

# ONCOTHERMIA JOURNAL

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# Editorial



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

I am pleased to introduce the 24<sup>th</sup> volume of our Oncothermia Journal (OJ). I am glad to present you the Proceedings of the recent, 36<sup>th</sup> Annual Conference of International Clinical Hyperthermia Society. The conference had two very intensive days of presentations and discussions, profoundly covering the most important topics of the scientific and medical aspects of the present and future of hyperthermia. The six sessions covered the topics of the hottest areas of the clinical and laboratory researches: the challenges, the clinical achievements, the recent technical situation, the immuno-oncological aspects, the integrative clinical approach and the molecular biology of the thermal effects. The key-notes were delivered by highly renowned experts as Prof.Y. Datta, Prof.S. Bodis, Prof.P. Wust, Prof.K-W Chi, Prof.C. Pang and Dr.T. Krenacs. The keynotes and the following presentations were intensively discussed; sometimes heated debates were developed. The participants discussed the topics actively in the coffee-breaks, lunches, and dinner too. The great challenge of the definition of oncological hyperthermia and the clinical dosing made the audience excited, sometimes running out of the predefined duration of the presentations. The present volume of OJ gives an insight into the successful conference, providing dedicated knowledge of the practical and theoretical issues of oncological hyperthermia, showing some non-oncological applications of heat-therapy as well. The new line of oncology, the immune-activities are also presented showing the extreme adaptability of oncological hyperthermia to the most modern oncotherapies.

The present proceeding speaks for itself: the high level of scientific and medical presentations represented the best values of the hyperthermia community and it well shows the great development possibilities, as well as the bright future of the method.

I am giving this volume to you to enjoy the achieved results, to learn the challenges and complications and to find the future of oncological hyperthermia. I devote this volume to all experts and interested medical professionals for reading and getting ideas on how to go further, how we may offer better, more effective and lower risk for patients.

Sincerely yours,

**Prof. Dr. Andras Szasz**

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

Ich freue mich, Ihnen den 24. Band unseres Oncothermia Journals (OJ) und die Ereignisse der 36. Jahrestagung der Internationalen Klinischen Hyperthermie Gesellschaft (International Clinical Hyperthermia Society - ICHS) vorstellen zu können. An zwei Tagen fanden mehrere Vorträge und Diskussionen statt, in denen die wichtigsten Themen der wissenschaftlichen und medizinischen Aspekte der gegenwärtigen und zukünftigen Hyperthermie ausführlich behandelt wurden. Die sechs Sitzungen umfassten die neusten Themen im Bereich der klinischen Forschung und Laborforschung: die Herausforderungen, die klinischen Erfolge, die neuste technische Situation, die immunonkologischen Aspekte, der integrative klinische Ansatz und die Molekularbiologie der thermischen Effekte. Zu den Keynote Sprechern gehörten renommierte Experten wie Prof.Y. Datta, Prof.S. Bodis, Prof.P. Wust, Prof.K-W Chi, Prof.C. Pang und Dr.T. Krenacs. Die Keynotes und die Präsentationen wurden intensiv diskutiert; manchmal entwickelten sich sogar hitzige Debatten. Die Teilnehmer diskutierten die Themen zudem lebhaft in den Kaffeepausen und während des Mittagessens und Abendessens. Die große Herausforderung eine Definition für die onkologische Hyperthermie zu finden und das Thema der klinischen Dosierung hat die Zuhörer sehr begeistert und manchmal wurde dadurch die vorgeschriebene Dauer der Präsentationen überschritten.

Die neue OJ-Ausgabe gibt einen Einblick in die erfolgreiche Konferenz. Zudem bietet diese Ausgabe ein vertieftes Wissen über die praktischen und theoretischen Fragen der onkologischen Hyperthermie und zeigt auch einige nicht-onkologische Anwendungen der Wärmetherapie auf. Auch das Thema Immun-Aktivitäten wurde vorgestellt und zeigt die extreme Anpassungsfähigkeit der onkologischen Hyperthermie an die modernsten Onkotherapien.

Die gegenwärtigen Entwicklungen sprechen für sich: Das hohe Niveau der wissenschaftlichen und medizinischen Präsentationen repräsentierte die besten Werte der Hyperthermie-Gemeinschaft und es zeigt sehr gut die großen Entwicklungsmöglichkeiten, sowie die glänzende Zukunft der Methode.

Ich präsentiere Ihnen diese Ausgabe, um die erzielten Ergebnisse vorzustellen, um die Herausforderungen und Komplikationen zu erläutern und um über die Zukunft der onkologischen Hyperthermie zu informieren. Ich widme diesen Band allen Experten und interessierten medizinischen Fachkräften, damit Sie Ideen sammeln können, wie wir den Patienten eine effektivere und risikoärmere Behandlung bieten können.

Mit freundlichen Grüßen,

**Prof. Dr. Andras Szasz**

# Imprint

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# Rules for submission

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

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

## 1. Aims and Scope

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

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

Further information about the Journal, including links to the online sample copies and content pages can be found on the website of the journal: [www.Oncothermia-Journal.com](http://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 temperaturunabhängige Effekte, Ansprechen auf elektrisches Feld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von *Oncothermie* und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
- *Oncothermie-Techniken*. Technische Entwicklungen, neue technische Lösungen.
- Hypothesen, Meinungen, wie die *Oncothermie-* und *ECT-Methoden* verbessert werden können, um die Behandlung zu unterstützen.

## 2. Submission of Manuscripts

All submissions should be made online via email: [Oncothermia-Journal@oncotherm.org](mailto:Oncothermia-Journal@oncotherm.org).

### 2. Manuskripte einreichen

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- Abstracts. Abstracts müssen enthalten: Zielsetzung, Material und Methoden, Ergebnisse, Fazit.
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## **Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) Method**

**Magdolna Dank<sup>1</sup>, Gyonygver Szentmartoni<sup>1</sup>, Gyula Peter Szigeti<sup>3</sup>, Carrie Minnaar<sup>2</sup>, Marcell A. Szasz<sup>1</sup>**

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# Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) Method

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## Introduction

Modulated electro-hyperthermia (mEHT) is a new kind of hyperthermia in oncology. It is a further development of the conventional heating methods utilizing the capacitive setting. Thus, mEHT heats the malignant cells selectively instead of the complete isothermal heating of the tumor mass. The mEHT is widely accepted and applied, however, traditionally considered clinical indications are still in progress.

