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ONCOTHERMIA JOURNAL

ESHO Conference 2017

www.Oncothermia-Journal.com

Editorial

Dear Readers, Dear Fellow Researchers, Dear Colleagues,

It is my great honor to introduce the new volume of our Oncothermia Journal. I am pleased to recognize the important role of this open-access journal in the information exchange of the experts of the broad hyperthermia field and especially the information for its modern and state-of-art technology: oncothermia.
Our Editorial Board is always open for all the aspects of oncologic hyperthermia which wide attention is well mirrored in this volume too. We are happy to include the available open access abstracts of the European Society of Hyperthermic Oncology (ESHO) in the present issue of the Oncothermia Journal, hoping that it helps a lot for professionals all over the world. The historical remarks for Oncothermia together with the proofs how oncothermia made further development of hyperthermia is aired now showing also some medical reports of the applications for advanced malignant diseases of prostate, cervix, brain, lung, triple negative breast, and various oligometastatic cases. Special attention is taken on the ongoing Phase III cervix trial which provided very promising results in its present interim phase.
Hyperthermia in oncology is in crossroads. The other new oncological concepts (gene-therapies, immune-therapies, stem-cell therapies) together with new approaches and technologies (tomotherapy, proton-therapy, minimally invasive robotic onco-surgery, anti-body therapies, check-point inhibitors, etc.) challenge the hyperthermia method. We have to prove the validity of this traditional medical approach in the condition when new therapy concepts are introduced radically. This demand supports the high-level research in vitro and in-vivo, and the therapy combination with natural remedies originated from traditional Chinese medicine or widely used vitamin therapies in western practices.
We are delighted to publish the debate about basic hyperthermia parameters: dose and temperature as well as the validity of the rapidly developing planning software. I challenged Professor Dr. van Rhoon in this topic and we had a vivid intensive debate openly in the plenary session of our ESHO conference. The debate was not closed, we decided to continue it in smaller expert groups when the scientific discussions can lead to consensus. We would be more than happy, if we may initialize a forum about these debated topics and come to an agreement for the development in world-wide activity of the hyperthermia field. This is why we are publishing the debate-related info in this volume of the Oncothermia Journal.
I wish enjoyments to read this recent volume of our open-access forum and wish benefits of these published information for your research, your practices and for the patients, too.

Sincerely yours,

Prof. Dr. András Szász

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

es ist mir eine große Ehre, Ihnen den neuen Band unseres Oncothermia Journals vorzustellen. Ich freue mich, die wichtige Rolle dieser Open-Access-Zeitschrift im Informationsaustausch der Experten des breiten Hyperthermie-Felds und vor allem die Inhalte der Information für hochmoderne Technik zu erkennen: Die Oncothermie.
Unsere Redaktion ist immer offen für alle Aspekte der onkologischen Hyperthermie, die in diesem Band auch in großer Hinsicht wiedergespiegelt werden. Wir freuen uns, die verfügbaren Open Access Abstracts der European Society of Hyperthermic Oncology Konferenz (ESHO) in die aktuellen Ausgabe des Oncothermia Journal mit aufzunehmen, in der Hoffnung, dass die Inhalte vielen Profis aus der ganzen Welt weiterhelfen.
Die historischen Bemerkungen zur Oncothermie zusammen mit den Beweisen, wie die Oncothermie die weitere Entwicklung der Hyperthermie vorangetrieben hat, zeigen nun auch einige medizinische Berichte über die Anwendungen für fortgeschrittene maligne Erkrankungen von Prostata, Gebärmutterhals, Hirn, Lunge, Brust und verschiedene oligometastatische Fälle. Besonderes Augenmerk wird auf die laufende Phase-III-Zervix-Studie gelegt, die in ihrer gegenwärtigen Zwischenphase sehr vielversprechende Ergebnisse liefert.
Die Hyperthermie steht in der Onkologie an einer Kreuzung. DieKonkurrenz zu anderen neuen onkologischen Konzepte (Gen-Therapien, Immuntherapien, Stammzelltherapien) sowie neue Ansätze und Technologien (Tomotherapie, Protonentherapie, minimal-invasive Roboter-Onkochirurgie, Antikörper-Therapien, Kontrollpunkt-Inhibitoren usw.) stellt eine große Herausforderung für die Hyperthermie-Methode dar. Wir müssen die Gültigkeit unseres traditionellen medizinischen Ansatzes in dem Zustand nachweisen, in dem neue Therapiekonzepte radikal eingeführt werden. Diese Forderung unterstützt die hochrangige Forschung in vitro und in vivo, und die Therapiekombination mit natürlichen Heilmitteln stammt aus der traditionellen chinesischen Medizin oder weit verbreiteten Vitamintherapien in westlichen Praktiken.

Wir freuen uns, die Debatte über grundlegende Hyperthermie-Parameter zu veröffentlichen: Dosis und Temperatur sowie die Bedeutung der sich schnell entwickelnden Therapieplanungssoftware. Ich habe Professor Dr. van Rhoon in diesem Thema herausgefordert und wir hatten eine lebendige intensive Debatte im offenen Plenum unserer ESHO-Konferenz. Die Debatte wurde nicht abgeschlossen, wir beschlossen vielmehr, sie in kleineren Expertengruppen fortzusetzen, um einen wissenschaftlichen Konsens zu finden. Wir würden uns freuen, wenn wir ein Forum über diese diskutierten Themen initialisieren und eine Vereinbarung über die Entwicklung der weltweiten Tätigkeit der Hyperthermie-Gemeinschaft treffen könnten. Aus diesem Grund veröffentlichen wir in dieser Ausgabe des Oncothermia Journal die entsprechenden Infos aus der Debatte.
Ich wünsche Ihnen viel Freude dabei, diesen aktuellen Band unseres Open-Access-Forums zu lesen und hoffe Sie können die Vorteile dieser Informationen für Ihre Forschung, Ihre Praktiken und für die Patienten erfolgreich nutzen.

Mit freundlichen Grüßen,

Prof. Dr. András Szasz

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
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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.

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Oncotherm a company devoted for innovation in oncological hyperthermia from 1988

Oliver Szasz, PhD, assoc. professor
Oncotherm Group; Troisdorf, Germany
Department of Biotechnics, St. Istvan University, Budaors, Hungary

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-2.pdf

ESHO'2017

Oncotherm

a company devoted for innovation in oncological hyperthermia from 1988

Oliver Szasz, PhD, assoc. professor
Oncotherm Group; Troisdorf, Germany
Department of Biotechnics, St. Istvan University, Budaors, Hungary

Oncothermia is a further developed hyperthermia

Oncothermia (generic name modulated electro-hyperthermia mEHT) is hyperthermia with certain developments.

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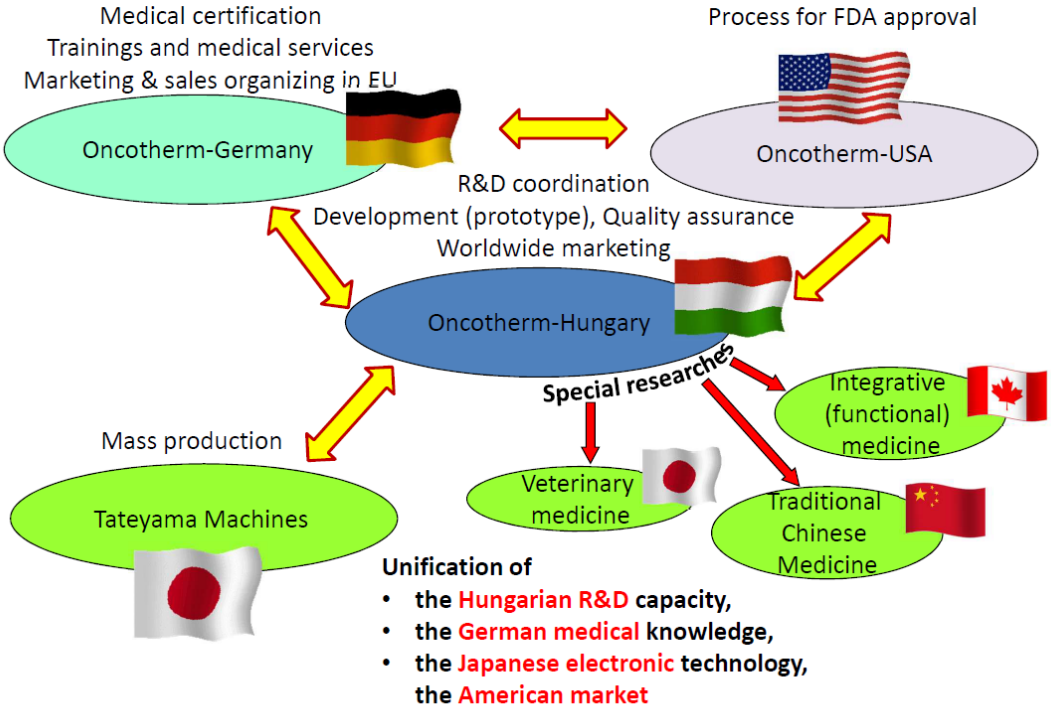
Presently processing: China, Japan, FDA (USA)

Oncotherm organization



Oncotherm worldwide

Australia
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Jordan
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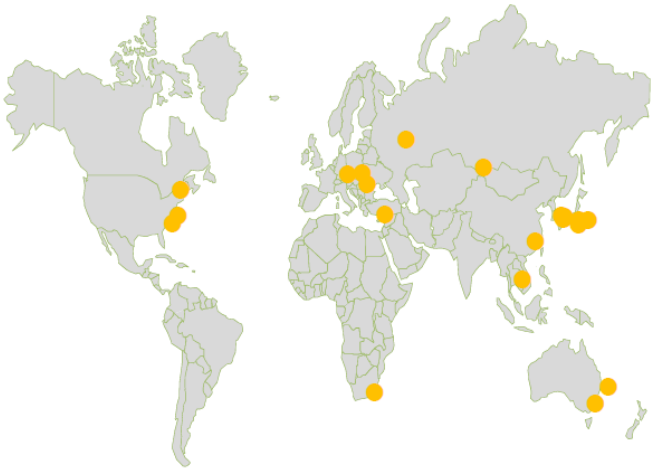
Pakistan
Poland
Romania
Russia
San Marino (IT)
South Africa
Pakistan
Spain
Switzerland
Taiwan
Thailand
Turkey
Ukraine
United Kingdom
USA
Vietnam

450+ devices,
In 30+ countries,
In 5 continents

25+ university activity in 12 countries

● University



Accession this year:
Algeria
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India
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Peru
Portugal
Saud-Arabia
Serbia
Sweden

200.000+ treatments/year

Oncothermia is a kind of hyperthermia. Hot topics: temperature, dose, selectivity

Andras Szasz, PhD; professor, Chair
Department of Biotechnics, St. Istvan University, Budaors, Hungary

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ESHO'2017

Oncothermia is a kind of hyperthermia.

Hot topics: temperature, dose, selectivity

Andras Szasz, PhD; professor, Chair

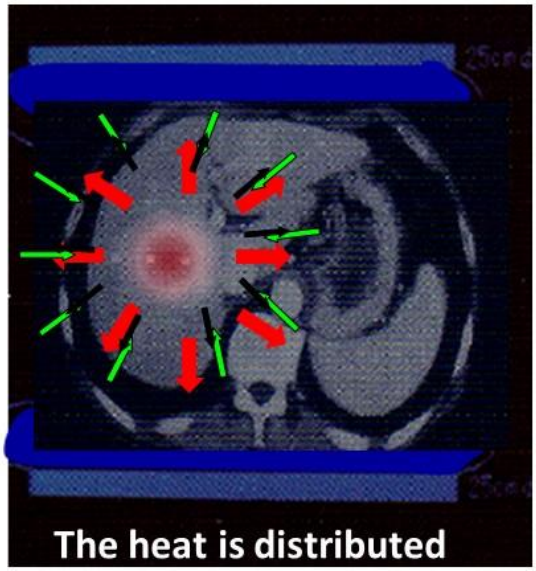
Department of Biotechnics, St. Istvan University, Budaors, Hungary

Outline

- ❑ Introduction
- ❑ Temperature
- ❑ Selection
- ❑ Dose

Origin of controversies in clinical results of hyperthermia

Energy could be well focused but the temperature can not be kept focused



Temperature spreads!

It increases the blood-flow trying to compensate the heating.

It is positive for complementary therapies

- radio [reoxygenization]
- chemo [drug delivery, and activity])

It is negative over the tresholds shown

Supplies extra nutrients for tumor

Risks the intensive dissemination

Outline

- ❑ Introduction
- ❑ Temperature
- ❑ Selection
- ❑ Dose

Oncothermia is thermal

Post-treatment 24 H, 30 min; Each point is 3 independent measurements

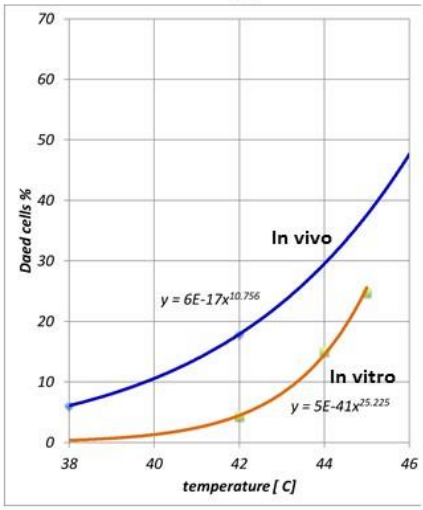
In vitro: U937 human lymphoma cell-line (10^6 cell/ml)

Andocs G, et al, Biology and Medicine 7(4):1-9,

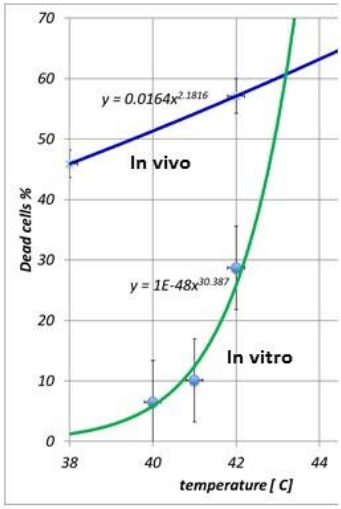
In vivo: HT29 human colorectal cancer xenograft

Andocs G et al. Radiology and Oncology (Strahlentherapie und Onkologie) 185:120-26 , (2009)

Conventional hyperthermia

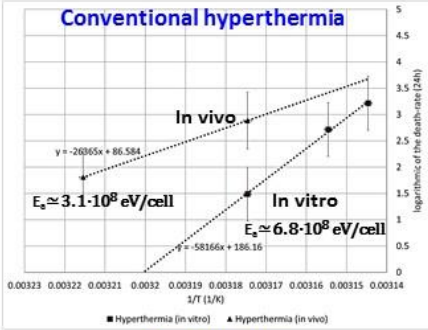


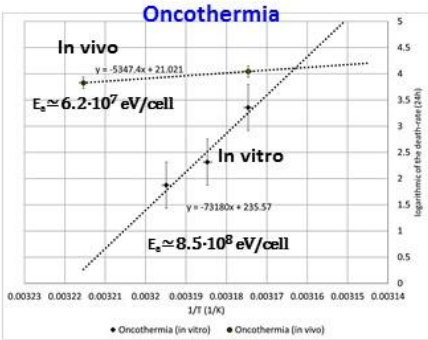
Oncothermia



Power-function

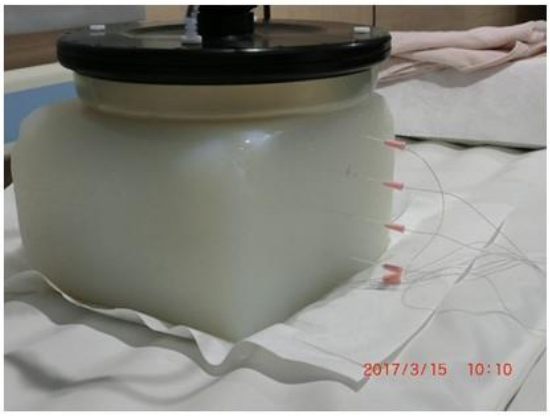
Arrhenius plots (thermal effect)

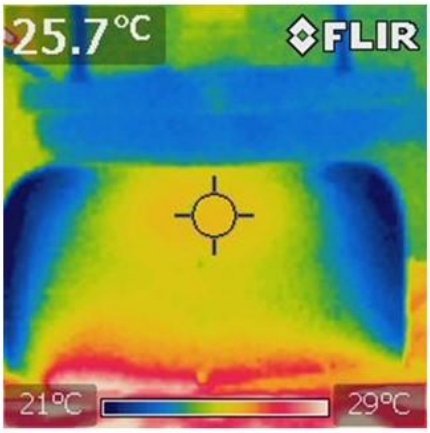




The activation energy is calculated

Temperature measurement Agar phantom





Device: EHY2000+; Applicator: 30cm
Power: 150W; treatment time:30 min
Agar-phantom: 6 kg, Size: 24*24*8.5 cm

Heating for ten minutes with 150 W with 30 cm electrode by EHY2000+ device

Observations:

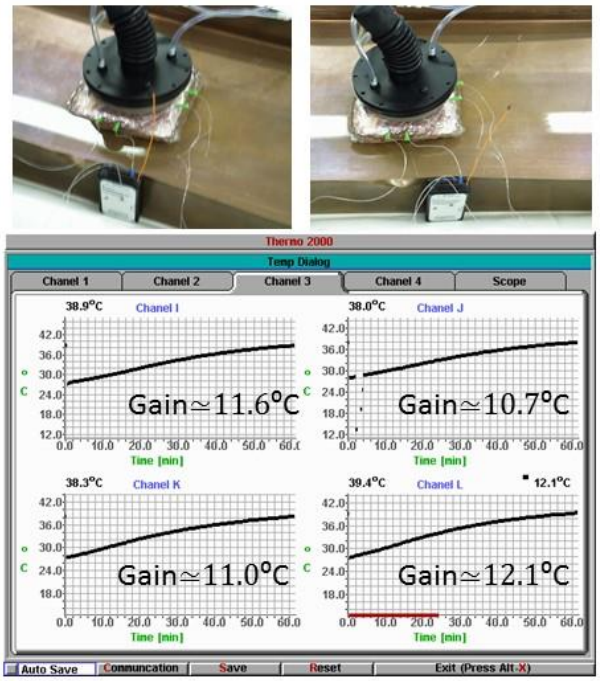
- The temperature was increased >3.5°C (with 150W, 10 min)
- The bulk material was heated, not the surface
- The heating shape is a truncated cone
- Spreading of the heated volume is less than 50% at the bottom

SAR≃24.5 W/kg

≈4.5 kg is heated, 110W was absorbed, ≃74 %

Prof. Dr. Kwan-Hwa Chi* and Dr. Samuel Yu-Shan Wang**
*Department of Radiation Therapy & Oncology Shin Kong Wu Ho-Su Memorial Hospital
**Molecular Medicine and Biochemical Engineering, National Chiao Tung University, Hsinchu, Taiwan

Meat-phantom experiements

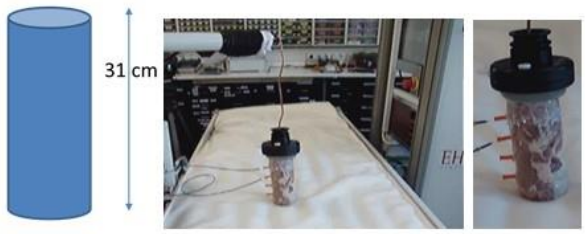


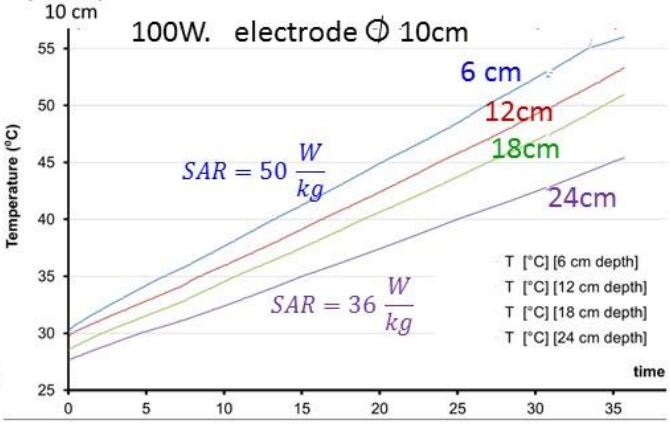
5 kg Pork meat

Start 27.3°C

Power 100W, 60 min

Muscle-fat mixture model





Complete absorbed power $= 92W$

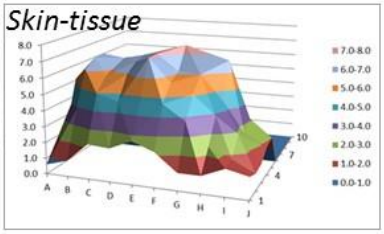
Nagy G. Meggyeshazi N. Szasz O (2013) Deep temperature measurements in oncothermia processes. Hindawi ;Conference Papers in Medicine. Volume 2013. Article ID 685264

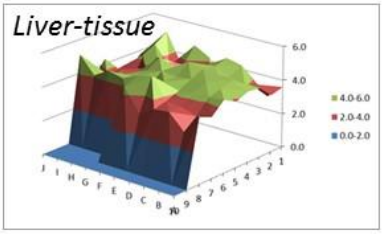
Local Hyperthermia – Oncotherm (Dr.Herzog)

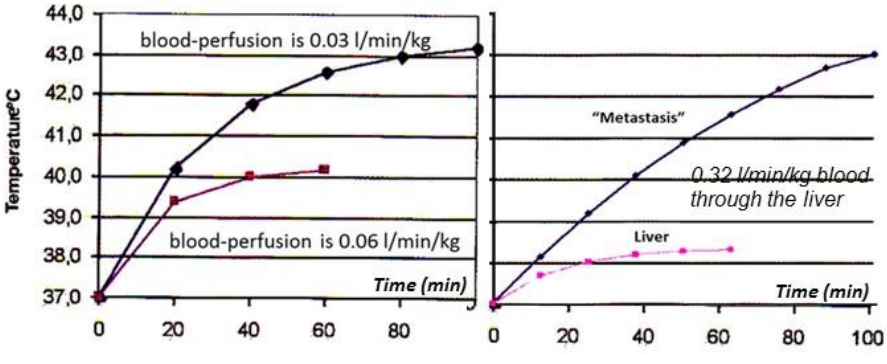
Herzog A (2008) Messung der Temperoturverteilung om Modell der nicht perfundierten Schweineleber bei lokoler Hyperthermie mit Kurzwellen mit I3,56 MHz; Forum Hyperthermie, Forum Medicine, 1/10, pp.30-36

electrode 20cm, 100W

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

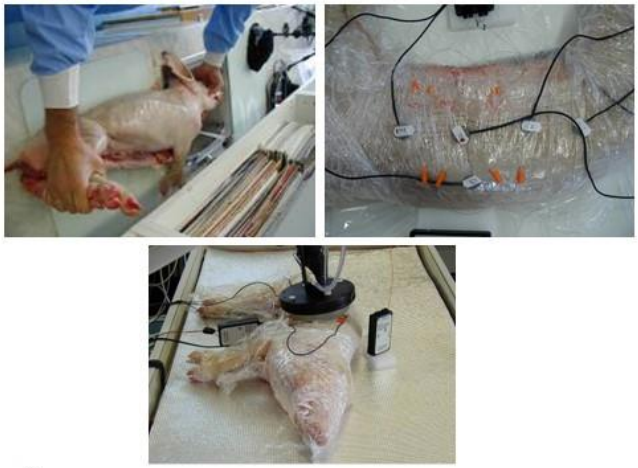


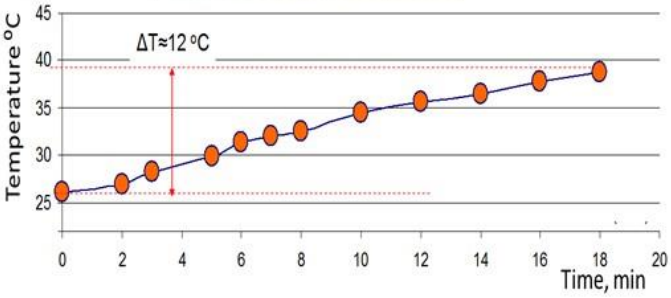




Pig experiments

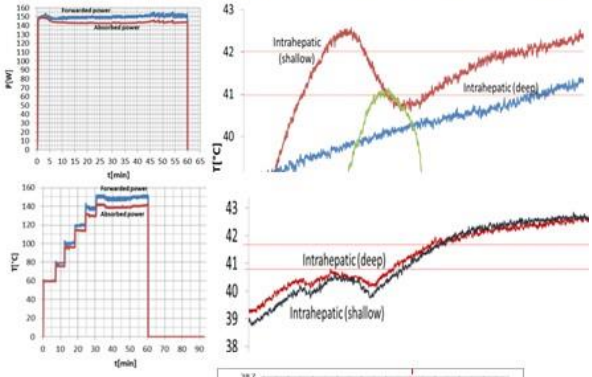
Ex vivo



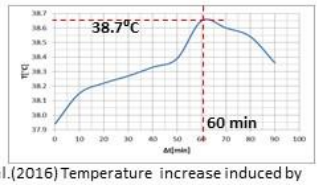


In vivo

Intrahepatic temperature measurement (alive)

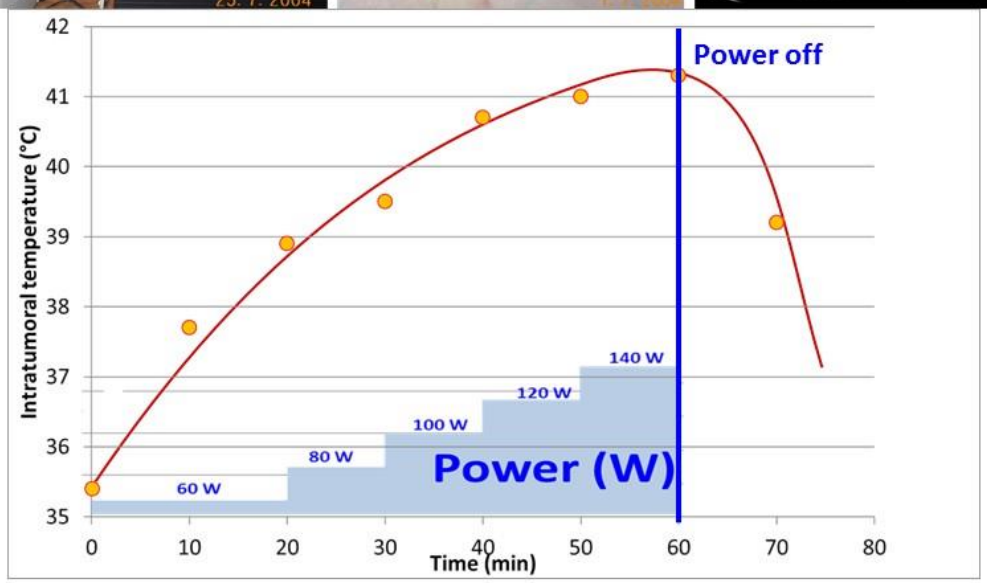


rectal

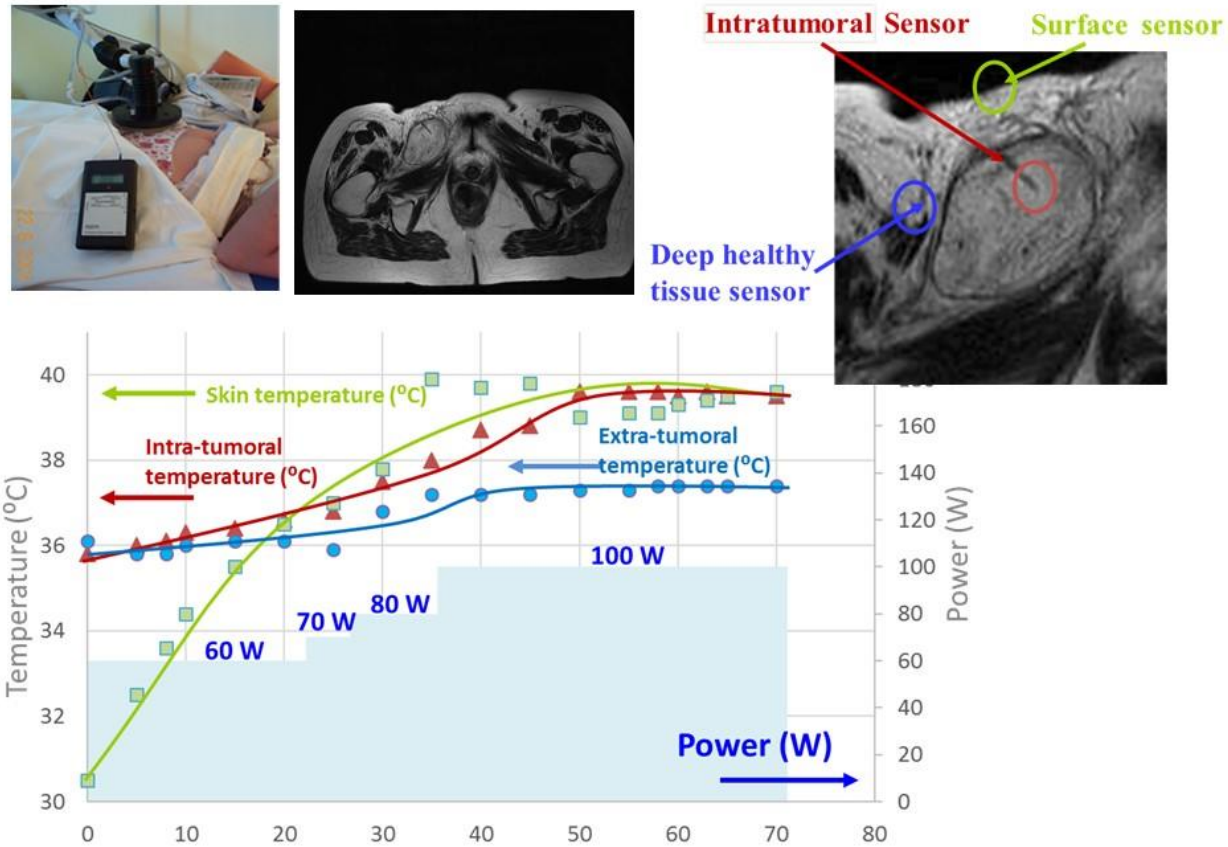


Balogh L, Polyak A, et al.(2016) Temperature increase induced by modulated electrohyperthermia (oncothermia®) in the anesthetized pig liver, Journal of Cancer Research and Therapeutics, 12(3):1153-1159

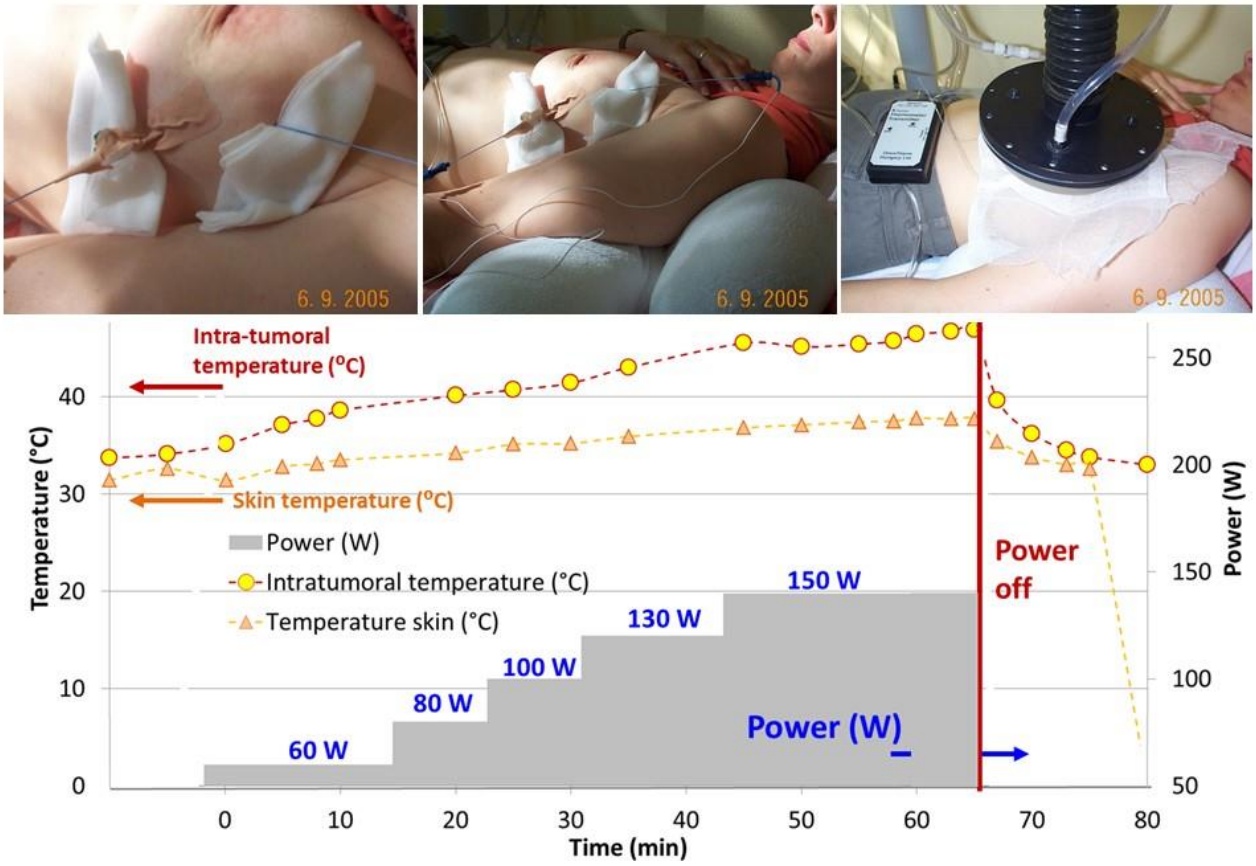
Human abdominal temperature measurement



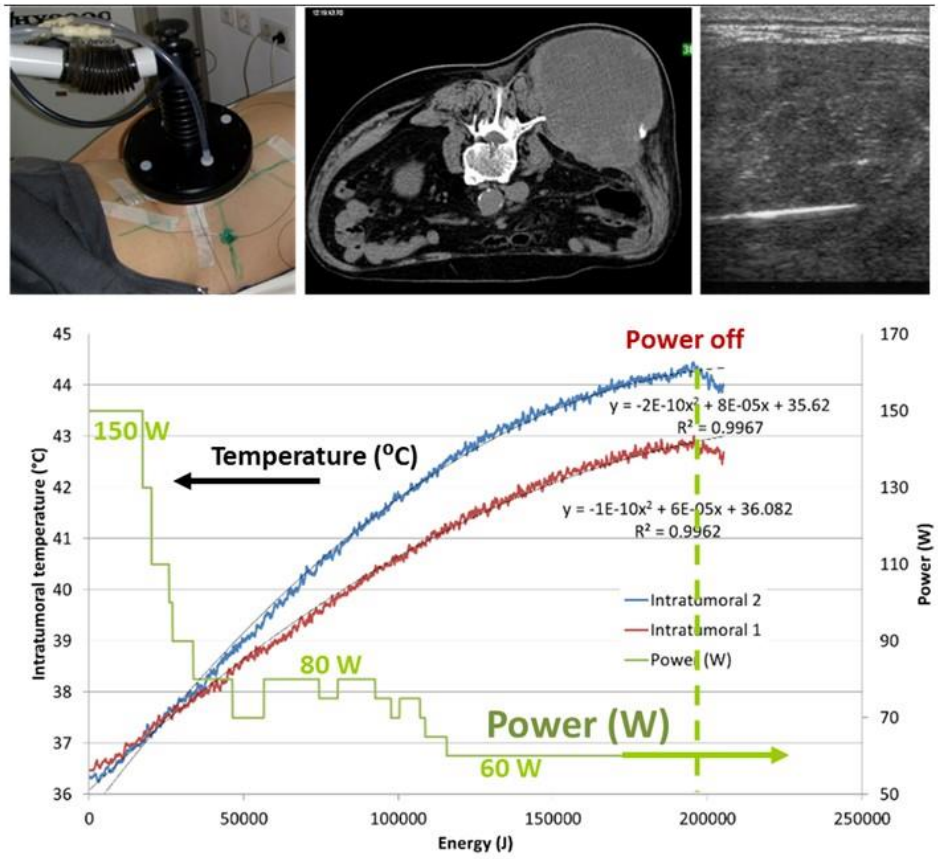
Temperature in ovary (Gronemayer Institute)



Mammary carcinoma measurement (Gronemayer Institute)



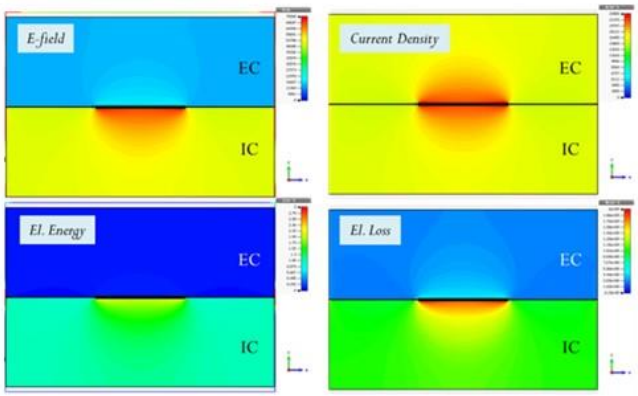
Temperature of sarcoma (Nurnberg University Hospital)



Outline

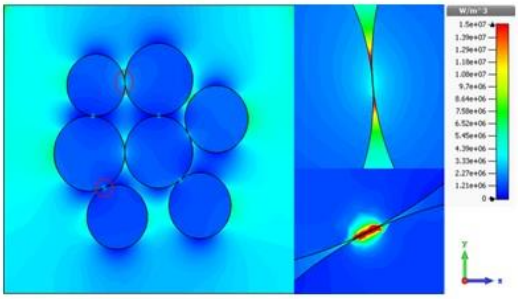
- ❑ Introduction
- ❑ Temperature
- ❑ Selection
- ❑ Dose

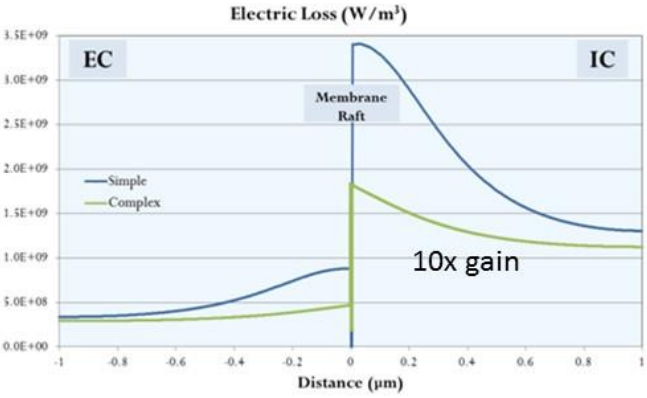
In silico model shows the raft-heating

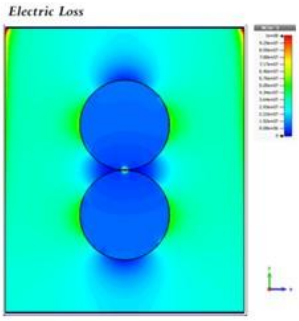


Additional extra energy loss by touching microdomains

12.5x gain



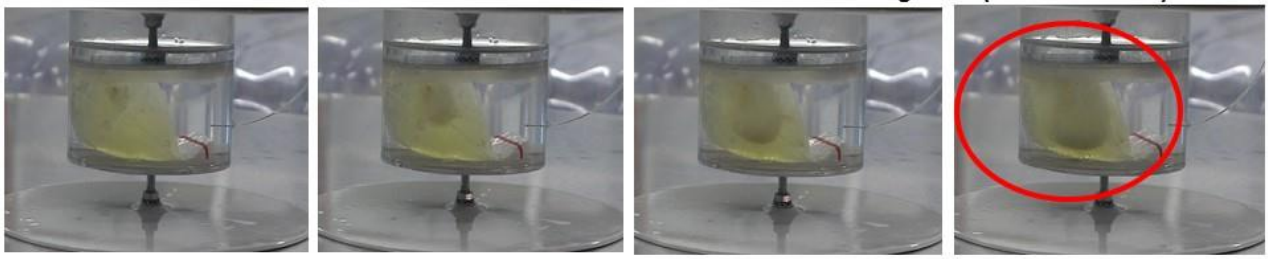




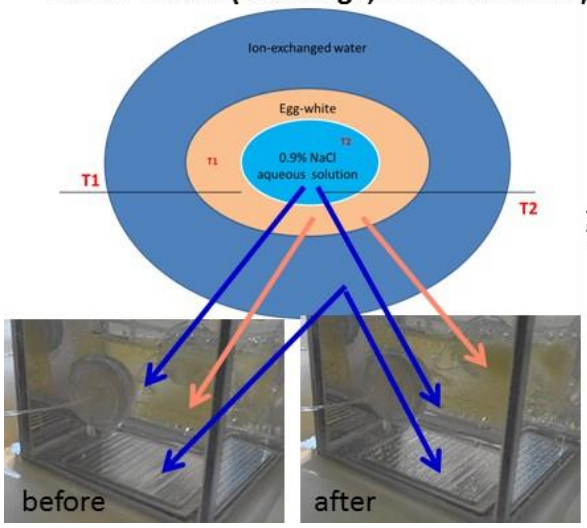
Egg-white in water-tank, heated by RF-current flow

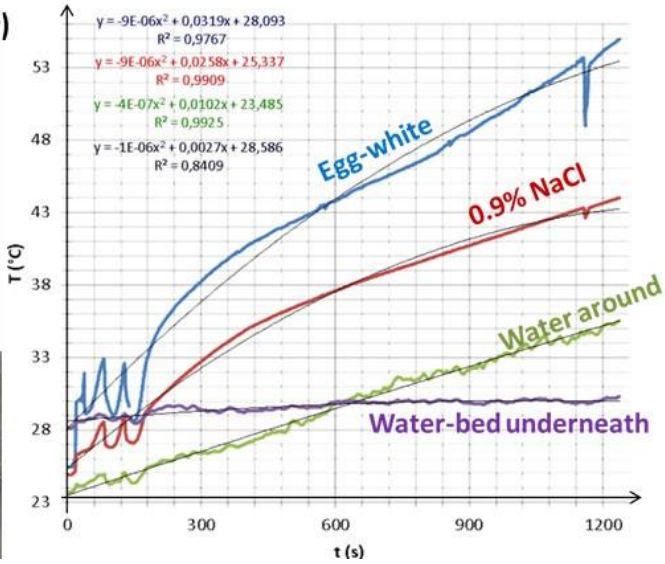
Tumor model (early stage)

The water was not heated-up, but the egg-white had been coagulated (from the center!)

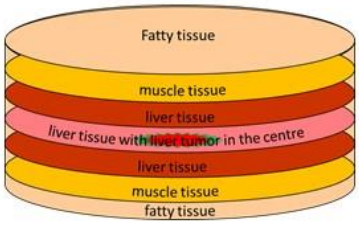


Tumor model (late stage, necrotic center)





Heterogeneous liver phantom

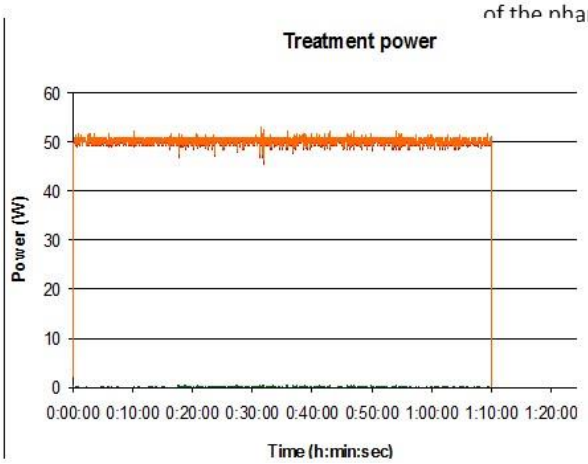


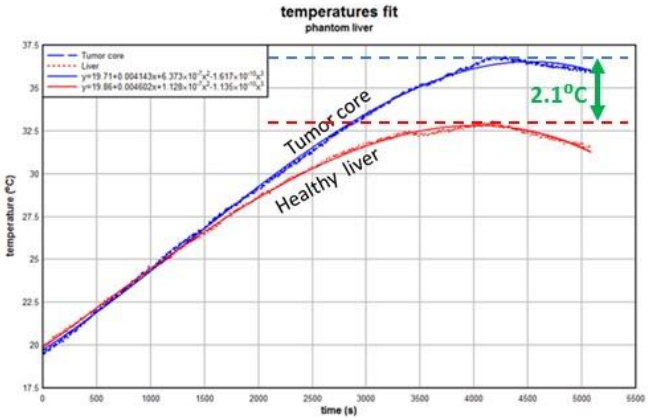
The structure of the phantom

Fat (down) and muscle layer (same on the top of the phantom)

Pig liver layer with cancer in the middle

Complete phantom with the electrode on its top





Oncothermia - cellular selectivity by active malignancies

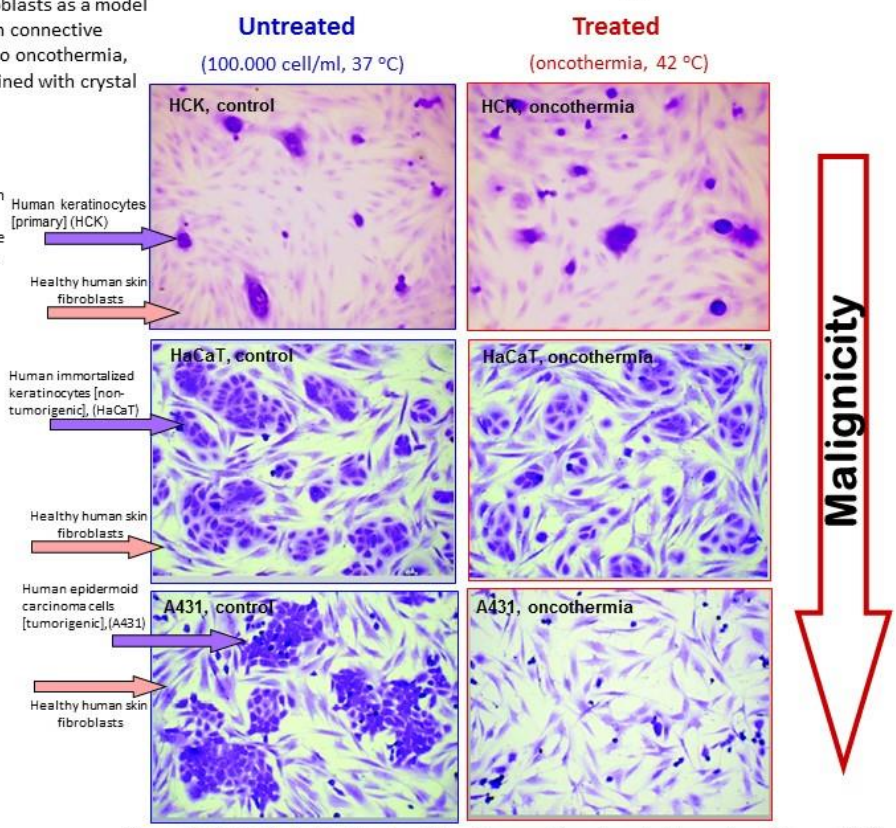
Co-culture with normal human skin fibroblasts as a model of a squamous carcinoma growing within connective tissue cells (100.000/ml) were exposed to oncothermia, incubated for 24 h at 37°C, fixed and stained with crystal violet

Cellular metabolic activity was measured using the MTT assay (standard colorimetric test) and quantitated at 630 nm. Data represent the mean value ± S.E.M. of 4-6 separate experiments assayed in triplicate, but some experiments were repeated up to 12 times to obtain reliable data.

Healthy tissue is unaffected

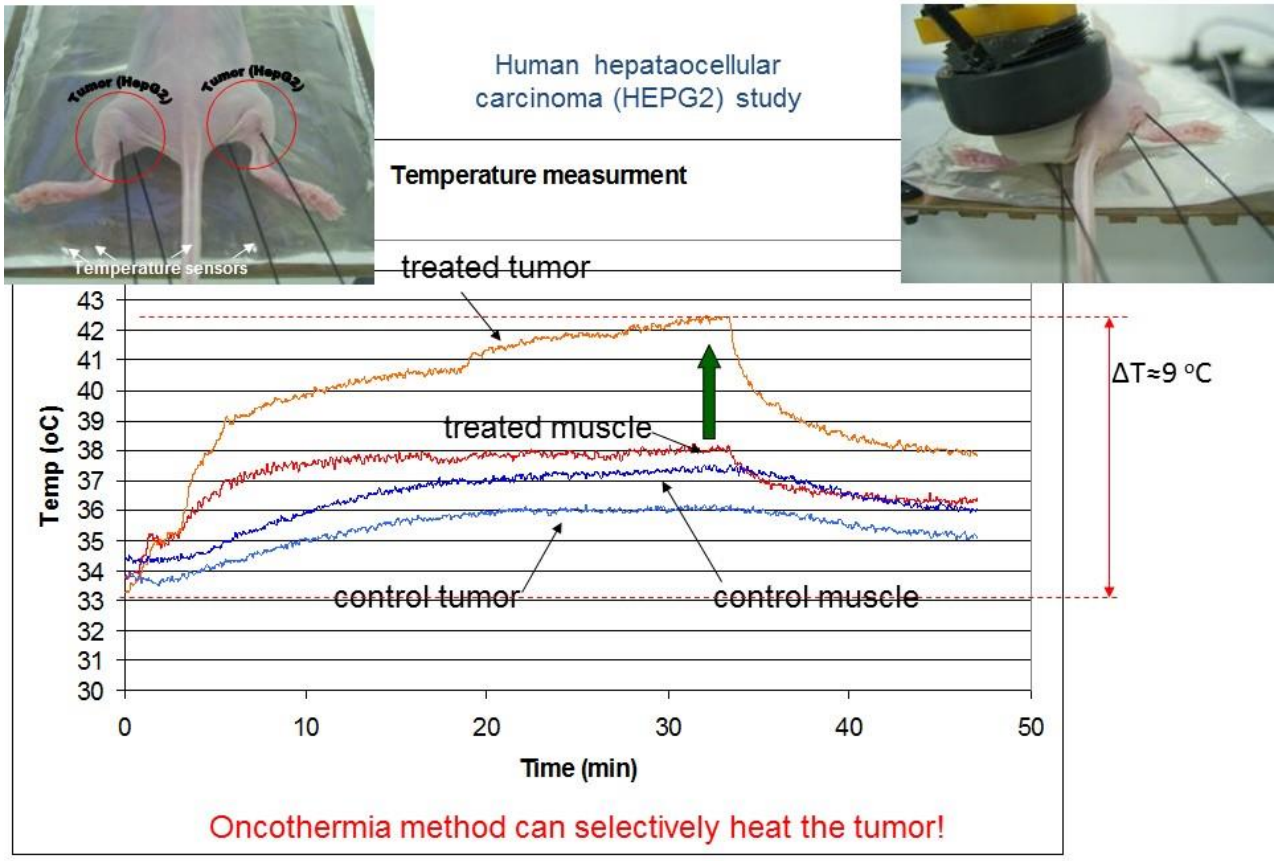
Highly proliferating tissue is slightly affected, but the healthy cells are intact

Malignant tissue is selectively treated, the malignance is destroyed, the healthy cells are intact



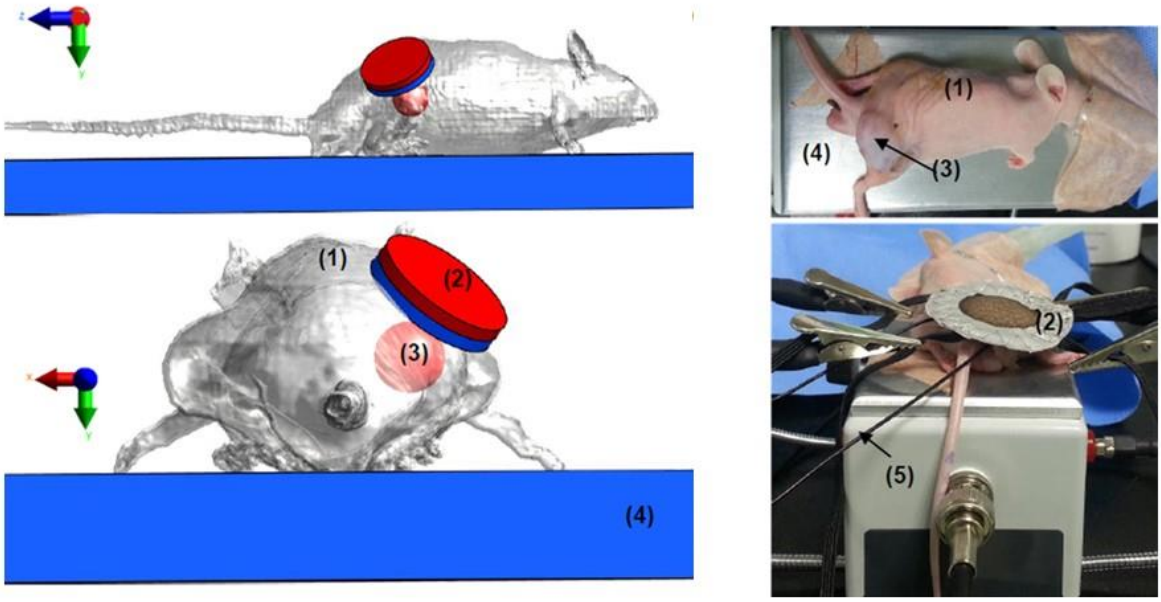
Brunner G, Klinik Hornheide, Munster Univ., Germany, Hyperthermia Symposium, Cologne, 2006

Selective macroscopic energy deposition



Temperature mapping

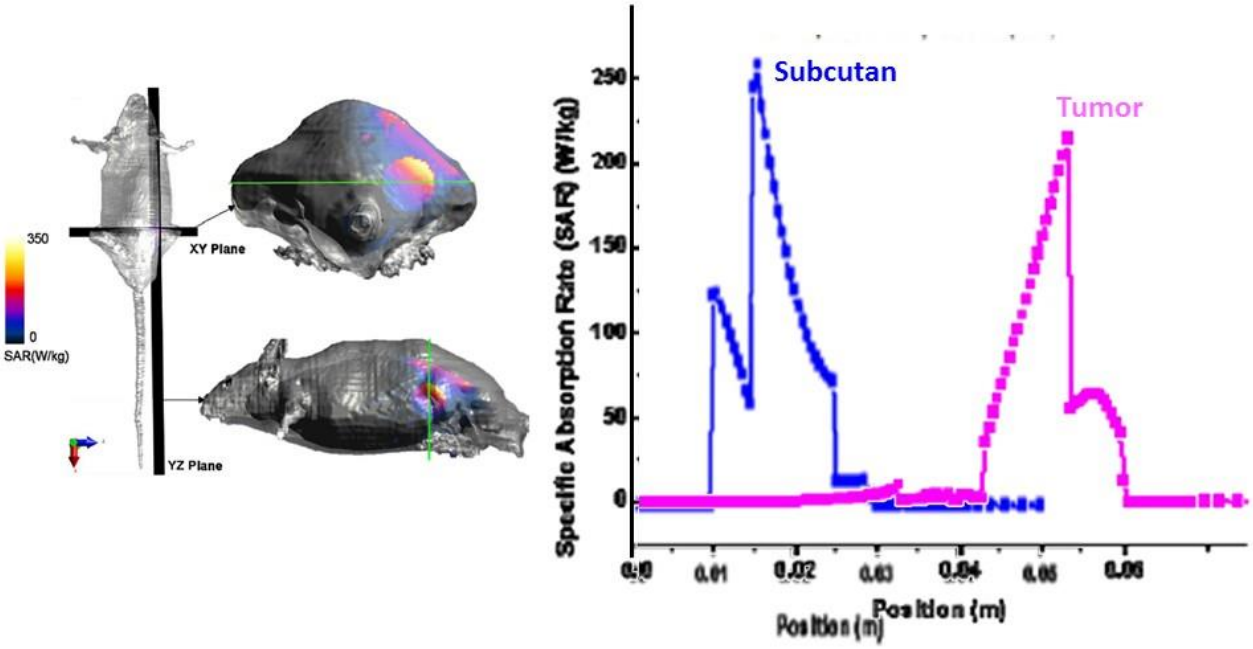
Jung Kyung Kim, Bibin Prasad, Suzy Kim; (2017) **Temperature mapping and thermal dose calculation in combined radiation therapy and 13.56 MHz radiofrequency hyperthermia for tumor treatment,** Proc. of SPIE Vol. 10047 1004718-1; Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXVI, edited by David H. Kessel, Tayyaba Hasan, Proc. of SPIE Vol. 10047, 1004718 © 2017 SPIE · CCC code: 1605-7422/17/$18 · doi: 10.1117/12.2253163



(1) Mouse (2) RF electrode (3) Tumor (4) Constant temperature bed (5) Fiber Optic Sensor

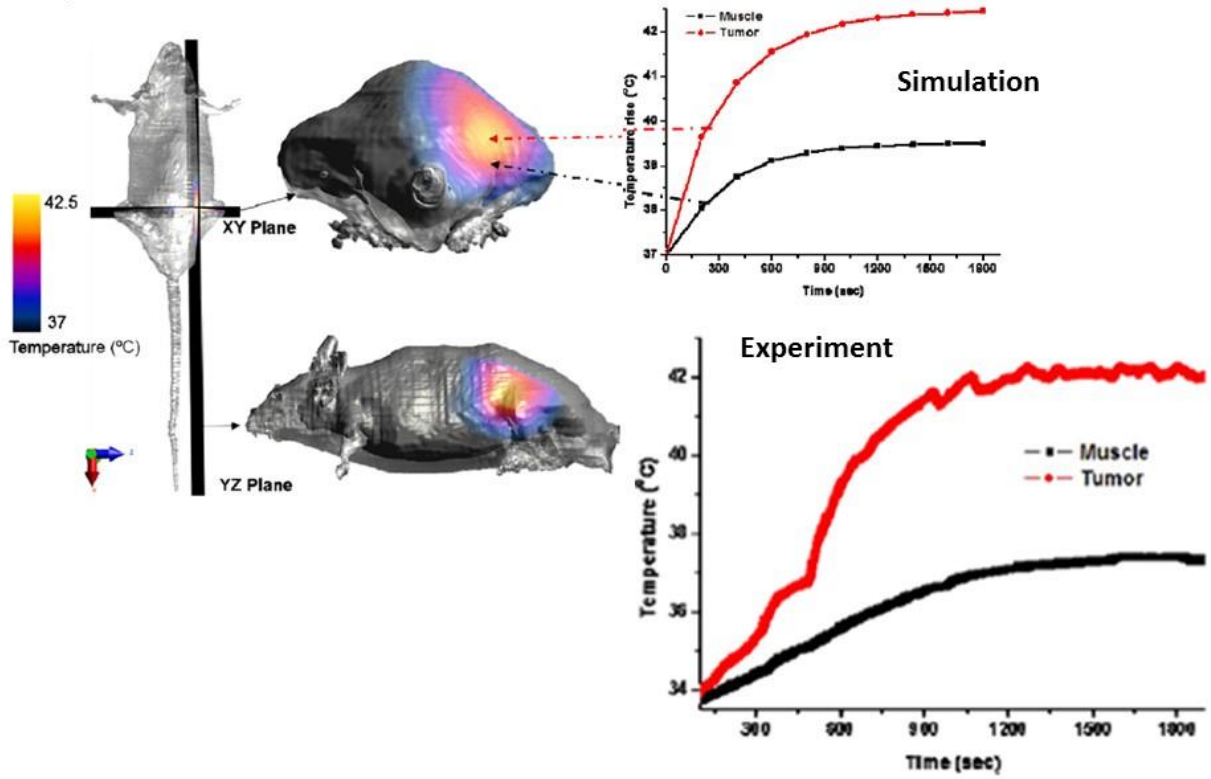
Temperature mapping

Jung Kyung Kim, Bibin Prasad, Suzy Kim; (2017) **Temperature mapping and thermal dose calculation in combined radiation therapy and 13.56 MHz radiofrequency hyperthermia for tumor treatment,** Proc. of SPIE Vol. 10047 1004718-1; Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXVI, edited by David H. Kessel, Tayyaba Hasan, Proc. of SPIE Vol. 10047, 1004718 © 2017 SPIE · CCC code: 1605-7422/17/$18 · doi: 10.1117/12.2253163



Temperature mapping

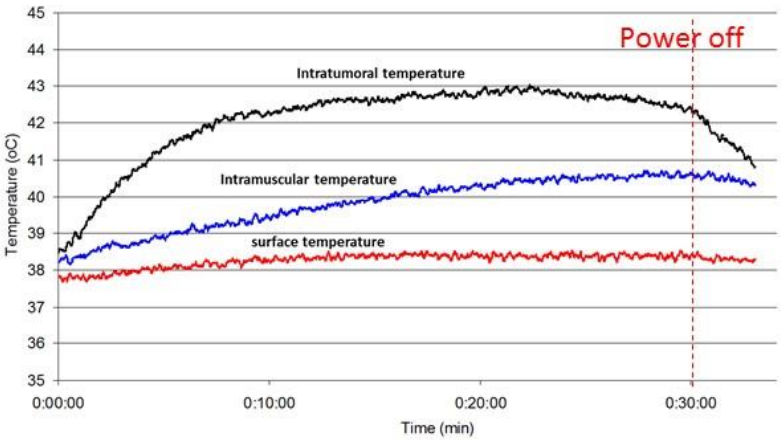
Jung Kyung Kim, Bibin Prasad, Suzy Kim; (2017) **Temperature mapping and thermal dose calculation in combined radiation therapy and 13.56 MHz radiofrequency hyperthermia for tumor treatment,** Proc. of SPIE Vol. 10047 1004718-1; Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy XXVI, edited by David H. Kessel, Tayyaba Hasan, Proc. of SPIE Vol. 10047, 1004718 © 2017 SPIE · CCC code: 1605-7422/17/$18 · doi: 10.1117/12.2253163



Tumor temperature in bull-terrier

Intratumoral temperature measurement using invasive fluoroptic temperature measurement sensors, 12 years old bullterrier, recidival epithelial cell carcinoma in the lower neck region, Oncothermia (10W)

Tottori University
Japan



Cases not possible with conventional heating

Investigator: Prof.Dr. A. Herzog,

Institute: Fachklinik Dr.Herzog, Nidda, (Bad Salzhausen), Germany;

Patient: 38 y, female

Diagnosis: Non-Hodgkin lymphoma, **Stage:** WHO IV,

Treatment: Oncothermia + Bendamustin,

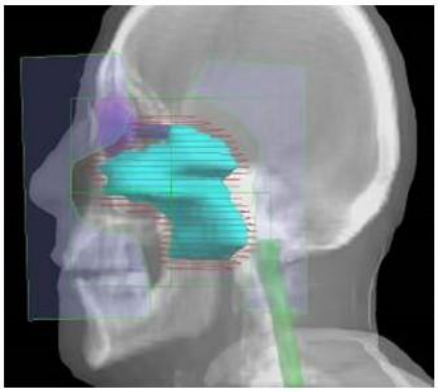
Results: Complete Remission, (CR),

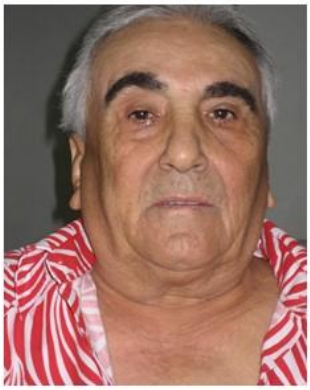
Cases not possible with conventional heating

Investigator: Prof.Dr.H. Renner,
Department: Klinikum Nord, Nürnberg, Germany,
Patient: REN1. 67 y, male.
Diagnosis: Sinus sphenoidalis, inoperable.
Histology: Squamous epithelium carcinoma.
Development: Complete right opthalmoplegy

Therapy: Radiotherapy, 54 Gy, fractional,
Oncothermia: 6 sessions, after radiotherapy

Result: complete remove of opthalmoplegy



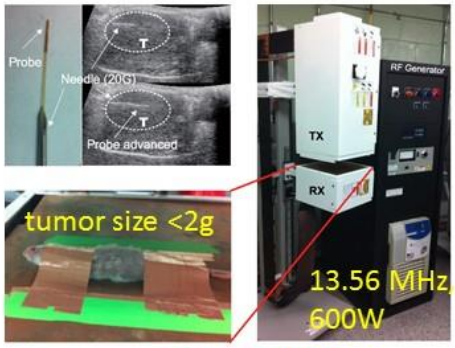


Outline

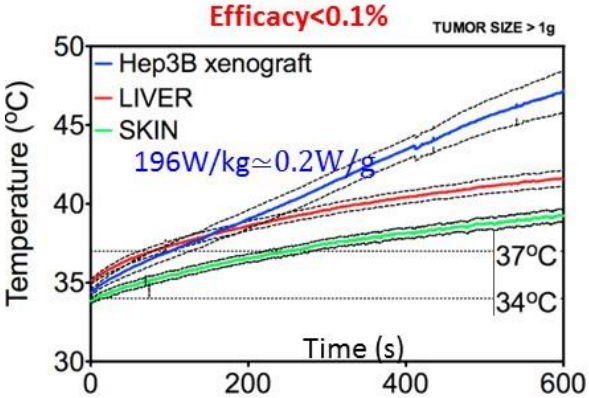
- ❑ Introduction
- ❑ Temperature
- ❑ Selection
- ❑ Dose

Experiments (energy cannot be the dose)

ThermMed, (LLC, Erie, PA, USA) [Kanzius generator]



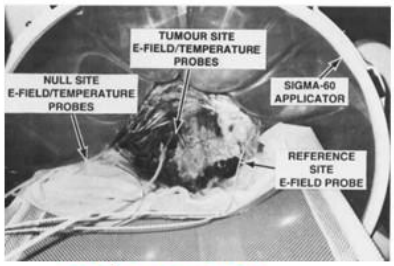
Efficacy<0.1%



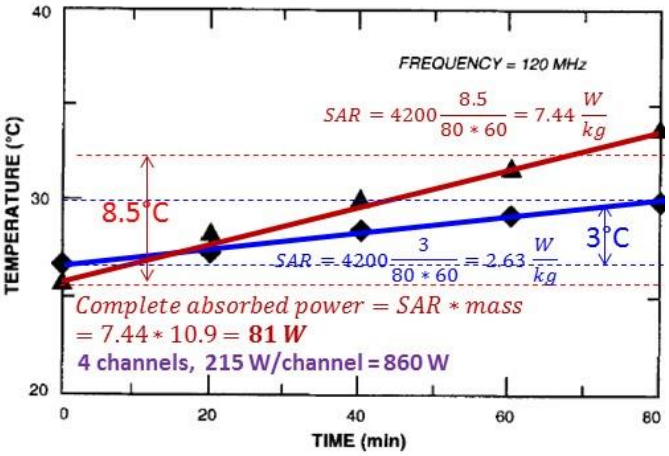
Raoof M, et al; (2013) Tumor Selective Hyperthermia Induced by Short-Wave Capacitively-Coupled RF Electric-Fields; Plos One 8:e68506 pp.9.

