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Abstracts of the XXXI. Conference of the International Clinical Hyperhtermia Society (ICHS)

Posters of the XXXI. Conference of the International Clinical Hyperthermia Society (ICHS)

www.Oncothermia-Journal.com

Editorial

Dear Reader,

at the end of last year we presented you a great variety of abstracts for talks and posters that were presented at the XXXI. Conference of the ICHS (International Clinical Hyperthermia Society) jointly held with the 2nd International Oncothermia Symposium. This large event – Oncotherm was the main sponsor -was held from October 12th-14th in Budapest, Hungary. Around 150 professors, doctors and experts from various disciplines came together representing 25 countries from all over the world in the beautiful Marriott Hotel, situated directly at the Danube. The proceedings of the conference with extended abstracts and some complete papers of the conference will be published in a peer-reviewed open-access journal: The „Conference Papers in Medicine“ very soon. In this issue of the Oncothermia Journal we are showing you the posters of the conference in the form as they were presented.

New president and directors of ICHS were elected in Budapest. Prof. Dr. Clifford L.K. Pang became the new president and will host this year's conference in Guangzhou, China from November 8th-10th, 2013. You can find more information about the ICHS and its structure in this magazine.

We are pleased to learn about Oncotherm's international success. However, our roots are in Germany. The smart German medical approach is still in our focus and is very important for the development of this method. We are proud to represent the high-tech German Medicine intenationally in 28 countries. In the knowledge of this this importance we organize again our German National Oncothermia-Symposium in the Pullman Hotel, Cologne on June 22nd. This event will be chaired as usually for the last ten years by Prof. Dr. Harald Sommer, the president of the German Hyperthermia Society (DGHT e.V.), a radiotherapist from the Ludwig-Maximilians-University in Munich. Prof. Sommer's scientific leadership is one of the traditional guarantees of the high scientific level of the event.
Oncotherm tries to inform the professional community by various channels of modern communication facilities. We publish regularly multiple articles in various journals and just now we casted new films about the treatment with the EHY-1000 and the Booster as specialised Oncotherm products. More films are yet to come. We will inform you when they are ready. You can find more information in our Oncothermia Journal. Also we present you herewith an overview of our devices, a list of information materials that you can order from our office and portraits of two German clinics.

Please let us know if there is anything we can assist you with or if there is any Oncothermia-related topic that you would like to write about.

Sincerely,

Prof. Dr. András Szász

Liebe Leser,

Ende letzten Jahres haben wir Ihnen eine große Auswahl an Abstracts zu den Vorträgen und Postern der XXXI. Konferenz der ICHS (International Clinical Hyperthermia Society) präsentiert, die gemeinsam mit dem 2. Internationalen Oncothermie-Symposium stattgefunden hat. Diese große Veranstaltung - Oncotherm was Hauptsponsor - wurde vom 12.-14. Oktober in Budapest, Ungarn abgehalten. Rund 150 Professoren, Ärzte und Experten verschiedener Disziplinen kamen zusammen und repräsentierten im schönen Marriott Hotel direkt an der Donau 25 Länder aus aller Welt. Die Ergebnisse der Konferenz mit erweiterten Abstracts werden demnächst in einem durch Fachleute überprüften Journal mit freiem Zugang publiziert: Den „Conference Papers in Medicine“. In dieser Ausgabe des Oncothermia Journals zeigen wir Ihnen die Poster der Konferenz so wie sie in der Konferenz präsentiert werden.
In Budapest wurden der neue Präsident sowie die Direktoren der ICHS gewählt. Prof. Dr. Clifford L.K. Pang wurde neuer Präsident und wird die diesjährige Konferenz vom 08.-10. November 2013 in Guangzhou, China ausrichten. Weitere Informationen zur ICHS und ihrer Struktur finden Sie in diesem Magazin.

Wir freuen uns über den internationalen Erfolg von Oncotherm. Trotzdem: Unsere Wurzeln liegen in Deutschland. Die klugen medizinischen Ansätze der Deutschen sind noch immer in unserem Fokus und von großer Bedeutung für die Entwicklung dieser Methode. Wir sind stolz darauf, die deutsche High-Tech-Medizin international in 28 Ländern zu repräsentieren. Im Wissen um diese Bedeutung organisieren wir in diesem Jahr wieder unser deutschces Nationales Oncothermie-Symposium im Pullman Hotel Köln am 22. Juni. Den Vorsitz hat wie in den letzten zehn Jahren Prof. Dr. Harald Sommer, Präsident der Deutschen Gesellschaft für Hyperthermie (DGHT e.V.), ein Strahlentherapeut von der Ludwig-Maximilians-Universität in München. Prof. Sommers wissenschaftliche Leitung ist eine der traditionellen Garantien für ein hohes wissenschaftliches Niveau der Veranstaltung.

Oncotherm versucht, die professionelle Gemeinschaft auf verschiedenen Kanälen moderner Kommunikation zu erreichen. Wir veröffentlichen regelmäßige Artikel in verschiedenen Magazinen und haben aktuell neue Filme über die Behandlung mit dem EHY-1000 und dem Booster als spezielle Oncotherm-Produkte drehen lassen. Weitere Filme werden folgen. Wir werden Sie natürlich darüber informieren wenn sie fertig sind. Mehr Informationen finden Sie in unserem Oncothermia Journal. Wir präsentieren Ihnen hier auch einen Überblick über unsere Geräte, eine Liste von Informationsmaterialien, die Sie in unserem Büro bestellen können sowie die Portraits zweier deutscher Kliniken.
Bitte lassen Sie es uns wissen, falls wir Ihnen irgendwie behilflich sein können oder falls Sie einen Text über ein mit der Oncothermie verwandtes Thema veröffentlichen möchten.

Mit den besten Grüßen

Prof. Dr. András Szász

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

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

1. Aims and Scope

The Oncothermia Journal is an official journal of the Oncotherm Group, devoted to support them, making a collective for using the results and making it common for general use. The Oncothermia Journal has an open-minded character, expecting the 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 oncothermia or electro cancer therapy (ECT) treatments, case-reports, practical considerations in complex therapies, clinical trials, physiological effects, Oncothermia in combination with other modalities, and treatment optimization.
- *Biological Studies:* Mechanisms of oncothermia, thermal-or non-temperature dependent effects, response on electric fields, bioelectromagnetic applications for tumors, Oncothermia treatment combination with other modalities, effects on normal and malignant cells and tissues, immunological effects, physiological effects, etc.
- *Techniques of oncothermia*: Technical development, new technical solutions, proposals.
- Hypotheses, suggestions, opinions to improve the oncothermia and electro-cancer-therapy methods, intending the development of the treatments.

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

1. Selbstverständnis und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale 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 temeperaturunabhängige Effekte, Ansprechen auf elektrisches Feld, bioelektromagnetische Anwendugen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologsche 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 at the Oncothermia Journal by email Oncothermia-Journal@oncotherm.org.

2. Manuskripte einreichen

Manuskripte können online eingereicht werden: Oncothermia-journal@oncotherm.org

3. Preparation of Manuscripts

Manuscripts must be written in English, but other languages can be accepted by special reasons, when it has an English abstract.

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

Manuscripts may be any length, but must include:

- *Title Page.* Title of the paper, authors and their affiliations, 1-5 keywords. At least one corresponding author should be identified, whose email address has to be provided with full contact details.
- *Abstracts.* Abstracts should include the: Purpose, Materials and Methods, Results, 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 reference to the text. Figure files will ideally be supplied as jpg-file (300dpi for photos).
- *References.* Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3], [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 Oncothermia 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.

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

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

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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 verhinden, müssen die korrigierten Texte innerhalb von 48 Stunden per Email oder Fax zurückgesandt werden.

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The Oncothermia Journal accepts advertising in any languages, but prefers English at least partly. The advertising must have connection with the scope of the Oncothermia Journal and must be legally correct, having controlled values and true info.

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

8. Legal responsibility
Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any actual publications. The Editorial Board has the right to reject any publications if its validity is not enough controlled or the Board is not convinced by the Authors.

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

9. Reviewing
The Oncothermia Journal has a special peer-review process, represented by the Editorial Board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of Reviewer will not be signed, her/his name will be handled confidentially. Papers which are not connected to the scope of the Journal could be rejected without reviewing.

9. Bewertung
Die Texte für das Oncothermia 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.

Contents

CONTENTS

Editorial

Cancer is a permanent fear for human kind from the ancient era. From the ancient times we have continuous fight against the malignant diseases, which one of the greatest challenges in the medical science for centuries. In 1971 “war” was declared in the United States against cancer. Nowadays, the oncology became one of the most interdisciplinary research fields: including the biology, biophysics, biochemistry, genetics, environmental sciences, epidemiology, immunology, microbiology, pathology, physiology, pharmacology, psychology, virology, etc. Moreover, a wide range of diagnostic and treatment methods are available to identify and destroy the malignant tissue. Enormous economic and human resources are involved in this field, but we reached only partial results. According to epidemic data the complete solution is still much awaited.

The 31st Annual conference of International Clinical Hyperthermia Society (ICHS) was a part of the “war”. The topic is not new, the hyperthermia is an ancient treatment, in fact the very first in medical oncology. After a long dormant period hyperthermia had renewed, when the delivery of the electromagnetic energy had given new perspectives. Definitely, hyperthermia promises a lot: a method with low toxicity and rare complications is a long-time dream and at the same time is one of great demands of the oncology practice. Completion of the biochemical approaches with biophysical methods could be perfect combination and giving synergy of the destruction of malignancy. Oncological hyperthermia is an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy and helps to desensitizing the previously non-effective treatments.

There are a great number of books, published up to date, devoted to the efficacy and the power of hyperthermia in oncology, [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20]. However, in contrary its long history, the state of oncological hyperthermia today is similar to that of therapies at their infancy. Like many early-stage therapies, it lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications. Promise of the hyperthermia applications in oncology is high, and it shown numerous positive impacts by it together with all the conventional and emerging new oncotherapies. The picture is very positive and it looks plausible that the method is in the center of interest among the specialists in oncology and related medical fields. But in fact, it isn’t! Doubts shadow the bright picture. Despite of the large number of published excellent clinical results, the challenge of hyperthermia in oncology is plausible from the perspective of a few thousand years. The medicine faces unsolved problems of hyperthermia, mainly by its controversial results obtained from the very beginnings. Together with the unexplained mechanisms of hyperthermia its control for efficacy and for safety remains unsolved as well.

The challenges look simple technical:

- deliver the heat to the deep targets in the body;
- have adequate and measurable feedback from the running treatment;
- select the malignant cells to treat;
- apply effective cell-killing and effective control of it;
- reduce the risk and be safe for the patient, lower the possible side effects;
- be safe for the treating personnel and for the environment;
- make relative simple procedure and acceptable treatment complications;
- have attractive cost/benefit ratio.

However these are only the surface of the problems. The challenge is complex, the physiological regulation has definite feedbacks answering on the hyperthermia constrains, the feedbacks try to reestablish the homeostatic control: spreading the temperature from the focus. This complexity causes the problem in all the technical challenging points.
Definite expectation with application of the hyperthermia is the same as the overall accepted paradigm in oncology: kill the tumor-cells.
Destroy the tumor or at least diminish the number of the malignant cells have criteria: find them selectively, without considerable damage in healthy tissue.

Probable hyperthermia is one of the subjects which have most questions in the titles of the published literature. Numerous definite questions were formulated, like:

- Is the community radiation oncologist ready for clinical hyperthermia? [21];
- Is there a future for hyperthermia in cancer treatment? [22];
- Is heating the patient a promising approach? [23];
- Hyperthermia: has its time come? [24];
- What is against the acceptance of hyperthermia? [25];
- Progress in hyperthermia? [26];
- Prostate cancer: hot, but hot enough? [27];
- What happened to hyperthermia and what is its current status in cancer treatment? [28];
- Where there's smoke, is there fire? [29],
- Should interstitial thermometry be used for deep hyperthermia? [30];
- If we can't define the quality, can we assure it? [31].

Questions pile up but the satisfactorily answers were missing yet. The real challenges are of course the sometimes obtained controversial results, addressing many further questions and raise the doubts. Further question is obviously arising: what do we have in hand? The aim of the present ICHS conference targets this question, together with the possible ways for further developments.

The presented material summarizes results from a large field of oncological hyperthermia, showing the update results of the classical focused electromagnetic heating, the focused mechanical energy delivery, the electric field promoted selections of the cells, the immune actions of the synergy of heat with electric field. Theoretical considerations of hyperthermia effects are well combined with different in-vitro, in-vivo, preclinical and even clinical realizations.

Various laboratory results together with the pre-clinical achievements are presented showing the newest biomedical basis of modern hyperthermia, successfully solving the challenges of focusing, selection and control of the hyperthermia process.
The clinical results show stable and high efficacy of the treatment of advanced malignancies even in refractory, relapsed, high-line cases as well. The monotherapy applications in cases when no other treatment could be applied impressively shows the high potential of the hyperthermia among the modalities of oncotherapies. The well documented synergy with integrated medical approaches like the traditional Chinese medicine (TCM) opens new perspectives in hyperthermia applications, together with the new efforts to treat such non-oncological diseases, which have no satisfactory results by the presently available other methods.

This proceedings of ICHS conference is an invitation to share the challenge of the new method, share the excitement to apply a new effective treatment, and share the enjoyment of the results.

May 5. 2013.

G. Baronzio,	M. Jackson,	DY Lee,	A. Szasz,
Terni (Italy)	Sydney (Australia)	Seoul (Korea)	Budapest (Hungary)

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Articles of the XXXI. Conference of the International Clinical Hyperthermia Society (ICHS)

Oncothermia Journal 7:19-19 (2013)

Transurethral hyperthermia in prostate cancer: a ten year observation study

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Introduction

Prostate cancer (Pca) is the most frequent cancer of men with approximately 31.500 new cases per year. The most important risk factor is age. Before age 50 clinically evident PCa are extremely rare and in most cases hereditary. More than 90% appears after age 60 and older. Between age 60 and 70 we expect that 50 of 100.000 men per year test positive for PCa and between age 75 and 85 approximately 400 men.

Method

Between 1999 and December 2000, 123 patients were treated with transurethral hyperthermia at our Prostate Cancer. They were retrospectively evaluated after 10 years. All patients had their prostate cancer verified by biopsy. The clinical stages were between T1-T3. All patients with verified metastases were excluded. None of the patients underwent surgery or radiotherapy. All had denied surgery or radiotherapy by their signature.

Hyperthermia was chosen because with our type of electrothermia it can selectively destroy cancer tissue. Hyperthermia induces apoptosis by inducting p53 and caspase 3 activity. Furthermor it preserves the healthy tissue and keeps it functional. Cancer tissue can be eliminatd totally so that the prostate is freed of cancer. Hyperthermia also mobilizes the body's own immunity. It is a non aggressive, non invasive form of treatment.

Our patients were also put on a hormone blockaded because PCa is hormone dependant and androgens stimulate proliferation. Complete androgene blockade inhibits proliferation and causes apoptosis, even in cancer cells outside the prostate e.g in the bone marrow.

Results

For 26 of the 123 patients (21,3%) a relapse of the PSA was documented. 22 patients (17,9%), 12 caused by cancer (9,5%). Twenty-six patients (21,3%) had later again a hormone therapy and for 8 patients (6,5%) later resectrion was necessary, but in no case was PCa documented. The proportion of surviving patients was as follows: 3 years: 97%, 5 years: 93%, 10 years: 87%. But most importantly, none of the patients died of PCa.

Conclusion

Transurethrale thermotherapy is a gentle none invasive treatment, which selectively can eleiminate cancer tissue from the prostate. Through a concomitant androgen blockade (CAB), this process can be positively supported, long term. The CAB will be finished after six months to one year. This treatment approach shows that after 10 years 87% of our patients are still without a relapse. If these results could be verified in randomized studies, this could lead to a paradigm change in the treatment of PCa.

Oncothermia Journal 7:21-22 (2013)

Early changes in protein expression releated to modulated electro-hyperthermia

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This article is under review at Hindawi.com and will be published here:
http://www.hindawi.com/cpis/medicine/pp/104671/

Early changes in protein expression releated to modulated electro-hyperthermia

Background

Modulated electro-hyperthermia (mEHT) is a widely used non-invasive technique for targeted tumor treatment [1-4]. The capacitive coupled modulated radiofrequency enriches in the tumor tissue (because of its dielectric differences [5]) without harming the sorrunding non-malignant tissues. Beside the temperature dependent effect mEHT causes in the tumor tissue, it has a non-temperature dependent tumor destruction effect, which is three times higher than the conventional hyperthermia with the temperature dependent outcome only [6]. Here our aim was to study early changes in protein expression either related or not to the temperature changes in tumors with a single shot of mEHT.

Method

HT29 human colorectal carcinoma cell line xenografted to both femoral region of BalbC/nu/nu mice. Tumors (approx.. 1.5 cm diameter) were treated with a single shot mEHT treatment (LabEHY, Oncotherm Ltd., Páty, Hungary) for 30 minutes. Temperature measurement was carried out during the treatment in the treated tumor core and subcutaneously, in the opposite (treated control) tumor core and rectally. The treated tumor core temperature was between
41-42 ^{o}C during the treatment. Sample was taken 0, 1, 4, 8, 14, 24 and 48 h after the treatment, each group containing 3 mice alongside with 2 untreated control animals (sample was taken simultaneously with the 24h treated group). Human genome U133 Plus 2.0 Array (Affymetrix Inc., Santa Clara, CA) was used on the 4h treated animals' both samples (teated and untreated side) and on the 24h untreated control samples to identify treatment related mRNA alterations. The results were analyzed by Bioconductor software. R&D Apoptosis array (R&D, Minneapolis, MN) was performed on the 8, 14 and 24 h treated and the 24h untreated control tissue samples. 35 apoptosis related proteins were observed. Results were analyzed by ImageJ. Immunohistochemistry was carried out on formalin fixed paraffin embedded (FFPE) tissue microarray (TMA) (3D HISTECH Ltd., Budapest, Hungary) slides to confirm and to identify the localization of the previously identified proteins. On whole cross sections Terminal deoxynucleotidyl transferase dUTP nick end labling (TUNEL) assay (Invitrogen, Carlsbad, CA) was carried out 24 and 48 h after mEHT treatment. The slides were digitalized with Panoramic Scanner and analyzed with Panoramic Viewer software (both form 3D HISTECH Ltd., Budapest, Hungary).

Results

According to the mRNA chip array, there were 48 genes showing significant differential expression related to the treatment, including heat shock protein isotypues (hsp70, hsp90, hsp60 and hsp40).

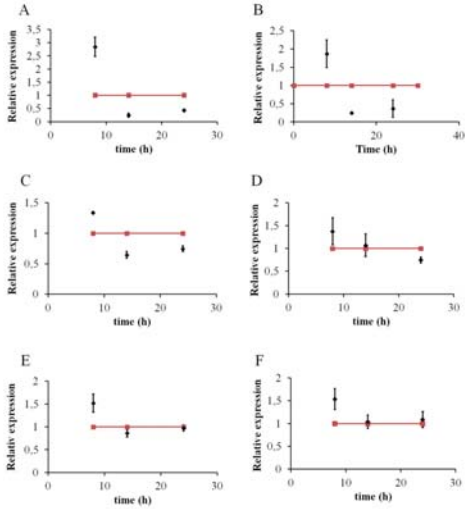

Figure 1. Relative protein expression of TRAIL-R2 (A), Fas (B), FADD (C), Bax (D), SMAC/Diablo €, HTRA2/Omi (F). The black rectangles show the treated sample relative protein expression while the red represent the relative control

Using apoptosis protein expression arrays the up regulation of death receptors (TRAILR2, Fas) and FADD (Fas associated death domain), Bc12 super family proteins (Bax.), mitochondrial apoptosis regulatory proteins (SMAC/Diablo, HTRA2/Omi) were observed 8h post treatment. In correlation with mRNA levels of heat shock proteins hsp70 and hsp60 were detected too (the array did not include hsp40 or hsp90).

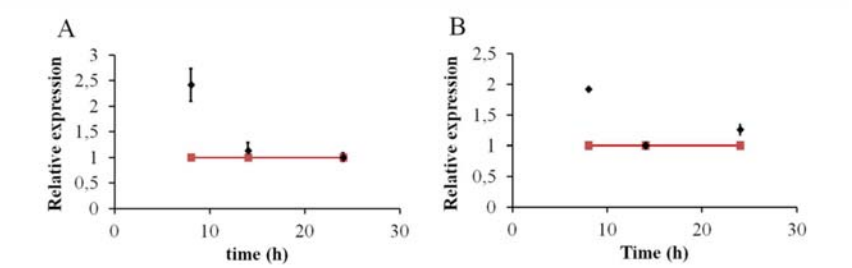

Figure 2. Relative protein expression of hsp60 (A), hsp70 (B). The black rectangles show protein levels in the treated samples, while the red represent the relative control levels

Elevation of hsp70 protein was also shown with immunohistochemistry starting from 14h post treatment. In situ protein detection using immunohistochemistry also confirmed the up regulation of the death receptor TRAIL-R2 between 8-14h post treatment along with cytochrome C release from the mitochondria to the cytoplasm between 8-10 h the nuclear translocation of apoptosis inducing factor (AIF) 14h post treatment. In line with these findings, TUNEL assay proved significant DNA fragmentation and elevated numbers of apoptotic bodies 24-48h post treatment.

Conclusion

A single shot mEHT treatment resulted in the up-regulation of a range of proteins related to apoptosis induction and heat shock response in HT29 colorectal cancer xenograft within 24 hours post treatment.

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Oncothermia in practice: quality assurance, applications, devices

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Oncothermia in practice: quality assurance, applications, devices

Introduction

Various kinds of hyperthermia devices are used in oncology, but the stable breakthrough of the applications has not been reached yet. Oncothermia offers strong scientific basis and good clinical practice as well. The very dynamic scientific and medical activity of Oncotherm is known in the scientific community through its many publications and accepted results. We are pioneering the electromagnetic treatments in oncology. The modulated electric field with RF carrier frequency of oncothermia is a leading method in oncologic hyperthermia by its treatment number all over the world. We are very active at all the international forums and conferences to make conditions risk-free and safe, ensure the patients of the safety of the treatment and your business also. The objective of this work is to show the oncothermia in practice and make sure the information about the actual safety regulations and certifications.

Method

Oncotherm is seriously concerned about the legal protection of its customers. All devices have market approvals (CE according to European Medical Device Directive) and the production has the well-known rigorous standards (ISO13485, ISO9001). For better services for suffering patients we are offering various specialized devices for special treatments like intraluminar (EHY1000 series) (mainly for prostate), loco-regional (EHY2000 series) and multilocal (EHY3000 series) equipments. We are more than happy to show the very new devices as the Androtherm for Peyronye diseases, the Booster, the special temperature measurement and the very new member of the Oncotherm devices: the new ECT series. According to the general information request, we have shown how the devices work, and answered the practitioners' questions. We have also shown some experiments to see how the devices work and which effects can penetrate deeply in the body at the treatments of various organs.

Results

Oncothermia follows the update demands of the modern oncology:

- It is personalized therapy,
- It is non toxic,
- It elongates the survival time of the patients,
- It completes the curative actions with increased quality of life,
- It has good cost/benefit ratio.

The introduced new paradigm by oncothermia solved the classical challenges:

- Challenge (1): "The biology is with us while the physics is against us" [1]
- ✓ *Oncothermia solution:* "The biophysics is with us"
- Challenge (2): "The biology and the physics are with us while the physiology is against us" [2]
- ✓ *Oncothermia solution:* "The fractal physiology is with us"
- Challenge (3): "Reference point is needed!" [3]
- ✓ *Oncothermia solution:* "Back to the gold standards, use the energy instead of temperature"

The task for future are challenging, and we are expecting professionals repeat our results and coming with us to fight in the war against cancer [4].

Conclusion

Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat-flow on the membrane supported by the electric field effects). It is natural, it is not against the homeostasis, physiology does not work against the action. Numerous case reports show the effect of Oncothermia well, so it has become a good weaponry in the war of cancer.

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Oncothermia research at preclinical level

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Oncothermia research at preclinical level

Background

Oncothermia method (OTM) has been applied in human oncology since 1989 [1]. Its clinical results excellently show the advantages of the method [2], however the details of its mechanism are being intersively investigated even now. Oncothermia research group conducts invetigations at all levels of scientific research, from in vitro studies to human clinical trials [3]. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven in vivo [4], but the complex electromagnetic paramters playing crucial role in achieving these antitumor effects have not yet exactly been determined. On the other hand in the veterinary oncology practice there is a huge need for an effective treatment to cure malignant diseases due to the increasing incidence of cancer in pet animals [5], and the lack of a really effective and relatively cheap method to cure. For these reasons, Oncotherm created a specialized research device for preclinical invetigations/veterinary clinical use, the VetEHY510 system, presented in Figure 1.

Figure 1. The VetEHY-510 system prototype and its main parts: A: Main unit, B: Metal treating table as a grounded counter-electrode, C: Active treatment electrode, D: Electrode holder arm, E: Patient box, F: Controlling computer, G: Table heater and electrode cooling water thermostat and pump unit

The VetEHY510 system was created to serve dual purposes:

1. To give a powerful, effective and easy to use device for veterinary oncologists to fight against pet cancer and to provide information about the treatment efficacy of oncothermia method for comparative clinical oncology.
2. To collect information and a wide range of measured electromagnetic parameters, which can help to optimize the treatment protocols and clarify the real role of electromagnetic treatment paramters which govern the best clinical outcome.

Material and methods

Using VetEHY device in Tottori University, Veterinary Medical Center we treated companion animals (dogs and cats) having different kind of tumors (liver tumor, soft tissue sarcomas, lung tumor, lymphomas, melanoma, etc.) under supervision of professional vet oncology specialists and kept the animal ethical regulations. The use of the dedicated veterinary device is shown in Figure 2.

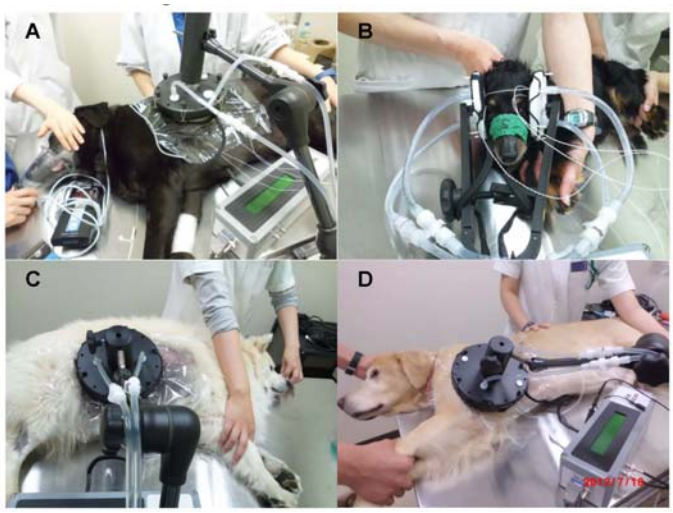


Figure 2. The VetEHY510 system in use, treating different companion animal cancer patients: A: Treatment of a dog having pulmonary metastasis, B: Tretment of a dog having brain tumor (glioblastoma) using a special forceps electrode system, C: Treatment of a dog having liver tumor, D: Treatment of a dog having a large lesion in the lung originated from a malignant lymphoma

These spontaneously occurring tumors are the best "models" of human malignant diseases. Getting treatment information and experiences on the behavior of these tumors from these pet patients are extremely valuable, transformed directly to human practice to improve the clinical results. (Figure 3.)

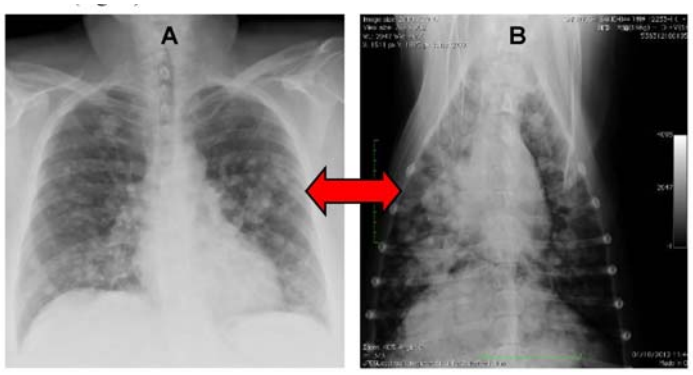


Figure 3. A representative example of the similarity of the clinical manifestation between humans and companion animals. A: X-ray image of he pulmonary metastases from recurrent melanoma in a human patient (image courtesy of Dr. D. G. Borgeson), B: X-ray image of the pulmonary metastases from melanoma in a Labrador dog (patient from our veterinary hospital)

Scientist in oncology are just starting to realize the importance of the involvement of veterinarians in a real preclinical research work. The newest edition of Withrow and Mac Ewen's Small Animal Clinical Oncology [5] briefly summarizes the aspects of companion animal cancer that enable attractive comparative models in a real preclinical investigation. To emphasize the real value the information which can be collected during the experimental treatment of companion animals, we would like to cite some points form the afore-mentioned book:

1. Companion dogs and cats are immunologically intact animals (like humans) as opposed to many experimental models of rodents and other animals.
2. Canceers seen in practice are spontaneously developing as opposed to experimentally induced and they recapitulate the natural human and veterinary condition better.
3. Companion species have a higher incidence of some cancers (e.g., osteosarcoma, non-Hodgkin's lymphoma) than humans.
4. Most animal cancers progress by more rapid rate than their human counterpart. This permits more rapid and less costly outcome determinations such as time to meatasis, local recurrence, and time of survival.
5. As fewer established "gold standard" treatments exist in veterinary medicine compared to human medicine, it is ethically acceptable to attempt new forms of therapy (especially single-agent trials) on an

untreated cancer rather than to wait to initiate new treatments until all “known” treatments have failed, as it is common in the human condition.
6. Companion species’ cancers are more skin to human cancers than are rodent tumors in terms of patient size and cell kinetics. Dogs and cats also share similar characteristics of physiology and metabolism for most organ systems such as surgery, radiation, and chemotherapy to be made between animals an humans.
7. Dogs and cats have intact immune systems as opposed to many rodent model systems, which allows immunologic assays and treatment approaches to be explored.
8. Companion animal trials are generally more economical to perform than human trials.
9. Companion animals live long enough to determine the potential late effects of treatment.
10. Dogs and cats are large enough for high-resolution imaging studies and multiple sampling opportunities, as well as for surgical intervention.

II. The VetEHY510 device contains many new technical solutions, which can ground the further development of the human clinical device. The main unit contains an E-class type resonant RF source operating at 13.56 MHz, and the high precision dual-directional coupler for precise forwarding and reflected RF power measurement. The main unit also contains a 6 bands wide range, real time automatic tuner system with autocalibration function for proper impedance matching for any kind of load impedance, according to the high variability of the companion animal’s body size and anatomical shape. This tuner system has an ultra-fast real time interfering dynamic element, so the continuous changes of the load impedance (for example according to the breathing movement of the animal) can be balanced every second, to keep the SWR (standing wave ratio) value in optimal range during the treatment (Figure 4.)

Figure 4. Newly developed technical solutions in the VetEHY510 system
The main unit contains a dynamic real time tuner system which can keep the SWR in optimal range during the treatment in real time

There is a very special part of the VetEHY510 system, the so-called patient box (Figure 5.) This device is a small box on the top of the treating table in a close proximity of the patient and makes the RF contact between the main unit and the treating electrode system. This unit is full with highly specialized measurement electronics and is able to mesure the extended amount of electromagnetic and thermal paramters durig the treatment. These are the electrode voltage, load current and their phase together with the impedance matching paramters and the temperature. This unit also contains a precise, four-channel temperature measurement system which is completely insensitive to the strong electromagnetic field according to its uique electronic solution, se tis system is able to measure temperature under the treating electrode.

Figure 5. The patient box and its display during treatment

The treating electrode system is also a new development. The shape-adapting electrode-holder bolus together with the flexible electrode material can be seen in Figure 6.

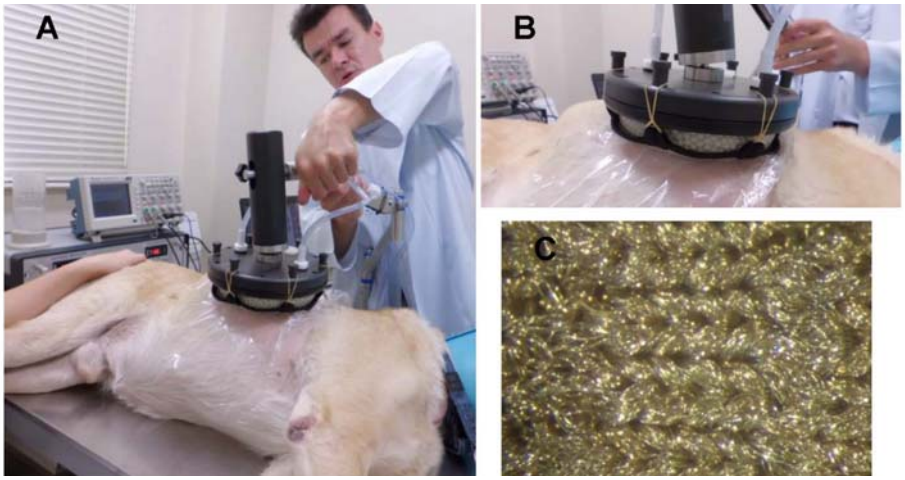


Figure 6. The treating electrode system
A: adjusting the electrode holder, B: the shape-adapting electrode-holder bolus and the flexible textile electrode in contact with the body, C: microscopic image of the fiber structure of the electroconductive textile material. The fibers are coated with palladium-copper-silver alloy

Results

1. Shrinkage of tumor size, decrease of the tumor-associated pain and improvement of the quality of life of the animals were observed after oncothermia monotherapy treatments. More emphasized beneficial effects were observed, when oncothermia was used in combination with low dose chemotherapy. Veterinary oncothermia clinical investigations are still in progress. To illustrate the clinical success in a relatively severe cases some case reports are presented.

Case 1.: Case No.: 12082,8 years old mini dax. Symptoms: severe ataxia, the dog was not albe to move and keep his balance. Diagnosis: supposed meningioma in the cervical region (C3) as revealed by MRI investigations. Treatment: oncothermia treatment as a monotherapy (1 session- 6 times in 2 weeks, after oncothermia treatment 1-2 times/month) using the special forceps electrode (Figure 7.)

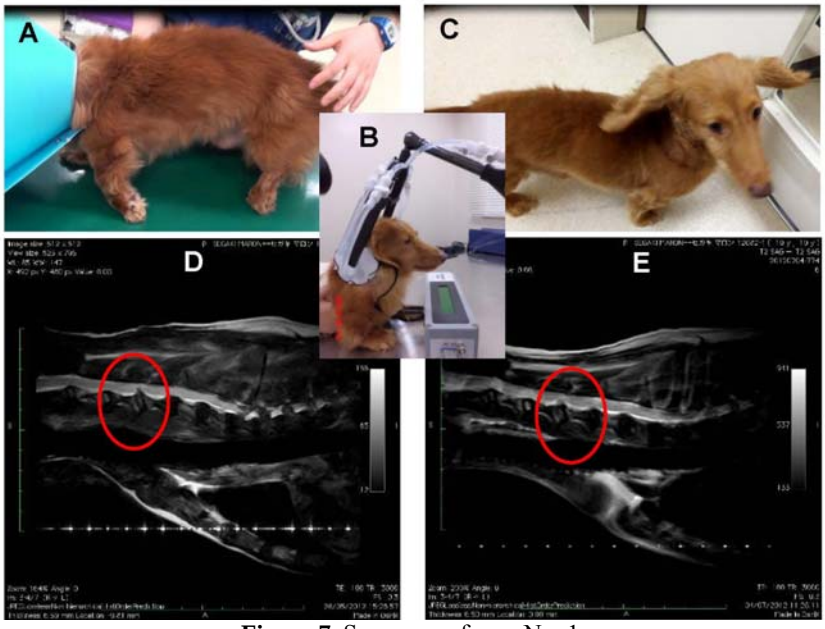


Figure 7. Summary of case No. 1.
A: at the time of the hospitalization the dog was suffering from severe ataxia and hemiparesis before the treatment, B: the dog during the oncothermia treatment, using a special forceps electrode, C: after several treatments the dog can walk and run again without any problem, D: before the treatment the MRI image showed a lesion in the cervical region (c3) which compressed the spinal cord causing the severe symptoms, E: after the first treatment session the size of the lesion was decreased as shown in this MRI image, and the spinal cord was released from the pressure

Case 2.: Case No.: 11461, a 8 years old castrated male Cocker spaniel. Diagnosis: melanoma was found on the toe of the right hind leg, which was surgically removed. Then severe lung metastases were developed. Treatment: low dose Carboplatine (2 times, 100 mg/m2, what is 1/3 of the prescribed dose) + Oncothermia treatment (10 times in 2-3 days interval)

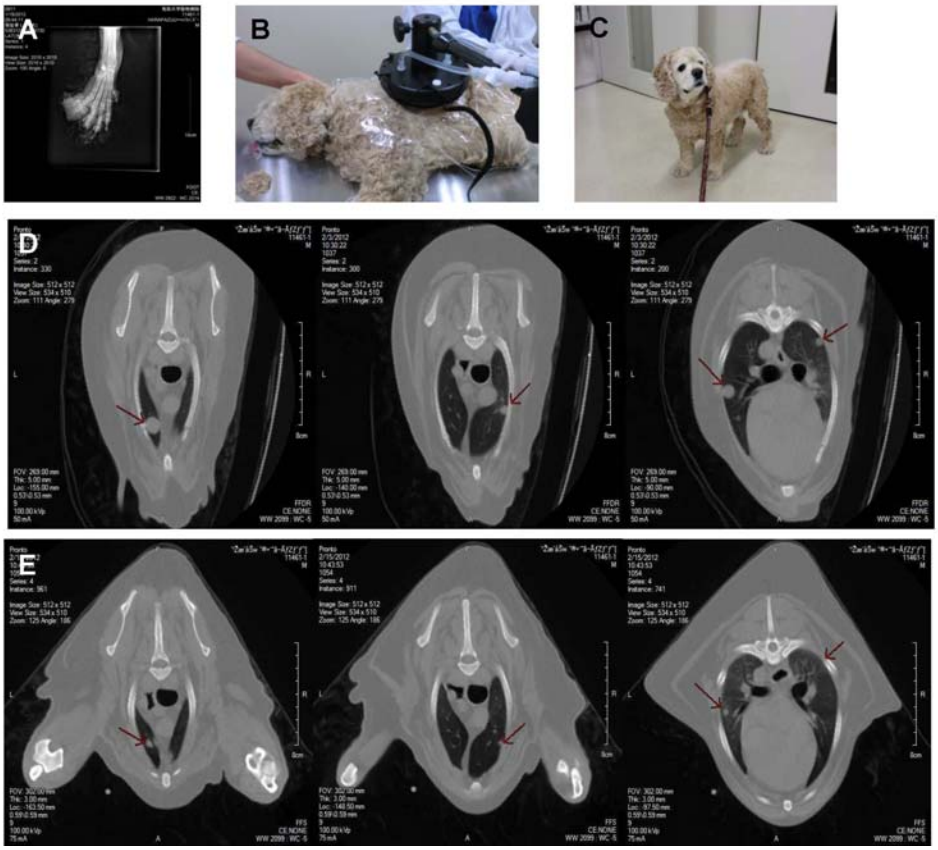
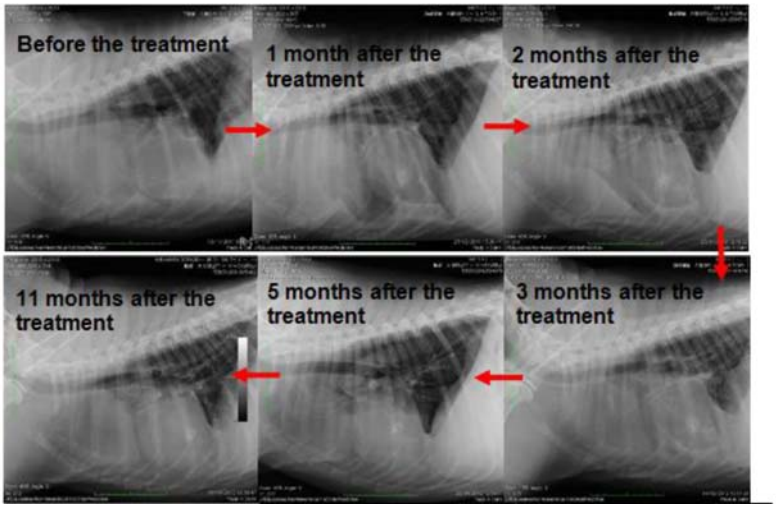


Figure 8. Summary of case No. 2.
A: X-ray image of the primary melanoma on the toe of the right hind leg, B: the dog during oncothermia treatment, C: the dog is still alive and has a good condition, without symptoms, D: CT image series in different slices of the lung before the treatment. Several large lesion can be visible in the lung, marked with red arrow, E: CT image series of the same slices of the lung after the treatment. The size of the lesions are dramatically decreased and in some cases completely disappeared

Case 3.: Case No.: 9417,9 years old, castrated male golden retriever. Diagnosis. Lymphoma in the thoracal cavity. Treatment: low dose COP (Cyclophosphamide-Oncovin-Prednisolon coctail, 2 times, 1/3 rd of the prescribed dose) + Oncothermia (15 times at the first session then 1-2 times / month)



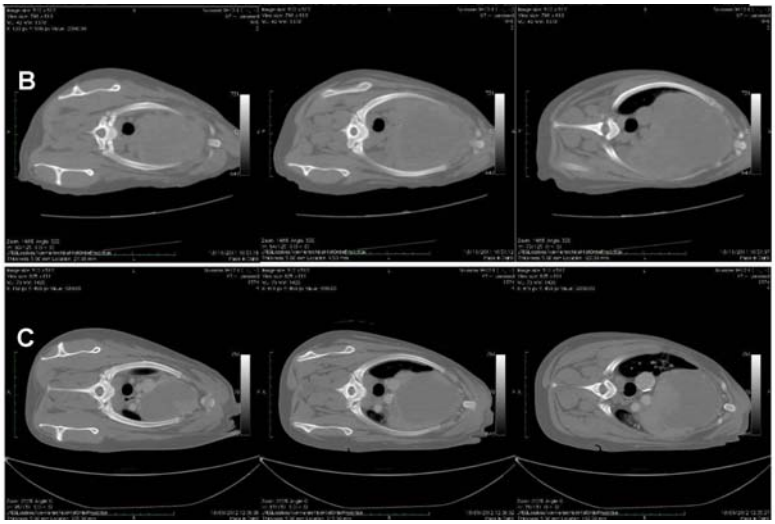


Figure 9. Summary of case No. 3.
A: In this X-ray image series the changes of the status of the lesion in the thoracal cavity can be tracked. B: CT image series in different slices of the lung before the treatment. The large tumor mass can be visible in the mediastinum, compressing the large part of the lung making serious difficulties in breathing. C: CT image series of the same slices of the lung 11 months after the treatment started. The size of the lesion significantly decreased, the lung was partially released from the compression

This case was a typical example of a rapidly progressing deadly disease becoming a managable chronic disease.

II. During these treatments we measured and collected many valuable electromagnetic parameters which can help to understand what is really happening during oncothermia treatment in electromagnetic sense.

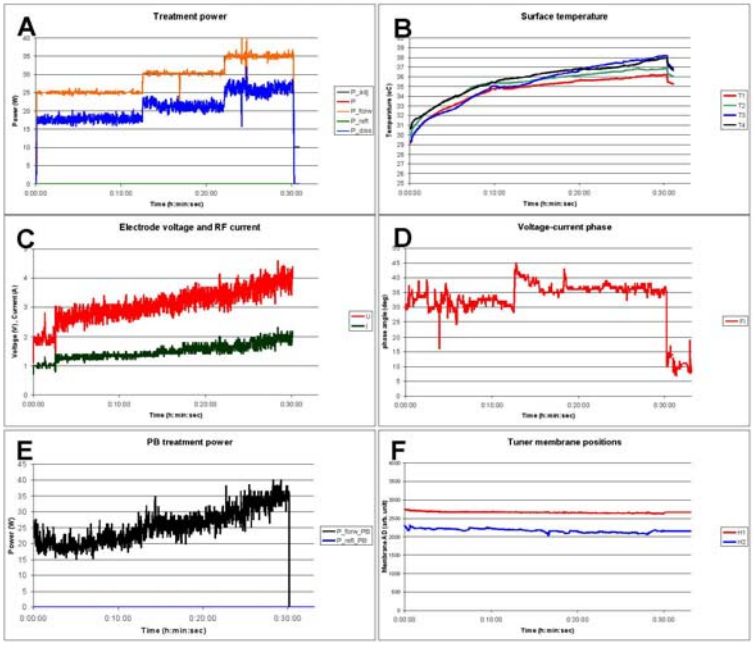


Figure 10.: Graph series of the most important measured electromagnetic and thermal parameters during a standard 30 min treatment. A: Treatment power (forwarding and reflected) measured in the main unit RF generator and dissipated power measured in the patient box. B: Skin surface temperatures under the treating electrode. C: Electrode voltage and load current measured in the patient box. D: The phase of the electrode voltage and load current. E: Treatment power measured by the power meter in the patient box. F: Tuner parameters

Our opinion is that the accurate analysis of these precisely measured treatment-related electromagnetic parameters can help to reveal the most critical electromagnetic parameter to achieve the best biological response. Using the results of these measurements we can optimize the technical solutions of further developments of the oncothermia devices for the human oncological applications and for the veterinary practice, too.

Conclusion

Oncothermia method and the VetEHY510 system is a new hope to effectively cure companion animal cancer patients, fulfilling the huge demand from veterinary market. The newly developed VetEHY510 device is a powerful research tool for comparative clinical oncology and to understand the role of critical electromagnetic paramters to improve the oncotehrmia method in human clinical practice too.

Acknowledgement

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Oncothermia Journal 7:33-33 (2013)

Russian Oncothermia Manual

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Though oncothermia is becoming the world-leading hyperthermia technique, there is no clear, exact and unified rules of its clinical application. The approach stating oncothermia as an individualized treatment which is not possible to manage 'in general' makes oncothermia rather an art than a technology. Such an art is impossible to use widely in modern technological medicine. We developed a comprehensive but simple and clear 'medical technology' of oncothermia usage for Russian market named 'Treatment of solid malignant tumors by oncothermia'. This technology is a stable basis for oncothermia use for any personnel, from nurse to artist-physician: it gives the exact and simple-to-use recommendations for the first and possibility of limitless creativity for the latter. It includes recommendations for all the tumor localizations and all the clinical regiments: chemo- and radiomodification, neoadjuvant, adjuvant and palliative treatment and rehabilitiation. The technology is approved by Russian Ministry of Health and is used in Russia since October 2011.

Oncothermia Journal 7:34-34 (2013)

Clinical application of Oncothermia against the tumors developed in deep tissue in Veterinary medicine

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Surgery, radiation, and chemotherapy are main tumor therapy in veterinary field as well as human medicine. However, there are some cases which we cannot inhibit recurrence and metastasis, or control good QOL. In particular, almost tumors developed in the deep tissues like abdomen and thorax are recognized as poor prognosis. We applied Oncothermia against 10 tumors which developed in abdomen and thorax. Treatment was performed 3 times per a week and 6 times in total. At pre- and post-treatment, CT examination was performed and measured the size of tumor. In 4 out of 10 cases, low dose chemotherapy was combined. As result, there was complete remission in 2 cases, partial remission in 2 cases, steady condition in 4 cases, and progressionin 2 cases. In 4 cases with combination therapy, the tumor size was decreased in 2 cases and tumor disappeared in 2 cases. These results suggest that Oncothermia is effective to the tumors developed in deep tissue in veterinary field. In particular, it was found that combination of Oncothermia and low dose chemotherapy is more effective than Oncothermia alone.

Oncothermia Journal 7:36-42 (2013)

Progress of research of hyperthermia integration with TCM in the treatment of cancer

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Progress of research of hyperthermia integration with TCM in the treatment of cancer

With the development of clinical oncotherapies, integrative treatments have generally been recognized by the Oncology Association. Hyperthermia has proven its effectiveness in the treatment of cancer which is different from surgery, radiotherapy, chemotherapy and biotherapy. Besides integration with the above therapies, using this with TCM is a unique approach.

The progress of research of hyperthermia integration with TCM in treating cancer will be presented according to the following six aspects:l

1. The advantages of hyperthermia in the treatment of cancer
2. The advantages of TCM in treating cancer
3. The advantages of hyperthermia in combination with TCM
4. An overview of the implementation of hyperthermia integration with TCM in treating cancer in Clifford Hospital
5. Clinical report of integrative therapy
6. The future of hyperthermia integration with TCM in treating cancer

1. The advantages of hyperthermia in treating cancer
   - 1.1. Hyperthermia is part of the field of Natural Medicine. It targets cancer cells directly, improves the immune system, induces apoptosis of cancer cells, suppresses the formation of cancer vessels, destroys cancer vessels, and relieves pain caused by cancer. At the same time, hyperthermia has demonstrated no damage to normal tissue.
   - 1.2. Hyperthermia can be utilized in conjunction with other cancer therapies and integrated into a comprehensive anti-cancer protocol.
   - 1.3. Hyperthermia not only enhances the sensitivity to radiotherapy and chemotherapy, but also reduces the side effects, which raises hope for solving of chemo drug resistance.
   - 1.4. Hyperthermia can improve the patient's quality of life and their confidence. It can be used on a long-time period.
   - 1.5. Modern science has contributed to the diverse modalities and methods of hyperthermia.
   - 1.6. Radiofrequency deep localized hyperthermia has broad applications and reliable therapeutic outcomes.

2. The advantages of TCM treating cancer
   - 2.1. The following are Anti-Cancer Mechanisms of Chinesse Medicine: Chinese herbs mentioned below perform different functions in cancer treatment
     - 2.1.1. Antimutagenicity: e.g. Ginseng, Fiveleaf gynostemma herb, green tea, scutellariae barbatae, astragalus, etc.
     - 2.1.2. Direct cytotoxicity: e.g. Oridonin, Ponicidin, Poria, etc.
     - 2.1.3. Inducing cancer cell apotosis: e.g. Tetrandrine, Berbamine, Rhizoma, etc.
     - 2.1.4. Suppressing proliferation and inducing differentiation: e.g. Epimedium, Tanshinone, Garlicin, etc.
     - 2.1.5. Suppressing the formation of cancer vessels: Coriolus versicolor polysaccharide, Lentinan, Cordyceps sinensis polysaccharide, Chinese thorowax root, Szechuan lovage rhizome, etc.
     - 2.1.6. Influence on membrane protein structure of cancer cells: croton, achyranthis, etc.
     - 2.1.7. Effect of Chinese herbal medicine photosensitizers on cancer: photosensitive and anti-tumorous effect of Coptis, Phellodendri, Sophorae flavescentis, Scutellaria, Fructus, etc. which are able to suppress the vitality and proliferation of cancer cells.
     - 2.1.8. Reversing the effects of multiple drug-resistance to cancer: vincristine, Tetrandrine, Emodine, Cepharanthine, Fructus, etc. These all have reversed the effects of drug-resistance, which improve the sensitivity of cancer cells to chemotherapies while impacting cancer cells.
   - 2.2. Long Term Treatment with Chinese Medicine
     - 2.2.1. Exerting bidirectional regulation of Chinese medicine to climinate pathogens and strengthen vital Qi. Use Chinese herbal medicine to invigorate to Qi and blood, nourish the

kidneys and liver, balance the Yin and Yang, etc, while at the same time climinating pathogens. It can decrease the rate of energy loss due to cancer, reduce toxic side effects resulting from radiotherapy and chemotherapy, and improve the body's immunity.

2.2.2. Application of the treatment according to differentiation: Prescription can be individualized based on the patient's immunity.

2.2.3. Multiple dosage forms: the delivery method of the medication can be adjusted according to the patient's condicitons.

2.2.4. Improving and maintaining the patients' quality of life.

2.2.5. Low toxicity with no side effects.

2.3. Acupuncture and Moxibustion

2.3.1. Acupuncture can modulate the meridians, balance the yin and yang, improve blood circulation, and boost the body's immunity.

2.3.2. Acupuncture can also regulate the body's cellular and immune system. It activates the body's immune surveillance system, and delays and inhibits the proliferation of abnormal cells.

2.3.3. It can improve the effect of radiotherapy and chemotherapy which include the improvement in bone marrow suppression and reaction in gastrointestinal tract.

2.3.4. Acupuncture and moxibustion is effective in alleviating pain.

3. The advantages of hyperthermia in combination with TCM

3.1. Anti-Cancer activity of TCM is increased through the Heating Process

The heating process increases the anti-cancer activity of certain Chinese medicines. e.g. Matrine could improve the therapeutic heating effect of hyperthermia on MA737 mouse mammary carcinoma; it could also induce more cancer cell apoptosis; e.g. Lithospermi preparation A-1 with heating has synergistic and suppressive effects on the growth of ECa109 cells.

3.2. The effect of hyperthermia integration with Chinese Herbal Medicine

A group led by Xie Yiying applied local hyperthermia with oral Chinese medicine decoction to 162 patients diagnosed with malignant cancer. The results showed that 93.2% of the patients had positive responses to the treatment. Zhang Qinyuan's group used whole body hyperthermia in combination with Chinese medicine on 54 patients with lung cancer. After 4 weeks of treatment, the experimental group demonstrated the best response on KPS, pain relief, focal change, and other aspects.

3.3. Hyperthermia integration with external use Chinese Medicine on malignant cancer

A research group headed by Zhong Dongwei, demonstrated that microwave irradiation can accelerate the penetration and absorption of Chinese medicine by compromising the stability of cellular membrane. Secondly, the effectiveness of Chinese medicine can be increased by the heating process. Mo Dingqun's group reported that patients with hepatic pain could be alleviated by microwave irradiation with TCM patches. 21 patients diagnosed with liver cancer received this treatment, with 11 patients displaying significant pain relief, and 9 patients had good responses to the therapy. The response rate was 100%.

3.4. Hyperthermia with Chinese Medicine injection

Kanglaite Injection(KLT) and hyperthermia: The research done by Deng Fuan studied the clinical efficacy of Kanglaite Injection(KLT) and ultrasound hyperthermia on 30 cases diagnosed with advanced liver cancer. The results suggested that the ratios of cancer pain elimination, symptom alleviation, cancer suppression, and overall survival in the experimental treatment group were significantly higher than in the control group. Compound Kushen Injection and hyperthermia: Gao Zhihong led a study of application of hyperthermia with Compound Kushen Injection on patients with stage III-IV malignant cancers. The results revealed that the experimental group had better responses in early symptom relief, improvement in the quality of life, and pain relief than the group that used Kushen Injection alone. Bolbcstemma Paniculatum preparation and hyperthermia: A study by Han Chengmin confirmed that the combined therapy can increase the inhibitory rate of the cancer cell Tca8113 and suppress the transformation of Tca8113 cell from G1 phase to S phase, resulting in increased cancer cell apoptosis rate and changes in the subcellular structure.

4. An overview of the implementation of hyperthermia integration with TCM in treating cancer in Clifford Hospital

Clifford Hospital is dedicated to the research of nontoxic integrative therapy on cancer. Clifford Hospital highlights the qualities of using TCM in treating different types of the diseases. It has achieved positive outcomes in cancer treatment by incorporating hyperthermia with natural therapies, including oral Chinese medicine, intravenous injection of Chinese herb, external application of Chinese medicine, Chinese medicine enema, acupoint injection, acupuncture, moxibustion, auricular acupoint therapy, compression of acupoint, catgut embedding, tuina massage, cupping, herbal bath, scraping, music therapy, Qigong, medical ozone, and chelation, among others.

The following are TCM and Natural Therapics available in Clifford Hospital.

4.1. Hyperthermia: We use the Oncotehrm EHY-2000 Local Electro-Hyperthermia Machine, NRL-002 Radiofrequency Field Thermo Therapeutic Machine, and Heckel – HT 2000 Infrared Whole Body Hyperthermia Machine.
4.2. Oral Chinese medicine: differentiated diagnosis and treatment made in accordance with TCM theory. Patients with cancer who sweat excessively during hyperthermia are considered to have an impairment of the Yin or Qi form heat. In these cases, the treatment should supplement the Qi and balance the Yin with Chinese Medicine Preparation Shengmaiyin, designed by Clifford Hospital.
4.3. External application fo Chinese medicine, once a day, every 4th hour. It can be used daily during the treatment. The Chinese medicine, which consists primary of Xiaoliu plaster, Xiaoshui plaster, and Zhitong Ding, is prescribed by senior TCM practitioners based on the patient's condition. These Chinese medicine are used to reduce the size of the cancer, climinate hydrothorax and ascites or local edema, and control cancer pain.
4.4. Chinese Medicine injection: frequently-used Chinese medicine injecitons include Kanglaite injection, Kangai injection, kkYadanzi Youru and Astragalus Membranaceus injection, etc.
4.5. Retention enema: includes Chinese medicine enema and coffee enema
4.6. Intracavitary hyperthermal perfusion: Hyperthermia perfusions can be performed to the chest, abdomen and bladder. Small dosages of chemo drugs and sodium bicarbonate are heated before the hyperthermia perfusion.
4.7. Acupuncture: Acupuncture is aided by electric acupuncture, infrared irradiation, and so on.
4.8. Moxibustion: Lukewarm moxibustion, festering moxibustion, warming acupuncture, herbs - partition moxibustion, and ginger moxibustion, etc.
4.9. Acupoint injection: Possesses antiemetic and pain-relieving effects with a longer efficacy than acupuncture.
4.10. Acupoint plaster: Medicine such as Pishu, Shenshu, etc. can be plastered on acupoints to increase WBC. Moxibustion and acupoint plaster possess better effects on alleviating patient's bone marrow suppression.
4.11. Ozone Therapy: There are different types of ozone therapies in Clifford Hospital, such as EBOO, major and minor hemotherapy, rectal ozone therapy, etc.
4.12. Chelation Therapy: It can effectively remove heavy metals from the body.
4.13. Herbal fumigation and bath: An ancient and effective external therapy in TCM. It is administered once a day during the treatment stage.
4.14. Medical Qigong: Medical qigong, the first mainstream culture in ancient China, which contributed more to society than the four great inventions, is now accepted as a top-rank therapy in Preventive Medicine and Rehabilitative Medicine in a number of countries. Patients at Clifford Hospital practice medical Qigong such as Tai Chi Wu Xing Gong, etc. under the tutoring of qigong practitioners.

5. Clinical report of integrative therapy

5.1. Case 1

Hyperthermia, oral Chinese medicine, western medicine and other treatments
Hyperthermia group：156 patients, from January, 2008 to December, 2011, radiofrequency deep regional hyperthermia in combination with oral Chinese medicine and western medicine.

Integrative Therapies: Radiofrequency deep localized hyperthermia: 1 hour each time, every other day, 15 treatments per course.
TCM Therapy: oral Chinese medicine, 100ml each time, b.i.d.; prescribed by senior TCM doctors based on the patient's condition.
Western medicine: We used methods with less adverse effects, such as oral chemotherapy, IPT chemotherapy, intra-abdominal hyperthermal chemotherapy, intravesical hyperthermial chemotherapy, etc.
Other treatments: acupuncture and moxibustion, etc.

Treatments	Subjects	CR	PR	NC	PD	Respond rate
Hyperthermia+ TCM	75	5	43	20	7	64.0%
Hyperthermia + TCM + chemo therapy	14	2	9	3	0	78.6%
Hyperthermia + TCM + abdominal cavity perfusion	42	3	23	11	5	61.9%
Hyperthermia + TCM + bladder perfusion	13	1	7	4	1	61.5%
Hyperthermia + TCM + radiotherapy	12	1	8	2	1	75.0%
Total	156	12	90	40	14	65.4%

Control group: 150 patients with advanced malignant cancer, who didn't receive hyperthermia, were randomly selected from January, 2008 to december, 2011

Treatments	Subjects	CR	PR	NC	PD	Respond rate
TCM + chemo therapy	51	4	31	8	8	68.6%
TCM + abdominal cavity perfusion	45	1	18	11	15	42.2%
TCM + bladder perfusion	24	0	12	3	9	50.0%
TCM + radiotherapy	30	1	15	5	9	53.3%
Total	150	6	76	27	41	54.7%

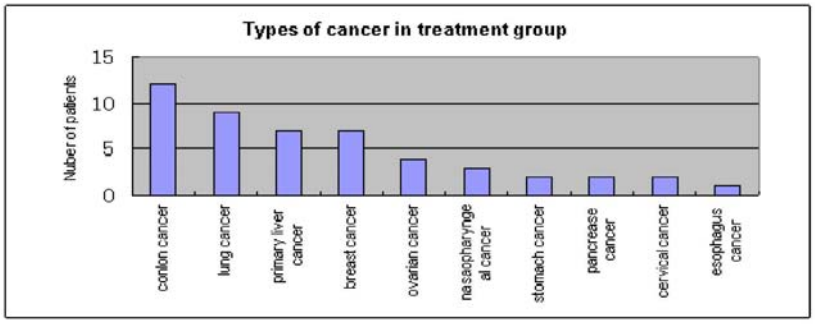
Results: Hyperthermia group: the overall response rate was 65.4% out of 156 patients. While is the control group: the overall response rate was 54.7%. There is statistically significant difference between two groups ($P<0.05$). There is no statistically differences in advense effect between the two groups.

Conclusion: Hyperthermia, in conjunction with TCM and other treatments can significantly improve the therapeutic effects of cancer treatment. Traditional Chinese medicine occupies a unique position in integrative therapies for cancer. The combination of hyperthermia with intra-abdominal and intravesical chemotherapy can produce a synergistic effect. Hyperthermia can improve the quality of life of the patient and does not increase toxic adverse effects from radiochemotherapy.

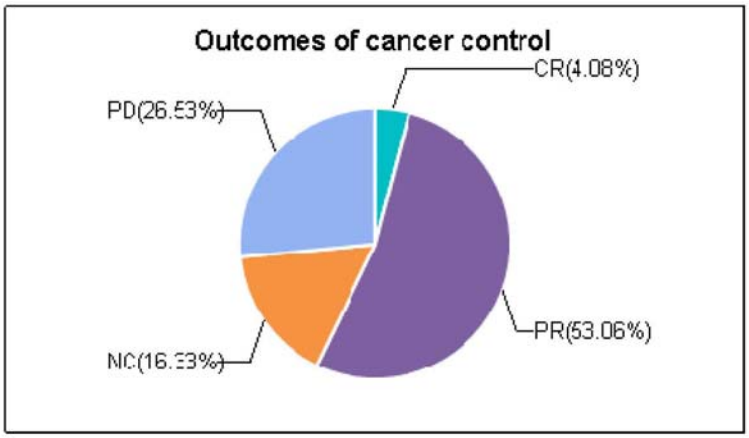
5.2. Case 1

Hyperthermia + oral Chinese medicine + external application of Chinese medicine + other treatments

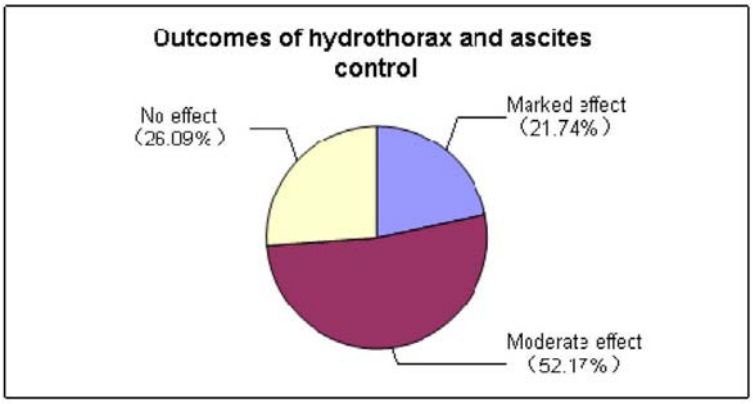
Participants: 49 cancer patients with chronic pain,and/or pleural or abdominal effusion, 21 males, 28 females,with a mean age of 54.0±7.2. They received 2 courses of deep regional hyperthermia, Chinese herbal medicine and External application of Chinese medicine.
Among these patients, 23 cases had pleural or abdominal effusion; 37 cases had chronic pain.



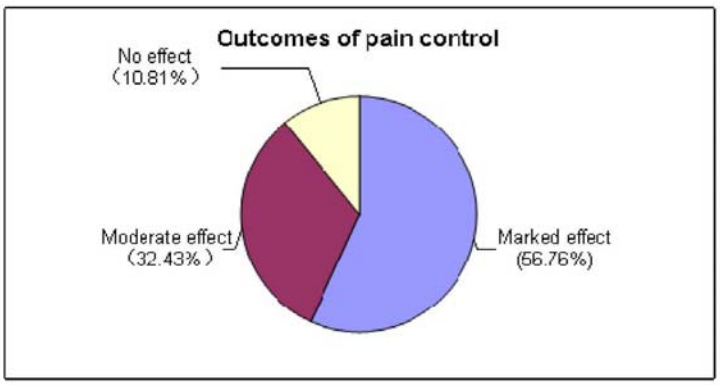
Results: cancer control: the overall response rate was 57.14%.



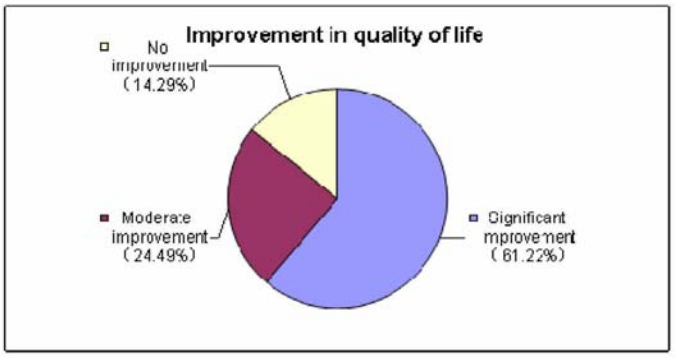
- Ascites and hydrothoax control: The overall response rate was 73.91%



- Pain control: The overall response rate was 89.2%



- Improvement in quality of life: The overall response rate was 85.7%



Conclusion: Hyperthermia along with internal and external use of Chinese medicine can: effectively control the progress of cancer, possess favorable efficacy on the control the pleural and abdominal effusion, effectively control pain and improve quality of life.

6. The outlook on hyperthermia integration with TCM in treating cancer

The integration of hyperthermia and TCM possesses unique advantages in treating cancer.
Clinical trials have demonstrated that patients had good responses when they received the integration of hyperthermia and TCM. The above therapies not only improved the immune function of the body and relieved the patients' symptoms, but also extended patients' life spans and improved their quality of life. TCM nourishes the Yin and Qi of the kidney, compensates for the depletion of the Yin caused by sweating during hyperthermia sessions. With the continuous development of biological mechanisms of anticancer medicine in hot environments and the impact of basic research on cancer cell, hyperthermia, in combination with TCM, will be utilized more extensively as a form of anti-cancer treatment.

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"Quo vadis" oncologic hyperthermia?

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“Quo vadis” oncologic hyperthermia?

Abstract

Hyperthermia was the very first first oncotherapy in human medicine based directly on sacral and philosophical roots in ancient cultures. The discovery of electromagnetism gave new hopes a century ago, however until up to now it has been suffering from lack of wide applications. Oncological hyperthermia struggles with multiple technical and medical problems which are far from the complete solution. Technically the deepheating, the precise focusing, the technical control and repeatability are challenging. The missing medical explanation of the phenomena, the missing acceptable and measurable dose, and the contra-feedback of physiology mechanisms block its acceptance. Multiple, most promising results and studies are mixed together with some negatives and controversial consequences, causing huge fluctuations of its applications. There are positive and negative “believers” of the method, but the decisional facts are missing. A new way gives shape to the development: heating in nano-range, which could solve most of the open problems in oncological hyperthermia.

Keywords: hyperthermia, oncology, nano-heating, focusing, selection, dose

Introduction

Hyperthermia is an ancient treatment. Hyperthermia means overheating of the living object completely (systemic) or partly (regionally or locally). “Overheating” is understood as “higher temperature than normal”. Hyperthermia is one of the most common therapies in “house” applications. It is applied according to unwritten traditions in every culture and every household. It is applied simply to prevent common cold but it is also good for its treatment, applied for various pains (joints, muscle-spasms, etc.), applied for better overall conditions and for simply relaxing, or sometimes for spiritual reasons. The various heat therapies are commonly used complementary with natural drugs (teas, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural and social events (ritual hot bath cultures), or to long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

The “prestige” of popular heat therapies is strongly supported by its corrective property: the person who has just received hyperthermia, feels the water-temperature most pleasant by hand when it is ~20 ^{o}C, while the 45 ^{o}C is pleasant for a hypothermic subject in the same experiment [1]. It seems that the heat therapy adjusts itself to the personal actualities; it is subjective, and adaptive.

These popular treatment applications of heating are types of “kitchen medicine”: the old recipes are “sure”, the patient takes it, and is cured when it is done according to the auricular traditional regulations. The meaning of “kitchen medicine” is, do it like in the kitchen, reading the process from the cookery-book: “heat it on the prescribed temperature for the prescribed time, and the success is guaranteed”. This type of thinking has its origin from the ancient cultures, when the Sun, the fire, the heat were somehow in the centre of the religious beliefs and philosophical focus.

This is “for sure” the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, “do it, get it”. However, the hyperthermia is not as simple as the traditions interpret it.

The fire and the radiation of the Sun had sacral significance in the ancient human cultures. In consequence the heat delivery was naturally on top of the curative possibilities. The ancient heat delivery however was ineffective and uncontrolled; deep heating was almost impossible. The method had its renaissance, when the modern electromagnetic heating techniques were applied controlling the heating process more precisely even in depth of the body. Important category of the hyperthermia was generated by electric fields [2], [3], which is even presently a hot topic in science [4], [5]. The electric conductive heating started in the late 19th century, called “galvanocautery” [6]. The method was further developed by D’Arsonval introducing the impedance (alternating current [AC], later higher frequencies, even sparkgenerated currents) calling it “Arsonvalization”, [7], and later a more modernized was “fulguration” [8]. The Arsonvalization method had fantastic popularity at the turn of the 19th -20th centuries, developing three different branches: the interstitial hyperthermia, including the galvanic heat-stimulation (electro-chemicalcancer- treatment), the ablation techniques and the capacitive coupling. The first capacitive coupled device on conductive basis was the “Universal Thermoflux”. It was launched on to the market by such a giant of the electric industry in that time as Siemens, which was later further developed, and the new device by the name “Radiotherm” was launched on the market in the early 1930s. The first start of the new capacitive-coupling technologies

was in 1976 by LeVeen [9] and has been widely applied since [10], [11], [12], [13]. Many hyperthermia devices use capacitive coupling since its application is easy and successful in clinical practices [14], [15], [16], [17]. The other line of the hyperthermia, based on radiative heat-absorption, form antenna array [18], [19]; showing many successful clinical studies too [20], [21].
From the late 1980s the heating up of the whole body or its certain region or a definite local volume started rapid development in the modern oncotherapeutic practices. The selective energy absorption has several favorable physiological and cellular effects promoting direct and indirect tumor-destructions without notable toxicity. Its main success lies in its complementary applications. Oncological hyperthermia is an ideal combination therapy; it provides synergies with most of the conventional treatment modalities, boosts their efficacy and helps desensitizing the previously non-effective treatments. Hyperthermia in oncology has been debated in an increasing number of books and high-ranking clinical publications. From the standpoint of oncology, the official policy was to avoid applying hyperthermia in oncotherapies. The repulsive opinion focused on the increase of dissemination of malignant cells and so supporting the metastases, [22], [23], [24]. There were also reports about the induced hepatitis by hyperthermia [25].
This is the reason, that in contrary its long history, the state of oncological hyperthermia today is similar to that of therapies at their infancy. Like many early-stage therapies, it lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.
This relatively simple, physical-physiological method has a phoenix-like history with some bright successes and many deep disappointments. What do we have in hand? Is it a brilliant, miraculous, non-toxic treatment or a quackery of some charlatans?

Many of the researchers evaluating the capabilities of oncological hyperthermia share the opinion, expressed in the editorial comment of the European Journal of Cancer in 2001: the biological effects are impressive, but physically the heat delivery is problematic. The hectic results are repulsive for the medical community. The opinion, to blame the "physics" (means technical insufficiency) for inadequate treatments is general in the field of oncological hyperthermia, formulated the following statement: "The biology is with us, the physics are against us [26]. In the latest oncological hyperthermia consensus meeting the physics was less problematic. However, in accordance with the many complex physiological effects a modification was proposed: "The biology and the physics are with us, but the physiology is against us" [27].
The present situation apparently supports the above opinions. Probably oncological hyperthermia hasthe most questions in the titles of published literature. Numerous definite questions were formulated, such as:
• Is the community radiation oncologist ready for clinical hyperthermia? [28];
• What happened to hyperthermia and what is its current status in cancer treatment? [29];
• Where there's smoke, is there fire? [30],
• Should interstitial thermometry be used for deep hyperthermia? [31];
• If we can't define the quality, can we assure it? [32].
• Is there a future for hyperthermia in cancer treatment? [26],
• What is against the acceptance of hyperthermia? [33];
• Progress in hyperthermia? [34];
• Prostate cancer: hot, but hot enough? [35];
• Is heating the patient a promising approach? [36],
• Hyperthermia: has its time come? [37];

Oncologists face multiple serious decisions when meeting a new patient. The staging and many other factors help the decision what to do: apply evidence-based protocols "A" or "B", or try something personalized. When application of hyperthermia arises, the dilemma widens: "to heat or not to heat"? Considering hyperthermia as a treatment option new challenges occur: "How to heat? What to heat? How to control? How to evaluate? We would like to show where we are in the field, and show a definitely new paradigm for oncological thermal-treatment and give its perspectives for the future.

Technical challenges

There are various concepts to heat-up the tumor locally of regionally or by heating up the whole body. The most intensive local actions are the extremely large specific absorption rate (SAR) in a small volume, heating the target rapidly and intensively to the ablation (coagulation) temperatures (see Figure 1/a. [38]). In this case the short time of action does not allow the temperature distribution in the connective tissues.

These ablation techniques due to their large and localized request of SAR are mostly invasive, only the superficial lesions can be ablated non-invasively.
The local hyperthermia is mostly a non-invasive focused deep heating, having longer time to reach the heat-effects due to the time-limited SAR administration in deep regions (see Figure 1/b,c.). Heating a part of the body (regional or part-body heating [39]) targets a larger volume with the aim to eliminate the regional dissemination and metastases (see Figure 1/d.), while there is a whole body treatment to heat up the complete body systemically (see Figure 1/e.).

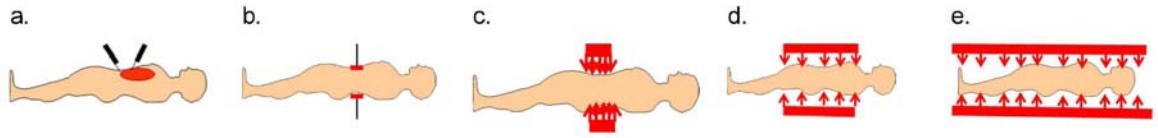

Figure 1. The main heating variations according to the targeted volume. The ablation (a) targets small volume with high SAR, while the local solutions (b. and c.) focus the electromagnetic energy from outside, and their SAR density is much lower, not making any coagulative processes, the part-body (d) and the wholebody (e.) treatments are non-focused techniques for temperature increase of a large targeted volume or the complete system

Thermodynamically the systemic and local/regional treatments differ in their energy-intake. The whole body treatment is based on the blood-heating (mostly heats up the subcutaneous capillary bed, or heats the mainstream of the blood directly with extracorporeal heater), while the local hyperthermia is definitely a tissue heating approach. This difference drastically divides the two methods from thermal point of view.
In whole body treatment the blood is a heating media, it delivers the heat to the tumor and heats it up; while in local treatment, the blood remains on body temperature during the local heating, so it is a cooling media (heat-sink) for the locally heated tumor, (see Figure 2.).

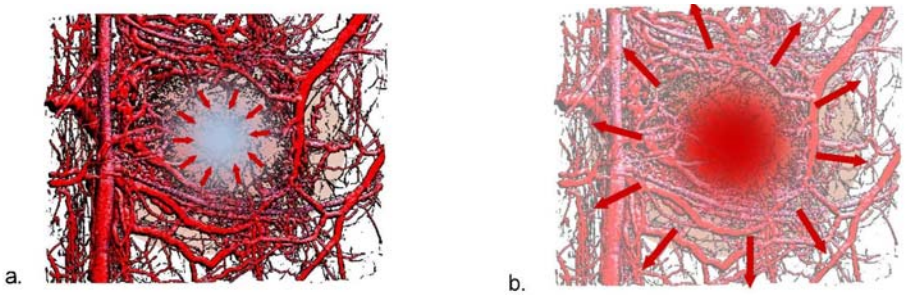

Figure 2. Opposite thermodynamic mechanisms of whole-body, systemic (a) and local (b) heating methods. The blood-heated tumor in whole body treatment reaches thermal equilibrium after a certain time, while the local treatment is always in non-equilibrium state, because the body temperature is lower than the heated tissue, creating intensive heat-flow from the target to the neighborhood

The whole-body heating could be solved by various ways, like steam, water or radiation heating. There are other possibilities as well (e.g. wax heating, hot-air heating, etc.) but the limited possible heat-flux and the poor technical realizations hinder these solutions. These are based on the blood-heating in the subcutaneous capillary bed, and the physiological reactions (vasodilatation and sweating) work well against the huge heat-flux into the body. The long heating time is also challenging (over an hour) to move the body away from the healthy homeostasis. The heat-flux is limited through the skin by the heat injuries (~0.5 W/cm 2 is the limit) so the contact heating with steam and water has definite problems. The radiation heating could be solved by special infrared wave (Infrared A) which penetrates deeper (~1-2 mm) into the subcutaneous layer, and could manage higher energy-flux without burn injuries. The method has many early descriptions [40], [41], [42], [43]; but the dominant systemic hyperthermia method is based on the infra-red radiation by multi-reflecting filtering [44], [45] or by water-filtering [46], [47], [48], [49]. In the followings we are going to concentrate on the local and regional heating techniques, which are mostly used in hyperthermia practices in oncology. Their various categories are roughly shown in Figure 3.

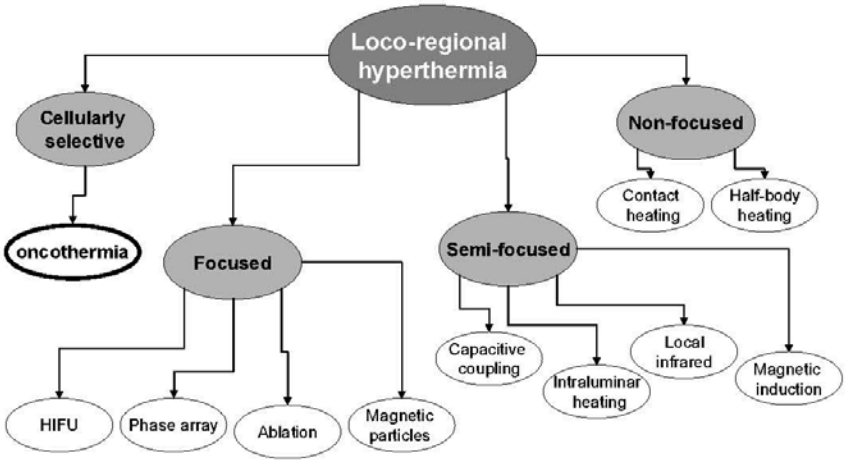

Figure 3. Various methods of the localregional hyperthermia with electromagnetic and ultrasound (HiFu) heating

The local/regional solutions are basically based on the electromagnetic effects, simple radiation (antenna effect) magnetic field application (coil effect) or electric field application (condenser effect), see Figure 4. These methods have high energy applications (kW range) to ensure the quick heating and the supply of the energy, which is gradually lost by the intensive cooling of the neighborhood of the target.

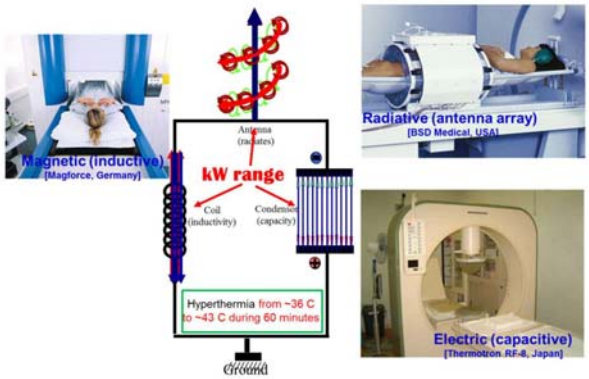

Figure 4. Electromagnetic fields are used in contemporary hyperthermia devices to heat up the body locally or regionally. All of these solutions are in range of kW energies, because the intensive physiological feedback tries to cool down the heated lesion

The race for the high power density in the focused area increases the risk of burns and the risk of misfocusing the fields resulting in hot-spots in the healthy volumes. The most part of the forwarded energy however is wasted due to the natural equalization of the temperature by the connected tissues to the target and by theintensive and steadily growing heat-exchanging mechanism of the blood-flow.

There are numerous electromagnetic hyperthermia methods applied. These are distinguished by the kind of the fields, frequencies, heated volume, conjunction with other methods, etc. In order to eliminate a part of the above challenges we try to go over the limits by technical tricks: cooling the surface to limit the surface load, focusing the energy on the lesion, controlling the hot-spots by imaging methods, etc. The main problems with the technical tricks are the loss of the basic control over the processes, requesting growing sophisticated methods to keep the pocess under control. This happen in the situation when we study the temperature which can be reached by any actual SAR energy. The blood-perfusion modifies the temperature, and even when the same energy is absorbed by the same volume, their temperature could be significantly different due to the different blood-flow through the target, see Figure 5.

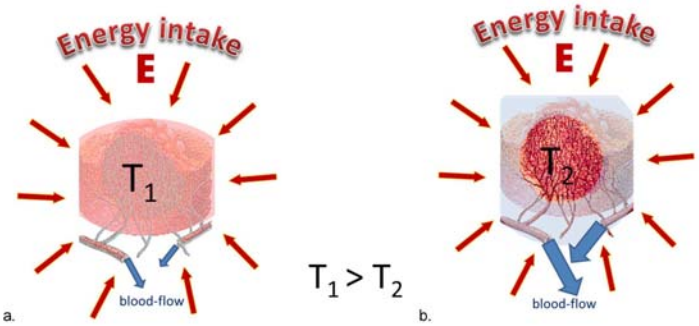

Figure 5. The same energy (**E**) is given to the same volume with different blood-flow. When the bloodflow is weak, (a), and strong (b) the reached temperature is high or low, respectively

Biological challenges

The original idea of the local hyperthermia was to force the tumor metabolism by heat. When the surrounding tissue is intact, it does not deliver more glucose for the forced metabolism Figure 6/a. The tumor very quickly deflates from nutrients, empties all its energies, suffers and burns away [50]; as well as the rapid increase of the lactate concentration [50] supports the cell destruction mechanism in the targeted volume.

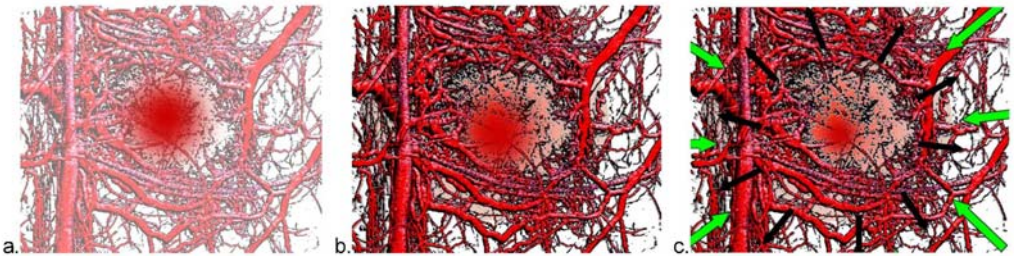

Figure 6. The focused local heating situation. (a) the local energy absorption impoverishes the ATP of the tumor, and it is destroyed. (b) The pumped energy has time to be distributed and heats up the surroundings, (c) the heated tissues deliver more glucose to supply the tumor and increase the risk of dissemination by increased blood-flow

When the heat delivery is intensive and short enough the local energy absorption heats up the target and ablation happens. If the energy is not enough for the coagulation, longer time is necessary for heating. In this case the locally absorbed energy heats up not only the chosen target but the surrounding tissue and even the whole body is heated up by the heat-exchanging mechanisms mainly by the blood-flow in the target Figure 6/b. The higher blood-flow delivers more glucose and nutrients to the tumor, causing opposite effect than the expected. In this way a competition starts: which one is quicker, the distortion or the supply, there is no control on the process Figure 6/c. Furthermore, the higher blood-flow is a real risk of the enhanced dissemination of the malignant cells (Figure 6/c.). This contradictory effect really blocks the controlling facilities of the processes, and so the result is incalculable and unpredictable. The real physical rule is that the energy can be focused precisely, but the temperature is not focusable, that is naturally distributed in the available volume trying to reach equilibrium (see Figure 7.).

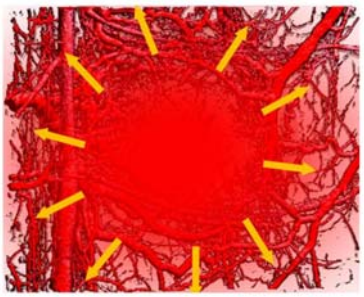

Figure 7. The locally heated volume heats up its neighborhood intensively. The energy is focused, but the temperature is not. The distribution of the temperature is forced by the physiological feedback trying to reestablish the homeostatic equilibrium

Complementary chemo or radiotherapy naturally helps controlling the process due to the higher chemoactivity [51]. The promoted, optimized chemo-intake helps to overcome on the fail of chemotherapies by the patient's intolerance (when it is not allowed to take big doses of drugs (for example at renal or liver insufficiency, insufficient blood-composition, etc.). In these cases the same results may be achieved by the combination of decreased chemo-dose and heat-therapy [52]. Hyperthermia supports the radioefficacy [53], [54] together with the applied heat. Hyperthermia has also been found to have pronounced advantages for surgical interventions. Through the hyperthermia induced inhibition of angiogenesis and heat entrapment, the outline of the tumor often becomes pronounced and the size of the tumor often shrinks making previously dangerous operations possible [55]. The feasibility of the preoperative application for locally advanced rectal cancer is well shown in a Phase II clinical trial [56]. Postoperative application of hyperthermia has also been thought to prevent relapses and metastatic processes [57]. Intraoperative radiofrequency ablation [58] and local hyperthermia [59] has also been used to improve surgical outcomes.

However, the complementary actions of other therapies in many cases could not compensate the bloodflow support of the tumor in a controlled way. Due to the physiological factors, the heat-treatment effects depend on the dynamism of the heat delivery, [60]. The quick heating acts differently on the local reactions and on the general thermoregulations from the slow one, because the physiological reaction time is relatively long. The highly non-equilibrium conditions in local-regional heating could not be stabilized, the stationer process is strongly influenced by the temperature regulation of the body. The measurements in humans evidently show the huge adaptability of the thermoregulation [61] (see Figure 8.).

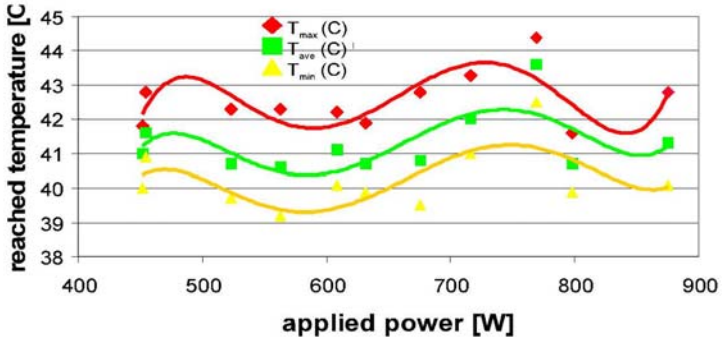

Figure 8. The homeostatic control keeps the temperature in a range, independently of the absorbed power

The temperature equalizing process naturally depends on the heat-exchange and heat conduction facilities, which are drastically enhanced by the growing temperature (see Figure 9. [62]).

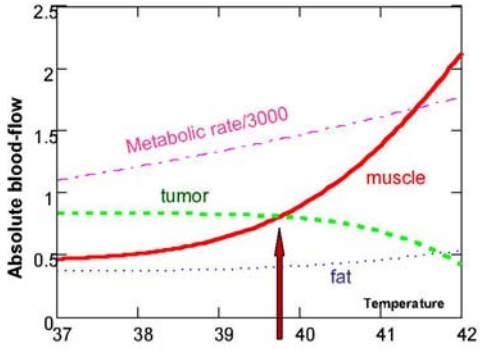

Figure 9. The blood-flow rapidly grows by the local temperature in the muscle tissue while the metabolic rate has linear increase only in the given temperature interval. The threshold (see text) is noted by an arrow

When the energy-transfer starts to heat up the whole body through the blood-heating of the target volume, new controlling processes (like sweating cutaneous vasodilatation, etc.) become active. The proper solution of hyperthermia would be when no increasing the complex feedback mechanisms against the heating action; having no unwanted gain of the blood-flow in the target. We have to act in the feedback loop mechanisms to reach the optimal situation, and not to excite the contra (negative feedback) actions, (see Figure 10/b.). The physiology acts against the local heating, which causes rapid heat-exchange of the target tissue with its connective tissues, and forces the body to make extra activity against local hyperthermia too. The reason for

the enhanced heat-conduction in the heated volume is simply physiological: the complex organism tries to reestablish the homeostatic equilibrium [63], it compensates the growing temperature with the higher cooling blood-flow (see Figure 10/a.). The absolute blood-flow values of the tumor and its connective neighborhood develops oppositely and turns over at threshold temperature value, allowing a drastic exponential increase of the blood-flow in the healthy tissue [64], [65].

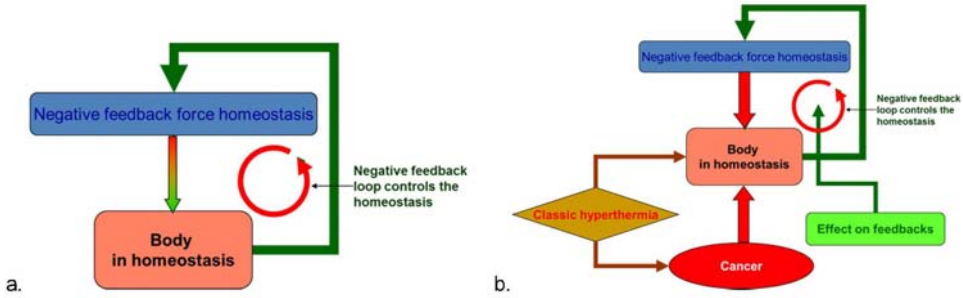

Figure 10. The feedback mechanisms of the complex living objects. (a) a definite

Hyperthermia in oncology has similar status that other medicaments, the difference between the medicine and poison is only the dose. There are certain energy-flow necessary for the deep heating, but of course the energy passing through the subcutaneous layers is limited by the toxicity, the burning. The blistering limit depends on the density of energy (W/cm^2) and the duration time of its application, Figure 11, [66].

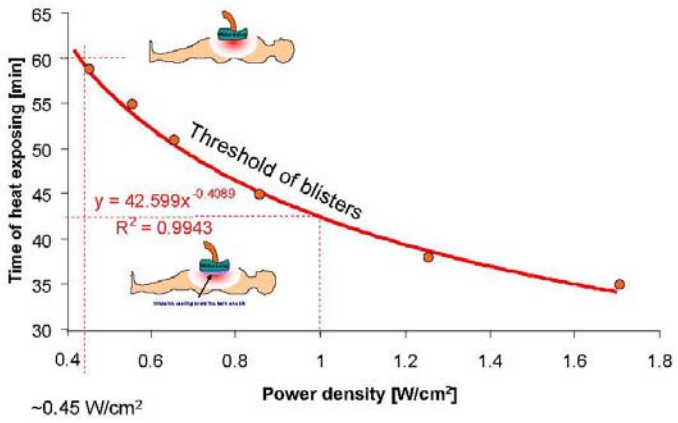

Figure 11. The blistering limit of the heating through the skin

To find the optimal path, it is necessary to fix the limits of the dosage. The lower limit is of course determined by the minimal effect by heating and the upper limit is determined mainly by the safety issues, like it is usual for overdoses. We have to consider that the modern hyperthermia is always complementary, so the other methods have to be considered at hyperthermia applications. The lower limit of the hyperthermia dose is probably the normothermia, where nothing else has action only the complementary treatment alone. With slight heating locally or systemically, it probably has no effect directly on the tumor, but it helps to increase the immune effects, enhances the complementary effects by the increased blood-flow and by the exponential temperature dependence of the chemical reactions (Arrhenius law). For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering shown above to the 0.5 W/cm2 , (60 min basis) the internal hot-spots could hurt the healthy tissue, and in the systemic application the physiology anyway limits it at 42 ºC. To avoid the overheating of the surface intensive surface cooling is applied in most of the electromagnetic hyperthermia techniques. In this case the physiology has negative feedback control again. In hot environment the subcutaneous layers have vasodilatation, high blood-flow helps the heat-exchange with the environment, it radiates out the excess body-heat, Figure 12/a. In cold environment the blood-flow is limited, the surface layer isolates the body Figure 12/b. Both cases change the heat- and electric-conductivity, as well as the dielectric properties of the skin layers. When the constrained forwarded power is applied, the voltage drops on the isolating (cooled) layer, it will be very high, a high voltage is necessary to pump through the requested constrain power. The relative high voltage lowers the current and less RF-current reaches the targeted deep-volumes.

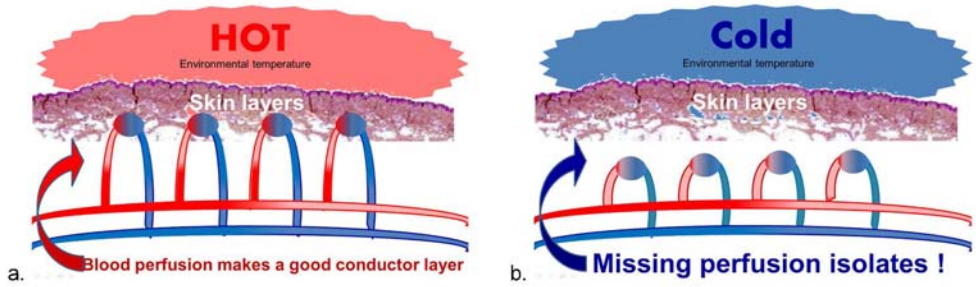

Figure 12. The environmental temperature significantly modifies the subcutane blood-perfusion. The hot environment (a) stimulates vasodilatation to cool down the body, while the cold environment works oppositely (b), definite vasocontaction helps isolate the body and avoids the loss of the body-temperature

On the other hand the high surface voltage will find the special conductive channels (blood-vessels, lymph passes, swealing paths, nerve-sensors, etc.) and like "sparking" passes through the isolating layer, causing electric bum despite the intensive cooling, see Figure 13.

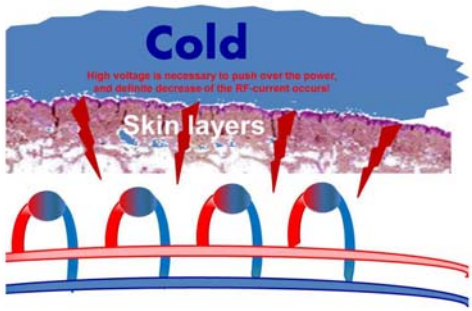

Figure 13. The constrained power produces high voltage on the skin layer. This finds narrow channels to go through, causing high risk of electric bum

The intensive cooling of the surface creates a further problem: the forwarded energy as parameter is not suitable when the cooling on the surface is intensive, because there is no idea about the energy lost by cooling. When we apply forwarded energy over one kW and the cooling has similar energy taken off, the control became very complex.
The other problem could be, when the energy heats mostly the bolus-liquid as the most energy-loaded surface layer and deeper seated body itself are not directly heated up. Again, the forwarded power does not give information about the real energy-load of the tumor.
Hyperthermia struggles with the technical problems above, and sometimes it hinders the biological factors.

The uncontrolled absorbed energy situation requests local control, the energy- intake which would be the natural dose measurement like in radiotherapy or like the chemical doses of medicine, cannot be applied here. Local, in-situ measurement is necessary to dose the treatment, and that only could be the temperature. The presently applied dose concept (CEM) is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in an extreme case reaches the 42 °C (even the 43 ºC is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start make vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40 °C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.
The ultimate challenge is to develop heat resistance, which could make the hyperthermia ineffective; the disease could become refractory for heating.

Medical challenges

Both the technical and biological challenges robustly appear in medical applications. However, some additional problems arise in medical considerations. The main point is connected to the inherent behavior of

the malignancy. The malignant tumor looks local but it is systemic; the main dangers of it are the dissemination of the malignant cells and the formation of distant, far away metastases. The survival prognosis is drastically worsens when the tumor is disseminated and metastasized. Considering this problem we have three-front fights:
1. Primary solid tumor, which proliferates and there is no natural block because the apoptosis is missing.
2. Dissemination transforms the local lesion to systemic disease. The dissemination occurrs mostly by missing adherent connections and missing cell-cell adhesions. When no dissemination happens the tumor is benign.
3. The formation of the distant metastases is the consequence of many various factors and one major is the missing immune reaction.

The dosing and control of the treatment is not only a technical and biological challenge. It is a hard problem of the medical application of hyperthermia. Without definite protocols it is a weak approach and has no possibility for comparison of the results and does not give reliable possibility for the patients. However the dose itself has numerous questions anywhere. The problem is mainly connected with the bio-variability which makes humans also individual. The dose has to be personalized, but then many points of the fixed protocol could not be fulfilled, as well as the collection of the cohorts for studies became complicated.
The dose in radiotherapy measured in Gy (J/kg), is a good quantitative parameter. However its efficacy depends on many physiological and technical parameters (like the oxygenation of the tissue, the focusing arrangement of the devices, the fractionating possibilities, etc. There are some surface burns representing the direct toxicity, which also can limit the application. Anyway the efficacy is measured by off-situ diagnosis (comparison of the before and after states), and the safety is fixed by the dose escalation studies, where the severe toxicity blocks the further increase.
The chemotherapy is definitely based on the toxicity limit. All the patients have the same dose depending on their surfaces. The dose is calculated by mg/m 2, irrespective of the size of the tumor, or any other personal specialties. We assume that the drug which is solved by blood is equally delivered to all of the body-volumes, and it is supposed that the tumor has been infiltrated by the drug in the same way as the other tissues do. The safety is again measured by dose-escalation studies. The concept is to apply the largest tolerable dose ("tolerable" means controllable side effects) and measure the efficacy off-situ later, in the same way (mainly by imaging) as the radiotherapy does.
In case of hyperthermia the highest tolerable temperature is defined, while the safety limit is also defined by the temperatures (hot-spots). Due to the long treatment time the patient roughly sensing the toxic dose (burning) so in hyperthermia the actual immediate correction of the dose could be done.
Another medical challenge of hyperthermia is its locality. The treatment is local, considering the tumor local too. But the malignancy is not local. Particularly it is not local when high-line treatment is applied after the failure of some earlier treatments, and the case is advanced, metastatic. In this point the local treatment alone is dubious even when the focusing is absolutely perfect and the action is concentrated completely on the desired target only.

Possible answers to the challenges

There is a new method emerging: oncothermia [69]. It is devoted to "pick up the gloves". It is a precise impedance (resistivity) matched system, Figure 14. This impedance fit is mainly based on RF-current and not on the voltage (potential) which is represented by a capacitor. Of course, this is also a capacitive coupling, but the electrodes of the capacitors are better conductors and promoting conductive behaviors than capacitors. While the capacitive coupling is based on dielectric loss of the material, the impedance matching is mainly Joule-heat, concentrating on the conductive part of the dielectric constant.

The capacitive coupling has two possible solutions: dominating the field (voltage) between the electrodes or dominating the current (ampere) from one electrode to the other. Oncothermia is this second type, using the current source instead of the voltage source. It is a special capacitive solution, using impedance matching for treatment. This heating is sensitive for the electrode direct touching, when they are not well connected to the body, the process stops, while the usual capacitive coupling acts when the certain high isolation (i.e. lifted electrode) is involved. The current-forcing solution forces the current through the target (starting from one electrode and finishing on the opposite, changing the situation by every period of the source). The two solutions have a lot in common, but the main difference is the current fixing. The same power has different effects, because the multiplication of the actual amperes and voltages define the constant power.

In conductive oncothermia the RF-current flows through the whole volume between the applied electrodes. In the oncothermia case the area of the cross-section that the RF-current flows through changes by depth, and it decreases the current density (current through a unit area). The energy deposition of the current in a unit volume, however, depends on the current density, which makes the energy absorption nonuniform in relation to depth.

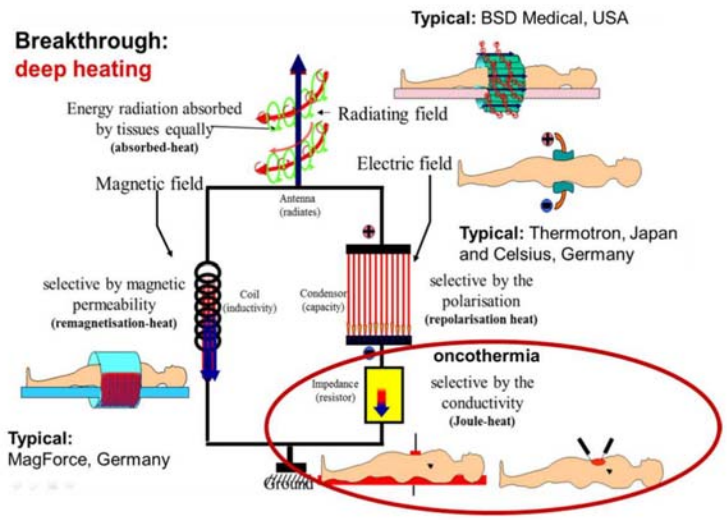

Figure 14. Impedance matching is the main factor of oncothermia

The better impedance coupling is supported by a technical trick, the asymmetric electrodes (see Figure 15.). The specific absorption rate (SAR) is much better in asymmetric solution starting on the surface, and the symmetric exceeds it in depth of 22 cm. Deeper than 22 cm the symmetric becomes better, which is for humans the full cross-thickness of a laying person.

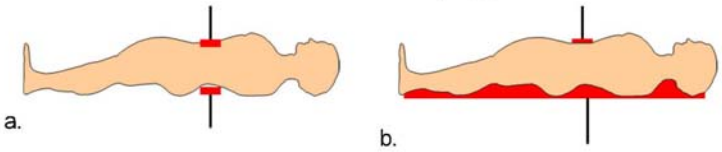

Figure 15. The symmetric (a) and asymmetric (b) electrode arrangement. The asymmetric arrangement has higher RF-current at same power

Oncothermia impedance coupling has special electrode construction to avoid any capacitive radiation, which could make non-controlled losses of unwanted shortage of penetration depth. It works by 13.56 MHz carrier frequency, applying definite, patented [67] time-fractal modulation with special template of its construction.

The complex modulated signal works effectively on the selection of malignant cells and promotes the heat-dispersion of the membrane bounded water-states. Together with the state of art fractal physiological considerations the concept is based on Warburg's principle of fermentative ATP production, and on Szent-Gyorgyi's principle of permittivity changes of malignant membranes [68]. There are numerous clinically proven advantages of oncothermia recognized [69]. The optimizing of dose, oncothermia uses the well-established gold-standard, the energy as used in the radiotherapies. The selection can heat up the malignant cells extremely high, without the same heating in the other parts of the tissue, Figure 16/a. However, by higher temperature the selection would be less emphasized, while the average is growing, see Figure 16/b,c.

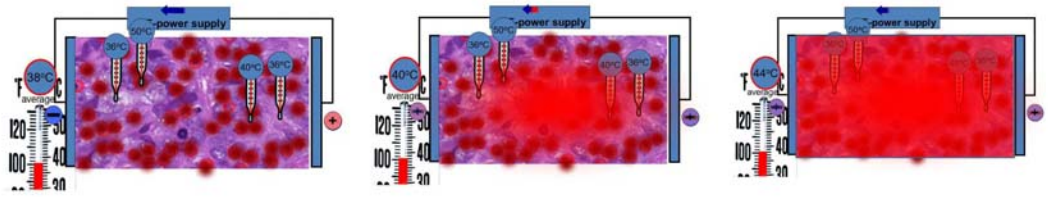

Figure 16. Heating with high selectivity in nano-heating process while the average temperature is kept low (a), incrasing the average temperature the selectivity lowers (b) and fixes the tissue in equilibrium, where no selectivity exists ever more (c)

The RF-current flows dominantly in the extracellular electrolyte, the cell-membrane is enough for the energy-absorption in it and in its surrounding thin electrolyte layers, see Figure 17.

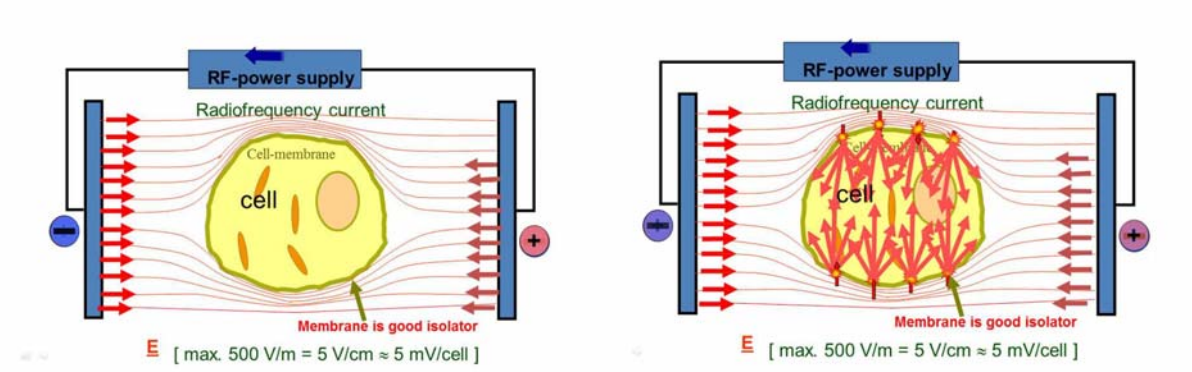

Figure 17. The RF-current penetrates into the cytoplasm only slightly, the majority of the energy is absorbed in the membrane and in its immediate vicinity (a). The temperature gradient excites the membrane (b)

The selection mechanisms [68] concentrate various effects on the membrane of the malignant cell, [70] Figure 18. The most important consequence of this excitation is the apoptosis which is formed in majority of the selective cell killing [71].

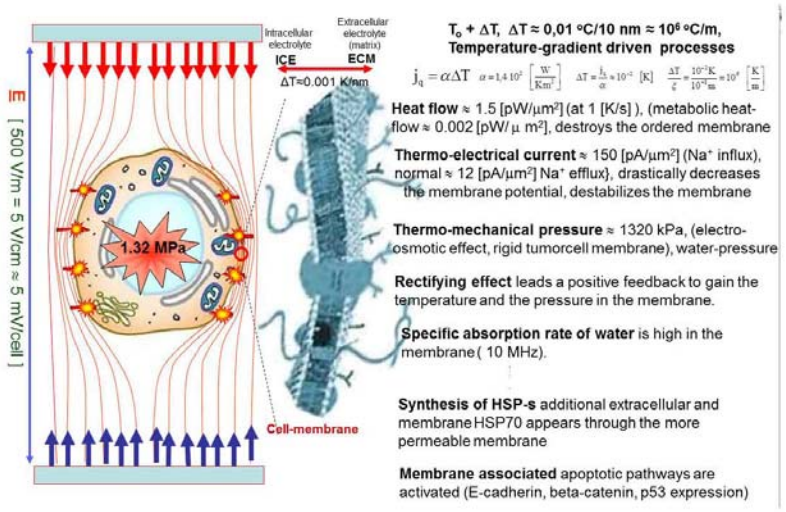

Figure 18. Various effects at the malignant cell are forced by the RF-field. The main effect is however to excite the pathways for apoptosis

An important observation shows the result of selection in oncothermia. While in conventional hyperthermia the relative cell-distortion is 17.9 % at 42 ºC, for oncothermia it is 57.1% in identical temperature, [72], Figure 19. Measurements were made by cooling the tumor intensively down to near body temperature (38 °C). In this measurement we take care of the same forwarded power as it was in the previous 42 °C process. It was intereting to observe the cell-distortion rate, which remained much higher than the conventional hyperthermia reaches in 42 °C.

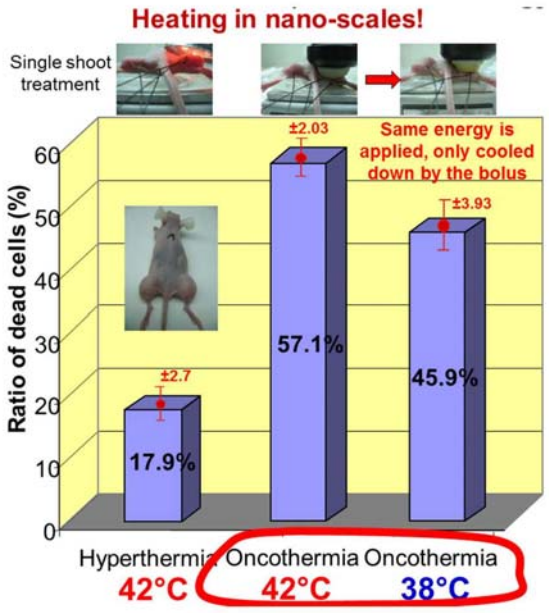

Figure 19. Oncothermia is more effective than conventional hyperthermia on the same temperature, and remains effective in case of lower average temperatures too

The careful, patented control of physiology of the skin at the treated volume [73] makes it possible to pump the highest available energy through the epidermis without toxicity. This lets us use the precisely matched and measured energy as control parameter; the cooling does not modify the energyintake.

The new technology allows using as much overall energy as necessary for the cellular heating, having no energy-loss by the heated non-cancerous volumes. The energy is selectively absorbed in nano-range of the membrane of malignant cells. The 1/10 th of the usually applied energy in similar devices is eligible to reach high quality results in preclinical and clinical use, mainly in survival time and quality of life. The main medical advantages of the method together with the effective selection and distortion of the malignant cells are the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. More details about this method were presented in this conference [68].

The dose is an important factor of efficacy safety and reproducibility in oncothermia. Conventional hyperthermia overemphasizes the temperature as a dose, which anyway is necessary for safety reasons, because the forwarded power and SAR do not correlate. The temperature is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic, average of the individual energies of the small units in the system. In chemo-therapy the cytotoxic remedies could cease very serious side effects, their safety has an emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or a complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.

When the medication definitely has no side effects (or the side effects are manageable) then the dose by their safety role has no upper limit. Anyway, when the dose is prescribed by fixed patient-independent protocol it is not realistically applied. When the prescribed energy is too high for the actual patient (high biovariability), the actually applied dose has to be lowered, trying to fit it for the actual patient.

Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) senses and notes the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much, actually it has to be modified on the personal requests. On the other hand, when the preset energy-dose is too small (the patients can actually tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety, and together with this, for the efficacy too.

Future tasks

There are numerous exciting tasks for the future of hyperthermia in oncology. Here is a list of them below without detailed description:

1. It is desired to extend to local treatment to whole-body effect, but affecting selectively only the malignant cells (irrespective of where they are in the body). This has numerous preliminary results by the bystander (abscopal) effect, which is definitely dose dependent and connected to the immune activation processes [74].
2. Oncothermia is completed by the preliminary results to solve the memory (vaccination) effect in situ prersonalized for the cancer patients. The memory effect was shown and used [75], [76], through T-cell activation.
3. More precise and specialized personalized effects have to be used by proper dose-adjustment and modulation-template [77].
4. More complementary applications have to be worked out. Conventional gold-standard therapies have to be widely applied in high line treatments too, working out the resensitizing processes for the previously refactory treatment. New therapies (dendritic-cell [78], stem-cell, [79], etc.) have to be involved in the combinative complementary processes.
5. There are multiple cases presented in this conference too [80], [81] showing the possibility to form the fatal cancer disease chronic, apply it for a long time (like dialysis) and make the patient's survival much elongated with good quality of life.

Conclusion

Nanoheating technology offers a renewing of the conventional hyperthermia. It is a synergy of the bioelectromagnetism with the fractal physiology. Oncothermia approach opens possibilities of stable controlled treatment without controversial challenges. It is a vivid way to solve the old-problems in hyperthermic oncology: it is a controlled, reproducible and reliable treatment.

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Oncothermia Journal 7:59-59 (2013)

War against cancer

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War against cancer

The author directs an information and consultation service for people with cancer and their famiilies. To better inform his clients and readers, he travels around the world in search of new or innovative treatments that are clinically available for patients willing to travel. This travel has taken him to Asia, Latin America, most EU contries as well as most regions of the US. In this presentation, he will review his findings in various states and countreis, highlighting the use of complementary and alternative medicine (CAM) in various societis. Some of the treatments to be discussed are chronomodulated chemotherapy, antineoplastons, Coley's toxins, sonophotodynamic therapy, newcastle disease virus vaccine, dendritic vaccine, immune pheresis, etc. The emphasis in the talk will be on clinics he has found that are using hyperthermia, and in particular Oncothermia, as part of their practice.

Oncothermia Journal 7:60-60 (2013)

Report of the single institute experience in treating head and neck cancer with hyperthermia and radiation as well as chemo-radiation

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Cancer accounts for 8 percent of death in India. Nearly 200,000 patients of new head and neck cancers are diagnosed in India. The overall survival of head and neck cancer has remained stable over 45-47% depending on race, socio-economic background and country. Organ sparing surgical techniques, and organ preserving approaches in the management of head and neck cancer are routinely practiced even in India. Hyperthermia despite being useful has not been a routinely available modality. At ACRO – Advanced Centre for Radiation Oncology of Nanvati Hospital, Mumbai, India, patients are offered hyperthermia as an adjunct to chemo-radiation or radiotherapy alone in all Stage of II-IV head and neck cancers, excluding that of Nasopharynx.

The present report will include the outcome of patients treated with hyperthermia and chemo-radiation as well as radiation therapy alone. The report will also include the data on a randomized trial of head and neck cancer to compare radiation with hyperthermia and radiation alone. More than 300 patients have been treated with hyperthermia alone so far. Hyperthermia is delivered by 8.2 MHz RF system and radiation with 5 Mv linear accelerator with or without IMRT, or on telecobalt equipment.

Oncothermia Journal 7:62-68 (2013)

Autoregulation of the brain temperature during whole body hyperthermia

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Autoregulation of the brain temperature during whole body hyperthermia

The aim of this study was revealing the temperature changes in rats brain tissue caused by whole body hyperthermia. Analysis of received results allow to conclude, that the brain has a highly secured system of temperature autoregulation against the exogenous temperature changes. The upper limit of this autoregulation (for rats, at least) is in the range 45 ^{o}C of environment. An important role in the normal functioning of the brain temperature autoregulation system belongs to Nitric Oxide the behavioral disorders, observed in animals after Whole Body Hyperhtermia (sure within the range of brain temperature autoregulation) is hardly associated with the canges in temperature of the Central Nervous System, but rather have to be mediated by impaired blood circulation and oxygen supply to the brain tissues, caused by the rapid deteriorationof the blood rheological properties.

Introduction

In our previous experimetnal studies significant morpho-physiological changes in the rat's brain tissue caused by Local Hyperthermia (43^{0}C, 60 min. exposure) have been revealed [4, 15]. On the **Figure1** we can see the clear-cut edge of damaged tissue in the rats' cerebral cortex. Analysis of the results allowed us to conclude that in the development of these changes essential role belongs to the mechanism associated with intense activation of Nitric Oxide Synthases (NOS), resulting (in the initial phase of Hyperthermic Exposure) in increased oxygenation of exposed brain tissue, and then (in the second phase of exposure), - to changes in blood rheological properties resulting in thrombosis of cerebral vessels [14].

Confirmation of this conclusion is presented on the Figure 2 (A and B). On the Figure2A we can see a sensory motor cortex of rats' brain with a lot of thrombosed cerebral vessels after 60 minutes of hyperthermic exposure in control rats brain and on Figure2B – the similar picture in experimental rats' brain with inhibited production of Nitric Oxide (we can see just a single thrombosed cerebral vessels).

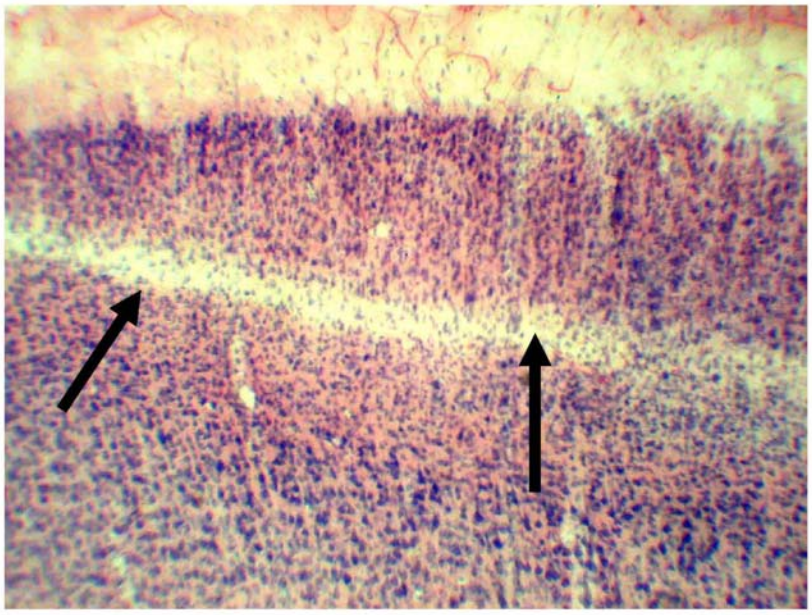

Figure 1. Sensory-motor cortex of rats' brain; 60 minutes hyperthermia (43 ^{o}C); Arrows show the clear-cut edge of damaged tissue. A – malignification: x15

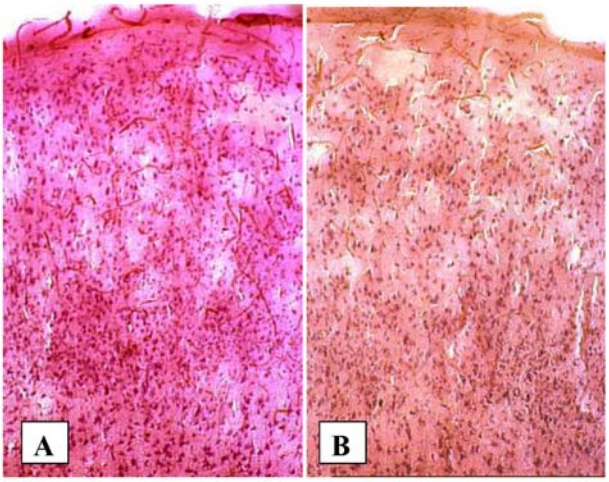

Figure 2. Sensory motor cortex of normal (A) and L-NAME injected (B) rats' brain (x10); 60 minutes hyperthermia (43^{o}C)

In the case of tumor tissue, we believe that the initial thermal hyperemia leads to a deterioration in the process of glycolysis due to increased oxygenation of tissues (Pasteur effect), and subsequent thrombosis leads to the sharp decrease in glucose delivery to tumor cells and to their unconditional death. Based on the foregoing, we attempted to evaluate the possible role of these phenomena in behavioral disturbances in rats observed after Whole Body Hyperthermia [13].
For this purpose, specially made thermocouple we implanted in the subcortical structures of the rats' brain, which allowed to record changes in temperature of brain tissue at different temperatures in HC.
Two series of experiments have beeen carried out - on intact animals, and on animals with previously administered (intraperitoneally) nonselective inhibitor of NOS (Nitro-L-Arginine Methyl Ester - L-NAME). The rectal temperature were also recorded. Raising the temperature in the HC up to 450C and its maintenance on this level during 1 hour, did not lead to temperature increase in the subcortical brain structures of intact animals above the 36-36.50C.. These results led us to temporarily suspend behavioral experiments and to more detailed study of this phenomenon - temperature homeostasis in the brain.

Materials and methods

The used approach was quite simple: specially designed (in Bicher Cancer Institute, Los Angeles, USA) for these experiments thin (300-400 mcm in diameter) teflon-covered thermocouples with a bared active tip (about 1.5-2 mm) were implanted into the brain of experimental animals (rats). Thermocouples were dipped in the subcortical structures (in the area of thalamic nuclei), and their connectors were fixed on the skull.

In one series of experiments on the third day after chronic implantation of a thermocouple, the animals were narcotized (0.15ml/100g, 4% solution of chloral hydrate) and placed in the HC (Figure 3), and by means of insulated cable the thermocouple was connected to the digital meter of temperature (Omega Engineering, Inc., USA). Two series of experiments were carried our: first – on animals wich before the hyperthermic exposure did not receive any pharmacological agents and the second series – on animals which 15 minutes before the beginning of hyperthermic exposure were intraperitoneally injected by nonselective inhibitor of Nitric Oxide Synthase Nitro-L-Arginine Methyl Ester (L-NAME, 50mg/kg).
The temperature in hyperthermic chamber, as well as in animals brain tissue was measured continuously, and the rectal temperature - discretely, in every 15-20 minutes.

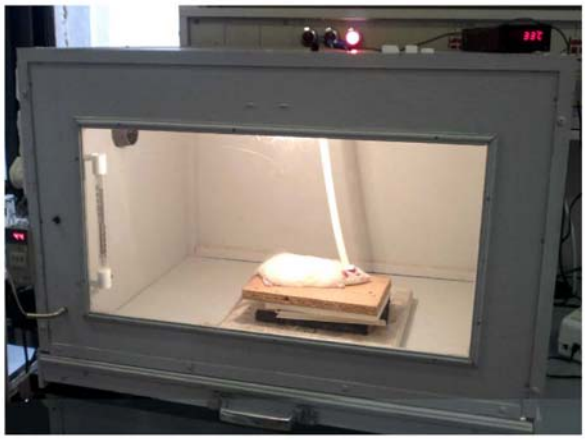

Figure 3. Hyperthermic chamber

The temperature in the hyperthermic chamber was gradually (in duration of 25-30 minutes) increased up to 45^0C and this level was automatically maintained for 60 minutes. Depending on the condition of the animals in some cases we continued the rise of temperature in chamber up to 48-50^0C.

In other groups of animals (without implanted thermocouple) - intacts and with a preliminary administered L-NAME (in the above-mentioned dose) an index of Red Blood Cells (RBC) aggregation - one of the most important rheological parameters of blood was determined at different temperatures in HC.

All received results were evaluated statistically and significance of differences between mean values were assessed by Student's Criterion.

Results

Changes in the brain tissue temperature, when the the temperature in the HC in duration of 30 minutes was increased from 38 to 45^0C, then was maintained on this level (45^0C) for 60 minutes and after that was slowly (in duration of 75 minutes) raised up to 500C, are presented in the Figure4. On this picture we can see the data on changes in temperature in the hyperthermic chamber (dark points) - which is automatically adjusted to a level that is specified by the experimenter, and in the rats' brain tissue (open circles) - continuously measured with a thermocouple implanted in the brain.

As seen on this figure, the temperature in the brain tissue of postoperative animals (before beginning of hyperthermia) is around of 33^0C and begins to rise with the onset of Whole Body Hyperthermia. And when the temperature in the chamber reaches 45^0C the brain temperature stabilizes on the level of 36-36.5^0C inspite of the fact that the 45^0C in the chamber lasts 60 minutes. If, however, we continue rising the temperature in the chamber even just on the one degree of Celsius, the stability of the temperature in the animals brain is disturbed and if we will continue temperature rising, the brain temperature almost linearly will follow to increasing temperature in the chamber. Practically, we were faced with a phenomenon that can be called as the autoregulation of brain temperature, or temperature homeostasis.

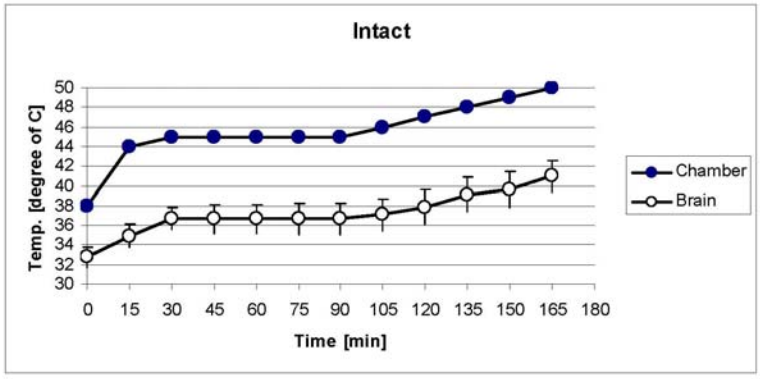

Figure 4. Data on changes in temperature in the hyperthermic chamber (dark points) and in the rats' brain tissue (open circles) – continuously measured with a thermocouple implanted in the brain

A fundamentally different picture is observed if prior to the hyperthermic exposure, the animal is intraperitoneally injected by nonselective Nitric Oxide Synthase inhibitor L-NAME (Nitro-LArginine Methyl Ester) at a dose of 50mg/kg. The results of measurements made on these animals are shown in the Figure 5. Variation of temperature in the hyperthermic chamber presented in this picture (both in duration and in the absolute values of the temperature) is identical to that of the previous picture. However, the dynamics of the temperature variation in the brain is fundamentally changed - a plateau that occurs on the corresponding curve in intact animals, is absent here. The temperature curve, recorded from the brain of animals with inhibited Nitric Oxide Synthase activity, starts smoothly and continuously grow with the onset of hyperthermia, and so lasts until the end of experiment, i.e. until the death of the animal, which usually occurs when the brain temperature reaches the range of 40-41^{0}C.

As for the dynamics of changes in rectal temperature in all experimental conditions we used, it is shown on Figure6. Here we can observe a mixed picture. Analysis showed that the statistical significant difference between the readings at different experimental conditions was observed only in the short time intervals of hyperthermic exposure and do not have a regular character.

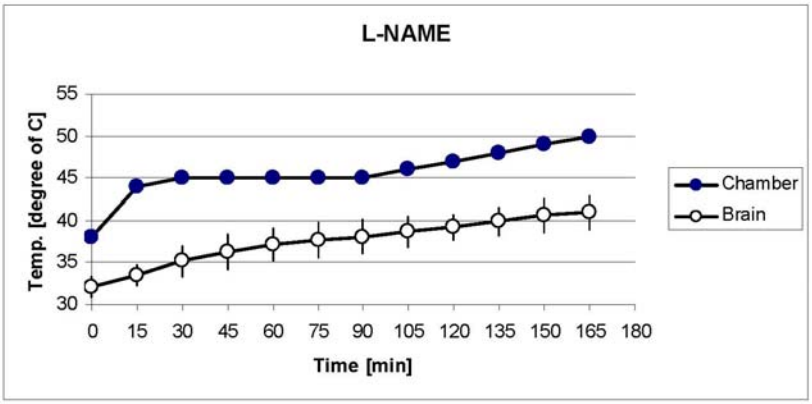

Figure 5. Changes in temperature in the Hyperthermic chamber and in brain tissue of animals that before the beginning of hyperthermic exposure have been intraperitoneally injected L-NAME (50 mg/kg)

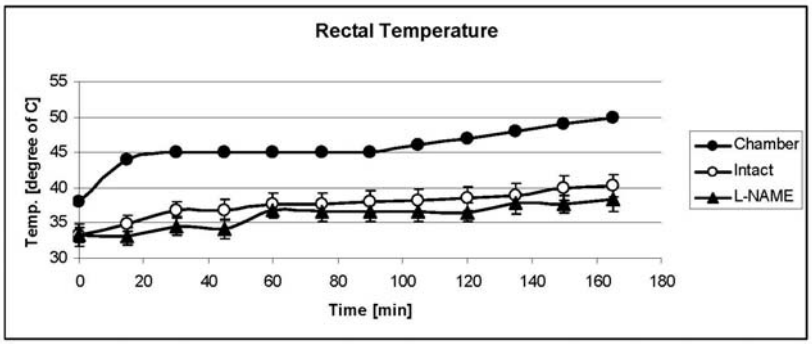

Figure 6. Changes it the temperature (rectal and in chamber) of intact group and in L-NAME (50 mg/kg) injected group of animals

A special series of experiments was conducted to determine the changes in the index of erythrocyte aggregation caused by hyperthermic exposure in intact and L-NAME-administered animals. The results of these measurements are presented in Table 1, where we can see the average values of this index at normal (room) temperature (21-23^{0}C), and 40, 43 and 45^{0}C.

Temperature in Chamber (^{0}C)	Intact rats	L-NAME injected rats
21-23	1.3±0.1	1.75±0.15
40	30.1±2.1	9.48±0.2
43	33.2±1.8	10.4±0.18
45	40.1±3.5	15.8±0.2

Table 1. The average statistical values and standard errors of RBC aggregation index in normal temperature and in conditions of WBH

Discussion

The bacis mechanisms underlying the regulation of body temperature in humans and animals has always been under the attention of scientists and it should be noted that in this area has been achieved significant progress, both in condition of norm and pathology [6, 9, 11, 22]. However, substantially different picture appears if we consider the issue of temperature regulation in the brain not only in case of external, but also in internal impacts (associated with changes in temperature caused by different levels of brain functional activity) [20].

There is an evidence that the direction of temperature changes in the brain of the cat during visual stimulation is dependent on the frequency of flashing light - at low frequencies, the temperature rised, and decreased at high frequencies [12]. It was also established that under normal physiological conditions, the temperature in the deep brain structures is higher than the temperature of arterial blood, and closer to the brain surface, due to exchange with the environment - the situation is diametrically opposite [17, 20, 24]. It is believed that quantitatively this phenomenon is regulated by the temperature shielding effect of blood flow, which protects the subcortical structures of the brain from penetration of "extracranial cold" [21], although would be more appropriate, instead of "extracranial cold" use the expression "ambient temperature changes."