## Aim

However, evidence is emerging, the proofs are of various evidence levels. Our overview in this presentation shows the clinical achievements, presenting the results of case presentations and clinical trials utilizing the mEHT method.

## Methods

Our review on data presents the collected experience with capacitive hyperthermia treatments with the EHY-2000+ device (OncoTherm Ltd., Germany). The essence of case reports with primary and metastatic tumors treated with mEHT (grouped into carcinomas of organ systems, and sarcomas of bone and soft tissues), case presentations of immunotherapeutic combinations with mEHT and also clinical trials of various natures were summarized and evidence is provided.

## Results

Based on clinical studies, the method mEHT is a feasible hyperthermia technology for oncological applications. Concomitant utilization of capacitive hyperthermia is now supported by the data from series of case reports up to randomized Phase III clinical trials.

Grant support: NVKP\_16-1-2016-0042



## Review of the Clinical Evidences of Modulated Electro-Hyperthermia (mEHT) Method

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*Presenter's name: Magdolna Dank MD,  
PhD*

*I have the Relationships with commercial  
interests:*

*Advisory Board: Lilly, Novartis, Pfizer  
Research: Celltrion*

CONFLICT  
OF INTEREST



mEHY treatment – easy to use and safe



# The Stories

Case-reports

# HCC

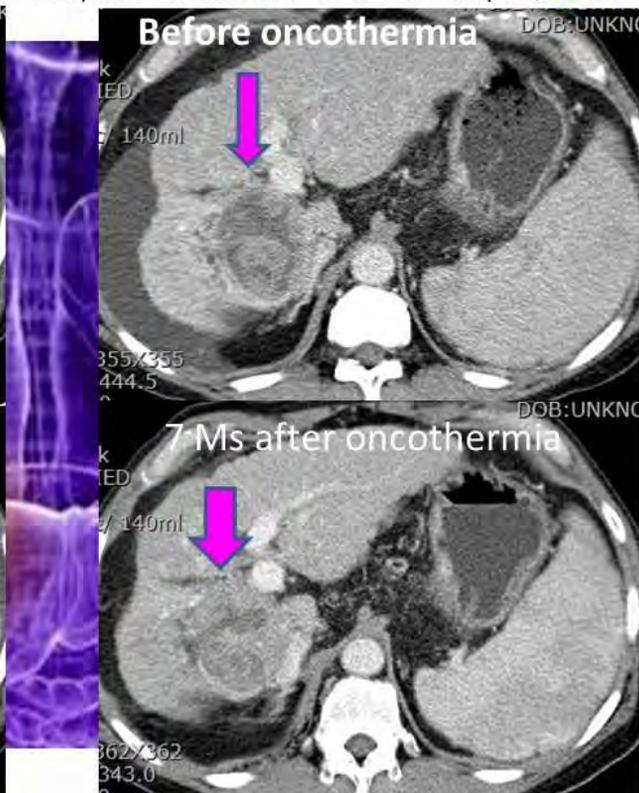
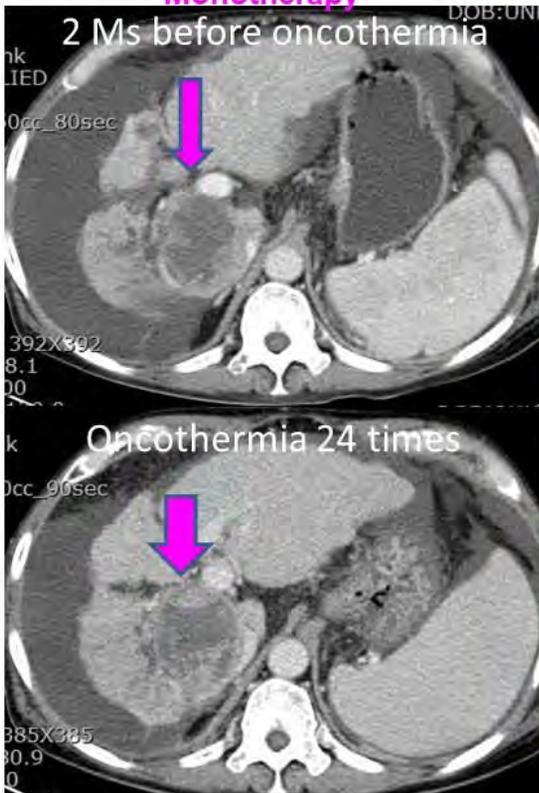


Navigation icons: back, forward, search, zoom, etc.

# HCC

(61y/M), Feb/2011, oncothermia 24 times,  
**Monotherapy**

**Investigator:** Prof.Dr.Taesing Jeung  
**Institute:** Department of Radiation Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital. **Published:** 31<sup>st</sup> ICHO Oct. Budapest, **2012**