BSD Medical Phase-array calibration

Beef phantom, weight is **10.9 kg**

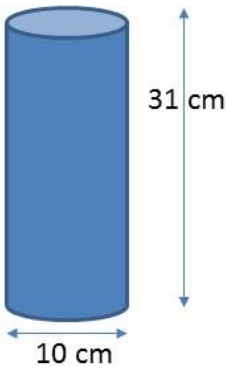


Efficacy <10%



Fenn AJ, King GA, Adaptive radiofrequency hyperthermia-phased array system for improved cancer therapy: phantom target measurements, Int. J. Hyperthermia, 10:189-208 (1994)

Energy is appropriate for the dose



Nagy G. Meggyeshazi N. Szasz O (2013) Deep temperature measurements in oncothermia processes. Hindawi ;Conference Papers in Medicine. Volume 2013. Article ID 685264

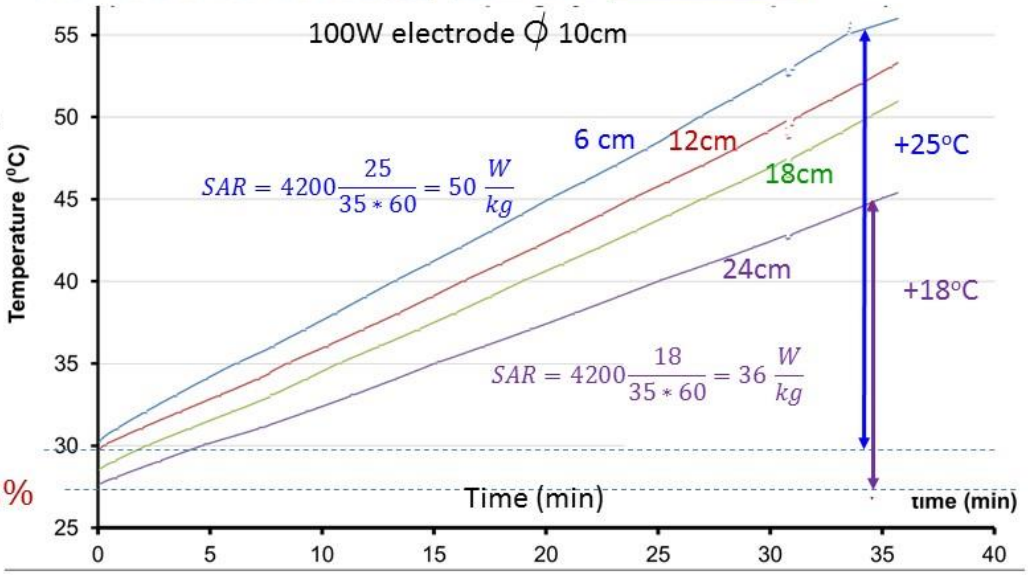
$V = 25 * 3.14 * 31$
$= 2434\ cm^3$

Mass $= 2.3\ kg$

Mean-energy $=$
$\mathbf{2.4\ kg * 40\frac{W}{kg} =}$
$\mathbf{= 92W}$

Reflected power is a couple of W.

Efficacy = 92%



Thank you for your attention.
Dr. Minnaar will continue with the clinical results.

Oncothermia in clinical practice

Carrie Minnaar, PhD candidate,
Dep. Radiation Sciences, University of the Witwatersrand

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-4.pdf

ESHO'2017

Oncothermia

in clinical practice

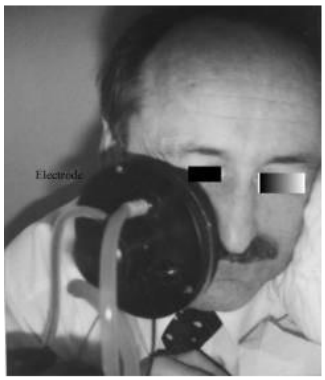
Carrie Minnaar, PhD candidate,
Dep. Radiation Sciences, University of the Witwatersrand

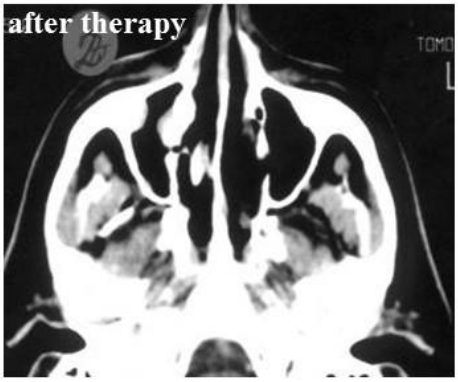
Outline

- ❑ **Case reports**
- ❑ **Studies**
- ❑ **Publications**

Adeno carcinoma metastases from colon

Investigator: Prof.D.Gronemeyer & Dr.H.Sahinbas
Department: Department of Radiology and Microtherapy, University of Witten-Herdecke, Bochum, Germany
Patient: 46 y, male
Diagnosis: Primary: Colon adenocacinoma, metastasised to the sinus infiltration in rectus internus and rectus internus infeior; inoperable
Therapies:
- **Chemotherapy:** Local chemoperfusion (May, 2000)
- **Oncothermia:** concomintantly (May,2005 – Jul 2000) (12x)



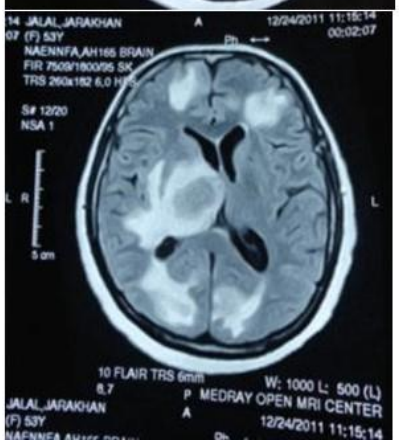


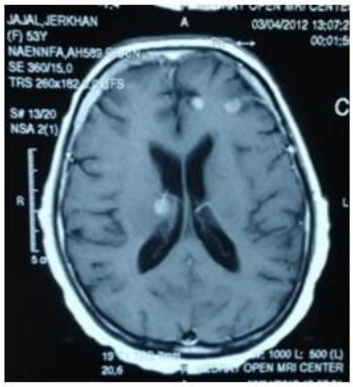
Result: Complete remission (CR)
Follow-up: tumor-free; last check-up Jul.2002, censored

Brain metastasis from breast cancer

Investigator: Dr. Marwan Akasheh; **Institute:** Dar Alshefa' Tumors Treatment Center, Amman, Jordan, **Patient**: female 53 y.

Before oncothermia

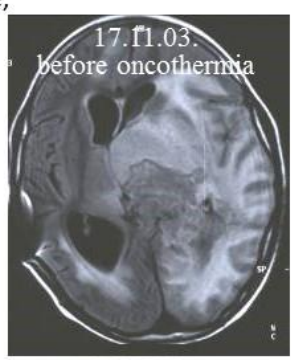


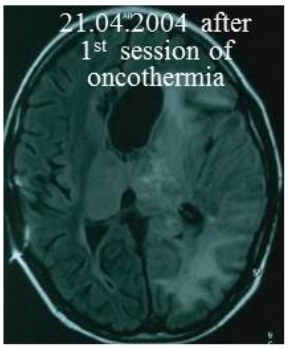


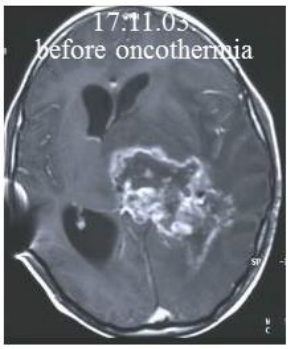
After oncothermia

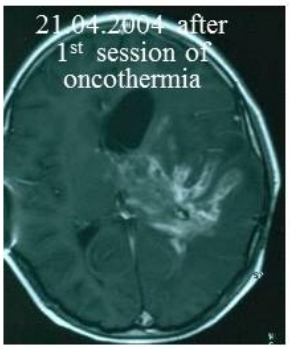
Cases not possible with conventional heating

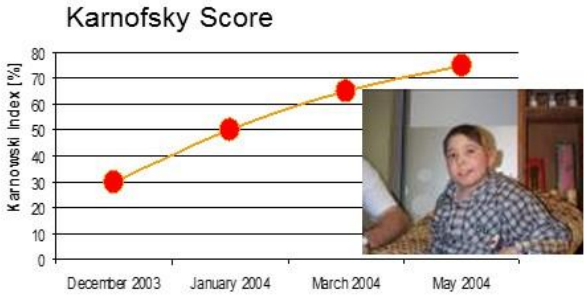
Investigator: Prof. Dr. D. Gronemeyer & Dr. H. Sahinbas
Institute of Microtherapy, University Witten Herdecke, Germany
Patient K.K. 10 y, (boy)
Diagnosis: progressive ependymoma, bithalamic
Stage: WHO III,
Treatments: conventional
1st line surgery,
2nd line chemotherapy,
3rd line radiotherapy and chemotherapy
Failed all, Karnowfsky score down to 30%
4th line: oncothermia monotherapy, 60 min, 2-3/week,







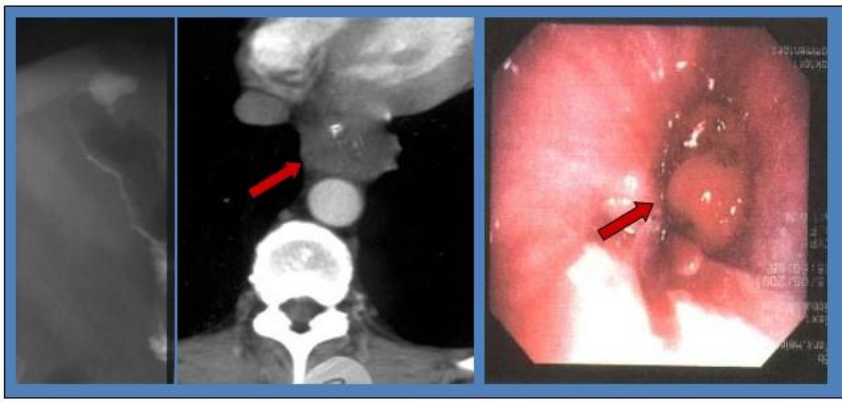


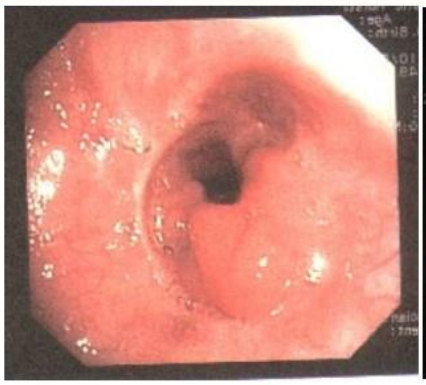


Cases not possible with conventional heating

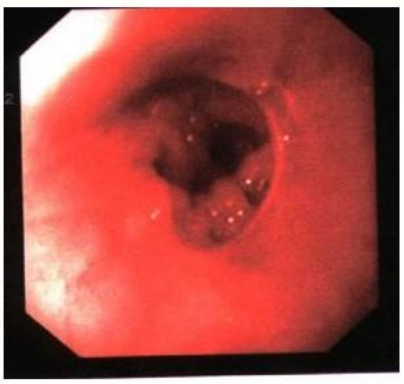
Investigator: Prof.D.Gronemeyer & Dr.H.Sahinbas
Department: Department of Radiology and Microtherapy, University of Witten-Herdecke, Bochum, Germany

Patient: M, 46 y, male
Diagnosis: Esophagus-Ca.
Therapies:
Surgery: +
Chemotherapy: Multiple CxT
Radiotherapy: (50 Gy) from
Relapse: Anastomose, Full block of food-passage in esophagus,
Oncothermia: monotherapy
Result: Complete remission (CR)
Free-food passage





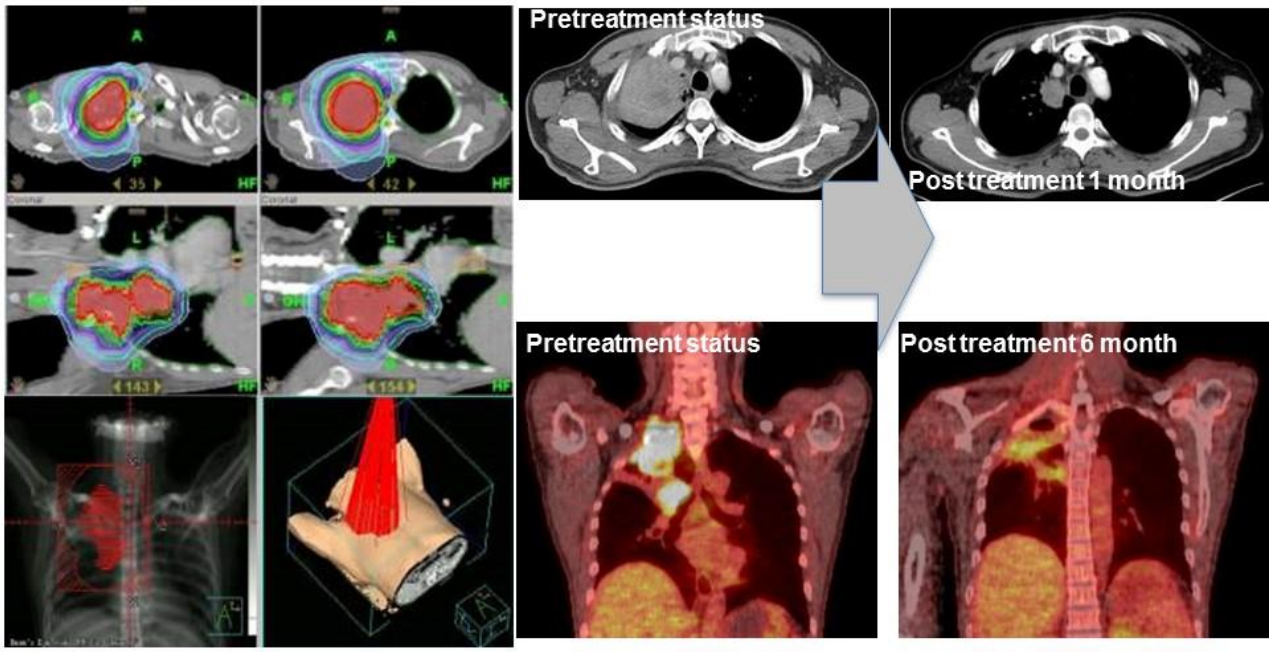
after 6x oncothermia



after 12x oncothermia

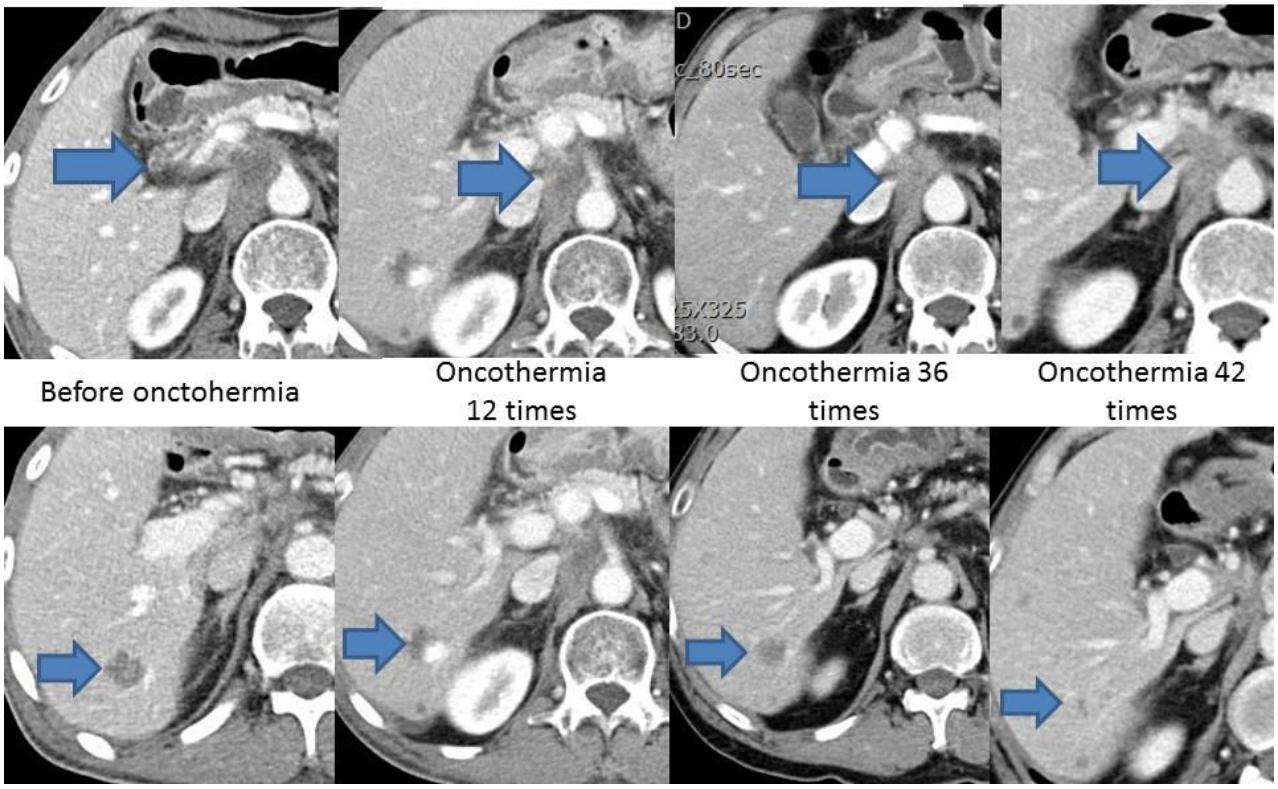
NSCLC Case

Investigator: Prof.Dr.Chang Geol Lee; **Institute:** Department of Radiation Oncology, Yonsei Cancer Center, Yonsei University Health System, Seoul, South Korea; **Presented** on KOSG'2013, Jeju
Patient: 51 years old, male patient; **Diagnosis:** NSCLC, RUL, AdenoCa, cT4N3M0; **T :** 6.5x3.7cm, right brachial plexus invasion; **N :** Both SCL, Lt. axillary LN; Referred for CCRT
Treatment: RT: 66 Gy/30 fractions; CTx: weekly paclitaxel/cisplatin; Oncothermia: 10 fractions/5 weeks



Pancreatic cancer and liver metastasis

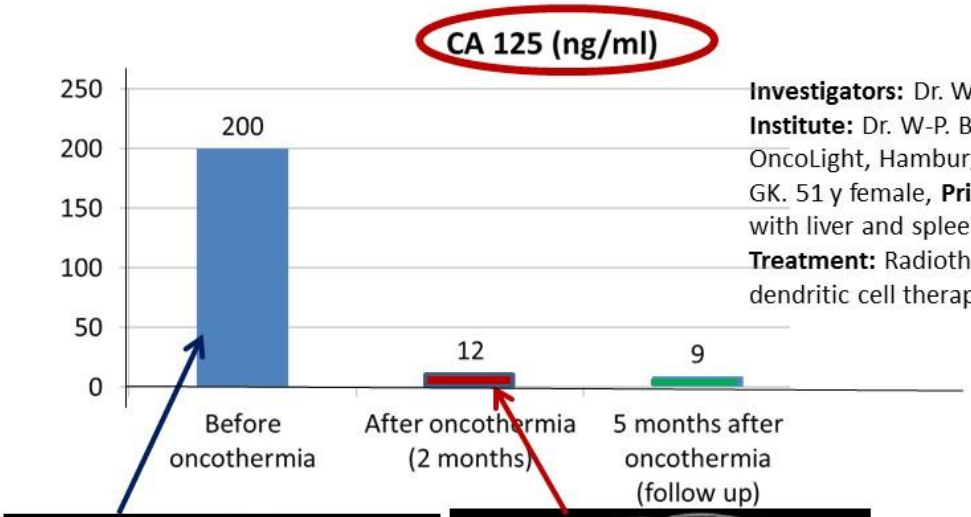
Investigator: Prof.Dr. Taesing Jeung; **Institute:** Department of Radiation Oncology, Kosin University,
Patient: male 58 y;, **Therapy:** Oncothermia **monotherapy**, 42 times



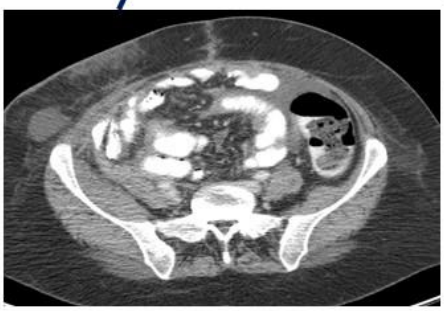
Cervix carcinoma

Investigator: Prof. H. Renner
Department: Klinikum Nord, Nürnberg, Germany
Patient: H.K, 61 y, female; Cervix carcinoma; cT4 cN0 M0 G3
Histology: Squamous cell carcinoma;
Therapy: bimodality therapy, Radiotherapy: 50.4 Gy; (5x1.8 Gy/weeks);
oncothermia: 6 sessions.
Control: 3 months later hysterectomy (Wertheim).
Result: pathologically complete remission ypT0ypN0

Ovary carcinoma with liver and spleen metastases

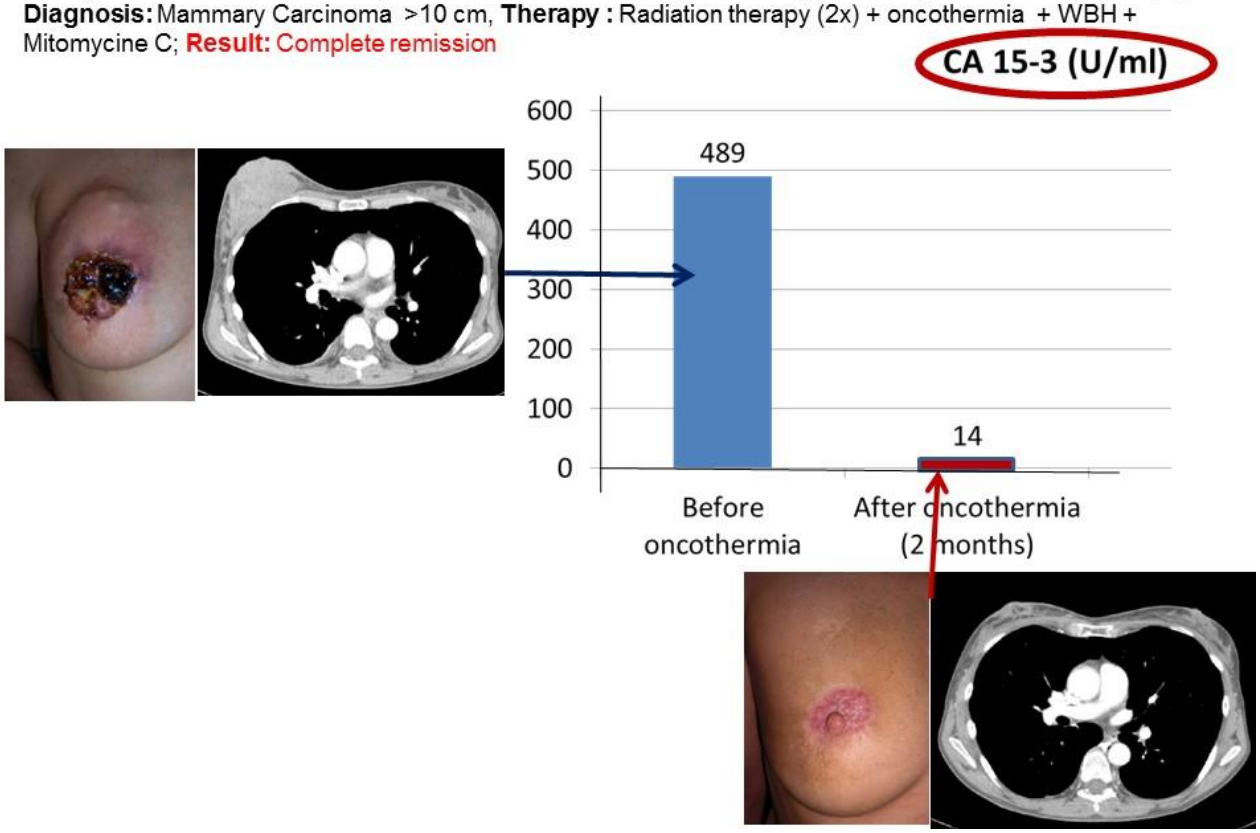


Investigators: Dr. W-P. Brockmann
Institute: Dr. W-P. Brockmann Institute OncoLight, Hamburg, Germany. **Patient:** GK. 51 y female, **Primer-tumor:** Ovarial-Ca with liver and spleen metastases,
Treatment: Radiotherapy 2x/day + local dendritic cell therapy + oncothermia



Metastsic mammary cacinoma

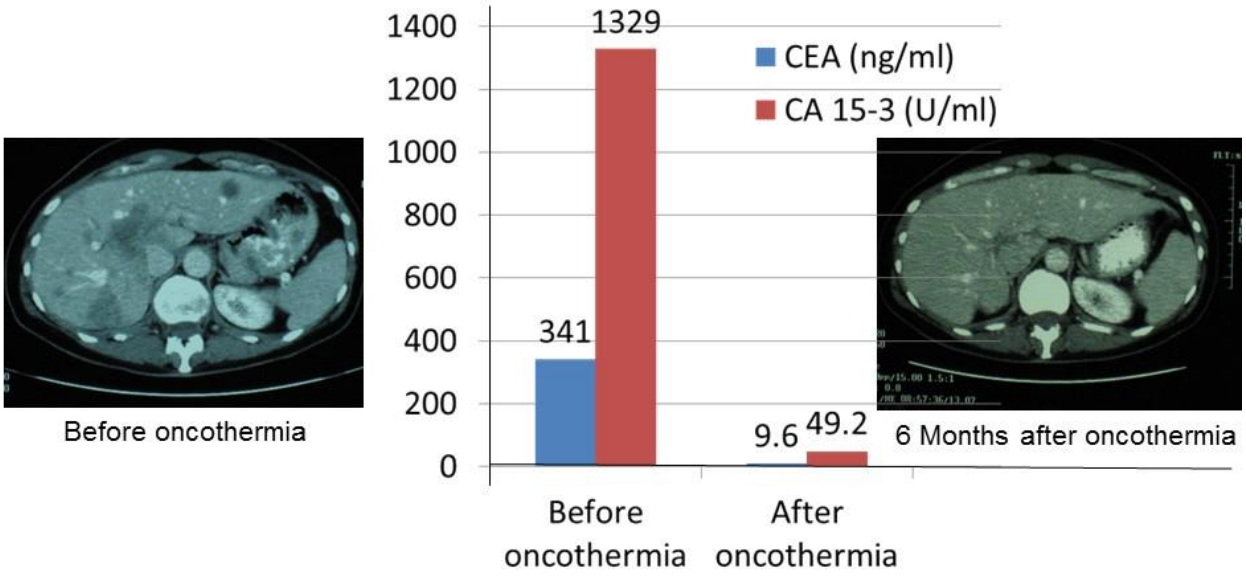
Investigator: Dr. W-P. Brockmann, **Institute:** Institute OncoLight Hamburg, Germany; **Patient:** 51 y, (M.S., ♀) **Diagnosis:** Mammary Carcinoma >10 cm, **Therapy :** Radiation therapy (2x) + oncothermia + WBH + Mitomycine C; **Result:** Complete remission



Metastatic mammary carcinoma (Liver)

Investigator: Prof.Dr.A.Herzog; **Institute:** Fachklinik Dr.Herzog, Nidda, (Bad Salzhausen), Germany; **Patient:** 43 y, female, (M.M.); **Diagnosis:** Mammary carcinoma, (fieve years earlier than the hepatic metastasis was diagnosed). **Symptoms:** liver pain, weakness. GOT 202 U/l, GPT 255 U/l, γ-GT 508 U/l; **Prior therapy:** adjuvant FEC 5 years earlier (HR negative, HER-2-pos). **Treatment:** reduced dose intensity of vinorelbine + Herceptin, accompanied by several sessions of oncothermia of the liver,

Result: complete remission (CR); absence of pain, transaminases within normal limits



Outline

- ❑ Case reports
- ❑ Studies
- ❑ Publications

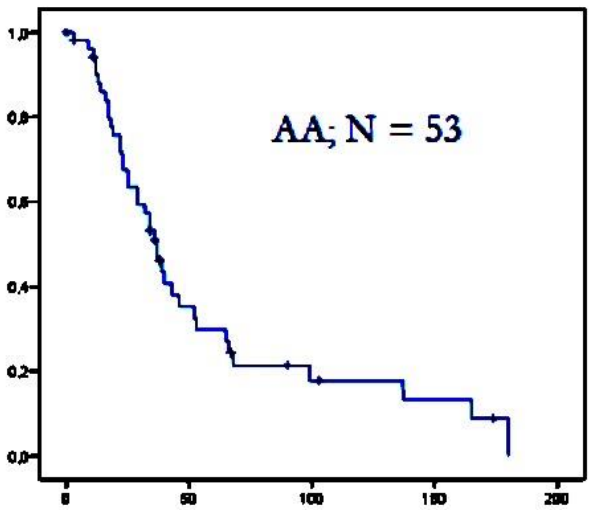
Glioma efficacy study (Phase II), (n=53+126) & (n=9+27)

Institute: Biomed Clinic, **Bad Bergzabern, Germany,**

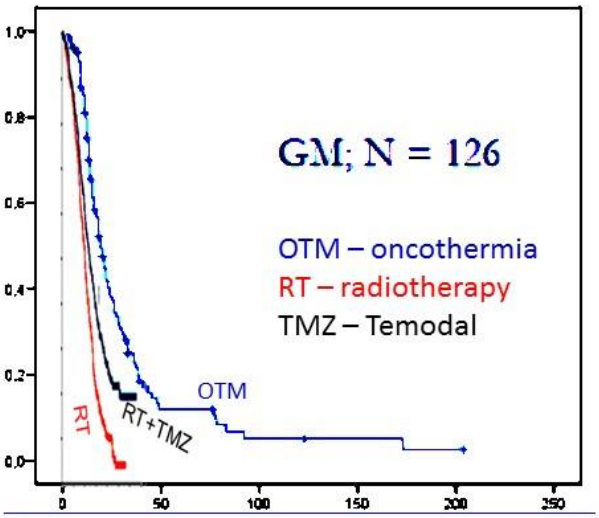
Investigator: Dr. Dr. D.Hager

Published: ASCO'2008

Astrocytoma median 103 m (n=53)



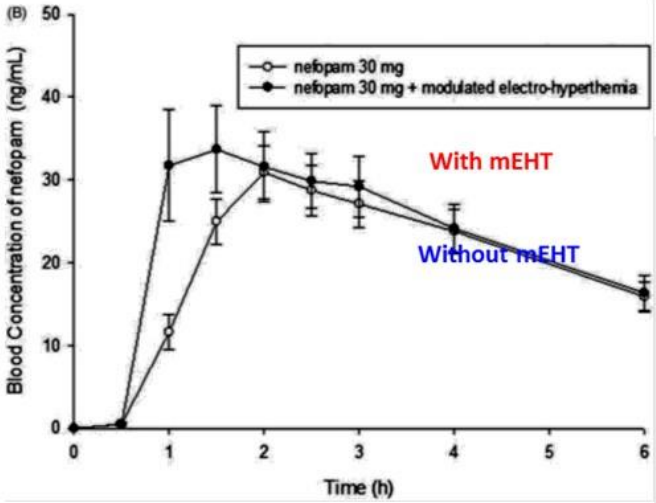
Glioblastoma median 16 m (n=126)

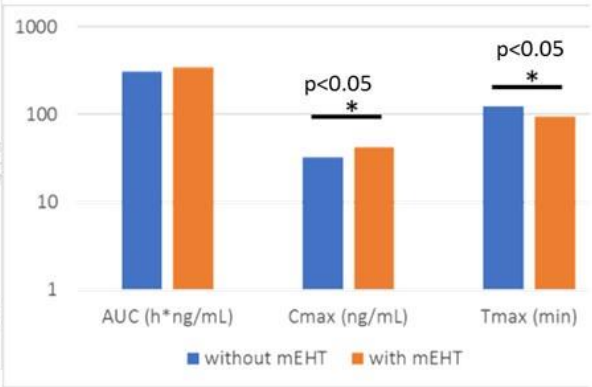


N Engl J Med 2005;352:987-96.

Randomized study with Nefopam pharmacokinetics

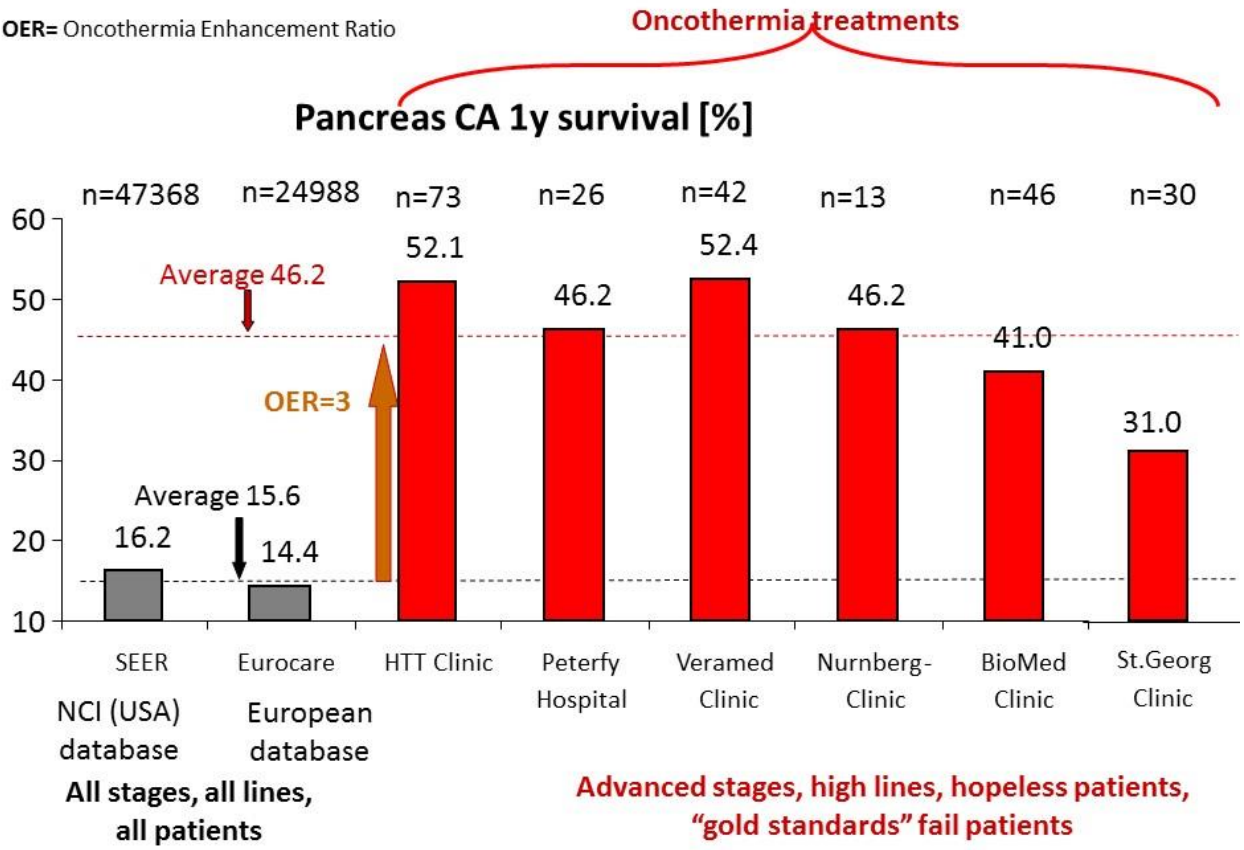
Lee SY, Kim M-G (2015) The effect of modulated electro-hyperthermia on the pharmacokinetic properties of nefopam in healthy volunteers: A randomised, single-dose, crossover open-label study; Int J Hyp, 2015;31(8):869





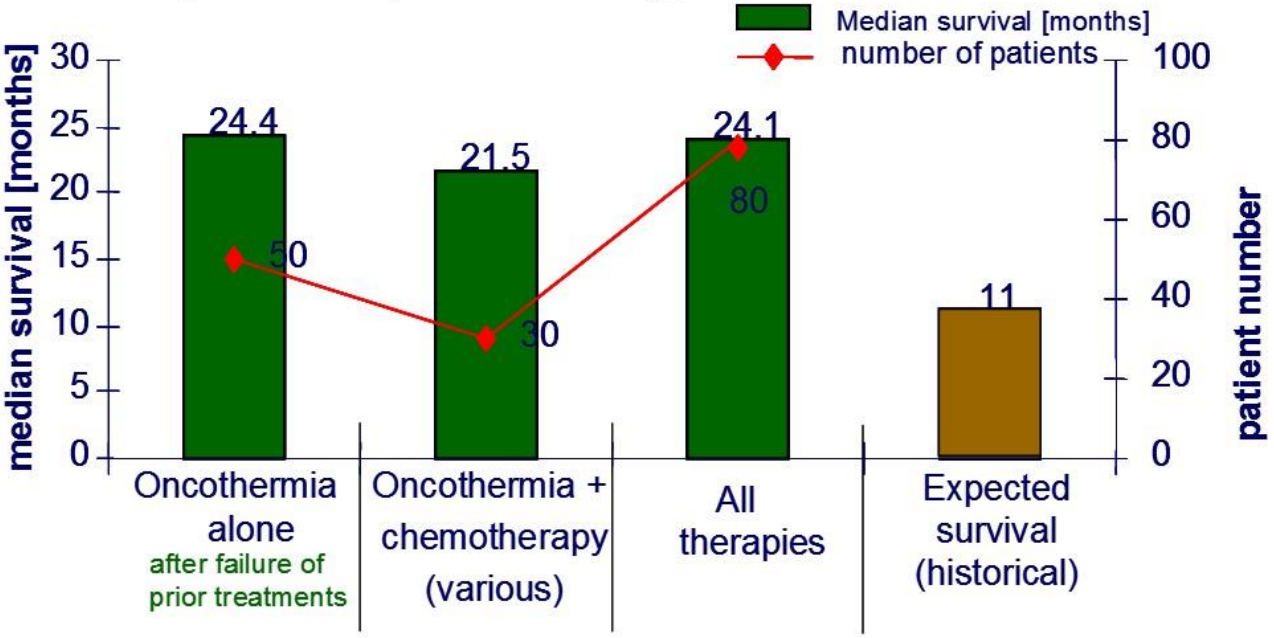
Comparison of pancreas studies

OER= Oncothermia Enhancement Ratio

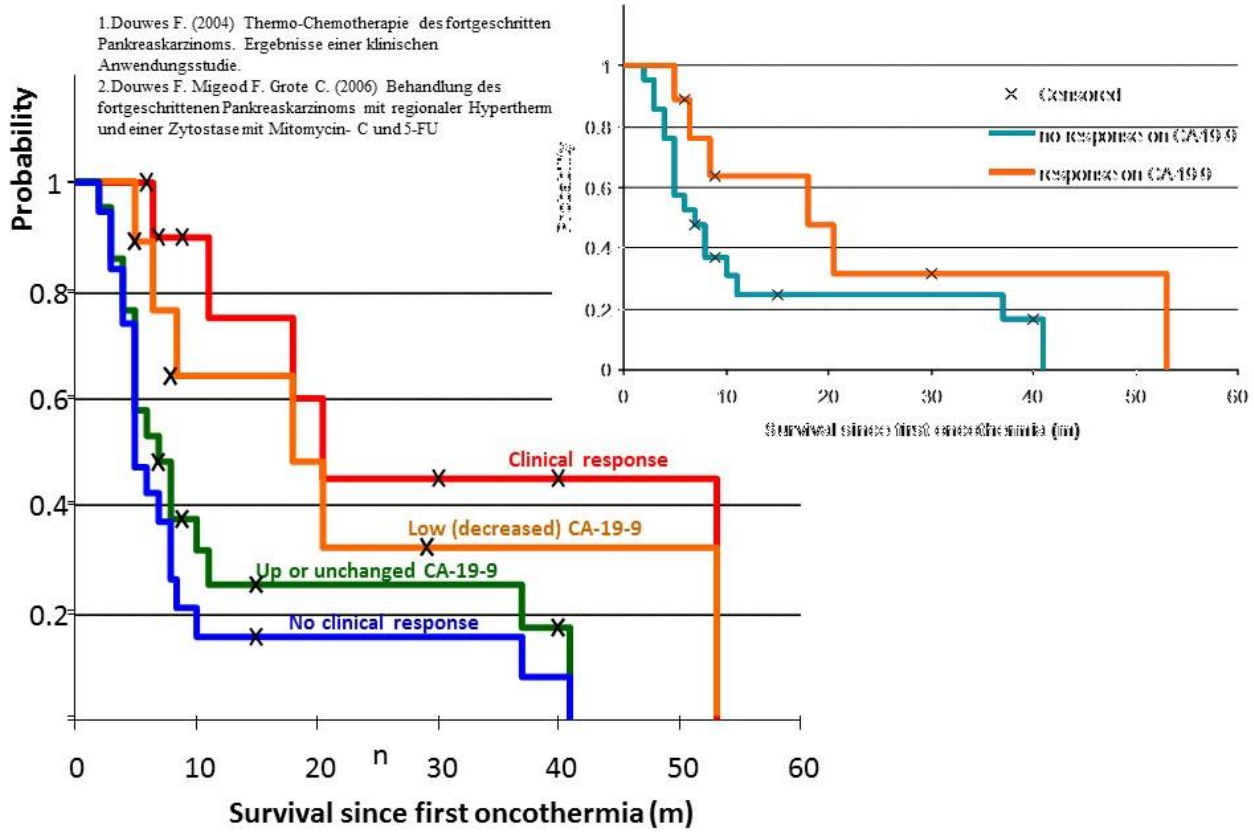


Liver metastases from colorectal cancer (Phase II study) (n=80)

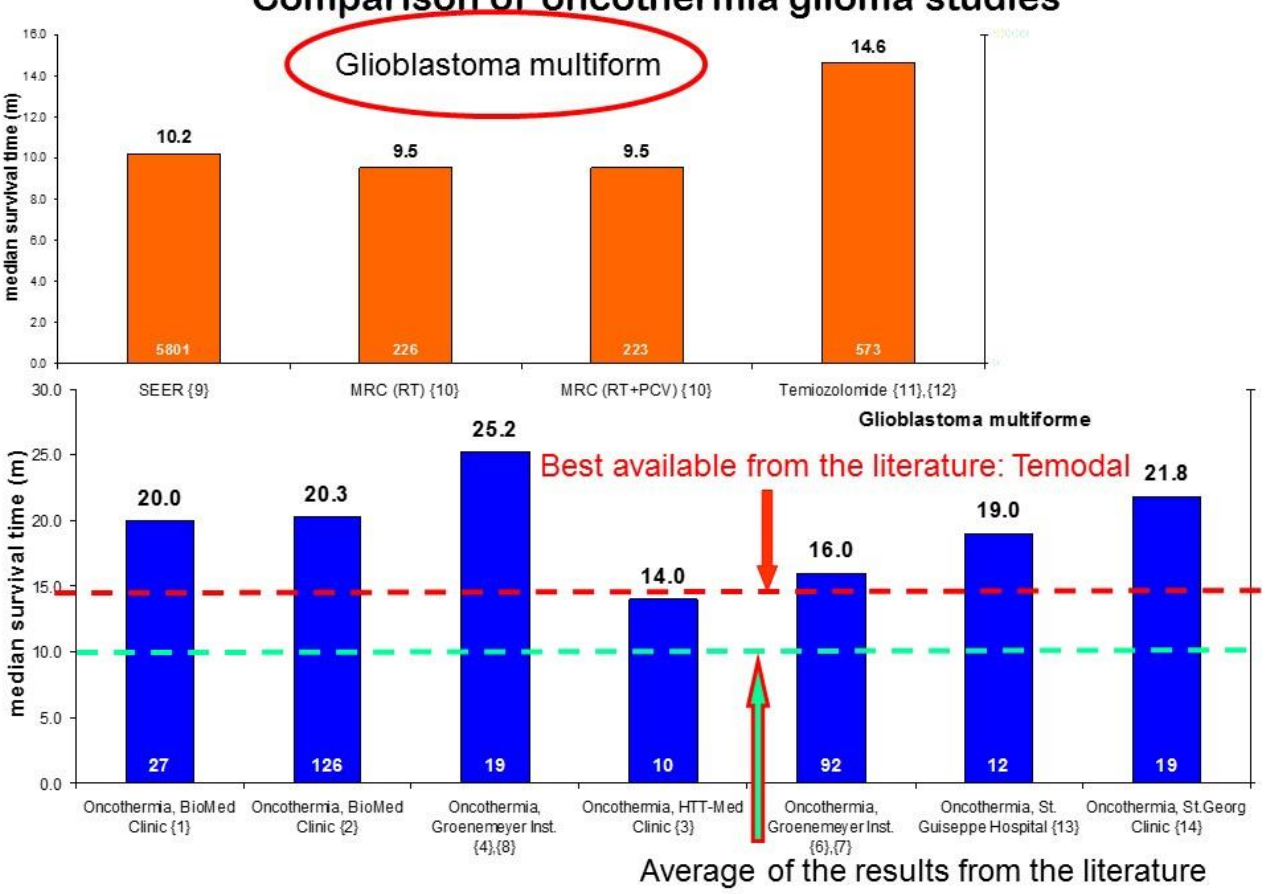
Investigator: Dr.D.Hager
Department: Biomed Clinic, Bad Bergzabern, Germany
Published: Hager ED, et al: Deep hyperthermia with radiofrequencies in patients with liver metastases from colorectal cancer. Anticancer Research 19(4C):3403-3408 (1999)
Histology: Adeno-carcinoma, Prior liver resection: 16%, All patients had metastases.
Prior chemotherapy unsuccessful, 37.5% of patients had palliative chemotherapy concomitantly with oncothermia, others had monotherapy (n=80)



Study of tumor-marker CA-19-9 for pancreas treatment



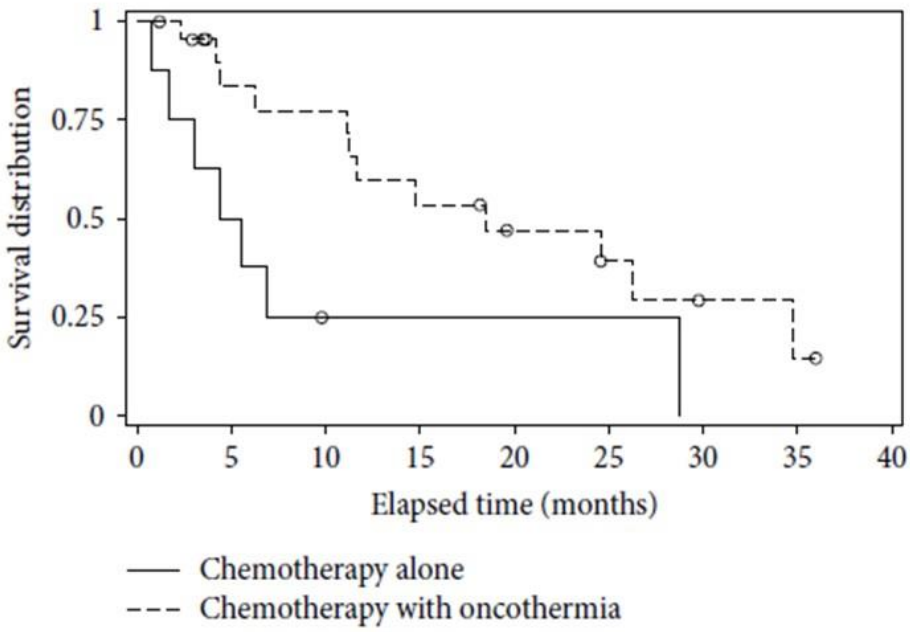
Comparison of oncothermia glioma studies



SCLC double arm prospective study

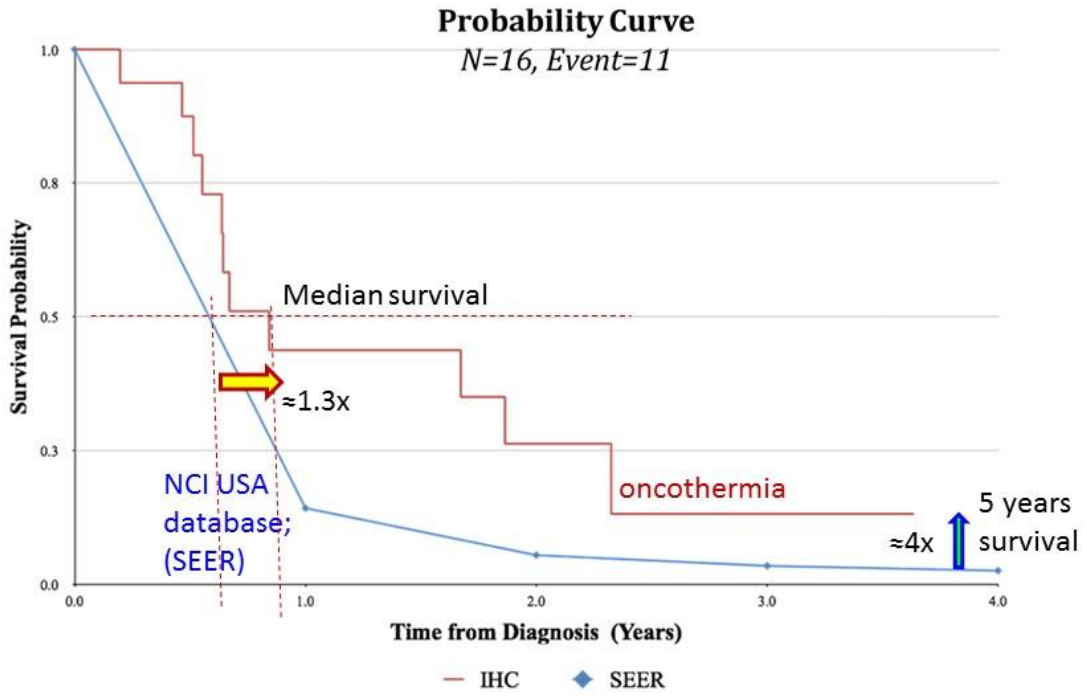
Investigator: Professor DY Lee, Kagnam Severance Hospital, Yonsei University, Seoul, S.Korea

The double arm study was applied with (n=23) and withou (n=8) oncothermia; complementary to chemotherapy of SCLC. Chemotherapy was in first line: Irinotecan (60 mg/m2), and Cisplatin (60 mg/m^2) three times. When the progression of tumor or metastases were detected the chemotherapy wa changed to Etoposide, (110 mg/m^2) and Cisplatin (70 mg/m in second line. Oncothermia wa performed from the first chemotherapy treatment perio up to 150 Watt, 1,490.5 kJ energy by 60 minutes, every second day, with rise in temperature to 38.5°C–42.5°C. In this study we used electrode 30 cm diameter applied for thorax, at least 12 sessions wer in 1 cycle.



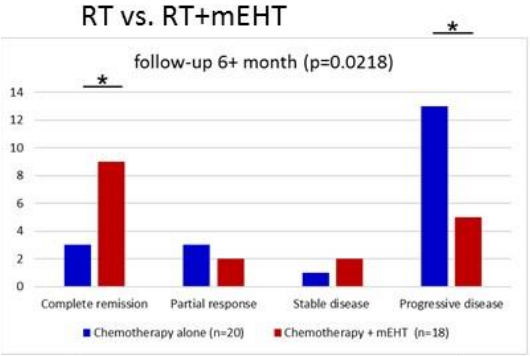
Non-resectable pancreatic adenocarcinoma

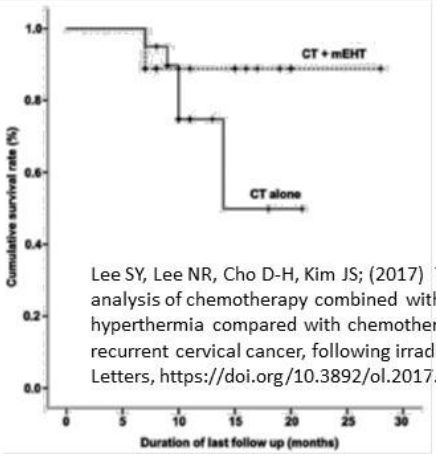
Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



Gynecological treatments

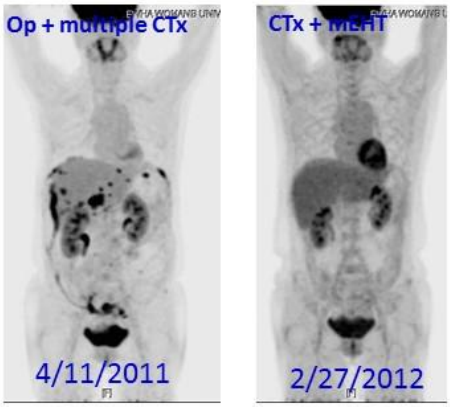
Recurrent cervix trial
Double arm, randomized,
RT vs. RT+mEHT





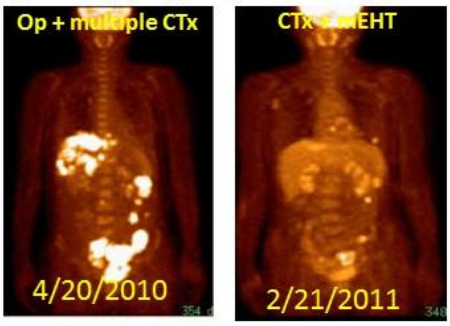
Lee SY, Lee NR, Cho D-H, Kim JS; (2017) Treatment outcome analysis of chemotherapy combined with modulated electro-hyperthermia compared with chemotherapy alone for recurrent cervical cancer, following irradiation, Oncology Letters, https://doi.org/10.3892/ol.2017.6117

Recurrent refractive progressive ovarian cancer. (55y).



Investigator:
YH Kim; Ewha Womans University Mokdong Hospital, Seoul, Korea

Invasive adenocarcinoma of ovary (grade 2) (33 y). Vaginal bleeding; G5P2



Ongoing phase III randomised cervix trial (interim results)

Investigators: Minnaar CA; Kotzen JA; Baeyens A.
Charlotte Maxeke Johannesburg Academic Hospital, S.Afrika.
Aim: to enrol 236 participants with FIGO stage IIB (initial distal parametrium involvement) to IIIB cervical cancer

Radiation: 25x2Gy external and 3x8Gy brachytherapy

Chemotherapy: 3x 80mg/m2 Cisplatin

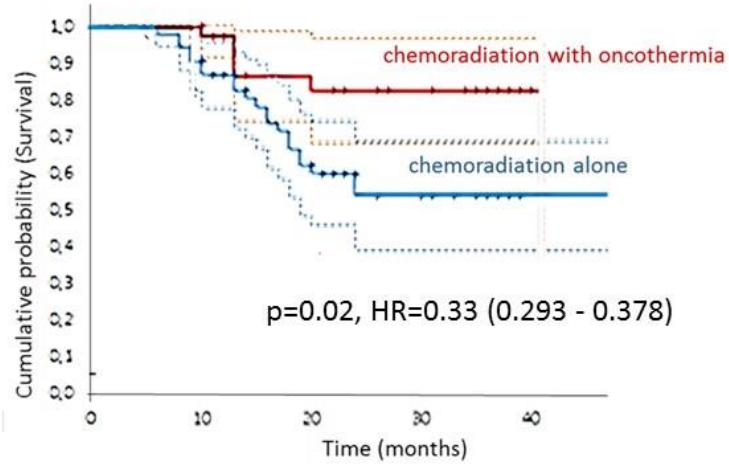
mEHT (oncothermia): 2x 55min/week (4 weeks)

Local control

Until now:
6 month Local Disease Control
70 patients completed 6 month PET scan.

