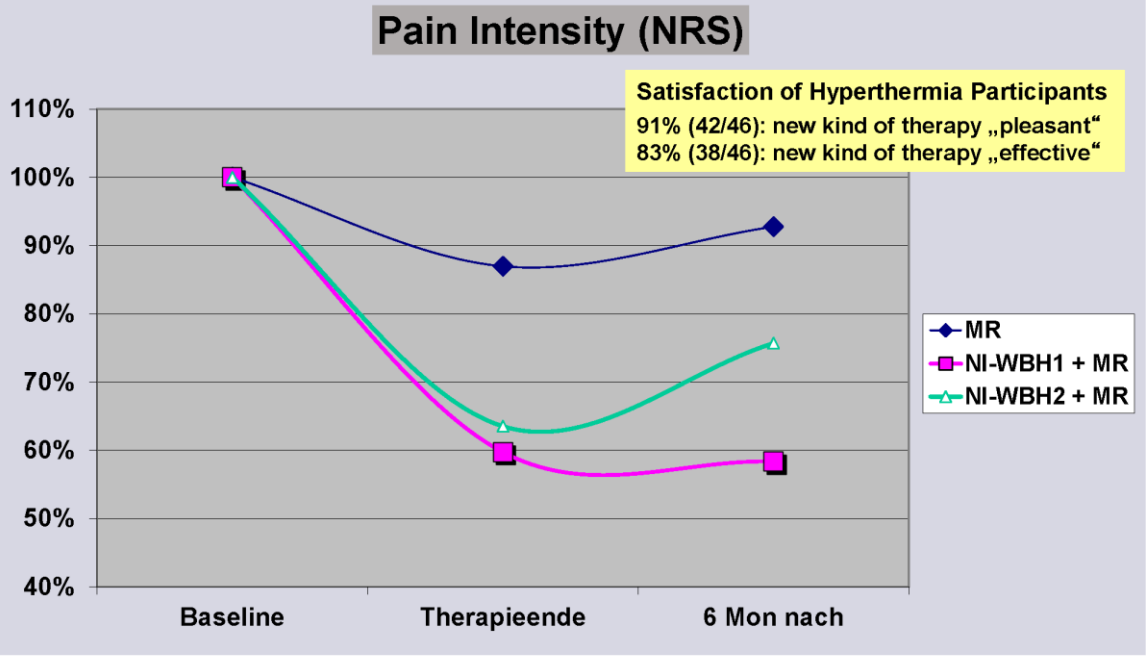

Microcirculation Abnormalities in Patients with Fibromyalgia

[Morf S, Vesti B, Forster A, Franzeck U, Koppensteiner R, Uebelhart D, Sprott H. Arthritis Res Ther 2005,7]

Unblinded Preliminary Case-Control Study

Patients

10 women (54,0 ± 3,7 years) with Fibromyalgia (**FM**), classified in accordance with criteria of ACR
3 control groups: 10 healthy women
10 women with Rheumatoid Arthritis
10 women with Systemic Scleroderma
} age-matched to FM

Method

Observation of microcirculation by intravital capillary microscopy and laser-Doppler fluxmetry

Result

- FM-patients had compared with healthy controls:
  - significantly fewer capillaries in nail fold ($P < 0.001$)
  - significantly more capillary dilatations in nail fold ($P < 0.05$)
  - significantly more irregular capillary formations in nail fold ($P < 0.01$)
- Peripheral blood flow in FM patients was much less than in healthy controls ($P < 0.001$), but did not differ from that of Systemic Scleroderma patients ($P = 0.73$)

„The data suggest that functional disturbances of microcirculation are present in FM patients and that morphological abnormalities may also influence their microcirculation.“

Small Fiber Pathology in Patients with Fibromyalgia Syndrome

[Üceyler N, Zeller D, Kahn AK, Kewenig S, Kittel-Schneider S, Sommer C. Brain 2013; 136:1857-67]

Prospective Case-Control Study

Patients

25 patients (59, 50-70 years) with Fibromyalgia (**FM**), diagnosed according to 1990 ACR-criteria
10 patients (50, 39-75 years) with monopolar Depression without pain

control group: 55 healthy subjects matched for age and gender related to FM-group

Method

quantification: intradermal nerve fibre density in skin punch biopsies of lower leg and upper thigh
examination: small fibre function by quantitat. sensory testing and pain-related evoked potentials

Result

FM-patients compared with healthy controls:

- signif. reduced total nerve fibres in skin biopsies at lower leg and upper thigh ($P < 0.001$)
- signif. increased neuropathic pain ($P < 0.001$)
- signif. impaired small fibre function ($P < 0.001$)
  with increased cold and warm detection thresholds
- signif. reduced amplitudes of pain-related evoked potentials ($P < 0.001$)
  upon stimulation of face, hands and feet

„All three methods used (in this study) *support the concept of impaired small fiber function in patients with fibromyalgia syndrome, pointing towards a neuropathic nature of pain in fibromyalgia syndrome."*

Our Hypothesis for the Cause of Fibromyalgia Syndrome

By living poor in exercise,
which is typical for the living style
of western industrial countries today,
the degeneration of microcirculation
is accelerated as one gets older.

abnormality of microcirculation

[Morf S, et al. Arthritis Res Ther 2005]

Consequence

The more and more reduced supply
of the intercapillary region generates
a pathological milieu in the tissues.
Hence, also the small fibers degenerate
and some die off. Probably in this phase
before they die off they signalize pain.

small fiber pathology

[Üceyler N, et al. Brain 2013]

2016

Message

A healthy microcirculation serves as **disease prevention**
by securing of a healthy milieu in the intercapillary region.

by

- a proper supply of all cells and tissues with H_2O, O_2, nutrients, immune cells, etc. but also
- a proper disposal of metabolic end products.

A healthy microcirculation is essential, to guide the humans
healthy through the life until their old age.

The broad **action spectrum of whole-body hyperthermia**,
based on sunlike heat radiation, can be a helpful instrument
in the orchestra of the future Integrative Medicine.

www.iratherm.de **Thanks**

Conventional, „standard" chemotherapy protocols for modulated electro-hyperthermia (mEHT, trade name: mEHT ®)

Dr. Szasz A. Marcell
Oncology Center, Semmelweiss University, Budapest, Hungary,
szasz.attila_marcell@med.semmelweis-univ.hu

Marcell A. Szasz (2019): Conventional, „standard" chemotherapy protocols for modulated electro-hyperthermia (mEHT, trade name: oncothermia ®), Oncothermia Journal 25: 131-
www.oncothermia-journal.com/journal/2019/Conventional_standard_chemotherapy.pdf

My objective to collect the standard protocols, which are conventionally in use together with modulated electro-hyperthermia (mEHT). These protocols do not contain the newest non-chemo-based therapies, like antibodies, gene therapies, immune-therapies, check-point-inhibitors, CAR T-cell therapy, etc., limited only on the classical chemotherapies, which are widely used in first- and second-line therapies. The protocols intended to help the mEHT professionals to choose the best protocol fort their patients. The protocols show only one cycle of mEHT fitted to the given chemotherapy at first. It could be repeated with continuous basis on the same composition, or when a longer period is in the protocol without administering chemo-therapy, but knowing the active effect on the disease, the mEHT could be continued at every send day as highest frequency of its application. When the toxicity of the chemo-therapy reaches its tolerance limit by repeated cycles, mEHT could be continued with control of its efficacy.

The collected protocols are:

7022 Chemotherapy, 5FU Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C18, C19H0, C20H0, C21

5FU 5FLUOROURACYL Dose: 500 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
5FU	5FLUOROURACYL	↑			
	mEHT	↑			↑

7024 Chemotherapy, ADM-Tegafur Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C16, C17, C18, C19H0, C20H0, C2100

ADM ADRIBLASTINA Dose: 25 (mg/m²)

FTOR FTORAFUR Dose: 400 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
ADM	ADRIBASTINA	↑						
FTOR	FTORAFUR		↑	↑	↑	↑	↑	↑
	mEHT	↑			↑			↑

Treatment days from the onset of the cycle:		8
ADM	ADRIBASTINA	
FTOR	FTORAFUR	↑
	mEHT	

7025 Chemotherapy, Holoye Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 16 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C70

BLM	BLEOMICIN	Dose:	15	[mg/m²]
CPH	CYCLOPHOSPHAMID	Dose:	100	[mg/m²]
MTX	METHOTREXAT	Dose:	10	[mg/m²]
5FU	5FLUOROURACYL	Dose:	400	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5
BLM	BLEOMICIN	↑	↑	↑	↑	
CPH	CYCLOPHOSPHAMID	↑	↑	↑	↑	↑
MTX	METHOTREXAT	↑	↑	↑	↑	↑
5FU	5FLUOROURACYL	↑				↑
	mEHT	↑			↑	

7026 Chemotherapy, Creagan Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C50, C56H0, C76

CPH	CYCLOPHOSPHAMID	Dose:	200	[mg/m²]
ADM	ADRIBLASTINA	Dose:	20	[mg/m²]
CDDP	CIS-PLATINUM	Dose:	20	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
ADM	ADRIBLASTINA	↑			
CDDP	CIS-PLATINUM	↑			
	mEHT	↑			↑

7027 Chemotherapy, Carboplatin-5-FU Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 24 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C76

CBP CARBOPLATIN Dose: 200 [mg/m²]

5FU 5FLUOROURACYL Dose: 500 [mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4
CBP	CARBOPLATIN	↑			
5FU	5FLUOROURACYL	↑	↑	↑	↑
	mEHT	↑			↑

7028 Chemotherapy, CEB Protocol + HT

Protocol Period : 5 [Day]

Interval between protocols : 25 [Day]

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C81

CCNU CYCLO-HEXYL-NITROSO-UREA Dose: 40 [mg/m²]

VP VEPESID Dose: 50 [mg/m²]

STER STER Dose: 30 [mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5
CCNU	CYCLO-HEXYL-NITROSO-UREA	↑				
VP	VEPESID	↑	↑	↑	↑	↑
STER	STER	↑	↑	↑	↑	↑
	mEHT	↑			↑	

7029 Chemotherapy, CVB Protocol + HT

Protocol Period : 15 [Day]

Interval between protocols 13 [Day]

Diagnoses:

C15

CDDP	CIS-PLATINUM	Dose:	60	(mg/m²)
VDS	VINDESINE	Dose:	2	(mg/m²)
BLM	BLEOMICIN	Dose:	10	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CDDP	CIS-PLATINUM	↑						
VDS	VINDESINE	↑						
BLM	BLEOMICIN	↑		↑	↑	↑	↑	
	mEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CDDP	CIS-PLATINUM							
VDS	VINDESINE	↑						
BLM	BLEOMICIN							
	mEHT	↑						

Treatment days from the onset of the cycle:		15
CDDP	CIS-PLATINUM	
VDS	VINDESINE	↑
BLM	BLEOMICIN	
	mEHT	↑

7030 Chemotherapy, EEP Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C16, C17, C18, C19H0, C20H0, C21

EPI	EPIRUBICIN	Dose:	15	(mg/m²)
VP	VEPESID	Dose:	100	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	20	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
EPI	EPIRUBICIN	↑	↑	↑	↑	↑
VP	VEPESID	↑		↑	↑	
CDDP	CIS-PLATINUM	↑		↑	↑	
	mEHT	↑			↑	

7031 Chemotherapy, ELF Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C16, C17, C18, C19H0, C20H0, C21

VP	VEPESID	Dose:	60	(mg/m²)
FOLINAC	FOLINSAV	Dose:	100	(mg/m²)
5FU	5FLUOROURACYL	Dose:	400	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
VP	VEPESID	↑	↑		↑
FOLINAC	FOLINSAV	↑	↑		↑
5FU	5FLUOROURACYL	↑	↑		↑
	mEHT	↑			↑

7032 Chemotherapy, Epirubicin-Cisplatin Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 19 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C45, C46, C47, C48, C49, C56H0, C76

CDDP	CIS-PLATIN	Dose:	25	(mg/m²)
EPI	EPIRUBICIN	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATIN	↑			
EPI	EPIRUBICIN	↑	↑		
	mEHT	↑			↑

7033 Chemotherapy, FAM Protocol + HT

Protocol Period : 35 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C16, C17, C18, C19H0, C20H0, C21, C25

5FU 5FLUOROURACYL Dose: 400 (mg/m²)

ADM ADRIBLASTINA Dose: 20 (mg/m²)

MMC MITOMYCIN C Dose: 5 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
5FU	5FLUOROURACYL	↑						
ADM	ADRIBLASTINA	↑						
MMC	MITOMYCIN C				↑			
	mEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
5FU	5FLUOROURACYL	↑						
ADM	ADRIBLASTINA							
MMC	MITOMYCIN C							
	mEHT	↑						

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
5FU	5FLUOROURACYL							
ADM	ADRIBLASTINA							
MMC	MITOMYCIN C							
	mEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26	27	28
5FU	5FLUOROURACYL							↑
ADM	ADRIBLASTINA							
MMC	MITOMYCIN C							
	mEHT							↑

Treatment days from the onset of the cycle:		29	30	31	32	33	34	35
5FU	5FLUOROURACYL							↑
ADM	ADRIBLASTINA			↑				
MMC	MITOMYCIN C							
	mEHT			↑				↑

7036 Chemotherapy, FAP/A Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C15

5FU	5FLUOUROURACYL	Dose:	400	(mg/m²)
ADM	ADRIBLASTINA	Dose:	15	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
5FU	5FLUOUROURACYL	↑	↑	↑	↑	↑	↑	↑
ADM	ADRIBLASTINA	↑						
CDDP	CIS-PLATINUM	↑						
	mEHT	↑			↑			↑

Treatment days from the onset of the cycle:		8
5FU	5FLUOUROURACYL	↑
ADM	ADRIBLASTINA	
CDDP	CIS-PLATINUM	
	mEHT	

7037 Chemotherapy, FEM Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C16, C17, C18, C19H0, C20H0, C21, C22, C23H0, C24, C25

5FU	5FLUOUROURACYL	Dose:	400	(mg/m²)
EPI	EPIRUBICIN	Dose:	30	(mg/m²)
MMC	MITOMYCIN C	Dose:	10	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
5FU	5FLUOUROURACYL	↑			↑
EPI	EPIRUBICIN				↑
MMC	MITOMYCIN C	↑			
	mEHT	↑			↑

7038 Chemotherapy, 5-FU INF.-CDDP Protocol + HT

Protocol Period : 1 (Day)

Interval between protocols : 6 (Day)

Diagnoses:

C18, C19H0, C20H0, C21

5FU	5FLUOUROURACYL	Dose:	300	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	20	(mg/m²)

Treatment days from the onset of the cycle:		1
5FU	5FLUOUROURACYL	↑
CDDP	CIS-PLATINUM	↑
	mEHT	↑

7039 Chemotherapy, FUEPI Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C18, C19H0, C20H0, C21

5FU 5FLUOUROURACYL Dose: 400 (mg/m²)

EPI EPIRUBICIN Dose: 20 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
5FU	5FLUOUROURACYL	↑	↑	↑	↑	↑
EPI	EPIRUBICIN	↑			↑	
	mEHT	↑			↑	

7040 Chemotherapy, induction Protocol (Head & neck-Tumors) + HT

Protocol Period : 28 (Day)

Interval between protocols : 13 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

5FU 5FLUOUROURACYL Dose: 400 (mg/m²)

BLM BLEOMICIN Dose: 10 (mg/m²)

MMC MITOMYCIN C Dose: 4 (mg/m²)

HU HYDROXI-UREA Dose: 100 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CDDP	CIS-PLATINUM	↑						
5FU	5FLUOROURACYL	↑		↑	↑	↑		↑
BLM	BLEOMICIN							
MMC	MITOMYCIN C							
HU	HYDROXI-UREA							
	mEHT	↑			↑			↑

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CDDP	CIS-PLATINUM							
5FU	5FLUOROURACYL							
BLM	BLEOMICIN							↑
MMC	MITOMYCIN C							
HU	HYDROXI-UREA							
	mEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
CDDP	CIS-PLATINUM							
5FU	5FLUOROURACYL							
BLM	BLEOMICIN							
MMC	MITOMYCIN C							
HU	HYDROXI-UREA							
	mEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26	27	28
CDDP	CIS-PLATINUM							
5FU	5FLUOROURACYL							
BLM	BLEOMICIN							↑
MMC	MITOMYCIN C							
HU	HYDROXI-UREA	↑	↑	↑				
	mEHT	↑						↑

7041 Chemotherapy, MBC Protocol + HT

Protocol Period : 14 (Day)

Interval between protocols : 14 (Day)

Diagnoses:

C15

MTX METHOTREXAT Dose: 20 (mg/m²)

BLM BLEOMICIN Dose: 10 (mg/m²)

CDDP CIS-PLATINUM Dose: 30 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
MTX	METHOTREXAT	↑						
BLM	BLEOMICIN	↑						
CDDP	CIS-PLATINUM				↑			
	mEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
MTX	METHOTREXAT							↑
BLM	BLEOMICIN	↑						↑
CDDP	CIS-PLATINUM							
	mEHT	↑						↑

7042 Chemotherapy, Platinum-5-FU Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C76

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

5FU 5FLUOUROURACYL Dose: 500 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
CDDP	CIS-PLATINUM	↑				

5FU	5FLUOUROURACYL	↑	↑	↑	↑	↑
	mEHT	↑			↑	

7044 Chemotherapy, 5FU+LV low dose Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C18

5FU 5FLUOUROURACYL Dose: 500 (mg/m²)

FOLINAC FOLINSÄURE Dose: 100 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
5FU	5FLUOUROURACYL	↑	↑	↑	↑	↑
FOLINAC	FOLINSÄURE	↑	↑	↑	↑	↑
	mEHT	↑			↑	

7046 Chemotherapy, 5FU+LV II. Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C18

5FU 5FLUOUROURACYL Dose: 400 (mg/m²)

FOLINAC FOLINSÄURE Dose: 400 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
5FU	5FLUOUROURACYL	↑	↑	↑	↑	↑
FOLINAC	FOLINSÄURE	↑	↑	↑	↑	↑
	mEHT	↑			↑	

7047 Chemotherapy, Irinothecan (campto) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C18

CPT-11 IRINOTHECAN (CAMPTO) Dose: 200 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPT-11	IRINOTHECAN (CAMPTO)	↑			
	mEHT	↑			↑

7048 Chemotherapy, CDDP+MTX+BLM+VCR Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 13 (Day)

Diagnoses:

C00, C01H0, C02, C03, C04, C05, C06, C07H0, C08, C09, C10, C11, C12H0, C13, C14, C30, C31, C32, C76

MTX METHOTREXAT Dose: 20 (mg/m²)