In accordance with our above described results, the rat's brain has a sufficiently effective system of thermoregulation in case of sharp rise in environmental temperature and the upper limit of this autoregulation is 450C. Further increase of temperature in the hyperthermic chamber (above 450C) leads to disruption of this autoregulation - the temperature in the brain increases in a linear function of chambers' temperature and when it reaches 40-410C – animal dies.

We completely agree with Zhu et al. [25]. who in their study concluded that the depth of the thermal shielding of the brain is critically dependent on cerebral blood flow. This is clearly evidenced by our data

showing that the preliminary (15 minutes prior to hyperthermic exposure) administration of a nonselective inhibitor of Nitric Oxide Synthase (L-NAME, 50mg/kg), completely disrupts the autoregulation of temperature in the of brain tissue and from the very beginning of hyperthermic exposure its dynamics linearly follows the changes of temperature in the chamber.

It is known that a sharp decrease in the synthesis of Nitric Oxide (if not its complete blockade) leads to the same sharp decrease in blood flow and increase in systemic arterial pressure (approximately on 60%) [5]. We know as well that in norm the endothelial Nitric Oxide Synthase controls basal vascular tone, and that the Nitric Oxide is involved in neurogenic vasodilation in response to a rise in body temperature [23]. In addition, it was found that LNAME inhibits the norepinephrine-induced increase of blood flow in brown adipose tissue – in the main thermogenic organ [16]. All the above confirms that Nitric Oxide is an important component in the system of thermoregulation not only for the brain but also for the whole body.

The intensity of the circulation, and hence the degree of maintenance of temperature homeostasis is largely dependent on the rheological properties of blood [8], one of the most important indicators of which is an index of erythrocyte aggregation However, this parameter itself is extremely temperature dependent, which is mainly due to the influence of temperature on the viscosity of the plasma and inter-erythrocyte interaction, promoting their aggregation [18].
Increased blood viscosity, adversely affecting its fluidity, further facilitates the aggregation and such an avalanche-like development of processes leads to formation of vascular thrombosis. This is one of the main and intended purpose of the local hyperthermia in case of tumor tissue, but it is a matter of special consideration and analysis.

Based on the fact that our study was conducted on rats, it is necessary to recall that between species of vertebrates the index of RBC aggregation varies greatly [7] and the lowest is in the rats that have very poorly defined tendency to aggregation of RBC [3]. There is strong reason to believe that Nitric Oxide plays an important role in the regulation of blood rheology, particularly in the phenomenon of RBC aggregation, and that disruption of this regulation is one of the factors causing the development of L-NAME-induced hypertension [3]. It is believed that Nitric Oxide-induced improvement in the deformability of RBC and decrease in their aggregability are the results of Nitric Oxide direct action on RBC, which is considered as a sufficient reason for use of Nitric Oxide donors to improve blood fluidity [19]. But it should be emphasized that this applies only to Nitric Oxide produced by activation of the constitutional forms of NOS, primarily the endothelial one (eNOS).

In 1987 by Maeda et al [10] showed that at increase in temperature (in a range of 5 to 430C) velocity of fibrinogen-induced RBC aggregation increases. Our data presented in Table 1 show that increase of temperature in hyperthermic chamber leads to multiple, statistically significant increase in the rats' RBC aggregation index, which in contrast to other vertebrates, as already noted, in the norm probably is very low [2]. On the background of NOS inhibition by L-NAME we recorded (see Table 1) statistically significant ($P < 0.05$) decrease in RBC aggregation index at all temperature regimes of hyperthermia. Is this in contradiction with the above-mentioned effect of Nitric Oxide on the aggregation of RBC? We believe that there is not contradiction, because it is well known that hyperthermia stimulates the excessive production of Nitric Oxide, as it causes a significant activation not only constitutional isoforms of NOS, but also the inducible one (iNOS) [1] which is accompanied with sharp intensification of free-radical processes and formation of peroxynitrite.
Along with this, dramatically increases the xanthin oxidase-induced generation of reactive oxygen species [3]. These effects primarily influence the process of RBC aggregation. Free radicals' attack leads to damage not only the membrane of red blood cells, but their cytoplasmic structures also, which leads to an increase in the index of aggregation, to the durability of aggregates and, consequently, to a considerable increase in the shear rate required for their disaggregation [3]. Increased blood viscosity, adversely affecting its fluidity, further facilitates the aggregation and such an avalanche-like development of processes leads to formation of vascular thrombosis. This is one of the main and intended purpose of the local hyperthermia in case of tumor tissue, but it is a matter of special consideration and analysis.

Based on the foregoing it is clear that non-selective inhibition of all isoforms of NOS by means of L-NAME on the background of hyperthermia results (in our experiments) to the reduction of red blood cell aggregation indwx.

Conclusion

The analysis of all the above data led us to the following conclusions:

1. The brain has a highly secured system of temperature autoregulation against the exogenous temperature changes.
2. The upper limit of autoregulation (for rats, at least) is in the range 45^0C of environment.
3. An important role in the normal functioning of the brain temperature autoregulation system belongs to Nitric Oxide.
4. Behavioral disorders, observed in animals after Whole Body Hyperthermia (sure within the range of brain temperature autoregulation) is hardly associated with the changes in temperature of the Central Nervous System, but rather have to be mediated by impaired blood circulation and oxygen supply to the brain tissues, caused by the rapid deterioration of the blood rheological properties.

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Clinical trials in breast and bladder cancer: Thermally enhanced chemosensitization and drug delivery

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Over the past decade, hyperthermia (HT) researchers have made cutting edge advances in HT augmented delivery of liposomal drugs. The performance characteristics of temperature sensitive liposomal formulations containing chemotherapeutic agents are far superior to other formulations largely because of the rapid release characteristic at temperatures between 40 and 42°C and a significant improvement in drug delivery. Several preclinical studies provided compelling rationale to initiate a number of clinical trials that will be presented. In a phase I trial of low temperature sensitive liposomal Doxorubicin (Thermodox) and HT for breast cancer patients with chestwall recurrence, toxicities have generally been those that are typical for doxorubicin and no dose limiting toxicities have been observed thus far. With respect to clinical response within the heated fields, results are quite encouraging. In a Phase I/II study, neoadjuvant liposomal Doxorubicin, Paclitaxel, and HT was shown to be a safe and effective strategy for improving pathological response rates and surgical outcome in patients with LABC. The encouraging results from a pilot study of external HT and intravesical Mitomycin C (MMC) to treat recurrent bladder cancer after resection and standard adjuvant therapy are likely due to the effects of HT on bladder permeability as well as synergistic interaction between HT and MMC to enhance cytoxocity of MMC. This trial has established the basis for a subsequent trial using thermally targeted intravesical drug delivery which could further improve local control rates beyond what is achievable with the current best conventional therapy.

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Local and whole body hyperthermia in chemoresistant ovarian cancer

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Introduction

The prognosis for patients with advanced ovarian cancer remains bleak. 5-year survival in stage III is 5-10%. Primary and acquired resistance of tumor cells to antineoplastic drugs is a major cause of the limited efficiency of chemotherapy. In our retrospective analysis we present the treatment results for patients with advanced ovarian cancer using whole body hyperthermia (WBH) in combination with a second line or palliative chemotherapy.

Methods

13 patients with pathologically verified epithelial ovarian cancer were eligible for the retrospective analysis (selection of patients was done in accordance with the following criteria: advanced ovarian cancer after surgical procedure and previous chemotherapy). Median patients age 53,7. Nine (69%) patients had had a relapse. Number of organs with evidence of disease: metastases in 1 organ by 3 (23%), 2 organs by 8 (61,5%) and 3 organs by 2 (15,4%) patients.
All patients received palliative chemotherapy during the WBH with a core temperature of 41.5º - 42ºC).

Results

15,4% of patients showed a response to the therapy (1 CR, 1 PR). No change was noted in 7 patients (53,8%). The subjective status of the majority of the patients improved significantly three to four days after WBH. The tumor symptomatic subsided briskly. Ascites reduction was by four of the five patients clearly perceptible. Median Remission duration was 6,1 months. At the time of survival analysis, the median follow-up duration for all patients was 11,7 months (range 2,5 to 22). 7 of 13 patients died of disease relapse and one patient with diffuse liver metastases of liver insufficiency after chemotherapy.

Conclusion

Our results confirm the effectively of WBH in the treatment of patients with advanced ovarian cancer after extensive multiple chemotherapies: the response at 69,2% and remissions at 15,5% were registrated. The overall tolerance of this treatment was good. Priority for all patients was an improvement in life quality, which was seen three to four days after WBH.

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Application of transurethral prostate hyperthermia in benign and malign prostate hyperplasia and chronic prostatitis

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Benign and malign prostate hyperplasia and chronic prostatitis (CP) pose a constant challenge in urology due to the known limitations and risk of transurethral resection of the prostate gland and in the limitations of antibiotic therapy in CP. New treatment approaches therefore are warranted. The transurethral prostate hyperthermia has undergone enormous technological improvements in the last 20 years, particularly in the area of localized hyperthermia. Based on the current knowledge of radio frequencies and short waves the hyperthermia treatment of the prostate has proven to be a promising, effective and safe therapy option for treatment of prostate diseases. The first three year retrospective analysis will be presented.

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Critical analysis of randomized trials on hyperthermia: dubious effect and multiple biases

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Critical analysis of randomized trials on hyperthermia: dubious effect and multiple biases

Abstract

Hyperthermia in oncology still remains an experimental treatment with no realistic future in clinical cancer therapy, though declaration of the undisputed efficacy of hyperthermia is a common place in every hyperthermia paper. We've studied available randomized trials on hyperthermia from the position of 'null hypothesis' to confirm or refuse the efficacy and safety of clinical hyperthermia, taking into account also the possible biases. Unfortunately, the careful analysis of 14 randomized clinical trials doesn't confirm a clinical benefit of hyperthermia independently of its type: superficial, deep of whole-body. We haven't found any positive trial not affected with biases. With correction to distortions, there is no trial with obvious long-term positive effect of hyperthermia. Effect of hyperthermia could be shown in an experimentally designed clinical trial or versus inadequate comparator. In clinical setting and provided that the study design is correct, hyperthermia is not effective at all or not effective enough to justify its obvious disadvantages: toxicity and labor-intensity. Thermal concept of hyperthermia seems to be irrelevant. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance.

Modern hyperthermia starts from the first paper on local hyperthermia of F. Westermark1 published in 1898, more than 110 years ago. 80 years ago in the early 30s, electromagnetic hyperthermia started with Whitney Radiotherm. 50 years ago, studies of Selawry and Crile launched the modern period of hyperthermia history, and almost 40 years have already passed since von Ardenn and LeVeen introduced local electromagnetic hyperthermia. Regardless of the starting point, hyperthermia is one of the oldest known treatment modalities in oncology.

In 2007, Horsman and J Overgaard[2] started their meta-analysis with the words: "Hyperthermia is generally regarded as an experimental treatment with no realistic future in clinical cancer therapy. …", and then added: «… This is totally wrong». Thus, the eminent hyperthermicians voiced the general opinion of the medical community on hyperthermia. This opinion was articulated by Hornback3 already in 1987 when he wrote: «Clinical hyperthermia today is a time-consuming procedure, done with relatively crude tools, and is an inexact treatment method that has many inherent technical problems. Certainly, excellent research work can be accomplished by private radiation oncologists working in the community. If the individual is willing to commit the time and effort required to participate in clinical studies in this interesting, challenging, exasperating, and not-too scientific field; then he or she should be encouraged to do so. The field is not without its risks and disappointments, but many cancer patients with recurrent or advanced cancers that are refractory to standard methods of medical care can unquestionably be helped by hyperthermia. It is not, as some have suggested, the fourth major method of treating cancer after surgery, radiation and chemotherapy. It may be innovative, but it still is an experimental form of therapy about which we have much to learn». Nowadays, clinical hyperthermia is still a time-consuming procedure, done with relatively crude tools, and is an inexact treatment method that has many inherent technical problems; it's an interesting, challenging, exasperating, not-too scientific field; it's already far not innovative, but is still an experimental form of therapy about which we have much to learn. If nothing changed for 25 years, something is wrong with hyperthermia.

Horsman and Overgaard[2] wrote then: «Although the role of hyperthermia alone as a cancer treatment may be limited, there is extensive preclinical data showing that in combination with radiation it is one of the most effective radiation sensitizers known. Moreover, there are a number of large randomized clinical trials in a variety of tumor types that clearly show the potential of hyperthermia to significantly improve both local tumor control and survival after radiation therapy, without a significant increase in side-effects». The simple question: if this is true, why is hyperthermia still not a standard method of treatment in oncology?

To answer this question, we studied all randomized clinical trials on hyperthermia published after 1990. We didn't include non-randomized clinical trials taking into account the well-known fact that such trials usually show much higher effect. It was clearly demonstrated, for instance, in the famous RTOG trial on thermoradiotherapy of superficial tumors when 68% complete response rate was reported in phase I/II non-randomized trial[4] and only 32% in phase III randomized trial[5]. Editorial of Brizel[6] clearly shows inconsistency of such non-randomized trials.

We reviewed 14 randomized clinical trials: 7 on superficial local hyperthermia (see Table 1.), 6 on deep loco-regional hyperthermia (see Table 5.) and 1 on whole-body hyperthermia. We proceeded from the "null

hypothesis", i.e. considering hyperthermia not effective and/or not safe. From this point of view, we analyzed trials for 1) efficacy by endpoints, 2) toxicity, 3) biases. With the "null hypothesis", the negative trial result does not need any explanation. Therefore, only positive trials were subjects to our analysis.

Superficial hyperthermia clinical trials

The clinical trial of Perez et al.[5] (RTOG protocol 8104) published in 1991 compared thermoradiotherapy (TRT) versus radiotherapy only (RT) in a well-designed and large (307 patients with tumors of chest wall, neck nodes and melanoma) randomized trial sponsored by Radiation Therapy Oncology Group (RTOG). Complete local response (CLR) was reached in 32% of patients in TRT arm and in 30% of RT arm; the difference was statistically insignificant. There was no effect to overall survival. Despite the demonstration of stronger thermal enhancement of RT in tumors <3 cm, the result was disappointing.

Three clinical trials with similar design were published nearly simultaneously from 1990 to 1993, comparing efficacy of different TRT protocols: Kapp et al.[7] compared the effect of 2 and 6 hyperthermia sessions; Emami et al.[8] and Engin et al.[9] compared the effect of 4 and 8 sessions (see Table 1). The difference between 'short' and 'long' protocols was negligible, and Engin et al. even showed lower efficacy of 'long' protocol: CLR was 55% in 8 sessions arm and 59% in 4 sessions arm (not significant).

Trial		Kapp et al.[7]	Perez et al.[5]	Emami et al.[8]	Engin et al.[9]	Vernon et al.[10]	Overgaard J[11]	Jones et al.[12]
Organization		Stanford University	Mallinckrodt Institute of Radiology	Mallinckrodt Institute of Radiology	Thomas Jefferson University	Some European and Canadian centers	Danish Cancer Society	Duke University
Country		USA	USA	USA	USA	Europe/Canada	Europe	USA
Year of publication		1990	1991	1992	1993	1996	1996	2005
Design		Monocenter	Monocenter	Monocenter	Monocenter	Multicenter	Multicenter	Monocenter
Nr of patients		70	307	173	41	236	70	108
Nr of tumors		179	N/D	240	44	N/D	134	N/D
Type of tumors		Chest wall, neck nodes, melanoma	Chest wall, neck nodes, melanoma	Superficial	Chest wall, neck nodes	Chest wall	Melanoma	Chest wall, neck nodes, melanoma
Therapy	HT+	RT + HT 42.5°C (6 HTs)	RT + HT 42.5°C x 45-60' (2 HTs)	RT + HT 42.5°C (8 HTs)	RT + HT 42.5°C (8 HTs)	RT + HT 42.5°C	RT + HT 43°C x 60' (3 HTs)	RT + HT 10<CEM43°C T_{90}<100 (10 HTs)
	HT-	RT + HT 42.5°C (2 HTs)	RT only	RT + HT 42.5°C (4 HTs)	RT + HT 42.5°C (4 HTs)	RT only	RT	RT
Complete local response (%)	HT+	52%	32%	57.8%	55%	59%	62% (immed.) /46% (2yr)	66%
	HT-	51%	30%	54.7%	59%	41%	35% (immed.)/ 28% (2 yr)	42%
Overall survival	HT+	N/D	Statistically insignificant	Statistically insignificant	N/D	Statistically insignificant	Statistically insignificant	Statistically insignificant
	HT-							
Disease-free survival	HT+	N/D	Enhanced	N/D	N/D	Enhanced	N/D	Enhanced
	HT-							
Burns	HT+	N/D	30%	N/D	40%	11%	N/D	46%
	HT-		0%		40%	2%		5.7%
Complications (overall)	HT+	5% needed medication, 3% needed surgery	N/D	18% of severe complications	N/D	Pain	27% pain, incl. 8% moderate and 6% severe	16% needed pause of treatment
Authors estimation		Negative	Negative	Negative	Negative	Positive	Positive	Positive
Final estimation		Negative	Negative	Negative	Negative	Dubious	Dubious	Dubious

Table 1. Randomized clinical trials on superficial local hyperthermia published after 1990

In 1996, Vernon et al.[10] a trial was published showing significantly better CLR rate for TRT arm (59%) than for RT only arm (41%) without any effect to survival. Unfortunately, despite the big enough sample size, this result couldn't be considered relevant because of the incorrect trial design. This was a combination of 5 different European and Canadian clinical trials merged to reach statistical significance. Different protocols are hard to compare, and choice of patients is not excluded, and there are controversial data. For example, Vernon et al. report only 11% of burns whereas other trials report 30-45% burns, but at the same time "some" patients in Vernon et al. trial didn't fulfill the protocol due to pain whereas there were no such patients in other trials with much higher share of burns. We consider this trial "semi-randomized" and consider its result dubious because of low reliability.

In the same year, a clinical trial of Overgaard et al.[11] was published. It was multicenter (11 centers in 6 countries) randomized controlled trial on 70 patients with metastatic or recurrent skin melanomas. 128 lesions were evaluated (63% ≤ 4 cm, 37% > 4 cm). RT was applied by 3 large fractions (8/9 Gy) with subsequent hyperthermia (43°C, 60 min) directly following the RT. Immediate CLR rate in TRT arm was 62% versus 35% in RT only arm (gain 77%, p=0.003), and 2 year local control rate (LCR) in TRT arm was 46% versus 28% in RT only arm (gain 64%, p=0.008).

Despite being good at first sight, Overgaard et al. trial leads to many questions. The sample of the trial is too small, especially considering its multicenter design: 11 European cancer centers enrolled only 70 patients for 6.5 years, i.e. less than 1 patient per center annually. Taking into account that melanoma is a quite frequent tumor, this creates ideal terms for pre-selection of patients, on the one hand, and for special attention to treatment of hyperthermia arm, which usually leads to much better clinical results. Though the trial seems to be well-randomized, the latter bias should obviously be presented with such a small sample. And, surely, such a small sample is not representative. The authors justify that such a small sample as it is, is enough for the statistically significant result but the approach which is correct for experimental trial is not suitable for clinical trial where the sample size and especially its proportion to general sample is a significant factor of the representativeness of the results. Additionally, in this trial not the patients but the tumors were subject to randomization. This is also typical for a rather experimental design. As a result, the trial looks like in vivo radiobiology experiment in clinical trial shell.

The main bias of the study is an incorrect comparator which is known as a typical bias in clinical trials. The best or at least standard control treatment is the implied demand for clinical trials. The usual RT dose for skin melanoma treatment, as well for other superficial lesions, is 40-50 Gy per site[5,9] with common dose not more than 100 Gy, and it's commonly known that low doses significantly reduce the effect of RT[26]. 24/27 Gy total doses (TD) used in this trial are certainly low, especially considering the well-known radioresistance of melanoma. The median number of tumors per patient was 2; therefore there was no reason to lower dose per site because of high common dose. Also, the usual fractionation for skin melanoma is 10-20 fractions of 2-5 Gy each. Hypofractionation used in this trial (3 fractions 8-9 Gy each) is rare. Such choice of comparator has only one logical explanation: this protocol is ideal for thermal modification. With three doses only, each dose is modified and it's simpler to coordinate HT and RT; and the larger single RT dose is, the better modification effect is. Low common dose allows showing hyperthermia effect because standard high-dose radiotherapy usually makes hyperthermia effect insignificant[19]. This once again demonstrates that this is not a clinical trial but in vivo radiobiology experiment without clinical significance.

This impression is enforced by lack of proper survival analysis. Of course, survival analysis is a core for any clinical trial but not for radiobiological experiment. All known in this trial is that immediate local control in hyperthermia arm was better and remained better after 2 years, but it's still unknown, which overall survival was in both groups 2 years later. Overall, 5-year survival was 19% which is far worse than the average level for metastatic skin melanoma, but there is no answer to the main question – which survival was in TRT and RT arms and which group had a better survival rate? There is a very detailed survival analysis by local response, number of tumors, sex, even by general control of all diseases – everything except the primary goal of the trial, the survival by groups – and it looks like hiding the negative results. There is another reason to suppose that negative results in this trial are incompletely reported: for instance, there is not a word about burns, though these are obviously reported in other trials, and it is usually more than 30%.

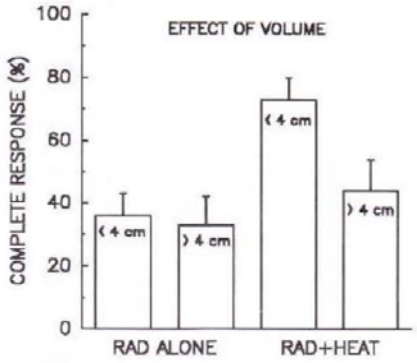


Figure 1. Effect of tumor volume on complete response rate (Overgaard et al., 1996[11])

It's also not clear, why 4 cm was used as a border for small tumor size? All the other randomized studies for superficial tumors used 3 cm as a border size, and this is absolutely correct because superficial tumors generally considered as so, if they are less than 3 cm deep. In RTOG 8104 trial[5], 77% of tumors were more than 3 cm. In Overgaard et al. trial, 63% of tumors were less than 4 cm and this distribution couldn't be compared with other trials because of the different criteria of tumor size. Therefore, it's impossible to say

exactly, whether there was pre-selection of small tumors in this trial. It was already known to that moment that TRT is significantly more effective in small tumors. The authors tried to prove that tumor size impact was statistically insignificant (p=0.21), but it seems to be not correct. As it's seen in Figure 1, the impact of tumor volume is much stronger in TRT arm, and the only reason why it's not statistically significant is the 4 cm limit. With a 3 cm limit, this difference would be higher and probably statistically more significant, as it is in other trials.

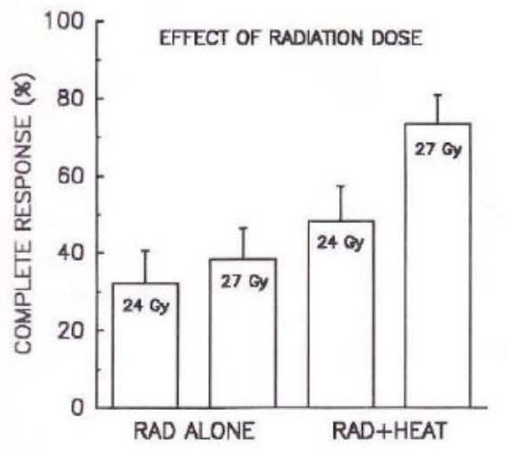


Figure 2. Effect of radiation dose on complete response rate (Overgaard et al., 1996[11])

Moreover, 2 different RT protocols with TD 24 and 27 Gy were used in the trial. There was no reason to include two RT protocols to examine HT efficacy: in this case all other factors should be equal. It's obvious that authors intended to show that thermal enhancement rises with the increase of TD (Figure 2) with subsequent extrapolation of the conclusion to the higher (normal) doses. This is an absolutely incorrect approach. The results of other trials show that with normal/high TD, the effect of thermal modification becomes insignificant or disappears[5,7,8,9] or even reverses[19], therefore the extrapolation is incorrect. RT strength in this trial was much higher than HT strength: CLR rate was 56% for 27 Gy vs. 25% for 24 Gy (Gain 124%, p=0.05), i.e. twice stronger than HT effect (Gain 64%). This also supposes that with rise of TD of RT, the relative thermal enhancement will diminish soon. The displayed thermal effect was rather the effect of single dose difference (9 Gy vs 8 Gy) than the effect of TD because the higher thermal effect to higher single doses is well-known in radiobiology. Finally, statistics do not look correct because the authors report only 1.17 odds ratio for RT versus 1.73 for HT.

The above mentioned is enough for drawing the conclusion:

- The trial is in fact in vivo radiobiological study without clinical significance.
- The trial seems to be especially designed for demonstration of hyperthermia efficacy to the detriment of practical value.
- The trial uses an incorrect comparator.
- The actual survival outcome of the study is hidden.
- Negative data seems to be reported incompletely.

Apparently, this is the reason why the study had no consequences: further studies on TRT of malignant melanoma are absent and there is not any clinical application. That is why we consider this trial result as dubious.

Characteristic	No HT (n = 52)		HT (n = 56)	
	No. of Patients	%	No. of Patients	%
Age				
Median	59.3	-7 years	52.4	
Range	38.4-83.8		18.2-90.9	
Sex				
Male	13		14	
Female	39		42	
Site of disease				
Breast/chest wall	33	63	37	66
Head and neck	6	12	8	14
Melanoma	6	12	5	9
Other	7	13	6	11
Multiple HT fields	7	13	18	32
Prior XRT	17	33	22	39
RT dose, Gy (given on protocol)				
Median	50	+10%	55	
Range	18-70		20-70	
Metastasis at enrollment	17 of 51	33	16 of 52	31
Additional systemic therapy	34	65	33	59
Hyperthermia dose, CEM 43°C T_{90}				
Median	0.74		14.3	
Range	0.07-1.49		0.57-36.21	

Abbreviations: HT, hyperthermia; XRT, external radiation therapy; RT, radiation therapy; CEM, cumulative equivalent minutes.

Table 2. Patient characteristic and treatment summary from Jones et al.[12] clinical trial

In 2005, the most famous and the most cited superficial hyperthermia study of EL Jones at al.[12] from Duke University was published. This trial deserves a very careful analysis because of its impact on hyperthermia application. This was a prospective, randomized, controlled, and monocentric study on 108 patients with superficial tumors of chest wall, neck nodes and melanoma. TRT with CEM43°C T90 =10-100 was studied versus fractionated RT alone (single dose 1.8-2 Gy, total dose 30-70 Gy). CLR was the main endpoint and it was significantly higher in TRT arm – 66.1% vs. 42.3% than in RT alone arm (p=0.02).

Even the first look at the patient characteristic (Table 2) reveals biases. The median age for TRT arm was 7 years less than for the RT only arm (52.4 vs. 59.3 years). Such difference is impossible with proper randomization for a more than 100 person sample. Incorrect randomization is a well-known defect of randomized trials. Some other points also suggest improper randomization: e.g., radiation dose in TRT arm was 10% higher. As it is shown above, 10% increase of RT dose in Overgaard et al.[11] trial led to 124% gain of 2 year local control rate. This improper randomization was further distorted by pre-selection of "heatable" patients: after test heating, 13 patients from 122 (11%) were considered "non-heatable" and didn't enter the trial. This pre-selection could not be considered as a defect if trial conclusion refers to "heatable" patients only, but it doesn't include such remark.

Factor	Value	Possible CLR Gain
Pre-selection of "heatable" patients	11%	+10%
Pre-selection of RT-resistant patients	36%	+10%
RT dose bias	10%	+50-100%
Median age	-7 years	Unpredictable gain
Tumor size	Unknown	+30-50%[5,7-9]
Total weight:		**>60%**

Table 3. Analysis of impact of biases in Jones et al[12] clinical trial

There is no tumor size data in the trial, though tumor size analysis is always present in any clinical trial as one of the major predictors of RT success. Taking into account the obvious defects of randomization, lack of tumor size data, pre-selection of "heatable" patients and slow enrollment (122 patients per 7 years, i.e. 1.5 patients per month), selection of patients with small tumors is highly probable. One more distortion factor is the high percentage of RT-pretreated patients (36%).

These patients were radioresistant: whereas in TRT arm their CLR rate was virtually equal (68.2% in pre-treated and 65% in not pre-treated), CLR rate in RT only arm was significantly lower in the pre-irradiated group (23.5% vs. 51%). Simple analysis shows that 36% share of RT-pretreated patients adds 10% difference in favor of TRT arm. This is not an obvious defect but well-designed trials usually exclude such known disturbing factors, enrolling either pretreated or not pretreated patients.

We tried to analyze the possible impact of all the above mentioned biases on CLR rate (see Table 3). The result shows that only accountable factors – pre-selection of "heatable" and RT-resistant patients and RT dose bias, – could add at least 60% to the effect in TRT arm, whereas the measured CLR gain in the trial is

57%. With regard to the known younger age of TRT arm and possible tumor size bias, the total impact of biases could be even stronger. In other words, it's possible that hyperthermia really didn't improve the radiotherapy effect but, vice versa, it worsened that. Taking into account the results of the previously reviewed trials, this conclusion doesn't look impossible.

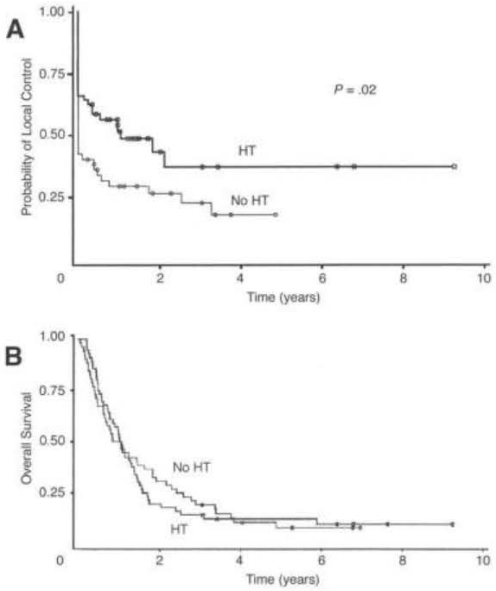
Local Control Rate (LCR) was the only positive (+57%) and statistically significant (p=0.02) effect of the study (see Figure 3, A). Long-term LCR is fully explained by initial LCR gain because the hazard of progression had become equal in both arms already in the 1st year (see Figure 3, C). Overall survival (see Figure 3, B) was the most disappointing endpoint: it was worse in TRT arm from the 1st year to the end of the trial, though statistically insignificant (p=0.84). With respect to known significant biases in favor of TRT arm, these results are threatening. This negative impression is further aggravated by attempts to hide the negative course of the trial. Table 4 is demonstrative in this respect. In fact, patients in TRT arm more patients died but with perfect local control (see Figure 3, A-B). In the table, a very favorable picture of better local control in TRT arm is shown but without detailed information which could spoil the impression. This is an obvious example of data manipulation. Finally, safety in this trial was the worst among all previous trials: 46% of burns, incl. 3% of 3rd degree; 11% of complications of catheterization, incl. 3% of grade 3 toxicity. 16% of patients had to pause the treatment due to toxicity.

Status	No HT (n = 52)		HT (n = 56)	
	No. of Patients	%	No. of Patients	%
Local recurrence				
Less than CR	30	58	19	34
Later failure	9	17	10	18
Death (without local treatment failure)	11	21	21	37
Alive with local control	1	2	5	9
Censored: additional local surgery	1	2	1	2

Abbreviations: HT, hyperthermia; CR, complete response.

Table 4. 2yr Local Control Status from Jones et al.[12] clinical trial

The authors' conclusion - "Adjuvant hyperthermia with a thermal dose more than 10 CEM 43°C T_{90} confers a significant local control benefit in patients with superficial tumors receiving radiation therapy", - seems irrelevant. We consider the result of the trial dubious. The observed local control benefit could be fully explained by the reported biases, and with regard to the biases survival gain in TRT arm seems to be negative.



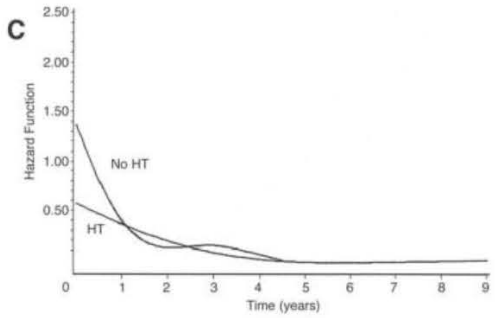


Figure 3. Clinical results of Jones et al[12] clinical trials. A – Probability of Local Control. B – Overall Survival. C – Hazard Function

In 2007, a paper of Jones et al.[13] was published advocating the use of hyperthermia as a radiotherapy sensitizer for treatment of chest wall recurrences: "Data from several randomized trials suggest that the addition of hyperthermia to radiation can increase the response rate for such local recurrences". The same year, the National Comprehensive Cancer Network (NCCN) included consideration of the addition of hyperthermia for women with recurrent locoregional advanced breast cancers after first-line surgery or if the radiation failed. The NCCN guidelines stated that, "while there is heterogeneity among the study results, a recent series with strict quality assurance demonstrated a statistically significant increase in local tumor response and greater duration of local control with the addition of hyperthermia to radiation compared to radiation alone (Jones et al., 2005[12])". The NCCN guidelines noted that the addition of hyperthermia generated substantial discussion and controversy among the NCCN panel members and is a category 3 recommendation (the recommendation is based upon any level of evidence but reflects major disagreement). The counterpoint was stated by B McCormick[14] from Department of Radiation Oncology of Memorial Sloan-Kettering Cancer Center who said: "Although HT in chest wall recurrences has been used for several decades, recent reports are few. Unresolved issues of radiation dose, optimal temperature and timing of HT, and quality assurance problems with thermometry are apparent from these studies. Although clearly an effective treatment option in this clinical scenario, more research on HT and radiation is needed before this treatment combination can be considered standard care".
Thus, from 7 reviewed randomized clinical trials on superficial hyperthermia, 4 are considered negative by the authors themselves (Perez et al.[5], Emami et al.[8], Kapp et al.[7] and Engin et al.[9]). Of the 3 remaining trials which are considered positive by their authors, Jones et al. trial was biased and dubious, Vernon et al. trial had incorrect design and controversial data and Overgaard et al. trial was not representative, it was biased and clinically insignificant.

These trials showed that superficial TRT is effective:
- for small tumors only (≤3 cm, thermal enhancement ratio (TER)=1.2-2) with no effect for big tumors (≥3 cm, TER=0.9-1.1);
- for those tumors only which are possible to heat adequately (20'≤Tmin 42.5°C);
- for 'heatable' tumors only;
- only with effective thermal control;
- with large RT fractions but much less effective or not effective with typical hyperfractionated protocols;
- only in special setting – HT shortly after RT.

Even in this setting, HT statistically significantly improves only the CLR rate (+30-60%) and the short-term local control rate (1-2 years). Total local control rate (complete + partial local remission) improvement and long-term local control rate (>2 years) are generally statistically insignificant. The major prognostic factors for duration of local control were tumor histology, then RT dose, then tumor size, then minimum temperature in the tumor (much less significant). The recent retrospective study of de Bruijne et al.[53] showed that with respect to tumor volume, thermal dose was not associated with any clinical endpoint. There is no influence on overall survival; sometimes it tends to be worse with HT[12]. Even these small and partial successes of superficial hyperthermia look clinically insignificant because small tumors represent smaller part (25-35%) of superficial tumors and could be easily ablated or removed by surgery (methods of choice). These are big superficial tumors, which are interesting for hyperthermia treatment, but it is ineffective in this regard. Major part of these tumors is hardly heatable because of localization, body shape, sensitivity, etc. Hard thermal control used in 'positive' clinical trials is impossible in clinical practice (for example, 24-channel thermometry is routinely used in Erasmus university HT center); bad thermal control

significantly reduces both efficacy and safety – up to reversal of the ratio. Hypofractionated RT protocols, which are optimal for thermal modification, are much less used in practice. Optimal sequence of RT and HT is hard or impossible to manage in real practice; suboptimal sequence makes the combination much less effective or ineffective. The level of toxicity (≥30% of burns), which is applicable in clinical trials, is impossible in clinical practice.

Conclusion on superficial hyperthermia:

- There has been no clear evidence of overall efficacy of hyperthermic radiotherapy modification of superficial tumors so far.
- Existing positive results are biased and/or clinically insignificant.
- Superficial hyperthermia is still an experimental treatment with limited applicability in clinical practice.

The conclusion of hyperthermia society opinion leaders is vague: "In a select group of patients, the addition of hyperthermia to radiotherapy increases the eradication of local tumor, with a modest increase in largely self-limited toxicity. While attainment of CR is a worthwhile study endpoint, one must also consider the need to address palliation of symptoms, in that the majority of these patients will ultimately succumb to their distant disease. In the modern era of 'targeted' therapy, the issue of local control will increasingly become more important. Future applications of hyperthermia combined with radiotherapy should include the addition of targeted biological agents in the hopes of increasing the CR rate and hopefully translating into prolonged disease-free survival. Liposomal doxorubicin has been combined with radiotherapy and hyperthermia by one group and warrants further evaluation in the future. Efforts must be taken to provide reproducible, efficacious heating of tumors so that the synergistic effect of combining radiotherapy and hyperthermia can be optimized. With rigorous thermal dosimetry and careful treatment technique, the addition of heat to radiotherapy can result in long-term local control of breast cancer chest wall recurrences"[15].

Having been translated from Aesopian language, this means that hyperthermic radiotherapy modification is effective only in a selected group of patients, and it causes primarily palliation of symptoms by improved local control without any effect to survival, because metastatic process is not affected by this treatment, and this local effect could be achieved only upon conditions of effective heating, rigorous thermal dosimetry and careful treatment technique, and hyperthermia increases the toxicity of the treatment, and its future application of TRT depends on the targeted biological agents which could increase its effect. Thus, this conclusion also contains a hidden confession of insufficient efficacy of superficial TRT of breast cancer and chest wall recurrences, and these limitations would keep hyperthermia far from clinical practice.

Clinical Trial		Emami et al.[16]	van der Zee et al.[17]			Mitsumori et al.[18]	Vasanthan et al.[19]	Issels et al.[20]	Harima et al.[28]
Sponsor		RTOG	Dutch Deep Hyperthermia Group			IAAE	IAAE	ESHO, EORTC, NIH	N/A
Year of publication		1996	2000			2007	2005	2010	2001
Enrollment period		1986-1992 6.5 years	1990-1996 6 years			1988-2002 3.5 years	1998-2002 3.5 years	1997-2006 9.5 years	1994-1999
Nr of patients		184 (173)	358			80	110	341	40
			114	143	101				
Age	HT+		51	62	73		50	51	65
	HT-		50	64	69		45	52	62
Tumor type		Deep-seated tumors of head & neck and pelvis	Loc. adv. cervical cancer	Loc. adv. rectal cancer	Loc. adv. bladder cancer	Locally advanced NSCLC	Locally advanced carcinoma of the uterine cervix	Soft tissue sarcoma	Loc. adv. cervical cancer
Pretreatment		Heavy: 84% RT, 45% surg, 34%ChT	No			No	No	No	No
Comparison		TRT vs. RT alone	TRT vs. RT alone			TRT vs. RT alone	TRT vs. RT alone	TChT vs. ChT in complex treatment	TRT vs. RT alone
Base treatment		EBRT TD ≤100 Gy	EBRT+BT TD=65Gy	EBRT TD 66-70 Gy	EBRT TD 66-70Gy	EBRT	EBRT + BT TD=84 Gy	ChT (EIA) → surgery → RT → ChT (EIA)	EBRT + BT TD=82.2 Gy
HT unit(s)		N/A	3 units: BSD2000, TEM, 4-guide			Thermotron-RF8	Thermotron-RF8	BSD2000	Thermotron-RF8
HT protocol		42.5°C x 30-60', 1 (before RT) or 2 (bef/aft RT) HTs	42°C x 60', 5 HTs after RT 1/week			42°C x 60', 5 HTs after RT 1/week	42°C x 60', 5 HTs after RT 1/week	42°C x 60', 16 HTs interval 3 days	42°C x 60', 3 HTs after RT 1/week

Complete Local Response (CLR)	HT+	CLR 55%	CLR 55% (p<0.001)			Statistically insignificant (p=0.49)		CLR+PLR=34% (p=0.02)	80%
			CLR 83%	St.insign.					
	HT-	CLR 53%	CLR 39% (p<0.001)					CLR+PLR=16% (p=0.02)	50%
			CLR 57%	St.insign.					
Overall Survival (OS)	HT+	34% (2 y)	51% (3y)			Statistically insignificant (p=0.868)	73.2% (3y) (p=0.19)	79 mnth (p=0.43)	58% (3y)
	HT-	33% (2 y)	27% (3y)					74 mnth (p=0.43)	48% (3y)
Local Progres-sion Free Survival (LPFS)	HT+					significantly better (p=0.036)	68.5% (3yrs) (p=0.58)	66% (4y) (p=0.003)	
	HT-							55% (4y) (p=0.003)	
Progression Free Survival (PFS)	HT+							32 mn (p=0.011)	
	HT-							18 mn (p=0.011)	
Common toxicity	HT+	3-4 Grade - 22%					17% Gr2, 1% Gr3	96.4% (p=0.005)	
	HT-	3-4 Grade - 12%					4% Grade 2	78.5% (p=0.005)	

Table 5. Randomized clinical trials on deep local hyperthermia published after 1990

Hyperthermia of deep-seated tumors

The phase III RTOG clinical trial on deep hyperthermia of Emami et al. was published in 1996[16]. This was a prospective, randomized, controlled, multicenter trial. 184 heavily pre-treated patients with deep-seated tumors of head & neck and pelvis were enrolled. TRT with HT 42.5°C for 30-60' applied after RT vs. RT alone (cumulative dose ≤100 Gy) was tested. CLR rate was 55% in TRT arm and 53% in RT only arm. 2-year overall survival was 34% in TRT arm and 33% in RT only arm. Acute 3-4 grade toxicity was 22% vs. 12% and late toxicity 20% vs. 12% in TRT and RT arms respectively. Thus, complete response rate increment was negligible and statistically insignificant; toxicity increment was substantial, both acute and late, but statistically not significant.

The authors concluded that "Interstitial hyperthermia did not show any additional beneficial effects over interstitial RT alone. Delivery of HT remains a major obstacle. The benefit of HT in addition to RT still remains to be proven in properly randomized prospective clinical trials after substantial technical improvements in heat delivery and dosimetry are achieved".[16]

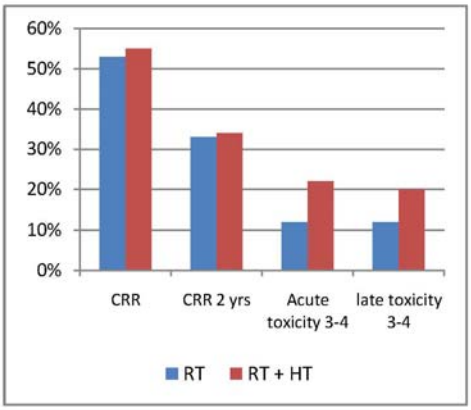


Figure 4. Clinical results of Ememi et al.[16] trial. (CRR – Complete Response Rate)

In 2000, Dutch Deep Hyperthermia Group (DDHG) published a prospective, randomized, controlled, multicenter phase III trial of Van der Zee J et al.[12]. 358 not pretreated patients were enrolled in 11 Dutch centers and randomized for TRT (182 patient) and RT only (176 patient). RT was applied as External Beam RT (EBRT) + Brachytherapy (BT) with total dose 65 Gy. 5 sessions of deep HT (42°C for 60' up to 90' of total time) was administered weekly 1-4 hrs after RT. CLR rate and Local Disease-Free Survival (LDFS) were the endpoints.

The trial included three sub-groups (see Figure 5.):

- Advanced cervical cancer 8114 patients)
- Advanced rectal cancer (143 patients)
- Advanced bladder cancer (101 patients)

Though overall CLR rate was statistically significantly increased in TRT arm (55% vs. 39%, p<0.001) and duration of local control in TRT arm was also significantly longer (p=0.04), there were great differences between the subgroups. There was no statistically significant effect in rectal cancer group, and OS in TRT

arm was worse there, though being statistically insignificant. In general, the result in rectum cancer group was negative. The bladder cancer result was better but the improved local control disappeared during the follow-up, and there was no effect to OS. In general, this result was dubious.

Cervix cancer group was the only one with statistically significant improvement of all CLR (83% vs. 57%, p=0.003), LDFS (3y LDFS 61% vs. 41%, p) and OS (3year OS 51% vs. 27% in RT only arm, p=0.009). Therefore, only cervix cancer results were further reported[21]. In 2008, Franckena et al.[22] published the impressive result of long-time follow-up: 12-year local control rate was 56% in TRT arm vs. 37% in RT arm (p=0.01); 12-year overall survival in TRT arm was 37% vs. 20% in RT arm (p=0.03). Median overall survival was 2.64 years in TRT arm vs. 1.78 years in RT arm. Local recurrence rate was 25% in TRT arm vs. 31% in RT arm. Distant metastases rates were the same in both arms (31% and 32%).

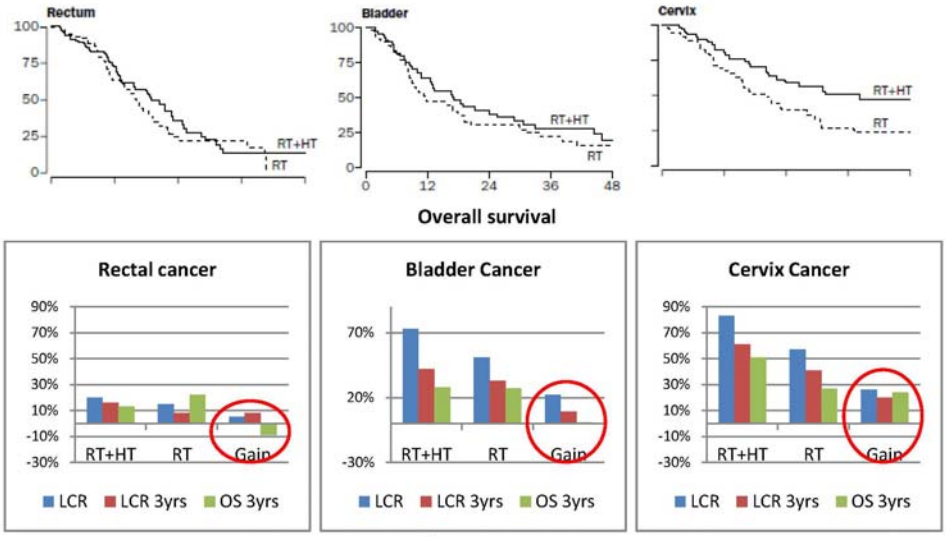


Figure 5. Clinical results of DDHG trial of Van der Zee J et al.[17]: LCR – Local Control Rate, OS – Overall Survival

First of all, interpretation of the trial result provokes disagreement. The statements like "in this trial, a beneficial effect from adding hyperthermia to standard radiotherapy was demonstrated, particularly for patients with cervical cancer"[23] or "the overall result showed a substantial benefit for whole group but only 114 patients with cervical cancer were included in the published reports of this trial"[24] are incorrect. In fact, beneficial effect was demonstrated only in cervical cancer sub-group. Results in the other two sub-groups were negative (rectal cancer) or dubious (bladder cancer).[25] Therefore, for correct analysis of trial results we consider it consisting of three sub-trials where only one was successful.

Secondly, it seems that the trial used incorrect comparator – RT with total dose 67 Gy vs. 75-95 Gy in successful RT trials. It's impossible to say which part of the TD was targeted to tumor mass in this trial because it's not specified. It's known only that "para-aortal nodes were routinely included in the external radiotherapy field"17, therefore TD to tumor mass was less than 67 Gy (estimated not more than 60 Gy). This point was widely criticized and authors' attempts to justify that the comparator look weak. The position that such dose "is considered adequate treatment"23 is unsatisfactory because it was not adequate but it was the best available or standard treatment is demanded by default for control treatment in a III phase trial. Inadequacy of low doses was obviously showed by Perez et al. trial26: in Stage III unilateral lesions, the 10 year pelvic failure rate was about 50% with ≤70 Gy to tumor mass versus 35% with higher doses, and in bilateral or bulky tumors it was 60% with doses ≤70 Gy and 50% with higher doses. Therefore, higher RT dose could add 25-30% and more to long-term local control rate and there is not any ground to consider total dose less than 70 Gy adequate, especially for control group in clinical trial. Combination of an external-beam RT (EBRT) with a brachytherapy (BT) with total dose of 75-85 Gy to tumor mass has been widely accepted since the mid-70s[26,27] whereas enrollment to DDHG trial started in 1990. Advocacy that the low dose was a consequence of the fact that not all patients received full RT is disproved by the study protocol. According to the protocol, EBRT was applied to whole pelvis by 23-28 fractions of 1.8-2.0 Gy to TD 46-50.4 Gy; then HDR BT 17 Gy in 42 patients or LDR BT 20-30 Gy in 49 patients was applied[17,21]. It follows that, at least in 42 patients TD couldn't exceed 67 Gy and in the other 49 patients it could vary in the range of 66-80 Gy. Therefore it seems that the really achieved TD of 67-68 Gy

is a planned target TD of the trial and not a result of a not full RT. Another attempt is to change the focus from the problem of insufficient RT dose to the general change of cervix cancer paradigm to chemoradiotherapy after the start of DDHG trial[25]. This is really true but it doesn't answer the question of RT dose inadequacy in any way. As it's obviously seen from Table 6, the clinical results in DDHG trial control (RT) group were 1.5-2 times worse than the best results available, and even much worse than the old results of Fletcher received in 1954-1963 on the very first megavolt linear accelerators with TD=90 Gy for IIIB stage. That is, it's evident that DDHG trial used incorrect comparator which is considered a serious bias.

The authors explain the worse clinical results by the relatively young age, bulky tumors and nodal involvement. The first reason is not convincing. Median age 50-51 is equal to age of the first diagnosis of cervix cancer in Northern Europe (50-52) and of necessity nearly equal to any other North-European study enrolling non-treated patients. Also, though in this trial the immediate CLR rate was better for older patients[21], other studies show that younger age is associated with better long-term results and survival[30,34]. Two other reasons look acceptable but not evident enough. Though the average tumor size in DDHG trial is really big, in terms of survival this is a significant factor for stage I but not for more advanced stages where parametria involvement and nodal status are significant[26,30]. Nodal involvement in DDHG trial, though seemed to be more extensive than in other trials (70% vs. 30-40%) was assessed in 44% of patients only[21], therefore it is not evident. To summarize, there are some grounds to consider DDHG sample more severe than in other clinical trials but it's not evident. Anyway, the use of stage of disease is valuable and correct for comparison (see Table 6.). And the question remains: why was a so gentle RT schedule used which is obviously inadequate to severity of the sample?

Trial	Van der Zee at al., 2000[17,21,22]		Harima et al., 2001[28]		Vasanthan et al., 2005[19]		Perez et al., 1998[26,29]	Nishiguchi et al., 1994[27]	Barillot et al., 1997[30]		Fletcher, 1968[31]	
Stage	TRT	RT	TRT	RT	TRT	RT	RT	RT	RT		RT	
Parameter	IIIB (IIB-IVA)		IIIB		IIIB (IIB-IVA)		III	III	IIIA	IIIB	IIIA	IIIB
CLR	83%	57%	80%	50%	80%			80%				
3y LDFS	61%	41%	80%	49%	68.5%							
3y OS	51%	27%	58%	48%	73.2%							
5y LDFS	61%	37%							65%	59%		
5y OS	41%	23%						47%	69%	48%	45%	36%
10y LDFS	61%	37%					68%					
10y OS	37%	20%					45%				36%	30%

Table 6. Comparison of clinical results of TRT trials with best results of only RT – trials for cervical cancer CLR – Complete Local Response, LDFS – Local Disease-Free Survival, OS – Overall Survival

However, the most impressive fact is that the clinical results in TRT arm of DDHG trial are also worse than the best results reported with RT only (see Table 6.) with total dose to tumor mass 75-90 Gy. As it was discussed above for Overgaard et al. trial, the use of low RT dose is convenient for radiobiological demonstration of hyperthermia effect but leads to clinical insignificance of any clinical trial. This is what we see in this DDHG trial: it's impressive in demonstration of low-dose radiotherapy modification but clinically insignificant because of low overall effect. As it's obvious from other hyperthermia trials, the effect of hyperthermic RT-modification becomes statistically insignificant or disappears completely in comparison with standard high-dose RT[5,16].

The inadequate comparator is not the only problem of the DDHG trial. There are also huge heterogeneity in RT and HT coupling, difference in the used HT-equipment, poor analysis and incomplete safety analysis. The trial combines data of two independent studies completed by Amsterdam Medical Center (AMC) and by University Hospital Rotterdam (UHR). Whereas the AMC trial was monocentric, the UHR collected patients also from 9 other RT-centers. As a result, if in AMC HT followed RT an hour later, in UHR the usual delay was 3-4 hours because of logistics. It's well-known that RT-modification time interval lasts not longer than 1.5 hours. Thus, there was an RT-modifying coupling in AMC but not in UHR, where concomitant instead of the combined treatment was applied. It seems that efficacy of such different applications should be quite different. The authors indirectly confess inapplicability of classic RT-modification criteria in this case: "Probably the main gain of hyperthermia is a direct effect on the hypoxic tumor cells. This extra cell kill will be clinically relevant in a small proportion of patients only, and studies of more patients are required to establish such an improvement"[17]. This coupling difference is further aggravated by the difference of the equipment used: it was BSD2000 system (BSD Corp., USA) in UHR, 4-

waveguide applicator system in AMC and TEM applicator in Utrecht (all being custom-built). There is not any comparison of the systems except of short phrase "for the three systems, similar energy distribution in human pelvic size phantoms has been demonstrated" [17]. Taking into account the significant difference in technologies (e.g., TEM applicator uses frequency range 10-80 MHz[32] whereas BSD2000 uses 80-120 MHz; these regions have very different properties), there is very low probability that these systems are clinically equal. But no publication on the trial contains separate analysis of efficacy and safety by centers or HT-units. There are no separate data about AMC and UHR, not even about the number of patients in these two trials. But such generalized data are useless from practical point of view because it's unknown, which type of application is effective in such wide range of application modes. It's even unknown, which temperatures were used in the trial because temperature analysis is absent. When Dahl and Mella[24] talk about thermometry data in DDHG trial, they just quote the data from another trial of Harima et al.[28], and this is an obvious confusion. It's also known from another source in Rotterdam (Fatehi, 2000[33]) that intratumoral temperature in cervix carcinoma with BSD2000 system never reaches 40°C, thus the 42°C stated in the trial protocol is a misinformation. Even the tumor-volume dependency analysis is missing which is vital in any HT-trial analyses. In fact, this trial is a 'black box': we know only the input and output parameters but we absolutely don't know 'how it works'. Thus, we don't know how to use it, and that is why DDHG trial is useless from practical point of view.

Additionally, safety analysis seems to be incomplete and biased. This is the only HT-trial which reports more 3-4 grade toxicity in TRT arm (2.2%) than in RT arm (5.9%), which is very dubious. At the same time, authors reports about 12% (20/170) of subcutaneous burns, which needed up to 2 weeks to heal; 3% (5/170) of skin burns, including 1 case (0.58%) of grade 2 burn and 2 cases (1.2%) of grade 3 burn, which demanded the interruption of HT-treatment; and 2 cases (1.2%) of severe deep burns of skin and subskin. Additionally, 'some' patients suffered from catheter-dependent infections17. Therefore, there were at least 18% (30/170) cases of HT-related toxicity which should cause the interruption of HT-treatment, whereas according to the authors' information, treatment was delayed only for 7 patients in TRT arm.
Refusal from treatment is one more source of safety information. It's reported that 41% of patients refused to undergo all 5 HT treatments, 25% received 1-3 treatments only, and 9% didn't receive any HT-session. It's declared that the main reason for refusal is that patients had known about "experimental nature of this treatment"[21]. This is quite a strange explanation because patients were recruited "after verbal informed consent had been obtained" 17, therefore the patients should have been initially informed about experimental nature of treatment; also this doesn't explain 9% of patients (16) who didn't receive any HT session at all. The most probable reason for not receiving HT-treatment is the toxicity. After all considerations, we assess HT-dependent toxicity near 30% with HT-limiting toxicity not less than 10%. These data are hidden.

Therefore, our conclusion on DDHT trial is as follows: Of three DDHT sub-groups, rectum results were clearly negative, bladder results were dubious and only cervix arm showed statistically significant response. This response was received despite the use of an inadequate comparator and was worse than those reported in the best trials with RT only, including long-time control and survival. The study design does not allow speaking about TRT, rather about the HT and RT co-treatment. Poor data presentation and analysis don't allow to understand the reasons of the study results. Toxicity analysis is incomplete. The results of the trial are clinically insignificant and practically inapplicable.

Shortly after the DDHG trial, a small Japanese trial of Harima et al.[28] was published in 2001. It was a prospective, randomized, controlled, and monocentric trial. Between 1994-1999 40 patients with FIGO stage IIIB cervical cancer were enrolled and randomly allocated for TRT and control RT group with 20 patients in each group. RT was applied with 6MV EBRT and iridium-192 HDR BT to TD 82.2 Gy. Hyperthermia was applied within 30 minutes after RT session by Thermotron RF8 capacitive system with the output power of 800-1500W. The trial showed excellent results in favor of TRT arm: CLR rate was 80% in TRT arm vs. 50% in RT only arm, 3 year LDFS and OS were significantly better in TRT arm (80% and 58% respectively) than in RT only arm (49% and 48% respectively).

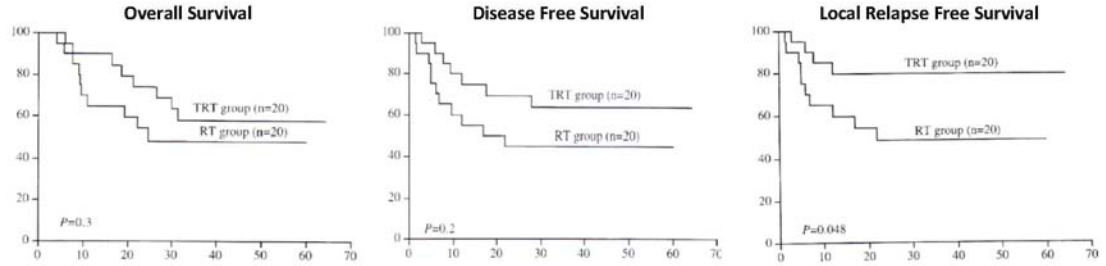


Figure 6. Survival data of Harima et al. clinical trial[28]

The trial stands apart from other trials and is unique in many respects. First, authors calculated the minimum volume of the sample (2x20 patients) from the hypothesis that TRT would give 80% of CLR versus 50% in Rt only. Then, they received the exact as planned result (80% and 50%) with the planned sample volume. Such exact coincidence of trial plan and result is really unique. Secondly, the sample of the trial was the oldest of all mentioned trials: mean age in TRT group was 64.9 years, and these were previously untreated patients. It's very uncommon because according to Ioka et al.[34] trial made on 8966 cases of cervical cancer diagnosed between 1975–1996 (Harima et al. enrolled patients between 1994-1999) who lived in Osaka Prefecture of Japan, the average age in time of the first diagnosis was 54.6 years. It seems that it's hard enough to obtain 10 years older sample of first time diagnosed patients randomly. Thus, pre-selection of aged patients is obvious. The reported fact that local control after TRT is significantly better in older patients[17] could be a reason for selecting such an older sample. At the same time, the average tumor volume in this trial was at least 1.5 times less compared to DDHT trial though the stage of the disease is the same and both trials enrolled previously not treated patients. Moreover, in Harima et al. trial the patients were 14 years younger (64.9 vs 51 years) than in TRT group of DDHT trial. It's well-known that effect is higher for smaller tumors. Third, though TD 82.2 Gy seems to be adequate, in fact it's not so. TD to tumor mass was only 60.6 Gy (30.6 Gy EBRT to whole pelvis and 30 Gy of BT to point A), while 21.6 Gy dose was applied to parametria with central shielding. Therefore, TD to tumor mass was nearly the same as in DDHG trial, but OS in RT group was much better than in DDHG trial (3y OS 48% vs. 27%, 5y OS 48% vs. 23% respectively) and was on the level of the best RT-only trials with TD 75-85Gy to tumor mass (see Table 6.), and it's also amazing. Effect of low-dose comparator and clinical significance of such comparison were discussed above. And, at last, the mentioned trial of Ioka et al.[34] showed that older age is associated with much lower survival: relative 5-year survival for cervical cancer was 88.6% in <30 years, 78.1% in 30–54 years, 67.7% in 55–64 years and 54.4% in 65+ years. In Harima et al. trial, 65-old sample had much higher survival than 15 years younger sample with 1.5 times less tumors in DDHG trial (see Table 6.), and this is once again amazing. We didn't find any reproduction of Harima RT-results with respect to its unique features.

So, there is the unique (not reproduced) small chamber trial made on pre-selected aged sample (10 years older than expected) and with low enough RT dose to tumor mass (60 Gy only, inadequate comparator), but with good result, which is better than in the 15 years younger comparator (van der Zee et al.), and is statistically significant in spite of the extremely low sample (20+20), and this result coincides with the study hypothesis in each and every point. This is an alarming result.

The trial seems to be specially designed to show the effect of TRT like it was shown earlier in the Overgaard et al.[11] trial: much older patients (+10-15 years) and low-dose TD to tumor mass (60.6 Gy) as a comparator with exact RT-HT coupling, and high-dose RT (21.6 Gy) to parametria. Older age and low-dose RT comparator could explain statistical significance of differences. Large dose to parametria, on the one hand, masks inadequacy of the RT-comparator because the total dose 82.2 Gy looks adequate, and, on the other hand, markedly improves overall survival (is improved in both RT and TRT arms compared to van der Zee trial), which is significant because older age favors better local control but doesn't contribute to better survival[34]. To summarize, the trial with so many amazing features should be made on much larger sample and preferably should be reproduced in independent trials for evidence. Until confirmation, the significance of Harima results should be considered as dubious.

It is a reproduction of the effect which is the main problem of Harima et al. trial evidence, because the attempt to reproduce its result was disappointing. In 2005, clinical trial on cervical cancer of Vasanthan et al.19 was published. This was a prospective, randomized, controlled, multicenter phase III trial sponsored

by International Agency of Atomic Energy. Between 1998-2002 110 patients with FIGO IIb-IVa stage of cervical cancer were enrolled in 5 centers in 4 countries. The OS at 3 years was 73.2%, and the local control rate was 68.5%. There were no significant differences between the patients treated with RT and TRT, either with regard to the OS ($p = 0.1893$) or to the rate of local control ($p = 0.58$). At the same time, OS was significantly worse in patients with stage IIb disease in TRT arm ($p = 0.0162$) however, there was no difference in their rate of local control ($p = 0.7988$). Acute Grade 2-3 toxicity was seen in 18% of patients in TRT arm and in 4% in RT arm ($p = 0.01$). Authors concluded that "this study failed to show any benefit from the addition of hyperthermia to radiotherapy in the treatment of locally advanced carcinoma of the uterine cervix". It's important to note that Vasanthan et al. study had an intermediate design between DDHG and Harima trials: HT was performed in patients with IIb-IVa stage disease with the average age of 50 years, in average 5 times (like in DDHG trial) 1/week by Thermotron RF8 units just after RT (like in Harima trial).

It's interesting to analyze the results of cervical cancer hyperthermia studies because there are many trials which make such analysis possible. It's also interesting because cervical cancer really looks thermosensitive. There was success in cervical cancer treatment, which started an interest in hyperthermia in oncology. In 1898, Swedish gynecologist F Westermark[1] published a report on use of long-term (48 hours) local (by virtue of intravaginal metal coil heated with circulated water to 42-44°C) and regional (hot tubs) hyperthermia for treatment of various gynecological diseases. He described several excellent results in inoperable cancer of the cervix. It was the first time when the ability of long-term heating to destroy tumors without damaging of healthy tissues was shown. Gottschalk[35] in 1899 confirmed the success of hyperthermia in cervical cancer. Thus, it is not amazing that at the end of XX century the center of oncologic hyperthermia application returned to cervical cancer.

Authors	Publ.	Country	Type	Design	Nr of patients	Heating	CLR		LPFS		OS		Assessment	
							TRT	RT	TRT	RT	TRT	RT	Authors'	Our
Datta et al.[36]	1987	India	Monocenter	TRT vs. RT	52	Convect.	74%	58%	NR	NR	NR	NR	Positive	NA
Sharma et al.[37]	1989	India	Monocenter	TRT vs. RT	50	Convect.	NR	NR	70%	50%	NR	NR	Positive	NA
Chen et al.[38]	1997	China	Monocenter	TRT vs. TChRT vs. ChRT vs. RT	120	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Negative	NA
Van der Zee et al.[17]	2000	Netherlands	Multicenter	TRT vs. RT	114	EM	83%	57%	61%	41%	27%	51%	Positive	Dubious
Harima et al.[28]	2001	Japan	Monocenter	TRT vs. RT	40	EM	80%	50%	80%	49%	58%	48%	Positive	Dubious
Vasanthan et al.[19]	2005	India-S.Korea-Ukraine-China	Multicenter	TRT vs. RT	110	EM	80%		69%		73%		Negative	Negative

Table 7. Available randomized clinical trials on TRT of cervical cancer

TRT – thermaradiotherapy, RT – radiotherapy, TChRT – thermochemoradiotherapy, ChRT – chemoradiotherapy, N/A – Not Available, NA – Not Assessed, NR – Not Reported, EM – Electromagnetic, Convect. – Convectional

We've found six randomized trials on TRT of cervical cancer (see Table 7). Among them, two early Indian trials of Datta et al. and Sharma et al. were not assessed because they used intravaginal convectional heating, which is clinically insignificant method; additionally, they were too small and reported better local control without effect to survival. The trial of Chen et al. is in Chinese which is a problem. But its result is negative in terms of TRT: the authors reported that of 4 subgroups in this trial, only combination of RT, ChT and HT had shown significant improvement, whereas differences between all other 3 groups (RT only, TRT and ChRT) were not significant. Because of the absence of translation, we haven't included Chen et al. trial in the final record (see Table 14.).

Design and results of the three remaining trials have already been analyzed above and summarized in the table below.

	Harima et al., 2001[28]		Vasanthan et al., 2005[19]		Van der Zee et al., 2000[17]	
Country	Japan		India, S. Korea, China, Ukraine		The Netherlands	
Centers	1		5		11 (2 subtrials)	
Enrollment period	1994-1999 (5y)		1998-2002 (4y)		1990-1996 (6y)	
Submitted for publication	2000 (+1)		2003 (+1)		1999 (+3)	
	TRT arm	**RT arm**	**TRT arm**	**RT arm**	**TRT arm**	**RT arm**
Patients characteristics						
Prior treatment	Not pretreated		Not pretreated		Not pretreated	
Age	64.9	61.6	50	45	51	50
Number of patients						
Total	40		110		114	
By groups	20	20	55	55	58	56
FIGO stage						
IIb			29 (52.7%)	27 (49.1%)	11 (19.0%)	11 (19.6%)
IIIa			6 (10.9%)	3 (5.5%)	0 (0.0%)	1 (1.8%)
IIIb	20 (100%)	20 (100%)	19 (34.5%)	23 (41.8%)	40 (69.0%)	40 (71.4%)
Iva			1 (1.8%)	2 (3.6%)	7 (12.1%)	4 (7.1%)
Tumor characteristics						
Size	5.9	6.1	[4.6]	[4.9]	[7.1]	[7.0]
Volume	[107]	[118]	49.5	60.3	[187]	[179]
Histology						
Squamous cell carcinoma	17 (85.0%)	18 (90.0%)	52 (94.5%)	51 (92.7%)	51 (87.9%)	46 (82.1%)
Adenocarcinoma	3 (15.0%)	2 (10.0%)	1 (1.8%)	3 (5.5%)	4 (6.9%)	7 (12.5%)
Other			2 (3.6%)	1 (1.8%)	3 (5.2%)	3 (5.4%)
Hyperthermia						
Nr of sessions						
0			>0%		7 (12.1%)	
1-3					11 (19.0%)	
3	20 (100%)					
3-7			<100%			
4-6					40 (69.0%)	
Technology						
HT-system	Thermotron RF8		Thermotron RF8		BSD-2000 TEM 4-waveguide	
Technology	Capacitive		Capacitive		APAS, TEM, 4-WG	
Outside heating	100%		100%		100%	
Intracavitary heating			49%			
Frequency	8 MHz		8 MHz		10-120 MHz	
HT treatment parameters						
Power	800-1500W		450-?W		N/A	
RT-coupling	30' after RT		just after RT		1-4 hr after RT	
Heating period	20'		[20']		<30'	
HT-period	60'		60'		60'	
HT sessions	3		5		5	
Frequency	1/week		1/week		1/week	
Thermal control						
Thermosensors	Intratumoral		Intratumoral & Intraluminar		Intraluminar	
Measuring points	4-point		2-point (IL+IT)		1 point	
Measurement	100%		~2.5 times per course		Only part of sessions	
Tmax	41.8		42.1		N/A [40.0][33]	
Tave	40.6		41.6		N/A [39.5][33]	
Tmin	39.6		41		N/A	
Radiotherapy						
Coverage	100%		N/A [90%?]		98%	96%
Total dose (TD)	82.2 Gy		≈84 Gy		68 Gy	67 Gy
to tumor mass (TMD)	60.6 Gy		≈72 Gy		N/A (<68 Gy)	N/A (<67 Gy)
External-beam Radiotherapy (EBRT)						
Technology	6MV		6-18 MV (>70%), ^{60}Co (<30%),		Linear accelerators	
Single dose	1.8 Gy		2 Gy		1.8-2.0 Gy	
Total dose	52.2 Gy		≈62 Gy		46-50.4 Gy	
to whole pelvis	30.6 Gy		≈50 Gy		N/A (<46-50.4 Gy)	
to pelvis wall	21.6 Gy		≈12 Gy		N/A	
Brachytherapy (BT)						
High-dose-rate (HDR)	100%		49%		33%	
Low-dose-rate (LDR)			51%		46%	
Coverage	100%		N/A		79% (for others EBRT boost was used)	
single dose	7.5 Gy					
total dose	30 Gy		22 Gy		17 Gy (LDR), 20-30 Gy (HDR)	
BT % TD/TMD	37%/50%		26%/30%		25-44%	
Clinical results						
CLR	80%	50%	80%		83%	57%
LDFS 3y	80%	49%	69%		61%	41%
OS 3y	58%	48%	73%		51%	27%

Table 8. Analysis of available randomized clinical trials on TRT of cervix cancer

Vasanthan et al. trial, despite the negative results for TRT arm, had an excellent common result: CLR rate 80%, 3y LDFS 69% and 3y OS 73%. As it's seen from Figure 7, Vasanthan LDFS was average between Harima and van der Zee but OS was much better. It's very demonstrative that OS in TRT arm in all three trials was close enough but OS in RT only arms was very different (79% vs. 48% and 27%, respectively).

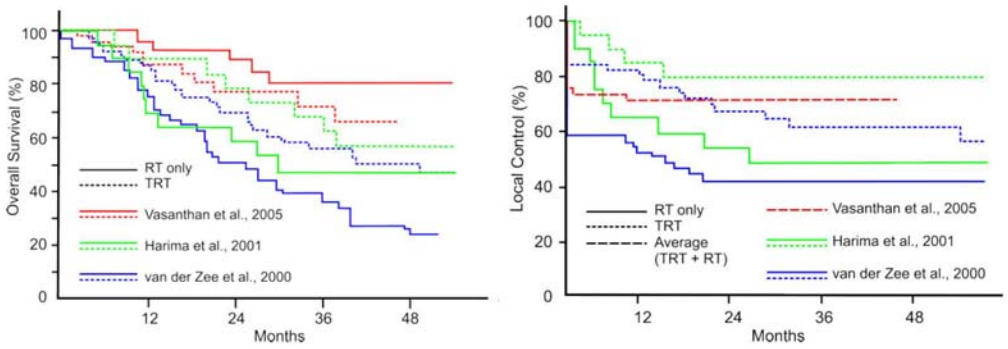


Figure 7. Comparative results of cervical cancer trials

There were two principal differences between Vasanthan trial on the one hand and Harima and van der Zee trials on the other hand: RT dose and tumor volume. In Vasanthan trial, dose to tumor mass was near 72 Gy (with TD=84 Gy), i.e. 20% more than in both Harima and van der Zee trials (TD≈60 Gy). The pattern of these three trials is rather typical: TRT versus low-dose RT gives significant effect, and it's not effective versus high-dose RT.

The second principal point is the tumor volume. As it's seen from Table 8, tumor volume in Vasanthan et al. trial (50-60 cm^3) is two times less than the estimated tumor volume in Harima et al. trial (107-118 cm^3), and is three times less than the estimated tumor volume in van der Zee et al. trial (179-183 cm^3). This is absolutely natural because 50% in Vasanthan trial were patients with IIb stage whereas there were only IIIb stage patients in Harima trial and in van der Zee trial patients could also be considered IIIb stage because IIb and IVa patients were counterbalanced. As anticipated, smaller tumor size led to better local control in Vasanthan et al. trial contemporary to van der Zee at al. trial (see Figure 7.) (the local control in Harima trial seems to be even better but the above-mentioned specificity of the trial design could easily explain it). Local control rates for IIb stage patients were also better than in IIIb stage patients (see Figure 8.). But – suddenly, - the overall survival rate in IIb stage patients was higher and significantly worse compared to both IIIb subgroups and RT control (p=0.016) (see Figure 8.). Therefore, it seems that smaller size is associated with better local control but also with much worse survival rates. Vasanthan et al. didn't analyzed the reasons of enhanced mortality in IIb stage patients saying just "further analysis is necessary to determine if the difference in survival is due to a greater incidence of distant metastases or some other cause"[19]. Significantly higher incidence of distant metastases after TRT (17.3% (4/23) vs. 4.3% (1/23) in RT group) has already been reported earlier by Sharma et al.[37] and it's known also that this trial included both II and III stage patients. It could be hypothesized therefore that in smaller tumors with relatively higher initial perfusion, hyperthermia-induced increase of blood flow could enhance tumor dissemination. On the other hand, neither DDHG[22] nor Harima et al.[28] reports higher metastases rates in TRT group, but they enrolled predominantly advanced stages of the disease (IIIB-IVA).

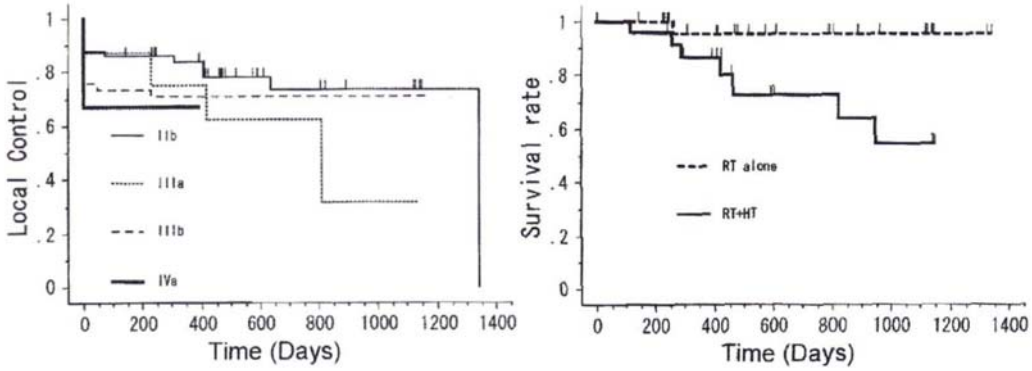


Figure 8. Local control and survival in FIGO IIb stage patients in Vasanthal et al.[19] trial

In 2007, a prospective, randomized, controlled, multicenter phase III trial of Mitsumori et al.[18] made on 80 patients with non-small cell lung cancer (NSCLC) was published. In fact, Vasanthan and Mitsumori trials were two arms of one IAAE sponsored trial. The result was the same: difference between CLR and OS rates in TRT and RT arms was statistically insignificant (p=0.49 and p=0.868, respectively), though Local

Progression Free Survival was significantly better in TRT arm (p=0.036). The authors concluded that "although improvement of LPFS was observed in the RT+HT arm, this study failed to show any substantial benefit from the addition of HT to RT in the treatment of locally advanced NSCLC".

The most recent and the most fundamental randomized trial on deep hyperthermia was published by RD Issels et al.[20] in 2010. This prospective, randomized, controlled, multicenter III phase trial was sponsored by European Society for Hyperthermic Oncology (ESHO), European Organization for Research and Treatment of Cancer (EORTC), US National Institute of Health (NIH), German Cancer Society, Helmholtz Association and private sponsors. 341 patients with localized high-risk soft tissue sarcomas (STS) (≥5 cm, FNCLCC grade 2 or 3, deep to the fascia) were enrolled at nine centers in Europe and North America for 9.5 years (1997-2006). The trial was designed to study HT efficacy in complex treatment of STS by the most effective protocol: neoadjuvant chemotherapy (NAChT) → definitive surgery → adjuvant RT → adjuvant chemotherapy (AChT). Chemotherapy (ChT) was applied by EIA protocol (etoposide 125 mg/m^2 and ifosfamide 1500 mg/m^2 x 4 days + doxorubicin 50 mg/m^2 on Day 1) in 8 cycles: 4 before surgery and 4 after RT. 169 patient were randomly assigned to receive thermochemotherapy (TChT) instead of ChT. Regional HT (42°C x 60') by virtue of BSD-2000 hyperthermia units were applied on the 1st and 4th day of each ChT cycle. The following results were reported: there was no effect to overall survival (median survival was 79 month in TChT arm vs. 74 month in ChT arm, p=0.43) but short-term local response rate (CLR + PLR) was twice higher in TChT arm (34% vs. 16%, p=0.02), and Local Progression Free Survival (LPFS) was significantly enhanced in TChT arm (32 months vs. 18 months (p=0.011); 76% vs. 61% after 2 years (p=0.003) and 66% vs. 55% after 4 years (p=0.003)).

Unfortunately, careful analysis of the trial gives disappointing results. There is a systematic bias in favor of TChT arm. 5 possible points of possible distortions were identified: Tumor Size, Grade of Disease, Surgery, RT and ChT. All the points were distorted to various extent but unidirectionally in favor of TChT arm, which forms obvious systematic bias. We've attempted to estimate the possible distortion which could be caused by this systematic bias (see Table 9.). The method of estimation is as follows. 'Δ%' is a relative increment of every parameter calculated as a difference between percentages of the parameter for TChT and ChT arms (or the value of the parameter if there is no percentage) divided by the percentage (value) of the less parameter. The impact of a parameter is considered 'direct' if its increase adds to the effect of the treatment, otherwise a parameter has 'reverse' impact. 'Weight' of a parameter is calculated as the sum of patients involved in the parameter assessment in both arms divided by the total number of patients on the sample (341), and represents an impact of this parameter on the general sample. Final distortion ('Dist%') is calculated as a product of 'Δ%' and 'Weight', therefore representing a parameter increment corrected for its weight. Distortion is considered positive if it favors the TChT arm. It's obvious that every parameter has different strength of impact on treatment effect but we didn't do any correction because of its subjectivity. Also, every parameter was assessed by minimum value. For instance, the impact of tumor size, not the tumor volume was assessed, though this 2.7% difference of tumor size means 8.4% difference of tumor volume.

	Arm →	TChT		ChT		Distortion (→TChT)		
	Pat Nr →	Nr	%	Nr	%	Δ%	Weight	Dist%
Factors	Impact ↓	169	49,6%	172	50,4%			
General Factors								
Tumor Size	Reverse	11		11,3		2,7%	100%	2,7%
3 Grade	Reverse	84	49,7%	94	54,7%	10,0%	52%	5,2%
Total						**12,7%**		**7,9%**
Chemotherapy								
Number of ChT-treated	Direct	165	97,6%	167	97,1%	0,6%	97%	0,5%
Median Nr of cycles	Direct	8		5		60,0%	97%	58,4%
Total						**60,0%**		**59,0%**
Surgery								
Overall Surgery (including previous)	Direct	155	91,7%	154	89,5%	2,4%	91%	2,2%
Definitive Surgery	Direct	104	88,9%	102	81,0%	9,8%	60%	5,9%
Measurable Disease without Surgery	Reverse	13	11,1%	24	19,0%	71,4%	11%	7,8%
R0 Surgery + Amputation	Direct	60	35,5%	51	29,7%	19,7%	33%	6,4%
R1 Surgery	Reverse	35	20,7%	36	20,9%	1,1%	21%	0,2%
R2 Surgery	Reverse	9	5,3%	14	8,1%	52,8%	7%	3,6%
Total						**154,9%**		**23,9%**
Radiotherapy								
Nr of Radiotherapies	Direct	108	63,9%	106	61,6%	3,7%	63%	2,3%
Radiotherapy Average Dose	Direct	53,2		52,7		0,9%	63%	0,6%
Total						**4,6%**		**2,9%**
TOTAL:								**93,7%**

Table 9. Estimated distortion of Issels et al.[20] trial results caused by impact of systematic bias

Thus, every parameter of the estimation favors to TChT arm: tumor size (+2.7%), grade of STS (+5.2%), RT (+2.9%), surgery (+23.9%) and ChT (+59%). In surgery, every sub-parameter is also distorted in favor of TChT arm: overall number of patients who underwent surgery, including previous surgery (+2.2%), number of definitive surgeries in this trial (+5.9%), number of patients with measurable disease left without surgery (+7.8%), R0 surgery and amputation (+6.4%), R1 (+0.2%) and R2 (+3.6%) surgeries. It can be assumed that higher percentage of R0 surgery in TChT group is caused by the success of neoadjuvant (induction) treatment but the success of induction treatment also could be contributed to the impact of systematic bias rather than an effect of HT (see Table 10) because total weight of induction distortion is higher than the received effect (18.5% vs. 8.5%). In turn, impact surgery is only a smaller part of the total distortion, which exceeds 90% and greatly overweighs the received increment of LPFS (11-15%).

	Arm →	TChT		ChT		Distortion (→TChT)		
	Pat Nr →	Nr	%	Nr	%	Δ%	Weight	Dist%
Factors	Impact ↓	169	49,6%	172	50,4%			
General Factors								
Tumor Size	Reverse	11		11,3		2,7%	100%	2,7%
3 Grade	Reverse	84	49,7%	94	54,7%	10,0%	52%	5,2%
Total						**12,7%**		**7,9%**
Chemotherapy								
Number of ChT-treated	Direct	165	97,6%	167	97,1%	0,6%	97%	0,5%
4 cycles	Direct	151	89,3%	146	84,9%	5,3%	87%	4,6%
1-3 cycles	Reverse	14	8,3%	21	12,2%	47,4%	10%	4,9%
0 cycles	Reverse	4	2,4%	5	2,9%	22,8%	3%	0,6%
Total						**76,0%**		**10,6%**
TOTAL:								**18,5%**
Immediate Local Response								
No Measurable Disease	Direct	52	30,8%	46	26,7%	15,1%	29%	4,3%
Measurable Disease	Reverse	117	69,2%	126	73,3%	5,8%	71%	4,1%
Total						**20,9%**		**8,5%**

Table 10. Estimated distortion of neoadjuvant (induction) treatment results of Issels et al.[20] trial

It's absolutely obvious that with such significant systematic bias, the effect of the trial cannot be attributed to HT, and it's impossible to exclude that without HT the result in this arm would be even better because HT treatment was associated with high toxicity.

Analysis of toxicity (see Table 11.) shows that toxicity in TChT group increased drastically: general toxicity was 3 times higher (225% vs. 78.5%) and severe toxicity was 20 times higher (24% vs. 1.2%) than in ChT arm. It is especially significant to note that this huge rise of toxicity was minimally conditioned by potentiation of ChT toxicity (factor 1.2-1.5). The major part of toxicity was the own toxicity of hyperthermia: thermometry complications, burns, tissue necrosis, pain, pressure of the bolus and others. In this regard, the authors' conclusion looks irrelevant: "Our results indicate that regional hyperthermia combined with the three-drug-regimen EIA can be given safely with moderate toxicity".

Impact of this 'moderate toxicity' to the course of the trial could be traced. During induction treatment, full HT treatment (7-8 sessions) was performed at 76% patients, 20% of patients received 1-6 sessions and 4% of patients didn't receive any session. During adjuvant HT, full HT treatment was performed at 36% patients, 17% of patients received 1-6 sessions and 38% of patients didn't receive any HT session. Authors declared toxicity as the only reason for non-receipt of the HT treatment. Therefore, this 'moderate' toxicity was HT-limiting in 24% of untreated patients and 55% of impaired patients (factor 2.3). Critical toxicity which forces to cancel HT-treatment became 9,5 times higher (4% to 38%) in impaired patients. This level of toxicity could be unacceptable for clinical practice

Parameter	TChT		ChT	
	total	severe	Total	severe
Common toxicity	96,40%	1,80%	78,50%	1,20%
Thermometry complications	4,30%	1,20%	-	-
Burns	18,40%	0,60%	-	-
Pain	44,80%	4,30%	-	-
Tissue necrosis	6,80%	2,50%	-	-
Pressure of the bolus	31,30%	4,90%	-	-
Other	22,70%	8,60%	-	-
	224,70%	23,90%	78,50%	1,20%
	x3	**x20**		

Table 11. Analysis of toxicity in Issels et al.[20] trial

Finally, we compared the clinical results of the trial with data of Sarcoma Meta-analysis Collaboration (SMAC)[39]. The data are derived from 14 randomized trials made between 1973-1990 on 1568 patients with high-grade sarcomas of extremities and trunk. All the patients had definitive surgery followed by adjuvant RT (47%) and adjuvant doxorubicin-based ChT (100%). Compared to Issels et al. trial, this sample had 14% more STS of extremities (58% vs. 44%), 10% more surgeries (100% vs. 90%), 16% less RT (47% vs. 63%) and didn't have neoadjuvant ChT (see Table 12.). The overall impact of all distortions could be considered as nearly equal.

Factor	Issels[20]	SMAC[39]	Distortion
STS of extremities	44%	58%	14%
Surgery	90%	100%	10%
RT	63%	47%	-16%
Neoadjuvant ChT	97%	0%	-97%
Adjuvant ChT	58%	100%	42%
Total:	**352%**	**305%**	**-47%**

Table 12. Comparison of distortion factors of SMAC and Issels et al. samples

Figure 9. demonstrates that clinical results of Issels et al. trial are uniformly worse than SMAC results. The most impressive fact that even the best results in TChT arm are worse than SMAC results in control arm, despite the fact that this arm didn't have ChT at all. Therefore, the clinical value of Issels et al. result is minor. Thus, it could be concluded that after correction to systematic bias, long-term effects of the Issels et al. trial is dubious and clinically insignificant. Toxicity level of the treatment is unacceptable for clinical practice. But according to the authors' opinion, "regional hyperthermia combined with preoperative or postoperative chemotherapy should be considered as an additional standard treatment option for the multidisciplinary treatment of locally advanced high-grade STS"[40]. This is an extremely doubtful conclusion.

It should be noted that systematic bias of Issels et al. trial was not intended and it was not incorporated in the design of the study initially. In fact, the trial has a brilliant design and is excellently reported. It seems that the problem of the study is rather a common problem of all prospective trials, when investigators pay excessive attention to the study group and much less attention to the control group. As a result, the volume of treatment in control group could decrease so much that the groups become incomparable. Taking into account the hard and complex protocol of Issels trial, its multicenter design, large sample size and long term of the trial, this defect was virtually inevitable. Probably, they designed 'the most effective' treatment protocol which appeared too hard to fulfill. Anyway, this is not an excuse for investigators who just didn't notice this great systematic bias when reporting the results (defect of interpretation).

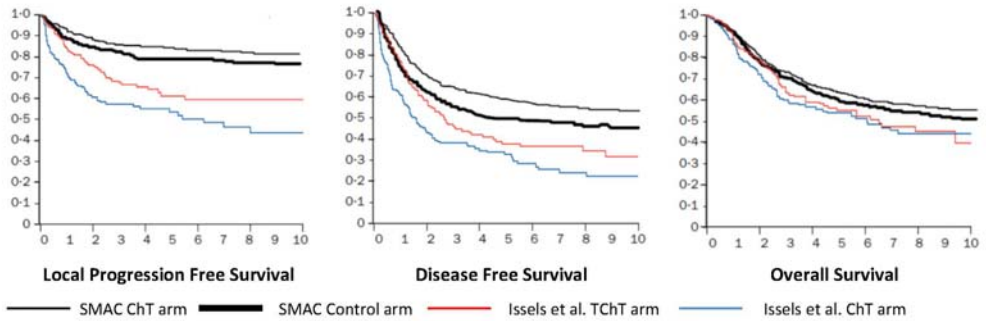


Figure 9. Comparison of clinical results of Issels et al.[20] trial (1997-2006) and SMAC[39] meta-analysis (1973-1990)

As a conclusion, hyperthermia of deep-seated tumors could be effective only versus inadequate comparator. In correct design of a trial, hyperthermia is not effective et all or not effective enough to prove its obvious disadvantages: toxicity and labor-intensity. Clinical efficacy of hyperthermia of deep-seated tumors is still not proven in randomized trials.

Authors	**Bakhshandeh et al. 2003[41]**	**Bakhshandeh et al. 2004[42]**	
Phase	II	III	
Design	Prospective, monocenter, single-arm	Prospective, randomized, controlled	
	TChT	TChT	ChT
Whole-body hyperthermia	Extreme		
Interval between sessions	3-4 weeks		
Number of procedures	4		
Temperature on plateau	41.8°C		
Time on plateau	60'		
Heating method	IR-C		
Unit	Aquatherm		
Anesthesia	IV deep sedation		
Artificial ventilation	No		
Chemotherapy	ICE: ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 150 mg/m^2 every 4 weeks	ICE: ifosfamide 4.5 g/m^2, carboplatin 270 mg/m^2, etoposide 135 mg/m^2 every 4 weeks	
Nr of patients	27	31 (27 randomized)	
		14	13
Median age	18-65	58	
Disease	Pleural mesothelioma	Pleural mesothelioma	
Stage	I-III	0-II	
Prior chemotherapy	0%	0%	
Metastases	0%	0%	
Immediate Efficacy (CR+PR)	20%	15%	31%
Complete remission (CR)	0%	0%	0%
Partial remission (PR)	20%	15%	31%
Stable disease (SD)	56%	57%	38%
Progression of disease (PD)	24%	28%	31%
Time to progression	6.9 months	5.6 months	9.2 months
Overall survival	17.9 months	11.5 months	15 months
1 year	68%		
2 year	20%		
Toxicity ¾ grade			
Neutropenia	74%	36%	30%
Thrombocytopenia	33%	37.7%	15.3%
Treatment-related deaths	1 (3.7%), sepsis		

Table 13. Randomized trials on Whole-Body Hyperthermia

Whole-body hyperthermia

The fact that there is only one phase III randomized trial on WBH is very demonstrative itself, because WBH has much longer history of application in oncology than local hyperthermia. Results of multiple phase II WBH trials usually don't justify III phase trial. Bakhshandeh et al[41] trial is demonstrative in this respect. In this II phase trial, 20% of partial remission and 20% 2 year survival in 27 patients with I-II stage malignant pleural mesothelioma was shown after TChT (ICE + WBH); extensive myelosuppression (75%

of 3-4 grade) with 3.7% mortality was reported. Meanwhile, it's known that efficacy of majority of chemotherapies is also 15-20% but on heavier samples, and efficacy of the gemcitabine+cisplatin combination had demonstrated 48% partial remission with less toxicity (not more than 30-40% of 3-4 grade toxicity).[43] Thus, Bakhshandeh et al.[41] phase II study showed more than dubious clinical efficacy with undisputedly higher toxicity, that could hardly be considered a basis for further studies. Anyway, authors had considered these results "promising" and initiated a phase III trial. Preliminary results of this predictably negative randomized phase III study, reported in 2004, exceeded expectations, and was sharply negative[42]. WBH didn't improve the results of chemotherapy, but significantly worsened them in all respects: half less PR, (15% vs. 31% in ChT only arm), significant decrease of OS (11.5 months vs. 15 months) and DFS (5.6 months vs. 9.2 months). It should be mentioned that this phase III trial was done on easier sample than the previous phase II trial (WHO 0-II instead of I-III in phase II trial) and with 10% less ChT dose. This allowed to reduce myelotoxicity significantly (36% vs. 74% in phase II) and to avoid deaths, but it also led to a reversal of clinical results: previously dubious results became clearly negative. Authors concluded that "this preliminary data from a randomized study show little, if any, beneficial effect mediated through hyperthermia" and that "conclusive judgment has to be postponed until completion of this trial" though in fact they just had to stop the trial. Moreover, the results didn't prevent the authors from publishing a review of the current state of WBH, which reports intention of Interdisciplinary Working Group on Hyperthermia to build clinical guidelines on the basis of "promising results of phase II trials" as well as on the basis of this phase III trial in 2005.[44]

The general impression is that the combination of ChT with extreme WBH can, in some cases (20-40%), overcome chemoresistance and provide a partial remission, but without any effect to overall survival. Also, clinical efficacy seems to be reversely connected with toxicity: a clinical benefit is associated with high toxicity; toxicity reduction leads to inefficacy or it worsens the effect of ChT. Since the results obtained in TChT studies have never exceeded the best results without WBH, there is a concern on feasibility of WBH at all, since similar or better effect can be obtained by applying high-dose ChT or polychemotherapy at a lower level of toxicity.

Guidelines on the WBH published by the Universities of Luebeck and Wisconsin in 2000 are more than cautious in terms of efficiency and safety of WBH. In particular, it is postulated that efficiency of WBH is only supposed and is based on very limited clinical data; that separate administration of WBH doesn't make sense because it provides only a minimal increase in overall survival (days, maximum weeks), and only with thermosensitive tumors[45]. These guidelines are intended for research only. The paper of HI Robins, the former head of the WBH program at the University of Wisconsin, immediately preceded these guidelines, was even more skeptical.[46] It is noteworthy that Robins, who was the chairman of the International Working Group on systemic hyperthermia and had published over 80 articles on WBP since 1983, completely stopped his activities in hyperthermia field and hasn't published any paper on the topic since 2003. With such sudden and complete cessation of research activity on WBH, one can assume that the true result of this 20-year activity is not encouraging.

Type	Authors	Year	Localization	Sponsor	Conclusion	
					Resume	Estimation
Superficial HT	Kapp et al. [7]	1990	Superficial	Independent	No Significant Effect	Negative
	Perez et al. [5]	1991	Superficial			Negative
	Emami et al. [8]	1992	Superficial			Negative
	Engin et al. [9]	1993	Superficial			Negative
	Vernon et al. [10]	1996	Superficial	Hyperthermic	Significant Effect	Dubious
	Overgaard et al. [11]	1996	Melanoma			Clinically insignificant
	Jones et al. [12]	2005	Superficial			Dubious
Deep HT	Emami et al. [16]	1996	Deep seated	Independent	No Significant Effect	Negative
	Van der Zee et al. [17]	2000	Rectum	Hyperthermic		Negative
			Bladder			Negative
			Cervix		Significant Effect	Clinically insignificant
	Harima et al.[28]	2001	Cervix			Dubious
	Vasanthan et al. [19]	2005	Cervix	Independent	No Significant Effect	Extremely Negative
	Mitsumori et al. [18]	2007	NSCLC			Negative
	Issels et al.[20]	2010	ST sarcomas	Hyperthermic	Significant Effect	Dubious
WBH	Bakhshandeh et al.[42]	2004	Pleural mesothelioma		No Significant Effect	Extremely Negative

Table 14. Final record of randomized clinical trials on hyperthermia in oncology

Biases of hyperthermia trials

The must common biases of hyperthermia randomized clinical trials are summarized in the table below.

Author	Year	Locali-zation	DIstortions						
			Inadequate comparator	Randomization defects	Pre-selection of patients	Incomplete data presentation	Incorrect design	Systemic distortion	Inadeqate analysis
Vernon et al.[10]	1996	Superficial	?	?	?	X[1]	X[2]	?	?
Overgaard et al.[11]	1996	Melanoma	X[3]	-	?	X[4]	X[5]	-	X[6]
Jones et al.[12]	2005	Superficial	-	X[7]	X[8]	X[9]	-	?	X[10]
Van der Zee et al.[17]	2000	Cervix	X[11]	-	-	X[12]	X[13]	-	X[14]
Harima et al.[28]	2001	Cervix	X[15]	-	X[16]	-	-	-	-
Issels et al.[20]	2010	STS	X[17]	-	-	-	-	X[18]	X[19]

Table 15. Summarized biases of positive randomized clinical trials on hyperthermia

Notes: 1 – incomplete safety data; 2 – combination of some trials with different design; 3 – TD 24/27 Gy; 4 – overall survival by groups is absent; 5 – experimantal design (randomization of tumors instead of patients); 6 – incorrect survival analysis; 7 – median age and TD RT differs >10%; 8 – pre-selection of thermosensitive patients; 9 – tumor size effect analysis is absent; 10 – inadequate analysis of efficacy, ignorance of bad survival; 11 – TD RT 67 Gy, TD to tumor mass <60 Gy; 12 – temperature analysis is absent, safety data are hidden; 13 – combination of two studies with very different protocol; 14 – effects of temperature, tumor volume and protocol are not analysed; 15 – TD to tumor mass 60.6 Gy; 16 – pre-selection of aged patients (+10 years of expected); 17 – volume of base treatment in the control group is twice lower than in the study group; 18 – all the parameters effecting the results are distorted in favor of hyperthermia group (+100%); 19 – masking of systematic distortion, and inadequate toxicity evaluation

Inadequate comparator is the most often and significant bias in RT-based HT trials[11,17,28]. Standard RT has its special efficacy which significantly and not proportionally falls with lowering of the total dose. If HT is added to such low-dose RT, it causes some gain in local the effect but in comparison to effect of the standard high-dose RT, this HT-added effect is at least not better[5,7,8,16] but it is often is worse[9,18], sometimes significantly[19]. At the same time, toxicity of TRT is usually 3-5 times higher than toxicity of RT only. The main problem is that TRT vs standard high-dose RT is not effective because RT itself is a much more potent factor than HT, and HT effect disappears at high-dose RT. The inadequacy of comparator in Issels et al. trial20 is of another nature and caused by the less volume of treatment in the control arm as it was discussed above.

Obvious defect of randomization is revealed only in Jones et al. trial[12], alongside with open pre-selection of patients, which is considered a bias because the resume of the trial refers to all patients and is not limited to 'heatable' patients only. Another hidden type of pre-selection of aged patients was revealed in Harima et al. trial28 where the not pre-treated patients in study group were 10 years older than the expected age of the first diagnosis in Japan. Three trials have incorrect designs. Overgaard et al. trial is in fact a clinical radiobiological trial without clinical significance. Vernon et al. and van der Zee et al. trials combines some different trials with incompatible protocols, different equipment, etc. Also, the data in the majority of the trials are presented incompletely, and virtually all the trials suffer from inadequate analysis. This refers not only to positive trials only. For example, the extremely negative Vasanthan trial is reported and analyzed poorly. For instance, authors just refused to analyze the possible reasons of significantly enhanced mortality in IIb stage group though this is of the great interest. The analysis of reasons of negative trials of 90th was also incomplete and incorrect as it will be discussed below.

The problem of sponsorship influence deserves a special attention. As it known from the literature, the clinical trials sponsored by industry have at least 5 times more probability to be successful (positive) than independent trials. As it is obvious from Table 14, independently sponsored HT clinical trials always reported no significant effect. On the contrary, trials sponsored by hyperthermia societies were successful in majority of cases with only two exclusions. Bladder and rectum cancer groups in van der Zee trial with negative and dubious results were just hidden by low-reporting and by referring to the entire trial as successful. The extremely negative intermediate results of Bakhshandeh et al. trial was reported only once at ASCO meeting. The final result of the trial is absent.

There is a serious interpretational bias. Namely, hyperthermia community tends to consider the negative trials of the early 90s as not significant because of insufficient heating and imperfect technique. This is absolutely incorrect. All the modern hyperthermia technologies were introduced before the 90s: microwave

superficial heating (433 MHz, 915 MHz, 2.4 GHz, etc.) and capacitive 13,56 MHz heating (LeVeen) are in use since late 70s, APAS technology of BSD has been in use since 1982 and 8 MHz capacitive technology of Thermotron has been commercially available since 1985. Erasmus university hyperthermia center has been using 433 MHz technology since 1985 to the date[47]. All the randomized trials of the early 90s were executed in leading US universities with the best available equipment. Therefore, the technique of heating in these trials was adequate from the modern look. It's confirmed by high temperature reached in these trials. For instance, in Kapp et al. trial[7] the minimum temperature in superficial tumors was 40.2°C, the average was 42.5°C and the maximum was 44.8°C. Modern guidelines of Erasmus university[47] for superficial tumors recommends to reach minimum temperature of 40°C and maximum of 43-44°C. It should be considered that in terms of heating and technique the negative trials of the early 90s were absolutely adequate.

Finally, the publication bias is significant. 7 positive trials are well reported, frequently quoted by hyperthermia society and included in all meta-analyses and reviews. Some of them are published sometimes[17,21,22]. On the contrary, the negative trials are poorly quoted and often not mentioned in meta-analises and reviews. This creates the wrong impression of hyperthermia success.

Hyperthermia problems

Despite more than 100 years of development, hyperthermia still doesn't have an acceptable explanation. Current hyperthermia concept is based solely on the temperature concept but clinical results often directly contradict this concept (see Table 16.). Particularly, the significantly stronger radiotherapy modification effect for smaller tumors[5,11] (less than 3-4 cm) is unexplainable from the thermal concept of hyperthermia. Perez et al.[5] explained that "they are easier to heat", and this explanation is commonly accepted now, but already in 1963 G Crile Jr[48] had convincingly demonstrated that, vice versa, bigger tumors could be heated much easier than smaller ones. This difference is very simple to understand because the main predictor of heating is tumor blood flow, which is high enough in small tumors and significantly reduced in big tumors, which play as "heat trap". Also, small tumor is cooled effectively enough by high blood flow of surrounding healthy tissues. Hiraoka et al trials confirmed that bigger tumors are heated better than smaller ones[49] and, at the same time, smaller tumors are cured better with HT[50]. Thus, this phenomenon clearly shows inconsistency of thermal concept of HT: the better heated tumors show worse clinical effect. Instead of initiate discussions about the validity of thermal concept of radiomodification, all the authors[5,8,9,11,16] had made the simplest and presumably wrong conclusion about a better heating of smaller tumors. This wrong conclusion led to logical consequence that insufficient heating is the reason of the trials fail, and that improvement of heating technology could correct a situation.

Results of 3 randomized clinical trials published before 1996 (Kapp et al.[7], Emami et al.[8] and Engin et al.[9]) had blocked the only possible thermal explanation of Perez et al.5 trial fail: one could hypothesize that 2 HT sessions is not enough for demonstration of HT effect. These trials clearly showed that longer protocols with 6 and 8 HT sessions are not more effective and even could worsen effect9. Though Engin et al.[9] had found that some temperature parameters (namely, median minimum tumor temperature, and minimum tumor temperature during the first heat treatment) were prognostic factors predictive of duration of response (though, together with tumor volume), Kapp et al.[7] didn't find such dependence: only tumor histology, radiation dose and tumor volume had correlated with duration of local control. Complete response rate seemed to be not correlated with temperature parameters at all[7,9].

	Hyperthermia theory	Premise	Hypothesis	In fact
1	HT is the most effective in hypoxic areas	Large tumors are mainly hypoxic	Effect of HT should be much stronger in large tumors	Effect of HT is much weaker in large tumors[5,7,31]
2	Higher temperature means stronger effect	Large tumors are easier to heat		
3		In van der Zee et al. trial[17], average temperature in cervix was <40°C and near 1°C lower than in rectum and bladder[33]	Effect of HT in cervix cancer should be worse than in rectum and bladder cancer	Effect of HT in cervix cancer was much stronger than in rectum and bladder cancer[17]
4		In Vasanthan et al. trial[19], the average temperature in cervix was >41°C	Effect of HT in Vasanthan[19] et al. trial should be stronger then in van der Zee et al.[17]	Effect of HT in Vasanthan et al. trial was much worse[17,19]
5		In Vasanthan et al. trial[19], the average temperature in Chennai group was 41.8°C and in Pusan group only 38.1°C	Effect in Chennai group should be much stronger (see Figure 10)	2 year local control was the same[19]
6	HT promotes cell cycle synchronization, thus enhancing the effect of RT	If exists, the synchronization should progress with more sessions	The more HT sessions, the stronger effect should be	Effect of multiple HT sessions is not stronger[8,9]
7	Hyperthermia damages or enhances the RT-damage of malignant tissues	If exists, the damage should accumulate		
8	Moderate HT (<42°C) leads to enhancement of tumor blood flow and oxygenation	Overwhelming majority of trials use HT after RT	Use of HT after RT is not effective because of insufficient temperature and could compensate RT damaging by improving tumor metabolism in view of better blood flow and oxygenation	Thermoradiotherapy trials are mainly unsuccessful[5,7,8,9,16,18,19] but some of them shows remarkable success[11,28]
9	Extreme HT (≥42°C) leads to hypoxia, acidosis, energy deprivation	Average maximum temperature in tumor never exceeds 42°C		
10	Thermal dose (CEM43°C T90) is a main factor of HT success	Thermal dose is a temperature multiplied to duration of exposure	Higher temperature should provide stronger effect	Higher temperature doesn't mean stronger effect (rows 2-5)
11			Longer exposure to heat should provide stronger effect	Effect of multiple HT sessions is not stronger[8,9]

Table 16. The contradictions of the classical theory of hyperthermia and data of randomized clinical trials

These results heavily affected the concept of thermal dose offered by Oleson and developed by Sapareto and Dewey[51] in the mid-80s. The explanation of long protocols fail was extremely weak: thermotolerance was called a reason. It seems to be incorrect because thermotolerance pattern has been well-known since early 60th[48]: it falls to initial level in 72 hours. Therefore, HT sessions 2 times a week, as it was in all the trials, should not be affected by thermotolerance. The subsequent hyperthermia trials of the 2000s[12,20] also used 2 times per week protocols.

Thus, five negative clinical trials of 1990-1996 (see Table 14.) were interpreted incorrectly in terms of reason of the fail: instead of revision of hyperthermia rationale, "insufficient heating" concept was offered. It would be incorrect to say that these results of the randomized trials were surprising: as it's clear from the Hornback paper quoted above[3], clinical oncologists had made their unambiguous decision about hyperthermia on the basis of previous clinical results already in mid-80s. Together with the fail of another RTOG deep hyperthermia trial, these trials' results led to disappointment of the medical community in oncological hyperthermia.

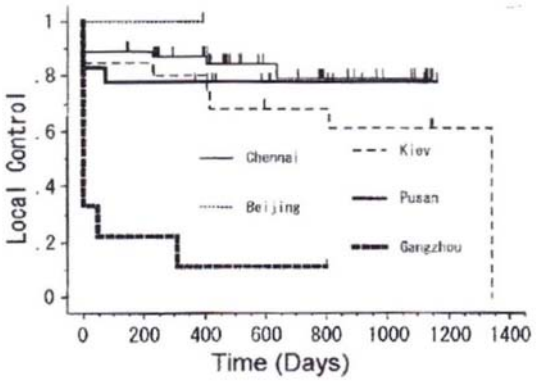


Figure 10. Local control rates in different subgroups of Vasanthan et al.[19] trial

Temperature analysis of cervical cancer studies also gives contradicting results. Average temperature in Vasanthan et al.19 trial was the highest among the main three cervical cancer trials (41.6°C vs. 40.6°C in Harima et al.28 trial and estimated <40°C in van der Zee et al.[17] trial), and the effect of TRT in Vasanthan trial was worse than RT only, though in the other two trials with lower temperature, the effect of TRT was significantly better than in RT control. Also, within Vasanthan et al 19 study, extremely low average temperature was used in the Pusan subgroup (38.1°C) but 2 year local control in this subgroup was the same as in Chennai and better than in the Kiev subgroup, where much higher average temperatures were used (41.8°C and 42.0°C, respectively).

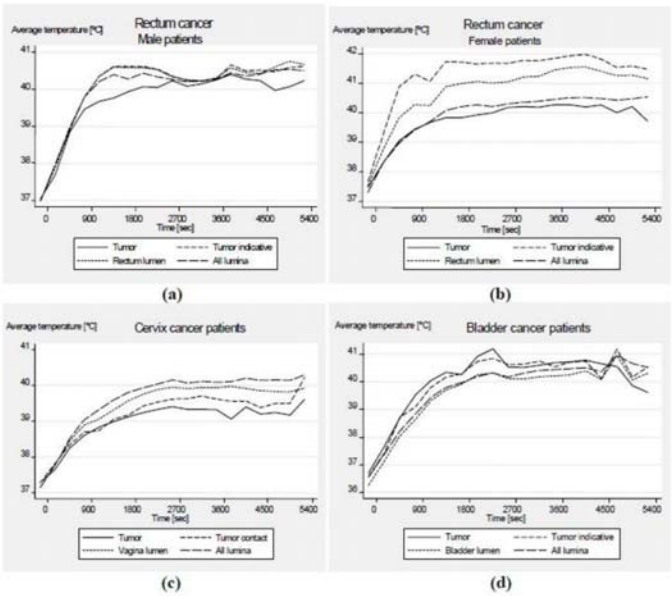


Figure 11. Technical quality of deep hyperthermia using BSD-2000 unit on rectal, bladder and cervical cancer[33]

As it was stated above, there is no temperature analysis in van der Zee et al.[17,21,22] trial but there is a doctoral thesis of D Fatehi[33] from Rotterdam University who was a co-author in later DDHG study[52]. His patients were collected between 2000-2002, i.e. 4 years after completion of the van der Zee trial. This paper refers to technical quality of deep hyperthermia using BSD-2000 unit on rectal, bladder and cervical cancer (see Figure 11.). It's known from the van der Zee paper that it was the Rotterdam University Hospital with its BSD-2000 unit, which was responsible for the larger part of patients enrolled in DDHG study. Therefore, technical results of Fatehi could be considered relevant. It's easy to see that temperature in cervix is less than in rectum and bladder (see Figure 11.), but it was cervical cancer which was effectively treated with TRT whereas TRT of rectum and bladder cancers were not effective[17]. Finally, in 2011 de Bruijne et al.[53] have convincingly demonstrated in a retrospective study that, after the correction of the tumor size, CEM 43°C T90 thermal dose was not associated with any clinical endpoint (CLR, LDFS, OS). Thus, even the central point of hyperthermia concept – the temperature, – has got many contradictions. This means that in fact hyperthermia doesn't have a theoretical base. Clinical results show that hyperthermia is in a dead end. Program papers on hyperthermia show that opinion leaders don't understand what to do and where to move, once again supposing only old thermal solutions[54,55] which should have been discredited already since the mid-90s. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance. The most impressive papers report the history of hyperthermia as a history of uniform success, they don't mention the negative results at all and declare heating as the only and exclusive technical problem of hyperthermia[56]. Such approach looks not scientific.

Conclusion

The careful analysis of the 14 randomized clinical trial doesn't confirm a clinical benefit of hyperthermia application independently of its type: superficial, deep or whole-body. We haven't found any positive trial not affected with biases. With correction to distortions, there is no trial with obvious long-term positive effect of hyperthermia. Effects of hyperthermia could be shown in experimental setting and in experimentally designed clinical trials or versus an inadequate comparator. In clinical setting and correct study design, hyperthermia is not effective at all or not effective enough to prove its obvious disadvantages: toxicity and labor-intensity. Hyperthermia thermal concept seems to be irrelevant. Nevertheless, multiple publications of positive trials, reviews and meta-analyses create an impression of hyperthermia renaissance.

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Phase II clinical study on relapsed malignant gliomastreated with electro-hyperthermia

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The purpose of this study was to evaluate the activity and toxicity of electro-hyperthermia (ET) on relapsed malignant glioma patients. Twenty four patients with histologically diagnosed malignant glioma entered the study. Sixteen patients had glioblastoma multiforme, four had anaplastic astrocytoma grade III and four had anaplastic oligodendroglioma. All patients were pre-treated with temozolamide-based chemotherapy and radiotherapy. Hyperthermia with short radiofrequency waves of 13.56 MHz was applied using a capacitive coupling technique keeping the skin surface at 20 degrees C. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumours was above 40 degreees C for more than 90% of the treatment duration. Two complete remission and 4 partial remission were achieved, with a response rate of 25%. The median duration of response was 10 months (range 5-88). The median survival of the entire patient population was 9 months, with 25% survival rate at 2 year. ET appears to have effectiveness in adults with relapsed astrocytoma and malignant glioma.

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Hyperfractinated thermoradiotherapy (HTRT) is more effective and less invasive than radiation or chemoradiation in heatable cancers – a meta analysis

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Hyperfractinated thermoradiotherapy (HTRT) is more effective and less invasive than radiation or chemoradiation in heatable cancers – a meta analysis

Intruduction

It has been proven in malignant cancers, that in case of metastatic nodes in the head and neck region [1, 2, 3, 4, 5, 6] and in several other locations [8, 9, 10] hyperthermia potentiates radiation therapy. Due to these early findings, clinical applications were limited to recurrent advanced or metastatic cancers [11, 12, 13]. However, prospective randomized trials in the
1990's demonstrated the effectiveness of thermoradiotherapy not only in superficial tumors but also when deeper structures were affected [14, 15], provided these tumors could be effectively heated. The addition of heat roughly doubles the effectiveness of radiation, but also the fact that hyperthermia may increase tumor oxygenation [16, 17, 18] make hypoxic tumors such as sarcomas or glioblastomas more susceptible to thermoradiotherapy [19]. In previous publications [19, 20] we described a treatment regimen based on protractions of the radiation fractionation combined with daily hyperthermia treatment coinciding with each radiation dose. This regimen seems to be effective in eradicating tumors with diminished toxicity.
A remarkable projected 5-year survival rate was reported in the 80-90% of the region in to superficial heatable tumors (breast, head and neck and prostate) [20] In the current investigation we undertook update the current results as well as to perform a meta-analysis corresponding survival rates using HTRT with conventional radiation (EBRT) or chemo radiation.

Material and methods

Hyperthermia was delivered using either Microwaves (BSD-100 or Cheng Laboratories) or Ultrasound (Labthermics) FDA approved equipment with the appropriate applicators. Thermometry was done using micro-thermocouples placed in the tumor region (BCIW, LA, CA) for prostate tumors only ultrasound was used. Radiation was delivered by a 12 MEV Siemens Mevatron Machine adapted for IMRT and IGRT with a Lina-Tech system for computer planning and collimator alteration. Fractionation used involved daily hyperthermia treatments in conjunction with each radiation fraction. The daily doses of radiation are progressively decreased from 180cGy to 100cGy resulting in the isoeffect biological equivalent dose by 15% to 25%. According to Ellis TDF formula, (see Table 1.)

200 x 25 = 5,000	TDF = **82**	35 x 200 = 7,000	TDF = **115**
Protracted Hyperfractionation			
[cGy]	TDF	[cGy]	TDF
180 X 10 = 1800	28	180 X 10 = 1800	28
150 X 10 = 1500	21	150 X 10 = 1500	21
120 X 10 = 1200	15	120 X 10 = 1200	15
100 X 5 = 500	6	100 X 10 = 1000	11
		50 X 30 = 1500	12
35 Fx = 5000	**70**	70 Fx = 7000	**87**

Comparison of Radiation Bioligoical Effectiveness (TDS #) between Conventional and Protracted Fraction Regions.

Table 1. Radiation therapy fractionation conventional fractions

This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment was continued until an objective complete response was attained, or failure determined. 40 breast patients, 27 head and neck and 22 prostate patients were treated with a follow up of two to five years. All patients were in early stage (III-a or less) the total dose was adapted to the clinical situation. To this effect, the use of objective end results parameters was introduced, including MRI, MR Spectroscopy [21], PET Scanning, Tumor Markers and PSA levels. Typically, the treatment was continued with further reduced doses until all the objective parameters confirmed a complete response or failure was determined. Therefore, as opposed to classic radiation therapy, patients were treated to effect as objectively demonstrated, instead of to a pre-determined radiation dose or number of fractions.

Patient Population Patients included in this study belong to a subpopulation that refuses all standard medical treatments, including clinical radiation therapy, surgery and chemotherapy. All signed appropriate consent forms. The recruitment period was from January 1999 to July 2010.

Statistics

All tests were done with Graph Pad Prism 4 software (Graph Pad Software Inc., San Diego, (USA) using the method of Kaplan and Meier. Meta-analysis was done by directly extrapolating published survival date [28, 29, 30, 31] for each type of tumor and by comparing the current results with HTRT.

Results

1. Toxicity was minimal considering the biological equivalent of radiation doses given. Dermatitis and occasional thermal burns (61 % of treatments in breast patients); nausea, vomiting and occasional diarrhea and cystitis were experienced when treating pelvic fields in prostate patients; mucositis, thickness of saliva and altered taste were experienced during the head and neck treatment. Hyperthermia did not seem to add to the radiation early effects. In all, the treatment was well tolerated on the vast majority of the patients. There were fewer side effects than with curative radiation therapy alone. No Grade IV toxicity (Common Toxicity Criteria was observed of note patients treated for prostate cancer exhibited less sexual dysfunction than it was reported after conventional radiation.
2. Complete response rates were gratifying results of thermoradiotherapy of or our previous experience [21-27]. Breast tumors, showed a complete response rate (CR) of 82%. The CR rate for head and neck tumors was 88% and for prostate tumors it was 93%. Meta-analysis comparing HTRT with conventional radiation shows a 30 to 50% advantage for HTRT in terms of 5-year survival and response rate. Survival rates with HTRT were around 80% warranted treating early superficial tumors with HTRT alone.
3. Projected 5-year survival in this updated series remain at a very high level for early stage breast head and neck and prostate tumors (see Figure 1.) (see Table 2.) upwards of 80%.

Head And Neck	88%
Prostate	87%
Breast	80%

Table 2. Five year overall survival rate

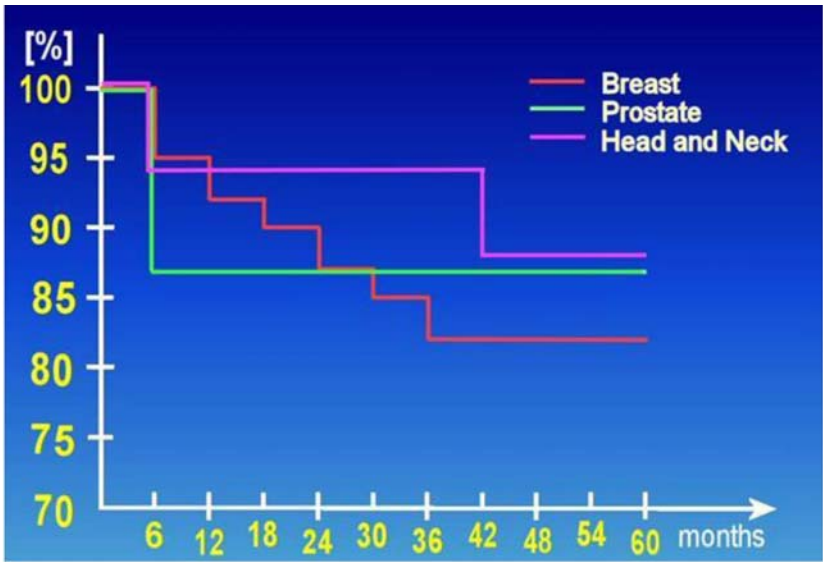

Figure 1. Percentage survival overtime breast, head ands neck, and prostate

4. Comparison survival after treatment with HTRT versus chemo-radiation or EBRT (external beam radiation therapy). (see Figures 2., 3., and 4.) depict the comparison in projected 5 years survival time between the 3 modalities (HTRT, EBRT and chemo-radiation)

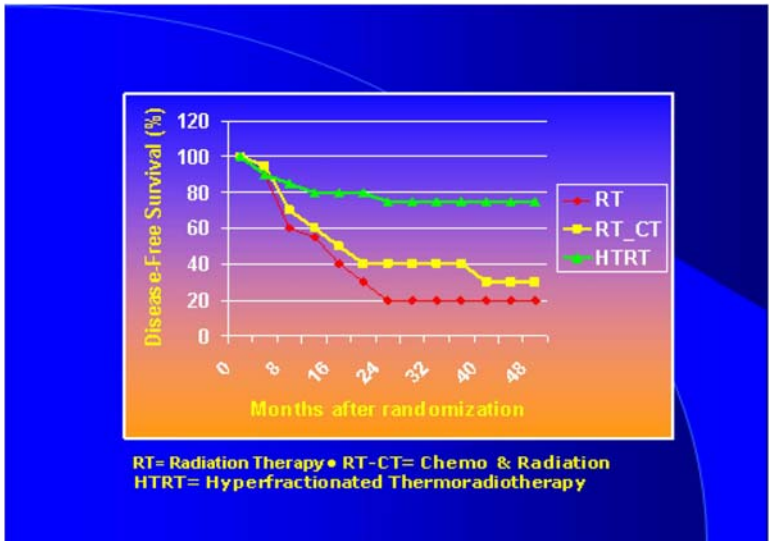

Figure 2. Percentage survival overtime head and neck tumors – Callais, Q [28]

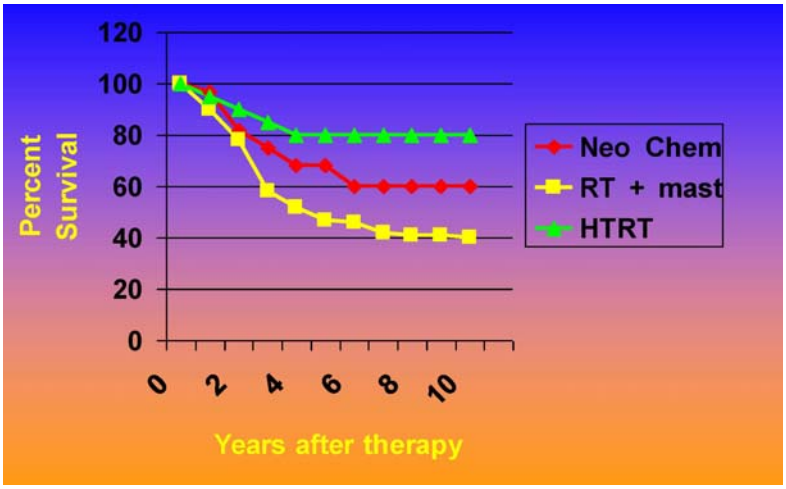

Figure 3. Percentage survival overtime breast tumors – Perez, C [29]

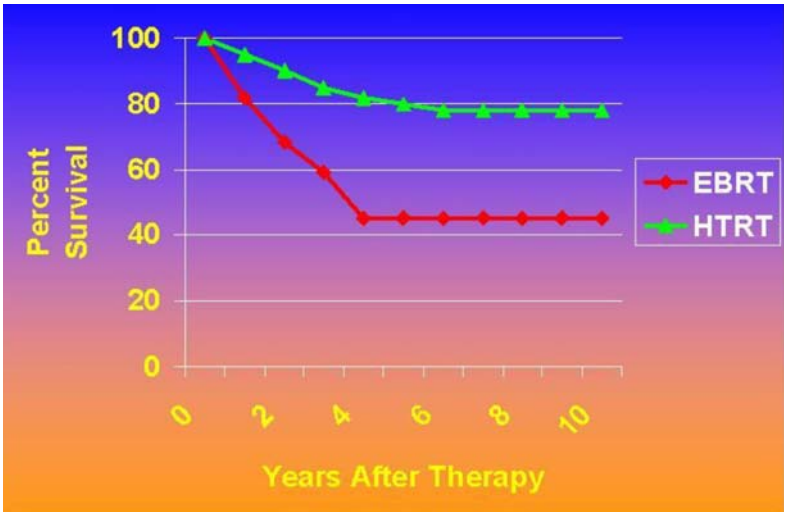

Figure 4. Percentage survival overtime prostate tumors – Perez C and Bradely [30]

In regard to treatment of disseminated prostate tumors, it should be noted that in patients able to obtain and maintain prior treatment, 90% could be treated without developing impotence, as compared with 50% that lost sexual ability when treated with EBRT, as depicted in Figure 5.

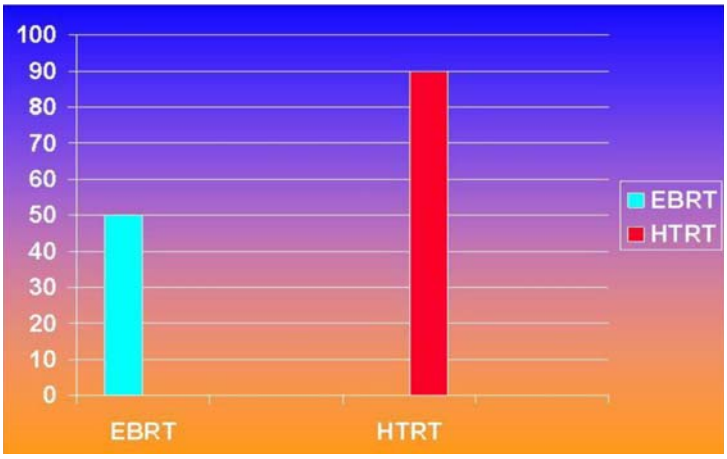

Figure 5. Percentage of patients able to obtain and maintain erection one year after treatment with HTRT and eBRT of prostate tumors – Siglin, A [31]

Discussion

A method is designed to treat superficial heatable tumors (head and neck, breast and prostate with curative intent when at early, non-disseminated stages – Higher response and survival rates can be achieved with less, more moderate toxicities than with EBRT or chemoradiation, as shown by Meta analysis, therefore we reached the following tentative conclusions.

The new and the old new oncology goal

Old: dump and pray

- Give maximum dose of toxic treatment modality
- Pray for results

New:

- Use less toxic thermoradiotherapy
- Treat to effect, objectively documented

Conclusion

Protracted RT hyperfraction with daily hyperthermia

- Decreases the radiation dose by 15 to 25%
- Decreases the side effects of radiation therapy
- Allows treating to effect using objective and point parameters (tumor markers, PET scans, MRI, etc.)
- Accomplishes a high percentage of complete responses in superficial tumors
- Accomplishes a high 5-year survival rate in the 80-90% range in early superficial tumors
- Is potentially curative in early stage breast, head and neck and prostate cancers
- Is more effective and less toxic than radiation or chemotherapy

The future of hyperthermia

1. Treat with curative intent
2. Find a niche where Hyperthermia will be included in the guide lines for the NOVO therapy. Suggestions: Head and Neck, Prostate, Breast, Sarcomas
3. Become part of institutional tumor boards to implement these objectives and accrue patients.

4. Emphasize the proven palliative effectiveness of Hyperthermia. Especially pain palliation (eg. bone, pain, chest, wall recurrences, etc.) Design prospective, randomize multi-institutional trials to prove points 1, 2, and 4

Summary

HTRT consists of daily Hyperthermia treatments in conjunction with each radiation fraction. Radiation daily doses are progressively decreased from 180 to 100 cGy resulting in protracted treatment time that decreases the isoeffect biological equivalent dose by 15% to 25%. This decrease is compensated by the increased number of hyperthermia fractions which potentiates each radiation dose. Treatment is continued until an objective complete response is attained, or failure is determined. 60 breast patients, 35 head and neck and 25 prostate patients were treated with a follow-up of two to five years. All patients were early stage (less than III).

Conflict of interest

The author declares no conflict of interest from the research plan and results with any commercial entity mentioned in the paper.

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Oncothermia Journal 7:108-108 (2013)

Strategies for the cancer treatment with hyperthermia

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Abstract

In the recent years many new cancer clinics are using hyperthermia for the treatment of cancer
We treat patients by an empirical way: One hour each session, Every other day
one month, two months, more? Alone or combining with other treatment methods.
What are the best ways to use the hyperthermia?

A.Should we combine hyperthermia devices?:
WBH+Local-Regional Hyperthermia
EHY 3000+EHY 2000
Transurethral Hyperthermia+Local-Regional Hyperthermia.
Superficial+Deep Hyperthermia
Multiple fields with the same device

B.Should we combine hyperthermia with conventional methods?
Should we use hyperthermia alone
Should we combine hyperthermia With:
Chemo, RT, Hormones, Biologic agents, Cryo, conventional drugs, Gene therapy, Photodynamic Therapy (PDT), immunotherapy, PDT

C. Should we combine hyperthermia with CAM methods
IPT, High dose Vit-C, supplements,

D.What should be our treatment Strategies
Treatment length, Treatment power, Session length, Treatment frequency, Adjuvant treatments, How we can prevent thermo-resistance, Treatments sequence
As there are no large studies available to indicate what are the superior strategies, frequent hyperthermia meetings with exchange of information and experience is the best way to select the best strategies for hyperthermia use.

Oncothermia Journal 7:109-109 (2013)

Whole body hyperthermia in water bath: technical-physical aspects and clinical experiences

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It is accepted that the increase in core body temperature above 41.5 ° C may help to destroy tumor cells. Life of cancer patients is particularly threatened by the metastasis. Therefore systemic treatments are preferred. The discussion of the last two decades showed that every tenth of temperature increase helps to improve the damage of cancer cell. Studies by Suvernev et al confirmed efficient reduction of viruses infected individuals at temperatures above 42.5° C. So close to the available methods and their predictive success one should verify the feasibility of a whole-body thermal therapy.

Professor von Ardenne started the development of the extreme whole body hyperthermia in water. After use of short-wave (Selectotherm) he perfected whole body hyperthermia by water filtered infrared-A-radiation, while discussions with other celebrities in research.
Thus temperatures could certainly be achieved up to 42,5^{o}C, in the routine up to 42.3 ^{o}C.
While the effort to increase these temperatures, the work fell to the resarch group led by Professor Suvernev from Novosibirsk (Russia), which are specialized for various reasons, turn on the water as a heat source. After the transfer of know-how, a prospective observational study was initiated to evaluate which of the two competing systems - perhaps Heatheal © procedure or IRATHERM®-2000 - will be suitable, safe and well tolerated, to escalate the temperature above 42.5 ^{o}C. In focus of the investigations are the temperature controls, the anesthesia, the safety and tolerability, all things considered the feasibility as the requirement of therapeutic efficiency. Later, the question has to be clarified whether it is better to escalate the temperature significantly (43.0 ^{o}C) or even in extreme temperatures (42.3 ^{o}C) with a distinct plateau time (> 60 min> 41, 8 ^{o}C) to linger and work out for what goals which method will be more suitable.