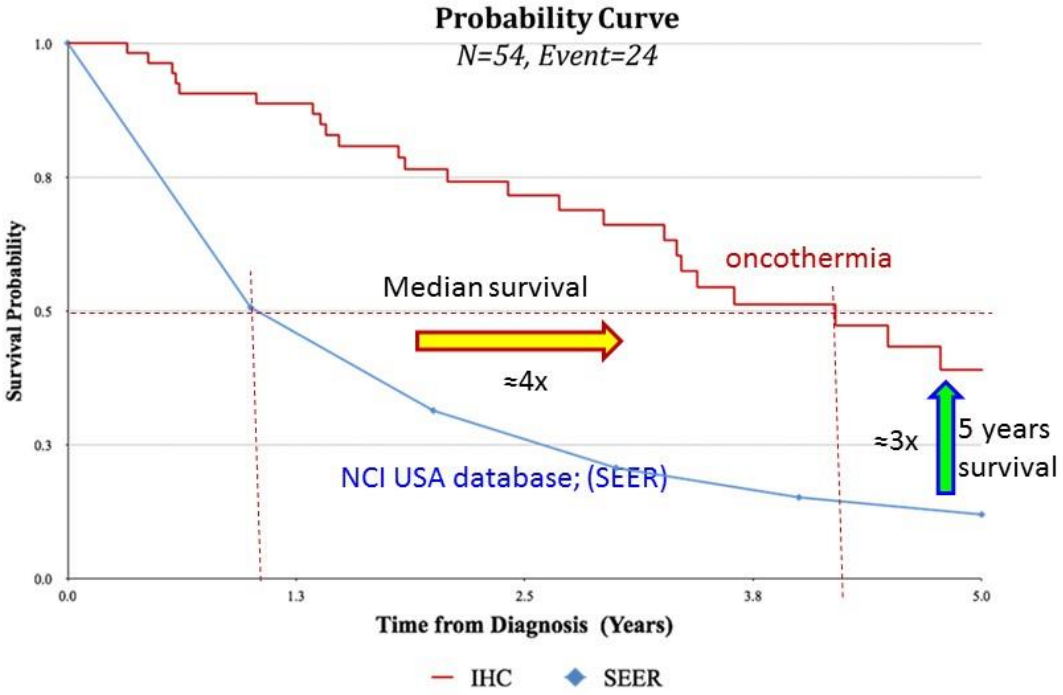
	Chemoradiotherapy with mEHT		Chemoradiotherapy alone	
	Total n	26 %	Total n	44 %
1. Complete response	13	50%	17	39%
2. Partial response	10	38%	10	23%
3. No change	2	8%	2	5%
4. Local progression	0	0%	7	16%
5. Death d/t disease	1	4%	8	18%

Survival time control



Metastatic colorectal cancer

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015

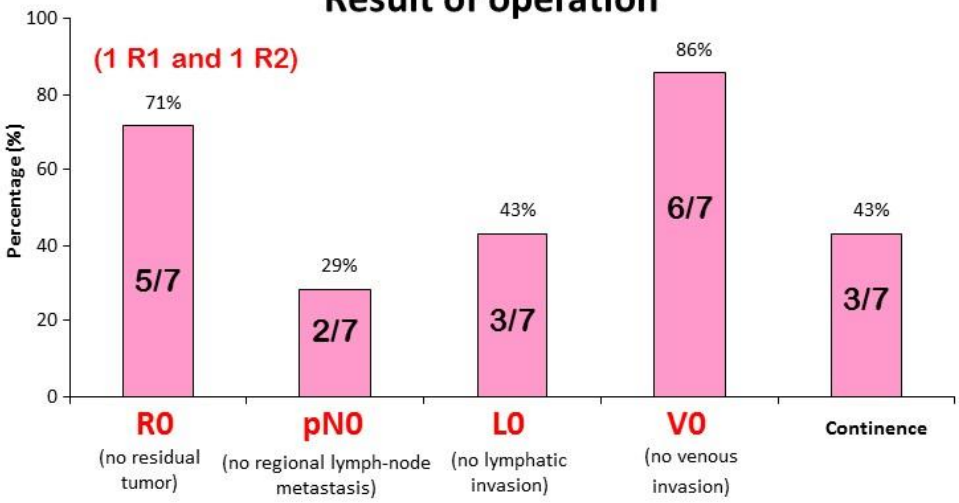


Neoadjuvant trimodal therapy of inoperable rectum CA

Investigator: Prof.H.Renner,
Institute: Klinikum Nord, Nürnberg, Germany
Published: Renner H: Simultane RadioThermoTherapie bzw.RadioChemoThermoTherapie; Hyperthermia Symposium, Cologne, Germany October 2003
Primer-tumor: Rectum carcinoma, inoperable (**R2**)
Number of patients: n=7
Radiotherapy: 45+5 Gy, (fractional)
Chemotherapy: 5-FU/Mitomicine-C (2x)
Oncothermia: 60 min, diam.30 cm (8-10x)
Result: patients were eligible for operation

After oncothermia patients became operable!

Result of operation



Brain safety study (prospective single-arm Phase I/II, (n=24))

Institute: Neurology Clinic,
Regensburg University, Germany,
Investigators:
Prof. Dr. U. Bogdahn & PD.Dr. P.Hau

Group	Number of Patients	Chemotherapy (single close of a 6 week cycle)	Oncothermia (4 of 6 week cycle)
1	3 (6)	ACNU 90 mg/m2	Oncothermia 2x /week
2	3 (6)	ACNU 90 mg/m2	Oncothermia 3x /week
3	3 (6)	ACNU 90 mg/m2	Oncothermia 4x /week
4	3 (6)	ACNU 90 mg/m2	Oncothermia 5x /week

Advanced glioma (3rd & 4th line)
Dose excalation study (Phase I)
Number of patients: 24

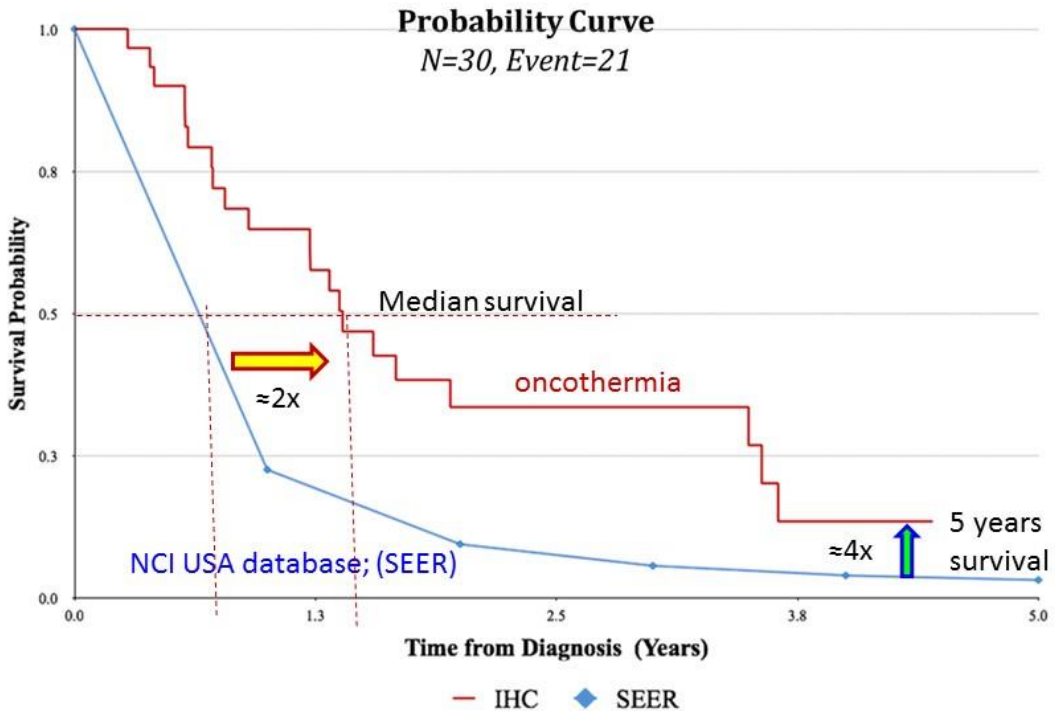
No additional side effect of oncothermia was observed. (Side effects were not more than with Nimustine alone!)

Publications:

1. Wismeth C et al (2006) Loco-regional hyperthermia in patients with progressive astrocytoma WHO III or glioblastoma WHO IV (RNOP-10) – a prospective single arm phase I/II study; EANO
2. Wismeth C et al (2009) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsing high-grade gliomas – Phase I clinical results. Expanding the Frontiers of Thermal Biology, Medicine and Physics Annual Meeting of Society of Thermal Medicine, Tucson, USA, 3-7 April 2009
3. Hau P. (2010) Transcranial EHT & alkylating chemotherapy in relapsed high-grade gliomas: phase I clinical results, 1st International Oncothermia Symposium, Cologne, Germany
4. Wismeth C. Dudel C. Pascher C. Ramm P. Pietsch T. Hirschmann B. Reinert C. Proescholdt M. Rümmele P. Schuierer G. Bogdahn U. HauP. (2010) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas - Phase I clinical results, accepted Journal of Neuro-Oncology *98:* 395-405, 2010

Metastatic lung

Investigator: Dr. Gurdev Parmar
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.
Published: 33st ICHS Nidda, Germany; 2015



Side effects, contraindications

Side effects

- Light erythematic redness (<8%)
- Surface burn (very rare)
- Adipose burn (<3%)

Does not gain (mostly suppresses) the side-effects of other complementary applied therapies.

Contraindications

- Organ transplants or vanished immune-reactions
- Missing thermal sensing
- Inability to communicate
- Woman in pregnancy
- Pacemaker or other electric implants (?)

Sedation, analgesia or anesthesia is not allowed when oncothermia is applied!

High care is necessary

- Epileptic or electric sensitivity
- Ascites or other free-electrolytes
- Large metallic implants

Applicable in most of the cases, when normal heat-therapies are not.

Applicable in hopeless cases for the gold standards

Outline

- ❑ Case reports
- ❑ Studies
- ❑ Publications

Oncothermia Research Information

Information about the results are available in

Many academic publications (>>100)

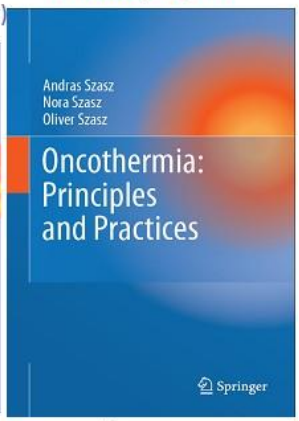
NEWSLETTER

News • Kongresse • Intern • Angebote

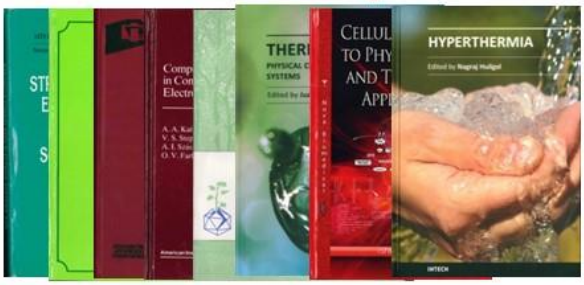
Medical journal

Open access for professionals distributed in printed form (ISSN number)

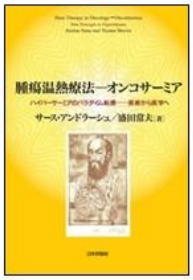
Oncothermia monographs

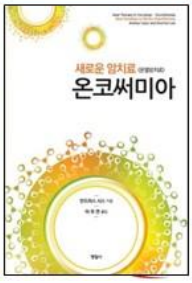


Numerous book-chapters



Own books





Outline

Thank you for your kind attention

Treatment of advanced metastatic prostate cancer by oncothermia(EHY-2000)

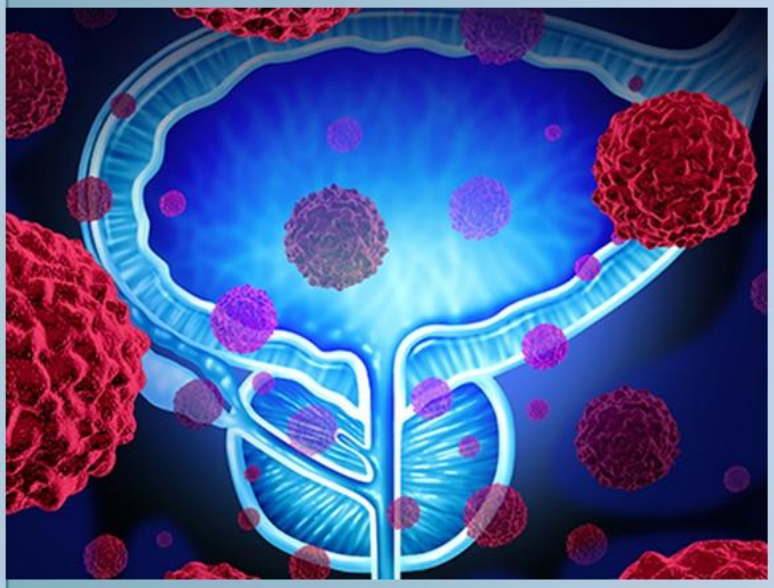
Michael Maragkos, Lazaros Danilidis, Ioannis Vakalis, Petros Kouridakis
Aias Papastavrou, Alfred Barich

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-5.pdf

WELCOME

Michael Maragkos
Αρχίατρος
Ακτινοθεραπευτής-Ογκολόγος

fppt.com



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2. Aias Papastavrou
3. Alfred Barich

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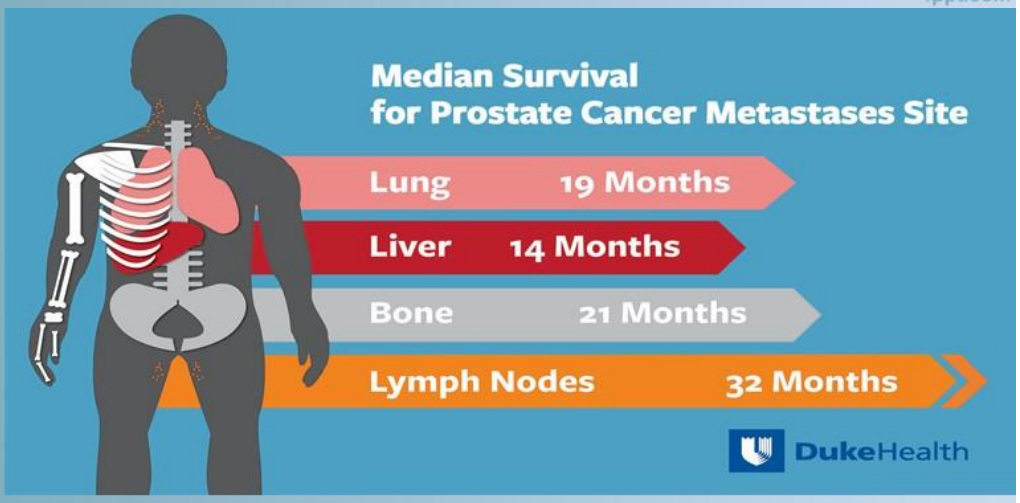

INTRODUCTION:

Multiple Pulmonary metastases are difficultly managed and almost impossible to eradicate completely, even with Chemotherapy

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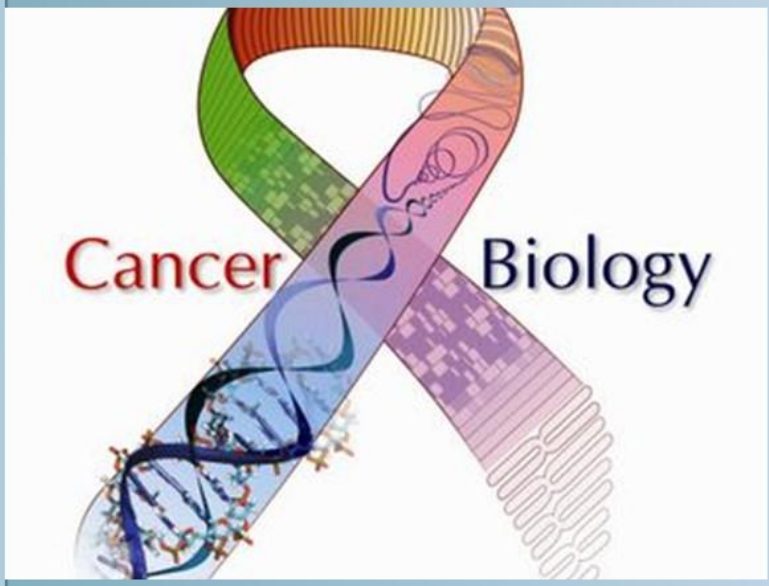
OTHER MODULES

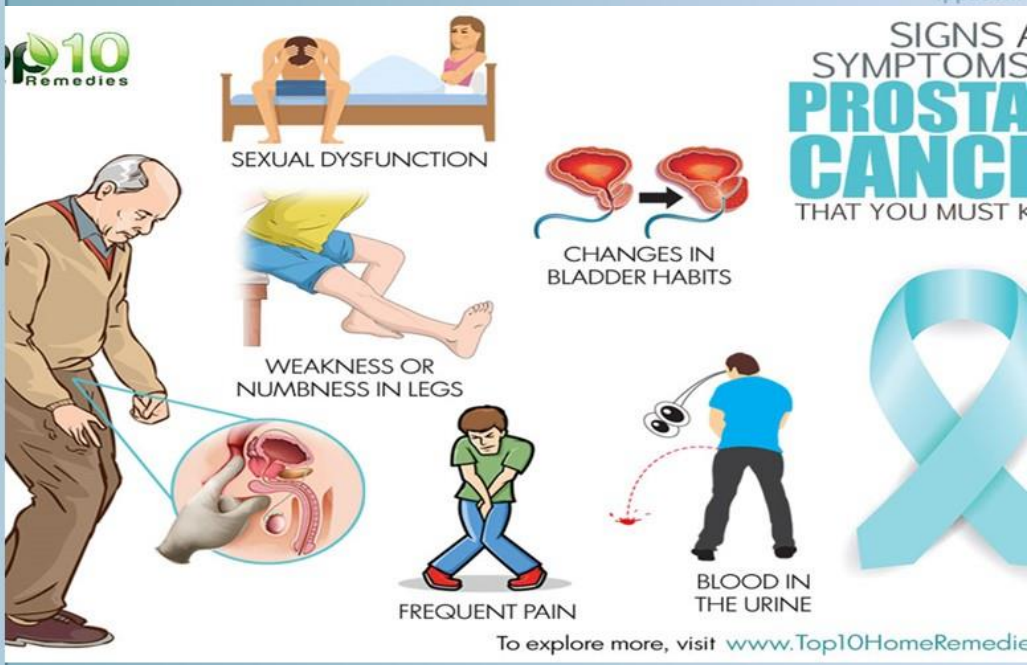
Solitary metastatic nodules have been successfully managed with metastasectomy.

HORMONE THERAPY

Effective management with androgen deprivation has given partial results only in patients from Japan as indicated by respective studies.

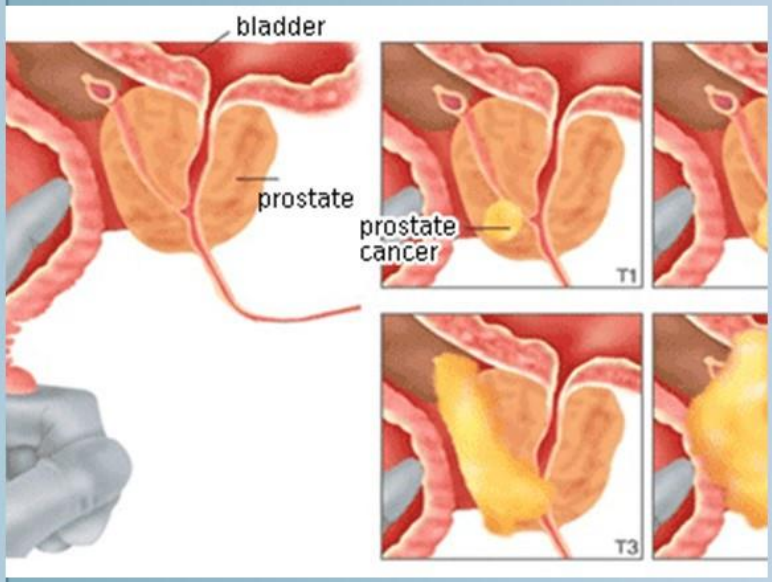


Pulmonary multiple metastases without previous bone mets is also very rare.



Case Presentation:21-10-2014

Our patient is a 75yr old man that was diagnosed with prostate cancer almost simultaneously with the lung metastases. Biopsies were performed for both sites, verifying the diagnosis.



Case Presentation:21-10-2014

Biopsies were performed for both sites, verifying the diagnosis

Αποσταλέν υλικό: **α) Βιοψία υποϋπεζωκοτικού οζού (δεξ.) πνεύμονα - γ) Βιοψίαυποδιαφραγματικής μάζας (αρ.) - γ) Συμπληρωματική βιοψία πνεύμονα**

Κλινικές πληροφορίες

Ιστορικό Ca προστάτη - Απεικονιστικά πολλαπλές εστίες εντός του πνευμονικού παρεγχύματος δεξιά - Υποδιαφραγματική μάζα κοιλιακής χώρας αριστερά.

ΜΑΚΡΟΣΚΟΠΙΚΗ ΕΞΕΤΑΣΗ

Για ιστολογική εξέταση παραλάβαμε:

α) δύο ιστικούς κυλίνδρους λευκωπής χροιάς και συνολικού μήκους 2 εκ.,
β) έξι ιστικούς κυλίνδρους λευκωπής χροιάς και συνολικού μήκους 2,5 εκ. και
γ) τέσσερις ιστικούς κυλίνδρους λευκωπής χροιάς και συνολικού μήκους 1 εκ..

ΜΙΚΡΟΣΚΟΠΙΚΗ ΕΞΕΤΑΣΗ

α-γ) Πολλαπλές τομές έδειξαν κυλινδρικά ιστοτεμαχίδια πνευμονικού παρεγχύματος τα οποία εμφάνιζαν στο σύνολό τους εκτεταμένες διηθήσεις από κακόηθες επιθηλιακό νεόπλασμα του τύπου του αδενοκαρκινώματος. Πιο συγκεκριμένα το τελευταίο αποτελούνταν από αδενοειδείς καρκινωματώδεις βλάστες σε πυκνή διάταξη μεταξύ τους, προσδίδοντας εν μέρει ηθμοειδή μορφολογία. Οι εν λόγω βλάστες επαλείφονταν από κυλινδρικού ή χαμηλού κυλινδρικού σχήματος νεοπλασματικά κύτταρα με βασίφιλους ωοειδείς βαθυχρωματικούς πυρήνες και ηωσινόφιλο κυτταρόπλασμα. Σπάνιοι πυρήνες έφεραν εμφανές πυρήνιο. Το διάμεσο στρώμα ήταν ινώδες.

Ανοσοϊστοχημικός έλεγχος

Τα νεοπλασματικά κύτταρα ήταν στην πλειονότητά τους θετικά στο PSA, στην AMACR, ενώ σπάνια κύτταρα εμφάνιζαν πυρηνική θετικότητα στο TTF1. Οι χρώσεις για CK 7 και Napsin A, ήταν αρνητικές.

β) Πολλαπλές τομές έδειξαν κυλινδρικά ιστοτεμαχίδια που αντιστοιχούσαν σε τμήματα ώριμου χόνδρινου ιστού, με συμμετοχή ινομυώδους ιστού.

Στοιχεία μεταστατικής νόσου δεν αναγνωρίστηκαν.

ΣΥΜΠΕΡΑΣΜΑ: **α-γ)** Ιστολογικά και ανοσοφαινοτυπικά ευρήματα μεταστατικού καρκινώματος του προστάτη στον πνεύμονα.

β) Ιστολογικά ευρήματα που θα μπορούσαν να

Initial PSA(21-10-2014) was 104.085ng/ml

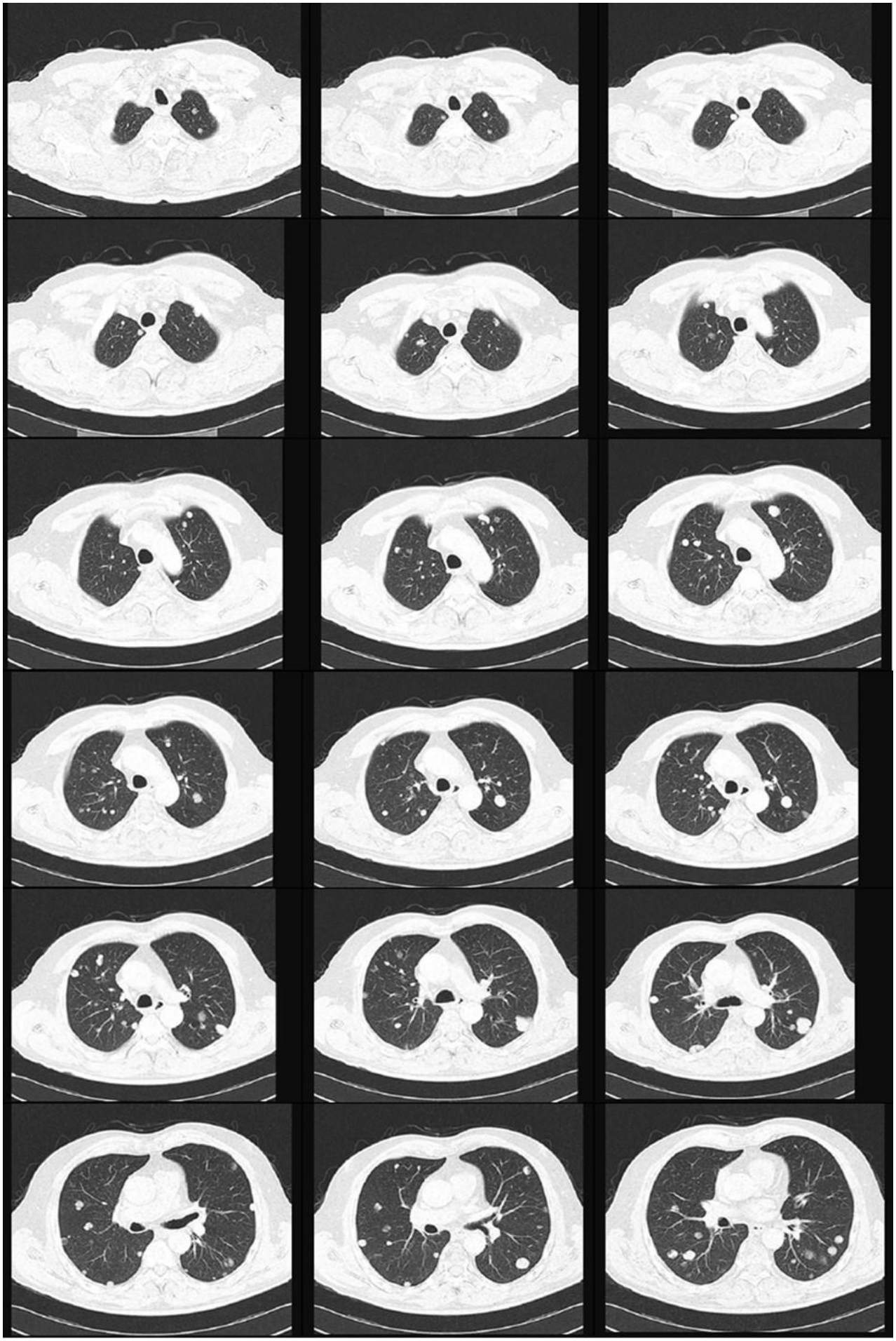
With Gleeson score 3+3

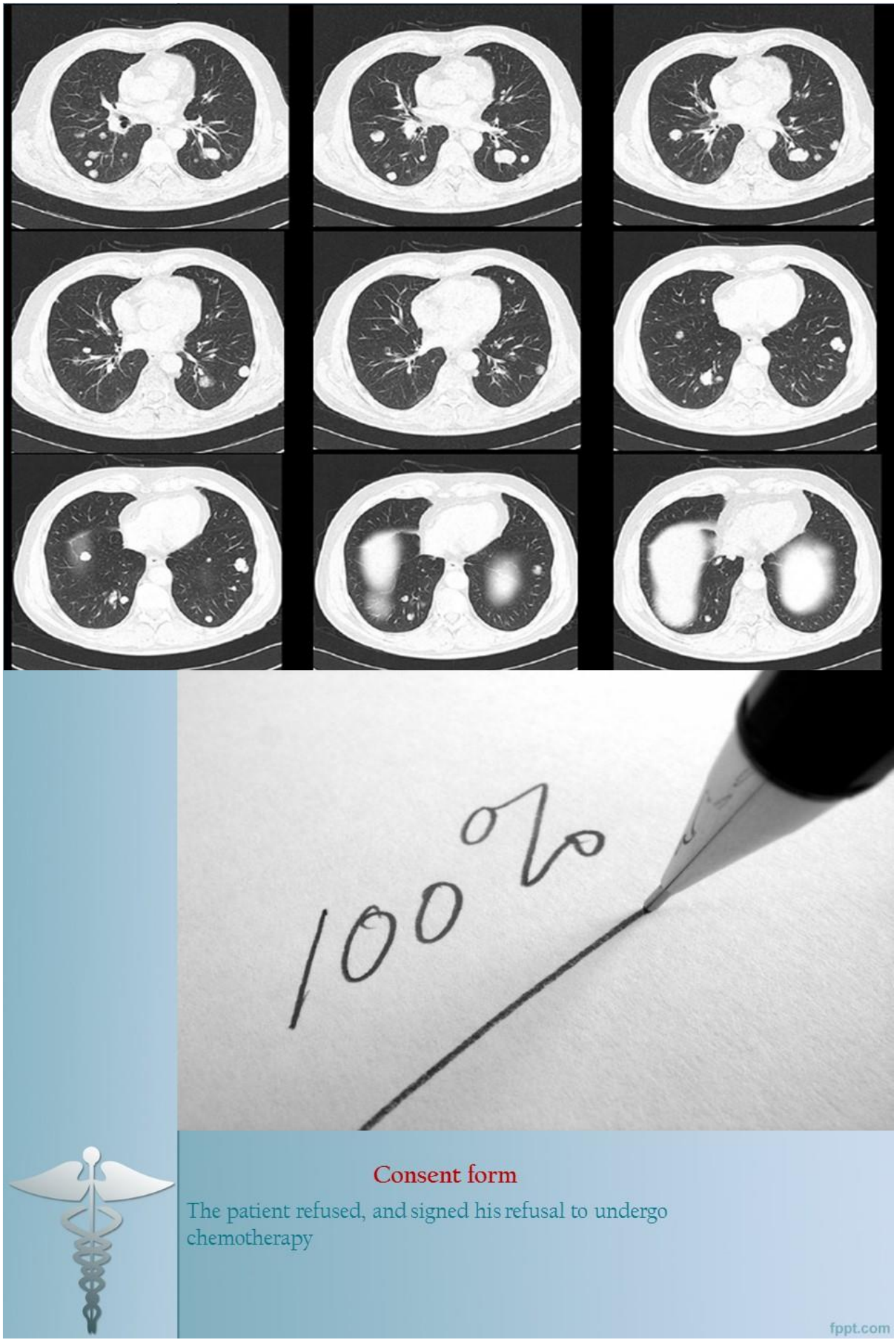
(The biopsies were histologically and immunophenotypically identical)

Upon verification 12-9-2012

The patient had only these multiple lesions without Bone mets

Initial CT's (12/9/14) showed clearly multiple metastatic lesions of both lungs.




100%
Consent form
The patient refused, and signed his refusal to undergo chemotherapy
fppt.com

Subsequently

He commenced androgen deprivation with an LHRH antagonist (degarelix).

HYPERTHERMIA

Parallel to this he commenced Hyperthermia (mEHT) of lungs and prostate

EHY-2000

Σύστημα τοπικο-περιοχικής Υ/Θ EHY-2000
hightech medicine plus

fppt.com

Within four months

fppt.com

The PSA values

From 104.085 to 0.202ng/ml. to

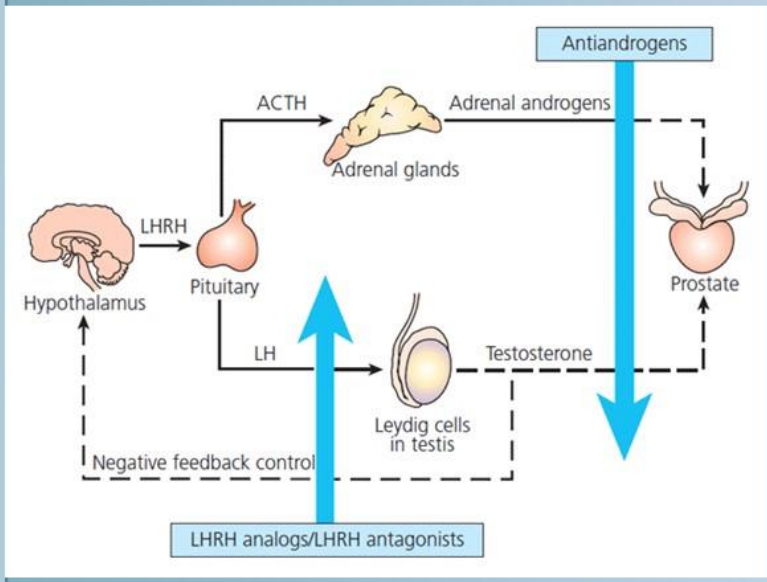
PSA (4-11-2014) : 3,392 ng/ml to

PSA (today) : =‹0,1 ng/ml

: ΜΠΑΝΤΙΜΑΡΟΥΔΗΣ ΑΘΑΝΑΣΙΟΣ Ημερομη

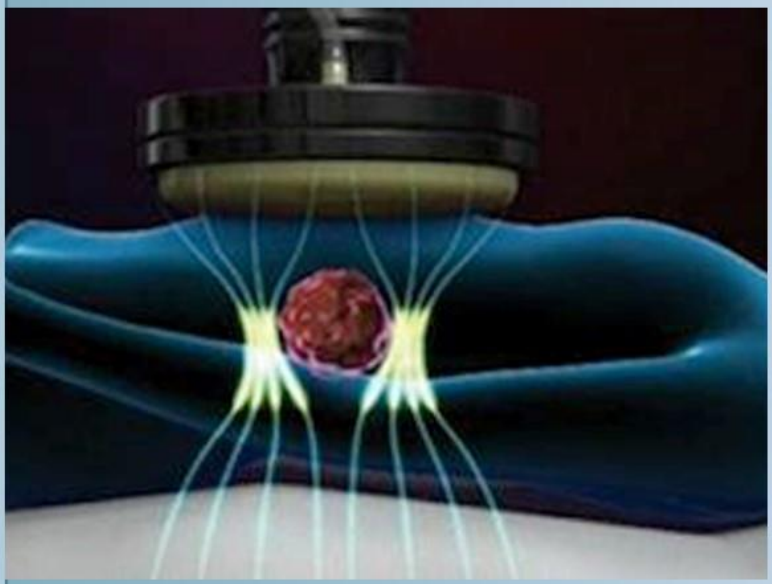
ΝΕΟΠΛΑΣΜΑΤΙΚΟΙ ΔΕΙΚΤΕΣ

Η	ΑΠΟΤΕΛΕΣΜΑ	ΜΟΝ.ΜΕΤΡ.	ΦΥΣΙ
	0,036	ng/ml	<4 Υπερτρ



Methods:

The therapeutic regimen consisted of degarelix injections every 28 days and mEHT on both sites .



The pulmonary field underwent mEHT for 90 minutes reaching an energy focus of mean 600KJ at 42.5 degrees Centigrade in target area twice a week for six weeks while the prostatic field was for 60 minutes twice a week giving a mean 400KJ at 42.5 deg. Cent. At target area.

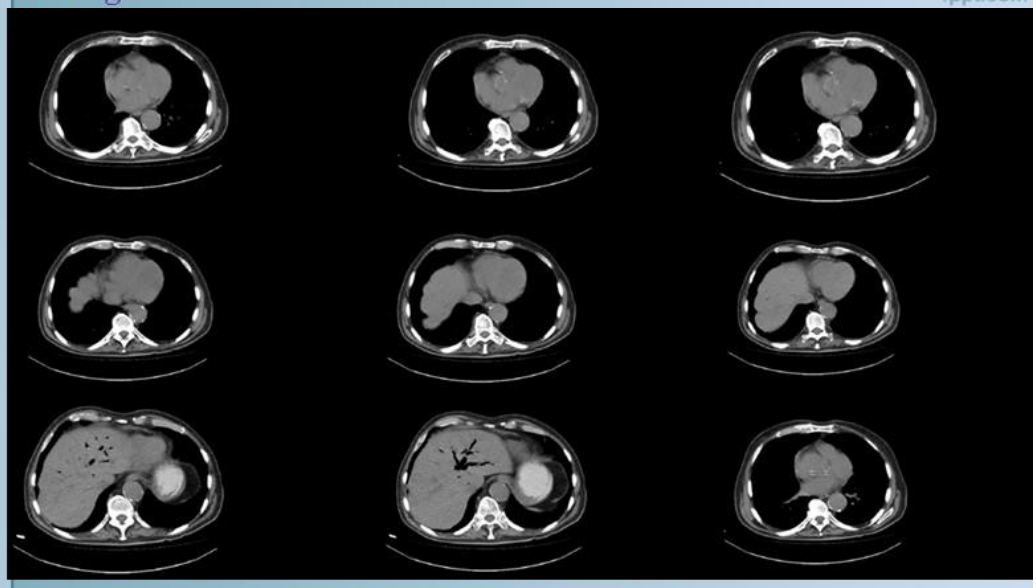
Follow up procedure

PSA readings
X-rays
CT's of the lungs for the duration of the regimen.

Results:

PSA levels at the time (11/9/14) were 104.085.

PSA levels dropped impressively : 9/1/15 PSA: 0.202ng/ml, 20/5/15 PSA: 0.048ng/ml, 18/4/16 PSA: 0.134ng/ml, 9/9/16 PSA: 0.622ng/ml and 18/2/17 PSA: 0.198ng/ml.



The pulmonary mets were reduced and within one year had completely disappeared

The CT's showed complete remission from 21/10/15 until today

The same applies to the intermediate chest X-rays that were taken.

Conclusions:.

The combination of mEHT and Androgen Deprivation gave unexpectedly good results, with long lasting complete remission of this rare expression of metastatic disease from prostate cancer

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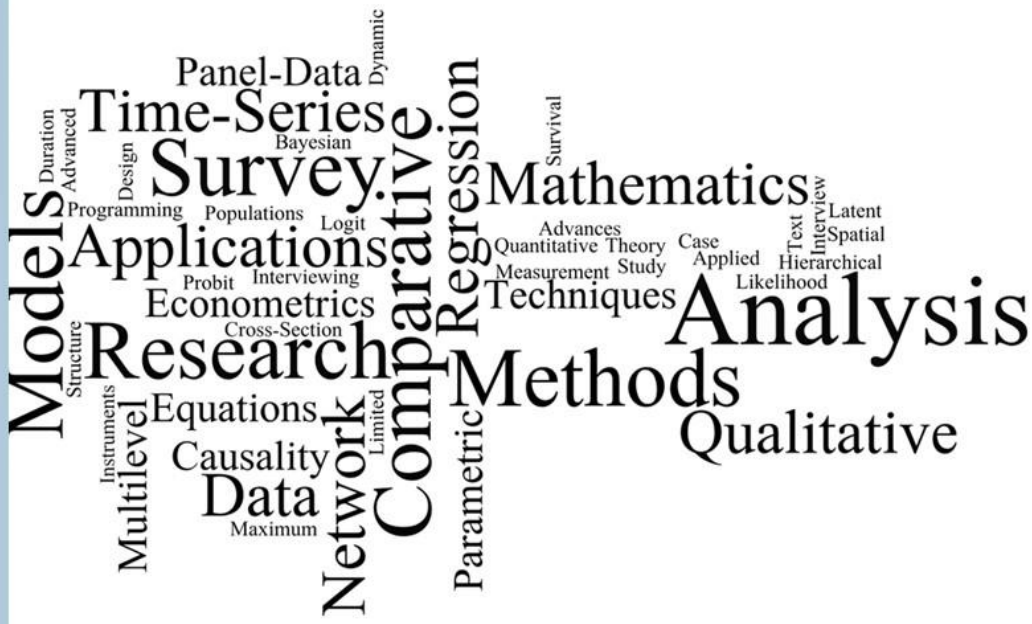
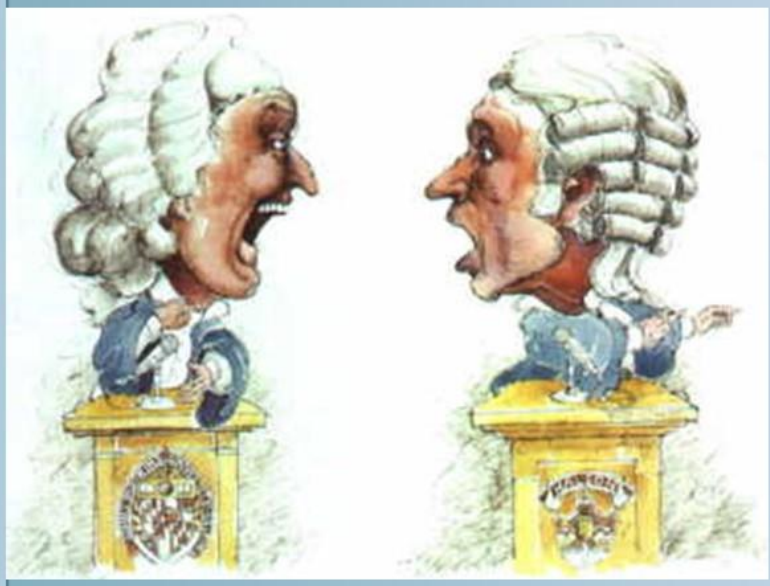


This warrants further study of the interaction of Hyperthermia on multiple pulmonary metastases from prostate cancer and its impact on therapeutic response in various regimens.

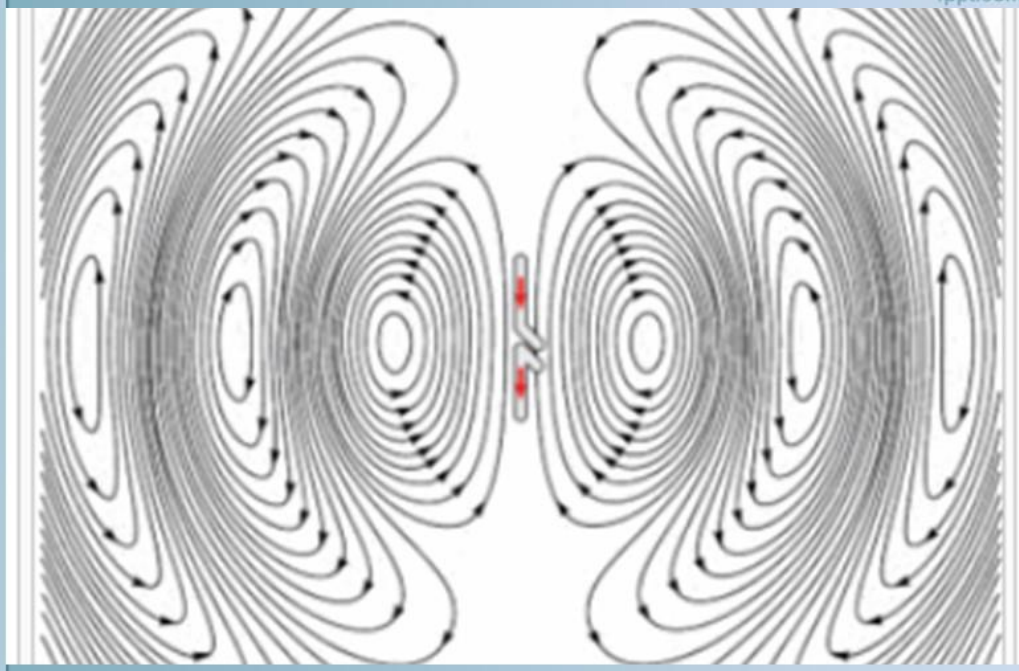
fppt.com



Discussion:

Despite the rarity of multiple pulmonary mets without other metastatic bone sites, the existing literature depicts poor prognosis and response to both androgen deprivation and chemotherapy with the exception of two Japanese studies.

(one ofthem a case report and the other being a study of twenty patients, but withconcurrent other metastases).



This gives us the incentive to further study the combination of Androgen deprivation and Hyperthermia for patients with multiple pulmonary metastases.

FINALLY

The patient continues in remission with an exceptional quality of life enjoying his grandchildren

Advanced cancer cases treated by combination of EHY-2000 and EHY-3010

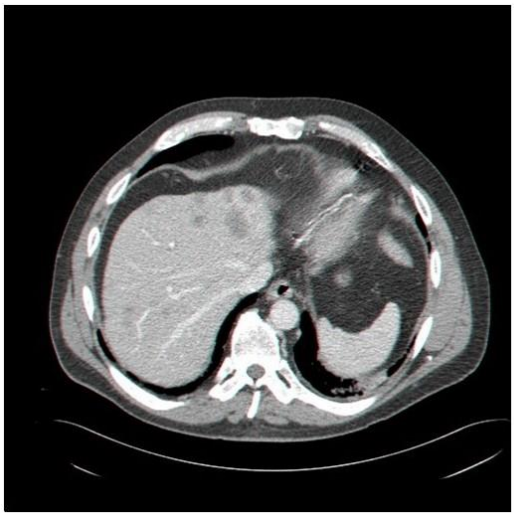
Dr. Joseph Brenner

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-6.pdf

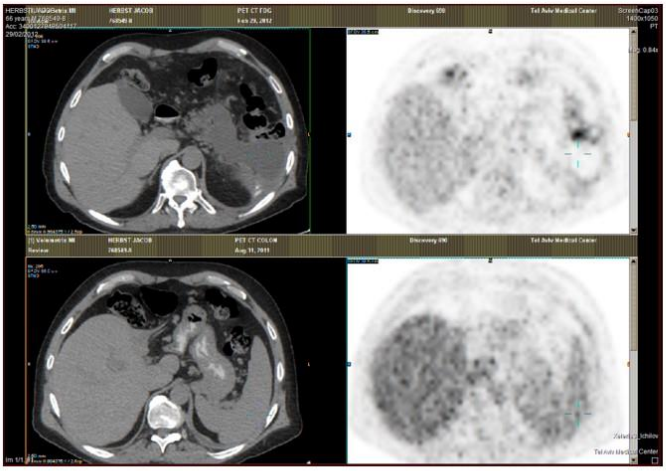
Dr. Joseph Brenner
ESHO 2017. 21- 23 June, Athens

Local recurrence of breast cancer to the whole chest wall: treatment with EHY-3000 to the whole chest, with EHY-2000 to the massive recurrent mass in the left chest wall and treatmet with superficial hyperthermia to the skin.

Complete response of the chest wall disease



Pancreatic cancer, intra-abdominal spread, liver metastasis.



The above patient after treatment with EHY-3000 to the whole abdomen and with EHY-2000 to the liver area.

Treatment to the chest, abdomen and pelvis with EHY-3000

Localized treatment to liver area with EHY-2000

EHY-2000 Treatment to a localized area up to 30 cm in diameter

EHY-2000 Treatment to a localized area up to 30 cm in diameter

Cervical cancer: What we have learned from clinical trials (Phase III study)

C.A. Minnaar; J.A. Kotzen
Department of Radiation Sciences, University of the Witwatersrand,
Johannesburg, South Africa

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-7.pdf

ESHO 2017

21-23 June

Ethniki Asfalistiki Conference Center Athens, Greece

Cervical cancer: What we have learned from clinical trials (Phase III study)

C.A. Minnaar; J.A. Kotzen

Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa

DISCLOSURES:
The study has been funded by the National Research Foundation (South Africa) and the device used has been supplied by Oncotherm Gmbh

AIM

To determine the clinical and economic benefit of the addition modulated electro-hyperthermia (mEHT) to standard treatment protocols for locally advanced HIV positive and negative cervical cancer patients in State healthcare in South Africa.

- 5 year survival rates for cervical cancer are much lower in developing countries (as much as 50% lower according to WHO)
- Due to poor health, poverty, HIV incidence, low resources
- There is an urgent need for a way to increase treatment efficacy without
  - Increasing costs,
  - complexity of treatments or
  - adverse effects is

METHODOLOGY

Randomisation Stratum: HIV, FIGO stage and Age group

Treatment:

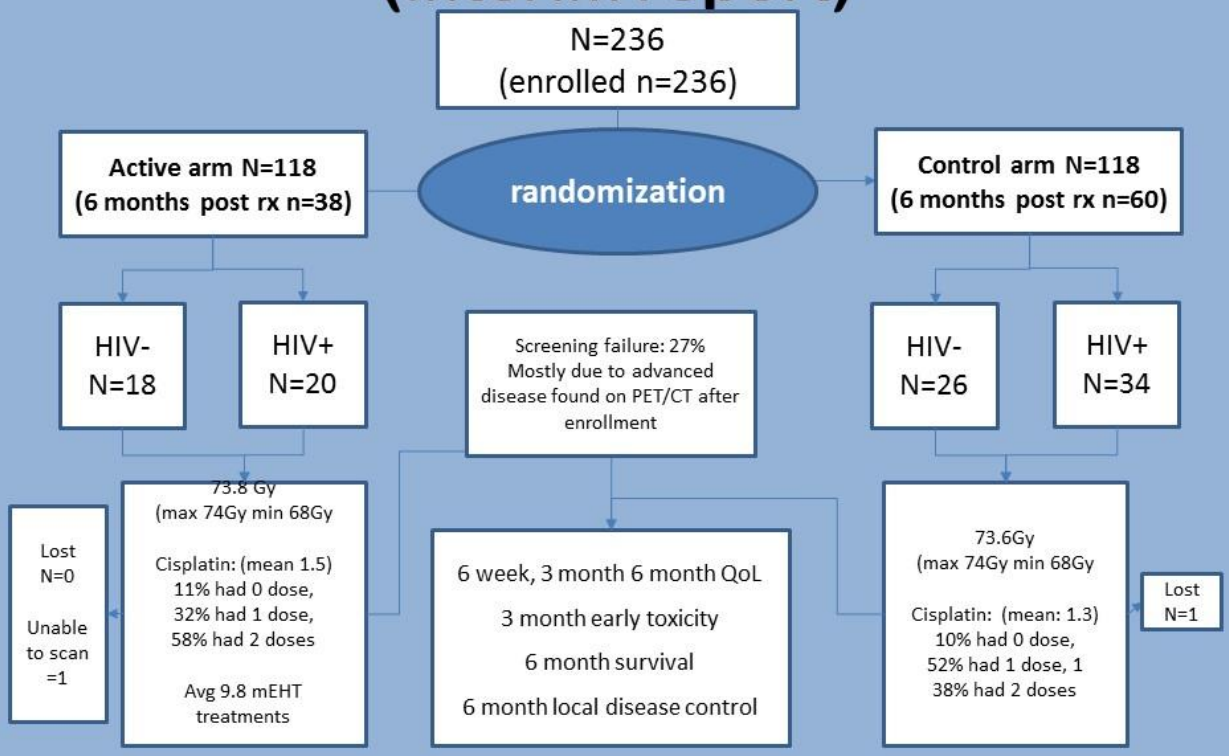
- 50Gy External Beam Radiation
- 3 x 8Gy HDR doses
- Cisplatin 80mg/m2 (1-2 doses)

Hyperthermia: 2 x 55 minutes mEHT /week (130W) directly before EBR

OUTCOMES

- Local disease control at 6 months (PET/CT)
- Adverse events + Early toxicity (CTCAE v4)
- Late toxicity from 6 months onwards
- Quality of life (EORTC + EuroQoL)

Randomized Phase III study (interim report)

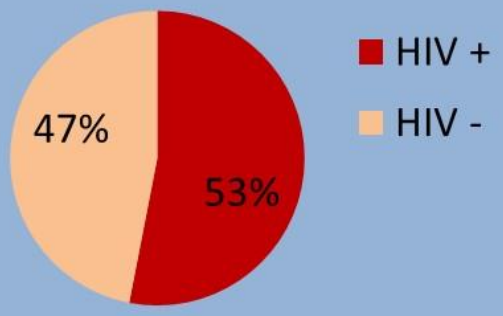


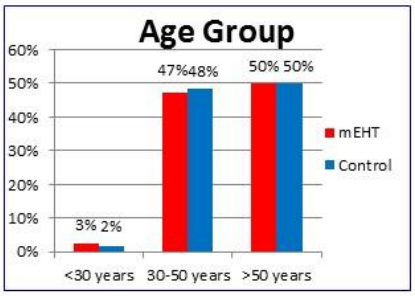
RESULTS

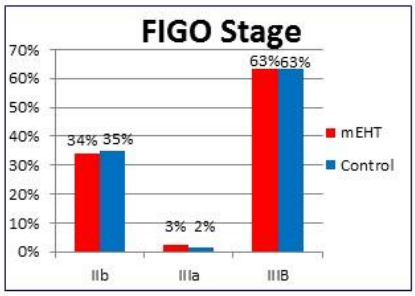
No correlation found between:

No. of cisplatin doses and outcome

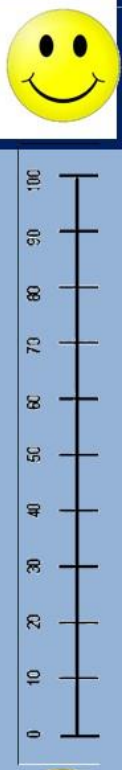
BMI and response to CRT+mEHT







QUALITY OF LIFE



Some South African Optimism:

30% of participants at initiation report 100% on visual analogue scale, despite pain and harsh socioeconomic conditions. When questioned, they answered:

"But I am alive, what more can I ask for?"

QUALITY OF LIFE

6 WEEKS

mEHT had significant improvement in:

- Social functioning
- Nausea and vomiting

Control had significant worsening in:

- Emotional function
- Appetite

Both showed a significant worsening in fatigue, insomnia and pain, Body image, Symptom experience, menopausal, financial difficulties

QUALITY OF LIFE

3 MONTHS

mEHT: showed significant improvement in:

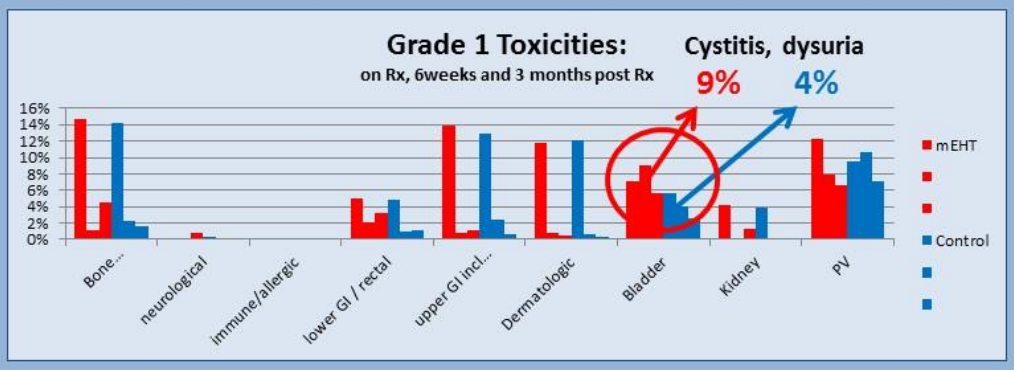
- Emotional functioning
- Mobility
- Global health
- Pain
- Diarrhoea

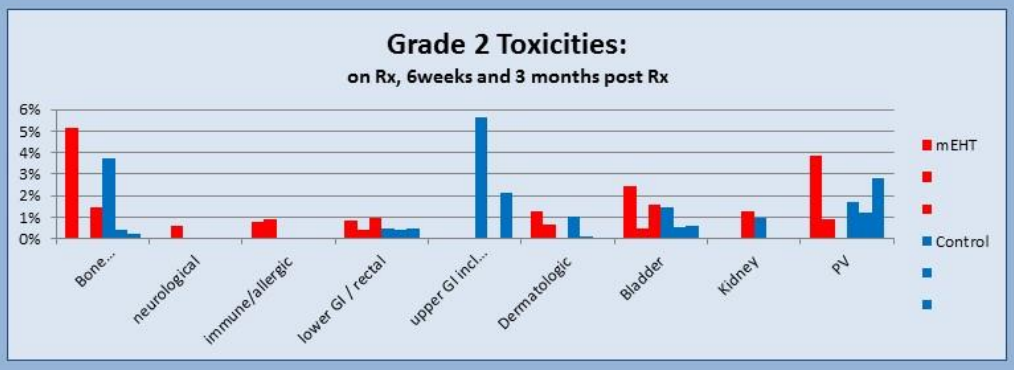
Both showed improved body image.

Both showed worse symptom scores and worse insomnia at 3 months.

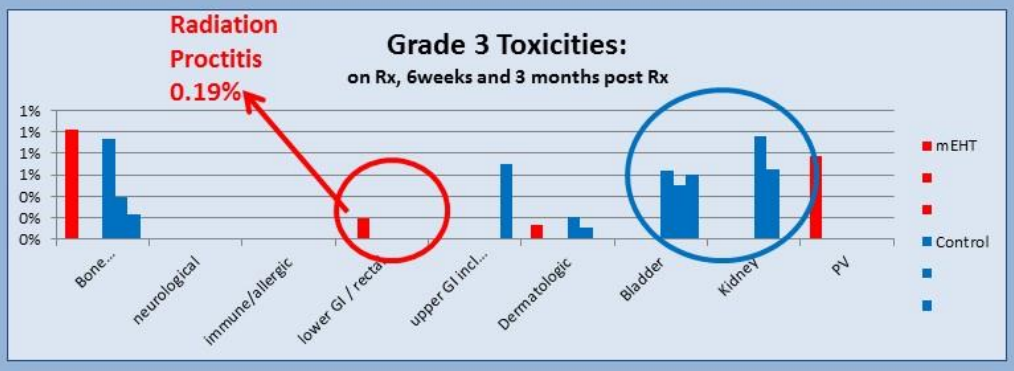
Only 5 responded to the sexual health and sexual worry questions.

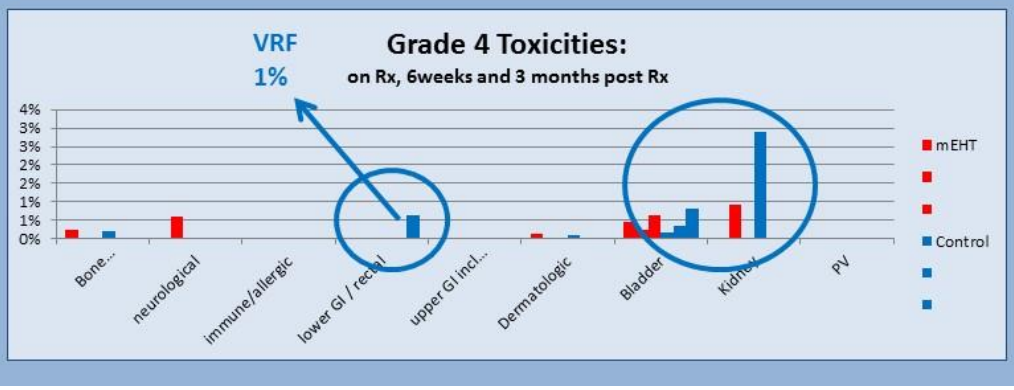
EARLY TOXICITIES: Gr 1 and 2





EARLY TOXICITIES: Gr 3 and 4



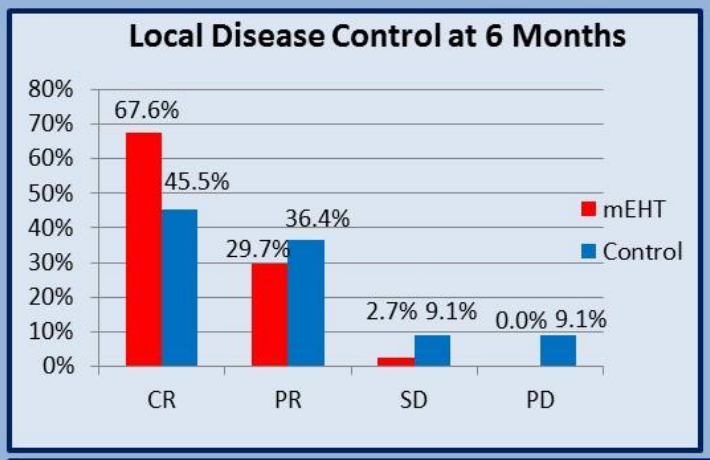


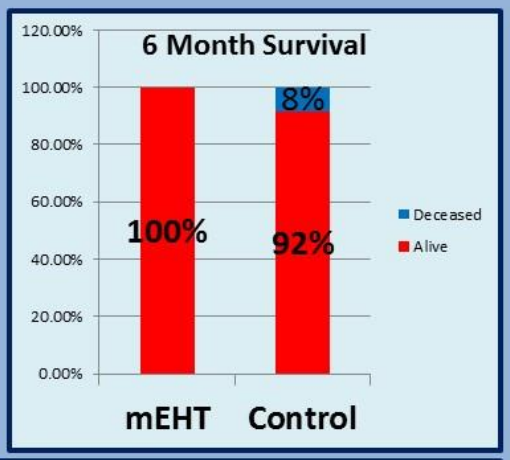
LATE TOXICITY

No Significant difference between late toxicity at 6 months between the mEHT/Control group or between the HIV+/- groups:

- **Bone**
- **Kidney**
- **Bladder**
- **Skin**
- **Subcutaneous**
- **Mucous membrane**
- **Gastrointestinal**

LOCAL DISEASE CONTROL





93 participants have survived 6 months post treatment and had PET/CT.

1 participant was unable to have PET/CT due to renal failure.

5 participants died before 6 months from disease progression. ***(Non ca related deaths excluded)***

Local disease control is assessed by PET/CT at 6 months post completion of treatment.

CONCLUSION

Preliminary results show a benefit in local disease control in the mEHT group without any unexpected early toxicities or adverse events. These results will be confirmed with a longer follow up.

mEHT may be a useful addition to treatment protocols for locally advanced cervical cancer patients in low resource settings and for whom chemotherapy as a radiosensitiser may not always be possible.