BLM BLEOMICIN Dose: 10 (mg/m²)

VCR VINCRISTIN Dose: 1 (mg/m²)

CDDP CIS-PLATINUM Dose: 25 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
MTX	METHOTREXAT	↑						
BLM	BLEOMICIN	↑						
VCR	VINCRISTIN	↑						
CDDP	CIS-PLATINUM				↑			
	mEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
MTX	METHOTREXAT							
BLM	BLEOMICIN	↑						

VCR	VINCRISTIN	↑						
CDDP	CIS-PLATINUM							
	mEHT	↑						

Treatment days from the onset of the cycle:		15
MTX	METHOTREXAT	↑
BLM	BLEOMICIN	↑
VCR	VINCRISTIN	↑
CDDP	CIS-PLATINUM	
	mEHT	↑

7049 Chemotherapy, Ralitrexed (tomudex) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C18

RAL RALITREXED (TOMUDEX) Dose: 1,5 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
RAL	RALITEXED (TOMUDEX)	↑			
	MEHT	↑			↑

7071 Chemotherapy, CAMP Protocol + HT

Protocol Period : 10 (Day)

Interval between protocols : 18 (Day)

Diagnoses:

C34

CPH CYCLOPHOSPHAMID Dose: 200 (mg/m²)

ADM ADRIBLASTINA Dose: 10 (mg/m²)

MTX METHOTREXAT Dose: 10 (mg/m²)

PCZ PROCARBAZIN Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CPH	CYCLOPHOSPHAMID	↑	↑	↑	↑	↑	↑	↑
ADM	ADRIBLASTINA	↑	↑	↑	↑	↑	↑	↑
MTX	METHOTREXAT	↑	↑	↑	↑	↑	↑	↑
PCZ	PROCARBAZIN	↑	↑	↑	↑	↑	↑	↑
	MEHT	↑			↑			↑

Treatment days from the onset of the cycle:		8	9	10
CPH	CYCLOPHOSPHAMID			↑
ADM	ADRIBLASTINA			↑
MTX	METHOTREXAT			↑
PCZ	PROCARBAZIN	↑	↑	↑
	MEHT	↑		↑

7072 Chemotherapy, CEP-METC Protocol + HT

Protocol Period : 29 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C34

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
EPI	EPIRUBICIN	Dose:	25	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	40	(mg/m²)
MTX	METHOTREXAT	Dose:	20	(mg/m²)
VP	VEPESID	Dose:	100	(mg/m²)
CCNU	CYCLO-HEXYL-NITROSO-UREA	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CPH	CYCLOPHOSPHAMID	↑						
EPI	EPIRUBICIN				↑			
CDDP	CIS-PLATINUM	↑						
MTX	METHOTREXAT							
VP	VEPESID							

CCNU	CYCLO-HEXYL-NITROSO-UREA							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
CDDP	CIS-PLATINUM							
MTX	METHOTREXAT							
VP	VEPESID							
CCNU	CYCLO-HEXYL-NITROSO-UREA							
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
CDDP	CIS-PLATINUM							
MTX	METHOTREXAT							
VP	VEPESID							
CCNU	CYCLO-HEXYL-NITROSO-UREA							
	MEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26	27	28
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
CDDP	CIS-PLATINUM							
MTX	METHOTREXAT							
VP	VEPESID					↑		
CCNU	CYCLO-HEXYL-NITROSO-UREA							
	MEHT					↑		

Treatment days from the onset of the cycle:		29	
CPH	CYCLOPHOSPHAMID		
EPI	EPIRUBICIN		
CDDP	CIS-PLATINUM		
MTX	METHOTREXAT	↑	
VP	VEPESID		
CCNU	CYCLO-HEXYL-NITROSO-UREA	↑	
	MEHT	↑	

7073 Chemotherapy, CEVET Protocol + HT

Protocol Period : 7 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C34

CPH	CYCLOPHOSPHAMID	Dose:	500	(mg/m²)
EPI	EPIRUBUCIN	Dose:	30	(mg/m²)
VCR	VINCRISTIN	Dose:	1	(mg/m²)
VP	VEPESID	Dose:	100	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CPH	CYCLOPHOSPHAMID	↑						
EPI	EPIRUBICIN	↑						
VCR	VINCRISTIN	↑						
VP	VEPESID				↑	↑		↑
	MEHT	↑			↑			↑

7076 Chemotherapy, CDDP-VNB Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C34

CDDP CIS-PLATINUM Dose: 40 (mg/m²)

VNB VINORELBIN Dose: 15 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CDDP	CIS-PLATINUM	↑						
VNB	VINORELBIN	↑						
	MEHT	↑						

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CDDP	CIS-PLATINUM							
VNB	VINORELBIN	↑						
	MEHT	↑						

Treatment days from the onset of the cycle:		15
CDDP	CIS-PLATINUM	
VNB	VINORELBIN	↑
	MEHT	↑

7077 Chemotherapy, ECO-ETP Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 5 (Day)

Diagnoses:

C34

EPI EPIRUBICIN Dose: 20 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 400 (mg/m²)

VCR VINCRISTIN Dose: 1 (mg/m²)

VP VEPESID Dose: 100 (mg/m²)

CDDP CIS-PLATINUM Dose: 40 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
EPI	EPIRUBICIN	↑			↑			

CPH	CYCLOPHOSPHAMID	↑			↑			
VCR	VINCRISTIN	↑						
VP	VEPESID	↑	↑	↑				
CDDP	CIS-PLATINUM				↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
EPI	EPIRUBICIN							
CPH	CYCLOPHOSPHAMID							
VCR	VINCRISTIN	↑						
VP	VEPESID							
CDDP	CIS-PLATINUM							
	MEHT	↑						

Treatment days from the onset of the cycle:		15
EPI	EPIRUBICIN	
CPH	CYCLOPHOSPHAMID	
VCR	VINCRISTIN	
VP	VEPESID	
CDDP	CIS-PLATINUM	↑
	MEHT	↑

7078 Chemotherapy, EPI-CDDP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C34

EPI EPIRUBICIN Dose: 30 (mg/m^2)

CDDP CIS-PLATINUM Dose: 30 (mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
EPI	EPIRUBICIN	↑			
CDDP	CIS-PLATINUM				↑
	MEHT	↑			↑

7079 Chemotherapy, EPICO Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 7 (Day)

Diagnoses:

C34

EPI EPIRUBICIN Dose: 20 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 400 (mg/m²)

VCR VINCRISTIN Dose: 1 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
EPI	EPIRUBICIN	↑			↑			
CPH	CYCLOPHOSPHAMID	↑			↑			
VCR	VINCRISTIN	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
EPI	EPIRUBICIN							
CPH	CYCLOPHOSPHAMID							
VCR	VINCRISTIN	↑						
	MEHT	↑						

Treatment days from the onset of the cycle:		15
EPI	EPIRUBICIN	
CPH	CYCLOPHOSPHAMID	
VCR	VINCRISTIN	↑
	MEHT	↑

7080 Chemotherapy, FOMI-CAP Protocol + HT

Protocol Period : 29 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C34

5FU	5FLUOROURACYL	Dose:	400	(mg/m²)
VCR	VINCRISTIN	Dose:	1	(mg/m²)
MMC	MITOMYCIN C	Dose:	5	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	200	(mg/m²)
ADM	ADRIBLASTINA	Dose:	20	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
5FU	5FLUOROURACYL	↑	↑	↑	↑			
VCR	VINCRISTIN	↑						
MMC	MITOMYCIN C	↑						
CPH	CYCLOPHOSPHAMID							
ADM	ADRIBLASTINA							
CDDP	CIS-PLATINUM							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
5FU	5FLUOROURACYL							
VCR	VINCRISTIN							
MMC	MITOMYCIN C							
CPH	CYCLOPHOSPHAMID							
ADM	ADRIBLASTINA							
CDDP	CIS-PLATINUM							
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
5FU	5FLUOROURACYL							

VCR	VINCRISTIN							
MMC	MITOMYCIN C							
CPH	CYCLOPHOSPHAMID							
ADM	ADRIBLASTINA							
CDDP	CIS-PLATINUM							
	MEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26	27	28
5FU	5FLUOROURACYL							
VCR	VINCRISTIN							
MMC	MITOMYCIN C							
CPH	CYCLOPHOSPHAMID							
ADM	ADRIBLASTINA					↑		
CDDP	CIS-PLATINUM							
	MEHT					↑		

Treatment days from the onset of the cycle:		29
5FU	5FLUOROURACYL	
VCR	VINCRISTIN	
MMC	MITOMYCIN C	
CPH	CYCLOPHOSPHAMID	↑
ADM	ADRIBLASTINA	
CDDP	CIS-PLATINUM	↑
	MEHT	↑

7081 Chemotherapy, IFO-Carbloplatin Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C34

IFO HOLOXAN Dose: 2500 (mg/m^2)

CBP CARBOPLATIN Dose: 200 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
IFO	HOLOXAN	↑			
CBP	CARBOPLATIN				↑
	MEHT	↑			↑

7082 Chemotherapy, IFO+CDDP+VP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C34

IFO HOLOXAN Dose: 2000 (mg/m²)CDDP CIS-

PLATINUM Dose: 25 (mg/m²)

VP VEPESID Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
IFO	HOLOXAN	↑			
CDDP	CIS-PLATINUM	↑	↑		↑
VP	VEPESID	↑	↑		↑
	MEHT	↑			↑

7083 Chemotherapy, IFO+CDDP+CBP Protocol + HT

Protocol Period : 7 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C34

IFO HOLOXAN Dose: 1000 (mg/m²)

CBP CARBOPLATIN Dose: 200 (mg/m²)

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
IFO	HOLOXAN	↑			↑			↑
CDDP	CIS-PLATINUM				↑			↑
CBP	CARBOPLATIN	↑						
	MEHT	↑			↑			↑

7084 Chemotherapy, IVP Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C34

IFO HOLOXAN Dose: 1000 (mg/m²)

VP VEPESID Dose: 60 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
IFO	HOLOXAN	↑	↑	↑	↑	↑
VP	VEPESID	↑	↑	↑	↑	↑
	MEHT	↑			↑	

7085 Chemotherapy, LCAET Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C34

CCNU CYCLO-HEXYL-NITROSO-UREA Dose: 30 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 500 (mg/m²)

ADM ADRIBLASTINA Dose: 30 (mg/m²)

VP VEPESID Dose: 100 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CCNU	CYCLO-HEXYL-NITROSO-UREA	↑			

CPH	CYCLOPHOSPHAMID	↑			
ADM	ADRIBLASTINA				↑
VP	VEPESID	↑			
	MEHT	↑			↑

7086 Chemotherapy, PACCO Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C34

CDDP	CIS-PLATINUM	Dose:	30	(mg/m^2)
ADM	ADRIBLASTINA	Dose:	30	(mg/m^2)
CPH	CYCLOPHOSPHAMID	Dose:	200	(mg/m^2)
CCNU	CYCLO-HEXYL-NITROSO-UREA	Dose:	30	(mg/m^2)
VCR	VINCRISTIN	Dose:	1	(mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
ADM	ADRIBLASTINA				↑
CPH	CYCLOPHOSPHAMID	↑			
CCNU	CYCLO-HEXYL-NITROSO-UREA	↑			
VCR	VINCRISTIN				↑
	MEHT	↑			↑

7087 Chemotherapy, PETCE Protocol + HT

Protocol Period : 29 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C34

VP	VEPESID	Dose:	150	(mg/m^2)

CDDP	CIS-PLATINUM	Dose: 30	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose: 500	(mg/m²)
EPI	EPIRUBICIN	Dose: 30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VP	VEPESID			↑	↑	↑		
CDDP	CIS-PLATINUM	↑	↑					
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VP	VEPESID							
CDDP	CIS-PLATINUM							
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
VP	VEPESID							
CDDP	CIS-PLATINUM							
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN							
	MEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26	27	28
VP	VEPESID							
CDDP	CIS-PLATINUM							
CPH	CYCLOPHOSPHAMID							
EPI	EPIRUBICIN					↑		
	MEHT					↑		

Treatment days from the onset of the cycle:		29
VP	VEPESID	
CDDP	CIS-PLATINUM	
CPH	CYCLOPHOSPHAMID	↑
EPI	EPIRUBICIN	
	MEHT	↑

7088 Chemotherapy, PEV Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C34

CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)
EPI	EPIRUBICIN	Dose:	30	(mg/m²)
VP	VEPESID	Dose:	50	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
EPI	EPIRUBICIN				↑
VP	VEPESID	↑			
	MEHT				

7089 Chemotherapy, VICE Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C34

CBP	CARBOPLATIN	Dose:	200	(mg/m²)
IFO	HOLOXAN	Dose:	2500	(mg/m²)

VP	VEPESID	Dose: 60	(mg/m²)
VCR	VINCRISTIN	Dose: 1	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CBP	CARBOPLATIN	↑						
IFO	HOLOXAN	↑						
VP	VEPESID	↑			↑			
VCR	VINCRISTIN							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CBP	CARBOPLATIN							
IFO	HOLOXAN							
VP	VEPESID							
VCR	VINCRISTIN							
	MEHT					↑		

Treatment days from the onset of the cycle:		15
CBP	CARBOPLATIN	
IFO	HOLOXAN	
VP	VEPESID	
VCR	VINCRISTIN	↑
	MEHT	↑

7090 Chemotherapy, VPI Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 14 (Day)

Diagnoses:

C34

IFO	HOLOXAN	Dose: 1000	(mg/m²)
VP	VEPESID	Dose: 50	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
IFO	HOLOXAN	↑						
VP	VEPESID	↑	↑	↑	↑	↑	↑	↑
	MEHT	↑			↑			↑

7091 Chemotherapy, CAV (small-cell Lung carcinoma) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C34

CPH CYCLOPHOSPHAMID Dose: 1000 (mg/m²)

ADM ADRIBLASTINA Dose: 50 (mg/m²)

VCR VINCRISTIN Dose: 2 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
ADM	ADRIBLASTINA				↑
VCR	VINCRISTIN	↑			
	MEHT	↑			↑

7092 Chemotherapy, CBP+ VP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 18 (Day)

Diagnoses:

C34

CBP CARBOPLATIN Dose: 300 (mg/m²)

VP VEPESID Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CBP	CARBOPLATIN	↑			
VP	VEPESID	↑	↑		↑
	MEHT	↑			↑

7093 Chemotherapy, CE (small-cell lung cancer) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 18 (Day)

Diagnoses:

C34

CBP CARBOPLATIN Dose: 200 (mg/m²)

VP VEPESID Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CBP	CARBOPLATIN	↑			
VP	VEPESID	↑	↑		↑
	MEHT	↑			↑

7094 Chemotherapy, CEV (small-cell lung cancer) Protocol + HT

Protocol Period :4 (Day)

Interval between protocols: 18 (Day)

Diagnoses:

C34

CPH CYCLOPHOSPHAMID Dose: 500 (mg/m²)

EPI EPIRUBICIN Dose: 30 (mg/m²)

VP VEPESID Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
EPI	EPIRUBICIN	↑			

VP	VEPESID	↑	↑		↑
	MEHT	↑			↑

7095 Chemotherapy, GEM+CCDP Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 13 (Day)

Diagnoses:

C34

GEM GEMCYTABINE Dose: 700 (mg/m²)

CDDP CIS-PLATIN Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
GEM	GEMCYTABINE	↑						
CDDP	CIS-PLATIN	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
GEM	GEMCYTABINE	↑
CDDP	CIS-PLATIN	
	MEHT	↑

7096 Chemotherapy, MMC+IFO+CDDP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C34

MMC MITOMYCIN C Dose: 3 (mg/m²)

IFO HOLOXAN Dose: 2000 (mg/m²)

CDDP CIS-PLATIN Dose: 40 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
MMC	MITOMYCIN C				↑
IFO	HOLOXAN	↑			
CDDP	CIS-PLATIN	↑			
	MEHT	↑			↑

7097 Chemotherapy, PE (small-cell lung cancer) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 18 (Day)

Diagnoses:

C34

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

VP VEPESID Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
VP	VEPESID	↑	↑		↑
	MEHT	↑			↑

7098 Chemotherapy, IEC (small-cell lung cancer) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Diagnoses:

C34

IFO HOLOXAN Dose: 600 (mg/m²)

VP VEPESID Dose: 40 (mg/m²)

CDDP CIS-PLATINUM Dose: 10 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
IFO	HOLOXAN	↑	↑	↑	↑

VP	VEPESID	↑	↑	↑	↑
CDDP	CIS-PLATINUM	↑	↑	↑	↑
	MEHT	↑			↑

7099 Chemotherapy, TAX+CBP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20(Day)

Diagnoses:

C34

TAX TAXOL Dose: 100 (mg/m²)

CBP CARBOPLATIN Dose: 200 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL	↑			
CBP	CARBOPLATIN	↑			
	MEHT	↑			↑

7101 Chemotherapy, ADOC Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Diagnoses:

C37H0

ADM ADRIBLASTINA Dose: 20 (mg/m²)

CDDP CIS-PLATINUM Dose: 30 (mg/m²)

VCR VINCRISTIN Dose: 1 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 400 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
ADM	ADRIBLASTINA	↑			
CDDP	CIS-PLATINUM	↑			

VCR	VINCRISTIN				↑
CPH	CYCLOPHOSPHAMID				↑
	MEHT	↑			↑

7102 Chemotherapy, PAC Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C37H0

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

ADM ADRIBLASTINA Dose: 50 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 500 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
ADM	ADRIBLASTINA				↑
CPH	CYCLOPHOSPHAMID	↑			
	MEHT	↑			↑

7121 Chemotherapy, by Metastases ADIC Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C40, C41

ADM ADRIBLASTINA Dose: 30 (mg/m²)

DTIC DACARBAZIN Dose: 150 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
ADM	ADRIBLASTINA	↑				

DTIC	DACARBAZIN	↑	↑	↑	↑	↑
	MEHT	↑			↑	

7122 Chemotherapy, VAMFA (adjuvant) Protocol + HT

Protocol Period : 26 (Day)

Interval between protocols : 10 (Day)

Diagnoses:

C40, C41

VCR	VINCRISTIN	Dose:	1	(mg/m²)
ADM	ADRIBLASTINA	Dose:	15	(mg/m²)
MTX	METHOTREXAT	Dose:	10	(mg/m²)
FOLINAC	FOLINSÄURE	Dose:	100	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VCR	VINCRISTIN	↑	↑					
ADM	ADRIBLASTINA			↑	↑	↑		
MTX	METHOTREXAT							
FOLINAC	FOLINSÄURE							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VCR	VINCRISTIN					↑		
ADM	ADRIBLASTINA							
MTX	METHOTREXAT							
FOLINAC	FOLINSÄURE							
	MEHT					↑		