The Heatheal© procedures accomplished in the gisunt® clinic with its gisunt® Hyperthermia Center are critically analyzed and were presented experts of hyperthermia for the first time to discuss further questions while continued leading investigations.

Oncothermia Journal 7:111-114 (2013)

Complete responses after hyperthermic ablation by ultrasound guided high intensity focused ultrasound (USgHIFU) plus cystemic chemotherapy (SC) for locally advanced pancreatic cancer

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Complete Responses after systemic chemotherapy (SC) plus hyperthermic ablation by high intensity focused ultrasound (HIFU) for locally advanced pancreatic cancer

Abstract

We describe results in unresectable pancreatic tumors treated with USgHIFU hyperthermia ablation plus adjuvant chemotherapy. Materials and Methods: 32 cases of non resectable pancreatic tumors were treated from March 2010 to March 2012, and all of them underwent systemic chemotherapy. Clinical responses (thermical ablation achieved) were measured by image techniques. They were 23 Stage III cases and 9 Stage IV cases. Complications were also analyzed.

Results: Clinical responses (ablation obtained) were 82% in all cases, sustained at 8 weeks of the procedure. We obtained 8 complete responses (25%) at the end of the combined treatment, 7 from stage III patients and 1 from stage IV. Major complications included severe pancreatitis with GI bleeding (1), skin burning grade III that required plastic surgery (2). No deaths were registered. Median Survival was 12.5 month (6 mo – 2.5 year)

Conclusion: HIFU plus SC is a potentially effective and safe modality for the treatment of unresectable pancreatic cancer.

Keywords

Pancreatic cancer, High-intensity focused ultrasound ablation, HIFU, Gemcitabine, Chemotherapy

Introduction

Despite continuous scientific advances in the field of oncology, pancreatic cancer has a poor prognosis nowadays. A significant part of cases are considered unresectable at diagnosis due to late detection of the disease or to invasion of great vessels surrounding the tumor [1]. Therefore, treatments with chemotherapy and in lesser grade radiotherapy are the only tools suitable to be offered to the patients with locally advanced disease [2]. Overall survival is around 6-10 months in stage III patients and only 3-6 months for stage IV cases [1].

At present, there is no ablative technique suitable for pancreatic lesions. High Intensity Focused Ultrasound (HIFU) is a minimally invasive surgical technique that has proven to improve the local control in different types of tumors. Several studies in animals and humans have shown the efficacy of this technique to cause a coagulative necrosis than is able to diminish or even ablate tumoral masses. Previous reports of the treatment of pancreatic masses by HIFU have been published recently, specially underlining its role as a good concomitant treatment associated to gemcitabine based chemotherapy protocols.

The HIFU Unit in Hospital Universitari Mutua Terrassa was established in 2008. First cases were exclusively uterine fibroid tumors. Since January 2010 a wide variety of malignant tumors had been treated at our institution. The HIFU device at this Unit is Ultrasound guided JC 200 device from HAIFU Chongqing (China). The purpose of this study is to evaluate retrospectively the results of HIFU treatment in a group of advanced pancreatic cancer patients managed in our center.

Material and methods

From March 2010 to March 2012 thirty-two cases of non-resectable pancreatic tumors due to locally advanced disease were treated with HIFU in our institution. Most patients were referred from the oncology or surgery departments of different Spanish hospitals, although three of them came from other European institutions. All of them had a pathology confirmed diagnosis of pancreatic cancer and underwent systemic chemotherapy with a Gemcitabine based combination prior to HIFU treatment. Patient's ages ranged from 32 to 79 years old (median= 63). They were 23 Stage III cases and 9 Stage IV cases, according to TNM International classification. HIFU treatment was administered at least 4 weeks after chemotherapy was discontinued. Previous Doppler color Ultrasound was obtained and simulation procedure was performed in all cases. Two cases were excluded fro the initial selection because the ultrasound image was not able to

obtain a good identification of the tumoral mass and therefore treatment was not performed. All patients were under general anesthesia to manage the procedureassociated pain and to obtain a better control of the respiration movements during treatment.
In thirty patients HIFU treatment was performed only once, but in two cases the procedure was repeated 2 months later to ablate the remaining tumor. The median intensity of treatment was 350 Watts, which corresponds to a median temperature of 70 degrees Celsius. The HIFU device in Clinical responses (thermical ablation achieved of the pancreatic tumor) were measured at 4, 8, 12 and 16 weeks by CT Scans, MRI and PET image techniques, all of them available at our hospital. Response was considered positive if an ablation of more than 60% of the tumoral mass was achieved. Two experienced radiologists reviewed results. Patients with poor hematologic conditions, previous radiotherapy treatment or poor Karnofky's index were excluded. Responses obtained were measured under RECIST criteria. The complications were also analyzed.

Results

Clinical responses in terms of ablation obtained were 82% in all cases, confirmed and sustained at 8 weeks of the procedure. We obtained 8 complete responses (25%) at the end of the combined treatment of HIFU plus systemic chemotherapy, 7 from stage III patients and 1 from stage IV. The longest survival since treatment is 2.5 year. At the time of this writing, twenty-two patients had died and ten were alive. The overall median survival time was 12.5 months (range, 6–30 months). Patients died as a result of cachexia, hepatic dysfunction caused by liver metastases untreated with highintensity focused ultrasound, peritoneal carcinomatosis or other systemic progression of the disease.
Major complications were registered including severe pancreatitis with GI bleeding (one case), skin burning grade III that required plastic surgery (2 cases). No deaths were registered due to the procedure. None of the patients needed emergency surgical procedures due to complications. During the hospital stay, no signs of tumor hemorrhage, large blood vessel rupture, or gastrointestinal perforation were detected in any patient. No dilatation of the common bile duct or pancreatic duct was visible at follow-up imaging. There was no evidence of post-interventional peritonitis, or jaundice in any patient during the follow-up period.

Discussion

US-guided HIFU is a feasible technique with no mortality, low morbidity and promising results. At present, there are several ablation techniques employed to treat tumors in different locations. Radiofrequency, cryotherapy, ethanol injection, or embolisation are considered for tumors in several locations except pancreas tumors. Recently, several papers have emphasized the use of HIFU for pancreas tumors [3, 4, 5]. Anatomical locations of these types of lesions preclude the use of the above-mentioned procedures but allow the treatment with HIFU. In our study, the high percentage of responses obtained in terms of meaningful ablation achieved (82%) confirms this assumption. Hyperthermic ablation techniques role in cancer patients need to be defined.
The increased prevalence of pancreatic tumors as well as the better results obtained with the combination of chemotherapy plus best supportive care of these patients, raise the issue of cytoreductive treatments addressed to control loco-regional progression of the disease. Ablation techniques in those cases, and HIFU among all of them, may play an interesting role, supported by its results and low morbidity obtained. In our study no significative morbidity was added to decrease the quality of life on our patients. Longer survival compared with the statistics reported in the literature reinforces our tumor ablation program with HIFU.
Where surgery does not arrive. There is a subgroup of patients that can be specially benefited with HIFU ablation techniques [6]. Patients with stage III tumors due to minimal vascular invasion that are not candidates to surgical resection may become free of disease after HIFU ablation. In our results 7 patients from our group of Stage III patients achieved a complete response, 4 of the still alive at the writing of this article. Need for multicentric studies: reporting, assessment and duration of response remain as controversial issues that need to be clarified in the coming studies.
There are difficulties to analyze percentage of response with tumors in the pancreas head. PET Scans are still difficult to evaluate when SUV is in its limits. In those cases inflammation and tumor recurrence are not clearly distinguished. Because 90% of the patients with pancreas tumors are diagnosed with regional or distant disease and do not have effective modalities of treatment, we are very encouraged with the results of our experience. We suggest that HIFU is a feasible, safe and effective technique to control local disease in stage III pancreas tumors that need to be tested in randomized clinical trials.

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Figures

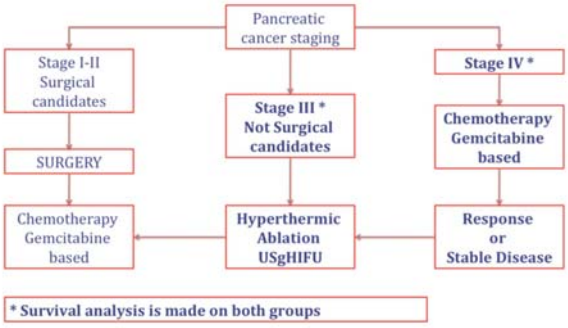

Figure 1. Pancreas cancer clinical pathway

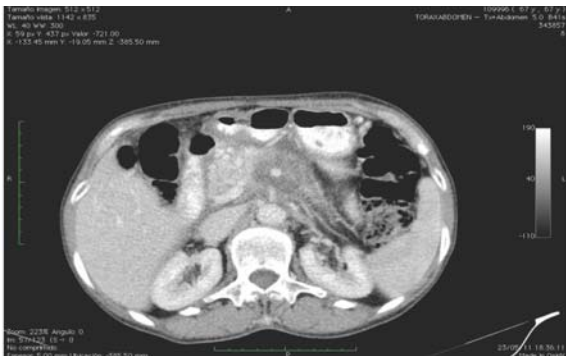

Figure 2. CT scan of tumor ablated in pancreas body preserving superior mesenteric artery

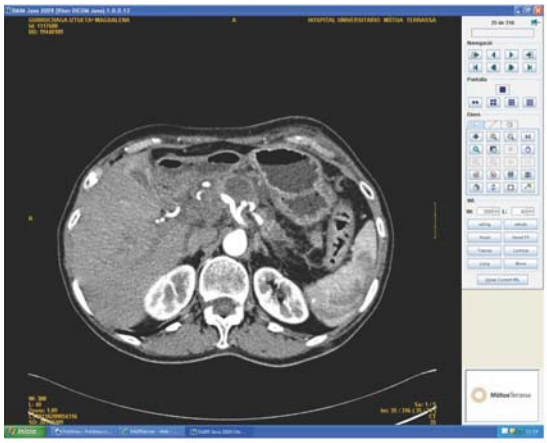

Figure 3. CT scan of tumor ablated in pancreas body above celiac trunk

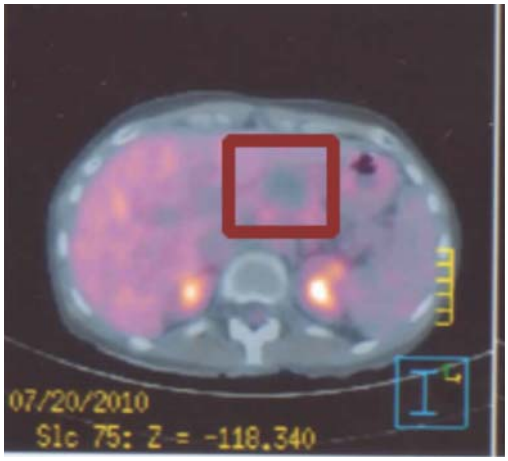

Figure 4. Pet scan of the Figure 2. case showing complete response on the tumor site

Figure 5. The US-guided HIFU device JC 200

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Chemotherapy combined with regional hyperthermia in locally advanced unresectable pancreatic cancer: clinical and anthropological benefits

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Chemotherapy combined with regional hyperthermia in locally advanced unresectable pancreatic cancer: clinical and anthropological benefits

Today the adenocarcinoma of the pancreas shows a significant increase of incidence, mainly in western countries. This tumor tends to affect mainly the male population, smokers and has a marked effect in proportion to the increase of age. Recent studies have shown a correlation between pancreatic cancer and diets high in animal fat and protein, and the role of coffee is discussed. The symptomatology is often delayed and is mostly characterized by obstructive icterus, in the case of localization in the head, and of pain for involvement of nerve fibers both in the retroperitoneal tumors of the head and body-tail. It frequently turns out to be the weight loss caused by maldigestion to reduced synthesis and transit of pancreatic enzymes. The prognosis of this cancer is poor, with lower survival than 12 months. Regardless of treatment, these tumors are often surgically inoperable forcing the surgeon to palliative shunt, moreover chemotherapy and radiation therapy are of little prognostic impact. The clinical radiofrequency hyperthermia (HT) shows, in recent experimental studies, to have anti-tumor effects in combination with chemotherapy based on new drugs. The treatment with capacitive hyperthermia (HT) shows antitumoral effects associated with chemotherapy (CHT) treatment which consists of gemcitabine (GEM) alone or it is in association with oxaliplatin, cisplatin, or 5-FU (1, 2, 3, 4, 5). This method presents a considerable operational simplicity and a very low incidence of complications, as well as, with equipment of recent introduction excellent tolerability by patients. The interest in hyperthermia has been growing in recent years, as it has been shown that drugs commonly used in cancer therapy may have greater efficacy at the same dose, or retain the same efficacy with lower doses when administered in association with hyperthermic techniques.

The advantages of the results can be summarized as follows: a more simple use of chemotherapy and radiotherapy, then undoubtedly better tolerated by patients, and in a stimulation of the immune reactivity, notoriously depressed in neoplastic patient. For these reasons the radiofrequency hyperthermia is considered a viable technique of enhancement of the action of other therapies (chemotherapy, immunotherapy, radiotherapy) allowing in many cases a stoppage phases of the disease for a more or less long time, allowing the maintenance of conditions of survival satisfactory, and in some cases even a reduction of the tumor mass. The current technology has allowed the development of highly sophisticated equipment, equipped with liquid-cooled and flexible antennas, thus allowing us to prolong the treatments without discomfort for patients and with no particular side effects.
The aim of this study was to evaluate the action of CHT associated with regional Hyperthermia (HT) tested on a group of 25 patients suffering from locally advanced unresectable pancreatic carcinoma (LAPC).

Materials and methods

We used a radiofrequency hyperthermia equipment SYCHROTERM RF 13.56 MHz, equipped with a liquid-cooled flexible antennas with a diameter of 26 cm, positioned in epigastrium-mesogastrio at the Center for Clinical Hyperthermia, Policlinico Tor Vergata, University of Rome "Tor Vergata". The treatment was based on a median of 3 cycles structured in 8 sessions of 45 minutes each, on alternate days, using about 250 W for a session. The group of 25 patients treated (12 male and 13 female) was selected on the basis of the characteristics of inoperability of the tumor (locally advanced unresectable pancreatic cancer) with a life expectancy of ≤ 12 months. At the same time patients underwent chemotherapy based on gemcitabine and fluorouracil, in period from 02/2001 to 07/2009. The outcome of the treatment was determined by CT, preliminary and 20 days after the last session of chemo-hyperthermia. We considered responding patients who reported reduced or stable disease.

Results

The study was performed on 25 patients, at our center clinical hyperthermia in the period 01/2001-07/2009, suffering from locally advanced unresectable pancreatic cancer (LAPC). The group consisted of 12 males and 13 females with a mean age of 64 years. All patients received chemotherapy according to the protocol

gemcitabine-oxaliplatin. Median overall survival (OS) was 16 months in the group CHT+HT vs 8-11 months as reported in literature.
Survival was 19 patients (76%) at 12 months, 12 patients (48%) at 18 months, 11 patients (44%) at 24 months of and 9 patients (36%) over 24 months (see Table 1.).

n.	Survival	n. patient	%
1	Survival 12th month:	19 pts	76%
2	Survival 18th month:	12 pts	48%
3	Survival 24th month:	11 pts	44%
4	Survival over 24th month:	9 pts	36%

Table 1.

We did not observe effects or increase toxicity in CHT.

Conclusion

Anticancer nucleoside Gemcitabine, Oxaliplatin and 5 FU have dose limiting toxicities (DLT)Major side effects of Gemcitabine include bone marrow suppression, flu-like syndrome and severe hepatic toxicity.(6, 7, 8, 9, 10)
The application of Regional Hyperthermia (HT) on this restricted group of patients has given out very interesting results. The HT + CHT can reduce the tumoral increase, can raise the survival of the patients and, above all, the HT can improve general conditions of the patients that have been treated with this kind of associated therapy. The results justified further evaluation in a large number of patients to confirm the benefit.
The Hyperthermotherapy improved the quality of life of all responding patients.
Compared to the severe physical, existential and esthetic impact of the chemotherapy alone, patients with Hyperthermia do not experience particular side effects. As a consequence of that, patients are less anxious in facing the treatment; they establish a fruitful empathic relation with cares and doctors. So, the anguish proceeding the moment of cares (CHT) turns now into a necessary but not threatening and foreboding moment (11, 12, 13, 14, 15). Physiotherapy intervention, too, has something to offer throughout the whole cancer journey, including for patients who are not curable and whose life is limited.

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New cancer paradigm and new treatment: the example of METABLOC

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New cancer paradigm and new treatment: the example of METABLOC

Abstract

Hyperthermia has long been known to interfere with the tumor metabolism. The goal of this presentation is to review the potential of metabolic therapy and to suggest that its combination with hyperthermia may be of interest.

Objective

In a land mark article, John Bailar published in the "New England Journal of Medicine" in 1997 the article: Are we losing the war on cancer? We recently confirmed that is still the case. We obtained mortality from the World Health Organization time-series data of 20 countries over 45 years (1961-2005). During these 45 years the age standardised cancer death rate has varied little (-4%). There has been a slight decrease in breast cancer (-6.5%), lung cancer in men (-2.5%), prostate cancer (-1.7%) but there was a sharp decrease for stomach cancer (-77%).These data confirm the preliminary results of Bailar and contradicts the notion of a breakthrough in cancer prevention, early detection and cancer treatment (Summa 2012). Today, as before, metastatic cancer to the notable exception of some childhood malignancies and of lymphoma remains almost universally fatal.

Today cancer is thought to be an invasion by malignant cells which deserve to be killed either by surgery, radiation therapy or chemotherapy. The screening of new drugs is done by assessing their efficacy in killing cancer cells. Modern drugs target one specific pathway in order to kill the malignant cell. But the logic is still the same: killing the cancer cell. None of these new drugs can be credited in having significantly changed the survival pattern. For example, the overall response rate to Herceptin (a so called magic bullet) when administered alone is less than 5%.

In the meantime the cost of cancer drugs has been increasing exponentially. It is highly probable that we are witnessing a "bubble" based more on goodwill, and hope than on results.

There is an obvious need for change of paradigm. This change is not only scientific (in reassessing what cancer really is) but we also need to change the way we conduct clinical trials. This change of paradigm will be a dramatic change in medical strategy and in the financial cost to society.

Cancer is widely thought to be the consequence of genetic abnormalities such as oncogene activation or tumor suppressor inactivation. This is correct but it is only a partial view of the disease. For example, there is oncogene activation in normal cells or during development of benign inflammation. There are alternative ways to understand cancer. The most promising is considering cancer as a metabolic disease, as a disease related to diabetes.

Metabolic aspects of cancer: Otto Warburg

Cancer is not only a genetic disease but also a disease of the metabolism. Since the work of Nobel Prize winner Otto Warburg, we have known that the metabolism of cancerous cells clearly differs from that of normal cells (Warburg 1956; McKnight 2010). Cancerous cells consume higher amounts of glucose than they are able to fully degrade (Van der Heiden et al. 2010). This is the actual basis for PET scan imagery, in which the intravenous injection of a radioactive substance similar to glucose is used to visualize the cancer and its metastases. This fact, which had long been forgotten, is starting to surface again. A considerable amount of recent work, including our own, shows that this metabolic disorder could be the source of the cancer development process (ref in Israel & Schwartz 2011).

Otto Warburg, published his observations regarding a metabolic alteration frequently observed in cancer cells in the 1920's (Warburg). Warburg reported that the cancer cells he investigated metabolized glucose directly to lactic acid, as opposed to the pyruvate being converted to water and carbon dioxide in the mitochondria via the tricarboxylic acid (TCA) pathway. This metabolic property of cancer cells bears his name, that is, the Warburg effect. It is also referred to as aerobic glycolysis, as it takes place in cancer cells even under normoxic conditions.

Interest in the Warburg effect has been waning considerably for a long period of time. Part of the reason was the fact that Warburg was convinced that the altered glucose metabolism in cancer cells was actually

the cause of cancer and that the most likely explanation for his observation was the damage to the mitochondria (Warburg). Since then, modern molecular biology has demonstrated that cancer cannot originate without a change to a cell's genome and that, at least in most cases means damage to the mitochondria and it is not the explanation for why many cancer cells adopt aerobic glycolysis as the principal pathway for glucose metabolism (Robey, Moreno-Sanchez). However, during the last 15 years or so, there has been a considerable increase in interest regarding the Warburg effect and its role in cancer.
As a result, some seminal publications have elucidated the role that the Warburg effect plays in cancer, and there are a number of recent excellent reviews as well (Van der Heiden, Feron, Kroemer). Warburg understood that there is a prevalent defect in the anabolic pathway. He did not understand that the oxidative pathway (catabolism) is also flawed.

Change in metabolism explain prominent features of cancer such as carcinogenesis and response to chemotherapy

There is a wide consensus today on the importance of metabolism in cancer (Van der Heiden, Feron, Kroemer). Prominent features of cancer can probably be summarized by metabolic changes. For example the oncogene targets the metabolic pathway (for review see Israel and Schwartz: cancer as a dysmethylation syndrome). A retrovirus can capture a gene, from a host cell and transmit it to a new host. Retroviral oncogenes disturb a major signaling pathway: the MAP kinases mitogenic pathways while the different steps of PI3 kinase pathway are targets for DNA viruses. Oncogene can thus be seen as metabolic perturbator.
To confirm the role of metabolism in carcinogenesis, we exposed normal melanocytes (from adolescent's foreskin) to high dose glucose and insulin. The proliferation increased (doubling time: 2.7 vs 5.6 days). After 3 weeks of exposure to glucose or after 3 weeks followed by 4 weeks culture in standard medium, melanocytes were able to grow in soft agar colonies, a feature of cancer cells (Morvan 2011).
Most anticancer drugs target the DNA, but their precise mechanism of action is debated. It is clear that even when the treatment is effective in patients with large metastatic disease, there are no signs of cell death. Minutes after the beginning of a small cardiac infarct, there is an increase of intracellular protein in the circulating blood. This is not the case after chemotherapy. However, the first sign of response of treatment is a decrease of glucose uptake as demonstrated by the PET scan. Cancer drugs can kill cancer cells (it is what they are selected to do), but when a cell survives it stops to grow for days or weeks. This resting phase has not been studied deeply, it is technically difficult (only a few cells survive) and time consuming. We were able to demonstrate that this growth arrest was because of a switch in metabolism (Guenin 2007).

Targeting cancer metabolism: background

There is considerable logic in targeting metabolic changes as an approach to the development of pharmaceutical agents to treat cancer despite the fact that these changes are not causal in nature. A relatively recent publication has shown that the genes involved in glycolysis are over-expressed in at least 24 different types of cancers that correspond to approximately 70% of all cancers (Altenberg). It has been hypothesized that this widespread prevalence is because aerobic glycolysis provides a competitive advantage to cancer cells, allowing the synthesis of compounds (ribonucleotides and lipids) required for proliferation (Gatenby 2004, Bui, Gatenby 2006).
A number of specific inhibitors of key enzymes involved in the aerobic glycolytic pathway have been evaluated as potential anti-cancer drugs (see reviews Yeung, Pelicano,Michelakis). However, with rare exceptions none of these compounds has been used clinically. Michelakis reported that treatment of five patients with glioblastoma multiforme using dichloroacetate, an inhibitor of pyruvate dehydrogenase kinase, resulted in tumour regression in three individuals. Berkson treated four pancreatic cancer patients with a combination of lipoic acid and naltrexone with excellent results. The first patient treated was still alive and well 78 months after presentation. Somewhat coincidentally, α-lipoic acid is also known to be an inhibitor of pyruvate dehydrogenase kinase just like dichloroacetate.
Naltrexone, on the other hand, is an opioid receptor antagonist and is primarily used for the treatment of alcohol and opioid dependence, although there are limited data suggesting its potential role in cancer inhibition.

This relative lack of success suggested to us that a single inhibitor of cancer cell metabolism might be insufficient to significantly inhibit cancer proliferation. Given the extreme plasticity of malignant tissue, it

seemed logical to attempt to use at least two different compounds, each one targeted to interact with enzymes catalyzing different steps. We adopted a strategy to use compounds already proven to be nontoxic in humans.

Screening for a "universal" metabolic combination

In 2004, we started collaborating with other scientists, among them was Dr. Maurice Israel, we focused their efforts to discover a way to take advantage of one of the weaknesses of cancer: its poorly effective metabolism. Instead of targeting the mitotic process, they chose to target the metabolism of the cell (Israel & Schwartz, 2005).

In June 2007, the second phase of this work began with the selection of about a hundred molecules potentially active from literature analysis. Focusing on the metabolic alterations of cancer cells, we identified molecules that have been described to act on enzymes which activities are known to be affected in cancer. Our second selection criteria was the existence of data on human administration for these molecules. This approach allowed us to select 27 different molecules.

In the first animal study (Schwartz 2010), a detailed literature analysis was conducted from which the first library of twenty-seven drugs that are known to target pathways potentially implicated in cancer was developed. We conducted in vitro tests on these molecules to determine their antiproliferative capacity on four cells lines at concentrations consistent with published human plasma levels. The data, summarized in Table 2, showed that 5 molecules were not effective, 11 molecules were weakly effective, while 11 molecules were significantly effective.

Thus, this preliminary study (see Schwartz et al. 2010 for details) suggested that a combination of ALA with HCA may have a high antitumoural potential. This efficacy was similar on whatever the cell line was tested. Our group tested 15 combinations of two drugs based on the seven effective and least toxic molecules. Seven combinations showed a strong antiproliferative effect (< 20% of viable cells after 24 hours). They were: acetazolamide and hydroxycitrate, lipoic acid and dichloroacetate, lipoic acid and hydroxycitrate, acetazolamide and miltefosine, albendazole and dichloroacetate, dichloroacetate and hydroxycitrate, lipoic acid and miltefosine.

In vivo antitumoural effect

We then proceeded to test these seven most effective combinations in vivo using mice bearing syngeneic MBT-2 bladder carcinoma. The majority of the combinations were not or only weakly effective (data not shown). The most effective treatment was the hydroxycitrate and lipoic acid (designated as METABLOC™) (Schwartz 2010). The efficacy of this combination was confirmed in B16-F10 melanoma and LL/2 Lewis lung carcinoma. This combination both drugs slowed growth of the tumour and increased survival with an efficacy was similar to conventional cytotoxic chemotherapy. This combination is effective whatever the tumor model is like, suggesting that these metabolic pathways are crucial for cancer survival.

The compositions were tested against different murine tumour models (MBT-2 bladder carcinoma, LLC Lewis lung carcinoma and B16F10 melanoma implanted in syngeneic C3H mice (MBT-2 cells) or C57Bl6 (LLC and B16F10 cells). Tumour cells were inoculated in the flank of the mice and the tumour developed for few days before the beginning of the treatment. After randomization, the combination and also the control compositions were administered intraperitoneally, for 21 days. The change in tumour development was monitored by measuring the size of the tumours with a Vernier caliper and monitoring the survival of the animals during the experiment. The mice used in this study were treated in accordance with the ethical regulations in force. In the described results, the following doses and schedule of administration were used: alpha-lipoic acid 10 mg/kg, twice a day; hydroxycitrate 250 mg/kg, twice a day.

The combination was used to treat mouse syngeneic cancer models: MBT-2 bladder transitional cell carcinoma, B16-F10 melanoma and LL/2 Lewis lung carcinoma. The efficacy of this combination appears to be similar to conventional chemotherapy (cisplatin or 5-fluorouracil) as it resulted in significant tumour growth retardation and enhanced survival (see Figure 1.) (for details see article by Schwartz 2010).

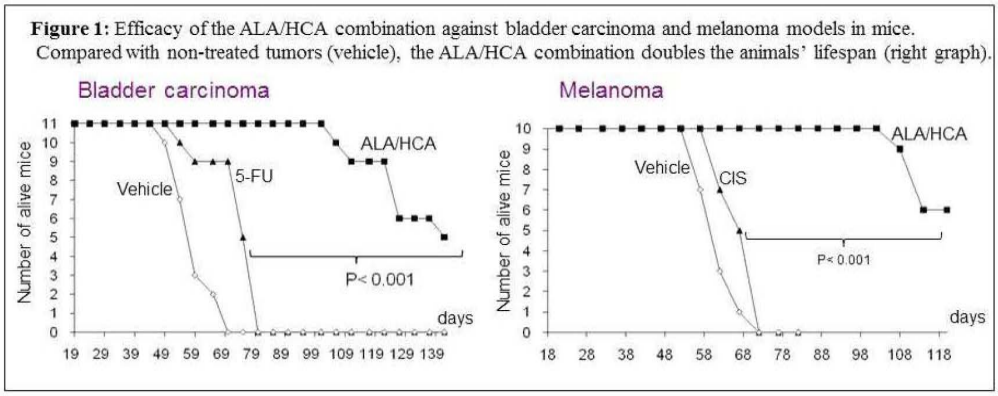

Figure 1.

These complementary studies suggest that combination of ALA anc HCA is efficient against cancer cell proliferation.

The addition of a forth molecule (see Figure 2.), capsaicin was responsible for tumor regression (Schwartz invest New Drugs 2012). None of these four different compounds is known to target the DNA. The all interfere with the metabolism.

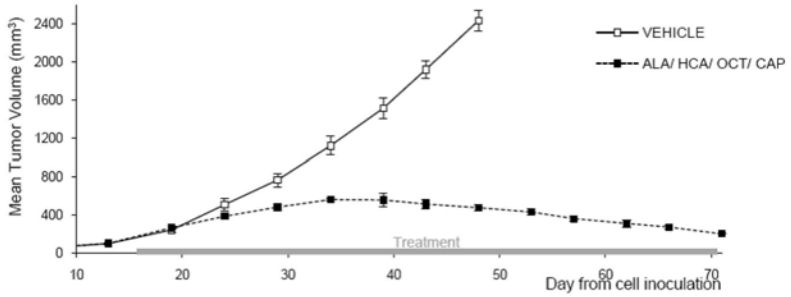

Figure 2. Anti-tumor activity of the alpha-lipoic acid, hydroxycitrate, capsaicin and octreotide combination in the melanoma model

Clinical data obtained with metabloc

At this stage, there is only preliminary data on the combination of these two molecules. The toxicity trials were conducted using increasing dosage of oral lipoic acid and hydroxycitrate. This treatment was added to standard anti-cancer cytotoxic chemotherapy. There is no trial using intra-venous combination of these drugs.

Eleven patients, five males and six females, were treated according to the standard protocol in use for their cancer type and stage between January 2009 and July 2011.

In addition to the normal chemotherapeutic regimen, a combination of ALA and HCA was administered to patients, after the informed consent was obtained, and both the results and side effects were registered. All patients had a histologically proven malignant disease. Follow- up data on patients was collected at a mean interval of 65 days, with a large range (40-90 days) for those patients with disease stabilization.

The minimum oral dose administered for ALA was 0.4 g/day, and the maximum dose was 1.8 g/day. The minimum dose for HCA was 1.2 g/day and the maximum dose was 3g /day.

The recorded side effects were related to the respective chemotherapies administered except for gastrointestinal disorders of mild intensity. Three patients (1 male, 2 females) out of 5 (3M, 2 F) treated with higher doses of ALA and HCA, 1.8 g/day and 3 g/day respectively, had a number of grade 1 to 3 side effects including stomach pain, diarrhea, nausea, and in 2 cases weight loss.

These side effects disappeared on using proton pump inhibitors, such as esomeprazole or lansoprazol, or by decreasing the dose. Seven patients (3M, 4F) tolerated the ALA plus HCA treatment without side effects. Two of these patients were administered proton pump inhibitors as part of their treatment, but the other five had no accompanying treatments. The minimum duration of a treatment was two months while the maximum duration was 21 months.

The patient affected by a pancreatic adenocarcinoma with liver metastases displayed tumour regression during a few months. She then spontaneously stopped her treatment and subsequently died. However, her survival was prolonged up to 18 months (Guais et al. 2010 for detailed description). Another patient with widely metastatic colon adenocarcinoma four years after the start of the treatment (Schwartz, 2012 submitted); however, the cancer finally recurred. Most of the patients receiving treatment for more than 6 months displayed partial regression or stabilization. Of the eleven patients, 5 were characterized by partial regression, 3 by a stable disease, and 3 by disease progression.

The combination of oral ALA and HCA with chemotherapy is well-tolerated. Side effects are primarily restricted to the gastrointestinal tract and can be avoided by decreasing the doses or preferentially by using proton pump inhibitors. The optimum dosage remains to be established by more clinical cases and a controlled clinical trial. However, these preliminary treatments support that METABLOC™ can be used safely with various common standard chemotherapeutic regimens (Baronzio 2011).

Conclusion

Since the work of Nobel Prize winner Otto Warburg, we know that the metabolism of cancerous cells clearly differs from the normal cells. Cancerous cells consume higher amounts of glucose than they are able to fully degrade. The changes in metabolism are universal features of cancer. This is the actual basis for PET scan imagery, in which the intravenous injection of a radioactive substance similar to glucose is used to visualize the cancer and its metastases. While Warburg described the effect that now bears his name, he did not understand the very reason behind it. We have probably understood it. It is probable that cancer is a simple metabolic disease closely related to diabetes.
To this day, we have outlined the enzymatic anomalies responsible for the Warburg effect and determined the therapeutic targets. We have devised a strategy against cancer by blocking the few metabolic pathways that feed its development.

Our work (theoretical and experimental) demonstrates that restoring the normal fluxes decreases tumor growth. This work conducted over the past eight years has enabled us to identify therapeutic targets and active molecules. Combinations of two of these compounds have revealed to be efficient in murine tumor models: alpha lipoic acid and hydroxycitrate. There is, as of today, no resistant cell line both in vivo and in vitro. Accordingly this combination slows tumor growth in every tumor model (lung cancer, bladder cancer and melanoma). These data were confirmed in an independent second laboratory. These molecules have an excellent safety profile that has already been approved for other medical applications than cancer. Early clinical work confirms an excellent safety profile and strongly suggests efficacy.

The long forgotten cancer metabolism, is now reaching headlines with tens of new molecules being developed, one at a time, both by the industry and by the academia. Our approach is different. We focus on the combination of well established and inexpensive drugs or food supplement in order to speed the clinical development. If effective the treatment should not be limited to a peculiar primary tumor site.

An other way to interfere with metabolism is oncothermia. It is highly probable that the combination of these non toxic approaches will yield great results.

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Hypoxia, Immunity, Metabolism and Hyperthermia

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Hypoxia, Immunity, Metabolism and Hyperthermia

Keywords
Hypoxia, innate immunity, immune-suppression, glycolysis, tumor metabolism, hyperthermia.

Introduction
The local inflammatory reaction is characterized by an initial increase in blood flow to the site of injury, by increased vascular permeability and by an ordered influx of different effector cells, recruited from the peripheral blood and bone marrow to the site of lesion (1) Another characteristic of the inflammatory reaction is the presence of hypoxia and its modulation of innate immunity (2).
In this overview, we will analyze the influence of the hypoxic state on inflammation and compare its interaction in diverse disease states including cancer. Interestingly, the body's response to hypoxia in different pathological situations seems to be quite similar.

Hypoxia as a homeostatic response
Once hypoxia has developed, the undernourished and hypoxic cells present trigger signals, in order to obtain new blood vessels, in order to satisfy their ever-increasing demands. The principal signal activates an ancestral oxygen sensor, the hypoxia inducible factor (HIF). HIF is a conserved mechanism of defense present in mammals, aimed at reestablishing a supply of oxygen and nutritive substances.
After its nuclear translocation, HIF triggers a series of mediators such vascular endothelial growth factor (VEGF), and chemokines such as Stromal derived growth factor -1 (SDF-1), which orchestrate a series of processes able to recruit, from bone marrow, into the hypoxic (tumour) milieu, several immature myeloid, mesenchymal and endothelial progenitors cells (2-6). The bone marrow derived cells are of 4 types:

a) Circulating Endothelial Cells (CECS) (7,8);
b) Endothelial progenitor cells (EPCs), which are precursors of blood vessels (9,10);
c) Mesenchymal stem cells (MSCs) (11,12);
d) Immature myeloid derived cells (MDSCs) (13,14,15,16).

CECs and EPCs are cells able to form new blood vessels. MDSCs concur with them to support and promote all the reactions useful to angiogenesis, but are unable to form the neovessels alone. MSCs, have the ability to transform into fibroblasts, to coordinate the inflammatory reaction, and also to support cells of the stroma (17). In addition , MSCs play an important role in the repair of tissues with lesions and fractures. In the tumour, the excessive presence of IL-1 and PGE2 triggers an autocrine process that leads to tumor progression (18). The behavior of MSCs in tumour tissue is different than in myocardial infarction and stroke, where they cooperate to repair the lesion and reducing the inflammatory reaction. In fact, they behave differently in the primary tumour than in metastases, and usually give rise to the tumor associated fibroblasts (CAFs) and pericytes (19), that ultimately form a favorable stroma more useful to tumor progression and with immunosuppressive activity.

When MSCs become triggered by HIF, they participate in the repair of several diseased tissues and organs such as in myocardial infaction (4), stroke (20), fractures (21), rheumatoid arthritis (22), Alzheimers (23), Parkinson (24) ulcerative colitis(25) and kidney disease (26).
In a certain sense, it is possible to demonstrate that the reaction of the organism to a pathogen or other danger signal is a normal law of homeostasis and is tightly regulated (see the box below).

Hypoxia → HIF→ SDF-1-VEGF → CECs-EPCs-MSCs-MDSCs → Neutrophils→ Macrophages
→ repair / or remodeling → Hypoxia resolution

In fact, four to six hours after the start of the ischemic or hypoxic state, partly resident neutrophils provided by MDSCs begin to produce a series of free radicals and proteases. In both the heart and the brain, areas of ischemia show these reactions which initially seem harmful, somehow sharpening the event (11, 27),

however after this cleaning operation they help to decrease the inflammatory reaction. In both stroke and myocardial infarction they collaborate through several known mechanisms (11, 27).

Neutrophils have a very limited life span, going rapidly into apoptosis and releasing among various other products lactoferrin. Lactoferrin has the ability to decrease the recruitment and the transmigration of neutrophils, permitting the arrival of macrophages. Macrophages not only act as scavengers but they also produce abundant immunosuppressive cytokines (TGF-ß; IL-10). Macrophages also produce decoy receptors of chemokines that participate to further decrease the inflammatory reaction (26, 28). A more recently discovered class of substances able to reduce the inflammatory response have been called Resolvins. (29, 30). In summary, the termination or the partial reduction of inflammation coincides with; the return of oxygenation, the coordination of leukocyte recruitment followed by macrophage recruitment, and finally the production of anti-inflammatory factors including resolvins.

Tumour hypoxia

Hypoxia is common in solid tumors, and areas deprived of oxygen and nutrients can develop in many different zones of the tumor, including those with strong vascularization (Fig.1). One of the reasons for its persistence is that neoplasia grows faster and at a pace not proportional to the neoangiogenesis (31-33). This persistence creates a vortex that continue to recruit neutrophils and MDSCs from bone marrow (34). In the tumour microenvironment MDSCs transform into type 2 macrophages, the so called M2 that produces an excess of molecules such as PGE2, TGF-ß and IL-10. These kinds of molecules can disorient the immune system to the point of making it ineffective (35). Furthermore the tumour is unable to produce resolvins in an adequate concentration (36- 38) for at least two reasons:

a) There is not an adequate concentration EPA and DHA in the cell membranes (principal substrates for resolvins).

b) There is an increase in COX-2 enzymes leading to overproduction of PGE2 (37, 38), which are not precursors for resolvins.

This is a circuit that continues to feed itself on the basis of a normal homeostatic response of the organism. Tumours follow the general pathways of several diseases in which hypoxia is implicated (i.e. myocardial infarction, stroke, etc.), but differs from them significantly in the persistence of this hypoxia and the lack of the off switch (resolvins) (Fig.2, 3).

Another factor that seems to maintain the inflammation is the osmotic pressure. The overproduction of VEGF induced by HIF leads to increased vascular permeability, with loss in the interstitial tissue of albumin and other proteins. This loss, leads to an increased osmotic pressure that elicits the release of pro-inflammatory cytokines by macrophages (39 - 41). This factor alone would justify the use of hyperthermia for its ability to decrease the interstitial fluid pressure (42, 43).

Tumour vasculature is not necessarily derived from endothelial cell sprouting; instead, cancer tissue can acquire its vasculature by alternative mechanisms, such as vasculogenic mimicry (VM). VM is the hypoxia-adaptation mechanism of tumour vascularisation. Hypoxia-induced VM play an important role in tumour progression (44, 45).

Hypoxia metabolism

HIF not only plays an important role in inflammation but it also determines the metabolic conversion in tumours to anaerobic glycolysis, the so called “Warburg effect”. This increased consumption of glucose and its incomplete and inefficient metabolism is due at least at two factors:

a) An increase in membrane receptors for glucose (Glut-1 membrane protein) and

b) Blocking of pyruvate dehydrogenase & suppression of pyruvate conversion to acetyl CoA (46-48).

Hyperthermia and immunity

Can hyperthermia be used to modify this destructive and cancer-promoting circuit of Hypoxia, Inflammation, and then Hypoxia? Is it possible that hyperthermia can affect HIF expression and beyond that, immunity against malignancy?

This association between hyperthermia and tumor hypoxia & pH response has been known since 1990, in large part because of the work of Koutcher JA and Gerweck LE on Glioblastoma and other tumours (49, 50). What's more, hyperthermia's activity as a radiation sensitizer is well known(51 -55). Hyperthermia, in almost every way it has been applied, consistently seems to affect immunity through several known mechanisms (56 - 58). Hyperthermia enhances the antigenic presentation to effector cells, recruiting macrophages, natural killer cells, regulatory cells and neutrophils to the tumour area (56-58). The association with radiotherapy and the favorable changes to the tumour microenvironment by hyperthermia, as outlined by Muthana, can affect regulatory cell behavior and macrophage activity (59). In fact, the concurrent use of hyperthermia with radiotherapy can decrease the recruitment of regulatory cells, compared to hyperthermia alone, and also the behaviour of macrophages seems to be affected by this association, ultimately decreasing their M2 types (60). The macrophage programming in the tumour microenvironment is a hallmark of cancer, with its auto - sustaining abilities regarding inflammation (58). The increase of heat shock protein (HSP) induced by hyperthermia (61), particularly HSP 70, has been found to act as a recognition structure for natural killer (NK) cells, increasing their activity (62 - 63). In vivo hyperthermia triggers innate and adaptive immunity aiding in tumour eradication (65 - 66).

Conclusions

The explanation of these specific components of tumour biology in this way is not meant as an oversimplification, but is meant as an effort to show that tumour biology is not all chaotic, but that they follow some normal routes of repair. Tumours exploit some of the weaknesses of the body, and profit from normal attempts of the body to repair and recover organ integrity and functionality. In the words of David B Lowe, by minimizing exposure to risk factors that contribute to chronic inflammation, and reconditioning the patient into a state of acute inflammation, we could have a significant decrease to cancer incidence and improvements to life prolongation (67). Hyperthermia in this context can have a significant role as an inducer of acute inflammation (65- 66).

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Electrochemical therapy of tumors

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Electrochemical therapy of tumors

Abstract

Application of electric current for the tumor-destruction has a long time history. The theory of the direct galvanic current (galvano-therapy, GT) is worked out by B.Nordenstrom in the frame of biologically closed electric circuits (BCEC). Later GT was extended by chemical considerations (EChT) and starting with pioneering work of Professor Xin YouLing, a wide, intensive application had been developed in China. My objective is showing the principles and practice of the EChT treatment modality for multiple advanced lesions.

1. Introduction

The efficacy of electrochemical therapy (EChT) in mice with implanted Jensen sarcoma tumors was reported in 1953 by Reis and Henniger [1]. However, the clinical application of this modality was initiated by the Swedish radiologist, Bjorn Nordenstrom. In 1983, he published a book in which he described his theory of biologically closed electrical circuits (BCEC) and the results of two decades of research on EChT treatment of malignancies in animals based on this [2]. He also reported the results of EChT in 20 lung cancer patients with 26 tumors in which he used the "skinny needle" he had developed for biopsy purposes as an electrode.

Follow-up after 2 to 5 years revealed that 12 tumors had either disappeared or were markedly reduced in size. This study stimulated interest in utilizing EChT for treating lung malignancies, and Japanese researchers subsequently confirmed Nordenstrom's results in animals and in several patients [3-7]. Anyway, the real application of the technique widely has begun in China (China-Japan Friendship Hospital as the center of this application) after it was introduced to the country in 1987. Electrodes which special produced by platinum were inserted into tumor and connecting its with an apparatus, the current arouse strong chemical reactions around electrodes and lead degeneration and necrosis of tumor cells. It is a new type method to treat tumor without surgical resection. The final result is caused by current inducing chemical reactions, so we call it EChT.

The advantages of EChT are that it is much safer, easier to administer, and less costly than surgical procedures and can be just as effective in certain instances. In addition, it provides an opportunity to treat tumors in those patients in whom surgery, radiation, and/or chemotherapy has not been successful or may be contraindicated.

2. Experimental studies on mechanism of EChT

It has been well established that tumor cells are more sensitive to certain changes in the environment than adjacent normal cells. Various treatment approaches, including radiation, chemotherapy, hyperthermia, microwave, laser, and antiangiogenesis strategies, are based on these differences.

Multiple pathological changes occur in the tumor tissue during EChT such as pyknosis of nuclei, disruption of cell membranes, disappearance of mitochondria, as well as coagulation and necrosis of nuclear proteins [2]

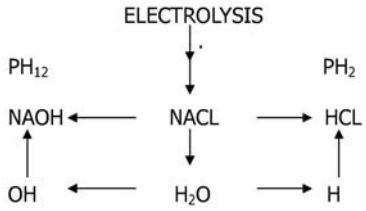
In animal experiments, histopathological studies have demonstrated that the killing effect of EChT on tumor tissue in the anode area differs from that around the cathode area. Tumor tissue at the anode shows coagulation necrosis with destroyed cellular structure, pyknosis of cells, and denaturation. Tumor tissue around the cathode has a different pattern, it is characterized by necrosis due to liquefaction, complete disruption of cell structures and accumulation of water molecules due to the presence of positively charged sodium ions, large protein molecules. Although the features of damage are different in anode and cathode areas, the extent of tissue destruction is about the same [8].

On the basis of large amount of animal experiments and clinical pathological examination, the mechanism of killing action of EChT is electrolysis by direct electric current induces pH changes in the environment.

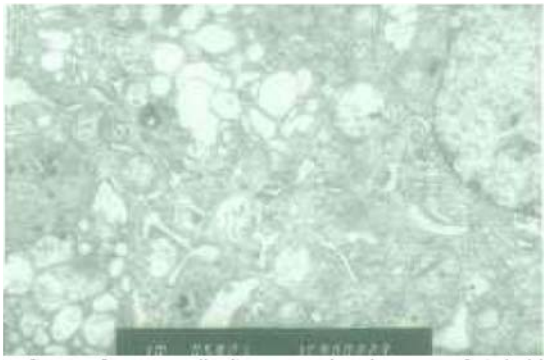
The killing action of DC per se is limited only around the surface of electrode. To expand the killing effect are the substances resulted from electrolysis of water and electrolytes, NAOH and HC1 that disseminate a certain distance from the electrode. Na+ formed after electrolysis will move toward the cathode and combine with OH ions to form NaOH which yields a strong alkaline environment (pH 12-14). Chloride ions accumulate around the anode and combine with H + to form HC1, which is strongly acidic (pH 1-2). The strong alkalinity and acidity are the main destructive mechanisms of EChT. During the application of

electrochemical therapy, large amount of foam ooze out from the surface of the electrode releasing Cl2 and H2O2 [9]. There are, however, additional mechanisms of action which are operative during EChT of tumors.

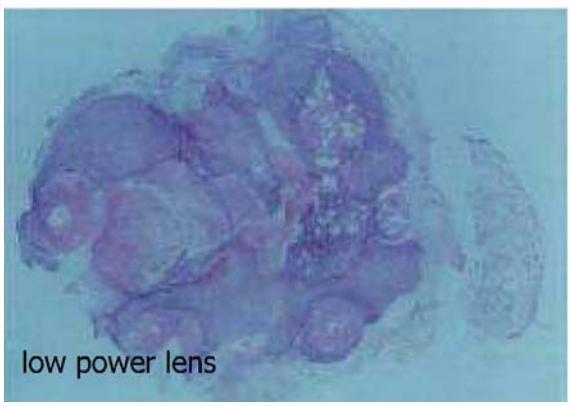
These can be summarized as follows:
The application of electric current increases the permeability of the cell membrane of tumor cells that allows ions to migrate inside cells and exert antitumor effects. Activity of enzymes in plasma can be released; proteins will be denatured and coagulated and precipitated whereby necrosis may be induced. Electrolysis changes the distribution of ions, which results in necrosis around the anode and edema around the cathode. That in turn, results in biological effects. Coagulation and extensive embolism may occur in blood vessels in the anode area, whereas significant edema in cathode area results in blockage of the microcirculation, and the blood supply to tumor cells is interrupted.
White blood cells and T lymphocytes accumulate in the anode area that may also have antineoplastic effects. At the same time, the negatively charged tumor cells are attracted to the anode so that metastasis of tumor cells may be hindered or prevented. Fragments of damaged tumor cells resulting from direct electric current application could serve as antigens and stimulate the body's immune system defences [4-7, 10].

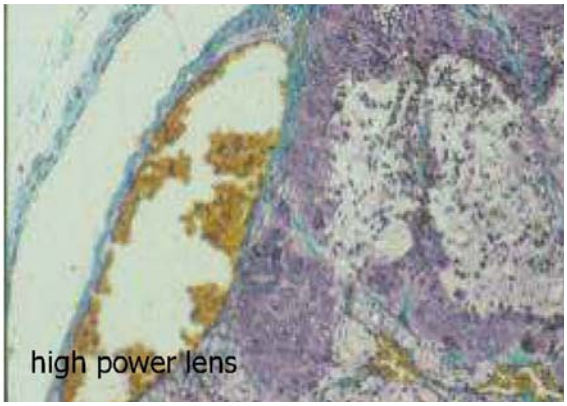


The strong alkalinity and acidity are the main killing factors of EChT.

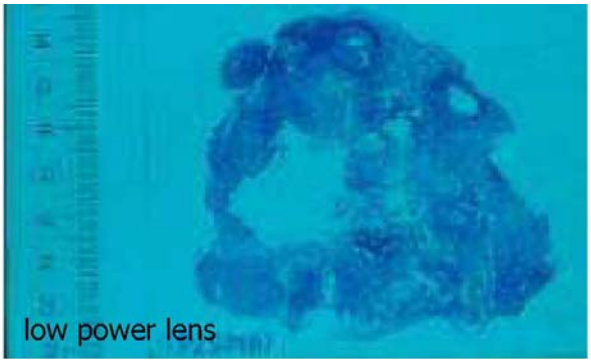


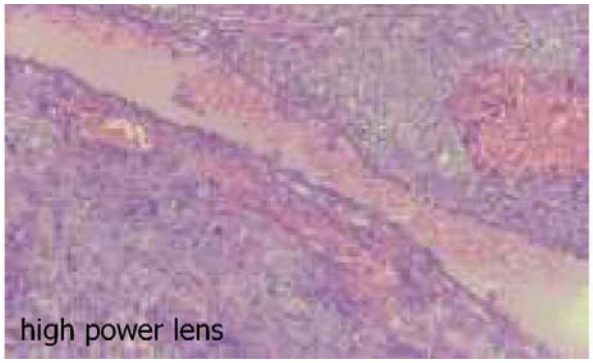
The figure of cancer cells disappeared and a mass of air bubbles came forth 10 minutes after beginning EChT.





The anode made tumor tissues dehydrated & carbonized, protein coagulated & necrosis.





Cancer cells were dissolved & breakdown, congestion & edema of tissue were representaed in the area of cathode.

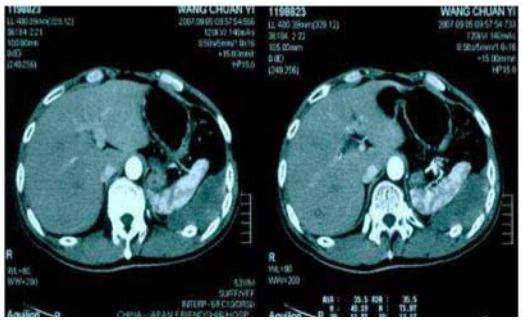
3. Clinical application of EChT

The clinical applications of EChT to treat cancer began in 1983. In that time Nordenström reported 20 cases of lung cancer (26 tumors in number) which he treated with EChT. There were only 10 cases (12 tumors in number) disappeared or obviously reduced.
From 1987, the China—Japan Friendship Hospital in Beijing took the lead to using EChT, and they have finished more than thousands therapy for many kinds of malignant and benign tumors.

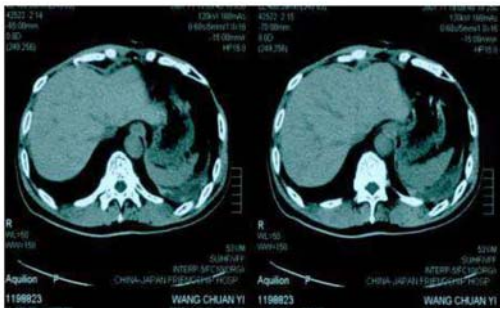
(1) Indication of EChT
When a cancer patient is not suitable for surgical operation, or radio-, chemotherapy are not effective, EChT may show its special effectiveness. The superficial tumors are well indication of EChT, such as cancer of head and face, breast cancer, parotid cancer, cancer of oral cavity, cancer of toque, cancer of superficial lymph node, melanoma, rhabdomyosarcoma, cancer of vulva, cancer of penis, etc.
Electrodes can be inserted accurately and arranged properly for those cases. Electric field for treatment can cover the whole cancer. Position and number of electrodes should be adjusted at anytime necessary. EChT could have satisfactory result if other treatment is ineffective.
Especially for late stage patients that have ulceration on the tumor (for example, local recurrence of operated breast cancer) which was not effectively treated in the past.
EChT can be a complementary method for surgical operation. For the cases which cannot be operated during thoracotomy (central type of lung cancer, mediastinal tumor), electrode could be inserted accurately to treat tumor.
It is the same for abdominal surgery and gynecological operation for cancers which could not be resected. (liver cancer, kidney cancer, pancreas cancer, ovarian cancer, etc.). Symptoms could be relieved and there is effectiveness to certain extent. [11-15]
The effectiveness of treating benign tumors is even admiring. In fact, EChT has been shown to be a unique therapeutic method and superior to surgery for treating venous malformation since there is no bleeding and no scar formation so that in addition to a good cosmetic result, function is maintained. [15, 16]

EChT was applied on breast hypotrophy and endometriosis in abdominal wall and satisfactory result has been achieved. [17]

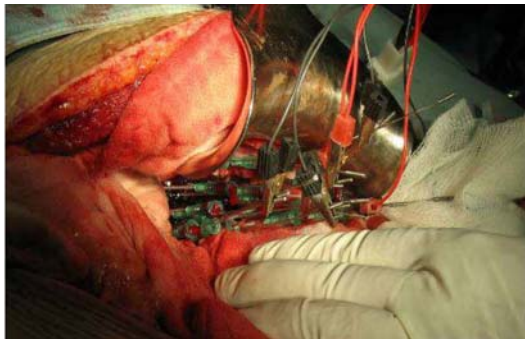
Before EChT



13ms after ECht



During EChT



Male, 53ys. Suffered from a left thoractic & abdominal tumor, 14x8x4 cm. Both thoracic and abdominal cavity was opened but the tumor could not be resected. Pathologic diagnosis: neurofibroma. EChT was performed. The patient was followed up for 13 months and recovered well

(2) Complication of EChT and its management

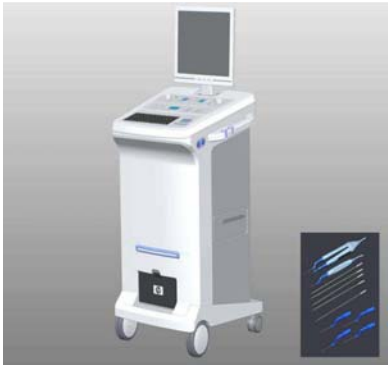
EChT is relatively nontraumatic so that even fragile patients are able to tolerate the procedure without difficulty. A moderate rise in body temperature and in white blood cell (WBC) count may occur but a return to normal generally takes place after 3-5 days. DC is not harmful under 30 V, so EChT can be considered to be quite safe. During EChT a voltage much lower than 30 V is used but if the insulation around the cannula is not properly arranged, surrounding normal tissue and skin may be damaged. Such damage is usually limited and typically restricted to an area of about 0.5-1.0 cm in diameter around the electrode, and no treatment is needed since spontaneous healing takes place [12].

4. The procedure of electrochemical therapy

(1) Selection of Instrument and Electrodes

Instrument: Computer controlled ZAY-B multifunctional instrument is used. It has two outputs with data storage and print function. Electric current, voltage and electric quantity needed could be pre-set. Alarm system could be started when short circuit or disconnection occurs.

Electrode: Electrodes are made of platinum with a 0.7-mm diameter and 160 mm in length with high electrical conductivity and good anti-erosive properties. Needles are also coated with plastic catheter for insulation to protect normal tissue against electrical injury and strict sterilization is necessary.

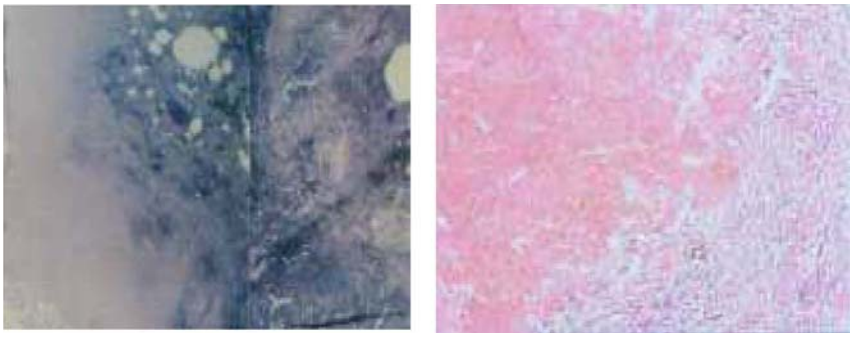


Electrochemical therapeutic apparatus and electrodes: ZAY-B electrochemical therapeutic instrument and platinum electrodes. Made of China

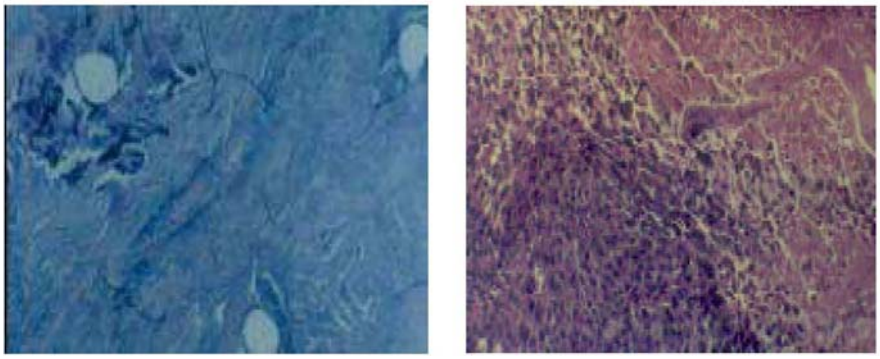
(2) Manipulation

Cathodes are usually placed in the center of tumor and anodes in peripheral. However, both the cathodes and anodes could be placed one besides the other, alternately. Electrodes must be covered the whole tumor to avoid incomplete treatment. Insulating plastic tubes are used to protect normal tissue from injury due to electrolysis. Then electrodes are connected to the instrument to start treatment

Based on the data obtained from our experiments, the destruction radius of each electrode is about 1.0 cm. Since the distance between two electrodes should be less than 1.5 cm, the number of electrodes can be calculated according to tumor size. [9, 18]
When treating tumors in the lower part of the body, epidural anesthesia is recommended. When treating tumors in the other part of the body, general anesthesia is preferable.



No cancer cells remained when electrodes' distance is shorten than 2 cm.



The distance of electrodes is over 3 cm, Cancer cells can be found in the remaining area

There will be a rupture drop area of electric field between 2 electrodes when the distance of electrodes is over 2 cm. So 1.0~1.5cm will be the best choice of the distance between electrodes during EChT

(3) Requirement of electric current, voltage and electric quantity
Voltage usually used is 8—12 V and electric current is in a range of 80—180 mA. Electric quantity is determined by tumor size, usually 100 coulombs per 1.0 cm diameter of tumor mass.

(4) Duration of treatment
The concept of increasing electric current to high level in order to shorten treating time is wrong. That is because the action of EChT is electrolysis which needs time to perform the action. According to animal experiment, 4 V voltage and 20 mA is enough to have killing effect.

To improve the effectiveness of EChT for treating malignant tumors, following measures are recommended: [19,20**]**

(A) For patients with advanced tumor who can not be treated with other therapies, EChT might relieve their sufferings. And their life quality could be improved
(B) For large tumor mass, more electrodes should be needed. If short circuit does not occur, the distance between electrodes could be reduced to 1.0cm in order to increase killing effect
(C) EChT should be combined with radio-chemotherapy, because EChT could make tumor cells more sensitive to radio-chemotherapy. Positively charged antitumor agents, such as adriamycin and bleomycin, could be injected into the tumor, whereby the electric gradient will move the chemotherapeutic agent toward the cathodic area and destruct tumor cells. Systemic chemotherapy, interventional therapy, and immunotherapy could also be considered in combination with EChT
(D) Chinese herbs could improve immune system and inhibit growth of tumors, and may be a supplementary treatment to be combined with EChT.

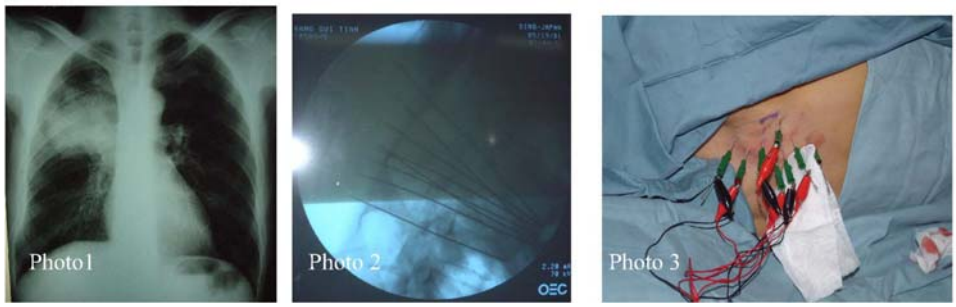
The technical aspects are important. If possible, the needles should be inserted under direct vision. And the distribution of and the distance between electrodes should be rational and adjusted when necessary. The electric quantity should be adjusted to the type and the size of the tumor.

5. Summary

In 1987, Professor BJ Nordenström was invited to come to Beijing giving lectures on BCEC theory and demonstrated the use of EChT on malignant tumor.
Following three years of animal and clinical practice in China, good therapeutic effectiveness has been achieved. It was approved as a new therapeutic method to be used and spread clinically by the Ministry of Public Health of China
Over ten thousand cases of various kinds of tumors have been treated with EChT in China within 20 years. It could be used not only for malignant tumors, but also for some benign tumors, such as cavernous venous malformations. The effectiveness of it is even admiring with no bleeding, no scars left and no harm to the appearance and function.
EChT was also applied on breast hypotrophy and endometriosis in abdominal wall and satisfactory result has been achieved.

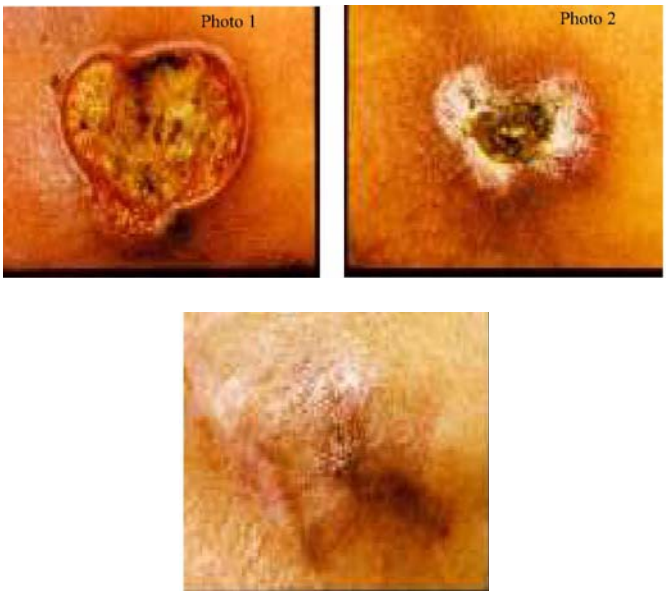
Typical cases

1.



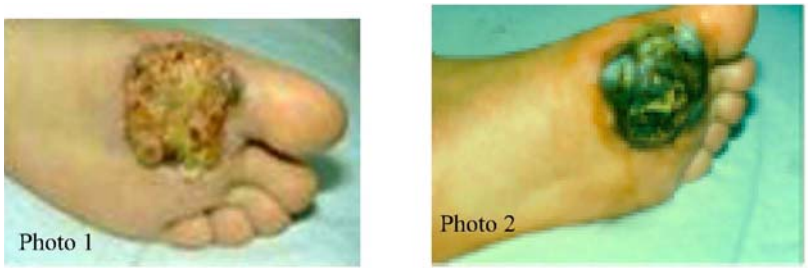
M. 67ys. Right up lung cancer (Photo 1). Electrodes were inserted to the tumor (Photo 2). During EChT (Photo 3).

2.

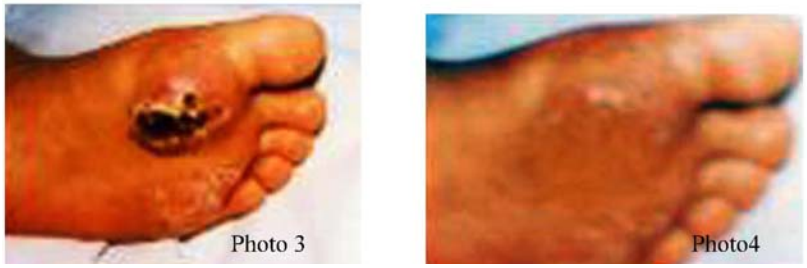


Male, 42y. Cancerous ulcer in right thingt. 5.5x8.0 cm. (Photo 1). After 2 times EChT (Photo 2). No recurrence through 6 years following up (Photo 3).

3.



M. 34y. Melanoma in left foot. Recurred after surgical resected. The wound didn't heal up and the tumor grew to 4.5x5.0 cm (Photo 1). 2 days after EChT (Photo 2).

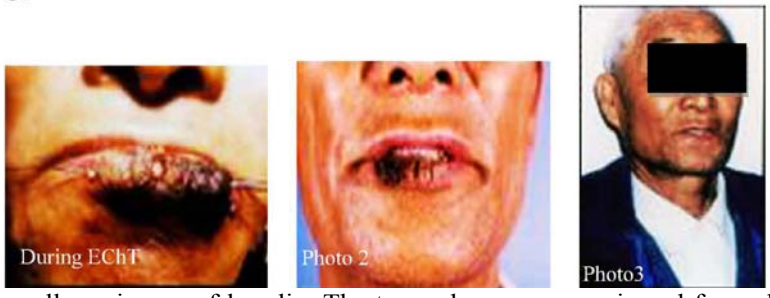


4 weeks after EChT (Photo 3). The wound healed 7 weeks after EChT and no recurrence developed through 4 years following up (Photo 4).

4

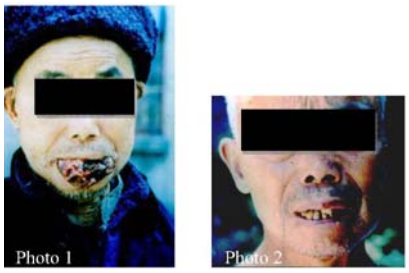
M. 30 ys. Right upper limb soft tissue sarcoma recurred after 2 times surgery combing pulmonary metastasis, 13x21 cm (Photo 1). Tumor turned necrosis and fall off 5 days after EChT. The wound was healed 6 weeks after EChT (Photo 2). He died of lung metastasis after following up 20 months.

5



M. 67 y. Squamous cell carcinoma of low lip. The tumor became necrosis and formed a scar after EChT (Photo 2). A good figure of the patient 12 months after EChT (Photo 3).

6

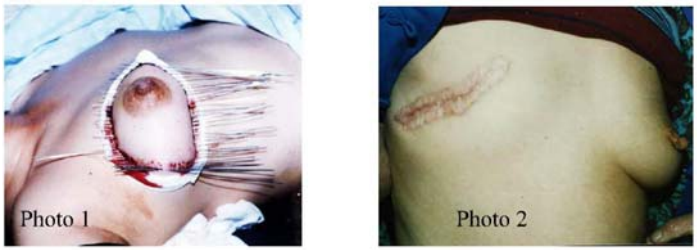


M. 67 y. Lower lip cancer of squamous epithelium, recurred after surgical resection (Photo 1). Photo 2 shows the result 1 year after EChT.

7

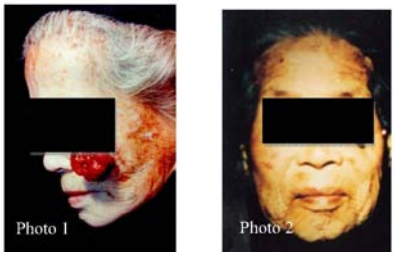
F. 52 y. Local recurrence after resection of right mammary cancer. Carcinoma ulcer grew to 12x10 cm (Photo 1). The tumor necrosed and surface of wound obviously reduced 7 weeks after EChT (Photo 2). The wound heated completely 9 weeks after EChT (Photo 3).

8



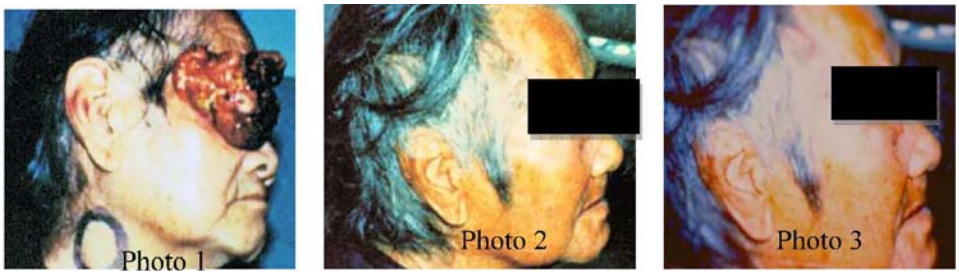
F. 62 ys. Breast cacner. Photo 1 shows the electrodes during EChT. Photo 2 shows the same patient 6 months after EChT.

9



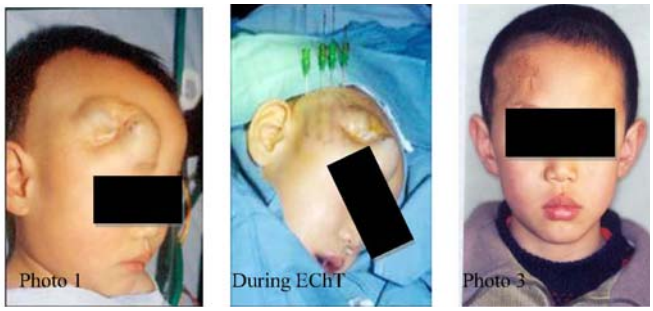
F. 92 ys. Melanoma in left face (Photo 1), 6 months after EChT (Photo 2).

10



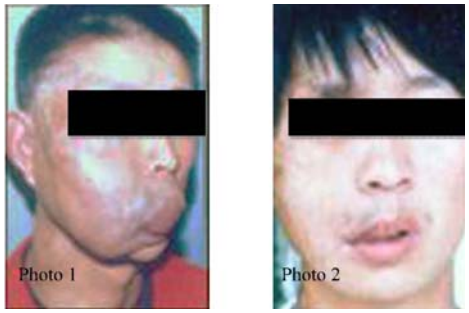
F. 61 ys. Recurrent cancer after operation on right eye (Photo 1). The tumor necrosed and dropped out after 1st EChT (Photo 2). The patient recovered well after second EChT was applied in 2 weeks later (Photo 3).

11



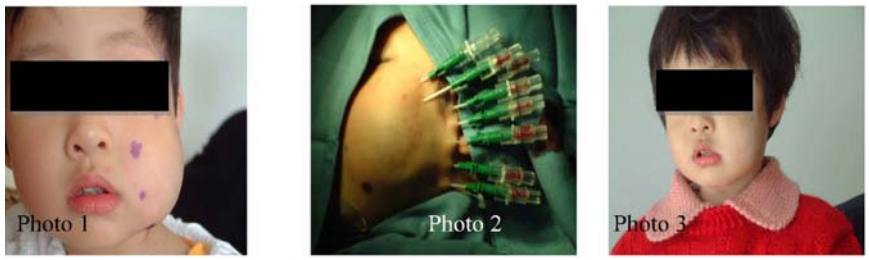
M. 4y. Venous malformations in right forehead. Operation failed due to uncontrolled bleeding. The diameter was 7.8x9 cm (Photo 1). The tumor disappeared and no recurrence developed after 3 years after EChT (Photo 3).

12



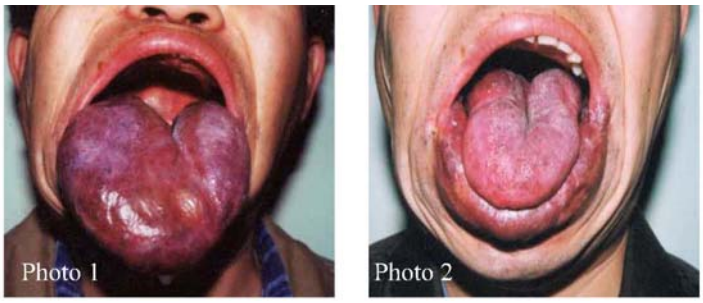
M. 32 y. Huge venous malformations in maxillofacial region. Many therapies had been tried but all failed (Photo 1). Photo 2 showed 1.5 years after EChT.

13



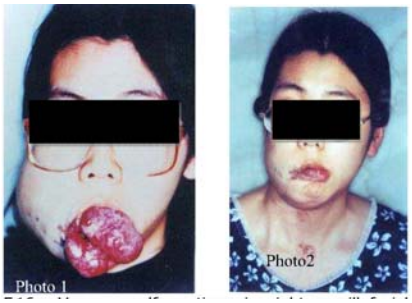
F. 2 y. Venous malformation in left maxillofactal region (Photo 1). During EChT (Photo 2), 2 years after EChT (Photo 3).

14



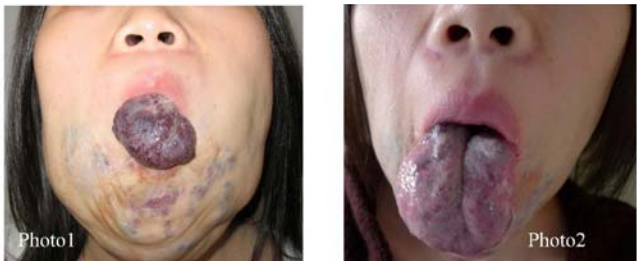
M. 32 y. Huge hemangioma in tongue. The tongue drop out of mouth and had a malfunction (Photo 1).

15



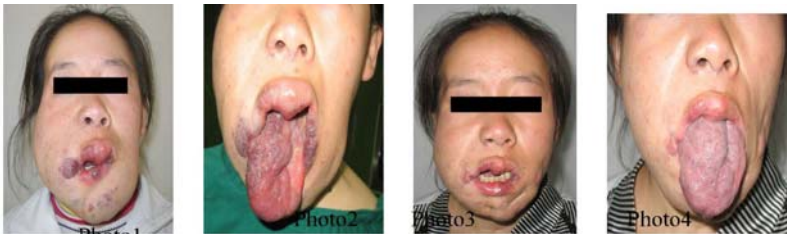
F.16y. Venous malformations in right maxillofacial region,tongue & lips. Speaking and foodintake were hindered (Photo1). 11 weeks after 1st EChT (Photo2). No recurrence for 3.5 years follow up. The well function of tongue and feature recovered.

16



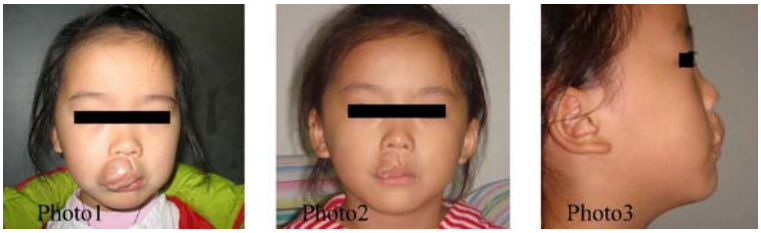
F. 19ys. Venous malformation in tongue (Photo1). 1year after EChT(Photo2).

17



F,21ys. Maxillofacial & tongue venous malformation (Photo1,2). One year after EChT (Photo3, 4).

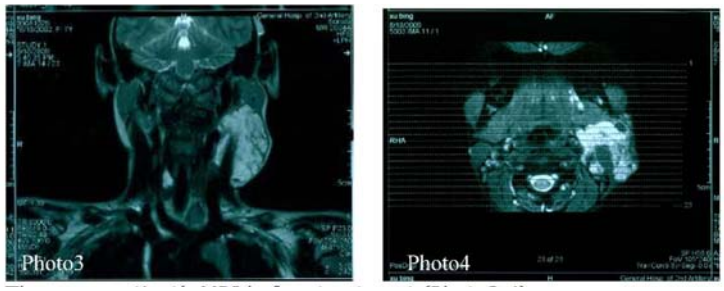
18



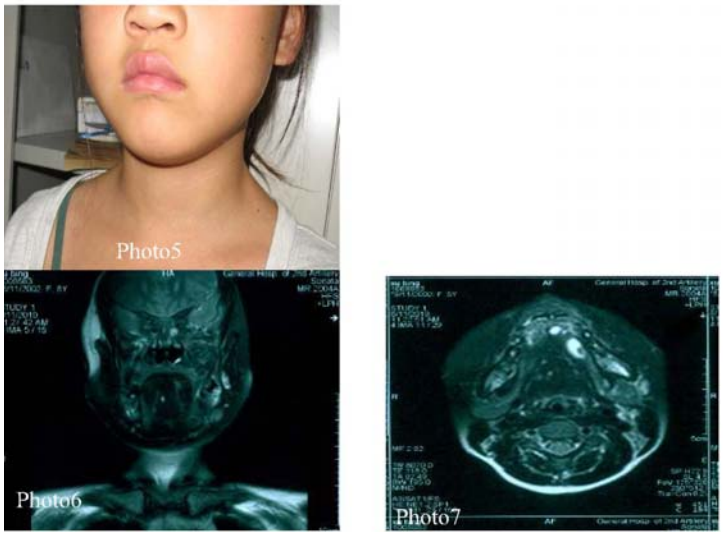
F.5ys. Up lip venous malformation reccured after surgical resection (Photo1). The patients' appearance after EChT (Photo 2, 3).

19

F. 7 ys. Venous malformation on left neck (Photo1, 2).

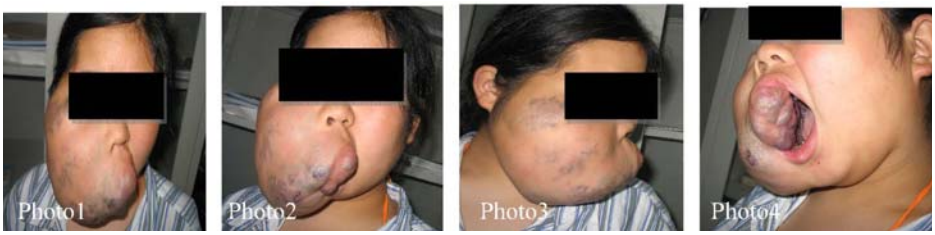


The same patient's MRI before treatment (Photo3, 4).

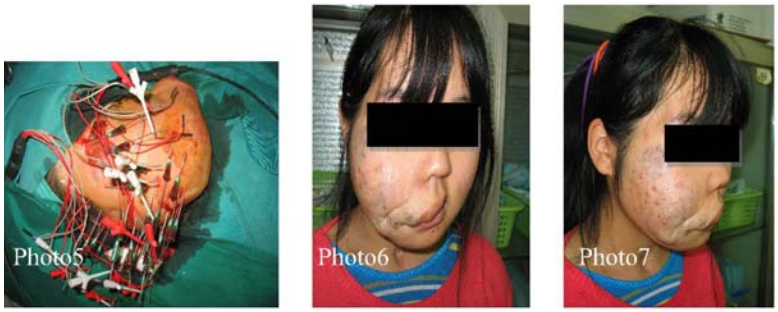


The same patient's appearance and MRI 1 year after EChT (Photo 5, 6, 7).

20



F. 14 ys. Severe maxillofacial vascular malformation (Photo1-4).



During EChT(Photo5). 3 years after 3 times EChT(Photo6,7).

21

M. 20 ys. Severe maxillofacial vascular malformation (Photo1-4).

During EChT (Photo5). 1 year after 3 times EChT (Photo 6). 3 times EChT and plastic surgery (Photo 7).

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Low back pain – complex approach of treatment CAM modalities (acupuncture and other type of dry-needling, "Targeted RF non invasive physiotherapy" for low back pain)

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http://www.hindawi.com/cpis/medicine/pp/104671/

Low back pain – complex approach of treatment by different CAM modalities (acupuncture and other type of dry-needing. "Targeted RF non invasive physiotherapy" for low back pain)

Absract

For at least 2,500 years, acupuncture has been an integral part of traditional Chinese Medicine. Recently more people have been diagnosed with chronic disease and many of them have been poorly treated with conventional therapies. Those patients frequently prefer other forms of complementary medical treatments. Based on the theory of homeostatic equilibrium being the basis of health, acupuncture focuses on restoring the homeostasis by manipulating the complementary and opposing elements of yin and yang. It is possible that by affecting afferent nerve signaling, acupuncture may influence the release of endogenous opioids to promote pain relief. Our objective is to give western trained physicians clinical applications together with acupuncture and modern physiotherapeutic - equipment (Booster) to accommodate accelerating interests in acupuncture and related techniques in modern complex treatment of chronic low back pain. In recent prospective Phase I/II study statistical data have verified the relevant end-points of the study: the safety, the quality of life (QoL), the rest time, duration of painless state, and the cost/benefit ratio.

Introduction

Thirty-five RCTs covering 2861 patients were included in a systematic review [1]. There was insufficient evidence to make any recommendations about acupuncture or dry needling for acute low back pain, but for chronic low back pain, results showed that acupuncture is more effective for pain relief than any treatment or sham treatment, in measurements taken up to three months. The results also showed that for chronic low-back pain, acupuncture is more effective for improving function than any other treatment, in the short term. [2] Acupuncture is not more effective than other conventional and "alternative" treatments. When different types of acupuncture were added to other conventional therapies, they relieved pain and improved function better than the conventional therapies alone with less intake of pharmacologic substances and had fewer side effects. In our randomized pilot study we were going to apply more complementary and alternative methods (CAM) and treatments for low back pain and evaluated their effect on visual analogue scale (VAS), & Quality of life (QoL) of patients [3]. CAM modalities including ―dry needling‖, the lately improved non- invasive RF therapy appear to be a useful adjunct to other therapies for chronic low-back pain with individually developed life-style management. (Personalized medicine‖).

Although chronic low-back pain is usually a self-limiting and benign disease that tends to improve spontaneously over time, a large variety of therapeutic interventions are available for its treatment. Recovery time is different at each patient depending on his/her additional physical condition. Most patients are older due to developed degenerative soft-tissue damage which is a growing problem all over the world that should be treated [4].

Definitions for low back pains

Lumbar strain (acute/chronic) is a stretch injury to the ligaments, tendons, and/or muscles of the low back. The stretching incident results in microscopic tears of varying degrees in these tissues. Lumbar strain is considered one of the most common causes of low back pain. The injury can occur because of overuse, improper use, or trauma. Soft-tissue injury is commonly classified as "acute" if it has been present for days or for weeks. If the strain lasts longer than three months, it is referred to as "chronic." Lumbar strain most often occurs in people in their 40s, but it can happen at any age. The condition is characterized by localized discomfort in the low back area with onset after an event that mechanically stressed the lumbar tissues. The severity of the injury ranges from mild to severe, depending on the degree of strain and resulting spasm of the muscles of the low back.

What are common causes of lower back pain?

- protruding, herniated, or ruptured disc (operation is questioned)
- cauda equina syndrome (needs to be operated urgently)

- Sciatica is a condition in which a herniated or ruptured disc presses on the sciatic nerve, the large nerve that extends down the spinal column to its exit point in the pelvis and carries nerve fibers to the leg
- Spinal degeneration
- Spinal stenosis
- Osteoporosis
- Skeletal irregularities
- Fibromyalgia
- Spondylitis

According to recommendations of international guidelines in the modern diagnosis and treatment of low back pain there are more modalities that can be individually decided. Regarding diagnosis, it is very important to differentiate between - specific‖ and - aspecific‖ or -nonspecific‖ low back pain. The term "specific low back pain" includes all diseases and pathologies with well-defined aetiology and pathological process, including bacterial spondylitis, rheumatic spondylarthropathies, primary or secondary tumours, malignancies, myelon- or cauda equine compression, paresis, metabolic base diseases, pathological or nonpathological fractures which are suspected. The presence of the so-called - red flags‖ indicate - specific‖ low back pain. This type of low back pain requires quick and precise diagnosis and specific treatment. All other kinds of low back pain, even those with very painful radiculopathy, and without paresis, cauda- or myelon compression can be considered as aspecific, even if it is caused by a herniated disc, because there is no absolute indication of discectomy. In case of aspecific low back pain, there is no need for any diagnostic imaging methods, because they would not influence the treatment. Investigation and flow-chart of assessment have a rigorous algorithm: (see Figure 1.)

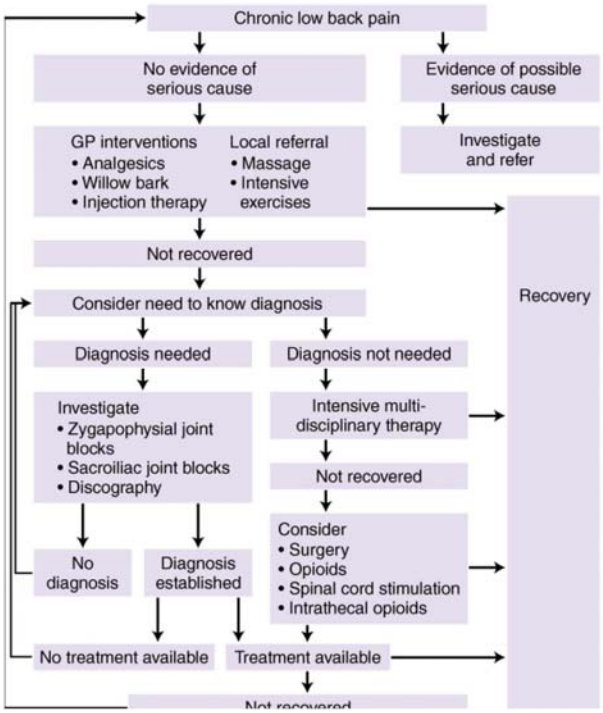

Figure 1. Flowchart of management for low back pain

Patient assessment should involve the following as a basic guideline for low back pain management:

- Algorythm for diagnose and treatment
- Identify low back diseases that place the patient at risk for pain
- Differentiate between chronic and acute pain and their treatment.
- Identify pain assessment tools used
- The basic neurophysiologic pain response
- Pharmacological and non-pharmacological approaches to pain management
- Differentiate between addiction, tolerance and dependence

- Discuss commonly performed nerve blocks and associated nursing implications
- Apply pain management instruments to practice situations
- The management of pain in the patient with cancer (recognized)

The course consists of diagnostic triage, Case history, Physical examination: Lasegue test and spinal palpation and motion tests, Imaging (not the first step), Electromyography and Prognostic factors. The main question is which of the following therapies is the best for the patient.

Our methodolical considerations

In our recent trial we have turned to acupuncture (with the application of a unique technic) and another non-invasive method. Our objective is to choose the effective acupuncture points and techniques, [4], [5]. We sort low back pain to the WEI Syndromes in TCM (in western terms: Polyneuritis, polyneuropathy, acute, chronic myelitis, periodical paralysis, hysteric paralysis, paresis)

WEI syndromes are characterized with following symptoms

- Cause: pathogenous Heat hurts the Lung, Yin fluid does not spread, nourish surface, tendons or muscles.
- Spleen-Stomach, Heat in Yang-Ming function-circle
- Additionally: Kidney Essence, Liver Blood Deficiency
- Weakness of muscles improved gradually...
- Excessive Heat in Lung, Stomach (acupoints for use [6] : Lu 5, UB 13, ST 44)
- Dampness-Heat Retencion (acupoints for use : UB 20, Sp 9)
- Yin Deficiency in Liver , Kidney (acupoints for use: UB 18, UB 23, KI 3)+ Huatuojiaji

Acupoints: St 31, St 34, St 36, GB 34, GB 30, GB 39, St 41

Damage and inhibited Qi and blood

Pathogenous Dampness – Cold in Kidney Channel have causes: (For pattern „Kidney Qi Deficiency": „Warming which is Cold, diminishes Dampness and Weat" (Huang Di Neiting, „The Yellow Emperor")

- Kidney Yin-Yang Xue (long-term diseases, sexual abuses, etc.)
- Stagnation of Qi and Blood
- Lumbar region: this is the „Palast of Kidney residence‖ Kidney-UB : both of them attacked
- Other importance: Du Mai Channel (Stability, Permanence, ―standing ability‖ in mental too)

Dampness and cold in kidney

- Rapid start, lumbar rigidity, pain, weakness
- Warming collaterals, warming Cold, dissolving Dampness, (UB-TaiYang)
- Acupoints: UB 23, DU 3, UB 26, UB 32, UB 40
- DU3+ UB 26+UB32: regulation of Kidney Qi, activating Yang Qi, DU Mai

Kidney deficiency (Yin and Yang)

Longer time persisting pain, leading to legs, cold extremities, tiredness, weak knees

- Basic aim is : strenghten Kidney Qi-, mainly with DuMAi , UB, Kidney points

Acupoints: UB 23, DU4, UB 52, KI3, UB 40, Warming and strengthening Kidney Deficiency: UB52+DU4+ KI3

Pain due to traumatic injury

- Basic: helping the better blood circulation, block- removing from channels and collaterals,
- pain-killing UB-TaiYang and Ahshi points
- Acupoints : Ahshi: „where is pain‖, UB 17, UB32, UB 40, SI3
- In case of "Strong pain": Du26

In literature, each of the acupuncture (dry needling) modalities (true, sham, and placebo) associated with conventional treatment achieved clinical improvement after 3 weeks which was greater than that achieved

by conventional treatment alone in patients with acute/chronic low back pain, although there were no significant differences among the different forms of stimulus. [7] Which techniques should be chosen among the CAM facilities listed bellow?

- Acupuncture (permanent technique / short time needling), trigger point AP, e.t.
- Acupuncture microsystem (Ear [8], ECIWO, Scalp-Chinese, YNSA-Japanese)
- IMS (intramuscular stimulation)
- Neuraltherapy—(according to Hunecke, Germany: small dosage of analgetics)
- MESOTHERAPY-Guna (inj. „Lumbar", „Ischias", „Matrix"), Milano Univ. Italy
- Moving-massage therapy (Manual Medicine, Tuina, Qi-gong)
- Electrotherapy, TENS
- Additional „Targeted RF Stimulation with „-Booster [9]

Our target was to assess the effects of acupuncture and other CAM therapies for the treatment of non□specific low□back pain and dry-needling combined with targeted RF stimulation (Booster) for myofascial, musculoscleteal pain syndrome in the low-back region with randomized controlled trial. [10], [11]. Intradiscal Radiofrequency Thermocoagulation (IRFT) and Intradiscal Electrothermal Therapy (IDET) are known as invasive forms of thermotherapy. Radiofrequency (RF) lesions not only target the rami dorsales to relieve facet pain, but also aim to reduce the nociceptive input from painful intervertebral discs. [12]. Percutaneous Intradiscal Radiofrequency Thermocoagulation (IRFT) has been used for this purpose. In this procedure a RF cannula is placed in the center of the disc and a lesion is then made here. Intradiscal electrothermal therapy (IDETTM) consists of heating the outer annulus of the intervertebral disc. A flexible intradiscal catheter with a temperature controlled thermal resistive coil is passed through a trocar into the annulus of the disc and is heated to a temperature of 70 degrees centigrade. This procedure has been developed as an alternative treatment to spinal fusion for patients with unremitting pain hypothesized to be caused by internal disc disruption (IDD).

Our aim was to introduce additive and non-invasive heat therapy for chronic low back pain. The purpose of the "Booster" equipment is to increase the blood flow in the treatment area. Selection at cellular level does not occur, only a heating of the deep layers of tissue in the region where the electrode is positioned superficially. (not invasive). The deep-heating effect is a result of Joule-loss and leads to vascular dilatation in the treatment area, that, in turn, improves blood perfusion and thus the drugs (and more oxygen) are transported to the treatment area. The temperature in this area is 37-39°C (moderate, so-called classic "Hyperthermia"), and this is the optimum temperature for the Booster's effect. The Booster must be adjusted to the pharmacokinetic parameters of the drugs used to achieve the maximum effect. The deep moderated "Hyperthermia" activates the microcirculation to and into the capillaries (capillary filtration capillary pressure etc.), increases micro-vascular perfusion, the local oxygen content in the tissue, and the nutrients and phagocytes in the treatment area. The increased temperature also regulates the cell cycle by changing the calcium ion binding. In addition, the following effects in the blood and tissue can also be achieved [13]:

- Increased fibroblast activity and increased capillary growth
- Increased nutrient concentration and metabolic activity
- Synergetic increase in the field-dependent effects (optimization of membrane stimulation and
- Activation of signal channels
- Increased reactions to heat and field exposure (mainly the development of Heat Shock Proteins, HSP 70)
- Increased venous and lymphatic flow
- Changes in the physical properties of the tissue

Recruitment commenced between 2011-2012, after 499 patients had been enrolled (249 to receive acupuncture + Booster treatment and 250 for control). 249 consecutive patients admitted to the rehabilitation unit were included in the study after informed consent. Other 250 patients received conventional pain killer pills and physiotherapy (Galvanic, Ultra sound treatment, and Infrared Soft Laser. Inclusion criteria were the following: 1) Diagnostic triage, 2) Case history, 3) Physical examination: Lasegue test and spinal palpation and motion tests, 4) Imaging, CT, MRI 5) B) Prognostic factors, age: 25-85, excluding criteria: ruptured disc, Caudal-syndrome which needs urgent operation. All patients gave

informed consent to participate in the study, which was performed according to the guidelines of the local ethics committee. The participants were not informed of the possibility of being assigned to either the acupuncture or to the no-acupuncture group. Ethics Committee approval was granted and the trial was performed in accordance with the Declaration of Helsinki. All the recruited patients went under rheumatic rehabilitation program using the Hungarian standard rehabilitation protocol. 249 of the patients received additional acupuncture therapy using the permanent dry needling method plus loco-regional heat therapy, and these patients were regarded as the "Acupuncture-Booster" group.

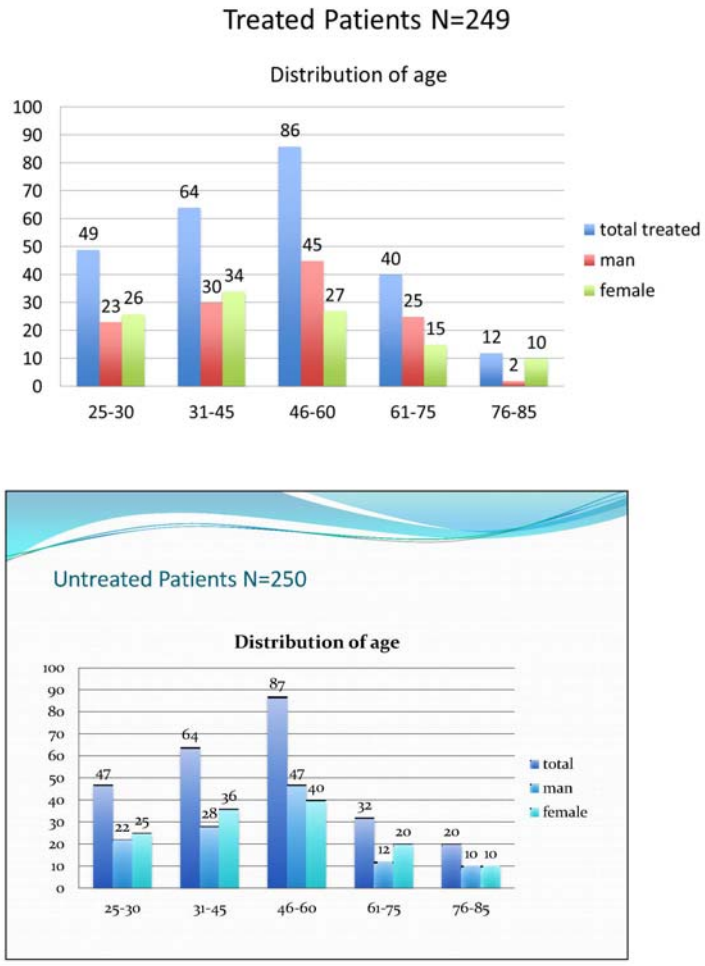

Figure 2. Distribution of patient (gender, age) treated and untreated

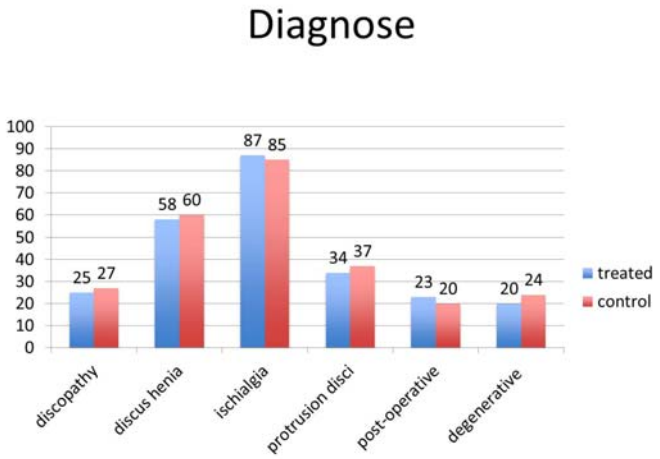

Figure 3. Diagnose in western medicine

Procedure

A prospective, assessor-blinded randomized controlled trial was carried out in an outpatient rehabilitation unit with day hospital service in Yamamoto Centre [14], Budapest, Hungary. After inclusion, patients were stratified into a control group and an acupuncture + Booster group. A simple randomization method was performed to create an acupuncture group and a control group. (Embedding acupuncture with MAXON-M Monofilment implantation) [15] and Booster Equipment.[16] After 3 months all patients went for a control to the same rheumatologist specialists as before starting the procedure in the Physiotherapy Department of Yamamoto Institute.

Patients in the Acupuncture+ Booster group

This group of patients had been treated once a month during the whole period of the clinical trial using the permanent dry needling method according to the correct TCM pattern. The period was 3 months of trial. The "time release" dry needling system with the inserted and permanently entered insertion with the help of a special needle was applied. The length of the special stainless-steel needle is 10.8 cm, and the diameter of the lumen is 0.7mm. The threads (MAXOL-M Monofilamentum, USA) were cut into 0.7–1-cm pieces and then applied with the needle. The threads were placed into this needle and the material was applied to the "acupoints". Loco-regional heat (Booster) was applied 2 times a week during treating course. Twelve needles were inserted into every subject per session. The depth of thread insertion was 0.7–0.9 mm. There was no other needle manipulation performed. The insertions of monofilament were applied once a month based on the total absorption time of the previous threads being 4 weeks.

Patients in control group

Physiotherapy in our department, (Institute of Complementary and Alternative Medicine, University of Pecs), as in many rehabilitation centers in Hungary, chronic backache rehabilitation was mainly based on the rheumatic protocol method in an attempt to restore normal movement and improve strength, alleviate pain condition, achieve less rest from work in younger patients. Each patient received certain modalities of treatment (3 times a week: UV, infrared soft laser irradiation, massage) as decided by the supervising senior physiotherapist according to the patient‘s need at different stages of recovery.

Results

Data collection and analysis

Two authors independently assessed methodological quality and extracted data. The trial was combined using analyses method or levels of evidence. Categorical variables were analyzed using the v2 test or Fisher‘s exact test for small samples. Measurement data were analyzed using two-tailed t-tests. All recorded data were input using Epi Info software (CDC, Atlanta, GA) and statistically analyzed using SPSS 11.5 statistical software (SPSS, Chicago, IL). For all analyses, $p < 0.05$ was considered to be statistically significant. Chisquare analysis of the acupuncture+Booster group and control group was also performed to determine homogeneity between both groups in terms of age, gender, and pretreatment measurement outcomes. A subjective index (VAS) from painful condition (1-10) treated and control group, respectively, $p < 0.05$ at 3 months, and later too was also determined during the follow-up period. The VAS scale was also enhanced in all cases, but the members of the acupuncture+ loco-regional heat by Booster group had more efficient function than the control group in painless condition. In summary, according to the above-mentioned results, changes of the index are better in the acupuncture group than in the control group. The intervention was well tolerated by patients. Any "throw-out reaction" of monofilament and side-effect was not observed under the treatment.

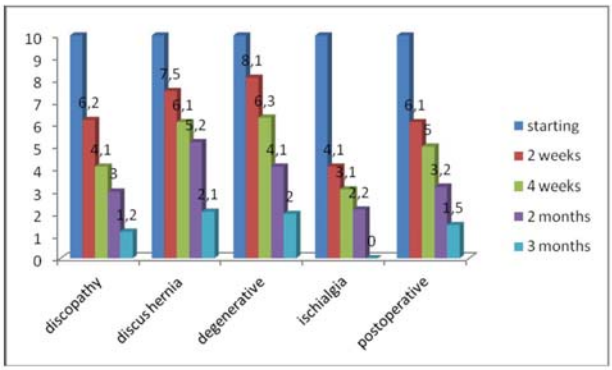

Figure 4. VAS result in different diagnose in treated groups

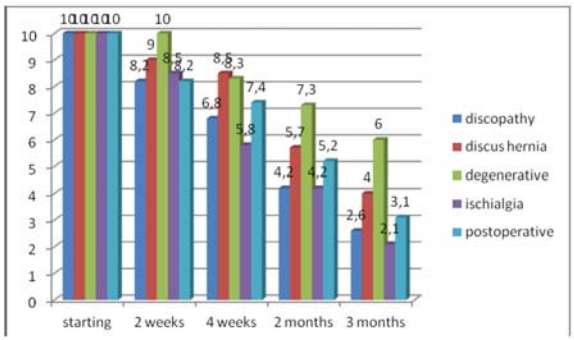

Figure 5. VAS result in untreated group

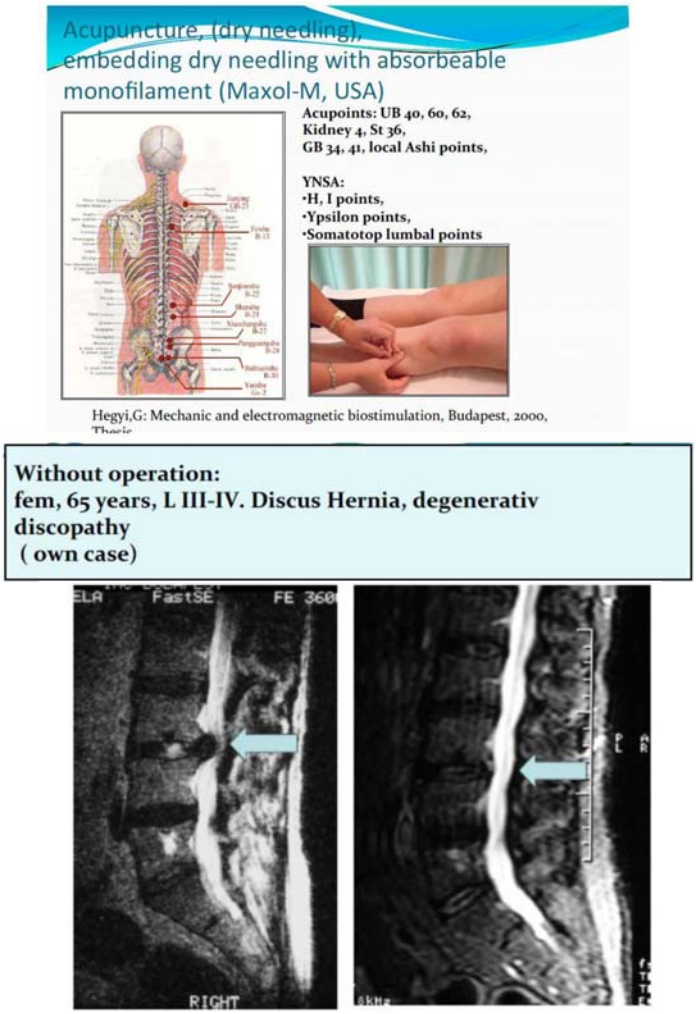

Figure 6, 7, 8. embedding acupuncture procedure, needle insertion, tissues slide [17]

According to our experience, the holistic treatment of low back pain needs a complex approach in which important points are summarized to take into daily practice as follows:

- Orthostatic correction, no "bed-rest"!
- Postural position improvement
- Developement of muscle ballance
- Motility habilitation
- Sitting, standing,walking,moving exercises- daily performed
- Isometric exercises
- Yoga, Tai-Qi, Qi-Gong, Swimming (on back only!)
- Proper diet (if weight loss is necessary…)
- Ethic treatment choosing, performing with skillfulness
- Neuraltherapy (using less dosage of anaestheticums) [18], [19]
- Acupuncture, proper physio-physicotherapy („boostering effect")

There is evidence for chronic low-back pain, for pain relief and functional improvement for acupuncture, compared to no treatment or sham therapy. These effects were observed immediately after the end of the sessions and at longer-term follow-up. There is evidence that acupuncture, added to other conventional therapies, relieves pain and improves function better than the conventional therapies alone. However, "dry needling" (special embedded form) and RF non-invasive physiotherapy treatments appear to be a useful adjuncts to other (pharmacological substance) therapies for chronic low back pain, decreasing their dosage avoiding unnecessary side effects. We recognized after trial period during controls to decrease number of medical visit of treated patients and also less oral analgesic's intake (less cost in 35 %). Between the ages of

35-60 there was significant improvement to have less sick-list. Clear recommendations should be made about the most effective acupuncture technique and exact, correct application of RF non-invasive treatment for shortening time of convalescence avoiding improvement of worsening or long-term pain development. (the energy-dosage and technique are important). We find that according to our protocol for "Booster" loco-regional deep heat applied for low back pain group, the required time was 20-25 minutes with 25-Watt power. The positive and negative electrodes can not be connected to avoid burning effect on the skin. There are some contraindications to apply the Booster: Pacemaker, Missing Heat-feeling,Large implantatum, PregnancySignificant big size of Ascites in abdomen (changing conductance of electricity)

Conclusion

The recent data allow firm conclusions about the effectiveness of acupuncture for (sub)acute and chronic low back pain. For chronic low back pain, acupuncture is more effective for pain relief and has more functional improvement than any treatment or sham treatment immediately after treatment and in the longer run. Simple acupuncture is not more effective than other conventional and "alternative" treatments. The data suggest that permanent acupuncture so called "dry-needling" with combination of RF targeted therapy (heat "Boostering") may be useful adjuncts to other therapies for chronic low back pain instead of invasive RF method. [15], [17]. The most important duty is to enhance the quality of life of patients suffering from longer-term pain. We should consider applying any treatment taking into account less necessary intervention, taking longer time of patients for result because most of the studies were of lower methodological quality, there certainly is a further need for higher quality trials in this area. Our results with non-invasive special heat "boostering" application are the following: it is easy to work with the instrument, it was well tolerated by all patients, we noticed additionally positive effects due to treating (according to reports of patients in other accompanying „cold-dampness symptoms" - diseases (COPD, asthma!) The Booster equipment is a product innovation in the field mainly of complementary cancer treatment [20], its use enhances the effect of both chemotherapy and other drugs. This „boostering function‖ is developed and used mainly for oncology but it can be successfully used for other medical fields such as rheumatology, neurosurgery, dermatology and analgesic pain-killer therapy.

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Deep regional hyperthermia combined with Traditional Chinese Medicine in treating benign diseases in Clifford Hospital

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Deep regional hyperthermia in combination with Traditional Chinese Medicine in treating benign diseases in Clifford Hospital

Abstract

Objective: To analyze the effect of Deep Regional Hyperthermia in combination with Traditional Chinese Medicine (TCM) in treating benign diseases in Clifford Hospital.

Methods: We had 143 cases with chronic pelvic inflammatory disease, 36 cases with chronic prostatitis, 21 cases with prostatic hyperplasia, and 35 cases with chronic bronchitis, and we performed the treatments as planned. The following treatments were given: Radiofrequency (RF) hyperthermia, TCM, Acupuncture, Antibiotic therapy.

Results: Effective rate in treating chronic pelvic inflammatory disease reaches 95%, which is significantly higher than with patients using TCM only. Effective rate in treating chronic prostatitis reaches 100%. Combining hyperthermia with TCM and Western Medicine is more effective than using Western Medicine only. Among the 21 cases of prostatic hyperplasia, there was significant improvement after two courses of treatments. Symptoms were relieved for the 35 chronic bronchitis patients and the patients' physical showed significant improvements after they received deep regional hyperthermia and TCM. Conclusions: Deep Hyperthermia Combined with Traditional Chinese Medicine in Treating Benign Diseases is safe and effective, painless and convenient with minimal side effect and has broad application range. Keywords: Deep Regional Hyperthermia, TCM, Benign Diseases

Apart from treating cancer, deep hyperthermia could also be used for treating non-neoplastic diseases, and the treatment proved to be effective. In combination with TCM in treating various benign diseases such as chronic pelvic inflammatory disease, chronic prostatitis, benign prostatic hyperplasia and chronic bronchitis, RF hyperthermia has led to satisfactory results. The followings are the statistical reports.

1. Chronic Pelvic Inflammatory Disease

Chronic Pelvic Inflammatory Disease is a type of common disease, usually caused by acute inflammation. It could lead to infertility, tubal (ectopic) pregnancy, chronic lower abdominal pain, thus affecting women's daily life and reproductive health. At Clifford Hospital, deep regional hyperthermia in combination with TCM was applied in treating chronic pelvic inflammatory disease. It has been demonstrated that the results are satisfactory. The followings are the statistical reports.

1.1. Materials and Methods

1.1.1. Ceneral information 283 patients with chronic pelvic inflammation who were diagnosed at Clifford Hospital from January 2010 to December 2012 and who had no RF hyperthermia contraindications were recruited. They were divided into 2 groups randomly. 14 subjects, aged 24-43, average age was 33±8, duration of the disease was 6-8 months, of which 47 patients suffered from infertility, 52 from menstrual disorder, 96 from thickened adnexa and tenderness, 23 from pelvic effusion, were in treatment group given RF hyperthermia, TCM and acupuncture. Meanwhile, 140 candidates, aged 23-45, average age was 32±7, duration of the disease was 4-8 months, of which 43 complained about infertility, 50 from menstrual disorder, 82 from thickened adnexa and tenderness, 52 from pelvic effusion, were in the control group who was given TCM and acupuncture. The two groups do not have statistical significance regarding the age, duration of disease or stage of the disease（P>0.05. TCM diagnosis: ① 36 cases of stagnation of dampness and heat: lower abdominal pain, tenderness radiating to the lumbosacral roots, increased intensity of pain and tenderness when feeling tired or during the menstruation, excessive secretion of the leucorrhea, yellowish, thick and smelly, on-and-off low fever, chest distress, poor appetite and dry mouth, yellow urine, dry and hard stool, red toungue nature, yellowish fur, thready and slippery pulse; ② 72 cases of Qi stagnation and blood stasis: lower abdominal swelling and stabbing pain, increased intensity of the pain when feeling tired or during the menstruation; excessive secretion of the leucorrhea; menstruation disorder, atropurpureus with clots, reduced pain when the clots are expelled, premenstruation depression, breast swelling pain, dark tongue nature with ecchymosis and petechiae, whitish

coating on the tongue, slippery pulse; ③ 67 cases of dampness stagnancy due to spleen deficiency: lower abdominal dull pain, lassitude, tiredness; excessive secretion of the leucorrhea, whitish and thin; tongue with ecchymosis and petechiae, pale tongue; ④ 83 cases of Congealing cold-dampness: lower abdominal crymodynia that usually deteriorated during the menstruation whereas relieved when heated, excessive secretion of the leucorrhea, thin and whitish, lumbosacral root pain, tiredness, dark tongue, pale fur, thready and slippery pulse; ⑤ 25 cases of Kidney Yang deficiency: dull pain in a certain part of the lower abdominal which is relieved when heated, soreness of waist, weakness of the knees, pale or dark complexion, dizziness and tinnitus, thin and whitish leucorrhea, pale tongue, whitish coating on the tongue, deep and thin pulse.

1.1.2. Treatment method

1.1.2.1. Deep Hyperthermia: NRL-002 radiofrequency field thermo therapeutic machine was used. We used only the upper and the lower electrode plate: 15 by 20 cm, the voltage was set 140-160V. Hyperthermia was given once a day, 40 min each time, 10 times per course, 2 courses in total.

1.1.2.2. Chinese Dialectical Therapy There are 5 patterns and the according prescriptions are as follows: ① Modified Discharge-Checking Formula for stagnation of dampness and heat: objectives, to clear heat and promote diuresis, to promote blood circulation to remove blood stasis; prescription: root of common peony 15g, moutan bark 15g, the root of red-rooted salvia 15g, plantain seed 15g, rhizoma alismatis 15g, Cape jasmine 10g, herba patriniae 20g, honeysuckle flower 20g, rheum officinalec10g, fructus aurantii 12g; ② Modified Pelvitis Formula for Qi stagnation and blood stasis: objectives, to promote blood circulation to remove blood stasis and to regulate Qi to alleviate pain; prescriptions: angelica sinensis 12g, root of common peony 15g, moutan bark 12g, the root of red-rooted salvia 20g, nutgrass galingale rhizome 12g, elecampane 9g, fructus aurantii 12g, plantain seed 15g, field pennycress 15g, pubescent holly root 20g; ③ Modified Discharge-Ceasing Formula for dampness stagnancy due to spleen deficiency: objectives, to invigorate spleen to eliminate dampness and promote blood circulation to remove blood stasis; prescriptions: the root of red-rooted salvia 15g, root of common peony 12g, Angelica sinensis 12g, Poria cocos 12g, Codonopsis pilosula 15g, radix curcumae 15g, rhizoma cyperi 12g, plantain seed 15g, rhizoma atractylodis 10g, honey-fried licorice root 6g. ④ Modified Shaofu Zhuyu Decoction for congealing cold-dampness: objectives, to relieve dampness stagnancy, and to promote blood circulation to remove blood stasis; prescriptions: cassia twig 10g, fennel 6g, Angelica sinensis 15g, Ligusticum wallichii 10g, root of common peony 12g, the root of red-rooted salvia 15g, Poria cocos 20g, Rhizoma Atractylodis Macrocephalae 15g, the root of three-nerved spicebush 12g, corydalis tuber 12g. Modified Internal Nourishing Pill for kidney Yang deficiency: prescriptions: monkshood 9g, cinnamon 1.5g (baked), fructus psoraleae 15g, herba epimedii 12g, the seed of Chinese dodder 15g, Astragalus mongholicus 20g, Rhizoma Atractylodis Macrocephalae 15g, Poria cocos 20g, Angelica sinensis 15g, Mantis Egg-case 9g. TCM was decocted and orally taken once a day for 20 days.

1.1.2.3. Acupuncture: on the basis of the theory of meridian and collateral, various points such as the Zhongji (RN3), Zigong (EX-CA1), Sanyinjiao (SP6), Qihai (RN6), Shenshu (BL23), GuanYuan Yu (BL26) were selected as the acupuncture points. Acupuncture was done once a day for 20 days. This could treat the patients from the outside to the inside and help them with the blood flow in the pelvic, thus relieving their pain.

1.1.3. Evaluation of Effectiveness: Complete recovery: symptoms and signs disappeared with laboratory and radiological test results in normal rages. Partial recovery: most symptoms and signs disappeared. Slight recovery: symptoms and signs were relieved in different degrees. No effect: the symptoms and the signs remained.

1.1.4. Statistical tool: The data was processed using SPSS13.0 software, $\chi 2$ was appied for the enumeration data.

1.2. Results

1.2.1. All cases were treated according to the treatment plans.

1.2.2. Comparison between the two treatment groups is as the following:

group	complete recovery	partial recovery	slight recovery	no effect	effective rate (%)	$\chi 2$	P
treatment	66	42	28	7	95.1	19.	$P<0.01$
control	42	34	36	28	80.0	75	

Table 1. Comparison of the two groups
* Comparison to control group, P<0.01

According to Table1, there is a statistical significance between the treatment group and the control group(P<0.01). Neither groups had any adverse reactions. 47 out of 143 subjects in treatment group were infertile and 36 of them conceived 3-6 months after the treatment, which accounted for 76.6%. Among the control group, 43 were sterile, of which 22 had a successful pregnancy 3 to 6 months after the treatments, meaning 51.2% of the controlled group were successfully treated. 23 cases of pelvic effusion in treatment group felt significant relief.

1.3. Discussion

Pelvic inflammation disease is a type of commonly seen gynecological diseases that is usually chronic in nature and frequently recurring. Conventional antibiotics do not work well for pelvic inflammation disease [1]. In particular, chronic pelvic inflammation disease, due to its long-term inflammation, could lead to fibrous hyperplasia and adhesions on these inflammatory organs, thus causing various symptoms and complications [2].

The cause of pelvic inflammation disease is quite complicated, which usually includes modified Discharge-Checking Formula for stagnation of dampness and heat, modified Pelvitis Formula for Qi stagnation and blood stasis, modified Shaofu Zhuyu Decoction for congealing cold-dampness, and modified Internal Nourishing Pill for kidney Yang deficiency. It often manifests itself with poor blood circulation, abdominal pain, leukorrheal disease, post-labor fever, dysmenorrhea and infertility. TCM in combination with acupuncture could treat both the cause of the disease and its the symptoms. It could be a beneficial treatment option for pelvic inflammation disease. Deep regional hyperthermia could reach the deep tissues, while promoting the blood circulation of the pelvic, improving the nutrition support and oxygen supply, boosting the metabolism and resolving the inflammation. Hyperthermia has an anti-inflammatory effect which can increase the absorption of exudates in pelvic cavity and retard the adhesion of inflammatory tissues[3]. Hyperthermia in combination with TCM can improve the effect in treating pelvic inflammatory disease and female infertility induced by inflammation. Deep regional hyperthermia is an effective method for treating pelvic inflammatory disease.

2. Chronic prostatitis

Chronic prostatitis is one of the most common urological diseases. It could cause secondary vegetative nerve dysfunction, sexual disturbance, male infertility etc. Due to limited knowledge of its mechanism, etiology and risk factors, there are few effective and safe treatments or therapies available to date. We adopted hyperthermia therapy along with western medicine and TCM, which has led to a promising outcome.

2.1. Materials and methods

2.1.1. General information form jan. 2010 to dec. 2011, a randomly selected 36 cases of diagnosed Chronic prostatitis patients formed the treatment group, aged between 23 to 42, on average 30±4 years old, illness course was between 6 months and 3 years, all demonstrated various degrees of pain or discomfort from low abdominal, inguinal and testis areas. The treatment group was given hyperthermia therapy in combination with Western medicine and TCM, while the randomly selected control group of 36 cases, aged from 25 to 40 years, on average 32±3 years, the illness course was from 5 months to 4 years, was given only Western medicine in the meantime. There are no significant differences in terms of age, course and symptoms between the two groups. (P>0.05) TCM diagnosis differentiations: ① 6 cases of Damp heat descending type: Demonstrated by frequent, urgent, painful urination. ② 11 cases of Qi and blood stagnancy type: Demonstrated by inguinal swelling pain, complaning about pain in testis, penis, lower abdominal and back areas; urination with signs of interruption, pain; purple color or dark

spots on tongue; pulse signs: tight or weak, rough; ③ 6 cases of Kidney insufficiency type: urine signs: cloudy white, interruption, more frequent. hyposexuality, sexual impotence, dizziness, tinnitus, soft, sour back and knee, insomnia, white tongue texture with few moss; slow, weak or fast pulse signs ④ 13 cases of Qi stagnation in liver type: lower abdominal pain, testis discomfort pain, depression, nervousness, insomnia, hyposexuality or sexual impotence.

2.1.2. Treating method

2.1.2.1. Deep hyperthermia treatment: apply EHY-2000 radio frequency hyperthermia machine with selection of diameter 20 cm electrode panel, switch of modulation, output 60-90W. The heat therapy lasted 4 weeks, 40 min per course, 3 times per week.

2.1.2.2. Chinese Dialectical Therapy: Chinese medicine diagnose differentiations: divided into four types with different medicines used. ① For Damp heat descend type: treatment methodology used is clear heat and expel dampness, Prescription: yam rhizome 15g, semen coicis 30g, rhizoma smilacis glabrae 30g, soapstone 30g, moutan bark 12g, rhizoma alismatis 12g, Tetrapanax papyriferus 12g, golden cypress 12g; ② For Qi and blood stagnancy type: treatment methodology is to propel Qi and relieve pain, to motivate stagnant blood, Prescriptions: fennel 6g, rhizoma zingiberis 6g, corydalis tuber 6g, myrrh 12g, Angelica sinensis 18g, Ligusticum wallichii 12g, cinnamon 6g, root of common peony 12g, pollen typhae 18g, trogopterus dung 12g; ③ For kidney insufficiency type, treatment methodology used to nourish kidney and benefit Qi, Prescription: pill of six ingredients with rehmannia, Radix rehmanniae 32g, Chinese yam 32g, dogwood 16g, rhizoma alismatis 12g, moutan bark 12g, Poria cocos 12g; ④ Qi stagnant in liver type: treatment methodology used to resolve liver drainage and dissolve sediments, Prescription: radix bupleuri, pericarpium citri reticulatae 6g, Ligusticum wallichii 5g, radix paeoniae alba 6g, honey-fried licorice root 2g, rhizoma cyperi 5g. Oral intake once daily for 4 consecutive weeks.

2.1.2.3. Western medicine: oral intake of quinolones, 0.2 g per time, twice a day, receptor inhibitor terazosin 2mg, once every night, for 4 consecutive weeks of the two medicines.

2.1.2.4. Efficacy evaluation

Symptoms: the indicators used are in accordance with the NIH-CPSI (for chronic prostatitis, prostatitis and CP) made by the American National Health Research Institute; EPS routine exams including white cell count[4], treatment efficacy evaluation standards are as follow: complete recovery: Symptom evaluation points are 90% less than the pre-treatment evaluation points. WBC count<10个／HP; partial recovery: Symptom evaluation points are 90% less than that of the pre-treatment. WBC count is 50-89% less than that of pre-treatment or WBC <15/HP; slight recovery: Symptom evaluation points are 30-50%less than that of pre-treatment. WBC count less than 25-49% that of pre-treatment; no effect: Symptom evaluation points are 30% less than that of pre-treatment. WBC count is less than 25% that of pre treatment.

2.1.2.5. Statistic analysis: SPSS 13.0 software was used, data was analyzed by $\chi 2$ function.

2.2. Results

2.2.1. All cases have completed their treatment courses as planned.

2.2.2. Efficacy comparison between the control and treatment groups (Table 2)

group	complete recovery	partial recovery	slight recovery	no effect	effective rate (%)	$\chi 2$	P
treatment	15	13	8	0	100*	17.32	$P<0.01$
control	6	10	7	13	63.9		

Table 2. Comparison between the two treatment groups (n=36)
* Comparison to control group, P<0.01

As table 2 shows, treatment group has statistic significance when in comparison with the control group (P<0.01).

2.2.3. Side effects: 8.3% of cases in treatment group experienced various minor gastrointestinal reactions such as gastric discomfort and nausea. 8.6/ of cases in control group had the symptoms of gastric raction. Both groups showed minor side effect that did not affect ongoing treatments.

2.3. Discussion

Chronic prostatitis is a syndrome caused by various factors. Current studies have revealed that it is related to infection of pathogen neurological secretion, immunology, psychiatric factors and nearby organs' pathological changes, physical and chemical factors, and to the reduction of Zinc reserve. A current and widely adopted treatment is the antibiotic treatment. The first line choice is quinolones which can infiltrate the prostate membrane, accompanied by highly selective α-receptor inhibitor to resolve bladder and rear urethra and smooth the muscle of prostate spasm to reduce urethra resistance, improve micturition, relieve symptom, but in general, treatment results are unsatisfactory, therefore, the current clinical strategy is to promote combined treatments. TCM believes that Chronic prostatitis is in its disease concept of cloudy lymph, cloudy sperm, cloudy white, which have complex pathology, recurrence, prolong course, weak Qi in kidney, and insufficient bladder Qi generation, damp heat drains down at lower body as its consequence. For these reason, variations of disease types are common, damp heat, stagnant blood and weak kidney are the key pathological factors [5]. Therefore, it is essential to differentiate the types of symptom signs and treat them accordingly. For example, to clear heat and drain damp, propel Qi and reconnect LUO, mobilize blood and melt stagnancy, nourish kidney and benefit Qi, liver drainage and dissolve sediments. These treatment methodologies can effectively reduce chronic prostatitis syndromes such as damp heat with stagnancy and weakness. Modulating body Qi as whole is one of the important key elements in combined treatments. Through electric negative field, deep hyperthermia can improve prostate tissue blood circulation, expedite the metabolism and relieve the inflammation and the edema of the tissue, thereby relieving the symptoms of chronic prostatitis. This study indicates that combined treatments through multi-channel, multi- mechanism, and multi-process helped to form and maintain effective drug concentration rate, meanwhile improving the body and gland immunity. Patients had quick, significant improvement over their discomforts in the lower abdominal and groin areas, which contributed to the enhanced effectiveness of using only western medicine. No adverse side effects were noted.

3. Prostatic hyperplasia

Prostatic hyperplasia is one of the common diseases for senior males, and the risk increases as they age. Along with aging, the compression on the urethra and bladder orifice will increase from the hyperplasia of the prostate, thus various complications such as frequent urination, urgent urination, difficult urination, more night urination, urinary system infection, bladder stone and hematuresis may occur. Though various treatments have been available in the clinics, it is quite essential to find some treatments that could delay the progression of prostatic hyperplasia. This could play a significant role in enhancing elderly men's quality of life. At Clifford Hospital, deep regional hyperthermia was applied to 21 cases of prostatic hyperplasia. The following is the report:

3.1. Materials and methods

3.1.1. General information 21 patients with prostatic hyperplasia were treated by hyperthermia and TCM in Clifford Hospital from January 2010 to December 2012. They were aged from 59 to 78, average age was 68±5, duration of the disease was 3 to 12 years, and they were all experiencing symptoms of urination with difficulties such as frequent urination, urgent urination and nighttime urination as well. The test showed the residual urine volume was（PVR）> 50ml. The results of their medical history, physical examination of the rectum and B ultrasound did not reveal any contraindications to hyperthermia. TCM diagnosis differentiation: ① 3 cases of Damp heat descent type: frequent, interruptive or even dripping urination. Yellow hot urine, urethra burning pain, lower abdominal swelling pain, thirsty and dry mouth or no desire for water; red tongue with yellow, sticky moss, pulse signs: stressed, fast, or slippery fast; ② 6 cases of Qi and blood stagnancy type: interruptive urine, narrowing or dripping urine line, or block of urethra, tapping pain on lower abdominal areas, dark purple color tongue or ecchymosis on tongue. Pulse signs, stressed or rough ③ 5 cases of Spleen and kidney deficiency: frequent and or retaining urine, weak micturition, narrowing or dripping

urine line. Worse conditions including night time enuresis, fatigue, shortness of breath, lack of words, poor apatite, pale complexion, or procptoosis by Qi descent. Colorless tongue, whitish coating, Pulse signs: feeble weak; ④ 4 cases of Kidney yang deficiency type: frequent urination particularly at night time, feeble micturition, dripping or blocking urination, fatigue, lower limb temperature, pale facial skin, pale tongue, thin whitish coating, pulse sings slight and deep; ⑤ 3 cases of Kidney ying deficiency type: frequent and interruptive urination, retaining urine, hot and filthy oliguria, fatigue, tinnitus dizziness, feeble on waist and knee thirstiness and sore throat, red tongue with less coating or thin, yellow coating, pulse signs slight and fast.

3.1.2. Treating method

3.1.2.1. Deep hyperthermia EHY-2000 RF hyperthermia device: electrode plate diameter – 20 cm, modulation switched off, output 60-90W, hyperthermia once a day, 40 min per time, 4 week duration.