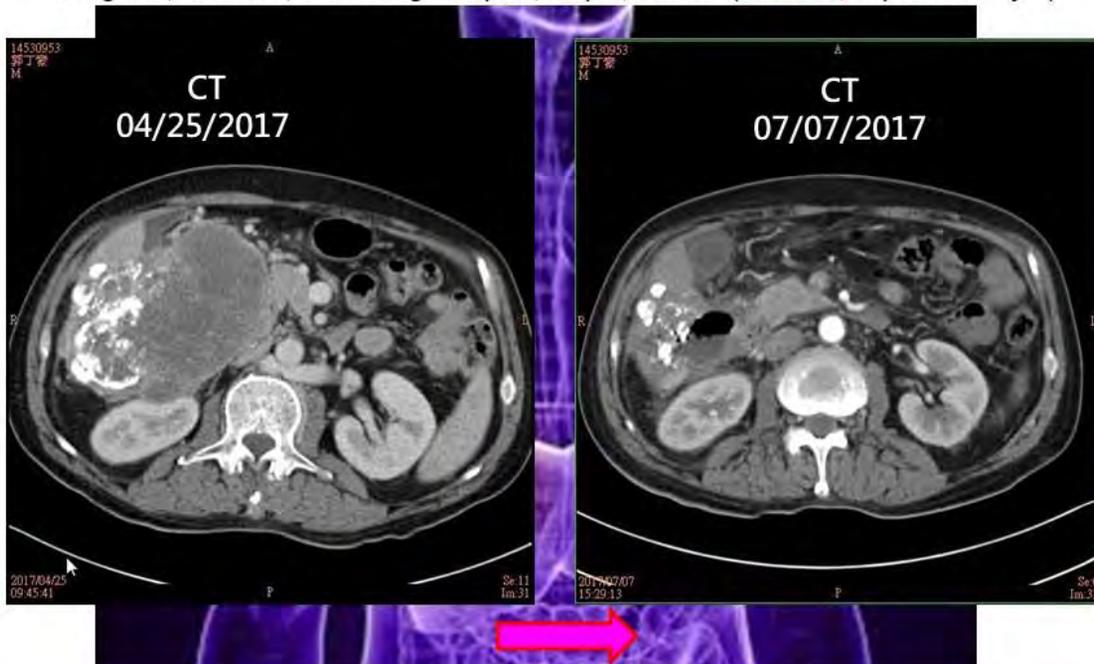
## Hepatocellular carcinoma (HCC)

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



## Hepatocellular carcinoma (HCC)

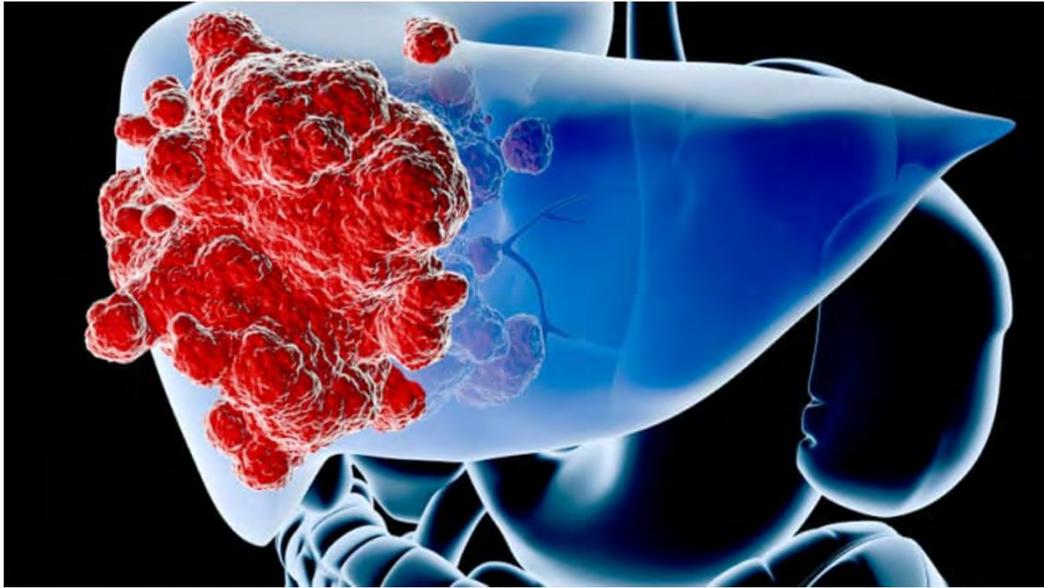
Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



RT 46 Gy/23fx + Oncothermia x 5 (1/week) + Lipodox 20mg x3

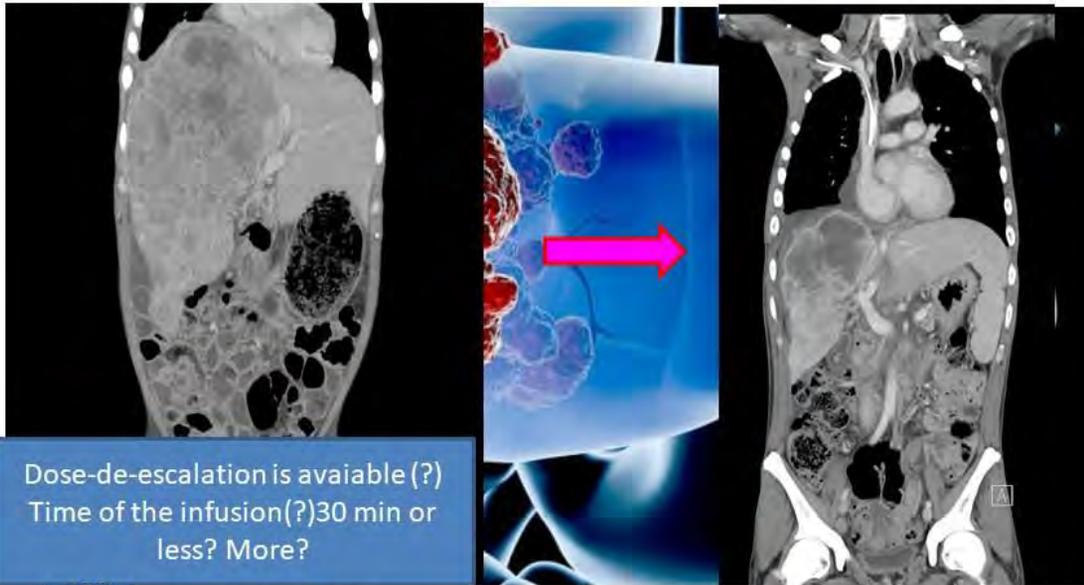
## Advanced hepatoma

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



## Advanced hepatoma

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



Dose-de-escalation is available (?)  
Time of the infusion(?)30 min or  
less? More?