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
VCR	VINCRISTIN							↑
ADM	ADRIBLASTINA							
MTX	METHOTREXAT							

FOLINAC	FOLINSÄURE							
	MEHT							

Treatment days from the onset of the cycle:		22	23	24	25	26
VCR	VINCRISTIN					
ADM	ADRIBLASTINA					
MTX	METHOTREXAT		↑	↑		
FOLINAC	FOLINSÄURE				↑	↑
	MEHT		↑			↑

7151 Chemotherapy, CAD Protocol

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C45, C46, C47, C48, C49

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
DTIC	DACARBAZIN	Dose:	200	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			↑
ADM	ADRIBLASTINA	↑			
DTIC	DACARBAZIN	↑			↑
	MEHT	↑			↑

7152 Chemotherapy, CYVADIC Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C45, C46, C47, C48, C49

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
VCR	VINCRISTIN	Dose:	1	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
DTIC	DACARBAZIN	Dose:	150	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
CPH	CYCLOPHOSPHAMID	↑	↑			
VCR	VINCRISTIN	↑	↑	↑	↑	↑
ADM	ADRIBLASTINA	↑				
DTIC	DACARBAZIN	↑	↑	↑	↑	↑
	MEHT	↑			↑	

7153 Chemotherapy, IFO-ADM/A Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C45, C46, C47, C48, C49, C50

IFO	HOLOXAN	Dose:	3000	(mg/m²)
ADM	ADRIBLASTINA	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
IFO	HOLOXAN	↑			
ADM	ADRIBLASTINA	↑			
	MEHT	↑			↑

7154 Chemotherapy, IFO-ADM/B Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 19 (Day)

Diagnoses:

C45, C46, C47, C48, C49

IFO	HOLOXAN	Dose:	2000	[mg/m^2]
ADM	ADRIBLASTINA	Dose:	30	[mg/m^2]

Treatment days from the onset of the cycle:		1	2	3	4
IFO	HOLOXAN	↑			↑
ADM	ADRIBLASTINA	↑			↑
	MEHT	↑			↑

7201 Chemotherapy, BOLD Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C43, C44

DTIC	DACARBAZIN	Dose:	100	[mg/m^2]
BLM	BLEOMICIN	Dose:	10	[mg/m^2]
VCR	VINCRISTIN	Dose:	1	[mg/m^2]
CCNU	CYCLO-HEXYL-NITROSO-UREA	Dose:	40	[mg/m^2]

Treatment days from the onset of the cycle:		1	2	3	4	5
DTIC	DACARBAZIN	↑	↑	↑	↑	↑
BLM	BLEOMICIN	↑			↑	
VCR	VINCRISTIN	↑			↑	
CCNU	CYCLO-HEXYL-NITROSO-UREA	↑				
	MEHT	↑			↑	

7202 Chemotherapy, DTIC+CDDP+BCNU+TAMO Protocol+HT

Protocol Period : 21 (Day)

Interval between protocols : 0 (Day)

Diagnoses:

C43, C44

DTIC	DACARBAZIN	Dose:	100	(mg/m²)
CDDP	CIS-PLATIN	Dose:	20	(mg/m²)
BCNU	CARMUSTIN	Dose:	80	(mg/m²)
TAMO	TAMOXIFEN	Dose:	20	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
DTIC	DACARBAZIN	↑	↑		↑			
CDDP	CIS-PLATIN	↑	↑		↑			
BCNU	CARMUSEN	↑						
TAMO	TAMOXIFEN	↑	↑	↑	↑	↑	↑	↑
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
DTIC	DACARBAZIN							
CDDP	CIS-PLATIN							
BCNU	CARMUSEN							
TAMO	TAMOXIFEN	↑	↑	↑	↑	↑	↑	↑
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
DTIC	DACARBAZIN							
CDDP	CIS-PLATIN							
BCNU	CARMUSEN							
TAMO	TAMOXIFEN	↑	↑	↑	↑	↑	↑	↑
	MEHT							

7203 Chemotherapy, DVP EORTC Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C43, C44

DTIC	DACARBAZIN	Dose:	300	(mg/m²)
VDS	VINDESINE	Dose:	2	(mg/m²)
CDDP	CIS-PLATIN	Dose:	30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
DTIC	DACARBAZIN	↑						
VDS	VINDESINE	↑						
CDDP	CIS-PLATIN	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
DTIC	DACARBAZIN	↑
VDS	VINDESINE	↑
CDDP	CIS-PLATIN	↑
	MEHT	↑

7204 Chemotherapy, oncotherapy Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 15 (Day

Diagnoses:

C43, C44

DTIC	DACARBAZIN	Dose:	150	(mg/m²)
EPI	EPIRUBICIN	Dose:	20	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
DTIC	DACARBAZIN	↑	↑	↑	↑	↑		
EPI	EPIRUBICIN	*						
	MEHT	*			*			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
DTIC	DACARBAZIN	↑						
EPI	EPIRUBICIN	*						
	MEHT	*						

Treatment days from the onset of the cycle:		15
DTIC	DACARBAZIN	
EPI	EPIRUBICIN	*
	MEHT	*

7205 Chemotherapy, oncotherapy Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 16 (Day)

Diagnoses:

C43, C44

DTIC DACARBAZIN Dose: 250 (mg/m^2)

CDDP CIS-PLATINUM Dose: 50 (mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4	5
DTIC	DACARBAZIN	↑	↑	↑	↑	↑
CDDP	CIS-PLATINUM	↑				
	MEHT	↑			↑	

7231 Chemotherapy, AC/A Protocol + HT

Protocol Period : 6 (Day)

Interval between protocols : 15 (Day)

Diagnoses:

C50

ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	150	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6
ADM	ADRIBLASTINA	↑					
CPH	CYCLOPHOSPHAMID			↑	↑	↑	↑
	MEHT	↑			↑		

7233 Chemotherapy, CEF/A single-use CPM Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C50

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
EPI	EPIRUBICIN	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
EPI	EPIRUBICIN	↑			
	MEHT	↑			↑

7234 Chemotherapy, CEF/B continuous CPM Protocol + HT

Protocol Period : 14 (Day)

Interval between protocols : 14 (Day)

Remark: continuously CPM Dose for 14 Day

Diagnoses:

C50

EPI	EPIRUBICIN	Dose:	40	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	50	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
EPI	EPIRUBICIN	↑						
CPH	CYCLOPHOSPHAMID	↑	↑	↑	↑	↑	↑	↑
	MEHT	↑			↑			↑

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
EPI	EPIRUBICIN							
CPH	CYCLOPHOSPHAMID	↑	↑	↑	↑	↑	↑	↑
	MEHT	↑			↑			↑

7235 Chemotherapy, classic CMF Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

CPH	CYCLOPHOSPHAMID	Dose:	400	(mg/m²)
MTX	METHOTREXAT	Dose:	30	(mg/m²)
5FU	5FLUOROURACYL	Dose:	400	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CPH	CYCLOPHOSPHAMID	↑						
MTX	METHOTREXAT	↑						
5FU	5FLUOROURACYL	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
CPH	CYCLOPHOSPHAMID	↑
MTX	METHOTREXAT	↑
5FU	5FLUOROURACYL	↑
	MEHT	↑

7236 Chemotherapy, EC Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

EPI EPIRUBICIN Dose: 40 (mg/m^2)

CPH CYCLOPHOSPHAMID Dose: 400 (mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
EPI	EPIRUBICIN	↑			
CPH	CYCLOPHOSPHAMID	↑			
	MEHT	↑			↑

7237 Chemotherapy, FAC Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

5FU	5FLUOROURACYL	Dose:	300	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
5FU	5FLUOROURACYL	↑						
ADM	ADRIBLASTINA	↑						
CPH	CYCLOPHOSPHAMID	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
5FU	5FLUOROURACYL	↑
ADM	ADRIBLASTINA	
CPH	CYCLOPHOSPHAMID	
	MEHT	↑

7238 Chemotherapy, FEC Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
EPI	EPIRUBICIN	Dose:	50	(mg/m²)
5FU	5FLUOROURACYL	Dose:	300	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
EPI	EPIRUBICIN	↑			
5FU	5FLUOROURACYL	↑			
	MEHT	↑			↑

7239 Chemotherapy, Withoxanthron-IFO Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 18 (Day)

Diagnoses:

C50

WITHX WITHOXANTRON Dose: 6 (mg/m²)

IFO HOLOXAN Dose: 1500 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
WITHX	WITHOXANTRON				↑
IFO	HOLOXAN	↑	↑		↑
	MEHT	↑			↑

7240 Chemotherapy, MMM/A MITOMYCIN C Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Remark: Between two days once MMM/B without MITOMYCIN C am 21.Day

Diagnoses:

C50

WITHX WITHOXANTRON Dose: 5 (mg/m²)

MTX METHOTREXAT Dose: 30 (mg/m²)

MMC MITOMYCIN C Dose: 5 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
WITHX	WITHOXANTRON	↑			
MTX	METHOTHEXAT	↑			
MMC	MITOMYCIN C	↑			
	MEHT	↑			↑

7241 Chemotherapy, MMM/B Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

WITHX WITHOXANTRON Dose: 5 (mg/m²)

MTX METHOTREXAT Dose: 30 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
WITHX	WITHOXANTRON	↑			
MTX	METHOTHEXAT	↑			
	MEHT	↑			↑

7242 Chemotherapy, TAC Protocol + HT

Protocol Period : 7 (Day)

Interval between protocols : 22 (Day)

Remark: TAMO continuously p.os

Diagnoses:

C50

TAMO TAMOXIFEN Dose: 10 (mg/m²)

ADM ADRIBLASTINA Dose: 20 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 150 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
TAMO	TAMOXIFEN	↑	↑	↑	↑	↑	↑	↑
ADM	ADRIBLASTINA	↑						
CPH	CYCLOPHOSPHAMID			↑	↑	↑		↑
	MEHT	↑						↑

7243 Chemotherapy, Taxol-ADM/A Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

TAX	TAXOL	Dose:	100	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL	↑			
ADM	ADRIBLASTINA	↑			
	MEHT	↑			↑

7244 Chemotherapy, Taxol-ADM/B Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

TAX	TAXOL	Dose:	100	(mg/m²)
EPI	EPIRUBICIN	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL	↑			
EPI	EPIRUBICIN	↑			
	MEHT	↑			↑

7245 Chemotherapy, Taxotere-Adriblastina Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

TAX	TAXOL	Dose:	50	(mg/m^2)
EPI	EPIRUBICIN	Dose:	50	(mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL	↑			
EPI	EPIRUBICIN	↑			
	MEHT	↑			↑

7246 Chemotherapy, Taxotere-Adriblastina/B Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C50

TAX	TAXOL	Dose:	50	(mg/m^2)
ADM	ADRIBLASTINA	Dose:	30	(mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL	↑			
ADM	ADRIBLASTINA	↑			
	MEHT	↑			↑

7301 Chemotherapy, BIP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Diagnoses:

C53

BLM	BLEOMICIN	Dose:	15	(mg/m^2)
CDDP	CIS-PLATINUM	Dose:	30	(mg/m^2)
IFO	HOLOXAN	Dose:	3000	(mg/m^2)
MESNA	UROWITHEXAN	Dose:	2000	(mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4
BLM	BLEOMICIN	↑			
CDDP	CIS-PLATINUM	↑			
IFO	HOLOXAN				↑
MESNA	UROWITHEXAN				↑
	MEHT	↑			↑

7302 Chemotherapy, Carboplatin-IFO Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C53

CBP CARBOPLATIN Dose: 200 (mg/m²)

IFO HOLOXAN Dose: 3000 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CBP	CARBOPLATIN	↑			
IFO	HOLOXAN	↑			
	MEHT	↑			↑

7303 Chemotherapy, VAC (recidive Sarcoma) Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 23 (Day)

Diagnoses:

C54

CPH CYCLOPHOSPHAMID Dose: 300 (mg/m²)

VCR VINCRISTIN Dose: 1 (mg/m²)

ACTD ACTINOMYCIN-D Dose: 1 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
CPH	CYCLOPHOSPHAMID	↑				
VCR	VINCRISTIN	↑				
CPH	CYCLOPHOSPHAMID					↑
ACTD	ACTINOMYCIN-D					↑
	MEHT	↑				↑

7304 Chemotherapy, neoadjuvant Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 7 (Day)

Diagnoses:

C53

CDDP	CIS-PLATINIUM	Dose:	30	(mg/m²)
VCR	VINCRISTIN	Dose:	1	(mg/m²)
BLM	BLEOMICIN	Dose:	15	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINIUM	↑			
VCR	VINCRISTIN	↑			
BLM	BLEOMICIN	↑	↑		↑
	MEHT	↑			↑

7305 Chemotherapy, VPB/D (recidive Collumkarzinom) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C53

VCR	VINCRISTIN	Dose:	1	(mg/m²)
CDDP	CIS-PLATINIUM	Dose:	30	(mg/m²)

BLM BLEOMICIN Dose: 10 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
VCR	VINCRISTIN	↑			
CDDP	CIS-PLATINIUM	↑			
BLM	BLEOMICIN	↑			
	MEHT	↑			

7306 Chemotherapy, CAP-BLM Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 13 (Day)

Diagnoses:

C53

CPH CYCLOPHOSPHAMID Dose: 300 (mg/m²)

ADM ADRIBLASTINA Dose: 30 (mg/m²)

CBP CARBOPLATIN Dose: 200 (mg/m²)

BLM BLEOMICIN Dose: 10 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CPH	CYCLOPHOSPHAMID	↑						
ADM	ADRIBLASTINA	↑						
CBP	CARBOPLATIN	↑						
BLM	BLEOMICIN	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
CPH	CYCLOPHOSPHAMID	
ADM	ADRIBLASTINA	
CBP	CARBOPLATIN	
BLM	BLEOMICIN	↑
	MEHT	↑

7307 Chemotherapy, CMVB Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C53

CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)
MMC	MITOMYCIN C	Dose:	6	(mg/m²)
VCR	VINCRISTIN	Dose:	1	(mg/m²)
BLM	BLEOMICIN	Dose:	6	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
MMC	WITHOMXCIN C				↑
VCR	VINCRISTIN	↑			
BLM	BLEOMICIN	↑			
	MEHT	↑			↑

7309 Chemotherapy, FAP/B Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C53

5FU	5FLUOROURACYL	Dose:	300	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
5FU	5FLUOROURACYL	↑			
ADM	ADRIBLASTINA	↑			
CDDP	CIS-PLATINUM	↑			
	MEHT	↑			↑

7312 Chemotherapy, CDP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C54

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
ADM	ADRIBLASTINA				↑
CDDP	CIS-PLATINUM	↑			
	MEHT	↑			↑

7313 Chemotherapy, CDDP+MTX+BLM Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 19 (Day)

Diagnoses:

C53

CDDP	CIS-PLATINUM	Dose:	40	(mg/m²)
MTX	METHOTREAT	Dose:	40	(mg/m²)
BLM	BLEOMICIN	Dose:	15	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM				↑
MTX	METHOTREXAT	↑			
BLM	BLEOMICON	↑			
	MEHT	↑			↑

7331 Chemotherapy, BECA Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 16 (Day)

Diagnoses:

C56H0, C62

VP	VEPESID	Dose:	50	(mg/m²)
CBP	CARBOPLATIN	Dose:	200	(mg/m²)
BLM	BLEOMICIN	Dose:	15	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
VP	VEPESID	↑	↑	↑	↑	↑
CBP	CARBOPLATIN	↑				
BLM	BLEOMICON		↑			
	MEHT	↑			↑	

7332 Chemotherapy, BEP Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 6 (Day)

Diagnoses:

C62

CDDP	CIS-PLATINUM	Dose:	20	(mg/m²)
VP	VEPESID	Dose:	100	(mg/m²)
BLM	BLEOMICIN	Dose:	15	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
CDDP	CIS-PLATIN	↑	↑	↑	↑	↑		
VP	VEPESID	↑	↑	↑				
BLM	BLEOMICIN	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
CDDP	CIS-PLATIN							
VP	VEPESID							
BLM	BLEOMICIN	↑						
	MEHT	↑						

Treatment days from the onset of the cycle:		15
CDDP	CIS-PLATIN	
VP	VEPESID	
BLM	BLEOMICIN	↑
	MEHT	↑

7333 Chemotherapy, Carboplatin-Cyclophosphamid Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 27 (Day)

Diagnoses:

C56H0

CPB CARBOPLATIN Dose: 200 (mg/m²)

CPH CYCLOPHOSPHAMID Dose: 400 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPB	CARBOPLATIN	↑			
CPH	CYCLOPHOSPHAMID	↑			
	MEHT	↑			↑

7334 Chemotherapy, Cisplatin-Carboplatin-IFO Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C56H0

CPB	CARBOPLATIN	Dose:	200	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)
IFO	HOLOXAN	Dose:	1000	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPB	CARBOPLATIN	↑			
CDDP	CIS-PLATINUM		↑		↑
IFO	HOLOXAN	↑	↑		↑
	MEHT	↑			↑

7336 Chemotherapy, VIP/A Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 16 (Day)

Diagnoses:

C56H0, C62, C63, C64H0, C65H0, C66H0, C67, C68, C69, C70, C71, C72, C73H0, C74, C75, C76, C77, C78, C79, C80H0, C81, C82, C83, C84

IFO	HOLOXAN	Dose:	1000	(mg/m²)
VP	VEPESID	Dose:	50	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	20	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
IFO	HOLOXAN	↑	↑	↑	↑	↑
VP	VEPESID	↑	↑	↑	↑	↑
CDDP	CIS-PLATINUM	↑	↑	↑	↑	↑
	MEHT	↑			↑	

7337 Chemotherapy, VIP/B Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 16 (Day)

Diagnoses:

C56H0, C62

IFO	HOLOXAN	Dose:	1000	[mg/m²]
VP	VEPESID	Dose:	50	[mg/m²]
CBP	CARBOPLATIN	Dose:	200	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5
IFO	HOLOXAN	↑	↑	↑	↑	↑
VP	VEPESID	↑	↑	↑	↑	↑
CBP	CARBOPLATIN	↑				
	MEHT	↑			↑	

7338 Chemotherapy, VPB with cisplatin Protocol + HT

Protocol Period : 16 [Day]

Interval between protocols : 14 [Day]

Diagnoses:

C62

VBL	VINBLASTIN	Dose:	4	[mg/m²]
BLM	BLEOMICIN	Dose:	15	[mg/m²]
CDDP	CIS-PLATINUM	Dose:	20	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VBL	VINBLASTIN	↑	↑					
BLM	BLEOMICIN		↑					
CDDP	CIS-PLATINUM	↑	↑	↑	↑	↑		
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VBL	VINBLASTIN							
BLM	BLEOMICIN		↑					
CDDP	CIS-PLATINUM							
	MEHT		↑					