3.1.2.2. Chinese dialectical therapy: ① Modified Bazheng Powder for damp-heat invasion of lower energizer: to clear the heat and promote diuresis, prescriptions: plantain seed 12g, dianthus superbus 12g, Polygonum aviculare 12g, soapstone 12g, Cape jasmine 12g, honey-fried licorice root 10g, akebiaquinata 12g, rheum officinale 12g; ② Modified Chenxiang Powder for Qi stagnation and blood stasis: to promote Qi circulation and activate blood flow, to achieve diuresis, prescriptions: tambac 15g, pyrrosia lingua 15g, soapstone 15g, the seed of cowherb 15g, Angelica sinensis 15g, coastal glehnia root 20g, radix paeoniae alba 20g, liquorice 10g, orange peel 10g; ③ Modified Buzhong Yiqi Decoction for Qi deficiency of spleen and kidney: to tonify the spleen and warm to kidney, to promote the circulation of the Qi, to achieve diuresis, prescriptions: Astragalus mongholicus 15g, ginseng 15g, Rhizoma Atractylodis Macrocephalae 10g, honey-fried licorice root 15g, Angelica sinensis 10g, pericarpium citri reticulatae 6g, rattletop 6g, radix bupleuri 12g, ginger 9 pieces, 6 Chinese dates; ④ Modified Jisheng Shenqi Pills for kidney-yang exhaustion: to warm and invigorate the kidney Yang, to promote the circulation of Qi, prescriptions: prepared rehmannia root 20g, Chinese yam 10g, dogwood 10g, rhizoma alismatis 8g, moutan bark 8g, Poria cocos 8g, cinnamon 6g, radix aconiti lateralis preparata 6g, the root of bidentate achyranthes 10g, semen plantaginis 10g; ⑤ Modified Zhibai Dihuang Pills for kidney-yin deficiency: to nourish the kidney Yin, to induce urination, prescriptions: prepared rehmannia root 20g, Rhizoma Dioscoreae 10g, dogwood 10g, rhizoma alismatis 8g, moutan bark 8g, Poria cocos 10g, rhizoma anemarrhenae 10g, golden cypress 10g. TCM was decocted and orally taken once a day for 20 days.

3.1.2.3. Western medicine: oral intake of Finansteride tablets, 5mg once a day, orally.

3.2. Results

Among 21 cases, 8 cases were given an indwelling catheter due to urination difficulty, 1 case with catheter removed 4 days after hyperthermia started, 4 cases 6 days after hyperthermia started, 3 cases 7 days after hyperthermia started. 13 cases with the symptoms of urgent, frequent and night time urination showed improvements 2-4 days after the hyperthermia started, and after 2 cycles of hyperthermia, their symptoms were almost resolved and no complications were noted.

3.3. Results

In addition to Western medicines and TCM in the treatment of prostate hyperplasia, it is also documented that hyperthermia in combination with Western and Chinese medicine could also be applied [6]. Chronic inflammatory cell infiltration is commonly found in prostatic hyperplasia [7], [8], [9]. Inflammation may have played a major role in causing or aggravating prostate hyperplasia, whereas prostatic hyperplasia may have worked the other way around, namely, causing or aggravating prostatitis. Chronic inflammation and hyperplasia of prostate are mutually induced.

Hyperthermia could promote the elimination of local inflammation and the diminishing of prostate volume; symptoms of patients are therefore improved. Hyperthermia could not only relax detrusor urinae muscle and urethral sphincter, but also relieve spasm. This study shows that hyperthermia in combination with Western medicine and TCM could alleviate the symptoms related to prostatic hyperplasia. In 8 cases the patients who were given an indwelling catheter due to urination difficulty had their catheters removed 4-7days after the hyperthermia started, much sooner than the conventional time which is 7-14 days. Those

with more serious symptoms, they showed improvements for their symptom 2-4 days after hyperthermia started, and they did not complain about any obvious discomfort. Therefore, deep regional hyperthermia could be one of the combined treatments for the patients who suffer from prostate hyperplasia. However, it is still not clear if regular hyperthermia for senior males could delay the progression of prostate hyperplasia. Further studies are required.

4. Chronic bronchitis

Chronic bronchitis is a type of commonly seen disease in clinical medicine, characterized by cough, expectoration, shortness of breath and frequent recurrence. The disease usually progresses slowly accompanied by obstructive pulmonary diseases, which could lead to pulmonary artery pressure, pulmonary heart disease, and pulmonary encephalopathy. Antibiotics remain the primary treatment. However, long-term use of the antibiotics could lead to resistance, which in turn would affect the effectiveness. In Clifford Hospital, deep regional hyperthermia in combination with TCM and acupuncture were applied in treating chronic bronchitis, which resulted in a promising outcome. The details are as follows:

4.1. Materials and methods

4.1.1. General information among those who underwent hyperthermia in the Clifford Hyperthermia Centre from January 2010 to December 2012, 35 patients presented with a diagnosis of chronic bronchitis, 21 males, 14 females, aged from 27 to 72 with an average age of 48±6, course of disease was 4-15 years. No contradiction to hyperthermia was known. There was no control group.

TCM diagnosis: ① 3 cases of Wind-cold syndrome: persistent cough, hoarseness, throat itching, thin and whitish phlegm, blocked and runny noses, chill, fever, headache, whole-body general soreness, thin and whitish coating on the tongue, floating and tense pulse. ② 3 cases of Wind-heat syndrome: dry cough, ropy and yellowish phlegm, thirst and throat soreness, turbid nasal discharge, fever, headache, sweating, red tongue nature, think and yellowish coating on the tongue, shallow and quick pulse. ③ 5 cases of Phlegm-heat syndrome: constant cough with excessive phlegm, ropy and yellowish phlegm, dry cough, fever, thirst, restlessness, small volume and yellowish urine, dry and hard stool, yellowish and greasy coating on the tongue, wiry, rolling, rapid pulse. ④ 7 cases of phlegm-dampness syndrome: persistent and heavy cough, excessive phlegm, thin and whitish, throat gurgling with sputum, chest distress, poor appetite, tiredness, sleepiness, red tongue nature, whitish coating on the tongue, slippery pulse. ⑤ 8 cases of Qi deficiency syndrome: lack of strength in expelling phlegm, thin and whitish, pale complexion, shortness of breath, sluggishness, low voice, chill, sweating, light and tender tongue nature with some indentations, thin and weak pulse. ⑥ 9 cases of Yin deficiency syndrome: dry cough without phlegm, or minimal sticky phlegm, blood phlegm, hard to be expelled out, thirst and dry mouth, itching throat, hoarseness, hot flashes in the afternoon, red tongue nature, less mosses, thready and rapid pulse.

4.1.2. Treating method

4.1.2.1. Deep hyperthermia EHY-2000 RF hyperthermia device, electrode plate: diameter – 30 cm, modulation switched off, power 130-150W, hyperthermia once a day, 40 min per time and 10 times per course, 2 courses totally.

4.1.2.2. Chinese Dialectical Therapy: ① Modified Mahuang Decoction for wind-cold syndrome: to relieve the chill and cough; prescriptions: ephedra 9g, cassia twig 6g, almond 6g, honey-fried licorice root 3g; ② Modified Folium Mori and Chrysanthemum Decoction for wind-heat syndrome: to resolve fever and cough, prescriptions: folium mori 8g, chrysanthemum 3g, almond 6g, fructus forsythiae 5g, Mentha haplocalyx 3g, Platycodon grandiflorum 6g, liquorice 3g, Reed Rhizome 6g; ③ modified Qingjin Huatan Decoction for phlegm-heat syndrome: to remove heat from the lung, dissolve phlegm and resolve the cough, prescriptions: Scutellaria baicalensis 12g, jasmine 12g, rhizoma anemarrhenae 15g, trichosanthes kirilowii Maxim 15g, Fritillaria thun-bergli 9g, tuber of dwarf lilyturf 9g, tangerine 9g, Poria coco 9g, Platycodon grandiflorum 9g, liquorice 3g; ④ Sanao Erchen Decoction for phlegm-dampness syndrome: to relieve cough and reduce sputum, prescriptions: ephedra sinica Stapf 12g, almond 12g, liquorice 12g, Processed Rhizoma Pinelliae 15g, tangerine 15g, Poria cocos 9g, honey-fried licorice root 5g; ⑤ Modified

Liujunzi Decoction for Qi deficiency syndrome: to strengthen the spleen and to supplement to lung, to invigorate the Qi and dissolve the phlegm, prescriptions: ginseng 12g, Rhizoma Atractylodis Macrocephalae 12g, Poria cocos 12g, honey-fried licorice root 9g, pericarpium citri reticulatae 6g, Processed Rhizoma Pinelliae 5g; ⑥ Modified Shashenmaidong Decoction for Yin deficiency syndrome: to nourish the Yin and Moisten the lung, and to relieve the residual heat; prescriptions: radix glehniae 12g, radix polygonati officinalis 10g, Radix Ophiopogonis 15g, radices trichosanthis 12g, hyacinth bean 10g, folium mori 5g, Licorice Roots Northwest Origin 3g. TCM was decocted and orally taken once a day for 20 days.

4.1.2.3. Acupuncture: Feishu, Lieque, Hegu, Dingchuan, Acupuncure was done once a day for 20 days.

4.1.2.4. Western Medicine. Antibiotics were determined by the bacterial culture and drug allergy results.

4.1.2.5. Treatment effect assessment the effect was evaluated according to the standards as listed in Practical Internal Medicine [10], TCM Criteria for Disease Diagnosis, and Proposed Criteria for Treatment Effect Assessment [11]. Cured: the symptoms including cough, phlegm and shortness of breath were controlled, the patients' conditions were stabilized, no reported recurrence; significant effectiveness: the patients' conditions were stable, the frequency of recurrence was reduced, the general conditions improved; effective: the conditions were still not stable, yet, the frequency of recurrence and the state of the disease were both relieved and the general conditions were improved; ineffective: no improvements for either the recurrence frequency, state of illness or general condition, or even deterioration.

4.2. Results

4.2.1. Clinical effect: 8 cases were cured, 11 with significant response, 9 with response, 7 failed to respond, to overall response rate was 80%.

4.2.2. Time for extinction of symptom: coughing was resolved in 4.5±1.3 days, gasp 3.5±0.5 days, whereas expectoration 4.5±0.5 days. It was shorter than the time reported by other studies. After the treatments, the phlegm became much easier to be expelled out, and the lung rale was significantly reduced [12].

4.2.3. Improvements of the Symptom: After hyperthermia, it became much easier to expel out the phlegm, and the pulmonary moist rales were significantly reduced compared to that of before hyperthermia.

4.3. Discussion

It has been well-documented in literature that an integration of Traditional Chinese Medicine and Western Medicine could treat chronic bronchitis[13]. In this study, hyperthermia in combination with TCM and acupuncture was applied in treating chronic bronchitis. This is new clinical trial. Hyperthermia could boost pulmonary blood circulation and lymphatic return, alleviate edema, facilitate effusion absorption and accelerate clearance of inflammatory metabolic products and bacterial toxins. Hyperthermia increased the drug concentration in the focus, thus enhancing the therapeutic efficacy of the drugs, bettering the gasp and eliminating pulmonary rales significantly. Hyperthermia in combination with Western Medicine, TCM and acupuncture demonstrated a promising result in treating chronic bronchitis, pneumonia and other pulmonary diseases. The study also revealed that hyperthermia worked very well in relieving various chronic bronchitis symptoms, particularly in reducing the pulmonary rale. No adverse side effects were noted. A combination of hyperthermia, TCM and acupuncture could also be applied in treating other pulmonary diseases such as pneumonia. However, further clinical trials and studies are needed.

5. Conclusion

Modern technologies not only have made deep hyperthermia a reality, but also have promoted a more widespread application of it. Regional deep hyperthermia in combination with other conventional treatments such as TCM and natural therapy could be an alternative for benign diseases. It is safer, pain-free, more effective and convenient and has far less side effects.

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Oncothermia Journal 7:167-169 (2013)

Regulation of Tonglian decoction on cell cycle and signal pathway mediated with NF-kB in cell line MGC-803 of gastric carcinoma

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Regulation of tonglian decoction on cell cycle and signal pathway mediated with NF-kB in cell line MGC-803 of gastric carcinoma

Abstract

Gastric Cancer (GC) is one of the most critical diseases around the world. Population of its morbidity reaches 1,000,000 every year, among which 42% patients are in China. Thus, both the incidence and the mortality of GC are twice as much as the average level in the world. Clinical practitioners and basic researchers have been working on it for years, trying to find effective and long-acting therapeutic method focusing on GC. Till nowadays, no one can deny that radio-chemotherapy and operation have non-negligible side effects. At the same time, national medicine is showing more and more predominance in treating GC. Chinese herbs have been applied in China for thousands of years. Uncountable clinic cases indicate that it can be a considerable means to try on GC. Based on classic formula—Tongyou Decoction---combined with the modern pharmacological theory, our research team has created a proprietary compound, named Tonglian Decoction (TD), aiming to treat gastric cancer.

Objectitve

To investigate the effect of TD on proliferation of gastric carcinoma cell line MGC803 by ascertaining the cell morphology through inverted microscope, the cell cycle by PI dye and one of its signal transductions mediated by NF-κB to explore the mechanism of TD and to discuss the contents of blood stagnation and heat-toxins of gastric cancer in molecular biology.

Methods

Human gastric carcinoma cell line MGC803 is cultured with 10% calf serum at 37□ in a 5% CO2 incubator, treated with TD, compared with 3 controlled drugs, including 5-fluorouracil (5-Fu), cisplatinum complexes (CP) and Xiaoaiping Injection (XAP) which have been widely applied in clinics to anti-cancer. Cell proliferation is assayed by MTT, cell morphology is observed through microscope, cell cycle is measured with Flow CytoMeter (FCM) by PI labeling and regulation mechanism is investigated with western blot of NF-κB signal pathway.

Results

Doses for 50% cells inhibition rates (IC50) of TD, 5-Fu, CP and XAP are 192.75, 21.22, 1.10 and 23.61 $\mu g \cdot mL^{-1}$, respectively(Figure 1). TD and 5-Fu inhibit cell proliferation predominantly(Figure 2). In FCM determination, rates of G1 phase in four groups get to 59.72%, 74.01% , 28.79% and 63.74%, respectively. Cells number in S phase treated with TD, 5-Fu and XAP has significant difference from that in CP group ($P<0.05$)(Figure 3). In western blot, compared to the controlled group, in signal pathway mediated with NF-κB proteins in 4 groups express slightly differently, among which TD and 5-Fu have much better effect, showing great significant difference from the other two groups ($P<0.05$) (see Figure 4).

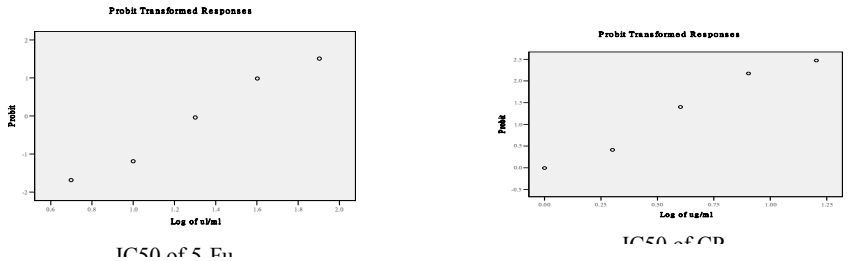
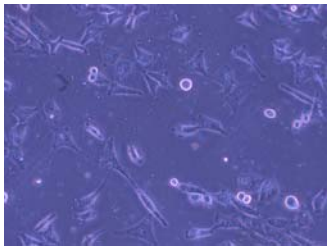
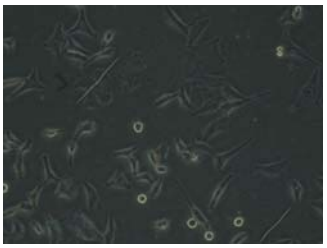


Figure 1. IC50 fitting curve of dose-effect dependence

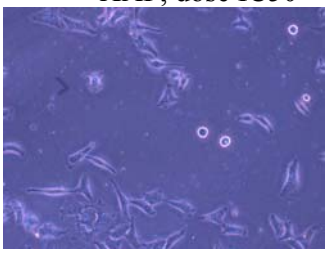


TD, dose IC50



XAP, dose IC50

5-Fu, dose IC50



CP, dose IC50

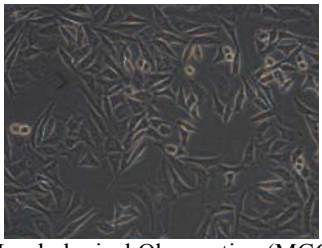
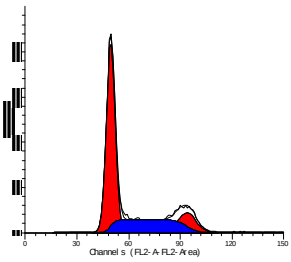
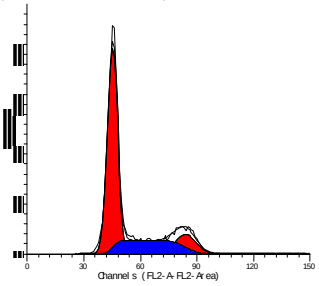


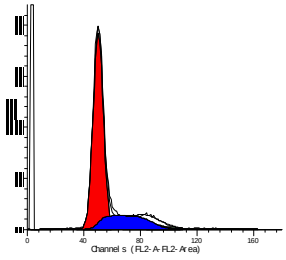
Figure 2. Morphological Observation (MGC803, 200×)



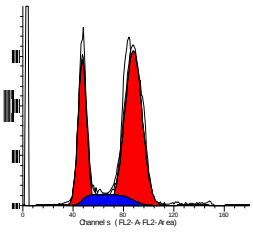
Diploid: 100.00 %
Dip G1: 59.72 % at 49.62
Dip G2: 12.46 % at 93.84
Dip S: 27.82 % G2/G1: 1.89
%CV: 5.17 Group TD



Diploid: 100.00 %
Dip G1: 63.74 % at 45.21
Dip G2: 12.11 % at 83.94
Dip S: 24.15 % G2/G1: 1.86
%CV: 5.94 Group XAP



Diploid: 100.00 %
Dip G1: 74.01 % at 49.91
Dip G2: 3.72 % at 88.77
Dip S: 22.27 % G2/G1: 1.78
%CV: 7.07 Group 5-Fu



Diploid: 100.00 %
Dip G1: 28.79 % at 47.13
Dip G2: 61.15 % at 87.58
Dip S: 10.07 % G2/G1: 1.86
%CV: 7.14 Group CP

Note: Cells calculation 20,000, analyzed by MODIFIT, BD Co. USA.

Figure 3. Phases of cells cycle for MGC803 regulated by four drugs analyzed with FCM

TD Control XAP CP 5-Fu

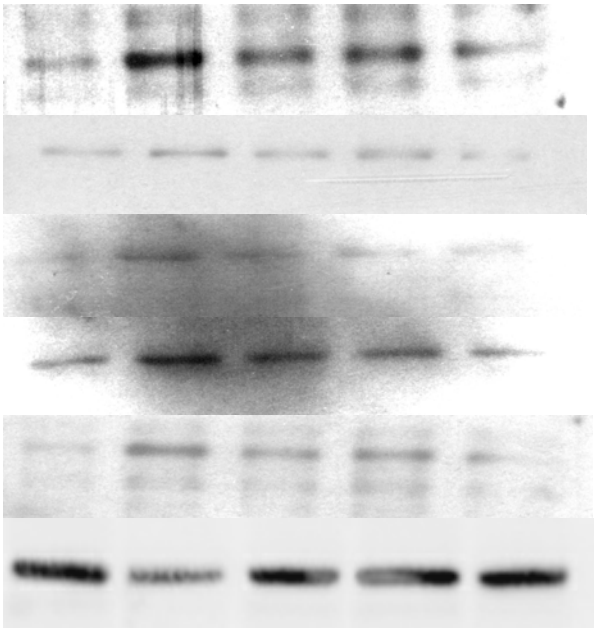


Figure 4. Expression of proteins in signal pathway mediated with NF-κB

Conclusions

1. TD can be used to regulate MGC803 carcinoma cells proliferation by inhibiting cells entering the S phase. 2. 5-Fu has little effect on cell cycle of MGC803, indicating that this anti-cancer drug is selective to regulate different cancers in digestive tract. 3. The intracellular mechanism of TD inhibiting MGC803 is connected to genes expression mediated with NF-κB.

Oncothermia Journal 7:170-170 (2013)

A novel dendritic cell therapy with oncothermotherapy mediated by abscopal effect

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Objective

The abscopal effect on the tumor is a distant antitumor activity induced by local treatments. The study was to observe the induction of abscopal effect by the combination of dendritic cell therapy with oncothermia therapy.

Methods

SCCVII (mouse squamous cell carcinoma) cells were injected into C3H/He mice at two separate sites, defined as a "primary" site that was treated and a "secondary" site outside the field of treatments. When both tumors were palpable, mice were randomly assigned to four groups receiving dendritic cell (DC) therapy or oncothermia therapy. The mice were treated with local intra-tumor injection of DCs combined 30 minutes heating at 42□. Mice were followed for tumor growth.

Results

In the models tested, the combination of DC therapy and either fractionated oncothermia therapy regimens achieved enhanced anti-tumor response at the primary site. Moreover, an abscopal effect, defined as a significant growth inhibition of the tumor outside the field, occurred in mice treated with the combination of DC therapy and oncothermia therapy.

Conclusions

The abscopal antitumor effect could be induced by the combination of DC therapy and onthermia therapy and this new technique could be a new strategy for the treatment of squamous cell carcinoma.

Oncothermia Journal 7:171-171 (2013)

Infrared WBH for relapse prevention in cancer

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Whole body hyperthermia plays an important role in the concept of biological cancer therapy, mostly in palliative situations. In the adjuvant setting, there has only been casuistic data until now.

The talk shows the immunology during / after chemotherapy and provides an overview of the immunological significance of fever, which most cancer patients have not experienced for many years before the disease. Since the opening of the praxis in early 2002, a collective of now > 60 patients (mainly breast cancer) has been observed. These patients were adjuvant treated with at least two whole body hyperthermia treatments. The follow-up so far shows a high number of patients with tumor-free survival even in high-risk constellation. The tumor after treatment should follow and evaluate this approach to a greater extend.

Oncothermia Journal 7:173-176 (2013)

Treatment of a High Grade Glioma (GBM) with four different oncolytic viruses (Parvo HI, VSV, NDV-Nothabene and Sindbis-Virus), elected by the symptoms, delivered via an Intra-arterial Port-a-Cath-System and controlled by repeated MRIs

Arno Thaller[1]
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Treatment of a High Grade Glioma (GBM) with four different oncolytic viruses (Parvo HI, VSV, NDV-Nothabene and Sindbis-Virus), elected by the symptoms, delivered via an Intra-arterial Port-a-Cath-System and controlled by repeated MRIs

Summary

This is the first case report using different viruses to attack one tumour. They were chosen by the very unique method of human medicine: The patient, i.e. the highest authority, was asked to observe the development of the most conspicuous tumour associated symptoms in the course of therapy. The tumour was located in the gyrus cinguli on the right side of the frontal lobe, depressing the right ventricle and causing weakness of the left arm and leg. At the beginning of treatment the degree of these symptoms was estimated as 100%. Improvement was noted by a number below one and worsening by a number above 100%.

This simple method allowed the election of four different viruses that showed to be effective to influence the leading symptoms. In the beginning of the therapy the tumour growth was 100% within 5 weeks. At the first control 5 weeks later the growth slowed down to 50%. The second and third control showed "stable disease" and the following controls showed an increasing relief of pressure on the side ventricle accompanied by the reduction of the tumour-size.

History

The first observation that virus can lead to healing of even the advanced cancer was made by an Italian gynaecologist in 1904 called "peace": DePace.[1]

The 20th century gained a lot of experience, that naturally occurring viral diseases and deliberately applied viruses can influence the course of malignant diseases even to a point that we can call "cure"![2]

Quite often, however, the initial response was followed by a failure due to the well-known ways of escape: antibody production and selection of resistant clones. Both mechanisms have to be considered to help virotherapy on the way to success.

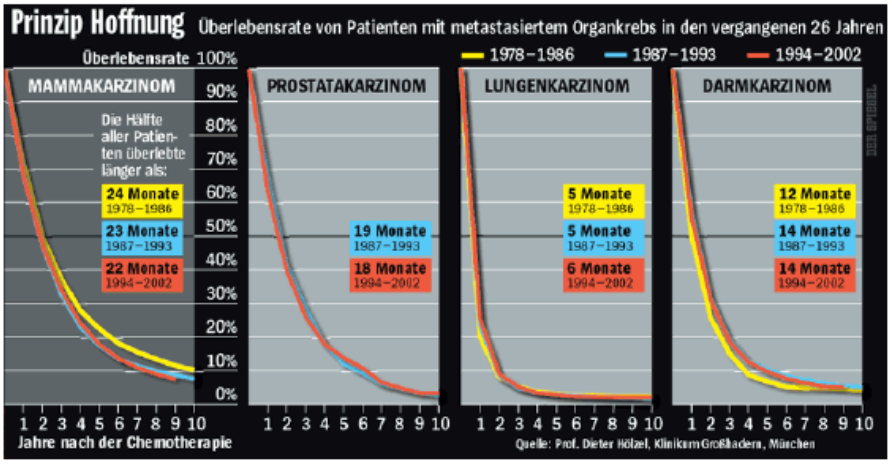
One simple strategy is to change the virus or the other is to combine several viruses in face of the fact that the tumour certainly consists of different clones with different degrees of "sensitivity" or rather "resistance".

At present there are 72 clinical trials being performed worldwide to evaluate different oncolytic viruses, mostly REO-Virus and a lot of genetically engineered Vaccinia-Viruses.

Chemotherapy was the great hope that suppressed all other approaches like fever and virotherapy.

At the end of this warring century we must confess: We have lost the "war against cancer". [3] There must be something wrong in our approach!

This is the Oath of Disclosure: „Poisoning without Benefit": It is the sober end result of a century's fight against cancer!



Spiegel 41/2004

Philosophy

It is very simple: Cancer behaves like a parasite, e.g. like a bacterium.
We have abundant knowledge about how to fight against parasites: to elaborate an "antibiogram".
The tradition of this knowledge forces us to elaborate a "virogram" in order to find out the most potent viruses for a given tumour!
The "virogram" is undoubtedly the solution of the problem, but it is not easily achieved.
We have to establish a cell line of the patient's own cancer.
The cancer cells that easily grow in tissue cultures, however, are not necessarily identical with the original tumour. It might be merely a laboratory adapted tumour strain without any significance in the clinical situation!
The solution of this problem is the comparison of the original tumour with the cultivated tumour cells with the help of molecular genetics in order to guarantee the identity. At least the hormonal status and the proliferative status must coincide!

Mostly we do not have tumour material of sufficient vitality at our disposal to establish a long term cell line and to perform an "in-vitro-virogram". This forces us to rely on the three clinical criteria of tumour response: symptoms, tumour markers and imaging, in order to elaborate an "in-vivo-virogram".

In the future we have to find out molecular patterns of the tumour cells that signalize "sensitivity" like in the case of K-ras-mutation and REO-virus type 3. For most types of tumours and viruses it is unfortunately yet unknown.

In our case we neither had living tumour material nor a tumour marker. This reduced our tools to "symptoms" and "imaging".

Method

Like in the case of the antibiosis of an unknown micro-organism we have to rely on the literature and on our own experience.

Parvo H1 is a virus which naturally occurs in rats. It does not even cause any symptoms in the natural host, not to mention the people. This virus is currently investigated by the German Research Institute in relapsing GMB.

VSV is the acronym of Vesicular Stomatitis Virus, causing a disease in cattle resembling foot-and-mouth-disease. Farmers are usually not afflicted. Sometimes they get a fever attack. It is clinically investigated in primary Hepatocelllular Carcinoma. An animal study showed high efficacy in GBM.[4]

Sindbis-Virus is endemic in Scandinavia and causes a disease in wild birds.
The Wollmanns animal study was also fairly effective in the case of GBM, even though to a lesser extent compared with VSV.

Newcastle-Disease-Virus (NDV) is the causative agent of atypical fowl-plague. It has been intensively investigated by Csatary since the sixties of last century in different tumours among others GBM6. They named their strain MTH-68/H, an acronym for "**M**ore **T**han **H**ope" in the year 1968 in Hungary. This strain is genetically nearly identical with the NDV-strain Mukteshvar.
Our strain is a mutant of MTH-68/H. It showed to be the most effective compared with four other strains in terms of oncolytic capacity and immune stimulating properties.7

The case report

10/10	First symptom: Grand Mal seizure MRI: Tumour in the right frontal lobe
05.10.10	Operation: Macroscopically complete resection (University of Regensburg) Histology: (UKR, H 23573/10): Glioblastoma WHO Grade IV, MGMT-Promotor methylated (100%), confirmed by the Reference Institute for Brain Tumours, Bonn, R-46851.

10-12/10	Radio-Chemo-Therapy until 60Gy, accompanied by Temozolomide 75mg/m2 daily together with radiation and Cilengitide 2g i.v. 2 times per week (Centric-Trial, Verum-arm). Cilengitide is a cyclic pentapeptide, that inhibits integrin, a trans-membrane protein essential for signal transduction, leading to an inhibition of angiogenesis.
1-7/11	Adjuvant Chemotherapy with Temozolomide 200mg/m2 d1-5/28 and Cilengitide 2g i.v. 2 times a week (six cycles)
7/11	MRI Relapse in the region of the right gyrus cinguli
15.07.11	Stereotactic radiation 6 x 5Gy
30.07.11	Intensified chemotherapy with Temozolomide 100 mg/m2 d1-7, 15-21/28 (4 cycles)
15.11.11	MRI: PD
19.11.11 1.	Cycle CCNU 110 mg/m2 d1/42, plus Procarbazin 60 mg/m2 d8-21/42, termination after the first cycle because of myelotoxicity (thrombocytopenia)
23.12.11	MRI PD: 26 x 20 x 30 mm = 16 ml, i.e. doubling of the tumour-volume within 5 weeks
23.12.11	Start of "specific detoxification"8
09.01.12	Start of virotherapy with Parvo-H1
30.01.12	MRI: PD: 27 x 26 x 31 mm = 22 ml, i.e. slowing down of the rapid volume increase from 100% to 50% within five weeks
07.02.12	Port implantation into the Aorta thoracica, ascending part (via the right subclavian artery)
02.04.12	MRI: Tumour volume 30 x 22 x 33 mm = 22 ml, i.e. stable disease since 8 weeks
08.06.12	MRI: SD since 12 weeks
25.07.12	MRI: Minimal regression
01.10.12	MRI: Further minimal regression. The ventricular system is "blooming up".

Fig. 2, 3, 4, 5

Summary

This case report is the proof of principle that clinical signs can be beneficial to choose an appropriate virus for an individual patient.
With the first virus (Parvo-H1) the increase of strength could be noticed after 3 – 4 days of daily administration.
With the second virus (VSV) the response was very dramatic: Within two hours the patient felt an increase of weakness in the left leg from 50% to 200%. It reached its climax after two more hours:

The patient fell down when trying to reach the toilet. Then the worsening slowly subsided within 12 hours, the final level of weakness was 40%.9
The response to the other viruses was not as conspicuous.
A second sharp rise of weakness was noted in connection with an inadvertent flu. The causative agent, however, remained in the darkness of clinical reality.
The hypothesis underlying this compassionate treatment, where all other modalities failed, is very simple:
The tumour behaves like a parasite. Oncolytic viruses share some common features with antibiotics.
These are the common features:
1. Resistance can occur, either primary or as a consequence of selection in the course of therapy.
2. A standardized "virogram" in analogy to the antibiogram could be of great help to choose the right virus for an individual tumour.10
3. In the case of "escape" we have to change the virus or to combine it with other viruses.

The main difference is the response of the immune system:
In the case of antibiosis it may lead to allergic reactions, due to the production of antibodies and cytotoxic lymphocytes.
In the case of virotherapy the immune response is ambivalent:
Antibodies antagonize the viruses, thereby diminishing their efficacy.11
The cytotoxic lymphocytes on the other hand work synergistically with the viruses: They do not directly attack the viruses but the virus-infected tumour cells.

"Modern times" are ruled by "trials", double blind if possible!
The status of "case reports" is steadily declining.
Biologists have taken over the fate of medical research.

This is a very doubtful evolution last but not least from a philosophical point of view:
The trial only throws light on the "collective" aspect of man.
It leaves the "individual" out of consideration.
The "individuality", however, is the essential difference between humans and animals, apart from "freedom" and "philosophy".

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7. Apostolidis, L., Schirrmacher, V., Fournier, P., Host mediated anti-tumoreffect of oncolytic Newcastle disease virus afterlocoregionalapplication, International Journal of Oncology 31: 1009-1019, 2007
8. The term „specific detoxification" refers to the application of homoeopathic preparations of those poisons that are likely impairing the immune systems, e.g. all past chemotherapies. As a consequence the side effects are promptly improved and quite often also tumour markers to a certain extent. This is a matter of fact even though the mode of action is completely unclear.
9. In Wollmanns animal experiment VSV was the fastest virus. Nevertheless the velocity of clinical response is difficult to explain.

However, medicine is an empirical science:

Facts do have priority

We cannot reasonably question the facts without declaring the patient an idiot. The lack of explanation cannot be the reason to deny somebody the soundness of mind. The lack of explanation is first of all my own deficiency! Facing the fact that 100.000 chemical reactions are taking place each second in a single cell, i.e.1018 in the whole organism (1 million times 1 million times 1 million!), it is not very surprising that unexpected events occur, on the contrary: It is very surprising, that any of our predictions really occur!

10. It is very amazing that this natural aim has not even been contemplated by the leading cancer research institutes. A generalpractitionerhasbroughtforththisidea:
    Thaller, A., Tumortherapie mit onkolytischen Viren unter Leitung der PCR zur Erstellung eines Virogramms und zur Therapiekontrolle, Wien 1999.
    In the absence of a standardized individual virogram we have to elaborate molecular patterns to predict "sensitivity" and "resistance".
11. They never cause allergic reactions against the virus itself but rather against contaminations by the culture medium, e.g. against egg proteins in the case of NDV cultured on egg cells and not on human tumour cells.

Oncothermia Journal 7:178-180 (2013)

Lyme disease and Oncothermia

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Lyme disease and Oncothermia

Abstract

Lyme-Disease is a tick-borne disease with multiple organ failure and systemic disorder. Dramatic change becomes apparent in the chronic phase of the disease. Chronic fatigue syndrome, lapse of concentration, depression, joint pain, muscle pain are a few, but major clinical symptoms characterizing the disease. The human immune-system is defenseless. Borrelia uses various mechanisms to escape from immuno-attacks or antibiotic therapies. This „stealth phenomenon“ needs new therapeutic principles to be interrupted. Our objective in this paper is to study the effect of oncothermia, which is a well-established oncological therapy, in Lyme disease. First, in our present work, we definitely concentrate on the quality of life of the patients.

Background

Lyme borreliosis (LB), or Lyme disease, is transmitted by ticks of the Ixodes ricinus complex. Its manifestations had been documented [1]. The etiologic agent, Borrelia burgdorferi, was firs isolated from the vector tick Ixodes dammini (now I. scapularis) [2]. Borrelia burgdorferi is a bacterial species of the spirochete class of the genus Borrelia, which has a double-membrane envelope [3]. Borrelia burgdorferi is one of the few pathogenic bacteria that can survive without iron, having replaced all of its iron-sulfur cluster enzymes with enzymes that use manganese, thus avoiding the problem many pathogenic bacteria face in acquiring iron. It takes more than 24 hours of attachment for transfer of Borrelia burgdorferi. Huge development was made during the past 20 years understanding Borrelia burgdorferi, and its consequent illness. Its microbiology [4], epidemiology [5], diagnosis [6], [7] and clinical practices [8], [9], [10] are studied in details.

Clinical symptoms of Lyme disease are serious. Listing only some major of them: fatigue syndrome, lapse of concentration, depression, joint pain, muscle pain, erythema chronicum, as well as myocarditis, cardiomyopathy, arrythmia, arthritis, arthralgia, meningitis, neuropathies and facial nerve palsy.

Borrelia burgdorferi infections have been linked to non-Hodgkin lymphomas, [11]. Oncothermia, well known in cancer-therapy [12], might be an adequate method for treatment of Lyme disease. The applied bioelectromagnetic energy absorption acting on the cellular membrane [13] and on its regulation [14], tuning the parameters to the membrane destruction [15]. The applied interaction radiofrequency (RF) range, (RF carrier with LF modulation [16], [17]); coupled by impedance (capacitive) mode could act on the cell-membrane states of the bacteria. The huge temperature gradient on the membrane could modify the HSP structure shown by DNA array involving first of all the HSP60 and HSP70 chaperones proteins [18]. Borrelia burgdorferi is especially sensitive on the membrane-states of these HSPs [19], [20], so the effect is expected. Furthermore, the applied modulation of oncothermia [21] could be a useful tuning parameter for selection of the bacteria.

Method

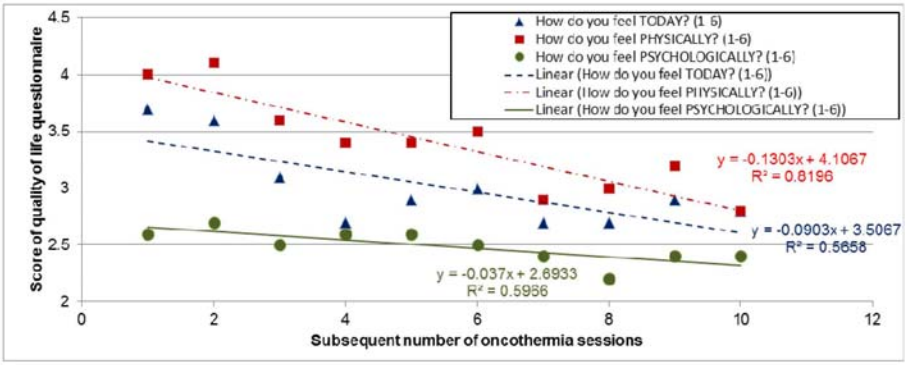
12 patients (8 male and 4 female; mean age 55 y, [39÷76]) suffering from lyme-disease the influence of oncothermia on healing processes was examined in this pilot-study. Their medical history was the cohort forming ability. Tick bite was recognized for 75% (9/12) patients, erythema migrants 50% (6/12), antibiotics pretreatment was made for all (12/12) and the typical symptoms of lyme-disease/lyme-neuro-disease was registered for all (12/12). All the patients were ELISA positive (12/12) and WesternBlot positive (12/12) as well. LTT positive was 42% (5/12) and positive in their cerebrospinal fluid was in 17% (2/12). Due to the complicated and very expensive laboratory tests, the effects were measured on the quality of life of the patients. For this measurement a special questionnaire was prepared, concentration on three questions: general feeling today, feeling physically and feeling psychologically. Valuation was made in grades on a 1-6 scale, (1=excellent, 6=inadequate/very bad).
Treatments were done by oncothermia method (EHY3000, Oncotherm GmbH, Germany), the duration was 60 min pro session. Treatments were 3 times in a week, and all together 10 sessions were provided. The heting protocol was a step-up heating (70/100/130/150 W) with modulation, using electrode 40x70 cm area,

applied it for the trunk of the patients. As drug-support Minocyclin/Hydrochloroquin were used when indicated.
Complementary supportive therapy was applied: HighDose VitaminC 7.5 gr; Vitamin B12; Glutathion; Homoepathics to support emunctories; Medicated Mushrooms (Capsule); Supplementary like VitaminD, Calcium, Magnesium.

Results

The evaluation of the development of the quality of life shows remarkable improvement (see table and figure, points are averages of the 12 patients answers).

questions/number of oncothermia sessions	1	2	3	4	5	6	7	8	9	10
How do you feel TODAY? (1-6)	3,7	3,6	3,1	2,7	2,9	3,0	2,7	2,7	2,9	2,8
How do you feel PHYSICALLY? (1-6)	4,0	4,1	3,6	3,4	3,4	3,5	2,9	3,0	3,2	2,8
How do you feel PSYCHOLOGICALLY? (1-6)	2,6	2,7	2,5	2,6	2,6	2,5	2,4	2,2	2,4	2,4



In the majority of cases dramatic improvement in physical state occurred, a better respond to other therapeutic treatments. Especially neurological disorders could be influenced positive. Patient feels as good as never before, can do housekeeping again, and could do her/his work again. Who was frequently absent form the school after the treatment regularly visited the lessons again,
etc. Adverse effects were sometimes headache and rarely neuropathic symptoms during the treatment.

Conclusion

Oncothermia is an important module in treatment-concept of Lyme disease. Mechanism of action against stealth development should be objectified. Procedure of Oncothermia-treatment (power/treatment-time/treatment frequency) should be defined. Synergies with other treatments should be objectified. Oncothermia should become a vital component in therapeutical treatment of lyme-disease.

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AndroTherm application for “La Peyronie” disease

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AndroTherm application for “La Peyronie” disease

Peyronie’s disease is characterized by a scarring fribrosis within the tunica albugina of the penis that could lead to penile length loss, narrowing, curvature, erectile dysfunction, pain with erection.

Prevalence

La Peyronie disease (Induratio penis plastic), is a developmental condition with acquired fibrotic changes and development of a fibrous plaque (fibrous inelastic scar) on the tunica albuginea of the penis. The Peyronie disease is mostly observable at the men of their middle ages (50-60 years) in Caucasian race (1). The prevalence, commonly reported, is about 3-9% (2), but according to the autopsy statistics the disease would be present in more than 20% of men (3). It can also be an asymptomatic finding in almost 4% of male population seeking medical attention (4, 5). In general the men, 40-60 aged, are affected by Peyronie’s disease in 2-3% (6). We think in fact that shame, fear and poor possibilities of healing (WEBSITE) are the main causes of reduced demand for medical consultation, although it also causes unpleasant side effects such as not agree to the modifications of the penis, reduction of self-esteem, impaired job performances, increased interpersonal conflicts and depression. Now, thanks to the many sources of information, the patient is aware of the limited possibilities of therapy and knows perfectly well that there is little chance of spontaneous recovery (15% of second Mulhall) (7).

Pathophysiology

Relatively little is known about the source of the disease, but nowadays is growing consensus on the possibility of an external stress received, most likely in the erect state, during sexual intercourse or masturbation. Trauma during sexual activity can occur for several reasons: vehement and prolonged masturbation, instinctive and sudden movement of the penis, accidental contrast of the penis against the female perineum, difficulty in penetration due to lack of lubrfiication of the vagina, lack of penile erection. The abrupt penis deformation during sexual intercourse may disrupt small vessels within the tunica albuginea with blood trapping between layers of the tunica. The hematoma is responsible for excessive release of cytokines, of Transforming Growth Factor (TGF beta1), as a reaction to an autoimmune response. It follows an overproduction of collagen, high production of extracellular matrix, accumulation of fibroblasts and myofibroblasts and decrease of elastic fibers (8). This process, characterized by an abnormal healing of hematoma with production of scar, implies the coexistence of an autoimmune process probably leading to a genetic factor. In 75% of patients affected by Peyronie's disease were shown high levels of antielastin antibodies (9) and a higher incidence of histocompatibility antigens HLA-27 (10). The autoimmune reaction may have, in some individuals, a certain degree of genetic predisposition. Some searches have demonstrated in fact, on cultured cells derived from plaques from Peyronie's disease, chromosomal abnormality, during metaphase, in which the chromosome Y seems the more involved. The actual trauma could lead to inflammation Bleeding and releasing of a number of chemicals that lead to inflammation (12). The closed , layered structure of the tunica may limit the ability to drain the produced inflammatory mediators away from the site of injury, leading to prolonged inflammation (when the inflammation became chronic it could block the healing process) (13,14). Nowadays no effective therapy exists for this disease, although there are continuous and ever new attempts. There are many non-surgical treatments for Peyronie’s disease like Vitamin E, Carnitine, Colchicine, Pentoxyphilline, and various herbal and complementary remedies like Acetyl-L-Carnitine (ALC) and Dymethyl Sulfoxide (DMSO), or the “ Tracker formula “; enzymes like Wobenzym, Fibrozym, Vitalzym, and Neprinol; as well as the minimally invasive (local in-situ injection) treatments of Verapamil, Interferon, Collagenase, and various steroids (e.g. Glucocorticoids) could be applied. All of the treatments applied have no or poor efficacy. There are various surgical options to solve this problem (15).

There are huge interest to treat this disease worldwide (16) and also comprehensive books published in the topic (17,18). The transdermal electrophoresis (19) could be effective for the treatment combined with definite drug-therapy called“ trasdermal electromotive drug-therapy“ (EMDTA) (20). This placebo controlled, double-blind study used Orgotein (8mg), Dexamathasone (8mg), Lydocain (120mg) for 20 min three times a week in three weeks duration. The plaque reduction was 79%, the curvature improvement 62% and the pain reduction 100%. Others had also used EMDA with Dexamethasone+Verapamil

combination (21), also campared to Lidocain effect alone (22). EMDA application with Verapamil alone (23) also was effective.

Contrary the new review of non-surgical solutions to treat Peyronie's disease (24), hyperthermia also was applied with success for Peyronie's disease (25). They studied 60 Patients with Peyronie's disease, having a comparison between application of Verapamil and Hyperthermia. The chosen cohort groups were identical in their main relevant parameters (see Figure 1.). Hyperthermia was applied for 20 minutes, twice a week for 5 weeks. A 2nd cycle was made after a 1 month having 10 treatments. The control group received 10mg injection of Verapamil once a week for 3 months. The Verapamil group had no real benefit of the treatment (see Figure 2.). It was significant relief of both subjective and objective symptoms in Hyperthermia treated group, without any adverse side effects (see Figure 3.). The penil curvature decreased by 55,9% with Hyperthermia, while only 3,8% with Verapamil, and the plaque size decreased 42,1% and 2,2% with Hyperthermia and Verapamil, respectively. Similar controlled clinical study is in progress to repeat the results (26). The clinical trial compares the only heat treatment and the treatment group is receiving a combination of Vitamin D and Testosterone injections additional to heat by infrared heating. Learning the failures of many applied conventional treatments and seeing the possible applicability of the heat and the electric field based on current knowledge of the pathophysiological mechanisms involved in the formation of plaque, we developed a new device for treatment of the penis disorders, including Peyronie's disease.

The collected evidences based research data indicate inflammation processes, like the " primum movens " of the cascade process of healing that includes the inflow of platelets, macrophages and mastcells. It has subsequently the release of numerous substances: interleukin, tubular necrosis factor (TNF α), platelet-derived growth factor (PDGF), transforming growth factor (TGF β), which trigger the scarring process by means of the proliferation of fibroblasts, differentiation of myofibroblasts, the deposition of collagen tissue and the transformation of "stem cells" of the tunica albuginea in osteoblasts (27, 28). On this basis the Peyronie's disease plaque is more similar to keloids than to scars. About the formation of keloids is important to note that at the wound site there is a production of heat shock proteins in response to an inflammatory process in order to modulate the intensity of inflammation and the synthetic responses to stress toward the healing of the wound. Overexpression of HSPs can, however, lead to an increase in the inflammatory process and an uncontrolled synthesis process. In some cases, genetic factors, individual predisposition, and physical factors (a particularly aggressive inflammatory process) can play an important role in the formation of keloids. It was reported a high expression of HSPs 27, 47 and 70 within the keloid tissue compared to healthy tissue, which induces both an exaggerated proliferative effect (HSPs 70) and production of matrix (HSP 27.47). (29). In Peyronie's disease has been noted up-regulated expression of certain proteins such as the 'alpha-actin, beta-catenin, and Heat shock proteins (Hsp47), which are established components of fibrosis and wound healing (30).

It is a benign tumor (31), in which:
1) Plaque fibroblasts are immortalized cells.
2) Plaques and normal tunica albuginea have chromosomal differences.
3) Induced immune response by the plaque fibroblasts and their products.
4) Mitochondrial dysfunction is observed in plaque fibroblasts.

In coherence of the above conditions it is not a surprise that apoptotic processes can play definite role in plaque formation and its elimination. There is a finding that apoptosis activation (32) albuginea plaques occurs. This, at least, in part is realized via extrinsic pathway (33). Peyronie's disease in known to be associated with Dupuytren's disease (34). Main characteristic of the Dupuytren's disease is palmar aponeurosis hyperplasy and contraction which leads to finger flexion contracture (35). Peyronie's and Dupuytren's diseases have common pathophysiology (36). The imbalance between proliferation and apoptosis, producing malignant growth was thus confirmed for fibrosarcoma, but not the same form for Dupuytren's disease, (37), because this is benign as well, similary to Peyronie's. However both can be regarded as system disease, (38), because the immune system is involved. It was hypothesize that periostin, secreted by Dupuytren's disease cord myofibroblasts into the extra-cellular matrix, promote the transition of resident fibroblasts in the palmar fascia toward a myofibroblast phenotype, thereby promoting disease progression (39).

Method

The traditional hyperthermia had good benefit in treatments of Peyronie's disease, however it is controlled the only single thermodynamic intensive parameter, with the temperature. Onchothermia is a special hyperthermia (40), working on the action of the modulated electric field in the locally treated lesion. It has long experience in the oncology (41). Its idea to use the benefit of electric field makes feasible applying it for Peyronie's disease, unifying the effects of EMDA and heat in a specialize treatment. Our objective is to perform a pilot study with application of a special (adaptively modified) kind of oncothermia for Peyronie's disease, called androthermia. The metod is based on the paradigm of the energy-dose control, replacing the single temperature concept (42, 43, 44). With this approach the oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which can not regarded as dose (the temperature does not depend on the volume or mass), Oncothermia uses the energy (Kj/Kg=Gy), like the radiation oncology uses the same (Gy) to characterize the dosing of the treatment. The requested job is to change the structure of the target, for what a definite energy dose is necessary (45). The historical energy-dose-like control (temperature multiplied by its application time) is physically incorrect, and operates with an overall energy average in the area, instead of a directed and well measurable energy-dose (measured in Kj). So these points are realized, and called this procedure modulated electro-hyperthermia or oncothermia (46) and specialized now for andrology. The presently applied radiative hyperthermia device, operating on order of magnitudes higher frequency than oncothermia, are in fact capacitive-coupled, because the applicators are definitely in the near-field arrangements. It is a well designed capacitive coupling on 13,56 MHz free-frequency (47). The process is controlled by the changes of the impedance, and by the absorbed energy, which both are accurately measured. Androtherm device, is the product of Onchotherm GmbH, Troisdorf, Germany (see Figure 1.).

Figure 1. Androtherm device (Treat-therm trade-mark)

It was developed for Peyronie's disease, concentrating the plaque dissolution, using all the experiences and achievements from the past 20 years. A set of special electrodes were developed for best performance (see Figure 2.)

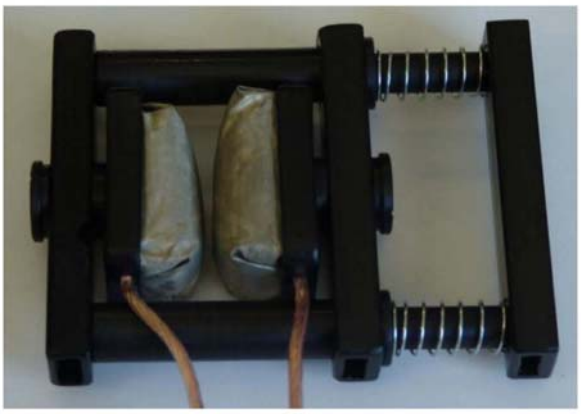

Figure 2. The electrode setup for penile treatment of Peyronie's disease

Protocol of treatments

The proposed and tested protocol of treatment was made 30 min two times a week, overall treatment number was 30 treatment/case in 3 cycle (10 sessions in each). One of the actual treatment setup is shown in Figure 3.

Figure 3. The fit of the electrode on the penis during the treatment

The treatments were used only as monotherapy, studying first the effect on the new method alone. All the Patiens were advanced stages, and their symptoms were measured in standard methods.
The practical parameters to observe the expected changes were:

- Size plaque
- Curvature of the penis
- Pain reduction at erection
- Erection function

Results

30 Patients were studied: one of them was withdrawn, 5 patients have not completed the whole course of treatments, at present we have the final data of 22 Patients. The age distribution was shifted to elderly categories (between 65 and 70 years). The plaque size decreased, after the treatments, about 50%, the Figure 4. Shows the plaque size before and after Androthermia. We evaluated the extendt of the plaques with ultrasound scans before and after the treatments.

PLAQUE SIZE

Dataset	1	2
Number in sample	22	22
Average	12,2818	6,2136
Standard Dev.	7,2447	4,3274
t	**3,3728**	
gradi di libertà	**42**	
P (level of significance)	**0,0016**	

The difference between the observed means is significant for p<0,01

Figure 4. The plaque size reduction after Androthermia

Only 15 Patients had curvature of the penis during erection, Figure 5 shows the average of curvature of the penis before and after Androtherm treatment. We estimated the curvature degree of the penis, during erection, before and after treatments, with a goniometer (Figure 5 shows our method of measurement in a Patient with a curvature very noticeable).

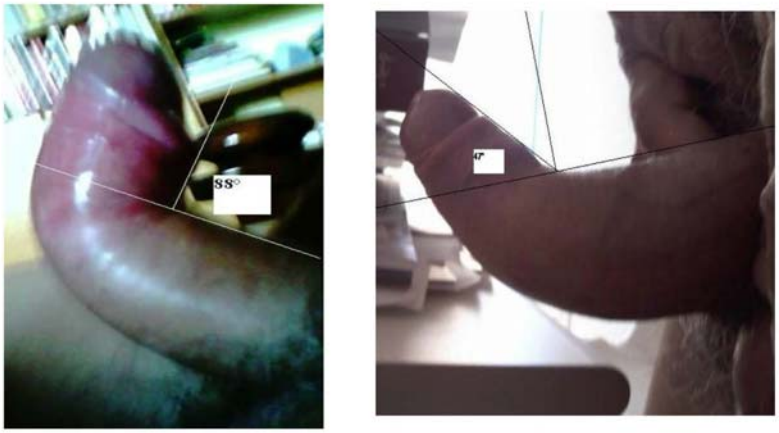

Figure 5. Patient with an extreme curvature of the penis, before and after treatment

CURVATURE OF THE PENIS

Dataset	1	2
Number in sample	15	15
Average	35,8000	23,6667
Standard Dev	16,3016	10,1236
t	**2,4489**	
gradi di libertà	**28**	
P (level of significance)	**0,0209**	

The difference between the observed means is significant for p<0,05

Figure 6. Results on curvature

10 Patienti reported the coexistence of an erectile dysfunction which was evaluated by the administration of questionnaires IIIEf 5, 15, before and after the treatments. Figure 6 shows the improvement of sexual performances obtained after treatments with Androthermia.

ERECTIL DISFUNCTION

Dataset	1	2
Number in sample	10	10
Average	46,1000	57,5000
Standard Dev	13,5438	9,5248
t	**2,1772**	
gradi di libertà	**18**	
P (level of significance)	**0,0430**	

The difference between the observed means is significant for p<0,05

Figure 7. Improvement of the average IIEF

All Patients who presented with pain during erection, reported the complete disappearance of symptoms.

Conclusions

Based on the results obtained we can say that the ANDROTHERMIA can be considered a very promising new therapy for the treatment of Peyronie's disease. The study is still in progress and the results of new cases in treatment confirm the validity of the method. The data until now obtained, could pave the way for new therapeutic approaches for others diseases of the penis.

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Where, when and why hyperthermia went wrong way?

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'Those who cannot remember the past are condemned to repeat it'.

Geroge Santayana, 'Life of Reason I'

'The great tragedy of Science – the slaying of a beautiful hypothesis by an ugly fact.'

Thomas Henry Huxley

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Where, when and why hyperthermia went wrong way?

Abstract

'Hyperthermia is generally regarded as an experimental treatment with no realistic future in clinical cancer therapy' – Horsman and Overgaard said in 2007, though, trying to combat this statement. It's difficult to find another method in medicine which remains experimental after 40 years of research and application. Hyperthermic community usually claims to technical problems of heating and heating control to justify this failure. To our mind, the problem is the 'temperature concept' of hyperthermia. Electromagnetic hyperthermia was finally derived from electromagnetic therapy near 1935, after 30-year fight between thermal and non-thermal concepts of electromagnetic fields application. It was based on a belief that only thermal effect has value, and temperature is the only parameter of efficacy (thermal/temperature dogma). Non-thermal (temperature independent) effects were denied. Initial concept of extreme hyperthermia of 1970th was based on the wrong premise of higher thermal susceptibility of malignant cells. Therefore, it was believed that hyperthermia has a broad therapeutic range which allows to kill tumor cells by above-threshold (>43°C) temperature without damage of healthy tissues. Proofs of inadequacy of this concept were received already in 1980th when it become obvious that really this therapeutic gap is minor or absent, which makes the extreme hyperthermia impossible. To correct it, the concept of 'thermal dose' was introduced. This was based on ungrounded extrapolation of biochemical Arrhenius equation onto living matter. Series of randomized clinical trials of early 90s showed inefficacy of the extreme hyperthermia and called into question the thermal dose concept, but the latter was ignored. Instead of the extreme hyperthermia, the concept of moderate hyperthermia based on the same thermal dose concept was introduced in 2000s: it was believed that moderate hyperthermia could enhance tumor perfusion and subsequently enhances radio- and chemo-efficacy. Though it's declared that this approach was fruitful and its effect was confirmed in randomized clinical trials, it's not correct. The careful analysis of these trials has shown multiple biases. After correction to the distortions, the efficacy of the moderate hyperthermia is not confirmed. Ignorance of the special features of tumor bloodflow was the reason of this failure. Therefore, there are some points when and where hyperthermia had gone the wrong way: 1) 1930s when temperature was equated to thermal energy and non-thermal (temperatureindependent) effects were denied; 2) 1960s when greater thermal sensitivity of tumor cells was incorrectly postulated; 3) 1980s when incorrect 'thermal dose' concept was introduced; 4) 1990th when obvious proofs of inconsistency of temperature concept were ignored; 5) 2000s when moderate hyperthermia concept was introduced. As a result, during the last 20 years, the 'temperature' hyperthermia is in stalemate. Since 1970s, growing evidence of non-thermal effects and their broad application in different fields (dielectrophoresis, bioelectric effect, electroporation, galvanotherapy, etc.) caused a development of some non-thermal field cancer treatment techniques. Hyperthermia concept should be cardinally re-evaluated now with respect to obvious bankruptcy of the temperature concept and development of non-thermal concept.

Introduction

The treatment of an alcoholic begins from the recognition of the problem. 'I'm John, I'm alcoholic' – this is a start of return. There is no any hope for cure without this recognition. Hyperthermia is in crisis already for two decades, but still there is no awareness of the problem. This is the main reason, why hyperthermia in its current state cannot be cured. First, we have to state unequivocally: 'Hyperthermia is in deep crisis'. Only a blind can't see it. If we remember how many top class US medical research centers were active in hyperthermia field 20-30 years ago, and how many of them show residual activity now, the conclusion is obvious. After 50 years of intensive development, having more trials and publications than any modern popular pharmaceutical, hyperthermia is not accepted in any branch of oncology. One-two occasional inclusion in one-two guidelines as a 'the last hope therapy' with many controversies is a demonstrative result of this development.

Such a pity situation necessarily should have objective reasons. It's not enough to claim for lack of money, competition with radiology and chemotherapy and so on. Our recent analysis of hyperthermia randomized trials1 clearly showed the real reason of the situation: the lack of real clinical effect. This is the problem and this should be recognized by hyperthermia community the first. Then, the next question arises: we know that hyperthermia has very strong biological and experimental rationale. How could it do not work in practice? Where is an error?

To understand this point, we should overview the theory and history of hyperthermia. We should return back in time to understand, where, when and why hyperthermia went wrong way, and is there a solution. Because modern hyperthermia is an almost exclusively electromagnetic treatment, we should trace the development of both hyperthermia and electromagnetic treatment to understand the state-of-the-art.

Hyperthermia and electromagnetic therapy before 1950: early stage, radiofrequences and formation of 'thermal dogma'

Hyperthermia before 1950: early stage

History of oncological hyperthermia is originated from some evidences of cancer cure by concomitant febrile diseases described in XVIII-XIX centuries. It seems that inhibition of tumor growth by high fever caused by malaria was for the first time described by de Kizowitz (France) in 1779. In 1866, Busch[2] (Germany) described the complete remission of histologically confirmed face sarcoma after two Erysipelas with a subsequent 2-year disease-free survival. He then used intentional contact with erysipelas infection to treat several patients. Apparently, in the second half of XIX century practice of infectious febrile therapy was quite common, and not only in Germany and France, but even in Russia[3], and it was used to treat a wide range of diseases, including mental diseases. In 1882, Fehleisen discovered Erysipelas agent - Streptococcus pyogenes[4]. He inoculated live bacteria to seven cancer patients and achieved complete remission in 3 cases. Bruns in 1887 reported a case of complete remission in a patient with multiple recurrent melanoma after Erysipelas with temperature over 40°C for several days, with 8-year disease-free survival[5]. He also collected 14 reported cases of erysipelas in proven malignant disease: in most cases there was complete and stable remission. The method was called febrile therapy and hyperthermia per se was only one component of the complex body reaction, and it was not considered as a separate treatment modality.

Systematic school of cancer febrile treatment began to emerge at the end of the XIX century, and associated with the name of William B. Coley[6], a bone surgeon in New York Memorial Cancer Hospital (now the Memorial Sloan-Kettering). In 1893, Coley described 38 patients with confirmed advanced cancer who have had erysipelas with high fever; in 12 of them, tumors had disappeared, and 19 displayed an improvement; in 2 of 10 patients with locally advanced sarcomas treated by Coley, complete remission occurred[7]. Coley had created a so-called 'Coley toxin' or 'mixed bacterial vaccine' (MBV), the first specialized bacterial antitumor pyrogen with standardized composition, which subsequently was produced industrially. American Medical Association (AMA) was sharply negative to Coley method: whereas JAMA editorial in 1893[8] gives a generally positive review of Coley therapy, the editorial in early 1894[9] explicitly declares ineffectiveness of such therapy. Since that time, it remains the official position of AMA.

Start of Coley toxin practice coincided with scientific and technological revolution in oncology: almost simultaneously, at the end of the XIX century, X-rays (1895) and radium (1898) were discovered, and in a few years oncology was armed with radiotherapy and brachytherapy, which displaced all other methods to far periphery of scientific interest. Despite the fact that the first results of radiotherapy in oncology were far not favorable[10], its understandable physical mechanism caused the belief that the results must necessarily follow, and the only problem is an improvement of the method. Because of sharply negative attitude of AMA and the newly formed American Cancer Society (ACS), approximately in 1915 Coley's work was suspended, although many oncologists in US and Europe continued to use Coley toxins for many years.

Unlike radiotherapy, study of mechanisms of action of febrile therapy and thermotherapy at all started only at 40-50th of XX century, when fundamental papers on thermal damage of Moritz et al.[11,12,13] were published and, on the other hand, building of the scientific foundation of immunology started. Coley left a lot of works and enormous amount of materials on the application of his toxins, which had been processed by his daughter Helen Nauts. In 1946, she published a retrospective study of 484 cases of cancers treated with Coley vaccine: in 312 inoperable patients, 5-year survival was 43%, and in 172 resectable - 61%[14]. In another example, 25 of 30 patients with advanced cancer showed 10- year disease-free survival[15]. It would seem, there was a good situation for revival of the method, but the position of AMA and ACS had not changed. Very soon, development of chemotherapy had pushed the febrile treatment again to the periphery of oncology.

The attitude of medical community to febrile therapy was mainly skeptical. In 1949, famous German surgeon Bauer in his book «Das Krebsproblem» wrote that 'these methods strongly impress patients, but not their cancers.'[16] Coley himself has never singled out the temperature as the primary mechanism of antitumor effect, considering the effects of its vaccine complex. Nevertheless, he repeatedly stated that the higher and the longer the fever, the better the effect of the treatment.[17]

The idea of separate use of heating for treatment of cancer had matured almost simultaneously with the idea of Coley bacterial toxins: already in 1898, Swedish gynecologist F Westermark[18] published a report on use of long-term (48 hours) local (by virtue of intravaginal metal coil heated with circulated water to 42-44°C) and regional hyperthermia (hot tubs) for treatment of various gynecological diseases.
He described several excellent results in inoperable cancer of the cervix. He was the first who had shown the ability of long-term heating to destroy tumors without damaging of healthy tissues.
Gottschalk[19] in 1899 confirmed the success of hyperthermia in cervical cancer and suggested the use of higher temperatures and reduced exposure time. In 1910, Doyen[20] reported on the successful treatment of a number of cancers by heating to high temperatures (55°C). Percy[21] in 1916 reported a 3-7-year survival in inoperable cancer of the uterus after local hyperthermia above 45°C; Balfour confirmed these results[22]. In 1918, Rohdenburg[23] summarized the available literature data on spontaneous remission and found fever, heating or severe infections in 72 cases out of 166. In 1932, Goetze[24] reported about the effectiveness of a hot bath in cancer of penis.

Attempts of hyperthermic radiosensitization started shortly after the introduction of radiotherapy. Already in 1913, Muller[25,26] reported 100 cases of combination of X-ray and diathermy: there were 32 complete remissions and 36 partial remissions. In 1935, Warren[27] study was published on thermoradiotherapy in hopeless cancer: by combining radiotherapy with different types of long-term induced fever, he had achieved considerable effect in 29 of 32 patients. The same time, Doub[28] reported on the effectiveness of thermoradiotherapy in osteogenic sarcoma; Doub[29] and Delario[30] declared a radiosensibilizing effect of induced febrile therapy. In 1941-42, Shoulders[31,32] reported on the effectiveness of combination of radiotherapy with febrile therapy in advanced cancer. In 1948, Korb[33] reported result of thermoradiotherapy with internal control: from two basal cell skin carcinomas in one man, one was treated with radiotherapy only without effect, and the second after thermoradiotherapy underwent complete regression.

Experimental study of hyperthermia started immediately after the first clinical results. In 1903, Loeb has shown that fragments of rat sarcoma treated at 45°C for 30 min didn't grafted. Jensen received similar results in mouse tumors treated at 47°C for 5 min. It seems, he was the first who suggested a higher heat sensitivity of tumor cells compared to normal cells. In 1907, Erlich reported higher heat sensitivity of carcinomas in comparison with sarcomas. In 1908, Haaland reported that 30-minute treatment at 44°C inhibits both sarcomas and carcinomas. In 1911, Vidal reported about increased survival of mice with tumor grafts at higher temperatures. In 1916-1921, Prime and Rohdenburg[34] reported the first systematic study on thermosensitivity of tumors made on 2000 mice inoculated with Crocker murine sarcoma, previously incubated at different temperatures. 100% growth inhibition was observed after treatment at 42°C for 180 min. and at 44°C for 90 min. In 1927 N Westermark initiated experimental study of hyperthermia on rats.[35]

	Year	Animal	Tumor	Criterion	Method of heating	6 hr	3 hr	1.5 hr	1 hr
Prime and Rohdenburg[34]	1921	Mice	Crocker sarcoma	Inability of grafting	Water bath in vitro		42°C	44°C	
Westermark[35]	1927	Rats	Flexner sarcoma Jensen sarcoma	Complete regression	Diathermia in vivo		44°C	45°C	
Johnson	1940	Rats	Jensen sarcoma	Inability of grafting	Water bath in vitro		43.5°C		45°C
				Complete regression	Diathermia in vivo	43.5°C			45°C (50%)

Table 1. Some results of in vivo experiments on hyperthermia cancer treatment

Electromagnetic treatment before 1950: radiofrequency era and formation of 'thermal dogma'

History of electromagnetic treatment started from works of Nicola Tesla in USA and Arsen d'Arsonval in France. It was d'Arsonval who is considered a father of electromagnetic therapy[36,37,38] d'Arsonval itself considered his treatment conditioned by electromagnetic field effects, though it was clear from just a beginning that 'undesirable heating' is an inevitable consequence of the electromagnetic impact[39] as Tesla

clearly predicted[40]. Because of the field concept, d'arsonvalization used low currents and high voltage to diminish 'undesirable heating' and to enhance 'field effects' [41].
Near 1905, diathermia was invented by von Zeyneck[42] and then widely promoted and advertized by Nagelschmidt[43]. Diathermia was targeted only for heating and used high currents with low voltages for this purpose. Between 1910 and 1920, diathermia was established in its classical form as a method of deep capacitive heating with a frequency of 0.5-2 MHz and a current strength of 1-3 A[44,45]. Use of such diathermia for hyperthermia was limited by overheating of subcutaneous tissues. Nevertheless, there were some reports of combination of diathermia and roentgen-therapy with promising results[25,26].

After 1917, works of Julius Wagner von Jauregg on treatment of paresis, syphilis and some other diseases by malaria had raised again an interest for febrile treatment[46]. It was revealed shortly that febrile treatment is effective for treatment of wide range of somatic diseases. It was also revealed soon that hyperpyrexia caused, for instance, by intramuscular injection of sulfur or oils, is also effective for treatment contemporary with infectious fever. That is, hyperpyrexia was identified as a separate curative factor. From this understanding, only one step remained to external hyperthermia.

In 1920, magnetron was invented which allowed to receive frequencies up to 150 MHz and started radiofrequency era in electromedicine. In 1928, W.R. Whitney, vice-president of General Electric, revealed that body temperature of those who are close to short-wave transmitters rises for 2-3 centigrades. This was a discovery of irradiant radiofrequency heating[47], which soon led to development of Radiotherm in 1931, the first true hyperthermia device. Though still called a febrile therapy, this was a new method of external heating of the body instead of internal heating of the classic febrile therapy.
This was an external hyperthermia. Whitney Radiotherm was widespread in USA in 30th and it was used for treatment of many disorders[48], including cancer[49], with some impressive results. For 1935, more than 100 articles on hyperthermia were published[50], including the first comparative study of different methods of hyperthermia[51]. In 1937, Manhattan hosted the first international conference on hyperthermia[52].

Under this external cover, there was internal struggle between thermal and non-thermal concepts of electromagnetic therapy. d'Arsonval was the first who tried to show non-thermal effect on the bacteria and toxins, but the result was inconclusive. Tesla announced the lethal non-thermal effect of high-frequency field on Mycobacterium tuberculosis[53] d'Arsonval did not come to a conclusion on the mechanism of action of high frequency currents, but he was sure that it is not limited by heat, suggesting the influence on the chemical reactions[54]. Rise of diathermia as a pure thermal-dependent method after 1910 was connected mainly with the name of Nagelschmidt. It was Nagelschmidt who declared first that heating is the only treatment modality of electromagnetic impact[43]. From that time, the competition of thermal and non-thermal concepts of electromagnetic treatment started.

Since 1920, after the start of radiofrequencies use, non-thermal effects of RF-heating were many times shown in vitro and in vivo by many researchers. Gosset et al. (France, 1924) exposed different plant cells with to 150 MHz RF-field and displayed cell death after initial growth acceleration; the effect was mainly or entirely non thermal dependent[55]. In 1926, an American surgeon Schereschewsky reported about lethal effect of 8.3-135 MHz RF-field (with maximum at 20-80 MHz) on mice without substantial heating[56]. He suggested a specific action of RF fields based of high-frequency vibrations. Having received a position in Harvard Medical School, Schereschewsky continued his research, and in 1928 reported on destruction of tumor grafts in mice, once again without substantial heating[57]. At 67 MHz, there was 23% of complete remission in HT group vs. 0% in the control group. Exposure to 135 MHz didn't show antitumor effect. Schereschewsky concluded that there is a special cell-destructive frequency range 20-80 MHz.

Schereschewsky papers caused a strong 'thermal' opposition. In 1927-1929, some program diathermia papers were published by Christie and Loomis from Rockfeller Foundation defending 'thermal purism'[58,59,60,61,62,63]. The main thesis was 'All those who claim to any other biological effects of high frequency currents, except of heat production, must prove it'64. From this time, this statement has become the official position of the western electromagnetic medicine.

A careful analysis of the Christie и Loomis paper[64] reveals inconsistency of such categorical statements, which were made on insufficient grounds and with disregard of many facts. In particular, they revealed that lethality of 8-50 MHz field exposure was nearly the same but it was sharply reduced over 50 MHz. This was explained by any changes of dielectric constant of mouse which allegedly led to a decrease of 'current

induced in mice'[65]. Though this statement was not explained, this did not affect the categorization of the final judgment. Now the fallibility of this statement is obvious because an increase of tissues conductivity with increasing frequency is well-known. At the same time, the authors displayed that thermal production in NaCl solution didn't diminish but increased over 50 MHz in the same extent as the lethality dropped[66]; this fact hadn't received any explanation. The study design was unsatisfactory. The authors tried to investigate the impacts of four different factors – frequency, current, time of exposure and distance between electrodes – simultaneously and in two options: intravital and postmortem. As a result, the groups were too small (2-10 mice, averaged 5±2.6) to receive significant differences. All the data are fragmented due to imbalance of groups. Moreover, the thermometry was extremely imperfect which was recognized by the authors themselves. There was no any statistical processing of the data, except of calculation of averages, although the methods of correlation analysis were described in detail by Pearson in the early XX century[67] and were extensively used in 20th. The authors didn't try to reveal any trends though they were easily noticeable. E.g., in table I[68] the tendency of decreasing of lethal temperature with increasing current is traceable, and in graph 7[69] the same tendency is visible with increasing of the frequency. Only the most rough and approximated tendency of thermal dependence of the lethal effect was noticed by the authors, and it was declared as the only dependence without any sufficient grounds. It's obvious from just the tone of Christie works than he didn't admit the existence of nonthermal effect axiomatically, and was initially blinkered. Sure, Schereschewsky work[56] causes a lot of critisizm, first of all in terms of thermometry, but it was impossible to deny the existence of non-thermal effects on the base of very controversial and inconsistent trials of Christie and Loomis64. However, it happened. In 1933, Schereschewsky, being under a strong 'thermal' pressure, abandoned his 'unscientific' non-thermal point of view and recognized the thermal essence of his findings[70].

In 1930, US biologist McKinley reported a lethal non-thermal effect of RF-field on wasps71, and later – on growth of seedlings and nervous reactions of frogs72. It was resumed in the last paper that high frequencies and heat are not synonymous in any way, and though electric field leads to internal heating as a side effect, there is another and still not studied reaction. The same year, Szymanowsky and Hicks reported a non-thermal inactivation of diphtheria toxin by RF-field73 and then confirmed this result in 193274. In their last paper they resumed that though non-thermal effect of AEMF is obvious, its low intensity and hard traceability makes it insignificant in clinical research75.

In 1928, German physician Erwin Schliephake also revealed a lethal effect of RF-fields on flies, mice and rats. Later, suffering from painful nasal furuncle, he received a sharp relief after an RFexposure[76]. Soon, Schliephake and his colleague physicist A. Esau had developed a 'short-wave therapy'. In 1932, the monograph 'Short-wave therapy'[77] was published in Germany, marking the born of the first commercial non-thermal technology. Already in 1935 it was re-published in English, and generally it was reprinted in Germany six times (until 1960). Wide use of the method and apparatus of Schliephake in the US led to the intervention of the American Medical Association in 1935[78]: 'huge sales of the new type of high-frequency devices' was discussed in preliminary report of physiotherapeutic council and it was stated that extensive use of these machines could lead only to insufficient results and discreditation of diathermia as a useful treatment method. The final report once again confirmed the position of medical community about exclusively thermal effect of AEMF[79].

In 30th, a confrontation between supporters of the thermal and non-thermal effects had become a political line. Non-thermal concept was supported in Nazi Germany. In 1933, Reiter who later became one of the most famous Nazi criminal physicians, reported the non-thermal RF effects on the metabolism of tumors in vitro[80], which caused two responses of Western opinion leaders in Nature[81,82] in 1936, again confirming the official position of the western medical community about lack of 'specific' and non-thermal effects of RF exposure. In the late 30th, 'non-thermal resistance' in anglo-saxon world was finally broken, and heat production was considered the only biological effect of high frequency fields.

Thus, in the late 30th, all the known methods of electromagnetic heating were already known and used; heating was officially recognized as the only biologically significant effect of high-frequency electromagnetic fields; hyperthermia was recognized as separate treatment modality, and some promising results were received with RF-heating; also, non-thermal effects of RF-heating was demonstrated many times, and first non-thermal RF-technology was widely recognized, though being denied by official science. In about 1937, triode was created and magnetron was refined, and in 1939 Varian brothers developed the first klystron at Stanford. These inventions allowed to receive EM radiation of gigahertz (UHF) range and

opened the microwave era. But in 1940, magnetrons and klystrons became not available for medical purposes – the war was approaching, and all the forces were sent to the development of radars. So, the first works on microwave diathermy appeared only in late 40th, after the war.
Thus, the period before 1950 was the early stage of both hyperthermia and electromagnetic treatment. Hyperthermia was mainly still not recognized as a separate method and existed predominantly in the form of febrile therapy, where thermal effect was a part of a complex body reaction. Its use was sporadic and totally enthusiastic. Despite of a general success of hyperthermia in late 30th, its use in oncology remained very limited. Electromagnetic hyperthermia made its first steps into the frameworks of radiofrequency range (0.5-50 MHz), though some promising results had showed; it was purely empirical and suffered from lack of theory. Despite of multiple evidences of non-thermal effects of alternating electric fields, 'thermal dogma' became the official position of the western science: it stated that heating is the only biologically significant effect of high-frequency electromagnetic field and denied any biological value, and even existence, of non-thermal effects. With this baggage of knowledge and technologies, hyperthermia entered the second half of XX century.

Hyperthermia and electromagnetic treatment in 1950-1985

Hyperthermia in 1950-1965: concentration

After 1950, the modern period of hyperthermia development as a separate treatment modality started. Period since 1950 to 1965 could be characterized as a 'concentration stage', when the first isolated attempts of hyperthermia use and research were made, and 'concentration' of hyperthermia research rose gradually as a necessary prerequisite for the following crystallization. In 1950, Gessler et al. [83] reported the successful destruction of spontaneous mammary tumors in mice by microwave hyperthermia (2,450 MHz) without significant damage to the animals. In 1957, Gilchrist et al. 84 used radiofrequency inductothermy for destruction of metastases in lymph nodes in vivo in dogs.

Development of chemotherapy creates new possibilities for hyperthermia. Because of high toxicity of first chemotherapeutics, they were administered initially mainly by regional perfusion. This was ideal design for heating use. Already in 1960 Woodhall et al85 from Duke University performed regional hyperthermic perfusion with alkylating agents in patients with head and neck tumors with 10% of complete response. Then, also in Duke, Shingleton studied effect of local hyperthermia (42°C) during chemoperfusion of intestine by means of capacitive radio frequency systems (27.12 MHz), and found a much more significant accumulation of alkylating chemotherapies in the heated tissues than in unheated[86]. Rochlin received similar results on the limbs of dogs[87].

Selawry et al. in 1957 revealed the basic patterns of hyperthermic impact to cell lines heated with water bath in vitro: acceleration of cell growth under 39°C with a maximum at 38°C, then interruption of the mitotic cycle at metaphase in the range of 39-40°C with the subsequent development of irreversible cellular damage over 40°C; lethal range at 42°C-46°C; development of thermotolerance above 39°C and long-term (up to 3 months) thermoresistivity in cells that survived after hyperthermia[88]. These findings laid in the basement of modern hyperthermia but unfortunately they are mainly misinterpreted. In particular, common belief in the danger of low temperature (≤39°C) heating during hyperthermia as it able to enhance tumor growth, and considering temperatures over 40°C as safe in this regard, is not grounded because it doesn't consider the time factor. According to Selawry data, the above mentioned temperature ranges are actual for long-time heating only (some days) and not applicable for short-time minute-range of hyperthermia procedure. As Selawry showed, the rise of mitotic index in 12 hours was much higher at 41°C than at 38°C (10.4% vs. 4.2%) and dropped to zero at 41°C only in 24 hours. In 6 hours, mitotic stimulation was nearly equal in the range 38-41°C (3.7-4.1% vs. 2.3-2.8% at 36°C), and only temperatures above 42°C stopped entering a new cells in the mitotic cycle. Therefore, the entire range of hyperthermia (≤42°C) is potentially tumor grows stimulating and higher temperatures could be even more dangerous in this regard. Low heating becomes more dangerous in regard of tumor growth only provided that it lasts more than 24 hours. Selawry also reviewed all the existing data about thermoradiotherapy.[89]

The true foundation of modern oncological hyperthermia was laid by Crile in his remarkable series of in vivo experiments on mice in 60th [90,91,92]. It was Crile who already in 1962 reported all known patterns of hyperthermia in vivo: ability of tumors to 'trap' heat due to decreased perfusion, start of tumor damage at

42°C, half-decrease of lethal exposure time per each centigrade above 42°C, better radiosensitivity and lower thermosensitivity of small tumors and reverse ratio for big tumors, development of thermotolerance after sublethal exposure, enhancement of thermosensitivity by serotonin injections, additive or synergic effect of combination of heat and irradiation. These results were obtained in tumors implanted in feet of mice and heated in a water bath. Two moments are important to notice on Crile results. First, serious toxicity of the effective hyperthermia: in fact, rise of temperature over 42°C led to damage both of tumor and healthy tissues. Sure, the probability of tumor damage was higher but share of mice which lost their feet after treatment was also significant. Second, though Crile showed that 44°C 30 min hyperthermia led to half-decrease of irradiation isodose, radiosensitivity of healthy tissues rose in the same extent as of a tumor. Crile, therefore, resumed that thermoradiotherapy has dubious advantage over radiotherapy per se and is indicated only for radioresistant tumors. Thus, just in the beginning of oncologic hyperthermia development as a separate modality, the problem of limiting toxicity was clearly shown.

Hyperthermia in 1965-1975: whole-body period and crystallization

The 1965-1975 period was the 'crystallization stage' of hyperthermia development, when stable hyperthermic schools and trends began take shape. It marked by name of Manfred von Ardenn, who was a prominent German physicist acting in oncology. Von Ardenn example is very demonstrative to show the inner patterns of hyperthermic evolution because of some reasons. First, he was a man of extraordinary mind, usually moving step ahead the world hyperthermia, who easily changed concepts and technical solutions if they were ineffective. Second, his physical and technical knowledge were absolutely superior all over the world, and his technical facilities were virtually unlimited. Third, he was independent researcher in socialistic East Germany, therefore his researches and practice were not affected by commercial biases, and were not bound to any technology and its commercialization as it inevitably happens in western world. Fourth, he was a CEO in his own research institute, and therefore had absolute freedom in research. Fifth, it seems that his researches were not limited financially. Sixth and very importantly, he was not limited to hyperthermia in any manner because he looked for cancer treatment at all. Complex impact of these factors created the extraordinary medium for hyperthermia research and development, and it's very interesting to examine which result was reached in these circumstances.

Von Ardenn started his activity in oncology in 1965 when he developed two-chamber hyperthermic bath with head cooling. Already in first experiments in vitro made in 1965 he confirmed selective thermosensitivity of tumors[93], and soon presented in Heidelberg university his concept of multistep cancer chemotherapy [94,95] based on combination of extreme hyperthermia and tumor acidification by DL-glyceraldehyde. It was 'the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia' in 1966, [96] which started worldwide 'hyperthermic race'.

The general tone of the first von Ardenne works suggests that he initially thought hyperthermia independent, non-toxic and selective treatment of cancer, and, apparently, had Napoleonic plans of one-step solution of cancer treatment problems on the basis of hyperthermia. Meanwhile, it seems, already in 1967, von Ardenne stumbled upon the phenomenon of non-comparability of results in vitro and in vivo[97], and also faced a problem of lack of effect of hyperthermia, which was reflected in an active search of termosensibilizers. Many of them were tested between 1967 and 1969, including menadione, which effect was, in turn, strengthen by methylene blue[98]; aterbin[99], progesterone[100] and dimetilstilbestron[101], Tween 80[102], vitamin A103, dimethyl sulfoxide[103] and antibodies. Finally, von Ardenne tried to attack cancer by a cocktail of modifiers[102], including radiotherapy[104].

It seems that the idea of tumor acidification by virtue of hyperglycemia had arisen not earlier than in 1968[105]. It received full theoretical explanation as hyperglycemic modifications in 1969[106], although search for other acidifiers still continued in 1970[107]. At the same time von Ardenne has moved from extreme to moderate hyperthermia (40°C)[108]. We can only hypothesize that the only possible reason of such change is toxicity of extreme hyperthermia. Therefore, von Ardenne realized 'a moderate reload' 25 years earlier then the world hyperthermia did. The other possible reason was that he soon revealed that hyperglycemia is a stronger factor of tumor killing than hyperthermia, and became to consider hyperthermia as an auxiliary modality. In 1969, he started experiments in vivo on mice based on the combination of hyperthermia, hyperglycemia and soft X-ray[109], and immediately reported the high effect[110].

In 1972, von Ardenne presented a complete concept of 'selective multiphase cancer therapy' (sCMT)[111], in which 'long-term acidification through activation of glycolysis' was the first time mentioned as the primary mechanism of cancer treatment, whereas mild hyperthermia (40°C) was considered only as an auxiliary modality. Under the theory of von Ardenne, hyperglycemia induces activation of anaerobic metabolism in tumor tissue, which leads to the accumulation of lactate and acidification of the tumor; erythrocyte membranes in acidic environment become rigid, which prevents their normal passage through the capillaries and lead to their blockage and fall in blood flow through the tumor. At the same time, lowering pH to 6.5 and below leads to the destabilization of lysosomal membranes, and hyperthermia leads to the following release of lysosomal enzymes and autolysis of the tumor. However, the whole-body hyperthermia can also lead to increased metabolism of healthy tissue, which aerobic nature requires a high oxygen consumption; oxygen is also required for recovery after hyperthermia. As a consequence, in 1973 the concept of von Ardenne was replenished with the last component – the multi-step oxygen therapy[112] considered as multiplier of sCMT[113]. As a result, to the end of 1973 sCMT concept was completed as the combination of long-term, high hyperglycemia followed by moderate hyperthermia with concomitant hyperoxygenation[114,115,116]. Von Ardenne paid much attention to the sequence and the intervals between the different stages, taking into account both synchronization of the cell cycle[117] and thermotolerance as a result of repeated exposures[118], and even circadian rhythms. Simultaneously, he investigated the mechanisms of cell damage in hyperthermia: peroxidation processes[119], denaturation of proteins[120], activation of lysosomal enzymes[121]. The sCMTconcept of 1974[122] also included chemotherapy and radiotherapy. Period of 1975-1976 was devoted to study of combination of sCMT with chemotherapy[123,124] and, at the same time, to the search of enhancers of hyperglycemic acidification (particularly, NAD[125,126] and sodium nitroprusside1[27] were used). In 1976, the idea of selective anticancer drugs activated by acidic environment of the tumor128 was published. An attempts were made to implement it by creating 'selectines' – a targeted agents released in the tumor tissue due to increased activity of beta-glucuronidase129. This idea is now being actively developed, that is von Ardenne was once again ahead of his time for 20-30 years.

Meanwhile, the western world, mainly influenced by the work of von Ardenne, also entered the hyperthermic race. In 1967, American Cancer Society issued a separate release on the method of von Ardenne130, confirming that its clinical application in the US started almost before it was applied by von Ardenne himself in GDR, and that information about inventions of von Ardenne called as 'top European scientist'131 appeared in the US synchronously132. In 1969-1973, 4-8 years after the first publications of von Ardenne, some fundamental works of Italian[133,134,135,136] and British[137] researchers were published, which laid the foundation for a systematic theory of hyperthermia.

Since 1967, Stehlin et al. in the US started a research on regional hyperthermic perfusion based on extracorporeal heat exchanger[138] (though von Ardenne developed such exchanger about 1966). Careful analysis of that trial shows that heating was associated with local control whereas survival mainly depended on tumor eradication (surgery + amputation). The British pioneers of the whole-body controlled hyperthermia Pettegrew and Henderson[139,140] (1971-1974) explicitly refer to the earlier works of von Ardenne, though questioning many of his considerations. It seems, it were Pettegrew and Henderson who first time detected the 'toxicity threshold' of WBH – 41.8°C. Study of local hyperthermia was continued: Cerino et al. 141 in 1966 investigated the local effects of ultrasound in bone cancer in vivo and concluded that the effect was mediated by heating. J Overgaard and K Overgaard (1972)[142] used short-wave diathermy for local heating.

Thus, from 1965 to 1975 hyperthermia has experienced considerable progress. Whole-body hyperthermia and regional hyperthermic perfusion technologies were developed, and study of local hyperthermia continued. Solid scientific base of hyperthermia was established, and the concept of extreme hyperthermia based on the use of temperatures above 42.5°C was clearly formulated. Some hyperthermia schools had arisen, namely von Ardenne school, Italian, British and US schools and Russian school inspired by von Ardenne.

At the same time, negative results had been accumulated. The initial enthusiasm of 'virtually unlimited selectivity' of hyperthermia quickly gave way to the understanding of inefficiency of hyperthermia as a separate method, as it is clearly seen from von Ardenne research progress. By 1975, the limitations of whole-body hyperthermia had become increasingly accepted in view of inability to increase system temperature above 42°C without high toxicity, high complexity and labor-intensity[139,140]. Nevertheless, the nature and feasibility of the hyperthermia seemed to be obvious, and the general opinion was that only the

correct technical solutions are required. The attraction of an attention of world oncology by hyperthermia was the main result of that early period.

Hyperthermia in 1975-1985: local period and structuring

The next decade since 1975 to 1985 was a stage of structuring of modern hyperthermia. During this period, world hyperthermia obtained its internal organizational structure represented by different hyperthermic societies and the journal. Hyperthermia trials became usual, and network of institutions engaged in hyperthermia research enlarged significantly. Modern scientific base of hyperthermia was mainly completed. Thermal chemo- and radiomodification and the role of tumor microcirculation in pathogenesis of tumor damage were a scientific mainstream. All the main hyperthermia technologies were developed that time, and main manufacturers of hyperthermia equipment were established. Refusal of whole-body and convection-heating hyperthermia at all, which was the main mode of hyperthermia in previous period, in favor of electromagnetic localized applications, was the main technological trend of the decade.

Though western 'scientific machine' with its distributed structure quickly stepped forward with US as a world leader, von Ardenne Institute maintained leadership in many aspects. His sCMT concept with moderate hyperthermia was safe but suffered from insufficient efficacy. The next von Ardenne's solution was an extreme local heating against the background of moderate whole-body heating. His first paper on local hyperthermia was published in 1977[143], and the same year a new Selectotherm concept was introduced: a combination of local heating by virtue of radiofrequency (27.12 MHz) scanning irradiator with concomitant long-term (4 hours) systemic exposure of near infrared range (IR-A) irradiation[144,145]. In 1978, just after von Ardenn Selectotherm concept, a similar Pomp-Siemens machine was introduced combining whole-body and local heating. Instead of infrared heating, it used microwave heating by dipole antennas operating at 433 and 2450 MHz[146]. The concept appeared ineffective and soon Siemens left hyperthermia race forever. The similar idea of microwave WBH was tried to realize by Gelvich in Russia in early 80th and it also failed. Instead of it, concept Yakhta-5 was developed in Russia near 1985 by combination of RF (13.56 MHz) WBH and RF (40.56 MHz) local heating.

Contrary to all his contemporaries which considered hyperthermia a stand-alone factor, von Ardenne considered local hyperthermia only an amplifier of tumor acidification[147] in Selectotherm concept. The phenomenon of complete blockade of tumor blood flow at pH 6.1 and 41°C was discovered soon[148]. About 10 papers were published by von Ardenne on the selective inhibition of microcirculation in tumor tissue. In particular, he examined the role of pH-modified red blood cells[149] and change of their size in hyperglycemic environment[150], role of clogging of blood vessels by red cells[151], increased perfusion pressure[152], microvascular permeability[153], low blood pressure[154], platelet aggregation[155], also the mechanisms of involvement of the vascular wall in the disorders of microcirculation[156]. In 1985, the impact on microcirculation was acknowledged by von Ardenne as a central mechanism of sCMT[157]. It should be noted that von Ardenne microcirculation studies were much more practical than contemporary studies of western teams[158], first of all because of he studied microcirculation at real HT temperatures range <42°C while others operated with temperatures more than 43.5°C which they erroneously considered possible to achieve.

Thus, the technology of whole-body infrared hyperthermia was technically realized by von Ardenne already in 1977, whereas similar development was initiated by the US National Cancer Institute only in 1978[159], and working prototype was built in 1983 only[160], but in local hyperthermia von Ardenne already was not a leader. In 1976, LeVeen et al.161 in US reported some interesting clinical results on local hyperthermia of some deep tumors, including lung tumors, made by virtue of his own prototype of capacitive radiofrequency device (13.56 MHz). Nevertheless, conceptually von Ardenn was still far ahead his contemporaries for two decades: while they dreamed about more than 43°C fantastic heating with local 'dream machines', he was already aware of the impossibility of such local heating. He considered a combination of local and systemic heating as the only possibility to achieve a homogenous local heating.

Since use of microwaves for superficial heating was simple and clear from just the beginning (2450 MHz, 915 MHz and 433 MHz were used[83,142,251]), heating of deep-seated tumors was a challenge. Delivery of hyperthermia range heat into the deep tissues is a serious technical problem till now. Capacitive, inductive and irradiating heating could be used for this purpose.

Between 1976 and 1978, development of all the major technologies for deep heating started. Capacitive and inductive technologies as the most simple methods which was already proven at diathermic applications,

were historically used for deep heating the first[86]. Inductive technologies (Magnetrode[162] and other solutions) showed their heating inefficacy (<20% of successful heating) already at the early stage and were mainly disregarded, though there are an attempts to reanimate the method from time to time[163,164].

In 1976, LeVeen et al. reported the eradication of tumors in animals and substantial regression in 21 patients using 13.56 MHz capacitive machine161. This was capacitive coupling 13.56 MHz machine with three pairs of 'cross-firing' electrodes located around the 'zone of interest'. Power was targeted to each pair of electrodes in series by short bursts (0.1 s). As a result, center zone between electrodes was permanently heated with this 'cross-fire' whereas superficial fat was heated 0.1 s only during each 0.3 s cycle. It's very interesting to note that already in 1979 Sugaar and LeVeen[165] reported some effects which developed with this machine only but not with other frequencies and heating modalities and seems to be not heat-dependent. In particular, alongside with the expected heat degeneration of tumor cells, significant changes in the tumor's stroma happened as well resembling lesions in acutely rejecting organ allografts. In 1977, Marmor and Hahns also reported some promising experimental results with this technology which couldn't be explained by temperature only166. Unfortunately, later some 'fantastic' results were reported by Storm et al.[167] with this machine: 75% of human sarcomas were heated ≥45°C and 50% ≥50°C without damage of healthy tissues with huge 8-10°C temperature difference between tumor and healthy tissues[227]. From the modern point of view, these results are absolutely impossible. LeVeen machine remained a prototype.

In 1976-1978, radiofrequency 8 MHz capacitive technology (Yamamoto Vinita Co. Ltd., Japan) was elaborated and marketed under Thermotron trademark. Since 1980, Thermotron-RF8 unit with power 1200W became commercially available. From the heating point of view, easy to use and manufacture are nearly the only advantages of capacitive technology while there is a number of disadvantages: high subcutaneous fat heating, instability of low-frequency RF field and its dependence from electrodes size, position and distance and tissues parameters, with easy hot-spot formation. Thermotron used high-intensive surface cooling (up to -5°C) to compensate subcutaneous fat heating.

Field disturbances were minimized by exact fixation of electrodes on gentry to always ensure their parallel and symmetrical position. Though not being perfect, Thermotron was the first stable hyperthermia machine designed with clear understanding of advantages and disadvantages of capacitive technology.

Majority of European and US specialists initially rejected capacitive concept considering its known disadvantages. Instead of it, surrounding irradiative solutions with interference heating were introduced in 80th. The idea was to achieve a steerable heating focus in the deep tissues due to interference of irradiation from some surrounding sources without substantial surface heating. Base calculations were done by Guy[239,168] in early 70th. It was clear that such system is highly frequencydependent because lower frequencies (less that 40 MHz) with long wavelength flatten a peak of SAR in deep tissues, and higher frequencies (more than 150 MHz) with shorter wavelength dissolve the peak because of insufficient penetration depth. Looking ahead, this problem had not been solved in full.

Some irradiative technologies were developed nearly simultaneously at 1978-1980: 'annular phased-array' (APA) 50-110 MHz technology of BSD Corp., coaxial 10-80 MHz TEM technology of Lagendijk et al.[286] and 4-waveguide 'matched phased array' (MPA). The first technology was marketed as BSD-1000 system, the two latter ones remained prototypes though Lund (Sweden) was about to market TMP technology as Variophase system. At phantom testing, all the techniques showed nearly the equal ability to create deep heating focus169. Unfortunately, in clinical practice the selective heating of deep focus never was achieved. Moreover, TEM and MPA technologies showed insufficient heating efficacy (<50% of heat-successful treatments).

BSD1000 system included 16 coupled (8 couples) horn applicators arranged on two octagons fed synchronously by 50-110 MHz amplifier. Early reports were very optimistic reporting more than 70% of heat-successful treatments (≥42°C). Later trials on larger groups were much less promising: only 30-50% of patients received heat-successful treatments.

The hyperthermic community had been structuring. In 1975, Washington hosted the first International Symposium on Cancer Therapy by Hyperthermia and Radiation, followed by the second one in 1977, third in 1980 and fourth in 1984[170,171]. Near 1981, US National Cancer Institute (NCI) offered a Hyperthermia Equipment Evaluation Contract for evaluation and comparison of different types of existing hyperthermia

equipment. At least three universities were contracted (Stanford, Utah and Arizona) and more than 20 types of equipment were tested. In 1981, the North American Hyperthermia Society (NAHS) was founded, and in 1985 International Hyperthermia Journal was founded. In 1978, Hyperthermia Study Group was founded in Japan followed by establishment of Japanese Society of Hyperthermic Oncology (JSHO) in 1984. Since 1985, hyperthermia treatment in Japan is covered by insurance. Together with abundant grants of Japanese government for hyperthermia research, this caused the fast development of hyperthermia in Japan.

Electromagnetic treatment after 1950: microwave era

Electromagnetic treatment in 1950-1960: early microwave period

As it was mentioned above, first work on microwave diathermy of Mayo Clinic appeared only in 1947, just after the war. Raytheon Microtherm was the first commercial microwave device with 1,2-2,5 GHz frequency and a power of 125W. Since 1948 to 1953, some works on microwave diathermia were published, followed by a long silence caused by detection and recognition of the adverse effects of microwaves.

Actually, these effects – cataracts in dogs and rabbits and testicular degeneration in rats – were discovered already in 1948, just after the start of microwave research, but it took time to accept them and realize the potential danger of the new devices. At the same time, evidence of danger of microwave radiation was received from military and industry. As a result, since 1953 to 1960, research activity in the field of microwaves completely shifted from medical use to development of security standards. In 1957-1960, the so-called Tri-Service program was implemented in US under the auspices of the U.S. Department of Defense to develop safety standards of microwave exposure.

Electromagnetic treatment in 1960-1985: maturing of microwave technology and rise of non-thermal effects

Major contributor to the development of the theory of biological effects of electromagnetic fields was Herman Schwan, a German physicist contracted by U.S. Defense Department. Near 1953, Schwan began a systematic study of the mechanisms of absorption of microwave radiation and found that it is uneven and depends on the frequency properties of tissues and their components[172]. Schwan has shown that microwave exposure should be based on rigorous biophysical calculations, that the 'efficiency of existing microwave devices is unpredictable from a practical point of view', and experimental methods are extremely dubious[173,174]. Electromagnetic medicine required adequate biophysical basis which has not yet been established[175]. As it's evident from the materials of the symposium on biological effects of microwaves, which took place in June 1970 in Richmond (USA), that time there were only initial presentation of the merits, which were subject to refinement in practically all areas[176]. Susskind[177] figuratively compared microwave devices of that time to 'gun shooting in the dark room'. Establishment of the scientific basis of microwave therapy was mostly completed around 1985, when the theoretical basis of interaction of high-frequency AEMF with biological tissues was completed and dielectric properties of various tissues and organs were determined[178,179].

Period between 1950 and 1960 as it mentioned before was poor enough for medical findings in electromagnetic treatment, but this had significant consequences. 10 years of research on the dangers of EMF in 50th cooled the medical community to the use of microwaves, which, in turn, changed the approach from applied research (heating) to the fundamental ones, and data about non-thermal effects of EMF began to accumulate more intensively. It allowed to move from their demonstration to their study. In 1959, researchers from the Mayo Clinic found the effect of 'pearl-chain formation'[180]: fatty drops in diluted milk were aligned into chains at high-frequency irradiation. The effect was inexplicable in terms of heating. Indeed, the effect was not new: it was described in 1927 by Muth[181], and later in 1939 by Lebesny[182] in blood emulsion. Also in 1959, a similar effect was observed by Heller et al.183: weak constant electromagnetic field caused the alignment of single-cell micro-organisms in the line. Moreover, depending on the frequency organisms could line-up alongside or across the field lines. In an earlier experiment, Heller et al.[184] has shown that 5-minute non-thermal effect of EMF on embryos of garlic in distilled water led to chromosomal abnormalities after 24 hours, similar to exposure to ionizing radiation and anti-mitotic agents. He assumed that the reason was the orientation effect of EMF. Also in 1959, a study of Humphrey and Seal[185] was published about use of DC to treat cancer, initiating the development of electrotherapy of

cancer, though a papers on galvanization of 1875[186] and 1886[187] had already shown the mature understanding of the technology. That time galvanization was used mainly for treatment of superficial lesions like hemangiomas[188] and lost its significance after invention of cauterization to reborn in XX century as cancer treatment modality. Already in 1951 Pohl[189] found that dielectric particles in AEMF are not only aligned, but also move alongside the gradient of the AEMF, and this phenomenon was called dielectrophoresis (DEF). In 1966, he used DEF for separation of alive and dead cells[190]. In 70th the method was developed in details[191,192]. In 1970, a lethal effect of the weak (10- 200 mA) AC (50Hz) for Escherichia coli was detected by Pareilleux and Sicard[193]. Then, this effect was rediscovered in 1992 by Canadian researchers[194] and called 'bioelectric effect' (BEE). In 1972, the increase in membrane permeability was detected by Neumann и Rosenheck[195] after a pulse of direct current, which led to the development of technology known as electroporation (EP). It was theoretically grounded in 1973-1974 by Crowley[196] and Zimmermann[197], and it firmly entered the arsenal of cell biology from the mid 70th. It is remarkable that even in 1977, a discussion of electrical breakdown begins with grounding of non-thermal nature of the effect. Later in 1989, Chang[198] has applied alternating radio frequency current for electroporation and obtained more efficient transfection at a substantially smaller percentage of irreversible cell damage[199]. Since 1978, Nordenström[200,201] reported the first clinical trials of galvanization called by him 'electrocancer therapy' on lung cancer.

In 1982, Schwan[202] summarized all the data on non-thermal effects available at the time, and highlighted the following described phenomena: 1) the formation of 'pearl chains', 2) the spatial orientation of nonspherical particles and cells, 3) dielectrophoresis 4) deformation of cells, 5) destruction of cells, 6) cell fusion, 7) rotation of cells.

It is important to notice that all the main technologies of electromagnetic hyperthermia have been developed between 1975 and 1985, that is at a time when biophysical basis of electromagnetic treatment was not entirely completed. This had determined inevitable technological bugs which will be analyzed in details below, as well as the fact that modern hyperthermia technologically operates mainly by representations of 70th or, the better case, of early 80th.

Hyperthermia and electromagnetic treatment after 1985

Hyperthermia in 1985-1995: unsuccessful local attack and WH return

Meanwhile, the understanding of hyperthermia problems rose. In 1987 Hiraoka et al.[203,204] reported their results on Thermotron use. Whereas a maximum temperature ≥43°C was reached at 38% of tumors and 42-43°C in 23% of tumors (totally 61% ≥42°C), the intratumoral temperature differences exceeded 2°C and minimum temperature more than 42°C was reached only in 11% of tumors. These was far not the favorable results for extreme hyperthermia concept. In 1988, institutional reports on NCI Hyperthermia Equipment Evaluation Contract were published by Stanford[205] (21 devices compared), Utah[206] (10 devices compared) and Arizona[207] universities. Stanford reported only 14% of treatments with minimum temperature ≥41°C while 56% of all treatments were associated with acute toxicity. The most interesting fact: maximum temperature (<42.5°C) was limited by toxicity, and 14% of treatments were necessitated to diminish temperature in view of toxicity. Average temperature 39.6-42.1°C in deep tumors was obtained only with three devices. In 1989, a report on BSD-1000 use[208] was published. Average temperature was 41°C and toxicity, both systemic and local, was directly named as the reason of the insufficient heating. The same year, very large phase I study on BSD-1000 APA technology appeared[209]. Since 1980 to 1986, 353 patients were treated with 1412 HT treatments in 14 US medical centers. The clinical effect was less than average with 10% of CR and 17% of PR, and thermal dose was not a significant parameter, while RT effect was significant (p=0.001). It seems that acute treatmentlimiting toxicity was 42%.

Thus, though hyperthermia remained a mainstream and 'hot topic' in scientific journals, practical oncologists and radiologicts and even many researchers in US had cooled to the method. Already in 1987, Hornback[210] wrote: 'Clinical hyperthermia today is a time-consuming procedure, done with relatively crude tools, and is an inexact treatment method that has many inherent technical problems. Certainly, excellent research work can be accomplished by private radiation oncologists working in the community. If the individual is willing to commit the time and effort required to participate in clinical studies in this interesting, challenging, exasperating, not-too scientific field; then he or she should be encouraged to do so.

The field is not without its risks and disappointments, but many cancer patients with recurrent or advanced cancers that are refractory to standard methods of medical care can unquestionably be helped by hyperthermia. It is not, as some have suggested, the fourth major method of treating cancer after surgery, radiation and chemotherapy. It may be innovative, but it still is an experimental form of therapy about which we have much to learn'.

This was the evidence of divergence of 'scientific' hyperthermia and clinical practice. This hidden disappointment of clinicians with scientists was prepared by the fact that clinical practice didn't confirm the scientific concept: hyperthermia appeared not so efficient but toxic and extremely time and labor consumptive. Practical fail of whole-body hyperthermia was already evident. Scientists believed that these were temporary problems and development of technologies will solve them. Clinicians felt that hyperthermia problems are deeper than just a technology. Hyperthermia gains in leading practical oncology centers, i.e in Kettering-Sloan Memorial, were modest.

Scientific evidences contrary to hyperthermia concept also accumulated. Already in early 70th, Burger[211,212] showed that damage of healthy tissues starts from 40.5°C, that is the thermotolerance of the healthy tissues doesn't differ from that of malignancies. This was a serious challenge to just a basis of hyperthermia concept based on the axiom of much higher thermosensitivity of malignant tissues contemporary to the healthy ones. Cautious attempt of Upjohn company to assess hyperthermia prospects ended with paper of Bhuyan[213]: despite of possibility of greater sensitivity of neoplastic cells to hyperthermia as compared to normal cells was called 'very promising', it was clearly indicated that early results on cell lines were very dubious because of the possible mistakes. These weak signals were ignored.

Understanding of limitations of local hyperthermia, especially of the impossibility to heat tumors homogenously, forced investigators to return to whole-body concept with its homogenous heating. In 1983, US company Enthermics Medical Systems in collaboration with Wisconsin University developed system for extreme infrared hyperthermia[214] which later became Aquatherm system[215]. Almost simultaneously, Texas University started whole-body program. Later in 1995, International Systemic Hyperthermia Oncological Working Group (SHOWG) was established[216] under leadership of HI Robins from University of Wisconsin.

At 1985/87 von Ardenne rejected Selectotherm WBH+LH concept and replaced it with IRATHERM concept based on whole-body infrared hyperthermia only. Multistep oxygen therapy received a new rationale: it was considered as immunostimulator[217,218]. In 1991 von Ardenne Clinic for Systemic Multistep Cancer Therapy (sCMT) was launched based on von Ardenne Institute of Applied Medical Research in Dresden, allowing systematic clinical trials. In 1992, new system for extreme wholebody hyperthermia IRATHERM 2000 was launched, and in 1993 the final version of sCMT was completed[219] extreme whole-body hyperthermia + selective thermopotentiation + supportive hyperoxemia.

Meanwhile, hyperthermia was ready for battle for recognition.
In 1988, the small trial of Valdagni et al[220] was published comparing thermoradiotherapy (TRT) with RT alone on 44 N3 metastatic squamous cell cervical lymph-nodes though only 36 nodes were included in the assessment. Hyperthermia was delivered by 280-300 MHz applicator MA-150 (BSD Corp.) Later in 1994, the report on long-term follow-up[221] was introduced. Excellent short-term and long-term results were reported both for local control (83% vs. 41%) and 5-year survival (53% vs. 0%), though thermal analysis failed to show a significant correlation between heating parameters and endpoints. The RT dose was high and nearly equal in both groups (67.5 Gy vs. 68 Gy). Some points limit the acceptability of these results. First of all, this is small size of the trial and the fact that it was initial enrollment only because the trial was terminated 'by ethical reasons'. Second, immediate results looks brilliant if to compare CR only but comparison of total effect (CR+PR) gives dubious results: 89% vs. 81% in RTcontrol. In this regard, survival effect looks absolutely decisional but there is a significant remark: such unbelievable effect was never reproduced not before not after. In all later randomized trials[222,223,224,225,250,252,258], there was no significant effect to survival. Moreover, it tended to be worse in TRT arm in some trials[250,258]. The extremely low survival in the RT-control provided that highly effective RT was used is also questionable. Therefore, Valdagni et al. effect to survival has not been confirmed in later trials and looks dubious enough. At the same time, it should be noted that this trial reported the highest tumor temperature among all the others superficial trials: mean maximum temperature was 43.3°C and minimum 40.4°C. It could in some extent explain the clinical results but absence of correlation of the endpoints with thermal parameters makes

this explanation weak. The highest temperature reached 48-52°C. Very surprisingly, in such a high temperatures, 'only one burn' was reported and both acute and late toxicity in TRT arm were equal to that in RT-control. This is an extremely alarming result because later Perez et al.[223] showed 30% of burns in TRT arm vs. 0% in RT only arm, Engin et al.[225] reported 40% of burns and Jones at al.[258] – 46% of burns vs. 5.7% only in RT only arm, and all these trials used less heating. It's also surprising that after such an excellent results and many reasons do not trust in Valdagni et al results.

Since 1984, five big randomized clinical trials on TRT with superficial[222,223,224,225] and deep HT[226] were launched in the leading US research institutions. The common belief in the success of the trials was so strong that only two of them[223,226] compared TRT with RT alone whereas other three ones compared different protocols of TRT as if its efficacy is already proven. The result was absolutely disappointing: any trial didn't show the effect of hyperthermia.

It was a good time for reassessment of hyperthermia rationale. There were enough facts to question the hyperthermia concept. Unfortunately, it was not done. All the researchers refused to review the hyperthermia rationale. Insufficient heating in view of inadequate technique was considered the only reason of the trials fail and it was a false conclusion. Toxicity was the reason of the insufficient heating as it was directly stated earlier in Stanford[205] and Shimm et al.[208] reports. This was not a technical problem and not a problem of thermometry: this is the inherent problem of hyperthermia itself and its real name is the narrow therapeutic range.

Hyperthermia community now tends to consider the negative trials of early 90th as not significant because of insufficient heating and imperfect technique. This is absolutely incorrect. All the modern hyperthermia technologies as it clearly stated above were introduced before 90th. All the randomized trials of early 90th were executed in leading US universities with the best available equipment. Therefore, the technique of heating in these trials was adequate from the modern look. It's confirmed by high temperature reached in these trials. For instance, in Kapp et al. trial[222] the minimum temperature in superficial tumors was 40.2°C, average 42.5°C and maximum 44.8°C. Modern guideline of Erasmus university[251] for superficial tumors recommends to reach minimum temperature 40°C and maximum 43-44°C. In the modern trials on deep-seated tumors, average temperature never reaches 42°C while it was reached usually in trials before 1995[203,205]. Also, the deep heating with 'second generation devices', namely BSD2000 with its SIGMA applicator, was lower that with old BSD1000 APA system.

It should be considered that in terms of heating and technique the negative trials of early 90th were absolutely adequate. They were inadequate to anticipation of early 80th based on incorrect concepts: it was anticipated that tumors could be homogenously heated to more than 43°C with high selectivity (5-10°C of difference between tumor and surrounding tissues was reported by Storm et al. in 1979[227]) without significant damage of healthy tissues due to 'almost endless selectivity between cancer cells and healthy cells'. Though, inadequacy of these 'heating anticipations' was shown already before 1990.

The trials showed that it's impossible to heat tumors homogenously more than 42°C. Less than 50% of entire tumors were heated up more than 42°C in average with more than 2°C difference of temperatures within a tumor, but the reason was not technical. There was no any obstacle even to evaporate tissues with existing techniques. Toxicity was the limiting factor. In fact, these clinical trials had just displayed the critical problem of hyperthermia: absence of therapeutic range. Damage of healthy tissues went alongside with damage of tumors and limited extent of heating. Ineffective thermal control was not a reason. Effective thermal control would only additionally restrict the heating.

The possibility of correction of hyperthermia rationale was lost. Since that time, hyperthermia was derived from the reality, as earlier it was derived from the practice. It moved to a dead-end.

Technology

In general, near 30 different hyperthermia prototypes were tested by 1985[205,206,207], though only few of them were marketed later. There was no substantial progress in hyperthermia technologies after 1985 despite of significant activities. Contrary, in some cases technical improvements even worsen the results. Though some new hyperthermia machines were introduced that time (Synchrotherm-RF (Italy) local machine,

Aquatherm (USA) and Heckel HT3000 (Germany) whole-body systems), such strong and versatile players like Bruker (Oncocare) and ODAM (Jasmin) left the market.

Near 1985, two 13.56 MHz capacitive hyperthermia systems were introduced: Oncocare of Bruker and Jasmin 3.1000 of ODAM (France). Both systems had very short history and in fact remained prototypes. Jasmin deserves a special attention because of more complex design: it was a powerful system with one upper and two capacitively coupled lower applicators with appropriate fixation, each having separate 600W RF-generator (totally up to 1,800W). The system was able to move a deep heating focus by changing output energy of each applicator[228]. Though good heat distribution was shown on phantoms, and 41-42°C was reached in deep tumors in clinical trials with enough safety[229], the clinical effect was more than modest[230]. Oncocare was a classical design 13.56MHz/600W capacitive system with two symmetrical electrodes, and showed the similar clinical results[231]. Both systems were withdrawn soon after publication of the first clinical results in 1989-1996, and both Bruker and ODAM had left the hyperthermia field.

Thermotron a little changed since its development. Total power of the system was enhanced from 1200W to 1500W. It seems that it didn't enhance its efficacy.

BSD-2000 concept with an entirely new SIGMA-60 applicator was introduced in late 80th instead of BSD1000[232,233]. Horn irradiators were replaced to 8 coupled dipole antennas with a little different frequencies range (70-100 MHz instead of 50-110 MHz in BSD-1000) and improved PC-guided electronic phase and amplitude steering. Despite of the better technical parameters of the new BSD2000 system[234], the deep-heating capacity of BSD1000 was nearly the same[235] or even better236. Toxicity had remained the same: acute toxicity was treatment-limiting in 50% of treatments and systemic stress was treatment-limiting in 30% of the treatments[235]; it looks that a little changed to mid-2000th[277]. Returning to the beginning, it seems that initial heating calculations of Turner et al.[237,238] from BSD Corp. were done with too favorable parameters, and Guy[239] calculations showing less central heating and much more superficial heating were more practical[286].

IRATHERM WBH concept had been developed by von Ardenne and dermatology department of Charite Clinic near 1985. The concept was based on use of near infrared irradiation (IR-A, 760-1400 nm). IR-A ability to penetrate to subcutaneous vascular network and heat it up was displayed already in 1931. Contrary, IR-B (1.4-3 mcm) and IR-C (3 mcm - 1 mm) are mainly absorbed in the upper skin layer.240 IR-A is separated by water filters[241]. IRATHERM 2000 system uses 5 groups of irradiators: 2 ventral and 3 dorsal. Active resistance of body to heating is the main problem of the IRATHERM concept. The power of perspirational cooling could reach 1400W, leading to long heating period (up to 2 hrs before reaching 42°C) and significant loss of fluid (up to 2 liters), dehydratation and electrolytic disorders. This causes the necessity of effective monitoring of electrolytic balance and vital functions[242].

Aquatherm concept developed in Wiskonsin university by Robins et al.214 near 1985 and introduced as Aquatherm system near 1995[215] was the entirely new WBH concept based on IR-C heating. It had been initially developed with respect to perspiration factor and seemed superior to IR-A concept from some points of view. Patient (except of the head) is placed in hollow metal cylinder which surface is heated up to 65°C (55-70°C), and therefore becomes the infrared irradiator (mainly IR-C). The temperature of the air at skin surface reaches 45-55°C. Because of high humidity (>90%) in the cylinder, perspiration is blocked and loss of heat with breathing and convection is insignificant. As a result, heating is soon (<80 min) and could be achieved with low power (500-1000 W) and without significant fluid loss.

Heckel HT3000 IR-A WBH system was introduced in 90th[243]. This is in fact a simplified analogue of von Ardenne IRATHERM system with only 4 IR-A irradiators located from the ventral side only. This narrows the 'gate' for irradiation and theoretically should enhance heating time and skin toxicity. Though, the HT3000 system uses a conventional functional bed with convenient mattress instead of rigid IRATHERM couch which often causes decubitus (8% of grade III-IV)[244]. There is no evidence-based confirmation of the efficacy and safety of HT3000 machine.

The series of hyperthermia machines under trademark Yakhta were produced in Fryazino (Russia) since 1985. There were some superficial machines: 2.450 MHz Yakhta-2, 915 MHz Yakhta-3 and 533 MHz Yakhta-4. Yakhta-5 concept mainly repeated earlier von Ardenne Selectotherm concept with combination

of WBH and local heating, though using 13.56 MHz radiative solution instead of IR for systemic heating and 40.68 MHz capacitive unit for local heating instead of 27.12 MHz in Selectotherm.
Though a number of these devices had been produced in USSR and then in Russia since 1985, only few of them are in use now. Two 40.68 MHz capacitive prototypes named Supertherm and Extratherm (with scanning electrodes) were developed in Obninsk, Russia near 1995. Though less superficial fat heating is reported, there are no enough data about their efficacy and safety.

Generally, there were a lot of solutions designed that time. Breakthrough Medical, Genemed (Japan), Labthermex, Lund Scientific (Sweden), SMA (Italy), Getis (Germany), HPLR 27[245] (France) presented their concepts, sometimes looking very promising, but all of them remained prototypes.

Hyperthermia in 1995-2005: reaction

Reaction of hyperthermia community and industry followed soon.
Just after the fail of the first RTOG deep-heating study (84-01[226]), the attempt was made (RTOG 89-08[246]) to compensate the damage based on use of 'second generation' equipment (BSD2000). Though it was a phase I/II trial which usually show much better results (like it was in phase I/II trial of 84-01 study[247]), this time the results was modest. CR+PR rate was 34% with less than 2 HT sessions per week and 16% only with 2 HT sessions. Response was not correlated with maximum tumor temperature but a strong association with radiation dose was revealed: 54% CR with ≥45 Gy versus 7% with <45 Gy ($p < 0.0001$). The toxicity of treatment was less than earlier (18% of acute toxicity vs. 68% in the previous trial) but it could be associated with caution of researchers which that time didn't run for temperature. As a result, the temperature distribution was even worse than in the previous trial, especially for minimum temperature (38.5°C only). There was no III phase trial initiated with such weak results, and RTOG discontinued its hyperthermia activity but once again without any final decision concerning this 15 years of in vain activity. Nevertheless, remarkable in all respects monograph of Seegenschmiedt et al.[248,249] was issued in 1995-1996 without any respect to negative results. It looked like hyperthermia is still a promising and highly effective modality ready to acceptance.

In 1996, Matsuda had proudly reported about hyperthermia status in Japan. At the time, Japan was the world leader in clinical hyperthermia with 215 units of equipment installed, established national market leader Thermotron-RF8 (more than 120 units) for deep-heating, extensive membership in JSHO, grant-in-aid by the Japanese government and coverage by insurance for hyperthermia. Deep-seated tumors share was 60% of treatments, while this percentage was negligible in Europe and USA.

In 1989-1991, before the fail of the trials of early 90th, five more randomized trials on superficial TRT were launched under the umbrella of International Collaboration Hyperthermia Group (ICHG). After the first fails of above mentioned trials, they were merged together. The common results were published in 1996[250]. Despite of the three of five arms displayed negative results, survival in hyperthermia group was worse and dissemination was more severe, these results were hidden. Overall statistics was favorable for HT group due to the excellent local control in the two remaining groups, though this success was bought for the sake of 2-fold growth of dissemination and 2.5 growth of mortality. Also, after publication of van der Zee et al. paper in 2010[251] it could be assumed that these good results were received due to pre-selection of patients and incorrect randomization. Nevertheless, the trial was announced as successful and became the cornerstone of hyperthermia evidences.

The next publication of Overgaard et al. trial on TRT of skin melanoma[252] in 1996 introduced a method to display the effect of hyperthermia based on use of inadequate comparator – low dose radiotherapy. Total dose 24 and 27 Gy with hypofractionation (8/9 Gy x 3 sessions) was used for treatment of malignant skin melanoma. This was near 50% of standard 50 Gy dose usually used for treatment of superficial tumors and 35% of 68 Gy dose in Valgany et al.[220] study, and it was absolutely clinically ineffective dose taking into account well-known radioresistance of melanoma. Naturally, the trial was a clinical radiobological study without clinical significance. The local control in TRT group was less than average and survival data were hidden. This trial was once again considered as successful.

In 1998, Sneed et al.[253] trial was published on brachytherapy (BT) with vs. without interstitial HT in multiform glioblastoma. The trial was excellent in all respects with only one but decisive bias: while the arms were excellently equalized in all aspects, 69% of patients were re-operated in HT arm vs. 58% only in

BT control, and the influence of reoperation rates (Δ11%) was not assessed. Reoperations started from 13-14 weeks with median time of reoperation 32-45 weeks. As it is clearly seen from time-toprogression (TTP) graph, initially the two arms were equal, and divergence started nearly at 25 weeks and reached its maximum nearly 40-45 weeks. Coincidentally, 45 weeks was a median time of reoperation for HT arm. Then, convergence of the arms started and nearly reached the equality at 65-70 weeks. Then, divergence started again but it seems that effect of the later peak of reoperations in HT arm should last longer. The final difference between two arms was near 10%, that is 3-4 patients (taking into account 33 and 36 patients in the groups) which is less than difference in quantity of reoperated patients (6 patients). Also, 2-year survival probability was 31% vs. 15% in the control group, and this 15% difference once more constitutes 4-5 persons which is less than 'reoperation impact'. It's obvious that with respect to 'reoperation bias', the result could become insignificant, that is this bias could have decisive impact for the result of the trial. Therefore, the results of the trial couldn't be accepted without appropriate recalculation.

Next to Overgaard et al. trial, the series of randomized trials with inadequate comparator were launched. In 2000, Dutch Deep Hyperthermia Group trial (van der Zee at el.[254]) was published. Total dose 67 Gy (≤60 Gy to tumor mass) was used for treatment of IIIB stage bulky cervix cancers, though itwas known that such low doses significantly decrease treatment effect[255], and doses less than 70 Gy to tumor mass are inadequate in cervix cancer, and 75-90 Gy to tumor mass was a standard treatment. The study showed good gain in TRT group both for local control, disease-free and overall survival[256] but these results were significantly worse than those received with standard high-dose radiotherapy, which makes them clinically insignificant. Also, the study was designed in the manner which doesn't allow to separate the effective mode of application among the number of treatment schedules and equipment types used (APAS, TEN and MPA systems were used). The trial is considered successful.

In 2001, Harima et al.[257] trial on TRT of cervix cancer was published having the improved design. Inadequate dose to tumor mass (60.6 Gy) in this trial was masked with by high enough total dose (82.2 Gy) because 21.6 Gy was targeted to parametria with central shielding. This allowed to show effect of hyperthermia by local control vs. low-dose RT from the one side, and at the same time to improve the survival which was the weak point of all the previous hyperthermia studies. This trial also included one more Innovation – pre-selection of aged patients. It's well-known that local control after hyperthermia is better in older patients. In Harima trial, sample of not-pre-treated patients in TRT group was 10 years older (64.9 years) than anticipated age of the first diagnosis of cervix cancer in Japan (55 years) and 14 years older than in DDHG trial (51 years). In the final reported results (with all the biases), the trial was extremely successful.

In 2005, Jones et al. trial on TRT of superficial tumors was published[258]. Though good enough gain of local control was displayed (66% vs 42% in RT control), some serious biases don't allow to consider this trial positive. Incorrect randomization is revealed which led to 10% more RT dose in TRT group. This dose difference alone could explain the received clinical effect. Other biases were high percentage of pre-treated patients and pre-selection of 'heatable' patients. Survival in TRT arm was worse during all time of the trial. As usual, this trial was announced as successful.

In 2003, the results of II phase SHOWG trial on thermochemotherapy (TChT) of malignant pleural mesothelioma by virtue of Aquatherm machine were published[259]. Despite of very mild effect (20% of partial remission only), it was decided to initiate III phase trial. In 2004, disappointing preliminary results of the trial were reported on ASCO meeting[260]. Despite of less severe sample (0-II stage instead of I-III stage in II phase study), the effect in TChT group was twice worse than in ChT control (15% vs. 30% of partial remission) but with much higher toxicity. After 2003, International SHOWG discontinued and its leader Robins finally left hyperthermia field. Instead of it, German Interdisciplinary Working Group on Hyperthermia[261] was created with its base in Charité (Berlin). IWGH was mainly targeted to von Ardennes CMT research, whereas Von Ardenne Institute and Clinic had stopped nearly the same time. Though it was announced that this is because the institute had reached its goals, absence of randomized results makes this reason inconclusive. Fail of SHOWG trial together with termination of von Ardenne Institute could be considered as the fall of whole-body hyperthermia.

It should be specially noted that von Ardenne 'Systemic Cancer Multistep Therapy' (sCMT) is not a real WBH. In fact, sCMT is a combination of two different modalities, hyperthermia and hyperglycemia, where hyperglycemia is the more potent factor because it per se could entirely block tumor perfusion[262] whereas

hyperthermia per se never blocks tumor perfusion entirely at temperatures ≤43.5°C. Hyperthermia following hyperglycemia causes higher tumor temperature and significant decrease of pH while without hyperglycemia this pH decrease is insignificant[263].

Therefore, above conclusions about fall of WBH refers to WBH per se, not to sCMT which potential still have not been evaluated evidently. Therefore, despite of a number of 'positive' trials and some meta-analyses on hyperthermia, medical community soundly didn't consider these results evident. Hyperthermia was not approved as a standard method of treatment in oncology. Without any error analysis and bereft of any correction of its rationale, hyperthermia stubbornly tried to break through the wall of evidence-based medicine, becoming more and more divorced from reality.

Resume of the International Kadota Forum on hyperthermia held in 2004[264] in Japan is very demonstrative. After usual reference to excellent laboratory results, the authors referred to 28 randomized trials on hyperthermia though only 18 'positive' trials were displayed in the corresponding table, and only 14 of them were really randomized. Concerning the rest of the trials, there was the only phrase: 'Nine randomized studies failed to show a significant benefit from addition of hyperthermia'. There was no even an attempt to explain the negative results, though these were the most extensive and reputable studies. There was no any analysis of so-called 'positive' studies which in fact were almost uniformly biased. Therefore, the advocacy of hyperthermia was based on dubious data while reputable and evidence-based but negative data were just disregarded. At the same time, the problem with hyperthermia acceptance was claimed because of 'limited availability of equipment, the lack of awareness concerning clinical results, and the lack of financial resources'. This was s beginning of 'hyperthermia low acceptance in view of low attention and money' myth. It seems that medical community was very well acquainted with results of hyperthermia but trusted to the most reputable trials which were uniformly negative. Lack of financial resources was absolutely natural after a huge funds and forces were just wasted in 80th-90th without any reimbursement. Limited availability of equipment was in high extent caused by the reluctance of doctors to use it.

Technology

Flexible capacitive applicators were introduced near 1995 by Synchrotherm-RF 13.56 MHz capacitive system. The similar applicators were used earlier in Russian Yachta hyperthermia machines, though at 533 MHz and higher frequencies. Taking into account a well-known instability of lowfrequency RF-field, Synchrotherm flexible solution seems controversial because field inhomogeneity (and hot-spots formation) increases significantly in any deviation of electrodes from pure flatness. Idea of 'field concentration/focusing' by virtue of flexible electrodes which is actual for far-field in microwave range doesn't work in the near-field at 13.56MHz: contrary, dominating electrostatic interactions cause high tangential and side currents, thus decreasing the heating in the field of interest and creating multiple hot-spots. Probably, this was a reason of later Synchrotherm decay.

The new applicator SIGMA-Eye for 3D steering was introduced for BSD-2000 system[265] in 2000th in view of insufficient focusing of the previous 2D SIGMA-60 applicator. Alongside with triple quantity of antennas (24 totally in 3 groups), the frequency was enhanced to 100 MHz to reach a smaller central peak. Though better steering was reported[266], the heating efficacy had appeared near 2-2.5 times lower than that of the previous SIGMA-60 applicator[267]. Practical results show that BSD-2000 still don't allow to heat-up the desired volume selectively because hot-spot before the target region is virtually inevitable[268], localization of other hot-spots is almost unpredictable[269], and in general the heating looks rather like a homogenous heating of the entire volume than as a selective heating of target volume[270].

It seems that BSD-2000 concept experiences problems. The toxicity of the technology still demonstrated in clinical trials[277] looks like its inherent feature because the interference of fields in the near-field region is not completely controllable and is inevitably connected with multiple floating hotspots formation (which, by the way, was obvious initially). Real-time thermometry is the only possibility to control the process but there is no a satisfactory technical solution. In fact, MR-thermometry is just the only possibility but it is still relatively applicable only for extremities and small pelvis with many limitations[267]. Sure, due to hyperthermia research, MR thermometry develops soon but it doesn't develop hyperthermia itself which in fact is 'sitting and waiting' while MR-thermometry matures. And it looks rather like flee from the problem because even MR thermometry is satisfactory, it doesn't solve the problem. The same situation already happened in 80th-90th: without effective thermometry, the heating was high enough and there were some clinical results though with high toxicity; with more effective thermometry, the heating and toxicity became

lower but clinical effect disappeared. There is no any premise for another end in this case. Taking into account the final results1 of the STS trial[277] where HT was ineffective even in the best heated and thermocontrolled case of extremities, thermometry far not looks the main problem of the technology. At last, in-built MR-thermometry finally makes BSD-2000 the 'research only' technology. It's impossible to imagine in clinical practice a modifier which is more expensive and labor-intensive than a modifying modality itself.