200  
mg

10/16/2016 CT

05/25/2017 CT

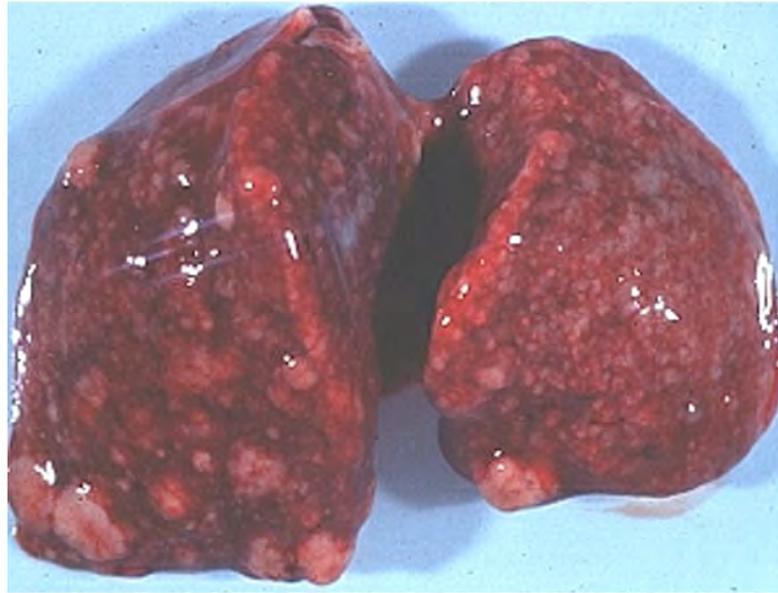
Keytruda 50mg Q3W +  
Lipodox 20mg Q2W  
+ liver RT



Oncothermia for liver 15 times

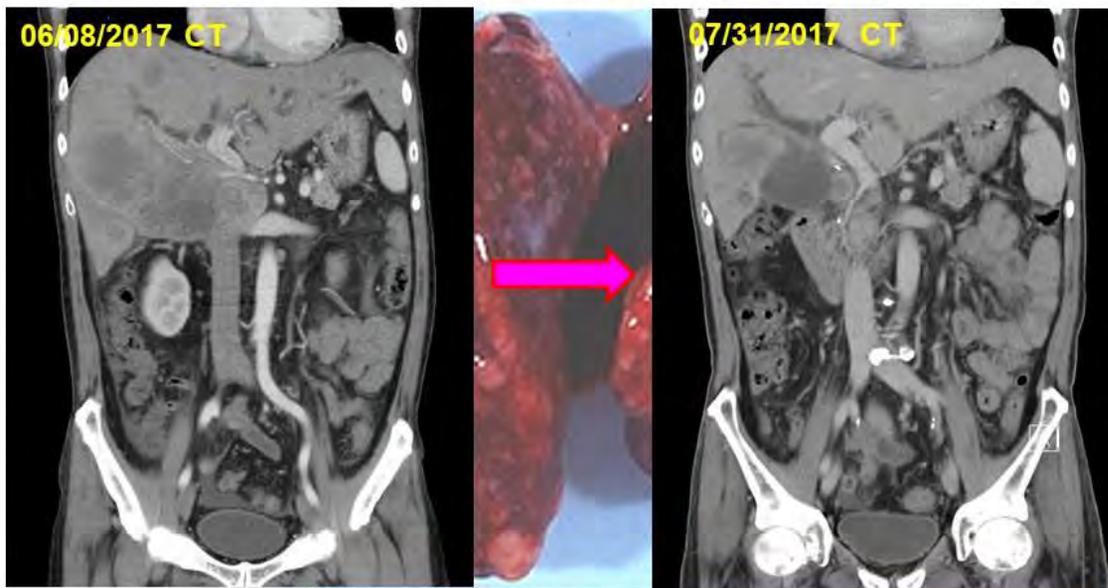
## Cholangiocarcinoma

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



## Cholangiocarcinoma

Wang Y-S, Chi K-W, Shih-Kong Hospital, Taipei, Taiwan (11.2017; unpublished yet)



D1: Avastin 200MG  
D2: Gemzar 500MG/M2 , D2~D4: 5-FU 500MG/M2  
D5: Keytruda 150mg  
RT (Cholangiocarcinoma): from 6/15 to 7/5, total 30Gy/15Fx.  
**Oncothermia** : from 6/28 to 7/31, total 10 times