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The study has been funded by the National Research Foundation (South Africa) and the device used has been supplied by Oncotherm Gmbh

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THANK YOU FOR YOUR KIND ATTENTION!

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

Systematic Review of Brain Glioma and Lung Cancer Trials with Modulated Electro-Hyperthermia, with Meta-Analysis and Economic Evaluation (Level II Evidence)

Sergey V. Roussakow, MD, PhD
Director, Galenic Research Institute

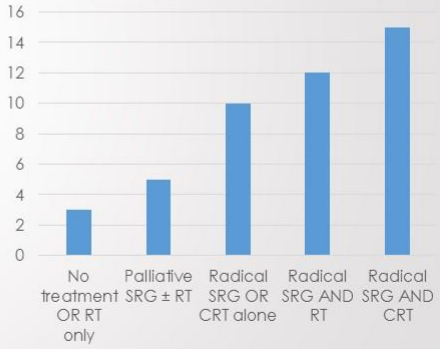
Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-8.pdf


ESHO
2017
21-23
June
SYSTEMATIC REVIEW OF BRAIN GLIOMA AND LUNG CANCER TRIALS WITH MODULATED ELECTRO-HYPERTHERMIA, WITH META-ANALYSIS AND ECONOMIC EVALUATION (LEVEL IIA EVIDENCE)
Sergey V. Roussakow, MD, PhD
Director
Galenic Research Institute
31st Annual Meeting of European Society for Hyperthermic Oncology
Athens, Greece
21st June 2017
Systematic Review of Recurrent Brain Glioma Trials with Modulated Electro-Hyperthermia, with Meta-Analysis and Economic Evaluation (level IIA evidence)

Background: GBM incidence and survival

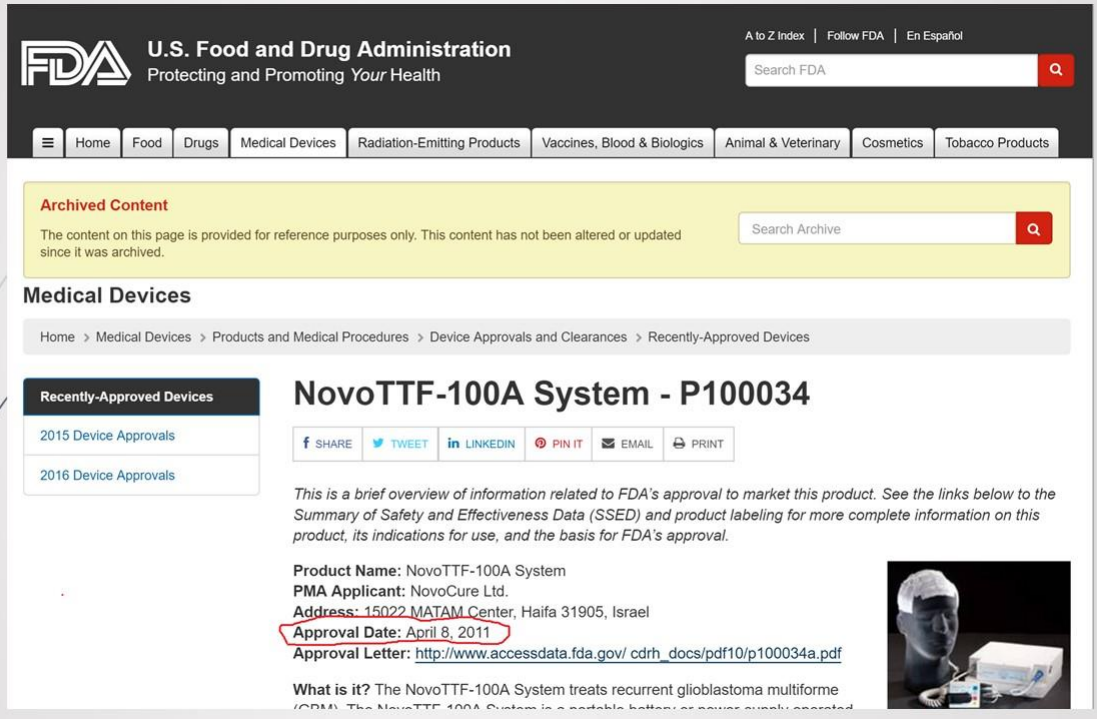
- Gliomas hold 80-81% of all brain malignancies.
- Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor, accounting for 45-54% of all adult gliomas.
- About 10,000 new cases of GBM are diagnosed annually in the US and about 2,200 cases in the UK.
- Median survival time (MST) of GBM after maximal treatment (radical surgery + chemoradiation (CRT)) is about 15-18 months.
- 5-year survival is 6.2% in the US and 10% in Japan.
- Probability of relapse of GBM is close to 100%.
- MST after relapse is 3-6 months only.

Median survival time (MST) of GBM patients depending on the treatment (UK 2007-2011)



Background: GBM treatment

- Standard-of-care first-line treatment for GBM (Stupp regimen):
  - maximal possible resection consistent with the preservation of neurologic function
  - 6 weeks of concurrent chemoradiotherapy:
    - focalized fractionated RT (60 Gy)
    - oral temozolomide (TMZ) 75 mg/m²/day for 5 days of week (5/7 d)
  - up to 6 months of adjuvant TMZ 150–200 mg/m² for the first 5 days in each 28-day cycle (5/28 d)
- No standard of care for recurrent GBM.
- Treatment options for recurrent GBM:
  - Re-resection (limited by location and performance status)
  - Re-irradiation (limited by total dose and performance status)
  - Chemotherapy (limited by performance status):
    - TMZ (incl. ddTMZ)
    - Nitrosoureas
    - Bevacizumab (BEV) and other anti-angiogenic agents
  - Novel treatments



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NovoTTF-100A System - P100034

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This is a brief overview of information related to FDA's approval to market this product. See the links below to the Summary of Safety and Effectiveness Data (SSED) and product labeling for more complete information on this product, its indications for use, and the basis for FDA's approval.

Product Name: NovoTTF-100A System
PMA Applicant: NovoCure Ltd.
Address: 15022 MATAM Center, Haifa 31905, Israel
Approval Date: April 8, 2011
Approval Letter: http://www.accessdata.fda.gov/ cdrh_docs/pdf10/p100034a.pdf

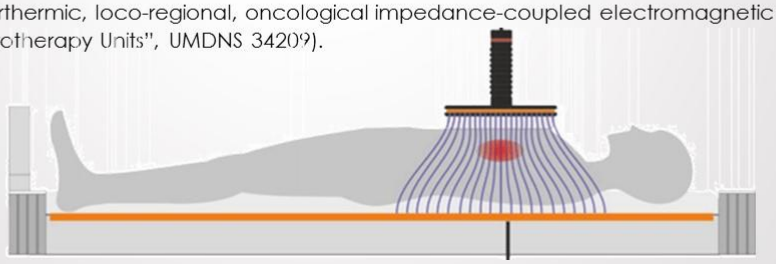
What is it? The NovoTTF-100A System treats recurrent glioblastoma multiforme

Novel treatments: Tumor-Treating Fields, FDA-approved non-thermal technology

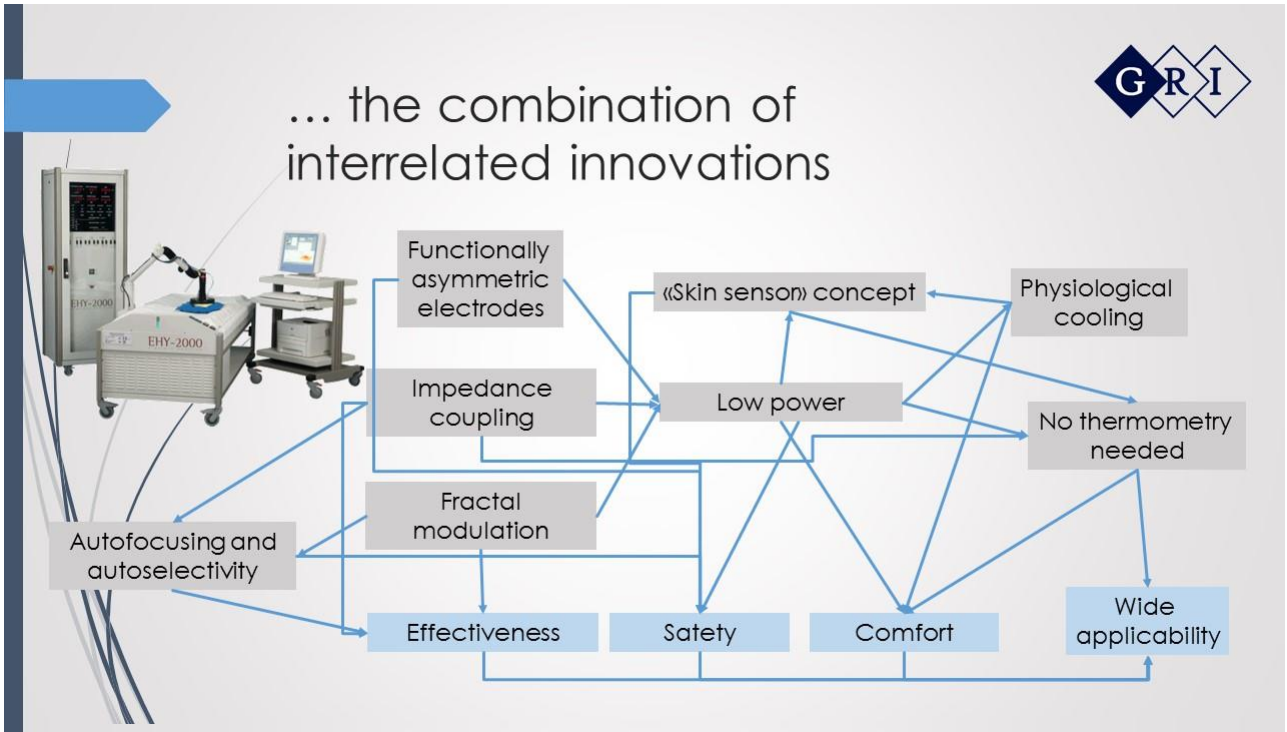
- TTF (Tumor Treating Fields) technology was approved by FDA as a chemotherapy enhancer in brain gliomas in 2011.
- TTF is based on long-term impact of alternating EM field of 100-300 kHz with low intensity (1-3 V/cm) and without heating.
- III phase RCT was preliminary ended in view of early confirmation of clinical efficacy and safety of TTF.

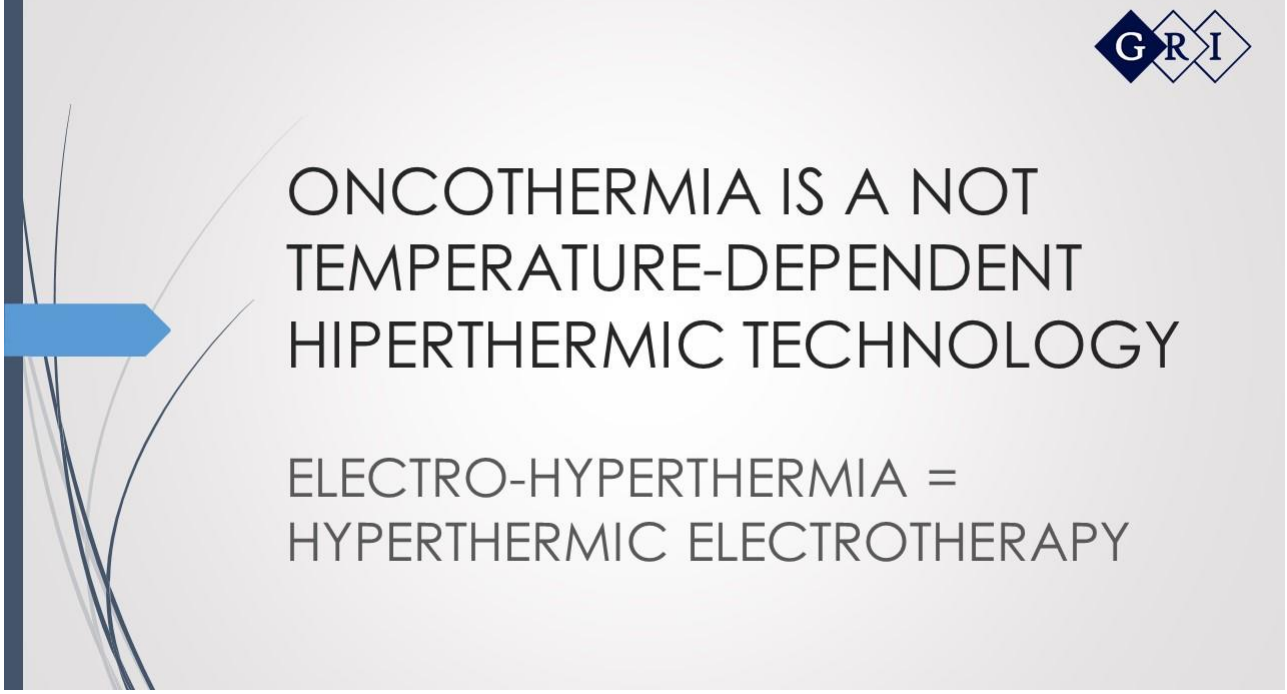
Intervention of interest: Oncothermia

- **DEFINITION**
  Oncothermia™ is a complementary treatment of solid malignant neoplasms by localized application of high-frequency electromagnetic field (13.56 MHz), modulated by 0-5 kHz fractal harmonic oscillations, using impedance-coupled, functionally asymmetric electrodes.
- **SYSTEMATIC NAME**
  An electromagnetic, radiofrequency, impedance-coupled, loco-regional oncological hyperthermia ("Hyperthermia Units, Radiofrequency", UMDNS 12066 / GMDN 40782).
- **BRIEF SYSTEMATIC NAME**
  Modulated electro-hyperthermia (mEHT).
- **ALTERNATIVE SYSTEMATIC NAME**
  A hyperthermic, loco-regional, oncological impedance-coupled electromagnetic therapy ("Electrotherapy Units", UMDNS 34209).

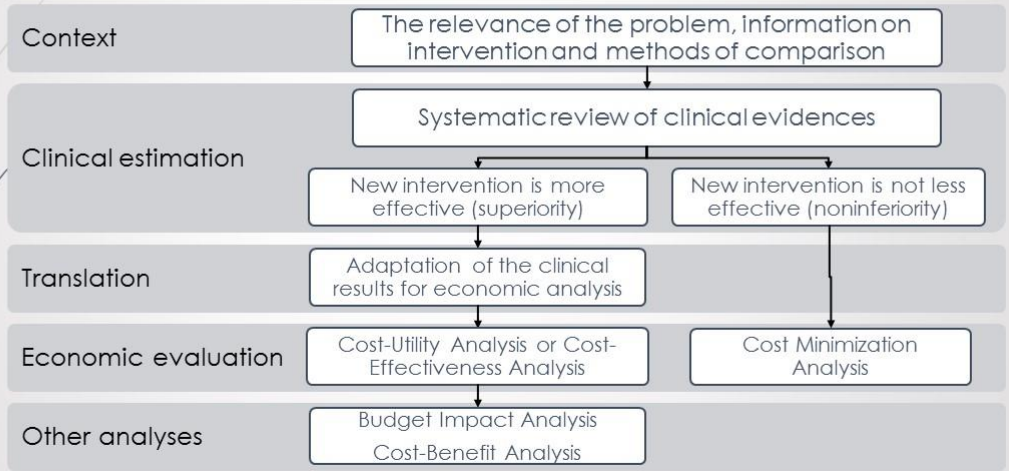


Oncothermia system EHY2000 Plus: a combination of innovations


... the combination of interrelated innovations
EHY-2000
Functionally asymmetric electrodes
«Skin senson» concept
Physiological cooling
Impedance coupling
Low power
No thermometry needed
Fractal modulation
Autofocusing and autoselectivity
Effectiveness
Satety
Comfort
Wide applicability


ONCOTHERMIA IS A NOT TEMPERATURE-DEPENDENT HIPERTHERMIC TECHNOLOGY
ELECTRO-HYPERTHERMIA = HYPERTHERMIC ELECTROTHERAPY

Structure of Study



Systematic search

- In accordance with PRISMA and CHSRI recommendations.
- Search by keywords: *([oncothermia] OR [electro-hyperthermia] OR [electrohyperthermia] OR ([electro] AND [hyperthermia]))*
- Databases:
  - US NIH (http://clinicaltrials.gov/)
  - EudraCT (https://www.clinicaltrialsregister.eu/)
  - UMIN (http://rctportal.niph.go.jp/)
  - MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed)
  - Cochrane Library (http://www.cochranelibrary.com/)
  - BMC (http://www.biomedcentral.com/)
  - Wiley Online Library (http://onlinelibrary.wiley.com/).
- Other sourses:
  - Oncothermia Journal (http://www.oncothermia-journal.com/journal/)
  - Conference Papers of ICHS, DGH, ESHO, STM, JSHO

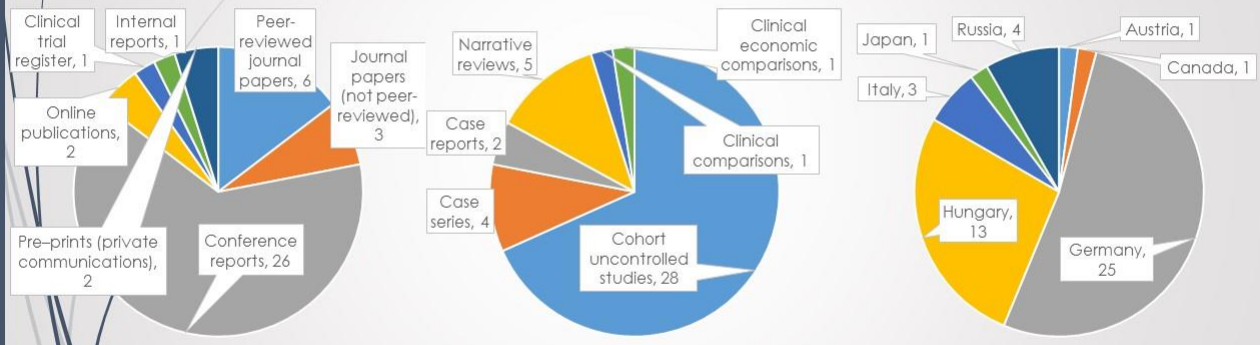
Systematic Review: Endpoints

- Primary Endpoints:
  - Overall Survival
- Secondary Endpoint:
  - Health-related Quality of Life (for QALY* calculation)

* QALY – Quality-Adjusted Life Year

Systematic search results

41 publications were identified



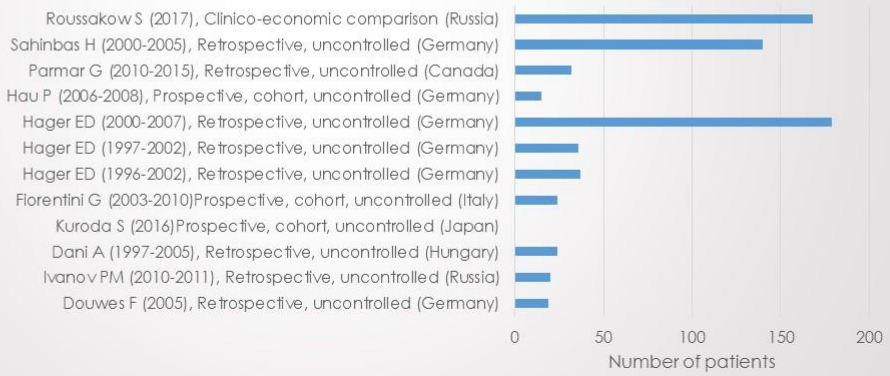
Distribution by publication type | Distribution by study type | Distribution by countries

Extracted trials

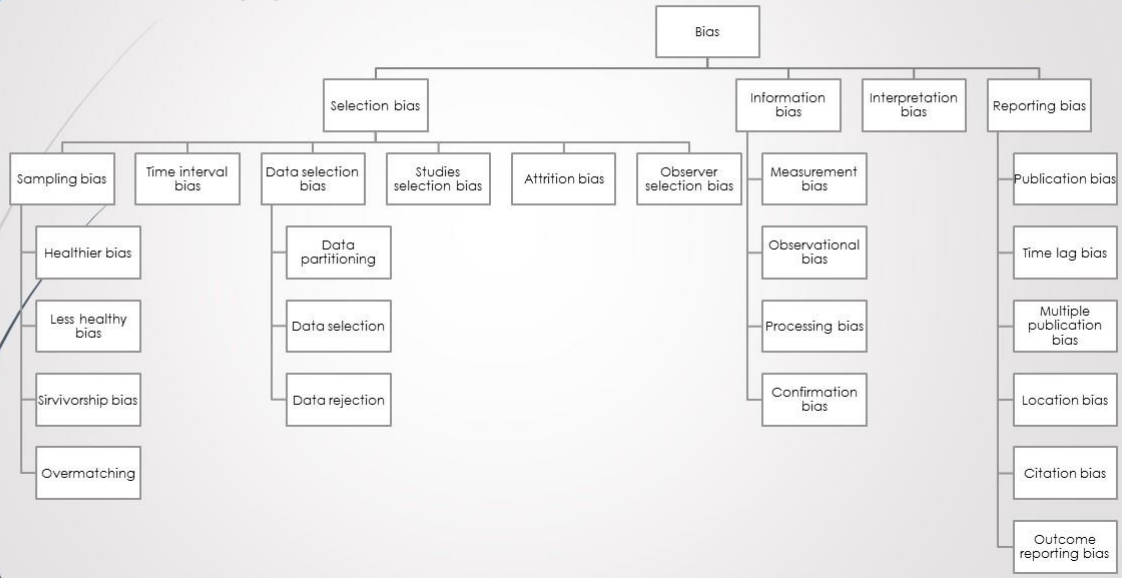
12 original Phase I/II clinical trials:

- Prospective, cohort, uncontrolled: 3 (one is recruiting)
- Retrospective, uncontrolled: 8
- Clinico-economic comparison: 1

694 patients recruited (mean 63, median 28 (15 – 179)) from 1997 to 2015.



Data appraisal and bias assessment



Levels of Evidence

NCI Dictionary of Cancer Terms: Levels of evidence. US DHHS-National Institutes of Health. Available at: https://www.cancer.gov/publications/dictionaries/cancer-terms?CdrID = 446533. Cited 23 Apr 2017.

Level	Type of evidence
1A	Systematic review of Randomized controlled trials (RCT)
1B	Individual RCT (with narrow confidence intervals)
1C	Low quality RCT (e.g. <80% follow-up)
2A	Systematic review of cohort studies and /or non-randomized controlled studies
2B	Individual cohort study or non-randomized controlled study
2C	Low quality cohort study or non-randomized controlled study (e.g., "outcomes" research)
3A	Systematic review of case-control studies
3B	Individual case-control study
4	Case series (and poor quality cohort and case-control study)
5	Expert opinion based on physiology bench research or mechanism-based reasoning

Appraisal of trials

Trial	Selection bias	Information bias	Interpretation bias	Reporting bias	Level of evidence
Roussakow S (2017), Russia	Low	Low	Low	Low	2a
Hau P (2006-2008), Germany	Low	Average	Low	Low	2b
Douwes F (2005), Germany	Low	Average	Average	High	2c
Sahinbas H (2000-2005), Germany	Low	High	Low	High	2b
Fiorentini G (2003-2010). Italy	Low	High	Average	High	4
Dani A (1997-2005), Hungary	Low	High	Average	High	4
Parmar G (2010-2015), Canada	Low	High	Average	High	4
Ivanov PM (2010-2011), Russia	High	Low	Low	High	4
Hager ED (1996-2002), Germany	High	Average	Average	High	4
Hager ED (1997-2002), Germany	Duplicate				Rejected
Hager ED (2000-2007), Germany	Duplicate				Rejected

Study 1

Roussakow S (2017)
Clinical and economic evaluation of dose-dense temozolomide 21/28d regimen with and without concurrent modulated electro-hyperthermia in the treatment of recurrent glioblastoma: a retrospective comparison of cohort trials

(level 2a evidence)

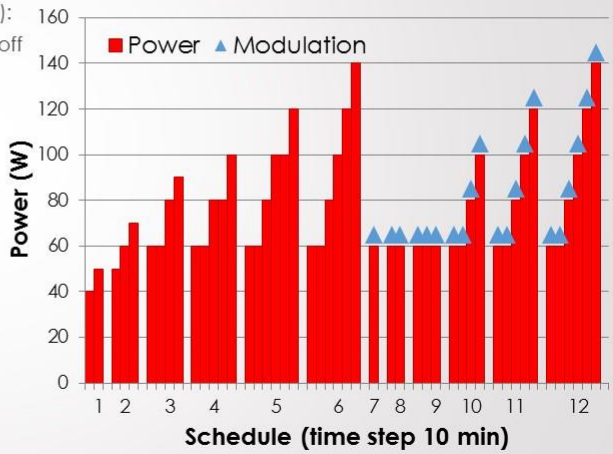
Material and Methods

- STUDY DESIGN
  Retrospective clinical and economical evaluation based on a retrospective, single-arm, two-center, phase II cohort study of Sahinbas et al. (2000-2005)
- INCLUSION AND EXCLUSION CRITERIA:
  - patients with relapsed, or progressed after incomplete resection, or progressive inoperable, histologically confirmed GBM or gliosarcoma (WHO IV) after complete conventional 1st-2nd-line pre-treatment (surgery + CRT)
  - ddTMZ 21/28d in combination with mEHT (with or without supportive therapy)
  - no re-irradiation and/or re-surgery and/or other CTX.
  - No exclusion criteria were applied.
- OUTCOMES
  - Median Survival Time (MST) since recurrence (primary).
  - Objective response rate (McDonald), adverse events rate (CTCAE) (secondary).

Intervention

Concurrent oncothermochemotherapy (up to three months):

- CTX: Oral TMZ 100 mg/m²/d q.d. for 21 days with 7 days off (21/28 d regimen)
- MEHT (EHY2000 device, Oncotherm Kft, Hungary):
  - On each 3rd day
  - Step-up heating 60 -> 150 W in 60 min
  - $T_{50} \geq 40$ °C
  - Dose-escalating schedule during first two weeks (no modulation):
    - Power increase 40 -> 150 W
    - Session time increase 20 -> 60 min
  - Adding of modulation from the third week.
- SUPPORTIVES:
  - Boswellia caterii extract 6 g/day p.o. t.i.d.
  - Misletoe extract 15 ng/day SC 3Xw
  - Selenium 300 µg/day p.o.



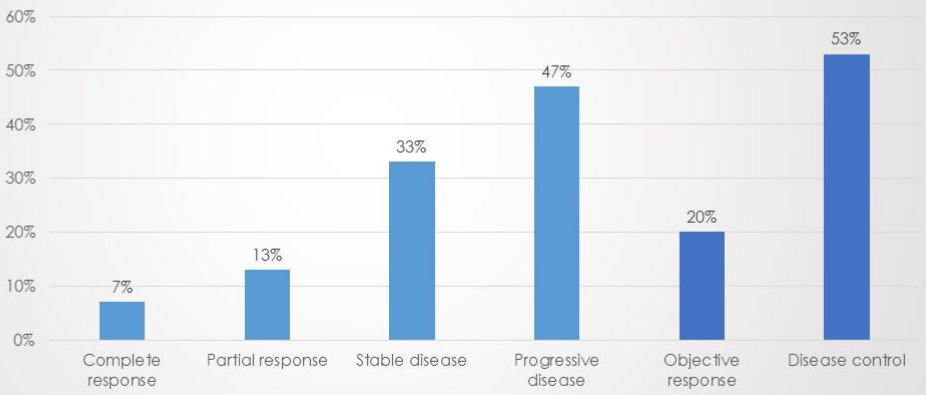
Patients' characteristics

- PATIENTS CHARACTERISTICS
  - 54 patients matched the inclusion criteria:
    - GBM (n = 53)
    - gliosarcoma WHO IV (n = 1).
  - Age:
    - mean 48.7 ± 1.5 years,
    - median age 49.8 years (range: 25.9 – 68.2; 95%CI: 42.2 – 52.8)
  - Male/female: 33/21.
  - Time from diagnosis:
    - mean 12.9 ± 2.1 months
    - median 9.5 months (0.2 – 94.2)
- PRE-TREATMENT
  - trimodal (surgery + CRT): 42 (78%)
  - Surgery + RT: 4 (7%)
  - surgery + CTX: 4 (7%)
  - RT only: 3 (6%)
  - CRT: 1 (2%).
- By modalities:
  - Surgery: 50 (93%)
  - RT: 50 (93%)
  - CTX: 47 (87%)

TREATMENT DETAILS

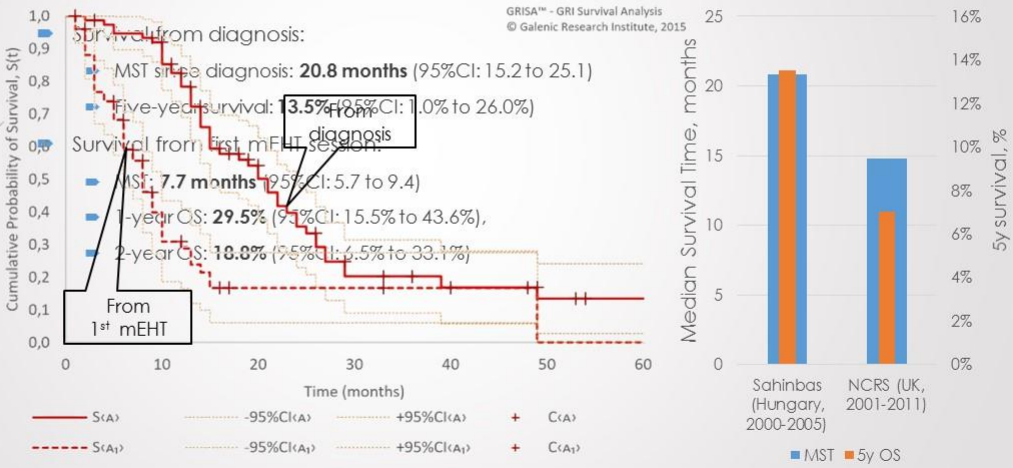
- ddTMZ + mEHT: 54 (100%)
- Supportives: 43 (80%)
- Number of treatment cycles: 84.
  - Mean 1.6 ± 0.1 cycle per patient
  - Median 1.0 cycle (range: 1.0 – 5.0; 95%CI: 1.0 – 1.0).
- Duration of treatment:
  - Mean 2.7 ± 0.6 months
  - Median 1.1 months (range: 1 day – 26.4 months; 95%CI: 0.8 – 1.5 months).
- Treatment terminated: 8 (15%) (progressive disease).

Response Assessment



Response assessment of 15/54 (28%) patients.

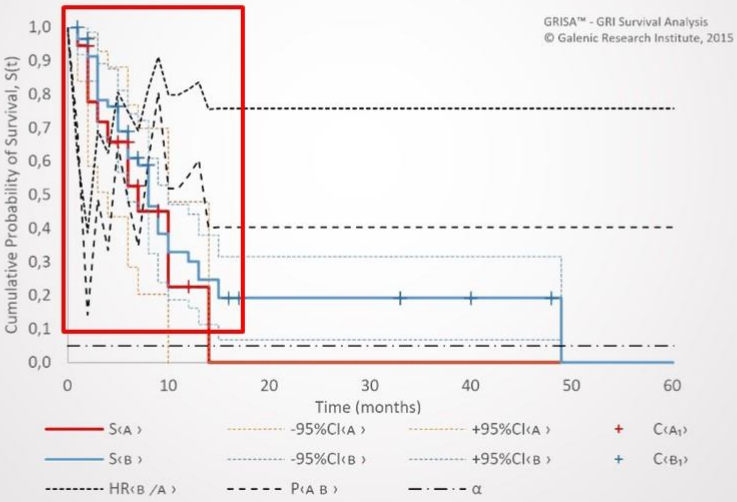
Survival Assessment



Toxicity Assessment

- No grade III-IV toxicity
- Grade I-II toxicity: <30%
  - Short-term (<2h) asthenia after treatment: 10%
  - rubor of skin: 8%
  - subcutaneous fibrosis: 1%
  - burning blisters: 2%
  - headache, fatigue and nausea (1-2 days): 12%.

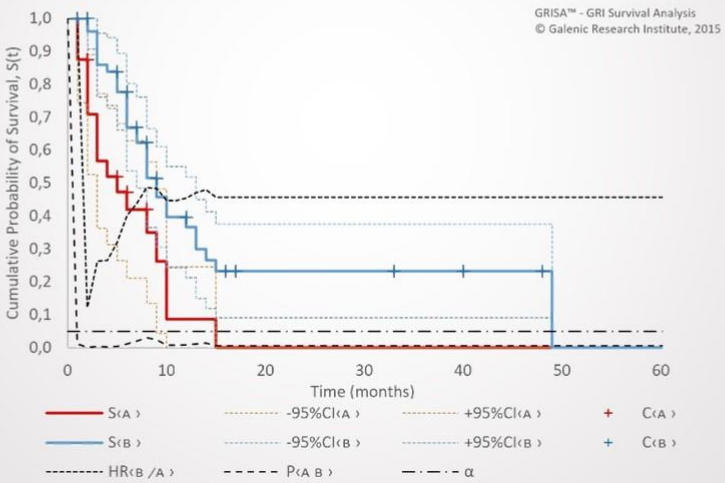
Covariate analysis: mEHT only versus CTCT



	mEHT only	CTCT
MST, months	7.7	6.4
ORR	57%	53%
Age	59.1	49.8

Survival since 1st mEHT session (Kaplan-Meier estimate) of "mEHT only" and combination (CTCT) treatment samples. (A) combination treatment (n = 43); (B) mEHT only (n = 11); C - censored.

Covariate Analysis: Low-Dose versus High-Dose mEHT



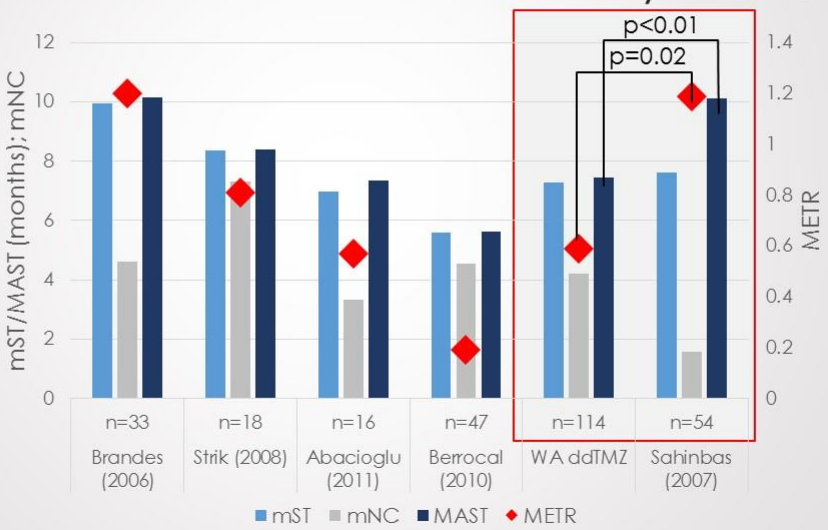
	HR	P-value
MST	2.19	0.007
ORR		0.003

Survival since 1st mEHT session (Kaplan-Meier estimate) of patients treated with LD-mEHT and HD-mEHT. (A) LD-mEHT (n = 24); (B). HD-mEHT (n = 52).

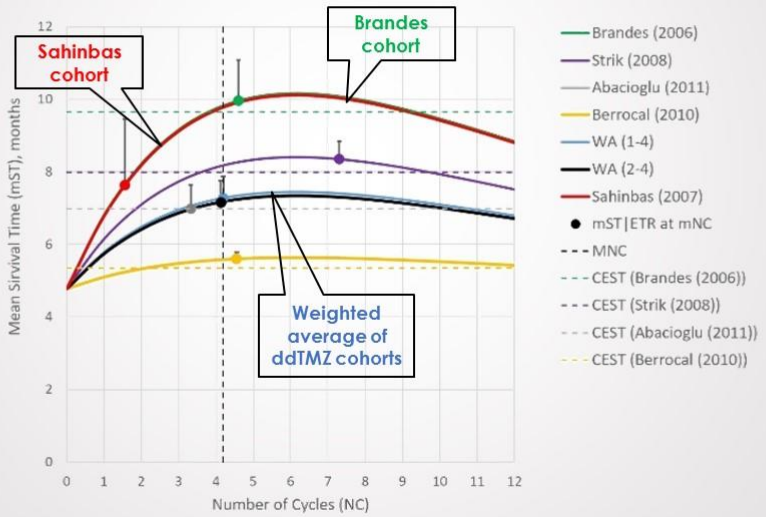
Selection of Comparison Group

Study	NOP	MNC	MST from	
			Dx	mEHT
Brandes (2006)	33	4,6	N/A	9,1
Strik (2008)	18	7,3	16,4	8,35
Abacioglu (2011)	16	3,3	N/A	7
Berrocal (2010)	47	4,55	N/A	5,1
~~Norden (2013)~~	~~55~~	~~N/A~~	~~11,7~~	~~N/A~~
~~Brada et al. (2010)~~	~~111~~	~~5~~		~~6,6~~

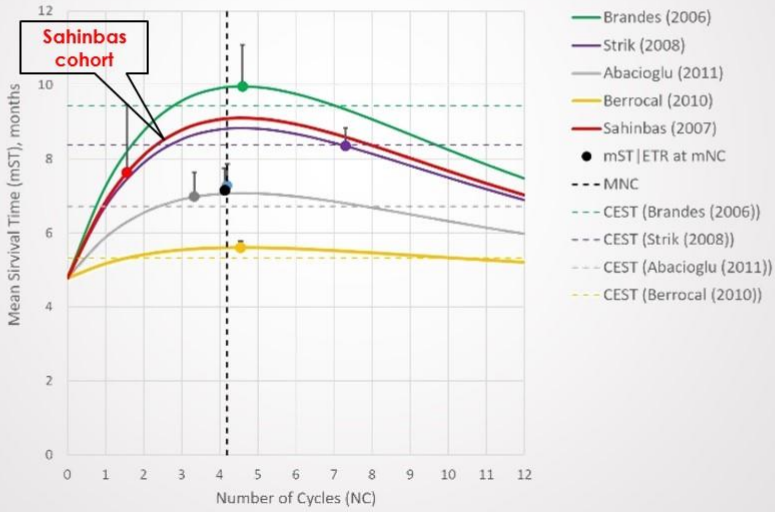
Data analysis: ddTMZ + mEHT vs. ddTMZ only at RGBM



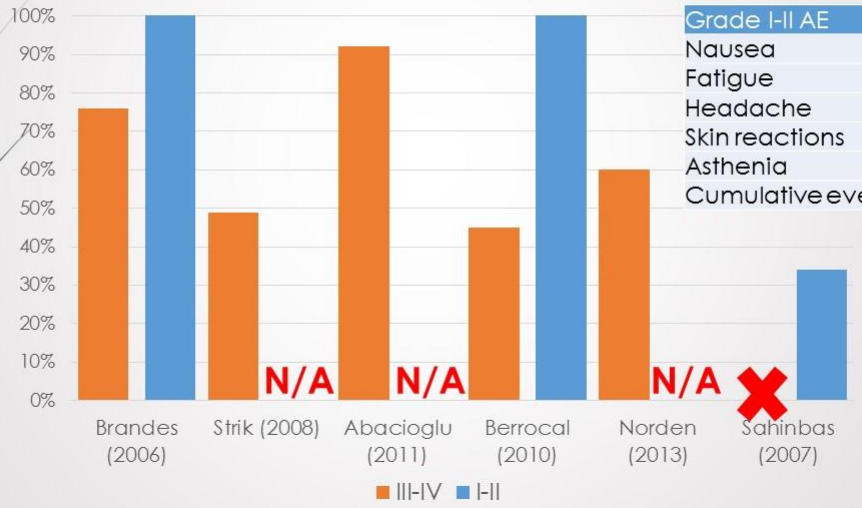
Data analysis:
ddTMZ + mEHT vs. ddTMZ only at RGBM



Data analysis:
ddTMZ + mEHT vs. ddTMZ only at RGBM



Data analysis: ddTMZ + mEHT vs. ddTMZ only at RGBM



Grade I-II AE	%
Nausea	4%
Fatigue	4%
Headache	4%
Skin reactions	12%
Asthenia	10%
Cumulative events	34%

Bias analysis

Study	Selection bias	Extra treatment	Understatement of MST	Overstatement of MST
Brandes (2006)	High	Average	Low	High
Strik (2008)	High	High	Low	High
Abacioglu (2011)	Low	Average	Low	High
Berrocal (2010)	Low	Average	Low	High
Sahinbas (2007)	Low	Low	High	Low

Conclusions

- Oncothermia suggests strong and significant enhancing of the efficacy of the dose-dense TMZ 21/28d regimen:
  - median effect-treatment ratio (METR) of the ddTMZ+mEHT regimen significantly surpassed that of the pooled ddTMZ alone (1.19 LMG/ccl (95% CI: 0.59 to 2.40) versus 0.57 LMG/ccl (95%CI: 0.39 to 0.85), p = 0.011).
  - METR of ddTMZ+mEHT in CTX-pretreated patients with median KPS 70% was the same as in the selected cohort of CTX-naïve patients with median KPS 90%, and significantly better compared to the TMZ-pretreated cohorts ($p \leq 0.015$).
- Maximum attainable MST of ddTMZ+mEHT regimen is estimated of 10.10 months (95%CI: 9.10 to 11.10).
- Sensitivity analysis shows that the results are robust.
- The ddTMZ+mEHT regimen has displayed a significantly less toxicity compared to the ddTMZ regimens:
  - no grade III-IV toxicity versus 45% – 92%, respectively) because of the shorter TMZ course (mean 1.56 versus 3.98 cycles).
- MEHT *per se* has displayed high safety with mild grade I-II toxicity
  - 30% of events), mainly presented with mild skin reactions (12%) and short (<2h) post-treatment asthenia (10%).

Study 2

Hau P (2006-2008)

Transcranial Electro-Hyperthermia Combined With Alkylating Chemotherapy in Patients With Relapsed High-Grade Gliomas: A Phase I Study

(level 2b evidence)

Trial design

Phase I; Monocenter; Prospective; Cohort, Uncontrolled; Not randomized; Open label; Single-arm; four-regimens clinical trial.

- Trial sponsor: OncoTherm Kft (Hungary).
- Center: Department of Neurology, University of Regensburg Medical School, Regensburg (Germany).
- Primary endpoints: dose-limiting toxicity (DLT), maximal tolerable dose (MTD).
- Secondary: adverse events rate (AER); time to progression (TTP); overall survival (OS); response rate (RR).
- Follow-up: up to the stopping rule.
- Stopping rule for individual patients:
  - PD (increase of tumor >25%);
  - second independent tumor;
  - DLT or other intolerable toxicity.
- Study stopping rule: if 2 DLTs occur, study stops and the dose below stopping considered maximal tolerable dose (MTD).
- Launched in Jan-2006. Completed in Mar-2008.

Intervention

- Locoregional mEHT was applied by EHY2000 Plus unit with step-up heating from 50 W to 140 W during a 60 minutes session. Dose-escalation protocol was applied as it was described in the previous study.
  Four mEHT regimens (groups) were applied:
  - 2 times per week (2Xw) (Group 1);
  - 3Xw (Group 2);
  - 4Xw (Group 3);
  - 5Xw (Group 4).
- CTX: i.v. ACNU (nimustin) 90 mg/m^2 on day 1 of 42-days cycle, up to 6 cycles.
- Supportives: corticosteroids (CS) and mannitol in case of increased intracranial pressure.

Inclusion criteria

- Inclusion criteria:
  - nonresectable, high-grade glioma WHO III (anaplastic astrocytoma (AA), oligoastrocytoma (AOA), or oligodendroglioma (AOD)) or IV (glioblastoma (GBM));
  - age 18–70 years;
  - KPS ≥ 70%;
  - first or second relapse after prior treatment (at least RT+CTX).
- Exclusions:
  - second diagnosis of tumor;
  - intolerance to nitrosoureas;
  - pacemakers of any origin;
  - prior treatment with nitrosoureas;
  - prior treatment with hyperthermia;
  - competitive participation in other clinical studies.

Patients' characteristics

Recruited:	15 pts.
Groups 1-3:	4 pts each
Group 4:	3 pts
Median age:	57 yrs (range 45-73)
M/F	11/4
Histology:	
GBM	13
Anaplastic astrocytoma	1
Anaplastic oligodendroglioma	11
Median relapses:	2 (range 1-3)
Median prior resections:	2 (range 0-2)
Medial KPS:	80% (range 50-100)

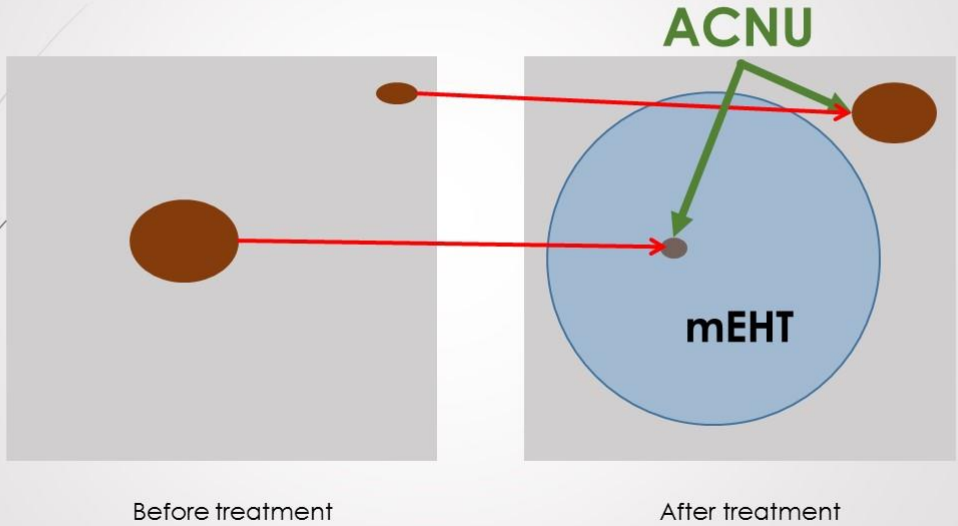
Treatment details

- Median CTCT cycles: 2 (range 1-5)
- Median mEHT sessions: 20 (range 11-77)
- Full dose escalation (all sessions of 140W): 4/15 (26.7%)
- Maximum power (total sessions):
  - 140W: 299/499 (67%)
  - 120W: 107/499 (24%)
  - 100W: 28/499 (6%)
  - <100W: 12 (2.6%)

Response assessment

- The best response throughout the follow-up:
  - CR: 0%
  - PR: 1/15 (6.7%)
  - SD: 8/15
  - PD: 6/15 (40%)
  - beneficial response rate (BRR): 9/15 (60%)
- Three patterns of progression described:
  - true progression: enlargement + enhancement;
  - pseudoprogression: enlargement with less enhancement;
  - mixed response: objective response (CR/PR) in the mEHT-treated lesion while PD in the not treated area.

Mixed response



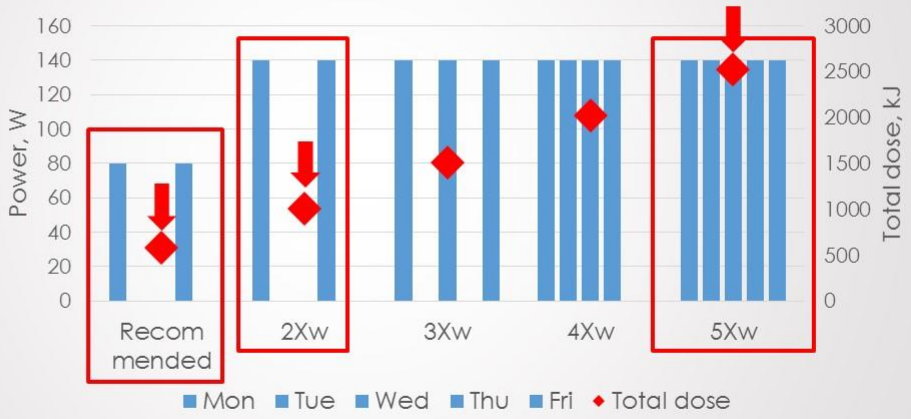
Survival assessment

- **MST (Kaplan-Meier estimate): 8.96 months.**
- MTTP: 3.2 m (14 w, range 6-40).

Conclusions

- No DLT occurred.
- In some patients, the administration of mannitol or long-term use of corticosteroids was necessary to resolve increased focal neurological signs or symptoms of increased intracranial pressure.

No DLT with 1.75-4.3-fold exceeding of the dose



Study 3

Douwes F (2005)

Hyperthermia in combination with ACNU chemotherapy in the treatment of recurrent glioblastoma

(level 2c evidence)

Trial design

- Phase II; Monocenter; Retrospective; Cohort, Uncontrolled; Not randomized; Open-Label; Single-arm; Single-regimen clinical trial.
- Center: Klinik St. Georg, Bad Aibling (Germany).
- Primary endpoints: overall survival (OS), response rate (RR).
- Secondary endpoints: adverse events rate (AER). Follow-up: until progression

Intervention: Concurrent thermochemotherapy (CTCT)

- CTCT was applied for three weeks followed by three-week interval (42-day cycle), until progression.
- Concurrent CTX (i.v. ACNU, 60 mg/m2) was applied one time a week, 30 min before OT session.
- Oncothermia (OT) was applied with EHY2000 unit for 60 min per session (step-up heating) for each 3rd day, twice a week: with ACNU and without it.
- Supportives: 20 mg of dexamethasone p.o. 6 hours before OT and 500 ml of mannitol (20%) i.v. 30-60 min. before OT.

Patients' characteristics

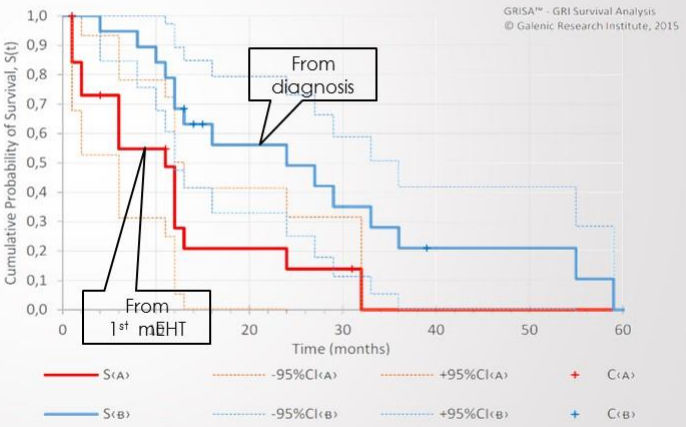
- 19 patients recruited:
  - histologically or radiographically verified recurrent GBM (WHO IV)
  - measurable lesion (MacDonald 1990).
- Age:
  - mean 53 ± 2.2 years (95%CI: 48.68 to 57.29),
  - median 55.3 years (range: 33.0-67.3, 95%CI: 50.6 to 59.7).
- Median KPS: 70% (range: 30 – 90%, 95%CI: 60 – 80%).
- Pretreatment:
  - resection and RT (100%)
  - CTX (8/19, 42%).

Treatment details

- No of CTCT cycles:
  - mean: 2.4 ± 0.42 (95%CI: 1.58 to 3.26);
  - median: 1 (range: 1 – 7, 95%CI: 1 to 3).

Survival assessment (Kaplan-Meier estimate)

- MST:
  - from diagnosis: **23.9 months** (95%CI: 11.8 to 35.1);
  - from 1st OT: **10.8 months** (95%CI: 5.1 to 12.0);
- MTTP: **7.5 months** (range: 3 – 21).
- OS from 1st OT:
  - 1y: **27.8%** (5.4% – 50.2%),
  - 2y: 13.9% (-3.7% – 31.5%),



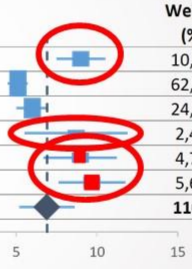
Toxicity

- Leucopenia:
  - G1: 6/19 (31.6%),
  - G2-3: 2/19 (10.6%),
  - G4: 1/19 (5.3%);
- Thromobocytopenia:
  - G1: 5/19 (26.3%),
  - G2: 1/19 (5.3%),
  - G3: 3/19 (15.8%),
  - G4: 1/19 (5.3%).
- No oncothermia-related toxicity reported.

Oncothermia-dependent enhancement of nitrosoureas

Meta-analysis of nutrosoureas in treatment of recurrent GBM

No Study, cohort	Single-arm M/No	Mean survival time	Weight (%)	p-value 1	2	3	4	5	6	7
1 Jungk (2016), BCNU	9,0/34	9,00 (7,49 – 10,51)	10,6%	1,00	0,00	0,00	0,87	0,98	0,61	0,07
2 Reithmeier (2010), BCNU	5,1/35	5,10 (4,48 – 5,72)	62,6%	0,00	1,00	0,14	0,03	0,00	0,00	0,05
3 Glas (2009), ACNU + VM26	6,0/35	6,00 (5,01 – 6,99)	24,4%	0,00	0,14	1,00	0,12	0,02	0,00	0,37
4 Heiland (2016), BEV + CCNU	8,7/18	8,70 (5,51 – 11,89)	2,4%	0,87	0,03	0,12	1,00	0,90	0,62	0,33
5 Hau (2010), ACNU+mEHT, salvage	9,0/15	8,96 (6,69 – 11,23)	4,7%	0,98	0,00	0,02	0,90	1,00	0,65	0,16
6 Douwes (2005), ACNU+mEHT	9,7/19	9,68 (7,61 – 11,75)	5,6%	0,61	0,00	0,00	0,62	0,65	1,00	0,04
7 Pooled (1 - 4)	**7,20/122**	**6,90 (5,19 - 8,61)**	**110%**	**0,07**	**0,05**	**0,37**	**0,33**	**0,16**	**0,04**	**1,00**



Random effect model (I^2=0,0%, p=0,59)

GRIMA™ (GRI Meta-Analysis)
© Galenic Research Institute, 2015

Thus, although the number of comparable studies is limited and the power of the analysis is low, the significant advantage obtained on such limited cohorts suggests the survival benefit of combination of mEHT with nitrosoureas.

Overall survival at recurrent GBM

Median survival time of GBM trials

No Study, cohort	Single-arm M/No	Mean survival time	Weight (%)	p-value 1	2	3	4	5
1 Dani (1997-2005), Hungary	13,9/11	13,90 (11,70 – 16,30)	30,9%	1,00	<0.01	<0.01	0.34	<0.01
2 Parmar (2010-2015), Canada	21,0/32	21,00 (18,09 – 23,91)	12,0%	<0.01	1,00	0,39	<0.01	0,06
3 Sahinbas (2000-2005), Germany	19,6/76	19,58 (16,90 – 22,30)	51,1%	<0.01	0,39	1,00	<0.01	0,06
4 NCRS (2007-2011), England	14,8/2008	14,80 (14,20 – 15,40)	970,9%	0,34	<0.01	<0.01	1,00	<0.01
5 Pooled (1 - 3)	**17,32/2127**	**17,99 (16,98 – 19,00)**	**1071%**	**<0.01**	**0,06**	**0,06**	**<0.01**	**1,00**

Fixed effect model (I^2=89,7%, p=<0.01)

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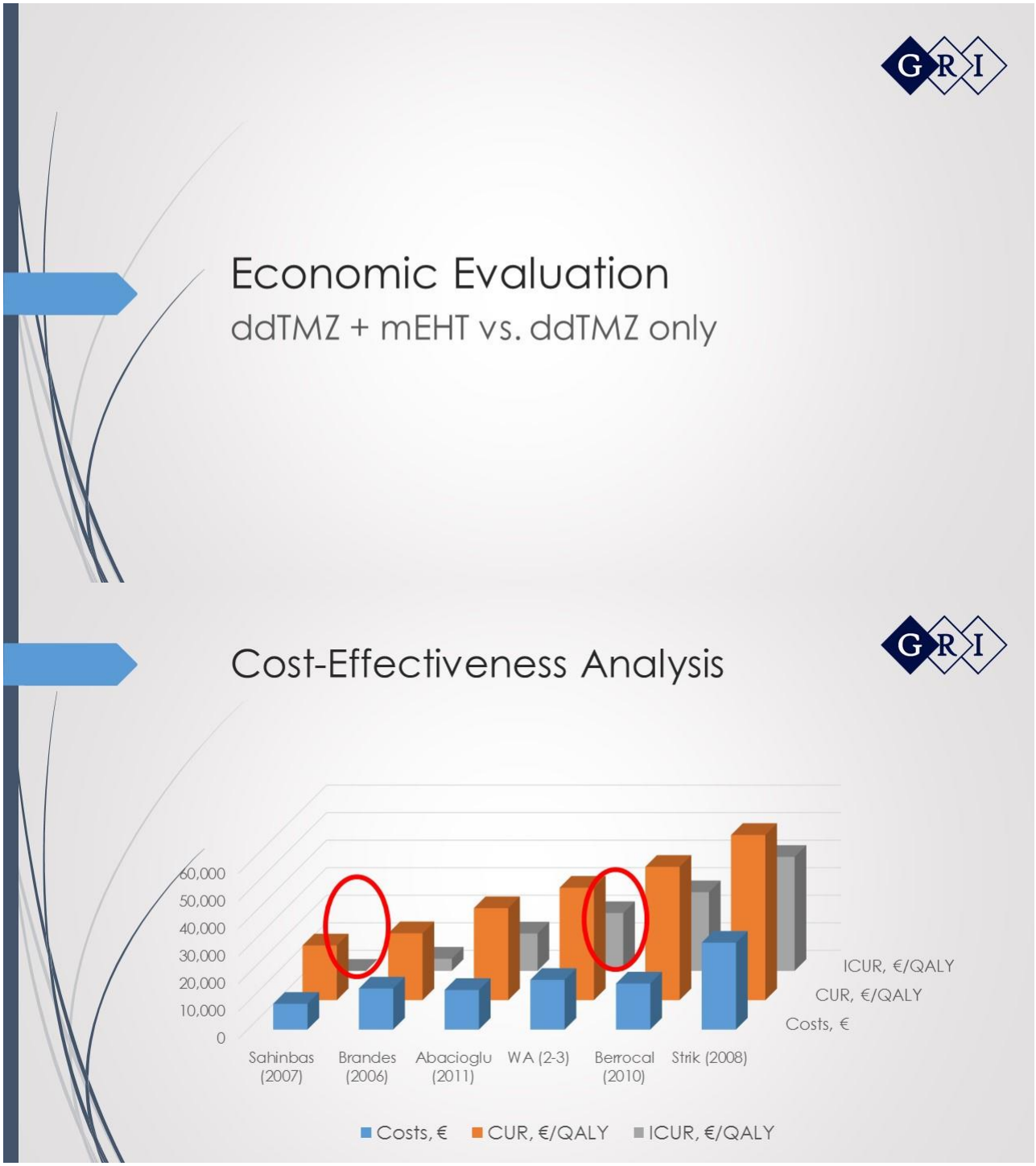
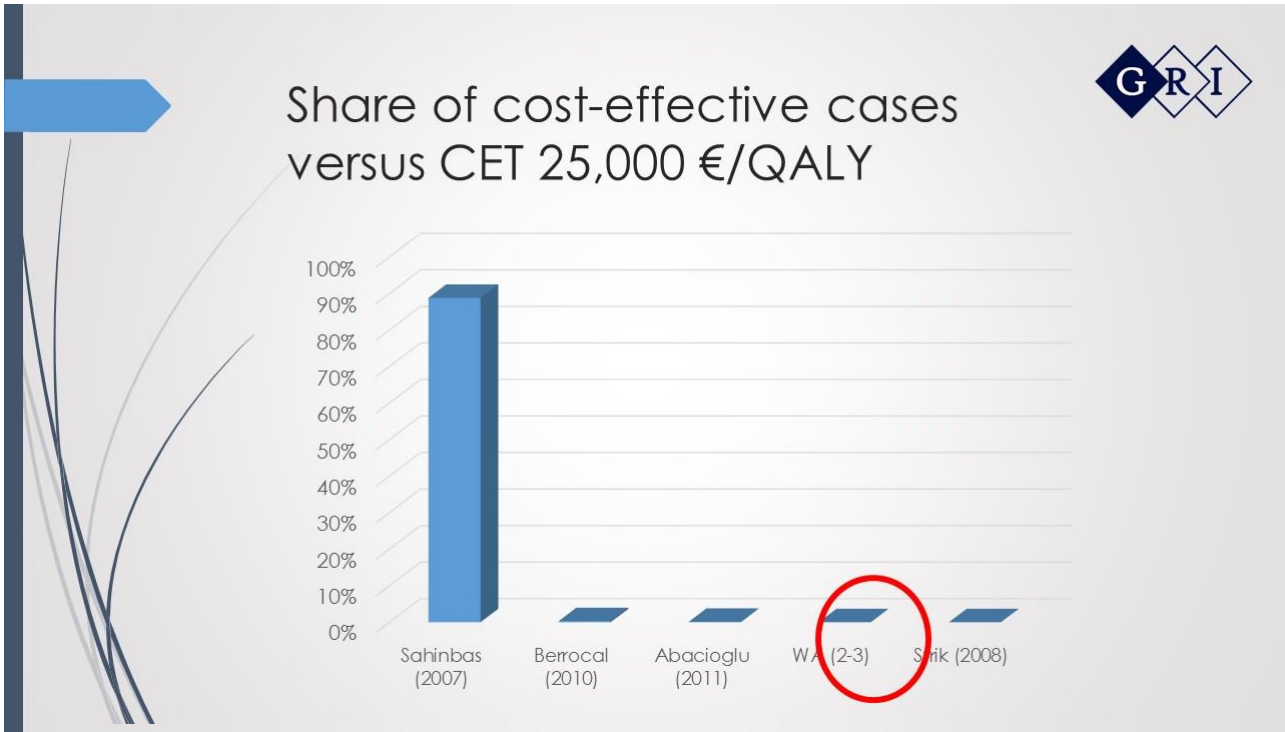
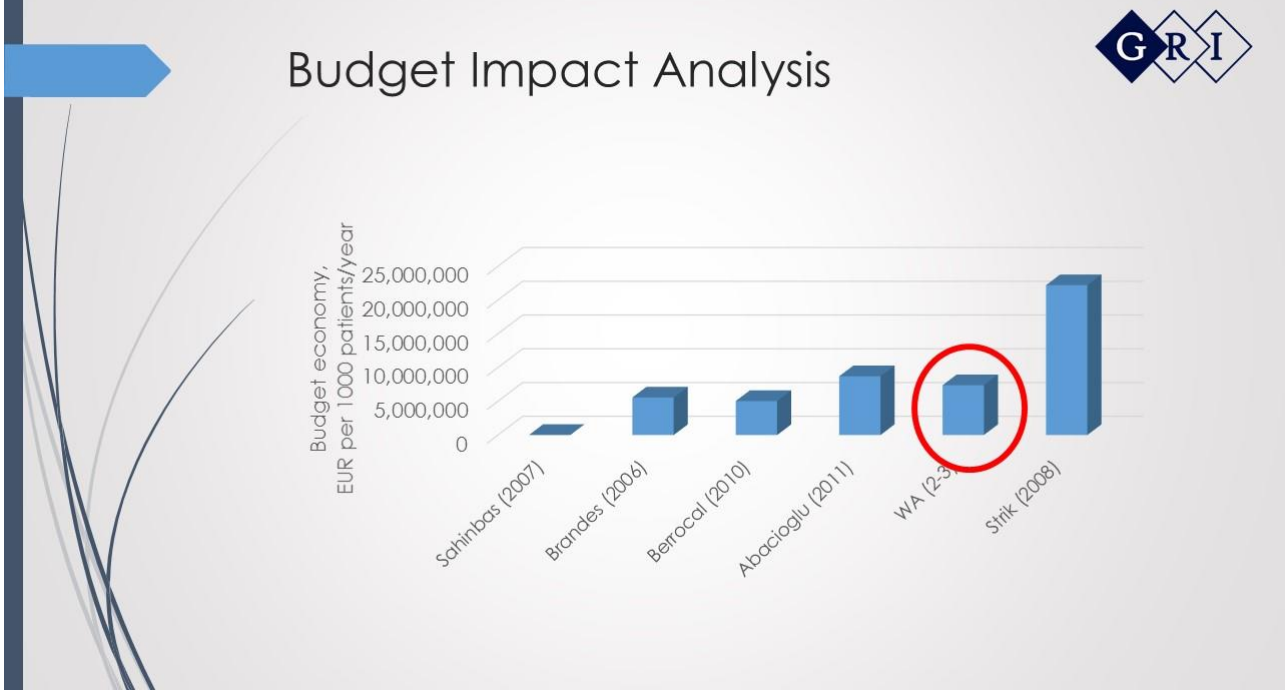
Inclusion of oncothermia in the complex treatment of recurrent GBM suggests the significant improvement of overall survival.