Near 2000, an innovative Oncotherm EHY2000 unit was introduced, based on the new modulated electro-hyperthermia (oncothermia) technology. The main idea of the technology was the rejection of the central role of the temperature. Instead of it, not-temperature-dependent effects based on the extracellular heating and modulation were the core of the technology. The classic capacitive design was cardinally re-evaluated. Instead of high-power/intensive cooling concept, low-power approach with mild physiological-range cooling was offered. Concept of 'skin sensor' abandoned the most problematic point of all hyperthermia machines – necessity of thermometry. Functionally asymmetric electrodes with grounded lower one provided necessary field stability and enhancement of heating in the 'zone of interest'. Special fractal modulation of the carrying frequency markedly enhanced selectivity of power deposition in tumor tissue. Thus, looking from outside like a regular 13.56 MHz capacitive solution, EHY2000 was a principally new electro-hyperthermia machine and technology. Detailed description of oncothermia technology, science and trials is beyond the range of this essay devoted to classical oncological hyperthermia only.

Hyperthermia since 2005: crisis, reload, dead-end and decay

In 2005, Vasanthan et al.[271] randomized multicenter (5 centers in 4 countries) trial on TRT of cervix cancer was published. Contrary to previous trials sponsored by hyperthermia societies and industry, this trial was independently sponsored by International Agency of Atomic Energy (IAAE). In this trial HT was studied vs. adequate RT dose to tumor mass (72 Gy, TD 84 Gy). The result was disappointing: TRT didn't differ from RT only by local control but showed worst survival. In IIb stage group, the worsening of survival was statistically significant. The subsequent trial of Mitsumori et al.[272] on TRT of non-small cell lung cancer (also sponsored by IAAE) also didn't show the effect of hyperthermia.

There was one more unpleasant surprise of Vasanthan trial: it was the 'most hyperthermic' study among all deep heating studies held before. The average tumor temperature reached 41.6°C (40.6°C and 40°C in Harima and DDHG trials correspondingly). The pure hyperthermic approach was ineffective, though it was clear already after early 90th negative trials. There was no possibility to wait with reassessment of hyperthermia rationale any more. In 2005 the program paper on re-setting of hyperthermia rationale was published[273]. Unfortunately, it was not a real reassessment. The paper once again speculated on 'successful' trials in the frame of the old concept of 'thermal dose' which is in fact the 'dose of temperatures'. Hyperthermia fails were not assessed accordingly and central place of temperature was even not discussed. It was just recognized at last that extreme hyperthermia concept is impossible. Instead of it, moderate hyperthermia concept (40-42°C) was offered based on effect of hyperthermia to bloodflow and tumor oxygenation, studied by Song et al.[274] to the moment. In fact, it was just an attempt to give another justification for temperature concept, a face lift instead of the capital reconstruction.

In 2007, paper of Jones et al.[275] was published advocating the use of hyperthermia as a radiotherapy sensitizer for treatment of chest wall recurrences based on the same 'positive' trials. The same year, National Comprehensive Cancer Network (NCCN) included consideration of the addition of hyperthermia for women with recurrent locoregional advanced breast cancers after first-line surgery or radiation failed, after substantial discussion and controversy among the NCCN panel members and as a category 3 recommendation (the recommendation is based upon any level of evidence but reflects major disagreement). In particular, McCormick from Department of Radiation Oncology of Memorial Sloan-Kettering Cancer Center was a counterpart[276]. This small success was too insignificant to compensate the harm from sound fail of IAAE trials in 2005[271] and 2007[272]. Crisis of hyperthermia was obvious.

'The last hope' of hyperthermia community was associated with Issels et al. trial[277]. This was the largest and the most complex trial for all the history of hyperthermia, the real 'crusade'. The prospective, randomized, controlled, multicenter III phase trial was sponsored by European Society for Hyperthermic Oncology (ESHO), European Organization for Research and Treatment of Cancer (EORTC), US National Institute of Health (NIH), German Cancer Society, Helmholtz Association and private sponsors. 341

patients with localized high-risk soft tissue sarcomas (STS) were enrolled at nine centers in Europe and North America for 9.5 years (1997-2006). The trial was designed to study HT efficacy in complex treatment of STS by the most effective protocol: neoadjuvant chemotherapy (with and without HT) → definitive surgery → adjuvant RT → adjuvant chemotherapy (with and without HT). Regional HT was applied by virtue of state-of-the-art BSD-2000 hyperthermia units. In 2010, the following results were reported: there was no effect to overall survival but short-term local response rate (CLR + PLR) was twice higher in HT arm (34% vs. 16%), and Local Progression Free Survival was significantly enhanced in HT arm (32 months vs. 18 months; 76% vs. 61% after 2 years and 66% vs. 55% after 4 years). Unfortunately, this result was totally based on systematic bias: all the possible points of distortion (tumor size, grade of disease, volume of surgery, RT and chemotherapy) were distorted to various extent but unidirectionally in favor of HT arm. Total distortion rate exceeded 90% while efficacy gain didn't exceeded 25%. The only difference in volume of chemotherapy (8 cycles in HT arm versus 5 cycles in the control arm, +60%) more than explains the gain of effect in HT group. In comparison with earlier results of Sarcoma Meta-Analysis Collaboration (SMAC), the best results in HT arm of Issels et al. trial were substantially worse than results in control arm of SMAC. With respect to the distortions and SMAC comparison, the another question arises: whether hyperthermia worsen the results of conventional treatment? Nevertheless, the result was as usual announced as positive, and the authors advocated that 'regional hyperthermia combined with preoperative or postoperative chemotherapy should be considered as an additional standard treatment option for the multidisciplinary treatment of locally advanced high-grade STS'[278].

Meanwhile, the new basement of 'reset' hyperthermia had been collapsing. 'When hyperthermia is applied in vitro, no fundamental differences can be seen between the response to normal and tumor cells'. This phrase of Kelleher and Vaupel[279] explicitly reflects the modern look on the problem and confirms the old 'open secret' of absence of difference in thermal resistance between healthy and malignant cells. But may be the authors didn't aware that this phrase is a final judgement to extreme hyperthermia concept. Extreme outer hyperthermia, both local and systemic, is impossible without significant difference in thermal sensitivity between normal and tissue cells because otherwise heat-damage of healthy tissue is inevitable. At equilibrium steady-state phase, difference between healthy and tumor tissues doesn't exceed 1°C for capacitive solutions. It seems that for interference irradiative solutions, a tumor is virtually always heated less than the surrounding tissues[270].

Kelleher and Vaupel also revealed that gain in tumor oxygenation due to hyperthermia is modest and transient and can't be used for enhancement of radiotherapy effect[280]. This confirms the data of immunohistochemistry study of Sun et al.[281] from Memorial Sloan-Kettering Cancer Center with hypoxia markers showing that real effect of moderate hyperthermia on microcirculation is bidirectional and inconclusive. Because the 'reset' concept of moderate hyperthermia is entirely based on the idea of better oxygenation of tumors, this could be a final judgement to mild/moderate hyperthermia concept. Though we still see some rapturous opinions[282] concerning promises of mild hyperthermia based on Song and team works[274], and they are still reporting these results[283], the new data makes these results questionable which would be discussed below.

As the last shot, in 2011 de Bruijne et al.[284] from Erasmus Hyperthermia Center had demonstrated in retrospective study that, after correction to tumor size, CEM 43°C T90 thermal dose is not associated with any clinical endpoint (CLR, LDFS, OS). This looks like the final judgement to temperature concept of hyperthermia at all. As a result, after more than 100 years of development hyperthermia is based on the dubious fundament and bereft of a rationale.

Technology

There were a few new machines developed in Western counties after 2005. Celsius TCS hyperthermia system was introduced in 2006 in Germany. Despite of being declared as 'innovative', this was just a replica of traditional 13.56 MHz/600W capacitive scheme with two rigid symmetrical electrodes and intensive cooling similar to Oncocare and Synchrotherm-RF. The most impressive feature of the system was just an absence of any innovation. This was a typical 'me too' approach, similar to a rising trend in the modern pharmacy, the attempt to present the old solutions in the 'new skin'. It seems that this solution if far from perfection. First of all, because it's hard to await that a regular 13.56 MHz concept would be successful after fail of many much more perfect predecessors like LeVeen machine, Oncocare, Jasmin, Synchrotherm (discontinued in 2011) and many other solutions. The second, use of not properly fixed electrodes seems to be a serious defect of a capacitive machine. Instability of lowfrequency RF-field and

hot-spot formation together with high superficial fat heating form the 'Procrustean bed' of the capacitive technology. The main possibility to relatively stabilize the field between symmetric capacitive electrodes is their rigid fixing to keep them always parallel and symmetrical, which is the Thermotron solution. It seems that any capacitive solution which uses not exactly fixed electrodes is not safe enough. For example, in Celsius TCS pre-clinical report[285] an intensive hot-spot was displayed in 1 of 4 clinical examples: at prostate cancer treatment and at low power 80- 120W, the temperature in rectum where thermometer was placed (that is, out of interest zone) suddenly raised to 45-46°C and remained at the level for 20 minutes. This is a typical hot-spot of tissuedamaging level. It seems that it should be the typical defect for any low-frequency capacitive system with not properly fixed electrodes.

Unexpectedly, hyperthermia become a 'hot topic' in China. Since 1995 many new hyperthermia machines were presented there by companies HY SenMo, ZD, ZRL, NRL, MoreStep and others. Majority of them are just replicas of Thermotron though acting at 13.56 MHz open ISM frequency with an attempt to enhance the classical design. Because two problems of capacitive technology are high superficial fat heating and lower deep heating, high 'superposition' field strength on the crossing of paired electrodes fields could allow to reach enough heating while surface heating is low. This is in fact a low-frequency capacitively coupled version of the earlier APAS-TEM idea[286] and repeat of LeVeen design[165]. It was then implemented by Synchrotherm-Pulsar system having 2 pairs of electrodes and double power 1200W. There is no data about its efficacy and safety. The majority of Chinese manufacturers develop a similar idea of 'double Thermotron'. It's hard to say, could any of these solutions be more effective than existing classic Thermotron capacitive solution.

Looking from outside it's clearly seen that this 'hyperthermic enthusiasm' is based on the uncritical acceptance of the above mentioned 'just heat it' appeal of hyperthermic community. Because Chinese haven't received 'hyperthermia vaccination', like Western world did, and haven't appropriate historical memory, this simple and attractive appeal will necessarily find acceptance.

Hyperthermia at 2010th: decay goes to renaissance?

World hyperthermia lies in ruins. It's especially obvious if to compare the current state with 80th and 90th. United States which was a worldwide leader in hyperthermia research and development, and where almost every big university was involved in these researches, now is virtually a 'free of hyperthermia' zone. Dr. Beecher institute, Duke University and some activity in Texas University – these are a pathetic remnant of the former boiling activity. 'Hyperthermia vaccination' was so strong in US that BSD2000 machine still can't receive FDA approval (since 1990). It seems that there is no any FDA approved machine for deep hyperthermia. Only superficial hyperthermia is accepted but it was accepted before 1990.

Japanese cluster based mainly on Thermotron is silent after sound fail of IAAE trials in 2005- 2007. There is no any development and research activity decreased markedly. After that fail, Thermotron-RF8 is not already an engine of Japanese hyperthermia and this place remains vacant.

Residual hyperthermic activity remains in Europe. German IHWG studies sCMT von Ardenne concept and tries to elaborate a concept of 'critical' whole-body hyperthermia (more than 42.5°C) offered by Russian doctor Souverniov. It seems that this direction is problematic enough. ESHO powered by BSD Corp. is still active, at least on a conference level. DGH is mainly powered by German private market based on insurance payments for hyperthermia treatment. Danish cluster seems to be inactive. The last review of van der Zee et al.[251] shows that the oldest and the most reputable in Europe Dutch cluster stopped its development. English school of hyperthermia decayed already after Pettigrew and Henderson at 70-80th and finally evaporated after 'successful' ICHG study[250] in mid-90th. Italian cluster, one of the oldest in Europe, shows some potential for development but in frame of the old hyperthermia concept, therefore without any future.

42 of 46 existing manuals and monographs on hyperthermia were published before 1996 and 33 – before 1990. Excellent Seegenschmiedt et al. monograph[248,249] completed this 'before 1996' period without any mention of any negative results. In fact, hyperthermia is still based on the old-fashioned ideas and concepts of 80th.

At the same time, we see the second wave of interest to hyperthermia worldwide. Quantity of publications is a good indicator. In 1991, just before the crisis of 90th, near 350 papers on hyperthermia were published (Pubmed). At 2000th, this quantity dropped to 200 papers per year, and have returned to pre-crisis level 300 papers in 2009th. Some new monographs have been published. We see three main reasons of this renaissance. The first, 'the throne is never vacant'. There is a strong request for universal modifier of conventional treatments which efficacy is obviously insufficient. There is still no any candidate to this position except of hyperthermia. Second, the new generation of scientists and physicians came into oncology which is free of 'hyperthermic disappointment', haven't an experience of hyperthermia usage and don't remember hyperthermia fails, but studied about hyperthermia from the textbooks based on very simple and attractive concepts of 80th.

Third, there was no any cardinal solutions made concerning hyperthermia, and hyperthermic community together with the industry made everything possible to 'smooth the blows' and keep it safe. They produced some myths about hyperthermia: hyperthermia is of course effective, the negative studies are not valid, the reason of hyperthermia unacceptability is evidence-base medicine barrier and competition of Big Pharma, and the main problem of hyperthermia is the lack of attention and money and some technical points like thermometry[264]. An article in Polish Journal of Environmental Studies287 is an excellent sample of such mythology. All these myths are wrong. Evidence of hyperthermia effect is based on dubious data, the negative trials were adequate, and extremely much funds and forces were invested in hyperthermia research and development. More than 12,000 publications and >700 clinical trials with near 30 randomized trials among them are much more than necessary for acceptance of any drug or treatment method. When 10 randomized trials on hyperthermia started in 1984-1991, evidencebased barrier was absent because the concept of EBM was offered in 1991 only, and even this barrier didn't object to launch a tremendous Issels et al. trial at 1996-2006. All the necessary technical solutions appeared many years ago. Thermometry is not a point at all because of fail of temperature concept.

As it clearly seen from the mentioned papers[287,264] the most impressive feature of hyperthermia community is a great interpretational bias in the form of complete disregard of any negative results: only positive results are considered valid while negative ones are just not mentioned. We see the same disregard, for instance, also in the remarkable Seegenschmiedt monograph: for example, Fig. 10.13 on page 213[248] presents effect of TRT vs. RT only. Among many phase II non-randomized 'estimation' trials which results should be considered with great caution[288], the only randomized trial of Perez et al.[223] is displayed. This trial was negative for hyperthermia arm (32% of CR vs. 30% with less toxicity in RT only group) and only small tumors (<3 cm) showed a TRT-gain. Only <3 cm subgroup positive results are displayed in the figure to confirm TRT effect and the negative arm is disregarded. As a result, there is an impression of uniform success of TRT though it's absolutely not correct: much more negative results of randomized trials[222,224,225] were received to the moment (reference up to 1995 are present in the monograph) but they are also not mentioned. This interpretational bias is characteristic for all the hyperthermia publications after 1991.

Therefore, the only reason of hyperthermia unacceptability is 'temperature-based' hyperthermia itself, namely its low efficacy, high toxicity and labor-intensity. This open conclusion should be done at last, otherwise we'll see the second wave of hyperthermia with the same result as the first one, just a prolongation of the agony with more expenses. This already happens. 'Temperature race' lasts though it should be stopped more than 10 years ago – it's just moving from 'vaccinated' Western countries to neophytes – China is becoming the main hyperthermia market. But term of the 'vaccination' expires even in Western countries with change of generations, and those who cannot remember the past are condemned to repeat it.

Technology

In 2011, Due.R srl, the manufacturer of Synchrotherm-RF system, dissolved after some years of collapsing (-10% of market every year), though recently one more 'me too' Synchrotherm-like Androtherm system came into the market. The problems of 'me too' machines are discussed above.

Electromagnetic treatment since 1985: stagnation of diathermia, non-thermal renaissance and problems of non-thermal research and applications

Diathermia of 1973 states: 'It is the opinion of FDA and the consensus of experts that pulsing the output of r.f. diathermy (as opposed to continuous wave) produces no extra beneficial therapeutic effects. Any

physiological responses produced by pulsed r.f. diathermy are attributable to heat produced by the average power output'[289]. Therefore, non-thermal development of diathermia was blocked by institutionalized thermal dogma just at the intention level. Only recently this opinion was soundly questioned: non-thermal nature of different pulsed patterns at diathermia was displayed[290].

Non-thermal effects are the mainstream of electromagnetic research since 1985. Since 90th, research of extremely low-frequency AEMF (ELF, <300 Гц) produced by electric lines and equipment started. Some of them displayed the possibility of oncogenic effect of ELF-AEMF: it was shown in vivo that medium-term effect facilitates tumor growth, especially of breast cancer, and long-term effect could provoke a spontaneous cancer development[291,292]; resistance of breast cancer to tamoxifen rises under the influence of 50/60 HZ, 1.2 mcT AEMF[293,294]. The rising quantity of such studies forced WHO to convene an international workshop in 1997[295]. Experts resumed that high-intensive ELF-AEMF could be dangerous, though low-intensity influence (<2T) characteristic for everyday exposure is not dangerous, though claiming for insufficient knowledge and necessity of further studies. Further studies displayed also anti-proliferative effect of ELF-AEMF[296,297]. Despite of number of publications on ELF-AEMF effects, their effect on human being remains controversial.

Since 1995, tremendous and rising quantity of trials is devoted to exposure of high-frequency AEMF of extremely low power (ELP) connected with use of mobile phones[298]. In general, it's considered safe but final conclusion is not possible. ELP-AEMF reported to be connected to children leukemia, brain tumors,breast cancer, gene toxic effects, neurological disorders and neurodegenerative diseases, allergic diseases, miscarriage and some cardiology disorders[299].Therefore, thermal-dependent safety standards elaborated in 50th are considered not enough and should be replaces by the new standards based on non-thermal effects.[300]

AEMF affects cell proliferation, and this effect is frequency-dependent resembling resonance. In 2009, Barbault et al. paper was published301. 1524 tumor-suppressing frequencies were revealed in the range from 0.1 Hz to 114 kHz. Most frequencies (57-92%) were specific for a single tumor type. The newly developed and FDA-approved tumor-therapy fields (TTF) technology is also efficient in suppressing tumor growth[302,303]. There are some possible explanations of this effect. Authors of TTF technology explain it on the basis of intracellular orientational effect of AEMF: AEMF-induced ponderomotoric forces inhibit an assembly of mitotic spindle[304]. Another explanation was offered by Vodovnik et al.[305]: external AEMF leads to hyperpolarization of membrane on the one side with simultaneous hypopolarization on the another side of a cell; membrane potential of dividing cells is diminished comparing to resting cells; following to fast complex and non-linear processes of hyperpolarization and depolarization and resulting changes of ion currents, membrane potential of dividing cells rises which inhibits proliferation.

Currently, non-thermal effects of AEMF of high enough power could be classified as follows: 1) ponderomotoric effects due to polarization of dielectrics: a) dielectrophoresis; b) rotation of cell and nucleus; c) orientational effect ('pearl-chain' formation); 2) membranotropic effects: a) electropermeabilization and electroporation; b) cell fusion; c) changes of transmembrane transport; d) changes of membrane structure; e) membrane destruction; 3) genotropic effects caused by direct impact of AEMF for DNA. Summation of these micro-effects led to development of non-thermal macroeffects: 1) effect on cell proliferation; 2) cell death: a) necrosis; b) apoptosis; c) 'mitotic catastrophe'; 3) disturbance of microcirculation.

Delicate sub-cellular mechanisms of ELP-AEMF are not clear still. Effect to DNA is suggested[306]. DNA could be a fractal antenna possessing electronic conductivity and autosymmetry. It could interfere with AEMF at low-frequency and radiofrequency range[307]. It was shown that exposure of DNA to ELPAEMF leads to expression of heat-shock proteins (HSP70)[308]. Astumian et al. displayed that proteins could act as molecular machines transferring energy from one form to another by virtue of cyclic conformational transitions[309] and these molecules could absorb AEMF energy. This especially refers to enzymes which action is based on cyclic conformational transitions; AEMF acts as an external energy source allowing to shift the reaction from equilibrium[310]. Tsong team showed that AEMF affects Na+/K+- ATPase: ionic transport in their experiment depended rather of AEMF frequency and amplitude then of ATP concentration[311]. The peak effect on K+ transport was near 1 kHz and near 1 MHz for Na+ transport. It's reported that non-thermic effect of ELP-AEMF (53 GHz, 0.06 mW/cm^2) inhibits growth of E.coli and

affects transmembrane Na+/K+-transport[312]. Antibiotics enhance the effect. The effect is considered membranotropic. Effect on redox status is suggested[313].

To the end of XX century, the number of non-thermal publications reached the critical mass (more than 20,000 publications), which explains the inevitable transition to practical application. Currently, there are a number of directions and technologies based on non-thermal effects: 1) dielectrophoresis; 2) electroporation; 3) bioelectric effect; 4) galvanotherapy; 5) electrotherapy; 6) electric field therapy; 7) magnetotherapy; 8) electro-hyperthermia. Some non-thermal technologies have been commercialized or close to commercialization (см. Table 2.).

Technology	Trademark	System	Inventor	Implementation	Company	Since
Electro-hyperthermia	Oncothermia (Modulated Electro-Hypethermia)	EHY2000 EHY3000	A Szasz (Hungary)	Approved in EU (CE), Russia, China	OncoTherm Group (Germany-Hungary)	1988
Electroporation	ECT (Electro Chemo Therapy)	Cliniporator	LM Mir (France)	Approved in EU (CE)	IGEA Srl (Italy)	~1980
		EndoVe	D Soden (Ireland)	I/II phase[314]	Mercy University Hospital (Ireland)	
	EGT (Electro Gene Therapy)	MedPulsar	GA Hofmann DP Rabussay Z Zhang (USA)[315]	Approved in EU (CE)	Genetronics Biomedical Corp. (USA)	~1997
		TriGrid	RM Bernard	FDA-approved for clinical trials	Ichor Medical Systems Inc. (USA)	1994
Electric Field Therapy	TTF (Tumor Treatment Field)	NovoTTF-100A	Y Palty (Israel)	Approved by FDA[316] after III phase trial[317]	NovoCure Ltd (Israel)	2000
Magnetotherapy	TEMF (Therapeutic Electro-Magnetic Field)	-	Wascher RR Williams D Bouldin FE (USA)[318]	I-II?	EMF Therapeutics Inc (USA)	~2000
Galvanotherapy	ECT (Electro Cancer Therapy)	ECTplus	Н/Д	Approved in EU (CE)	CUTH Meditech GmbH (Germany)	2006
		NEUFLO	Schroeppel EA, Kroll MW	Approved by FDA for research	Ionix Medical Inc (USA)	~2000
			(USA)[319]			

Table 2. Commercialized non-thermal AEMF-technologies in clinical oncology

About 2010, some momentous events had happened. In 2009, it had been first time displayed in oncothermia study[320] that under the mask of 42°C hyperthermic heating, temperature was responsible only for 25% of general cell-destructive effect while 75% of cell deaths were caused by non-thermal (not temperature dependent) effects. In 2011, non-thermal TTF technology received FDA approval for treatment of brain tumors in combination with chemotherapy[316]. A non-thermal device for less than two years received approval for deep-seated tumors treatment, which the leading US hyperthermia manufacturers can't receive since 2000. In 2012, oncothermia device was installed in Prince of Wales Hospital, Australia. Australia is a 'zone free of hypertermia' since the case of Dr. Holt. It's very symbolic that it was oncothermia, the technology based on non-thermal effects, which run the blockade.

It seems that interest to non-thermal effects is rising more and more in XXI century. Girgert et al.[294] revealed pro-oncogenic effect of ELF-AEMF (50 Hz, 1.2 mT) at breast cancer. This effect was multigene, complex and unidirectional[321,322,323]. Novikov et al.[324] revealed Erlich tumor eradication in mice after exposure to weak ELF magnetic field (42 mT); characteristic patterns 1 Hz/300 nT, 4.4 Hz/100 nT, 16.5 Hz/150-300 nT were revealed. Berg et al.[325] revealed that ELF magnetic field (50 Hz, 15-20 mT) selectively affects cancer cells: induction of apoptosis, depression of angiogenesis, necrosis and synergy with hyperthermia and chemotherapy are reported. Wen et al.[326] revealed synergy of ELPF magnetic field (100 Hz, 0.7 mT) and radiotherapy.

It should be mentioned that the use of non-thermal effects is still questionable for many reasons, and many problems could happen on this way. First, there is a controversy in non-thermal effects direction. Pro-oncogenic and anti-proliferative properties are often reported by different researchers for the same EMF applications. Second, the vast diversity of non-thermal effects creates a fallacious impression that almost any electromagnetic exposure could have cancer treatment effect. With this trend, even 'toaster cancer treatment' appearance is not excluded. Indeed, it seems that there is a limited number of combinations of field parameters and technologies of their application which are suitable for cancer treatment. Third, there is

a trend to uncritical extrapolation of different known effects of EMF despite of power level and field type. For instance, Tello et al. (2001)[327] explain effects of constant EMF by effects of AEMF which is incorrect. Indeed, there is no any electromagnetic modality which applies all the known EMF mechanisms. Effects of EMF are dispersed at entire frequency spectrum and each effect has its frequency optimum. Other wide-spread mistake is the use of ponderomotoric effects which demand high enough field strength for explanation of ELP-AEMF effects, which looks at least controversial. Demodulation, molecular, atomic and subatomic effects of ELP-AEMF are becoming a hot-topic in research[328] but the real significance of such an 'informational' effects is still questionable. Next, problem of EBM barrier is becoming more and more critical for development of a new medical technologies. Now, it's expensive enough to receive even pre-clinical evidences. In case of electromagnetic treatments with great versatility of frequency-power-modulation combinations, it could be the insoluble problem.

At last, a great 'systematic error' still present in the non-thermal research with its roots coming from the 'thermal dogma'. As it follows, e.g., from the Kaiser paper[329], non-thermal effects are positioned only in the 'non-thermal range', when there is no macroscopic temperature elevation, that is in ELP range. This is the incorrect and fruitless approach. Thermal and non-thermal effects develop simultaneously, and 'it's impossible to reach enough non-thermal effects with those field strengths which don't cause substantial heating'. This old sentence of Schwan should be a slogan of any 'nonthermal' research and application. The 'non-thermal' applications of 30th[77] failed for this reason – trying to remain 'pure non-thermal', – and this is also a danger for the new non-thermal applications. It seems that oncothermia technology is the only one which realizes this problem in principle and can reasonably divide thermal and non-thermal investments into general effect at hyperthermic-range temperatures[320], though we see emerging understanding of this problem even in diathermia[290].

Another dimension of this problem is a maniac desire to see thermal effects everywhere. There is something sacral in this 'thermal belief': thermal effects go deeper and deeper, to molecular level and beyond of the measurable limits, but they are still considered 'thermal' in their nature – 'week thermal' or 'quazy-thermal'. The ideas of 'molecular thermometers' which register those temperature changes which are not registered with thermometers[330] or of 'resonant heating in micro hot-spots'[331] are examples of this type of thinking, and it turns the problem of relationship of 'thermal' and 'non-thermal' into a scholastic problem of the same nature as the ancient problem of 'a hen and an egg'. It's obvious that any process is accompanied with thermodynamic changes but it doesn't mean that it's 'thermal' in its nature. Any mechanical process could be scholastically reduced to thermodynamics, but could thermodynamics explain a mechanical process? Could it be described correctly in terms of temperature, enthalpy and entropy instead of mass, force, velocity and acceleration? Of course not, but this is what radiofrequency physics in its 'thermal dogmatic' form tries to do for more than 70 years.

These are non-thermal effects which are the front line of development of physical factors application in medicine now, whereas thermal concept has exhausted for a long time, and stagnate since the early 90th. Despite the fact that thermal concept remains the only officially recognized[289], and it's still early to resume the triumph of non-thermal approach, since 2000th hyperthermia finally went from the front line of research in oncology, and in fact lost its positions in practical application.

Sure, it is still early to say about success of non-thermal technologies. Though TTF technology is already FDA-approved, its III phase clinical results are far not so favorable as it was awaited. Despite of oncothermia is currently the world leader with more than 250 devices installed, it's impossible to resume its final success prior to obtaining of III phase trials results, because there was the same 'success' with other hyperthermia technologies before III phase trials. Anyway, the answer will be received in the nearest future.

The true history of hyperthermia

The initial hyperthermia concept of 60th was simple and straightforward. It was totally based on the known imperfection of tumor bloodflow: hypovascularization makes tumor a 'heat trap' and allows to overheat it more than surrounding tissues in view of their cooling with thermo-enhanced bloodflow; heating over 43-44°C causes tumor death, though its exact mechanism was unknown [90,91,92]. Toxicity of this heating approach also was well-realized, and Crile directly wrote that hyperthermia could be used only in case of radioresistant tumors.

Everything had changed in mid-60th after Manfred von Ardenne came into the topic. He loudly announced 'the discovery of a field of almost endless selectivity between cancer cells and healthy cells in cancer therapy with extreme hyperthermia' and run the global 'hyperthermic race'. This was the main error of the initial hyperthermia concept: huge overestimation of heat-resistance of healthy tissues and contemporary underestimation of heat-resistance of malignant tissues. This error came from laboratory and was entirely based on results of early experiments with cell cultures which were fallacious because of bad understanding of very different properties and behavior of cell cultures and real tissues. Loss of malignancy of cultured malignant cells and, vice versa, malignant-like behavior of cultured healthy cells and loss of viability are only small part of these problems[213]. Though von Ardenne itself very soon had changed his mind which was reflected in the feverish search of hyperthermia enhancers, this change of mind was not announced and the initial slogan was not cancelled. It had been already accepted as a basement of a new 'hyperthermia belief'.

Hyperthermia was more belief than a science from just the beginning. Von Ardenne acted as a messiah, a mysterious 'top European scientist' for USA and Japan, not less mysterious 'Soviet scientist' for Western Europe, and even more mysterious 'secret German nuclear physicist' for USSR, and his words were the revelation. There was a real impression that hyperthermia is that thread, pulling which the cancer knot could be unleashed, and the magic wunderkind and great physicist specified the true path at last. Any reasonable skepticism was rejected, any supportive data were accepted with delight and without any criticism. Even now, when this belief is already bereft of any ground, it hasn't changed in principle.

Sure, it was not von Ardenne who started hyperthermia. Hyperthermia started long before he came and developed gradually and very cautiously. von Ardenne also was not a believer. He was a real scientist who trust only facts, but he was in a great extent a 'scientific showman', who produced new ideas and technical solutions with lightning speed, absolutized raw results and easily changed his mind without any excuse. He was a genius physicist in the inert medicine, another consciousness, another 'phase state'. When the facts had changed soon, von Ardenne just followed them, and in fact he left the hyperthermia field almost just after he entered it because his systemic cancer multistep therapy (sCMT) is not a hyperthermia. But 'hyperthermic belief' already didn't need him: it became all-sufficient.

Von Ardenne was just a strong catalyser who had almost turned a modest marginal direction in the scientific mainstream. Why 'almost'? Because hyperthermia was initially based on wrong premises, and a short enough time was given from the first excitation to understanding and cooling: 30 years since 1966 to 1996.

Science was opposite to 'hyperthermic madness' from just a beginning. Many scientists initially concerned the higher thermal resistance of healthy cells in vitro[332,333,334] – the wave of belief had just swallowed these single opinions. In Seegenschmiedt et al. monograph248 of 1996, these 'marginal' opinions were referred as an unfortunate necessity and curiosity. Burger already in 1967 showed that healthy tissues in vivo are damaged already over 41°C[211,212] – this quiet voice from the far-away South Africa was disregarded. Even in 1998, it was believed that brain tissues could tolerate up to 44°C[253]. Currently dominant position is simple and unequivocal: there is virtually no difference in thermosensitivity of healthy and malignant cells in vitro[279]. This gets an understanding of the question of the therapeutic range of hyperthermia: does it exist at all? There are some theoretical considerations which suppose that it could be even negative.

It's well-known that the direct cell-damaging effect of hyperthermia is connected with protein denaturation. Slight functional and reversible denaturation of proteins mainly connected with change of tertiary structure of proteins starts already above 41°C, which is a physiological limit of body temperature; it becomes significant over 43-45°C [335,336]. It's also well-known that the main mechanism of restore of damaged tertiary structure of proteins is intracellular chaperons, namely heat-shock proteins (HSP)[337], and that malignant cells express much higher levels of HSPs than normal ones[338]. Therefore, malignant cells are better protected from the moderate heat-stress then normal cells, and single papers report that normal cells are less resistant to moderate heating than malignant cells. Moreover, 2-3-day and more intervals between HT sessions allow to restore the initial level of thermal sensitivity of normal tissues because their thermal induced resistance reverses in 72 hours. It should be mentioned also that tumor cells thermoresistance and vascular thermoresistance of tumor tissues lasts an order of magnitude longer than that of normal cells. This fact good enough explains many results when HTcourses with more sessions were less effective than shorter ones. Over 43°C, tumor bloodflow cut-off becomes the main factor of tumor damage, but at the same time the direct thermal damage of healthy tissues grows. The acute toxicity of whole-body

hyperthermia over 42°C clearly shows, what happens when the temperature of healthy tissues exceeds 42°C. It's also well-known now that selectivity of tumor heating usually doesn't exceed 1°C[203]. Therefore, there is a small range between 42°C and 43°C, where malignant cells theoretically could be damaged in more extent than the surrounding healthy tissues. This is a very narrow and critically instable therapeutic region which works correctly only provided that tumor is heated homogenously. Unfortunately, tumors are mainly heated up very unequally: the reported difference of temperatures within a tumor exceeds 2°C[203]. The situation is compounded with the fact that those 'low-heat' areas are those well-perfused and effectively enough cooled by bloodflow regions of tumor where active and proliferating malignant cells are located, which therefore could survive. At last, taking into account that real effect of extreme hyperthermia starts from 43°C, at which the temperature in surrounding tissues reaches critical level 42°C, the therapeutic range disappears at all.
The simple conclusion follows: extreme hyperthermia could be either effective but toxic or not toxic but ineffective. Though being suggested already since mid-80th, the definite conclusion on negative therapeutic range of the extreme hyperthermia was made for the first time only in 1991: it was displayed that thermo-enhancement rates (TER) of toxicity of some chemotherapies at WBH outweight the TER of their efficacy[339]. It took one more 14 years before this had led to a change in hyperthermia rationale[273], though the fact itself has still not accepted by hyperthermic community.

But initially nothing seemed foretold troubles. In 70th, the new 'basement error' of hyperthermia was developed: the illusion of 'virtually endless selectivity of extreme heating' was created predominantly by Storm et al.[340] works. Unbelievable 8-10°C difference between normal and tumor tissues was reported. It's hard to say now, was it a thermometry mistake or something else, it doesn't' matter. It is important that, together with dogma of 'endless selectivity of thermal resistance', this already looked like nearly a 'final solution' in cancer treatment.

Now the real hyperthermia race had started. At the turn of 70th and 80th, new hyperthermia machines were springing up like mushrooms overnight. Almost every big US university medical center had its hyperthermia group and many of them offered their own technical solutions. Those who hadn't a machine, heated with any suitable warmer[341,342]. Near 1980, US National Cancer Institute (NCI) launched a contract for evaluation of hyperthermia equipment trying to control this boiling activity and supporting hyperthermia development at the same time. Simultaneously, multiple clinical trials started.

The first wake-up calls sounded in late-80th when institutional reports on NCI contract were reported. Heating is not enough, toxicity is limiting, 43°C in unreachable in view of toxicity – this was a resume of Stanford report[205]. Impossibility of extreme temperatures questioned the entire concept of extreme hyperthermia. 'Thermal dose' concept[343] was offered in advance. Thermal dose, designed to replace the rapidly losing its value temperature, which is in fact just a 'dose of temperatures', was an artificial construction based on an extrapolation of in-vitro Arrhenius dependence of heat-damage to living tissues. To that date it looked grounded, because difference in gain rate over and under 43°C was known since 60th. To the moment, futility of this parameter is obvious[284].

Though hyperthermia problems were already obvious to the most advanced users and scientists[210], it still looked very strong before 1990. Extreme hyperthermia concept was finally furnished after explanation of tumor bloodflow[274]: heating over 42.5°C causes 'cut-off' of tumor bloodflow with subsequent hypoxia, acidosis and following necrosis of tumor tissue. Hyperthermic activity reached its maximum: the record number of 8 monographs and 350 papers were published in 1990. Ten big randomized III phase 'trials for recognition' sponsored by RTOG and leading US universities were launched. Hyperthermia triumph was almost in hands – but it didn't happen.

Instead of the triumph, the huge disappointment awaited the hyperthermic community: all the trials[222,223,224,225,226] failed to show hyperthermia benefit. Nothing was confirmed: thermal parameters mainly didn't correlate with the endpoints, heating was not enough in frame of the extreme HT concept, toxicity was too high and number of sessions didn't influence the effect. The result of the 25-year boiling activity was – nothing. Hyperthermia has not ever recovered from this blow. This was a beginning of the dawn of hyperthermia.

Though, the dawn promised to be long because the great inertia continued to push hyperthermia ahead. A number of international and national hyperthermic societies with thousands of members, some big research

world clusters with hundreds of hyperthermic opinion-leaders, the specialized international hyperthermia journal and the industry behind of this structure – this couldn't fall in a day. And – may be the most significant factor, – hyperthermia was already included in advance in the base manuals on radiotherapy. As the time has shown, may be this was the strongest factor of its survival.

First of all, conclusions on the negative trials were unexpectedly mild. Despite all the trials were equivocally negative, there were no the cardinal resume. Whereas earlier Stanford institutional report conclusion was simple and clear, these conclusions left hyperthermia alive. Though it was already obvious that the core problem is the narrow (absent) therapeutic range and this is a problem of the method per se, all the conclusions referred only to the technical problems of heating and heating control, remaining to the industry a possibility to recover them. Then, RTOG attempted to recover the situation and had launched the new deep hyperthermia trial[246] with 'second generation' equipment before the first negative trial[226] was published. This phase I/II trial results were negative again, and RTOG left the topic forever.

This was the turnover point. After independent sponsors – RTOG and the big universities, - finally left hyperthermia trials in 1996, and hyperthermic societies took the trials in their hands, the trend momentarily turned out. Since the moment, all the trials had been becoming positive. Conspirology of this turnover is not the topic of this essay but the basic moments should be called. Due to EBM, it's well-known now that industry-sponsored clinical trials are often biased and have 5-20 times more probability of positive result. Interrelations of the hyperthermic societies with hyperthermic equipment manufacturers is an 'open secret' – it's enough just to visit ESHO web-site. Even without respect to these interrelations, both industry and hyperthermic societies that time were united with the common aim – survival, - though had common interests. Our earlier critical analysis displayed that all the hyperthermia-sponsored trials since 1996 were heavily biased[1] and their results were either dubious or clinically insignificant.

First, International Collaboration Hyperthermia Group (ICHG) had merged the resting five just launched randomized trials, at least 3 of those obviously moved to negative result. Surprisingly, in 1996 a 'very positive' trial was published from this merge. Though 3 of 5 arms remained negative1, this fact even didn't get the abstract. Simultaneously published 'positive' Overgaard et al trial[252] was clinically insignificant1 in view of inadequate control. Surprisingly, the fundamental Seegemschmiedt et al. monograph[248] was published in 1996 'like nothing happened'.

Understatement of negative results is a common problem, which forms a 'positive bias' in the entire modern medicine: because nobody interested in negative results, they are poorly published and quoted. Often, negative trials even not published. The published papers are usually brief and of lower quality. They are never reprinted and very rarely commented. Contrary, positive trials are usually often quoted and referred, they are reprinted and commented, discussed in letters and editorials. As a result, looking from the pages of medical journals, the medicine per se looks much more successful than it is really. Concerning hyperthermia, this 'conspiracy of silence' is elevated to the rule: if problem isn't mentioned, it's absent.

1996 was the turnover year in one more meaning: this was the last year of scientific hyperthermia. As it clear from the above, before 90th the hyperthermia was a scientific hypothesis, albeit with a touch of belief, though it's quite usual for a nice and promising hypothesis. In 90th, the usual 'great tragedy of Science' happened: the slaying of a beautiful hypothesis by an ugly fact. In the frame of scientific paradigm, there were two further options only: either to explain the facts and change the hypothesis accordingly for the new testing, or to withdraw it. In 1996, hyperthermia had chosen the third way: ugly facts were just declared inadequate, disregarded and understated. Nothing had changed in the hypothesis per se – the methods of obtaining proofs had been changed instead of it. Among many biases described by EBM, almost all were used in these hyperthermia-sponsored trials: inadequate comparator, defects of randomization, pre-selection of patients, selective data reporting, incorrect analysis, selective data publication, systematic bias, etc[1]. This already was not a scientific approach. Without continuous correction to distortions (ugly facts), any hypothesis becomes a subject for unguided process of errors accumulation, and finally turns into pseudoscience. Ignorance or distortion of facts, which are known to the authors but contradict to their concepts; refusal of attempt to compare theoretical concepts with real results when it possible; use in the basement of theory of incorrect data, not proved statements or erroneous data – all these signatures of pseudoscience were more and more obvious in hyperthermia since 1996.

The next ten years since 1996 to 2005 were a decade of the gradual and cautious hyperthermia revanche. Only 3 randomized clinical trials on external electromagnetic hyperthermia were held during this decade[254,257,258]. All of them were sponsored by hyperthermic societies and all were considered positive. In fact, all the results once again were dubious and/or clinically insignificant[1]. Anyway, accumulation of such 'positive' results allowed meta-analyses[275,344,264], the first step to evidence, but these meta-analyses had inevitable and obvious weak place: there were a number of negative trials without any explanation. It's not enough just to say 'Nine randomized studies failed to show a significant benefit from addition of hyperthermia'[264] – this should be explained. Anyway, even such weak evidences allowed hyperthermia to reach some acceptance: it was once mentioned in NCCN guidelines in US and agreed for advanced cervix cancer treatment in Dutch.

On the other side of Pacific Ocean everything went well. Thermotron obtained an acceptance in Japan without III phase trials. Government supported it with grants, the treatments were covered with insurance. After US hyperthermia failed in 1996, Japan became a real world leader with more than 200 hyperthermia units installed. As a result, world Kadota consensus meeting in 2004 was held in Japan. This was the highest point of hyperthermia rise after catastrophe of 90th. Though consensus claimed for low acceptance, lack of money and equipment, and low acquaintance of physicians with 'possibilities of hyperthermia', the future once again looked promising: fails of 90th were nearly forgotten, new trials were accepted, Japan looked as a bright example.
As usual, a fly in the ointment didn't hesitate to appear. In 2004, a grand failure of the first and the only randomized trial on whole-body hyperthermia happened: the result in hyperthermia arm was twice worse than in chemotherapy control[260]. It could be a burst but everything was done to blow off steam without explosion. These preliminary results were reported only once orally at ASCO meeting. It was promised to continue the trial but though it was sponsored by International Systemic Hyperthermic Oncological Workgroup, the result was so strikingly negative that there was no any possibility to correct it. The trial had been terminated. Noone paper was published on the result, and this result never was commented or referred. ISHOW had dissolved silently. The result should be erased by understatement.

Nobody awaited that it is Japan where the next powerful blow will come from soon. New ugly facts came in 2005 from the old trouble-maker – independent trials. In late 90th, two big randomized clinical international multicenter trials[271,272] were launched under the sponsorship of International Agency of Atomic Energy (IAAE). Both had appeared negative. The longest day has an end. Fail of Vasanthan et al. cervix cancer trial published in 2005 was the most painful. First, the highest temperature was reached in this trial but results in HT group were for worse than in RT-control, and it was impossible to explain. Second, the design of the trial was close to two previous 'positive' trials[254,257] which were already included in the 'golden database' of HT evidences. Therefore, these evidences were becoming questionable. It's not surprising therefore, that hyperthermic opinion-leaders rushed to explain why their trials were successful whereas Vasanthan trial failed, but it was inconclusive[345]. Third, all the old 'sins' of hyperthermia were remembered.

This ugly fact was impossible to ignore any more. The situation demanded urgent actions – and in 2005 hyperthermic opinion-leaders announced the 'resetting of hyperthermia rationale'[273] at last: extreme hyperthermia is impossible – moderate (mild) hyperthermia (MHT) based on thermal dose calculation was announced the actual concept.

The name of the event is demonstrative itself. Not 'reassessment', not 'correction' – it was a remarkable attempt of exactly the 'reset': to cancel everything happened before with one action and start from zero without any burden of former sins. And – this is principal, - without necessity to change anything; the same equipment, the same procedures, just less temperatures. Taking into account that 'hyperthermic temperatures' were in fact moderate already for more than decade (and in some meaning from just the beginning[346]), this was just a legitimization of the de-facto state-of-the-art with simultaneous trial to disown all the old fails and sins. It was a genius action in all respects. History shows that a new technology has got at least 20-30 years from hypothesis to disappointment or acceptance. With this reset, hyperthermia which time was up soundly considered for one more 20-30 years of existence in its 'mild' version. The desperate attempts of hyperthermic establishment to keep hyperthermia safe would deserve respect if these were scientific action. Unfortunately, it looked rather like an attempt to save hyperthermia by any means.

Anyway, the maneuver was successful. Revival of hyperthermia was visible, sometimes rapturous[282]. New rationale looked obvious and visible. Number of publications had been rising. Publication of the second

negative IAAE trial[272] in 2007 already didn't hurt hyperthermia too much – it looked like a 'greetings from the past'.

Unfortunately, this once again was only a temporary relief. The reset was fallacious and ineffective.

First of all, though hyperthermia had refused old extreme concept as ineffective, its ‘golden database’ included only ‘positive’ data received in frame of the old and ineffective extreme concept[287]. New evidences were slow to emerge. It was an obvious contradiction. Second, it was many times showed that thermal parameters are not connected with endpoints in any way and thermal dose is of lowest significance. Next, nothing changed in the hyperthermia practice. In Erasmus Medical center nothing had been changing since 1985, and hyperthermia remained extreme[251] – they just hadn't noticed any 'resetting' of the rationale. Manufacturers still recommend to heat tumors from 40°C to 45°C[347]. Was it a 'tactical’ reset without real changes, a real ‘maneuver’?

But the main problem of the ‘resetting’ was that the new hyperthermia concept was built on dubious premises and once again seemed to be fallacious. It was totally based on Song team works[274,348,349,283] which reported ‘abundant evidence’ that MHT (39-42°C) leads to significant enhancement of tumor bloodflow and long-lasting (1-2 days), sustained enhancement of tumor oxygenation[348]. According to Song et al., this rise of oxygenation at MHT was stronger than at extreme HT (16 mmHg vs 12 mmHg[274]), and MHT was more potent radiosensitizer than carbogen breathing and nicotinamode[348], and this effect is a stable platform for using MHT as general-purpose radio- and chemo sentisizer[349]. This was a discovery of one more magic ‘almost endless’ effect of hyperthermia and once more it seems to be fallacious.

First, the effect of the significant, sustained and long-lasting improvement of tumor oxygenation by MHT was revealed only by Song laboratory and was not supported by other groups, which haven’t revealed a sustained increase of both tumor bloodflow and oxygenation after MHT[280,350]. According to Vaupel and Kelleher, the real effect of MHT on tumor bloodflow and oxygenation is limited and transient, and can’t be used for radio sensitization. These are contrary points of view. Second, Song’s effect is very controversial because in fact ‘better oxygenation without better perfusion’ concept was declared without any satisfactory explanation of the effect. The offered explanation[349] is extremely weak and was entirely built on wrong premises and unwarranted suggestions. Understanding of tumor physiology could help in explaining of these controversies.

Special features of the tumor vasculature are well-known. Tumor vessels are partly a normal host vessels included in the tumor structure, and partly the newly developed tumor vessels. The normal vessels dominates in the smallest tumors and became rare as tumor grows; they have a normal structure with dense endothelium, basal membrane and muscular layer. In the dominating newly developed vessels, there is an endothelium-like lining without dense contacts and with gaps between cells, and there is no basal membrane (at least constant one) and a muscular layer. As a result, the newly developed vessels are highly permeable, and there is 5-10% of plasma loss during every passage of blood through a tumor[351]. Sometimes, the vascular wall is absent and blood lacunas are formed adjacent to the vessels. In general, the tumor bloodflow is described as ‘unclosed’. As a result, the enhanced interstitial pressure[352] which rises as tumor grows[353], is the obvious feature of a tumor. Alongside with the enhanced vascular permeability, lack of adequate drainage, tumor growth and hypoxic swelling of cells are the reasons of the tumor interstitial pressure growth. Because normal lymphatic vessels located at tumor borders are the main collectors of tumor interstitial fluid, this fluid is delivered from inner areas of tumor by convective flow. In view of inhomogeneity of tumor interstitial matrix formed by alternation of ‘liquid’ and ‘gelatinous’ areas, this flow exists in the form of sustained ‘currents’. Phenomenon of different calibers of tumor vessels is wide-spread: newly developed thing vessel often precedes a much larger ‘normal’ vessel, thus limiting its bloodflow. Tumor capillaries are twisted, atonic and enlarged in diameter, and highly permeable. In tumor, virtually there is no reserve capillaries: all of them are always open and perfused. There is a number of shunting vessels (which are not metarterioles in a usual meaning) responsible for shunting of the major part of tumor bloodflow bypassing capillaries[354]. The tumor shunting capacity could be so great that causes refractory hypoxemia at lung tumors in view of great intrapulmonary shunting[355,356]. Finally, the absence of the muscular layer makes impossible the usual regulation of bloodflow by vasoconstriction and vasodilatation. Bypass shunting is the main type of regulation of the tumor bloodflow. The major part of tumor vessels and capillaries are always dilated and atonic[355].

Let's hypothesize, what happens in a tumor during mild hyperthermia. Tumor hasn't its own inflow and outflow vessels and is fed by the bloodflow of the surrounding tissues. Taking into account the smallest ability of tumors for muscular regulation (see above), the changes of tumor perfusion are just a reflection of the changes of surrounding tissues perfusion, which grows exponentially as a temperature rises. But vasodilatation of tumor vessels is negligible, therefore the main mechanism of perfusion enhancement is the rise of blood velocity. First, this speed-up is limited by development of vascular turbulence and the subsequent rise of resistance, from the one side, and by different calibers of tumor vessels with number of bottlenecks in the network, from another side. The turbulence could block microvessels both functionally and physically (sladge). As a result, the major part of the enhanced bloodflow is just shunted through the tumor shunting vessels. Second, the speed-up of capillary bloodflow deteriorates the capillary gas exchange. In normal capillaries, erythrocytes are in close contact with a capillary wall for some time. This contact is necessary for an effective gas exchange. In the enlarged tumor capillaries, there is no close contact of erythrocytes with capillary walls which leads to significant decrease of gas exchange efficiency and is the major reason of tumor hypoxia. Slower tumor capillary bloodflow and prolonged time of the passage are a relative compensation of the defect. The speed-up of capillary bloodflow significantly worsens the situation: due to the limited time of passage, the gas exchange is limited, and functional shunting[357] develops alongside with abovementioned anatomic shunting, looking like 'arterialization' of tumor blood-flow. Turbulent sladge of blood cells could block capillaries at all. As a result, bidirectional changes of tumor microcirculation at MHT could both to improve tissue oxygenation or have no changes, or to deteriorate hypoxia. Also, it could be supposed that perfusion and oxygenation at MHT significantly rise in the initially wellvasculated regions and clusters, whereas in the previously hypoxic and hypoperfused badly vasculated regions and clusters, the bloodflow doesn't rise or even decreases. At the same time, oxygen mass transfer will always and significantly rise, and this is registered by 'macro photo' with the existed oxygen tension measurement methods. The size of polarographic microcell of usual oxygen-measuring electrode is 300 micrometers and it averages oxygen tension in adjacent area near 1 mm3. This is a too big scale to register a real microcirculation changes but it's enough to measure oxygen mass transfer. Additionally, the rise of tumor perfusion at MHT will inevitably lead to enhancement of intratumoral pressure, strengthening of interstitial currents and rise of probability of lympogenous dissemination.

Fortunately, there is an excellent paper of Sun et al.[281] from Memorial Sloan-Kettering Cancer Center clarifying the problem. Immunohistochemistry staining with hypoxia markers allowed to receive a 'micro photo' of tissue hypoxia status and has confirmed all the above suggestions. It's obvious that changes of tumor microcirculation are multidirectional from just the beginning of heating: some microvessels functions and hypoxia decreases, some of them functions with no changes in hypoxia status, some are blocked with deterioration of hypoxia. The average result looks like some improvement of hypoxia status during moderate heating but this improvement mainly ceased in 1 hr after treatment. The most interesting: it seems that 24 hrs after a treatment the tissue hypoxia becomes heavier than it was before the treatment.

This could be the only rationale of Song et al. phenomenon of 'long-term better oxygenation after MHT'. If microcirculation status of tumor becomes worse after MHT, that is if many capillaries and vessels are blocked and shunting proportion rises, then oxygen mass transfer rises in view of diminishment of tumor oxygen uptake. With a 'macro photo', it will be detected like 'better tumor oxygenation', and the better this 'oxygenation' looks, the worse the real hypoxia status of the tumor. It seems therefore that 'long-term better oxygenation after MHT' reported by Song et al. actually could be 'a long-term worsening of tumor hypoxia after MHT', that is the absolutely contrary effect.

This makes the suggested oxygen-dependent radiosensitization effect of MHT dubious. Better oxygenation of previously well-oxygenized areas doesn't lead to enhancement of radiosensitivity, whereas aggravation of hypoxia significantly reduces it. Shunting oxygen is useless for radiosensitization. This also refers to chemopotentiation effect: if microcirculation is worsen by MHT, delivery of drug will be less effective, though total drug clearance through the tumor will rise for the account of bypassing, making an impression of the better treatment[354].

Therefore, it seems that the moderate hyperthermia concept of Song and his followers is incorrect. The hyperthermia state-of-the-art could be formulated as follows: hyperthermia always causes enhancement of perfusion during the session (1 phase) and worsening of microcirculation afterwards (2 phase); the amplitudes of the both phases effects are proportional to the heating temperature, at least up to 44°C[280]. In this meaning, extreme HT is always more effective than MHT. Radiosensitizing effect of MHT, if exists, is caused rather by the usual hyperthermic destroy of the tumor microcirculation than by the effect of tumor re-oxygenation.

For seven years since the re-setting, there is no any evidence of MHT efficacy. Surprisingly, in the later work[283] Song et al. once again operate with extreme 42.5°C heating though calling it 'mild hyperthermia'. This is a logical end of the resetting: just change of the name and replacement of the explanation without any change in practice and procedure. What is the most impressive in this resetting: the self-consistent and well-grounded rationale of extreme hyperthermia was replaced with inconsistent and controversial MHT rationale. This is the essence of mid-00th 'resetting maneuver': impossibility of extreme HT and lack of results caused an attempt to 'face lift' by virtue of the artificial MHT concept; bankruptcy of the face-lift caused hidden return to the initial extreme concept under the mask of MHT; the result is an impression of hyperthermia renovation without any real changes.

'The second coming' of the extreme hyperthermia does not inspire any optimism. This is the one more consequence of the inconclusive decisions concerning hyperthermia. Because until now the extreme hyperthermia (>42.5°C) was never reached, it could be still hypothesized that if it would be possible to reach technically, it would be effective. This was an implied conclusion of negative trials of 90th.

The results of experiments on combination of whole-body and local heating (WBH+LH) deny this opinion. It was obviously shown in 90th that this combination really provided much better heating up to 42.9°C vs. 41.3-41.7°C at WBH and 39.9°C at LH (p=0.0012), and WBH+LH heating was much more uniform[358]. Thermal dose CEM 43° T90 in combination group was 12 times higher than in local HT group (49 min vs. 4 min)359. Unexpectedly, this near to ideal heating led to much worse experimental results at dog sarcomas than LH only: time of local control didn't differ (p=0.59) but metastases developed sooner (p=0.02), and probability of metastases development was 2.4 times higher in the WBH+LH group at higher toxicity[359]. These data contradict thermal dose concept and thermal concept of HT at all and suggest that the extreme hyperthermia could be a miracle even if it's technically possible. Some other results support this point of view: particularly, Hiraoka et al. reported that clinical effect at <43°C heating is better than at >43°C204, von Ardenne soon refused his Selectotherm WBH+LH concept, and similar Pomp-Siemens machine was clinically insuccessful. The most likely reason is that at temperatures over 42°C, toxicity of HT significantly outweights its benefits.

As it discussed in details above, 'the last crusade' of hyperthermia in form of Issels et al. tremendous STS trial[277] led to fiasco1. Despite the official 'positive' result of the trial, the huge systematic bias in view of the doubled treatment power in HT-arm vs. control arm, and poor clinical results cause the question: Whether hyperthermia worsened the clinical results?

Resuming, currently we see hyperthermia bereft of acceptance, rationale and evidences. It's the time to terminate this prolonged experiment.

At the same time, the history of electromagnetic therapy in oncology is only at its beginning. Recognition of inconsistency of thermal dogma would release significant forces and funds which are now being spent for support of agonizing hyperthermia, and would remove the intentional block created by this dogma. New methods of electromagnetic treatment, some of which already exist and some are in development, will replace hyperthermia and, probably, we'll see the fourth basic method of cancer treatment at last. Possibly, it will be associated with hyperthermia-range heating, but let it don't deceive you: the 'temperature hyperthermia' is over.

Conflict of interests

The author is the General Consultant of OncoTherm Group in Russia and CIS countries and the Secretary Treasurer of International Clinical Hyperthermia Society.

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Essentials of Oncothermia

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Essentials of Oncothermia

Abstract

Oncothermia is a method of hyperthermia in oncology, controlling the locally applied deep-heat by selectively targeting the cellular membrane of the malignant cells. The selection of the method is based on various biophysical and biochemical achievements. There are various differences between the malignant and healthy cells, which could be used for their selection by heat targeting. The primary selection factor is a different metabolic activity which creates distinguishable environments of the malignant cells. The other factor is the clear difference of dielectric properties of the membrane and near membrane extracellular electrolytes, marking off the malignancies. There is also a structural factor also, which is clear in the different pathological patterns of the malignancy from their healthy counterparts. This last is described by fractal pattern evaluation technique, which dynamic time-fractal transformation is used for further discernment of the malignancy. My objective is to show a new heating method, which makes oncological hyperthermia controllable and effective.

Keywords: oncology, hyperthermia, heat, nanothermia, oncothermia, selectivity, cell-membrane, Warburg, Szent-Gyorgyi, fractal, radiofrequency, modulation, beta-dispersion

Introduction

Oncological hyperthermia is the overheating of the malignant tissues locally or systemically. The method is deduced from the ancient medical practices, where the heat-therapies had a central role in medicine.

The local hyperthermia by the radiation of red-hot iron was the first known oncological treatment applied by Hypocrites, who described the method [1]. The main idea was originated from sacral considerations formulating the overall force of the "fire". However, physiological consideration was also behind that together with beliefs: the local heat accelerates the metabolic activity without extra supply of this action from the unheated neighboring volumes. This physiological mechanism is accompanied by severe hypoxia and it finally kills the target by acidosis. The working idea has been recently shown, proving the impoverishment of ATP and enrichment of lactate in the locally heated tumor tissue, [2]. Due to the primitive heating techniques the ancient radiative heat is only rarely applied in real cases. The central point of the locally applied oncological hyperthermia is the selective heat-delivery into the deep-seated tumors. The discovery of the electromagnetic heating gave new perspectives for deep heating, and hyperthermia started its first "golden era" in oncology. It was among the first modern curative applications of modern techniques in oncology, [3] and was followed by a controlled clinical study involving 100 patients as early as 1912. It showed remarkable benefit of the combined thermo-radiation therapy [4]. The method was further developed in three various branches: the interstitial hyperthermia, including the galvanic heatstimulation, the ablation techniques and the capacitive coupling. The first capacitive coupled device was launched by Siemens. The skeptical opinion about oncological hyperthermia was also typical: "All of these methods impress the patient very much; they do not impress their cancer at all" [5]. After a small dormant period the phoenix life of hyperthermia in oncology started again. The first start of the new capacitive-coupling technologies was by LeVeen [6] in 1976 and has been widely applied since then [7], [8]. Its efficacy was discussed and proven in the relevant literature in its time, [9], [10], [11], [12], [13].

Treatments with coils (magnetic and inductive) are relatively rarely used due to the negligible magnetic permeability of living systems [14]. In order to improve the magnetic energy absorption within the target tissue, magnetic materials, such as micro-particles [15] and ferrite rods [16] are usually injected into the targeted area [17]. Other inductive heating is typically achieved without inclusion of extra magnetic material into the tumor, it uses only induction of Eddy-currents [18], [19], [20]. The emerging application of magnetic treatments was started by the nano-particle magnetic suspensions [21] and other magnetic liquids.

A method for electromagnetic energy delivery, that has been widely used recently is the antenna-array coupling [22]. Its subsequent developments are the annular phase array [23], the matched phase array [24], the Sigma60 [25], and Sigma-Eye [26], where the applicators use high-frequency RF (60 – 150 MHz). Nevertheless, multiple controlled clinical trials have shown the efficacy of this method [27], [28], [29], [30]. This rapidly emerging period was shadowed by skeptic opponents, they emphasized the increased

dissemination of the malignant cells which supports metastases by hyperthermia, [31], [32], [33]. Direct negative opinion was formulated about the mistakes of hyperthermia investigations [34]: "The mistakes made by the hyperthermia community may serve as lessons, not to be repeated by investigators in other novel fields of cancer treatment." Many researchers had been doubtful and unsettled questioning the future of hyperthermia accepting the impressive biological effects, but blaming the physical realization of the heat-delivery [35]. Annals of Surgical Oncology formulates in the actual clinical experiences of mesothelioma [36]: "The results of adjuvant intrapleural chemotherapy for mesothelioma with or without hyperthermia have been less than hoped for." One of the flagship clinical studies of hyperthermic oncology was published about cervical cancer, with excellent results [37], the method emerged again, [38]. The control study five years later was disappointing [39].

What is the problem [40]? Why are conventional hyperthermia with high preciosity of focusing made by modern techniques of radiofrequency and microwave applications not able to serve the proper deep heating requests? The answer is plausible: the temperature spreads into the neighboring volumes independently of how precise the focus of the energy is. The problem is, that because of the misleading aim we get uncontrollable temperature as a dose and we ignore the physiological reactions of the patient. The published temperature patterns of the heating show the problem well: the energy is well focused, but the temperature seeking to be equalized and the focused energy-intake will heat up the tissue outside the focus as well. For example, a tumor is heated in the pelvis, and the elevation of the temperature in the tumor is 4.2 oC after 57 min, with as high power application as 1300 W [41]. The overall heating is obviously show unwanted hot-spots on the MRI pattern. The elapsed time smears the relative focused temperature. The temperature increase in the tumor was in average 4.2 oC, while in the surrounding muscle it was 3.8 °C [41]. (Note, a standard speedy electric tea kettle uses 1300 W to boil a cup of water within a couple of minutes. The increase of the temperature for the ~ 0.3 liter water is ~75 ºC. In these cases we apply the same power reaching a temperature increase of ~7 ºC during 60 minutes for the same volume of tumors as the cup of water in the kettle.) Analyzing the temperature pattern in details shows that the mean tumor-size was less than half a liter (419 ml), the necrosis in the tumor was 36 ml. The volume ratio of the body's cross section and the bolus show, that the bolus has 157% more cross-sectional area than the body. The applied frequency was 100 MHz in average, which loses its 66% of the initial energy (penetration depth definition) within max. 5 cm, so the main energy-absorption was in the water of the cooled bolus. Other publications show the same problem of the heating [42]; [43]; [44]. Comparison of the clinical responses also clearly shows the problem of the bolus heating. The cases of non-responders have higher bolus temperature, the tumor is not heated [45], [46].

The same problems arise by typical capacitive coupling hyperthermia solutions. It pumps enormous energy also (1200 W) into the target and the rise of temperature was 4.8 oC after 45 min. The selection by temperature between the malignant target and the non-targeted healthy tissue was approx. 1 oC [47].

This large volume temperature rise was observed in other capacitive applications too, [48].

All of these problems are caused by the massive heating of the target, which has a physiological reaction to cool it down and to reestablish the homeostatic equilibrium. The complex physiological effects badly modify the desired effects [49]. Even when the focus is proper, the heat is distributed to the full available volume. Furthermore, the same volume heating with the identical absorbed energy will be heated to different temperatures when the blood-flow in the targeted volume is different. This is why the patterns of the specific absorption rate (SAR) of the energy and the temperature are so different in a given fixed heating process, [50]). There are multiple other points that modify the temperature distribution in the body:

- Not only the temperature equalizing process, but the natural, technically non-followable movements of the patients (i.e. due to the breathing) modify the focus.
- The heat flow to the surroundings can damage the healthy neighborhood.
- The enlargement of the sphere having certain temperature gradients increase the area of the injury current, and this supports the cell-proliferation.

Compensating these effects, the acceleration of the heating with high energy has to be applied, when the incident energy might burn the skin. In consequence, certain surface cooling is necessary. The heat-sink of the surface decreases the incident power, but its quantity has no measurable parameters. This way we lose the control of the treatment process by the incident energy, because the missing part by cooling is uncontrolled. It has serious consequences in the vigilance of the process: temperature measurement in situ is necessary to fix the dose of the energy. This measurement is mostly invasive, causing multiple complications, including inflammation, bleeding, infection, dissemination of the cells, etc. The unwanted hotspots are created by the electromagnetic interferences and are uncontrollable with the dynamic changing

of physiologic parameters. These could be controlled only by a large volume temperature pattern, which requires costly and complicated MRI measurements parallel with the hyperthermia
treatments for control.
The physiological feedback of the large volume temperature equalizing is the increased blood-flow. The high blood-flow promotes the glucose influx (delivery), and supports the malignant proliferation by this supply. The increased temperature anyway gains the metabolic rate and the proliferation even by the cells in dormant (G0) phase. The higher blood-flow creates other malignant danger too: the risk of the forced disseminations and metastases, decrease the prognostic factors of survival of the patient.
The well-focused local hyperthermia treatment creates a competitive pair of effects: killing the tumor-cells by heat and support them by nutrients together with the risk of dissemination. The result of this competition is unpredictable and depends on the patient and on the applied techniques as well. The explanation of the controversial results of local hyperthermia in oncology may be simple: a reference point was missing, [51]; the temperature is not a correct reference.
The present main-stream thinking of oncological hyperthermia is a typical loss of aims by illusions, believing the overall control of temperature. The temperature however is only a condition for the treatment and not its aim. The question "Tool or goal?" has become relevant to study the temperature alone. Take a simple example of mixing the tool and the goal in our everyday life: the graduation is a tool for our professional life, however when somebody regards the certificate of studies as a goal, its application, the aim of the study is lost. Mixing the tool with the action creates false goal in hyperthermia application: increase the temperature alone. This "auto-suggestion" creates such a situation in which magnetic resonant imaging (MRI) is applied to control the temperature during the treatment instead of using this capable imaginary method to see what is happening in the tumor indeed.
Our tasks are finding the correct heating and control the hyperthermia process. For this we have to precisely select the malignant cells and we must not heat up all the materials in the targeted tumor, only the membrane of the cancerous cells. This selected nanoscope energy-absorption liberates not as much heat energy which heats up all the mass equally, so its efficacy could be significantly higher. The main advantage however is its independent action from? the physiologic feedbacks, no contra-action starts to compensate its effect.
Furthermore, the membrane excitation could excite special cellular signal-transduction pathways, which are connected with the natural apoptotic cell-death, and so the negative feedback loop of the complex living system is supported. (The conventional hyperthermia by its overall heating excites negative feedback mechanisms act against the temperature growth, so the system starts "fighting" against the healing process.)
The temperature as the average of kinetic energy in the system has a double role in the control of the heatabsorption.
It characterizes the heat-absorption, when the heating is homogeneous (see before), and its gradients (non-homogeneities) are the driving forces of the dynamic processes in case of microscopic (non-homogeneous) heating. The average temperature does not inform us about the distribution of the real energy-absorption (see Figure 1.).

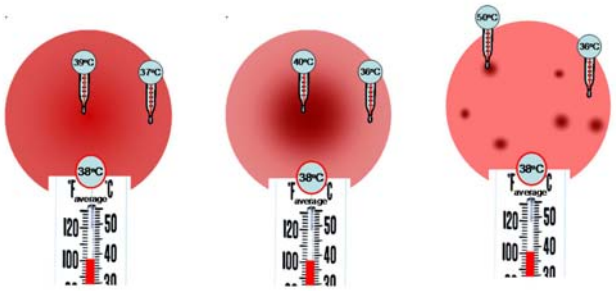

Figure 1. The average temperature is not able to characterize the thermodynamic situation. The internal temperature differences could serve as driving forces of various processes on the same average temperature of the system

Method

The efficacy of the energy depletion intended to be pumped into the tumor is limited by the energy loss outside the malignant target. The main factors of the useless energy absorptions are:

- The absorbed energy by the tissues transfers the effect to the deep-seated tumor.
- The heat-exchange by the blood-flow.
- The heat exchange by the heat-conduction from the tumor to the surroundings.

These heat-sinks modify the overall performance of the treatment and make the full heating process for the malignancy uncontrolled. The real effect, which is used for the intended treatment is less than the losses, and the efficacy is usually less than 25%, which is very low. The problem of this is not only that the large part of energy is wasted, but also the useless energy part could be dangerous by overheating the healthy tissues as well as increasing the metabolic rate and also having physiology reaction to this effect which tries to break the homeostasis. The massively heated tumor volume intensifies the control of physiology, and weakens the expected effect.

The adequate corrective actions for these challenges would be the more precise targeting, decreasing the losses in the surrounding and avoiding the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increas the efficacy:

- Apply the electric field as carrier of the energy, and that field cannot be compensated by homeostatic control.
- Apply a correct microscopic targeting, using the cell-by-cell energy-absorption efficiently.
- Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- Apply a mechanism, which carries info that disseminated cells have to be blocked.

Oncothermia changes the paradigm of local hyperthermia in oncology to solve the above problems [52].

This hyperthermia technology heats non-equally; concentrating the absorbed energy to the extracellularelectrolytes [53]. This method creates inhomogeneous heating, microscopic temperature differences are far liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis. The synergy of electric field with the thermal effects effectively and selectively does the job [54]. Oncothermia uses nano-heating technology to select and heats effectively the membrane of the malignant cells. The heating is concentrated mostly on the cellmembranes, so the nano-range energy-liberation could be precisely controlled without considerable wasted energy and without having disadvantages by the heating of the tumor-environment in average.

The general idea of microscopic heating is simple: the heating energy is not liberated in a sudden single step, but regulated and multiple small energy liberation does the same job, Figure 2. In our case, the forwarded energy selectively targets the most influential areas. Instead of the high, general energy pumping into the lesion, the energy is liberated at the membranes of the malignant cells.

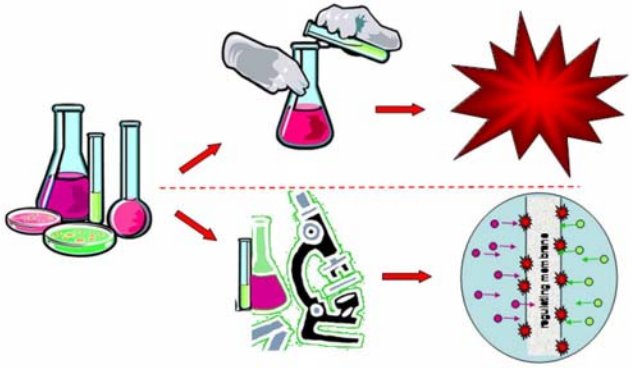

Figure 2. The difference of macro- and micro-liberation of energy. The efficacy of the last one is much better

The precisely targeted power and its efficacy are usually not connected. The microscopic effects, instead of the large energy liberation, is one of the most update thinking in energy source developments. The relatively low efficacy combusting engines are intended to be replaced by the fuel-cell energy-sources and electric motors, which are based on the membrane regulated microscopic reactions of gases. (Mostly hydrogen and oxygen gases are in use.)

Good examples are the standard incandescent bulb and the energy saving fluorescent ones, using a fraction of the power for the same light. The incandescent bulb creates light by high-temperature filament, which heats up the environment, having only 10% efficacy, while the fluorescent has more than 40%. It could be developed further by the higher nanoscopic energy-liberation, when not the molecules but the electrons are directly involved in the light-production. These are the LED bulbs, having more than 90% efficacy in producing light.

Oncothermia [55] is a kind of hyperthermia with nanoscopic heating processes. Instead of the undistinguished cells by the classical overall heating of hyperthermia, oncothermia nanoscopically selects and attacks the malignant cells. It has a simple setup. The modulated radiofrequency current (RF) flows through the targeted lesion, see Figure 3.

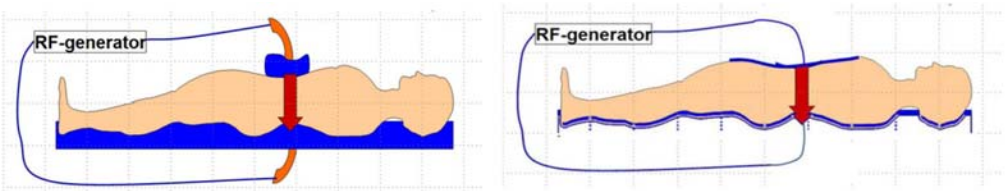

Figure 3. Oncothermia setup. The cell-culture/animal/human is a part of the electric circuit. Energy is carried by 13.56 MHz RF-current, (fractal-modulated) (a) EHY2000 local/regional treatment, (b) EHY3000 multilocal treatment

The radiofrequency current (RF-current) flows through the body and delivers energy to the malignant cells. The frequency is low (13.56 MHz) chosen to satisfy multiple requests:

- It is a free-frequency for medical applications in hospitals and clinics, as well as in general use of for example RF-identification.
- It is in the range of the beta-dispersion which is one of the selection factor of oncothermia.
- It is low enough to have long wavelength for near-field use with high penetration into the body when the impedance matching [56] is fixed.
- It is high enough to be modulated by time-fractal fluctuations.

The discussion of all these behaviors is seen below.
The current which flows through the chosen part of the body starts from one electrode and ends on the other one, periodically changing its direction according to the carrier frequency. The current is directed by the impedances inside the targeted volume, the current automatically flows to the "easiest" direction, where the conductance and dielectric conditions are optimal. Oncothermia uses three factors to direct the current to select malignant cells, i.e. those current paths which include malignant cells are favored. Certainly, the biophysical behaviors have to be studied to fix the optimum. The first selection factor is the well-known metabolic differences between the malignant and healthy cells. Due to the high energy demand of the malignant proliferation, the malignant cells metabolize more to supply their needs. Furthermore, the process to produce ATP differs in malignant cells from the normal ones. While the dominance of the mitochondrial ATP production characterizes the healthy tissue, when 36 ATP is produced from one glucose molecule during the complete cycle, the fermentative ATP production dominates the metabolism of malignant cells, only two ATPs are produced from one glucose molecule [57]. Consequences of this huge difference are enormous: the requested glucose influx of malignant cells is considerably higher, which is standardly measured by Positron Emission Tomography (PET). The considerable glucose consumption certainly produces high concentration of adducts, the extracellular electrolytes enriched by metabolites and lactates in the vicinity of the malignant cells, robustly enhances the ionic concentration in the connected electrolytes. The applied RF-current naturally flows with higher density in the areas where dense ionic conditions allow the easy flow, Figure 4. This could be measured by current density images with MRI [58], by simple impedance measurements in vitro [59] and in vivo too [60].

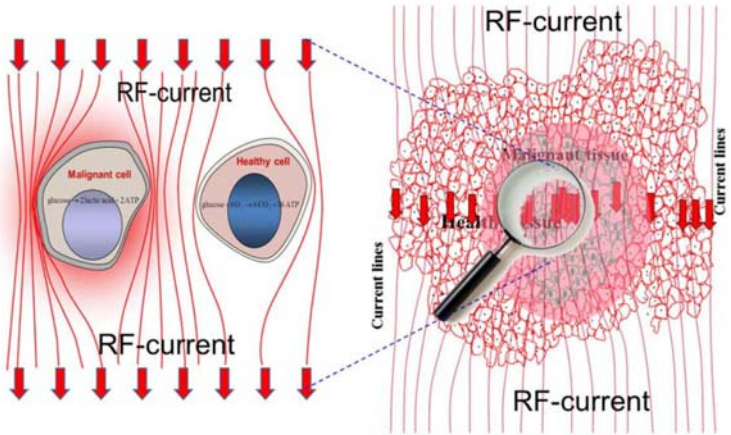

Figure 4. The radiofrequency currect is focused on the tumor lesion, and microscopically flows into the extracellular electrolytes around the malignant cells

This gives us a possibility to distinguish the malignant cells automatically and individually, see Figure 5. This automatic focusing makes it possible for the current density to follow any movements (breathing, heart-beats, muscle-movements) in the target tissue.

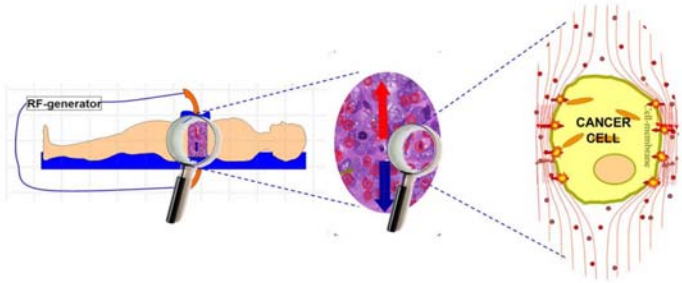

Figure 5. The microscopic heating of the extracellular electrolyte around the malignant cells excite the membrane and makes temperature gradient in a few nanometer distance

The above selection is based on the conductive component of tissue impedance. The permittivity component is also selective. Malignant cells differ from their healthy counterpart not only by their metabolic processes, but their collective behavior sharply identifies them. The malignant cells are autonomic, they are individual ”fighters”, having no collective driving of their activity, while the healthy cells have social signals [61]. These connections commonly regulate and control their life.
These cells are specialized for work-division in the organism, and their life-cycle is determined by the collective “decisions”. This requests definite order in the connective electrolytes. Indeed, the order was proven, [62], [63], [64], [65]. Contrary, the malignant cells which have no such order in their immediate extracellular connections, Figure 6. The disorder increases the electric permeability of the electrolyte near the malignant cells, [66]. The higher permittivity is also a selection factor, which is used to distinguish the malignancy by Szent-Gyorgyi’s cellular categories alpha- and beta-states, [67], [68].

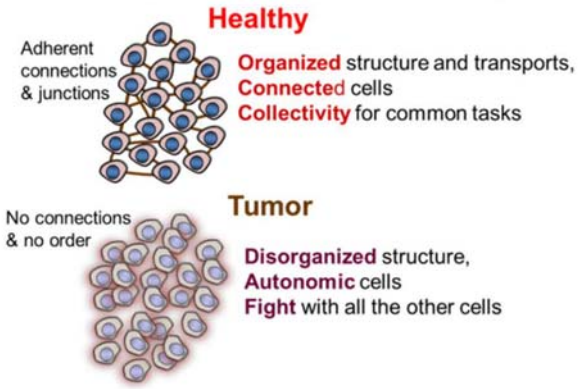

Figure 6. The difference of the healthy and malignant tissue is well observable by their organization structure

This dielectric differences are well completed by the specialties of the cell-membrane of the malignant cells.

- The efficacy of the ATP production in cancerous cell is low. The large ATP demand for the proliferative energy-consumption allows less ATP for active membrane stabilization by K+ & Na+ transport, so the membrane potentiating weakens [69].
- The cellular membrane of cancerous cells differ electrochemically also from the normal, its charge-distribution also deviates [70].
- The membrane of the cancerous cell differs in its lipid and sterol content from their healthy counterpart [71].

The membrane-permeability is changed by the above differences. In consequence of these the efflux of the K+, Mg++ and Ca++ ions increases, while the efflux of Na+ decreases together with the watertransport from the cell. Consequently, the cell swallows, its membrane potential decreases further [72]. (The efflux of K+ regulates the pH of the cell, takes the protons out from the cytosol.) The concentration of Na+ increases in the cytosol, and parallel to this the negative ion-concentration also grows on the glycocalyx shell, decreasing the membrane potential and the tumor will be negatively polarized on average, [73]. This fact was well used for direct current treatment (electro-

chemical cancer therapy (ECT)) by Nordenstrom [74], [75], and others [76], [77], [78].
There is a further selection based on complex impedance, the β -dispersion [79] (Maxwell-Wagner effect). [80]. The bound water to the membrane has the upper part of the β-dispersion, (denoted by δ, [81]), which has a further selection role in oncothermia. The treatments have to be chosen in the frequency-range of β-dispersion, promoting it with amplitude modulated pink-noise, expecting most of the changes in the complex system [82]. The carrier frequency and its modulation are selected by the membrane properties difference between the malignant and healthy cells [83], [84], [85].
Oncothermia selects by the above electromagnetic differences, and heats up the membrane of the malignant cells. The RF-current, which flows through the cancerous lesion is automatically focused by its lower complex impedance [86], it will flow mainly in the extracellular electrolyte (see Figure 7/a.), because the cells are electronically capsulated (isolated) by their membrane by more than one-million V/m fieldstrength. (The membrane is a good isolating lipid (fatty) layer). The membrane disruption is one of the targeted aims [87], [88], [89], so that is why many research groups deal with the electric field action on the cellular divisions [90], [91], [92], [93]. The main advantage of the electric field application is the missing control of the organism, physiology control over this effect; no physiology feedback limits directly the electric field, only its consequences could be regulated. The process made by oncothermia has its main energy delivery into the extracellular liquid, heating it up, and creating a little (1/1000 ^{o}C) difference between the inner and outer temperature of the cell. This looks only a small difference, but regarding the very tiny membrane layer (5 nm), the small difference in standard conditions is high: ~200,000 ^{o}C/m! The system is far from thermal equilibrium [94]. This starts a prompt heat-flow from outside to the cell through the membrane, and permanently acts till the temperature difference exists. Despite the quick heat-flow through this tiny membrane, the heat-current is long-lasting, till the full cellular interior is not heated up to the same temperature as outside. The not so high radiofrequency (13.56 MHz) is absorbed in all the electrolytes, but the main energy absorption is in the membrane and the extracellular electrolyte [95]. This creates an extreme SAR between the cells, which makes temperature gradient through the membrane [53]. The treated tissue will be inhomogeneously heated, the heat flows from the extracellular to the cytosol through the membrane, accompanied with definite other thermodynamical and chemical changes [53]. These definite thermal currents will be continued till the extra- and intracellular temperature reaches equilibrium, so the intracellular electrolyte is heated up to the equal level (see Figure 7/b.).

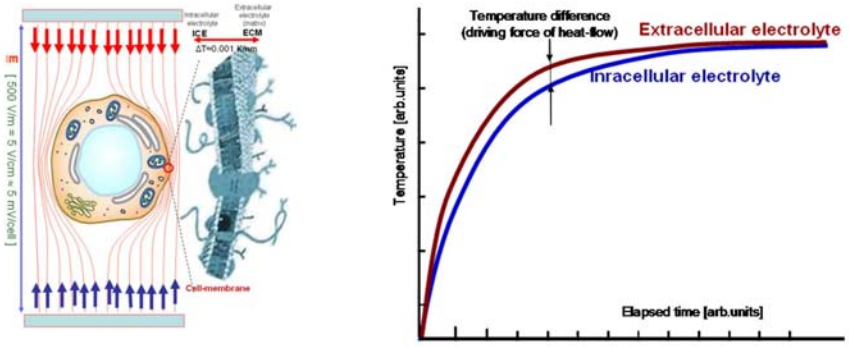

Figure 7. Oncothermia delivers its energy mainly into the extracellular electrolyte, creating a temperature gradient through the cellular membrane (a). The thermal gradient action due to the non-homogenous heating is active until the thermal equilibrium equalizes the temperature (b)

The cell killing needs energy, and afterwards the overall energy of the system would be decreased from a well ordered (bounded) state (which was in the case of the living cell) to a disordered chemical state with some broken chemical bonds. The transition from the ordered (chemically higher energy) state to the disordered (chemically lower state) arrangement of the well- known gap energy must be pumped. This gap-energy has different components. For hyperthermia, the heat energy gives the full energyconsumption, however, in oncothermia, a significant field effect takes part in the distortion mechanism [53].
This simple method allows easier cell-destruction by oncothermia, (see Figure 8.); similar to the wellknown catalytic reactions.

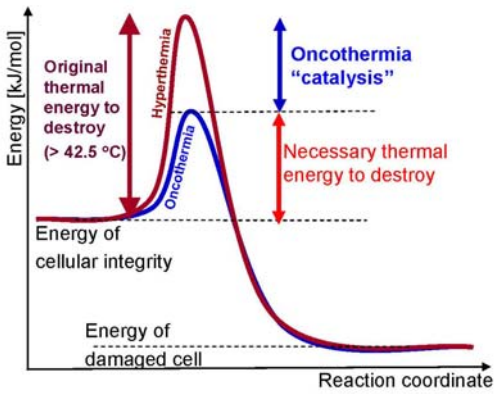

Figure 8. Oncothermia needs less thermal energy to make the same distortion as the classical hyperthermia does

The missing connections (adherent bonds, junctions) are selected not only by the dielectric properties of the cells, but they also affect the energy-absorption and the cellular protections against the energy overload. The absorbed energy by a healthy cell can easily be shared by the connections with the neighboring cells, damping the effect of the energy-overload. The malignant cells have no such possibility, the no network distribution could protect them from the energy-overload.

The large extracellular SAR makes not only thermal, but also the electric inhomogeneity in the tissue; the extracellular matrix has higher current density than the other electrolytes. The current density gradient is accompanied with the gradient of the electric field, which could reorient the high-dielectric constant proteins in the extracellular liquid. The orientation of these protein molecules would be constrained perpendicular on the membrane surface. By this effect, the lost adherent connections could be rebuilt between the malignant cells, which were indeed shown experimentally, [96]. This effect helps to suppress the metastatic dissemination and it also promotes the intercellular signals to activate the natural cellkilling mechanisms. Not only the heating makes the effect, but also the electric field itself has a strong synergy with this [97].

An important and unique specialty of oncothermia is the modulation of the carrier frequency. This timefractal pattern carried by the basic frequency distinguishes in similar way as the pathological evaluation does. The famous Adey-window was the first proof of the special modulation effects [98], [99], published in the early 1990s. The modulation of RF-carrier frequency started to be used [100], and became an important new method for cancer therapies [101]. Numerous clinical results show its efficacy [102], [103], [104], [105],[106], [107], and oncothermia has been applying it since the beginning. Biopsy specimens are evaluated by pattern-recognition of the experienced pathologist. One of the modern pattern-description is measuring the fractal dimension of the actual pattern. The malignancy has characteristic fractal dimension differences, the cancer has its own fractal structure, [108]. The analysis of fractal structures could even indicate the stage of the disease [109]. Careful fractal analysis can make predictive information, making a significant prognostic value, [110].

The fractals in patterns are accompanied by fractal dynamics. This new discipline is the "Fractal Physiology", ([111], [112], [113], [114]), which has a fundamental role in the structure of the healthy organism and is a basis of the self-similarity in biology, which is well-recognizable in the scaling behavior of the living objects, [115], [116], [117].The time fractal which characterizes the healthy tissue is the 1/f fractal-fluctuation. This is the modulation which we apply in the tumor-cure. The effect is simple: the system, which easily emits a frequency fluctuation can easily absorb it as well. So the applied modulation helps to localize the tumor-boarder, helps to "clear" the contours, and (most importantly) helps to select (self-focus) the energy-intake. Simply speaking, it works like the hammer on the drill, when you would like to make a hole in the concrete wall: it makes the action more effective. You may also switch off this modulation. Why? Because, you must not use the modulation in the sensitive organs (like the brain) from the very beginning. It causes head-ache and severe pain. In these cases from the third treatment the doctor starts the modulation in subsequently increased time, reaching the permanent modulation regime at the 8th treatment (if the patient has not complained). I propose to use the modulation in all the "usual" cases, but be careful when treating brain, spinal-cord, and head-and-neck cases. In non-tumorous applications the modulation has no role at all.

The fractal modulation, which is applied by oncothermia selects and re-establishes the apoptotic path-way functions. A day after oncothermia a definite difference can be detected between the anyway identical oncothermia treatments which are different only in the application of the modulation. Both

treatments cause the same effect immediately after the application, however a day later definite differences appear. The treated lesion by non-modulated signal started to re-grow, the ratio of dead-volume in the tumor decreased. At the same time the modulated treatment caused the opposite: the dead volume increased and in two days the complete tumor was almost destroyed after a single shot treatment reaching 42 °C in average in both the modulated and non-modulated cases.
Oncothermia selects the malignant cells and acts differently from the physiological homeostatic reactions (heat-flow on the membrane is supported by the electric field effects). It is natural, it is not against the homeostasis, physiology does not work against the action [118]. The main task is to direct the physiology in the standard way, and act on such normal line. The positive feedback loops (the avalanche effects), which may destroy the normal homeostatic equilibrium have to be stopped.

Results

Using the modern achievements of the physiology, oncothermia answers positively on the doubts about the conventional hyperthermia. The experimental and preclinical results are described in other articles presented in this conference [119], [120], [121], [122], [123], [124], [125], [126], so I summarize the clinical results only. Remarkable amount of retrospective and prospective clinical studies are available to indicate the oncothermia effect in humans [127], [128]. 62 studies were performed with altogether 3790 patients, from six countries (Hungary, Germany, Korea, China, Italy, Austria). The collection outlook is shown in Table 1, 2.

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)	Resposnding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of non-responding patients (m)
Brain studies	10	521	73.99	22.19	44.09	51.31	15.88
Pancreasa studies	6	184	47.04	11.02	53.05	28.09	7.58
Lung studies	5	636	64.76	15.79	25.73		
Bone	3	79		40.10	90.90		
Liver metastasis	7	267	86.00	18.06	80.00		
Colorectal	7	447			63.18	109.80	23.20
Gynecology (pelvic)	5	100	93.22	33.25	44.82	89.36	21.70
Breast	1	103	97.10	52.10	45.00	274.80	10.90
Esophagus	2	19	41.70	55.64	35.00	29.40	8.50
Somach study	1	68	58.90	14.40			
Kidney cancer	1	39	84.60	35.90	48.00	78.40	33.70
Urinary bladder cancer	1	18	85.00	36.50	73.00	42.00	22.60
Head and neck	1	64	92.20	26.10			
Soft tissue sarcoma	1	16	100.00	35.90	31.00	115.30	31.30
Prostate	3	135	88.90	38.80	72.00	53.40	7.60
SUM	54	2796			51.63		

Table 1. Collection of the studies (Phase II) made by oncothermia in combinantions with various conventional oncotherapies. (Data are wighted avarages of the study-results)

Miscelleonous Study	Number of patients (n)
Borreliosis	12
General oncology	277
TCM general oncology	306
Abdominal effusion	49
Peyronie's disease	25
Chronic pelvic inflammation	283
Asthma	7
Chronic bronhitis	35
SUM patients	994

Table 2. Collection of the miscellaneous studies made by oncothermia in combinantions with various other therapies

The survival time connected data, response rate connected data, the quality of life connected data, and tumor-maker connected data are collected in Tables 3, 4, 5 and 6., respectively.

Study	Number of patients	1st year survival (%)	Median overall survival (m)	Responding patients/ratio (%)	Median overall survival of responding patients (m)	Median overall survival of non-responding patients (m)	Reference
Brain gliomas	27	86.2	23.6	43	66.2	18.2	[129], [130]
Brain-glioma study Phase II,	140	71.7					[131], [132]
Astrocytoma	40		25.8	80	40.2	20.2	
Glioblastoma	92		16	73	21.*9	13.1	
Diffuse astrocytoma	8		52.9				
Glioma (WHO IV) Study, Phase II, prospective, two arms	45		15				[133], [134]
Passive arm	36	40	11				
Active arm	9	65	14.5	43	66.2	18.2	
Recurrent glioblastoma study, Phase II	19	68.0	21.8	59	32.6	12.4	[135]
Glioma study, Phase II,.	36	60.0					[136]
Astrocytoma	9		106				
Glioblastoma	27		20				
Glioma study, Phase II,.	179						[137]
Astrocytoma	53	100	103				
Glioblastoma	126	76	16				
Advanced, relapsed brain gliomas, Phase II	12		10	25			[138]
Advanced, relapsed brain gliomas, Phase II	24	55	12	25			[139]
Brain glioma WHO III-IV, Phase I, safety prospective	24						[140],[141], [142], [143]
Metastatic brain tumors study, Phase II	15	90.0	46.2	73	48.2	16.1	[138]
Head and neck study, Phase II.	64	92.2	26.1				**[133]**, [144]
Bone-metastases, monotherapy, Phase II	6	100	40.1				**[133]**, [144]
Refractory bone-metastases study, Phase II	11			90.9			[145]
Kidney cancer study, Phase II	39	84.6	35.9	48	78.4	33.7	**[133]**, [144]
Urinary bladder cancer study, Phase II	18	85.0	36.5	73	42.0	22.6	**[133]**
Non-small cell lung cancer meta-analysis.	311						[146]
Passive arm	53	26.5	14				
Active arm	258	67.0	15.8	21	53.4	18.1	
Non-advanced (WHO<III)	77		11	17			
Advanced (WHO≥III)	140		14.7	88			
Small-cell lung cancer	28						
Passive arm	9	29					[147]
Active arm	19	58					
Lung carcinoma study, Phase II	61	67.2	16.4				**[133]**, [148]
Breast cancers	103	97.1	52.1	45	274.8	10.9	**[133]**, [144]
Soft tissue sarcoma study, Phase II	16	100	35.9	31	115.3	31.3	**[133]**
Esophagus study, Phase II	12	41.7	28.5	35	29.4	8.5	**[133]**, [149]
Esophagus study, Phase II	7		6.8	100			[150]
Liver metastases from various origin, Phase II	25		20.5				[151]
Liver metastases from various origin, Comparative study, Phase II,	28						[145]
With radiotherapy	16			81			
With chemotherapy	8			38			
Monotherapy	4			25			
Liver metastasis form colorectal origin, Phase II,	80	86.0	24.1				[152]
Passive arm		53	11				
Active arm	80	91	24.1				
With chemotherapy	30	80	21.5				
Monotherapy	50	92	24.4				
Liver metastasis form colorectal origin, Phase II	15		23	80			[153]
Liver metastasis form colorectal origin, Phase II	22		28				[154]

Liver metastasis	29			86			
Liver metastasis form colorectal origin, Phase II	30		22				[155]
Pancreas tumor study, Phase II	26	46.2	11.6				[156]
Pancreas tumor study, Phase II,	107						
Passive arm	34		6.5				[148]
Active arm	73	52.1	9.93	58	25.5	8.4	
Pancreas tumor study, Phase II	30	31.0		41	34.4	5.6	[157], [158]
Pancreas tumor study, Phase II	42	52.4	12.3				[159]
Pancreas tumor study, Phase II	13	40.0	11.9				[160]
Stomach cancer study, Phase II	68	58.9	14.4				**[133]**
Colorectal cancer ()	218	84.9	28.5				**[133]**,
sigma	12			34.1			[144]
rectum	92			57.1	58	21	
colon	114			44.2	109.8	23.2	
Colon cancer study, Phase II, prospective, three arms, randomized	154						
Clifford TCM	53			75			[161] [162]
Monotherapy	50			81			
Combined therapy	51			91			
Rectum cancer study, Inoperable→operable, Phase II	7			71			[150]
Rectal cancer, non-operable, Phase II	65			96			[163]
Pelvic gynecological cancer studies, Phase II	74						
Cervix	38	86.8	27.6	25	63.5	20.9	[164]
Ovary	27	100	37.8	67	132.7	19.4	
Uterus	9	100	61.5	62	68.5	32.0	
Ovary, advanced, relapsed	26						[165]
Heavily pretreated	13		14.3				
Not heavily pretreated	13		27				
Prostate cancer study, Phase II	18	88.9	38.8	72	53.4	7.6	[149]

Table 3. Summary of the studies made by oncothermia treatment (End-points are survival connected)

Study	Number of patients	Complete remission (CR) [%]	Partial remission (PR) [%]	No change (NC) Stable disease (SD) [%]	Overall response rate (CR+PR+SD) [%]	Reference
Colorectal inoperable, liver metastasis	60					
CDDP	28	0	3.57	3.57	7.14	[166]
OXALI	32	0	15.63	15.63	31.25	
Ovary (relapsed, advanced epithelial	26					[165]
Heavily pretreated	13	0.00	23.08	38.46	61.54	
Not heavily pretreated	13	30.77	23.08	38.46	92.31	
General oncology	277		21.50	37.00	58.50	[167]
TCM general oncology	306					
Oncothermia + TCM	75	6.67	57.33	26.67	90.67	[168]
Oncothermia+TCM+i.v.CTx	65					
Passive arm	51	7.84	60.78	15.69	84.31	[168]
Active arm	14	14.29	64.28	21.43	100.00	

Oncothermia+TCM+bladder perfusion	37					
Passive arm	24	0	50	12.5	62.50	[168]
Active arm	13	7.69	53.85	30.77	92.31	
Oncothermia+TCM+RTx	42					
Passive arm	30	3.33	50	16.67	70.00	[168]
Active arm	12	8.33	66.67	16.67	91.67	
Abdominal effusion +oncothermia	49	4.08	53.06	16.38	73.52	[168]
Chronic pelvic inflammation	283					[169]
Passive arm	143					
Active arm	140	46.10	29.40	19.60	95.10	
Chronic bronhitis, TCM + oncothermia	35	30.00	24.30	25.70	80.00	[169]
Colon cancer study, , Phase II, prospective, three arms, randomized	154					[168]
Clifford TCM	53	5.7	28.3	18.9	52.90	
Monotherapy	50	10	26	26	62.00	
Combined therapy	51	13.7	45.1	23.5	82.30	
Colon operability	7	71			71.00	[170]
Prostatitis	72					[169]
Passive arm	36	16.70	27.80	19.40	63.90	
Active arm	36	41.70	36.10	22.20	100.00	
Prostate study	184	49.5	15.2	15.8	80.50	[171]
Prostate cancer (Kleef) (Gleason Score 2-6	16					[172]
Oncothermia +hormone therapy	8				50	
Oncothermia monotherapy	8				37.5	
Prostate cancer (Kleef) (Gleason Score 7-9	17					[172]
Oncothermia +hormone therapy	11				81.82	
Oncothermia monotherapy	6				33.33	
Peyronie's disease	25				100	
Pancreas	42		23.8	31	54.80	[159]
Pancreas	30	3.3	33.3	40	76.60	[157], [158]
Esophagus		8	50	42	100.00	[150]
CRC - liver	22	5		23	28	[154]
CRC liver	15		20	60	80.00	[153]
CRC liver Oxalyplatin	12				8.3	[155]
CRC liver cisplatin	18				27.8	
Advancer liver	28					[173]
Oncothermia + RTx	16		31	50	81	
Oncothermia + CTx	8		13	25	38	
Oncothermia monotherapy	4			25	25	
Brain	19		11	32	43	[135]
Asthma	7		75	10	85	[174]
Small-cell lung cancer (SCLC)	38		44.7	15.8	60.5	[175]
Benign tumors oncothermia+TCM	35	54.3	25.7		80.00	[169]

Table 4. Summary of the studies made by oncothermia treatment. (End-points are response connected)

Study	Number of patients	Pain-reduction [%]	increasing performances [%]	better overal QoL [%]	Reference
Colorectal inoperable, liver metastasis	60				
CDDP	28	17.86	39.29	57.14	[166]
OXALI	32	46.88	7.86	100.00	
Borreliosis	12		100.00	100.00	[176]
Abdominal effusion +oncothermia	49	88.88	73.91	85.70	[168]

Colon cancer study, , Phase II, prospective, three arms, randomized	154				[168]
Clifford TCM	53	37.7	13.73	58.49	
Monotherapy	50	36	23.53	60	
Combined therapy	51	58.8	62.75	86.28	
Prostate study	184				[171]
Prostate study	115		76.2	94.1	[177]
Colon operability	7		86	43	[170]
CRC liver	15				[153]
CRC liver Oxalyplatin	12	66.7		83.3	[155]
CRC liver cisplatin	18	11.1		27.8	

Table 5. Summary of the studies made by oncothermia treatment. (End-points are quality of life connected)

Study	Number of patients	Tumor-marker decrease [%]	References
Colorectal inoperable, liver metastasis	60		[166]
CDDP	28	14.29	
OXALI	32	37.50	
CRC liver Oxalyplatin	12	58.30	[155]
CRC liver cisplatin	18	5.60	

Table 6. Summary of the studies made by oncothermia treatment. (End-points are tumor-marker connected) Further clinical trials are in progress on advanced ovary, esophagus, breast, and pancreas tumors

Conclusion

Oncothermia is the cellular selective, highly effective nanoscopic heating of malignant cells. It is a feasible treatment for oncology in all phases of malignant diseases. This nanothermia application solved the uncontrolled controversies of the conventional hyperthermia in oncology. Numerous new ways of research can be initialized by the presently achieved results. Further basic research and clinical studies are in progress.

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Burden of oncothermia – Why is it special?

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Burden of oncothermia – Why is it special?

Abstract

There are many contradictory opinions about conventional hyperthermia in oncology. The main points are the physical, technical imperfection of classical heating, as well as the limits of the natural physiological feedback of the organism. We would like to present the definitive differences between oncothermia conventional hyperthermia, explaining the new line of problem-solving in this important field of oncology.

Keywords: hyperthermia, oncothermia, nanotheremia, non-equilibrium, modulation

Problem

General opinion among the specialists, that the physics limits the deep heating [1]. The limit is formed by the heat-conduction and other thermodynamic factors. The imperfect thermal conditions are combined with insufficient electrodynamic facilities to concentrate the energy focused in depth. This skimpiness appears in the unwanted hot-spots and the overheated surface when the actually necessary energy is pumped through.

Some experts evaluated the situation a bit differently, blaming the biophysical, physiological factors having technic inefficiencies. According to this position the physiological negative feedbacks seeking to reestablish the thermal homeostasis are blocking the proper job, [2].

Certainly, both the physical and physiological deficiencies are involved in the hindrance of the success and probably it is accompanied with a factor of improper references also. In case of comparison of various heating methods the only one factor is measured as relevant: the temperature in the targeted volume. However, this reference has various complex shortages and could lead to misleading consequences. The high temperature ablation in a small volume for short time cannot be compared with a longer time local or regional heating or even less comparably with the whole body heating on the same temperature. When a local or regional heating reaches 41.5 °C homogeneously in the target that could be a therapeutic indicator of success, but the same homogeneous temperature reached by whole-body treatment gives completely different results, and also the expectation of the expert therapist is different. The temperature alone is not a reference point [3], because the physiological conditions modify the actual state even when the temperature is equal. Typical example is the difference of the blood-heating approaches and tissue heating ones. In blood-heating cases (e.g. limb perfusion, subcutane radiative heating), the hot blood heats up the tumor. In case of the tissue–heating the blood remains cold (stays on body temperature). This difference makes huge deviations in the thermal and physiological actions: in the first case the heat flows from the blood to the target, while in the second case it is completely the opposite. In the first case the static thermal equilibrium can be reached after a definite time, while in the second case the thermal equilibrium remains dynamic always, the heat-flow is always active from the heated volume to the other body-parts by the blood-flow. In this second case the heated volume (tumor) is a hot heat-source to heat the body up. Measurement of the intensive thermodynamic parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)

The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept. Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead of its elimination. (These processes: like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.) Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

When the temperature is not enough then the standardly used absorbed energy (specific absorption rate; SAR), could be the solution. However, this is again problematic. Due to the variability of the blood-flow of the parts of the body, the same SAR could heat up the same volume to completely diverse temperatures. The actual blood-flow cools down the target and sinks the energy by indefinite level,

because the bloodflow is non-linearly controlled by the physiologic feedback system.
In consequence, the simple temperature characterization of the therapy has numerous problems, like

- Temperature heats up the vicinity of the tumor, it can not be kept locally focused,
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.),
- Temperature requests the increase of the safety-cooling on the skin,
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely,
- Temperature increases the blood-flow in the region, in consequence increases the dissemination,
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy,
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemo-penetration into the tumor (vasocontraction or blood-vessel blockage in the tumor),
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues),
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient.

Additionally to the temperature as reference we have challenges from the variation of the patient's individual behaviors. We have to calculate not only the physiology of the patient, but the psychology as well, not forgetting, that the treated body-part organ belongs to somebody. The personal differences are modified by the previous treatments and tolerances, and by the personal tolerance limits. Most of the decisions in serious cases need medical experience, we not apply automatically the prescribed protocols formulated for average patient.

Solution

The physiology is an interdisciplinary subject, it applies numerous principles and discoveries. The electronic structure approach of solid state physics (e.g. Szent-Gyorgyi, [4], [5]), the superconductivity (e.g. Cope, [6]), the electromagnetism (e.g. Liboff, [7], [8]), the thermodynamics (e.g. Schrodinger, [9], Katchalsky & Curran [10]), etc. are all parts of the physiology, and make it really complex as the phenomena of life itself is. The living organism develops itself, rearranges, reorganizes the incoming chemicals and builds up its own structure, consequently lowers the entropy. Various modern approaches are developed in the last decades on this complexity, like self-organization ([11], [12], [13], [14],), fractal physiology ([15], [16], [17], [18]), and the bioscaling ([19], [20], [21]). These modern achievements are used for solutions of the above problems of hyperthermia in oncology.
There are special biochemical and biophysical changes caused by the above differences of the malignant cells and used for oncothermia specialties:

- their extracellular matrix has different concentration of ions [22], which can be measured by positron emission tomography, PET[23];
- they have different conductive behaviors [24] which can be measured by electroimpedance tomography (EIT) [25];
- their electromagnetic environment (how they conduct the electromagnetic currents and waves) is different, [26], [27]. This can be measured by Cole-Cole impedance measurements [28].
- order of their electrolyte (aqueous solution) differs, [29]. The healthy tissue has ordered water-states [30], in extracellular matrix [31], [32], while malignancy decreases the order of the electrolyte matrix, decreasing the cell-cell adhesion promoting the proliferation [33].
- The dynamical process has special self-organization [34], forming special structures [35], [36], bioscaling [37], and noise spectrum [38], which certainly differs in cancerous state. The information to recognize the tissue is well coded in the order of those [39], [40].

The solution of the problems of conventional hyperthermia is the nanothermia, it targets the cellmembrane of the malignant tissue, and do not waste the heat (energy) to the volumes which are irrelevant in the point of view of destroying the malignant cells. This nanothermia heating (concentration of nanoscopic range of the target) is the oncothermia [41], using the distinguished points of the

differences between the malignant and healthy cells. The clue to find the mechanisms, which could create the requested optimization, selection and control of the energy intake is based on the clear biophysical differences between healthy and cancerous cells, finding the biophysical property to focus the energy on the desired cellular membranes. The hyperthermia is macro heating, it heats a given volume of the target equally, and distributes the SAR in conductive and convective ways. The result is that the heated volume will be a massive heat-source to elevate the temperature of the complete neighboring tissues, unselectively.
The efficacy of the energy depletion intended to be pumped into the tumor is limited by the energy loss outside the malignant target. The main factors of the useless energy absorptions are:

- The absorbed energy by the tissues transfers the effect to the deep-seated tumor,
- The heat-exchange by the blood-flow,
- The heat exchange by the heat-conduction from the tumor to the surroundings.

These heat-sinks modify the overall performance of the treatment and make the full heating process for the malignancy uncontrollable. The real effect, used for the intended treatment is less than the loss, and the efficacy is usually less than 25%, which is very low. The problem of this is not only that the large part of the energy is wasted, but also the useless energy part could be dangerous by overheating the healthy tissues as well as increasing the metabolic rate and also gives physiological reaction on this effect which tries to break the homeostasis [42]. The massively heated tumor volume intensifies the control of physiology, and weakens the expected effect.
The adequate corrective actions for these challenges would be the more precise targeting, decreasing the loss in the surroundings and to avoid the physiological corrections to suppress the desired effect. To construct the solution some new effects have been used to increase the efficacy:

- Apply the electric field as carrier of the energy, and that field cannot be compensated by homeostatic control.
- Apply correct microscopic targeting, using the energy-absorption cell-by-cell efficiently.
- Apply such mechanisms, which initialize natural effects to kill the malignant cells.
- Apply mechanism, which carries info for disseminated cells to be blocked.

Oncothermia uses these new approaches to fit it for the best curative performance. This new approach (the fractal physiology) is applied for oncothermia. The carrier electric field is delivering the time-fractal structure to the tissues, enhancing considerably the selection between the connected healthy cellular community and the individual autonomy of the malignant proliferation. In this application there is no considerably heat-flow to the blood-stream, no gain of the feedback of electrolyte balancing-loop. Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, it does not constrain for false defense. Thermal gradients make dynamism in a very local area of the cell-membrane of malignant cells. The applied selection focuses on this thermal nonequilibrium.
The applied fractal modulation [43] makes possible the selecting and supporting of the natural processes to activate the natural healing mechanisms and reestablish the healthy “social signal’ between the isolated cells, promoting the anti-malignancy collectivity. The carrier frequency delivers the information (modulation frequencies), for what the cancer cells are much less “transparent” than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy. What makes the difference on the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special “social” signals [44] commonly regulating and controlling their life. They are specialized for work-division in the organism, and their life-cycle is determined by the collective “decisions”. The cancerous cells behave non-collectively; they are autonomic. They are “individual fighters”, having no common control over them, only the available nutrients regulate their life. The order, which characterizes the healthy tissue is lost in their malignant version, the cellular communications disappeared [45].
By modulation the cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination. Selection is solved on cellular level suppress the dissemination of the malignant cells. The method is similar to the process when the light goes through the windows-glass. When the glass is transparent to that specific set of colors (visible light, definite interval of frequencies), its absorption is almost zero, all the energy goes through it. However, when it has any bubbles, grains, precipitations etc. those irregularities will absorb more from the energy, their transparency is locally low, their energy absorption is high, they are heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. Cellmembrane permeability is increased by the nanothermia process, expressing the HSP on the outer

membrane signalizing the cell malignancy for the systemic immune actions. Cell-membrane is excited to ignite various communication pathways in the cells. Relatively slow "step-up" heating keeps the non-equilibrium conditions stable for long time for action. Advantage of the step-up heating protocol is that it does not create considerable physiological contraactions, the slow heating makes the healthy tissue adapted to the growing temperature, and does not generate high stress and following stress-reactions. Oncothermia is mainly regulated by the patient's tolerance. Its control is based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoiding to burn the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient's natural defending/protective system.

Oncothermia heats the target like the fuel cells liberate the energy. The selection of malignant cells is made by their metabolic activity according to Otto Warburg [46], a Nobel-Laureate in Physiology. Warburg recognized the metabolic difference between the malignant and healthy cells: the malignant cells have much higher flux of glucose than their healthy counterparts do. The higher glucose metabolism needs larger ionic fluxes in the vicinity of the individual tumor-cells. The RF-current, which flows through the cancerous lesion, automatically focused by its lower impedance, will flow mainly in the extracellular electrolyte, because the cells are electronically capsulated (isolated) by their membrane by more than one-million V/m field-strength. (The membrane is a good isolating lipid (fatty) layer). The membrane disruption is one of the targeted aims [47], [48], [49], as well as many research groups are dealing with the electric field action on the cellular divisions [50], [51], [52], [53]. The main advantage of the electric field application is the missing control of the organism, there is no physiologic sensor and control of this effect. No physiologic feedback limits the electric field directly, only the consequences of its action could be regulated. The process made by oncothermia has its main energy delivery into the extracellular liquid, heating it up, and creating a little (1/1000 oC) difference between the inner and outer temperature of the cell. This is only a small difference, but regarding the very
tiny membrane layer (5 nm), the small difference in standard conditions is high: ~200,000 oC/m! The system is far from the thermal equilibrium [54]. This starts a prompt heat-flow from the outside to the cell through the membrane, and permanently acts till the temperature difference exists. Despite the quick heat-flow through this tiny membrane, the heat-current is long-lasting, till the full cellular interior is heated up to the same temperature as outside.
The large extracellular SAR makes not only thermal, but also electric effects in the tissue; the extracellular matrix has higher current density than the other electrolytes. The current density gradient is accompanied by the gradient of the electric field, which could reorient the high-dielectric constant proteins in the extracellular liquid. The orientation of these protein molecules would be constrained perpendicular on the membrane surface. By this effect, the lost adherent connections could be rebuilt between the malignant cells, which were indeed shown experimentally, [55]. This effect helps to suppress the metastatic dissemination as well as promoting the intercellular signals to activate the natural cell-killing mechanisms.
Development of the thermo-tolerance, such as heat-shock protein (HSP) production [56], is one of the suppressors success of hyperthermia, [57]. From the point of view of the thermo-tolerance, one of the most prominent chaperone proteins is the HSP72. The concentration of this HSP is 5-10 times lower in the healthy cells than in the malignant ones, [58]. However, responding to the heat treatment, their concentration in healthy cells became 8-10 times higher, while the same heat treatment of the HSP72 multiplication creates only 1.2-1.5 times higher concentrations in malignant cells, [58]. Oncothermia is a highly personalized, energy-dose dependent, nano-scale heating technology, which can solve all the debated problems of the conventional hyperthermia. Oncothermia uses higher thermal load on cellular membrane than any other hyperthermia can do, but its physiological feedback remains low, due to the nano-scale capability of the treatment. Also the excited apoptotic pathways, reestablished adherent connections and controlled abscopal effect makes the job.

Oncothermia is personalized; the heat delivery has numerous important physiological controls. The objectivity of the treatment definitely depends on the radiofrequency current and its gained voltage on the given impedance on the tumor. This current is well-regulated by the skin-conductance and by the connected physiological changes. The inconvenient feeling of RF-heating defines a pain-limit, which depends on many objective and individual factors. A good approach is to regard the nerve-cell sensitivity objective (the cellular processes are well unified), and regard the personal differences as influence of physiological factors. The main factor for heat-sensitivity are the blood-perfusion and blood-flow in the subcutaneous layers where the heat-sensing nerves are located. The high blood-flow is an effective heat

exchanger, it cools the given volume, and the nerves tolerate higher energy-flow through the layer. The high blood cooling is not only the facility to have higher energy-flow, but also to get more current through the volume. The higher current density excites the nerve-sensing, and the feeling again is an overheating, requests down-regulation. In case of low blood-perfusion the current is small, so the nerves can tolerate more intensities than in any other situations. The crucial point is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature is kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. A detailed mathematical model has been worked out for this regulation mechanism, and applied in oncothermia treatment.

The other factor is connected to the psychological interaction with the treatment process as well. In any protocols, when the temperature is described as a dose, then the required temperature cannot be achieved. Then of course it is forced by the power, so the incident energy is not limited in this case. In fact, the opposite reaction has to happen: if the patients cannot tolerate the prescribed power (and required temperature), then a lower one has to be applied. The pain in the body depth is independent of the temperature sensing nerves, the pain there has other mechanisms, which are not part of the prevention of damage (like the temperature sensing), but sensing the actual damage itself. Consequently, blocking the surface heat sensors is a high risk factor, which is never made in oncothermia therapies.

While the temperature has physiological blood-flow response, the current (electric field) has no such homeostatic regulation, it has only pain-response from the skin. This pain tolerance is constant (saturated) at 13.56 MHz [59]. This allows an objective pain sensing by the current, which depends on the thickness of the adipose layer. This creates negative feedback signal: when the fat is thick, the temperature grows and makes a temperature pain limit which increases the blood-flow by vasodilatation by step-up heating. The current in this way grows, but when the blood-conductance becomes too high, the pain from the current will limit the process again, and controls the personal merit, which is pretty objective due to the saturation of the current sensing.

Conclusion

Oncothermia is a feasible method to treat any solid malignant tumors, irrespective its primary or secondary status and irrespective of the advanced stage of the disease. The only two parameters which are considered as useful for measuring the treatment efficacy: the survival time and the quality of life.

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Oncothermia application for various malignant diseases

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Oncothermia application for various malignant diseases

Abstract

Oncothermia was introduced to our hospital in 2010. Our objective is to report results of 277 patients treated by oncothermia during 20 months. We present some characteristic cases and statistical study of the overall results. We concluded state the feasibility of oncothermia to treat high variety of malignant diseases also in their very advanced (T4N3M1) stages.

Background

Hyperthermia is a long time used treatment in oncology, having debates about its applicability and working mechanisms. There are numerous technical solutions [1], [2] but the results are mostly controversial like the cervix studies are, (the positive [3] and the opposite effect [4] of hyperthermia was published). The basic problem is the missing control, due to the simple fact of the focusing possibilities. The sophisticated technologies are concentrating the localized and focused energy to the target, however the temperature is distributed from any sharply focused volume, naturally trying to be equalized in its neighborhood. The smearing of the temperature is accelerated by the physiologic feedback to cool down the specially heated volume by the extra blood-flow in the heated part of the body [5], [6]. The extra blood-flow naturally supports the tumor by nutrients (mainly glucose) and increases the risk of dissemination. The focusing and heating mechanisms are certainly different in various kinds of technical solutions, which reflects on the problem of the standardization, no reference point exists [7].

Method

Avoiding the controversies, oncothermia was used in our study. Oncothermia has realized the root of the problem: impossibility to localize the temperature in the desired volume. The solution was the nano-heating technology. Oncothermia selects and heats up very locally (in nanoscopic range) the membrane of the malignant tumors, [8]. This effect excites important pathologic pathways to promote apoptosis [9], and overcome on the main problem of the technical challenge by large energy intake but on a very well localized place. It needs 60 min to reach the general temperature equilibrium, which is the time of the active oncothermia session. The oncothermia in this line is working permanently by thermal non-equilibrium conditions. We collected all patients (n=277) who had at least one oncothermia treatment in time-interval Nov.2010 – July 2013 (20 months). The patient group had nM=125 males and nF=152 females. Average age was 53 y [7-84 y]. The various diseases and the number of patients involved in the study were heterogeneous, (see figure 1.) aiming to check the efficacy on the wide range of diseases and stages.

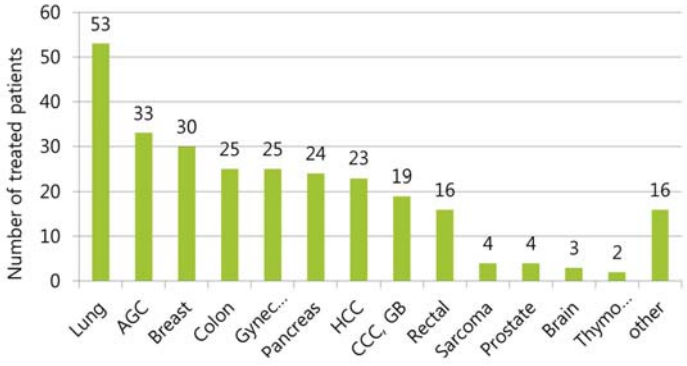


Figure 1. Diseases and the patients number who were involved in the present study

Major target areas were Lung 53, Stomach 33, Breast 30 and Colon 25. We assume the reason why lung cancer was the highest number. It is not only because lung cancer is the most common cancer in Korea but also other area's cancers easily metastasize to lung.

The treatment had step-up heating protocol [60W□150W], using 20 cm and 30 cm diameter electrodes. The step-up grades were fit by personalization, with careful control of the actual patient. Oncothermia

was applied 1~4 times a week (figure 2.). 47.9% of the patients got 3 times a week and the cases of 4 treatments a week was on multiple locations.

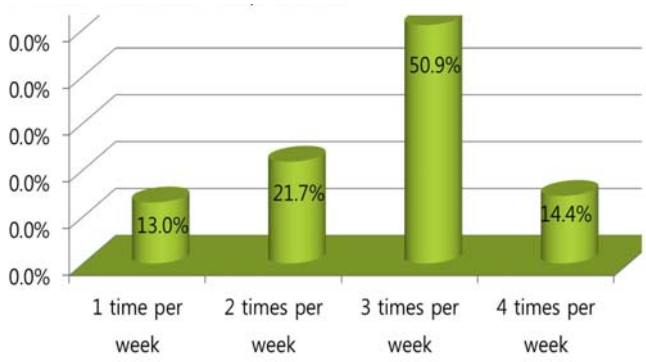


Figure 2. Distribution of the frequency of the oncothermia treatment

Oncothermia was applied in complementary combination with various chemo- radio-therapies, as well as trimodal (chemo-radio-thermo) application was also used. A certain part of the patients, where standard therapies were not applicable due to various reasons, had oncothermia monotherapy, (figure 3.) 38.3% of patients who received Oncothermia was concurrently treated with Immune Therapy or Orthomolecular medicine within the same hospital. 45.5% received chemo therapy, 5.8% received radiation therapy and 10.5% was with both chemo and radiation therapy. Oncothermia as monotherapy was applied to patients who were not in good condition to get other therapies.

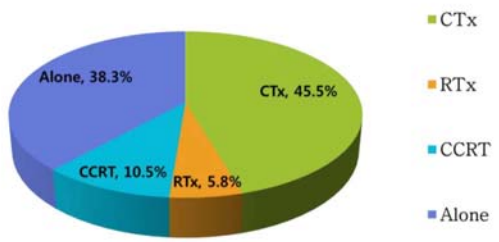


Figure 3. Oncothermia complementary to standard treatments. (CTx – chemotherapy, various kind; RTx – radiotherapy various kind; CCRT – concurrent chemo-radiotherapy various kind; alone – oncothermia monotherapy

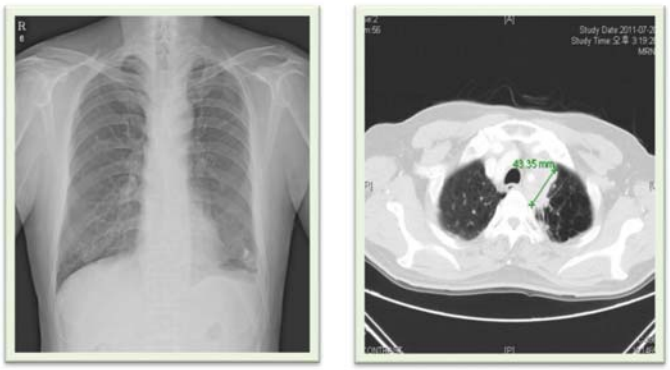
Distribution of the cumulative treatment numbers was heterogenic. 49% of the patients received less than 12 times, 24% was less than 24 times, 14% less than 36 times and 13% more than 36 times oncothermia treatment. The highest number was more than 200 times in a year, handling the fatal disease as chronic.

Case reports

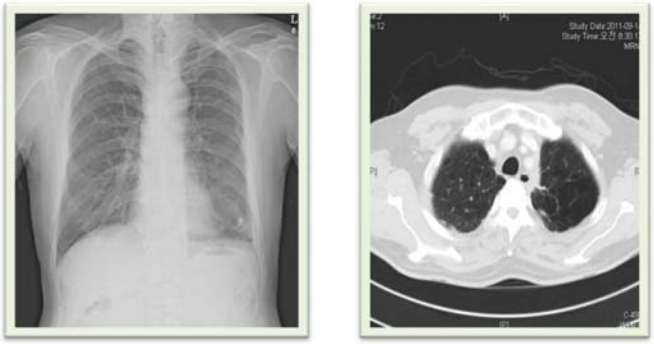
We show some characteristic case reports which are well demonstrating the forceful feasibility of oncothermia applications.

Small-cell lung cancer

A 66 years old male patient was diagnosed with small cell lung cancer in June 15, 2011. He received chemotherapy EPS #2 and oncothermia twice a week in one cycle. On September 14, 2011 good partial remission (PR) was observed.



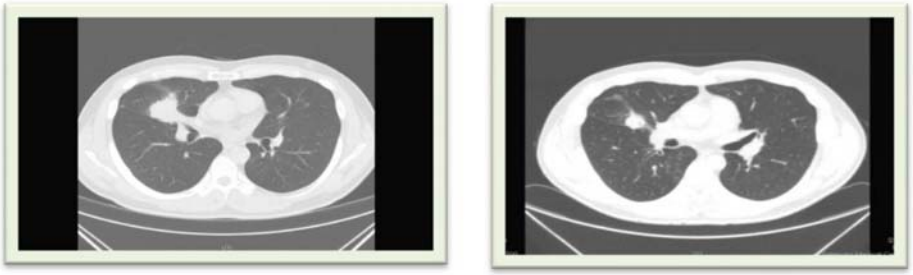
Before the complex therapy with oncothermia



After the complex therapy with oncothermia

Non small-cell lung cancer

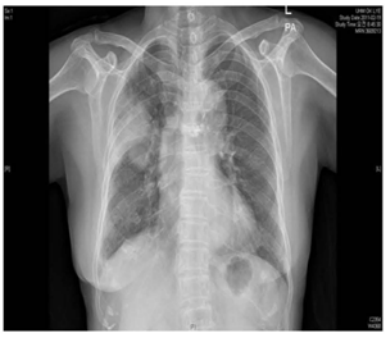
Non-small cell lung cancer was diagnosed in July 13, 2011 at the 40 years old male patient. He was treated with chemotherapy Iresa from August 2, 2011 and with oncothermia twice a week (10 times). Good partial remission (PR) was diagnosed in September 14, 2011.



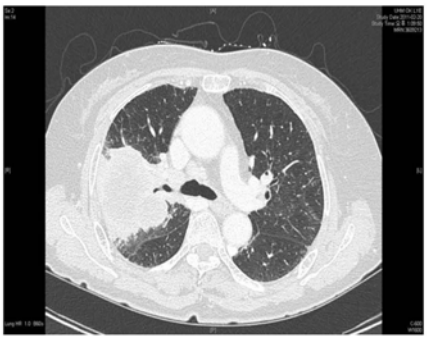
Before the complex therapy with oncothermia *After the complex theray with oncothermia*

Advanced non small-cell lung cancer

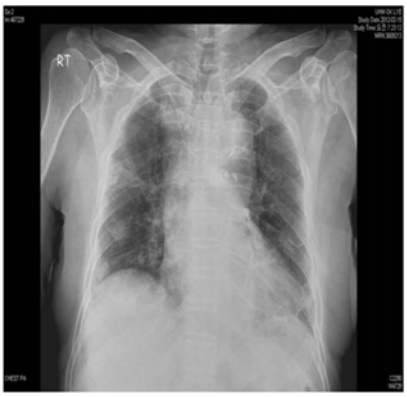
The 68 years old female patient was diagnosed with stage IV. non-small cell lung cancer. Stage cT4N2M1a, pleural seeding. She received chemotherapy 15th CTx (Paclitaxel and Cisplatin) from 02 March, 2011 to 15 February 2012. She also received 4 cycles of oncothermia. Good partial remission (PR) was observed in 09 May, 2012.



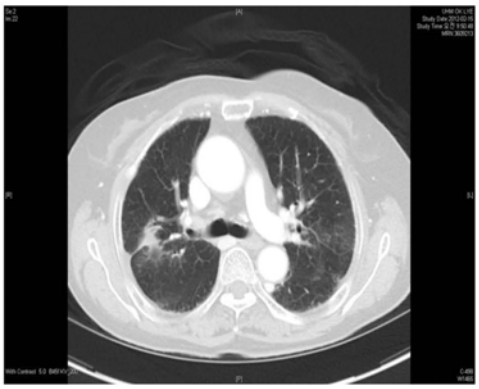
Chest PA before therapy (19 February 2011)



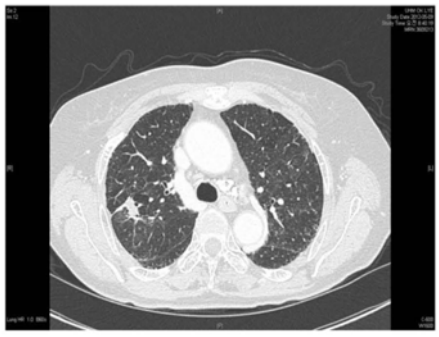
Chest CT before therapy (20 February 2011)



Chest PA during therapy (15 February 2012)



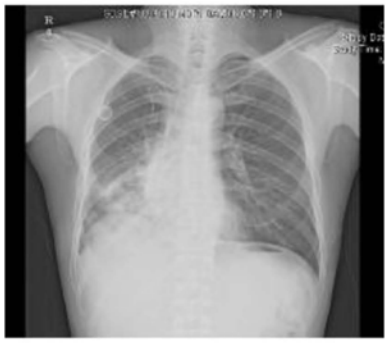
Chest CT during therapy (15 February 2012)



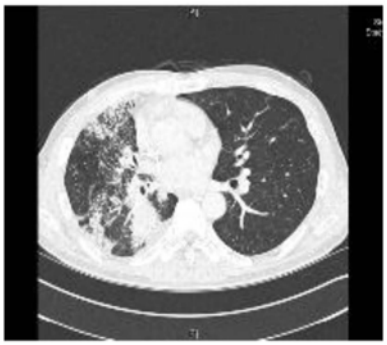
Chest CT after therapy (09-May-2012)

Advanced adenocarcinoma of lung

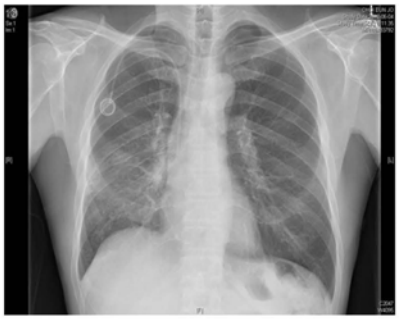
48 year old male was diagnosed with adenocarcinoma, stage IV lung cancer (cT4N3M1b). He received chemotherapy S/P 8th. CTx. -[Vinorelbine + Cisplatin] (07-July-2011~ 01-February-2012) and oncothermia complementary. Post-treatment Tarceva is being taken, also it is applied currently. Good partial remission (PR) was observed on 04 June, 2012.



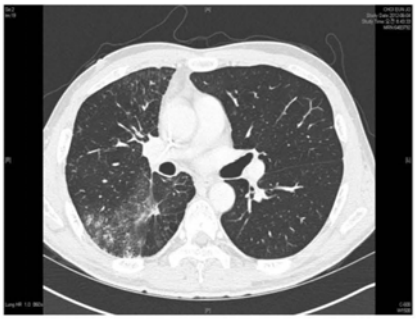
Chest PA before therapy (25-01-2012)



Chest CT before therapy (08-02-2012)



Chest PA after therapy (04-06-2012)



Chest CT after therapy (04-06-2012)

Study results

The half of the patients who was treated, was not evaluated, due to the therapy is in progress. The clinical response for all the patients (n=277) is shown of Figure 4.