Treatment days from the onset of the cycle:		15	16
VBL	VINBLASTIN		
BLM	BLEOMICIN		↑
CDDP	CIS-PLATINUM		
	MEHT		↑

7339 Chemotherapy, VPB with Carboplatin Protocol + HT

Protocol Period : 16 (Day)

Interval between protocols : 14 (Day)

Diagnoses:

C62

VBL VINBLASTIN Dose: 4 (mg/m²)

BLM BLEOMICIN Dose: 15 (mg/m²)

CBP CARBOPLATIN Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VBL	VINBLASTIN	↑	↑					
BLM	BLEOMICIN		↑					
CBP	CARBOPLATIN	↑	↑	↑	↑	↑		
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VBL	VINBLASTIN							
BLM	BLEOMICIN		↑					
CBP	CARBOPLATIN							
	MEHT		↑					

Treatment days from the onset of the cycle:		15	16
VBL	VINBLASTIN		
BLM	BLEOMICIN		↑
CBP	CARBOPLATIN		
	MEHT		↑

7340 Chemotherapy, CFP (first line therapy) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C56H0

CPH	CYCLOPHOSPHAMID	Dose:	300	(mg/m²)
EPI	EPIRUBICIN	Dose:	40	(mg/m²)
CDDP	CIS-PLATIN	Dose:	50	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
EPI	EPIRUBICIN	↑			
CDDP	CIS-PLATIN	↑			
	MEHT	↑			↑

7341 Chemotherapy, CPH+VP for treatment of recurrences+ HT

Protocol Period : 4 (Day)

Interval between protocols : 25 (Day)

Diagnoses:

C56H0

VP	VEPESID	Dose:	60	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	400	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
VP	VEPESID	↑	↑		↑
CPH	CYCLOPHOSPHAMID				↑
	MEHT	↑			↑

7343 Chemotherapy, TAX-CBP (first line th) Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 26 (Day)

Diagnoses:

C56H0

TAX	TAXOL	Dose:	100	[mg/m²]
CBP	CARBOPLATIN	Dose:	200	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4
TAX	TAXOL				↑
CBP	CARBOPLATIN	↑			
	MEHT	↑			↑

7345 Chemotherapy, VEP (bym rezidivierenden Ovarialkarzinom) Protocol + HT

Protocol Period : 5 [Day]

Interval between protocols : 23 [Day]

Diagnoses:

C56H0

VP	VEPESID	Dose:	50	[mg/m²]
CDDP	CIS-PLATINUM	Dose:	15	[mg/m²]
EPI	EPIRUBICIN	Dose:	40	[mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5
VP	VEPESID	↑	↑	↑		
CDDP	CIS-PLATINUM	↑	↑	↑	↑	↑
EPI	EPIRUBICIN	↑				
	MEHT	↑			↑	

7346 Chemotherapy, PEB (bym Ovarialkarzinom germinaler Ursprung) Protocol + HT

Protocol Period : 4 [Day]

Interval between protocols : 25 [Day]

Diagnoses:

C56H0

CDDP	CIS-PLATINUM	Dose:	50	(mg/m²)
VP	VEPESID	Dose:	50	(mg/m²)
BLM	BLEOMICIN	Dose:	10	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
VP	VEPESID	↑	↑		↑
BLM	BLEOMICIN	↑	↑		↑
	MEHT	↑			↑

7347 Chemotherapy, CPH+CDDP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C56H0

CPH	CYCLOPHOSPHAMID	Dose:	400	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	50	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CPH	CYCLOPHOSPHAMID	↑			
CDDP	CIS-PLATINUM	↑			
	MEHT	↑			↑

7348 Chemotherapy, Cisplatin-Taxol Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C56H0

CDDP	CIS-PLATINUM	Dose:	50	(mg/m²)
TAXOL	TAXOL	Dose:	100	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM				↑
TAXOL	TAXOL	↑			
	MEHT	↑			↑

7401 Chemotherapy, ABVC-BCG Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Remark: BCG Scarification an 8-15. Days 6x10U

Diagnoses:

C64H0

ADM	***ADRIBLASTINA***	***Dose: 30***	***(mg/m²)***
BLM	BLEOMICIN	Dose: 15	(mg/m²)
VCR	VINCRISTIN	Dose: 1	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
ADM	ADRIBLASTINA				↑
BLM	BLEOMICIN	↑			
VCR	VINCRISTIN	↑			
	MEHT	↑			↑

7402 Chemotherapy, CDDP+CPH+ADM Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 20 (Day)

Diagnoses:

C67

CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)
CPH	CYCLOPHOSPHAMID	Dose:	400	(mg/m²)
ADM	ADRIBLASTINA	Dose:	40	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
CDDP	CIS-PLATINUM	↑			
CPH	CYCLOPHOSPHAMID	↑			
ADM	ADRIBLASTINA				↑
	MEHT	↑			↑

7403 Chemotherapy, CMV Protocol + HT

Protocol Period : 8 (Day)

Interval between protocols : 14 (Day)

Diagnoses:

C67

VBL VINBLASTIN Dose: 5 (mg/m²)

MTX METHOTHREXAT Dose: 30 (mg/m²)

CDDP CIS-PLATINUM Dose: 60 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VBL	VINBLASTIN	↑						
MTX	METHOTHREXAT	↑						
CDDP	CIS-PLATINUM				↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8
VBL	VINBLASTIN	↑
MTX	METHOTHREXAT	↑
CDDP	CIS-PLATINUM	
	MEHT	↑

7404 Chemotherapy, MVEC Protocol + HT

Protocol Period : 22 (Day)

Interval between protocols : 7 (Day)

Diagnoses:

C67

VBL	VINBLASTIN	Dose:	5	(mg/m²)
EPI	EPIRUBICIN	Dose:	30	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	20	(mg/m²)
MTX	METHOTHREXAT	Dose:	30	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VBL	VINBLASTIN	↑						
EPI	EPIRUBICIN				↑			
CDDP	CIS-PLATINUM	↑						
MTX	METHOTHREXAT	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VBL	VINBLASTIN							
EPI	EPIRUBICIN							
CDDP	CIS-PLATINUM							
MTX	METHOTHREXAT							
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
VBL	VINBLASTIN	↑						
EPI	EPIRUBICIN							
CDDP	CIS-PLATINUM							
MTX	METHOTHREXAT	↑						
	MEHT	↑						

Treatment days from the onset of the cycle:		22
VBL	VINBLASTIN	↑

EPI	EPIRUBICIN	
CDDP	CIS-PLATINUM	
MTX	METHOTHREXAT	↑
	MEHT	↑

X001 Chemotherapy, ADM+CTX+CDDP Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 24 (Day)

Diagnoses:

C4490

ADM ADRIBLASTINA Dose: 30 (mg/m²)

CTX CITOXAN Dose: 300 (mg/m²)

CDDP CIS-PLATINUM Dose: 30 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
ADM	ADRI BLASTINA	↑			
CTX	CITOXAN	↑			
CDDP	CIS-PLATINUM				↑
	MEHT	↑			↑

X002 Chemotherapy, ADM+CDDP+BLM Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Diagnoses:

C4490

ADM ADRIBLASTINA Dose: 15 (mg/m²)

CDDP CIS-PLATINUM Dose: 15 (mg/m²)

BLM BLEOMYCIN Dose: 5 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
ADM	ADRI BLASTINA	↑	↑	↑	
CTX	CITOXAN	↑	↑	↑	↑
CDDP	CIS-PLATINUM	↑	↑	↑	↑
	MEHT	↑			↑

X003 Chemotherapy, VMB Protocol + HT

Protocol Period : 21 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C00, C0090

VCR VINCRISTIN Dose: 1 (mg/m²)

MTX METHOTHREXAT Dose: 20 (mg/m²)

BLM BLEOMYCIN Dose: 10 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
VCR	VINCRISTIN	↑						
MTX	METHOTHREXAT	↑						
BLM	BLEOMYCIN	↑			↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
VCR	VINCRISTIN	↑						
MTX	METHOTHREXAT	↑						
BLM	BLEOMYCIN	↑			↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
VCR	VINCRISTIN	↑						
MTX	METHOTHREXAT	↑						

BLM	BLEOMYCIN	↑			↑			
	MEHT	↑			↑			

X004 Chemotherapy, ADM+CDDP+ACTINOMYCIN-D Protocol + HT

Protocol Period : 1 (Day)

Interval between protocols : 28 (Day)

Remark: Only in the case of anaplastic CC

Diagnoses:

C32

ADM	ADRIBLASTINA	Dose:	30	(mg/m²)
CDDP	CIS-PLATINUM	Dose:	30	(mg/m²)
ACD	ACTINOMYCIN-D	Dose:	1	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4
ADM	ADRIBLASTINA	↑			
CDDP	CIS-PLATINUM	↑			
ACD	ACTINOMYCIN-D	↑			
	MEHT	↑			↑

X005 Chemotherapy, BLM+5FU+VLB Protocol + HT

Protocol Period : 5 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C15

BLM	BLEOMYCIN	Dose:	30	(mg/m²)
5FU	5FLUROURACIL	Dose:	400	(mg/m²)
VBL	VINBLASTIN	Dose:	3	(mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5
BLM	BELOMYCIN	↑			↑	
5FU	5FLUOROURACIL	↑	↑	↑	↑	↑
VBL	VINBLASTIN	↑				
	MEHT	↑			↑	

X006 Chemotherapy, MLP-F Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 28 (Day)

Diagnoses:

C16

MTX METHOTHREXAT Dose: 100 (mg/m²)

LV LEUCOVORIN Dose: 200 (mg/m²)

5FUi* 5FLUROURACIL-INF. Dose: 1000 (mg/m²)

5FUb 5FLUROURACIL-BOLUS Dose: 400 (mg/m²)

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

*/ 24 Hours

Treatment days from the onset of the cycle:		1	2	3	4
MTX	METHOTHREXAT	↑			↑
LV	LEUCOVORIN	↑	↑	↑	↑
5FUi	5FLUOROURACYL-INF	↑	↑	↑	↑
5FUb	5FLUOROURACYL-BOLUS	↑			
CDDP	CIS-PLATINUM	↑			
	MEHT	↑			↑

X007 Chemotherapy, MMC+5FU Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 17 (Day)

Diagnoses:

C21

In the case of epithelioma

MMC MYTOMICIN Dose: 6 [mg/m²]

5FU 5FLUROURACIL Dose: 500 [mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4
MTX	METHOTHREXAT	↑			
5FU	5FLUOROURACYL	↑	↑	↑	↑
	MEHT	↑			↑

X008 Chemotherapy, GEMZAR+5FU Protocol + HT

Protocol Period : 15 [Day]

Interval between protocols : 7 [Day]

Diagnoses:

C25

GMZ GEMZAR Dose: 600 [mg/m²]

5FU 5FLUROURACIL Dose: 500 [mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
GMZ	GEMZAR	↑						
5FU	5FLUOROURACIL	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
GMZ	GEMZAR	↑						
5FU	5FLUOROURACIL	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		15	16	17	18
GMZ	GEMZAR	↑			
5FU	5FLUOROURACIL	↑			
	MEHT	↑			↑

X009 Chemotherapy, GEMZAR+CDDP I. Protocol + HT

Protocol Period : 15 (Day)

Interval between protocols : 7 (Day)

Diagnoses:

C25

GMZ GEMZAR Dose: 600 (mg/m^2)

CDDP CIS-PLATINUM Dose: 15 (mg/m^2)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
GMZ	GEMZAR	↑						
CDDP	CISPLATINUM	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
GMZ	GEMZAR	↑						
CDDP	CISPLATINUM	↑						
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		15	16	17	18
GMZ	GEMZAR	↑			
CDDP	CISPLATINUM	↑			
	MEHT	↑			↑

X010 Chemotherapy, VIDE Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C4980, C4990

VCR	VINCRISTIN	Dose:	1	(mg/m²)
IFO*	HOLOXAN	Dose:	2000	(mg/m²)
MESNA*	MESNA	Dose:	2000	(mg/m²)
ADM	ADRIBLASTINA	Dose:	10	(mg/m²)
VT	ETOPOSID	Dose:	100	(mg/m²)

*4-hour i.v.

Treatment days from the onset of the cycle:		1	2	3	4
VCR	VINCRISTIN	↑			
IFO	HOLOXAN	↑	↑	↑	
MESNA	MESNA	↑	↑	↑	↑
ADM	ADRIBLASTINA	↑	↑	↑	
VP	ETOPOSID	↑	↑	↑	
	MEHT	↑			↑

X011 Chemotherapy, VAC Protocol + HT

Protocol Period : 4 (Day)

Interval between protocols : 21 (Day)

Diagnoses:

C4980, C4990

VCR	VINCRISTIN	Dose:	1	(mg/m²)
ACD	ACTINOMYCIN-D	Dose:	0,5	(mg/m²)
CTX	CITOXAN	Dose:	1000	(mg/m²)

MESNA* MESNA Dose: 2000 [mg/m²]

*by CTX 12-hours i.v.

Treatment days from the onset of the cycle:		1	2	3	4
VCR	VINCRISTIN	↑			
ACD	ACTINOMYCIN-D	↑	↑		
CTX	CITOXAN				↑
MESNA	MESNA				↑
	MEHT	↑			↑

X012 Chemotherapy, VCR+CDDP+BLM Protocol + HT

Protocol Period : 4 [Day]

Interval between protocols : 24 [Day]

Diagnoses:

C57

VCR VINCRISTIN Dose: 0,7 [mg/m²]

CDDP CIS-PLATINUM Dose: 30 [mg/m²]

BLM BLEOMYCIN Dose: 10 [mg/m²]

Treatment days from the onset of the cycle:		1	2	3	4
VCR	VINCRISTIN	↑			
CDDP	CIS-PLATINUM				↑
BLM	BLEOMYCIN	↑			
	MEHT	↑			↑

X013 Chemotherapy, GEMZAR+CDDP II. Protocol + HT

Protocol Period : 15 [Day]

Interval between protocols : 13 [Day]

Diagnoses:

C64

GMZ GEMZAR Dose: 600 [mg/m²]

CDDP CIS-PLATINUM Dose: 30 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
GMZ	GEMZAR	↑						
CDDP	CIS-PLATINUM				↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
GMZ	GEMZAR	↑						
CDDP	CIS-PLATINUM							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		15
GMZ	GEMZAR	↑
CDDP	CIS-PLATINUM	
	MEHT	↑

X014 Chemotherapy, M-VAC Protocol + HT

Protocol Period : 22 (Day)

Interval between protocols : 6 (Day)

Diagnoses:

C64

MTX METHOTREXAT Dose: 20 (mg/m²)

VBL VINBLASTIN Dose: 3 (mg/m²)

ADM ADRIBLASTINA Dose: 20 (mg/m²)

CDDP CIS-PLATINUM Dose: 50 (mg/m²)

Treatment days from the onset of the cycle:		1	2	3	4	5	6	7
MTX	METHOTREXAT	↑						
VBL	VINBLASTIN	↑						
ADM	ADRIBLASTINA	↑						

CDDP	CIS-PLATINUM				↑			
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		8	9	10	11	12	13	14
MTX	METHOTREXAT							
VBL	VINBLASTIN							
ADM	ADRIBLASTINA							
CDDP	CIS-PLATINUM							
	MEHT							

Treatment days from the onset of the cycle:		15	16	17	18	19	20	21
MTX	METHOTREXAT	↑						
VBL	VINBLASTIN	↑						
ADM	ADRIBLASTINA							
CDDP	CIS-PLATINUM							
	MEHT	↑			↑			

Treatment days from the onset of the cycle:		22	23	24	25
MTX	METHOTREXAT	↑			
VBL	VINBLASTIN	↑			
ADM	ADRIBLASTINA				
CDDP	CIS-PLATINUM				
	MEHT	↑			↑

Modulated electro-hyperthermia-enhanced liposomal drug uptake by cancer cells

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ORIGINAL RESEARCH

Modulated electro-hyperthermia-enhanced liposomal drug uptake by cancer cells

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Purpose: Modulated electro-hyperthermia (mEHT) stands to be a significant technological advancement in the hyperthermia field, utilizing autofocusing electromagnetic power on the cell membrane to create massive apoptosis. Since mEHT possesses the unique ability to excite cell membranes, we hypothesized that mEHT could enhance the uptake of liposomal drugs by enhancing phagocytic activity.

Materials and methods: Water bath control and mEHT were used to compare the enhancement of liposome-encapsulated doxorubicin (Lipodox®) uptake by cancer cells. Cancer cells were made visible by doxorubicin fluorescence to investigate drug uptake. Viable cell yield was determined via the Trypan Blue exclusion method. Various substrates were used to investigate the mechanism of drug-uptake enhancement. The murine colon carcinoma model, CT26, was used to confirm the tissue infiltration of Lipodox® and its therapeutic effect.

Results: mEHT treatment showed a significant enhancement of Lipodox® uptake of doxorubicin fluorescence compared with 37°C or 42°C water bath treatment. Tumor tissue sections also confirmed that mEHT treatment achieved the highest doxorubicin concentration in vivo (1.44±0.32 μg/g in mEHT group and 0.79±0.32 μg/g in 42°C water bath). Wortmannin was used to inhibit the macropinocytosis effect and 70 kDa dextran-FITC served as uptake substance. The uptake of dextran-FITC by cancer cells significantly increased after mEHT treatment whereas such enhancement was significantly inhibited by wortmannin.

Conclusion: The result showed mEHT-induced particle-uptake through macropinocytosis. mEHT-enhanced uptake of Lipodox® may amplify the therapeutic effect of liposomal drugs. This novel finding warrants further clinical investigation.

Keywords: hyperthermia, cancer treatment, liposome, doxorubicin, micropinocytosis

Introduction

Hyperthermia (HT) has a long history of use as a cancer treatment. One specific form of HT is modulated electro-hyperthermia (mEHT),[1–4] which utilizes capacitively (impedance) couplled 13.56 MHz amplitude-modulated radiofrequency energy.[4] The trade name for mEHT is oncothermia. The electric field energy can concentrate and accumulate in the tumor area due to the higher ionic conductivity around the cancer cell and induce cancer cell apoptosis in relatively low fever-range temperatures (at or below 42°C).[3–6] mEHT has been applied as clinical cancer treatment worldwide for more than 20 years.[7–9] Numerous clinical trials and retrospective analyses have shown that mEHT can be applied to multiple cancer types, including brain, gastrointestinal, gynecological, liver, lung, and pancreatic cancers.[10] mEHT has shown a synergistic effect with some chemotherapy agents.[11] In general, mEHT is not recommended as monotherapy, but rather in combination with radiotherapy, chemotherapy, or immunotherapy.