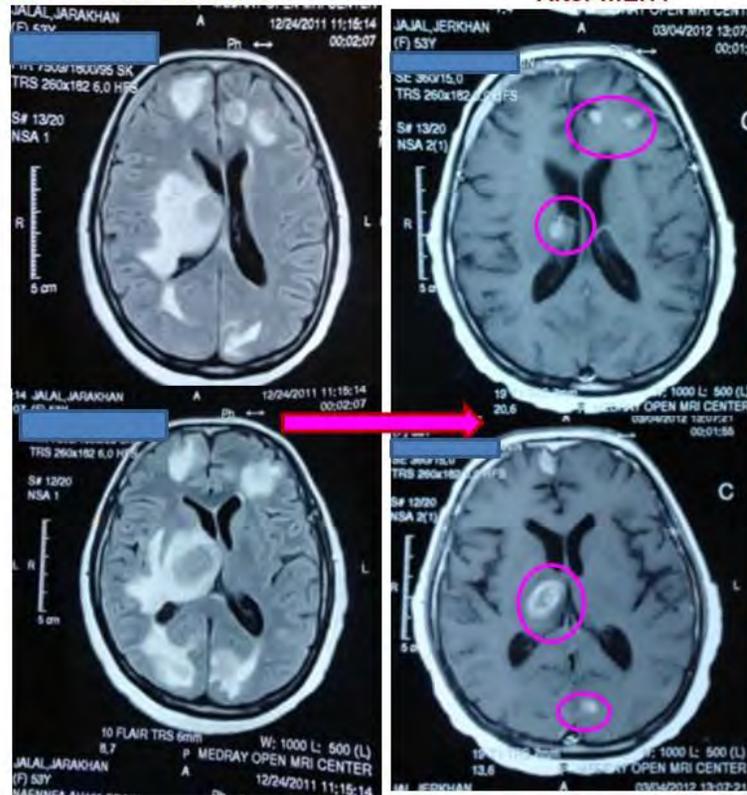
## Brain metastasis from breast cancer

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

**mEHT Monotherapy**

**Before mEHT**

**After mEHT**

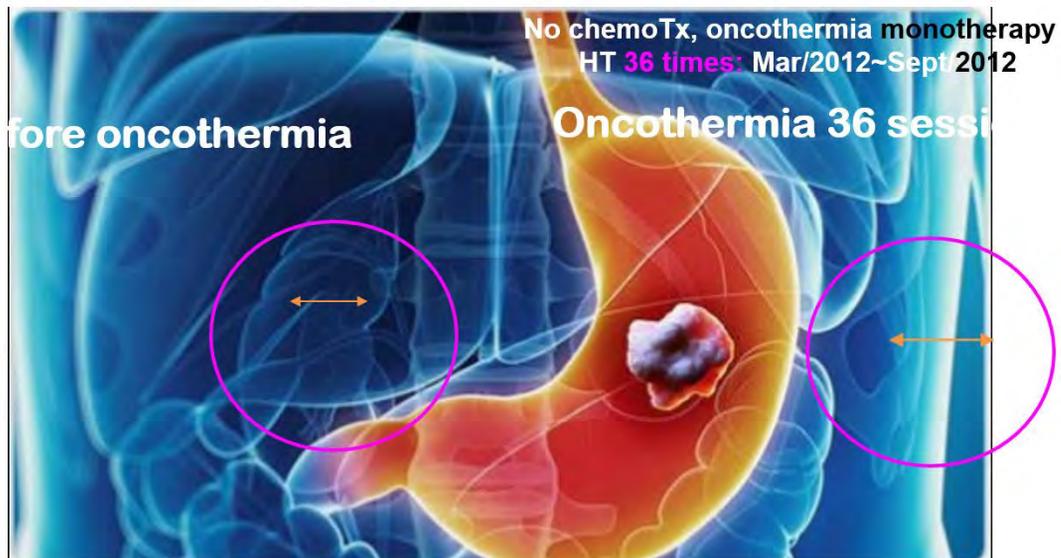


## Stomach Carcinoma, Stage IV; pts' preference

**Investigator:** Prof. Dr. Taesung Jeung

**Institute:** Department of Radiation Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital. Patient: (54y/F)

**Published:** 31<sup>st</sup> ICHO Oct. Budapest; 2012

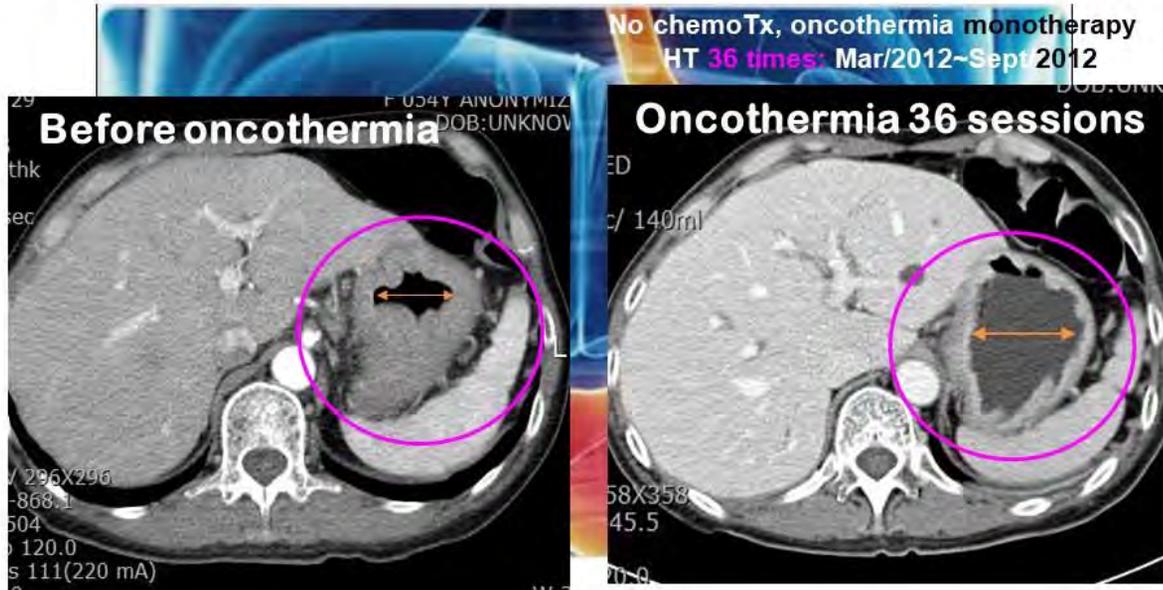


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**Investigator:** Prof.Dr.Taesing Jeung

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**Published:** 31<sup>st</sup> ICHO Oct. Budapest; 2012



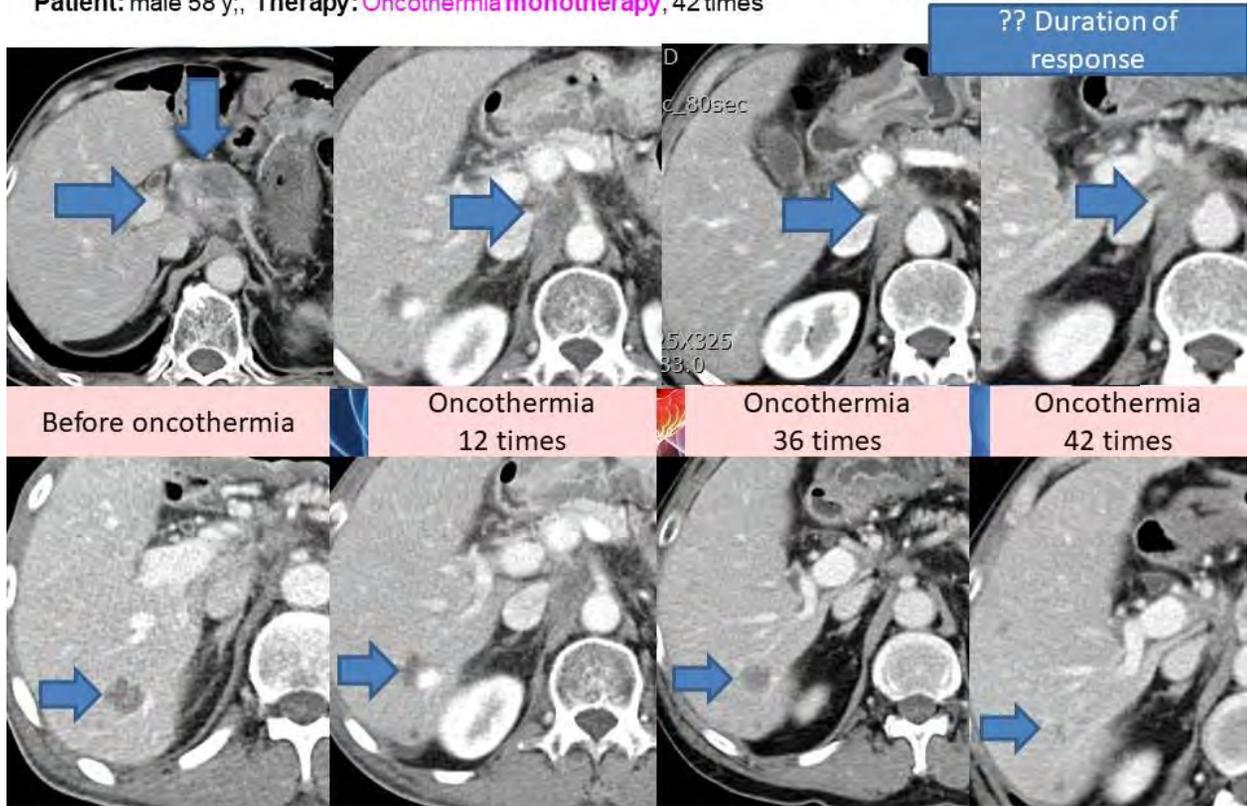
## Pancreatic cancer and liver metastasis