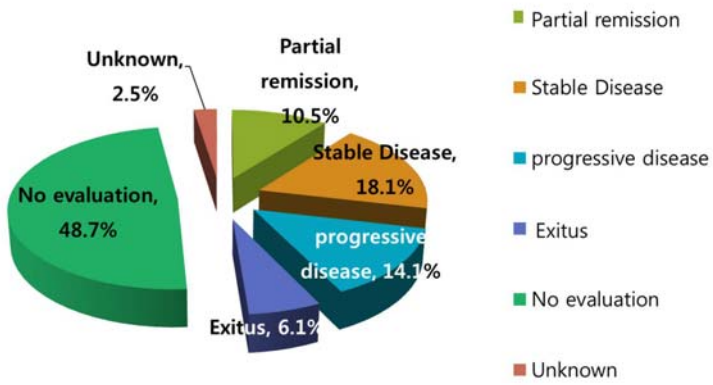


Figure 4. Clinical response for all the patients who was treated with oncothermia at least one times

The clinical response of the evaluated patients (n=142) shows more than half of the patients responded (Figure 5.). We analyzed the Oncothermia treatment results based on the CT images taken after the treatments. But only 52% of the entire group was subjected to result analysis. 48% was not traceable. The result of the 52% was, 21.5% PR, 36% SD, 28.9% PD and 12.6% exitus. So 58.5% of the patients showed either stable disease or partial remission. Given this was applied for end stage patients, this is very encouraging result.

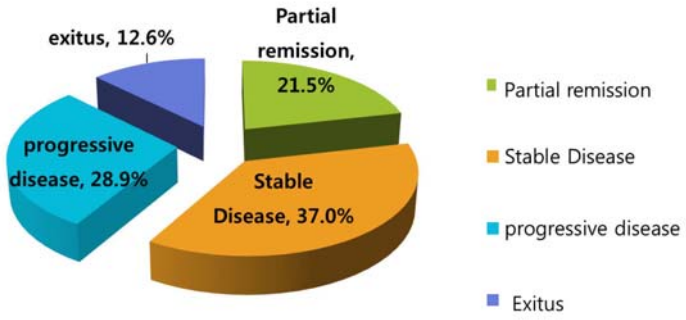


Figure 5. Clinical response of the evaluated patients (n=142)

No adverse effects were observed during the study.

Conclusion

As a conclusion, despite of being small number group and relatively not long period, it seems that oncothermia is feasible good therapeutic modality for the patients with end stages, who can no longer receive standard therapies.

Moreover, apart from the end stage patients, we observed improvement of the quality of life of the treated

patients, and we expect that oncothermia will show good result for general condition, pathological stage on early stage patients too. We expect increase of QoL and enhance of the clinical remission rate and to reduce of the frequency of recurrence and metastases.

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Cases that respond to Oncothermia monotherapy

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Cases that respond to Oncothermia monotherapy

Abstract

There is a long history of hyperthermia in oncology, but its wide range acceptance and application is missing even today. A new approach of oncological hyperthermia, oncothermia, looks promising modality of the complementary treatment of advanced malignant cases. Our present article is targeting this method, trying to answer on the question of its feasibility to treat various advanced cases in monotherapy process, as well as its applicability for a long, large number of treatment sessions protocols.

Background

Despite the hyperthermia was among the very first medical treatments in human medicine, this approach has ambivalent evaluation as a therapy. Hyperthermia is one of the most common therapy in "house" applications, a part of the "popular wisdom" of the traditional medicine. Heat is applied according to unwritten traditions in every culture. Heat treatment has high popularity in Korea for various preventive or curative intentions. It is applied for simple prevention or "cure' of common cold, applied to still various pains (joints, muscle-spasms, various orthopedic problems, etc.). Heat is applied for better overall conditions and for simple relaxing, or sometimes for spiritual reasons. The various heat therapies are commonly used complementary with natural drugs (tees, herbs, oils, aromas, etc.) or with natural radiations (sunshine, red-hot iron radiation, etc.) This popular medicine is sometimes connected with ritual, cultural and social events (ritual hot bath cultures), or to long-time continued chronic cures (like special spa treatments, hot-spring natural drinks, etc.).

These popular treatment applications of heating are types of "kitchen medicine": the old recipes are "sure", the patient takes it, and cured when it is done according to the auricular traditional regulations. This "for sure" is the disadvantage of the popular wisdom. It interprets this heating method as a simple causal process, "do it, get it". However, the hyperthermia is not as simple as the traditions interpret it. Internal source of heat is the fever as a reaction to infections [1] or pyrogens [2] or malignant hyperthermia [3] as well. The natural fever is induced by the living system [4]. The situation is quite different, when the heating is forced from outside of the body and it is intended to be applied as therapy. The forced heating works against the homeostasis and the body tries to keep the temperature normal, irrespective that the heating is local, regional or systemic. The interpretation of hyperthermia as therapy has various stumbling-blocks, because the effect caused by the absorbed heat is too complex: the applied, absorbed energy is usually depleted non-homogeneously and the intricacy of the living processes modifies the intended motive of application. Further complication is/in the heating process itself: the efficacy certainly differs by heat-sources and by the properties of the target volume and its physiological effects as well. A frustration in understanding of the differences between the natural and constrained heat-therapies and their consequent reactions characterizes the complete history of hyperthermia in medicine, and explains in majority why hyperthermia has no well deserved place in the professional medical armory to treat various diseases.
Hyperthermia as a treatment modality is battling for the step from the bio-medical experiment status to a clinically proven one [5], [6].

The central problem of the forced heating in a local/regional volume is the physiological feedback reaction acting to compensate the compulsory temperature elevation. The main physiological feedback mechanism is the active blood-flow in the heat-targeted volume, [7], [8], [9]. The intensified blood-flow is excellent heat-exchanger, cooling down the heated volume and effectively increasing the temperature in the sorrounding of the target. The high blood-flow delivers extra nutrients (malinly glucose) supplying the tumor, as well as increases the risk of dissemination of malignant cells by the blood-stream. Both effects are contrary to our direct aim to destroy the cancer. The situation is a competition now between the cellular distrotion by direct heat and the supply of the growth of the tumor together with its increasing dissemination ability. This is the origine of the contradictiong results and the missing satisfactory control on the oncological heat-treatments.
Technically a huge variety of heating could be applied by heat therapies [10]. Its energy-production, its selectivity, locality, kind of energy-delivery, locality invasivity control, applied frequency of the electromagnetic waves, as well as their medical applications and combination with other methods make

the heat-therapies different.
Oncothermia is a special heating, targeting the membrane of the malignant cells [11]. This nano-range heating makes possible to destroy the malignant cells by extreme temperature gradient on their membranes individually [12], without exciting of the physiological feedback mechanisms; without considerable blood-flow increase.
Our objective in this article is showing on actual cases how oncothermia works. The main addressed questions are:

1. Which adverse effects has oncothermia by dose-escalation (extended treatment duration)?
2. How the long treatment is effective in various cases of the disease?
3. Can we apply oncothermia as monotherapy for a long time?
4. Are we able to handle the fatal cancer cases as chronic disease in the style of dialysis?

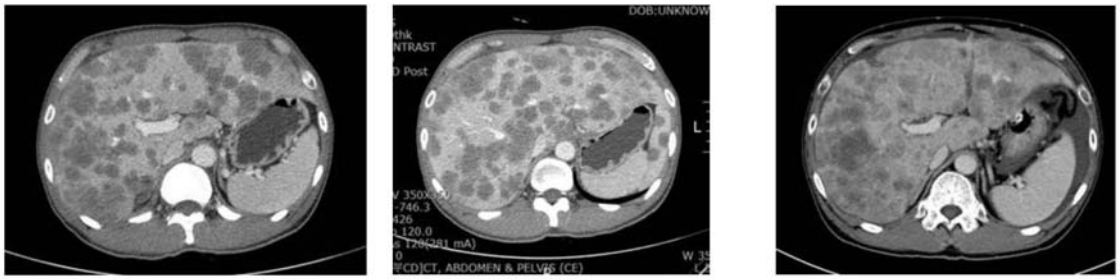
Method

There were chosen numerous cases, having complications with the gold-standard therapies, in high-line treatments. Oncothermia was applied or complementary to chemo- and/or radiotherapy or it was applied as monotherapy in the cases, when the combination was not feasible. The study was started in Dec. 2011, and summarizes the results until Sep. 2012.
Patients were the intention to treat (ITT) population, no cohort was formed, a retrospective data-collection is the basis of the evaluation. The study was performed in single-institute basis and the patients were rigorously diagnosed, checked and followed-up during the trial. All together 216 patients were treated in this time with 4263 sessions cumulatively. From this we had chosen 16 cases characteristically showing the results.
We used the EHY2000+ device (Oncotherm GmbH, Germany), applying the 20 and 30 cm diameter electodes in step-up heating protocol. The maximal energy was 150 W, duration of a session was 60 min each, 2 ~ 3 times/week, 12 times in one cycle. Average number of the treatment was 33 sessions or 4 cycles, the duration the time of the full cycles was over 6 months.

Case-reports

Rectosigmoid cancer with liver metastasis

A 43-year-old Asian man was diagnosed as Rectosigmoid Cancer with metastasis of liver in March/10/2012. and T-loop End Colostomy was performed on May/7/2012. Avastin-FOLFOX chemotherapy was given 3 times after operation and the second line FOLFIRI chemotherapy was given 3 times. He received Radiotherapy at Liver delivering 18 Gy in 10 fractions for 2 weeks from August/13/2012 to August/27/2012 and concurrent Oncothermia 37 times from July/20/2012 to Novemer/21/2012.



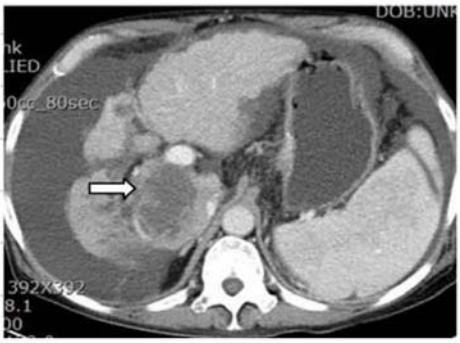
Before oncothermia After 12 times of oncothermia After 31 times of OncoTx

Tumor mass in liver was regressed and liver parenchyma increased gradually with concurrent small dose of radiation and oncothermia. No adverse effect originated from oncothermia was observed. This result gives the large possibilities of combined treatment of oncothermia with low dose of radiation for far advanced cancer for palliative treatment.

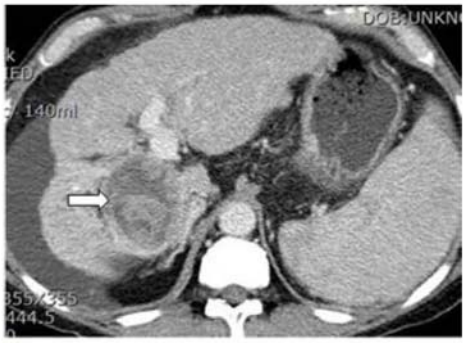
Hepatocellular carcinoma

A 61-year-old Asain man was diagnosed as Hepatocellular carcinoma. TACE was given on Feb/17/2011. He suffered from Type B virus-Hepatitis from 1992, and liver cirrhosis from 2001. TACE could not be

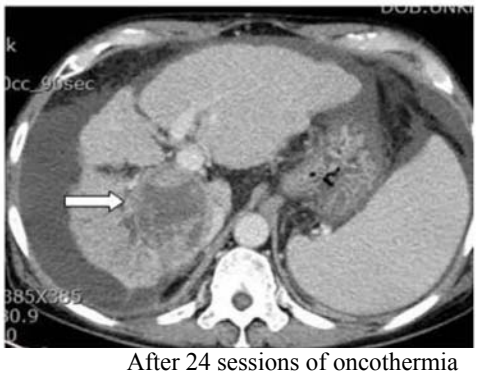
given anymore after one time even though HCC was aggravated with elevation alphafeto-protein level in serum. Regrowing cancer and rapid rising of alphafeto-protein (20.48 to 448.90) appeared in Nov/2011. 24 times of Oncothermia were given from Nov/21/2011 to Feb/27/2012.



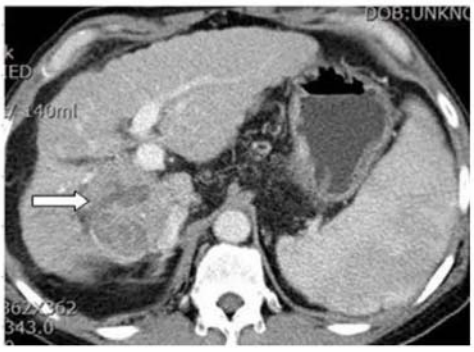
2 months before oncothermia



Just before oncothermia



After 24 sessions of oncothermia



7 months after oncothermia

Alphafeto-protein level was lowered and kept stable at 24.39 after oncothermia to July 2012. Tumor mass was stable until new lesion in liver found in Sept/2012 with the high elevation of alphafeto-protein to 697.40 after 7 months from oncothermia.

Pancreatic cancer

A 59-year-old Asian woman had been diagnosed as Pancreatic cancer in Aug/2010. Chemotherapy was given many times as much as possible at other hospitals.

She visited Kosin University first in Aug/2011 just only to relieve massive pain for serious carcinoma peritonei with conglomerated mass attached at anterior abdominal wall. Radiation therapy was given 30 Gy in 10 fractions(once/day, for 2 weeks) With IGRT technique to anterior abdominal wall mass in August/2011. Ascites was not at that time.

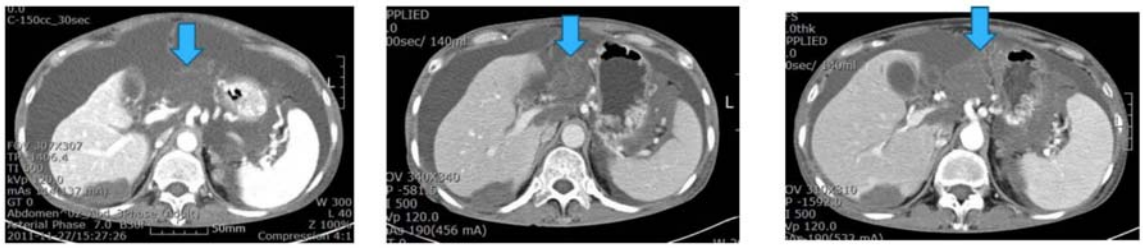
Abdominal pain was relieved much just after palliative Radiation Therapy but progressed gradually from Oct/2011.

Ascites and intestinal obstruction were developed. Intestinal bypass surgery was recommended by surgeon but was not performed. It was difficult to recover from the high risk of the operation since the patient had far advanced cancer and poor general condition.

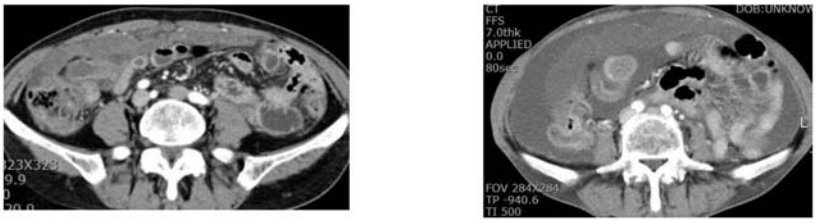
Oncothermia was started firstly in our hospital as soon as installed in November 2011. She could eat some food and ascites was controlled by medicine since 5 times of oncothermia were given. Cancer mass was regressed a little bit. Amount of analgesics intaken was reduced.

She maintained well with oncothermia to later June 2012. But her cancer became worse gradually. Eventually cancer metastasis to both pleural cavity was developed with both pleural effusion. Patient's general condition became worse gradually for pleural metastasis. That was drained often to reduce dyspnea. It was difficult to keep hyperthermia for 1 hour due to the poor general condition and inevitably carcinoma peritonei became worse from August 2012.

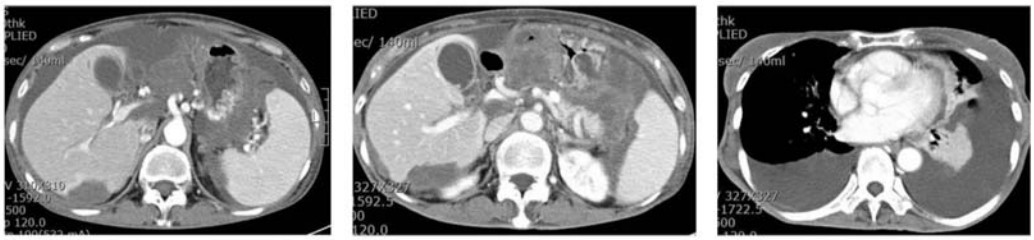
She died due to pneumonitis with massive pleural effusion on the early September 2012.



Before oncothermia | After oncothermia (30 sessions) | After oncothermia (60 sessions)



July 7, 2011 | Oct 16, 2011

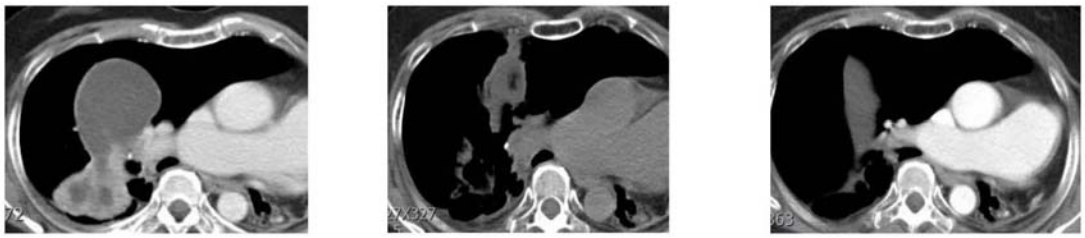


May/15/2012 | July/17/2012 | July/17/2012 (2)

Although she had a massive abdominal pain because of far advanced carcinoma peritonei, she lived for 10 months by controlling the massive abdominal pain with Oncothermia. She was the first patient to be applied Oncothermia. From her case, there are many possible cases applied to other patients of advanced cancer with oncothermia without any negative side effects.
Total 82 times of oncothermia to her were given by 2~3 times/week to her for 10 months. It can be possible to apply many times of oncothermia for advanced cancer without any complications.

Synovial sarcoma

This 48 years old female was diagnosed as synovial sarcoma and received operation of right thigh in 2004. She used to live well until the recurrent and metastatic cancer was known at the right lung in September 2011.
Radiation therapy 30 Gy in 10 fractions for 2 weeks to tumor mass at right lung mass with IGRT technique was given carefully in April 2012. She lost left lung by tuberculosis when she was young. Tumor mass regressed partially after radiation therapy but progressed in November 2011. She received oncothermia 39 times from November 2011 to April 2012.



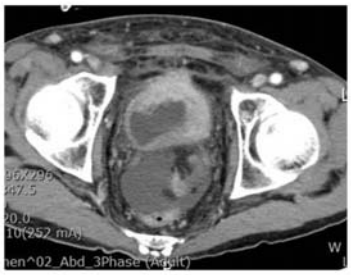
Just before OncoTx | 12 times of OncoTs | 36 times of OncoTx

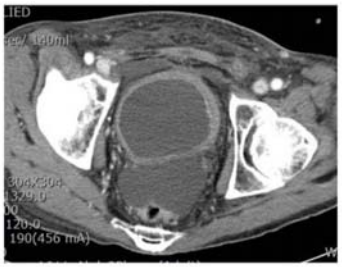
Metastatic sarcoma to lung was markedly regressded with oncothermia. Sarcoma has been already known to be sensitive to hyperthermia. And also Sarcoma is sensitive to oncothermia as well.

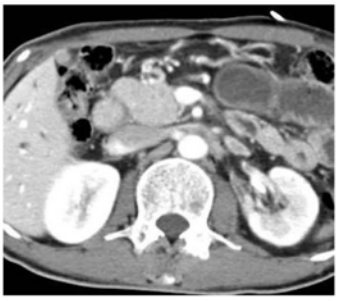
Pancreatic cancer

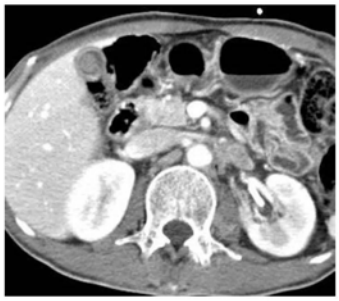
A 49-year-old Asian man has been diagnosed as Pancreatic Cancer in Nov/2011. Chemotheray was given in Mar/2012. Brain metastasis was developed and 30 Gy Radiation Therapy in 10 fractions to the whole

brain was given in Mar/2012. Urinary Bladder metastasis was found in May/2012.
Oncothermia 12 times(3 times/week) to pelvis for metastatic bladder cancer were given from May/14/2012 to June/13/2012. Oncothermia 26 times to pancreas were given from June/25/2012 to August/30/2012.


Before Oncothermia


After 12 times of oncothermia

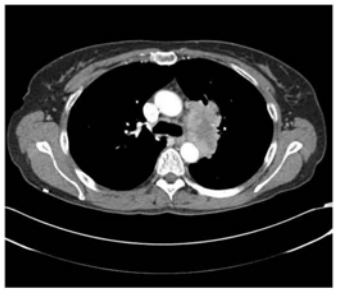

Before Oncothermia

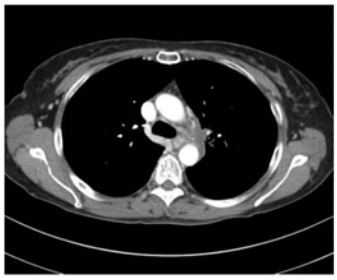

After 12 times of oncothermia

Metastattic bladder cancer was regressed prominently after 12 times of oncothermia. Pancreatic tumor mass was also reduced in the size prominently after oncothermia. If the primary tumor was sensitive to oncothermia metastatic cancer is also sensitive to the oncothermia. But she got sudden death on Sept/3/2012 due to brain edema for aggravation of metastatic brain tumor.

Adenoid cystic carcinoma

A 56-year-old woman was diagnosed as adenoid cystic carcinoma of submandibular gland and received operation(mass resection & right maginal mandibulectomy and reconstruction with forearm Free flap, Lt. and Lt. FTSG from Lt. forearm sural nerve graft) in June/1/2009.
She used to live well up to find recurrent cancer and metastasis to lung in May 2011. She refused any treatment like chemotherapy after she heard less effectiveness and greast negative side effects of chemotherapeutic agent for adenoid cystic carcinoma. Dyspnea and blood tinged sputum developed occasionally from May 2012.
She received Radiotherapy delivering 30 Gy in 10 fractions(once/day) for 2 weeks in June 2012 and concurrent Oncothermia 48 times(2~3 times/week) from June/12/2012 to October/2/2012.


May/31/2012(before OncoTx)

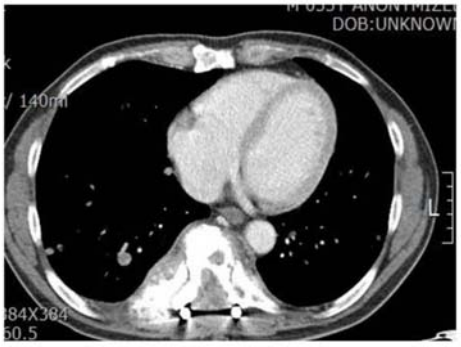

July/9/2012(after OncoTx & RTx)

Tumor mass at left hilum was regressed markedly in chest CT scan after 24 times of oncothermia with 30 Gy of Radiation therapy. Adenoid cystic carcinoma is generally resistant to Radiation therapy. But concurrent Radiotherapy and Oncothermia made these metastatic lung cancer reduced in size.

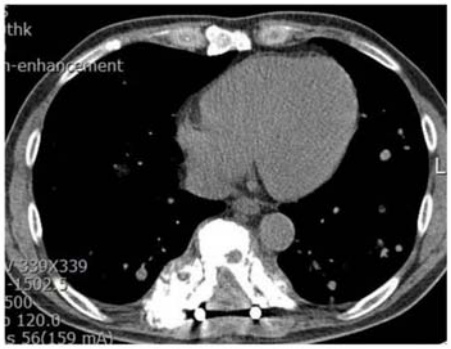
Lung cancer

A 55-year-old Asian man was diagnosed as lung cancer(adenocarcinoma) in March 2010 and received chemotherapy and target therapy.

He received Radiotherapy at regrowing lesion with invasion to spine at the operated site and Rib delivering 30 Gy in 10 fractions for 2 weeks in April 2011. tumor mass regrew and multiple metastatic lesions was appeared in both lung. Oncothermia was given 24 times(2~3 times/week) from April/10/2012 to July/12/2012.



Before HTx



After HTx 12 times

Tumor mass was regressed at the right lung and spine. However tumors were progressed in the left lung because oncothermia was not given at the left lung.

Back pain to the right chest was subsided after oncothermia. Many cases were shown the reduction of the metastatic bone pain with oncothermia.

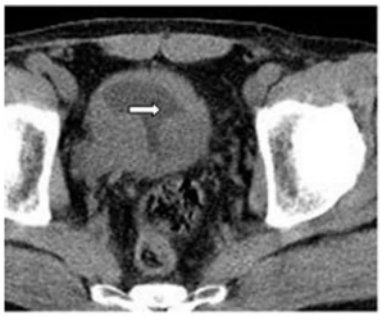
It is possible to apply oncothermia to reduce metastatic bone pain with a variety of cancer.

Bladder cancer

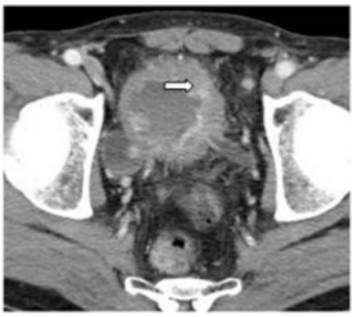
67-year-old Asian man was diagnosed as bladder Cancer(transitional Cell carcinoma) in April 2008, Operation and 6 cylces of chemotheray were performed in 2008.

Recurrent cancer in bladder was known in April 2011. Partial resection and chemotherapy were performed again after known recurrent cancer. But baldder cancer was progressed in spite of chemotherapy in April 2012.

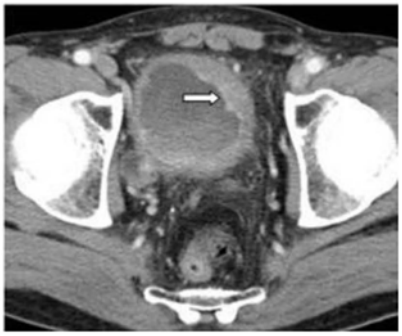
Oncothermia 24 times were given from April/30/2012 to July/31/2012.



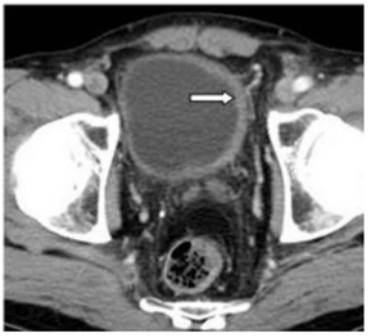
Before Oncothermia



After 12 times of oncothermia



After 24 times of oncothermia

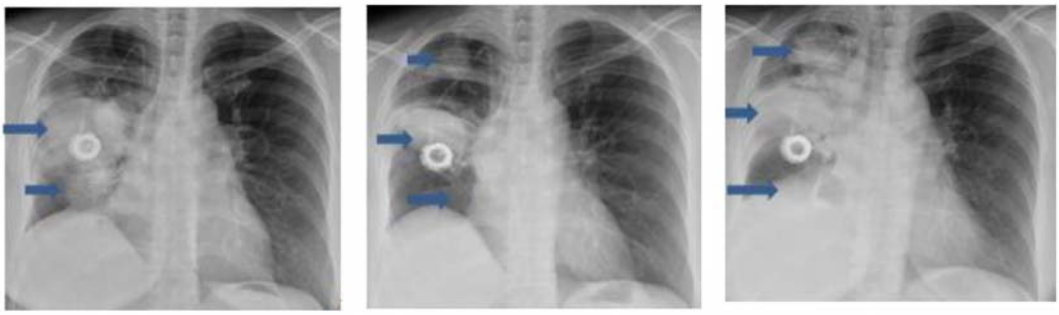


2 months after 24 times of oncothermia

Tumor mass of bladder was regressed after 24 times of oncothermia. As can be seen the result of CT scan taken after 2 months stopped oncothermia, the futher regression of the tumor mass was observed. That is, even though the oncothemia treatments was stopped, the effectiveness in the reduction of tumor mass was kept for 2 months.

Lung cancer

This 47year old female was diagnosed as Lung Cancer(adenocarnoma) in April/2010
Chmotherapy and target therapy were given up to Oct/2011. However, no longer those treatments were affected to the patient from the early Dec. 2011.
12 times of Oncothermia (2~3 times/week) were given from Dec/22/2011 to Feb/2/2012.

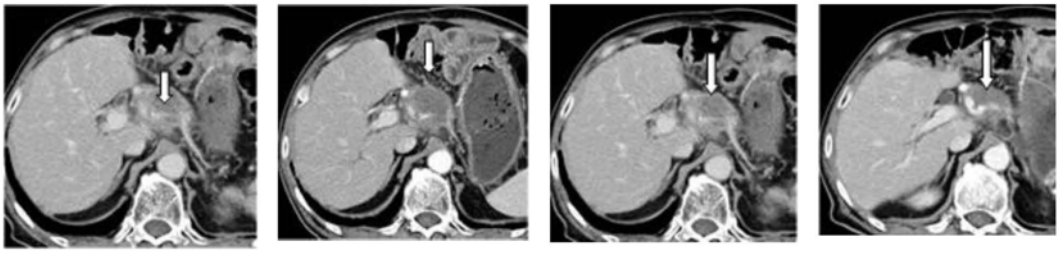


Before OncoTx After 12 times of OncoTs 4 Months from OncoTx

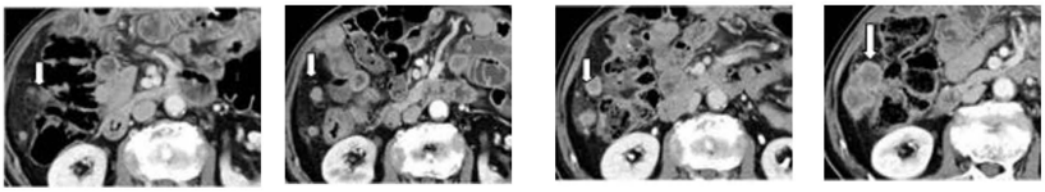
Tumor mass was regressed markdely just after oncothermia. However tumor mass was progressed rapidly in 4 months of stopping oncothermia. Original tumor mass in the area of oncothermia was regressed. But new lesion at the outside of oncothermia region was progressed gradually.
She died in Aug/2012 due to liver, brain, multiple bone metastasis and massive aggravation of the lung cancer.

Pancreatic cancer

A 68-year-old Asian man was one of patients who received many times of oncothermia. Pancreatic cancer was diagnosed in August 2011. He refused chemotheray from diagnosis. Operation was impossible to be performed at the time of the diagnosis. Oncothermia9@~3 TIMES/WEEK) was given 65 times from February/16/2012 to October/11/2012.



Before OncoTx. After OncoTx. 12 times After OncoTx. 24 times After OncoTx. 60 times



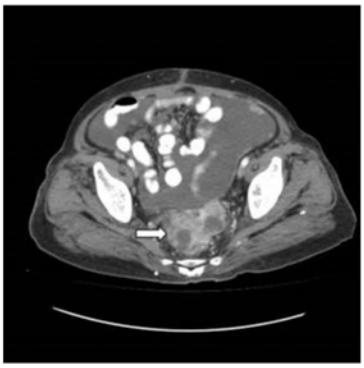
Before OncoTx. After OncoTx. 12 times After OncoTx. 24 times After OncoTx. 60 times

He was treated 65 times of oncothermia for pancreatic cancer without any negative side effects for 8 months. In the area of Oncothermia treatment, the tumor mass was gradually reduced. However, tumor mass in the outside of Oncothermia area was significantly increased. Therefore, Oncothermia monotherapy is available to reduce pancreatic cancer.

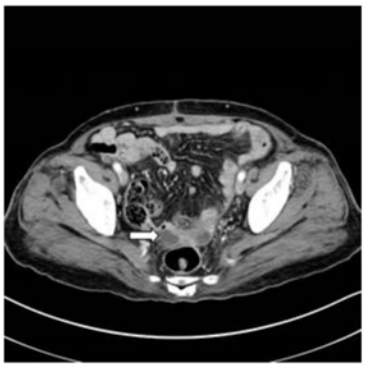
Ovarian cancer

A 70-year-old Asian woman was diagnosed as Ovarian Cancer and RAH with both salphingo-oophorectomy was performed on Oct/6/2011

Cisplatin chemotherapy was given once just after operation. But she refused further treatment due to toxicity of chemotherapy. No special treatment was given from Nov/2011. Regrowing mass at left ovarian site and carcinoma peritonei was known in Jan/2012. Oncothermia was given 12 times (3 times/week) from Feb/15/2012 to Mar/19/2012.



Before oncothermia

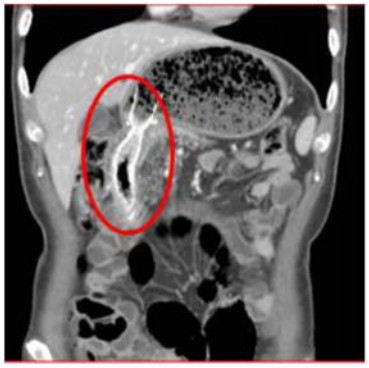


1 month after 12 times of oncothermia

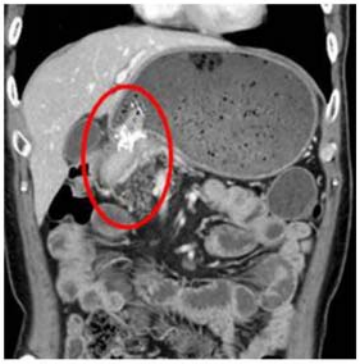
Tumor mass recurred from post ovarian cancer in pelvis was regressed markedly after oncothermia 12 times and ascites was improved and controlled by medicine.

Stomach cancer

This 50 years old man was diagnosed as stomach cancer(adenocarcinoma) and received operation(subtotal gastrectomy) in May 2009. Recurrent cancer has been found at anastomotic site of stomach and obstruction of duodenum was developed in April 2012. Stent was inserted into duodenum and antrum of stomach in April 2012. Radiation therapy delivering 30 Gy in 10 fractions(once/day) for 2week at stent site by IMRT was given between Aug/23/2012 and Sept/6/2012. Oncothermia was given 12 times by 2~3 times/week between Sept/4/2012 and Oct/20/2012 after radiation therapy. Tumor maker CEA in serum was decreased from 5.41(Aug/14/2012) to 4.44(Oct/30/2012).



Before Oncothermia



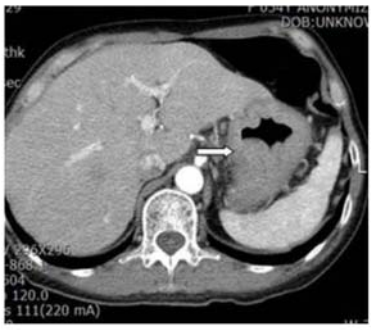
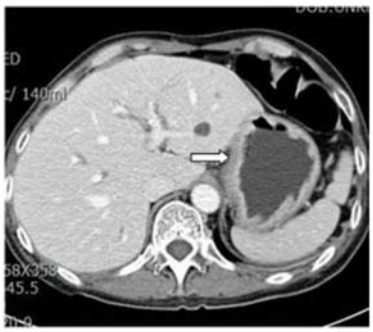
After 12 times of oncothermia

Any negative side effects were not appeared even though the high temperature had been expected at the metal stent site. Metal stent in the canal or duct is not absolute contra-indication for oncothermia.

Duodenal stent disappeared after oncothermia but patient could eat food well with good food passage through duodenum. Tumor mass maybe was also regressed by oncothermia.

Stomach cancer

54-year-old woman has been diagnosed as Stomach Cancer with metastasis to right ureter in Jan/2012. The patient had inoperable state and refused chemotherpy by herself. 36 times(2~3 times/week) of oncothermia were given from April/17/2012 to Sep/6/2012.

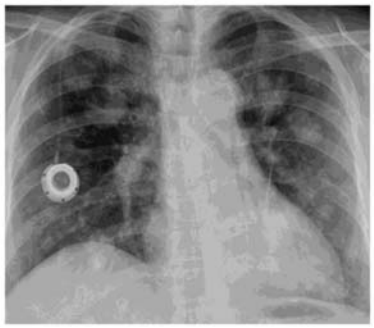
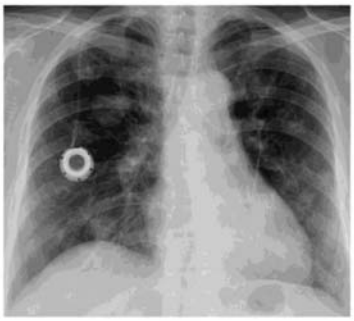
Before oncothermia After 36 times of oncothermia

Tumor mass was regressed prominently in stomach and she could eat food from 12 times of oncothermia. The total 36 times of oncothermia were given without any negative side effects.

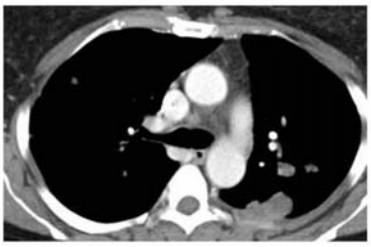
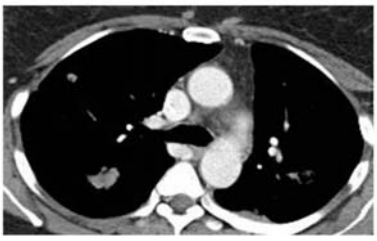
Rectal cancer

A 47-year-old Asian woman was diagnosed as rectal cancer and received operation in April 2010 and followed by chometherapy.

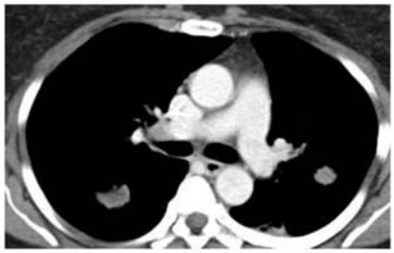
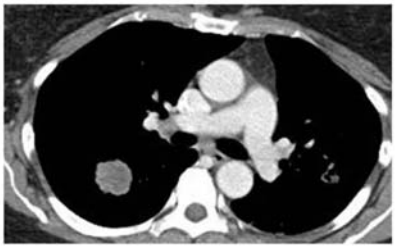
She lived well until multiple metastatic cancers were found at both lung in January 2012. She received chemotherapy and oncothermia at left lung for recurrent and metastatic cancer. Oncothermia was not able to be applied at both lung because of the limitation of RF plate. Oncothermia was given 23 times(2~3 times/week) from March/30/2012 to July/31/2012.

Before OncoTx. After 12 times of OncoTx.

Before OncoTx. After 112 times of OncoTx.

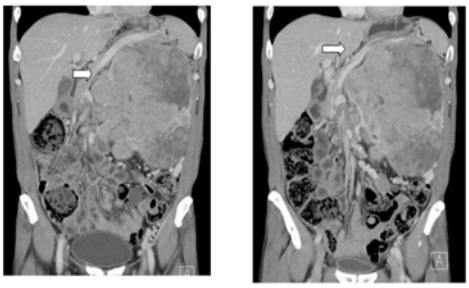
Before OncoTx. After 12 times OncoTx.

Chest X-ray checked at 12 times of Oncothermia revealed the regressed tumor masses at left lung prominently but ones in right lung were not reduced in size because oncothermia was not given at right

lung. CT scan was checked, too. Tumor mass regressed prominently at left lung. However those at right lung did not regressed in size, furthermore some progressed. And the pain posterior to left upper chest because of metastatic cancer with invasion to chest wall was also relieved after oncothermia. This case is not oncothermia monotherapy but It must be sure in this one film that the combined chemotherapy with oncothermia is more effective certainly.

Renal cancer

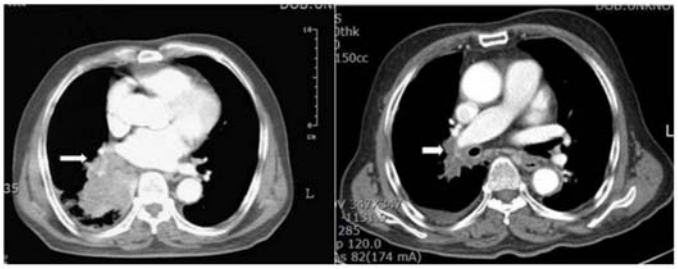
A 61-year-old man was diagnosed as renal cell carcinoma in Jan/2011. He refused to get any special treatment for cancer like chemotherapy, hormonal therapy, target therapy, operation and radiotherapy. He received only oncothermia 24 times(2 times/week) to tumor mass at left upper abdomen from Dec/2/2011 to Feb/23/2012 for 3 months.



Before oncothermia 24 times of oncothermia

Lung

A 86-year-old man checked Computerized tomography (CT) scan due to symptoms of the upper respiratory infection. CT scan showed a mass at the right lower lung and mediastinal area but we could not performed biopsy because of the high risk of procedure. The patient had inoperable state and refused chemotherapy by himself. He received Radiotherapy 30Gy in 10 fractions(once/day) for 2 weeks and concurrent oncothermia 22 times(2~3 times/week) from January/27/2012 to March/6/2012.



Before Oncothermia After 12 times oncothermia

Tumor was regressed after 22 times of oncothermia. Combined treatment of the small amount of radiation and oncothermia revealed the prominent regression of lung mass even through histologic type were not confirmed. Tumor makers of CEA 5.99 and NSE 38.97 were abnormal level in serum.

Conclusion

These cases together with the huge amount of other treatments answers on our questions, however of course further investigations and studies are mandatory. We had not observed oncothermia related adverse effects by dose-escalation. In negligible case skin erythema appeared, handled with appropriate cream. It did not terminated any further treatments.

Oncothermia could be applied in very severe cases, where other treatments are dubious or inapplicable. In this situation oncothermia could be applied as monotherapy with success. On the other hand the complementary applications of oncothermia had no any limitations for the oncothermia side of the therapy. We observed some cases which are not eligible for oncothermia, due to the mismatch of the electrodes, the bolus is not able to cover the surface smoothly. We had no contraindicated cases in our patient spectra.

The efficacy of the treatment was depending on the number of applied sessions. The long-time applications were positive for the patients in both the curative and quality of life meanings in advanced

diseases.
We observed long-time manageability of the serious stages of the cancer, making the anyway rapid fatal disease chronic, treated it longer than the anyway expected survival and the quality of life of the patients was excepted, better than in similar cases without oncothermia.
We observed feasibility and good perspectives of this method, and strongly recommend making higher evidence clinical studies for stronger approval.

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Abscopal effect: new perspectives in Oncothermia

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Abscopal effect: new perspectives in Oncothermia

Abstract

Radiotherapy has a relevant action on the tumor environment and its distant component. Abscopal effect is the bystander effect of radiotherapy observed at a site distant to the irradiated one within the same patient. Abscoopal effect even though described, is not a common clinical event. We are reporting a documented observation of an abscopal effect in one patient with lung cancer treated on target with radiotherapy and oncotehrmia. This is the first case in literature of abscopal effects in lung cancer, a synergistic action between radiotherapy and oncotheramia is suggested.

Introduction

The abscopal phenomenon is the effect of radiation therapy observed as response of metastases distant from the site of irradiation. The word abscopal is derived from Latin ab means "position away from" and "scopos meaning" a target for shooting at.

There is evidence of reactions occurring outside the defined zone of radiation field. First described in 1953 by Mole (1), who called these out-of-field events "abscopal effects", these distal effects rarely have been documented since then. It should be stressed that abscopal effects are not bystander effects in the traditional sense (2) but refer to radiation responses in areas separate from the irradiated tissue and are presumably mediated by secreted soluble factors.

In both radiotherapy patients and in external-beam-irradiated animal models, most reports on abscopal effects refer to antitumor consequences outside the radiation field (see Figure 1.). Much of the observed physiological abscopal effect has been associated with splenic irradiation (3). In the clinical setting, these include regression of hepatocellular carcinomas after radiotherapy to treat a tumor at the base of the spine and histologic changes in metastatic lymph nodes in some women treated for breast cancer but also in variety of malignancies including lymphoma, papillary adenocarcinoma, melanoma, adenocarcinoma of the esophagus, chronic lymphocytic leukemia (4-10).

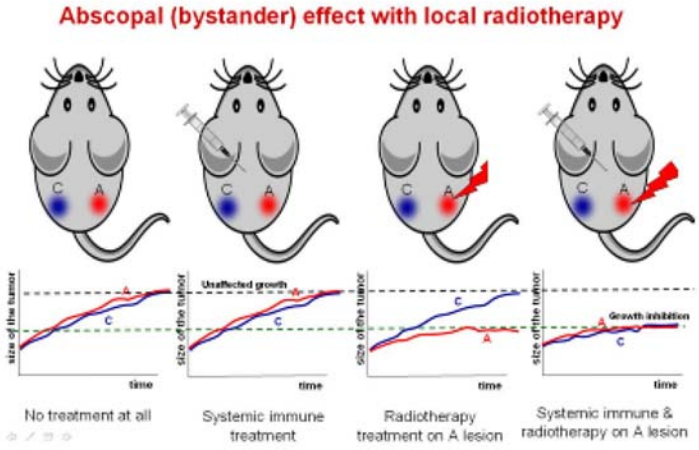

Figure 1. The mice have two distant tumors in left and right femoral region. The growths of the tumors are equal. When the mice were treated systemically with immune supporters, no change could be seen. When the A tumor was treated locally with radiotherapy, that tumor did not grow so quickly as the reference C. However, when we apply the systemic immune therapy and the local radiotherapy were applied for the only A-lesion, surprisingly the C lesion is also suppressed

Radiation-induced bystander effects are biologic responses in the cells that were not traversed by an ionizing radiation track and, thus, they were not subject to direct energy deposition; that is, the responses occur in nonirradiated cells. These bystander effects take place in the neighbors of irradiated cells or in other non irradiated cells that have received secreted signals from the irradiated cells. As such, bystander effects are somehow communicated from an irradiated cell to a nonirradiated bystander cell via cell-to-cell gap junctions (14) or by the secretion on shedding of soluble factors (14-16). The precise nature of factors that mediate the bystander effect is unknown, but reactive oxygen and nitrogen species and

various cytokines have been implicated. Radiation-induced bystander effects have been extensively documented in several recent reviews (17-18), which have described both detrimental (e.g., DNA stand cleavage, chromosomal damage, and cytotoxicity (11) and potentially beneficial bystander effects.
Although the bystander effect is widely considered a new concept, reports that biologic entities may be inactivated equally by ionizations within the entity or in the surrounding medium have existed since the 1950s(1), and clastogenic factors in plasma from radiotherapy patiens were first observed in the 1950s. Studies have demonstrated that bystander effects induced by high linear energy transfer (LET) – but not those induced by low LET – are dependent on cellular interaction and functioning gap junctions (14-18). It is suggested that the abscopal effect relates to immune response mediated by cytokines, but the mechanism remains unclear because this phenomenon is so rare and poorly understood in clinical practice, showing many controversies also and sometimes it is used complementary to other type of local therapies including surgery, hyperthermia and immunotherapy (19-23).We report a case of Abscopal effect in lung cancer. This observation has never been reported.

Case presentation

The Abscopal effect was shown in a patient, who is a 72 years old male with advanced non-small-cell lung carcinoma (classified as cT2 cN2 M0, stage IV), with metastases in sentinel and in distant lymphnodes was treated locally on the primary lung tumor. A trimodal protocol was applied. It consisted of fractional radiotherapy with 28 sessions delivering 1.7 Gy each, plus Oncothermia 6 sessions, one each week of irradiaton. As supportive treatment 250 microgram of GM-CSF (sargramostim) were given on weekly basis. Two months after treatment a Partial Remission has been observed in the primary lung tumor and evidence of Complete Remission in the distant lymphnodes metastases was reached. The patient felt increase of quality of life, and well being for prolonged time (see Figure 2).

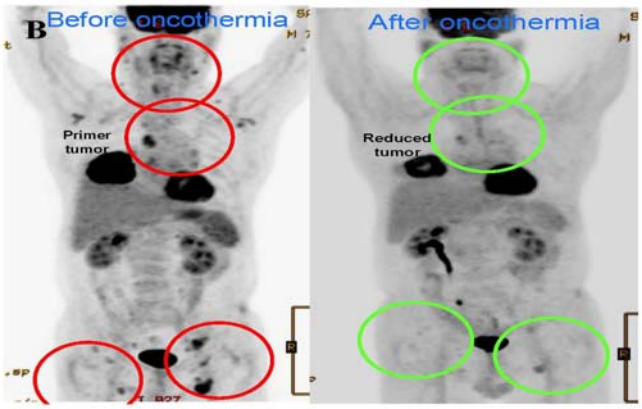

Figure 2. Patient with lung cancer before and after treatment: evidence of abscopal effect

Discussion

Numerous studies have assessed the relative effect of radiotherapy and dose rate on tumor cells, with conflicting results that may be dependent, in part, on tumor type and experimental model or design. When the existence of an inverse dose-rate effect was reported, and these findings were initially attributed to incomplete repair of DNA damage and arrest of cells in the radiosensitive, G2 phase of the cell cycle. Since then, there have been multiple reports of an inverse dose-rate effect in a variety of tumor types, with some studies demonstrating the absence of an association between G2 arrest and radiosensitivity and implicating other mechanisms of action.
There have been two main theories proposed to explain the abscopal antitumor effect. The first applies to leukemias and lymphomas, it is hypothesized that during splenic irradiation diseased lymphocytes circulate through the irradiated volume (spleen), and as the splenic size decreases the remotely located masses also decrease in size, giving an impression of a systemic antitumor effect from local treatment. The second applies to solid tumors, it is postulated that local radiation induces a release of mitotic inhibitors (cytokines) into the circulation that mediate a systemic antitumor effect. It has been demonstrated that an elevation of circulating tumor necrosis factor after radiotherapy that coincided with the regression of a hepatocellular carcinoma situated away from the radiation field (9). Others proposed

hypothesis is that the abscopal effect is mediated by the immune system. Irradiation of tumour in one site induces release of circulating tumor antigen or inflammatory factors that may then mediate an augmented immune response against non-irradiated, malignant lesions expressing similar tumor antigens (10-18). In our patient by virtue of this unusual presentation, we were able to predict and observe the rare abscopal effect in the site distant from the site of irradiation. Irradiation and oncothermia of the disease in the chest resulted in tumor mass regression in the untreated distant site. Strong synergy of heat and modulated electromagnetic field in tumor cell killing have been observed in animal models (19-21) and could be translated to humans in the routine therapy of cancer. Based on this experiemental and clinical case, we hypothesize that Abscopal effects could be observed in patients treated with radiotherapy, radiotherapy plus oncothermia or only oncothermia. Further studies are necessary.

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Oncothermia Journal 7:283-284 (2013)

Report of the pilot-study done for the proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

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Report of the pilot-study done for the proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Abstract

According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in in vitro assays. This fact is a very important using ascorbic acid as complementary drug with standard antitumoral therapy or in cases where currently no other potent treatment is possible. Although the specific method of action is still unclear: high concentration of ascorbic acid produces oxidative shock by H2O2 lethal for tumor cells beyond a certain level, however healthy cells can survive the same stress effect. The goal of our experiment was to determine the possible potentiating effect of application of high dose pH-neutralized ascorbic acid to the normal oncothermia treatment method. The NMRI mice were inoculated with C26 Murine Colon Carcinoma cell line subcutaneously at both of their femoral regions and kept till the tumors reach symmetrically the 10 mm in diameter. Four experimental groups were made, containing 4 female animals in each. The fromed groups of animals were: Gr1. no treatment (control), Gr2. only ascorbic acid treatment, Gr3. only oncothermia treatment, Gr4. both ascorbic acid and oncothermia treatment. Both vitamin-C and oncothermia treatment were applied once ("single-shut" treatment regime), ascorbic acid was pH-neutralized and applied intra-peritoneal in dose of 2 g/kg bodyweight. Oncothermia treatment was applied only to the right limb tumor, the other side was used as internal control. After the treatment the animals were sacrificed, all tumors were removed and analyzed histopatologicaly. The other organs were routinely checked as well. Our main question centered on the comparison of the cell-destruction ratio of the various applied treatment regimes, and study the possible synergy or additive crosspotentiating of the methods. In this pilot study results are showing that because of some unknown reasons, high dose ascorbic acid application showed no synergic or adjuvant effect with OTM therapy, even the combination decreased the effectivity of the OTM compared to the results of monotherapy. In the proposed, large number animal experiment results of this study should be considered.

Introduction

According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in in vitro assays. This fact is a very important using ascorbic acid as complementary drug with standard antitumoral therapy or in cases where currently no other potent treatment is possible. Although the beneficial effect of the ascorbic acid in anti-neoplastic therapy has some controversial reports in the literature [1-3] and the specific method of action is still unclear: high concentration of ascorbic acid produces oxidative shock by H2O2 lethal for tumor cells beyond a certain level, however healthy cells can survive the same stress effect [4]. As for the application, it was reported that intravenous ascorbic acid treatment is much more efficient, since this way more than 70-fold higher plasma concentration is elucidable than in case of oral application [5]. To achieve proper effect, high plasma level of ascorbic acid is required, so in human cases intravenous dosages are considered between 0,15 to 1,5 g/kg doses [6, 7].

Objective

The goal of our experiment was be to determine the possible potentiating effect of application of high dose pH-neutralized ascorbic acid to the normal oncothermia treatment method. The dose to use we considered to be 2 g/kg accordingly to human trials [7] and our intra-peritoneal acute toxicity test (not reported). We choose the intra-peritoneal application because the absorption from abdominal cavity is very fast and complete, nearly equal to intravenous application and it is much easier performable in mouse than IV application. However in this case only not irritative materials can be applied, so neutralization of ascorbic acid by sodium-hydroxide is necessary.

Method

The NMRI mice intended to inoculate with C26 Murine Colon Carcinoma cell line subcutaneously at both of their femoral regions and kept till the tumors reach symmetrically the 10 mm in diameter. C26 cells were be cultivated in RPMI 1640 Glutamax medium (Invitrogen, Carlsbad, California, USA). Inoculation was be done by 7500000 cell/ml concentration liquid cell suspension, using 0,1 ml

subcutaneously each side. Incubation time for tumor growth is expected to be around two weeks. Vitamin C solution of 1M in concentration was be created by using dry ascorbic acid (Sigma Aldrich, St. Louis, Missouri, USA) and sterilized purified water, and was be neutralized by 10M sodium-hydroxide solution (Sigma Aldrich, St. Louis, Missouri, USA). We created four experimental groups, containing 4 female animals in each. The formed groups of animals were: Gr1. no treatment (control), Gr2. only ascorbic acid treatment, Gr3. only oncothermia (OTM) treatment, Gr4. both ascorbic acid and oncothermia treatment.
Both vitamin-C and oncothermia treatment was applied once ("single-shut" treatment regime), ascorbic acid was pH-neutralized and applied intra-peritoneal in dose of 2 g/kg bodyweight. Oncothermia treatment was applied only to the right limb tumor, the other side was be used as internal control, the incubation period between vitamin C application and OTM treatment was 30 minutes. The animals were sacrificed 24 hours after the treatment, all tumors were removed and analyzed histopatologicaly. The other organs were routinely checked as well.

Results

In our pilot-study, we experienced that vitamin C as monotherapy did not do any change in tumor remission compared to the control samples. As for OTM as monotherapy, the treated side tumor showed greater dead tissue area than the both of untreated side and control animals, same level as experienced in earlier studies. The combinational therapy showed controversial result, as the dead tissue amount in the tumors was the same in both treated and untreated sides, and it was smaller than in case of OTM monotherapy at the treated side.

Conclusion

In this pilot study results are showing that because of some unknown reasons, high dose ascorbic acid application showed no synergic or adjuvant effect with OTM therapy, even the combination decreased the effectivity of the OTM compared to the results of monotherapy.
In the proposed, large number animal experiment results of this study should be considered. It is highly probable that "single shut" ascorbic acid application will not be appropriate to achieve any synergic effect. Also, incubation time between vitamin C application and OTM treatment should be greater than the applied 30 minutes.
According the results we have got in our experiment suggest us that we should turn our interest from ascorbic acid to other possible materials as potentiating agent for oncothermia treatment in the future.

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Programmed cell death induced by modulated electro-hyperthermia

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Programmed cell death induced by modulated electro-hyperthermia

Abstract

Background: Modulated electro-hyperthermia (mEHT) is a non-invasive technique for targeted tumor treatment.

Method: HT29 human colorectal carcinoma cell line xenografted to both femoral regions of BalbC/nu/nu mice treated with a single shot OTM treatment. Histomorphologic, and immunhistochemical analysis TUNEL assay and R&D Apoptosis array were performed on tissue samples.

Results: mEHT caused a selective tumor demolition. An up regulation of TRAIL-R2 and FAS was observed. Cleaved caspase-3 positive cells appear at the tumor periphery. Cytochrome c and AIF release was observed in line with massive TUNEL positivity.

Conclusion: In HT29 colorectal cancer xenograft mEHT caused massive caspase independent cell death.

Background

Modulated electro-hyperthermia (mEHT) is a non-invasive technique for targeted tumor treatment [1-4]. The capacitive coupled modulated radiofrequency enriches in the tumor tissue, because of its dielectric differences [5, 6], without harming the surrounding non-malignant tissues. The possible mechanism of action of conventional hyperthermia on tumor models was previously slightly investigated and have not been fully evaluated [7]. Already it was shown that mEHT has non-temperature dependent effect beside the temperature dependent one [8]. Here our aim was to detect the possible role of mEHT in tumor cell death.

Method

HT29 human colorectal carcinoma cell line xenografted to both femoral regions of BalbC/nu/nu mice were treated with a single shot OTM treatment (LabEHY, Oncotherm Ltd, Páty, Hungary) for 30 minutes into the approx. 1.5 cm diameter tumors. Sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 h in 3 mice in each group by keeping 5 untreated animals. The temperature measurement was carried out during the treatment using optical probes (Luxtron FOT Lab Kit, LumaSense Technologies, Inc. CA, USA). The treated tumor core (41-42°C was during the treatment) the surface subcutaneously, the untreated tumor core and the rectal temperature were measured. Histomorphologic (H&E), immunhistochemical analysis by cleaved caspase-3 (Cell Signaling, Danvers, MA), TRAIL-R2 (Cell Signaling), cytochrome c (Cell Signaling), AIF (Cell Signaling) was completed on formalin fixed paraffin embedded tissue microarrays (TMA, TMA Master, 3DHISTECH Ltd., Budapest, Hungary) prepared from all samples. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay (Invitrogen, Carlsbad, CA) was performed on TMA and 24h and 48h post-treatment on the whole sections. R&D Apoptosis array (R&D, Minneapolis, MN) was carried out on the 8h, 14h and 24h treated and 24h untreated samples. Results were analyzed using digital microscopy and were evaluated by ImageJ.

Results

Modulated EHT caused a selective tumor demolition proceeding from the tumor centre. An up regulation of TRAIL-R2 and FAS was observed 8 h post treatment.

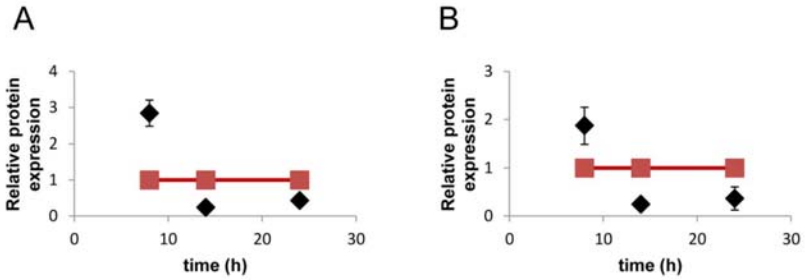

Figure 1. Relative protein expression of TRAIL-R2 (A) and Fas (B). An elevated expression can be noticed 8h post-treatment in both TRAIL-R2 and Fas proteins. The black rectangles show the treated sample relative protein expression while the red represents the relative control

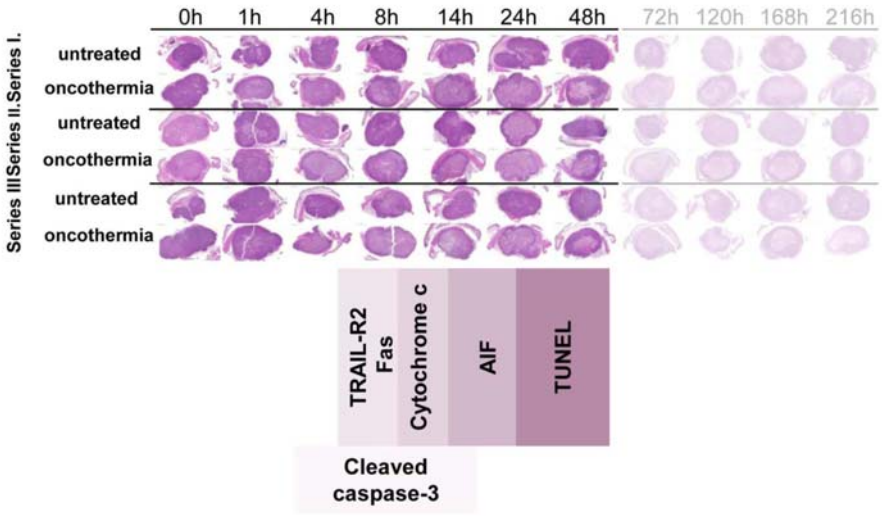

Figure 2. The summary of the possible mechanisms of actions of programmed cell death can be seen. Based on the immunohistochemistry results 8h post-treatment elevated TRAIL-R2 expression was observed, 8-14h post-treatment mitochondrial cytochrome c release was detected, in line with this AIF nuclear translocation was revealed on the14-24h samples. Between24-48h massive DNA fragmentation was identified by TUNEL assay

Cleaved caspase-3 positive cells (mostly leucocytes) appeared only at the tumor periphery 4-14h. Cytochrome c release was observed 8-14 h post treatment. AIF nuclear translocalisation occured 14-24h. Massive TUNEL positivity developed 24-48h post treatment. Heavy myeloperoxide and CD3 positive leukocyte infiltration ring showed 72-216 h possibly correlates to the tumor elimination.

Results

In HT29 colorectal cancer xenograft mEHT caused massive cell death, the occurrence of a caspase independent, AIF dependent programmed cell death subroutine.

Conflict of interest

Authors declare no conflict of interest in this project.

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Treatment of advanced cervical cancer with complex chemoradio - hyperthermia

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Treatment of advanced cervical cancer with complex chemoradio - hyperthermia

Abstract

This single arm, retrospective, single institution study investigated intention to treat patients (n=72) with advanced cancer of cervix of uterus. The study was performed in 2001-2010; providing 331 sessions. All patients had radiotherapies as fractional radiotherapy and intracavital brachytherapy. Some patients (n=34) received chemotherapy (Cisplatin 40 mg/m^2/week; concomitantly with teleradiotherapy) as well. Complementary to the tele-radiotherapy, oncothermia was used two times a week, targeting the pelvis. Applied energy dose was 45 W, 60 min. Oncothermia was applied immediately just after the infusion, when chemotherapy was also administered. Complete & partial remission were achieved in trimodal therapies for 73.5% of the patients, while we could stabilize the disease for 14.7% of the patients.

Introduction

Carcinoma of the cervix of uterus is the second deadly female malignancy after mammary carcinomas. Cervical cancer incident in Hungary, 21 incidences per 100,000 females (higher than the rate in Eastern Europe), and the mortality rate is 9.6 / 100,000 women /year, which is more than 500 deaths of women a year, [1].

Hyperthermia treatments are popular for gynecological applications [2], [3]. These focus on radiotherapy combinations [4], showing highly significant benefit of hyperthermia in overall survival, disease-free survival and local-relapse-free survival made by a randomized trial [4]. A large randomized controlled clinical trial of the radiohyperthermia was published in the Lancet [5], with great success. The results were very promising [5], but the control study [6] was disappointing. The explanation may be simple: a reference point was missing [7]. The chemotherapy combination (Cisplatin + hyperthermia for previously radiated cases) also shows feasibility [8] as well as the trimodal applications for cervix [9], [10], [11]. There are large debates in the topic [12], with counterpoints [13], and contras [14]. Our objective is to treat advanced cervical tumors with a new kind of hyperthermia (oncothermia) and add new results for the professional discussions.

Our department accepts patients from the three neighboring counties (Veszprem, Zala and Vas) for preoperative, postoperative, definitive and palliative treatments. In addition to the applied standard professional protocols since 2001 we have the possibility to apply complementary oncothermia treatments.

Method

A single arm, retrospective, single institution study investigated intention to treat patients (n=72) with advanced cancer of cervix of uterus. The study was performed from 2001 till 2010; involving 331 oncothermia treatment sessions.

After a complete medical check-up upon the decision of the conference of professionals (OncoTeam), the treatment protocol was prescribed and the patients were hospitalized. Patients with solid diagnosic proofs of advanced cervix carcinoma were involved in the study. The chemoradio-therapy was administered according to the standard protocol, and in the appropriate indications complementary oncothermia was used. All patients had radiotherapy. The CT based radiation with 3D conformity, targeting the pelvic regional lymph-nodes up to 30 Gy; it was followed by field-concentration in 1-2 steps until 50 Gy, in fractional solution by 2 Gy doses. Intracavital brachytherapy was applied complementary to teletherapy. After-loading technique was used once a week and three times altogether, providing 6-7 Gy/treatment. Additional chemotherapy was applied for n=34 patients, (Cisplatin 40 mg/m2/week; concomitantly with tele-radiotherapy). Complementary to the teleradiotherapy, oncothermia was used two times a week, targeting the pelvis. Two types of treatment devices were in use –'EHY 2000' and 'EHY 3000' (Oncotherm GmbH, Germany). Applied energy dose was 45 W, for 60 min. (In days of chemotherapy it was applied just after the infusion.) (The electrode positioning is shown on Figure 1.)

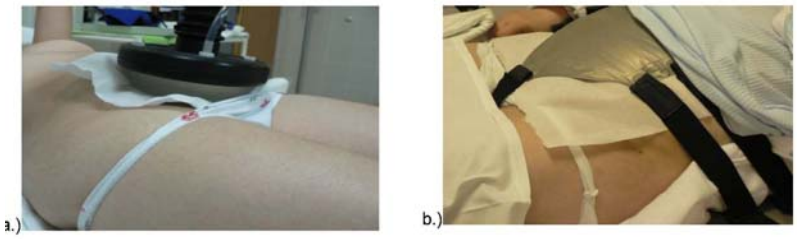

Figure 1. Arrangement of the treatment electrodes of oncothermia EHY2000 (a) and EHY3000 (b) type devices

The most important aspect of the treatment was the time schedule. The precise timing between chemo-, radio- and brachytherapy treatments was organized with high care, and oncothermia was applied immediately after chemo- or brachytherapy treatments, and at max 20 min before EBRT, and delivered during the whole course of the treatment schedule. The effectiveness was measured within confines of the oncological care. Imaging procedures as well as gynecological check-ups used to keep track of the development of the patients' status.

Note, this complementary treatment is currently not financed by the social insurance, therefore, patients had to pay privately for the oncothermia treatments. Unfortunately, this problem may affect the therapeutic plan in numerous cases, when the patient is unable to finance their own complementary treatment modality, even when the treatment is justified by professional aspects. In case of private cofinancing, the treatment plan of the commentary application is carefully designed to achieve the best available results.

Results

We first show a case report. The anamnesis of the 54 years-old female patient was G2,P2, with comorbidity hypertonia for 15 years. She had a stroke at the age of 54. She had vaginal bleeding symptom at the first diagnosis: Neopl.cerv.ut.std IIIB-IV; Fig. 2. Histology: carcinoma planocellulare. She rerceived the first external irradiation 2 Gy/day fractions, with 50 Gy complete dose. Additionally, afterloading brachytherapy was applied: 8 Gy, 5 Gy and 4.5 Gy, subsequently for three times.

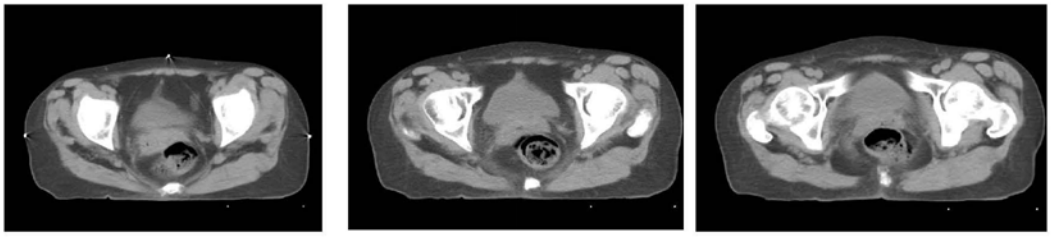

Figure 2. The diagnosis and the planning of the radiation and oncothermia complementary

Chemotherapy Cisplatin 40 mg/m2/week complementary to external radiation was performed, and oncothermia was given to her in 10 sessions. The result was a complete remission. With permanent checkup no evidence of disease (NED) can be found. The last control (four years after the finishing of the oncothermia) was NED again, Figure 3.

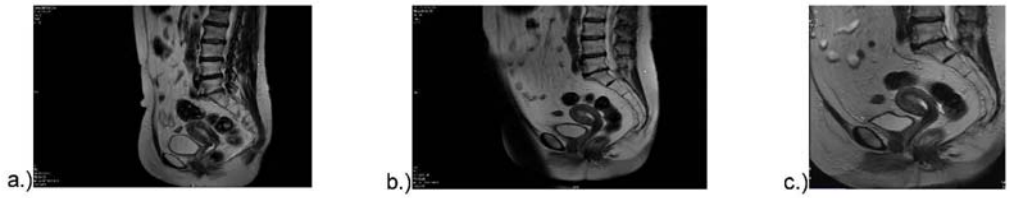

Figure 3. Control MRI of the patient: 1 months after oncothermia (a), one year after oncothermia (b), four years after oncothermia (c)

Patients had various number of treatments, Figure 4. in average 4.7 sessions were applied.

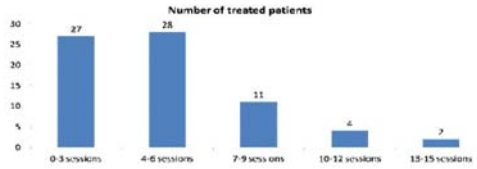

Figure 4. Distribution of the number of treatments for the patients (n=72)

The clinical response was measured in cases of trimodal applications (radiotherapy, chemotherapy and oncothermia, n=34). Results are promising: 73.5% (25/34) complete and partial remissions, 14.7% (5/34) stable disease and 11.8% (4/34) progressive disease, Figure 5.

Figure 5. Efficacy of radio-chemo-thermotherapy half year after finishing of the treatment

Our experience has shown that the addition of oncothermia had increased the effectiveness of conventional modalities, measured in the quality of life and survival elongation.

Conclusions

With a therapeutic plan prepared with due care and implemented precisely−especially the time between treatments and appropriate setting of treatment parameters−oncothermia can effectively complement the conventional oncotherapies. We will present our results in a case study, in which a patient's treatment was started only with palliative intent but at the end complete remission was available.

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Oncothermia Journal 7:293-294 (2013)

Experience in the treatment of liver metastases with special reference to the consequences of interruption of long-run treatments

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Experience int he treatment of liver metastases with special reference to the consequences of interruption of long-run treatments

Abstract

Approximately 800 metastatic liver cases were treated with oncothermia in our department. Many of them had long-time, cumulatively, huge number of treatments handled the disease a chronic for years. We investigated the long-time effects of the treatments, together with them interruption of the treatment serial for a few weeks. We are reporting a typical case: mammary carcinoma with liver metastases. The metastatic lesion was treated for four years, but the termination of the treatment for two months was fatal at the end.

Introduction

Our department had the opportunity to integrate oncothermia treatments into the treatment flow of oncological patients since 2001. We have treated nearly 1000 patients of whom 80 percent had malignant liver lesions, primary liver tumor or various liver metastases. Regrettably, not only the medical and the technical aspects but the patient's financial background have had a role when professionals are selecting the available modalities. We selected a subgroup of patients into a study (will be published elsewhere) who had had at least 60 treatments, investigating the effect of the long term treatment and its interrupts - at least 2weeks- on the overall local outcome (clinical response). In this subgroup of patients with liver lesions oncothermia was integrated into a combined treatment regime with chemotherapy. Only bimodal therapy was used, no radiotherapy was applied. The complementary oncothermia was administered immediately after the chemotherapy. The patient's status was evaluated with standard laboratory check-ups and imaging modalities. The frequency of the tests was determined according to the Hungarian Social Security guidelines taking into account the overall condition and complaints of the patient. The case study to be presented here is a patient who had two times complete remissions confirmed with imaging modalities -CT, PET, US- and had oncothermia treatments temporarily terminated. Relapsing of the tumor-growth was observed at both times, despite the continuous standard oncological care. In the inspected group of patients the malignant disease was handled like usually for chronic ones. The cases where the regular oncothermia treatments were interrupted – for more than two weeks – the diagnostic check-up showed progression of the lesions, despite the ongoing conventional chemotherapy. We are giving a case report in details showing the chronic treatment process for liver metastasis from mammary carcinoma.

Report

Mammary carcinoma of the female patient was discovered by a routine mammography when she was 34 y old. Breast-conserving surgery was successfully performed (R0) and post-surgical radiotherapy (50 Gy [fractionated on 2 Gy] plus 10 Gy electron boost) as well. During the diagnostics liver metastasis was discovered. Chemotherapy was started: Taxotere + Epirubicine. (see Figure 1.) Oncothermia was started with the device EHY3000 (Oncotherm GmbH, Germany), and 49 sessions were given by 60 W, 60 min, twice a week.

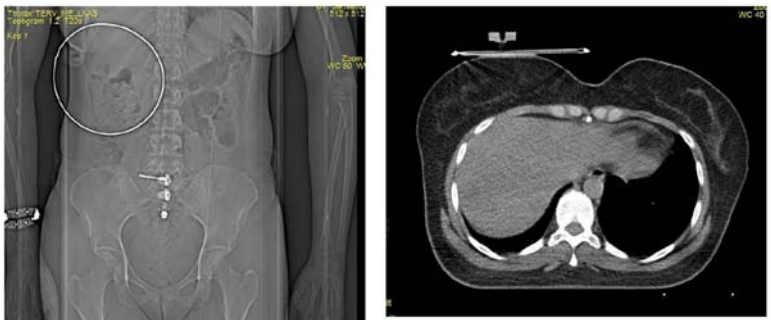

Figure 1.

During the oncothermia treatment regression was observed continuously and two month after finishing the oncothermia a PET/CT detected no evidence of disease (NED). The next checkup also found complete remission NED state, but a year later relapse was detected in the liver (see Figure 2.).

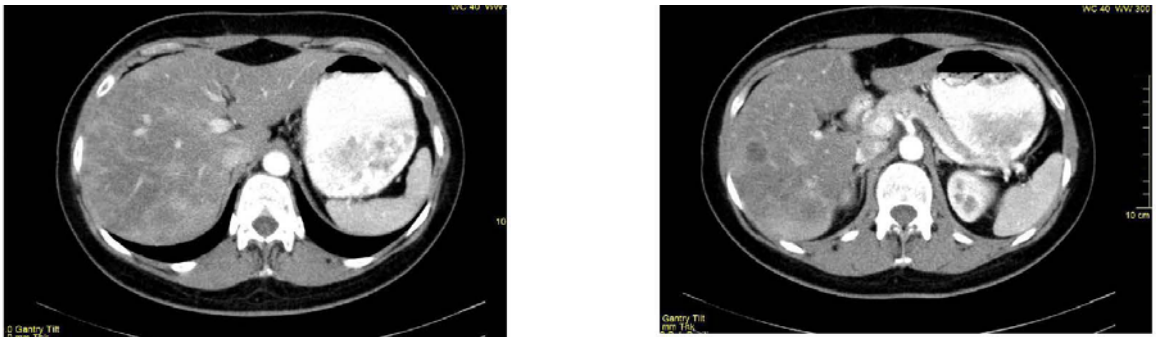

Figure 2.

Chemotherapy Taxotere +Xeloda followed by Taxotere + Paraplatin were administered, and complementary oncothermia 24 sessions once a week. A robust regression was observed in the follow-up period for one year (see Figure 3.).

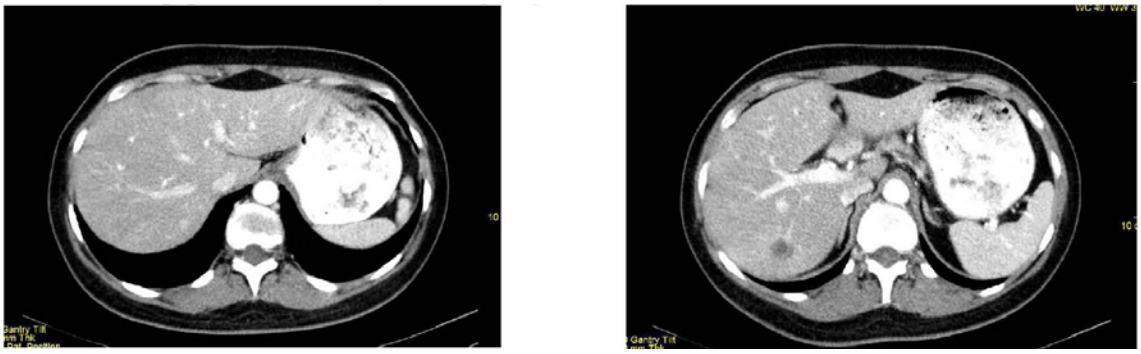

Figure 3.

When oncothermia was terminated, soon relapse was detected in the liver again with multiple lesions. The oncothermia was applied (60 W, 60 min, twice a week, 23 sessions), and the disease was stabilized. Oncothermia was terminated again, and only chemotherapy was applied (Taxol+ Gemzar). Rapid progression of the disease was observed (Fig. 4.), which led to exitus.

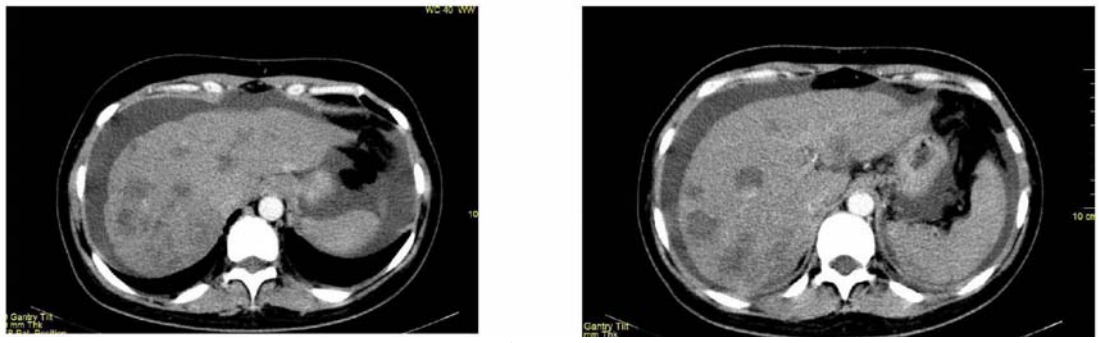

Figure 4.

Conclusion

Oncothermia can be applied for a long time, it handles the malignant liver tumor as chronic disease, but it should be continued during the whole chemotherapy course, or at least until the second negative control (2nd NED). Question arises: when should we to stop the oncothermia treatments and what diagnostic modality is suitable to confirm that there is no need for further treatments? The work is in progress.

Oncothermia Journal 7:296-300 (2013)

Oncothermia basic research at in vivo level. The first results In Japan

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http://www.hindawi.com/cpis/medicine/pp/104671/

Oncothermia basic research at in vivo level. The first results in Japan

Background

Oncothermia method (OTM) is a long time (since 1989) applied method in oncology [1] with great clinical success.[2] Oncothermia research group conducts investigations to reveal the basic mechanism of action of this tumor treatment method in basic research level performing a huge number of in vivo studies. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier and presented elsewhere [3], [4], as well as the recent in vivo results [5], [6]. In this paper we summarize the first results we have achieved in Tottori University, Japan.

Materials and methods

Study I.

In the first study we examine the effect of oncothermia treatment in a mouse tumor model. **Animal model:** Colon26 (murine colorectal cancer) cell line derived allograft mouse tumor modelwas used for this study with double tumors. The use of the mice and the procedures used in this study were approved by the Animal Research Committee of Tottori University.

Figure 1. Experimental mouse tumor model. Every animal had two tumors in both the femoral regions, the right side was teated, the left side was indivicual control

Experimental setup and treatment: A single shot 30min oncothermia treatment was done reaching maximum 42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement device (Lumasense m3300)

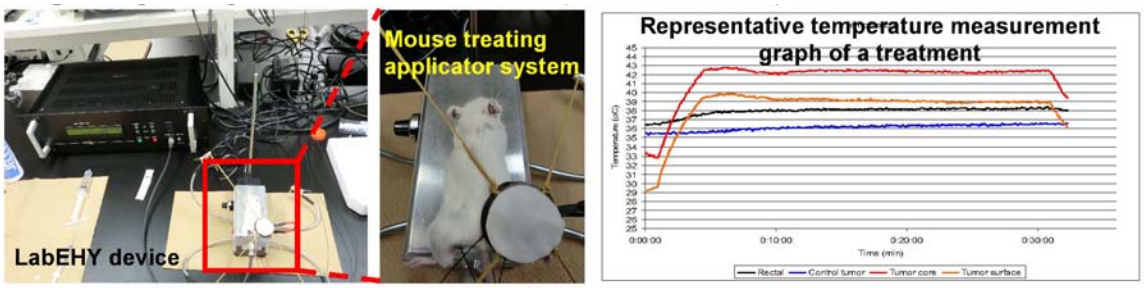

Figure 2. The experimental setup with the LabEHY system and a representative temperature measurement graph of the temperature curve of the tumors

Study design: A time course study was performed. After a single shot oncothermia treatment animals were sacrificed at 6H, 24H, 72H, and 120H later and tumors were removed. In all time-group there were 3 treated animals and 1 untreated control animal.

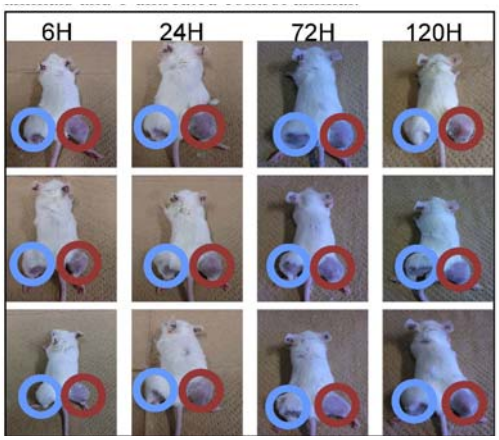

Figure 3. Oncothermia treated experimental animals in this study

Tumor sample processing: All the removed tumors were cut accurately at their centerline. After a standard histological process the samples were stained with HE and TUNEL reaction and Ki-67 immunohistochemical (IHCH) detection was performed (HE staining and IHCH detection were perfomed by Sapporo Byori Kensa Center, Japan). Samples were evaluated using complex histomorphological methods. Besides the qualitative analysis, a quantitative microscopical evaluation was also performed in the tumor samples stained with Ki-67. In ten randomly chosen high magnification (400x) microscopic view area of the living part of the tumor tissue samples the Ki-67 positive cell nuclei were counted, recorded and evaluated.

Study II.

In the second study we examined the effects of OTM to tumor oxigenization using a rat tumor model.

Animal model: 9L (rat glioma) cell line derived allograft rat tumor model was used. All animals had 2 tumors in both femoral regions. The use of the rats and the procedures used in this study were approved by the Animal Research Committee of Tottori University.

Oxygen level measurement: Tumor tissue oxigenisation level was measured using an O_2 sensitive electrode system (Eikon Kagaku Ltd. 150Dmodel).

Study design: In 11 rats, tumor tissue oxigenization level was measured using a pO_2 sensitive electrode system right before the treatment. The sensor probe of the system was inserted into the tumor tissue with the help and guidance of a teflone catheter, then the measured pO_2 value was recorded. Then the probe and the catheter were removed and a single shot, 30min oncothermia treatment was performed using a LabEHY system (Oncotherm Ltd.), reaching maximum 42°C intratumoral temperature. Right after the treatment the tumor oxigenization level was measured again.

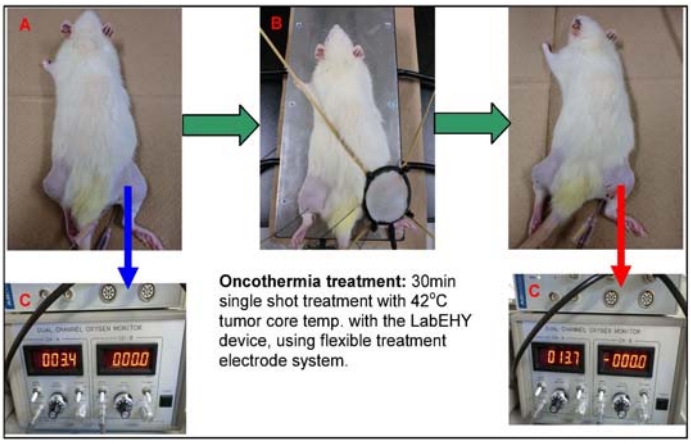

Figure 4. The study design. The 9L glioma cell line derived rat allograft tumor model (A), the oncothermia treatment procedure (B) and the tissue oxigenization measurement system (C)

Results

Study I.

1. A. Histomorphological changes in a qualitative and a quantitative way

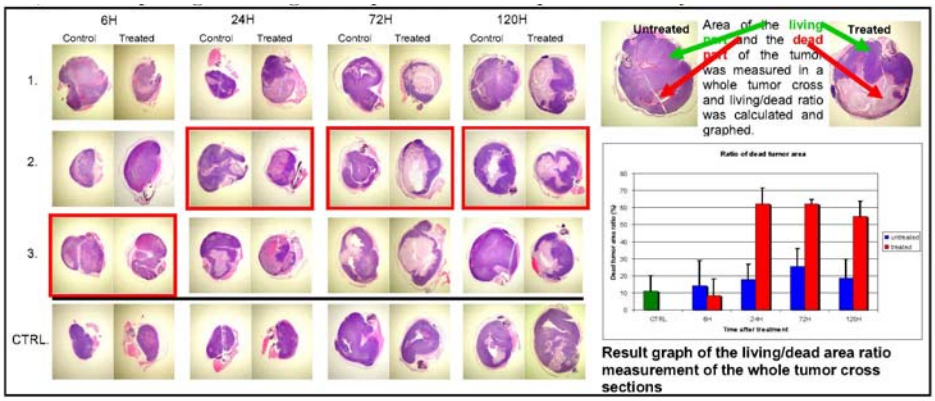

Figure 5. All the tumor samples involved in this study and the result graph of the quantitative analysis of the living/dead area ratio measurements. Drastic and selective tumor-destruction was detected adter a single shot oncothermia treatment. The tumor destruction was not immediate it had a time-delay. Samples marked with a red rectangle are evaluated in details

1. B. Histomorphological changes in details

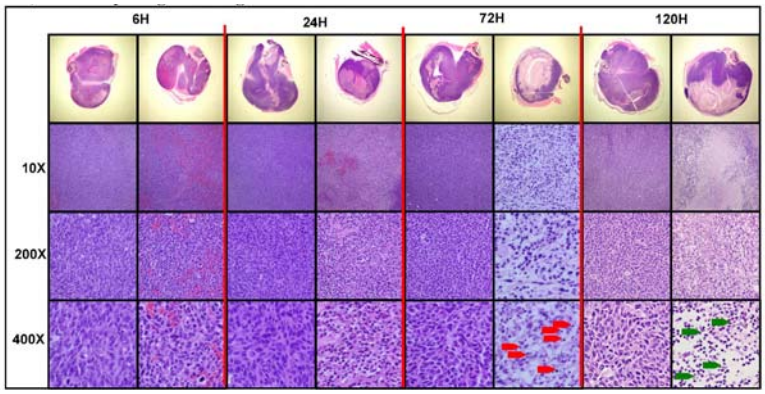

Figure 6. Detailed morphological analysis of the tumor samples marked with red rectangle in Fig. 5. 6H after the treatment the tumor cells look intact, but 24H after the treatment, the large part of the tumor is dead, the cells shrank with picnotic cell nuclei. In the 48H and 72H samples definite late morphological signs of apoptotic cell death was observed: extremely high number of apoptotic bodies (marked with red arrow). 120H after the treatment morphological signs of leukocyte (mostly neutrophiles, marked with green arrow) invasion is visible

2. TUNEL reaction

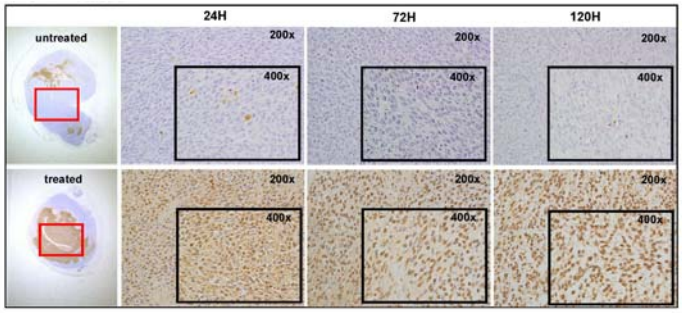

Figure 7. Result of the qualitative evaluation of TUNEL staining. TUNEL assay enzymatically labels the DNA fragments resulted by apoptotic cell death process. In the dead tumor area a huge number of TUNEL-positive cells were observed after a single shot OTM treatment

3. Ki-67 expression changes

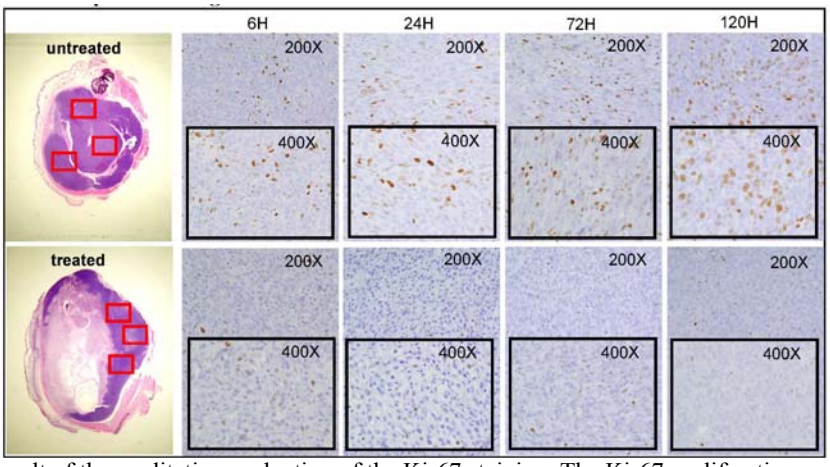

Figure 8. Result of the qualitative evaluation of the Ki-67 staining. The Ki-67 proliferation marker protein is expressed in the nuclear membrane only in the dividing cells. That is why sampling for Ki-67 positive cell analysis and counting were done from the living part of the tumors. The high magnification images from the living part of the tumor samples (marked with red rectangle in the whole cross sections)

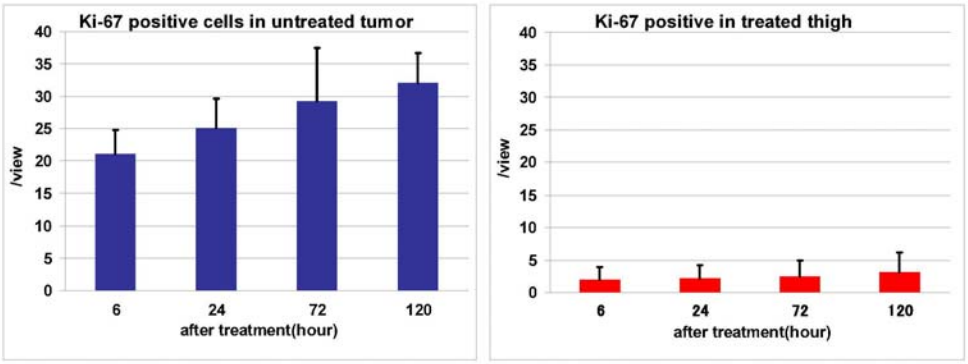

Figure 9. Result of the quantitative evaluation of the Ki-67 staining. Ki-67 positive cell nuclei were counted in 10 randomly choosen area of the living part of the tumor samples. In a very interesting way the number of Ki-67 positive cells were significantly decreased in the living part of the treated tumor compared to the control tumors

Study II.
Results of the tumor pO2 level measurement in a rat tumor model

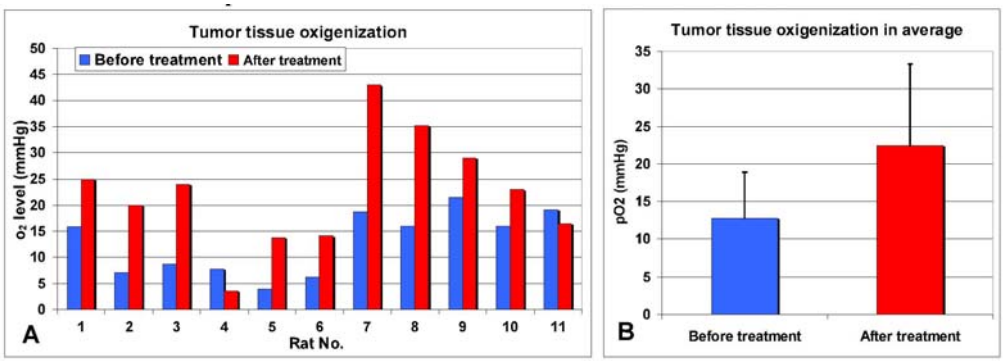

Figure 10. Result of the tumor tissue oxigenization level measurement in each animal (A) and in average (B). Tumor tissue pO_2 level was significantly higher right after the oncothermia treatment compared to the pO_2 level measured right before the treatment in case of 10 out of the total 11 animals. The pO_2 level was almost double after the treatment in average

Conclusions

1. In the mouse study, oncothermia treatment could significantly destroy the tumor tissue in a large volume of the tumor with only a single shot. Oncothermia treatment induce apoptotic cell death in the destroyed tumor tissue and effectively inhibit cell proliferation in the living part of the tumor.
2. In the rat study, oncothermia treatment could significantly increase the tumor tissue oxigenisation which created the basis of the strong synergism with radiotherapy and some chemotherapy.

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Oncothermia Journal 7:302-304 (2013)

Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

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Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

Introduction

Worldwide, breast cancer accounts for 22.9% of all cancers (excluding non-melanoma skin cancer) in women and it is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis.

Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment and geographical location of the patient. Survival rates in the western world are high, in developing countries, however they are much poorer.

The size, stage, rate of growth and other characteristics of breast cancer determine the kinds of treatment. Treatment may include surgery, hormonal therapy, chemotherapy (CHT), target therapy, radiotherapy (RT) and thermotherapy (hyperthermia).

Surgical removal of the tumour provides the largest benefit in many cases.

To increase the likelihood of cure, several chemotherapy regimens (Antracycline based or not) and target therapy are commonly given in addition to surgery. Chemotherapy may be standard, which means administered full dosage and scheduled bi-tri-weekly, or metronomic therapy, which refers to repetitive, low doses of drugs, designed to minimize toxicity (Dr. Harold J. Burstein of the Dana-Farber Cancer Institute).

Targeted therapy (TT) is a form of treatment that is designed to specifically inhibit molecules that provide advantageous growth signals to cancer cells.

Current targets: receptor tyrosine kinases, VEGFR inhibitors, EGFR inhibitors, endothelin receptors, KIT, BCR/ABL, PDGFR, growth factors, VEGF, estrogen, androgen, transcription factors.

Radiation is used after breast-conserving surgery and substantially improves local relapse rates and in many circumstances the overall survival too.

Some breast cancers are sensitive to hormones such as estrogen and/or progesterone, which makes it possible to treat them by blocking the effects of these hormones (Tamoxifene or Aromathase Inhibitors or Fulvestrant).

Hyperthermia is a type of cancer treatment in which the body tissue is exposed to high temperatures (40-42°C).

A research has shown that high temperatures can damage and kill cancers cells, usually with minimal injury to normal tissue. Hyperthermia increase blood flow to the warmed area, perhaps doubling the perfusion in tumours, while in the normal tissue the increase might be tenfold or even more. This enhances the delivery of medications.

Thermotherapy also increases oxygen delivery to the area, which may make radiation more likely to damage and kill cells, as well as preventing cells from repairing the damage induced during radiation session.

Numerous clinical trials have studied hyperthermia in combination with radiation therapy and/or chemotherapy. These studies focused on the treatment of many type of cancer, including breast cancer, and shown a significant reduction in tumour size when hyperthermia was combined with other treatments.

Materials and methods

In our long experience in Universitary Hyperthermia treatment of tumours associated with chemotherapy, we have observed that the response to the associated treatment determines the disease stabilization and significant clinical benefit for 24 months in 12 cases of metastatic breast cancer, whereas chemotherapy alone has turned out to be ineffective with disease progression causing bone marrow toxicity G3-4, fatigue G2-3, nausea and vomiting G1-G2, bone pain G3-4 and visceral pain G2-3. (see Table 1).

TOXICITY WITH CHT ALONE	TOXICITY WITH ASSOCIATED THERAPIES (CHT+HT)
Bone pain: G3-4	Bone pain: G1-2
Visceral pain: G2-3	Visceral pain: G1
Fatigue: G2-3	Fatigue: G1-2
Nausea and vomiting: G2	Nausea and vomiting: G1
Bone marrow tox: G3-4	Bone marrow tox: G1-2

Table 1. 2 of 12 patients underwent hormone therapy alone because of their allergy to chemotherapy drugs, other 10 patients underwent to CHT+/- Hormone Therapy according to the protocols seen in Table 2.

ID	Birth Date	Therapy
C. L.	25/08/1969	*Exemestane,*
C. C.	19/02/1947	*CMF, Docetaxel, Nolvadex, Enantone*
D.L.V.	01/05/1956	*Trastuzumab+CBDCA, Myocet+Gemcitabine*
C. P.	22/10/1956	*FEC, Trastuzumab, Vinorelbine, Capecitabine, Fulvestrant*
F. V.	15/03/1946	*Myocet+ Docetaxel, Myocet+Gemcitabine, Zoledronic Acid*
F.D.	20/08/1962	*Fulvestrant+Xeloda, CBDCA+TAX, NVB+GEM*
P.G.	11/12/1957	*Herceptin+NVB, Herceptin,Xeloda*
O.F.	14/09/1959	*Zometa+Tam*
M.D.	19/08/1956	*Xeloda+TXT+BEVA,CBDCA+GEM, TAXOL, NVB, Myocet*
L.G.	28/08/1921	*TXT+Letrozolo*
P.D.A.	24/03/1961	*Herceptin+CBDCA, Myocet+Gemcitabina*
M.C.	19/94/1954	*FEC,CBDCA+GEM, Herceptin+NVB, Lapatinib+Xeloda*

Table 2.

All patients underwent an average 30 cycles of capacitive hyperthermia, each consisting of eight 45-minute sessions every other day, using 300W per session. Heat was applied to a small or large area, site of the tumor or metastases, using radiofrequency (SYCHROTERM RF 13.56 MHz). External applicators two flexible antennas with a diameter of 26 cm) were positioned in area to be treated to raise its temperature.

Results

In these patients the improvement of perfomance status has allowed a return to regular life. This improvement of the quality of life showed a correspondent biochemical response, with a progressive reduction in tumor markers and showed also a diagnostic response with stabilization of disease: in some cases the reduction of size and/or number of metastases and in all cases with absence of metabolic activity disease (TB PET CT scan).

Conclusion

Our data confirms that the association CT-HT is positively viewed by most women treated for MBC perceiving it as helping them to feel healthier and experience a sense of freedom.

The most interesting finding was the observed beneficial effect of HT on pain and an improvement of Quality of Life (QoL).

The use of OT/CHT-HT combination may enhance efficacy vs CHT and OT alone. This surprising result may confer a small, but probably, clinically significant improvement survival and quality of life. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.

According to the studies on P.N.E.I.M (1, 6, 7), the results in the field of Clinical Pharmacology concerning drug abuse and medicines disuse, and the resulting recent studies in anthropology on cancer patients, all of our patients were treated at a preventive, therapeutic and post-treatment level with appropriate behavioural tests and drug treatments to avoid relapse. Clinical Pharmacology, in our opinion, considers every patient, according to the multidimensional approach (biopsychosocial), as a global being (8, 9, 10, 11).

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Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

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Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

Abstract

Aim: Investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa. **Objectives:** Evaluate the effect that the addition of oncothermia has on local disease control, progression free survival, overall survival at2 years, treatment toxicity, quality of life, economic impact and HIV status of participants. Radiobiology investigations will evaluate thermo-radiosensitivity and the molecular markers for thermo-radiosensitivity. **Methodology:** Phase III randomised clinical trial involving 236 HIV negative and positive stage IIb-III locally advanced cervical cancer patients. Treatment includes cisplatin, external beam radiation and brachytherapy. The study group will receive oncothermia treatments. Participants will be monitored for two years after completion of treatment. **Hypothesis:** The addition of oncothermia to standard treatment protocols will result in improved clinical response without increasing treatment toxicity in HIV positive patients or raising healthcare costs.

Introduction

More than 80% of hospital patients in Africa receive treatment in public healthcare facilities where resources and funding are limited.[1] The economic impact of cancer extends from the financial costs of treatment, rehabilitation, end-of-life care and loss of life to the economic costs of days off work, loss of productivity and the social-economic pressures on the family and community of cancer patients.[2] Sub-Saharan Africa has the highest HIV prevalence in the world.[3] It is a growing concern that the HIV status of a person and theanti-retroviral medications increase the patients' sensitivity to toxicity from radiation therapy and chemotherapy.[4,5,6] There is therefore a strong need for the investigation and application of technologies which can increase cancer treatment efficacy without increasing the treatment costs in Africa. Research from the Netherlands indicates that hyperthermia technology may increase the treatment efficacy whilst lowering the healthcare costs of cervical cancer patients.[7] The investigation of the use of affordable hyperthermia technology is therefore warranted.

Background

Cervical cancer is classified as an AIDS defining illness by the World Health Organisation. Over 80% of the 555 000 new cervical cancer diagnoses globally per year will occur in developing countries where HIV is prevalent.[8] Cervical Cancer is the second most prevalent female
cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published.[9] Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.10 cancer in South Africa with around 5 000 new cases diagnosed per year. This was 16.24% of all new cancer diagnoses in 2001, the year in which the last official national cancer statistics were published. 9Although recent statistics on cervical cancer in South Africa are lacking, doctors at the Charlotte Maxeke Johannesburg Academic hospital estimate that 20% of radiation oncology patients have cancer of the cervix, 60% of which are in stage IIIb at the time of diagnosis. An estimated 30% of the cervical cancer patients in public healthcare facilities are HIV positive.[10]

Aim

To investigate the clinical, economic and cellular effects of the addition of oncothermia to standard treatment protocols for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa.

Methodology

Study-design: Phase III randomised clinical trial. **Sample:** 236 HIV negative and HIV positive stage IIIb-III locally advanced cervical cancer patients will be recruited. This is based on the estimated required sample size for a two-sample comparison of survivors' function at two years. The statistical significance is defined as a two-sided alpha <0.05for a log–rank test, with a constant Hazard ratio of 0.5693, a statistical power of 90%, a 15% withdrawal rate and an estimated 140 events.We anticipate at least 50% of recruited participants will be in Stage III of the disease and around 30% of participants will be HIV positive. **Randomisation:** The participants will be divided into a control group (N=118) and a study group (N=118) and the sampling method used will be stratified random sampling (stratum: HIV status). Location: Charlotte Maxeke Johannesburg Academic Hospital, Gauteng, South Africa. **Treatment:** Participants from both groups will receive 3 doses of cisplatin (80mg/m2) administered three weeks apart, external beam radiation (50Gy administered over 25 factions of 2Gy) and 3 HDR intracavitary brachytherapy treatments of 8Gy each. The study group will receive two 60 minute modulated electro-hyperthermia (oncothermia) treatments per week during the external beam radiation therapy (total 10 treatments). **Duration:** The study is scheduled to start in early 2013 and the recruitment period is expected to take two years. Participants will be monitored for two years after completion of treatment protocols. The total study duration is expected to be four years. Preliminary results for the local disease control and radiobiology research are expected to be available within the first three years. **Radiobiology Research:** Radiobiology research will be conducted on tissue and tumour samples in order to study the effect that heating tumours has on the systemic and local response and toxicity resulting from treatment with ionising radiation.

Objectives

Primary Objectives: Evaluate the effect that the addition of oncothermia has on local disease control at 6 months (assessed by PET scans); progression free survival at 12, 18 and 24 months and overall survival at2 years (and the cause of death)in HIV positive and negative cervical cancer patients. Secondary **Objectives:**·To evaluate the adverse effects that can be directly attributed to oncothermia treatments. To evaluate the effects of oncothermia on tolerability andtoxicity of the prescribed treatments. To evaluate the economic impact of the addition of oncothermia to standard treatment protocols in public healthcare (based on quality adjusted life years). To evaluate the effect of the addition of oncothermia on the quality of life of patients (EuroQOL EQ-5D-5L questionnaire and the EORTC QLQCX23 cervical carcinoma specific questionnaire).·To evaluate the effect, if any, of oncothermia treatments on the HIV disease status of HIV positive participants by assessing the CD4 count; HIV viral load and the concurrent AIDS-defining conditions. To describe cervical cancer recurrence patterns in both groups by loco-regional and distant recurrences and by initial stage and suspicion for nodal metastasis pre-treatment. **Radiobiology:**·To evaluate thermo-radiosensitivity by measuring DNA damage (double strand breaks) in lymphocytes in response to ionising radiation combined with oncothermia. Haematological samples will be taken from patients in all four groups before and after the administration of radiation therapy. Double strand breaks will be measured using Micronucleus (MN) assays and the results will be analysed in order to determine whether the addition of oncothermia had an effect on the systemic toxicity of ionising radiation therapy in HIV positive and HIV negative cancer patients.· To investigate the molecular markers for thermo-radiosensitivity. This will be done by comparing gene expression profiles of cells extracted from biopsies of thermo-radiosensitive and thermo-radio-resistant tumours. Gene profiling of tumour samples will be used to identify potential molecular markers in the tumour cells which are associated with increased response or with resistance to radiochemotherapy combined with oncothermia.

Expected outcomes

It is expected that the addition of oncothermia to standard treatment protocols will result in improved local disease control and improved two year survival rates without increasing the treatment toxicity. We hypothesise that the addition of oncothermia will result in a reduction in healthcare costs associated with the treatment of cervical cancer.

Study rationale

This will be the first trial to date to investigate the effects of hyperthermia on HIV positive cancer patients and will be the first hyperthermia trial to be conducted in Africa. This will be the first phase III trial investigating oncothermia in cervical cancer patients and the first phase III trial investigating the trimodality treatment of cervical cancer patients. The study will investigate the economic impact of the addition of oncothermia to public healthcare protocols in Africa. The radiobiology research and genetic profiling is also unique in the field.

Acknowledgements

The hyperthermia device being used is the EHY2000 Plus which is being supplied by Oncotherm GmbH.

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Oncothermia as personalized treatment option

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Oncothermia as personalized treatment option

Abstract

Oncothermia is a nanoheating technology personalized for individual status depending on the state, stage, grade, and other personal factors. The guiding line of the treatment keeps the homeostatic control as much effective as possible. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. The applied step-up heating supports the physiological selection. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed. It has wide-range applicability for every solid tumor, irrespective of its primary or metastatic form. It could be applied complementary to all the known oncotherapy methods. It is applicable in higher lines of the therapy protocols, even in the refractory and relapsed cases as well.

Keywords: oncology, hyperthermia, oncothermia, personalization, Weibull-distribution, logistic-curve, response-time, surface-cooling

Introduction

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment using energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3], and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized [5]. The central task is to find the proper dose in the given application, and optimize the safety and curative limits of the applied dose. The lower limit is of course determined by the minimal effect by heating and the upper limit determined mainly by the safety issues, like it is usual for overdoses. The lower limit of oncothermia dose is indefinite, because in case of normothermia nothing else has action only the complementary treatment alone, which has no danger and has such curative effect as we expect from the gold-standards. For the upper limit however there are very definite technical and physiological parameters: the surface power-density of the signal is limited by the blistering to the 0.5 W/cm^2, (60 min basis) the internal hot-spots could hurt the healthy tissue, and in systemic application the physiology anyway limits at 42°C. The ultimate challenge is the developing heat resistance, which could make the hyperthermia ineffective, the disease became refractory of heating. The presently applied dose concept (CEM) in conventional hyperthermia is physically incorrect (temperature is not a dose) and due to its inhomogeneity concept it is hard to measure. The systemic (whole body) heating in extreme case reaches the 42°C (even the 43°C is applied sometimes in special conditions; CEM100%) but the expected distortion of the tumor does not happen. The high energy of the local heating (in most of the cases more than 1 kW is applied) at the start makes vasodilatation, which turns to vasocontraction over a definite physiological threshold at about 40°C. In consequence, over this threshold the high temperature blocks the complementary drug delivery and causes severe hypoxia, which is a severe suppress of the effect of complementary radiotherapy. Furthermore, the conductivity and permittivity of the skin is physiologically controlled by the blood-perfusion, which definitely modifies all the electromagnetic applications through it.

Hyperthermia overheats the actual target. It does not limit the target size at large (like whole-body hyperthermia) or at small (like heating with nano-particles) volumes. These methods are all characterized by the temperature, but they are characteristically different by their thermal state. In whole-body heating the thermal equilibrium drives the process, the body-temperature characterizes the treatment technically. However the body temperature characterizes the process less and less by decreasing the volume of the heated target, the body temperature becomes stable and almost independent from the local heating of a smaller volume in the body. Contrary to the thermal equilibrium in whole body heating, the nonequilibrium dominates in local treatments, and consequently thermal gradients will appear in the system.

Heating in nanoscopic range creates huge fluctuations of the local temperatures while the hot nanoparticles try to equalize their high temperature with their neighborhood. This process is typical for the commercial microwave heating, where not the extra nanoparticles, but especially the water-molecules are heated in their nanoscopic sizes, and those give the temperature to the entire volume by time. To

construct a nano-heating process the targeting of the nanostructures is a clue. Their selection from the other materials makes their controlled heating and also targeting the heat on the desired volume possible.
Extra nanoparticles could selectively absorb the electromagnetic energy heating up these small particles extremely in their neighboring spheres. Our approach is definitely similar, but by not using extra particles for selective energy absorptions. Our nanoscopic targets are naturally in the body, in the membrane of the malignant cells. The selection is based on the metabolic differences (Warburg effect), the dielectric differences (Szent-Gyorgyi effect) and beta-dispersion (Schwan effect) as well as uses the structural (pathological) differences (fractal effect) of the malignant lesions.
The main medical advantages of the method are its personalized targeting together with the effective selection and distortion of the malignant cells. The new direction of application focuses on the blocking of their dissemination as well as promoting the bystander (abscopal) effect acting on far distant metastases by a local treatment. The method is successfully developed in the direction of the immune-support, and a new patent covers an exciting area: cancer-vaccination with oncothermia.

Method

The physiological processes are determined by a dynamic equilibrium process-character, which is dominantly determined by special transports and logistics in the complex bio-systems. The distribution which is typical for general logistics, failure analyses and even for survivals is the Weibull distribution [6], which cumulatively looks

$$f(x) = e^{-(x/t_0)^a} \qquad (1)$$

where to is the unit time, when the value of the function is 1/e<0.63; the a-exponent in the distribution defines the shape (see Figure. 1.).

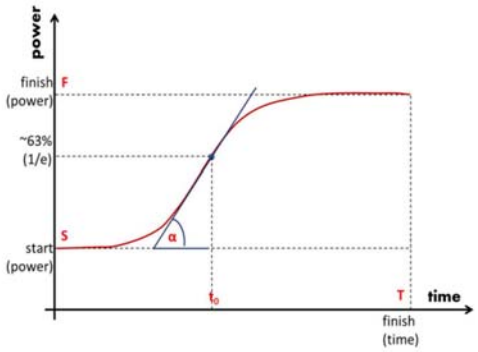

Figure 1. A special point of the Weibull function: the value, where t=t0 (1/e≈0.63). The derivative in the inflexion point equal (n/to)· (1/e)≈0.63*n, when to=1. The popular meaning of the parameters are: to is the stretching in x-direction (time-transformation), n is the stretching in y (incline of the curve). The parameters which has to be defined are the F, S, T, t0 and α, the finishing and starting power, the full treatment duration, the 63% of the power-increase and the slope of the power increase, respectively

The a-exponents were observed in various processes in wide range of applications. The generalized logistic function (sigmoid) could be constructed by various ways, but the so called Avrami-exponents (a, which is the exponent of the above Weibull function) are functionally appearing based on the extended works of FW. Cope [7], [8], there are some collected Avrami-exponents for various solid-state and biological processes show the universality of this logistic function.
The application of the Weibull distribution function approach multiple clinical applications and it is well established theoretically and practically, [9], [10], [11], [12]. It is used for a long time for survival description in gerontology [13], [14] and in oncology [15] as well.
The function has its inflexion point (where the tendency of decreasing changes) in t=t0 at 1/e (00.63) value. The derivative in this point is proportional to n. (The derivative there is exactly n/e [0-0.63n].) Therefore the parametric evaluation could be well checked in the t=t0 point. Note, the Weibull distribution could be well approached by normal (Gaussian) distribution over a>2. The area under the curve (shaded in the next figure) represents the complete energy-dose which is provided to the patient.

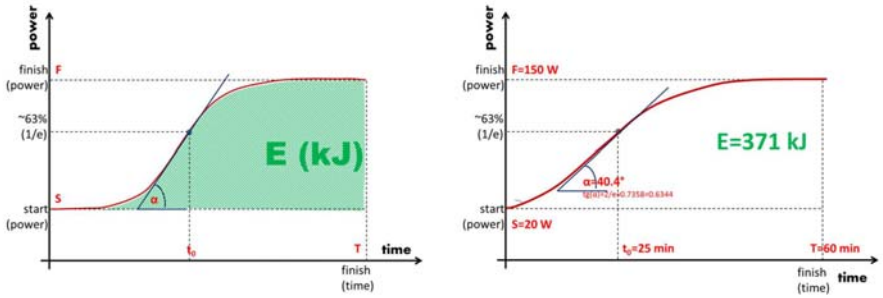

Figure 2. The provided energy is represented by the area under the curve (integral of the forwarded power, (a)), and the slope at the infexion point is proportional with the exponent "a", shown in numerical example (b)

However the continuous increase of the temperature does not fit to the homeostatic steady-state requests. Physiological response time (when the homeostatic equilibrium is reestablished after a definite disturbance) is 5-7 min. We propose at least 6 min on the definite chosen power level before the next increase step-up. Considering this transient as 6 min, the step-up heating is shown below. In this case the obtained dose is higher due to the upfitting rule, which we applied. In case of using 10 min relaxation time the protocol is shown on Figure 3.

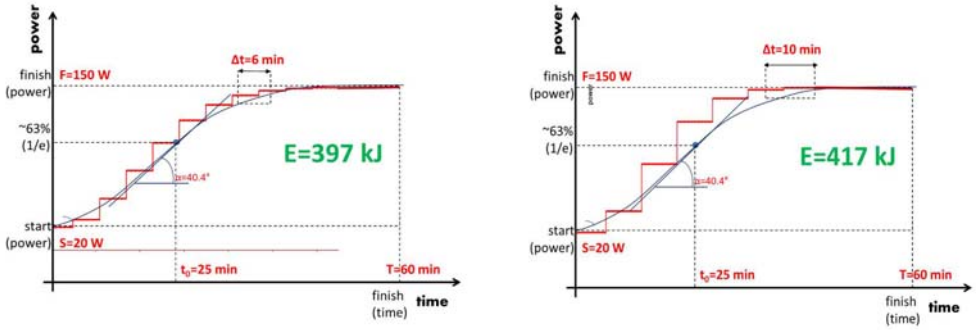

Figure 3. The step up heating follows the Weibull curve and keeps the steps until the homeostatic equilibrium. The provided cumulative energy could vary by the time-intervals of the steps

Difference between the poison and medicine is only the dose. In numerous cases people committed suicide taking medicine which would be useful in lower dosage in treatments. The dose is an important factor of efficacy safety and reproducibility too. In case of medication or radiation oncology we know the dose units as quantitative measurable values in mg/m2 or J/kg in chemo- or radiotherapies, respectively.
In hyperthermia the temperature is overemphasized as a dose, however it is not a quantitative parameter, it is a quality which makes the equilibrium spread all over the system. The temperature is an intensive parameter characteristic average of the individual energies of the small units in the system. In chemotherapy the cytotoxic remedies could cease very serious side effects, their safety has emphasized role in their applications. The chemo-doses are determined by the safety (toxicity) limits, independently of the person or the size of the tumorous target. The result (efficacy) is measured a definite time later, when the result is measurable or the toxicity (by personal variability) appears. Then the chemo-dose could be modified or complete change of the medication occurs. The actual dose varies in this second line, considering more the actual person and the actual situation.
When the medication definitely has no side effects (or the side effects are controlled) then the dose role has no upper limit by their safety, and also when the dose is limited but it is too high for the actual patient due to the biovariable poisoning limit, then the actually applied dose is of course lower, trying to fit it for the actual patient.
Oncothermia is governed by the very personalized way: the patient immediately (during the treatment and not a considerable time afterwards) sensing and note the toxicity limit: the heat-pain immediately limits the oncothermia dose. When the preset dose is too much actually it has to be modified by the personal requests. On the other hand, when the preset energy-dose is too small (the patients actually can tolerate more, the personalized toxicity limit is higher), then higher energy has to be applied until the personalized limit is indicated by the patient. Overheating is impossible, because the surface of the skin has the highest thermal load, and the heat-sensing is also there. This personalized dose regulation is the main factor of the safety and together with this for the efficacy too.

Results

Oncothermia has formulated a new paradigm [16], and made a pioneering job: it was the modulated electric field application, which later had good continuation in the literature in many laboratories worldwide. Its definite breaking results were on the modulated field effect combined with the thermal actions [17], showing large development in the present clinical practice. The electric field action was considered in serious manner in 2000 by Nature [18], and has been intensively applied in the clinical practice [19], [20]. The modulated electric field actions were applied for various accepted clinical trials [21], [20].

The second new approach was the controlled micro-heating, [22], which makes it possible to introduce the dose as the absorbed power [23], [24]; like it is used in the standard radio-therapy as well.

The third new important field which was pioneered by oncothermia is the immune-stimulative applications of the modulated electric field, showing the definite natural apoptotic cell-killing [25], [26] with activation of various leucocytes [27] to isolate [28] and kill the malignant lesion. The fourth pioneering field is the [29] abscopal (bystander) effect of modulated electric field. According to the remark of world-famous tumor vaccination researchers in their last conference, it could be a good basis to be involved in this very modern and promising field. This effect makes a great opportunity to make the local treatment systemic [30], like the locally observed tumor becomes systemic by its malignant progress.

In clinical point of view Oncothermia makes also important and unique steps to go forward with proving its trustful performance [31]. It has various levels of clinical evidences, has multiple studies including phases of the data development from the toxicity measure (Phase I), [32],[33], through the efficacy (Phase II) [34], and the wide range clinical applications (Phase III/IV) [35]. Oncothermia has many retrospective studies but also many prospective ones in Phase II and Phase III categories. The retrospective data are compared to the large databases, and compared to the multiple clinical institutions, making statistical evidences of the validity of the data.

Presently altogether oncothermia has 54 clinical trials for malignant diseases involving 2796 patients from six countries (Germany, Hungary, Italy, S.Korea, China, Austria). These trials cover 15 localization (see Table 1.) The patients were in advanced stages, mostly over the 3rd line treatment. The comparison with the large databases was made in multiple clinics relations, showing extremely large (minimum 20%) enhancement of the 1st year survival percentages.

Study	Number of studies	Number of patients (n)	1st year survival (%)	Median overall survival (m)
Brain studies	10	521	73.99	22.19
Pancreasa studies	6	184	47.04	11.02
Lung studies	5	636	64.76	15.79
Bone	3	79		40.10
Liver metastasis	7	267	86.00	18.06
Colorectal	7	447		
Gynecology (pelvic)	5	100	93.22	33.25
Breast	1	103	97.10	52.10
Esophagus	2	19	41.70	55.64
Somach study	1	68	58.90	14.40
Kidney cancer	1	39	84.60	35.90
Urinary bladder cancer	1	18	85.00	36.50
Head and neck	1	64	92.20	26.10
Soft tissue sarcoma	1	16	100.00	35.90
Prostate	3	135	88.90	38.80
SUM	**54**	**2796**		

Table 1. List of oncothermia studies. Some references of various localizations: Bone (metastatic) [36], [37]; Breast [38]; Colorectal [39], [40], [41], [42], [43]; Gliomas [44], [45], [46], [47], [48], [49], [50], [51], [52], [53], Esophagus [54]; Brain (metastatic) [55], Kidney [56]; Liver (primary) [57], Liver (metastatic) [58], [59]; Lung (NSCLC) [60], [61]; Lung (SCLC), [62], [59], Pancreas [63], [64], [65], [66].

Conclusion

Oncothermia has good clinical achievements in the clinical studies, making a stable basis of the clinical applications in various advanced primary and metastatic malignancies and giving the long time expected stable standard on oncological hyperthermia. Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes the accurate and personalized treatment possible by this method.

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Deep temperature measurements in oncothermia processes

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Deep temperature measurements in oncothermia processes

Abstract

Temperature in depth of in various model-systems was measured, starting with muscle and other phantoms. Temperature was measured by flouroptical system (Luxtron) in the various points of the phantoms. It was shown that the temperature can be selectively increased in the target. In water-protein phantom the protein coagulation (>60 °C) was observed selectively while the water temperature around it was a little higher than the room temperature.

Keywords: oncothermia, temperature, penetration-depth, hyperthermia, selectivity, phantom

Introduction

Research of oncothermia has wide range of temperature measurements from its origin in 1988. Numerous experiments were done in various model systems and phantoms, including various ex-vivo tissues and complex body-parts of various animals [1]. Independently from Oncotherm the temperature development was also measured in complex meat-phantom [2].

New model-experiments were performed recently to show the depth profile of heating and be sure on the deep heating facility by oncothermia devices. Some devices are using the size of the electrode pair for focusing, telling that the small electrodes have less penetration. It is true generally in the radiative approach, but our impedance heating is different. We had used the smallest available electrode (10 cm diameter) showing that even with this the impedance heating is effective in depth.

The problem of the controlled and focused heat-delivery to deep-seated tissues is a long-standing problem of the local hyperthermia in oncology, [3]. The multiple artificial methods to focus the temperature have numerous technical and physiological problems. The energy could be focused in a planned and accurate way, but the temperature spreads naturally. Further problem is the physiological control in living objects, which likely acts by negative feedback, limiting or blocking the temperature increase during the actual heating process.

Methods

The early (twenty years old) phantom measurements have been repeated under much more modern conditions, and have been checked with optical fiber thermo sensing method, and also the outside heating profile was controlled for visual pattern by a high-sensitivity thermo-camera system. The in-vivo models, as well as all the animal experiments, have used flouroptical temperature measurements in depth. The precise inserting of the sensors was controlled by imaging technologies in large animals and humans.

We had modeled various human sizes, [4], orienting waists [thickness] as: underweighted ~70 cm [~18 cm], healthy ~ 85 cm, [~21 cm] overweight ~114 cm, [~28 cm] obese ~152 cm [~33 cm] and used phantom thicknesses 15 – 32 cm depending on the patient's weight and the part of the body (see Figure 1.). The thickness of an average patient is around 22 cm. (see pictures below), so the asymmetric solution is better for humans than the symmetric. Probably there are many animals, (horses, cows, elephants, etc.) where the 22 cm is not enough, for these cases the symmetric solution is better. (We are using it in veterinarian solutions for these specialties).

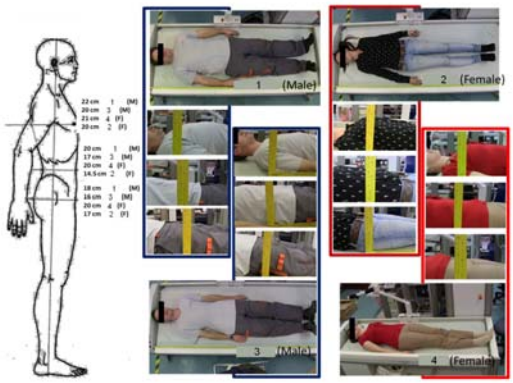


Figure 1. Typical human thicknesses of various healthy volunteers

First we measured in a 20cm phantom column, taking care on the heat-exchange with the environment and the cooling by the bolus and the water-bed. In the first experiment the phantom was mixed pork-meat taking care about the muscle and fat tissue combinations, modeling the living body complexity well. The phantom was a 10 cm diameter and 20 cm long cylinder, placed on the treatment bed, and heated by 60 W. (see Figure 2.) (20 cm was chosen for a thickness of an average suffering cancer patient.)

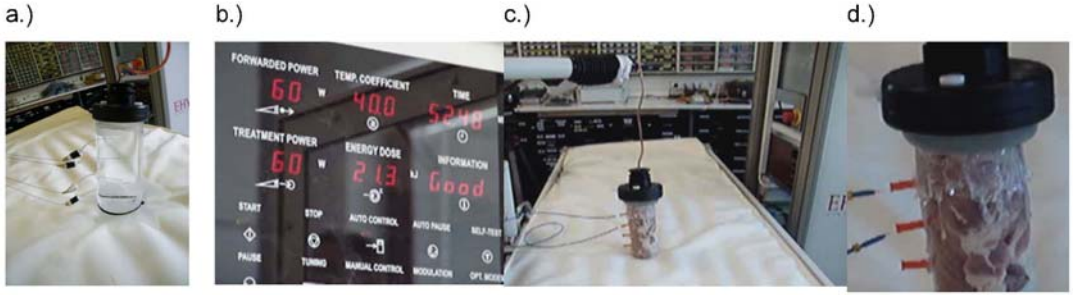


Figure 2. Typical experimental arrangement at EHY2000+ device. Experimental cylinder with the temperature sensors (a) Well turned device (b). The muscle phantom on the treatment bed (c) Muscle phantom with temperature sensors (d)

Other experiments were targeting the selection process of oncothermia. Various phantom materials were placed in distilled water and the system was treated by oncothermia, Figure 3.

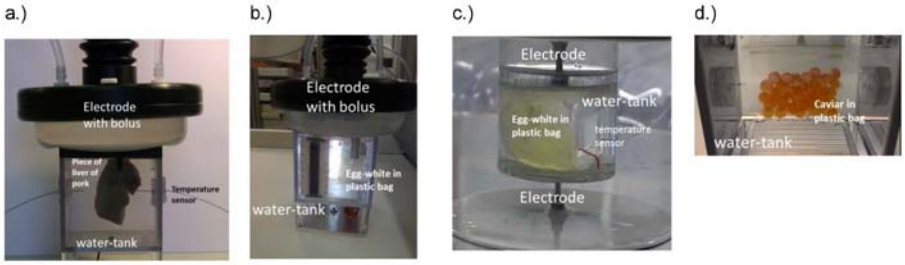


Figure 3. Various phantom arrangement for study the selection solutions. A piece of liver of pork (a), egg-white in rectangular water-tank (b), egg-white in cylindrical water-tank (c), caviar in water-tank (d)

Results

The deep temperature was rapidly enhancing, reaching the 42°C (from 24°C) increasing 18°C up, in the depth of 6 cm, (see Figure 4.).

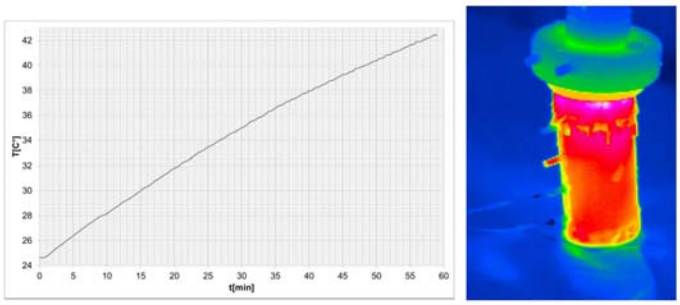


Figure 4. The temperature in depth was increased considerably. The outside temperature is of course lower, due to the cooling of the outside air on room temperature (22°C). The highest temperature in 6 cm depth (red temperature sensor in the thermo picture) was 42°C, which was reached from 25°C at start (17°C increase made by 60W, 60 min)

Approaching more the depth profile of the heating we measured the temperature in depths of 4, 8, 12, 16 cm depth. The same phantom system was used with chopped pork meat, (see Figure 5.) The power was 75 W. The measured temperatures were controlled by fluorooptical (Ipitek product) and thermistor sensors (Tateyama product). The starting initial temperature was 24°C. After 1 h the top sensor (4 cm depth) indicated over 54°C, while other depths of 8, 12 and 16 cm was developing 53°C, 51°C and 45°C. (The down electrode was cooled by the water-bed having much a loss of the heat. This temperature

development was 30°C the largest and 21°C the smallest values. Without water-bed the down-cooling was not effective, and the phantom was heated higher.