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In a previous study, we performed a three-armed, direct comparison between water bath, 8 MHz conventional HT (Thermotron RF-8), and mEHT. We observed the respective biological effects on tumor cell lines. In the same treatment conditions (42°C for 30 minutes), mEHT gave rise to a higher apoptosis rate than other HT methods. Moreover, mEHT also induced the release of Heat Shock Protein 70 (Hsp70) from cancer cell cytosol to its extracellular domain.[12] These results indicate that mEHT may trigger anti-tumor responses on cell membranes and disturb the biological effects of cell membranes. Liposomal chemotherapy drugs (chemo-drugs) are a relatively new form of chemo-drugs, with many years of clinical application. They have many advantages when compared with conventional chemo-drugs. The use of liposome-encapsulated doxorubicin (Lipodox®) allows the drug to become trapped within the tumor site, enhancing its killing effect on tumor cells. Lipodox® can also reduce side effects induced by conventional doxorubicin, specifically cardiac toxicity. Approved cancer indications for Lipodox® include Kaposi sarcoma, multiple myeloma, and breast and ovarian cancers. Lipodox® has not been approved as a substitute for conventional doxorubicin in adjuvant treatment of breast cancer.[13] Furthermore, therapeutic efficacy in application has not matched expectations from development phases.[14] Thus, there have been many studies conducted to enhance the therapeutic efficacy of liposomal chemo-drugs. Thermo-sensitive liposome, a new form of doxorubicin, has been proposed as remedy,[15] but this new formulation drug has yet to pass clinical trials, and is years away from clinical bedside application. As of now, no proven method is available to enhance the therapeutic efficacy of US Food and Drug Administration-approved Lipodox® or its class of liposomal chemo-drugs.[16]

mEHT has been mentioned as a nano-heating method on cell membranes without utilizing artificial nanoparticles.[17] The radiofrequency energy transmitted from mEHT could stimulate the membrane, specifically the membrane rafts of the tumor cells.[18] Thus, in this study, we hypothesized that the ability of mEHT to stimulate cell membranes may enhance the phagocytosis of cancer cells. This may apply to macromolecular drugs such as liposomal chemo-drugs.

Materials and methods

Cell culture

HepG2 (hepatocellular carcinoma) and A549 (lung carcinoma) cells were grown in DMEM (Thermo Fisher Scientific, Waltham, MA, USA) containing 10% heat-inactivated FBS with 100 units/mL penicillin and 100 μg/mL streptomycin (Thermo Fisher Scientific). U87MG (glioblastoma astrocytoma) cells were maintained in minimum essential medium (Thermo Fisher Scientific) containing 10% heat-inactivated FBS with 1 mM sodium pyruvate, 100 units/mL penicillin, and 100 μg/mL streptomycin. CT26 (murine colorectal carcinoma) cells were maintained in RPMI 1640 (Thermo Fisher Scientific) containing 10% heat-inactivated FBS with 4.5 g/L D-glucose, 10 mM HEPES, 1 mM sodium pyruvate, 100 units/mL penicillin, and 100 μg/mL streptomycin. All of the cell lines were purchased from Bioresource Collection and Research Center, Hsinchu, Taiwan (BCRC). The BCRC number of each cell line is listed as follows: BCRC 60025 (HepG2), BCRC 60074 (A549), BCRC 60360 (U87MG), and BCRC 60447 (CT26).

mEHT treatment

Electromagnetic heating was generated by capacitively-coupled, amplitude-modulated, 13.56 MHz radiofrequency (LabEHY, Oncotherm Ltd, Troisdorf, Germany). An in vitro heating model was set up in an electrode chamber (LabEHY in vitro applicator). The chamber contained a cell bag (1×10^6 cells) heated to 42°C for 30 minutes with average power of 10–12 W. Temperature was maintained at approximately 42°C on the treated side, as measured with optical sensors (Luxtron FOT Lab Kit, LumaSense Technologies, Inc., Santa Clara, CA, USA). The in vitro model setup was shown previously.[12] The power patterns were repeated three times. We checked the power pattern each time to verify the accuracy and similarity of the experiments. Our experiment followed the same precision procedure setup for experimentation with mEHT as used by Andocs et al.[19] For water bath control, 1×10^6 cells were placed in a tube with culture medium and incubated at 42°C for 30 minutes.

Viability assay

To determine cell viability, cells were cultured for 24 hours after treatment, and viable cell yield was determined via the Trypan Blue exclusion method.

Lipodox® size determination and doxorubicin concentration

Lipo-Dox® (Lipodox®) was purchased from Taiwan Tung Yang Biopharm (TTY Biopharm Company, Ltd, Taipei, Taiwan). Lipodox® contains 20 mg/10 mL of doxorubicin and 14 mol/mL phospholipid per vial. The lipid compositions included distearoylphosphatidylcholine, cholesterol, and polyethylene glycol-(average molecular weight, 2,000) derived distearoylphosphatidylethanolamine (molar ratio, 3:2:0.3).[20,21] The diameter of the Lipodox® was determined by dynamic

light scattering (DLS) (HORIBA SZ-100, HORIBA, Kyoto, Japan). Total doxorubicin content in the medium was detected fluorometrically using a 96-well microplate reader (Sunrise, Tecan, Männedorf, Switzerland) (excitation: 470 nm; emission: 582 nm). Fluorescence intensity was translated to doxorubicin concentration, by a standard curve prepared from doxorubicin original solutions. Results are represented by the mean and SD of at least three replicates for each experiment.

Doxorubicin-release detection

In this study, the doxorubicin-release detection was performed by flow cytometry and immunofluorescence. Cells were collected at 10 minutes after treatment. For flow cytometric analysis, the drug-loaded cells were washed with ice cold PBS twice and detected in the FL-2 channel depending on the red fluorescence of doxorubicin. In the inhibition experiments, different inhibitors for each endocytosis pathway were used and cells were pre-treated with them for 30 minutes prior to mEHT treatment, including 200 μg/mL NaN_3 (Sigma S2002, ATPase-inhibitor, Sigma-Aldrich Co., St Louis, MO, USA), 4 μg/mL filipin (Sigma F4767, caveolae-mediated pathway), 0.1 μM wortmannin (Sigma W3144, macropinocytosis), and 7 μg/mL chlorpromazine (CPZ) (Sigma C8138, clathrin-mediated endocytosis pathway). For immunofluorescence staining, the drug-loaded cells were washed with ice cold PBS twice and stained with DAPI for nuclear staining after fixing with 3.7% paraformaldehyde for 15 minutes. The fixed cells were washed with ice cold PBS twice, re-suspended in mounting solution, and dropped onto the cover slide for analysis by fluorescence microscopy (iRiS™ digital cell imaging system, Logos Biosystems, Inc., Seoul, South Korea).

Substrate assay

To investigate the increasing uptake ability by mEHT treatment, various endocytosis pathway substrates were used in this study including Alexa-fluor 488-conjugated transferrin (5 μg/mL, Invitrogen T-13342) for clathrin-mediated pathway, Alexa-fluor 488-conjugated cholera toxin subunit-B (2 μg/mL, Invitrogen C-34775) for caveolin-mediated pathway, and FITC-labeled 70 kDa dextran (1 mg/mL, Sigma 46945) for macropinocytosis. All these substrates were used for pre-treating cells for 10 minutes before mEHT treatment and analyzed by Accuri C6 flow cytometer and CFlow Software (Accuri cytometers Inc., Ann Arbor, MI, USA) at 10 minutes after treatment.

Western blot assay

For protein analysis, cells were lysed 10 minutes after treatment with RIPA buffer (Sigma R0278) containing phosphatase inhibitor (Hoffman-La Roche Ltd., Basel, Switzerland) and protease inhibitor (Hoffman-La Roche Ltd.). The total protein concentration was measured using the BCA protein assay kit (Thermo Fisher Scientific). Cell lysates (20 μg) were separated using SDS-PAGE. After transfer, proteins were probed with antibodies against p-EGFR, Tyr1068 (Cell Signaling Technology [#2234], Danvers, MA, USA), and α-tubulin (9F3) (Cell Signaling Technology, #2128). Bound antibodies were visualized using HRP-linked anti-rabbit antibodies.

Animal study

BALB/c mice were purchased from BioLASCO Taiwan Co., Ltd. (Taipei, Taiwan) and housed at 20°C–22°C, with 50%–60% humidity and 12-hour light/dark cycles. Sterile rodent food and water were given ad libitum. Five-week old mice at weights of 20–25 g were used. CT26 murine colorectal carcinoma cells were cultured as described previously. CT26 murine colorectal carcinoma cells (3×10^5) were injected subcutaneously in the right femoral areas of mice. The mice were used for experiments when their tumor volume grew to approximately 150–200 mm^3. The mice received local water bath or mEHT treatment (as described previously) immediately after 10 mg/kg Lipodox® intravenous injection through the tail vein as a one-time treatment. For water bath control, tumor-bearing legs were fixed on a rack to maintain a stable position in a water bath during the HT treatment. The size of tumors was measured on the day of experiment, and once every 2 days. Length (L) and width (W) were recorded and the tumor volumes were calculated as ($L\times W^2/2$). Mice were sacrificed when their tumors reached the maximum allowed volume of 3,000 mm^3.

Statistical analysis

All statistical analyses were performed using the statistical software program Prism 4 (GraphPad Software, Inc., La Jolla, CA, USA). Comparisons among groups were made with one-way ANOVA or unpaired Student's *t*-test (two-tailed). Differences were considered statistically significant at $P<0.05$. Data are given as mean and SD of experiments, independently repeated at least three times.

Ethics statement

The studies were approved by the Institutional Animal Care and Use Committee of the National Yang-Ming University prior to initiation (approval no. 1060602). The welfare of the animals was based on the *Guide for the Care and Use of Laboratory Animals*, 8th edition.

Results

mEHT enhanced cytotoxicity of Lipodox® in various cancer cell lines

In order to investigate the cytotoxicity of mEHT combined with Lipodox® in cancer cells, HepG2, A549, U87MG, and CT26 cells were treated for 10 minutes with or without 50 μM of Lipodox®, and then separated into groups to be either incubated in a water bath at 37°C (control), in a water bath at 42°C, and mEHT at 42°C for 30 minutes. After 24 hours incubation without Lipodox®, cell number was counted and the number relative to the 37°C control was indicated as cell viability. Cell viability of the mEHT group decreased in comparison with the 37°C control, whereas mEHT combination with Lipodox® treatment further decreased the cell viability to 10.7%±2.7% from 52.3%±6.2% with mEHT treatment alone in HepG2 cells (Figure 1A, $P<0.001$). This result was consistent among other cell lines. For A549 cells, cell viability under mEHT treatment with Lipodox® was 23.4%±4.1%, while without Lipodox® was 49.5%±13.2%, ($P<0.05$) (Figure 1B). In U87MG cells, cell viability was 45.0%±1.7% with mEHT treatment alone and 25.6%±4.9% with mEHT plus Lipodox®, ($P<0.01$) (Figure 1C). In CT26 cells, cell viability was 47.3%±8.7% with mEHT treatment alone and 22.3%±8.9% with mEHT plus Lipodox®, ($P<0.05$) (Figure 1D).

Size distribution and doxorubicin-release rate of Lipodox® unaffected by mEHT treatment

To investigate if mEHT treatment affects the liposomal size and structure of Lipodox®, Lipodox® was separated into groups and treated under three conditions: in a water bath at 37°C

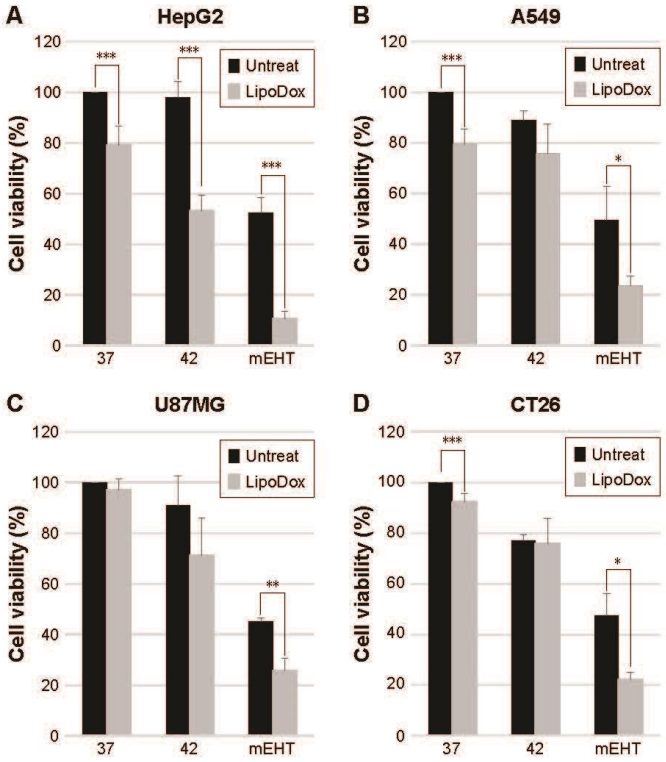

Figure 1 Inhibition of cell viability with mEHT plus Lipodox® treatment.
Notes: Cancer cells (**A**) HepG2, (**B**) A549, (**C**) U87MG, (**D**) CT26 were incubated under three conditions: in a water bath at 37°C as control, in a water bath at 42°C, and with mEHT at 42°C for 30 minutes. Cells for viability assay were cultured for 24 hours after treatment, and viable cell yield was determined by the Trypan Blue exclusion method. Histograms for the percentage of Trypan Blue-negative cells are shown. Data represent mean ± SD (n=3). *$P<0.05$, **$P<0.01$, ***$P<0.005$.
Abbreviations: Lipodox®, liposome-encapsulated doxorubicin; mEHT, modulated electro-hyperthermia.

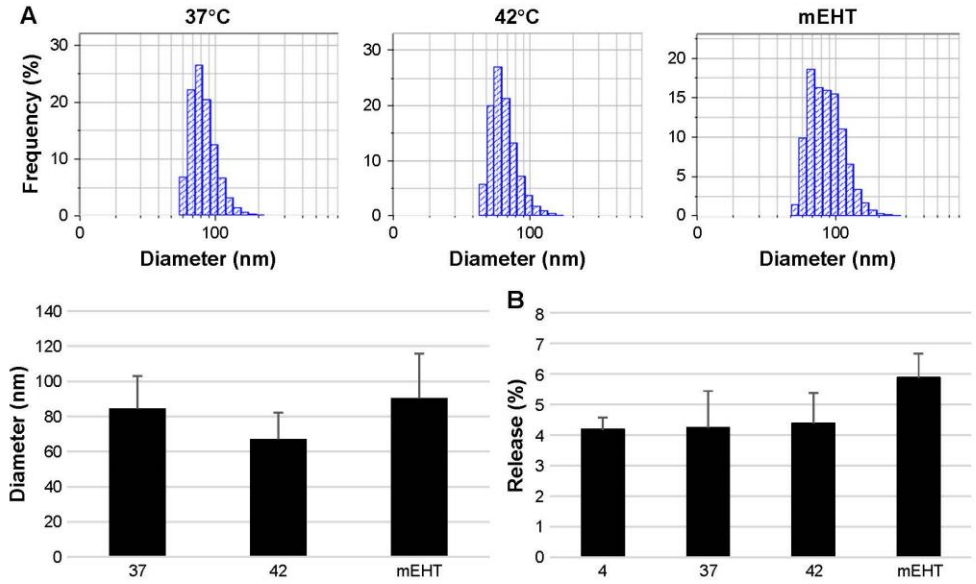

Figure 2 Size distribution and Lipodox®'s doxorubicin-release rate with HT treatment.
Notes: (**A**) The particle size of Lipodox® was measured by DLS after incubation under three different conditions: in water bath at 37°C as control, in water bath at 42°C, and with mEHT at 42°C for 30 minutes. (**B**) Free form of doxorubicin was measured in the Lipodox®-containing medium after incubation under different conditions: in water baths at 4°C, 37°C, 42°C, and with mEHT at 42°C for 30 minutes.
Abbreviations: DLS, dynamic light scattering; HT, hyperthermia; Lipodox®, liposome-encapsulated doxorubicin; mEHT, modulated electro-hyperthermia.

(control), in a water bath at 42°C, and with mEHT at 42°C for 30 minutes. Liposomal size was then measured by DLS. Size distributions showed no significant difference among the three groups, with 84.5±18.6 nm at 37°C, 67.2±15 nm in 42°C water bath, and 90.3±25.5 nm with mEHT incubation (Figure 2A). The release rate of doxorubicin concentration in medium also showed no significant difference among the three groups, with 4.24% at the 37°C water bath, 4.38% at the 42°C water bath, and 5.87% with mEHT treatment (Figure 2B). This result indicated that both HT treatment by water bath and mEHT did not affect the liposomal size and structure of Lipodox®. Therefore, we can confirm that the cytotoxic enhancement of mEHT plus Lipodox® was due to increased release of doxorubicin in medium.

mEHT enhanced Lipodox® uptake by cancer cells in vitro and in vivo

Lipodox® uptake by cells (HepG2, A549, U87MG, and CT26) was detected by the intracellular fluorescence intensity of doxorubicin by using flow cytometry and fluorescence microscopy. As shown in Figure 3A, mEHT significantly increased the uptake of doxorubicin in HepG2 (3.4±0.7 fold to 37°C), A549 (2.2±0.8 fold to 37°C), U87MG (1.8±0.3 fold to 37°C), and CT26 (1.5±0.2 fold to 37°C) in vitro. Flow cytometric assay for detecting fluorescence intensity showed that after mEHT treatment, Lipodox® uptake was significantly increased in all cell lines compared with the 42°C water bath and 37°C control (Figure 3A). Immunofluorescence further showed the uptake of Lipodox® in HepG2 culture water bath at 37°C, in 42°C water bath, and with mEHT treated with 50 μM of Lipodox® for 30 minutes. As shown in Figure 3B, cells cultured with mEHT showed the highest fluorescence intensity compared with the 37°C and 42°C water bath groups, indicating elevated uptake under mEHT treatment.

To investigate the mEHT-increased Lipodox® uptake in vivo, CT26-bearing mice were separated into three groups to be treated with a water bath at 37°C (control), water bath at 42°C, and with mEHT at 42°C for 30 minutes after Lipodox® intravenous treatment (10 mg/kg). The tumors were dissected and the concentrations of doxorubicin were detected. Figure 3C shows the doxorubicin concentrations water bath at 37°C, in 42°C water bath, and with mEHT were 0.35±0.1, 0.79±0.32, and 1.44±0.32 (μg/g), respectively, indicating that mEHT significantly increased Lipodox® retention in tumors.