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



## Pancreatic cancer and liver metastasis

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



## Recurrent uterine sarcoma with peritoneal seedings

Investigator: Prof. Chi K-W, Shih-Kong Hospital, Taipei, Taiwan  
 Presented on 35<sup>th</sup> ICCHS Conference, Guangzhou, China; Nov. 2017)

refractory to chemotherapy and salvage  
 with combined radiotherapy (45Gy/30fx)



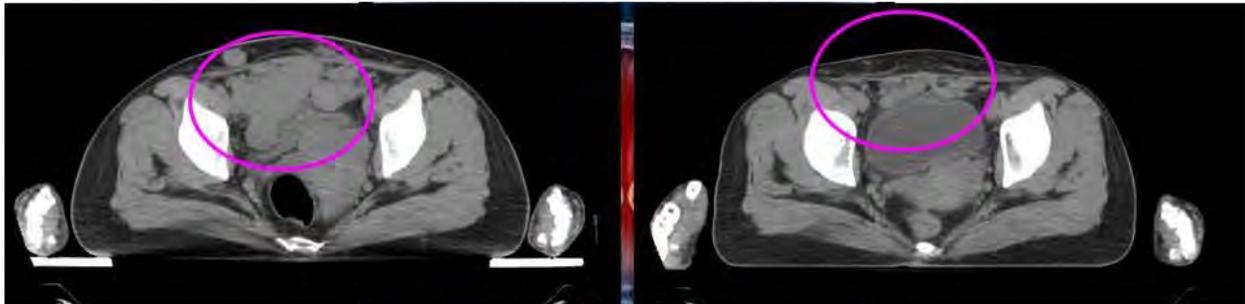
Evolution of partners in the  
 combo



## Recurrent uterine sarcoma with peritoneal seedings

Investigator: Prof. Chi K-W, Shih-Kong Hospital, Taipei, Taiwan  
 Presented on 35<sup>th</sup> ICHS Conference, Guangzhou, China; Nov.2017)

refractory to chemotherapy and salvage  
 with combined radiotherapy (45Gy/30fx)



Before treatment

After treatment

Evolution of partners in the  
 combo

Intratumoral ipilimumab 2.5 mg, i.v. nivolumab  
 50 mg and complementary with oncothermia 6  
 times (1 time/week)

## Abscopal effect

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

Recurrent refracter progressive  
 ovarian cancer. (55y).

Op + multiple CTx



4/11/2011

CTx + mEHT



2/27/2012

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

Op + multiple  
 CTx



4/20/2010

CTx +  
 mEHT



2/21/2011

Metastatic non-small-cell lung cancer (55y).

Investigator: Prof. Dr. Seong Min Yoon,  
 Division of Hematology-Oncology, Department of Internal  
 Medicine, Samsung Changwon Hospital, Sungkyunkwan University,  
 Korea

Patient: 72 y, male, Primer-tumor: NSCLC; Size: 9.5 cm right middle  
 lobe; Metastases: in sentinel and distant lymph-nodes; Tumor-  
 classification: cT2 cN2 Mx, stage IIIB

Treatment: 28x1.7 Gy; support: 250 microgram Leukine and  
 Oncothermia 6x



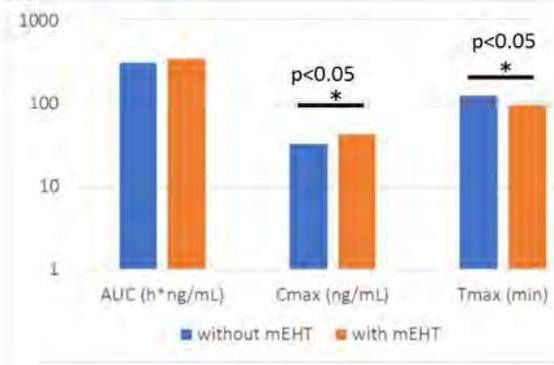
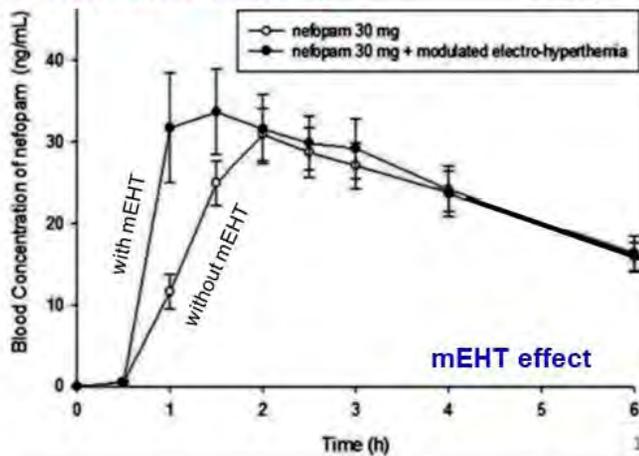
# Clinical studies