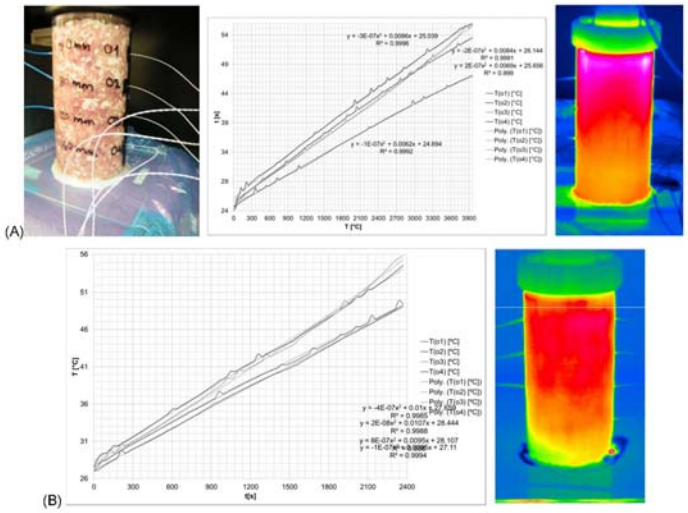


Figure 5. Depth profile with (A) and without (B) water-bed cooling effect. The temperature was about the same in both systems, when the heating time was 60 min and 40 min in the canse of water-bed and without water-bed cooling of the system. The deepest temperature however was over 45°C, (18°C increase) in 16 cm depth

The most realistic geometry was used when we put the experimental phantom 31 cm height, simulating an obese patient, (see Figure 6.). The in-depth measurements show definite increase of the temperature over 45°C (from 27°C) in depth of 24 cm applied 100 W heating power. The well increased temperature (peak) in depth of ~10 cm is well observable on the thermo picture.

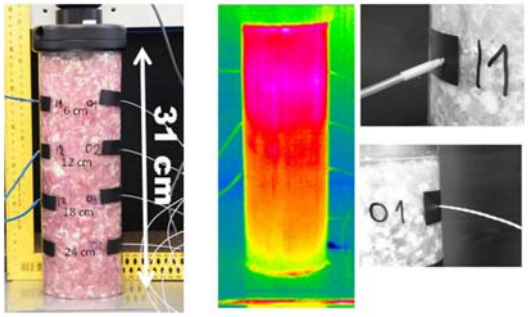
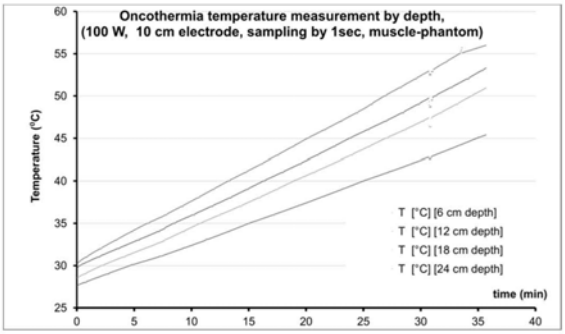


Figure 6. The phantom column, its thermo-picture during the treatment and the thermo sensors ("O" - Oncotherm-Tateyama system, "I" - Ipitek system for control). The thermo-picture shows a temperature distribution which has a maximum in depth of ~10 cm. The high temperature increase is proven in depth as much as 24 cm



The phantom experiments for demonstrating the selection process had shown well the selection mechanism of oncothermia. The liver experiment has shown a high temperature increase inside of the liver-piece, see Figure 7.

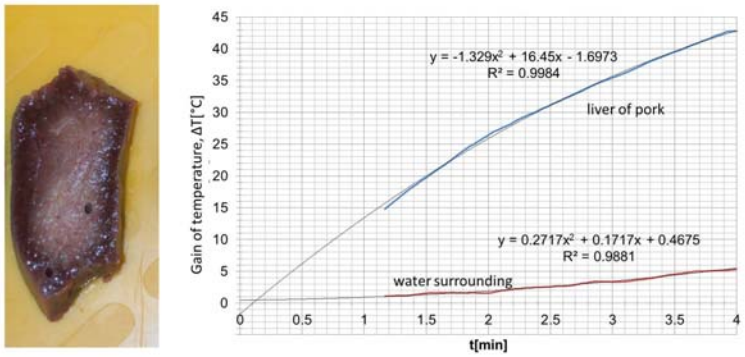


Figure 7.

The same selectivity was measured on egg-white in plastic bag surrounded with distilled water in two different-shape water-tanks (figure 8. and figure 9.). The temperature was as high as the protein coagulation happen (T>60 °C), while the water temperature was only slightly up (2°C over the room temperature 24°C), by the heat form the coagulated egg-white. The same was observed on the caviar phantom, when the balls were individually "cooked" without increase of the temperature of the surrounding water, see Figure 10.

Figure 8. Coagulation of egg-white starts in its inner-volume, while the water around remains cold

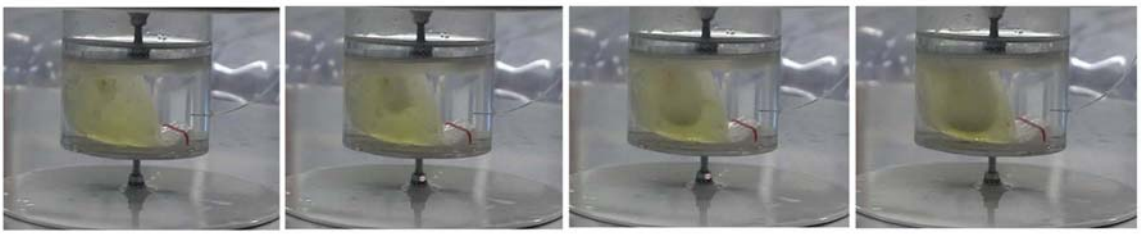


Figure 9. The development of the egg-white coagulaton is well seen in the cylindrical water-tank. The coagulation starts inside of the egg-white, the watr outside remains cold

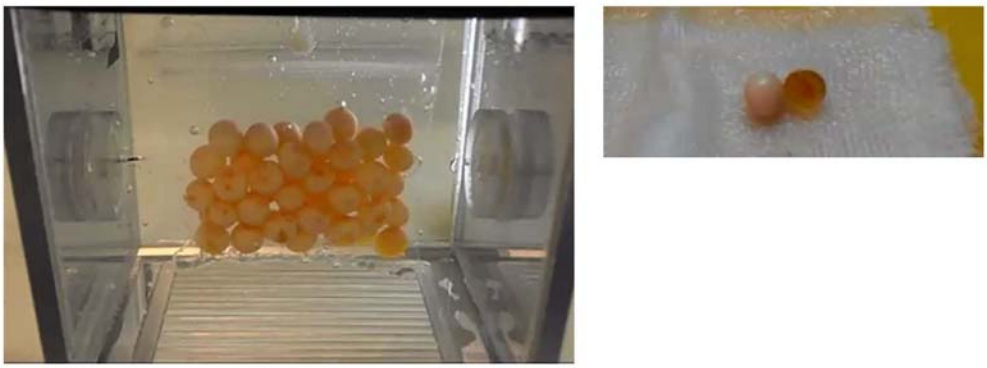


Figure 10. The caviar pieces are cooked, while the water had no temperature increase from room-temperature

Conclusion

Oncothermia is an effective deep heating method for tumor-lesions, increasing the temperature by a safe, controlled and well-targeted way. Phantom measurements proved the possibility of the selection when the local temperature can go up to ablative regime, without heating up the non-targeted volume. This is the basic of oncothermia selection and is expected to be effective in nanoscopic range at the membrane of the malignant cells.

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Modulation effect in oncothermia

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Modulation effect in oncothermia

Abstract

Conventional hyperthermia is based on the local or systemic heating, which is measured by the realized temperature in the process. Oncothermia applies nano-heating, which means high energy absorption in nanoscopic range of the malignant cell-membrane selectively. This high temperature and its consequent stress create special effects: it evolves possibility of chaperone proteins to be expressed on the outer membrane by softening the membrane, and starts various excitations for programmed cell-death of the targeted malignant cell. The process needs special delivery of the energy which selects as desired. A strict 13.56 MHz sinusoidal carrier frequency is amplitude modulated by time-fractal signals. The modulation is far from any sinus or other periodic patterns, it is a 1/f spectrum, having definite templates for its construction. In some personalized cases definite template is used for fractal pattern, which is copied from the actual character of the tumor-pathology or other specialty of the target.

Keywords: modulation, radiofrequency, hyperthermia, oncothermia, pink-noise, 1/f-spectrum, timefractal, apoptosis

Introduction

The understanding the principle of modulation starts with a simple everyday task: listening our favorite radiobroadcasts, like 107.1 MHz Cologne, 91.8 MHz Frankfurt, Radio Energy (Munich) 93.3 MHz etc. We choose the frequency (tune the radio to select it) and we enjoy the broadcast. The carrier frequency which was the basic of the tuning never meets the ear, it is too high for sensing, and anyway it would be a too monotonic sound, it is only a single frequency. Instead of monotony we hear the music or other information carried by this chosen frequency. The carrier-frequency delivers the real information coded in its modulation (see Figure 1.).

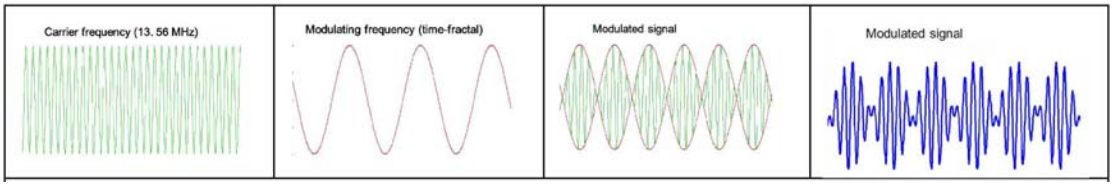

Figure 1. The amplitude modulation. Carrier frequency (a), modulation signal (b), modulated signal shown the frame of the modulator (c), modulated signal alone (d)

The carrier frequency carries two important information characters:
- its modulation finds the target on cellular level and
- its energy heats up the selected cells from outside by its neighboring extracellular matrix.

The modulation method is similar to the process when the light goes through the windows-glass. When the glass is transparent to that specific set of colors (visible light, definite interval offrequencies), its absorption is almost zero, all energy goes through it. However, when it has any bubbles, grains, precipitations, etc., those irregularities will absorb more part from the energy, their transparency will be locally low, their energy absorption will be high, they will be heated up locally. It is a self-selection depending on the material and the frequency (color) which we apply in the given example. The carrier frequency delivers the information (modulation frequencies), for which the cancer cells are much less "transparent" than their healthy counterpart is. Malignant cells are heated up by the selectively absorbed energy.
The applied time-fractal modulation is one of the specialties, which only oncothermia has in hyperthermia applications in oncology.

Method

The living material is not an ordered solid. Contrary to the crystals, it is hard to introduce the cooperativity. The living matter is in aqueous solution, which is mostly well ordered, [1] in the living

state. This relative order formed the "dilute salted water" into the system having entirely different mechanical, chemical, physical, etc. behaviors as the normal aqueous solutions. Indeed, the important role in the living systems of the so called ordered water was pointed out in the middle of sixties, and later it was proven, [2]. At first the ordered water was suggested as much as 50 % of the total amount of the water in the living bodies [3]. The systematic investigations showed more ordered water [4], [5] than it was expected before. Probably the ordered water bound to the membrane is oriented (ordered) by the membrane potential, which probably decreases the order of the connected water, so increases the electric permeability of the water [6], and so decreases the cell-cell adhesion and could be the cause of the cell-division of even for the proliferation [6]. According to Warburg's effect the metabolism gradually favors the fermentation in malignancy [7]. The end-products of both the metabolic processes are ions in the aqua-based electrolyte. The oxidative cycle products dissociate like 6CO2+6H2O 9 12H+ + 6CO32- while the lactate produced by fermentation dissociates: 2CH3CHOHCOOH 9 2CH3CHOHCOO- + 2H+. Assuming the equal proton production (by more intensive fermentation energy-flux) the main difference is in the negative ions.

The complex lactate-ion concentration grows rapidly, and increases its osmotic pressure. Keep the pressure normal, the dissolvent (the monomer water) has to be increased as well, seeking to solvent by non-ordered water. Indeed, it is measured in various malignancies that the water changed to be disordered, [8], [9], [10], so in these cases the ordered water concentration in cancerous cells is smaller than in their healthy counterpart. Consequently, the hydrogen ionic transmitter became weak, the removal of the hydrogen ions became less active. This decreases the intracellular pH and the proton gradient in mitochondria, which is directly worsening the efficacy of ATP production. To compensate the lowered proton-gradient, the membrane potential of mitochondria grows. This lowers the permeability of the membrane, decreases the mitochondrial permeability transition, which have crucial role in apoptosis, [11], [12]. (The high mitochondrial membrane potential and low K-channel expression had been observed in cancerous processes, [13]). These processes lead to apoptosis resistance, and for the cell energizing the ATP production of the host cell (fermentation) became supported. The free-ion concentration increases in the cytoplasm, and so the HSP chaperone stress proteins start to be produced. This process needs more ATP as well as it is anti-apoptotic agent, so the process could lead to the complete block of apoptosis. Rearranging (disordering) the water structure needs energy [14]. It is similar to the way, like the ice is melted with latent heat from zero centigrade solid to liquid with unchanged temperature conditions. This drastic change (phase transition) modifies the physical properties (like the dielectric constant) of the material without changing the composition (only the microscopic ordering) of the medium itself.

The decisional role of the two metabolic pathways (the oxidative and the fermentative) was studied by Szent-Gyorgyi [6], having etiology approach, and using additional formulation. His interpretation describes the cellular states by two different stages. The alpha-state of the cell is the fermentative status.

What makes the difference on the absorption? It is the missing collective order in malignancy. The healthy cells live collectively. They have special "social" signals [15] commonly regulating and controlling their life. They are specialized for work-division in the organism, and their life-cycle is determined by the collective "decisions". The cancerous cells behave non-collectively; they are autonomic. They are "individual fighters", having no common control over them, only the available nutrients regulate their life. The order, which characterizes the healthy tissue, is lost in their malignant version, the cellular communications disappeared [16].

The problem of the autonomy of the malignant cells makes the treatment very much complicated, because cancer has its own fractal structure, [17]. The analysis of the fractal structures of malignancies could even indicate the stage of the disease [18]. Careful fractal analysis can make predictive information for the prognosis as well, [19].

Results

The effect of modulation was measured on immuno-deficient nude mice xenograft model made by HT29 human colorectal carcinoma cell-line. The single shot oncothermia was used for 30 min keeping 42 °C in the tumor. A day after oncothermia a definite difference can be detected between the modulated and unmodulated effects, which became very emphasized after two days, (see Figure 2. [20]). This is one of the reasons, why we propose in the protocols of oncothermia the treatment frequency every other day.

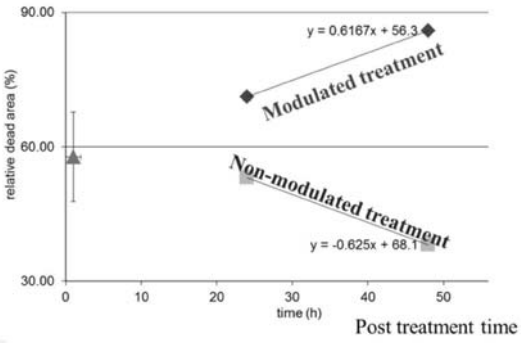

Figure 2. The modulation reestablsihes the apoptosis, the natural cell-killing process, and after 48 h the effect is obviously acting. (HT29 xenograft model on single-tumor-bearing mice, heating single shot, 30 min to 42 C. Animals were sacrificed 24 h after the treatment.)

The multiple fractal physiological proofs are extended by the oncothermia specialized experimental results too. We used the same xenograft model on a high number of nude mice (30 tumors were examined, 5-5 mice having double tumors in two arms, modulated (active) arm and non-modulated (passive arm)). The single shot experiment was also for 30 min, but the tumors were treated only on 40 °C. We know it from other experiments that this temperature is generally not enough to make hyperthermia effect in classical heating approach. The animals were sacrificed after 48 h, and the results (see Figure 3.) show well the modulation effect: the treated arm in modulated cases had 45.8% higher cell-distortion than the non-treated part, while the effect in the non-modulated mice was only 3,9%.

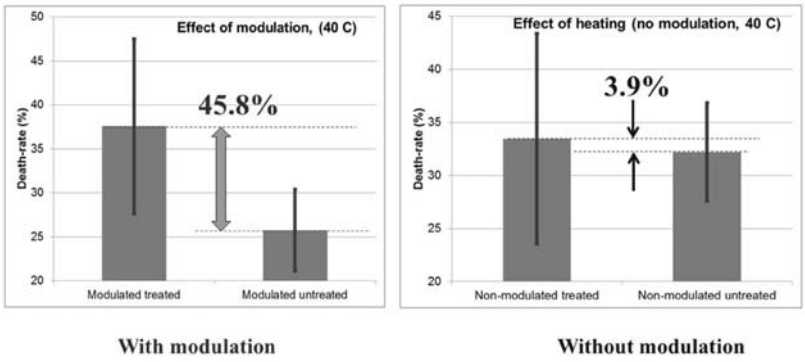

Figure 3. The modulation makes definitely and significantly higher tumor-destruction compared to the non-treated side than the non-modulated cases. (HT29 cell-line in nude mice, xenograft model, single shot for 30 min keeping at 40 C, 5-5 mice were used in both arms, sampling was taken 48 h after the treatment

More detailed explanation and background of the modulation applications in Oncothermia could be obtained from the Oncothermia book [21]. The modulation method has patent applications [22], [23], [24].

Conclusion

Oncothermia modulation is one of the three specialties of this treatment. Its efficacy and its role in the personalization process have introduced an effective tool for the apoptotic cancer-cell destruction.

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Synergy between TCM and Oncothermia

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Synergy between TCM and Oncothermia

TCM and cancer

Traditional Chinese medicine-based herbal medicines have gained increasing acceptance worldwide in recent years and are being pursued by pharmaceutical companies as rich resources for newer drug discovery. For many years, traditional Chinese medicines (TCM) have been applied for the treatment of cancers in China and beyond. Chinese medicine employed treatments for cancer for over two millennia. The book The Rites of the Zhou Dynasty (1100- 400 BCE) refers to physicians specializing in the treatment of swellings and ulcerations or necrosis and ulcerations. These terms are still utilized in the modern practice of traditional Chinese medicine to denote the study and treatment of tumors that are both benign and malignant.8 Early Chinese medical texts described different types of breast tumors and discussed their clinical appearance, physiological origin and severity. Over 100 names were recorded for tumors in early medical literature. Most of these terms represent conditions that would be regarded as early cancerous conditions in the Western medical literature. The most frequently cited term for breast cancer was breast rock12. In the Yellow Emperors Classic of Internal Medicine (written circa 250 BCE), the first clinical picture of breast cancer was described. The prognosis was estimated to be approximately ten years after diagnosis and the process of progression, metastasis and death was detailed.

The current trend in China is to integrate, or combine Western therapies with TCM in the treatment of cancer. There are no available statistics on the proportion of women using this approach. Our collaborators in China- Hebei University TCM Department- estimate that about 70%-80% of women diagnosed with breast cancer in the metropolitan areas, where Western medicine (WM) is favoured, are using the combined approach at some point during their treatment of breast cancer while a very small fraction of women use TCM as a sole therapy. The treatments employed by the TCM physicians are aimed at controlling side effects and toxicities attributed to cancer therapies, improving quality of life, preventing recurrence and prolonging survival.

Herbal medicines are generally low in cost, plentiful, and show very little toxicity or side effects in clinical practice. However, despite the vast interest and ever-increasing demand, the absence of strong evidence-based research and the lack of standardization of the herbal products are the main obstacles toward the globalization of TCM. In recent years, TCM research has greatly accelerated with the advancement of analytical technologies and methodologies (1). Cancerous conditions are well-known in the traditional Chinese medical system. In the classics of TCM, “Huang Di Nei Jing Di” (黃帝內經) published more than 2000 years ago, there are descriptions of the pathogenesis, appearances and treatment principles of tumors (瘤), such as muscle, tendon and bone carcinomas; however, this term does not differentiate between malignant and nonmalignant tumors. It was not until the Sung Dynasty (ca. 1300 AD) that the first reference to cancer - the Chinese word Ai (癌) meaning malignant carcinoma - first appeared in the ancient medical book “Wei Ji Bao Shu” (衛濟寶書). According to the theories of TCM, cancer is caused by imbalances between endogenous physical conditions of the body and exogenous pathogenic factors. The internal condition of the body plays a dominant role in the onset of cancer. In other words, factors can induce cancer only when the body's own defense system fails. Those pathogenic factors, in Chinese medicine terms, include accumulated toxins, “heat” and blood stasis, and they attack when a person is in a weak physical condition, without the strength to resist. Furthermore, malfunction of the body-mind communication network may also trigger the development of cancer (2) So, TCM expert doctors view cancer as a systemic disease associated with the state of the whole body (or disturbance of the signaling network, to use a modern term). “Systemic” in the TCM doctors' views, means “state of the whole body”. “Cancer is the manifestation of a breakdown in the body's ability to handle pathogenic factors, not a local disease of cells or organs.” Accordingly, the treatment philosophy and strategy of TCM emphasizes holistic modulation and improvement of the whole body rather than removing the tumor mass or killing the cancerous cells. This treatment strategy is particularly enforced for cancer patients at the late stages. In these stages, the focus of treatment is extending the life expectancy and improving the quality of life of the patient; in other words, the focus is on the patient not the tumor mass (帶瘤生存).The other major principle of TCM is the emphasis on an individual therapy. For the same type of cancer in different persons, the diagnosis and treatment schemes could be very different. This is called the principle of “treatment based on symptom pattern differentiation (辨證論治)”. In other words, TCM expert doctors make the diagnosis and prepare a treatment scheme based on the assessment of the pattern of symptoms manifest in each individual. When herbs are called for, most commonly, several are used together, and the whole herbs are used, not purified compounds. Thus, in the

prescription, there will be multiple effective components delivering a comprehensive, integrated treatment of cancer through multiple targets and their associated pathways. This approach is in line with the view of TCM that cancer is a systemic disease that requires a holistic approach and medicines that can produce therapeutic actions through multiple targets. While this approach differs from that of conventional medicine, the effects of treatment still come down to biochemistry. If treatments are effective, then there must be underlying mechanisms that can be investigated and verified scientifically. Understanding these mechanisms can help us expand the efficacy of both Western and Chinese medicines in a logical, rational way.

Future Prospect of TCM Herbal Medicines in Cancer Research

The cellular and animal studies have provided strong molecular evidences for the anticancer activities of the TCM herbal medicines, tested as pure compounds or as crude extracts of the single herbs or the complex formulas. However, several important questions remain to be answered. Do TCM-derived herbal medicines possess any special effects other than those often seen with conventional drugs for cancer treatment? There has been little investigation to make a side-by-side comparison. An earlier work was conducted on the anticancer effects of protodioscine (glycosides) from the rhizome of Dioscorea collettii var. hypoglauca, a Chinese herbal remedy for the treatment of cervical carcinoma, carcinoma of urinary bladder and renal tumor for centuries, against a 60 NCI human cancer panel (3), and it was found to be specifically effective for cervical carcinoma, bladder and renal cancer cell lines. Moreover, based on an analysis of the COMPARE computer program with protodioscin as a seed compound, no other compounds in the NCI's anticancer drug screen database have a cytotoxicity pattern (mean graphs) similar to those of protodioscin, indicating that a potential novel mechanism of anti-cancer action is involved. This may be one of many methods by which the unique properties of TCM can be revealed in a concise manner. The other question to be addressed in the future is whether the methodologies and the in vitro and in vivo biological models currently employed to investigate the therapeutic nature of traditional Chinese medicines are good enough. By now 66 herbs are known that have been used for anticancer studies all over the world. They were grouped these herbal plants into seven functional groups based on the traditional usage for cancer treatment. Interestingly only a small subset of herbs is considered toxic, grouped under the category of "medicinal with cytotoxic function", the majority is not. On the other hand, the majority of TCM-derived components shown above are in the same category as the conventional anticancer drugs which induce apoptosis. In a previous study (4), we used a cell system by which the inhibitory effects of non-cytotoxic chemicals were assessed by a focus formation assay upon transfection of ras oncogene to the host cells. Using this system, two well-studied medicinal mushrooms Ganoderma lucidum and Tricholoma lobayense with anticancer potential were examined for their possible adverse effects on cell transformation induced by ras oncogene. The results indicated that both species of mushrooms strongly inhibited ras-induced cell transformation. However, the inhibitory effect of the mushroom extracts was not due to a direct killing of the transformed cells; rather, it seems to have been mediated through the surrounding normal cells. This normal cell-dependent growth inhibitory effect is also observed with oleanolic acid isolated from Oldenlandia diffusa (5). These examples suggest that, at least some, TCM medicines exert their anticancer effects through mechanism(s) other than apoptosis. Looking forward, we have to see three specific issues that will require focused more attention:

(i) more well-designed clinical trials are required to support the effectiveness and the safety of TCM in the management of cancers/ applying together modern technology as oncothermia;

(ii) new parameters based on the unique properties and theory of TCM are needed to assess the clinical efficacy of TCM in clinical trials; and

(iii) new approaches to research may be needed, given the nature of TCM herbs as being fundamentally different from drugs. There is evidence that the reductionist approach, i.e., searching for one or a few active ingredients in an herb or formula, may not elucidate the efficacy of herbal medicines; a systems biology approach may be more appropriate and productive, in terms of developing effective treatment protocols.

Undoubtedly, the evaluation of the therapeutic effects and the benefits of TCM therapy for cancer patients is a significantly complex, albeit significant issue. TCM therapy, based on multiple medicinal herbs and an holistic approach to diagnosis as well as treatment, means that a clinical study of TCM treatment is more difficult and complicated than the study of single compound drugs. In addition to the conventional "standards" used for WM (western medicine) clinical trail, there is a need to develop a set of parameters

that are suitable to the assessment of TCM therapy. The effects, as well as the toxicity, of individual herbs or, especially, of single compounds derived from the herb cannot completely reflect the benefits and toxicity of the herbal combination. When whole herbs are not studied, improper or biased results and conclusions might be unavoidable (6). As a goal, to develop and involve TCM into rational cancer therapy together spin-off technology oncothermia, more well-designed intensive clinical evaluations and translational laboratory studies are absolutely needed. And, close collaboration between TCM and conventional Western medicine professions and a combination of TCM with modern multidisciplinary cutting-edge technologies like oncothermia, such as omic methodology on systems biology (7), would provide us with an attractive and effective strategy to achieve this goal for benefit patients.

Anti-cancer effects and underlying mechanisms of TCM – derived complex formulas – really a "great chellenge"

There are only a few mechanistic studies on the action of TCM formulas as anticancer agents. One study was on San-Zhong-Kui-Jian-Tang (8), a complex formula comprising 17 different herbs, which is used for cancer therapy in China. It was found to induce the mitochondrial apoptotic pathway by changing Bax/Bcl-2 ratios, cytochrome c release and caspase-9 activation, but did not act on Fas/Fas ligand pathways in two human breast cancer cell lines, MCF-7 and MDA-MB-231. A similar study was carried out by the same laboratory (9) on Huang-lian-jie-du-tang (HLJDT) known to possess anti-inflammatory activity. The in vitro study conducted in two human liver cancer cell lines, HepG2 and PLC/PRF/5, found that HLJDT caused cell arrest by up-regulating the inactive form of Cdc2 and Cdc25, and down regulating the levels of Bcl-2 and Bcl-XL.[1] Furthermore, HLJDT increased the ratio of Bax and Bak/Bcl-2 and Bcl-XL[2] and the associated cell survival pathways, and subsequently triggered the mitochondrial apoptotic pathway. It was the collective actions of the herbs in the formula that were inhibiting the growth of cancer cells tested both in vitro cell lines and in vivo in nude mice. Another study is the study of a classic formula, Guizhi-fuling decoction (GZFLD) (10). The formulation consists of five herbs: Cinnamomum cassia, Paeonia lactiflora, Paeonia suffruticosa, Poria cocos, and Prunus persica. Accordingly, GZFLD inhibited the growth of HeLa cells by activating the tissue inhibitor of metallo-peptidases (TIMPs) and causing the suppression of the activity of the matrix metallo-peptidase (MMPs) that play a key role in the degradation of the extracellular matrix and promotion of cell proliferation.

[1] BCL2: B cell leukemia/lymphoma 2, BCL-XL: B cell leukemia/lymphoma x
[2] MCL-1: myeloid cell leukemia sequence, 1MDM2: murine double minute 2

In the same study, GZFLD was also shown to inhibit tumor growth and angiogenesis in an in vivo animal model. Another report (11) concerned a classic formula "bojung-bang-dock--tang (BJBDT)" consisting of Astragalus membranaceus Bunge, Atractylodes japonica Koidzumi, Coiz lacryma-jobi Linne var. ma-yuen stapf, Dioscorea batatas Decaisne, Dolichos lablab Linne, Panax ginseng C. A. Mey, Polygonatum sibiricum Delar. ex Pedouté, Poria cocos (Schw.) Wolf. Two related studies (12, 13) found that BJBDT demonstrated anti-angiogenesis by blocking VEGF/VEGFR[3] activities in human umbilical vein endothelial cells. Interestingly, BJBDT can prevent cisplatin-induced toxicity and apoptosis in normal MCF-10A, but not in MCF-7 and MDA MB-231 breast cancer cells, suggesting the herbal formula can be applied as a cancer chemopreventive agent (14). The synergistic effects of herbs in a TCM formula were well illustrated in a new study, in which a TCM-based formula, Realgar-indigo naturalis (RIF), was applied in the treatment of acute promyelocytic leukemia (APL). The RIF formula has three components, realgar, indigo naturalis, and Salvia miltiorrhiza of which tetra-arsenic tetrasulfide, indirubin, and tanshinone IIA, respectively, are the major active ingredients. The study demonstrated that tetraarsenic tetrasulfide is the principle component of the formula, while tanshinone IIA and indirubin are the adjuvant ingredients. Together these herbs have shown a synergistic action against APL effective in both in vitro and human clinical studies.

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[3] VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor

Introduction of the international quality management systems by sample of Oncotherm Group

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Introduction: The most important aspect for the Oncotherm Group is that our medical devices are prepared according to the concerning international standards and fulfill the inquiries of our customers.
These standards are the followings:
_ ISO 9001:2008 Quality Management Systems. Requirements
_ ISO 13485:2003/AC:2009 Medical Devices. Quality Management Systems. Requirements for regulatory purposes
_ 93/42/EEC MDD (Medical Device Directive)

Method: I would like to introduce the organizational structure and processes of Oncotherm Group and the requirements which should be adapted (see above).
The Oncotherm Group consists of two parts: the Oncotherm Kft., which is in Hungary and the Oncotherm GmbH, which is in Germany, but these two firms are one unity.
They are working together and they have got common quality management systems.
The research, design and development, and the manufacturing are in Hungary, but the marketing, sales, costumer service and service activities are in Germany, so these two parts create one well operative company. The Company-Group is a marketing method (Oncothermia Method, OTM) which is in synergy with the devices (Oncothermia Device, OTD) and integratively presented on the market as Oncothermia System (OTS). This unification of the German medical and constructive knowledge with the general European manufacturing culture is based on European Medical Device Directive and ISO standards. We do everything in Europe and are proud on that high level production culture which is represented by our 21 years old company.

Summary: Our devices are prepared by team-working of Hungarian and German highly qualified specialists, and there is more than 20 years hard work, experience and knowledge behind the OncoTherm System, which are the basis of our recent approval by TÜV Süd Product Service GmbH.

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Production support by LabView-based data-acquisition systems

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Production support by LabView-based data-acquisition systems

Abstract

Medical devices are complex products requesting high level of safety and reliability because of their sophisticated functions. Automation of the quality control and the visualization of the steps of the production processes are useful supports of the production process. Our objective is to show a way of production support by LabView system.

Introduction

During the production of a product a lot of tests and measurements are done. First the electronic boards are checked separately, then the modules which are built from them are tested separately, and finally a lot of tests are conducted on the assembled system. During these test a lot of data could be acquired from the product, but – especially at the final testing of the product – the data acquisition could be difficult, because:

• The testing time is so long, that the continuous observation of the test is not possible
• If during the measurement more instruments are used, the simultaneous and continuous observation of all of them is not possible.
• Most of the measuring devices don't provide built-in data acquisition and storage
• Although some instruments have this function, it could be difficult to synchronize the data acquired by various instruments.

The solution of these problems is such a data collection system, that in real-time collects and synchronizes all of the information, that the used instruments provide during the actual measurement and then stores them into a common database, allowing the common processing of them. By this way the efficiency of the production could be greatly increased. For us at Oncotherm it is a priority to increase both the speed and the quality of the production of our products, so we started to develop integrated data-acquisition systems to support our production tasks.

Discussion

The main element of these systems is the LabView program suite, which has been developed especially for data-acquisition and instrument control and is provided by National Instruments. It can be used for a wide range of sophisticated tasks as watermonitoring [1], control of imaging [2], or bio-signals [3], even virtual laboratories can be constructed [4].

We know the LabView application is suitable for RF-controlling processes [5] and for complicated production as well [6]. Our objective is to support a production of the radio-frequency operating medical treatment device [7].

The main task of LabView is to control the NI's own DA units, but the products of the most important instrument manufacturers are controllable with the suite too. During our projects we use both NI instruments and the instruments of other manufacturers (Tektronix, Rhode&Schwartz) too.

One of our main ambitions is to monitor of the manufactured EHY-2000 oncothermia devices during their final tests, which means lots of test treatments continuously day and night. During these test treatments important data can be collected about the general behavior and the reliability of the system, which are the key factors concerning the quality of the product.

The device sends important information about its state by RS232 serial port and the inner signal lines of the device are monitored by NI data-acquisition devices.

A typical data acquisition system consists of the following instruments and provides us the following information:

• EHY-2000:
• By serial port: time after the start of the treatment, output power, reflected power and the states of the various protection signal lines
• By direct monitoring of signal lines: the control voltage of the amplifier and the voltages proportional with the forwarded and reflected power.
• R&S RF power meter: used as an external reference for the accuracy of the power measurement of the device.

• Multimeter: used as a current meter to monitor the correct consumption of the amplifier.
By using the data provided by the reviewed instrumentation we can get a clear picture of the energetic efficiency and the general behavior of the amplifier, which
– as the most difficult part of the device – needs the most testing.
Of course, the data-collecting systems always follow the demands of the current projects, capitalizing the flexibility of the LabView-based DA systems. On the bases of our experiences until now we have more ways of improvement in this field. The most important ones are:
• Research support: integrated data acquisition during laboratory experiments, focusing to collect data from the Lab-EHY laboratory device and the 4-channel thermometer also developed by Oncotherm.
• Production support: automated testing of our products by LabView-based instrumentations

Conclusion

The LabView based production and quality control of the RF-operating medical device are feasible. By realizing this conception we can both improve the quality of our products and the affectivity and the speed of our R&D projects, so we are committed towards these ways.

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Hyperthermia vervus Oncothermia: cellular effects in cancer therapy

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Hyperthermia versus Oncothermia: cellular effects in cancer therapy

Abstract

Hyperthermia means overheating of the living object completely or partly. The fact the hyperthermia is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the focusing of the heat-effect. The idea of oncothermia solves the selective deep action on nearly cellular resolution.

We would like to demonstrate the perspectives of oncothermia, as a highly specialized hyperthermia in clinical oncology. Our aim is to prove the ability of oncothermia to be a candidate to become a widely accepted modality of the standard cancer-care. We would like to show the proofs and the challenges of the hyperthermia and oncothermia applications to provide the presently available data and summarize the knowledge in the topic. Like many early-stage therapies, oncothermia lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

Introduction

In oncology, the term "hyperthermia" refers to the treatment of malignant diseases by administering heat in various ways. Hyperthermia is usually applied as an adjunct to an already established treatment modality, where tumour temperatures in the range of 40–46°C are aspired. Interstitial hyperthermia and whole-body hyperthermia are still under clinical investigation, and a few positive comparative trials have already been completed. In parallel to clinical research, several aspects of heat action have been examined in numerous pre-clinical studies [1, 2, 3].

The traditional hyperthermia is controlled the only single thermodynamic intensive parameter, with the temperature. Oncothermia, which is a "spin-off" form of the hyperthermia, is based on the paradigm of the energy-dose control, replacing the single temperature concept [4]. With this approach oncothermia returned to the gold standards of the dose concepts in medicine: instead of the parameter, which can not regarded as dose (the temperature does not depend on the volume or mass), oncothermia uses the energy (kJ/kg [=Gy]), like the radiation oncology uses the same (Gy) to characterize the dosing of the treatment [5].

For further information read the longer version of this paper which readable on-line: http://www.hindawi.com/journals/ecam/aip/672873/ and accepted for publication of the special issue of the Evidence-Based Complementary and Alternative Medicine (Translational Research in Complementary and Alternative Medicine).[6]

The concept of hyperthermia

The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumour and surrounding tissues is monitored throughout the hyperthermia procedure. The goal is to keep local temperatures under 44°C to avoid damage to surrounding tissues, and the whole body temperatures under 42°C, which is the upper limit compatible with life [5].

Cellular mechanisms induced by hyperthermia

The cellular effect of hyperthermia is more complicated [7, 8].Briefly, hyperthermia may kill or weaken tumor cells, and is controlled to limit effects on healthy cells. Tumor cells, with a disorganized and compact vascular structure, have difficulty dissipating heat. Hyperthermia may therefore cause cancerous cells to undergo apoptosis in direct response to applied heat, while healthy tissues can more easily maintain a normal temperature. Even if the cancerous cells do not die outright, they may become more susceptible to ionizing radiation therapy or to certain chemotherapy drugs, which may allow such therapy to be given in smaller doses. Intense heating will cause denaturation and coagulation of cellular proteins, rapidly killing cells within the targeted tissue. A mild heat treatment combined with other stresses (excitation of the appropriate signal-pathways) can cause cell death by apoptosis.

The potential importance of the hyperthermia for cancer treatment has been highlighted by Coffey et al.[7, 8].Specifically the review addresses four topics: (1) hyperthermia induced cell killing, (2) vascular, (3) cellular and intracellular mechanisms of thermal effects in the hyperthermia temperature range and (4) effects on proteins that contribute to resistance to other stresses, for example, DNA damage.

(1) Hyperthermia induced cell killing: It has been long recognized that hyperthermia in the 40–47°C temperature range kills cells in a reproducible time and temperature dependent manner. In the hyperthermic region there are three cellular responses for thermal therapy: cytotoxicity, radiosensitization and thermotolerance [9, 10].The intensity of cell death in hyperthermia is showed cell cycle dependence. Both S- and M-phase cells undergo a "slow mode of cell death" after hyperthermia. Cells during G1-phase may follow a "rapid mode of death" immediately after hyperthermia [11, 12, 13].
(2) Vascular:With higher heat temperatures there is a corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability [14, 15]. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death [16]. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases [17, 18].
(3) Cellular and intracellular mechanisms of thermal effects in the hyperthermia - Cell metabolism: hypoxia, pH, ATP and its consequences:Summarizing the relevant data, it can be stated that tumour temperatures >42.5oC and appropriate heating can reduce both intracellular and extracellular pH, which may further sensitize tumour cells to hyperthermia in the sense of a positive feedback mechanism [19]. Relevant pathogenic mechanisms leading to an intensified acidosis upon heat treatment (which is reversible after hyperthermia) are:

1. an increased glycolytic rate with accumulation of lactic acid,
2. an intensified ATP-hydrolysis,
3. an increased ketogenesis with accumulation of acetoacetic acid and b-hydroxybutyric acid,
4. an increase in CO2 partial pressures,
5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
6. an inhibition of the Na+/H+antiporter in the cell membrane [20, 21].

The ATP decline observed upon heat treatment is mostly due to

1. an increased ATP turnover rate (i.e. intensified ATP hydrolysis). As a result of an increased ATP degradation, an accumulation of purine catabolites has to be expected together with a formation of H+ ions and reactive oxygen species at several stages during degradation to the final product uric acid,
2. a poorer ATP yield as a consequence of a shift from oxidative glucose breakdown to glycolysis [19].

(4) Effects on proteins that contribute to resistance to other stresses, for example, DNA damage: At higher temperatures, inhibition of HSP-synthesis occurs above a distinct threshold temperature. In general, the temperature, respectively, thermal dose at which HSP synthesis is inhibited in a given experimental system varies between different cell types, but the respective threshold can be lowered when further (proapoptotic) stimuli are added. As lack of HSP-synthesis is associated with exponential cell death, it is generally accepted that HSPs prevent cells from lethal thermal damage. Recently, an additional role has been ascribed to HSPs which should be importance in hyperthermia as activators of the immune system [22, 23, 24, 25].

Problems with hyperthermia

The high energy application could cause controversies: the high temperature burns the malignant cells but it's missing selectivity.The healthy cells are damaged also and the hyperthermia starts unwanted physiological reactions as well as enlarged dissemination possibility. These conditions make the hyperthermia effect not controlled.

Change of paradigm – the concept of oncothermia

Oncothermia technology heats non-equally; concentrating the absorbed energy to the intercellular

electrolytes [26]. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis [27].
Oncothermia works with much less forwarded energy, by focusing energy directly on the malignant tissue using its impedance selectivity even by cellular resolution. This effect is based on the low impedance of the tumor, due to its metabolism, which is higher than that of its healthy counterpart's [28].
Based on microscopic effects, there not only the heating makes the effect, but the electric field itself has a strong synergy with this, having significantly larger cell killing in malignancy at 38oC, than the conventional hyperthermia has on 42oC. The process is selective. The radiofrequency current is choosing the "easiest" path to flow, and due to the high ionic concentration of the near-neighborhood of malignant cells, the current will be densest at the tumor cells. The experimental results well support this idea. In the case of healthy cells the load is equal for all the cells, no difference between the treated and control samples. When we gain the metabolism (immortalized cells) but not yet malignant acceleration, the effect is selectively higher but not significant. However, when the malignancy is present, the cellular growth is aggressive, the selection became effective, and kills the tumor cells without affecting the healthy ones in the coculture.
This electric field effect well demonstrates, that the average kinetic energy (temperature) has not decisional effect. The main action is the targeted energy-delivery, which could be done on such low average energy as the standard healthy body temperature.

Cellular mechanisms induced by oncothermia

Clinical oncothermia can induce the following cellular mechanisms:
(1) Oncothermia promotes the programmed cell-deaths of tumor: Detecting the double strains of DN and measuring the enzymatic labeled strain-breaks of DNA the apoptosis is highly likely in oncothermia [29]. Consequently the main effect in oncothermia is the apoptosis contrary to the conventional hyperthermia, which operates mainly by necrosis. Investigating the apoptosis by various methods (morphology, beta-catenin relocation, p53 expression, Connexin 43, Tunel, DNA-laddering etc.) the effects are indicating the same apoptotic process. This process is non-toxic (no inflammatory reactions afterwards) and promotes the immune reactions and not makes processes against those.
(2) Oncothermia limits the dissemination of malignant cell: Oncothermia blocks the tumor cell dissemination, avoid their motility due to the lazy connections to the tumor. Oncothermia makes it by the reestablishing the cellular connections, which is also great success to save the life. The built up connections could force not only the sticking together, but makes bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells.These are high efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart. It also produces higher concentration of HSPs in the outer membrane and in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis.

Legal note

According to European Medical Device Directive (MDD) oncothermia is certified by TUV, Munich by medical CE certificate; (both safety and efficacy are certified). All the devices are manufactured according to the ISO 9001 and ISO 13458.

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Bystander effect of oncothermia

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Bystander effect of oncothermia

Background

Oncothermia (OTM) is an electro-hyperthermia modality, a long time (since 1989) applied method, [1], used successfully in human oncology [2]. OTM changes the paradigm of hyperthermia by targeted microscopic heat-liberation at the membrane of the malignant cells. This method creates inhomogeneous heating, and the microscopic temperature greatly differs far from the thermal equilibrium. The tumor destruction efficacy and the role of temperature independent effects of the OTM were proven earlier by a laboratory research, and were presented elsewhere [3], [4]. Bystander effect (abscopal effect) means that a local tumor treatment can affect the behavior of the far distant metastases. It was first discovered by radio-oncologists and remained a highly controversial topic until recent years. [5], [6]. Intensive research is being conducted to reveal the immunbiological basis [7], [8], [9] and the mechanism of the action of this effect [10] and to use the benefits in the regular oncological practice. Our objective is to show the newest results of oncothermia in research of the bystander effect.

Materials and methods

Animal model

HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mice. The use of the mice and the procedures used in this study were approved by the Animal Experiment Ethical Committee of National Research Institute for Radiobiology and Radiohygiene.

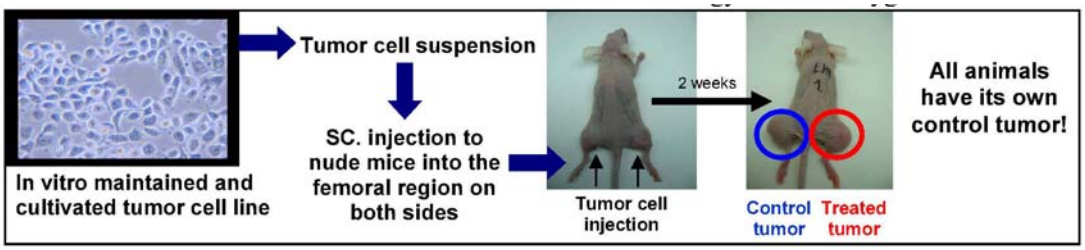

Figure 1. Process of the tumor induction of the experimental animals

Experimental setup and treatment

A single shot 30 min oncothermia treatment was done, reaching maximum 41-42oC intratumoral temperature, using the LabEHY system (Oncotherm Ltd. Germany), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense, Luxtron m3300).

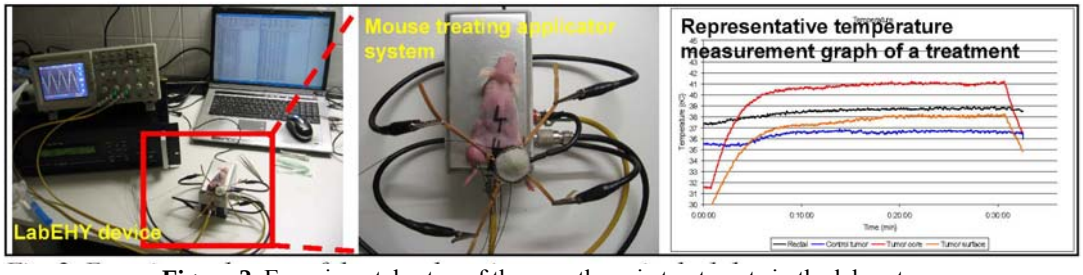

Figure 2. Experimental setup of the oncothermia treatments in the laboratory

Study design: Time course study was performed. After a single shot treatment, sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 hours. 3 mice were sacrificed at each time point, keeping 5 sham treated animals.

Figure 3. All the oncothermia-treated experimental animals involved in this study

Tumor sample processing: At the time of the sampling the single-treatment animals were sacrificed and both the control and treated tumors were removed and studied in pairs.

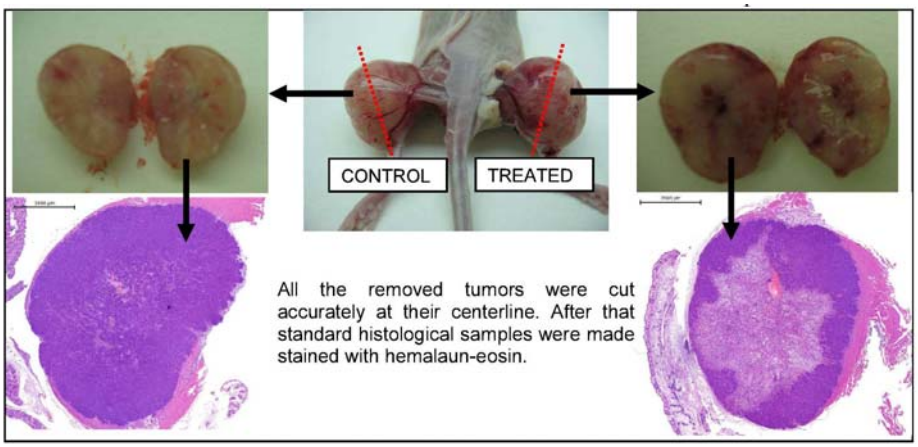

Figure 4. Method of the tumor sample processing

Due to the extremely high number of the tumor samples, tissue microarray (TMA) technology was used to perform accurate immuno-histochemical reactions on many samples in one block.

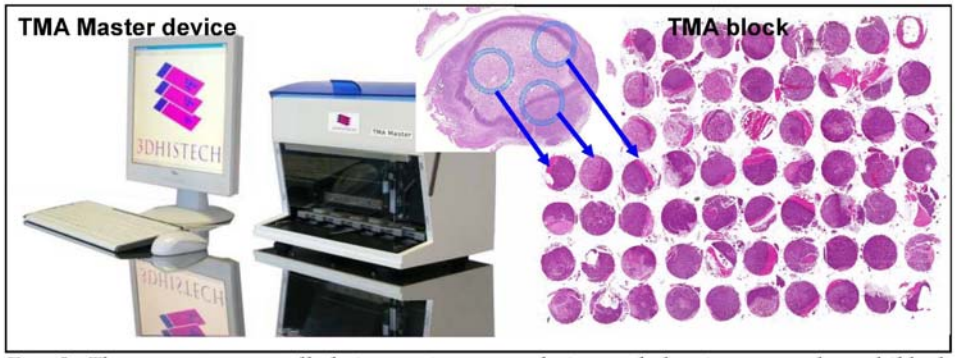

Figure 5. The computer-controlled tissue-microarray device and the tissue sample multiblock were created by the TMA Master device (3DhisTech). One multiblock contains many small representative tumor tissue samples, so really identical and highly standardized immunohistochemical reaction can be performed in all the samples. This is the real advantage of this technology

Immunohistochemistry (IHCH): The following reactions and IHCH analysis were performed on the TMA samples: TUNEL (Invitrogen); TRAIL-R2 (DR5) (Cell Signaling), HSP70 (Cell Signaling); Myeloperoxidase (Sigma); CD3 (Dako), CD4 (ABDSerotech).

Digital microscopy analysis: All histological slides were digitalized using Panoramic Slide Scanner (3D HisTech) and a special software was used for imaging and evaluation.

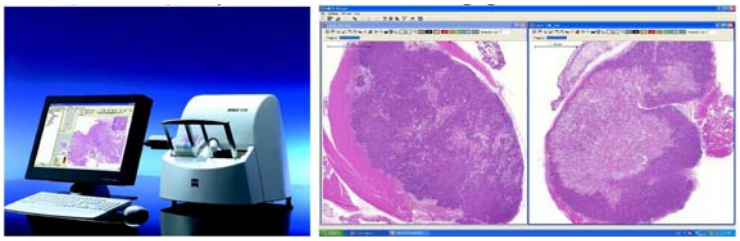

Figure 6. The panoramic slide scanner device and a screenshot from the panoramic viewer software, dedicated for prectise histomorphological analysis

Results

1. Histomorphological changes

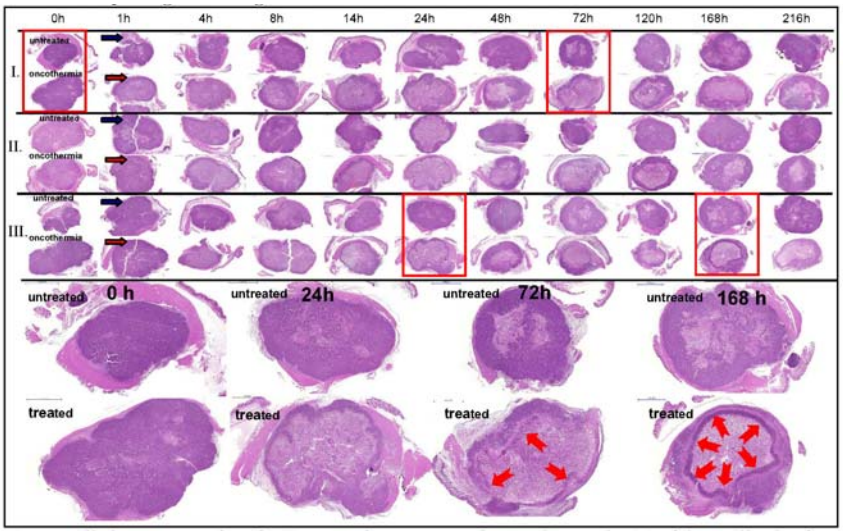

Figure 7. All the processed and HE stained tumor samples in this study. Morphologically the first significant sign of cell destruction was seen 8H after the treatment. Drastic and selective tumordestruction was detected 24H after OTM which became more emphasized after 48H. 72 hours after the treatment a significant leucocyte infiltration (marked with red arrows) appeared around the destructed tumor tissue and reached its maximum 168 hours after the treatment

2. Appearance of the hallmarks of immunogenic cancer cell death

2.1. Apoptotic body formation

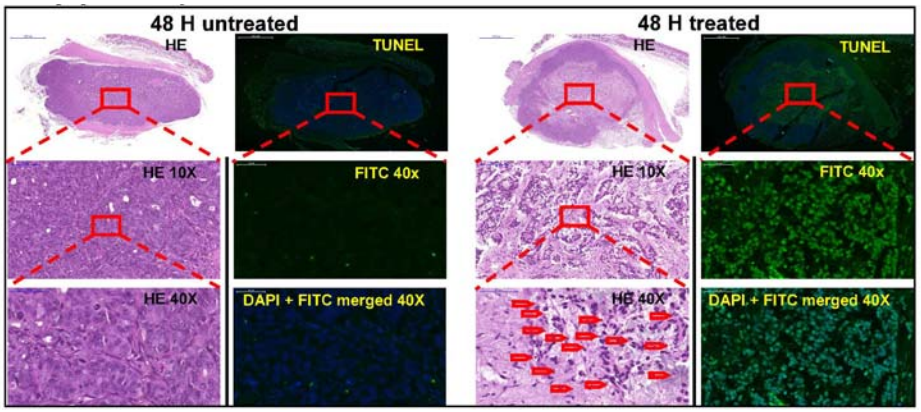

Figure 8. HE and TUNEL stained whole cross-section tumor samples 48H after the treatment. Oncothermia treatment induce apoptotic cell death, and this process is highly emphasized 48H after a single shot treatment. Almost all the cell nuclei of the killed tumor cells are TUNEL positive. In the process of this programmed cell death a huge number of apoptotic bodies were formed (marked with red arrows)

2.2. TRAIL-R2 (DR5) expression

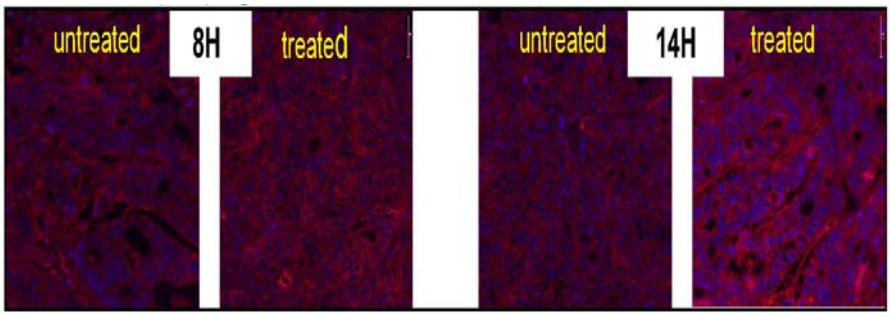

Figure 9. TRAIL-R2 detection IHCH from TMA multiblock TRAIL-R2 (DR5) is a highly immunogenic cell surface receptor. Expression was increased in the treated side 8H after the treatment and became more emphasized after 14H

2.3. HSP70 expression changes and molecular dynamics

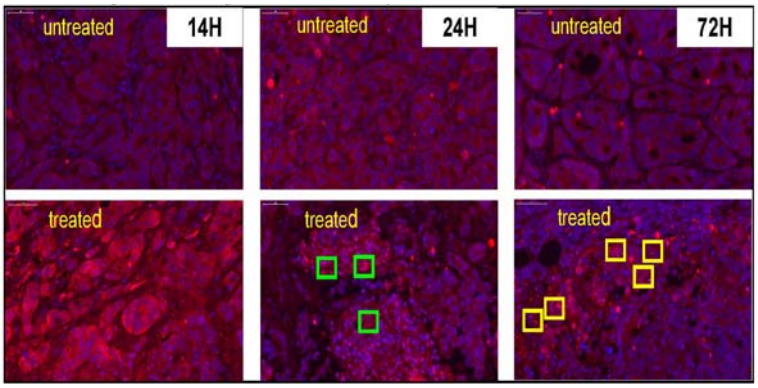

Figure 10. HSP70 detection IHCH from TMA multiblock. Definite increase of the HSP70 expression was observed 14 hours after the treatment. After 24 hours, unusual molecular dynamic changes of the increased amount of HSP70 can be visible: intracellular condensation (marked with green rectangle) and relocalization to cell membrane. After 72 hours the membrane relocalization of the HSP70 became more emphasized, especially in the region of the leukocyte invasion (marked with yellow rectangle)

3. Strong local immune reaction

3.1. Mycloperoxidase (MPO) detection

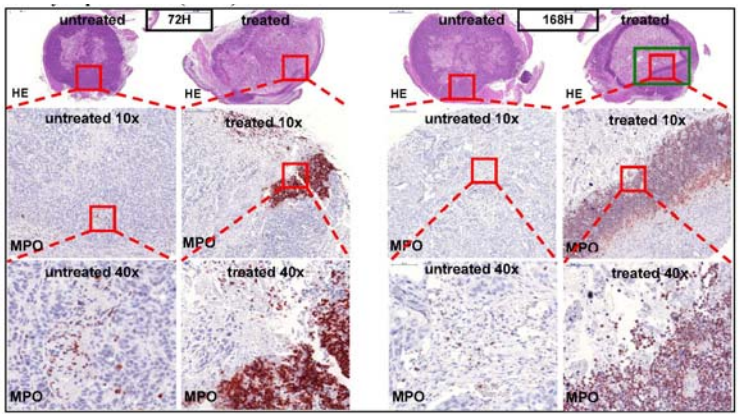

Figure 11. Myeloperoxidase (MPO) detection from TMA multiblock. MPO is a marker of neutrophyle granulocytes. The leukocyte invasion ring which appears at 72H and becomes very characteristic at 168H around the destructed tumor area, contains high number of MPO positive cells (neutrophils)

3.2. CD3, CD4 detection

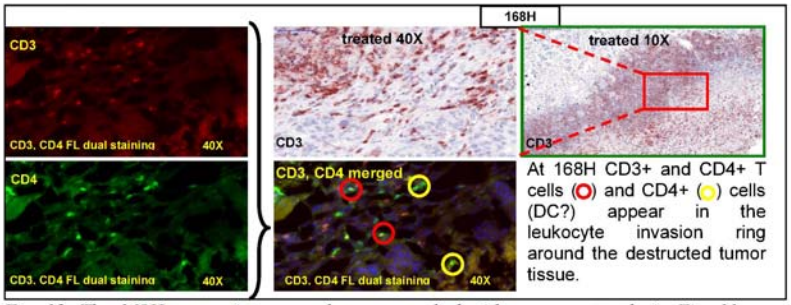

Figure 12. The 168H tumor tissue sample area, marked with green rectangle in Fig. 11. Was analyzed by CD3 IHCH staining and , CD3/CD4 dual fluorescent IHCH staining. The analysis showed that the invasion ring, beside the neutrophiles, also contains large amount of CD3+ T cells and CD4+ cells, probably dendritic cells

Conclusions

1. Oncothermia treatment can induce programmed cell death in the tumors which create many apoptotic bodies. Presence of apoptotic bodies in a destructed tumor tissue is essential to induce immunogenic reactions.
2. Oncothermia treatment induced cell death is highly immunogenic, showing all the key molecular pattern dynamic changes what is characteristic of immunogenic tumor cell death.
3. Oncothermia treatment can induce strong and very unusual local immune reaction at the site of the treatment, long time after the electromagnetic intervention.
4. The local antitumor immune reaction of oncothermia treatment might be systemic, if the host has an intact immune system, and a proper immune-stimulating agent is administered. This process can control the distant metastases by bystander effect, making the systemic control of the malignant disease possible with local treatment. Ongoing intensive research is in progress on immunocompetent tumor models, to investigate and reveal the mechanisms of the action of this controlled bystander effect.

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Oncothermia with chemotherapy in the patients with small cell lung cancer

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Oncothermia with chemotherapy in the patients with small cell lung cancer

Abstract

Small cell lung cancer constitutes approximately 13% of all lung cancer types & SCLC is one of the most aggressive and lethal forms of lung cancer. And so chemotherapy including radiotherapy would be standard for SCLC, but it has very poor median survival of less than 4 months. This is why another form of additional treatment to chemotherapy would be necessary and so oncothermia will be one of the additive treatment for prolonged survival time.

We made a 6 year-long study of 31 patients with small cell lung cancer at the department of Thoracic & Cardiovascular surgery Gangnam Severance Hospital, Yonsei University, College of Medicine, Seoul from April 2006 to March 2012.

23 patients were treated with chemotherapy and oncothermia and 8 patients were treated with chemotherapy only.

1. Cases who have survived more than 3 years were 3. They have been treated with chemotherapy and oncothermia
2. Out of 31 cases, 14 patients died during the treatment, 7 cases with chemotherapy only died, including one long survival case of 28 months, 7 cases with chemotherapy and oncothermia died, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are still alive: 4cases were treated with chemotherapy only, including one long survival case of 28.7 months, 11cases with chemotherapy and oncothermia including three long survival cases of more than 3 years
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value 0.0200). Combination of oncothermia treatment with chemotherapy enhance the effect of anticancer drugs to destroy cancer cells and is thought to be able to improve the survival of the patients with small cell lung cancer.

Introduction, background

Lung cancer is one of the most common causes of cancer-related deaths in both men and women worldwide. Its incidence as well as the mortality rates are high, and the prognosis is usually very poor, [1]. In 2006 its age-standardized incidence and mortality rates were estimated to be 75.3 and 64.8/100 000/year, respectively, in men, and 18.3 and 15.1/100 000/year in women in Europe, where the small-cell lung cancer (SCLC) accounts for 15%–18% of all cases [2].The small-cell lung cancer has a fast growth-rate, it quickly disseminates quickly around the mediastinal lymph nodes and forms distant metastases in late diagnosis, and then the median survival is only 2-4 months, the overall prognosis is very poor, [3], [4].

In almost all small-cell lung cancer cases, surgical treatment is not possible it could only be performed only in very limited disease (i.e. T1,N0) [2]; consequently, the main treatments are the chemo- and radiation therapy. In general case of SCLC, even if some reported long-term survival, the overall 2-year survival rate is less than 20%. 5-year survival rate is almost devoid. In limited SCLC, chemotherapy alone reached complete remission (CR) in 50% of relapse cases. Bulky primary tumors were completely destroyed but most of intrathoracic recurrence was difficult to discover. Added to radiation therapy [5] In this case, 30 - 60% recurrence rate has been reduced, radiation pneumonitis, esophagitis, and the overall survival rate was significantly improved. [6]. In addition, initially most of the extensive small-cell lung cancer with advanced small-cell lung cancer, chemotherapy response joteuna for anticancer drug resistance may occur and the overall survival rate was very poor, median survival was 7-10 months ,2-year survival rates of the less

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The most widely used chemotherapy is the Etoposide/Cisplatin (EP) treatment which has a median survival of 8-10 months for patients with extensive disease and 17-20 months for patients with limited-disease, [8].

The concurrent radiotherapy with chemotherapy is used as an optimal treatment for limited SCLC, [9].

Chemotherapy and radiation therapy were performed on the tumor after complete resection and the relationship did not cause death in 19 patients with autopsy and in 13 patients with small-cell lung cancer metastases have been cured [10]. The prognosis of SCLC is generally poor, because micro-metastases occur and surgical resection is not possible. There are frequently occurring insidious transitions [10], [11].

In a study of chemo- and radiation therapies [12] for 28 patients died of other causes than lung cancer has been reported, and 47% was clinically cured. The autopsy study [13] of patients who died from other causes than tumors found that residual cancer cells in the area of lung cancer and mediastinal lymph node regions are 64%.

The prognostic index was constructed for SCLC in Severance hospital, (Korea), retrospectively evaluation of 295 patients revealed 131 cases with limited and 164 cases with extended disease. The median survival was 20.4 months for limited and 7.7 months for extended disease, [14]. A prognostic index was constructed to create four classifications of SCLC considering the variables of the extension of the disease, the performance status, the CYFRA21-1 and the tumor-marker.

Heat therapy could be a feasible option to treat SCLC. The classical loco-regional heat treatment (conventional oncological hyperthermia) has a localized area selection [15]. This boosts the chemo-efficacy, [16], [17], [18] and also increases the effectiveness of radiation therapy [19], [20].

Some successful clinical trials had shown the feasibility of the hyperthermia method for lung cancer. Most of these are applied for non-small-cell lung cancer (NSCLC), combined with radiotherapy, having 14÷70 Gy dose in the given session. The measured response rate (RR) was surprisingly high RR=75%, (n=12, [21]), and RR=100% (n=13, [22]). Others had a comparison to a control-arm (not randomized), increasing the RR from RR=70% (n=30), and RR=53.8% (n=13), to RR=94.7% (n=19, [23]), and RR=76.9% (n=13, [24]), respectively. The second year survival also increased remarkably: from 15% and 15.4% to 35% and 44.4%, respectively. (The first year survival was measured as well, increasing from 30% to 55%, [23]).

The chemo-thermotherapy combination was also investigated for NSCLC with success. In preclinical trials the cisplatine was shown to be effective, [25], so the clinical studies were concentrating on this drug combination. A special case report showed the feasibility [26], and the median survival gain (from 15 (n=20) to 25 (n=32) months), [27]. The median survival was measured in another study [28], as 19.2 months, the RR=73% and the 1 year-survival is 75%. The 5year median survival was measured in another study [29], showing rather high numbers (24.5%, n=30).

However, a problem arises by the classical hyperthermia. The cancer tissue is more active than the surrounding normal tissue, its cell proliferation and metabolism require a lot of energy. When temperature tries to equalize itself in the surrounding, it grows around the tumor. In consequence the surrounding blood vessels expand, the blood flow increases delivers extra nutrition for tumor accelerating its stable proliferation. In this case, the temperature rise of the cancerous tissue will have more metabolic and proliferation activity. Furthermore, hyperthermia effects the intracellular Heat-Shock Proteins (HSP), developing thermo-tolerance of the cells, [30].

The extracellular matrix surrounding the tumor is overburden by ionic metabolites and final metabolic products, which changes their electric properties [31]. [32]. This is used by oncothermia when selecting

the tumorous region, and at the same time absorbing the energy selectively on the malignant cells. The temperature rises only very locally on the malignant cells, and does not rise all over the large volume and does not affect the surrounding normal tissue. In consequence no vasodilatation occurs, no extra proliferation is supported by the blood vessels, the absorbed energy concentrates on the job: destroy only the tumor [33].The method works by impedance tuned, capacitive coupled radiofrequency, with modulated 13.56 MHz.

One of the most advanced hyperthermia-modalities devoted to oncology is oncothermia [33]. The actions widely affect the targeted malignant cells: passing through the malignant cell membrane 1500 nW/μm2 heat-flow, while the normal tissue membranes have only 20 nW/μm2 Oncothermia treatment induces Na+ influx current 150 pA/μm2 while normal Na+ efflux is 12 pA/μm2, [34]. Na+ moves into the malignant cell, the water is also pumped in by electro-osmotic way, increasing the pressure within the cell. By these actions the cell membrane is destroyed and will destroy the cancerous tissue. [35]. For these reasons we expect the effect on the disseminated SCLC lesions with the combination of chemotherapy and radiation therapy. We supposed improved survival rates, when appropriate amount of energy, proper temperature, well-chosen doses, are used in the study [33].

In the preliminary reports [36], [37], [38] the feasibility of oncothermia application was demonstrated on NSCLC and some preliminary case reports and statistical summaries on SCLC were presented in local conferences too, [39], [40]. Systematic study of oncothermia applications for SCLC is still missing. Our present study tries to provide more details in this important field of oncology.

Materials and methods

A prospective, double arm, monocentric study for SCLC was performed. The small-cell lung cancer cases were treated with a combination of chemotherapy and radiation therapy, with complementary oncothermia in our study. It is considered that the applied complex protocol completed by oncothermia maximizes the effectiveness of chemotherapy and may improve the survival rate. We treated 31 patients in duration of 6 years, from April 2006 to March 2012.

7 out of 8 cases in control arm who underwent only chemotherapy were men, and in one case was a woman. The youngest was 54 years old and the oldest was 84 years old. The active arm, 23 patients had the combination of chemotherapy and oncothermia treatment, 19 males and four females. The youngest was 54 years old, the oldest was 79 years old (see table 1.). There was no significant difference between these two groups (Fisher's exact test:> 0.9999; t-test: p-value => 0.8665). The real end-point of the study was the survival time.

All patients had proven SCLC and received chemotherapy. 23 patient received oncothermia in combination with chemotherapy. Oncothermia was provided with EHY-2000 device (Oncotherm GmbH, Germany).

Anticancer drugs in the first-line were Irinotecan (60 mg/ m²) and Cisplatin (60 mg / m²) three times after the chest CT was taken. When the progression of tumor or metastases was detected we replaced the chemotherapy regime by Etoposide (110 mg / m²) and Cisplatin (70 mg / m²) in the second line.

Oncothermia was performed from the first anti-cancer drug treatment period up to 150Watt, 1,490.5 kJ energy by 60 minutes, every second day, with rise in temperature from 38.5°C-42.5°C. In this study we used a 30 cm diameter electrode applied for thorax. Other technical details are shown elsewhere [33], [41].

	CTX.* only			CTX. + Oncothermia			
Age	M	F	Total	M	F	Total	Total
51 – 60	2	-	2	5	1	6	8
61 - 70	4	-	4	8	2	10	14
71 - 80	1	-	1	6	1	7	8
81 - 90	-	1	1	-	-	-	1
	7	1	8	19	4	23	31

Table 1. Patient's profile

Characteristic cases

A male patient aged 67 who had visited our Department with chief complaints of slight fever and sputum in August 2008 was hospitalized for a thorough examination and then diagnosed as a case of limited small cell lung cancer. For treatment, Irinotecan (60mg/m²) and Cisplatin (60mg/m²) were administered 12 times and at the same time, oncothermia was given 24 times (2 cycles) in total, 2 times per week. Then, chest PA and chest CT revealed that he was in complete remission from small cell lung cancer. So, treatments of chemotherapy and oncothermia were stopped from October 2009 and then he was an outpatient follow-up on a regular basis. On Oct. 25th 2010 PET CT showed a normal finding. In April 2011 he was treated by chemotherapy in the Department of Urology, our hospital, for prostatomegaly. Because of the fact that PSA was increased to 4.96 in June 2011, he got a prostate tissue biopsy and was diagnosed with a case of adenocarcinoma. Finally he was treated with the prostate cancer resection using the Da Vinci robot in July 2011. Chest CT was done in July 2011, it found mediastinal lymphadenopathy, and after mediastinoscopy, he was diagnosed as a case of metastatic small cell lung cancer. For chemotherapy, Etoposide (110mg/m²) and Cisplatin (70mg/m²) were 12 times administered in replacement, and another one-cycle treatment of oncothermia was given. In Dec. 2011 and Feb. and April 2012, follow up chest CT found that the patient was in complete remission. During outpatient follow-ups in Sept. 2012, chest CT found multiple nodes in the left upper and lower lobes on possible suspicion of metastasis. Under the patient's personal circumstances including general weakness, chemotherapy and oncothermia were stopped, and he had been now observed in outpatient follow-up for more than 3 years. [6]

Three month later, the check up showed good partial remission (PR) on the lesion, (figure 1.), patient is free from symptoms.

Our case to present is a 67-year-old male, registered with symptoms of cough, low-grade fever in August 2009. The diagnosis was SCLC, (see Figure 1.).

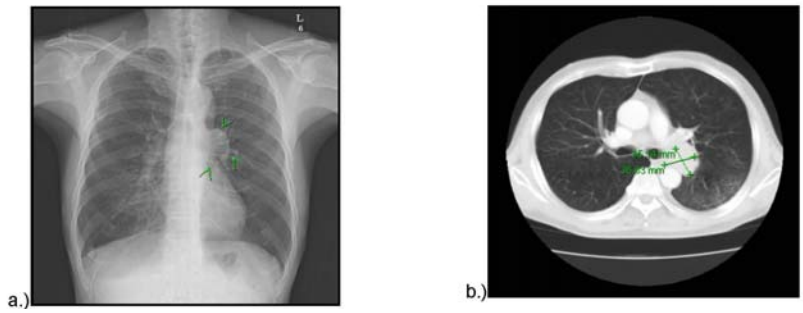

Figure 1. (a) Chest X-ray: in the left hilar lung tumors are found . (b) Chest CT: Left hilar lung tumor approved [21. Jul. 2009]

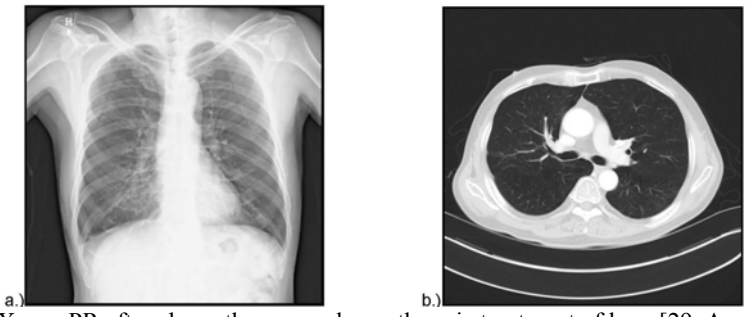

Figure 2. (a) Chest X-ray: PR after chemotherapy and oncothermia treatment of lung [29. Apr. 2010], (b) Chest CT: approved the PR [30th. Apr. 2010]

Nine month later PR was observed, (see Figure 2.), patient is free from symptoms.

Another case to present is a male patient 65 years old, registered in January 2010, diagnosed by SCLC, (see Figure 3.).

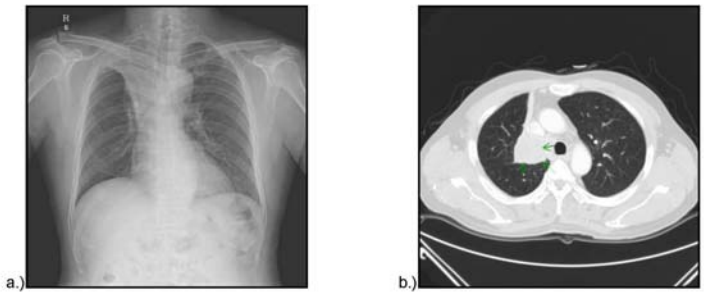

Figure 3. (a) Chest X-ray:: the right upper lobe bronchus obstruction due to cancer as atelectasis is observed, [6th. Jan. 2010]. (b) Chest CT: right upper lobe bronchus and bronchial cancer is proven in the right upper lobe atelectasis, [7th. Jan. 2010]

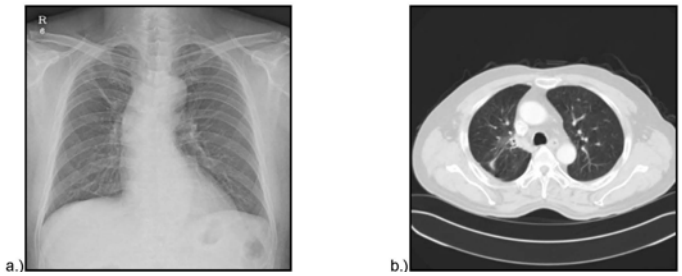

Figure 4. (a) Chest X-ray: after chemotherapy and oncothermia treatment of the right upper lobe atelectasis was not observable. (b) Chest CT: right upper lobe bronchus, bronchial cancer was disappeared [23. Nov. 2010]

Eleven months later we reached complete remission (CR), (see Figure 4.).
He is follow-up on OPD to now more than 1year after chemotherapy and oncothermia was stopped with good general condition for more than 3 years.

Study results

Chemotherapy alone (without oncothermia) was applied for eight cases. The survival time ranged from 2 months up to 29 months. With the combination of chemotherapy and oncothermia, the survival time was from 2 months to up to 36 months.
The treatment was terminated for only 1 patient. It was within 1 month after the diagnosis and treatment with chemotherapy only. All other 31 patients underwent chemotherapy and 23 had combined treatment with oncothermia.
1. Among 23 cases, one paient died within one month after the date of diagnosis, who was treated with chemotherapy only. Cases who have survived more than 3 years were 3, all of whom were treated with the combined use of chemotherapy and oncothermia.
2. Out of 31 cases, 14 died during the treatment; (i) 7 were treated with chemotherapy only, including one long survival case of 28 months, and (ii) 7 ones treated by the combined use of chemotherapy and oncothermia, including one long survival case of 26 months.
3. Out of 31 cases, 16 people are alive up to the present: 4 got chemotherapy only, including one long survival case of 28.7 months, and (ii) 11 were treated by the combined use of chemotherapy and oncothermia, including three long survival cases of more than 3 years.
4. The combined use of chemotherapy and oncothermia has significantly enhanced the survival rate in comparison with the use of chemotherapy only (Log-rank test: p-value = 0.0200)

The survival analysis shown by the Kaplan-Meier curve survival distribution (see Figure 5.) shows significant difference between the arms of chemotherapy with and without oncothermia. The log-rank test to compare survival distributions between the two groups, had hazard ratio and 95% confidence interval using Cox proportional hazard regression shown p=0.02. The summary is shown in Table 2.

Summary of the Number of Censored and Uncensored Values					
Stratum	Group1	Total	Failed	Censored	Percent Censored
1	chemotherapy	8	7	1	12.50
2	oncothermia in parallel	23	12	11	47.83
Total		31	19	12	38.71

Table 2. Comparison of the arms with chemotherapy without and with oncothermia in parallel

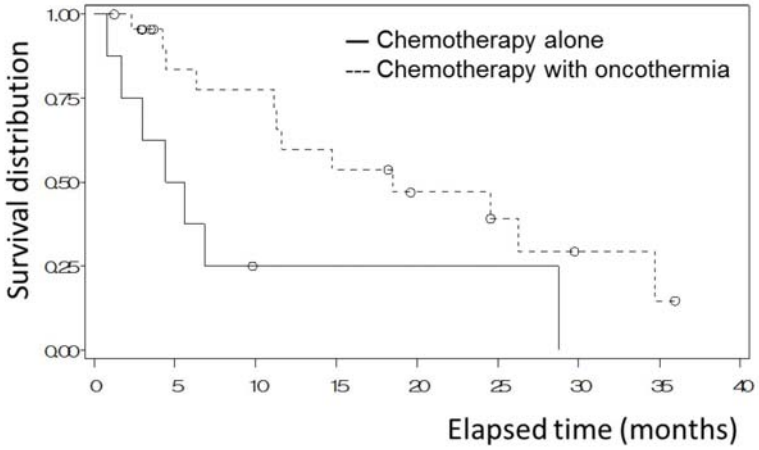

Figure 5. Kaplan-Meier survival curve. ⇒log-rank test, p-value=0.0200

Conclusion

1. In the cases of small cell lung cancer, we obtained a better treatment efficacy than with the treatment of chemotherapy only, by the combined use of chemotherapy and oncothermia (one hour per each time, 2 times per week, and more than 12 times (= one cycle)). Based on this, our thought is that the treatment of oncothermia, 3 times per week and more than 3 cycles, can create a good treatment efficacy
2. Small cell lung cancer can primarily be covered by chemotherapy (and radiotherapy sometimes), but tolerance against the anti-cancer agent is frequently created and then the return of the disease or metastasis takes place very often, which indicates a poor prognosis. We think that the combined use of oncothermia can enhance the treatment efficacy of chemotherapy, thus getting a higher rate of survival against small cell lung cancer.
3. However, we have some limitations of not so many cases with chemotherapy and oncothermia and short periods of follow-up. We consider that more cases and longer periods of follow-up are required for a good verification.
4. Several matters including the most suitable size of energy, time of administration and the number of administrations should be the subjects of subsequent studies.
5. Combination of oncothermia treatment applied to enhance the effect of anticancer drugs to destroy cancer cells is thought to be able to improve the survival of small-cell lung cancer. However, the author of chemotherapy and hyperthermia our case, less than the observation period is shorter than many cases and long-term follow-up will be necessary.
The hyperthermia dose, that is the amount of energy, and the appropriate time of administration, the number of doses, should be further studied.

Chemotherapy in SCLC, the authors and twice a week, one hour of treatment, more than 12 times (1 cycle), treatment with a combination of hyperthermia treatment effects compared to chemotherapy underwent example was good. It three times a week, 3 cycles or hyperthermia treatment effect is good thought.
In case of small cell lung cancer recurrence or metastasis, chemotherapy, and in some cases, radiation therapy may be added frequently, the anti-cancer drug for the treatment of resistant wounds, the prognosis is poor.

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Posters of the XXXI. Conference of the International Clinical Hyperthermia Society (ICHS)

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P-01: Giammaria Fiorentini, Carlo Milandri, Patrizia Dentico, Paolo Giordani, Vincenzo Catalano, Feissal Bunkeila (2012) Deep electro-hyperthermia with radiofrequencies combined with thermo-active drugs in patients with liver metastases from colorectal cancer (CRC): A phase II clinical study

DEEP ELECTRO-HYPERTHERMIA WITH RADIOFREQUENCIES COMBINED WITH THERMO-ACTIVE DRUGS IN PATIENTS WITH LIVER METASTASES FROM COLORECTAL CANCER (CRC): *A PHASE II CLINICAL STUDY.*

Giammaria Fiorentini[1], Carlo Milandri[2], Patrizia Dentico[2], Paolo Giordani[1], Vincenzo Catalano[1], Feisal Bunkeila[1]

[1]Dept. of Oncology Azienda Ospedaliera Marche Nord, Pesaro, Italy
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Purpose

- Increase palliation in patients with liver metastases from CRC
- Evaluate capacitatively coupled low-frequency 13.56 MHz deep hyperthermia combined with thermo-active drugs

Patients and methods

From April 2006 to February 2010, 60 heavily pretreated patients at advanced stage of CRC with not operable liver metastases have been cured with deep hyperthermia at an applied adsorbed power of 80-150 Watt equivalent to 41°- 47° for 60-75 minutes, 3 times/w for 3 weeks in combination with thermo-active drugs.

Thermo active drugs were:

cisplatin 30 mg/sqm on D 1,8, 15 in the first subset of 28 patients (Group A) then with oxaliplatin 50 mgr/sqm on D 1,8,15 in a second subset of 32 patients (Group B). Hyperthermia was achieved by arrangements of capacitative electrodes with a radiofrequency field of 13.56 Mhz (RF-DHT).

RESULTS OF HYPERTHERMIA AND THERMO- ACTIVE DRUGS (60pts)

	Group A CDDP	Group B OXALI	OVERALL	
	28pts	32 pts	60 pts	%
Partial responses	1	5	6	10%
stabilizations	1	5	6	10%
CEA reductions	4	12	16	27%
Increasing performances	11	19	30	50%
Reduction analgesics	5	15	20	33%
Better Q of L	16	34	50	83%

RESULTS OF HYPERTHERMIA AND THERMO-ACTIVE DRUGS (60pts) -TOXICITY

	Group A CDDP	Group B OXALI	OVERALL	
	28pts	32 pts	60 pts	%
Burns G2	3	4	7	12%
Leukopenia G2	1	5	6	10%
Nausea & V. G3	5	4	9	15%
Nefrotoxicity G2	4	0	4	7%
Neurotoxicity G3	1	5	6	10%

RESULTS OF HYPERTHERMIA AND THERMO- ACTIVE DRUGS (60pts)

Group A CDDP	Group B OXALI	OVERALL	%
28pts	32 pts	60 pts	

MEDIAN SURVIVAL TIME

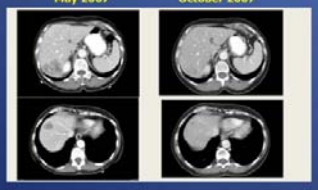
33 weeks (range 19-45)

MEDIAN DURATION OF RESPONSE

19 weeks (range 9-27)

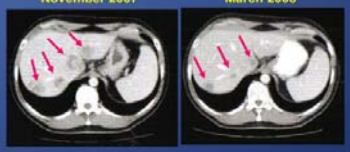
Metastases from CRC: PR lasting 22 weeks

May 2007 October 2007



Metastases from CRC: PR lasting 29 weeks

November 2007 March 2008



Conclusions

Capacitively coupled low-frequency 13.56 deep-HPT is feasible for chemo-refractory malignant liver involvement from CRC. Significant increase of QoL was shown. 12 pts reported a control of disease. Oxaliplatin showed a more effective thermo-enhancement respect cisplatin in liver metastases from CRC. Based on these results and on ethical reasons we abandoned cisplatin and we are planning a further randomized trial comparing FOLFOX 4 plus hyperthermia versus FOLFOX 4. These interesting results deserve to be confirmed in further clinical studies.

P-02: Gramaglia Alberto, Parmar Gurdev, Ballerini Marco, Cassuti Valter, Baronzio Gianfranco (2012) Liposomiated doxorubycyn (LD) and hyperthermia on glioblastoma relapsing after surgery, radiotherapy and two chemotherapy lines: a case report

LIPOSOMIATED DOXORUBYCYN (LD) AND HYPERTHERMIA ON GLIOBLASTOMA RELAPSING AFTER SURGERY, RADIOTHERAPY AND TWO CHEMOTHERAPY LINES: A CASE REPORT

Gramaglia Alberto [1], [*], Parmar Gurdev [2], Ballerini Marco [3], Cassuti Valter [3] and Baronzio Gianfranco [3]

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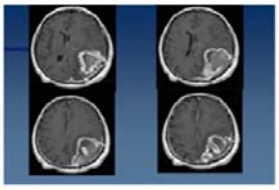
2. Integrated Health Clinic, Fort Langley, B.C., Canada.
3. Demetra&Lab Immune, Terni, Italy

Rationale for using liposomal doxorubicin.

Temozolomide is an imido-tetrazine readily absorbed orally and able to cross the blood brain barrier. TMZ has demonstrated activity against Glioblastoma and astrocytoma in various degrees, and in brain metastases (Reardon DA 2006, Addeo R 2011). Although TMZ has become the drug of choice in association with radiotherapy for Glioblastoma, many Glioblastoma patients develop resistance to the drug and become incurable. The complete reasons for why this resistance takes place is at the moment not completely understood, but seems linked to the presence of certain subpopulations of cancer-stem cells inside the tumor mass (Joannensen TC. 2012). This possible and eventual resistance to treatment has forced our group to look for other drugs active on GBM. We have chosen liposomal doxorubicin for various reasons that we will now describe. Liposomal doxorubicin (Caelyx®), is a formulation of hydrochloride doxorubicin wrapped in a film composed by phospholipids and polymers of methoxypolyethylene (mPEG) embedded in the lipid surface (Green AE. 2006). This association provides a favorable pharmacokinetic profile characterized by an extended circulation time, a reduced volume of distribution, thereby promoting an increased tumor uptake (Gabizon A. 2012; Holloway RW. 2010). Tumor abnormal microcirculation and permeability is responsible for the increased uptake and retention of liposomal drugs (Maeda H. 2006). This phenomenon of increased permeability is greatly increased by HT, as demonstrated by Ponce (Ponce AM.2006) and Dvorak (DvorakJ. 2004). Dvorak was one of the first to use the combination of Caelyx® and HT on hepatocellular carcinoma, reporting that the combination of HT and doxorubicin itself may be supra-additive, resulting in enhanced anti-tumor efficacy in the heated region and in decreased toxicity (DvorakJ. 2004). Caelyx® has been investigated by Koukoukaris (Koukourakis MI. 2000) in glioblastoma and in metastatic brain tumours. These authors are in agreement with the Chua and Lesniak group, who have concluded that Caelyx® selectively overcomes the blood brain barrier and accumulates 13-19 times higher in Glioblastoma tissue (Koukoukaris MI.2000; Chua SL. 2004; LesniakMS. 2005). Furthermore, Chua (Chua SL. 2004) has demonstrated the possibilities of using Caelyx® in association with TMZ in recurrent Glioblastoma. Liposomal doxorubicin has been associated with disease stabilization and a modest haematologic toxicity. These studies have convinced our group to test the use of pegylated doxorubicin in recurrent cases of GBM in our clinic. Our initial cases are thus briefly described hereafter.

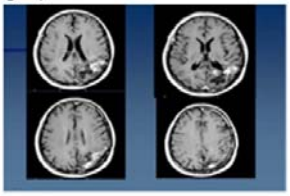
Case of patient treated with Caelyx. The patient (a right handed man) was first surgically treated (December 2005) for left posterior parietal Glioblastoma. The patient then underwent RT (45 Gy CFRT in 18 fractions) followed by a boost CFRT to reduced target (20 Gy in 4 fractions). He then started and continued Temodar (10 cycles) until progression (January 2007). This was followed by 2 cycles of ACNU, until progression (March 2007) (Fig.1). He was then started on Ionidamine and RadiofrequencyHyperthermia(HT). The initial cycles were done at 45 day intervals, then after an initial good response and apparent stabilisation, the GBL progressed the treatment was done at larger intervals of up to 9 CT+HT (the last treatment was done in Nov 2007).

Fig.1



The treatment was as follows: 12 mg/m^2 IV + steroids in glucose solution and on day 1200 mg of Quercetin p.o. one hour before HT, and repeated at least four hours later. From days 2 to 5 the patient underwent 4 consecutive days of more HT and quercetin treatment (100 mg before and after completion of HT).
HT was delivered by means of a 13.56 MHz radiofrequency capacitive device (Synchrotherm Duer) via two opposite plates at the maximum tolerated power for at least one hour for five consecutive days. Due to progression we decided to begin 20 mg of Caelyx® i.v. + HT, with the following schedule: after i.v. injection of Caelyx® an HT application lasting 1 h was done. Following a HT every day were applied for 10 times and a partial regression and stabilization was obtained (Fig..2) .

Fig.2



P-03: Csaba Kovago, Nora Meggyeshazi, Gabor Andocs, Andras Szasz (2012) Proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Proposed investigation on the possible synergic effect between high dose ascorbic acid application and oncothermia treatment

Csaba Kovago[1], Nora Megyeshazi[2], Gabor Andocs[3], Andras Szasz[4]

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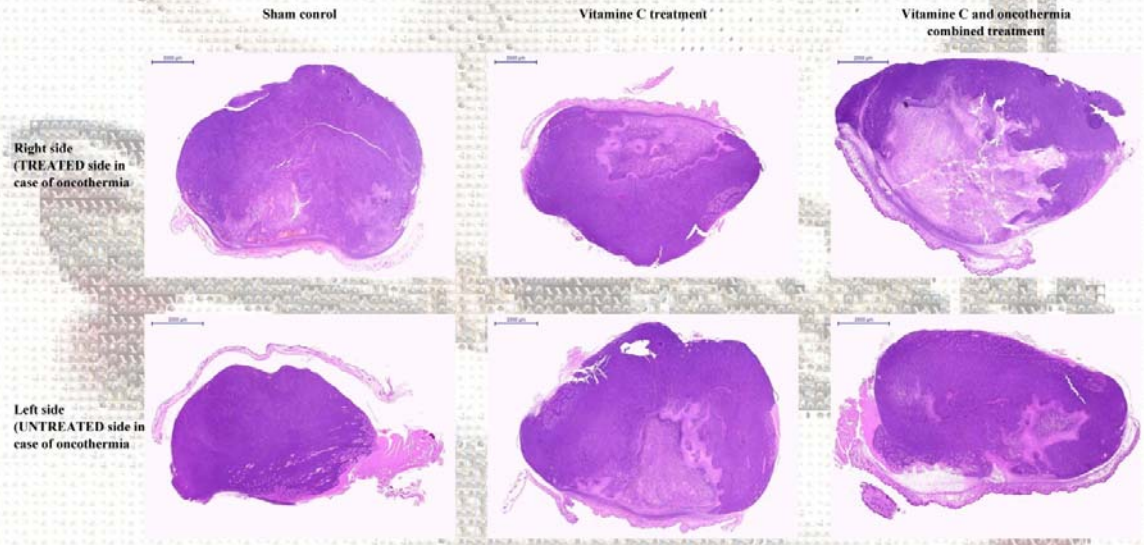
2: 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
3: Tottori University, Department of Clinical Medicine, School of Veterinary Medicine, Tottori, Japan
4: Szent Istvan University, Faculty of Mechanical Engineering, Biotechnics Department, Gödöllő, Hungary

Introduction - According to recent investigations, the parenteral application of ascorbic acid (vitamin C) at high doses has significant antitumor activity in in vitro assays. This fact is a very important using ascorbic acid as complementary drug with standard antitumoral therapy or in cases where currently no other potent treatment is possible. Although the specific method of action is still unclear: high concentration of ascorbic acid produces oxidative shock by H_2O_2 lethal for tumor cells beyond a certain level, however healthy cells can survive the same stress effect.

Objective - The goal of our experiment will be to determine the possible potentiating effect of application of high dose pH-neutralized ascorbic acid to the normal oncothermia treatment method.

Method - The NMRI mice intended to inoculate with C26 Murine Colon Carcinoma cell line subcutaneously at both of their femoral regions and kept till the tumors reach symmetrically the 10 mm in diameter. We plan to create four experimental groups, containing 5 male and 5 female animals in each. The formed groups of animals will be: Gr1. no treatment (control), Gr2. only ascorbic acid treatment, Gr3. only oncothermia treatment, Gr4. both ascorbic acid and oncothermia treatment. Both vitamin-C and oncothermia treatment will be applied once ("single-shut" treatment regime), ascorbic acid will be pH-neutralized and applied intra peritoneal in dose of 2 g/kg bodyweight. Oncothermia treatment will be applied only to the right limb tumor, the other side will be used as internal control. Animals will be held in total anaethesia during the time period of the treatment using ketamine-xylazine combination intraperitonealy (100 mg/bwkg ketamine and 10 mg/bwkg xylazine dose). Oncothermia treatment will be carried out using LabEhy equipment (Oncotherm Ltd, Páty, Hungary), output power set between 5-10 W (to keep the treated tumor core temperarture around 42 °C), treatment time planed to be 30 minutes.
The animals will be sacrificed 48 hours after the treatment, all tumors will be removed and analyzed histopatologicaly. Slides will be stained with hematoxylin-eosin protocol, the slides will be scanned by Pannoramic Scan digital slide-scanner (3DHISTECH Ltd, Budapest, Hungary). The digital images will be analysed by HistoQuant module of the Pannoramic Viewer software (3DHISTECH Ltd, Budapest, Hungary).
The other organs will be routinely checked as well. Our main question centers on the comparison of the cell-destruction ratio of the various applied treatment regimes, and study the possible synergy or additive cross-potentiating of the methods.

Results from a pilot study - The following slides originated from a previously made experiment, to test the idea of the investigation. As it can be seen the combined treatment of vitamine C and oncothermia resulted much larger tumor-tissue death than the vitamine C application alone.



Conclusion - The results of this experiment can help us to plan regimes to potentiate the known effects of the oncothermia methods with fewer side effects than in case of standard complementary chemotherapeutic applications. Our future plan to study further chemical materials, and herbal drugs in the same way in order to determine their possible synergic effects with oncothermia.
Using the results and experiences geathered from this experiment, further investigations are planed targeting herbal and synthetic materials to check the compatibility of these compounds with the effects of the oncothermic treatment.

P-04: Meggyeshazi Nora, Andocs Gabor, Krenacs Tibor (2012) Programed cell death induced by modulated electro-hyperthermia

Programmed cell death induced by modulated electro-hyperthermia

Meggyesházi Nóra[1], Andócs Gábor[2] , Krenács Tibor[1]

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Background: Modulated electro-hyperthermia (mEHT) is a non-invasive technique for targeted tumor treatment. The mEHT generated capacitive coupled modulated radiofrequency selectively accumulates in the tumor tissue without major effect in the surrounding normal tissues.

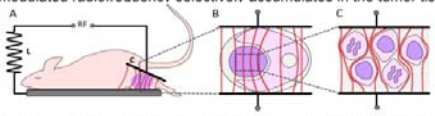


Figure 1: Scheme of the experimental set up and hypothetical effect of modulatated electo-hyperthermia treatment The radiofrequency (RF) generated electric field (red lines) is enriched in the tumor implant which is part of the circuit (A). Cross section through the mid-femoral region filled up by the tumor (violet lump) accumulating the current (B), which can not pass through cell membranes as it is depicted at the microscopic level (C). However, the electric field -alternating by 13.56 MHz- generates heat and interacts with ions in the extracellular space and any dipole molecular groups (non-thermal effect) causing them to rotate both in the matrix and cell membrane receptors. As a result of enhanced electric field and deregulated adaptive pathways in tumors, mEHT treatment can significantly interfere with the fate of tumor cells than normal cells and may trigger tumor cell destruction.

Method: HT29 human colorectal carcinoma cell line xenografted to both femoral region of BalbC/nu/nu mice was treated when reaching ~1.5 cm by using a single shot mEHT treatment (LabEHY, Oncotherm Ltd, Páty, Hungary) for 30 minutes. Sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 h in 3 mice each group by keeping 5 untreated animals. Histomorphologic, immunohistochemical and TUNEL assay results were tested in digital slides and analyzed semi-quantitatively. An apoptosis protein array was used to screen 35 apoptosis releated proteins, results were evaluated using the ImageJ software.

Figure 2: Double tumor model. Temperature (sub-cutaneous, tumor core, control side and rectal) was controlled <43°C.

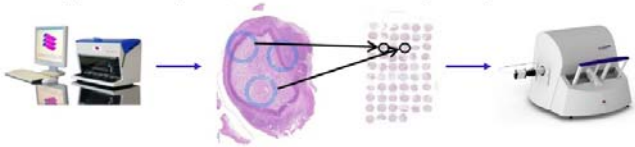


Figure 3: We have prepared tissue microarray (TMA), standard array selection based on digital slides. Followed by several immunofluorescence and immunohistochemistry with TRAIL-R2 , AIF, Cytochrome-C, and cleaved caspase-3 (all from Cell Signaling),and performed TUNEL assay.The slides were digitalised.

Results: mEHT caused programmed cell death related destruction from the tumor centre. TRAILR2 was up-regulated 8h post treatment. Cleaved caspase-3 positive cells appeared only at the tumor periphery between 4-14h. AIF nuclear translocalization at 14h and cytochrome c release from the mitochondria at 8-14h and massive TUNEL positivity at 24-48h indicated DNA fragmentation.

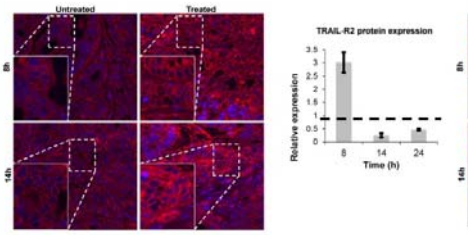


Figure 4. TRAIL-R2 expression in the tumor cell membranes is elevated both 8 and 14 hours post-treatment compared to the control side tumors. The elevation at 14h post-treatment appears only at the tumor periphery but not in the center, while evenly low TRAIL-R2 levels are seen throughout the control tumor. Insets show high power views.

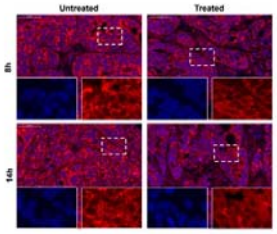


Figure 5: Cytochrome c was released into the cytoplasm from 8h post-treatment with a peak at 14h which disappeared by 24h on the treated sides. It remained mitochondrial in the untreated tumors.

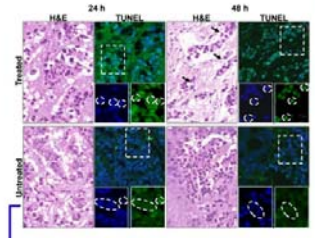


Figure 6: Both nuclear shrinkage and apoptotic bodies (arrows; H&E staining) as well as DNA fragmentation proved by the TUNEL assay (green fluorescence) became significantly elevated both at 24h and 48h after mEHT treatment (upper row) compared to untreated tumors of the opposite legs (lower row). Dashed rectangles highlight representative TUNEL positive areas at higher magnification in insets. Nuclear TUNEL positivity (dashed circles) was verified by showing DNA staining with DAPI in the highlighted identical cells. As a control, other DAPI positive cells particularly in the untreated tumors show only basic green fluorescence levels within dashed oval areas.

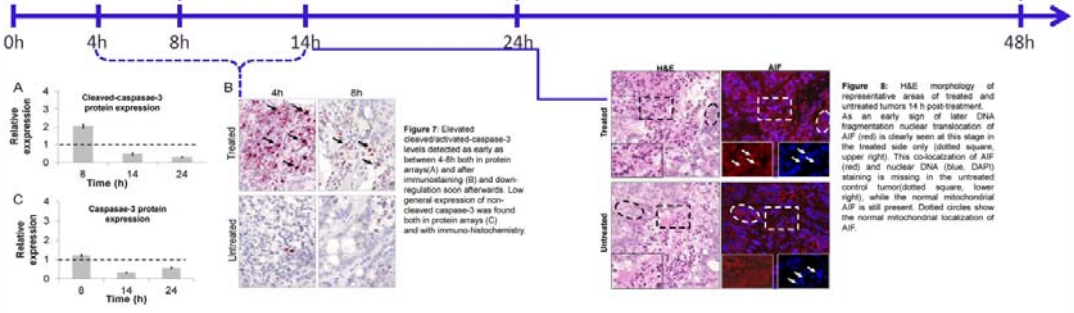


Figure 7: Elevated cleaved/activated-caspase-3 levels detected as early as between 4-8h both in protein arrays(A) and after immunostaining (B) and down-regulation soon afterwards. Low general expression of non-cleaved caspase-3 was found both in protein arrays (C) and with immuno-histochemistry.

Figure 8: H&E morphology of representative areas of treated and untreated tumors 14 h post-treatment. As an early sign of later DNA fragmentation nuclear translocation of AIF (red) is clearly seen at this stage in the treated side only (dotted square, upper right). This co-localization of AIF (red) and nuclear DNA (blue, DAPI) staining is missing in the untreated control tumor(dotted square, lower right), while the normal mitochondrial AIF is still present. Dotted circles show the normal mitochondrial localization of AIF.

Conclusion: In HT29 colorectal cancer xenograft mEHT (modulated electro-hyperthermia) caused programmed cell death. DNA fragmentation followed rather a caspase independent and AIF dependent subroutine with cytochrome c release.

Acknowledgement: Ivett Teleki, Edit Parsch, Péter Balla, Gergő Kiszner

In memoriam Réka Szász

P-05: Pesti L., Dankovics Zs., Lorencz P., Csejtei A. (2012) Complex treatment of advanced uterine cervix Chemo-radio-thermotherapy case report

Complex treatment of advanced uterine cervix
Chemo-radio-thermotherapy case report

Pesti L., Dankovics Zs., Lorencz P., Csejtei A.
Department of Oncoradiology
Markusovszky Hospital, Non-profit Co.Trust, Vas County, Hungary

Among malignant gynecologic diseases the morbidity of the squamous cell, planocellular carcinoma of uterine-cervix is 1300-1400 cases yearly, with mortality of 500 cases yearly in Hungary [approx. 10 million inhabitants].

We applied complex combination of various treatment modalities in inoperable, or only partially resectable cases:

RADIOTHERAPY (external-beam & brachytherapy) + CHEMOTHERAPY + HYPERTERMIA

Radiotherapy (ionizing radiation) treatment

Teletherapy: CT based radiation with 3D conformity, targeting the pelvic regional lymph-nodes up to 30 Gy; followed by field-concentration in 1-2 steps until 50 Gy, in fractional solution by 2 Gy doses.

Intracavital brachytherapy is applied complementary to teletherapy. After-loading technique is used once a week and three times altogether, providing 6-7 Gy/treatment.

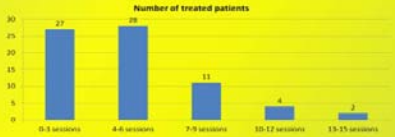
Chemotherapy

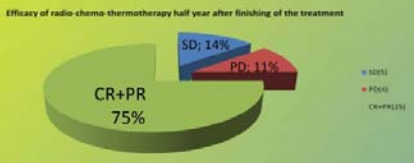
Cisplatin 40 mg/m²/week; concomitantly with tele-radiotherapy.

Local hyperthermia treatment

Complementary to the tele-radiotherapy, two times a week, targeting the pelvis.
Applied energy dose is 45 W, 60 min.
(In days of chemotherapy it is applied just after the infusion.)

We treated 70 patients with uterine cervix malignancies by the above radiotherapy-hyperthermia protocol between 2001 and 2010. All together 331 hyperthermia treatment-sessions were provided for these patients. 34 patients received additional complementary chemotherapy by above dose.





CASE-REPORT (57y old female)

Anamnesis: G2,P2, hypertonia for 15 years, stroke at age 54
vaginal bleeding (23.Dec. 2005), emergency hospitalization in our Department
Diagnose: Neopl.cerv.ut.std IIIB-IV Histology: carcinoma planocellulare kerat.

Teletherapy treatment
Dec.2005 – Feb.2006: external irradiation 2 Gy/day fractions, with 50 Gy complete dose

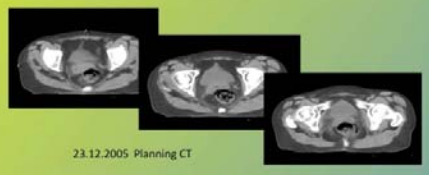
Brachytherapy (after loading treatments)
23.Dec.2005: Block of bleeding, after loading, 8 Gy
05.Jan.2006: After loading, 5 Gy
04.May 2006: After loading 4.5 Gy; targeting the residual tumor

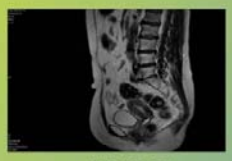
Chemotherapy
Dec.2005 – Feb.2006: 40 mg/m²/week Cisplatin complementary to external radiation

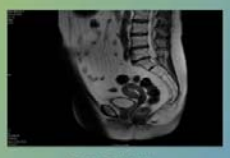
Hyperthermia treatments
Jan. – Feb.2006: 6 sessions
May-Aug.2006: 4 sessions

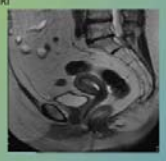
Last pelvic control by MRI: 17.Oct. 2010

NO EVIDENCE OF DISEASE (NED)


23.12.2005 Planning CT


24.03.2006 MRI


13.02.2007 MRI


17.10.2010 MRI

P-06: Peter Lorencz, Andras Csejtei (2012) Experience in the treatment of liver metastases, with special reference to the consequences of interruption of long-run treatments

Experience in the treatment of liver metastases, with special reference to the consequences of interruption of long-run treatments

Peter Lorencz, András Csejtei
Department of Oncoradiology, Markusovszky Hospital, Vas County, Szombathely, Hungary

Introduction: Our department has been dealing with oncothermia since 2001. It is used as one of the complementary treatments which are applied together with the gold-standards. We had treated more than thousand patients with this modality. 80% of the treated patients had primer or metastatic malignant liver tumors. We are intensively studying the long-term application of the hyperthermia, transforming the treatment of malignancy to the same as for one of the chronic-diseases. The cohort which we had chosen received more than 60 oncothermia treatments, and we are studying not only the long-time effects, but the response of long interruption (at least two weeks) of the treatment.

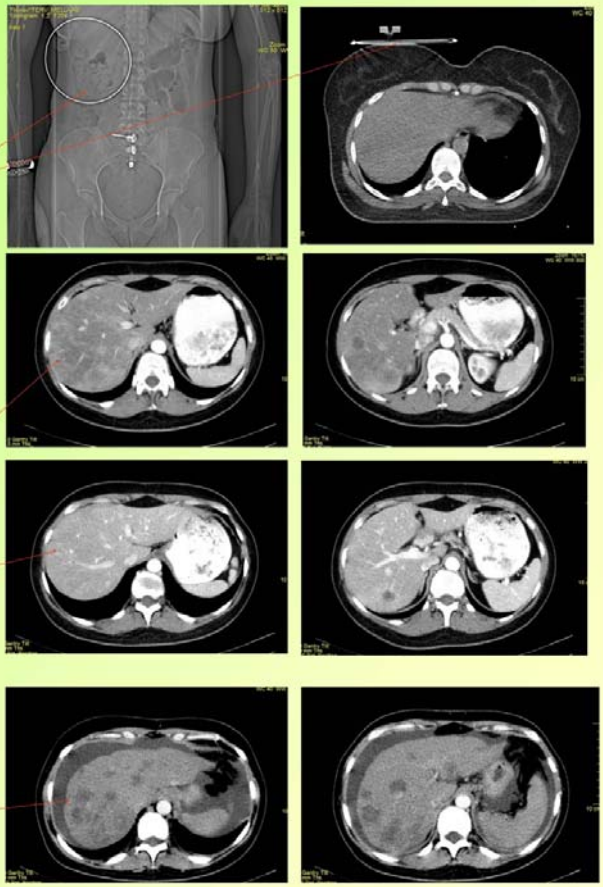
Objective of this presentation: We had chosen a mammary-carcinoma case with liver metastasis to show a typical effect of the interruption of the long-time treatment.

Method: The hyperthermia method was oncothermia, made by the EHY2000 and EHY3000 systems (Oncotherm Kft/GmbH). Oncothermia was applied always complementary to chemo-, radio- or combined therapies. In case of liver no radiation, only chemotherapy was applied. Patients received Oncothermia immediately after the chemotherapy. The control of the patients was made by standard imaging systems (CT, US, MRI).

Case-report: In 2005 a preventive mammography discovered a breast tumor in a female patient born in 1971. In preparation of the surgical intervention the liver metastasis was discovered too.

Applied therapy:

Dec. 22; 2005– breast-keeping surgery, R0
Jan. 2005 – radiotherapy on the breast: 50 Gy
(2 Gy fractioned)+ 10 Gy electron-boost
Jan. 05; 2006 – chemotherapy started (Taxotere + Epirubicine)
Jan. 06; 2006 – oncothermia is planned by CT simulator
Jan. 06; 2006 – Jul.14; 2006 oncothermia
49 sessions (60W, 60 min; 2x/week)
Mar. 06; 2006 – Regression detected by CT
May. 08; 2006 – Regression detected by CT
Sep.15; 2006 – Regression detected by CT
Oct. 18; 2006 – PET/CT negative, NED
Aug. 15; 2007 – NED by CT
No oncothermia is applied at this time
Jun. 06; 2008 – metastasis relapse in liver detected by CT
Jun. 10; 2008 – Chemotherapy (Taxotere +Xeloda)
Aug. 18; 2008 – Chemotherapy (Taxotere + Paraplatin)
Jun. 17; 2008 – Dec. 01; 2008 – 2nd cycle of oncothermia,
24 sessions; 60W.60min; 1x /week)
Jan. 07; 2009 – robust regression by CT
No oncothermia is applied at this time
Jul. 28; 2009 – multiple metastases detected in the liver by CT
Aug. 12; 2009 – Dec. 18; 2009 – 3rd cycle of oncothermia.
23 sessions; 60W, 60 min; 2x / week
No oncothermia is applied after this time
Sep. 26; 2009 – Chemotherapy (Taxol + Gemzar)
Feb. 08; 2010 – rapid progression detected by CT
Mar. 13; 2010 - exitus



Conclusion: Oncothermia has to be continued while the patient has chemotherapy, or at least until the second negative control (2nd NED).

P-07: Andocs G., Okamoto Y., Osaki T., Tsuka T., Imagawa T., Minami S., Balogh L., Meggyeshazi N., Szasz O. (2012) Oncothermia basic research at in vivo level. The first results in Japan

Oncothermia basic research at in vivo level
The first results in Japan

Andocs, G.[1], Okamoto, Y.[1], Osaki, T.[1], Tsuka, T.[1], Imagawa, T.[1], Minami, S.[1], Balogh, L.[2], Meggyeshazi, N.[3], Szasz, O.[4]

(1) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan
(2) „Frederic Joliot Curie" National Research Institute for Radiobiology and Radiohygiene, Budapest, Hungary
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
(4) Biotechnics Department, Faculty of Engineering, St. István University, Budapest, Hungary

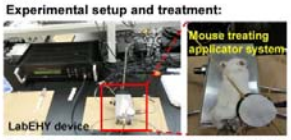
Background: Oncothermia method (OTM) is a long time (since 1989) applied method in oncology.[1] with great clinical success.[2] Oncothermia research group conducts investigations to reveal the basic mechanism of action of this tumor treatment method in basic research level performing a huge number of in vivo studies. The tumor destruction efficacy and the role of temperature independent effects of the OTM was proven earlier and presented elsewhere [3],[4], as well as the recent in vivo results [5],[6]. In this presentation we summarize the first results we have achieved in Tottori University, Japan.

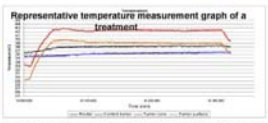
Methods

Study I. :
In the first study we examine the effect of oncothermia treatment in a mouse tumor model.

Animal model: Colon26 (murine colorectal cancer) cell line derived allograft mouse tumor model with double tumors. Every animal had two tumors on the femoral region, the right side (○) was treated, the left side (○) was individual control.

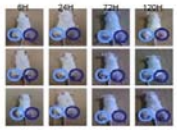
Experimental setup and treatment:





A single shot 30 min oncothermia treatment was done, reaching maximum 41-42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense m3300).

Study design:
Time course study was performed. After a single shot oncothermia treatment animals were sacrificed at 6H, 24H, 72H, and 120H later and tumors were removed. All time-group there were 3 treated animals and 1 untreated control animal.



Tumor sample processing:
All the removed tumors were cut accurately at their centerline. After a standard histological process the samples were stained with HE and TUNEL reaction and Ki-67 detection were performed. Samples were evaluated using complex histomorphological methods.

Study II.:
In the second study we examined the effects of OTM to tumor oxigenization using a rat tumor model.

Animal model: 9L (rat glioma) cell line derived heterotopic allograft rat tumor model with double tumors in both femoral region. Tumor tissue oxigenization was measured in the tumor on the right side.

Oxygen level measurement: pO_2 sensitive elektrode system (Eikon Kagaku Ltd.150D model)

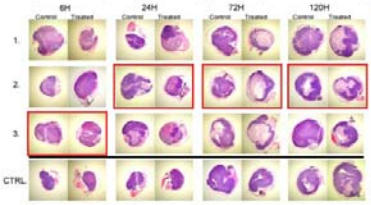
Study design:

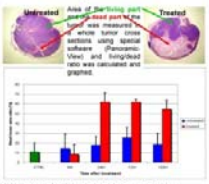
In 11 rats, tumor tissue oxigenization level was measured using a pO2 sensitive electrode system right before the treatment. Then a single shot, 30min oncothermia treatment was performed reaching maximum 42oC intratumoral temperature. Right after the treatment the tumor oxigenization level was measured again.

Results

Study I. :

1. A, Histomorphological changes in a qualitative and a quantitative way:





Result graph of the living/dead area ratio measurement of the whole tumor cross sections

Drastic and selective tumor-destruction was detected after a single shot OTM. The tumor destruction was not immediate, it had a time-delay. Samples marked with a red rectangle are evaluated in details.

References:

gandocs@gmail.com

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(http://www.springer.com/biomed/cancer/book/978-90-481-9487-1?changed=header) Heidelberg, Dordrecht
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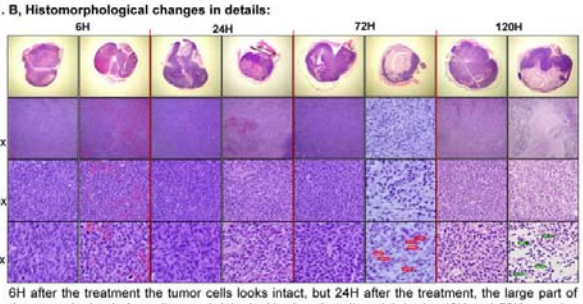
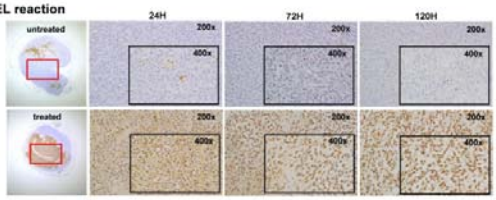
[6] Meggyeshazi N. : Early changes in protein expression released to modulated electro-hyperthermia. ICHS 2012

1. B, Histomorphological changes in details:



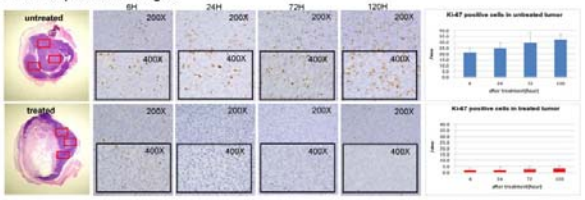
6H after the treatment the tumor cells looks intact, but 24H after the treatment, the large part of the tumor is dead, the cells are shrinked with picnotic cell nuclei. In the 48H and 72H samples definite late morphological signs of apoptotic cell death was observed: extremely high number of apoptotic bodies(▭). 120H after the treatment morphological signs of leukocyte (mostly neutrophiles ▭) invasion can be visible.

2.TUNEL reaction



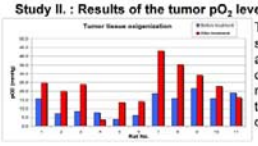
TUNEL assay enzymatically labels the DNA fragments resulted by apoptotic cell death process. In the dead tumor area a huge number of TUNEL-positive cells were observed after a single shot OTM treatment.

3. Ki-67 expression changes

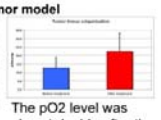


The Ki-67 proliferation marker protein is expressing in the nuclear membrane only in the dividing cells. That is why sampling for Ki-67 positive cell counting was done from the living part of the tumors (▭). In a very interesting way the number of Ki-67 positive cells were significantly decreased in the living part of the treated tumor compared to the control tumors.

Study II. : Results of the tumor pO_2 level measurement in a rat tumor model



Tumor tissue pO_2 level was significantly higher right after the OTM treatment compared the pO_2 level measured right before the treatment in case of 10 out of the total 11 animals.



The pO2 level was almost double after the treatment in average.

Conclusions

1. In the mouse study, OTM treatment can significantly destroy the tumor tissue in a large volume of the tumor even with a single shot way. OTM treatment induces apoptotic cell death in the destroyed tumor tissue and effectively inhibits cell proliferation in the living part of the tumor.
2. In the rat study, OTM treatment can significantly increase the tumor tissue oxigenisation which creates the basis of the strong synergism with radiotherapy and some chemotherapy.

Acknowledgement:

In memoriam Reka Szasz

TATEYAMA KAGAKU GROUP

P-08: Coletta D., Gargano L, Assogna M., Castigliani G., De Chicchis M., Gabrielli F., Mauro F., Pantaleoni G, Pigliucci GM (2012) Stabilization of metastatic breast cancer with capacitive hyperthermia plus standard-dose chemotherapy and/or metronomic

STABILIZATION OF METASTATIC BREAST CANCER WITH CAPACITIVE HYPERTHERMIA PLUS STANDARD-DOSE CHEMOTHERAPY AND/OR METRONOMIC

Coletta D.[1], Gargano L.[1], Assogna M.[1], Castigliani G.[1], De Chicchis M.[1], Gabrielli F. [2], Mauro F. [2], Pantaleoni G. [2] and Pigliucci G.M. [1]

[1] Department of Oncological Hyperthermia. University of Tor Vergata. Rome. Italy.
[2] Interfaculty Department for Scientific Research (D.I.R.S).- L.U.de.S. University. Lugano – Switzerland.

INTRODUCTION

In our long experience in Universitary Hyperthermia treatment of tumors associated with chemotherapy, we observed that response to associated treatment determines the disease stabilization and significant clinical benefit for 24 months in 12 cases of metastatic breast cancer, whereas chemotherapy alone had shown ineffective with disease progression, bone marrow toxicity G3-4, fatigue G2-3, nausea and vomiting G1-G2, bone pain G3-4 and visceral pain G2-3. (Table 1).

TOXICITY WITH CHT ALONE	TOXICITY WITH ASSOCIATED THERAPIES (CHT+HT)
Bone pain: G3-4	Bone pain: G1-2
Visceral pain: G2-3	Visceral pain: G1
Fatigue: G2-3	Fatigue: G1-2
Nausea and vomiting: G2	Nausea and vomiting: G1
Bone marrow tox: G3-4	Bone marrow tox: G1-2

TAB 1

MATERIALS AND METHODS

2 of 12 patients underwent hormone therapy alone because allergic to chemotherapy drugs, other 10 patients underwent to CHT+/- Hormone Therapy according to the protocols seen in Table 2.

ID	Birth Date	Therapy
C. L.	25/08/1969	*Exemestane*
C. C.	19/02/1947	*CMF, Docetaxel, Nolvadex, Enantone*
D.L.V.	01/05/1956	*Trastuzumab+CBDCA, Myocet+Gemcitabine*
C. P.	22/10/1956	*FEC, Trastuzumab, Vinorelbine, Capecitabine, Fulvestrant*
F. V.	15/03/1946	*Myocet+ Docetaxel, Myocet+Gemcitabine, Zoledronic Acid*
F.D.	20/08/1962	*Fulvestrant+Xeloda, CBDCA+TAX, NVB+GEM*
P.G.	11/12/1957	*Herceptin+NVB, Herceptin,Xeloda*
O.F.	14/09/1959	*Zometa+Tam*
M.D.	19/08/1956	*Xeloda+TXT+BEVA,CBDCA+GEM, TAXOL, NVB, Myocet*
L.G.	28/08/1921	*TXT+Letrozolo*
P.D.A.	24/03/1961	*Herceptin+CBDCA, Myocet+Gemcitabina*
M.C.	19/94/1954	*FEC,CBDCA+GEM, Herceptin+NVB, Lapatinib+Xeloda*

TAB 2

All patients underwent an average 30 cycles of capacitive hyperthermia, each consisting of eight 45-minute sessions every other day, using 300W per session.

RESULTS

In these patients the improvement of performance status has allowed a return to regular life. This improvement of the quality of life showed a correspondent biochemical response, with a progressive reduction in tumour markers and showed also a diagnostic response with stabilization of disease: in some cases reduction of size and/or number of metastases and in all cases with absence of metabolic activity disease (TB PET CT scan).

CONCLUSION 1

The use of OT/CHT-HT combination may enhance efficacy vs CHT and OT alone. This surprising result may confer a small, but probably, clinically significant improvement survival and quality of life. However the result of larger collaborative international adjuvant CHT-HT trials will be needed in order to determine the true value of this combination.

CONCLUSION 2

According to the studies on P.N.E.I.M (1, 6, 7), the results in the field of Clinical Pharmacology concerning drug abuse and medicines disuse, and the resulting recent studies in anthropology on cancer patients, all of our patients were treated at a preventive, therapeutic and post-treatment level with appropriate behavioural tests and drug treatments to avoid relapse. Clinical Pharmacology, in our opinion, considers every patient, according to the multidimensional approach (biopsycosocial), as a global being (8, 9, 10, 11).

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P-09: Sergey Roussakow (2012) Critical analysis of randomized trials on electromagnetic hyperthermia: doubful effect and multiple biases

CRITICAL ANALYSIS OF RANDOMIZED TRIALS ON ELECTROMAGNETIC HYPERTHERMIA: DOUBTFUL EFFECT AND MULTIPLE BIASES

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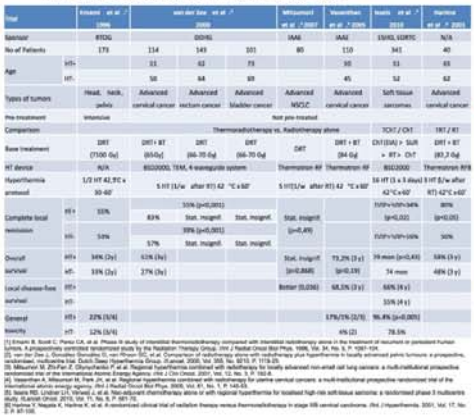
Tab. 1 RCT on superficial hyperthermia published after 1990

Tab. 2 RCT on deep hyperthermia published after 1990



INTRODUCTION

Hyperthermia in oncology had been extensively studied since 60th. Despite of more than 13 000 publications, 50 monographs and manuals and more than 1 200 clinical trials, hyperthermia is still not accepted as a regular cancer treatment. The current trial was performed for further explanation of this situation.

METHODS

All the available randomized controlled trials (RCT) on hyperthermia (HT) in oncology published after 1990 were studied: 7 RCTs on superficial HT (Tab. 1), 6 RCTs on deep loco-regional HT (Tab. 2) and 1 RCT on whole-body HT (altogether 14 RCTs). All the RCTs were studied from the position of "null hypothesis", i.e. considering HT not effective and/or not safe. These were analysed for 1) efficacy by clinical outcomes, 2) toxicity, 3) biases.

RESULTS AND DISCUSSION

8 of the 14 RCTs were recognized as negative by their authors (Tab. 3). HT significantly improved survival in 2 RCTs only. In other trials, HT didn't effect survival significantly, sometimes worsening it. Improvement of local control was the only significant and permanent effect of those positive RCTs. Careful analysis of all the positive RCTs revealed significant biases (Tab. 4) which affected their results.

Inadequate comparator was the most common bias. Typically this was a low-dose radiotherapy (RT) (Overgaard, 1996; van der Zee, 2000; Harima, 2001). As a result, clinical effect in HT-groups of the trials was worse than in other trials, where adequate RT doses (without HT) was used. Toxicity and expensiveness of thermoradiotherapy (TRT) were higher than of RT alone. Therefore, results of HT RCTs received with inadequate comparator were clinically insignificant. At the same time, HT worsened clinical outcomes when applied vs. adequate control (standard high-dose RT). At least in one case HT with adequate RT control significantly reduced overall survival (Vasanthan, 2005) (Fig. 4). Comparative analysis allows to hypothesise, that improvement of local control in the trials with inadequate comparator was achieved for account of significant decrease of overall survival in comparison with trials with adequate treatment (Fig. 3). Significance of RT dose was clearly demonstrated in the RCT of Overgaard et al. (1996) (Fig. 1): increase of RT dose for 10% led to 120% increase of 2-year local control rate, though effect of HT was 2 times less (60% only).

In Jones et al. (2005) trial, defect of randomization was revealed. As a result, RT dose in HT group was 10% higher than in the control RT group (55 Gy vs. 50 Gy). This difference can explain the received clinical effect in full. Additionally, pre-selection of thermosensitive patients was applied in this trial, though the conclusions of the trial were not limited to thermosensitive patients only. Clinical effect in Harima et al. (2001) trial also could be explained by pre-selection of aged patients (median age in HT group of previously untreated patients was 65 years, though the expected age of the first diagnosis is 55 years) and inadequate RT dose to tumor mass (60.6Gy). It's well known that local control after HT is much better among aged patients (Fig. 2).

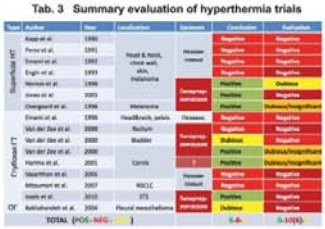
Some trials were incorrectly designed. In Vernon et al. (1996) trial, some different trials were combined in order to reach statistical significance level. Overgaard et al. (1996) trial was experimentally designed. In van der Zee et al. (2000) trial, different protocols were used which are impossible to average. Incomplete data presentation and inadequate analysis are typical biases.

In Issels et al. (2010) trial, systematic distortion in favor of HT group was revealed. As a result, intensity of base therapy in control group was twice lower than in HT group. This distortion excessively explains the received clinical effect without necessity of HT hypothesis. Also, the best results in HT group were much worse than those reported in meta-analysis of 14 earlier RCTs (without HT). This allows to hypothesise that HT possibly worsened the clinical results instead of improve them. This hypothesis is supported by the rise of toxicity in HT group. General toxicity rose 9 times and severe toxicity (treatment-limiting) rose 20 times vs. toxicity in the control group.

The only existing RCT on whole-body HT showed that HT significantly and strongly worsened clinical results comparatively with chemotherapy alone (Fig. 5).

All the RCTs considered as positive by their authors were sponsored by different hyperthermic societies. All the RCTs sponsored by independent organizations were negative.

Tab. 3 Summary evaluation of hyperthermia trials



Tab. 4 Evaluation of biasses in positive RCT

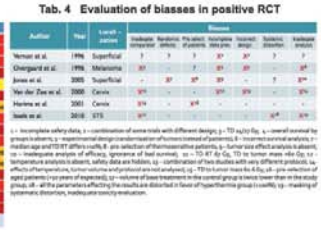


Fig. 1 Significance of radiotherapy dose - example of Overgaard et al. (1996) trial

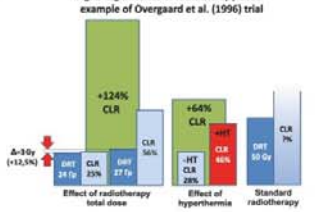
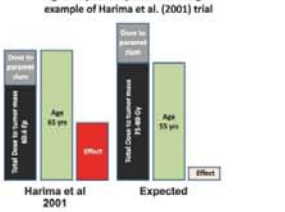


Fig. 2 Impact of special trial design - example of Harima et al. (2001) trial



2 year complete local remission rate (CLR) in the group with total dose (TD) 27Gy was 56% vs. 25% at TD=24Gy (+124%, p<0.05). Therefore, impact of TD for CLR was twice stronger that hyperthermia impact (CLR+46% in hyperthermia group vs. 28% in the control group, +64%). Obviously, with standard TD of DRT (50Gy) the effect of thermal potentiation would be statistically insignificant.

- **Inadequate control** (TD to tumor mass 60.6 Gy vs. 75-80 Gy with adequate radiotherapy) allows to show effect of thermal potentiation
- **Relatively high dose to parametria** (21.6 Gy or ~25% TD) makes impression of adequate TD (82.2 Gy), reduces relapses rate and makes better survival
- **Pre-selection of aged patients** (+10 years vs. expected age of 1st diagnosis) makes local control better.