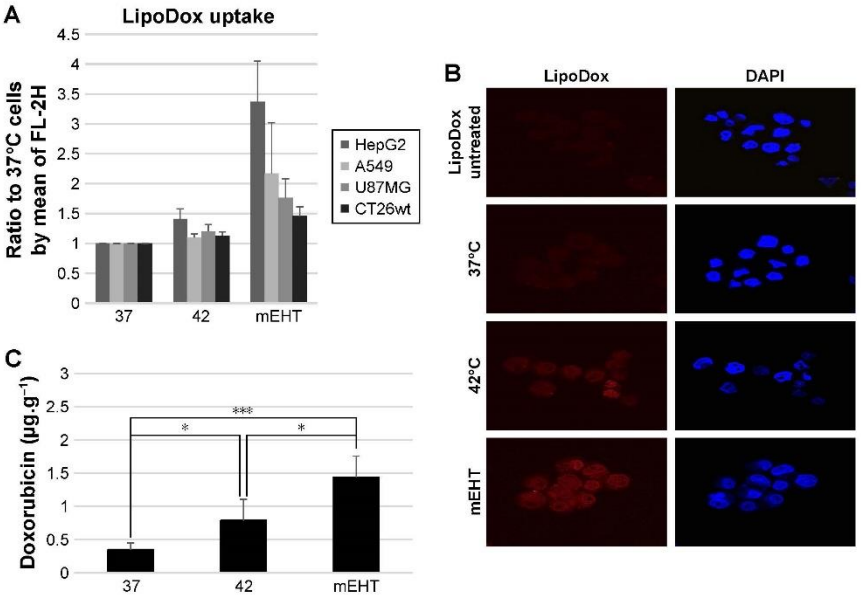

Figure 3 Increased Lipodox® uptake in vitro and in vivo due to mEHT treatment.

Notes: (**A**) Cellular uptake of Lipodox® by various cancer cells (HepG2, A549, U87MG, and CT26wt). Cells were treated for 24 hours with 50 µM of Lipodox® followed by either incubation in water bath at 37°C as control, in water bath at 42°C, and with mEHT at 42°C for 30 minutes. Flow cytometry was used to quantify the uptake of Lipodox® by the cells. Data represent results from experiments repeated three times independently. (**B**) Fluorescence microscopy images of HepG2 cells which were treated with Lipodox® at 50 µM for 24 hours, followed by incubation in water bath at 37°C as control, in water bath at 42°C, and with mEHT at 42°C for 30 minutes. Nuclei were stained with DAPI (blue), and doxorubicin was indicated by red fluorescence. Magnification 400×. (**C**) mEHT increased Lipodox® uptake in vivo. Four hours after Lipodox® intravenous treatment (10 mg/kg), CT26-bearing mice were treated in three groups under incubation in water bath at 37°C as control, in water bath at 42°C, and with mEHT at 42°C for 30 minutes. Fifteen mice were divided into three groups, each containing five mice. The tumors were dissected and the concentration of doxorubicin was measured by spectrofluorometry. *$P<0.05$, ***$P<0.005$.

Abbreviations: Lipodox®, liposome-encapsulated doxorubicin; mEHT, modulated electro-hyperthermia.

mEHT enhanced Lipodox® uptake by activation of macropinocytosis

Endocytosis pathways are subdivided into four categories: receptor-mediated endocytosis (clathrin-mediated endocytosis), caveolae-dependent endocytosis, macropinocytosis, and phagocytosis.[22] To explore which pathway was utilized in mEHT-enhanced Lipodox® uptake, various inhibitors were utilized to block pathways. By blocking energy by supplementation with NaN_3 (ATPase-inhibitor), both water bath and mEHT treatment showed a significant decrease of Lipodox® uptake (Figure 4A, $P<0.01$). Both CPZ (clathrin-mediated endocytosis-inhibitor) and wortmannin (macropinocytosis-inhibitor) significantly reduced the Lipodox® uptake in water bath and mEHT treatment (Figure 4B and C), whereas wortmannin induced a more inhibitory effect with mEHT treatment ($P<0.01$). Filipin (caveolae-mediated endocytosis-inhibitor) had no effect on both water bath and mEHT treatment groups (Figure 4D). These results indicated that the processes involved in translocation of Lipodox® across cancer cell membranes are energy-dependent and may include macropinocytosis.

The cytotoxic effect after Lipodox® plus HT treatment was further evaluated by wortmannin. Cytotoxicity of Lipodox® under water bath and mEHT treatment could be reversed by wortmannin (Figure 4E). Consistent with the observation of uptake inhibition, mEHT responded to wortmannin more significantly than water bath treatment ($P<0.01$ vs $P<0.05$, Figure 4E).

Various substrates for the investigation of endocytosis pathways

Multiple substrates were used for different pathways: cholera toxin subunit for caveolae-dependent endocytosis and transferrin for clathrin-dependent endocytosis were both utilized. Cholera toxin subunit was found to increase levels of substrate internalized significantly after mEHT treatment (Figure 5A, 1.21±0.08 fold compared to 37°C treatment, $P<0.05$).

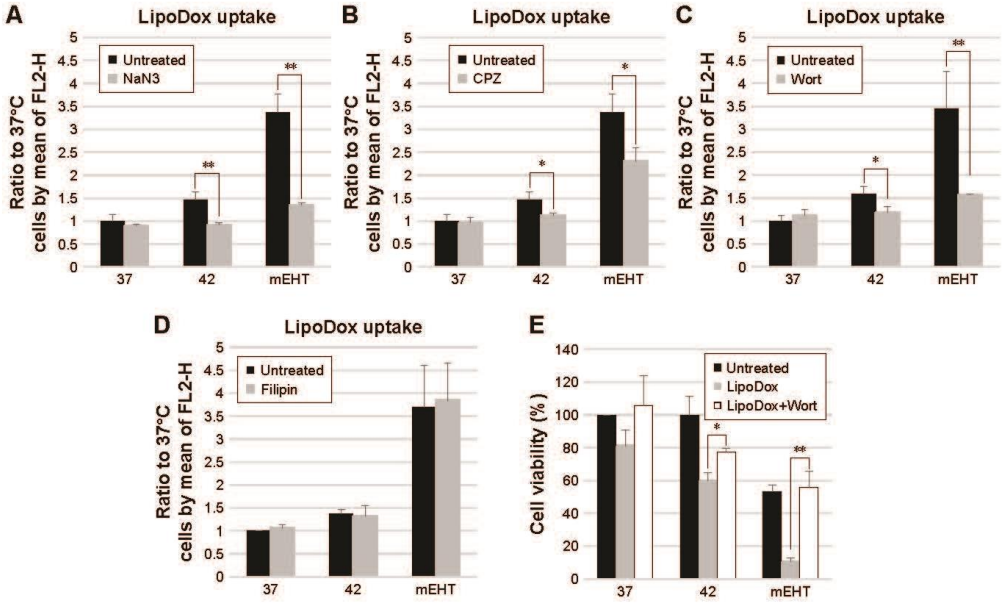

Figure 4 Effect of endocytic-inhibitors on accumulation of Lipodox® and cell viability in HepG2 cells.
Notes: Cells were either untreated or pretreated under separate conditions with various inhibitors. (**A**) NaN_3 as ATPase-inhibitor, (**B**) CPZ, (**C**) wortmannin, (**D**) filipin for 30 minutes at 37°C prior to adding Lipodox® (50 μM). The fluorescence signal was measured following incubation for 3 hours at 37°C in all cases. (**E**) HepG2 cells for viability assay were cultured for 24 hours after treatment, and viable cell yields were determined by the Trypan Blue exclusion method. Data represent mean ± SD (n=3). *$P<0.05$ and **$P<0.01$ compared to control.
Abbreviations: CPZ, chlorpromazine; Lipodox®, liposome-encapsulated doxorubicin; Wort, wortmannin.

Transferrin uptake was significantly enhanced with 42°C water bath (Figure 5C, 1.18±0.05 fold compared to 37°C treatment, $P<0.01$). The substrate of macropinocytosis, dextran, was significantly increased (2±0.5 fold compared to 37°C treatment) in cancer cells after mEHT treatment (Figure 5B). Since the increased uptake was higher in dextran, we further investigated the effect with the macropinocytosis inhibitor, wortmannin. Wortmannin also significantly reduced the internalized dextran under mEHT treatment (Figure 5D). It has been reported that macropinocytosis can be stimulated by triggering tyrosine kinase receptor.[23] The activation of EGFR after mEHT treatment was evaluated by Western blot. As shown in Figure 5E, EGFR was activated immediately from 10 minutes up to 6 hours and decreased in 24 hours after mEHT treatment. This result further confirmed that mEHT-induced endocytosis was macropinocytosis.

In vivo evaluation of therapeutic efficacy of the combination of Lipodox® and mEHT

The therapeutic effect of Lipodox® plus mEHT was further confirmed by a mouse cancer model. The effect of tumor growth inhibition was shown in Figure 6. There was no therapeutic effect in groups treated with water bath or with mEHT alone. Lipodox® alone inhibited tumor growth slightly. Lipodox® with water bath was found to increase tumor growth inhibition ($P<0.05$). Tumors treated with Lipodox® plus mEHT were significantly smaller than those of the control groups (untreated, with water bath alone, mEHT alone, Lipodox® alone, or Lipodox® plus water bath) ($P<0.05$).

Discussion

In this study, we found that mEHT could enhance the uptake of Lipodox® by disturbing physiologic activity within the cell membrane. A possible pathway to stimulate this endocytosis ability was also investigated. Uptake of particles is limited to a specific size during mEHT treatment. Uptake enhancement is positively related to the killing effect of cancer cells. Our in vivo study also showed a similar enhancement and therapeutic effect.

To the best of our knowledge, this is the first report that directly shows the enhancement of cellular uptake ability of clinical grade Lipodox®. Lipodox® is widely used for the

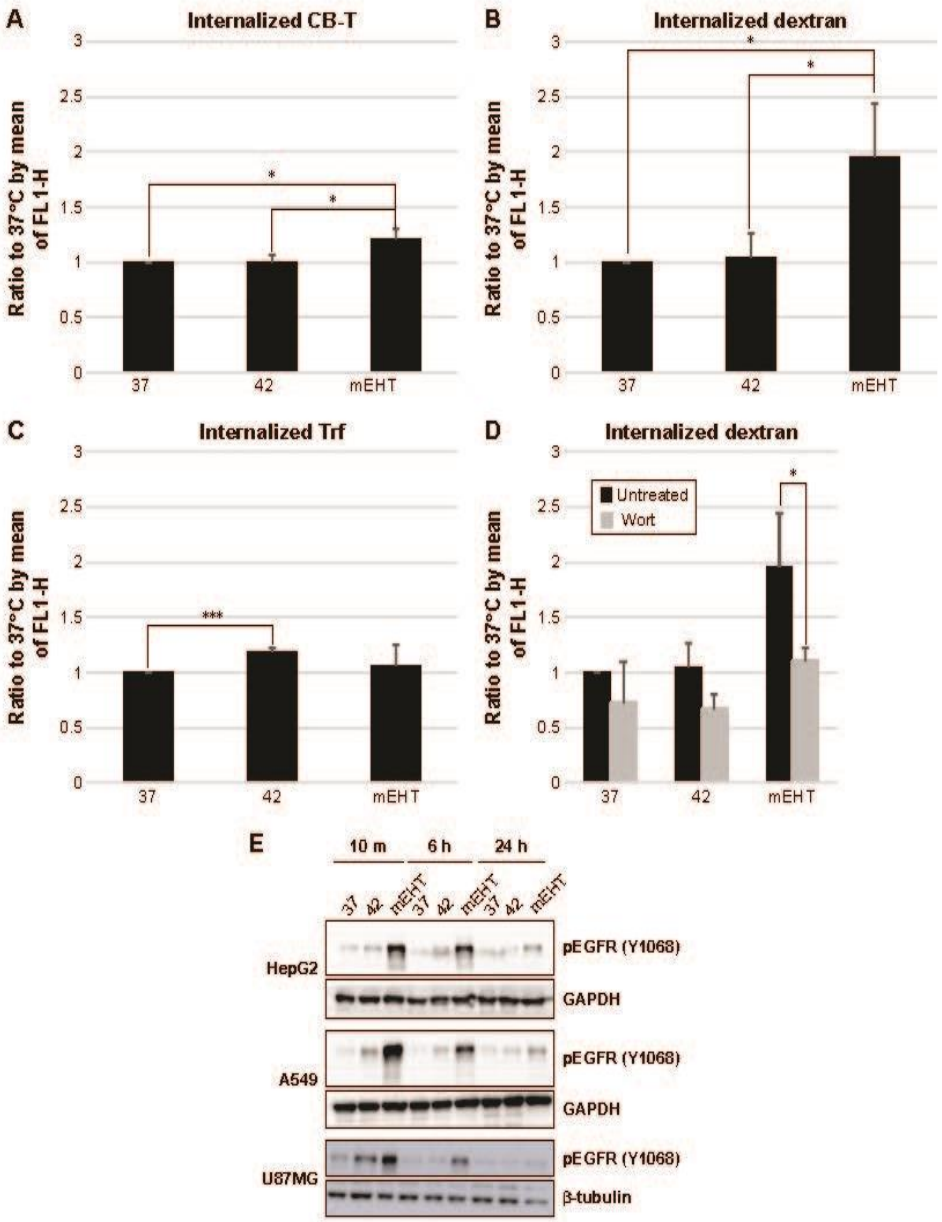

Figure 5 The stimulation of endocytosis signaling pathway with mEHT treatment.

Notes: The roles of (**A**) cholera toxin B subunit signaling pathway (caveolin pathway), (**B**) dextran (micropinocytosis), and (**C**) transferrin (clathrin pathway) in endocytosis of mEHT treatment in HepG2 cells were evaluated. (**D**) Wortmannin (0.1 μM) was used to observe the dextran uptake inhibition effect. (**E**) The activation of EGFR was determined by immunoblotting for Y1068 phosphorylation. Lysates of HepG2, A549, and U87MG were harvested after mEHT treatment at 10 minutes, 6 hours, and 24 hours. GAPDH and beta-actin were served as internal control. *$P<0.05$, ***$P<0.005$.

Abbreviations: mEHT, modulated electro-hyperthermia; Wort, wortmannin; CB-T, Cholera toxin B subunit; Trf, transferrin.

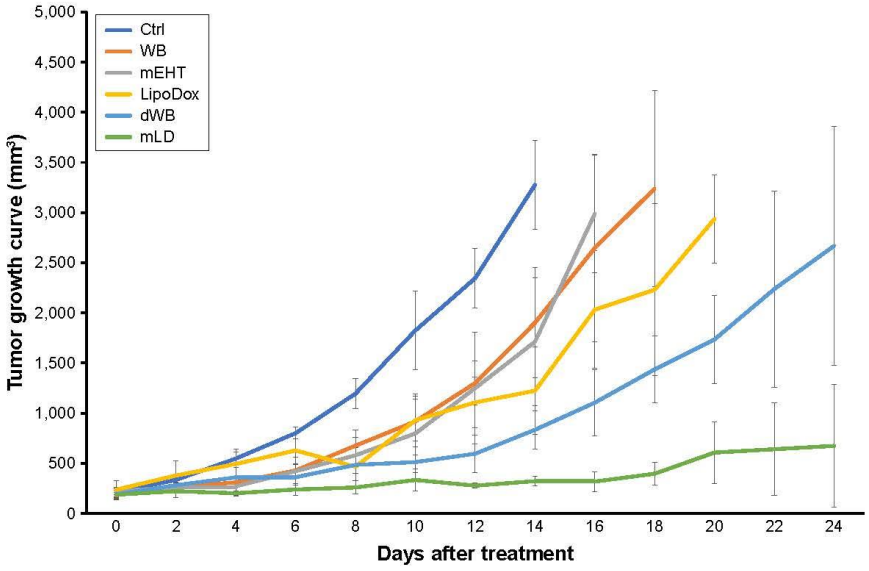

Figure 6 Decreased tumor growth with in vivo treatment of inbred colon cancer mice model.
Notes: CT26-injected BALB/c mice were untreated (control [Ctrl], n=6) or treated under different conditions: WB (n=6), mEHT (n=7), Lipodox® (n=7), dWB (n=7), and Lipodox® plus mEHT (n=7). Tumors were measured at days 0–24 after treatment. Tumor growth curves showed that Lipodox® plus mEHT treatments inhibited tumor growth significantly better than other groups.
Abbreviations: dWB, Lipodox® plus WB; mEHT, modulated electro-hyperthermia; mLD, Lipodox® plus mEHT; WB, water bath.

treatment of gynecologic cancer including cervical and ovarian cancers. However, the efficacy of Lipodox® in clinical bedside settings is not as high as expected based on clinical development findings. Although several studies reported that HT could enhance the therapeutic effect of Lipodox®, these studies focused on the tumor liposome extravasation induced by HT.[24,25] In this report, we utilized mEHT as a physical method to enhance the cellular uptake of Lipodox® in cancer cells, significantly increasing the killing effect on cancer cells. These findings show promise for future clinical applications.

The cell membrane is one important target for mEHT.[17] Due to the specific design of mEHT, the structure of lipid bilayer membranes serves as a good insulator for the cell from the electric field generated by mEHT. The heating of mEHT applies forward energy selectively to the most ionized areas in the tumor microenvironment. The RF current, which flows through the cancerous lesion of ionized areas, was electrically concentrated by its lower impedance. The mEHT generated energy is captured by the extracellular part of the cell membrane.[17] The membrane rafts, which are a cluster of functional proteins, have different electromagnetic properties when compared with other parts of the cell membrane. This property allows membrane rafts to absorb more mEHT energy than other lipid bilayer parts of the cell membrane. The higher energy absorption induces elevation of temperature on rafts during mEHT treatment. Therefore, the energy of mEHT could disrupt the membrane arrangement and enhance particles of specific size to penetrate cancer cells.

Conventional HT has been reported to induce hyperpermeable tumor vasculature environment that enhances the therapeutic efficacy of both Doxil and Lipodox®.[26] Conventional HT can induce a selective intratumoral accumulation of liposomal drugs, while HT increases vascular permeability in the tumor vasculature.[27] Conventional HT may also trigger the release of extravascular liposomal drugs from the liposomal structure, but the release of Doxil may increase the risk of toxicity in healthy tissues. For conventional HT as a treatment consideration for regional tumors, the temperature may need to rise to a higher level (above 41°C) to achieve intravascular drug release. This treatment lacks the selectivity for tumor tissues, thus increasing the possibility of side effects and toxicity to surrounding healthy tissues. Moreover, when compared to mEHT, conventional HT cannot enhance

the uptake of Lipodox® by tumor cells directly. mEHT may indicate a particular therapeutic benefit for tumor cells that have more resistance to chemotherapy by inhibiting transportation across the membrane.