## Randomized study (n=6+6) for pharmacokinetics

**mEHT (with Nefopam)**

Lee SY, Kim M-G (2015); Int J Hyp, 31:869; 2015



# Oncothermia is safe in heavily escalated dose too

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/m <sup>2</sup>	Oncothermia 2x /week
2	3 (6)	ACNU 90 mg/m <sup>2</sup>	Oncothermia 3x /week
3	3 (6)	ACNU 90 mg/m <sup>2</sup>	Oncothermia 4x /week
4	3 (6)	ACNU 90 mg/m <sup>2</sup>	Oncothermia 5x /week

Advanced glioma (3<sup>rd</sup> & 4<sup>th</sup> line)  
Dose escalation study (PhI)  
Number of patients: 24

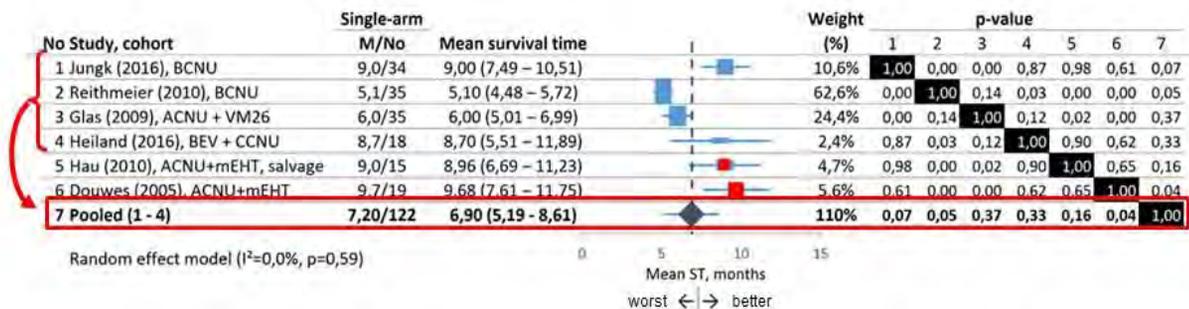
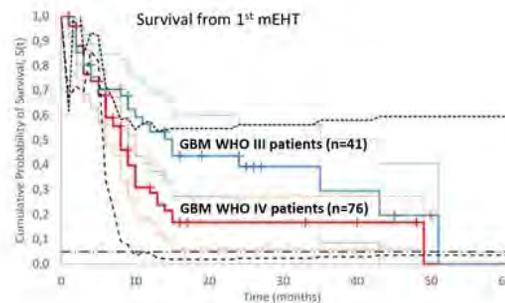
No additional side effect of oncothermia was observed. (Side effects were not more than with Nimustine alone!)

1. Wismeth C et al (2008) 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, Rummel P, Schuierer G, Bogdahn U, Hau P. (2010) Transcranial electro-hyperthermia combined with alkylating chemotherapy in patients with relapsed high-grade gliomas - Phase I clinical results, accepted Journal of Neuro-Oncology 98: 395-405, 2010



## Recurrent glioblastoma multiforme meta-analysis

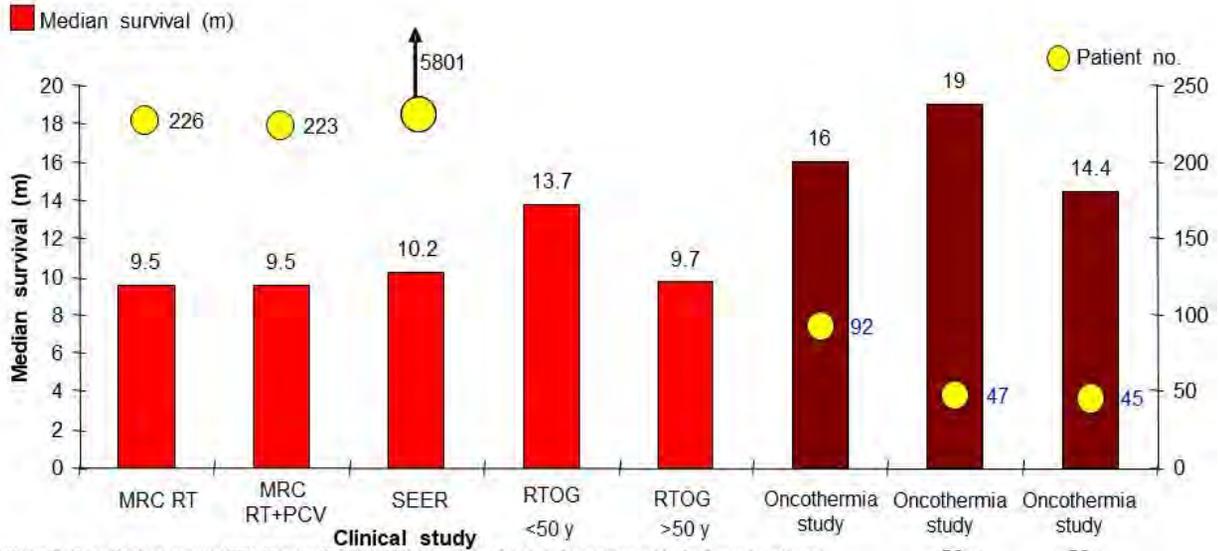
Roussakow S Clinical and economic evaluation of dose-dense temozolomide 21/28d regimen with and without concurrent modulated electro-hyperthermia in the treatment of recurrent glioblastoma: a retrospective comparison of cohort trials (2a level evidence) . [based on Publications of Gronemeyer et al. (2004)]; BMJ Open, 7:e017387.doi.1136/BMJ-open-2017-017387; (2017).