Toxicity summary

- There are no proofs that mEHT enhances toxicity of CTX.
- mEHT can reduce toxicity of combination treatment by enhancing CTX performance and shortening CTX course/dosage.
- In regular (non-forced) treatment per IFU, mEHT generates less than cumulative 40% of its own grade I-II toxicity with no grade III-IV toxicity.
- In case of the forced treatment (exceeds the IFU-recommended dose up to 4 times), mEHT can cause its own grade III-IV toxicity but it doesn't result in dose-limiting toxicity.


Economic Evaluation
ddTMZ + mEHT vs. ddTMZ only
Cost-Effectiveness Analysis
60,000
50,000
40,000
30,000
20,000
10,000
0
Sahinbas (2007)
Brandes (2006)
Abacioglu (2011)
WA (2-3)
Berrocal (2010)
Strik (2008)
ICUR, €/QALY
CUR, €/QALY
Costs, €
Costs, €
CUR, €/QALY
ICUR, €/QALY


Share of cost-effective cases versus CET 25,000 €/QALY
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Sahinbas (2007)
Berrocal (2010)
Abacioglu (2011)
WA (2-3)
Strik (2008)


Budget Impact Analysis
Budget economy, EUR per 1000 patients/year
25,000,000
20,000,000
15,000,000
10,000,000
5,000,000
0
Sahinbas (2007)
Brandes (2006)
Berrocal (2010)
Abacioglu (2011)
WA (2-3)
Strik (2008)

Cost-Benefit Analysis

- CBA was performed from the perspective of a large neurooncology center treating more than 150 patients with recurrent GBM per year with a one mEHT unit.
- Time horizon: eight years.
- Total revenues: €3,124,574 per 8 years.
- Total economic effect (economy + revenues): €5,700,034 per 8 years.
- mEHT device is profitable.

Negative results

Absent

CLAIMS

Claim	LOE	Reasoning
1. Oncothermia* is feasible as an enhancer for all ddTMZ regimens in the treatment of recurrent high-grade brain gliomas (HGG).	2a	Systematic comparison of cohort trials.
2. Oncothermia* is feasible as an enhancer of all TMZ regimens in the treatment of recurrent HGG.	2c	Retrospective cohort trial, inductive reasoning from claim 1.
3. Oncothermia* is feasible as an enhancer for ACNU and other nitrosoureas-containing regimens in the treatment of recurrent HGG.	2a	Two cohort trials, one prospective.
4. Oncothermia* enhances the anti-angiogenic treatments of recurrent HGG.	4	Case-report, extrapolation of the controlled cohort trial, reasoning.
5. Oncothermia* is feasible as an enhancer of all CTX regimens in the treatment of recurrent HGG.	5	Extrapolation of claims 1-3.
6. Oncothermia* applied per claim 1-5 is safe with no grade IV toxicity, and usually with mild grade I-III toxicity.	2b	Prospective cohort trial.
7. Oncothermia* is feasible as an enhancer of TMZ regimens in the treatment of newly diagnosed HGG.	5	Extrapolation of claims 1-3.
8. Oncothermia* in the combination treatment of recurrent HGG is suggested to have the same or better efficacy compared to alkylating drugs like TMZ and nitrosoureas.	2a	Two cohort trials, one prospective.
9. Oncothermia* in the combination treatment of recurrent HGG is feasible in patients with KPS ≥40%, providing the possibility to continue treatment when application of all the other conventional treatments is impossible.	2a	Three cohort trials, one prospective.
10. Oncothermia* is feasible as a single treatment of recurrent HGG in those patients, for which CTX is impossible in view of toxicity or bad performance.	2a	Follows from claims 8 and 9.
11. Oncothermia* is feasible as a salvage treatment of recurrent HGG after the failure of conventional treatments, in combination with CTX or alone.	2a	Prospective cohort trial; case-report; follows from claims 8, 9 and 10.
12. Oncothermia* as a salvage treatment can restore the patient's performance and chemosensitivity and allow to continue active CTX.	4	Case-reports.
13. There are no proofs that oncothermia* enhances toxicity of CTX.	2a	Six cohort studies.
14. Oncotehrmia* can reduce toxicity of combination treatment by enhancing CTX performance and shortening CTX course/dosage.	2a	Three cohort studies + systematic comparison.

Conclusions

- Oncothermia is feasible in the combination treatment of recurrent high-grade brain gliomas (HGG), including and especially of glioblastoma multiforme (GBM), as an enhancer of temozolomide (TMZ) regimens, nitrozoureas (NU) and anti-angiogenic agents (AAA).
- Oncothermia doesn't enhance the toxicity of CTX and can reduce toxicity of combination treatment by enhancing CTX performance and shortening CTX course/dosage.
- In regular treatment per IFU, oncothermia generates less than total 40% of its own grade I-II toxicity with no grade III-IV toxicity.
- In case of the forced treatment (exceeds the IFU-recommended dose up to 4 times), mEHT can cause its own grade III-IV toxicity but it doesn't result in dose-limiting toxicity.
- Oncothermia in the combination treatment of HGG is suggested to have the efficacy of the same order of magnitude as alkylating drugs like TMZ and NU.
- Oncothermia is feasible in patients with KPS ≥30%.
- Oncothermia is feasible as a single treatment in those patients, for which CTX is impossible in view of toxicity or bad performance status, and as a salvage treatment in combination with CTX or alone, after the failure of conventional treatments, with a possibility of restoration of the patient's performance and chemosensitivity and continuation of CTX.
- Oncothermia is suggested to be cost-effective in combination with all the modern CTX agents, namely TMZ, BEV and other AAA; it is budget-saving and profitable from the perspective of the enduser.

Why oncothermia is the optimal salvage treatment?

- well-tolerated
- non-toxic
- possesses the own efficacy of the same order of magnitude as the conventional treatments
- applicable at low performance status
- improves quality of life
- can restore the chemo sensitivity allowing to continue chemotherapy

Systematic Review Lung Cancer Trials with Modulated Electro-Hyperthermia, with Meta-Analysis and Economic Evaluation
(level IIA evidence)

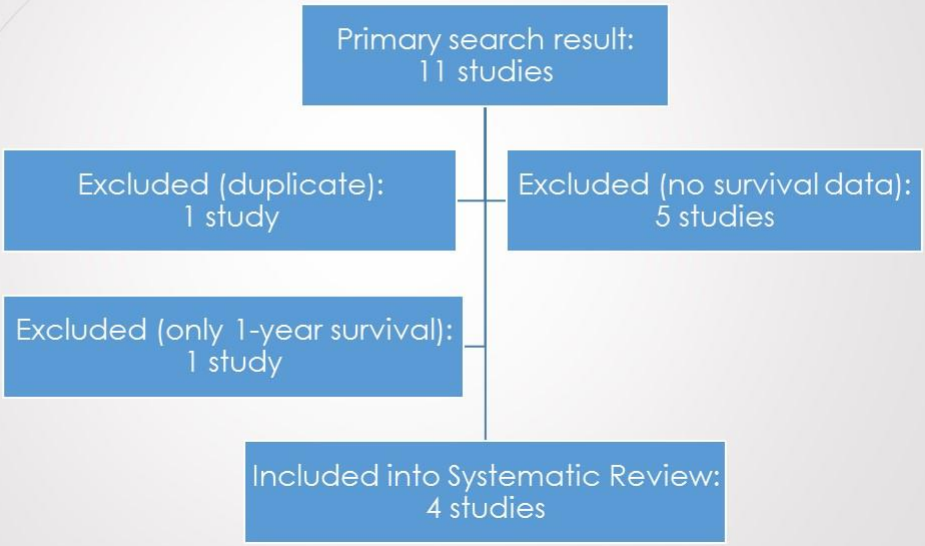
Pre-requisites of the study

- Lung cancer is a fatal disease with one of the least 5-year survivals among all cancers (14-17% in USA and 12-14% in EU).
- In Russia (2012), share of lung cancer is 18,7% in men and 3,6% in women, and it is the first reason of cancer mortality in Russia (17,3% of all cancer deaths).
- Current treatments show low efficacy and can't change the trend of high mortality.
- Thus, study of possibilities to improve the prognosis in lung cancer is of outstanding significance in oncology.

Methods

- Retrospective pharmacoeconomical observational study
- Systematic review of oncothermia trials on lung cancer treatment
- Cost-Utility Analysis

Search Flowchart



Accepted Studies

Name of Study	Country	Type	NOP	LOE	Publication
Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer	Korea	Prospective, cohort, phase II	31	2b	Lee DY, Haam SJ, Kim TH, Lim JY, Kim EJ, Kim NY. Oncothermia with Chemotherapy in the Patients with Small-Cell Lung Cancer. Conference Papers in Medicine. 2013: Article ID 910363, 7 p. doi:10.1155/2013/910363.
Clinical study for advanced non-small-cell lung cancer treated by oncothermia	Hungary	Retrospective, cohort, phase II	258	2c	Dani A, Varkonyi A, Magyar T, Szasz A. Clinical study for advanced non-small-cell lung cancer treated by oncothermia. Oncothermia J. 2011;3:39-49.
Retrospective matched-group clinical study for advanced NSC lung cancer	Hungary		186	2c	Dani A, Osvath M, Szasz A, Szasz N. Retrospective matched-group clinical study for advanced NSC lung cancer. Hyperthermia symposium Cologne, October 24-25, 2003.
A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting	Canada		48	2c	Parmar G. A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting. XXXIII Annual Conference of the International Clinical Hyperthermia Society (ICHS). 10-12 Jul 2015, Nidda, Germany.
TOTAL:			458	2a	

Study 1 (Dani et al., 2011): Description

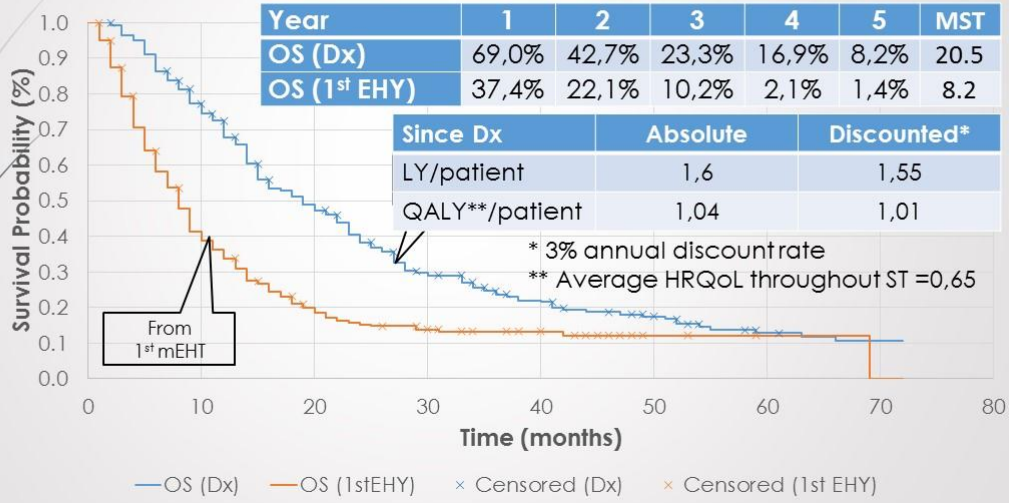
- Retrospective, 2-center, cohort, single arm study
- Non-small cell lung cancer (N=258):
  - Peterfy Hospital (Budapest) (PFY, n=61)
  - HTT-Med Clinic (Budapest) (HTT, n=197)
- Recruitment period: Oct 1997 - Dec 2003
- Average age 57.2±0.65 yrs, median 57 yrs (16-84), normal distribution
- Gender structure: 67.8% males
- Inoperable (St. IIIB-IV): 29% at Dx, 75% at 1st EHY (61% St. IV)
- Oncothermia included in the complex treatment
- Average time to start of oncothermia 11.9±1,07 m, median 6.2 m (0.2-142) or 49.8%±1,8% of OS), median 50.7% (0.68-99)
- Oncothermia applied in the III quartile of survival time

Study 1 (Dani et al., 2011): Survival

Year	1	2	3	4	5	MST
OS (Dx)	69,0%	42,7%	23,3%	16,9%	8,2%	20.5
OS (1st EHY)	37,4%	22,1%	10,2%	2,1%	1,4%	8.2

Since Dx	Absolute	Discounted*
LY/patient	1,6	1,55
QALY**/patient	1,04	1,01

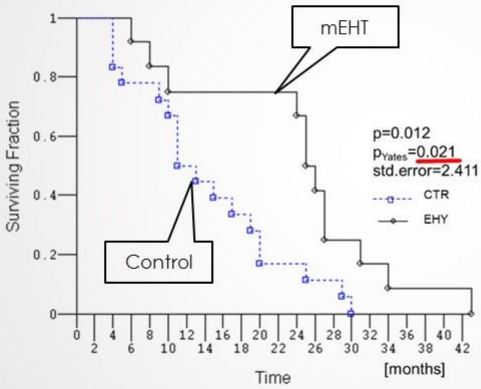
* 3% annual discount rate
** Average HRQoL throughout ST =0,65



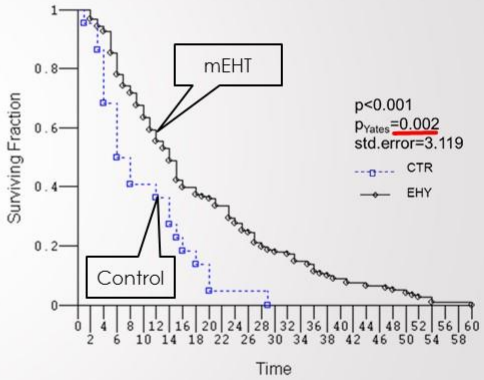
Study 2 (Dani et al., 2003): Description

- Retrospective, monocenter, cohort, double-arm study
- Non-small cell lung cancer (N=186) (Szent Barbala Hispital, Tatabánya):
  - Study arm (SA), standard treatment + oncothermia (n=147)
  - Control arm (CA), standard treatment only (n=39)
- Recruitment period: 1998 - 2001
- Average age: SA=57 yrs, CA=57.3 yrs
- Gender structure: SA=67.8% males, CA=79.2% males
- Metastatic cancer at Dx: SA=59%, CA=45%
- Metastatic cancer at 1st EHY: 88%
- Oncothermia included in the complex treatment

Study 2 (Dani et al., 2003): Survival

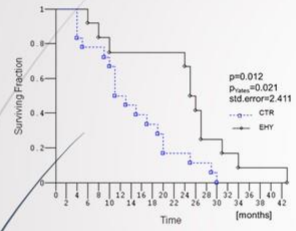


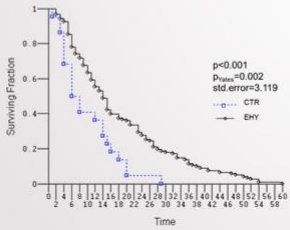
Stage IIIA (n=31/14)



Stage IIIB-IV (n=87/18)

Study 2 (Dani et al., 2003): Survival





Year	1	2	3	4	5	MST
OS (EHY)	58,0%	28,0%	12,0%	5,0%	1,0%	15
OS (Control)	36,0%	4,0%	0,0%	0,0%	0,0%	13.8

Since Dx	Study arm (EHY+)		Control arm (no EHY)	
	Absolute	Disc*	Absolute	Disc*
LY/pat	1,04	1,02	0,4	0,4
QALY**/pat	0,68	0,67	0,26	0,26

* 3% annual discount rate
** Average HRQoL throughout ST: SA=0,65, CA=0.55

Study 3 (Parmar, 2015)

- Retrospective, monocenter, cohort, single arm study
- Integrated Health Clinic (Fort Langley, BC, Canada)
- Non-small cell lung cancer stage IV (N=30)
- Recruitment period: Aug 2010 - Jun 2015
- Stage IV at Dx: 100%
- Oncothermia included in the complex treatment
- Oncothermia applied in the III quartile of survival time

Year	1	2	3	4	5
OS	64,8%	33,5%	33,5%	26,8%	13,4%

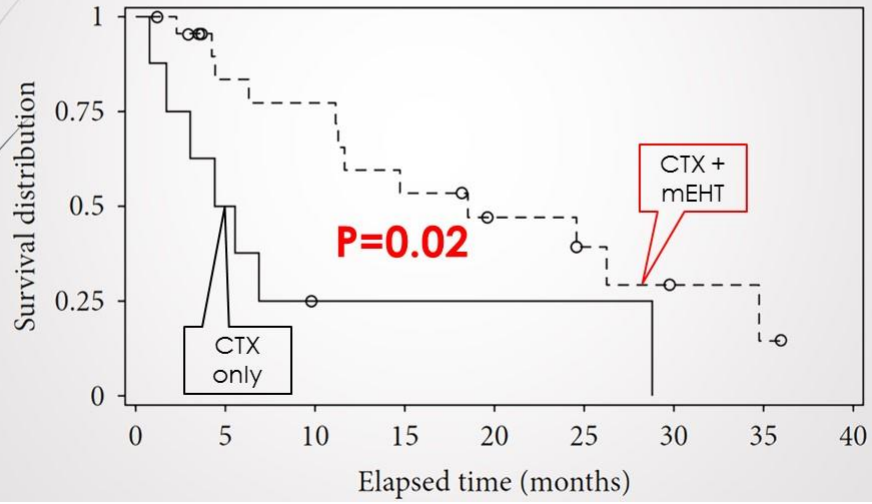
Since Dx	Absolute	Discounted*
LY/patient	1,72	1,65
QALY**/patient	1,12	1,07

* 3% annual discount rate
** Average HRQoL throughout ST =0,65

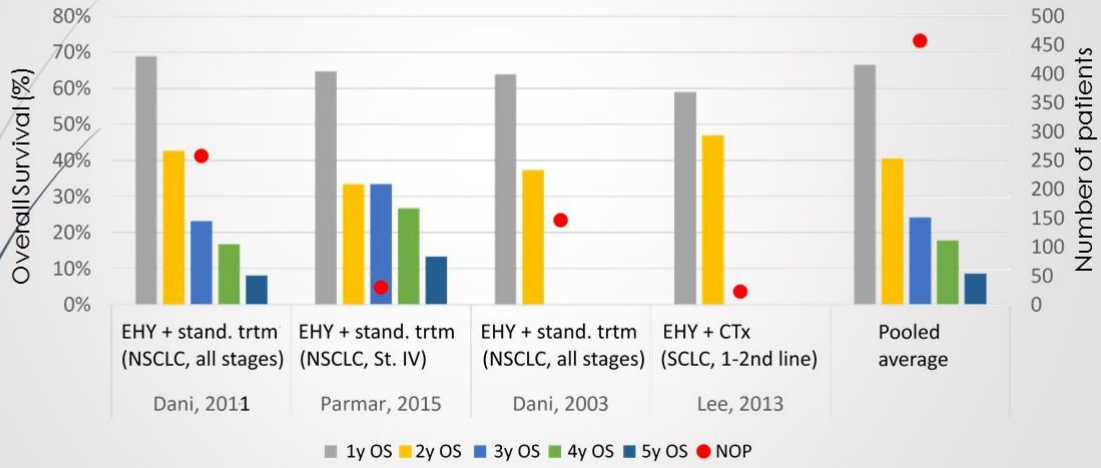
Study 4 (Lee, 2011): Description

- Prospective, monocenter, cohort, double-arm study
- Gangnam Severance Hospital, Yonsei Unoversity, Korea
- Small cell lung cancer (N=31):
  - Study arm (SA), chemotherapy + oncothermia (n=23)
  - Control arm (CA), chemotherapy only (n=8)
- Recruitment period: ongoing study
- Oncothermia in combination with chemotherapy in 1st-2nd line treatment of SCLC.

Study 4 (Lee, 2011): Survival



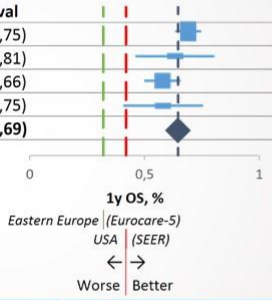
Synthesis of Survival Data



Comparison of Overall Survival

1-year survival of lung cancer trials with mEHT

No Study, cohort	Single-arm Ev/No	1-year survival	Weight (%)	p-value 1	2	3	4	5
1 Dani (2011), Hungary	178/258	0,69 (0,63 – 0,75)	58,4%	1,00	0,54	0,03	0,24	0,24
2 Parmar (2010-2015), Canada	19/30	0,63 (0,46 – 0,81)	6,3%	0,54	1,00	0,57	0,67	0,88
3 Dani (2003), Hungary	85/147	0,58 (0,50 – 0,66)	29,2%	0,03	0,57	1,00	0,98	0,14
4 Lee (2013), Korea	18/31	0,58 (0,41 – 0,75)	6,2%	0,24	0,67	0,98	1,00	0,47
5 Pooled (1 - 4)	**300/466**	**0,65 (0,60 – 0,69)**	**100%**	**0,24**	**0,88**	**0,14**	**0,47**	**1,00**



Fixed effect model (I^2=47,0%, p=0,13)

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Dataset	1	2	3	4	5
Oncothermia (pooled average)	66,6%	40,6%	24,3%	17,9%	8,7%
Standard treatment USA (SEER)	41,6%	26,8%	21,0%	17,9%	15,9%
Standard treatment EU (Eurocare-5)	39,0%	22,7%	17,1%	14,5%	13,0%
Standard treatment East. Europe (Eurocare-5)	32,4%	18,0%	13,7%	11,7%	10,6%
Best radiochemotherapy	54,2%	35,6%	23,8%	15,6%	15,1%

Incremental Utility of Oncothermia

	Best radiochemotherapy		Standard treatment		
	Sequencial	Combined	USA	EU	Eastern Europe
LYG/pat	0,36	0,14	0,35	0,52	0,72
Disconted LYG/pat	0,34	0,14	0,35	0,51	0,70
Added QALY/pat	0,23	0,09	0,23	0,34	0,47
Disc. Added QALY/pat	0,18	0,04	0,18	0,29	0,42

- Oncothermia provides increment of utility versus all comparators.
- The lesser increment is versus best combined chemoradiotherapy (0,04 QALY/pat)
- The maximal increment is versus Eastern European standard treatment (0,42 QALY/pat)

Cost-Utility Analysis

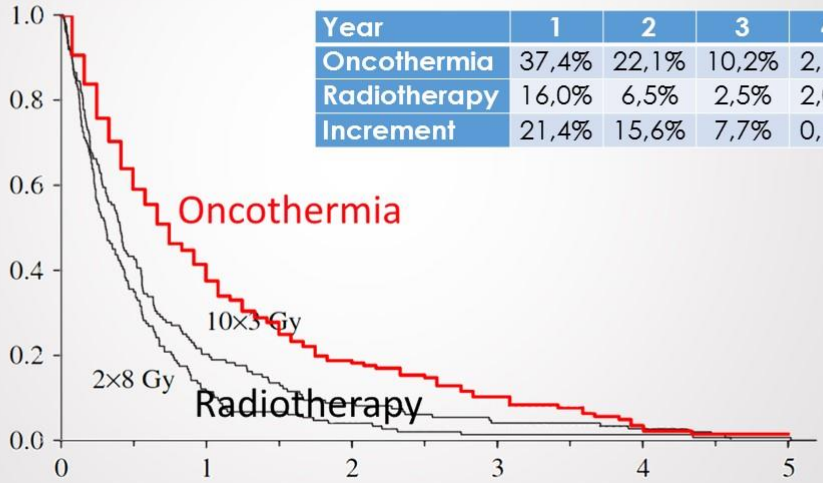
Cost-Utility Analysis of Oncothermia versus Radiotherapy in Treatment of Lung Cancer

Oncothermia vs Radiotherapy: Comparison of cohorts

	Oncothermia	Radiotherapy
Clinical Trial	Dani, 2011	van den Hout, 2006
Country	Hungary	Netherlands
Recruitment	1997-2003	2000-2003
Number of patients	258	297
Average age	**57.4**	69
Males	68%	80%
Stage IV	80%	**47%**
Treatment line	3rd-4th	**1st**
Time to treatment	11.9 months	**1 month**
Pre-treatment	2.69 courses/pat	**0.2 courses/pat**

Oncothermia vs Radiotherapy: Comparison of Survival

Year	1	2	3	4	5
Oncothermia	37,4%	22,1%	10,2%	2,1%	1,4%
Radiotherapy	16,0%	6,5%	2,5%	2,0%	0,0%
Increment	21,4%	15,6%	7,7%	0,1%	1,4%



Oncothermia vs Radiotherapy: Economic Assessment

- Life discounting 3%/year.
- Monetary discounting not used.
- Radiotherapy HRQoL=0.57.
- Though oncothermia always improves life quality versus radiotherapy, the equal HRQoL=0.57 was used for both trials.
- Radiotherapy costs = 3,869 $ /pat.
- Oncothermia costs = 1,727 $/pat:
  - Cost of 1 session EUR 140 (exchange rate 2005 = 1,4 $/EUR).
  - Direct non-medical costs calculated proportionally to radiotherapy costs.

Oncothermia vs Radiotherapy: Cost-Utility Analysis

	QALY/pat	$/pat	CER ($/QALY)
Oncothermia	0.408	1,727	4,230
Radiotherapy	0.151	3,869	25,619
Increment (OT – RT)	0.257	-2,142	-8,328

- **ICER = -8,328 $/QALY**
- This means that radiotherapy generates $8,238 extra costs per each QALY compared to oncothermia use.

Sensitivity Analysis

- Radiotherapy costs:
  - Average: 8,081 $/pat
  - Median: 8,609 $/pat
  - Minimum: 3,874 $/pat
  - Maximum: 14,491 $/pat
- Oncothermia costs:
  - Minimum: 1,283 $/pat
  - Average: 1,727 $/pat
  - Maximum: 3,095 $/pat (300 EUR/session)
- **ICER = -3,008 — -51,342 $/QALY**
- **Radiotherapy instead of oncothermia generates $3,000 — $50,000 of extra costs per QALY.**

Year	Country	$/pat
2003	Canada	9 060
2005	Netherlands	3 874
1999	Canada	4 086
1999	Canada	5 673
2012	Netherlands	8 291
2012	Netherlands	8 609
2012	Netherlands	9 143
2012	Netherlands	9 503
2012	Netherlands	14 491
	Average	8 081
	Median	8 609
	Minimum	3 874
	Maximum	14 491

Cost-Utility Analysis

Cost-Utility Analysis of Oncothermia versus Chemotherapy in Treatment of Lung Cancer

Oncothermia vs Chemotherapy

- Oncothermia of 3rd-4th line versus 1st line Chemotherapy
- Platinum-based Chemotherapy adds 0,49-0,63 LY/pat (average 0,585).
- Chemotherepy costs 5,932-202,176 $/QALY (average 42,841 $/QALY)
- ICER = -10,825 — -250,000 $/QALY
- **Chemotherapy instead of oncothermia generates >$10,000 of extra costs per QALY.**

Chemo	Year	$/unit	Unit	Added units
DOC	2010	48 978	QALY	
DOC	2001	98 493	LY	0,500
DOC	2003	22 181	LY	
DOC	2001	20 654	LY	
DOC (2nd line)	2001	25 442	LY	0,490
DOC средняя		42 412	LY/QALY	
ERL	2014	89 129	QALY	
ERL	2007	202 178	QALY	
ERL	2007	88 030	LY	
ERL	2009	75 710	LY	
ERL	2011	36 838	LY	
ERL average		98 377	LY/QALY	
GEF	2014	56 049	QALY	
GEM	2001	8 251	LY	0,580
GEM	2006	16 603	QALY	
GEM	2002	7 581	PFLY	
GEM+CARB	2014	37 030	QALY	
GEM+CIS	2001	14 559	LY	0,730
GEM+CIS	2014	49 789	QALY	
GEM average		27 123	Разл.	
PAX	2001	43 071	LY	0,540
PAX	2001	67 585	LY	0,540
PAX (135) +CIS	2001	12 379	LY	0,780
PAX (175) +CIS	2001	20 480	LY	0,730
PAX (250) +CIS	2001	17 551	LY	0,830
PAX average		32 213	LY	
PEM	2010	61 470	QALY	
PEM+CIS	2012	56 000	QALY	
PEM average		58 735	QALY	
VIN+CIS	2006	16 603	QALY	
VNB	2001	5 932	LY	0,590
VNB+CIS	2001	7 549	LY	0,700
VNB+CIS	2014	59 797	QALY	
VNB average		24 426	LYS	
CTx average		42 841		0,585
CTx minimum		5 932		0,490
CTx maximum		202 178		**0,626**

Negative results

Absent

Conclusions

- Oncothermia in the 3rd-4th line complex treatment of lung cancer provided better 1-3 year survival compared to any 1st line conventional treatment except of surgery, including the best chemoradiation treatment.
- Oncothermia provided virtually the same utility as the best concurred chemoradiation treatment (+0,04 QALY/pat) and the better utility than standard treatment in USA and Europe (+0,42 QALY/pat versus Eastern Europe).
- Oncothermia showed the better cost-utility compared to radiation therapy with ICER = -3,000 — -50,000 $/QALY.
- Oncothermia showed the better cost-utility compared to chemotherapy with ICER = -10,000 — -250,000 $/QALY.
- Thus, oncothermia is pharmacoeconomically preferable treatment versus either radiotherapy or chemotherapy in complex treatment of lung cancer.

Thank you for attention

Testing modulated electro-hyperthermia using C26 colorectal carcinoma cell line in vitro

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Testing modulated electro-hyperthermia using C26 colorectal carcinoma cell line *in vitro*

Eva Kiss[1], Tamas Vancsik[1], Gertrud Forika[1], Peter Hamar[2], Tibor Krenacs[1]

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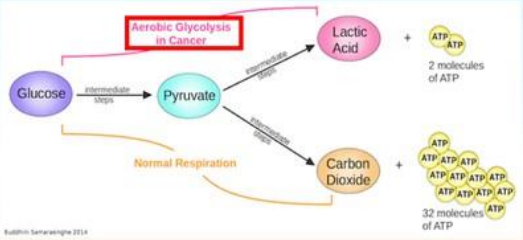
2017. 09. 12.

Modulated electro-hyperthermia (mEHT)

- complementary
- 13.56 MHz electromagnetic field
  - safe
  - optimal tissue penetration
- amplitude modulation (AM) of the carrier frequency
- 42 °C
- thermal effect
- high energy absorption
- tumor destruction

Modulated electro-hyperthermia (mEHT)

In a tumor tissue:
enhanced aerobic glycolysis
high water and ion concentration in EC



Modulated electro-hyperthermia (mEHT)

In a tumor tissue:
enhanced aerobic glycolysis
high water and ion concentration in EC

⇩

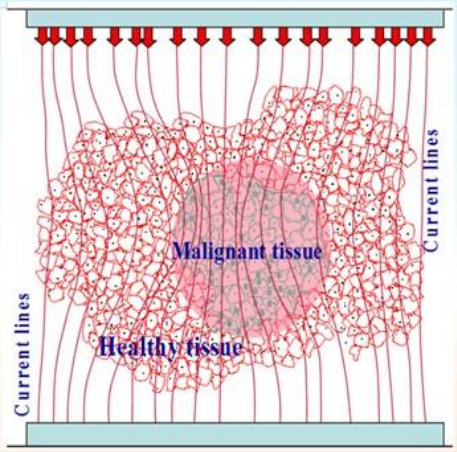
increased conductivity
lower electric resistance

⇩

The electromagnetic field **enriches selectively in the tumor**

Tumor destruction

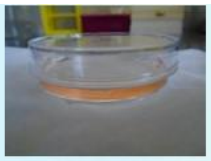
Modulated electro-hyperthermia (mEHT)

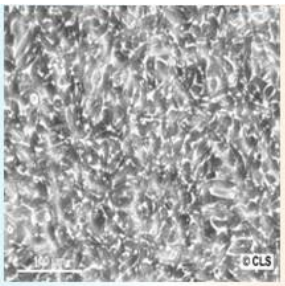


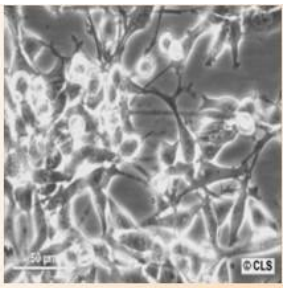
Aims

- ✓ **To set up** optimal and effective **experimental conditions for *in vitro*** studies
- ✓ **To test** mEHT induced
  1) **morphological changes**
  2) **cell death**, stress response & growth signaling related marker expression

Materials and Methods

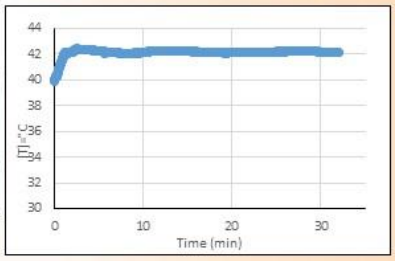


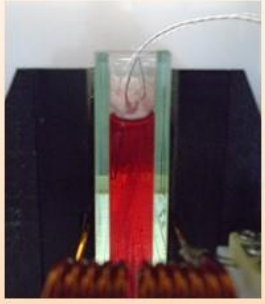


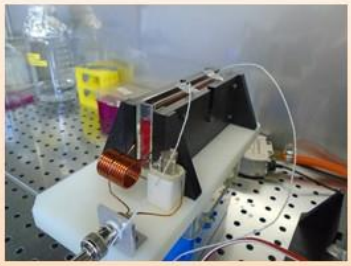


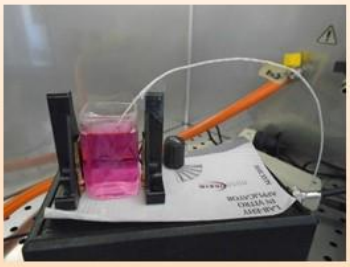
http://www.clsgmbh.de/artikeldet.php?proid=10486&sid=7kcd48a0aep4h0dc1jmotua2t6

- Mouse colorectal adeno-carcinoma (**C26**)
  - cultured in RPMI 1640 medium
  - on coverslips in Petri dishes (700 000 cell / 4 ml)
- Modulated electro-hyperthermia (**mEHT**)
  - LabEHY 100 (Oncotherm, Paty, Hungary)
  - ~42°C
  - **repeated treatments (2x30 minutes or 2x60 minutes)**
- Experimental groups:
  1. control (kept 37°C in incubator)
  2. modulated electro-hyperthermia (~42 °C)
- Sampling:
  - early (**3h**) and late (**24h**)
  - fixation in ethanol:acetone=3:1
- Morphological changes, stress response, apoptosis and growth signaling related markers were detected









I. 2x30 minutes mEHT treatment

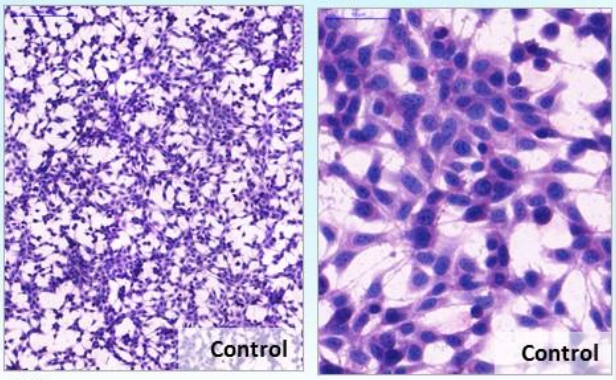
II. 2x60 minutes mEHT treatment

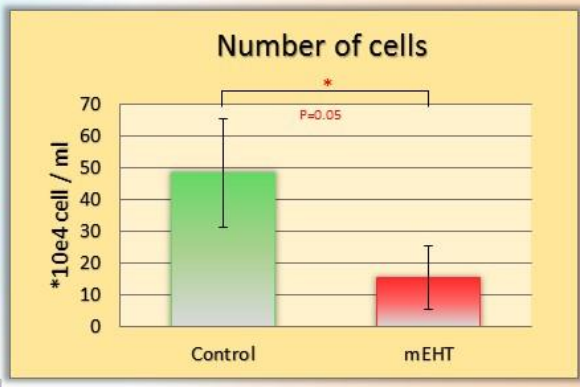
Results –
Tumor damage

2x30 min mEHT
24 h post-treatment

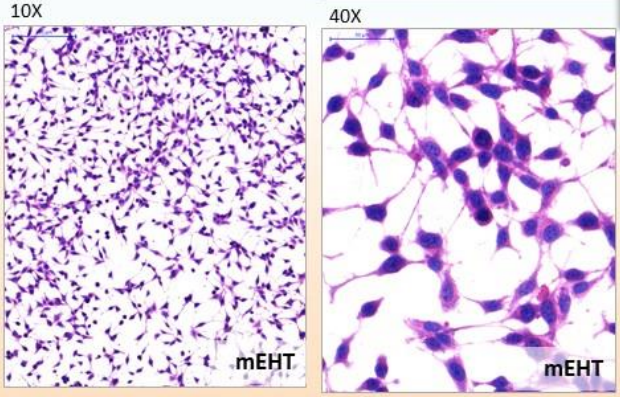
H&E

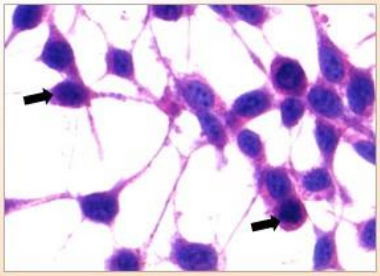
10X 40X





10X 40X





✓ Reduced tumor cell number
✓ Chromatin condensation → apoptosis

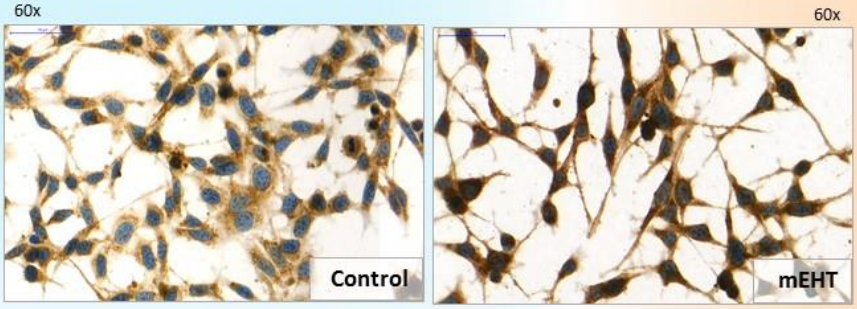
Results –
Immuncytochemistry

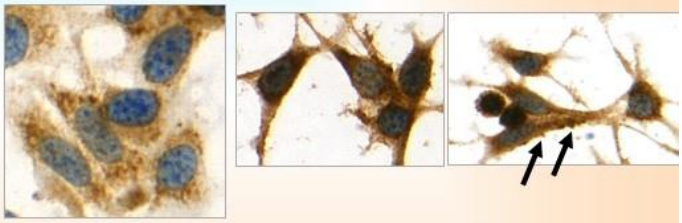
2x30 min mEHT
24 h post-treatment

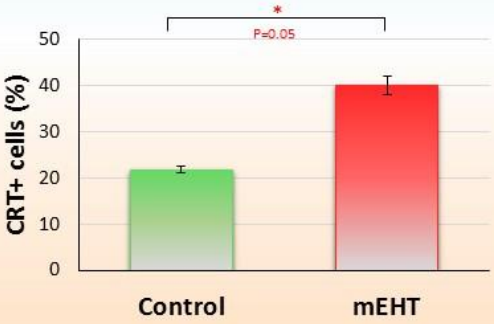
Calreticulin (CRT)

ER chaperone protein
Ecto-CTR is an early marker of apoptosis
ER → cytoplasm
member of DAMP (Damage Associated Molecular Pattern)

60x 60x



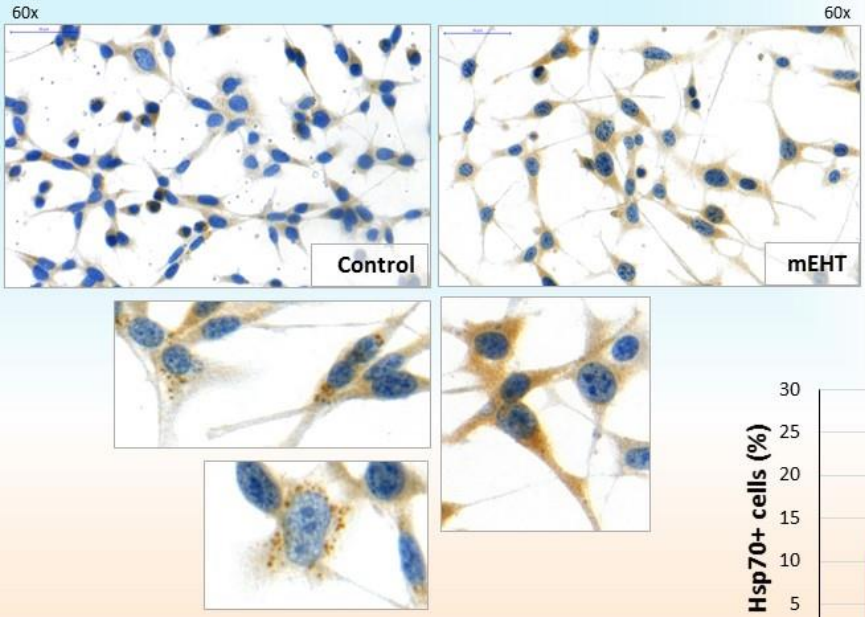




✓ Intensive CRT release after 2x30 minutes mEHT treatment 24h post-treatment

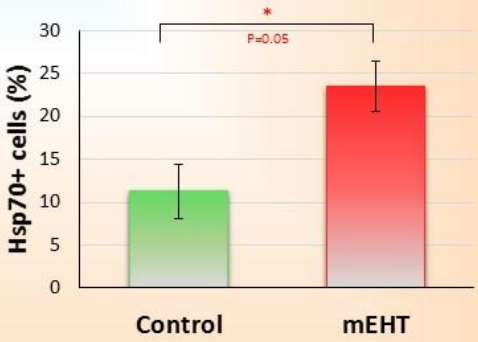
Results –
Immuncytochemistry

2x30 min mEHT
24 h post-treatment



Hsp70

granular → diffuse
heat shock protein
member of DAMP



✓ Visible granular location of Hsp 70 in the control
✓ Became a diffuse pattern due to mEHT treatment

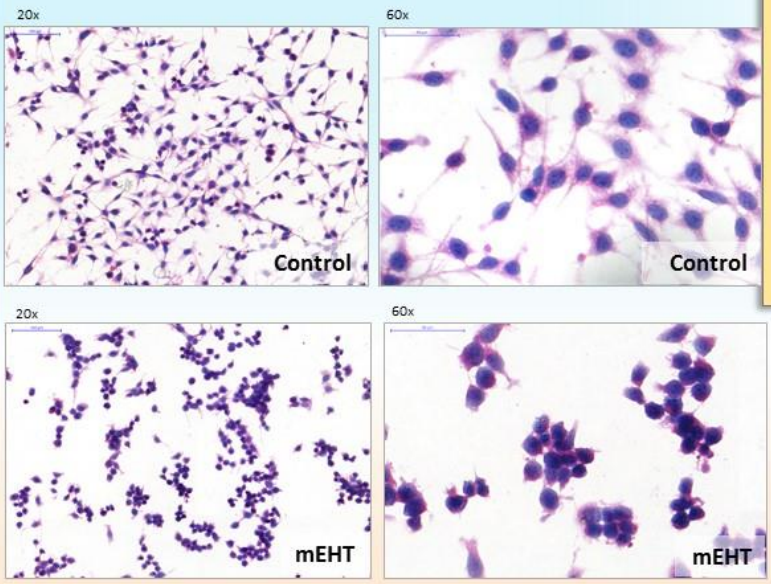
I. 2x30 minutes mEHT treatment

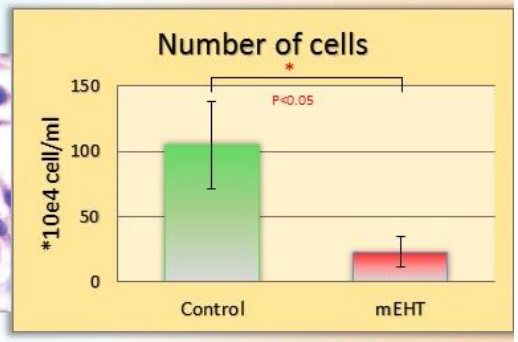
II. 2x60 minutes mEHT treatment

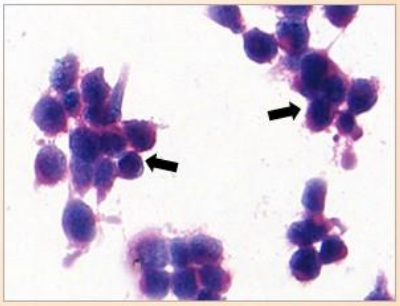
Results –
Tumor damage

2x60 min mEHT
3 h post-treatment

H&E





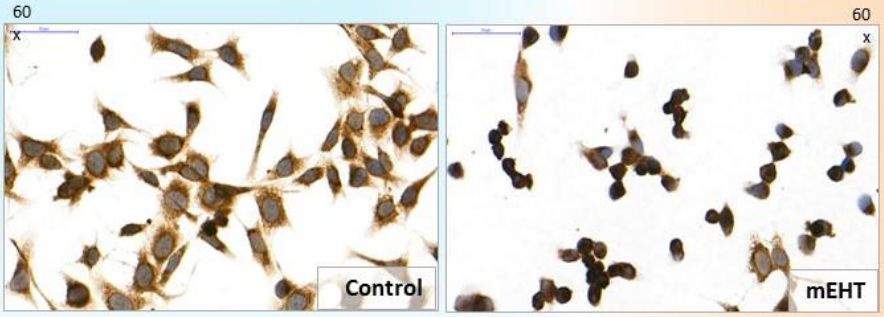


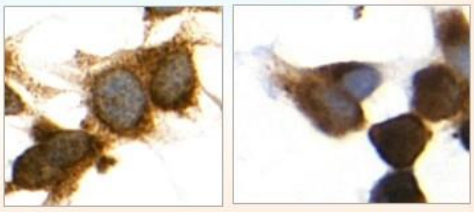
- ✓ Lost of tumor cell processes
- ✓ Reduction of tumor cell number
- ✓ Chromatin condensation → apoptosis

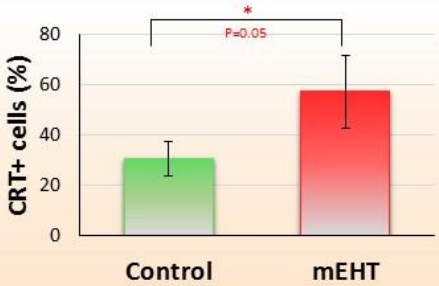
Results –
Immuncytochemistry

2x60 min mEHT
3 h post-treatment

Calreticulin (CRT)



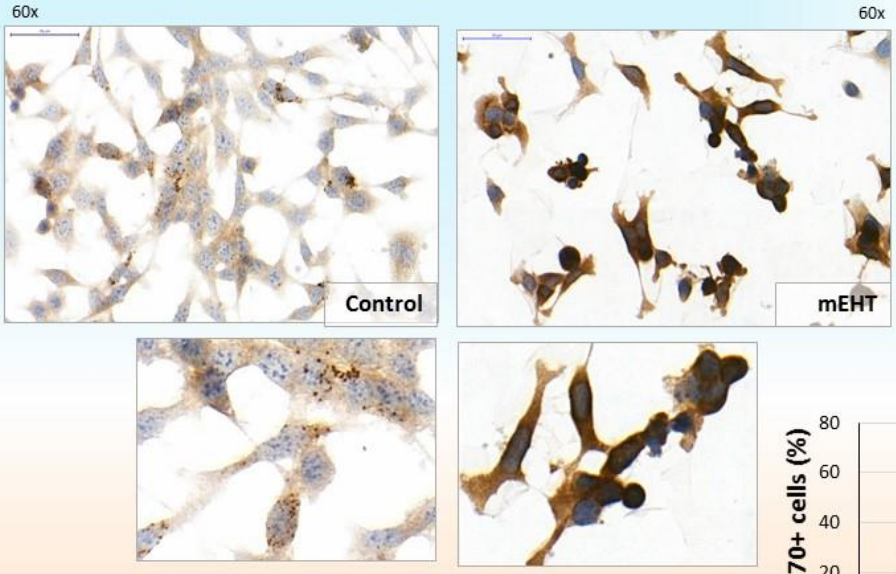




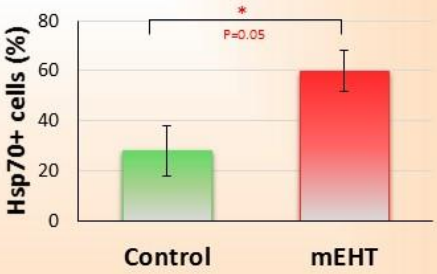
✓ mEHT causes more intensive CRT positivity after 2x60 minutes treatment

Results –
Immuncytochemistry

2x60 min mEHT
3 h post-treatment



Hsp70

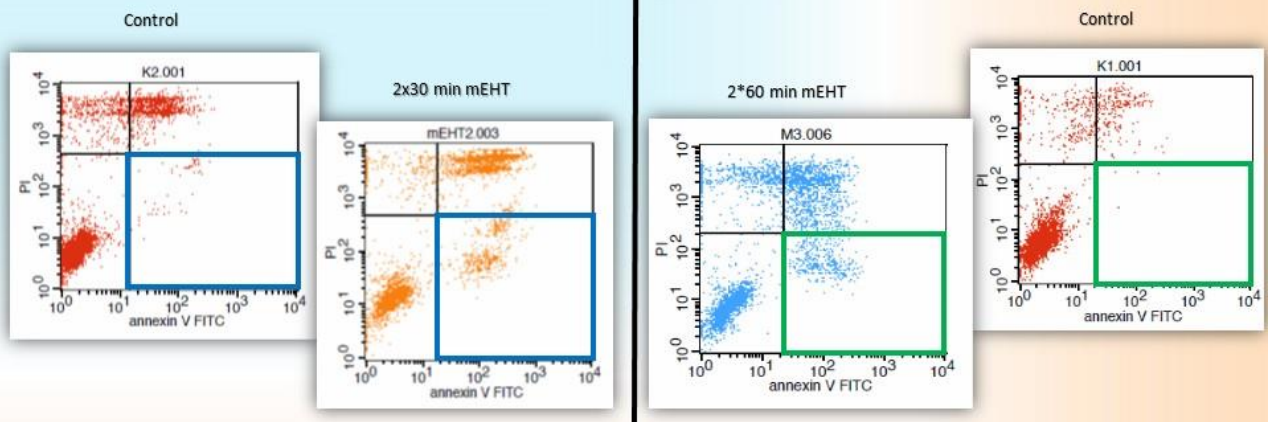


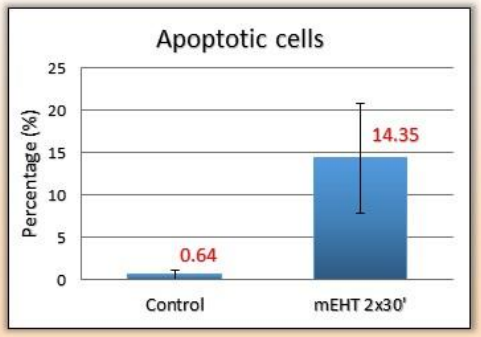
✓ **Significant increase of Hsp70 level after 2x60 minutes mEHT treatment compared to control**

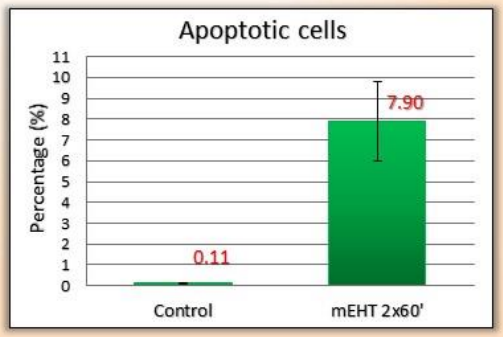
Results –
Flow cytometry

24 h post-treatment

2x30 min | **2x60 min**



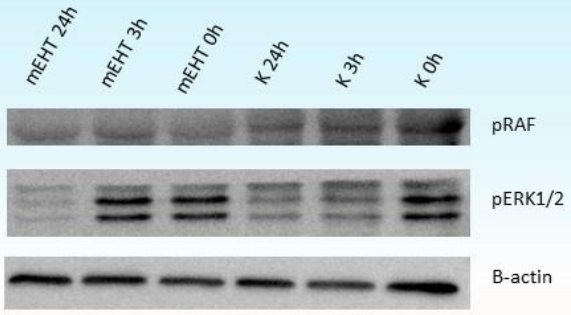


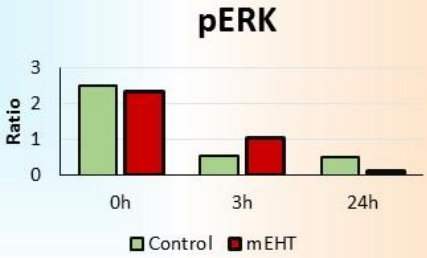


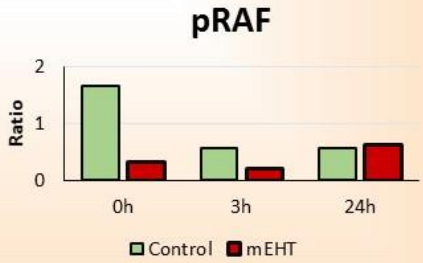
Results –
Protein analysis

2x30 min mEHT

Western blot







✓ **Inactivation of pRAF**
✓ **Activation of pERK 1/2**

Conclusion

According to our preliminary results we can summarize that:

- mEHT caused significant **apoptotic cell death** alone besides the release of such damage and stress associated molecular pattern proteins (CRT, Hsp70) which can potentially induce immunogenic response *in vivo.*

This study has been supported by the Hungarian National Research, Development and Innovation Office (NVKP_16-1-2016-0042).

The efficiency of modulated electro-hyperthermia may correlate with the tumor metabolic profiles

Gertrud Forika[1], Tamas Vancsik[1], Eva Kiss[1], Zoltan Hujber[1], Anna Sebestyen[1], Ildiko Krencz[1], Zoltan Benyo[2], Peter Hamar[2], Tibor Krenacs[1]
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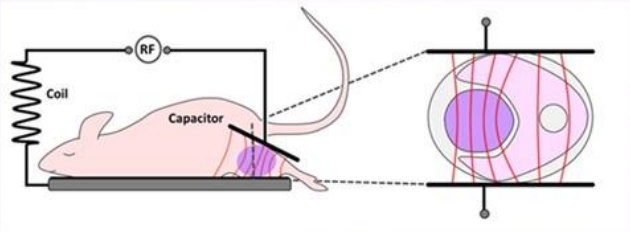
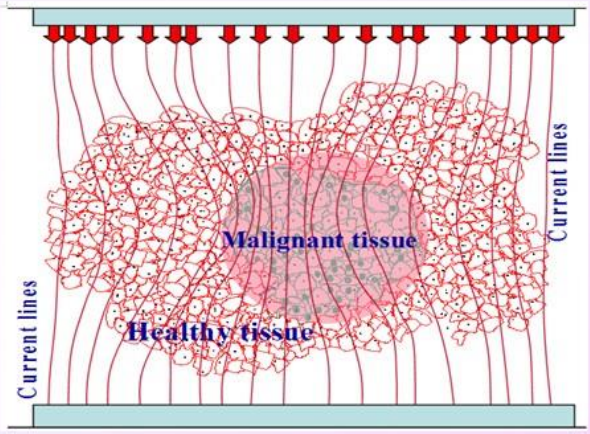
Modulated electro-hyperthermia (mEHT) – the method



- Loco-regional
- Non invasive
- Complementary therapy

Using 13.56 MHz radiofrequency it generates hyperthermia (~42°C) => Apoptotic cell death

The conductivity of electric field has an affinity to increased ion concetration tissue. Malignant tissues, due to their elevated glycolysis, results more ion particles (Warburg effect). So the treatment target these tissues and acts there.



mEHT and Warburg effect (elevated glycolysis)

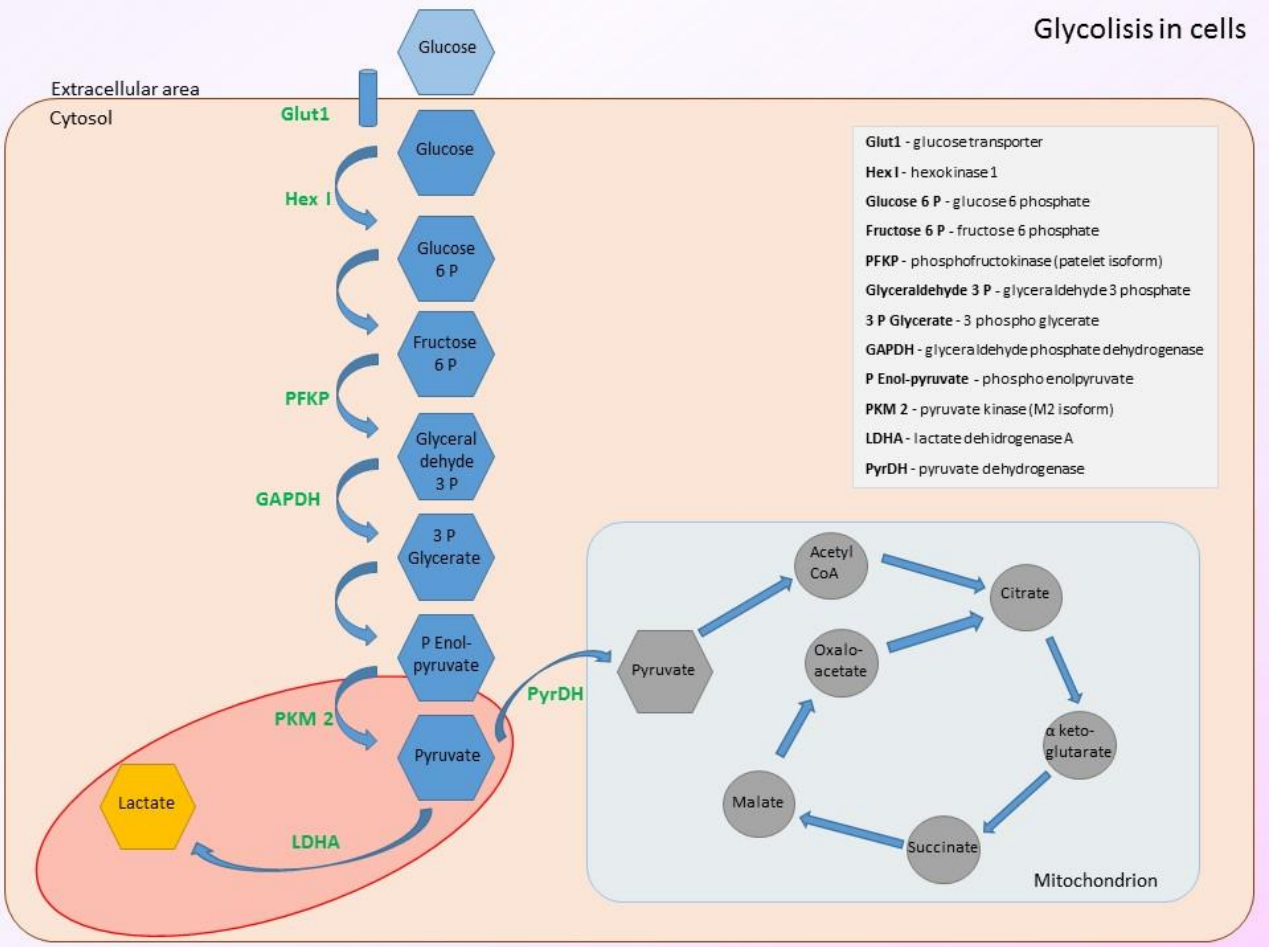
Elevated charged metabolite level existed in solid malignant tumors

- Lactic acid, other charged ions => acidic environement

- Better conductivity -> concentrate the electric field -> selectivity of tumor treatment
- The question arises: Can the glycolysis proprieters of tumor influence the tratment efficacy?