Macropinocytosis has been considered as growth factor-induced and actin-driven endocytosis that transfers particles or fluid from outside the cell into cytosol.[22] When compared with other cellular endocytosis pathways, macropinocytosis takes up particles in a nonspecific manner and could occur in most cells. This kind of endocytosis is usually triggered by outside stimulations that induce the activation of receptor tyrosine kinase. In this report, we showed that mEHT could be a stimulator to excite EGFR and may induce the formation of membrane ruffles. Dextran testing also confirmed that this mEHT-induced macropinocytosis is nonspecific endocytosis.

It has been reported that apoptosis can be induced in cancer cells by mEHT treatment alone.[12,28,29] The death receptors and caspase signaling pathway are activated in cancer cells after mEHT treatment. Although monotherapy with mEHT is not very promising in clinical applications, the ability of apoptosis induction by mEHT may contribute to the enhancement of cancer cell killing effect when doxorubicin is released from the liposome within cancer cells. Previous studies have shown that thermosensitive liposome-encapsulated doxorubicin (TLED) could achieve a similar therapeutic effect in doxorubicin-resistant cancer cells.[30] However, TLED still focuses on a local release of doxorubicin in the tumor site, which differs from our findings of enhanced cellular uptake of doxorubicin. Vujaskovic et al have reported neoadjuvant therapy with Lipodox® and HT as a feasible and well-tolerated treatment strategy in locally advanced breast cancer.[31] Their results are consistent with our animal study which showed that conventional HT (water bath) could elevate the therapeutic effect of Lipodox®. We found that mEHT enhanced the effect further.

There are several approaches to enhance the cellular uptake of doxorubicin through various methods of drug-loaded nanoparticles. Two recent studies have shown that treatment with MoS2 nanoparticles followed by photothermal therapy could accelerate drug release and increase efficacy of cancer treatment with doxorubicin.[32,33] The application of thermosensitive liposomal doxorubicin and mild HT produced by a clinical high intensity focused ultrasound system has undergone a clinical trial that showed improved anti-tumor efficacy.[34,35] These studies have shown the promise of utilizing physics-based therapies in combination with nanoparticle drugs for the treatment of cancer. Our studies also confirmed the value of this treatment approach. Furthermore, the use of clinically-approved Lipodox® and mEHT can have immediate clinical bedside applications without further need for trials.

Conclusion

mEHT treatment was designed to focus on low pH areas in tissues, but mEHT did not induce doxorubicin release from liposomes in the extracellular matrix. mEHT stimulated the activity of receptors and enzymes of cancer cells. Consequently, the uptake of Lipodox by cancer cells significantly increased after mEHT treatment and effectively enhanced the therapeutic effect of the drug. This novel finding warrants further study for application to clinical cancer therapy.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer

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Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer

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Disclosures can be found in Additional Information at the end of the article

Abstract

Triple-negative breast cancer (TNBC) is more aggressive and metastatic than other breast cancer types. Cytotoxic chemotherapy is presently the predominant systemic therapy for TNBC patients. This case report highlights the influence of metabolically supported chemotherapy (MSCT), ketogenic diet (KD), hyperthermia (HT), and hyperbaric oxygen therapy (HBOT) in an overweight 29-year-old woman with stage IV (T4N3M1) triple-negative invasive ductal carcinoma of the breast. The patient presented with an observable mass in her left breast detected during a physical examination in December 2015. Magnetic resonance imaging revealed a Breast Imaging Reporting and Data System Category 5 tumor and multiple lymphadenomegaly in the left axilla. A Tru-Cut biopsy led to the diagnosis of a triple-negative nuclear grade 2 invasive ductal carcinoma. The patient was admitted to ChemoThermia Oncology Center, Istanbul, Turkey in October 2016, and a whole body (18F)-fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT) scan revealed a 77 mm x 55 mm primary tumor in her left breast, multiple left pectoral and axillary lymph nodes, multiple widespread liver masses, and an upper left nodular abdominal lesion. The patient received a treatment protocol consisting of MSCT, KD, HT, and HBOT. A follow-up whole body 18F-FDG PET-CT scan in February 2017 showed a complete therapeutic response with no evidence of abnormal FDG uptake. The patient continued to receive this treatment protocol and in April 2017 underwent a mastectomy, which revealed a complete pathological response consistent with the response indicated by her PET-CT imaging. This single case study presents evidence of a complete clinical, radiological, and pathological response following a six-month treatment period using a combination of MSCT and a novel metabolic therapy in a patient with stage IV TNBC.

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Introduction

Breast cancer is the most frequently diagnosed cancer among women, with nearly 1.7 million

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new cases diagnosed worldwide in 2012. It ranks as the fifth cause of death from cancer overall (522,000 deaths) and is the leading cause of cancer death in women [1]. Breast cancer is a heterogeneous disease with several biologically distinct subtypes. Triple-negative breast cancer (TNBC) is defined by the absence of immunohistochemical expression of the estrogen (ER) and progesterone (PgR) receptors and a lack of amplification of the human epidermal growth factor receptor 2 (HER2)/Neu gene, accounting for approximately 20% of breast cancer cases. TNBC has a highly aggressive nature, develops among younger women, and has a higher risk of distant metastasis than other types of breast cancers. Its lack of molecular targets has contributed in part to the difficulty in managing TNBC. Cytotoxic chemotherapy is the only systemic therapy available for these patients. In the treatment of early-stage disease, chemotherapy is effective and pathologic complete response (pCR) rates exceed those of hormonal receptor-positive subtypes [2]. However, patients with metastatic disease experience rapid progression through several lines of chemotherapy. No prior studies have evaluated the influence of metabolically supported chemotherapy (MSCT), ketogenic diet (KD), hyperthermia (HT), and hyperbaric oxygen therapy (HBOT) as a therapeutic strategy for managing TNBC.

The rationale for MSCT is based on Warburg's hypothesis that "cancer is a disease of metabolic dysregulation" where aerobic fermentation compensates for insufficient oxidative phosphorylation for energy generation [3]. In practice, MSCT initiates with a 12-hour fast, the application of pharmacological doses of regular insulin, and the development of mild hypoglycemia prior to the administration of chemotherapy. As was previously demonstrated in a case report of rectal cancer and a case series in pancreatic cancer, MSCT may enhance the cytotoxic effects of chemotherapy [4-5].

The reduction in circulating glucose can exploit the dependency of cancer cells reliant on glycolytic fermentation. The KD, a high-fat, carbohydrate-restricted diet, decreases blood glucose levels and elevates blood ketone levels, thus slowing the progression of cancer [6]. HT exposes body temperature to 42°C or higher and exploits the heat sensitivity of cancer cells [7]. Tumor hypoxia increases the glycolytic dependency of cancer cells, and hypoxic environments have cancer-promoting effects. HBOT increases oxidative stress specifically in tumor cells and reverses the cancer-promoting effects of hypoxia [8]. We report here a case of stage IV TNBC in a patient that achieved a complete clinical, radiological, and pathological response after receiving a combination of MSCT, KD, HT, and HBOT.

Case Presentation

An overweight 29-year-old woman with a body mass index (BMI) of 28.1 presented with a lump in her left breast that was detected during a physical examination in December 2015. The patient was admitted to Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey in August 2016, with interval enlargement of the tumor. Magnetic resonance imaging revealed a 75 mm x 75 mm x 65 mm left breast mass (Breast Imaging Reporting and Data System Category 5) with irregular borders. Multiple lymphadenomegaly was seen in the left axilla with the largest being 27 mm x 20 mm. A Tru-Cut biopsy led to a diagnosis of a nuclear grade 2 invasive ductal carcinoma that was negative for ER, PgR, and HER2 receptors (Figures *1-4*).

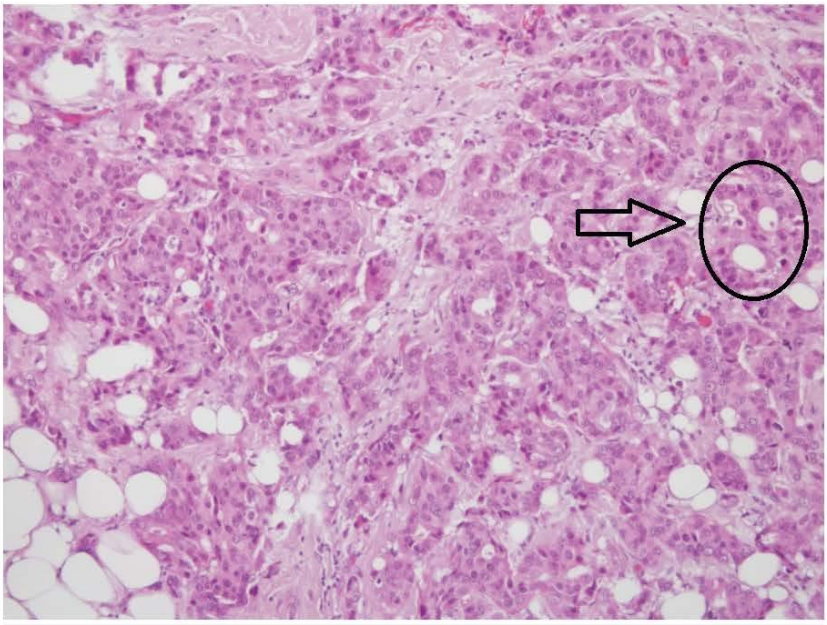


FIGURE 1: Histopathological examination showing a solid mass and gland forming atypical epithelial cells indicative of nuclear grade 2 invasive ductal carcinoma (x100)

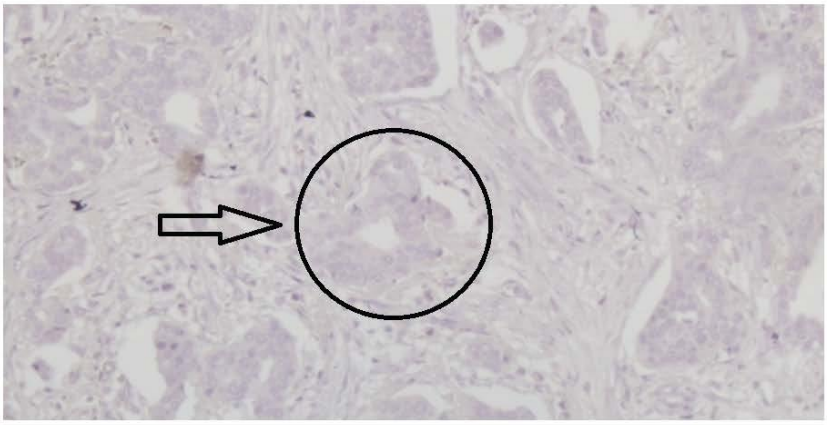


FIGURE 2: Immunohistochemical examination of the tumor showing negativity for estrogen receptors (x200)

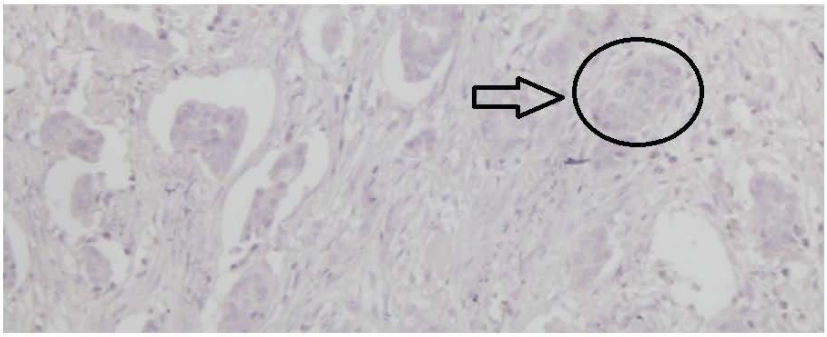


FIGURE 3: Immunohistochemical examination of the tumor showing negativity for progesterone receptors (x200)

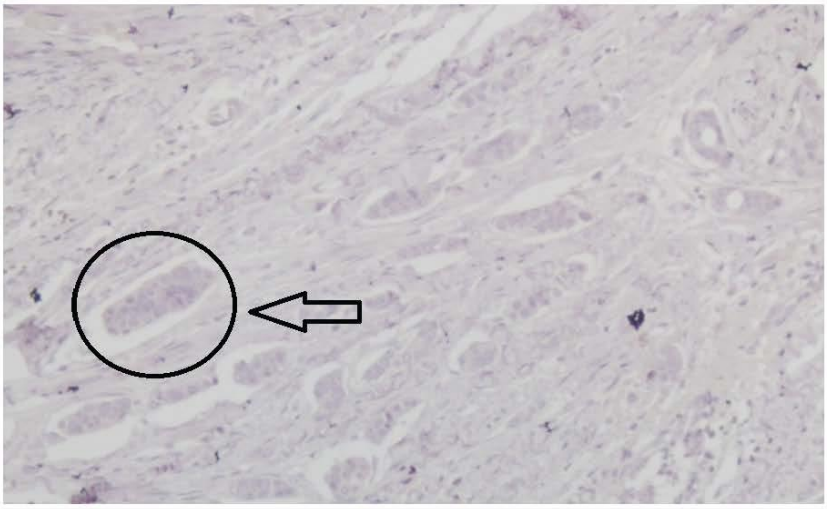


FIGURE 4: Immunohistochemical examination of the tumor showing negativity for human epidermal growth factor 2 receptors (x200)

The patient was admitted to ChemoThermia Oncology Center, Istanbul, Turkey on October 1, 2016 and was evaluated using whole body (18F)-fluorodeoxyglucose (FDG)-positron emission tomography-computed tomography (PET-CT). The PET-CT scan revealed a 77 mm x 55 mm primary tumor in her left breast (maximum standard update value [SUVmax]: 22.65), multiple left pectoral and axillary lymph nodes (SUVmax: 11.44), multiple widespread liver masses (SUVmax: 30.34), and an upper left nodular abdominal lesion (SUVmax: 5.94) (Figure *5*, Video *1*). The patient was diagnosed with stage IV (T4N3M1) triple-negative invasive ductal carcinoma of the breast.

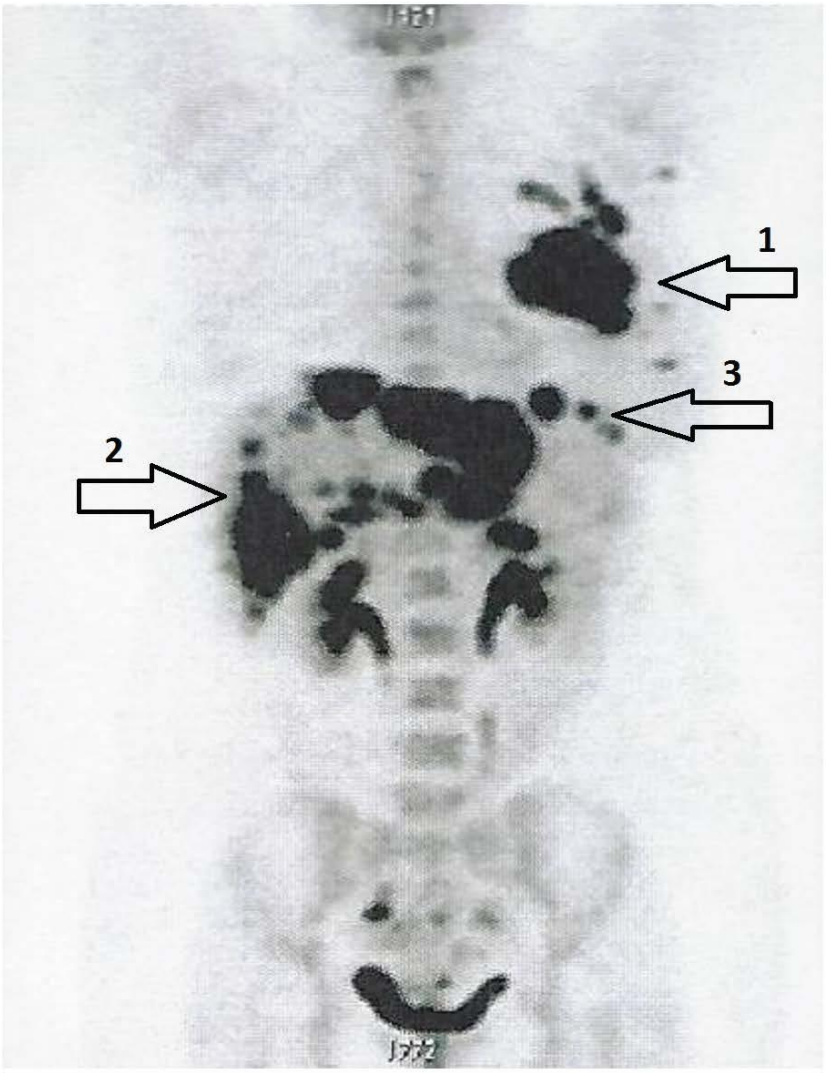
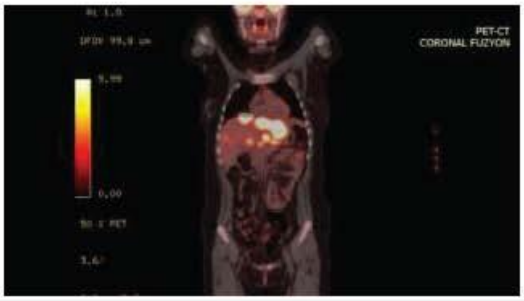


FIGURE 5: Whole body (18F)-FDG-PET-CT scan showing a 77 mm x 55 mm primary tumor in the left breast (arrow 1), multiple widespread liver masses (arrow 2), and an upper left nodular abdominal lesion (arrow 3).

The metastases are so widespread, the use of arrows is nearly insufficient. Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.



VIDEO 1: Coronal fusion video of the whole body (18F)-FDG-PET-CT scan done before treatment on October 1, 2016.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

View video here: https://youtu.be/Ox_DD5wOZD0

An MSCT protocol designed for the patient consisted of docetaxel (50 mg/m2), doxorubicin (20 mg/m2), and cyclophosphamide (250 mg/m2). This drug combination was administered following a 12-hour fast and the introduction of 5 to 10 units of regular insulin (Humulin R). Chemotherapy delivery was initiated at blood glucose levels of 50 to 60 mg/dL. With the patient's written and informed consent, this therapy was delivered on the first and eighth day of a 21-day cycle for a total of four months. Insulin delivery and chemotherapy infusions were delivered after assessing blood glucose levels upon arrival at the clinic, and the insulin dosage was sufficient to lower her blood glucose to approximately 50 mg/dL prior to delivery of the chemotherapy drugs.