Fig. 3 Comparison of RCT on cervix cancer

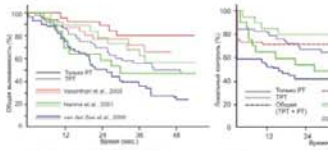


Fig. 4 Decrease of survival in HT group (Vasanthan, 2005)

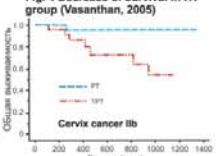
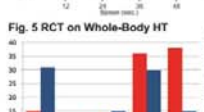


Fig. 5 RCT on Whole-Body HT



In RCT of Bakhshandeh et al. (2004), whole-body hyperthermia (WBH) did worsen effect of chemotherapy (CHT) in malignant pleural mesothelioma. Partial remission (PR) rate in thermo-chemotherapy group (TCHT) was decreased to 18% vs. 31% in control group (CHT only) together with significant decrease of overall survival (OS) (11.5 months vs. 15 months in control group) and disease-free survival (DFS) (5.6 months vs. 9.2 months) and increase of III-IV grade toxicity (neutropenia (NP) 36% vs. 30% in control group, thrombocytopenia (TP) 38% vs. 15% in control group).

Bakhshandeh A, Mosalaeinoori G, Zabel P, et al. Randomized trial with ICE (fosfamide, carboplatin, etoposide) plus whole body hyperthermia versus ICE chemotherapy for malignant pleural mesothelioma. //Journal of Clinical Oncology, 2004 ASCO Annual Meeting Proceedings (Post Meeting Edition). Vol. 22, No. 14S (July 15 Supplement), 2004: 7288.

ABSTRACT

Hyperthermia in cancer treatment still remains an experimental treatment without real clinical future. For further explanation of this situation, all the available randomized clinical trials (RCT) on electromagnetic hyperthermia (EMHT) were studied from the position of 'null hypothesis', taking into account the probable biases. The careful analysis hasn't confirmed a clinical efficacy of EMHT despite of its type: superficial, deep (locoregional) or whole-body. There is no any positive trial not affected with serious biases. After adjustment to the biases, there is no any trial with significant effect of EMHT. EMHT efficacy was shown either in trials with experimental design or versus incorrect comparator. In clinical setting and with correct comparator, EMHT was ineffective or not enough effective to counterbalance its obvious limitations – toxicity and labor-intensity. Since EMHT doesn't generally improve the results obtained with standard effective treatment protocols but significantly increases toxicity, its usefulness is doubtful in general, because an equal or even better effect could be obtained by applying a standard high-dose protocols of radiotherapy or chemotherapy, with lower toxicity and significantly lower labor costs.

Publication: 1. Reported on XXX annual ICHS meeting (Tbilisi, 9-11 сентября 2011 г.)
2. Submitted to «Medical Radiology and Radiation Safety» Journal

P-10: Strauss CA., Kotzen JA., Baeyens A., Mare I. (2012) Oncothermia in HIV positive and negative locally advanced cervical cancer patients in South Africa

Oncothermia in HIV Positive and Negative Locally Advanced Cervical Cancer Patients in South Africa

C-Therm Africa
Your partner in oncologic hyperthermia

Strauss C.A., Kotzen J.A., Baeyens A., Maré I.
University of the Witwatersrand
Medical School, Radiation Sciences

INTRODUCTION:

The investigation of technologies which can increase cancer treatment efficacy is driven by:

- The high prevalence of Human Immunodeficiency Virus (HIV) and cervical cancer in South Africa [1 2]
- The growing concerns that HIV infection and certain Antiretroviral Therapies (ARTs) increase the sensitivity to radiation therapy (RT) and chemotherapy, [3 4 5]
- The economic impact of cancer on the already over-burdened healthcare system and economy in Africa [6]

AIM: To investigate the clinical and economic benefits of the addition of oncothermia to standard treatment protocols for HIV positive and negative locally advanced cervical cancer patients in public healthcare in South Africa and to study the radiosensitising effects of the technology on a cellular level in these patients.

OBJECTIVES

PRIMARY:

Evaluate the effect of the addition of oncothermia on:

- Local disease control at 6 months (assessed by PET scans);
- Progression free survival at 12, 18 and 24 months;
- Overall survival at 2 years (and the cause of death)

SECONDARY:

- Evaluate adverse effects that can be directly attributed to oncothermia
- Evaluate the effects of oncothermia on tolerability and toxicity of the prescribed treatments
- Evaluate the economic impact of the addition of oncothermia in public healthcare (based on quality adjusted life years)
- Evaluate the effect of the addition of oncothermia on the quality of life of patients
- To evaluate the effect, if any, of oncothermia treatments on the HIV disease status of HIV positive participants as assessed by:
  - CD4 count
  - HIV viral load
  - Concurrent AIDS-defining conditions
- To describe cervical cancer recurrence patterns in both groups

RADIOBIOLOGY RESEARCH

- To evaluate thermoradiosensitivity by measuring DNA damage (double strand breaks), using Micronucleus (MN) assays, in response to ionising radiation combined with oncothermia before and after completing treatment in HIV positive and negative patients.
- To investigate the molecular markers for thermoradiosensitivity. This will be done by comparing gene expression profiles of cells extracted from biopsies of thermoradiosensitive and thermoradioresistent tumours. Gene profiling of tumour samples will be used to identify potential molecular markers in the tumour cells which are associated with increased response or with resistance to radiochemotherapy combined with oncothermia. This may eventually result in individualised treatment schedules and may be useful in separating patients with and without recurrence following oncothermia.

METHODOLOGY:

Study Type: Phase III randomised clinical trial. Sample: 236 HIV negative and HIV positive stage IIb-IV locally advanced cervical cancer patients will be recruited. This is based on the estimated required sample size for a two-sample comparison of survivors' functions at two years. The statistical significance is defined as a two-sided alpha<0.05 for a log-rank test, with a constant Hazard ratio of 0.5693, a statistical power of 90%, a 15% withdrawal rate and an estimated 140 events. We anticipate at least 50% of recruited participants will be in Stage III of the disease and around 30% of these participants will be HIV positive. Randomisation: The participants will be divided into a control group (N=118) and a study group (N=118) and the sampling method used will be stratified random sampling (stratum: HIV status). In each stratum there will be a random selection in order to ensure equal numbers of HIV positive and HIV negative women in each group. Location: The trial will be conducted at the Charlotte Maxeke Johannesburg Academic Hospital, Gauteng, South Africa. Treatment: Participants from both groups will receive 3 doses of cisplatin (80mg/m^2), external beam radiation (50Gy administered over 25 factions of 2Gy) and 3 HDR intracavitary brachytherapy treatments of 8Gy each. The study group will receive two 60 minute oncothermia treatments per week during the external beam radiation therapy. Duration: The study is scheduled to start in January 2013 and the recruitment is expected to take two years. Participants will be monitored for two years after completion of the treatment protocols. The total study duration is therefore expected to be 4 years.

EXPECTED OUTCOMES:

- The addition of oncothermia to standard treatment protocols will result in improved local disease control and two year survival rates in HIV positive and negative locally advanced cervical cancer patients without increasing the treatment toxicity.
- We hypothesise that the addition of oncothermia will result in a reduction in healthcare costs associated with the treatment of cervical cancer. This would significantly benefit the already over-burdened healthcare system and economy of South Africa and other developing countries.

ACKNOWLEDGMENTS: The EHY 2000 Plus device which will be used for the trial is being supplied by Oncotherm GmbH

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P-11: Jückstock J., Eberhardt B., Kirchner H., Müller L., Sommer H. (2012) Locoregional hyperthermia combined with chemotherapy for metastatic breast cancer patients – preliminary results of the Mammatherm-trial

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KLINIK UND POLIKLINIK FÜR FRAUENHEILKUNDE UND GEBURTSHILFE

Locoregional hyperthermia combined with chemotherapy for metastatic breast cancer patients – preliminary results of the Mammatherm-trial

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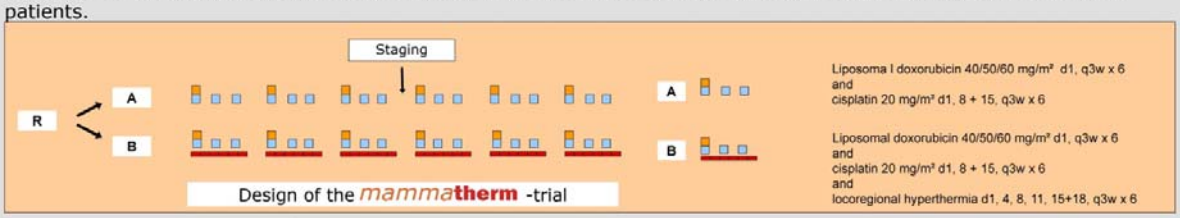
Background

Treatment options for patients with metastatic breast cancer should be as effective and preferably as little toxic as possible. To date there is no standard therapy available and treatment regimens for metastatic breast cancer vary largely. Locoregional hyperthermia might show additive effects to chemotherapy due to an increased perfusion and a simultaneous occurrence of interstitial acidosis in tumor tissue. In randomized clinical trials the addition of hyperthermia to radiation in advanced breast cancer was associated with improved outcome. To our knowledge so far there are no randomized clinical trials evaluating the effect of a combination of hyperthermia and chemotherapy in breast cancer patients.



Design of the mammatherm -trial

Fig. 1: Hyperthermia devices in the study

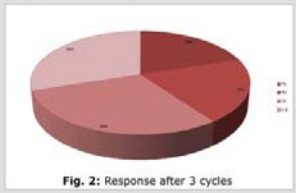


Fig. 2: Response after 3 cycles

Patients and Methods

Phase I of the multicenter German Mammatherm-trial was a dose-finding-study for liposomal doxorubicin administered in combination with cisplatin (20mg/m2) and locoregional hyperthermia. Patients received 6 cycles of therapy according to the following regimen:
liposomal doxorubicin 40 or 50mg/m2 i.v. d1 q22d and cisplatin 20 mg/m2 i.v. d1, 8, 15 q22d in combination with locoregional hyperthermia administered at d1, 4, 8, 11, 15, 18 q22d. Dosage escalation levels for liposomal doxorubicin were at 40/50mg/m2; an escalation up to 60mg/m2 was planned but not effected due to dose limiting toxicities (DLTs).
DLTs were defined as non-hematological toxicities > grade 2 NCI CTCAE (National Cancer Institute Common Terminology Criteria of Adverse Events), - except of nausea and vomiting -, or hematological side effects grade 3 or 4 NCI CTCAE leading to treatment postponement of more than 7 days, if those adverse events were at least possibly associated with the study therapy.
Here first results of the trial concerning the observed DLTs are presented.

Results

A total number of 10 patients were recruited into the trial between August 2007 and May 2011. The therapy was prematurely stopped in 6 patients. Therapy was discontinued in only one patient due to toxicity (adiponecrosis); all other discontinuations were required because of tumor progression. Dose limiting toxicities (DLTs) were observed in 2 patients and comprised liver toxicity in a patient with liver metastases, and, probably, but not proven, tumor-associated bone pain. A causal link to the administered chemotherapy could not be ruled out but appeared to be rather unlikely in both cases. None of these adverse events required treatment discontinuation. There were neither hematological nor hyperthermia related DLTs seen.

	grade 3	grade 4
leukopenia	6	
Neutropenia	3	
thrombopenia	-	
anemia	-	
GOT ↑		1
GGT ↑		1
Total of non-hematological toxicity	12	2
Burns	1	
SAE's	6	

Table 1: Incidence of grade 3/4-toxicities

Conclusion

The combination of locoregional hyperthermia and chemotherapy in pretreated metastatic breast cancer patients showed a tolerable toxicity profile. Data concerning the final toxicity analysis are pending.

12. Conference of the International Clinical Hyperthermia Society• Budapest, October 2012• Dr. Julia Jückstock
Klinikum Innenstadt Munich University, gynecology and obstetrics • Munich, Germany • julia.jueckstock@med.uni-muenchen.de

P-12: Oliver Szasz, Gabor Andocs, Nora Meggyehazi, Andras Szasz (2012) Oncothermia – personalized treatment option

Oncothermia - personalized treatment option

Oliver Szasz[1], Gabor Andocs[2], Nora Meggyeshazi[3], Andras Szasz[1]

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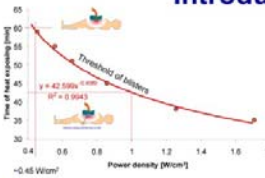
(2) Department of Veterinary Clinical Medicine, Faculty of Veterinary Science, Tottori University, Tottori, Japan

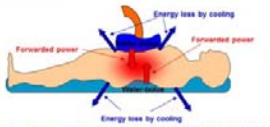
(3) 1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

Objective

The personalization of the oncological treatments is the new trend in modern medicine [1]. Oncothermia is a personalized treatment by tuned energy delivery to the targeted tumor [2]. This energy is well focused on cellular level [3], and makes the dose of energy optimal for cell destruction [4]. The personal feedback of the patient together with the natural homeostatic control of the treatment actions makes the treatment realistically personalized. [5]

Introduction

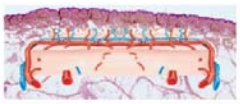


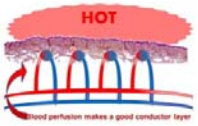


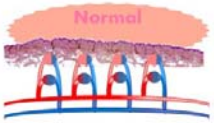
When the energy taken away by cooling and by the bolus is high and uncontrolled, than no control on the treatment as well.

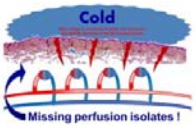
Discussion

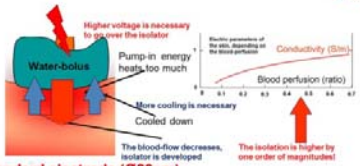
The main factor of the homeostatic control is physiological, based on the active homeostatic control of the blood-perfusion and blood-flow regulating the energy-intake and heat-exchange in the target. The high blood-flow is an effective heat-exchanger, cools the given volume. The well conducted treatment optimizes the current flow-density through the lesion, and optimizes the treatment. One of the crucial points is the surface heat-regulation, which has to be carefully done by the electrode systems. When the surface temperature kept constant, the nerves mainly regulate the current density, which is the clue of the objective regulation. This regulation is also stress dependent, and depends on the human race-variants as well. The step-up heating is important not only avoid the inconveniences, but regulate the adaptation mechanisms. Healthy cells can be adapted to the electric/heat-stress, while this adaptation is much less in the malignant lesions. The applied step-up heating supports the physiological selection and makes the contrast of the reaction definite. Recognizing the hysteresis type of SAR-temperature development the protocol could be well conducted. Using the Weibull distribution function of the transport processes as well as considering the typical physiological relaxation time of the tissues special protocols can be developed for all the deep-seated treatments of various organs.



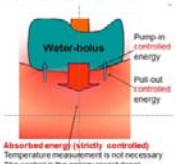






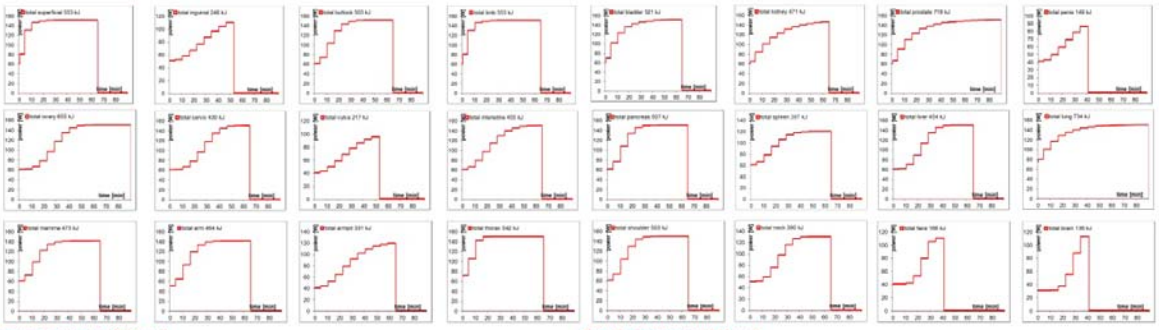


Standard electrode (Ø20cm)



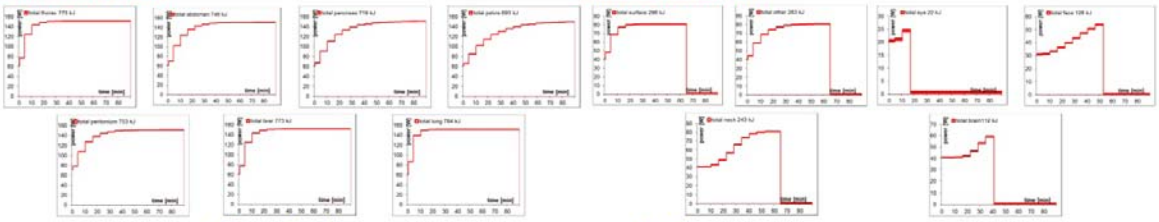
This patented technique makes possible

- ✓ Temperature measurement is not necessary, the energy control is valid
- ✓ We get the highest available RF-current, which does the decisional effect
- ✓ Oncothermia is extraordinarily safe and effective
- ✓ It is possible to make special protocol proposals for general use, and it modified by patients needs



Large electrode (Ø30cm)

Small electrode (Ø10cm)



Conclusion

Oncothermia with its surface stabilized sensing (patented action) uses the personal sensing in objectivity of the actual energy-dose. This makes possible the accurate and personalized treatment by this method.

In memoriam Reka Szasz

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P-13: Gabor Nagy, Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Deep temperature measurements in oncothermia processes

Deep temperature measurements in oncothermia processes

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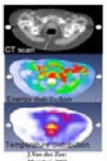
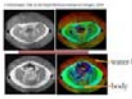
Introduction

The controlled and focused heat-delivery to deep-seated tissues is a long-standing problem of the local hyperthermia in oncology. [1]. The multiple artificial methods to focus the temperature has numerous technical and physiological problems. The energy could be focused in planned accurate way, but the temperature is naturally spread, as well as the physiological controls likely contra-effects the actual heating process. Our objective is to show how oncothermia makes the energy delivery in controlled way in depth.

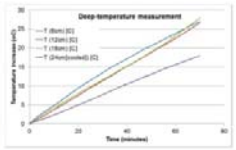


Electric Tea Kettle – 1300 Watts is boiling 2 cups of water in about 3 minutes from room temperature. Most of the hyperthermia devices with same energy heat up the same volume of tissue from 36°C to 43°C during 60 minutes

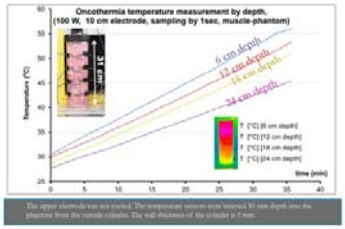
The energy-pattern far not correlates with the temperature pattern of the same treatment. The reason is the various blood-flow in the regions. (van der Zee, Conference in Mumbay 2005

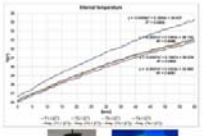


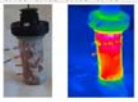
Many times the bolus is heated up more than the desired tissue



Impedance heating; (current flows through)

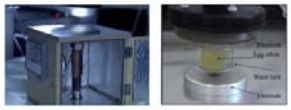






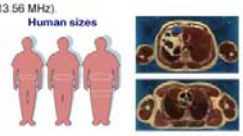
Method

The heating method is impedance –heating with modulated RF (13.56 MHz).



The RF-impedance heating easily heats up the loads to high temperature, and even coagulates the egg-white (without heating up the surrounding water).

Human sizes



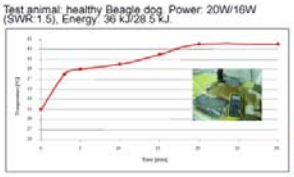
Human "thickness is ranging between 25-32 cm in average in lying-position

Applied equipment was EHY2000 device

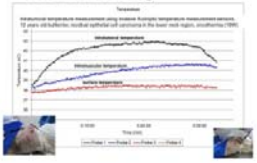
We measured the temperature in various systems, starting with muscle phantoms and with experimental in-vivo models, preclinical (veterinarian) cases and in human applications too. The early (twenty years old) phantom measurements were repeated by more modern conditions, and were checked with optical fiber thermo sensing method, as well as the outside heating profile was controlled for visual pattern by high-sensitivity thermo-camera system. The in-vivo models as well as all the animal experiments had used flouroptical temperature measurements in depth. The precise inserting of the sensors was controlled by imaging technologies in large animals and humans.

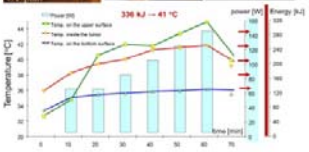
Measurements in physiological conditions

Test animal: healthy Beagle dog. Power: 20W/16W (SWR:1.5), Energy: 36 kJ/28.5 kJ.



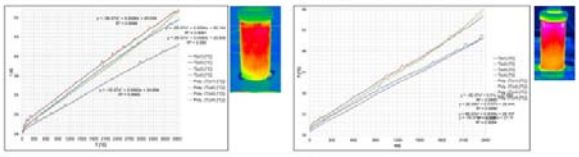
Treatment of tumorous dog

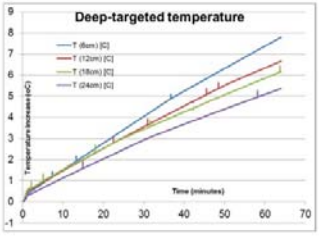




Results

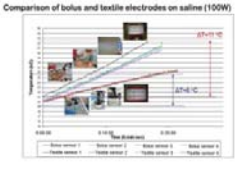
The experiments in phantoms shown a well increased temperature (at least 7 C in depth of 24 cm by 100 W in 60 min applied the 10 cm diameter bolus electrode) [2]. The animal experiments had shown the easy heating the tumor lesion to 42°C without heating the surrounding tissue [3]. The human probes had shown the desired temperature increase in depth, [4], [5]. Important observation is the safe application, no erythema or other dermatological toxicity was caused by the deep heating. This observation is supported by the fact, that the huge number of oncothermia applications worldwide (over 100.000 treatments/year) is free from toxicity or severe skin complications. Only approx. 3% of the all treatments causes light erythema, which could be eliminated by appropriate greasy cream for next day. Parallel with the overall temperature increase the active nano-heating is well measured reaching huge temperature gradient at the membranes of the malignant cells [5].





Heating in depth. 60W applied on 25 cm phantom (above) and 100W for 30 cm phantom .

Comparison of bolus and textile electrodes on saline (100W)



Conclusion

Oncothermia is effective deep heating method for tumor-lesions, increasing the temperature by safe, controlled and well-targeted way.

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In memoriam Reka Szasz

P-14: Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Oncothermia paradigm

Oncothermia paradigm

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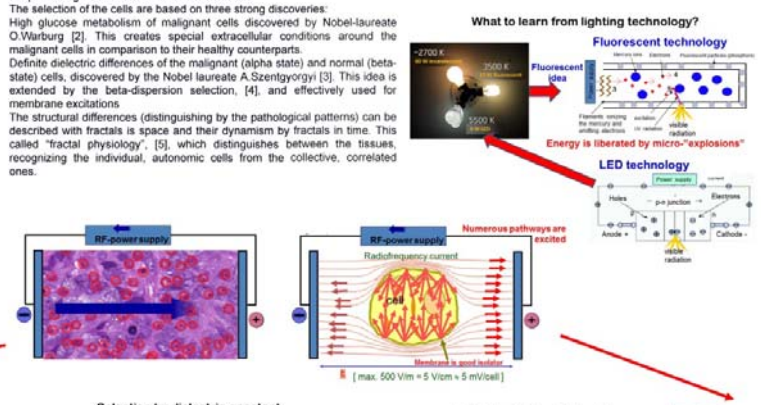
Objective

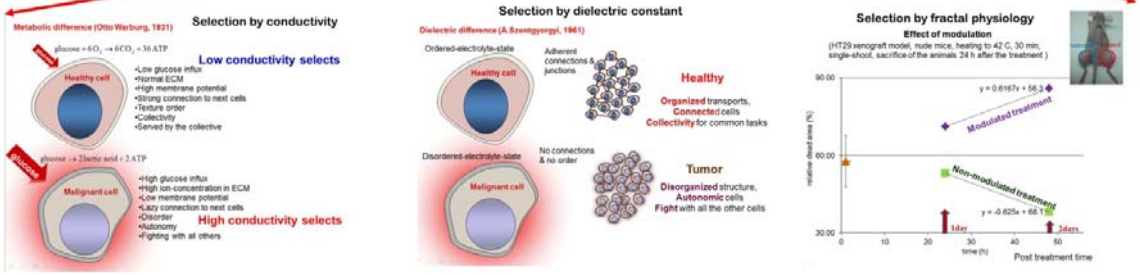
Oncothermia is a new type of cancer-treatment targeting the malignant cells on nano-range, at its membrane and exciting basic cellular signaling pathways, [1]. The front-line achievements explaining the cellular differences between malignant and healthy cells were well recognized in the last century, but unfortunately these were not used for selection in practical applications. Our objective is to show how oncothermia uses these brilliant and strongly proven results.

Philosophy of Oncotherm Research and Innovation

Method

Oncothermia excites many signaling pathways by electric field and huge temperature gradient at the cellular membranes.
The selection of the cells are based on three strong discoveries:
High glucose metabolism of malignant cells discovered by Nobel-laureate O.Warburg [2]. This creates special extracellular conditions around the malignant cells in comparison to their healthy counterparts.
Definite dielectric differences of the malignant (alpha state) and normal (beta-state) cells, discovered by the Nobel laureate A.Szentgyorgyi [3]. This idea is extended by the beta-dispersion selection, [4], and effectively used for membrane excitations
The structural differences (distinguishing by the pathological patterns) can be described with fractals is space and their dynamism by fractals in time. This called "fractal physiology", [5], which distinguishes between the tissues, recognizing the individual, autonomic cells from the collective, correlated ones.





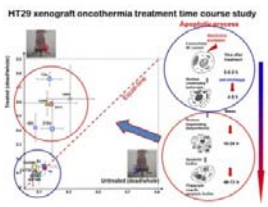
Results

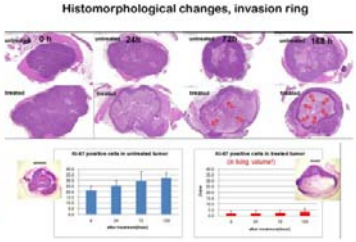
In consequence of the effects multiple changes are recognized in the outer cell-membrane:

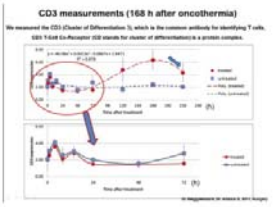
- Inducing apoptotic signal
- Forming membrane-HSP
- Higher transparency
- Higher motility of domains
- Rebinding E-cadherin
- Damages on membrane
- Rectification- demodulation

in the cytosol:

- Dilution of the cytoplasm
- Higher pressure developed
- Activated apoptotic pathways
- Activated death receptors
- The effects and their actions in the oncothermia treatment process can be measured in vitro and in vivo as well.







Conclusion

Oncothermia uses cellular nano-effects for targeting and eliminating the malignant cells. It is a feasible and well proven method for natural cell-killing and for immune activation as well.

In memoriam Reka Szasz

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P-15: Oliver Szasz, Gabor Andocs, Nora Meggyeshazi, Andras Szasz (2012) Modulation effect in oncothermia

Modulation effect in oncothermia

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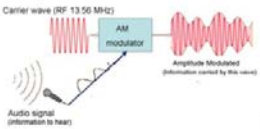
Objective

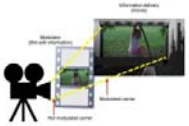
One of the most special and distinguished effect of oncothermia is the modulation. This special effect is important for selection and apoptotic action of oncothermia, applied on basic of multiple patents, [1], [2], [3]. The applied amplitude modulated signal is of course not simple. Presently the amplitude modulated electromagnetic applications have their renewing in the professional literature [Szasz et al Oncothermia, Springer, 2010]. Our objective is to show the oncothermia modulation which is a new way of the modulation technique.

Introduction

The carrier wave (13.56 MHz frequency) delivers the energy focused to the tumor-cells, but the information is delivered by the pattern carrying by the wave. The pattern is formed by the modulation (symmetric change of the amplitude of the carrier). The modulation is similar to the movie-projection. The beam originally starts from a white lamp source, which is the "carrier" of the info. When we see only this, only a white light-spot could be observed, no info is carried. The info is saved on a film, which is illuminated by the source light. The white light started to be "modulated" and the info from the "modulator" started to be carried by the beam. The transparent picture is projected to the silver-screen

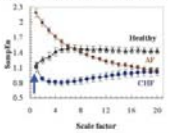
The amplitude modulation in radio-broadcast

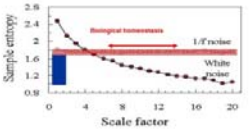




Amplitude modulation like projection (clearly similar to B&W)

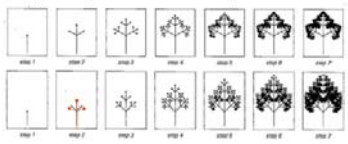
The information which oncothermia has to deliver is the collectivity. This information is characteristic on the healthy cells, they are existing in collective harmony. This harmony makes the full control on their apoptosis, which is the most important prevention against the malignant proliferation. The cellular connections coordinate the harmony, and "glue" the cells together in an integrative tissue, blocking their free movements out. There all are missing in malignancy, where the autonomic cells are able to disseminate by blood-stream and causing the metastases as the main mortality factor in cancer-statistics. The harmonic cooperation of the cells is characterized by the equal entropy in all the scales of the living tissue [Goldberger et.al, 1998]. This is far not the case in any unhealthy conditions, where the homeostatic equilibrium is broken. [Hegyi et.al. 2011] The proper homeostasis in living systems is characterized by the special time-fractal noise so called 1/f frequency. The system which has this noise-harmony, satisfies the constant entropy requirements. [Goldberger et al. 2000]

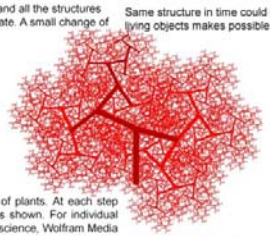




Fractals in space

Fractals in nature are widely appearing. The natural shapes of the living organisms, organs and all the structures are fractal0-like organized. The fractals in space are self-similar starting form a simple template. A small change of the template changes the final structure robustly.



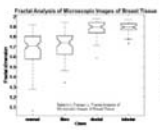


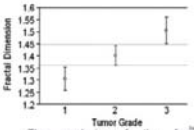
Steps in the evolution of substitution systems that provide simple models for the growth of plants. At each step every growing stem is replaced by a collection of three new stems according to the rules shown. For individual stems this type of branching is known in botany as monopodial. (S. Wolfram: A new kind of science, Wolfram Media Inc. 2002, pp.400)

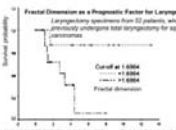
Fractals in time

Same structure in time could be constructed as exists in the space. Analysis of the time-fractals of the dynamism of living objects makes possible to control their wellness as well as to predict their failures.

Space-fractals characterize well main of the pathological statuses.







The problem of the autonomy of the malignant cells makes the treatment very much complicated, because the cancer has its own fractal structure. [Ballerini L Franzen L, Fractal Analysis of Microscopic Images of Breast Tissue]

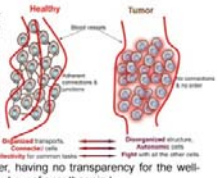
The analysis of the fractal structures of malignancies could even indicate the stage of the disease [Tambasco M, Magliocco AM, (2008) Relationship between tumor grade and computed architectural complexity in breast cancer specimens, Human Pathology, 39:740-746.].

Careful fractal analysis can make predictive information for the prognosis as well [Delides et al (2005) Fractal Dimension as a Prognostic Factor for Laryngeal Carcinoma. Anticancer Research 25: 2141-2144].

Method

In oncothermia a special amplitude modulated r by fractal is [2].

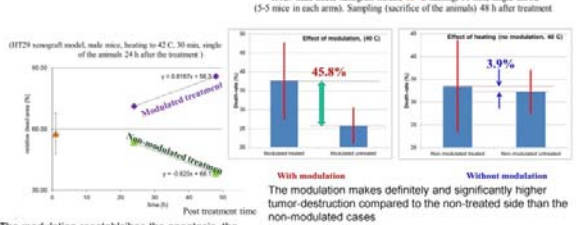
The modulation is far from any sinus or other periodic patterns, it is 1/f spectrum, having definite templates for its construction. The 1/f fluctuation characterizes all the harmonic sounds (like music as well), but of course all the musical pieces are different (even their interpretation could be different) despite of their identical 1/f spectrum. This is which we use for fractal modulation technique. The newest progress applies well established personalized template of the modulation [3], which based on the personal time-fractal of the patient and his own tumor pathology. The modulation electronically needs also special solutions, because the highly capacitive system (and capacitive coupling on impedance basic) could badly modify the spectrum.



The malignant absorption selects according to the disorder of the cancer, having no transparency for the well-chosen modulated RF carrier frequency (It is a patented method and know-how of oncothermia.)

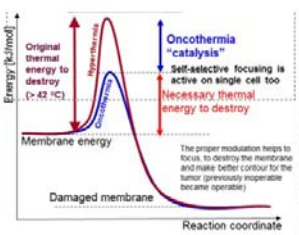
Results

Measurements in comparison the modulated and nonmodulated treatments in vivo show the differences. The modulated treatment side and the untreated side of double tumorous mice shows 45% distortion rate after single-shot (30 min) treatment on 40 C, between the treated and untreated sides of mice (three animals 6 lesions in one measurement point), while the same experimental setup in non-modulated treatment case makes only less than 4% difference between the treated and untreated lesions of the same animals. In study the time-course of the animals, we received also important data: the modulation starts the apoptotic process, and after one and two days the tumor-destructive process is developing, killing the tumor rapidly. In the same experimental setup, the non-modulated treatment makes only the usual destruction after the treatment.



The modulation reestablsihes the apoptosis, the natural cell-killing process, and after 48 h the effect is obviously acting. (HT29 xenograft model on single-tumor-bearing mice.)

The modulation makes definitely and significantly higher tumor-destruction compared to the non-treated side than the non-modulated cases



In memoriam Reka Szasz

Conclusion

Oncothermia modulation is one of the three specialities of this treatment. Its efficacy and its role in the personalization process introduced effective tool for apoptotic cancer-cell destruction.

More detailed explanation and background of the modulation applications in Oncothermia could be obtained from the Oncothermia book [Szasz et al, Springer 2010]. The method is patented

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P-16: Gabriella Hegyi, Oliver Szasz, Andras Szasz (2012) Synergy of oncothermia and traditional Chinese medicine

Synergy of oncothermia and traditional Chinese medicine

Gabriella Hegyi[1], Szasz Oliver[2], Andras Szasz[2]

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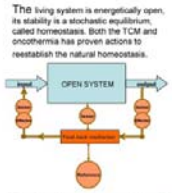
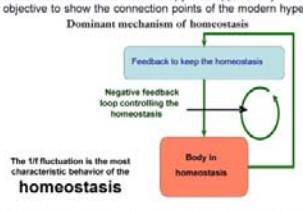
(2) Department of Biotechnics, St. Istvan University, Budapest, Hungary

Introduction - Objective

Hyperthermia is the very first oncological treatment [1], started probable on sacral basis. Later Hippocrates described it using physiological process, but surprisingly the other ancient medical approach, the traditional Chinese medicine (TCM, [2]) had not been combined by this method. Probable the philosophical approach was different. Hyperthermia applied constrain force to overheat the body or a part of it, forcing reaction from the system (physiologic changes like blood-perfusion, immune changes, pH or other environmental changes, etc.), and use this anyway unusual reaction for healing. The philosophy of TCM was opposite, not apply any constrains which are out of the normal control, apply only effects to reestablish the normal control, the homeostatic equilibrium. The homeostasis was characterized with a mystic (undefined) chi, which "flows" normally in the homeostasis, and blocked or overstimulated in diseases. Due to the undefined (mainly sacral meaning) categories TCM was not able to be integrated in Western medicine, while heat lost its mystic sacral meaning, and started to be accepted. However this is only the surface of our understanding. In fact the effects of the heating and its consequences remained unclear and so the heat therapy was applied only in home-cares, were categorized as "kitchen" medicine. Nowadays both therapies started to be further examined how integrate these to the modern medical processes. Our objective to show the connection points of the modern hyperthermia and TCM, with especial emphasis on the natural treatment options of malignant diseases



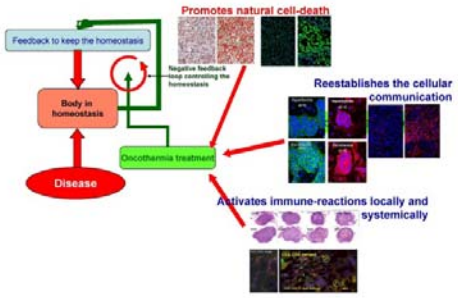


The Western approach to keep or reestablish the homeostasis of the healthy system and the TCM goal to make yin-yang equilibrium are identical in general meaning.

Method

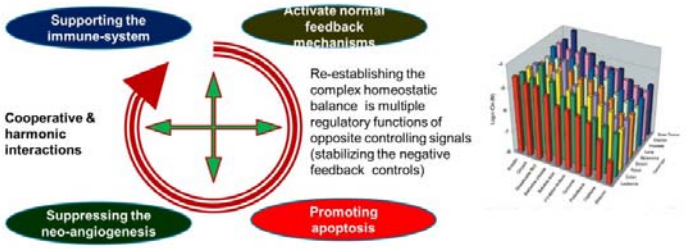
There are various herbal substances in TCM acing palliative or curative on tumorous diseases. These are in increasing interest of western medicine too. For example the pain reduction the "Senecio palmatus". For curative treatments special moxibustion techniques with various complex mixture of herbs could be applied [3]. Synergetic effects of oncothermia [13]. and TCM is expected due to their natural processes. Oncothermia is targeting the tumor cells by intensifying the natural homeostatic loops which is in its goal identical with most of the TCM targets too . [8], [9]. Applying the most modern approaches (of the structure of the living matter, [10], [11], combined with the new physiology ([7], [4], [5], [6]), gives strong point to build up a new synergy between Eastern and Western medicine. [12]

Dominant mechanisms of oncothermia



Dominant mechanisms of TCM

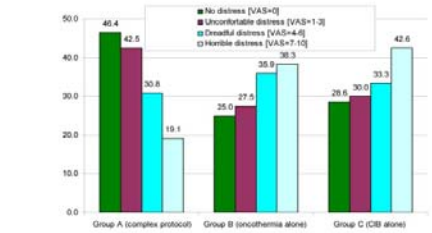
Pharmacogenomics of a Traditional Japanese Herbal Medicine (Kampo) for Cancer Therapy

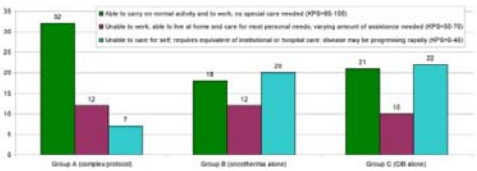


The living homeostasis is complex. Controlling it needs complex approach. Oncothermia is supporting the negative feedback controls of the complex stability. The natural remedies (herbs) are complexly ready for this control too. (this is well shown by the Japanese herbal medicine [13].

Synergy of the methods

[example applications] (Prof.Pang, Clifford Hospital) [14]





Conclusion

Potential of the synergy of high-tech oncothermia and TCM is feasible. Recognition of the distortions in the healthy tissue has some common principles and possibilities of the two methods. The synergy of the ancient knowledge and the high-tech state-of-art of western medical knowledge could be established with this research.

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P-17: Anett Gallne-Valyi (2012) Introduction of the international quality management system: Oncotherm Group

Introduction of the international quality management system: OncoTherm Group

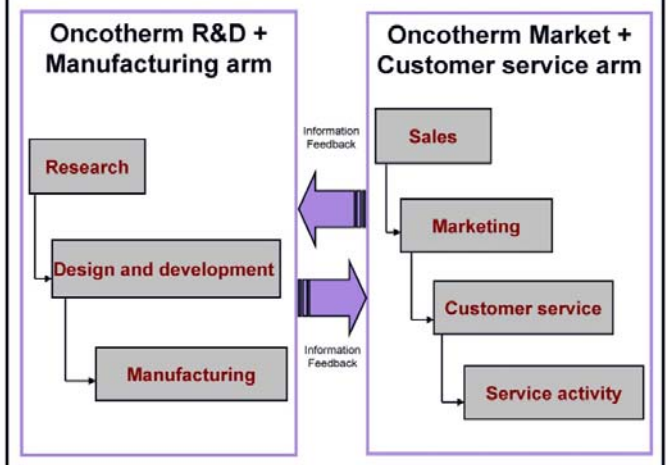
Anett Gállné-Vályi
Quality Manager of Oncotherm Group

OncoTherm Group

Common Quality Management System based on:

- **ISO 9001:2008** Quality Management System. Requirements
- **ISO 13485:2003/AC:2009** Medical Devices. Quality Management Systems. Requirements for regulatory purposes
- **93/42 EEC** Medical Device Directive (MDD)

Therefore we have a common quality system based on the concerning ISO standards and MDD, which provides that our processes are working in a well-controlled way and we advert all requirements/demands coming from our customers and from the national, international regulations.



Approval by TÜV Süd (Munich, Germany)

Oncotherm System (OS) =
Oncotherm Device (OD) + Oncotherm Method (OM)

Made in EU by German approval

Conclusion:

The OncoTherm Group is a marketing method which is in synergy with the devices and jointly presented on the market as a system. There is more than 20 years hard work, experience and knowledge behind the OncoTherm System which certifies that this system has stood the test of the time.

Objectives of the presentation:

- Show the basis of the permanent improvement of the efficacy of oncothermia combined with high quality and complete safety for the users and patients.
- Keeping up the trust of our users and potential customers

Basic points:

- ✓ Oncotherm devices are prepared by team-working of highly qualified experts
- ✓ This unification of the German medical and constructive knowledge with the general European manufacturing culture based on the concerning requirements
- ✓ Oncotherm established a perfect cooperation between the research, medical knowledge, marketing, manufacturing and services
- ✓ Oncotherm operates in the frame of strict common German quality management systems based on the below mentioned aspects:
  - Our devices are distributed for over fifteen countries worldwide, using the German medical knowledge and practical expertise.
  - Most medical feedbacks are coming from the smart German physicians from more than hundred oncothermia installations in the country. This is a good input for the research, design and development as well as an important help of the manufacturing and controlling channels.
  - Feedback from the service activity and the customer service is an integrative part of the company's progress. These pieces of information directly and permanently improve oncothermia method and its devices.
  - Oncotherm manufacturing facilities are organized reacting flexible and quickly on the market demands and challenges.
  - The oncothermia methods are in the focus of our marketing policy. The devices are serving this state-of-art methodology, giving effective weaponry in the hand of the medical staff for fighting in the war against cancer. This marketing strategy requests integrative and tight cooperation with research, design and development amalgamated by interdisciplinary approaches of modern technical and medical knowledge.

Oncothermia marketing and manufacturing arms are working like an integrative unit that makes us strong and effective on the market.

Our quality management systems are satisfying the highest European medical standards. The production process of the devices has ISO13485 medical standard and it is approved by **TÜV Süd Product Service GmbH (Munich, Germany),** who also certifies our products according to the European Medical Device Directive (medical CE-mark).

The business processes have also the highest standard (ISO9001) granted by the **TÜV Süd Management Service GmbH (Munich, Germany),** vouching for the standardized available processes to satisfy oncothermia users and potential customers.

TÜV Süd as the largest Notified Body for medical devices in EU justifies the operation of our quality management systems and keeps it well-controlled to fulfill every necessary European requirements .

CE 0123

Integrity:

We don't sell only a device but an **OncoTherm System** which consists of **OncoTherm Device** and **OncoTherm Method**.

Full process is controlled by unified overall leadership and unified overall quality system!

SZENT ISTVÁN UNIVERSITY

oncotherm

Essence of Oncothermia

Oliver Szasz, Andras Szasz
Department of Biotechnics, St. Istvan University, Budapest, Hungary &
Oncotherm GmbH, Troisdorf, Germany

What are the limits of the old hyperthermia approach?

New paradigm is necessary for oncology

Hyperthermia contradiction:
"The biology is with us while the physics is against us" (J.Overgard)

Oncothermia changes the paradigm:
"The biophysics is with us"

Hyperthermia contradiction:
"The biology and the physics is with us while the physiology is against us" (S.Osinsky)

Oncothermia changes the paradigm:
"The fractal physiology is with us"

Hyperthermia contradiction:
"Reference point is needed!" (J.van der Zee)

Oncothermia changes the paradigm:
"Back to the gold standards, use the energy instead of temperature"

Avoid from high temperature

"Physics is with us, when we use it well"

- Temperature heats up the vicinity of the tumor, it can not be kept locally focused
- Temperature increases the danger of burn of healthy parts in depth (misfocusing, conduction, etc.)
- Temperature requests the increase of the safety-cooling on the skin
- The increased surface cooling blocks the temperature sensing in the skin,
- The increased surface cooling makes the skin even more isolating, and so the electric burn is more likely
- Temperature increases the blood-flow in the region, in consequence increases the dissemination
- In complementary application with radiotherapy the forced high temperature suppresses the efficacy or blocks at all the effect of radiotherapy
- In complementary application with chemotherapy the forced high temperature suppresses the efficacy or blocks at all the chemopenetration into the tumor (vasocontraction or blood-vessel blockage in the tumor)
- In complementary application with chemotherapy the forced high temperature increases the cytotoxic side effects in the heated healthy tissues around by increased chemo-reaction rates (vasodilatation in the healthy tissues)
- The toxins from the necrotic cells are rapidly transported into the whole body, challenging the anyway low immune status of the patient

Temperature is not dose

"Physiology is with us"

- ✓ Moderate temperature avoids the natural contra-regulation effects
- ✓ Temperature does not exceed the systemic physiological limit (42 °C)
- ✓ Tumor selection is solved by non-temperature dependent way (electric concept)
- ✓ Focus is to be fixed to the tumor, moves together with the natural body movements (impedance control)
- ✓ Selection is solved on cellular level suppress the dissemination of the malignant cells
- ✓ Cellular connections (adherent connections, gap-junctions) of malignant cells are reestablished to avoid the further dissemination
- ✓ Cellular communication (social signal) is reestablished to promote the natural (programmed) cell death for malignant cells
- ✓ Possibility of the cellular molecular exchange (gap junctions) is reestablished to promote the normal function of the cells.
- ✓ The "master switch" (p53 gene) is activated promoting the natural way of various cell killing pathways
- ✓ Cell-membrane permeability is increased to express the HSP on the outer membrane signalizing the cell malignancy for the systemic immune actions.
- ✓ Cell-membrane is excited to ignite various communication pathways in the cells.
- ✓ Electric field blocks the positive feedback loop of tumor-supporting injury currents

Technical specialties of oncothermia

The nano-scale heating

- Target the cell-membrane in nano-scale (correct energy is mandatory)
- Personalized information-delivery is applied (patented)
- Surface cooling is controlled (patented)
- Low voltage large current (at given energy) is applied (patented)
- Time-fractal modulation is applied (patented)
- No temperature measurement is necessary (patented)
- Every parts are designed to the actual task (oncotherm-design)
- Easy to use, comfortable for patient, tailored for patient

Avoid the static approach

"thermostatical considerations are against us"

Measurement of intensive thermodynamical parameters (like temperature) supposes at least local equilibrium, which never could be realized due to the intensive contra-regulatory effects. (This concept however, became the main request of the classical hyperthermia approach in its guidelines.)

The forced equilibrium increases the heat-flow to the blood-stream, which is an effective cooling media trying to block the static concept.

The heat-flow to blood supports the positive feedback loop of the basic-acidic electrolyte balance, and promotes the intensive growth of the tumor by addressed oxygen delivery.

Static constrains try to block the natural dynamism of the living system, which mobilizes its forces to keep the dynamic equilibrium instead of the static one. This creates protection mechanisms of the actual status quo in the tissue, defending the tumor instead its elimination. (These processes like intracellular HSP development, like forced delivery of metabolic species [oxygen and nutrition], like systemic cooling control, like various stress reactions, etc.)

Process reaching equilibrium mobilizes higher level of physiological contra-actions and accelerates a competition between the constrains and the nature. This falsely mobilizes the natural healing forces. (Natural actions are gained against the actual treatment and not against the "common enemy", against the malignancy.)

Application of dynamic processes

"Thermodynamics and fractal physiology is with us"

- ✓ Oncothermia uses tumor killing approach, which is well fitted to the dynamism of the living system, does not constrain it for false defense.
- ✓ Control of oncothermia is natural, always fitted to the actual conditions (changes of the electrolytes determines its actions).
- ✓ No considerable heat-flow to the blood-stream by oncothermia, no gain of the positive feedback of electrolyte balancing-loop.
- ✓ Thermal gradients make dynamism in a very local area of the cell-membrane of malignant cells. The applied selection focuses on this thermal non-equilibrium.
- ✓ The relatively slow "step-up" heating keeps the non-equilibrium stable for long time for action.
- ✓ The slow heating up does not create considerable physiological contra-actions.
- ✓ The slow heating makes the healthy tissue adapted to the growing temperature.
- ✓ The slow temperature change does not generate high stress and following stress reactions.
- ✓ The applied electric field makes at least three times more effective cell killing than the temperature does.
- ✓ The applied fractal modulation makes possible selecting and supporting the natural processes to activate the natural healing mechanisms and reestablish the healthy "social signal" between the isolated cells, promoting the anti-malignancy collectivity.

Avoid automatisms in treatment guidelines

Guidelines are not "cookery books";
we are in the clinic and not in the kitchen

Everybody is different....

The actual disease is not simple the disease of an organ. This organ belongs to somebody.

The personal differences are modified by the previous treatments and tolerances

The definite similarities after the chemo- or other serious therapies are mainly due to the side effects...

Most of the decisions in serious cases need medical experience, not "only" book-based evidences.

The patients with advanced diseases are not "naïve" in most of the cases. Their high-line treatments need personal decisions, frequently no evidence-based protocols are available for their special cases.

Many times the palliation is necessary, which definitely needs personal decisions.

The psycho-factors are not negligible in the case of malignant diseases.

The personal decision is the responsibility of the experienced doctor...

Make personalized processes

Guidelines of the thinking for experienced physicians

- ✓ Oncothermia is mainly regulated by the patient's tolerance
- ✓ Oncothermia control based on thermal sensing of the patients, for safety and for efficacy reasons. Safety is avoid burning the tissue of the subcutaneous layers, the efficacy to apply such energy, which does not overload the patient natural defending/protective system.
- ✓ Oncothermia uses natural processes to cure, understanding and using these needs thinking doctors and their understandings.
- ✓ Oncothermia acts of natural physiology regulation, which needs understanding of the processes.
- ✓ Oncothermia needs permanent dynamic approach, follow-up well what is happening during the treatment.
- ✓ Step-up heating is the basic treatment approach, which requests permanent care on the process.
- ✓ The effect of the activated natural processes are not acting immediately. To have a control treatment-by-treatment is essential.
- ✓ The patient's well being during and after the treatment is necessary side of the well conducted protocol.
- ✓ Complete relaxation could be supported by relaxing music, video or sound effects during the treatment.

In memoriam Reka Szasz

Production support by LabView-based data-acquisition systems

Skrihár Gábor
Development engineer, Oncotherm Group

The necessity of integrated data-acquisition systems

During the production of a product a lot of tests and measurements are done. First the electronic boards are checked separately, then the modules which are built from them are tested separately, and finally a lot of tests are conducted on the assembled system. During these test a lot of data is acquired from the product, but – especially at the final testing of the product – the data acquisition could be difficult, because, because:

- The testing time is so long, that the continuous observation of the test is not possible
- If during the measurement more instruments are used, the simultaneous and continuous observation all of them is not possible.
- A lot of instruments don't provide built-in data acquisition and storing
- Although some instruments have this function, it could be difficult to synchronize the data acquired by various instruments.

The solution of these problems is such a data collection system, that in real-time collects and synchronizes all of the information, that the used instruments provide during the measurement and then stores them into a common database, allowing the common processing of them. By this way the efficiency of the production could be greatly increased. For us at Oncotherm is a priority to increase both the speed and the quality of the production of our products, so we started to develop integrated data-acquisition systems to support our production tasks.

The main element of these systems is the LabView program suite, which is developed especially for data-acquisition and instrument control and is provided by National Instruments. The main task of LabView is to control the NI's own DA units, but the products of the most important instrument manufacturers are controllable by the suite too. During our projects we use both NI instruments and the instruments of other manufacturers (Tektronix, Rhode&Schwartz) too.

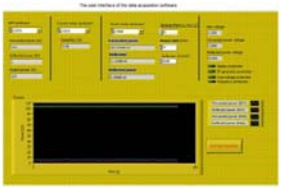
The instrumentation of a test treatment

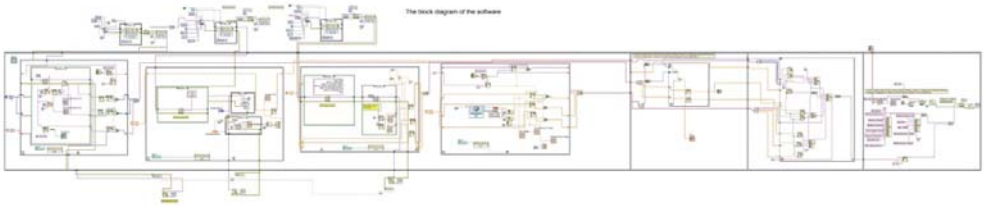
One of our main ambitions is the monitoring of the manufactured EHY-2000 oncothermia devices during their final tests, which means lots of test treatments continuously day and night. During these test treatments important data can be collected about the general behavior and the reliability of the system, which are the key factors of the quality of the product.

The device sends important information about its state by RS232 serial port and the inner signal lines of the device are monitored by NI data-acquisition devices.
A typical data acquisition system consists of the following instruments and provides us the following information:

- EHY-2000:
  - By serial port: time after the start of the treatment, output power, reflected power and the states of the various protection signal lines
  - By direct monitoring of signal lines: the control voltage of the amplifier and the voltages proportional with the forwarded and reflected power.
- R&S RF power meter: used as an external reference for the accuracy of the power measurement of the device.
- Multimeter: used as a current meter to monitor the correct consumption of the amplifier.

By using the data provided by the reviewed instrumentation we can get a clear picture about the energetic efficiency and the general behavior of the amplifier, which – as the most difficult part of the device – needs the most testing.





Other possible usages

Of course, the data-collecting systems always follow the demands of the current projects, capitalizing the flexibility of the LabView-based DA systems. On the grounds of our experiences until now we have more ways of improvement on this field. The most important ones are:

- Research support: integrated data acquisition during laboratory experiments, focusing to collect data from the Lab-EHY laboratory device and the 4-channel thermometer also developed by Oncotherm.
- Production support: automated testing of our products by LabView-based instrumentations

Realizing sing these conceptions we can improve both improve the quality of our products and the affectivity and the speed of our R&D projects, so we are committed towards these ways.

P-20: Gyula P Szigeti, Gabriella Hegyi, Oliver Szasz (2012) Hyperthermia versus Oncothermia: cellular effects in cancer therapy

Hyperthermia versus Oncothermia: Cellular effects in cancer therapy

Gyula P Szigeti*, Gabriella Hegyi**, Olivér Szász

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***Department of Complementary and Alternative Medicine, University of Pécs, Hungary*

ABSTRACT

Hyperthermia means overheating of the living object completely or partly. Hyperthermia, the procedure of raising the temperature of a part of or the whole body above normal for a defined period of time, is applied alone or as an adjunctive with various established cancer treatment modalities such as radiotherapy and chemotherapy. The fact the hyperthermia is not generally accepted as conventional therapy. The problem is its controversial performance. The controversy is originated from the complications of the deep heating and the focusing of the heat-effect. The idea of oncothermia solves the selective deep action on nearly cellular resolution.

We would like to demonstrate the force and perspectives of oncothermia, as a highly specialized hyperthermia in clinical oncology. Our aim is to prove the ability of oncothermia to be a candidate to become a widely accepted modality of the standard cancer-care. We would like to show the proofs and the challenges of the hyperthermia and oncothermia applications to provide the presently available data and summarize the knowledge in the topic. Like many early-stage therapies, oncothermia lacks adequate treatment experience and long-range, comprehensive statistics that can help us optimize its use for all indications.

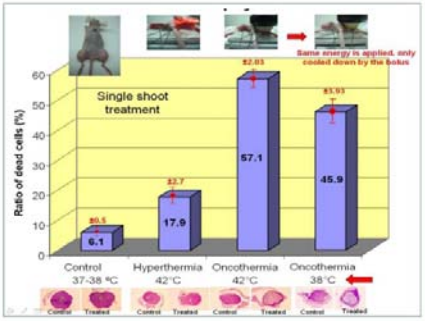

Figure 1.
The cell-destruction ability of oncothermia is three-times higher than hyperthermia at the same 42°C temperature. Pumping the same energy as for temperature 42°C, but cooling the lesion by outside water-bolus (to 38°C temperature), the efficacy of the cell-destruction remained much higher in oncothermia than in hyperthermia at 42°C temperature.

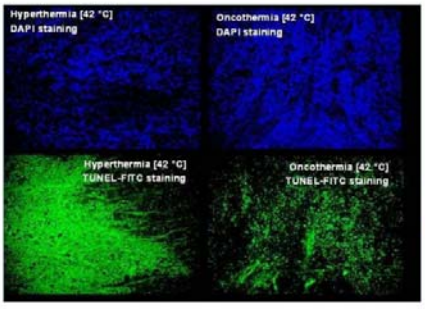

Figure 2.
Upper panel: DAPI staining (stains the double strains of DNA only), lower panel TUNEL-FITC staining (enzymatic label of the strain-break of the DNA).

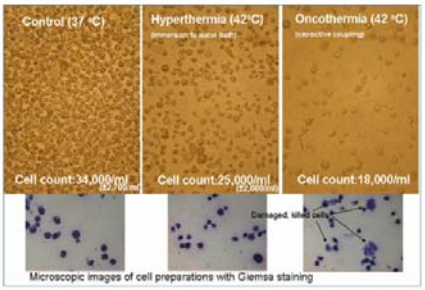

Figure 3.
Comparison of cell death induced by oncothermia with traditional hyperthermia (*in vitro* experiments with fixed sample): HL-60 leukaemia cell line.

ACKNOWLEDGEMENT

Authors acknowledge the experimental work and fruitful discussions of Dr. Nora Meggyeshazi and Dr. Gabor Andocs.

The concept of hyperthermia

The effectiveness of hyperthermia treatment is related to the temperature achieved during the treatment, as well as the length of treatment and cell and tissue characteristics. To ensure that the desired temperature is reached, but not exceeded, the temperature of the tumour and surrounding tissues is monitored throughout the hyperthermia procedure. The goal is to keep local temperatures under 44°C to avoid damage to surrounding tissues, and the whole body temperatures under 42°C, which is the upper limit compatible with life.

Mechanisms induced by hyperthermia:

- *Hyperthermia induced cell killing*
  It has been long recognized that hyperthermia in the 40–47°C temperature range kills cells in a reproducible time and temperature dependent manner. In the hyperthermic region there are three cellular responses for thermal therapy: *cytotoxicity, radiosensitization and thermotolerance.*
  The intensity of cell death in hyperthermia is showed cell cycle dependence. Both S- and M-phase cells undergo a 'slow mode of cell death' after hyperthermia. Cells during G1-phase may follow a 'rapid mode of death' immediately after hyperthermia.
- *Vascular*
  With higher heat temperatures there is a corresponding decrease in oxyhaemoglobin saturation, and these changes will result in a decrease in overall oxygen availability. This lack of oxygen will also give rise to a decrease in tumour pH and ultimately lead to ischemia and cell death. Normal tissues typically show a very different vascular response to heat, with flow essentially increasing as the temperature increases.
- *Cellular and intracellular mechanisms of thermal effects in the hyperthermia - Cell metabolism: hypoxia, pH, ATP and its consequences*
  Summarising the relevant data, it can be stated that tumour temperatures >42.5°C and appropriate heating can reduce both intracellular and extracellular pH, which may further sensitise tumour cells to hyperthermia in the sense of a positive feedback mechanism. Relevant pathogenetic mechanisms leading to an intensified acidosis upon heat treatment (which is reversible after hyperthermia) are:
  1. an increased glycolytic rate with accumulation of lactic acid,
  2. an intensified ATP-hydrolysis,
  3. an increased ketogenesis with accumulation of acetoacetic acid and β-hydroxybutyric acid,
  4. an increase in CO_2 partial pressures,
  5. changes in chemical equilibria of the intra- and extracellular buffer systems, and
  6. an inhibition of the Na^+/H^+ antiporter in the cell membrane.

  The ATP decline observed upon heat treatment is mostly due to
  1. an increased ATP turnover rate (i.e. intensified ATP hydrolysis). As a result of an increased ATP degradation, an accumulation of purine catabolites has to be expected together with a formation of H^+ ions and reactive oxygen species at several stages during degradation to the final product uric acid,
  2. a poorer ATP yield as a consequence of a shift from oxidative glucose breakdown to glycolysis.
- *Effects on proteins that contribute to resistance to other stresses, for example, DNA damage*
  At higher temperatures, inhibition of HSP-synthesis occurs above a distinct threshold temperature. In general, the temperature, respectively, thermal dose at which HSP synthesis is inhibited in a given experimental system varies between different cell types, but the respective threshold can be lowered when further (proapoptotic) stimuli are added. As lack of HSP-synthesis is associated with exponential cell death, it is generally accepted that HSPs prevent cells from lethal thermal damage. Recently, an additional role has been ascribed to HSPs which should be importance in hyperthermia as activators of the immune system.

Problems with hyperthermia

The high energy application could cause controversies: the high temperature burns the malignant cells but it's missing selectivity. The healthy cells are damaged also and the hyperthermia starts unwanted physiological reactions as well as enlarged dissemination possibility. These conditions make the hyperthermia effect not controlled.

Change of Paradigm - The concept of oncothermia

Oncothermia technology heats non-equally: concentrating the absorbed energy to the intercellular electrolytes. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The definitely large temperature gradient between the intra- and extracellular liquids changes the membrane processes, ignites signal pathways for natural programmed cell-death, avoiding the toxic effects of the simple necrosis.

Mechanisms induced by oncothermia

- *Oncothermia promotes the programmed cell-deaths of tumor*
  Detecting the double strains of DNA (DAPI staining, see *Figure 2.* upper panel) and measuring the enzymatic labeled strain-breaks of DNA (TUNEL-FICT, see *Figure 2.* lower panel) the apoptosis is highly likely in oncothermia. Consequently the main effect in oncothermia is the apoptosis contrary to the conventional hyperthermia, which operates mainly by necrosis. Investigating the apoptosis by various methods (morphology, beta-catenin relocation, p53 expression, Connexin 43, Tunel, DNA-laddering etc.) the effects are indicating the same apoptotic process. This process is non-toxic (no inflammatory reactions afterwards) and promotes the immune reactions and not makes processes against those.
- *Oncothermia limits the dissemination of malignant cell*
  Oncothermia blocks the tumor cell dissemination, avoid their motility due to the lazy connections to the tumor. Oncothermia makes it by the reestablishing the cellular connections, which is also great success to save the life. The built up connections could force not only the sticking together, but makes bridges between the cells for information exchange to limit the individuality, the competitive behavior of the malignant cells.
  These are high efficacy factors favor oncothermia over its temperature-equivalent hyperthermia counterpart, see *Figure 3.* It also produces higher concentration of HSPs in the outer membrane and in the extracellular matrix. The higher HSP concentration in the vicinity of the malignant cells together with the changes of the adherent connections between the cells induces apoptosis.

P-21: Gabor Andocs, Nora Meggyeshazi, Y. Okamoto, Lajos Balogh, Oliver Szasz (2012) Bystander effect of Oncothermia

Bystander effect of Oncothermia

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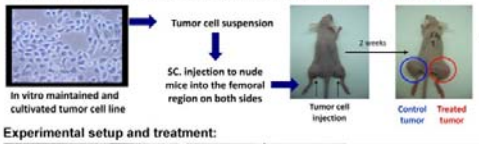
Introduction

Oncothermia (OTM) is an electro-hyperthermia modality, a long time (since 1989) applied method in oncology,[1] with great clinical success [2]. OTM changes the paradigm of hyperthermia by targeted microscopic heat-liberation at the membrane of the malignant cells. This method creates inhomogeneous heating, microscopic temperature differences far from thermal equilibrium. The tumor destruction efficacy and the role of temperature independent effects of the OTM was proven earlier by laboratory research, and presented elsewhere [3],[4].

Bystander effect (abscopal effect) means that a local tumor treatment can affect the behavior of the far distant metastases. It was first discovered by radio-oncologists and remained higly controversial topic until recent years. [5],[6]. Intensive research is conducting to reveal the immunbiological basis [7],[8],[9] and mechanism of action of this effect [10] and using the benefits in the regular oncological practice. Objective is showing the newest results of oncothermia in research bystander effect.

Methods

Animal model:
HT29 human colorectal carcinoma cell line derived xenograft tumor model in nude mouse.

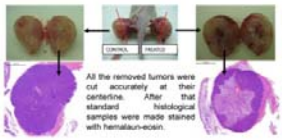


Experimental setup and treatment:

A single shot 30 min oncothermia treatment was done, reaching maximum 41-42°C intratumoral temperature, using the LabEHY system (Oncotherm Ltd.), under precise tumor temperature control using fluoroptic temperature measurement system (Lumasense m3300).

Study design:
Time course study was performed. After a single shot treatment, sampling was made after 0, 1, 4, 8, 14, 24, 48, 72, 120, 168, 216 hours. 3 mice were sacrificed at each time point, keeping 5 sham treated animals.

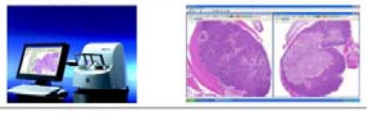
Tumor sample processing I.:
24 h later the single-treatment animals were sacrificed and both the control and treated tumors were removed and studied in pairs.



Tumor sample processing II.:
Due to the extremely high number of the tumor samples, tissue microarray (TMA) technology was used to perform accurate immono-histochemical reactions on many samples in one block.

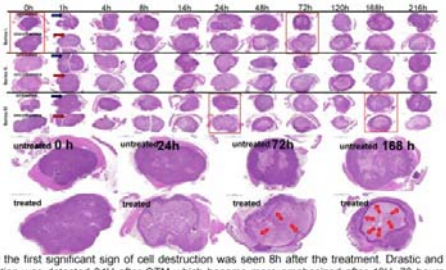
Immunohistochemistry (IHCH):
The following reactions and IHCH analysis were performed on the TMA samples: TUNEL (Invitrogen); TRAIL (DR5), HSP70 (Cell Signaling); Myeloperoxidase (Sigma); CD3 (Dako), CD4 (ABDSerotech).

Digital microscopy analysis:
All histological slides were digitalized using Panoramic Slide Scanner (3D HisTech) and special software was used for imaging and evaluation.



Results

1. Histomorphological changes:



Morfologically the first significant sign of cell destruction was seen 8h after the treatment. Drastic and selective tumor-destruction was detected 24H after OTM which became more emphasized after 48H. 72 hours after the treatment a significant leucocyte infiltration (marked with red arrows) appeared around the destructed tumor tissue and reached its maximum 168 hours after the treatment.

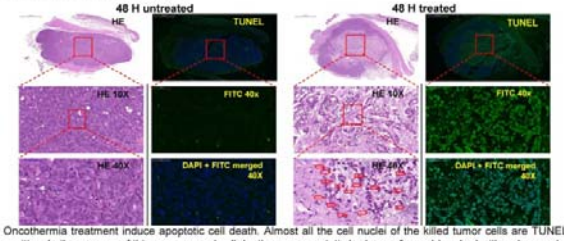
References:

(andocs@gmail.com)

In memoriam Reka Szasz

2. Hallmarks of immunogenic cancer cell death

2.1 Apoptotic body formation

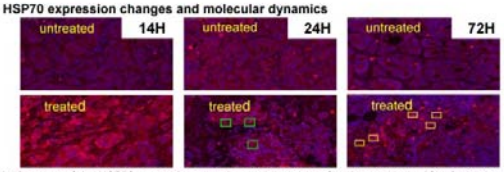


Oncothermia treatment induce apoptotic cell death. Almost all the cell nuclei of the killed tumor cells are TUNEL positive. In the process of this programmed cell death many apoptotic body was formed (marked with red arrows).

2.2. TRAIL (DR5) expression

TRAIL (DR5) is a higly immunogenic cell surface receptor. Expression was increased in the treated side 8H after the treatment and became more emphasized after 14H.

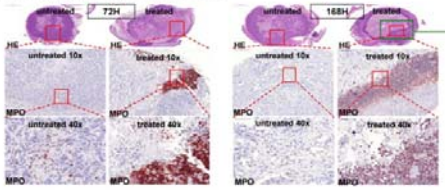
2.3 HSP70 expression changes and molecular dynamics



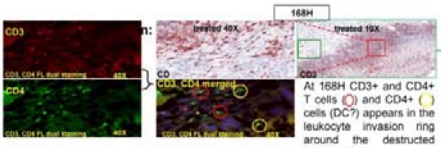
Definite increase of the HSP70 expression was observed 14 hours after the treatment. After 24 hours, unusual molecular dynamic changes of the increased amount of HSP70 can be visible: intracellular condensation ( ) and relocalization to cell membrane. After 72 hours the membrane relocalization of the HSP70 became more emphasized, especially in the region of the leukocyte invasion. ( )

3. Strong local immune reaction

3.1 Myeloperoxidase (MPO) detection:



The leukocyte invasion ring what appears at 72H and became very characteristic at 168H around the destructed tumor area, contains high number of MPO positve cells (neutrophiles, macrophages)



At 168H CD3+ and CD4+ T cells ( ) and CD4+ ( ) cells (DC?) appears in the leukocyte invasion ring around the destructed tumor tissue.

Conclusions

1. **Oncothermia can induce programmed cell death which create many apoptotic bodies**
2. **Oncothermia induced cell death is higly immunogenic, showing all the key molecular pattern dynamic changes what is characteristic of immunogenic tumor cell death**
3. **Oncothermia treatment can induce strong and very unusual immun reaction at the site of the treatment**
4. **The local antitumor immune reaction can be systemic, if the host has an intact immune system, and this process can control the distant metastases by bystander effect, making possible the systemic control of the malignant disease with local treatment.**

(The intensive research is in progress on immunocompetent models!)

Acknowledgement:

TATEYAMA KAGAKU GROUP

oncotherm highTech medicine

P-22: Yun Hwan Kim, Woong Ju, Cheol Kim (2012) Electro-hyperthermia for refractory ovarian cancer patient having bone marrowdepletion as a consequence of long-term chemotherapy: Case report

Electro-hyperthermia for refractory ovarian cancer patient having bone marrow depletion as a consequence of long-term chemotherapy
: Case Report

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Abstract

Modulated electro-hyperthermia is an emerging complementary treatment option for refractory solid tumor. Early experience suggests that it may have advantages over conventional hyperthermia with exceeding efficacy, and less complication. Herein, we describe a case of platinum-resistant, refractory ovarian cancer successfully controlled by the combination of electro-hyperthermia and dose-dense chemotherapy. On the way of repeated treatment for advanced or relapsed ovarian cancer, we finally encountered uncontrollable tumor growth simultaneously with multi-drug resistance and bone-marrow depletion. In this case, we observed stable disease over long time (1 year <) without any significant hematologic complications by applying electro-hyperthermia and weekly single chemo-agent. The gross lesion was disappeared on CT scan and PET imaging with the decline of serum CA-125 marker. Electro-hyperthermia combined with dose-dense chemotherapy could be a good treatment option for the selected, refractory ovarian cancer patients without significant hematologic complications.

Case

Refractory ovarian cancer patient aged 62 was transferred at May 2011.

2010.1.20 Debulking operation (Epithelial Ovarian cancer, Stage IIIc)

2010.1-2010.9 Paclitaxel-Carboplatin #9 ➔ Complete Remission

2011.1.4 Recurrence (liver metastasis was detected by PET)

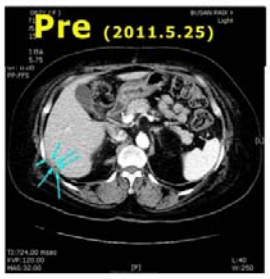
2011.1-2011.7 Belotecan-Cisplatin # 6 ➔ Partial Remission but suffered from severe bone marrow depletion

2011.7 Transferred for electro-hyperthermia (Oncothermia) treatment

2011.8~2012.2.20 Weekly Cisplatin #4 + Oncothermia (x3/week) ➔ Partial remission without hematologic complications

2012.3 Regimen changed to Weekly Paclitaxel + Oncothermia due to elevation of tumor marker ➔ Stable disease

Images & Tumor marker (CA 125)



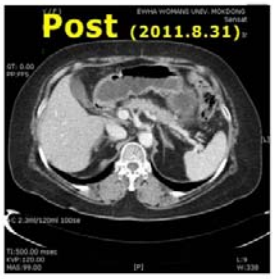


Figure 1. CT scan follow-up.

Liver metastasis was disapeared after dose-dense chemotherapy and concomitant oncothermia

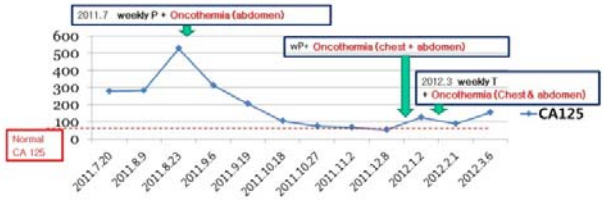


Figure 2. serum CA125 follow-up.

Serum level had declined after dose-dense chemotherapy and concomitant oncothermia

P-23: Doo Yun Lee, Hyo Chae Paik, Seok Jin Haam (2012) Hyperthermia in the patients with small cell lung cancer

Hyperthermia in the patients with small cell lung cancer

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Introduction

Small cell lung cancer (SCLC) has more rapid doubling time and earlier development of widespread metastasis than non-small cell lung cancer. SCLC is highly sensitive to initial chemotherapy (CTx) and radiotherapy (RTx) but, recurs or spreads quickly. In addition, the surgical role in SCLC is still insignificant. So, the new treatment modality besides conventional treatments is needed to get a better prognosis. The aim of this study is to evaluate the effectiveness of hyperthermia in SCLC patients

Materials and methods

We retrospectively reviewed the medical records of 28 SCLC patients who were diagnosed with SCLC from January 2004 to December 2012. Nineteen patients underwent the treatment of hyperthermia (hyperthermia group), and 9 patients did not undergo (control group). The patients who underwent < 1 cycle of hyperthermia or surgical procedures were excluded. For hyperthermia, EHY-2000 system (Oncotherm GmbH, Troisdorf, Germany). One cycle was defined as 12 times (1 hour per time, 2 times per week). The patients' characteristics and survival rates of each group were analyzed.

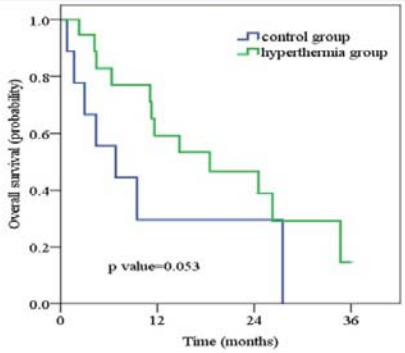
Results

Patients' characteristics

	Hyperthermia group	Control group	P value
Gender			0.615
Male	16	8	
Female	3	1	
Median age (range, years)	67 (52~79)	67 (58~84)	0.148
Concurrent treatments			
CTx	14	6	0.516
RTx	8	0	0.024
Median follow-up time (range, months)	14.7 (2.3~36.0)	6.8 (0.8~27.5)	0.442

The Gender distribution, median age, and median follow-up time were not statistically significant. The numbers of patients who underwent concurrent CTx were not different in each group but, more patients in hyperthermic group underwent concurrent RTx than control group

Overall survival rates



Comparing overall survival rates between hyperthermia group and control group, the survival rate of hyperthermia group was better than that of control group, but it did not have statistic significant (p value=0.053).

Discussions

Hyperthermia in SCLC has a lot of important advantages. 1) It is applicable to patients with poor functional status. 2) It can be performed with CTx and RTx. 3) It has very low morbidity. But, there are several limitations in this study. 1) Small number of patients was included. 2) There are bias of CTx and RTx.

Although the results of this study did not reach the statistic importance, hyperthermia may be good treatment option in the patients with SCLC.

P-24: Vakalis Ioannis, Kouridakis Petros, Daniilidis Lazaros, Natsouki Valentina, Kalyvas Spyros, Maragkos Michail, Dimitriadis Konstantinos (2012) Loco regional hyperthermia in Greece: A new treatment modality for treating deep seated tumors. Two years clinical experience from Thessaloniki hyperthermia's – Oncology operation center – New challenges

"LOCO REGIONAL HYPERTHERMIA IN GREECE: A NEW TREATMENT MODALITY FOR TREATING DEEP SEATED TUMORS. TWO YEARS CLINICAL EXPERIENCE FROM THESSALONIKI HYPERTHERMIA'S - ONCOLOGY OPERATION CENTER-NEW CHALLENGES"

ONCOHYPERTHERMIA OPERATION CENTER
TSIMISKI 82,THESSALONIKI HELLAS

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1.Surgeon.Department of surgery 424 General Army Hospital, Sub-director
2.Surgeon.Department of surgery 424 General Army Hospital, Director
3.Surgeon MD,MH,PhD
4.Dermatologist
5.General Practitioner
6.Radiotherapist-Oncologist.Department of oncology 424 General Army Hospital,MBA,Director.
7.Medical Oncologist. Department of Oncology,Theagenio cancer institute,Ex-Director.

We treated 75 patients with cancer between August 2010 and September 2012.We used the "OncoTherm 2000plus system (13,56 Mhz) medical device in our hyperthermia operation center.

REPORTING RESULTS

1.CENTRAL NERVOUS SYSTEM TUMORS

-3 Men with gliomas and 1 man with astrocytoma.We noticed general improvement as regarding to their performance status and reduction of their tumor mass in routine radiologic tests.

2.HEAD AND NECK-ORAL CAVITY

-1 Man suffering of tongue cancer who received 12 trials of local deep-heat (HT) treatment having received chemo-radiotherapy before. This man developed progressive disease with lung metastases in the end of the treatment.

-1 Man with epithelial (squamus cell-SCC) carcinoma who has been treated with HT together with Radiotherapy. His tumor has been reduced during therapy on the order of 90%.One year later this patient died having stopped any other therapy.

3.LUNG CANCER

-9 cases,3 Women-6 Men

-1 Woman having tumor at the right lower lobe. After 24 trials her tumor almost completely disappeared (no evidence of primary tumor).

-1 Woman having cancer at the left lower lobe after surgery and chemotherapy with x-knife. Her tumor has been reduced on the order of 40%.

-1 Woman having cancer at the right upper lobe. Her cancer has been partially responded to treatment and she is programmed to be operated.

-4 Men having medically inoperable pulmonary disease remained with no response to treatment

-1 Man having medically inoperable pulmonary disease paused treatment after his 3rd trial.

4.BREAST CANCER

-16 women having breast cancer,4 with early stage (stages II-III) and 14 with locally advanced and /or tumor recurrent disease (stage IV).

-Women from the first group received 12 trials HT and 3 of them are currently under careful medical supervision. The last one having cancer in both of her breast paused treatment during her 3rd trial.

- Amongst the women from the second group :

-1 of them having receiving 12 trials HT together with chemotherapy her tumor completely responded to treatment and demonstrates no evidence of primary tumor according to her MRI test.

-7 of them with liver metastases demonstrated stabilized response according to their radiologic exams.

-1 of them with liver metastases having receiving chemotherapy sessions ,she finally developed tumor necrosis syndrome and died.

-2 of them having pulmonary metastases, the one with no response to treatment and the other with minor reduction to her tumor size according to their x-ray tests.

5.STOMACH CANCER

-1 Man having stomach cancer after surgery having one meta lesion in his liver. After 12 trials performed partial response of his metastasis.

-1 Woman having medically inoperable stomach cancer 88 years old paused treatment after 1st session.

6.GIST

-1 Woman having GIST cancer 77 years old. After 12 trials she did not responded to treatment and she died 3 months later of anorexia nervosa.

7.LIVER CANCER

-1 Man having liver cancer and hepatitis-C having two main tumor lesion in his liver, one 12cm and the other 1cm over his left adrenal gland. He has had liver chemoembolization with about 60 trials. His first tumor lesion shrinked on the order of 50-60% while the other did not responded to treatment at all.

8.GALLBLADDER CANCER

-2 Men and I woman having cholangiocarcinoma.Amongst then 1 man and 1 woman having liver meta-lesions have been undergone cholocystectomy and adjuvant systematic chemotherapy (12 trials) did not responded well to therapy.

-1 Man having medically inoperable cholangiocarcinoma died after the 4th trial.

9.PANCREATIC CANCER

-Among 10 medically inoperable patients having pancreatic cancer,7 men and 3 women.

-2 of the men received over 30 trials HT together with adjuvant chemotherapy and they demonstrated partial response to therapy and they live up to now (2 years later) with good quality of life.

-1 Man died after 12 trials HT

-1 Man having metastases lesions in his liver and in the lungs from the beginning , died of intrabronchial hemorrhage.

-3 Men paused HT after 4-5 trials.

-1 Woman suffering of medically inoperable pancreatic cancer after 36 trials of adjuvant chemotherapy together with HT trials demonstrated a good performance status,her quality of life improved and 1.5 year later she died of acute renal failure.

-1 Woman suffering of inoperable pancreatic cancer paused therapy after 7 trials HT.

-1 Woman having medically inoperable pancreatic cancer with 27 trials HT and adjuvant chemotherapy despite the fact that her meta lesions in her liver and her tumor markers have been increased, performs up to now (about 13 months) an excellent quality of life.

10.COLON CANCER

-Among 8 incidences with colon cancer,5 men and 3 women developed meta lesions in their liver:

-1 Man with a single liver metastasis after ablation and 12 trials HT this metastatic lesion completely disappeared.

-1 Man received 12 trials.(We have no more data)

-3 Men paused trials in the middle of their treatment.

-1 Woman with meta lesion in the liver and in the lungs having received 12 double trials,she demonstrated improvement in her lung tumors according to her radiological exams during her follow-up.

-1 Woman with multi meta lesions in liver,ovaries,uterus paused treatment during the 3rd trial suffering of acute peritonitis and and acute abdomen.

-1 Woman suffering of tumor relapses in her abdomen paused treatment during 4th trial.

11.RENAL TUMORS-GRAWITZ

-1 Man with right Grawitz tumor 79 years old, with meta lesions in his lungs had 3 double trials. He paused treatment and some time later he died of acute respiratory inadequacy.

12.OVARIAN CANCER

-14 patients with ovarian cancer.

-Amongst them:

-13 received adjuvant chemotherapy.

-3 having undergone some trials HT, paused treatment.

-4 having liver metastases, demonstrated improvement in quality of life after 12 trials.

-3 having multiple metastases demonstrated progressive disease after 12 trials.

-1 Woman with tumor reccurence after 24 trials These died of allergic reaction to chemotherapy.

-1 Woman developed ascites after 24 trials and died of peritonitis and acute abdomen .

-1 Woman received 24 trials without chemotherapy performed complete remission to meta lesions.

-1 Woman stage IV after total hysterectomy with liver meta lesions,ascites and chemoprophylaxis with tamoxifen having received 139 trials HT.After therapy performed shrinkage of tumor lesions and a reduction to tumor markers levels showing evidences of a low density lesion with central necrosis in her previous tumor lesion according to her radiological findings .

13.ANUS CANCER

-1 Man and 2 women with anus cancer.

-1 Man with remission around the tumor bed after surgery having a meta lesion in the left upper lobe. He received 12 trials of HT with adjuvant chemo-radiotherapy. He demonstrated partial remission to therapy according to radiological images. He finally died of brain attack.

-1 Woman with anus cancer who did not want to be operated. She received chemotherapy and during her second trial she died of undiagnosed meta lesion in the brain.

-1 Woman paused after 1st trial.

14.SARCOMA

-2 women with sarcoma both paused treatment during trials the first one during 4th and the second during 5th trial.

CONCLUSIONS:

1.Hyperthermia combined with chemotherapy and/or Radiotherapy demonstrates significant clinical response rates as compared to chemotherapy and/or Radiotherapy alone in some cases.

2.Hyperthermia is quite well tolerated and does not significantly increases the toxicity of Radiation or combined modality therapy.

3.In contrast, estimation of the severity of late effects is often haphazard and incomplete depending on the sensitivity of the test used for detection. Over time treatment change frequently, making it difficult to evaluate the role of each component to the outcome. Indications show that life expectancy from the statistical point of view with the addition of hyperthermia may be improved. Hence:

3.More protocols is needed to be currently designed based on clinical experience randomizing chemo radiation therapy alone versus hyperthermia together with chemo/radiotherapy so that the role of hyperthermia in the neoadjuvant treatment of cancer may be better defined.

Oncotherm Group
Marketing & Sales Strategy

Janina Leckler, Marketing & Sales Manager, Oncotherm Group Germany/Hungary

SALES ORGANISATION

Organisation and coordination/support:

Oncotherm GmbH, Germany

Freelancer in Germany:

The Pockwood Corporation

International Distributors and their territories:

C-Therm Africa
South Africa, Angola, Botswana, Democratic Republic of the Congo, Ghana, Ivory Coast, Kenya, Namibia, Nigeria, Rwanda, Tanzania, Zambia, Zimbabwe, Angola

Ertesad Limited
Cyprus, Armenia, Azerbaijan, Belarus, Kazakhstan, Russia, Turkmenistan, Ukraine, Usbekistan

Hospi Co. Ltd.
South Korea, Australia

Instituto Di Medicini Biológica
Brazil

Oncocure Inc.
Canada, Belize, Costa Rica, El Salvador, Guatemala, Honduras, India, Mexico, Nicaragua, Panama

Tamer Corporation for Medical Supplies
Jordan, Iraq, Kuwait, Lebanon, Qatar, Saudi Arabia, United Arab Emirates

Tateyama Co. Ltd. (Thailand) / Tateyama Machine Ltd.
Japan, Thailand, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Singapore, Vietnam

TEK Grup Saglik Hizmetleri A.S.
Turkey, Cyprus (Turkish part)

The Pockwood Corporation
Belgium, Netherlands

Marketing Organisation

Head: Oncotherm GmbH, Germany

Assistance: Oncotherm Kft., Hungary

Marketing actions for the support of sales and customer satisfaction:

Monthly Newsletter with information on events, new developments and the science

Brochures about devices and the method for doctors, special patient brochures

Oncothermia Journal (published three times a year)

Website with special login-area for customers

Films about treatment and device use

Yearly Oncotherm Symposium

Oncotherm booth at national and international conferences and events

Publications (Oncotherm-books and many scientific articles)

Press Releases

Oncotherm Products Overview

Mr. Balázs Ács Executive Manager, Oncotherm Ltd.

Main products:

Booster

This product is new kind of innovations in the field of complementary cancer treatment. Its use enhances the effects chemo- and/or radiotherapies, as well as well applicable for drug-targeting and personalization of any other medications, irrespective its i.v, oral, injection or other introduction.

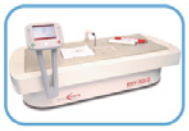
EHY-1020 IL

The EHY-1020 IL is a device specialized of intraluminar application mainly for tumorous diseases of prostate irrespective its malignant or benign character. Both malignant and benign tumors (BPH) can be treated using a highly specialized catheter system with built-in electrode and temperature control, and the treatment uses counter electrode(s) in the appropriate

EHY-2000plus

The EHY-2000 is the classical system for loco-regional deep oncothermia applications. This series has been used for treatment throughout the world for more than 20 years. Popular, versatile device, applicable for all kind of tumors.

EHY-3010 ML



The EHY-3010 ML is designed for the simultaneous multi-local treatment of advanced, metastatic disseminated, malignant and solid tumors. Within the range of Oncothermia systems, it is the pioneering breakthrough in the field of multi-local tumor therapy. Due to its highly flexible application electrodes (textile electrode), almost all tumor locations can be treated, even as large as the whole-body covering.

R&D:

Androtherm

This device is devoted for andrological treatment, mainly for the Peyronie's disease. Its special applicator and precise targeting uses the apoptotic effects combined with the plack-distortion with high efficacy. The penis curvature and the connected erectile disfunction treated with success by this device.

LabEHY

These kinds of devices are devoted for precise laboratory works in-vitro and in vivo research. The in vitro experiments can cover all the suspension and confluent layer systems, while the in vivo applicators are constructed for mice and rat experimental models. The device has revolutionary tuning system to follow even the extremely quick changes (like heart-rate of the animal), and extremely precise power adjustment. Temperature control and feedback measurements are also possible with the devices. All experiments can be completely documented electronically including the biological and electrical data.

VetEHY

These devices are developed for pet (cats dogs) treatment starting with a few dekagram to few tens of kilograms animals. Two devices are developed: one for the standard veterinary practice and pone for the veterinary research. Both have temperature measurements for precise documentation. Devices are equipped with data-handling and evaluation software.

ECT

This is the classical invasive device using pure electric-field invasively (needle application) or non-invasively (surface electrodes are applied). The precisely targeted tumor by the modulated electric field destroyed mixed way of necrotic and apoptotic processes. It is applicable for near-surface and easy-to-reach deeper tumors both in human and veterinary applications.

Accessories:

Temperature measurement unit

It measures the temperature intratumoral or extratumoral locations as well as on the surface of the skin. It is RF-independent even as high as 700W RF-power. Its sensitivity is 0.1 C, calibrated in the 36-55 C interval. The sensors are especially made for this purposes by Tateyama Kagaku, Japan.

Electromagnetic field sensor

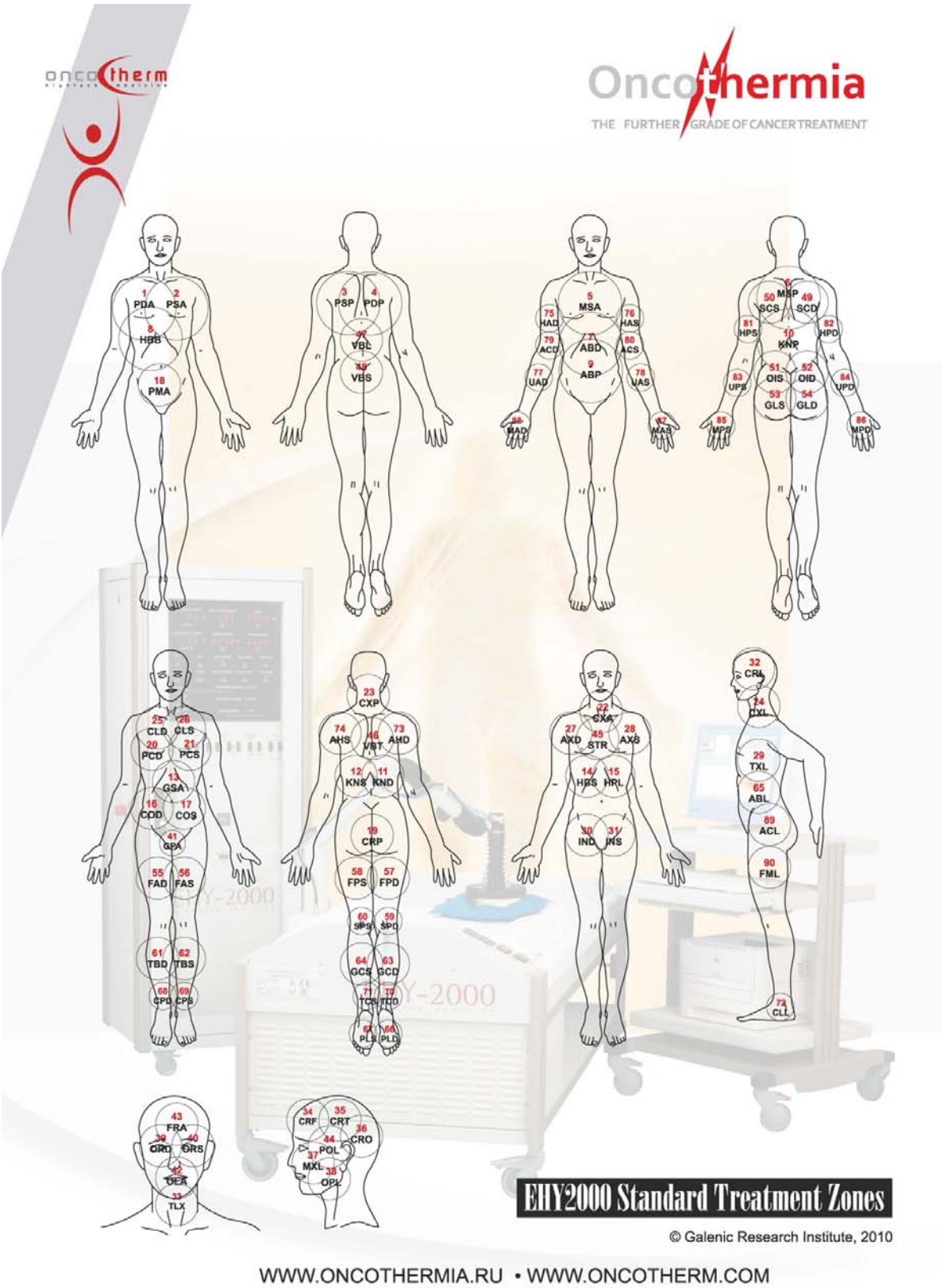
This devices is for the electromagnetic field detection. Useful accessory for all the oncothermia devices.

WEB-BOX

This device is a versatile adapter of the communication of any of Oncotherm devices to the web. It is data-safe and especially certified for medical data-security.

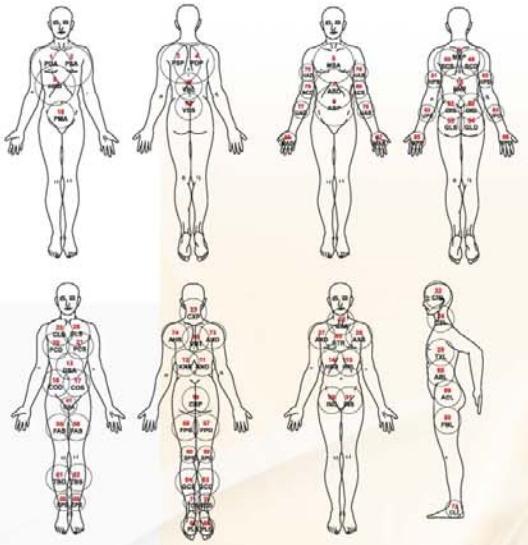
www.oncotherm.com

PI-03: Oncothermia.ru (2012) EHY-2000 standard treatment zones



Oncothermia
THE FURTHER GRADE OF CANCER TREATMENT

Summary Guidelines



EHY2000 Standard Treatment Zones

SUMMARY OF ONCOTHERMIA APPLICATION

Applicator

Applicator size should match the application zone and tumor size. Applicator is applied to the skin directly or through a thin fabric. In case of external fistulas, ulcers or weeping, applicator is applied through a thin moisture-absorbing paper. Applicator should be applied to that surface of the body which is closer to the tumor. Heating is the most effective at the 3-15 cm distance from the active (upper) applicator. Applicator should cover the entire projection of the tumor and adjacent tymph nodes, if possible. Applicator should be parallel to upper suftace of the couch (neutral electrode), if possible. If it's impossible, the angle between the applicator and the couch should be as small as possible and open toward the nearest wall. The entire surface of water bolus should be in a tight contact with the skin without any air interlayer. Loose contact between applicator and skin leads to energy losses, reducing the heating efficiency and increasing the likelihood of burns. Applicator should be fixed firmly but without unpleasant pressure to the patient. Only water bolus should contact the patient. Applicator body (black) and RF cable shouldn't contact patient's body as it may cause burns.

Position of the Patient

Patient position should provide the shortest distance between the upper applicator and the tumor. In deep tumors, the preferable position is that one where there is a minimum layer (between upper electrode and the tumor) of the following structures (in descending order of importance) a) fat, b) bone and c) neural structures. The posture should be comfortable to allow the patient to sustain it during entire procedure. The basic patient position is lying on his back. If the tumor is located closer to the dorsal surface of the body, the patient is laid on his stomach. Some tumor localizations require lateral position (head, neck, etc.) During the procedure, the patient, if possible, should be immovable.

Treatment Zones

On the human body, there is a finite number of treatment zones. Each zone is designed to act on specific organs. For each treatment zone, there are certain recommendations on the size of the applicator, power and mode of exposure. The map of the treatment zones is shown on the left. The table of treatment zones and modes of exposure is shown below (top number is the treatment time, lower number is MRP). The complete list of the treatment zones and modes of exposure in accordance with ICD10 is contained in Annex B for the Technology."

Power

EHY2000 PLUS maximum power is 150 W. Applied power depends of applicator size.

Size	Ø, cm	MSP, W	MRP, W	MSP, W	MPP, W
Small	10	25	80	120	140
Standard	20	40	120	150	150
Big	30	60	150	150	150

- **MSP - Minimum Start Power:** the power which does not cause pain in 99% of patients. Pain at MSP is a contraindication for oncothermia treatment.
- **MRP - Maximum Recommended Power:** the power limit, above which the balance shifts towards classical hyperthermia, reducing the effectiveness of non-thermal mechanisms. Below MRP, the possibility of side effects and complications is minimal (less than 3%). MRP value may vary in different tissues and organs.
- **MSP - Maximum Safe Power:** the power, above which the likelihood of surface tissues burns increase provided incorrect use of applicators. It is allowed to exceed MSP level only in the presence of a trained doctor and under his/her responsibility.
- **MPP – Maximum Permitted Power:** the power which is safe subject to highly qualified application. MPP application is justified when tumor is resistant to lower powers.

In practice, the principle of oncothermia treatment is «maximum tolerable power».

Maximum Tolerable Power (MTP) is an individual patient parameter, the threshold power of pain. Exceeding of MTP is associated with a high probability of adverse effects, particularly superficial and subcutaneous burns. MTP is an individual and dynamic variable. Typically, MTP increases during the treatment course and a session in view of adoptation of tissues to oncothermia impact. Usually the adoptation is completed in 3-9 sessions, but sometimes (rarely) MRP can not be reached. In this case the power should continue at MTP, increasing the duration of the session according to the following calculation:

$$t' = tMTP + (t' - tMTPM) * MRP/MTP,$$

were *t' – scheduled duration of the session; t' – corrected duration; tMTP – time to reach MTP*

Increment and Interval of power Increase

Oncothermia is targeted for continuity of heat-up, not to reach of the maximum «plato» temperature. Therefore, the increase of power is carried out gradually and incrementally. The gradual increase of power also allows tissues to adapt to higher temperatures and reduces the toxicity of the method.

Recommended increment of power is 10 W, minimum 5 W, maximum 20 W. Recommended interval of power increase is 10-15 minutes, minimum 5 minutes, maximum 20 minutes.

Modulation

Modulation is applied by default. Poor tolerance of oncothermia treatment is the only reason to disable modulation. It could happen mainly at brain treatment. In this case, the course should be started without modulation. Modulation starts gradually during the course, and then becomes constant. Adaptation of the patient to modulation is the target because it is modulation which allows to realize the full effect of oncothermia.

Duration and termination of a session

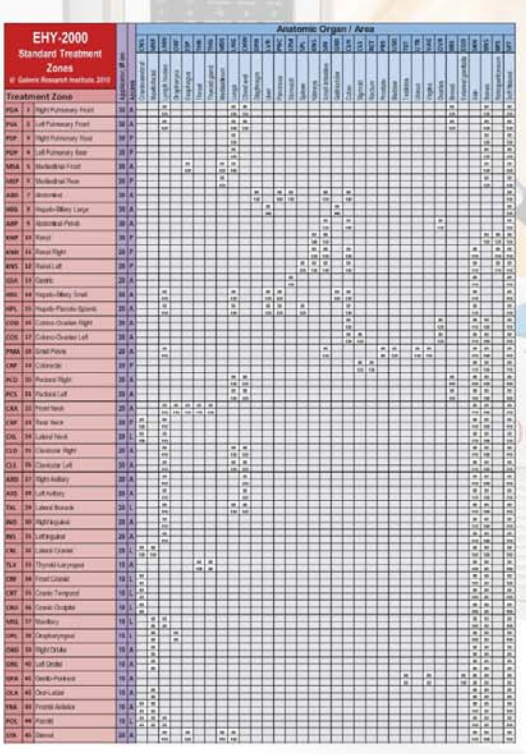
Standard duration of a session is 40-60 minutes for small applicator, 60 minutes for standard applicator and 90 minutes for big applicator. A session could be terminated after reach of scheduled time or dose. Maximum duration of a session with dose termination is 120 minutes.

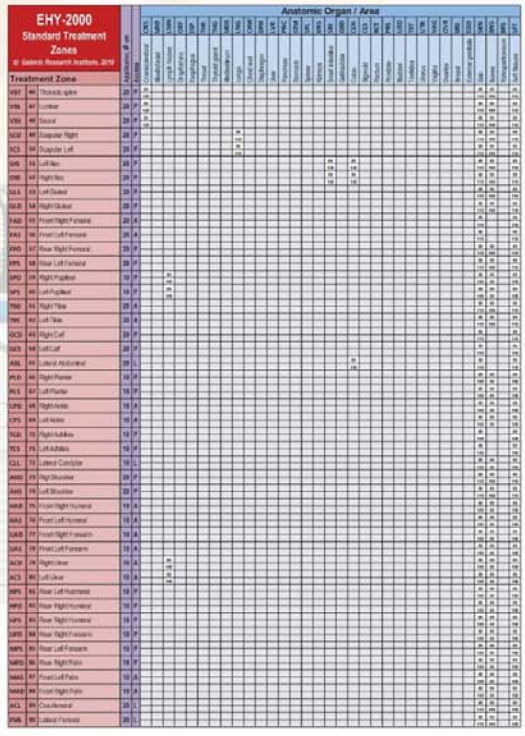
Interval between sessions

Recommended interval between sessions is 1-3 days (2-3 times a week). If necessary, the interval could be extended above 3 days. In combined treatment (chemo- and radiopotentiation), an interval between sessions is determined by the basic treatment. Daily use is possible.

Number of sessions and duration of the course

The average course consists of 6 treatments. The standard recommended course is 10 sessions, the minimum effective course is 5 sessions. The number of sessions for combined use (chemo- and radiopotentiation) is defined by a protocol of the basic treatment. Recommended course of oncothermia as a monotherapy is 15 sessions and more. The maximum number of sessions is unlimited. The longest described course for multiple liver metastases lasted for of 1030 days with more than 200 oncothermia sessions.





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Specialty Committee of Natural Therapy of World Federation of Chinese Medicine Societies (WFCMS)

World Federation of Chinese Medicine Societies (WFCMS) is an international academic organization voluntarily formed by group members in the world of Traditional Chinese Medicine and Natural Medicine. Currently, WFCMS has 220 society members in 58 countries and regions.

World Federation of Chinese Medicine Societies- Specialty Committee of Natural Therapy (WFCMS-SCNT) was established in May 2011. It aims to improve the world (regional) exchanges and cooperation between Natural Medicine groups, to raise the professional skill level of Natural Medicine practitioners, and to make positive contributions to human health. WFCMS-SCNT is based in Clifford Hospital of Guangdong Province which has the largest International Natural Medicine Center equipped with most comprehensive programs in the world.

Warmly welcome domestic and overseas personage experienced in Natural Medicine to join WFCMS-SCNT, and to visit International Natural Medicine Center .

Clifford Hospital International Natural Medicine Center

In May 2011, the First Meeting of The International Academic Conference on Natural Medicine was held in Guangzhou, China. Over 400 scholars from nearly 30 countries and regions attended the event.

Professor Clifford L.K. Pang, Chairperson of World Federation of Chinese Medicine Societies – Specialty Committee of Natural Therapy (WFCMS-SCNT) together with Andras Elek Szasz, Vice Chairperson of WFCMS-SCNT, and Stefan Matthias Heckel-Reusser, Executive Director of WFCMS-SCNT.

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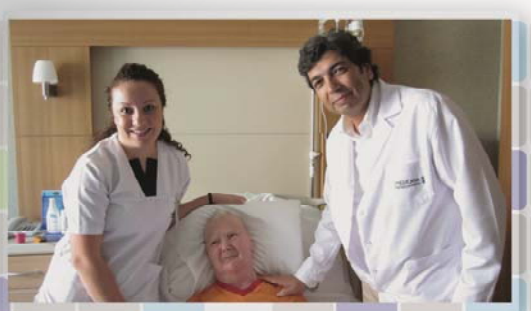
Post code: 511495
Website: http://www.clifford-hospital.org/Hospital%5F09/cn/znwen/
E-mail: WFCMS-NaturalTherapy@clifford-hospitol.org zrlfwyh@126.com
Fax: 0086-020-84518400

PI-06: Oncotherm (2012) Welcome poster

PI-07: Osmanoglu Hospital (2012) Oncology Center Istanbul

ONCOLOGY CENTER ISTANBUL
Osmanoğlu Hospital



Şişli Osmanoğlu Hospital is located in the heart of İstanbul, Sisli -İstanbul – Turkey. Şişli Osmanoğlu Hospital has 21 medical services. Oncology Service has 2 medical oncology physicians, 3 oncology nurses, 1 laboratory assistant , 1 coordinator and 1 secretary. The clinic works as a day clinic. Medical oncology physicians are Prof. Dr. Bülent Berkarda and Dr. Salih İyikesici.
Şişli Osmanoğlu Hospital Oncology Service has started doing hyperthermia treatment on July 2011 with Oncotherm EHY - 3010. They installed second Oncotherm EHY – 3010 device in the beginning of February 2012.

Prof. Dr. B. Berkarda
Onc. Dr. M.S. İyikesici

- Cancer Coaching
- Cancer Prevention
- Conventional Chemotherapy
- Metronomic Therapy
- Insulin Potentiation Therapy
- Hyperthermia

They usually apply hyperthermia with chemotherapy or hyperthermia alone. Only few of their patients had hyperthermia with radiotherapy. Also, some of them have insülin potentiation therapy (IPT).
They focus almost all of solid cancer types.
The physicians usually use the protocol of ten times one hour each.

oncotherm hightech medicine

TEK GRUP SAĞLIK HİZMETLERİ A.Ş.

PI-08: Seong Gi Min (2012) A case of clinically complete remission of lung with hyperthermia and concurrent 5th-line chemotherapy in a disseminated NSCLC patient

Zenith 제니스병원 HOSPITAL

A case of clinically complete remission of lung with hyperthermia and concurrent 5th-line chemotherapy in a disseminated NSCLC patient

Seong Gi Min, MD, Zenith Hospital, Seoul, Republic of Korea

Backgrounds

Lung cancer is the leading cause of cancer death worldwide. With combination chemotherapy, the median survival is 8~10 months. Besides chemotherapy, various modalities have been evaluated to get better survival. Hyperthermia is a new therapeutic approach and has synergistic effect with chemotherapy to control the disease and to improve the survival. Some clinical characteristics , i.e., female, adenocarcinoma, and never-smoker, show good prognosis. However, the efficacy of 5th-line chemotherapy for disseminated NSCLC is doubtful. Recently, we experienced the excellent response of one case of lung-to-lung metastatic NSCLC being clinically nearly complete remission of lung with hyperthermia (EHY-2000) and concurrent 5th-line chemotherapy.

Case presentation

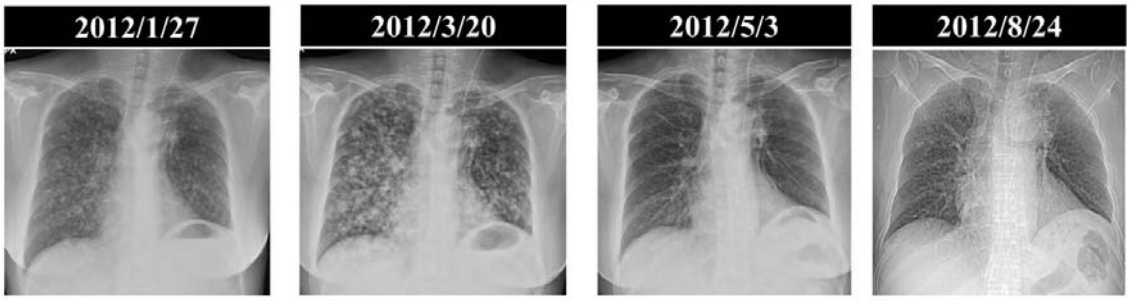
Patient : Female/53, never-smoker

Pathology, lung: adenocarcinoma, EGFR mutation (-) *The date of diagnosis:* May, 2007

Current status: metastases to lung-to-lung, brain, bone, pleura

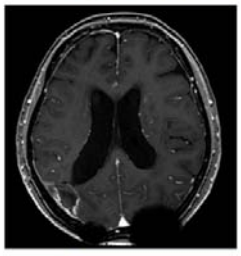
Past medical history & present illness: She had received LUL lobectomy on May/17/2007 followed by adjuvant CCRT. In May, 2009, the recurrence, brain, lung and bone metastasis was developed. After GKS on May/27/2009, palliative chemotherapy was administered. Those chemotherapeutic regimens were gemcitabine/cisplatin, gefitinib, and pemetrexed from August/3/2009 to November/3/2011. In June, 2011, she also had received craniotomy & tumor removal of right parietal lobe followed by whole brain radiotherapy (November/22-25/2011). Since January 2012, an agent in clinical trial had been administered. With progressive disease, the agent was switched to 5th-line palliative chemotherapy, docetaxel on March/21/2012. Hyperthermia, EHY-2000 system (Oncotherm GmbH, Troisdorf, Germany) had been applied on her chest since February/7/2012. *After 3rd cycle of hyperthermia, clinically nearly complete response was observed on chest X-ray and chest CT.*

Conclusion: The concurrent therapy of hyperthermia and chemotherapy would be promising in disseminated NSCLC.



Agent in clinical trial (2012/1/27-3/20) **Docetaxel** (2012/3/21-2012/8/24)

Hyperthermia (2012/2/7-2012/7/9)

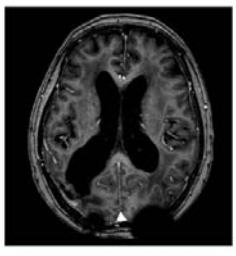


Metastatic Brain Tumor

June/ 2011
Controlled
Hydrocephalus with
Ommaya reservoir

Metastatic Brain Tumor

August/2012
Aggaravated
Hydrocephalus &
Leptomeningeal seeding



Non Hyperthermia

Clifford Hospital

Non-Toxic Integrative Cancer Treatments

Clifford Hospital is Asia's second and China's first large modern general hospital accredited by JCI (Joint Commission International). It's also rated National "Triple-A" Grade, recognized as a "Well-Known Traditional Chinese Medicine Hospital of Guangdong" in the country and accredited by JCI three times. It is equipped with 650 ward beds and over 40 specialities such as Internal Medicine, Surgery, Pediatrics, etc.

Bestowed the titles of National Education Base for Preventive and Curative Cancer Treatments, and Reputable TCM Oncology Center of Guangdong Province, Clifford Hospital Oncology Center achieved breakthroughs in medical treatment, utilizing modern techniques such as hyperthermia, chelation, medical ozone therapy and traditional therapies including Chinese Medicine, acupuncture, herbal cuisine, psychotherapy, medical Qigong, music etc, combined with the latest advanced medical procedures which are radiotherapy and chemotherapy of international standard, argon-helium cryoablation, bio-targeted therapy, immunotherapy and others. For different needs at different periods of cancer prevention, treatment, recovery and remission, individualized protocols are made by medical experts in Joint Case Conference according to the patient's specific conditions so as to strengthen the patient's immune system, prolong the patient's life and improve the patient's quality of life.

Clifford Hospital

Doctor Pang and specialists of varying fields hold Joint Case Conference to make the individualized treatment protocol.

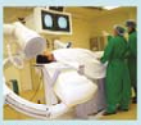
Over 30 international oncologists participate in Joint Case Conference, providing individualized protocols.

Dr. Clifford L. K. Pang, M.D.
Pioneer in the Non-Toxic Integrative Cancer Treatments
Founder and CEO of Clifford Hospital

Dr. Pang has rich clinical experience in Non-Toxic Integrative Cancer Treatments for cancers of the liver, stomach, intestine, thyroid and breast and others, with success in curing over 1,000 patients with various cancers. He has published several medical works including A Study of Non-Toxic Integrative Cancer Treatments.

Over 20 advanced procedures are available for cancer prevention, treatment, recovery and remission.

Over 10,000 cancer patients were cured without cancer metastasis and recurrence for many years.



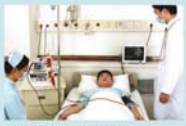
Minimally Invasive Interventional Therapy

Chelation Therapy

Whole Body (Heckel)

Bio-Cellular Therapy

Local Hyperthermia (Onco Therm EHY-2000)



Medical Ozone Therapy

TCM Therapy

Medical Qigong and Psychotherapy

Dietary Therapy

Acupuncture

祈福医院
CLIFFORD HOSPITAL
(国际JCI认证 / 国家三甲医院)

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Web Site: www.clifford-hospital.org
E-mail Address: adm@clifford-hospital.com.cn

National Oncothermia-Symposium

22th, June 2013. Köln, Germany

International Clinical Hyperthermia Society

8-10th, November, 2013, Guangzhou, China

Nationales
Oncothermie-Symposium

Freitag, 21.06.2013

19.00 Uhr Conference Dinner

Ort: Restaurant im Hotel Pullman

Kosten: 50,00 € pro Person

Anmeldeschluss: 01.06.2013

Samstag, 22.06.2013

9.00 - 18.00 Uhr Konferenz

Ort: Raum Belvedere (12. Stock)

Teilnahmegebühr: 100,00 € pro Person
(inklusive Konferenzmaterialien,
Kaffeepausen, Mittagessen)

Anmeldeschluss: 01.06.2013

Wissenschaftliche Leitung:

Prof. Dr. med. H. Sommer
Ludwig-Maximilians-Universität,
München

Hauptsponsor: oncotherm

Anmeldung / Organisation:

oncotherm

Frau Janina Leckler
Belgische Allee 9
53842 Troisdorf

Tel.: +49 (0)2241/319920
Fax: +49 (0)2241/3199211

Email: leckler@oncotherm.de

Tagungsort:

Hotel Pullman
Helenenstraße 14
D-50667 Köln

Anfahrt:

Nationales Oncothermie-Symposium

Programm

22. Juni 2013

Köln, Deutschland

Spezialthema:
„Tumor-Impfung und Oncothermie“

www.io-symposium.com

NATIONALES ONCOTHERMIE - SYMPOSIUM

Liebe Kolleginnen und Kollegen,
liebe Oncotherm-Anwender,

ich freue mich, dass wir uns in diesem Jahr der Oncotherm-Tradition folgend wieder in Köln treffen, um uns über Themen aus der Hyperthermie und Oncothermie auszutauschen und zu diskutieren.

Ein Schwerpunkt der Veranstaltung in diesem Jahr ist das hochaktuelle Thema der Tumorimpfung. Dieses wurde in den letzten Monaten in den Medien, in Fachkreisen und von Patientenorganisationen diskutiert und wird auch bei unserer Veranstaltung entsprechend gewürdigt. Aber auch weitere interessante Beiträge und neue Ergebnisse erwarten Sie bei unserem Symposium in Köln. Falls Sie uns kurzentschlossen noch mit einem Vortrag oder einem Poster für die Posterausstellung unterstützen möchten, freuen wir uns, von Ihnen zu hören.

Ich hoffe, viele von Ihnen bereits beim Conference Dinner am Abend vor der Veranstaltung begrüßen zu dürfen.

Wir freuen uns auf Sie!

Harald Sommer

Prof. Dr. med. Harald Sommer

Hauptsponsor: oncotherm

9.00-9.10	Begrüßung	Prof. Dr. H. Sommer, PD Dr. O. Szász
9.10-9.35	Lokale Hyperthermie wissenschaftliche und wirtschaftliche Aspekte und ihr Einfluss auf die Kostenübernahme durch die Krankenkassen	Prof. Dr. A. Herzog
9.35-10.00	Intraindividuelle Testung der Elektro-Hyperthermie	Prof. Dr. R. Klapdor
10.00-10.20	Kaffeepause	
10.20-10.45	Präklinische Ergebnisse	Dr. G. Andocs
10.45-11.10	Apoptotischer Zelltod	Dr. N. Meggyeshazi
11.10-11.35	Immunogener Zelltod	Dr. G. Andocs
11.35-12.00	Oncothermie und intermittierende Hypoxy-Hyperoy-Therapie	Dr. O. Zais
12.00-12.25	Chemo-Thermo-Therapie des metastasierenden Pankreaskarzinoms	Dr. F. Douwes
12.25-12.50	Tumor-Impfung—warum?	Dr. W. Stücker
12.50-13.50	Mittagessen	
13.50-14.15	Onkolytische Viren	Prof. Dr. V. Schirrmacher
14.15-14.40	Tumor-Impfung und Oncothermie	Prof. Dr. A. Szász
14.40-15.05	Die philosophischen Grundbegriffe der Medizin	Dr. A. Thaller
15.05-15.25	Kaffeepause	
15.25-15.50	TCM Synergie, XIAO-Aiping decoctum	Dr. C. Kovago
15.50-16.15	TCM Synergie	Prof. Dr. G. Hegyi
16.15-16.40	Erstattungsfähigkeit der Oncothermie	Dr. F. Breitkreutz
16.40-17.05	Systemische Candidose und Borreliose, eine Falldarstellung	Dr. O. Zais
17.05-17.35	Diskussion	
17.35-18.00	Ausblicke der Oncothermie: Vergangenheit und Zukunft	PD Dr. O. Szász

POSTERAUSSTELLUNG

Neben den Vorträgen wird auch in diesem Jahr wieder eine Posterausstellung Teil des Symposiums sein. Wir freuen uns auf Ihre Beiträge!

Bitte senden Sie Ihr Poster (A1: 594 x 841) bis zum 01.06.2013 an Frau Janina Leckler (leckler@oncotherm.de).

Alle Informationen auf www.io-symposium.com und auf www.oncotherm.de.

ANMELDUNG

Sie können sich für die Teilnahme am Symposium sowie am Conference Dinner bis zum 01.06.2013 anmelden.

Anmeldungen sind per Email an leckler@oncotherm.de oder per Fax an die Nummer 02241 31992 11 möglich.

Die Veranstaltung wurde von der Ärztekammer Nordrhein mit 8 Fortbildungspunkten zertifiziert.

ICHS NEWS

International Clinical Hyperthermia Society

Prof. Dr. Clifford L.K. Pang was nominated and accepted the nomination as the president of the ICHS for 2013.

The following representatives from each region were confirmed:

Secretary Treasurer: Dr. SV. Roussakow
Scientific Advisor and President Elect: Dr. J. Brenner
Past President: Prof. A. Szasz

American Vice President: Prof. JI Bicher
Asian Vice President: Prof. TS Jeung
European Vice President: Dr. F. Douwes
Australian Vice President: Prof. M. Jackson
African Vice President: Dr. CA. Strauss

Board of Directors:
Chairman: Prof. JI Bicher

Members:
Prof. A. Szasz
Prof. Dr. Clifford LK Pang
Dr. F. Douwes
Prof. N. Mitagvaria
Dr. A. von Ardenne
Dr. J. Brenner
Dr. N. Huilgol
Mr. M. Elderfield

The next ICHS Conference will take place in Guangzhou, China from November 8th-10th, 2013.

Request from DGHT

deutsche gesellschaft für hyperthermie e.V.

DGHT

Deutsche Gesellschaft für Hyperthermie e.V.
Mühlenweg 144 · D-26384 Wilhelmshaven

DGHT Geschäftsstelle
Mühlenweg 144
26384 Wilhelmshaven
Tel.: 04421-20944 80
Fax: 04421-20944 81
E-Mail: info@dght-ev.de
www.dght-ev.de

An alle Kollegen und Mitglieder der
Deutschen Gesellschaft für Hyperthermie e.V.

Datum
09.04.2013

Aufruf

Sehr verehrte Kollegen,

die letzte Mitgliederversammlung im September 2012 zeigte in einem Diskussionsbeitrag die Wichtigkeit und Notwendigkeit der wissenschaftlichen Anstrengungen. Herr Jörg Rawolle von der Firma The Pockwood hatte sich angeboten, eine faire und wahre lobbyistische Tätigkeit zu übernehmen, die mit ruhigem Gewissen auch unter ethischen Gesichtspunkten angenommen werden darf. Ich möchte Sie auffordern, diese zu unterstützen.

Wir benötigen dazu dringend exakt aufgearbeitete Best-Case, die zusammengefasst eine Häufung bei bestimmten Tumorentitäten erfassen lassen dürften. Nur mit Munition bewaffnet und harten Fakten und Daten gefüttert, werden sich Termine bei den Vorständen von Verbänden und Versicherungen, Krankenkassen und Regionaldirektionen lohnen, um auszuloten, wo Projekte, finanzierte Forschungen, Untersuchungen und Beobachtungen möglich werden. Nur auf solch eine Weise wird man erreichen können, dass die Ernsthaftigkeit der Bemühungen Schritt für Schritt nicht nur eine Freude im Falle des Erfolges für uns Anwender und den einzelnen Betroffenen ist, sondern in Regelmäßigkeit auftretend den Patienten verfügbar gemacht werden kann.

Insbesondere muss die historisch gewachsene Diskriminierung einzelner Hyperthermiesysteme durch harte Daten ad absurdum geführt werden! Erste Grundlagenforschungen wie Temperaturmessungen zeigten die Berechtigung. Weitere Studien mit identischen Systemen im Ausland unterstützen dieses Denken, so dass wir jetzt als Verband gefordert sind, die praxis- und klinikrelevante Hyperthermie in entsprechende Gremien zu tragen.

Dazu gehören sicherlich auch Ministerien, Verantwortungs- und Entscheidungsträger bei den verschiedenen Versicherern. Die inzwischen hocheffektive Geschäftsstelle der Deutschen Gesellschaft für Hyperthermie e.V. wird in der Lage sein, die Daten zu bündeln und mir als Arzt vorzulegen, so dass ich Herrn Rawolle mit entsprechend aufgearbeiteten Materialien versorgen und wissenschaftlich begleiten kann. Bitte nehmen Sie diesen Aufruf sehr ernst und durchforsten Sie Ihre Daten der Best-Case unter dem Aspekt regelmäßig guter Einflussnahmen. Übergeben Sie uns ggf. die Zusammenfassung, die Ihre Praxis-/Kliniktätigkeit mit Blick auf Hyperthermie- und Krebsbehandlungen hergibt.

Es wäre sehr schön, wenn durch Zusendungen die Datensammlung wächst, so dass ich vielleicht einen ersten Überblick zum Hyperthermie-Symposium in Köln geben könnte. Herr Rawolle steht zur Verfügung. Nutzen wir die Möglichkeit!

Ich werde mir erlauben, in regelmäßigen Abständen nachzufragen und hoffe sehr, dass mir Daten zugehen und es nicht nur bei der verbal signalisierten Bereitschaft bleibt, die zur Mitgliederversammlung im September der Grundtenor war.

So verbleibe ich mit kollegialer Hochachtung als Ihr

H. Wehner
Wissenschaftlicher Beirat / Pastpräsident

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E-Mail: praxisdrheinrich@gmail.com

Praxis für
Ganzheitsmedizin
Ursula Ehrhorn
Dr. med. Ralf Heinrich
Berlin, Germany

Ursula Ehrhorn (praktische Ärztin, Homöopathin & Coach) und Dr. Ralf Heinrich (Arzt für Naturheilverfahren) arbeiten seit Dezember 2012 in der Praxisklinik für Ganzheitsmedizin in Berlin mit dem EHY-3010 ML von Oncotherm.

Grundlage ihrer therapeutischen Arbeit ist die Betrachtung des Menschen in seiner Ganzheit aus Körper, Geist und Seele. Ziel der beiden Ärzte ist es, so auf allen drei Ebenen auftretende Belastungen, Mangelzustände und Erkrankungen zu erkennen und behandeln zu können.

Ziel ihrer Therapie ist es im Rahmen eines individuellen und ganzheitlichen Therapiekonzeptes den Menschen auf eine möglichst natürliche und schonende Art zu einem gesunden Gleichgewicht zurückzuführen.

Frau Ehrhorn und Dr. Heinrich kommen aus der Schulmedizin und haben die naturheilkundlichen Methoden zusätzlich erlernt. Falls notwendig oder gewünscht, arbeiten sie mit den rein schulmedizinisch ausgerichteten Kollegen zusammen. Zu den Schwerpunkttherapien der Praxisklinik zählen aber die Cellsymbiosistherapie, das Coaching, die Galvanotherapie und die Hyperthermie (Oncothermie).

Die Praxisklinik bietet neben der regulären Betreuung der Patienten auch regelmäßige Veranstaltungen sowohl für interessierte Laien als auch für Therapeuten an. Aktuelle Themen und Termine finden Sie auf der Website.

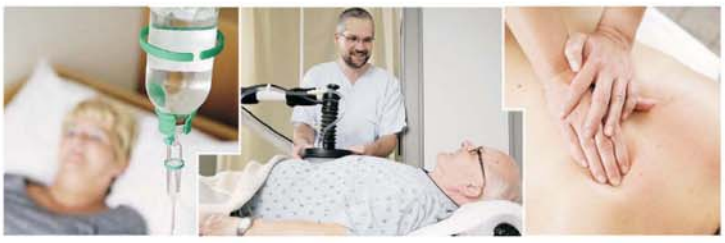
TimO
Therapiezentrum für integrative medizinische Onkologie
An der HELIOS Klinik Hüls
Chefärztin der Abteilung für Innere Medizin: Sabine Hellmer
Fette Henn 50
47839 Krefeld-Hüls
Telefon: +49 2151 739 285
Telefax: +49 2151 739 215
E-Mail: info@timo-krefeld.de
Web: www.timo-krefeld.de

TimO
Therapiezentrum für integrative medizinische Onkologie
Krefeld-Hüls, Germany

Die Krebs-Diagnose stellt im Leben der meisten Betroffenen einen tief greifenden Einschnitt dar. Nichts scheint mehr, wie es war. Die Situation ist geprägt von Ungewissheit und einem Wechselbad der Gefühle. Und dennoch müssen Entscheidungen von großer Tragweite getroffen werden. Wie geht es weiter? Was wird sich verändern? Viele Fragen beschäftigen sich mit der Zukunft, Vergangenheit und Gegenwart. Im Dschungel aus Hightech-Medizin und alternativen Heilmethoden ist das Therapiezentrum für integrative medizinische Onkologie – kurz TimO – als erfahrener und verantwortungsvoller Partner ein zuverlässiger Begleiter.
Da es den einen Krebs nicht gibt, stellt TimO die Therapie ganz individuell für jeden Patienten zusammen. In sorgfältiger Abstimmung werden konventionelle Methoden und wissenschaftlich anerkannte, komplementäre Ansätze zur bestmöglichen Krebstherapie kombiniert. Um die Kraft der eigenen Entscheidungen zu nutzen, orientieret sich das Zentrum an den persönlichen Wünschen und Möglichkeiten der Patienten.
Die Möglichkeiten der Krebsbehandlung und damit die Heilungschancen und Überlebenszeiten haben sich in den vergangenen Jahrzehnten dank moderner Therapieverfahren deutlich verbessert. Im TimO werden Patienten nach den aktuellen Standards der Fachgesellschaften, etwa der Deutschen Krebsgesellschaft, behandelt.
Unter konventionellen Tumortherapien werden tumorzerstörende Maßnahmen zusammengefasst, die im Wesentlichen aus folgenden Behandlungsformen bestehen:

- Chemotherapie
- Hyperthermie
- Chirurgie
- Strahlentherapie

Weitere Therapieverfahren, wie die Immuntherapie mit Antikörpern oder molekulare Therapien, finden zunehmend Eingang in die Tumortherapie.
Die medikamentösen und komplementären Behandlungen werden im Therapiezentrum für integrative medizinische Onkologie in der HELIOS Klinik Hüls durchgeführt. Für hochspezialisierte Untersuchungen wie Kernspintomografien oder Strahlenbehandlungen besuchen die Patienten die darauf spezialisierten Kliniken im HELIOS Klinikum Krefeld. Regelmäßige Taxidienste sorgen für einen bequemen und reibungslosen Ablauf, so dass die Patienten auch während dieser Behandlungen nicht auf die Fortführung der komplementären Therapien im HELIOS Klinik Hüls verzichten müssen.



New Oncotherm Customers

We are happy to welcome three new customers:

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Fax.: 905.508.4827
Email: info@mcne.ca

www.naturopathiccentre.com

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Praxisklinik Ganzheitsmedizin

Fasanenstr. 48
10719 Berlin
Fon: 030 – 790 16 53-3
Fax: 030 – 790 16 53-4

www.praxisklinik-in-berlin.de

National Cancer Institute, Thailand

268/1 Rama VI Road, Rajthevi
10400 Bangkok
Thailand

Tel.:+66 (2) 3547052
Fax.:+66 (2) 6449097

www.nci.go.th

Oncotherm Information Material and Publications

Dear Oncotherm-user, dear interested doctors,

with several offers we would like to present our method to make it wide known and to support you. We would like to introduce to you shortly our information material and our publications. You can order all presented brochures and the Oncothermia Journal as well as register for our newsletter (Tel.: +49 (0) 2241 31992 0, Email: info@oncotherm.de)

Oncothermia Brochures

We have a brochure about our method and one for each device in German and English language. All brochures can be downloaded from our website:

http://www.oncotherm.de/web/page/phy/prospects.ENG/?.

The Oncothermia-Book

„Oncothermia: Principles and Practices" was published at the beginning of 2011 by the famous Springer Publishing House and shows on 565 pages the scientific background of the method as well as several examples from the practical experience.

The Oncothermia Journal

It is published three times a year and gives Oncothermia users the possibility to present their scientific results and case studies.

The Oncothermia-Films

A collection of films and TV-broadcasts about Oncothermia can be found on

www.oncotherm.com/fp.php?id=videos. You can also ask a CD collection from our office.

The Oncothermia-Newsletter

The Oncotherm-Newsletter is released once a month and provides information about new products, scientific topics, current events and new publications. It is sent out via email. If needed we can also send you a printed version.

Events

Oncotherm participates in national and international exhibitions and congresses.

With talks we inform doctors worldwide about the results of the method. In our newsletter and on our website we inform you about the events that we are visiting.

The Oncothermia-Symposium

The Oncothermia-Symposium follows a long tradition. The event takes place once a year, alternating with either a national or international focus. You can find further information on www.io-symposium.com.