Objective

- To quantify the tumor destruction rate (TDR) on different cell lines after mEHT treatment
- To make a glycolysis profile for the cell lines
- To respond to the question if the tumor destruction rate is influenced by the glycolytic pathway activity

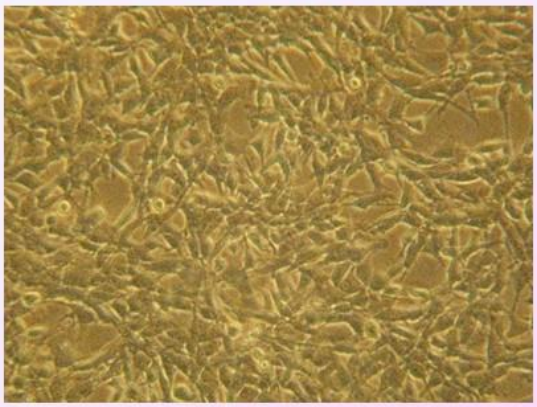


Used cell lines

HT29 - human colorectal carcinoma
HepG2 - human hepatocellular carcinoma
C26 - mouse colorectal carcinoma
C38 - mouse colorectal carcinoma

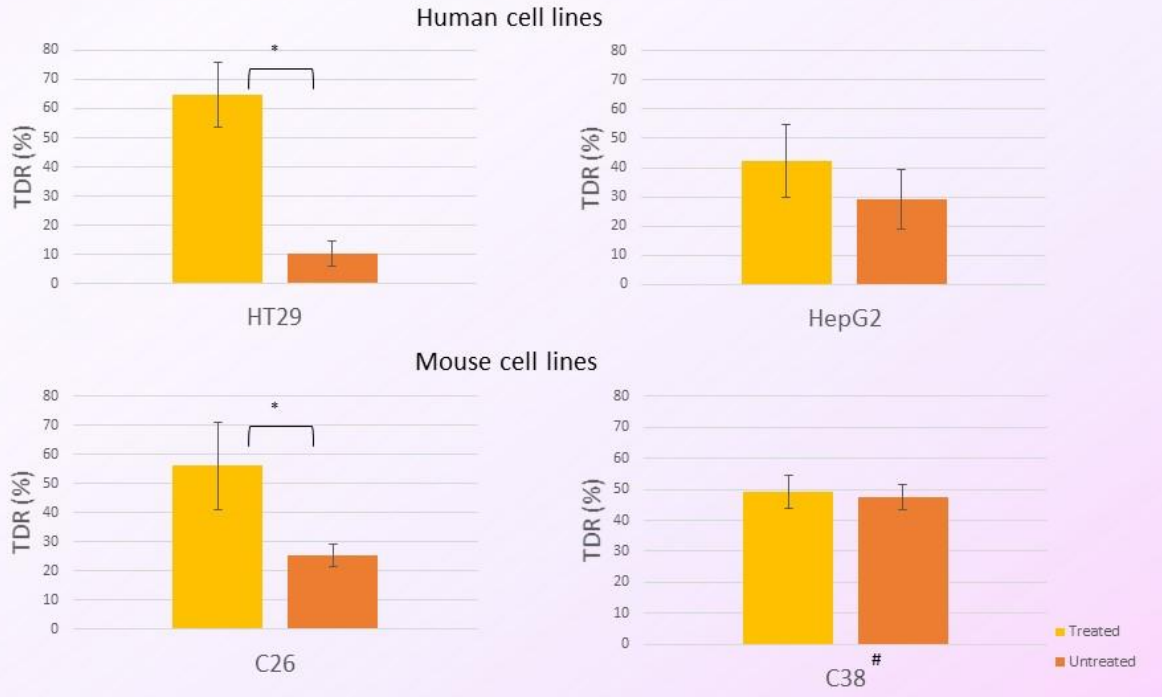
Cell glycolisis profiling:

- Intracytoplasmatic metabolits
- pH and buffer capacity measurements
- In situ glycolytic enzyme production



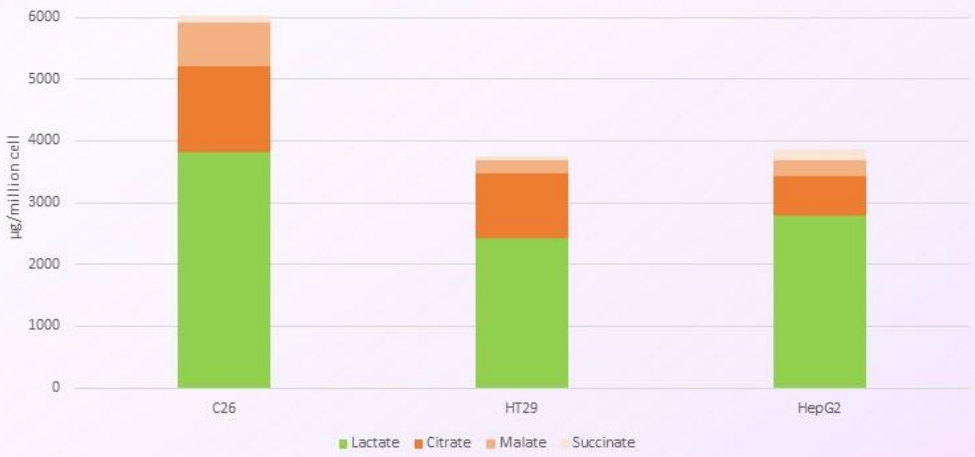
mEHT induced tumor destruction rate (TDR)

- Single shot, 30 minuters long mEHT treatment. Samples after 24 hours



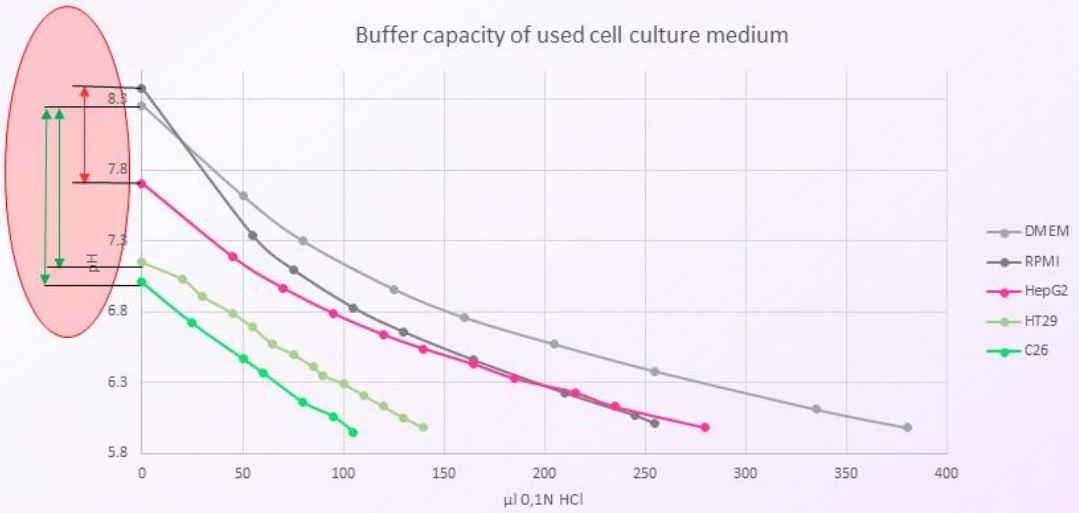
#at 96 hours sampling there was a bigger difference

Intracytoplasmic glycolysis metabolites



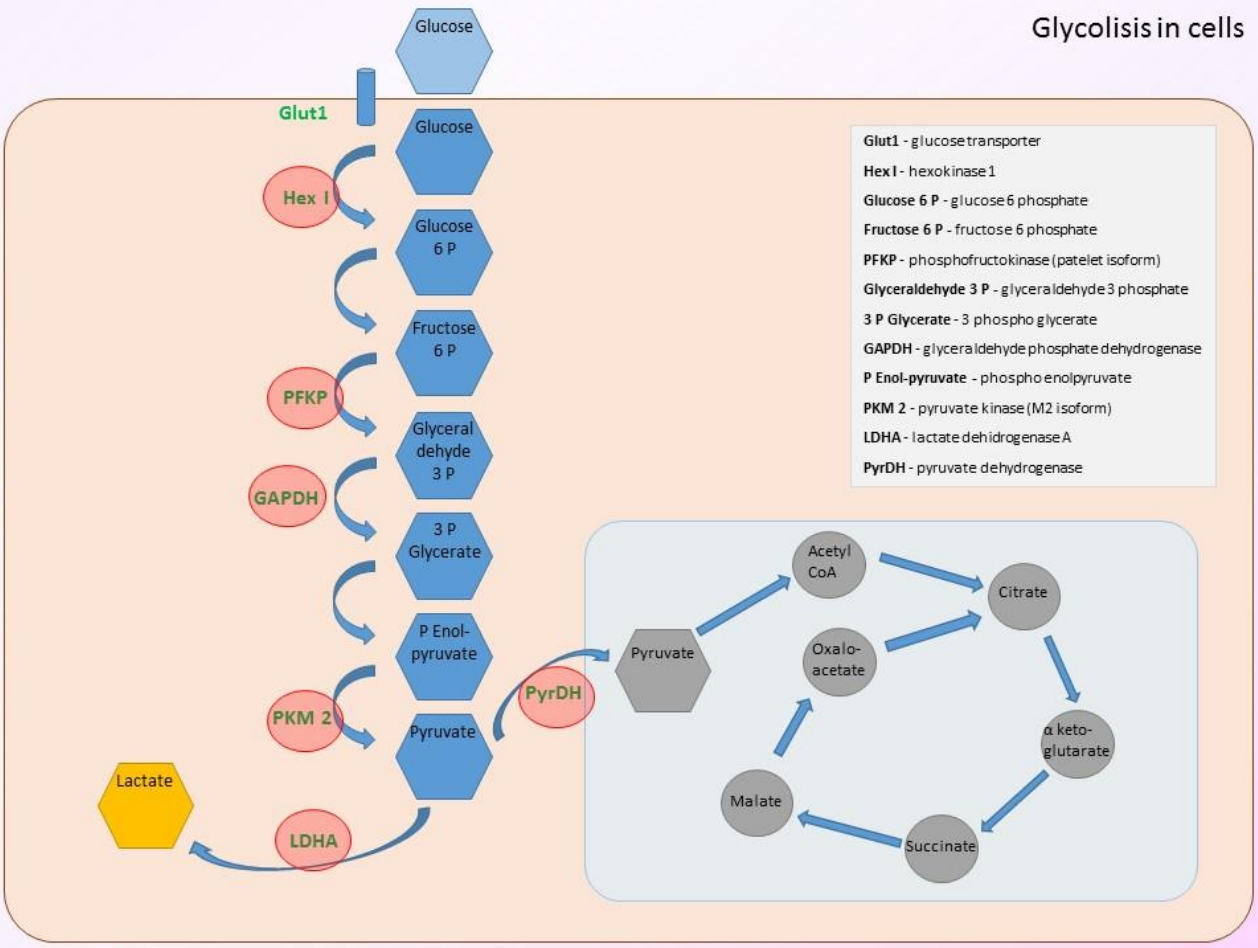
The intracytoplasmic level of lactate and some of Krebs cycle products are the same in the HepG2 and HT29 cell lines. The C26 has an elevated metabolit production

Extracellular acidification rate (ECAR)

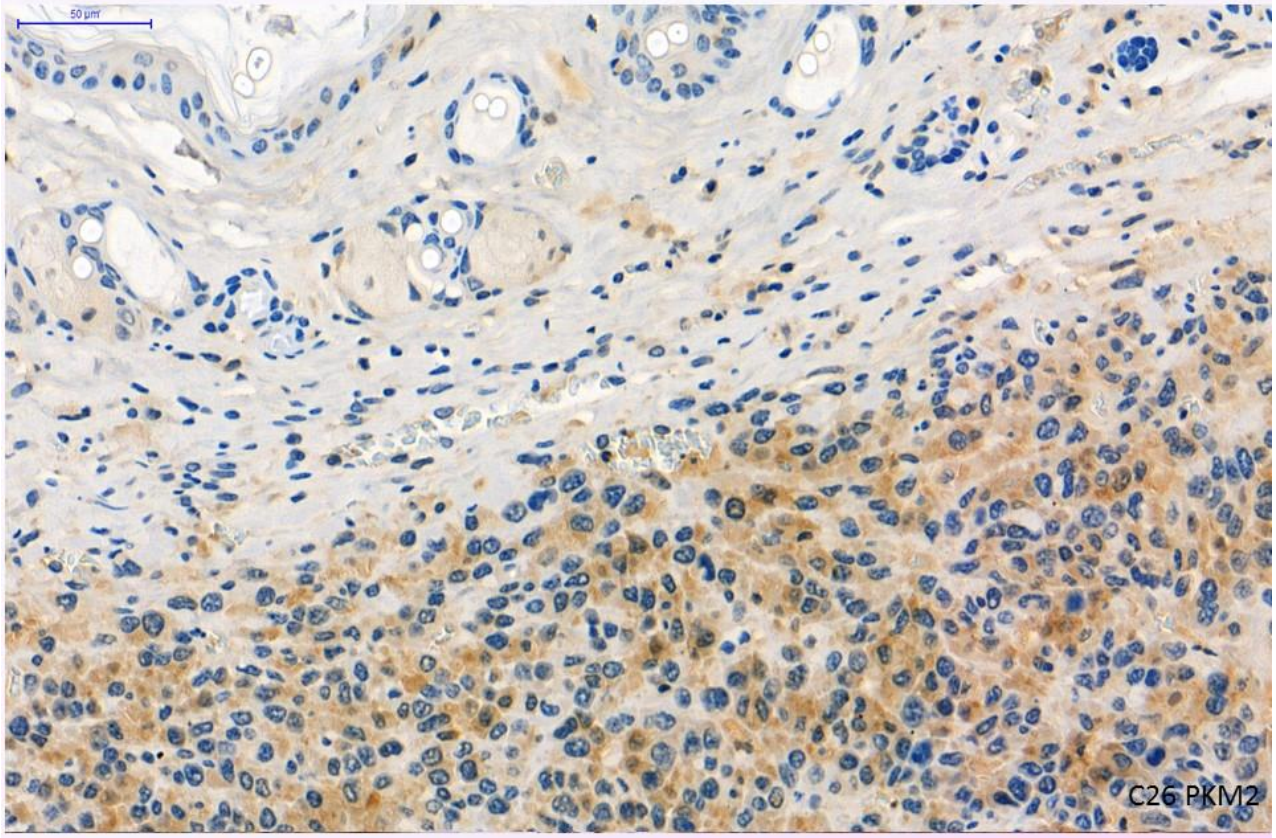


The culture mediums buffer capacity shows the ammount of acidic particles exported by cells. The medium used by HepG2 cell line was the less acidic, so the C26 and HT29 produced the most acidifying particles in the extracellular area.

- Cell culture media removed after the cell culture growth to confluent form (3 days)



Presence of glycolytic enzymes



Conclusion

- Warburg effect is present in the studied cell lines
- mEHT treatment efficiency varied among different tumor types based on TDE (*tumor destruction rate*)
- The intracytoplasmatic ion concentration may differ from the extracellular environement
- The extracelullar lactate amount can be a precise indicator for treatment efficiency
- The elevated ion concentration supports the accumulation of electric field


This study was founded by NKFIH-NVKP_16-1-2016-0042 grant

Inoperable multifocal intrahepatic cholangiocarcinoma treated with Hyperthermia, IV Vitamin C and ozonated blood autotransfusion

Michael Marangos, Lazaros Danilidis, Ioannis Vakalis, Petros Kouridakis
Aias Papastavrou, Alfred Barich

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http://oncotherm.com/sites/oncotherm/files/2017-10/Pages%20from%20Oncothermia%20Journal%20volume%2020-11.pdf

WELCOME

9/12/2017

1

Inoperable multifocal intrahepatic cholangiocarcinoma treated with Hyperthermia, IV Vitamin C and ozonated blood autotransfusion

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- 1. Thessaloniki Hyperthermia Center,
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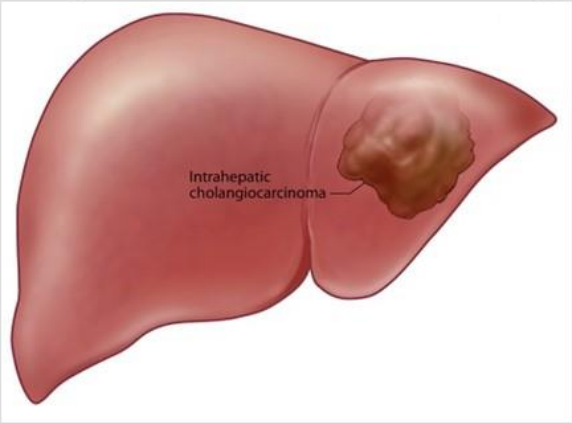
INTRODUCTION:

Intrahepatic cholangiocarcinoma is a rare (3/1000000) malignancy with a very poor prognosis. Even in the rare cases that are resectable (30%) more than half of them have lymphatic spread at the time of diagnosis.



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Chemotherapy and Radiation therapy have a purely paregoric role. In extensive disease, there is no more than 4% 1yr, and the mean survival is 8.5 months from diagnosis.

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CASE PRESENTATION:

This case is a 75 yr. old woman that presented with weight loss, anorexia, weakness, and intermittent low grade fever.

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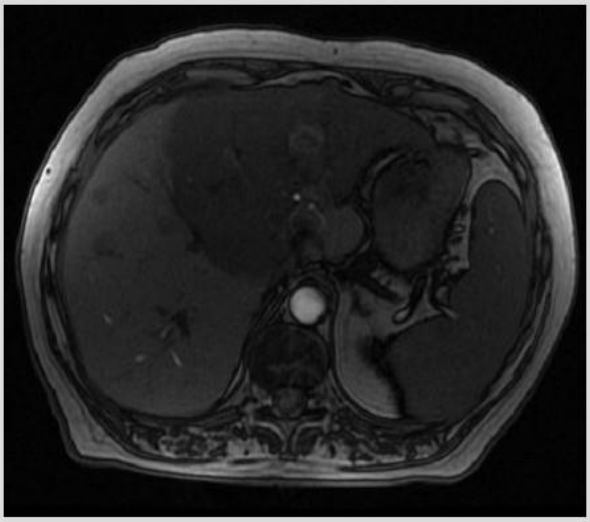
MRI RESULTS 31-10-2016

- Depicted a lesion covering half her liver , with concurrent satellite lesions



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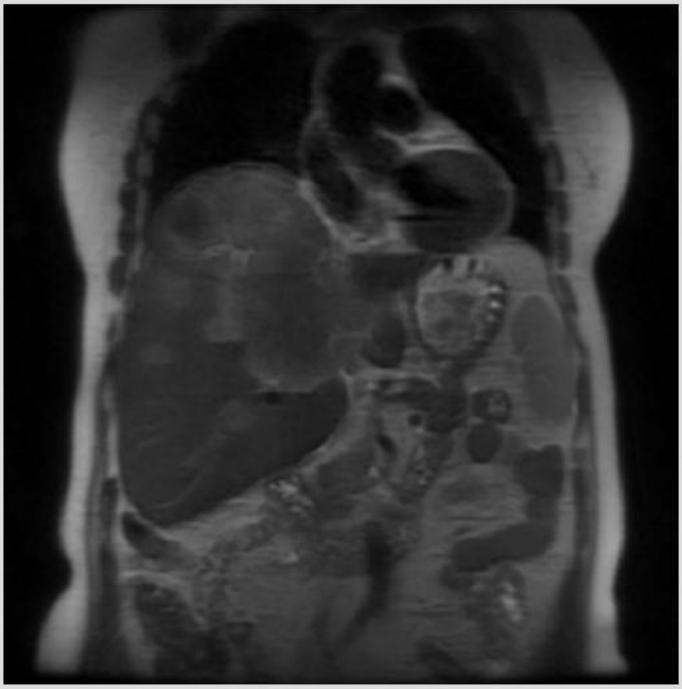
LUNG CT 31-10-2016

- No metastatic disease.



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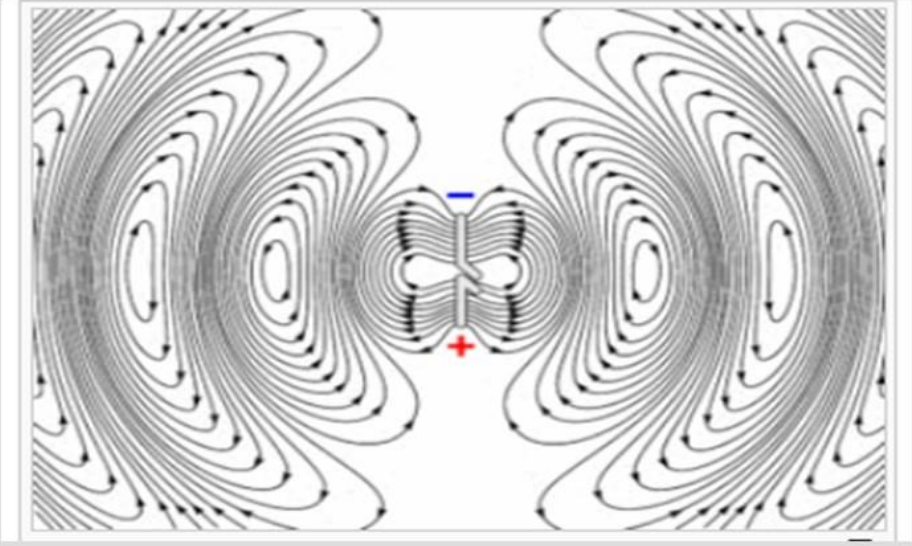
BLOOD TESTS

- Normal
- CEA levels were normal (0.53ng/ml).
- Monoclonal antibodies indicated the presence of the disease:
- CA 125- 121.8 U/ml,
- CA 19.9- 387.3 U/ml ,
- CA 15.3- 24.98 U/ml

Consent form

- Due to her age, she refused standard treatment modalities (chemo, radiation etc.)



- She was amenable only to our proposal to treat her with:
- Hyperthermia (mEHT),
- IV Vitamin C and
- Autotransfuion of ozonated blood .

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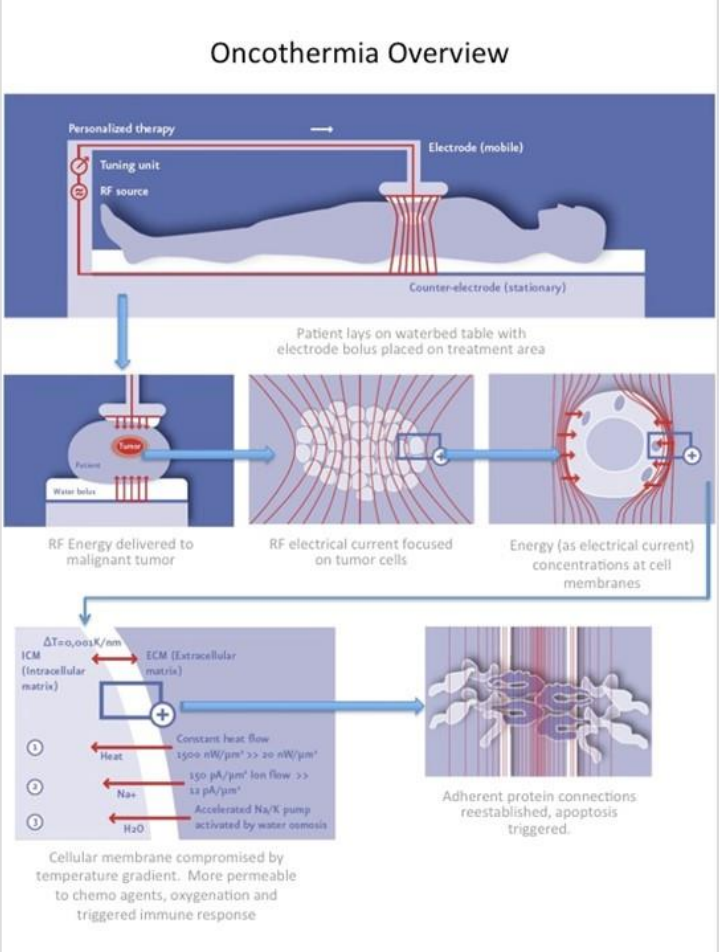
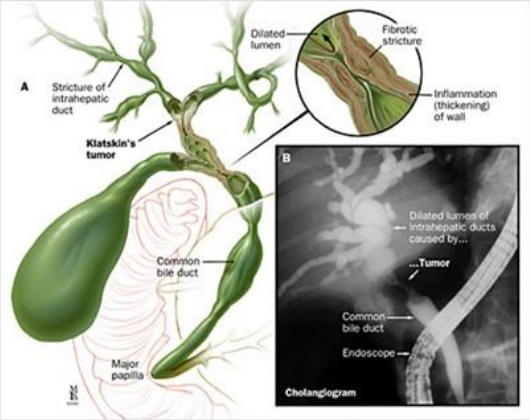


Methods Phase I :

- Treatment from 18/11/17 – 27/12/17 with
- mEHT for 60 minutes
- (Abdominal field covering all the liver area) with mean 450KJ energy field for six weeks with two sessions per week.



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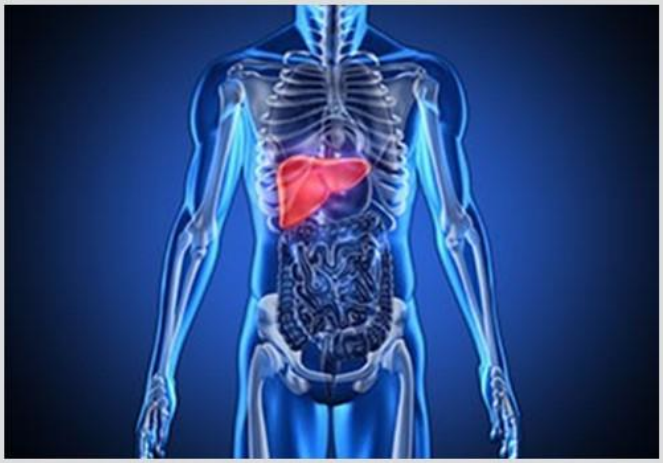
Methods Phase II :

- Treatment from 9/2/17 – 23/3/2017 with the same parameters as Phase I



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- The patient was tested for G6PD and TSH.
- Having secured normal IV 7gr. Vitamin C with Magnesium, alternating with Selenium 200μg and Zn every other session.
- Previous to this autotransfusion of ozonated blood was performed (125ml of her blood was taken , ozonated,and autotransfused).

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FOLLOW UP

- MRI GE Sigma Infinity 1.5 Tesla with EXCITE at the same diagnostic center with Transverse, Coronal and Saggital planes with T1-W pulse in and out of phase GRE, T2-W Fat Sat, 3D FAME with dynamic study and rapid IV infusion of radiopaque substance.

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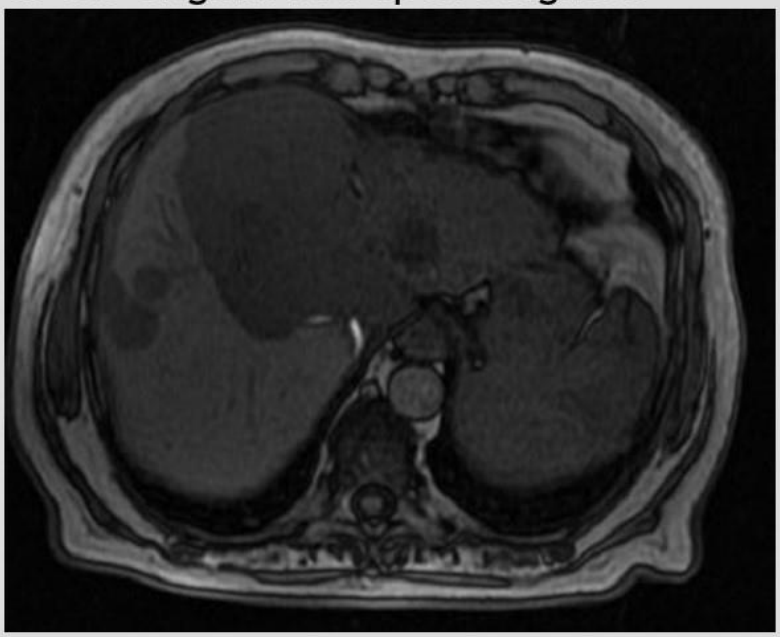
RESULTS:

- MRI results 18/1/17 : The findings are same as the original MRI upon Diagnosis



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RESULTS:

- MRI results 25/4/17 : The same findings of the primary tumor with differentiation of the satellite lesions which show **slight increase of diameter (3mm) with RO uptake in peripheral ring** and **necrosis in the middle**.

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- The patients QOL was significantly improved after therapy and she was able to return to normal life.
- Her fever stopped and her weakness receded, her anorexia stopped with result of weight gain due to normal eating habits.

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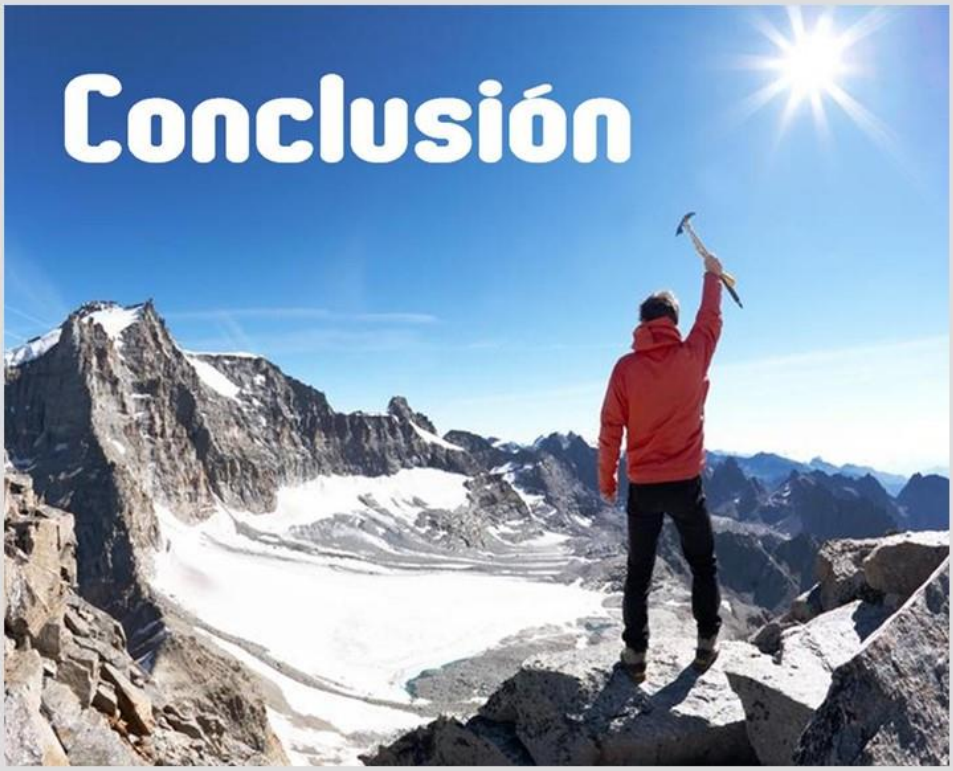

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-Hyperthermia (mEHT) may play a significant role in improving patients QOL, and may offer objective results in disease stabilization.

-We should consider various non-toxic protocols which may enhance patients immune systems and increase healthy tissue resistance to disease dissemination in conjunction with Hyperthermia.

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Further investigation is warranted into the best combinations for this purpose.


9/12/2017

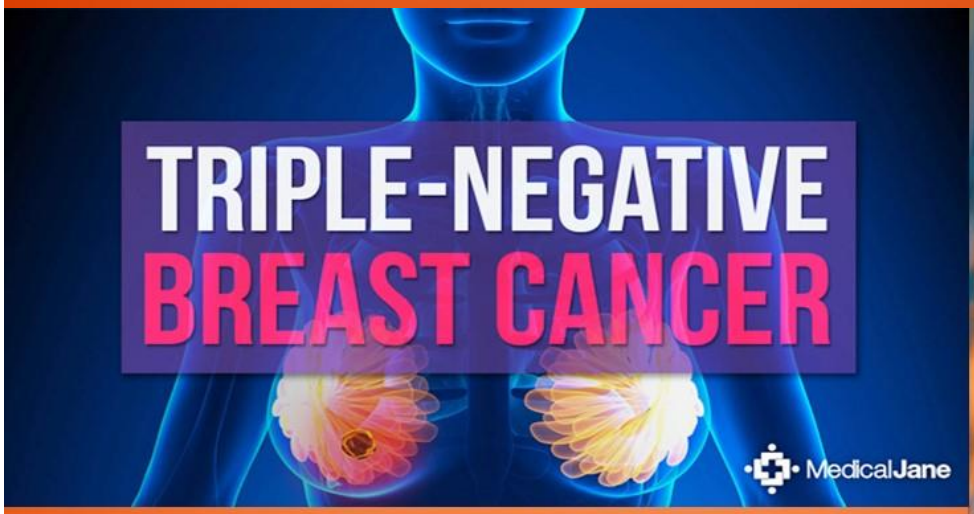

Thank you

Oncothermia case report on metastatic triple negative breast cancer

Alfred Barich

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/1.pdf

WELCOME



- Medical Full eradication of metatastatic site in cerebellum in 28year old patient……..

TRIPLE NEGATIVE BREAST CANCER

- ….. with triple negative breast cancer by radiation & hyperthermia and and partial remission in liver and pulmonary mets and stability in bone mets using Integrative therapeutical strategyTemplates 2003

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- 1. Thessaloniki Hyperthermia Center
- 2. IASO General Hospital-Athens
- 3. AHEPA Univ. Hospital-Thessaloniki.

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Introduction.

- Cancer is a complex and multi-facetted disease, but the overwhelming complexity of polymetastatic malignancy necessitates extra-complex, multi-modal treatment approaches, if it is to be successful at all.

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We present

- In this case report
- The usefulness of modulated Electrohyperthermia (mEHT) in the treatment of a Stage IV triple negative ,invasive ductal Ca of the left breast, Grade 3, treated in our facility in 2015

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Case presentation.

- Status post L. mastectomy with metastatic disease at the time of diagnosis (operated elsewhere). When presenting the patient also had multiple liver and pulmonary metastases.

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LIVER METASTASES 17-12-2015

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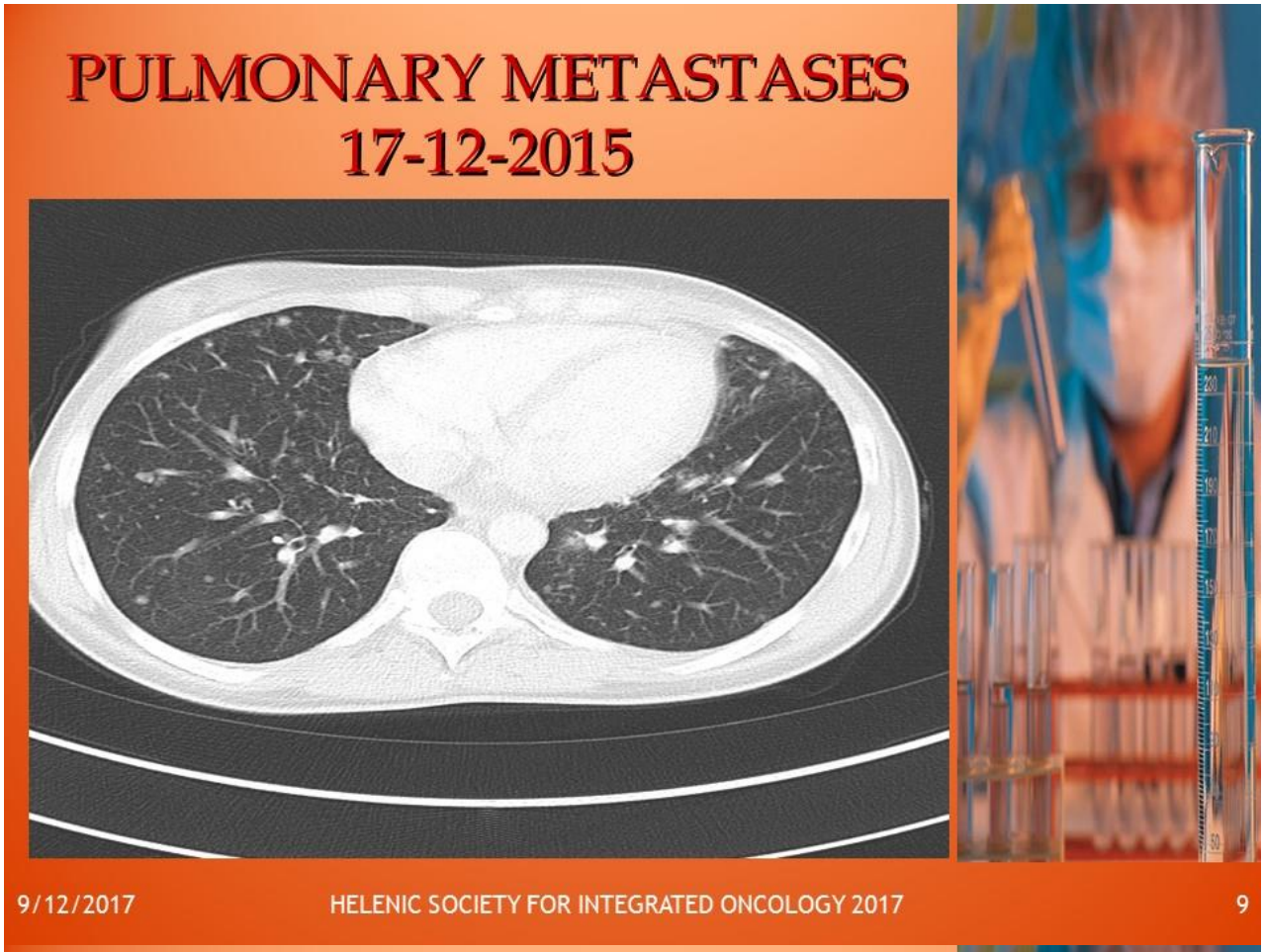
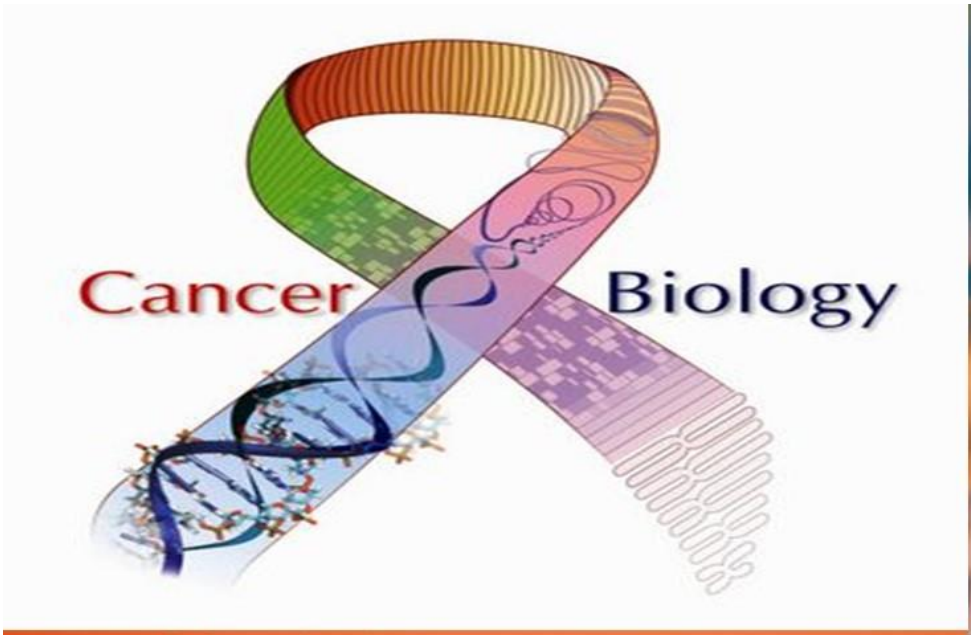

PULMONARY METASTASES
17-12-2015
9/12/2017
HELENIC SOCIETY FOR INTEGRATED ONCOLOGY 2017
9


BRAIN METASTASES
9/12/2017
HELENIC SOCIETY FOR INTEGRATED ONCOLOGY 2017
10

The molecular profile of the patient was established, based on molecular/genetic sensitivity test (R. G . C . C: Research Genetic Cancer Centre).

- Cell harvest count was 6.7 cells isolated /7.5ml (disease stability count at 5cells/7.5ml).



- High level of neo-angiogenesis was established through VEGFr, FGFr and PDGFr markers. MDR1 and MRP levels at 50%and 40% respectively.

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- Tumor markers: or markers:
- 0/10/2015-CA 15.3 : 453.0 IU-/ml,
- 14/1/2016

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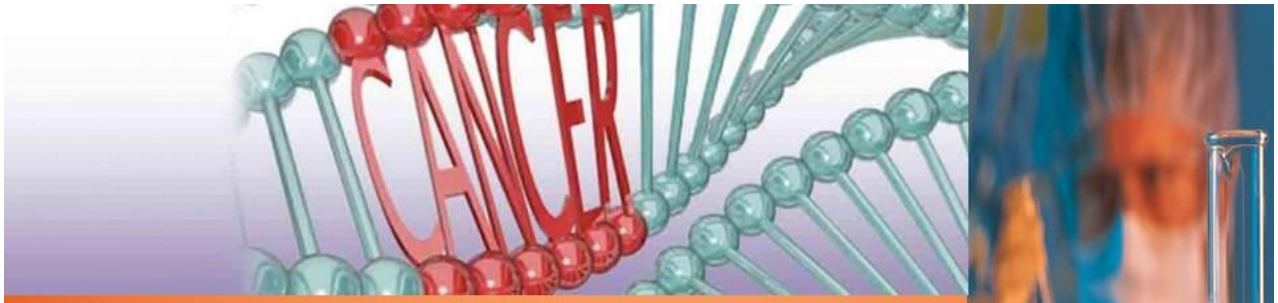


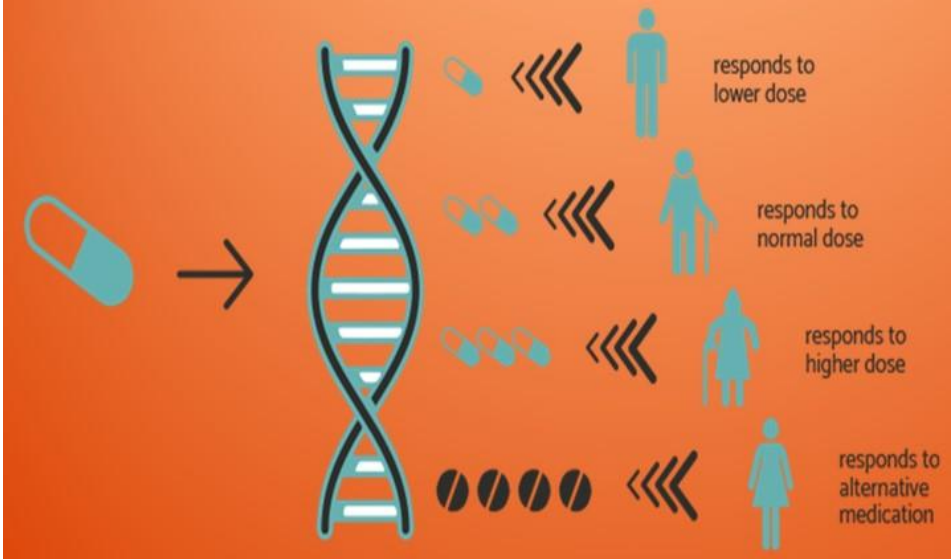
Tumor markers:

- 30/10/2015-CA 15.3 : 453.0 IU-/ml, 14/1/2016

Methods.

- Sensitivity to RT and mEHT were established by measuring levels of HSP27, HSP 72, HSP 90, with values 5%, 15%, and 25% downregulation respectively).

- Sensitivity to conventional CT agents was established. Sensitivity was also established for a wide range of biological molecules (vitamins, anti-oxidants etc).



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- The patient was submitted to RT to brain , delivered through linear accelerator (6 mV) and received :
- 6.5Gys,
- A complex, personalized CT scheme, based on her molecular/genetic profile,
- mEHT on metastatic sites (cerebral, hepatic and pulmonary) with two sessions /week and mean 350KJ/site except for brain which received 250KJ/session for a total of six weeks.

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Results.

- Computerized Tomography showed complete eradication of brain lesions compared with the initial examination. MRI examination corroborated on these findings.

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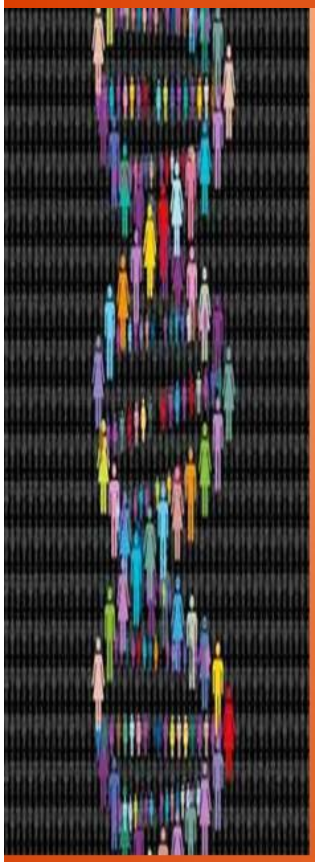

- ABCG2 resistance pump mechanisms were also measured to determine cancer cell resistance mechanisms (MDR1,MRP,LRP, GST) and upon determination,reistance pump inhibitors were used to reduce cancer cell resistance Tumor markers had also favorable.

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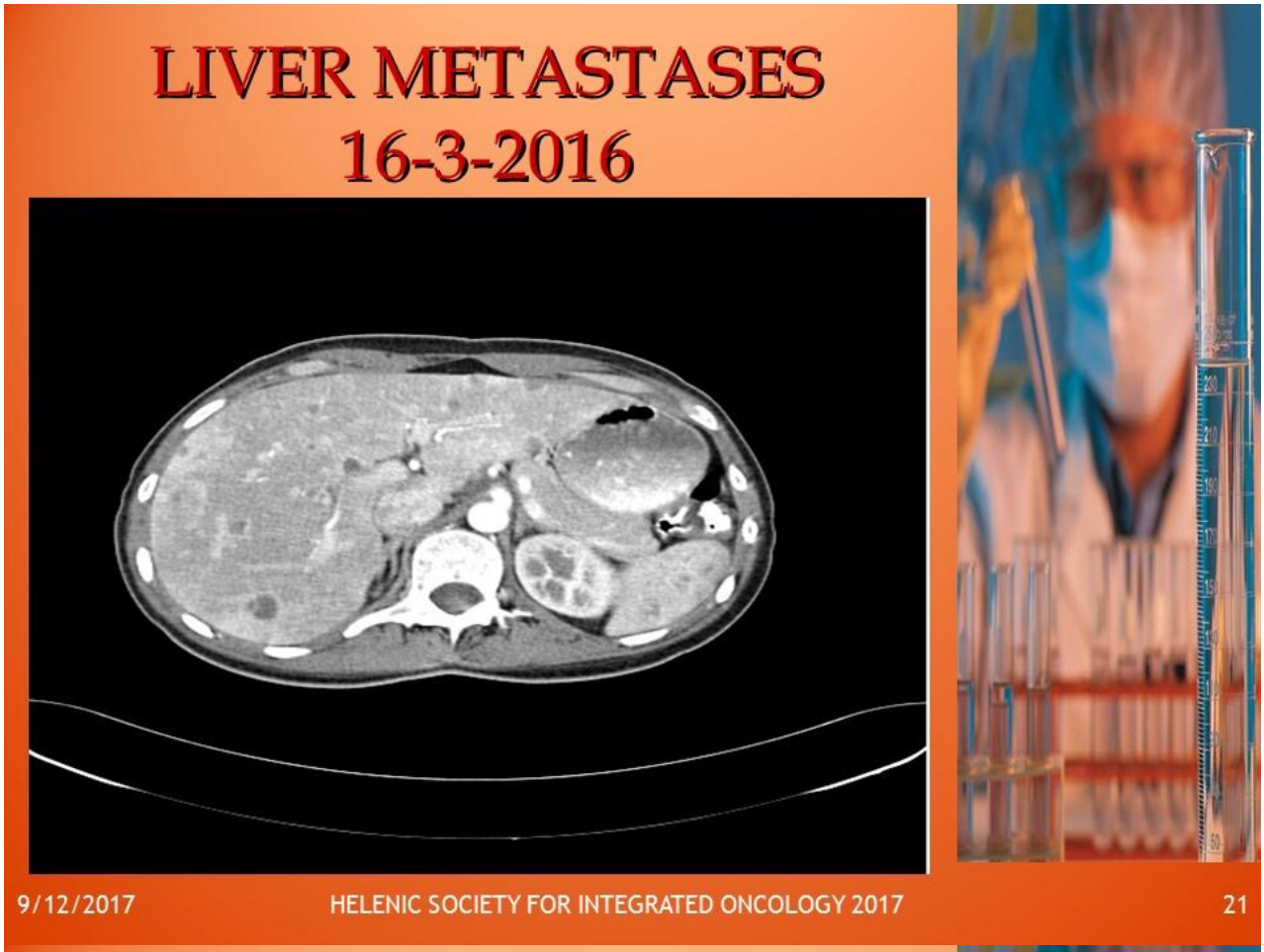
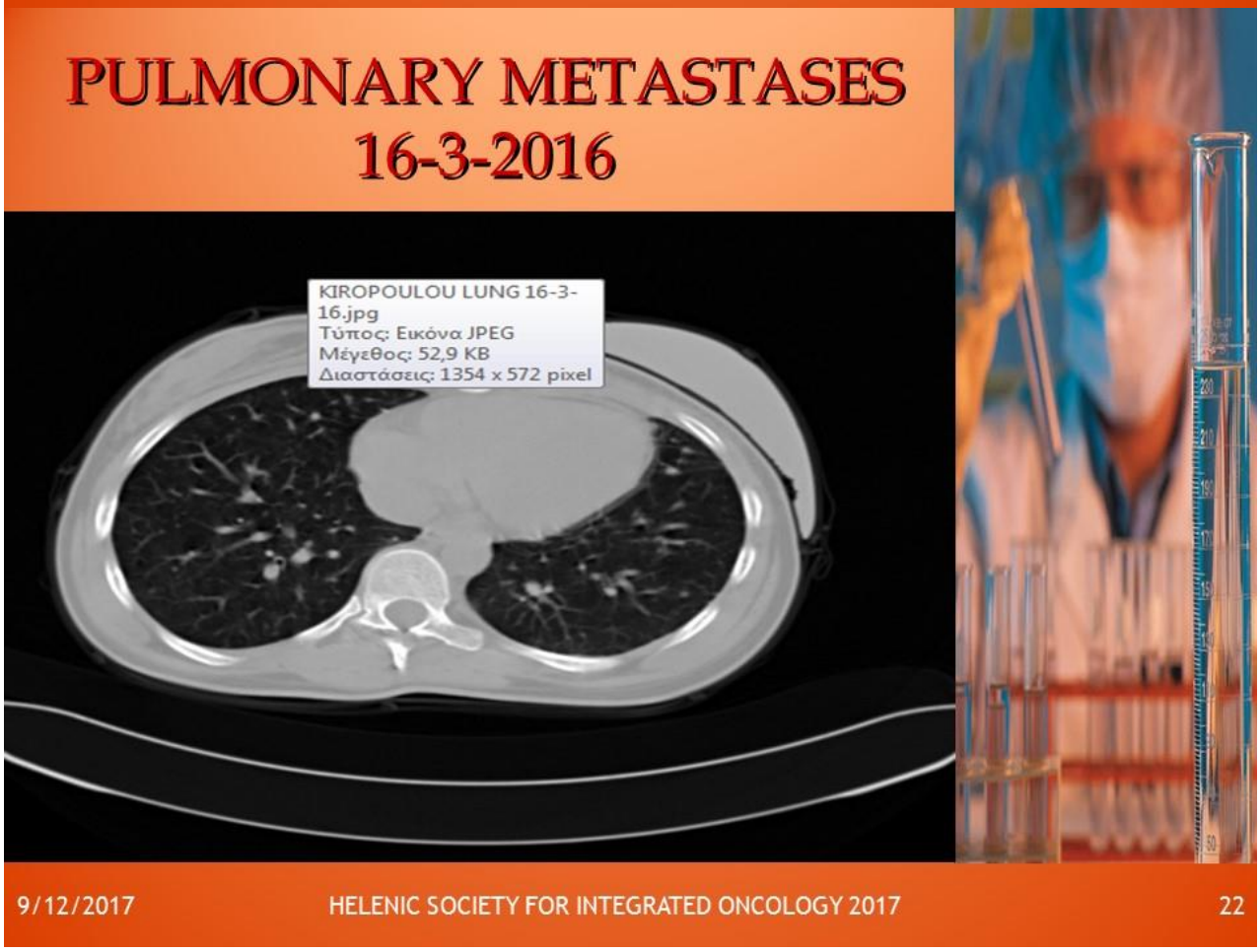
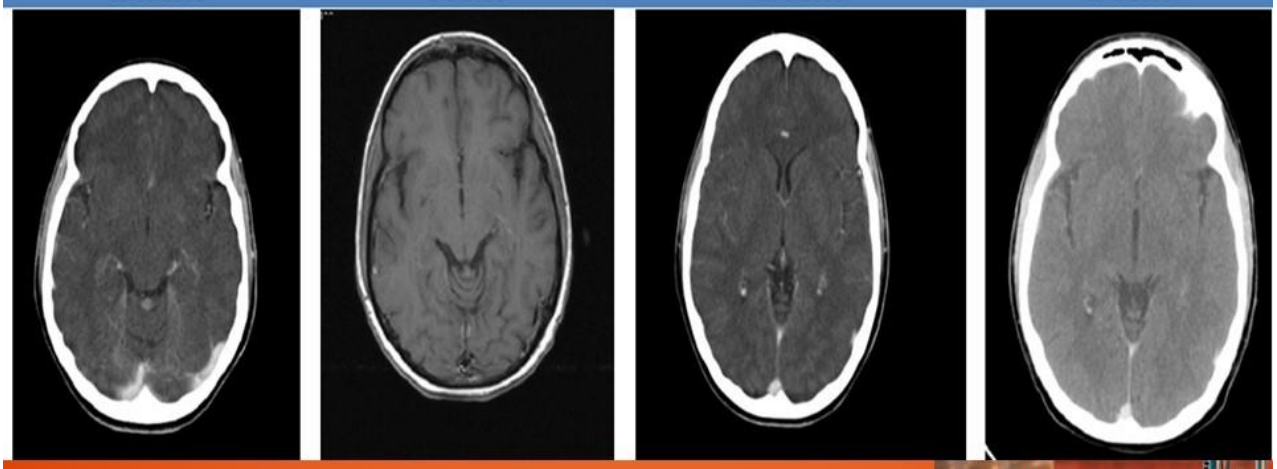

LIVER METASTASES
16-3-2016
9/12/2017
HELENIC SOCIETY FOR INTEGRATED ONCOLOGY 2017
21

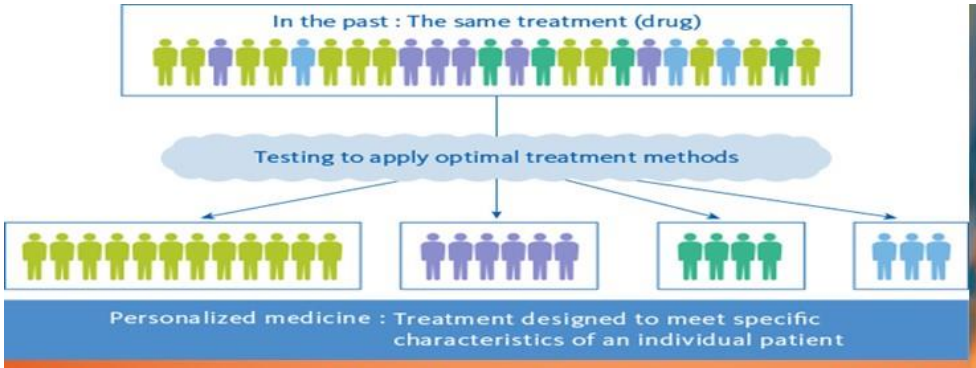

PULMONARY METASTASES
16-3-2016
KIROPOULOU LUNG 16-3-16.jpg
Τύπος: Εικόνα JPEG
Μέγεθος: 52,9 KB
Διαστάσεις: 1354 x 572 pixel
9/12/2017
HELENIC SOCIETY FOR INTEGRATED ONCOLOGY 2017
22

BRAIN MRI



Quality of life

- The quality of life of the patient was improved because of the reduction of tumor burden and complete eraditcation of the brain mets. …



- The personalization of treatment, which is achieved through the integrative oncological approach with inclusion of mEHT to the standard chemo and radiation protocols, can give us surprisingly good results even on the most aggressive and disseminated tumors.

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mEHT

- mEHT can safely be applied to the brain, without fear of edema and its complications. In similar cases without the use of Hyperthermia , with only the conventional modalities of treatment, literature has very disappointing results to show.

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Tumor specific stress and immune response induced by modulated electrohyperthermia in relation to tumor metabolic profiles

Tibor Krenacs[1] & Zoltan Benyo[2]
[1]1st Department of Pathology & Experimental Cancer Research
[2]Institute of Clinical Experimental Research Semmelweis University, Budapest, Hungary

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/2.pdf

Tumor specific stress and immune response induced by modulated electrohyperthermia in relation to tumor metabolic profiles

Tibor Krenacs[1] & Zoltan Benyo[2]

[1]1st Department of Pathology & Experimental Cancer Research

[2]Institute of Clinical Experimental Research

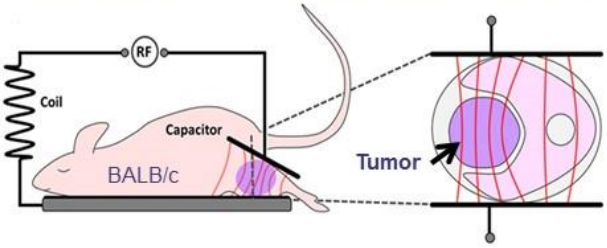
Semmelweis University, Budapest, Hungary

ESHO Congress
Athens, June 21-23rd 2017

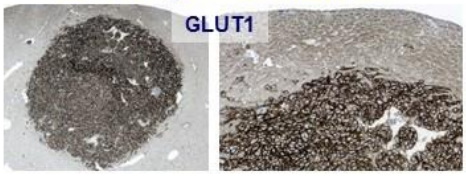
mEHT of 13.65 MHz – selective tumor destruction

- **Electric field can be selectively enriched in malignant tumors**

  Elevated permittivity, glycolysis, lactate and ion concentration (**Warburg-effect**)



LLT-H lung cc liver metastasis



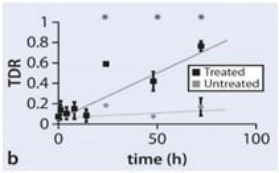
- **Xenograft HT29 CRC** *(HepG2 HCC)* **immuncompromised** (NUDE)
- **Allograft C26 CRC** *(C38 CRC, LLT-H, lung ADC)* **immuncompetent**

Symmetrical tumors

- **right leg - mEHT treated**
- **left leg - control**

- **Programmed tumor cell death in synergy of electric field & induced heat**

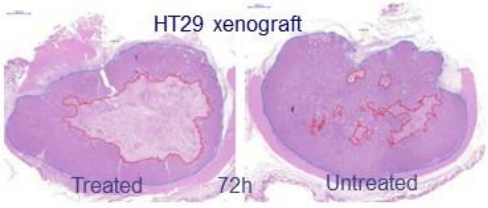
Tumor damage ratio (TDR)



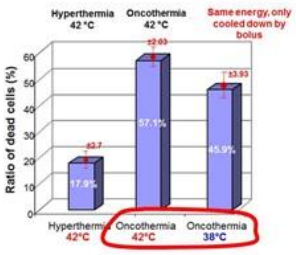
Progressive tumor damage

Single 30' shot of mEHT (~42°C)

HT29 xenograft

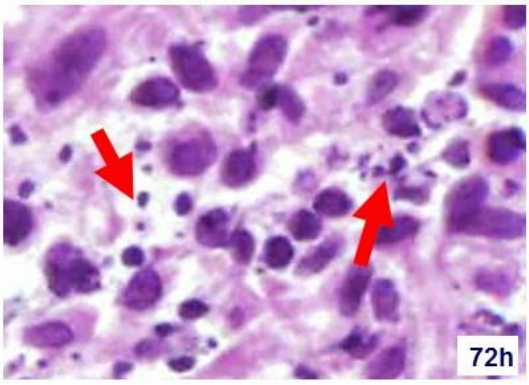


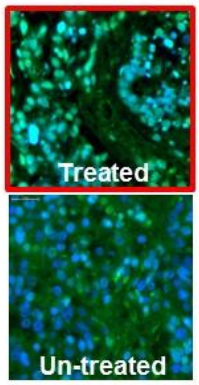
Andocs et al. Strahlenther Onkol. 2009, 185:120-126.