In addition to MSCT, the patient was encouraged to consume a KD. She received education regarding the diet restrictions and given food lists as noted in Table *1*.

Do Eat	Do Not Eat
Eggs	Bread
Leafy Greens	Pasta
Above ground vegetables	Rice
High Fat Dairy	Potatoes
Natural Fats	Sugar
Meats	Honey
Nuts and seeds	Fruits

TABLE 1: Ketogenic diet recommendations

The patient was not provided with specific recipes or meal plans. Instead, she was directed to modify familiar meals while incorporating more fats. Her blood glucose levels were assessed using a home blood glucose meter (Contour TS, Bayer Health Care, IN, USA). Her urinary ketone levels were also checked prior to each MSCT session and served as a measure of her dietary compliance. The patient remained compliant with the KD presumably because of her understanding of the poor prognosis of this disease and her oncology team's knowledge about the previously published papers reporting the efficacy and importance of the KD [6,9]. The patient also received local HT and HBOT after each MSCT session. The OncoTherm EHY-3010 HT device (OncoTherm, Troisdorf, Germany) was used to gradually increase her body temperature to 45°C for each hyperthermia session (12 sessions, 60 minutes each) according to the manufacturer's specifications. A mobile electrode measuring 40 cm x 50 cm was positioned on the thorax and abdomen that fully involved both the primary lesion and the liver metastasis. The Quamvis 320 hyperbaric oxygen chamber (OxyHealth, California, US) was used to produce an operating pressure of 1.5 atmospheres absolute (ATA; 12 sessions, 60 minutes each). The patient tolerated these combined therapies well with no evidence of toxicity or adverse events.

The evaluation of the patient's whole body (18F)-FDG-PET-CT scan (on February 20, 2017) following the 12 sessions of MSCT, HT, HBOT, as well as KD therapy, demonstrated a complete therapeutic response (Figure *6*, Video *2*). FDG uptake was no longer detected in any lesions present at the left breast, left axilla, liver, or upper left abdomen.

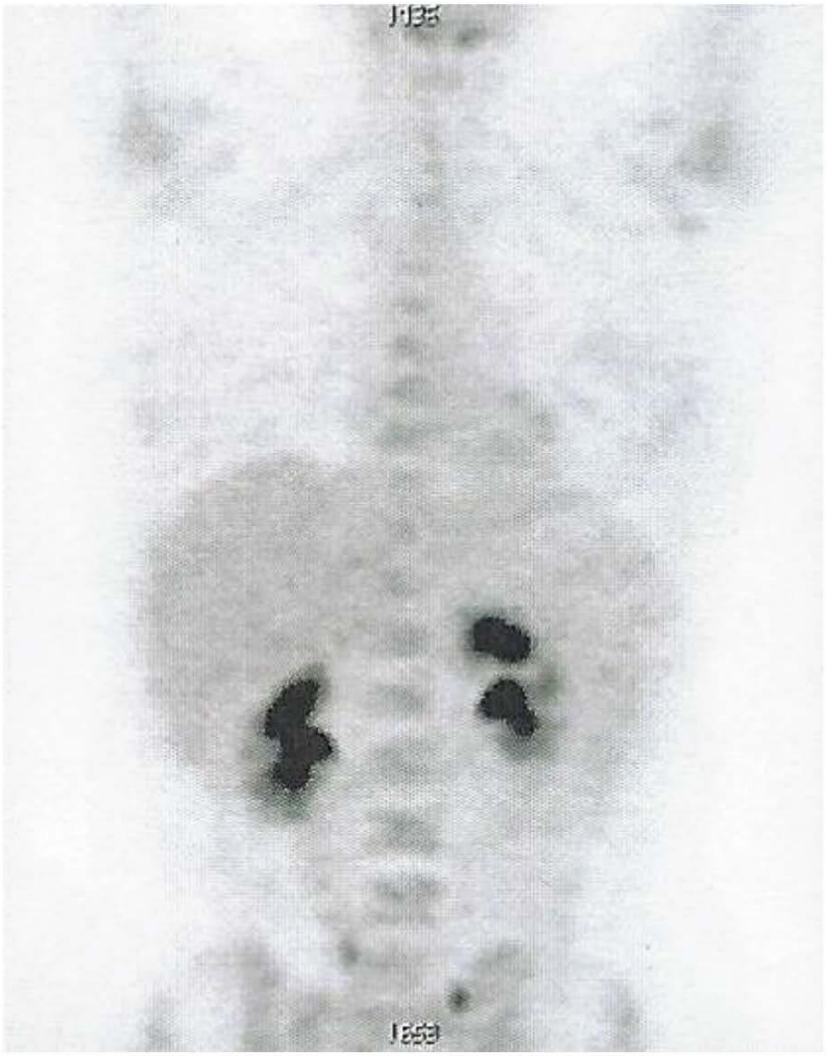
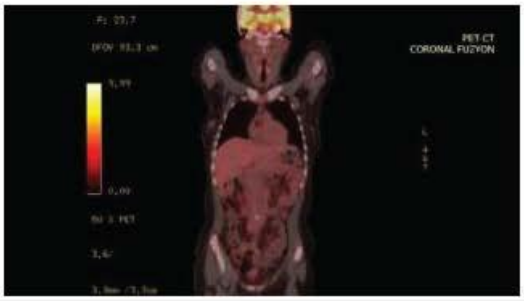


FIGURE 6: Follow-up whole body (18F)-FDG-PET-CT scan showing no pathological FDG uptake, indicative of a complete response.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.



VIDEO 2: Coronal fusion video of the whole body (18F)-FDG-PET-CT scan done following the 12 sessions of MSCT, HT, HBOT, as well as KD therapy on February 20, 2017.

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; PET, positron emission tomography.

View video here: https://youtu.be/W6NneJYTak4

The patient's blood glucose levels averaged 85 mg/dL, and urinary ketones were present at each evaluation (levels reported as 1 to 111). At the end of the study, the patient's BMI was 21.8, evidence that she had inadvertently restricted calories, which is known to enhance the metabolic effects of KD therapy [6]. Her self-reported quality of life and energy level had improved significantly compared to the beginning of treatment. The patient continued the same treatment protocol for an additional two months. She then underwent a mastectomy of her left breast with axillary dissection on April 28, 2017. The pathology report identified a 5 cm fibro-hyalinized lesion with no evidence of live tumor cells indicating a pCR consistent with the complete response reported on her PET-CT scan (Figures 7-8). A summary showing the timeline of events is given in Table 2.

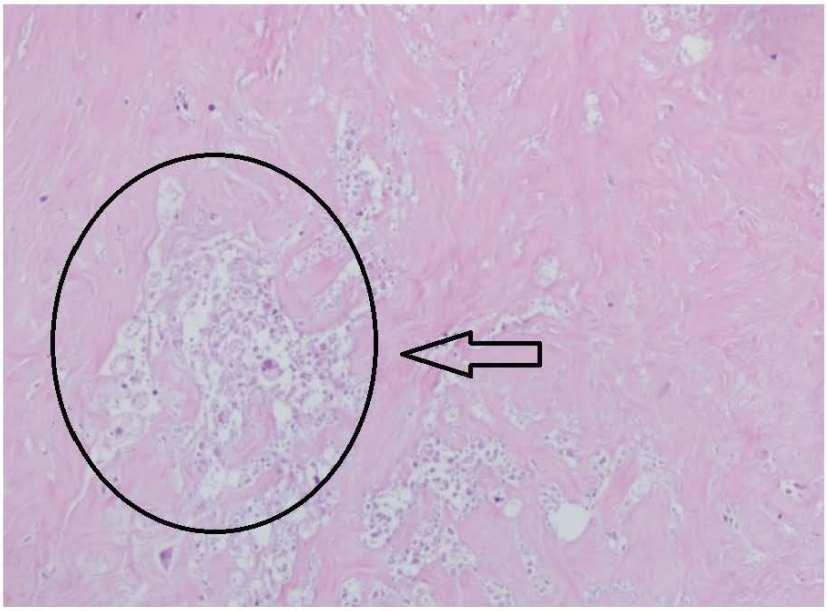


FIGURE 7: Mastectomy sample of the primary breast tumor area, totally necrotized, showing fibro-hyalinized tissue formed and no live tumor cells; indicative of a pathological complete response (x100)

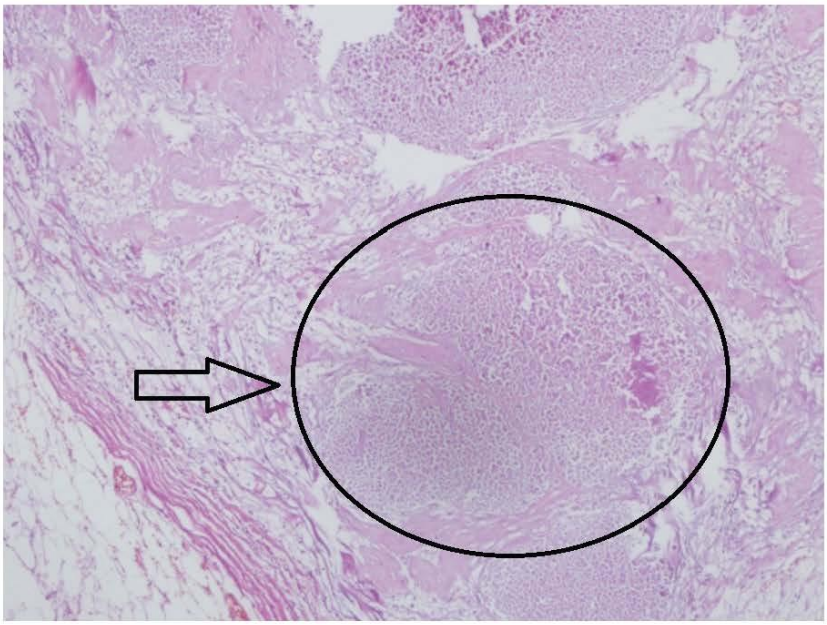


FIGURE 8: Lymph node sample of the metastatic axillar lymph node showing totally necrotized tissue with no live tumor cells (x100)

Date	Event
December 2015	Lump in left breast detected with physical examination.
December 2015 - August 2016	No further imaging is done.
August 2016	Admitted to Bakirkoy Dr. Sadi Konuk Education and Research Hospital, Istanbul, Turkey where MRI revealed a 75 mm x 75 mm x 65 mm left breast mass with multiple lymphadenomegaly in the left axilla.
August 2016	Tru-cut biopsy confirmed a diagnosis of stage IV TNBC.
October 2016	Admitted to ChemoThermia Oncology Center, Istanbul, Turkey where whole body (18F)-FDG-PET-CT revealed a 77 x 55 mm primary tumor in her left breast together with multiple left pectoral and axillary lymph nodes, multiple wide spread liver masses and an upper left nodular abdominal lesion.
October 2016 - February 2017	Received a treatment protocol consisting of MSCT, KD, HT and HBOT. She received MSCT on the first and eighth day of a 21-day cycle and following each MSCT session she received local HT and HBOT together with being encouraged to consume a KD.
February 2017	Whole body (18F)-FDG-PET-CT demonstrated complete therapeutic response with no malignant FDG uptake following 12 sessions of MSCT, HT, and HBOT together with KD therapy.
February 2017 – April 2017	Continued to receive the same treatment protocol for an additional six sessions.
April 2017	Underwent mastectomy of the left breast with axillary dissection which revealed a pathological complete response.

TABLE 2: Summary showing timeline of events

Abbreviations: CT, computed tomography; FDG, fluorodeoxyglucose; HBOT, hyperbaric oxygen therapy; HT, hyperthermia; KD, ketogenic diet; MRI, magnetic resonance imaging; MSCT, metabolically supported chemotherapy; PET, positron emission tomography; TNBC, triple-negative breast cancer.

After achieving this outcome, even though there is no evidence of disease, the presence of microscopic disease cannot be excluded. Consequently, we have decided to continue with the same treatment regimen of MSCT, KD, HT and HBOT to one full year from implementation,

taking care not to exceed the cumulative cardiac toxicity dose for doxorubicin, which is part of her MSCT regimen. During this period, the patient will undergo follow-up scans every three months.

Discussion

We have described a complete response to MSCT, KD, HT, and HBOT in a 29-year-old woman with stage IV (T4N3M1) TNBC that had metastasized to the lymph nodes, liver, and abdomen. There are, currently, no specific treatment guidelines for managing TNBC, and the lack of identifiable molecular targets makes management even more challenging. However, pCR is strongly correlated with a favorable long-term prognosis [10]. We proposed that the effect of standard chemotherapy drugs would be enhanced when combined with therapies that also target the metabolic weaknesses of cancer cells with the goal of achieving pCR. MSCT is a therapeutic strategy that builds on Warburg's theory that tumor cells lack metabolic flexibility and become dependent on the aerobic fermentation of glucose due to impaired respiration [3-5, 9]. In the case presented here, this therapeutic strategy included the induction of mild hypoglycemia achieved through a 12-hour fast and pharmacological doses of insulin prior to each administration of chemotherapy.

The strong dependence of cancer cells on glucose makes them vulnerable to KDs that lower blood glucose levels while elevating levels of circulating ketone bodies. Ketone bodies are water-soluble energy substrates derived from fatty acid metabolism. They cannot be utilized for energy in cancer cell mitochondria due to respiratory defects [9]. Although the KD has been used for decades as a treatment for intractable pediatric epilepsy, its potential as a therapy for targeting energy metabolism in cancer cells has only recently been explored [6]. The reduced blood glucose levels with elevated urinary ketone levels observed in this patient are theorized to have contributed in part to the patient's pCR.

In addition to the KD, HT and HBOT also targeted the defective energy metabolism of tumor cells. HT contributes to a therapeutic effect by aiding the uptake of drugs, increasing oxygen radical production, and inhibiting DNA repair in cancer cells, which leads to cancer cell death [7]. HBOT targets tumor hypoxia, which is associated with tumor aggressiveness and resistance to chemotherapy and radiotherapy [8]. Both HT and HBOT also exploit the reliance of tumor cells on glycolysis, a major contributor to the upregulation of antioxidant activity responsible for the tumor's increased resistance to pro-oxidant chemotherapy and radiation therapies [9]. Consequently, HT and HBOT will selectively increase oxidative stress in the tumor cells. Ketone bodies protect normal cells from this stress while also providing a substrate for energy production. We suggest that the synergistic effect of targeting cancer cell metabolism concurrent with the standard chemotherapy drugs contributed to the patient's pCR. Moreover, it is important to emphasize that the patient tolerated this treatment well and reported no discomfort or adverse event. This underscores the need to determine if our patient's response to this treatment was an isolated occurrence or if this response might also be seen in a larger cohort of patients with TNBC.

Despite the advanced stage of this disease, the therapeutic strategy of combining MSCT, KD, HT, and HBOT achieved a clinical and radiological complete response in this patient within four months. The treatment regimen was continued for an additional two months when pCR was further documented in tissue following her mastectomy.

Conclusions

TNBC is more aggressive and metastatic than other types of breast cancer and has a lack of molecular targets making it more difficult to manage than other cancers. Given the poor prognosis and adverse effects, women with advanced TNBC may be counseled to forego

conventional chemotherapy. This single case study presents evidence of a complete clinical, radiological, and pathological response following a six-month treatment period using a combination of MSCT and a novel metabolic therapy in a patient with stage IV TNBC. Given this patient's remarkable favorable outcomes, further research and randomized clinical trials exploring add-on therapies (such as KD, HT, and HBOT) that may enhance the efficacy of traditional cancer treatments by exploiting the metabolic weaknesses in cancer cells are warranted, especially for patients with poor prognosis of high grade and/or late-stage cancer that is not expected to respond to treatment. Furthermore, this patient did not experience the adverse effects that are commonly associated with the current standard of care and this improved quality of life should also be considered when designing research that compares outcomes of MSCT, KD, HT, and HBOT to traditional treatment. In conclusion, this combined metabolic approach appears effective in treating advanced TNBC, given this patient's complete response with a good quality of life.

Additional Information

Disclosures

Human subjects: Consent was obtained by all participants in this study. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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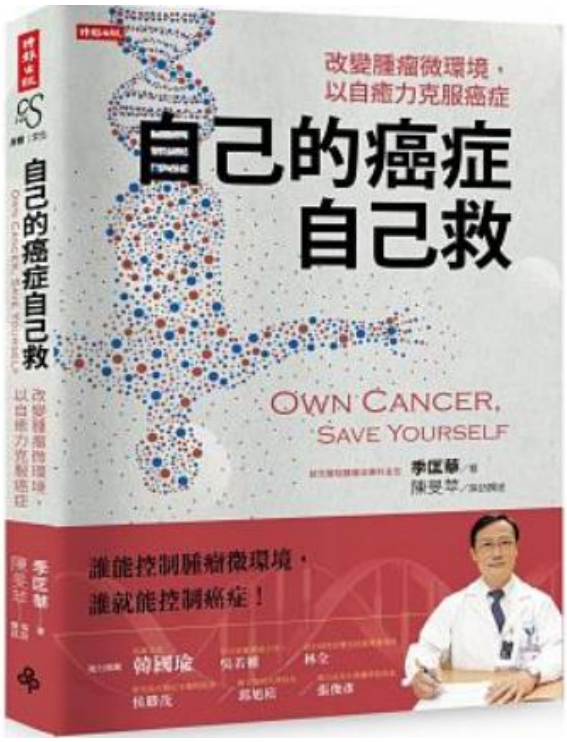

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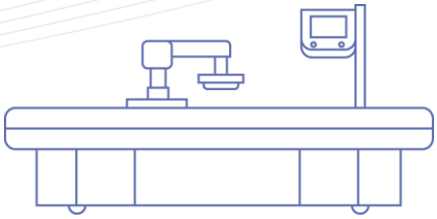

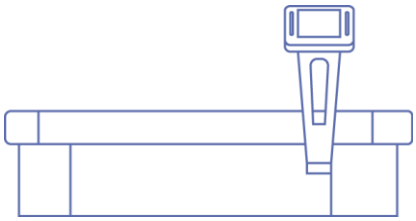

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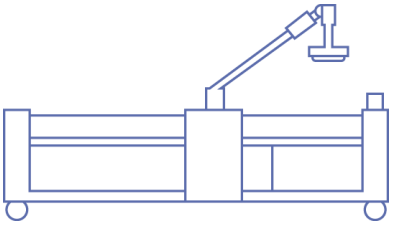

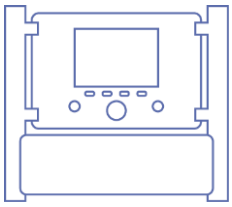

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