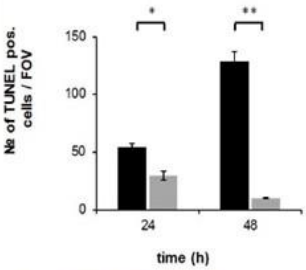
mEHT induced programmed cell death

HT29 (p53 mutant) CRC xenograft



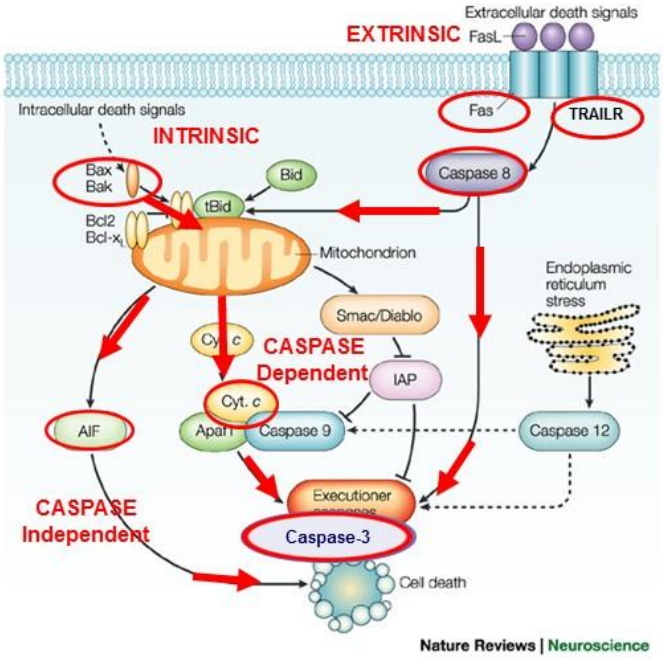


DNA fragmentation



Meggyeshazi, Andocs et al. Strahlenther Onkol. 2014, 190:815-822.

APOPTOSIS

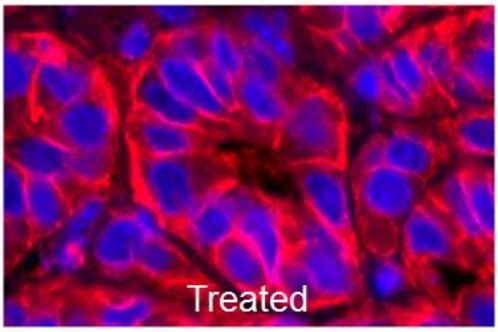


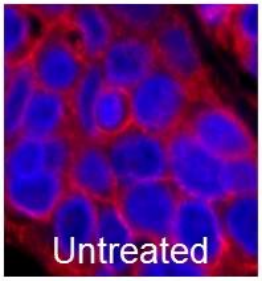
Vila-Przedborski: Apoptosis-2003

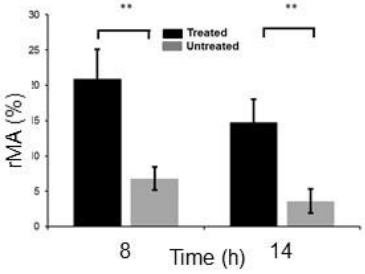
mEHT induced death receptor mediated extrinsic pathway

HT29 CRC xenograft

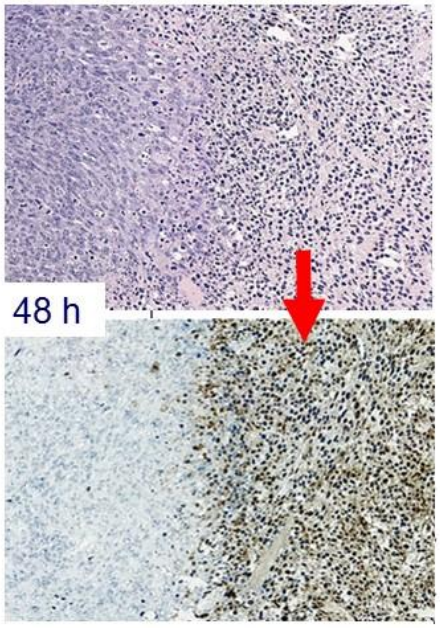
TRAIL-R2 (Death Receptor 5)







Cleaved-**Caspase 8**



H&E

IHC

Target therapy: rh-TRAIL and **MAbs** (*HGS ETR2/ lexatumumab*)

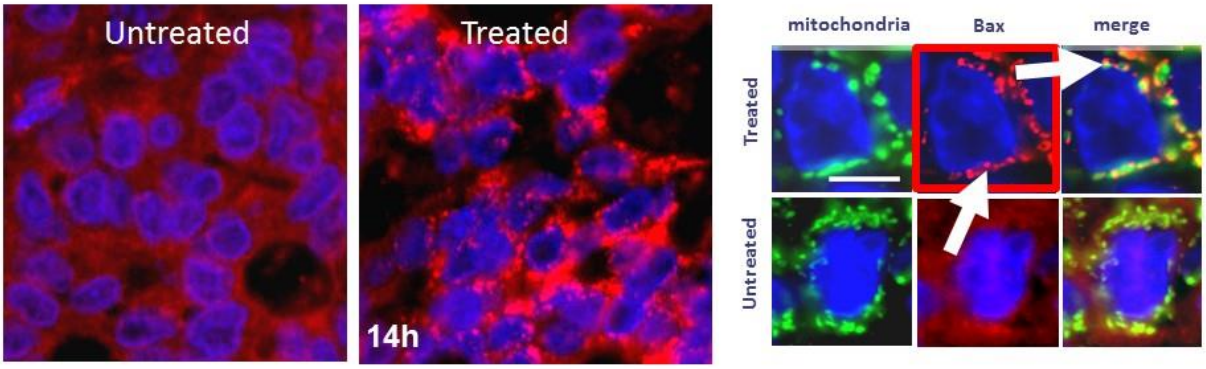
- **Synergy** with **cytotoxic chemo- and radiation therapy** in breast cancer & CRC
- **Phase-I-II** trials are running

Rajen. Transl Pediatr 2013; 2:66-69

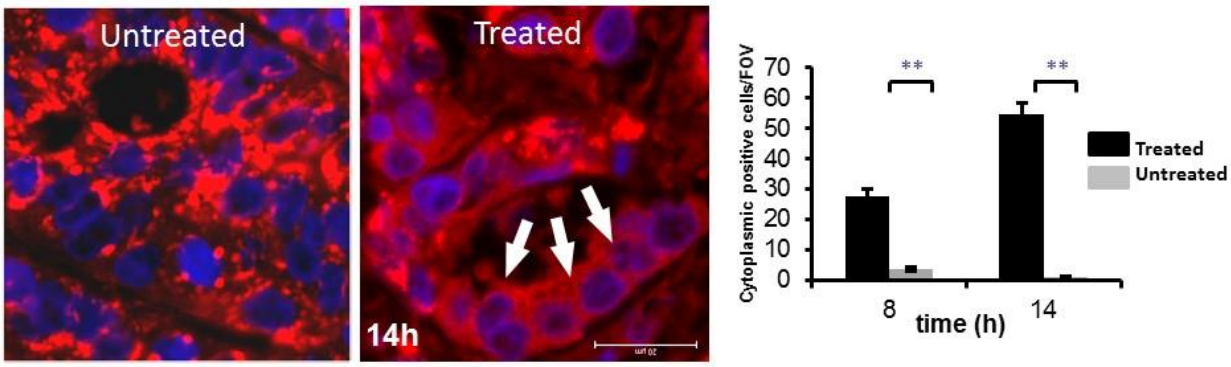
mEHT induced Caspase-dependent intrinsic pathway

HT29 CRC xenograft

Bax - mitochondrial translocation

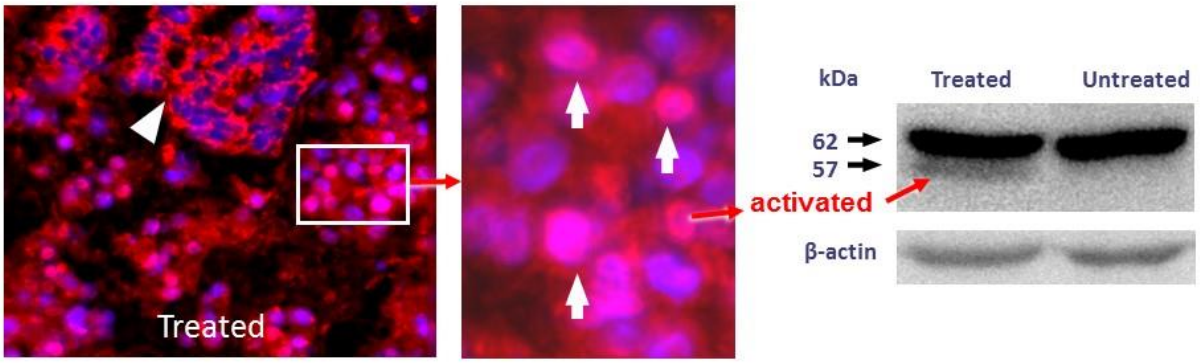


Cytochrome C - cytoplasmic release

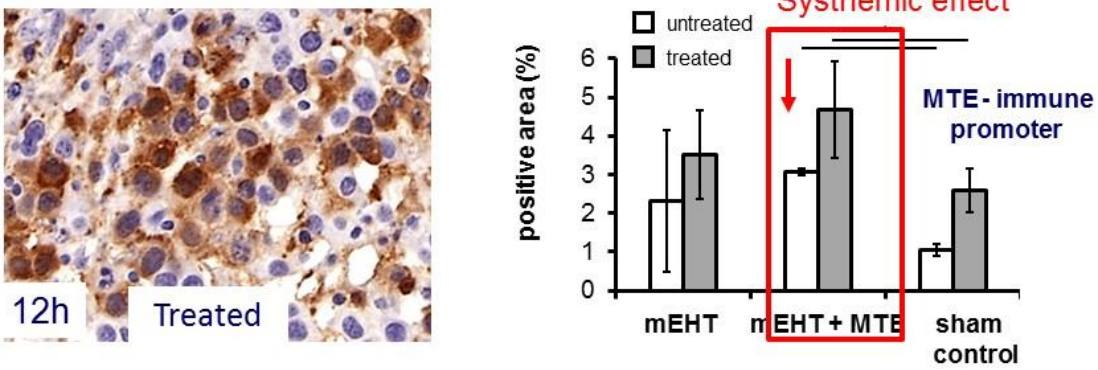


mEHT induced Caspase dependent & independent apoptosis

HT29 CRC **AIF** (apoptosis inducing factor) **translocation**



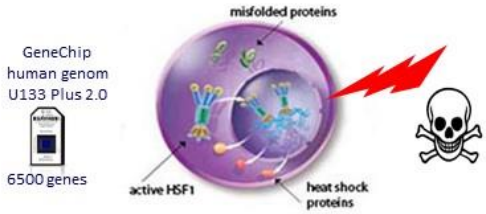
C26 CRC Cleaved-**caspase-3**



Heat shock/cell stress – chaperones – damage signaling

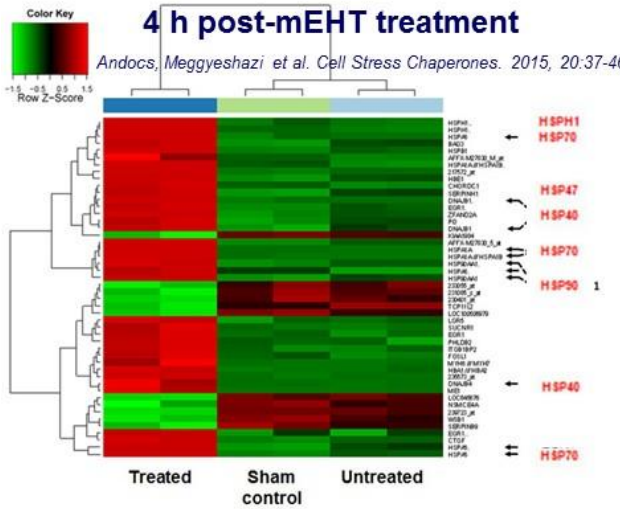
Human HT29 CRC xenograft

HEAT SHOCK + ELECTROMAGNETIC FIELD

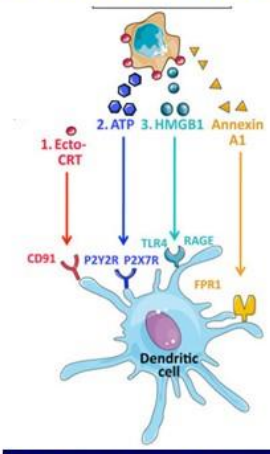


4 h post-mEHT treatment

Andocs, Meggyeshazi et al. Cell Stress Chaperones. 2015, 20:37-46.



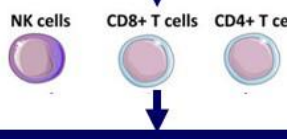
Damage associated molecular patterns (DAMP)



Hernandez et al. Oncogene. 2016, 35:5931–5941

- **Calreticulin (CRT)**
  „eat me" signal
- **ATP**
  „find me" signal
- **HMGB1**
  „danger"signal
- **HSP70**
  Granzyme B endocytosis

- DC maturation, activation
- Tumor antigen processing
- T-cell & NK-cell activation



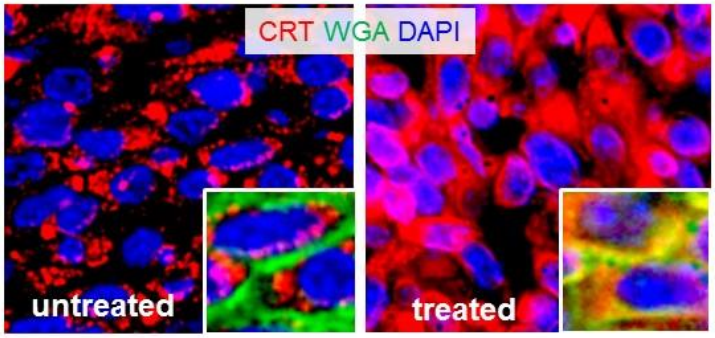
- **Antitumor immune response**
- **Immunogenic cell death (ICD)**

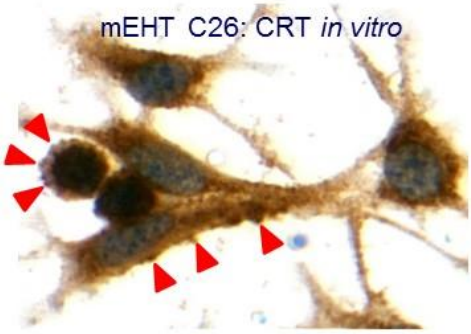
- **Antracyclins**
  Doxorubicin
- **UV or γ irradiation**
- **EGFR immunotherapy**
- **Capsaicin**

Spatiotemporal DAMP signaling – systhemic effect

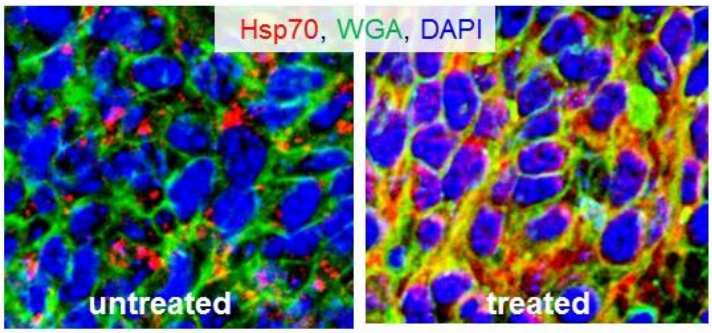
C26 CRC allographt

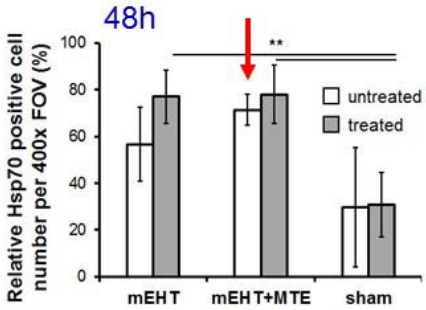
Calreticulin membrane translocation





Hsp70 membrane translocation

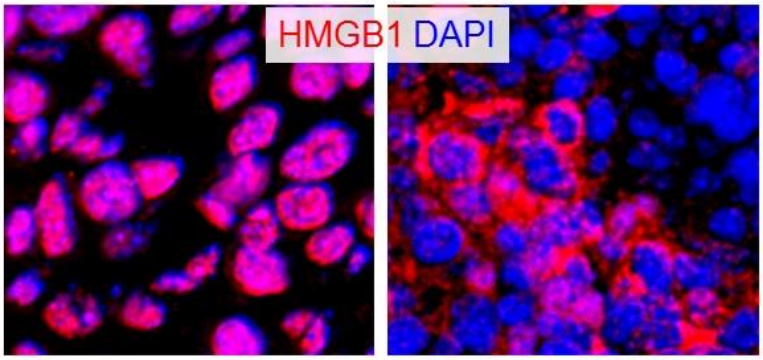


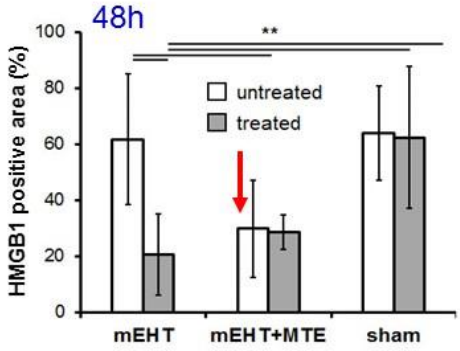


Spatiotemporal DAMP signaling – systhemic effect

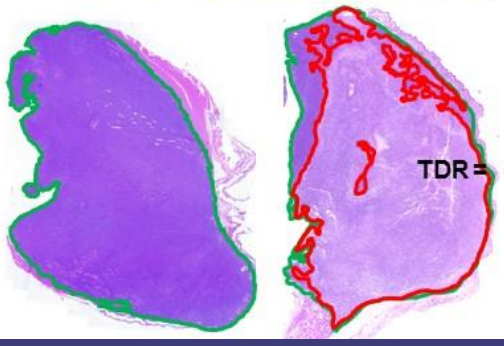
C26 CRC allographt

HMGB1 release – cytoplasmic & extracellular

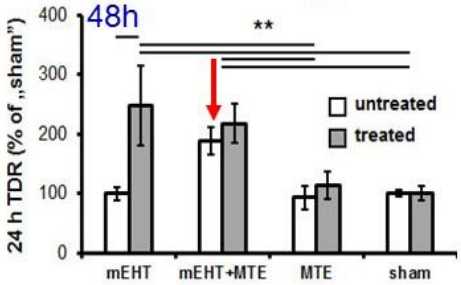




Tumor Destruction Ratio

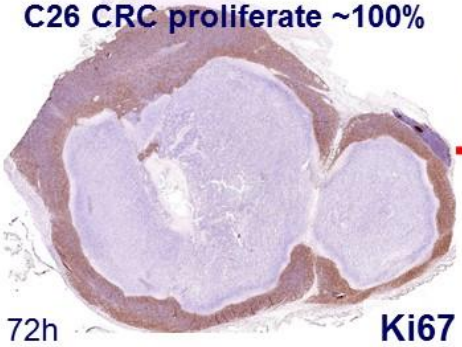


In mEHT tretead & mEHT+MTE treated
& in mEHT+MTE treated opposit site

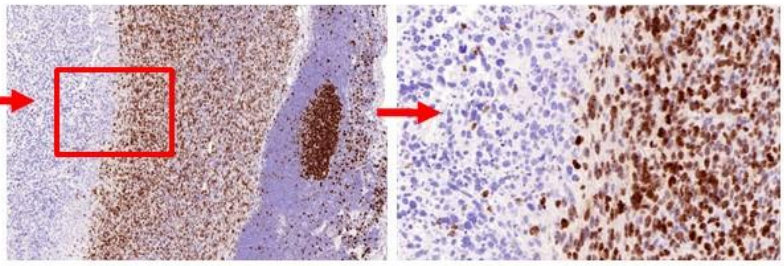


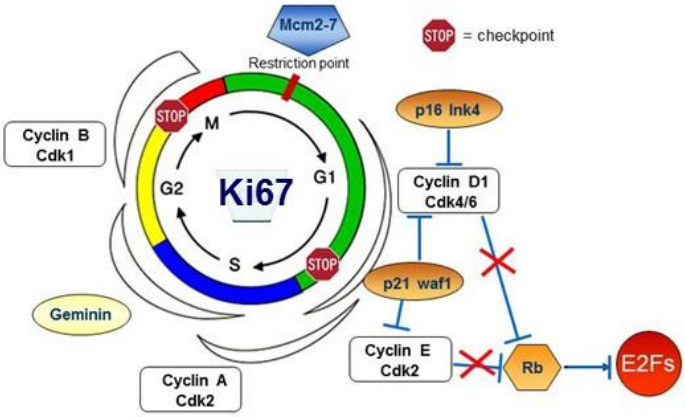
Complete cell cycle arrest – apoptosis

C26 CRC proliferate ~100%

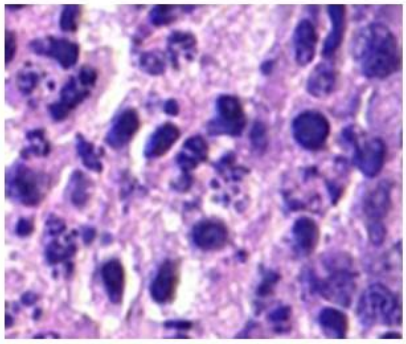


mEHT - Complete cell cycle arrest





Apoptosis vs DNA repair

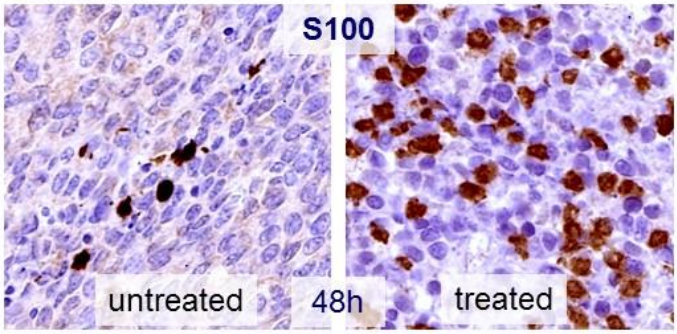


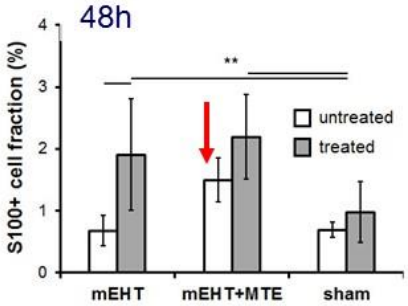
Ehrhardt et al. Cell cycle-arrested tumor cells exhibit Increased sensitivity towards TRAIL-induced apoptosis Cell Death and Disease (2013) 4, e661

Antitumor immune response - local and systhemic

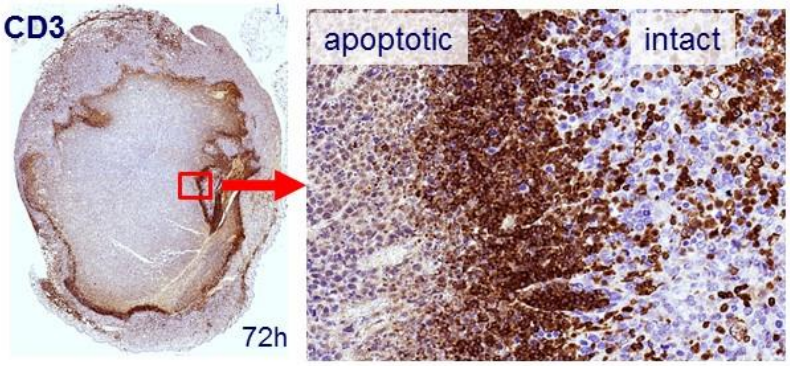
C26 CRC allographt

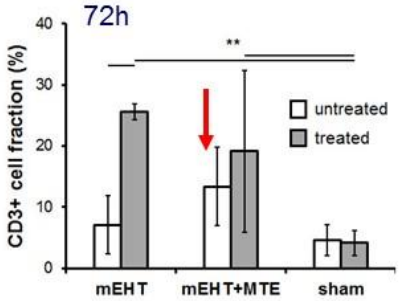
Elevated number of antigen presenting DC (APC)





Massive T-cell infiltration



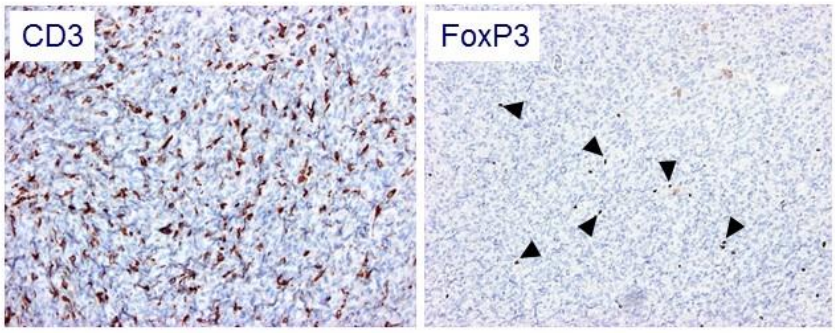


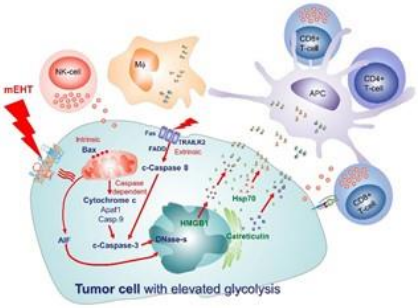
Antitumor immune response – immunogenic cell death

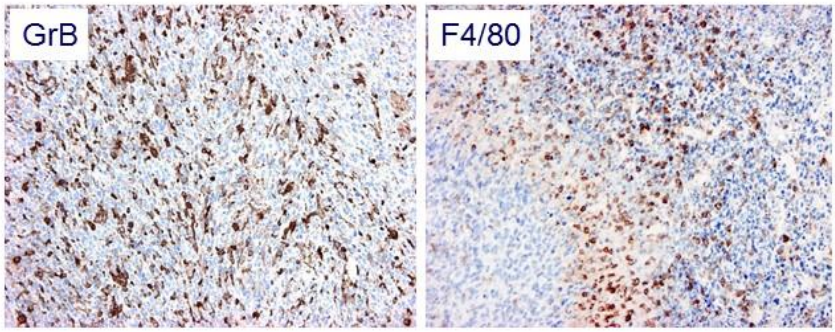
48 h post-mEHT

T-cell infiltration, negligible regulatory T-cells

C26 CRC allographt







Single mEHT shot

Progressive

- accumulation of immune cells &
- tumor damage

↓

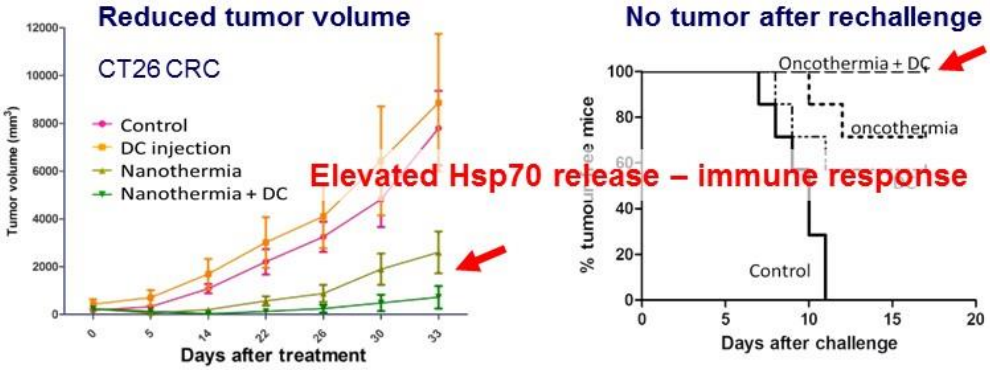
Immunogenic cell death ICD

Cytotoxic T-cells & NK cells + Macrophages

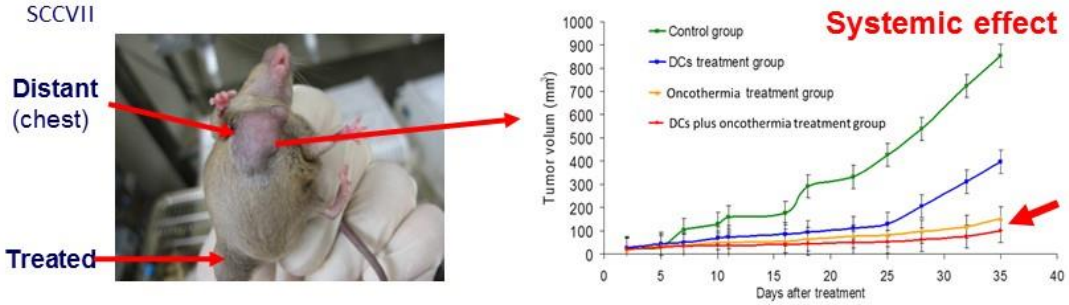
mEHT + DC therapy – protection & systhemic effect

In vivo allographts

Tsang et al. BMC Cancer, 2015, 15:708



Quin et al. Oncology Reports 2014, 32:2373-2379.



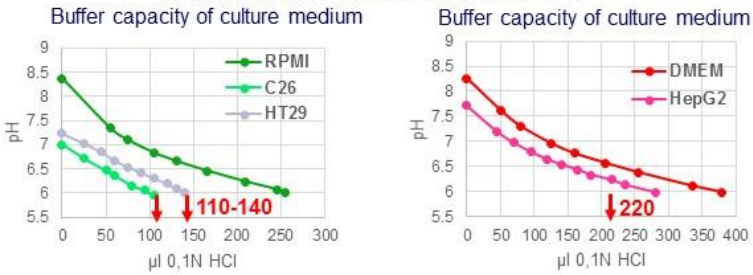
mEHT tumor selectivity – Elevated glycolysis (Warburg effect)

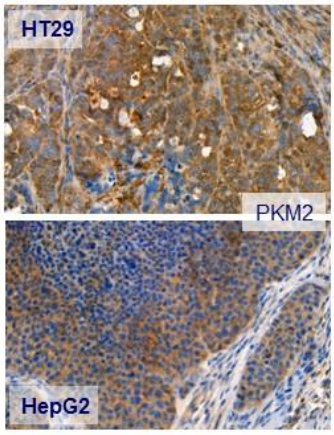
Glycolytic, metabolic activity

mEHT treatment efficiency

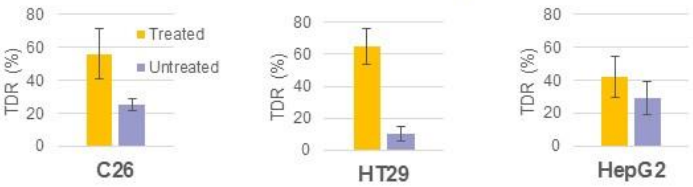
Lactate concentration ⇄ buffer capacity

Yamagata, M., et al. Br J Cancer. 1998, 77:1726-1731.



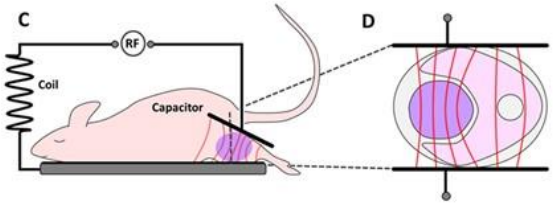


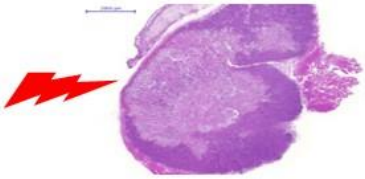
mEHT tumor destruction 24 h post-treatment



- Testing glycolytic enzyme levels *in situ* (IHC) and *in vitro* (Western blot)
- For predictive marker(s) of mEHT therapy

Conclusions: Oncothermia - *in vivo* model systems





- **Can induce selective, programmed tumor cell death (apoptosis)**
- **Upregulation of death receptors (TRAIL-R2 & Fas)**
- **Both the extrinsic and the intrinsic caspase-dependent pathway**
- **Preferred pathway depends on genetic/epigenetic predisposition:**
  - HT29 human CRC (p53 defficitent) - AIF
  - C26 mouse CRC - caspase mediated
- **The damage response generates DAMP signal sequence**
- **Progressive infiltration by APC, cytotoxic T-cells, NK-cells & macrophages**
- **Progressive damage – immunogenic cell death (IDC)**

Acknowledgements

Thank you!

Nora Meggyeshazi

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Peter Balla

Eva Kiss, Gertrud Forika

Edit Parsch†, Eva Balogh

Lajos Balogh, Andras Szasz

Oliver Szasz & Balazs Acs

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DEBATE treatment planning & thermometry

G. Van Rhoon[1] vs. A. Szasz[2]
[1]Erasmus University, Rotterdam, The Netherlands
[2]St. Istvan University, Godollo, Hungary

Cite this article as:
http://oncotherm.com/sites/oncotherm/files/2017-10/3.pdf

ESHO 2017

DEBATE
treatment planning & thermometry

G. Van Rhoon[1] vs. A. Szasz[2]

[1]Erasmus University, Rotterdam, The Netherlands
[2]St. Istvan University, Godollo, Hungary

A.S. has a possible conflict of interest:

- founder & CSO of company Oncotherm (1988)
- chair, professor, lectureship Biophysics at St. Istvan University
- lectureship Bioelectromagnetics at Pazmany Catholic University
- lectureship Fractal-physiology at Chiba University (Japan)

Thermometry (A. Szasz)

Thermometry is mandatory in the heating techniques where

a. the absorbed energy is not known (there are lot of energy losses), so the temperature guesses the absorbed energy in the target
b. it is for safety – avoid the risk to overheat the healthy tissues (like surface, deep hotspots, etc.)

The dose

a. It has to be proportional with mass and other extensive parameters, unlike temperature
b. The correct thermal dose is the absorbed energy (kGy=J/g), like in ionizing radiation

The task of the dose is presently upside-down

When we measure the temperature we may transform it to real dose: energy

Planning software (A. Szasz)

It is a necessary tool in the methods of heating techniques is external beam radiation with request of isodose in the target. Planning shows:

1. **how much energy is absorbed**
2. **where the energy is focused**
3. **maximizes the heating in tumor and minimizes the hot-spots in untreated regions**

Need of planning depends on the applied technique.

Like no planning necessary for

- brachy-therapy,
- ablation therapies,
- intraperitoneal hyperthermic chemotherapy,
- whole-body hyperthermia
- etc.

The technique decides about the request of planning software

Oncothermia does not need it

Theses for oncothermia technique (A. Szasz)

The absorbed energy is the dose. Its unit is the kGy=J/g

Realization:

1. Don't be isothermal (no homogeneous heating)
2. Heat the malignant cells selectively
3. Use high heating efficacy, less energy-loss

When the above conditions are realized, then:

Use adaptive treatment protocol instead of planning

1. regulate the process by actual site and stage of the disease
2. expand the local treatment to systemic (immune effects)
3. be adaptive for patients' complaints

Challenges of the hyperthermia dose → CEM43^{o}CT$_x$ (A. Szasz)

a. The concept is based on the thermal **necrosis**, which is incorrect

b. Estimation of **heterogeneities** (Tx) is very rough, and its concept is not dose-like

c. CEM43^{o}CT$_x$ is incorrect: T has unit [°C]; what is the unit of $\mathbf{R^{(T-43°C)}}$?

d. The CEM43^{o}CT$_x$ dose is calibrated **in vitro** (Sapareto & Dewey)

e. The **kink of Arrhenius** plot essentially depends on the complementary applications

f. Development of Arrhenius-law, the **Eyring reaction-kinetics** has to be applied

WBH

- heats everything homogeneously
- the extreme temperatures can be reached
- the CEM°43T$_{100}$ is definitely higher than at any local treatment

Inhibition of proliferation, induction of apoptotic cell death and immune response by modulated electro-hyperthermia in C26 colorectal cancer allografts

Vancsik Tamas[1], Eva Kiss[1], Dr. Csaba Kovago[2],Nora Meggyeshazi[1], Gertrud Forika[1], Tibor Krenacs[1]

[1]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary

[2]Pharmacology and Toxicology Department, Faculty of Veterinary Science, St. Istvan University, Budapest, Hungary

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http://oncotherm.com/sites/oncotherm/files/2017-10/4.pdf

Inhibition of proliferation, induction of apoptotic cell death and immune response by modulated electro-hyperthermia in C26 colorectal cancer allografts

Vancsik T[1], Eva Kiss[1], Dr. Csaba Kovago[2], Nora Meggyeshazi[1], Gertrud Forika[1] Tibor Krenacs[1]

[1]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
[2]Pharmacology and Toxicology Department, Faculty of Veterinary Science, St. Istvan University, Budapest, Hungary

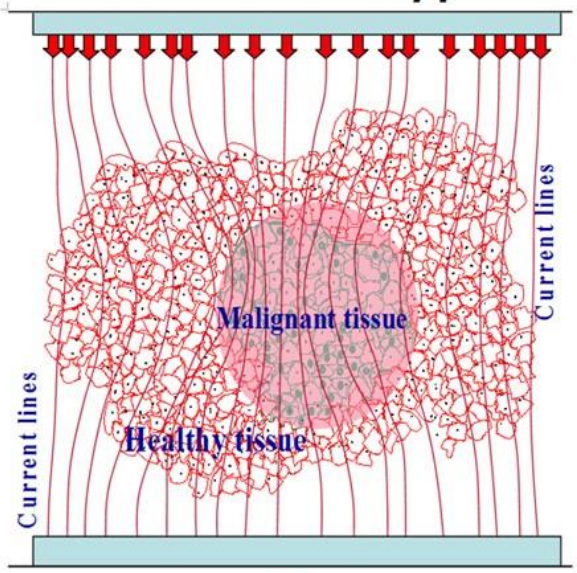
Modulated electro-hyperthermia

Tumor-tissue secificities:
Metabolism: **Warburg-effect**
Enchanced aerob glycolysis
High EC water and ion concentration

⇩

Higher conductance
Lower resistance

Modulated electro-hyperthermia



The electromagnetic field **selectively enriches in tumors**

Tumor destruction

Modulated electro-hyperthermia (mEHT)

Not ablation

Modulated electro-hyperthermia (mEHT)

Modulated electro-hyperthermia (mEHT)

- 13,56 MHz amplitude modulated electromagntic field (**mEHT**):
  - Safe (10 kHz<f<1GHz)
  - Optimal penetration (f<25 MHz)
- **<42 °C heat**
- In clinics eg.: osteosarcoma[1], head-neck squamous carcinoma[2], colorectal carcinoma[3]
- Thermal effect
- EM-related tumor destruction[4]


Strahlentherapie und Onkologie

Original Article

Strong Synergy of Heat and Modulated Electromagnetic Field in Tumor Cell Killing

4. Andocs G és mtsai., **Strong synergy of heat and modulated electromagnetic field in tumor cell killing.** Strahlenther Onkol. 2009 Feb;185(2):120-6

1. Rong Y, Mack P (2000) Apoptosis induced by hyperthermia in Dunn osteosarcoma cell line in vitro. Int J Hyperthermia 16:19–27
2. Shchepotin IB et al (1997) Apoptosis induced by hyperthermia and verapamil in vitro in a human colon cancer cell line. Int J Hyperthermia 13:547–557
3. Tamamoto T et al (2003) Heat-induced growth inhibition and apoptosis in transplanted human head and neck squamous cell carcinomas with different status of p53. Int J Hyperthermia 19:590–597

Aims

Tumor allograft in **Immunocompetent** animal:

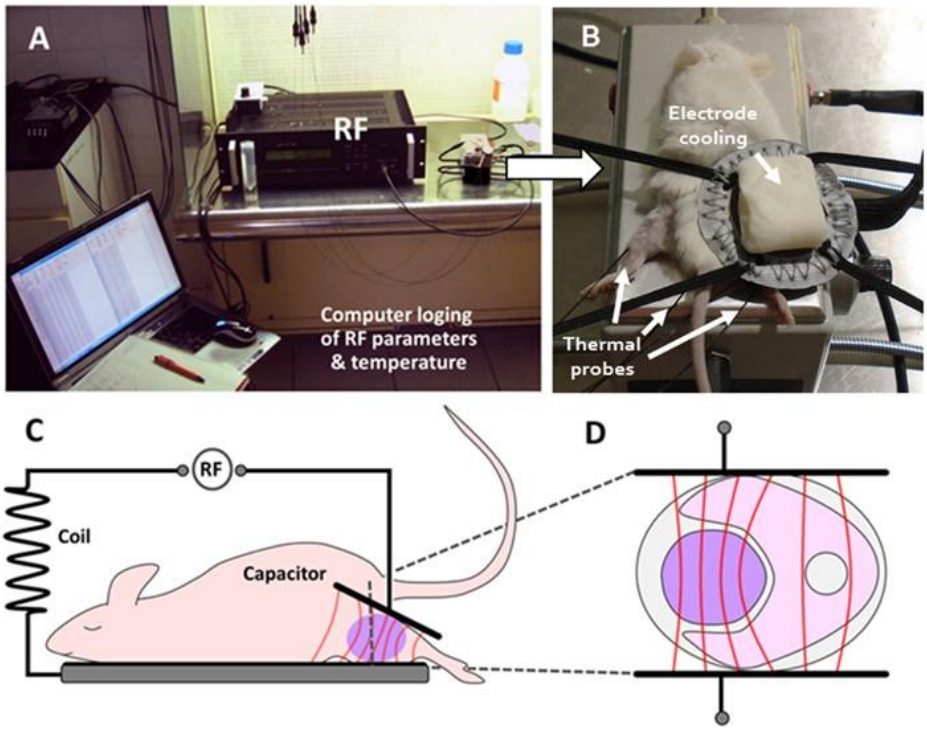
- Tumor-destruction
- Programmed cell death
- Cellular/tissue stress
- Immune response

Materials and methods

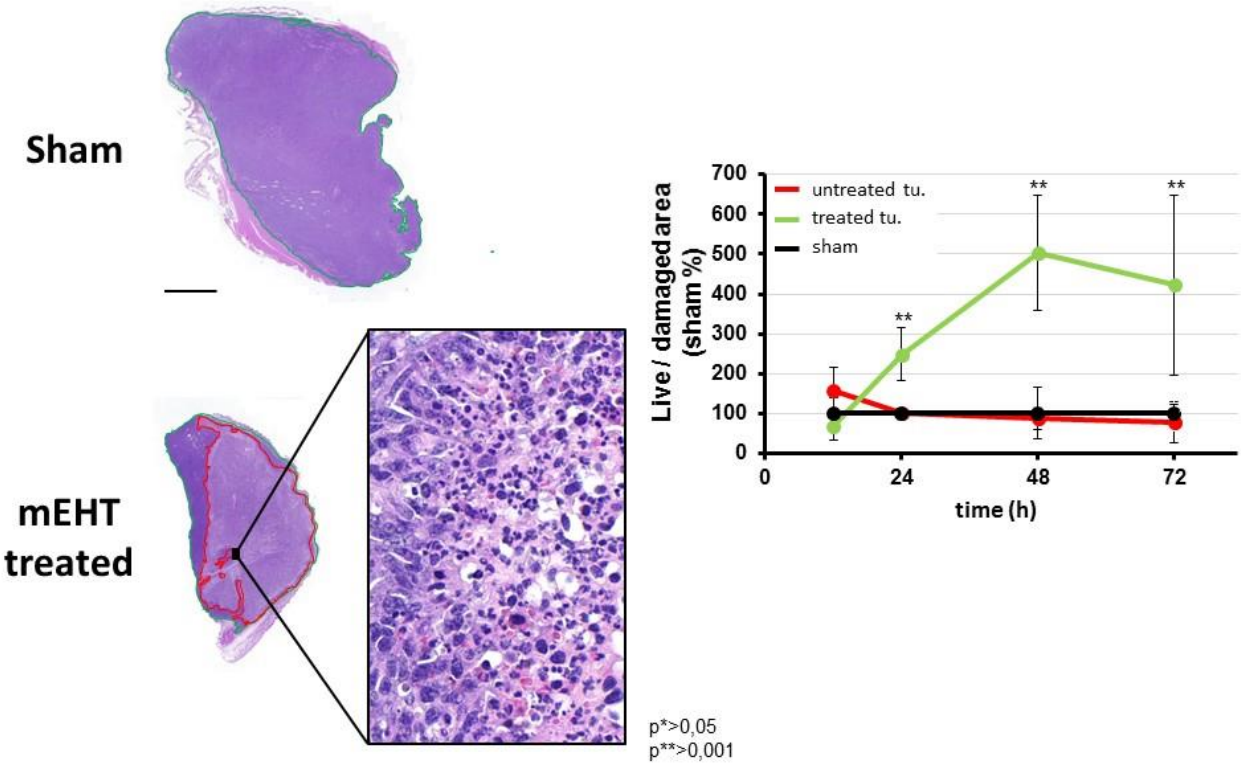
- C-26 mouse colorectal carcinoma in Balb/c mice
- Groups:
  - mEHT: modulated electro-hyperthermia

Materials and methods

- C
- G

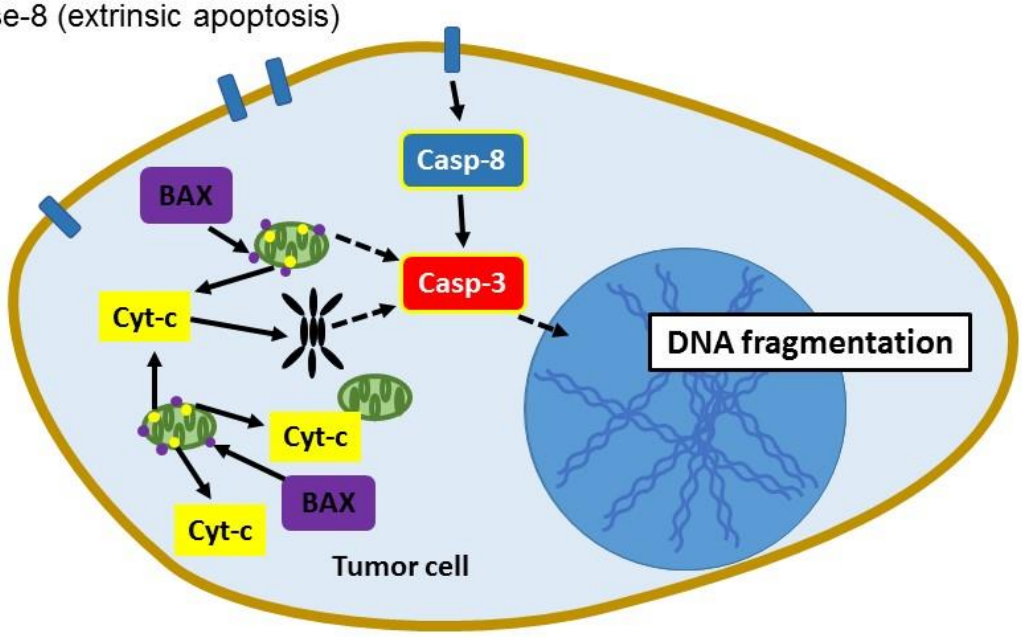


Tumor destruction

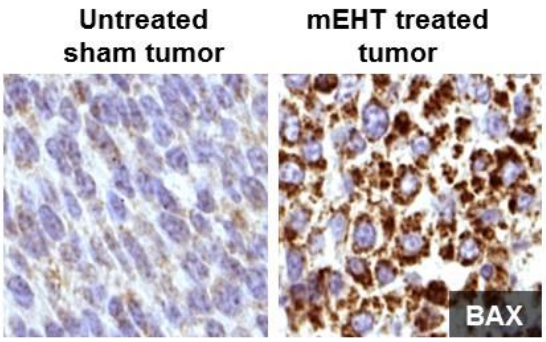


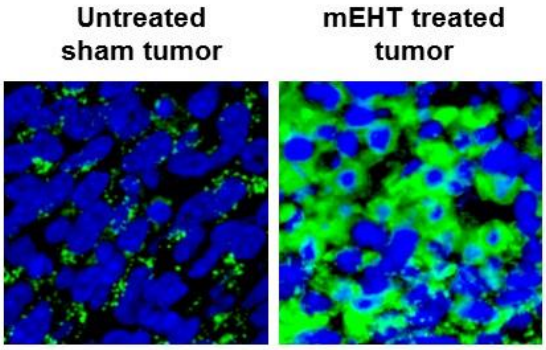
Programmed cell death

Apoptosis:
BAX (pore forming protein)
Cytochrome-c (apoptosome building)
Cleaved caspase-3 (common effector caspase)
Cleaved caspase-8 (extrinsic apoptosis)

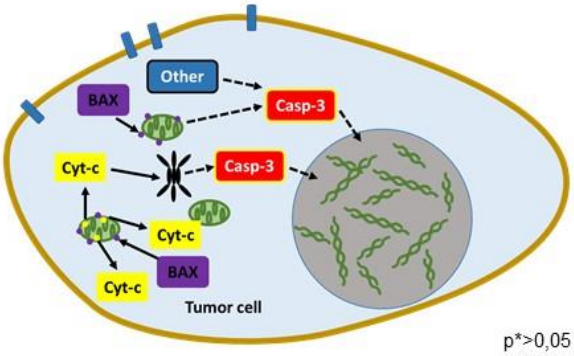


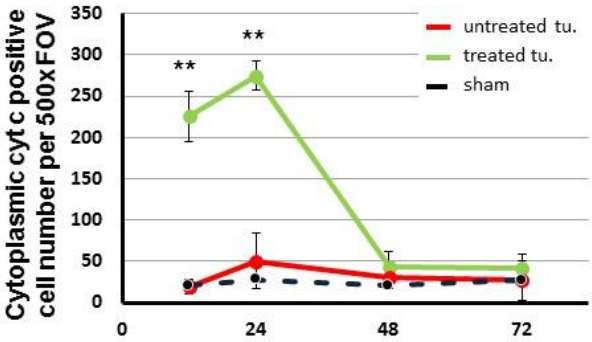
Induction of apoptosis





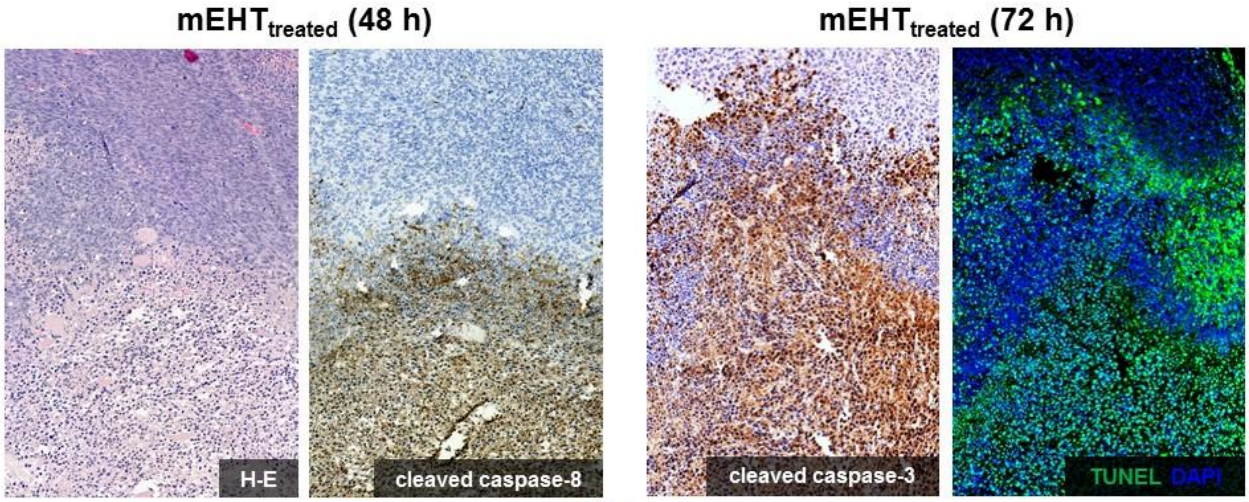
citochrome c, DAPI

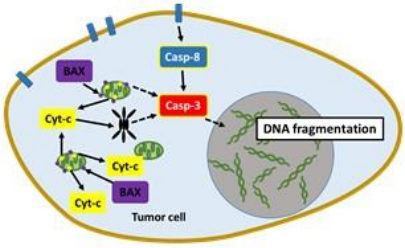




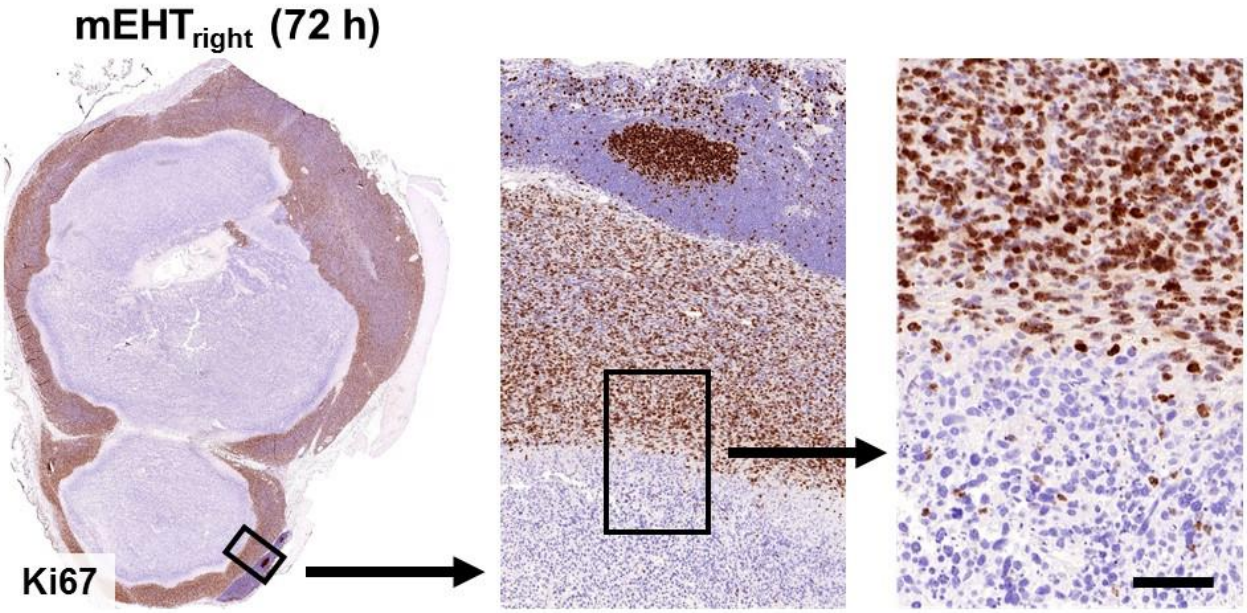
p*>0,05
p**>0,001

Cleaved caspase-3 / TUNEL



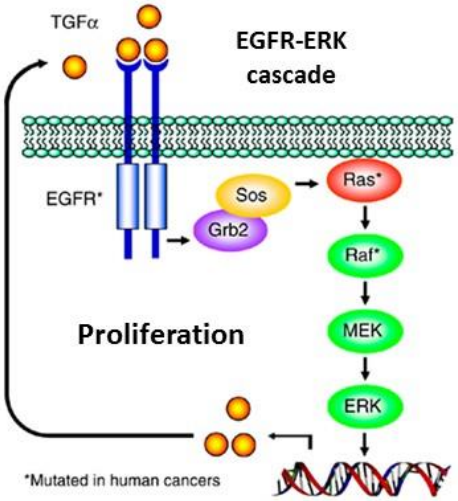


Inhibition of proliferation



- **Arrest of cell cycle**

Inhibition of proliferation



[1] Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. *Oncogene* (2007) **26,** 3291–3310. doi:10.1038/sj.onc.1210422

Role of ERK signalling:

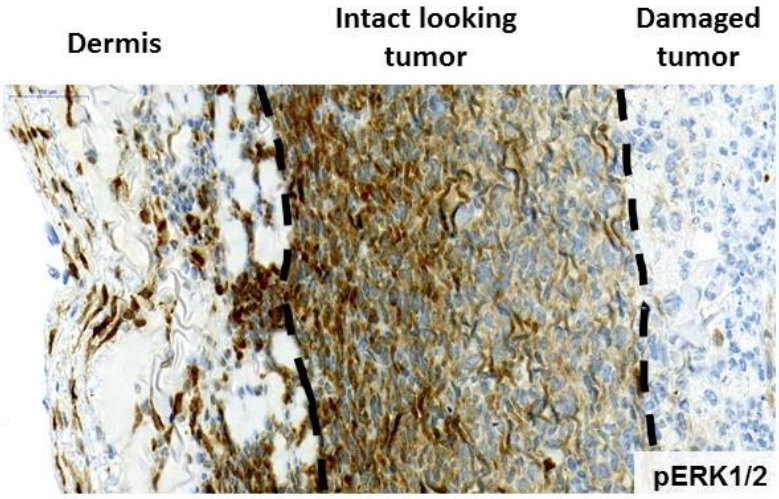
Active EGFR-ERK1/2 phosphorilation cascade supports **proliferation**[1]

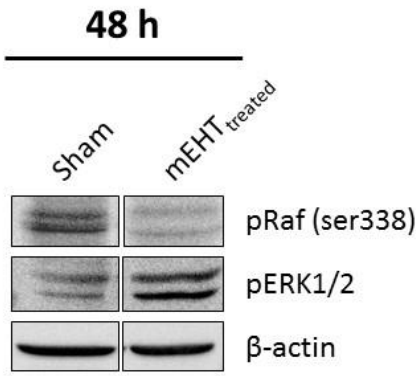
Elevated phosphorilated ERK1/2 level (and inactive upstream pathway) can also promote **apoptosis** [2] :

- with mitochondrial induction (BAX, cyt c) [3]
- inhibition of nuclear localisation impairs ERK-mediated survival [4]
- ERK could support extrinsic apoptotic pathway [5]

[2] Cagnol S, Chambard JC. ERK and cell death: mechanisms of ERK-induced cell death--apoptosis, autophagy and senescence. *FEBS J.* 2010 Jan;277(1):2-21. doi: 10.1111/j.1742-4658.2009.07366.x. Epub 2009 Oct 16.
[3] Lu Z, Xu S. ERK1/2 MAP kinases in cell survival and apoptosis. *IUBMB Life*. 2006 Nov;58(11):621-31.
[4] Mebratu Y , Tesfaigzi Y.How ERK1/2 activation controls cell proliferation and cell death: Is subcellular localization the answer? *Cell Cycle*. 2009-Apr 15;8(8):1168-75. Epub 2009 Apr 11.
[5] Kim YH et al. Quercetin augments TRAIL-induced apoptotic death: involvement of the ERK signal transduction pathway. *Biochem Pharmacol*. 2008 May 15;75(10):1946-58. doi: 10.1016/j.bcp.2008.02.016. Epub 2008 Mar 10.

Inhibition of proliferation



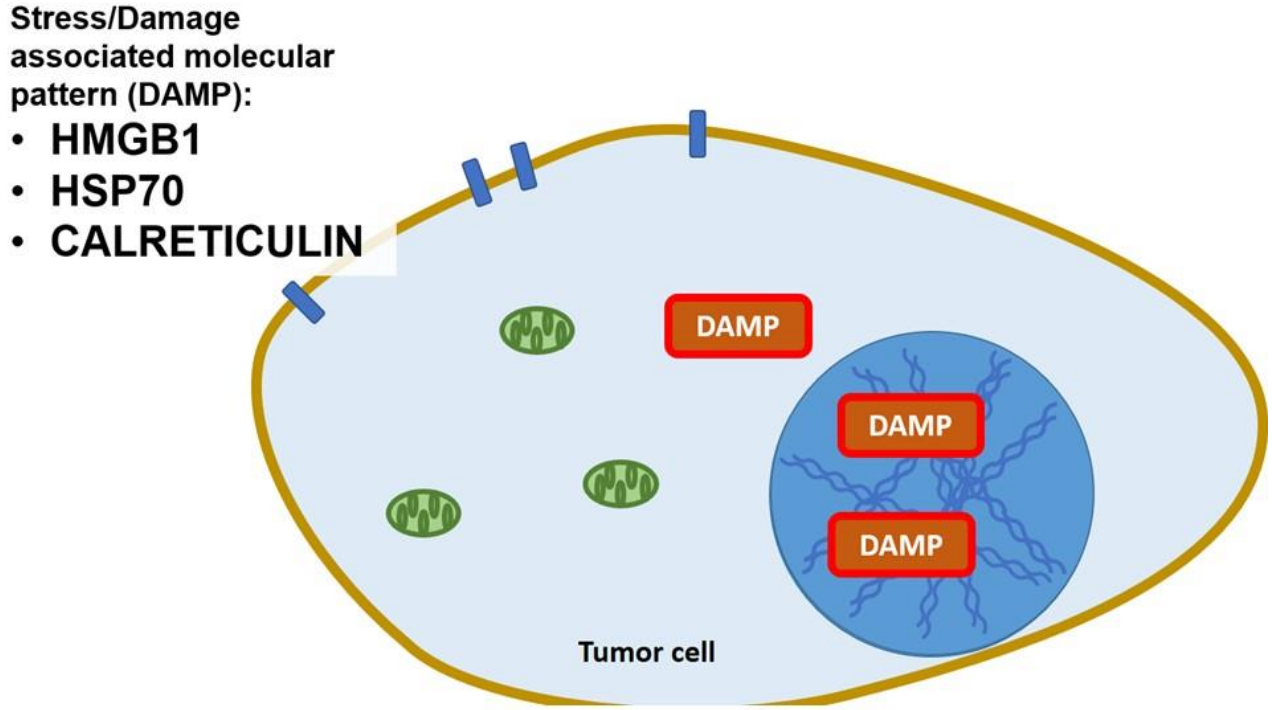


- Few nuclear reaction
- ERK1/2 positivity disappearace towards the damaged area

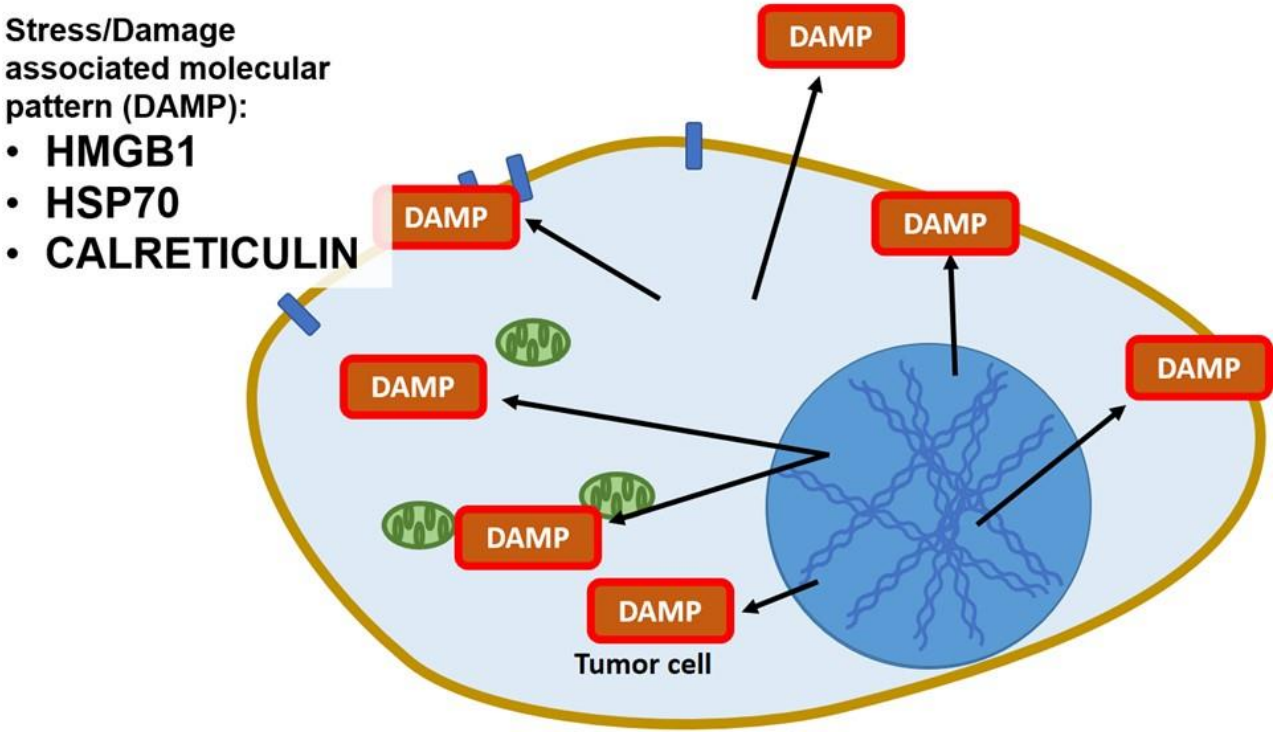
In damaged tumors:

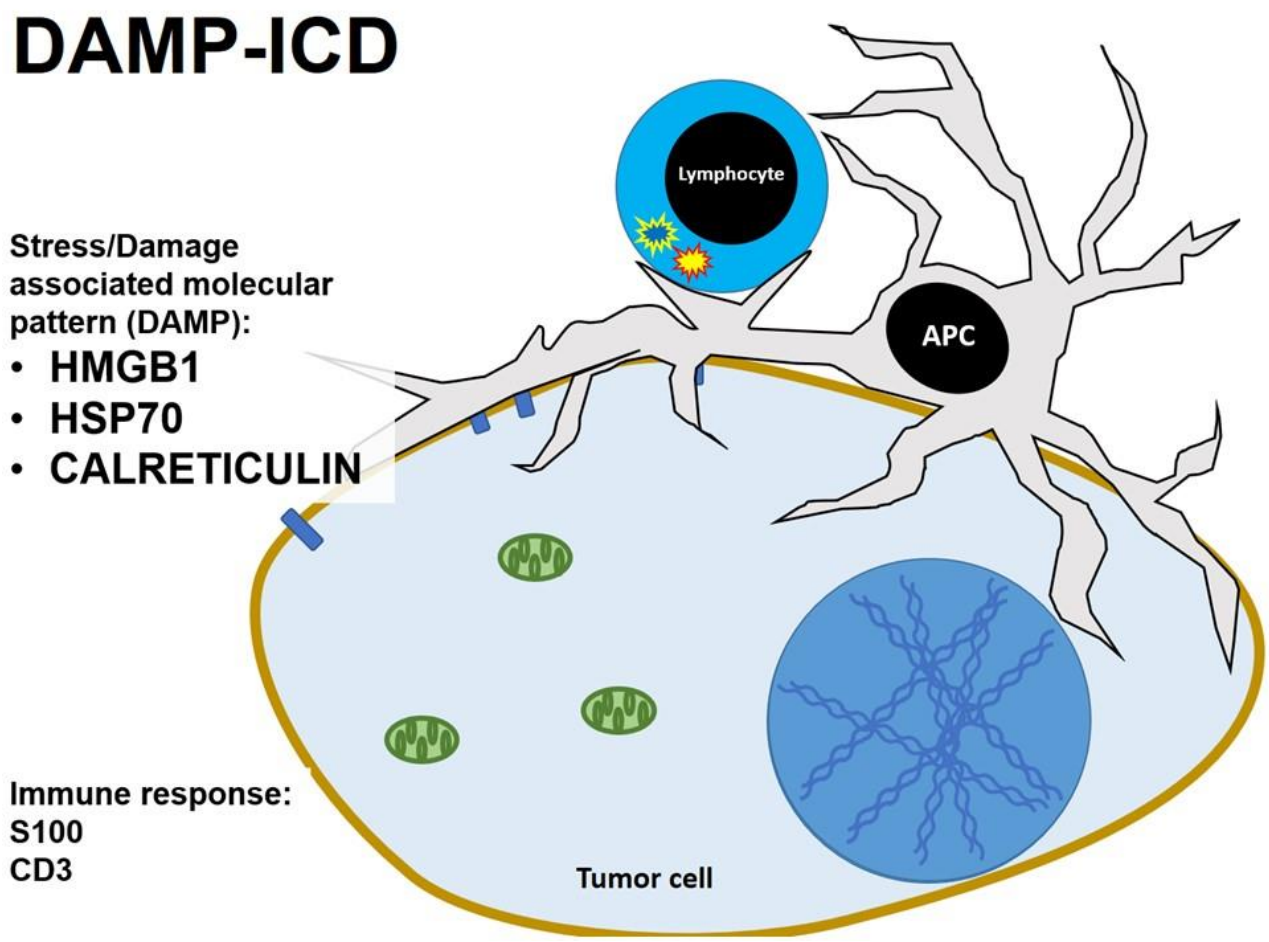
- Decreased pRaf,
- increased pERK1/2 levels

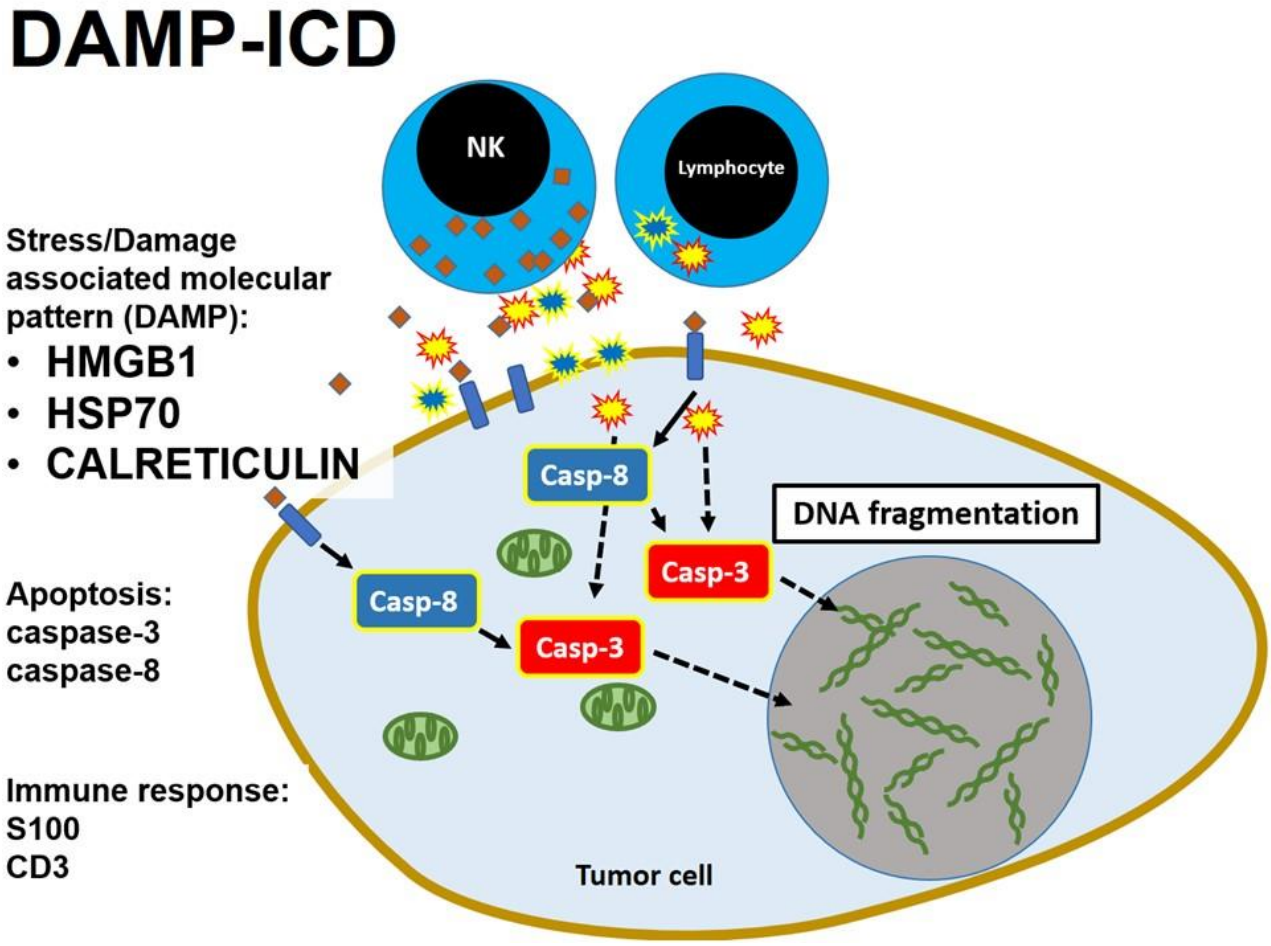
DAMP-ICD



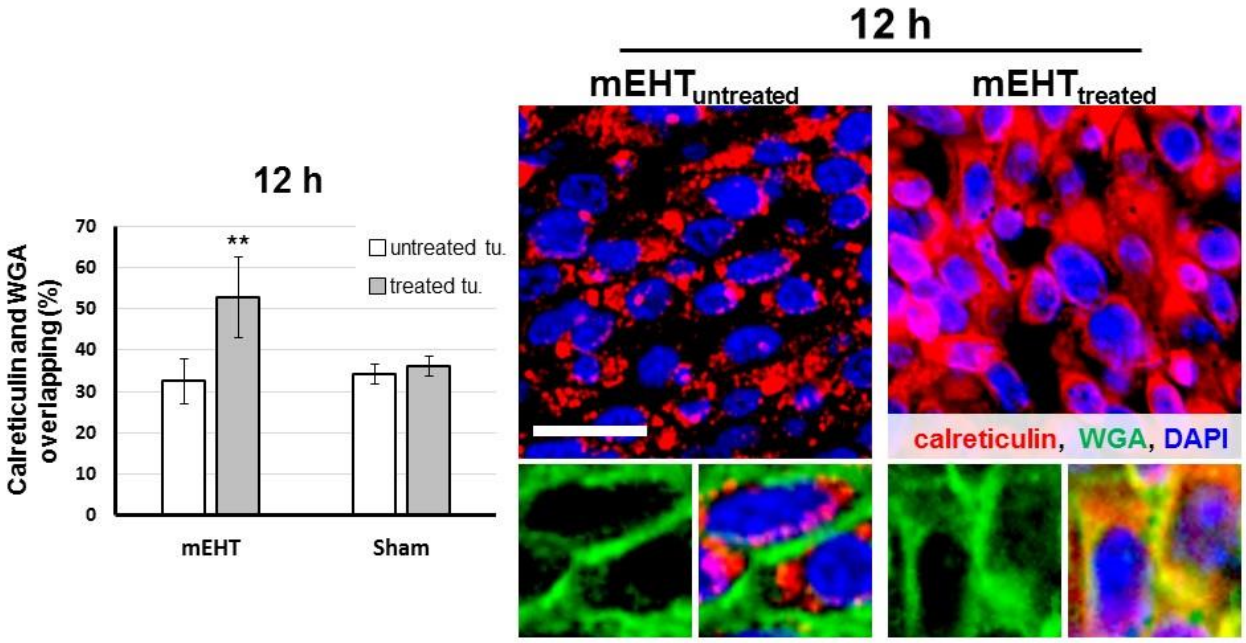
DAMP-ICD




DAMP-ICD
Lymphocyte
APC
Stress/Damage associated molecular pattern (DAMP):
• HMGB1
• HSP70
• CALRETICULIN
Immune response:
S100
CD3
Tumor cell

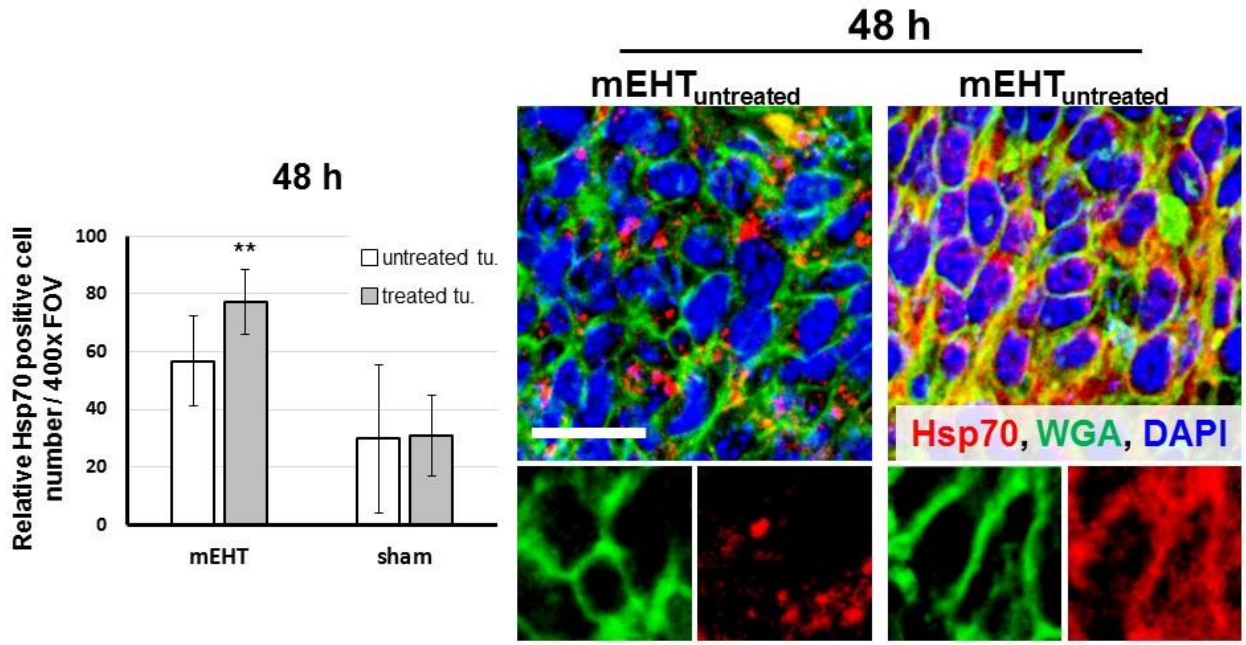

DAMP-ICD
NK
Lymphocyte
Stress/Damage associated molecular pattern (DAMP):
• HMGB1
• HSP70
• CALRETICULIN
Casp-8
DNA fragmentation
Casp-3
Casp-8
Casp-3
Apoptosis:
caspase-3
caspase-8
Immune response:
S100
CD3
Tumor cell

DAMPs: calreticulin



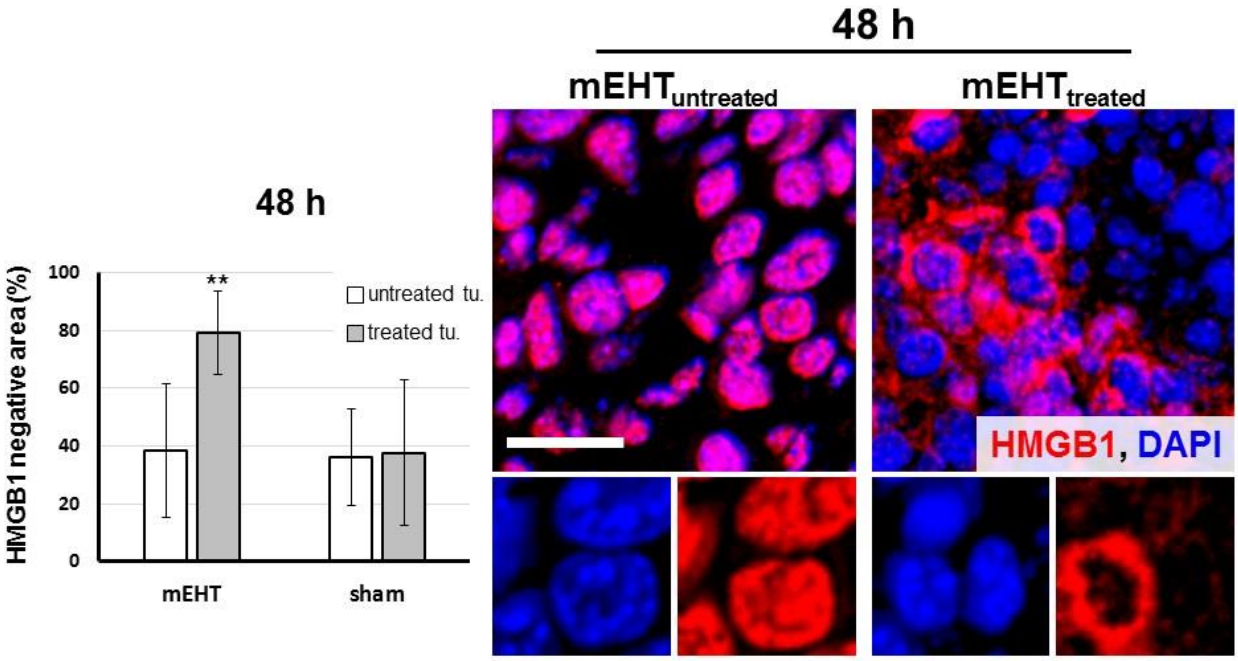
p*>0,05
p**>0,001

DAMPs: Hsp70



p*>0,05
p**>0,001

DAMPs: HMGB1



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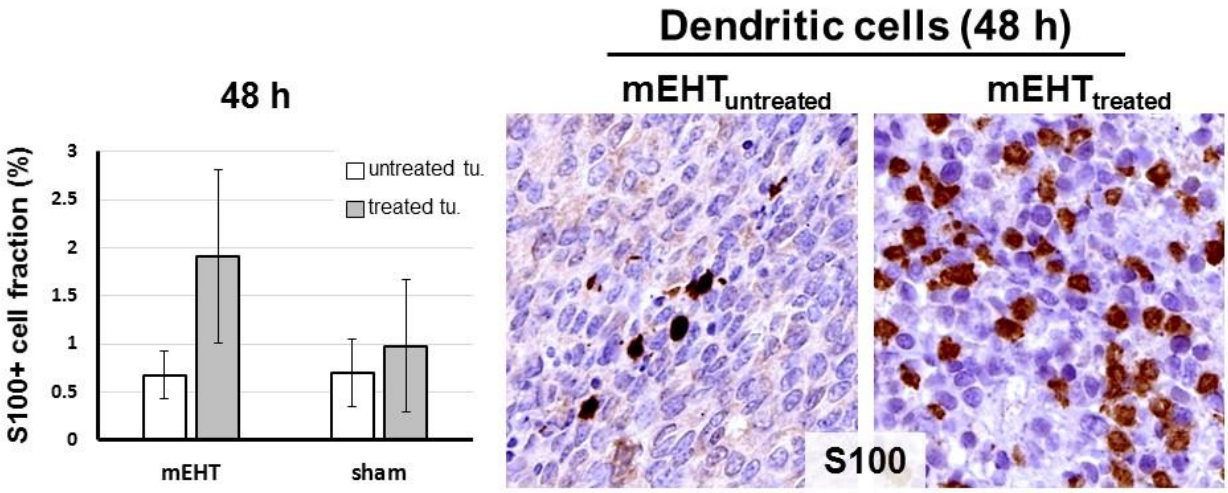
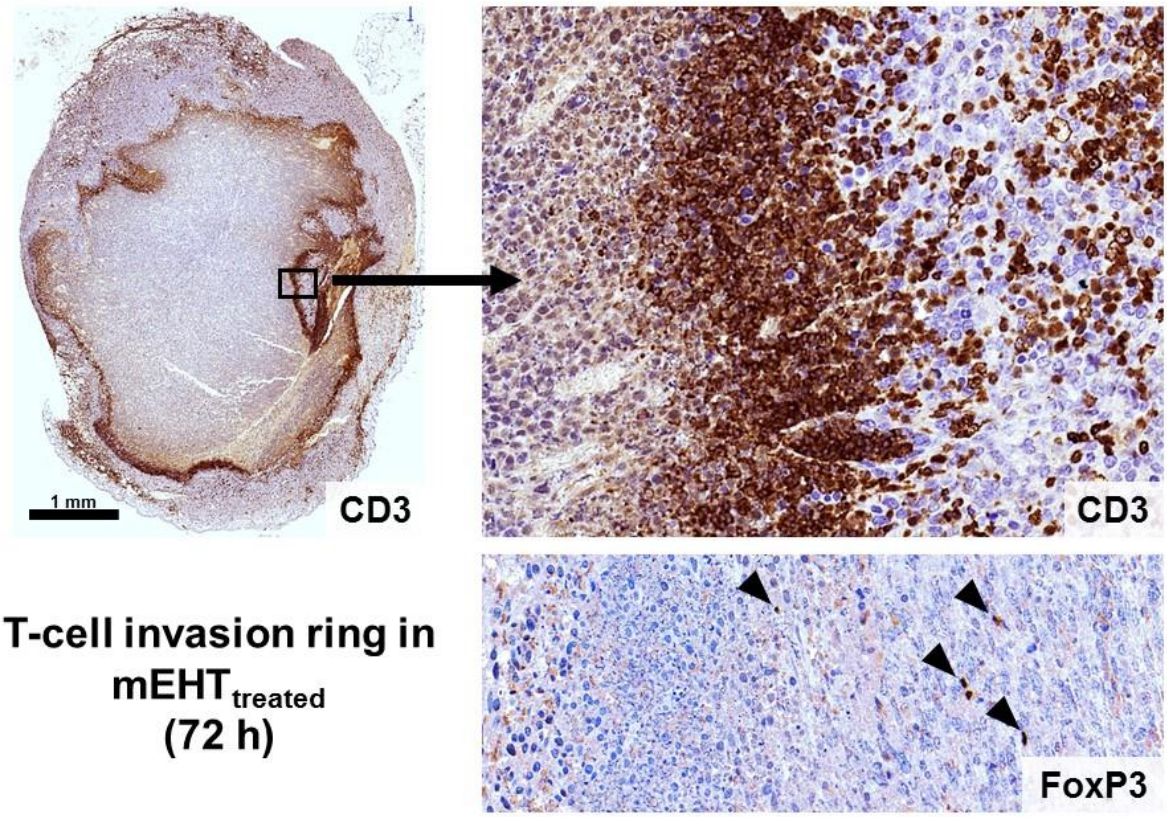
p**>0,001

Antigen presenting cells



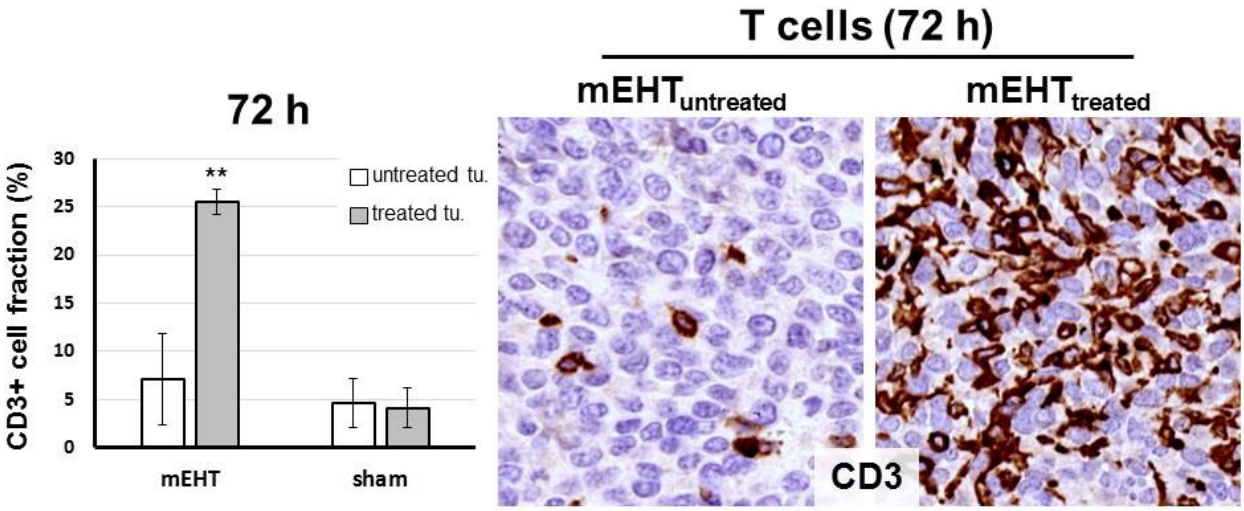
p*>0,05
p**>0,001

T-cells



T-cell invasion ring in $mEHT_{treated}$ (72 h)

T-cells



p*>0,05
p**>0,001

Summary

- mEHT caused significant and progressive tumor-destruction
- Induction by BAX and cytochrome c
- Inhibition of proliferation; eliminated Ki67
- Membrane localisated EGF receptors inhibition was suggested by reduced pRaf and elevated pERK1/2 could support the caspase-dependent apoptosis.
- Activation of APC by DAMPs
- T-cell mediated immunogenic cell death
- Extrinsic and intrinsic apoptotic pathways

Aknowlendgement:

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Matraine Balogh Eva
Zita Bratu
Zsibai Zsofia

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Thank you for your attention

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Whole Body Hyperthermia Clinical Trials

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President Hellenic Society for Integrative
Oncology

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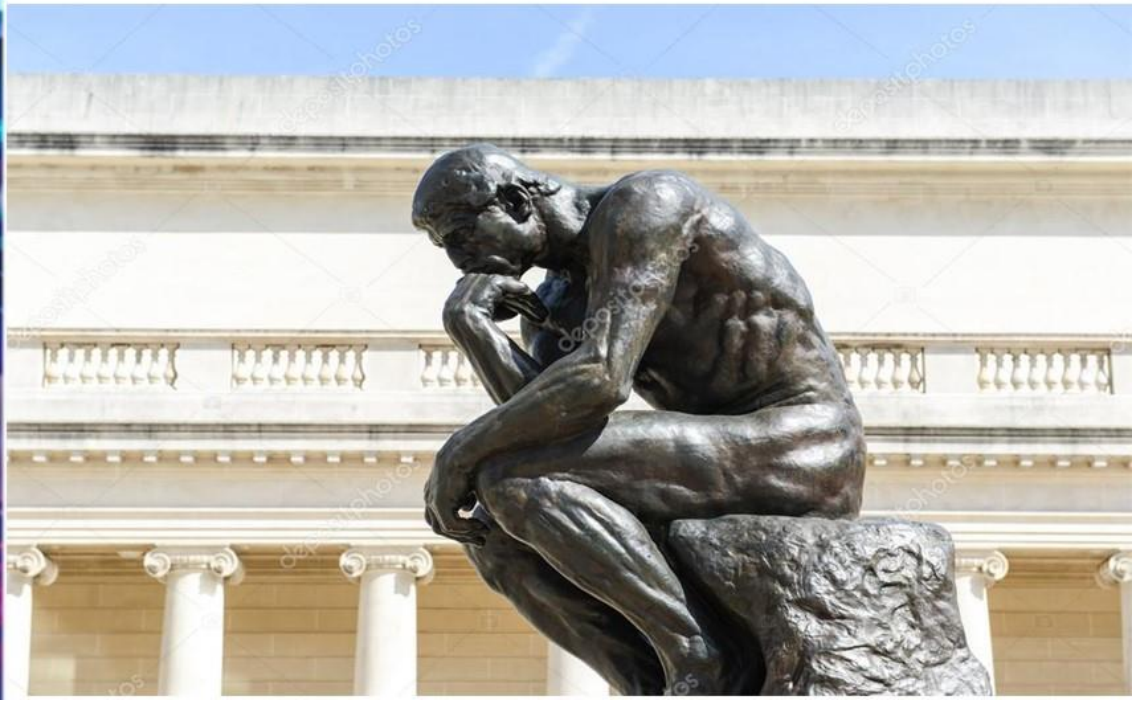
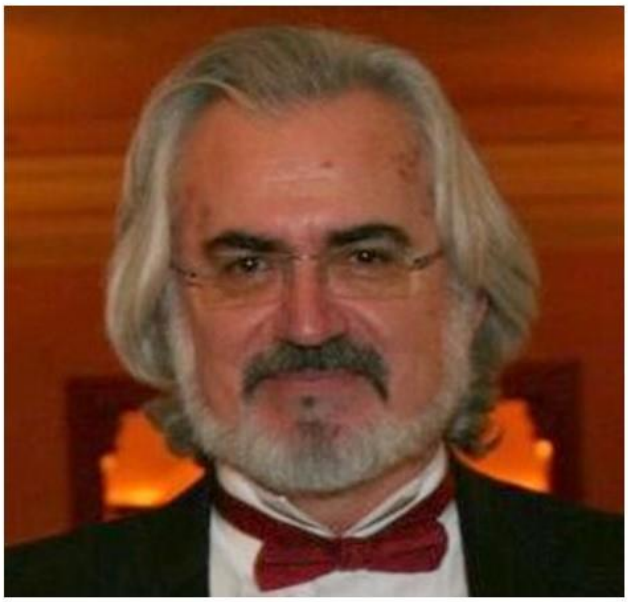
http://oncotherm.com/sites/oncotherm/files/2017-10/5.pdf

ARE THERE GUIDELINES FOR CLINICAL PRACTICE OF WBH, BASED ON CLINICAL TRIALS?

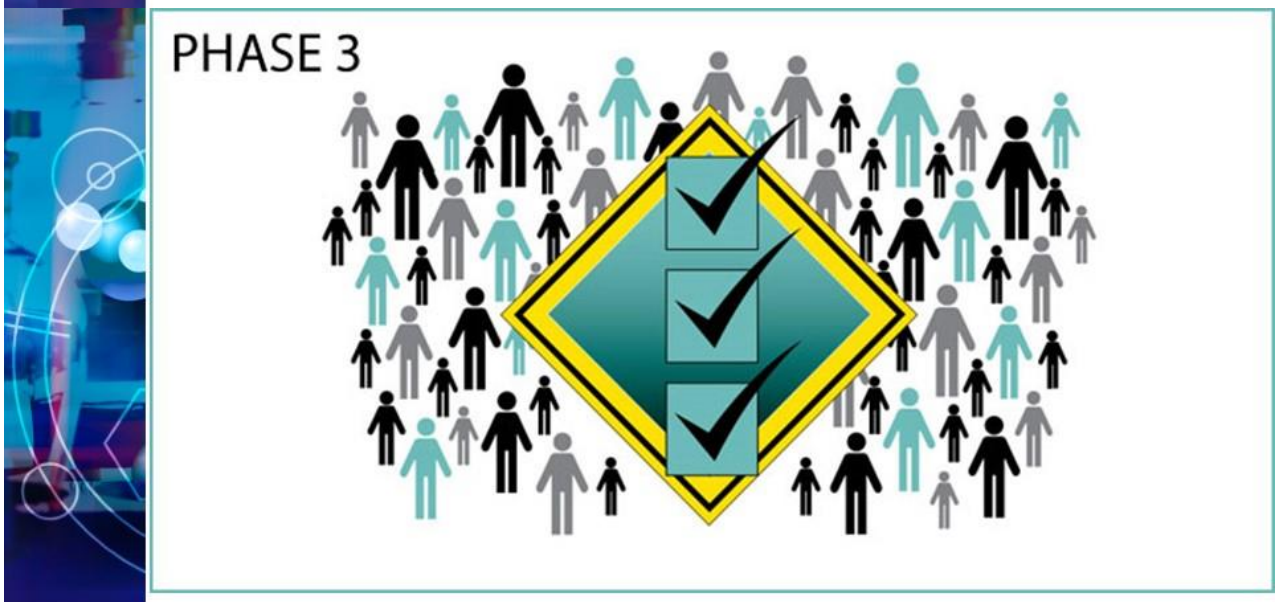




Dr. Alfred J. Barich,
Surgeon-Oncologist
AHEPA University Hospital / EUROMEDICA
President Hellenic Society for Integrative Oncology

Early phase I studies disclosed that most patients could only tolerate a systemic temperature of about 41.8°C for several hours before severe toxicity occurred .

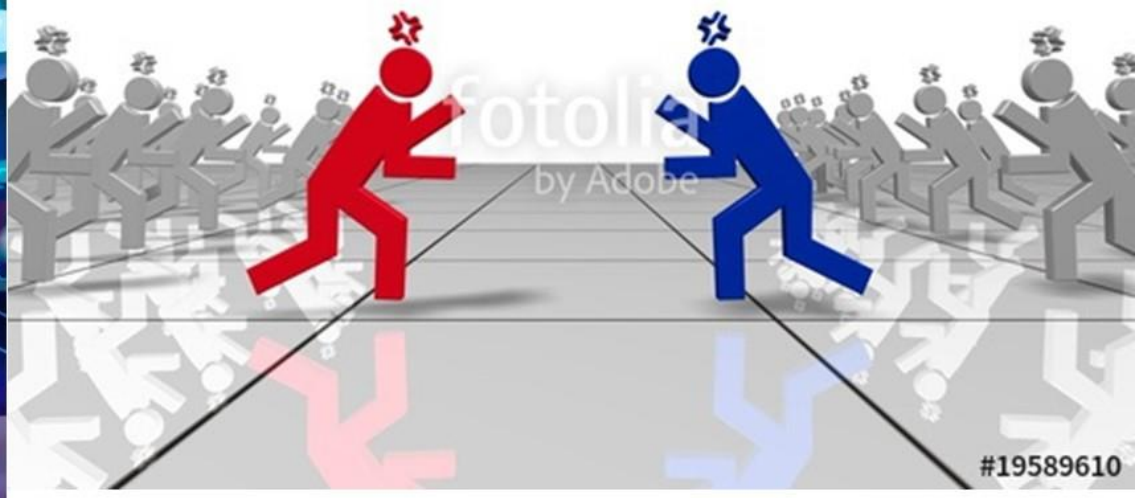
Most of the experience with the use of whole-body hyperthermia with systemic drugs is gained from phase I studies



In a phase III trial which included 44 patients with small cell lung carcinomas, standard chemotherapy with

doxorubicin,
cyclophosphamide and
vincristine (ACO regimen)

were given to the control group .

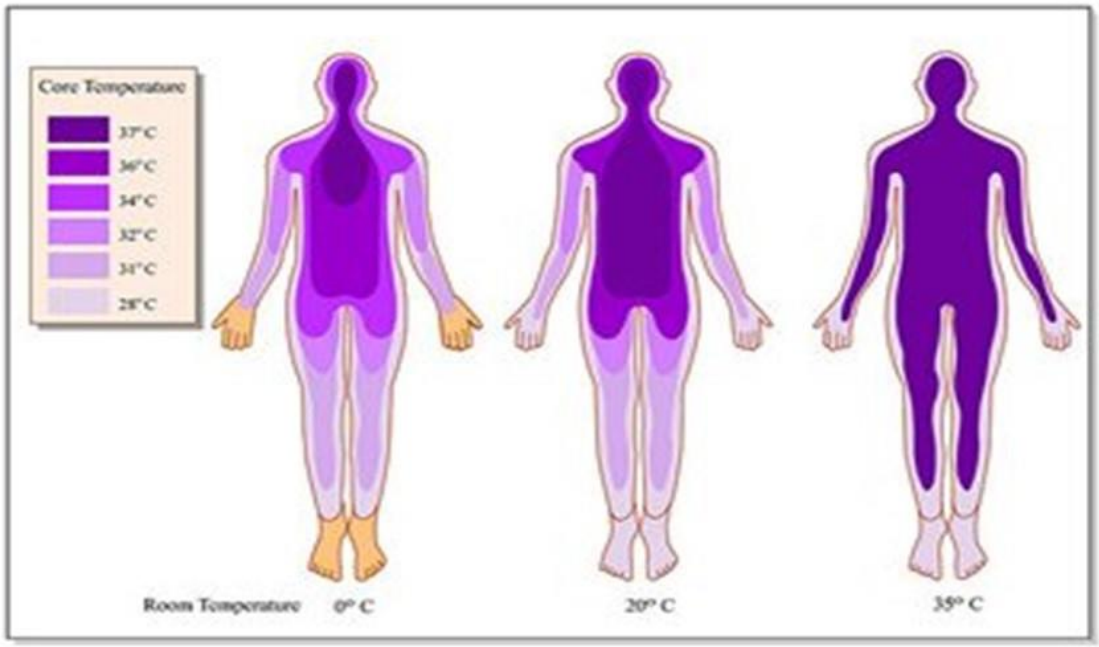


The other group received, in addition, whole-body hyperthermia, 41.5°C for one hour, during the first three of the six ACO cycles

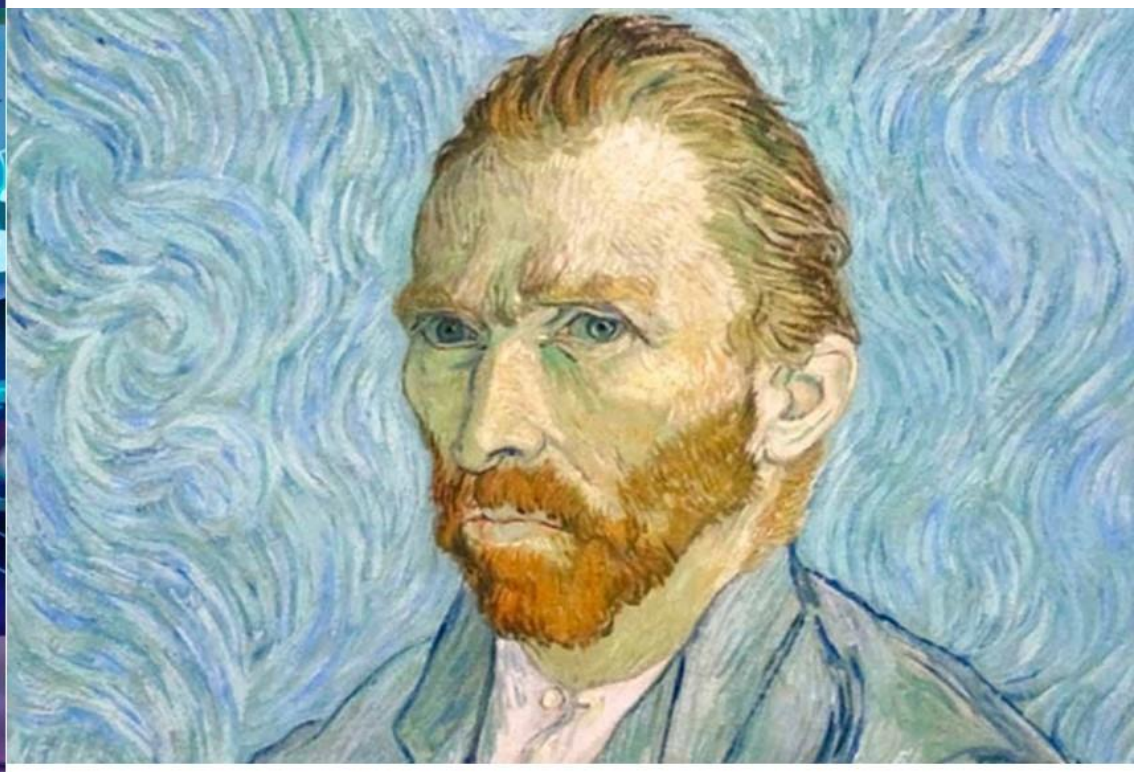
-The median duration of response was 105 days in the normothermic arm and 130 days in the hyperthermic arm.
-No impairment of renal, cardiac or liver functional occurred.
-Toxicity was similar in both groups.
- The development of whole-body hyperthermia has been hindered by a tendency to include patients in very advanced stages of the disease.

Currently, the procedure of applying whole-body hyperthermia is less burdensome for the patient and less demanding than procedures like high-dose chemotherapy with stem-cell support.

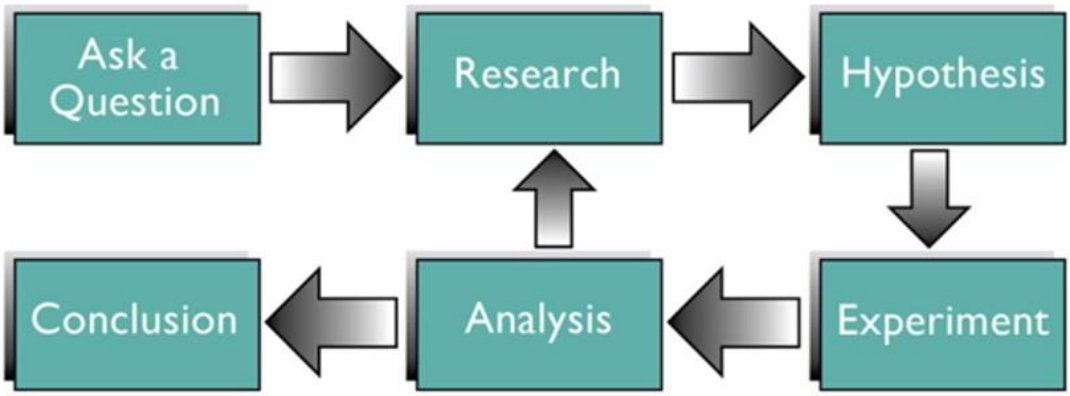
The first Guidelines for application of WBH as we know it today were formulated by the collaboration of the Medical University of Lubeck and University of Wisconsin Medical School within the auspices of Systemical Hyperthermia Oncological Working Group(SHOWG).



The application of WBH after the compilation of over 310 preclinical and clinical trials resulted in 28 state sponsored (Clinical Trials.Gov)



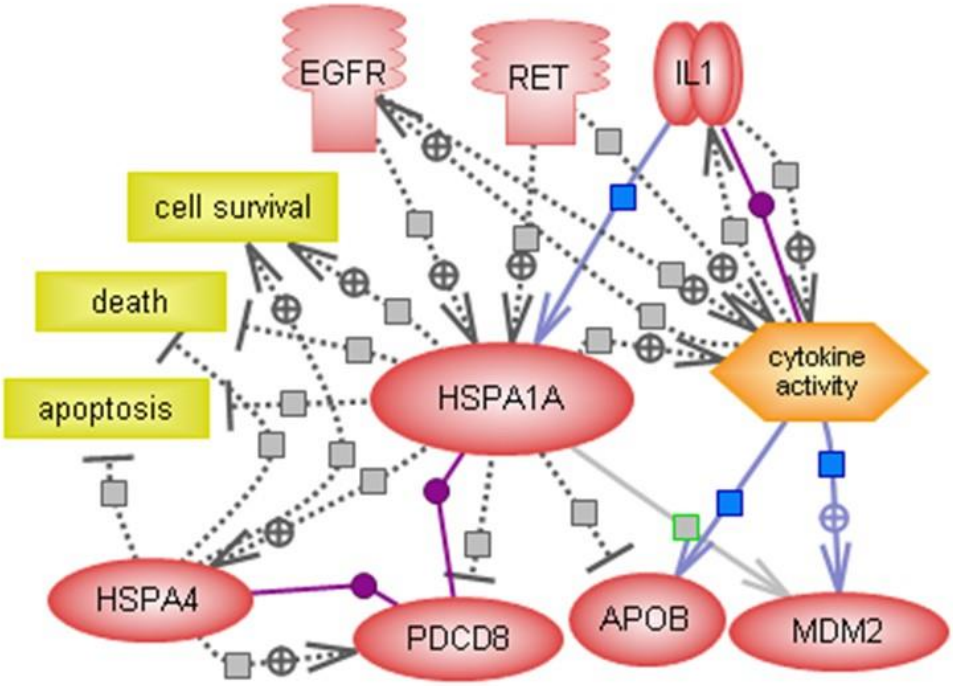
Clinical trials for studying the impact of WBH on cancer, and interestingly enough 6 trials studying the impact of WBH on Depression.
This indicates the degree of interest that is evoked from the results.



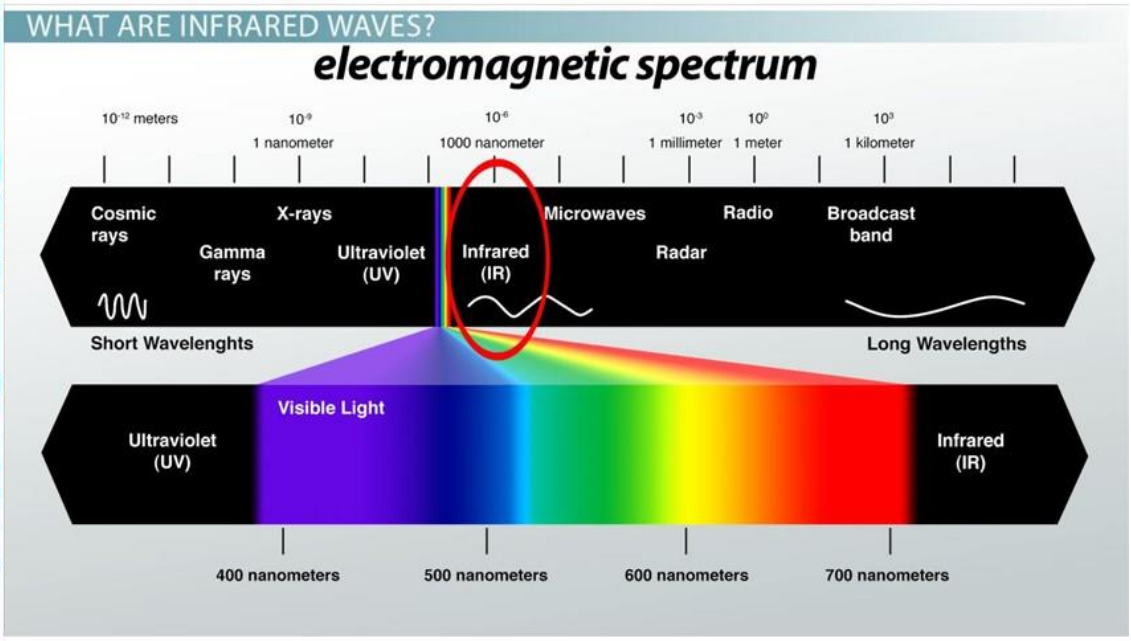
From this compilation of Trials a variation in the actual application protocols began to develop

ENDPOINTS OF THE DEVELOPING:

a) Extreme WBH temperatures reaching up to 42 C that were focused on maximizing cancer cell kill,



And
b) the Moderate WBH which focused more on the immunostimulation process that was incurred with the activation of Heat Shock Proteins (HSP).

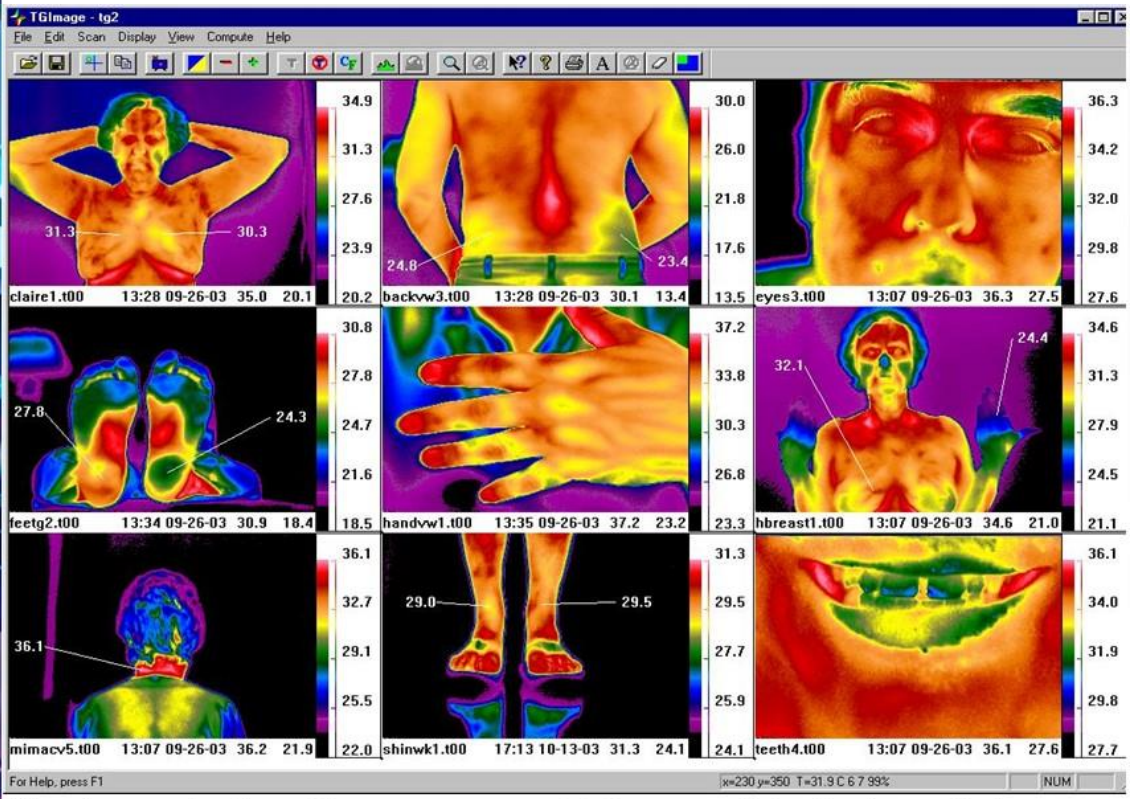


Also various modes of achieving these temperatures began to surface, with the most popular among these being the use of infrared energy to do the actual heating.

As the technology advances, and more variations are being introduced, it is becoming obvious that new Guidelines are becoming imperative.

WORLDWIDE CLINICAL TRIALS

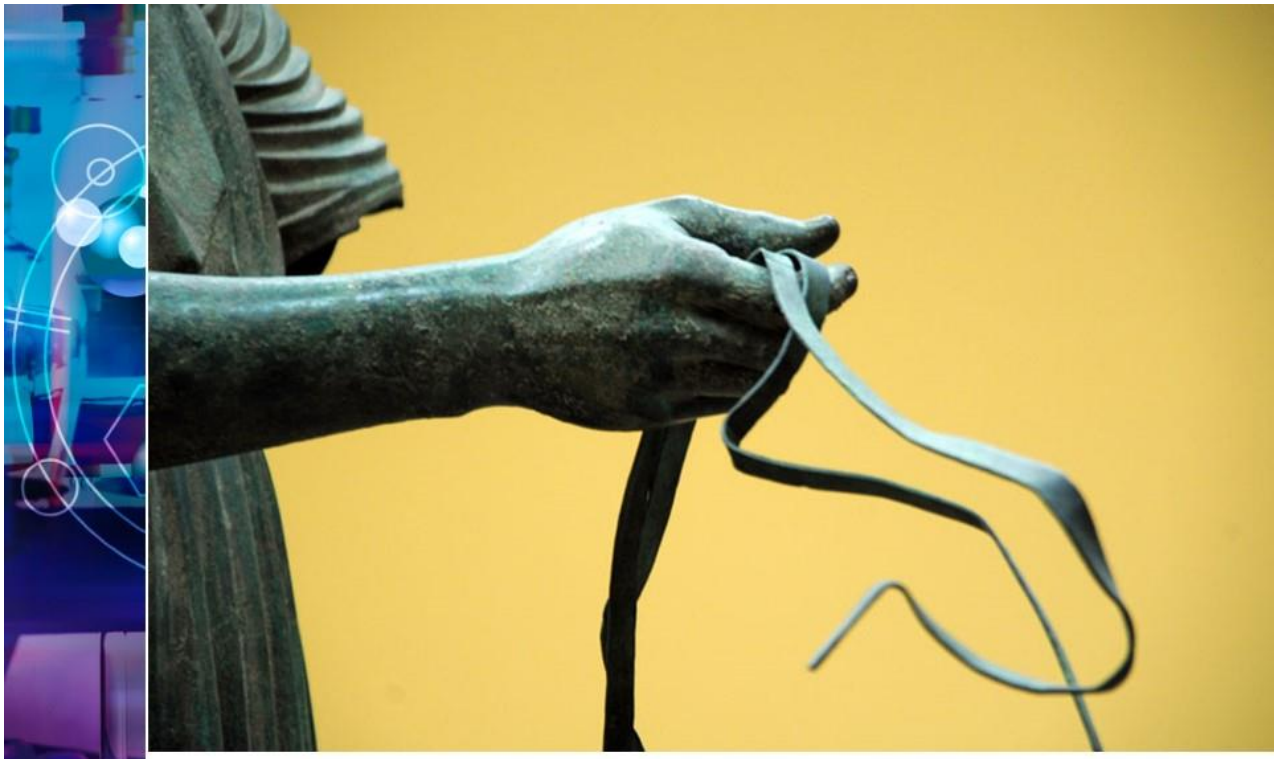
From the existing data we can conclude that :
Achievement of more level I/II evidence, with more well-designed randomised clinical trials, and high quality prospective trials are a mandate,as well as Incorporation of translational research in clinical trials.



Development of quality assurance guidelines must be implemented,as well as improvement of thermal dosimetry, when feasible, using non-invasive methods, and development of treatment techniques more user friendly for patients.

Revision of the original Kadota consensus treatment techniques and consensus to incorporate the knowledge and clinical experience that has been compiled

-Expansion of relationships with pharmaceutical and biotech companies, making a clear point that combination therapies with Hyperthermia esures better results, thus ensuring the tendancy for more targeted therapies through combinations.



More agressive promotion of the benefits of hyperthermia in the medical community and to the general public are necessary.

Modulated Electro-Hyperthermia in Oligometastatic Cancer Patients: initial experience and clinicopathologic evaluation

Forika G#, Borbenyi E, Szasz AM, Muhl D, Kiss E, Kvasnika M, Toth A, Torgyik L, Dank M

[#]1st Department of Pathology and Experimental Cancer Research, Budapest, Hungary;
Cancer Center, Semmelweis University, Budapest, Hungary

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#1st Department of Pathology and Experimental Cancer Research, Budapest, Hungary; Cancer Center, Semmelweis University, Budapest, Hungary

Intoduction

Modulated electro-hyperthermia (mEHY) has gained support in the treatment of cancer patients as **supplementary method** besides the standard treatment or for those who exhausted conventional treatment.

Patients and methods

Seventeen eligible patients were recruited based on clinical rounds decision since SEP-2, 2016.
Primary tumors of patients originated from the locations as follows: 7 pancreas, 4 colorectal, 3 breast, 2 lung and 1 kidney.
Patients who attended one treatment occasion and multiple primary tumors were excluded.
EHY-2000 instrument (Oncothermia Ltd., Budaörs, Hungary) was used and initial power of 60-150 W was applied.
The increments were set to 5-10 W in 5 minute steps.
Tumor markers CEA and CA19-9 and imaging studies were reviewed in light of duration of mEHY therapy.

Results

The patients' data was evaluated on APR-7, 2017.
Average number of metastases of the tumors were 2 (Figure 1).
Various chemotherapeutic protocols were administered to the patients as per guideline recommendations.

Average treatment time of each mEHY occasion was 59.5 minutes.
From the initial power to the final power on average 50W power increment was reached.
The patients underwent 18.7 cycles on average (range: 2-45).

Eight patients (4 pancreas, 1 colon, 1 breast and 1 kidney) had to discontinue the therapy due to progression, especially hydrothorax, ascites and severe pain, their treatment lasted on average 58.6 days.
Upon analyzing pancreatic tumor patients' data, elevated CEA but not CA19-9 levels correlated with progression of disease as confirmed by CT scans and eventual outcome.
The pancreatic cancer patients had an average of 130.6 days on mEHY treatment (Figure 2).
There was no significant difference in the duration of mEHY treatment between those possessing elevated CEA level and subsequently going into progression and those who remained free of symptoms and staying on mEHY therapy.

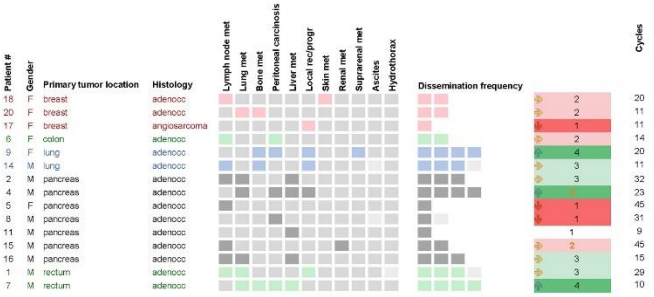


Figure 1. The patients included in the study, and their primary tumors with metastases upon inclusion in the mEHY therapy. Number of occasions of mEHY are listed on the right.

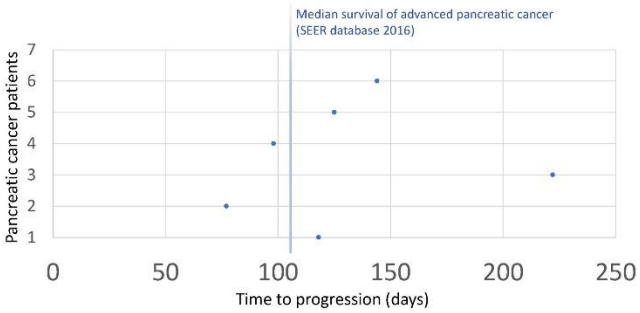


Figure 2. The period of pancreatic cancer patients included in the study spent with mEHY treatment. Three of them have still ongoing mEHY therapy.

Conclusion

Seventeen patients were treated at our mEHY therapy unit, which was established in the past months.
Patients with oligometastatic/inoperable tumors are likely the target population of this treatment approach, especially supplementing systemic therapy.
CEA and CA19-9 levels in pancreatic cancer patients are not predictive for response to mEHY therapy (yet patient numbers are low), thus, identification of better biomarkers is warranted.
In the next phase, we plan to recruit pancreatic cancer patients and identify predictive markers for response to mEHY therapy combinations.

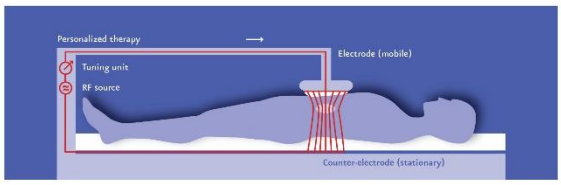
Acknowledgements

AMS was supported by the János Bolyai Research Scholarship of the Hungarian Academy of Sciences.
Supported by the NVKP_16-1-2016-0042 grant.

Advertisement

Information

Oncothermia-Method & Oncotherm-Devices



Oncothermia is based on the classical method of Hyperthermia, one of the oldest cancer treatment methods. Unlike conventional Hyperthermia, Oncothermia does more than simply warm up deep layers of tissue. It combines such warming with a modulated electric field, with a carrier frequency of 13,56 MHz, that is generated by two active electrodes.

EHY-2030

EHY-2030 is our latest development in the treatment of loco- regional tumors. The newly designed device includes the Smart Electrode System (SES), the plug-in Patient Management System (PMS-100) and a user-friendly touch screen display with full system control. The new RF generator with increased power has been developed with a new intelligent controlled step motor tuning system for the reachable fastest impedance matching.

EHY-3010

EHY-3010 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. Instead of a bolus electrode, this system uses textile electrodes, which are even more flexible to adjust to the treatment area.

EHY-2000plus

EHY-2000plus is a widely accepted system for locoregional deep Hyperthermia applications. This model has been used for treatment worldwide for more than 20 years. Popular, versatile device, applicable for all kinds of solid tumors. It has been improved by taking into account the experiences of our doctors and experts, and the requirements of patients and the people treating them. The EHY-2000plus is an easy to use and reliable device.

EHY-1020

EHY-1020 is our professional device for treating prostate diseases. Both malignant and benign tumors (BPH) can be treated using this system: a catheter with built-in electronics and counter electrode. The EHY-1020 system is compact and easy to use. The method has been successfully used by our customers for many years. The results of the treatment are excellent and nevertheless many unpleasant side effects that are known from other forms of treatment can be avoided.

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