## Comparison by international trials

SEER (Surveillance, Epidemiology, and End Results) by the National Cancer Institute USA, April 2000  
 MRC (Medical Research Council, Brain Tumor Working Party)  
 RTOG (Radiation therapy Oncology Group,  
 EORTC (European Organisation for Research and Teratment of Cancer)  
 RT = Radiotherapy, PCV = Procarbazine+CCNU(Lomustine)+Vincristine, TMZ = Temizolomide

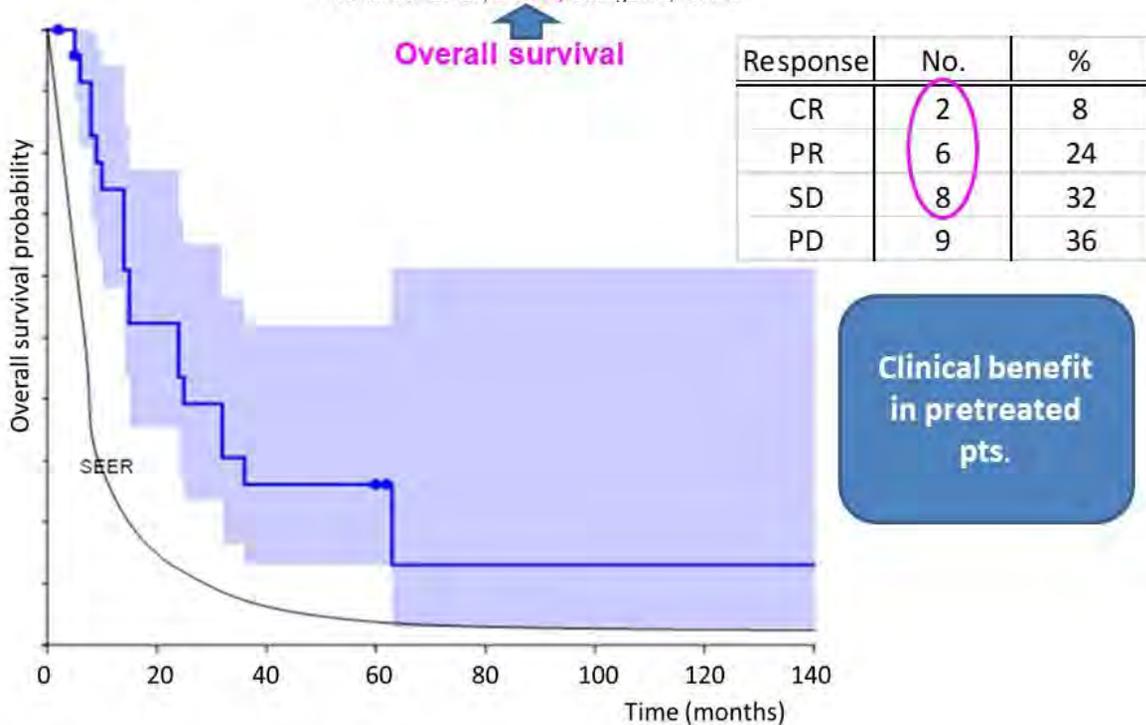
### Glioblastoma multiforme (WHO IV) clinical trial-results



Sahinbas H, Baier JE, Groenemeyer DHW, Boecher E, Szasz A: Retrospective clinical study for advanced brain-gliomas by adjuvant oncothermia (electro-hyperthermia) treatment, submitted for publication, BMC Cancer, 2006

### Relapsed gliomas survival (n=24)

**Investigator:** Prof. Dr. Fiorentini G.; **Department** of Onco-hematology, Azienda Ospedaliera Marche Nord, Pesaro, Italy. **Patients:** n=25, 19 glioblastoma, 6 astrocytoma, **Pretreatments:** all: temozolomide & radiotherapy, 22/24 surgery; **Published:** Fiorentini G. Oncothermia in brain tumors, Invited lecture on 35<sup>th</sup> annual conference of the International Clinical Hyperthermia Society (IChS), November 25-26, 2017, Guangzhou, China

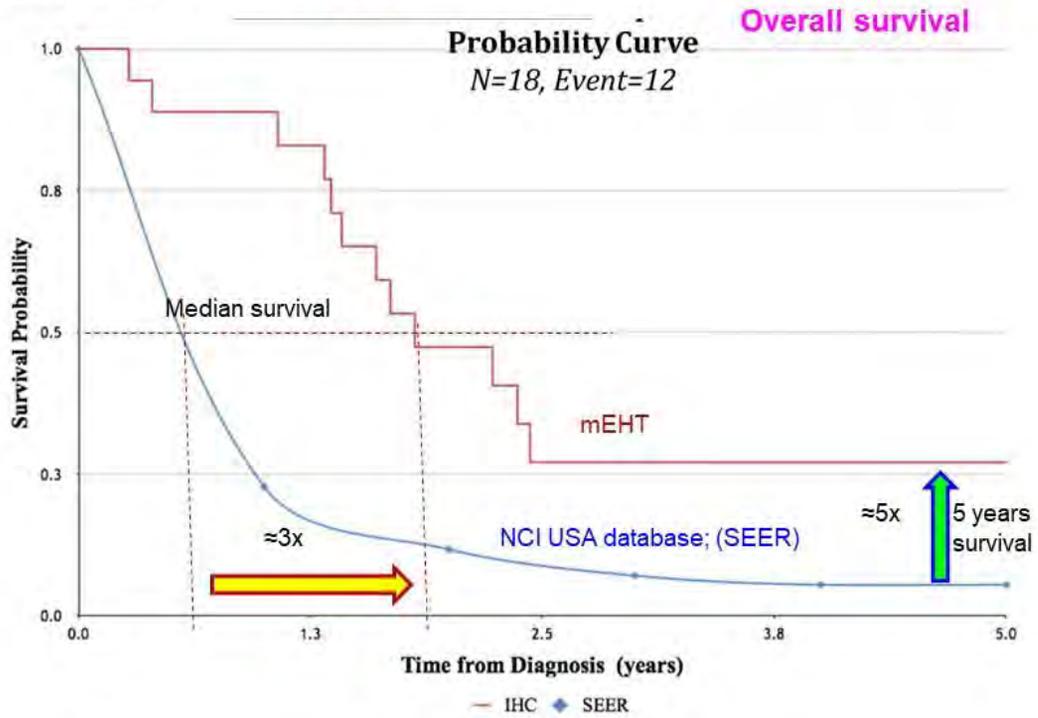


## Glioblastoma multiform

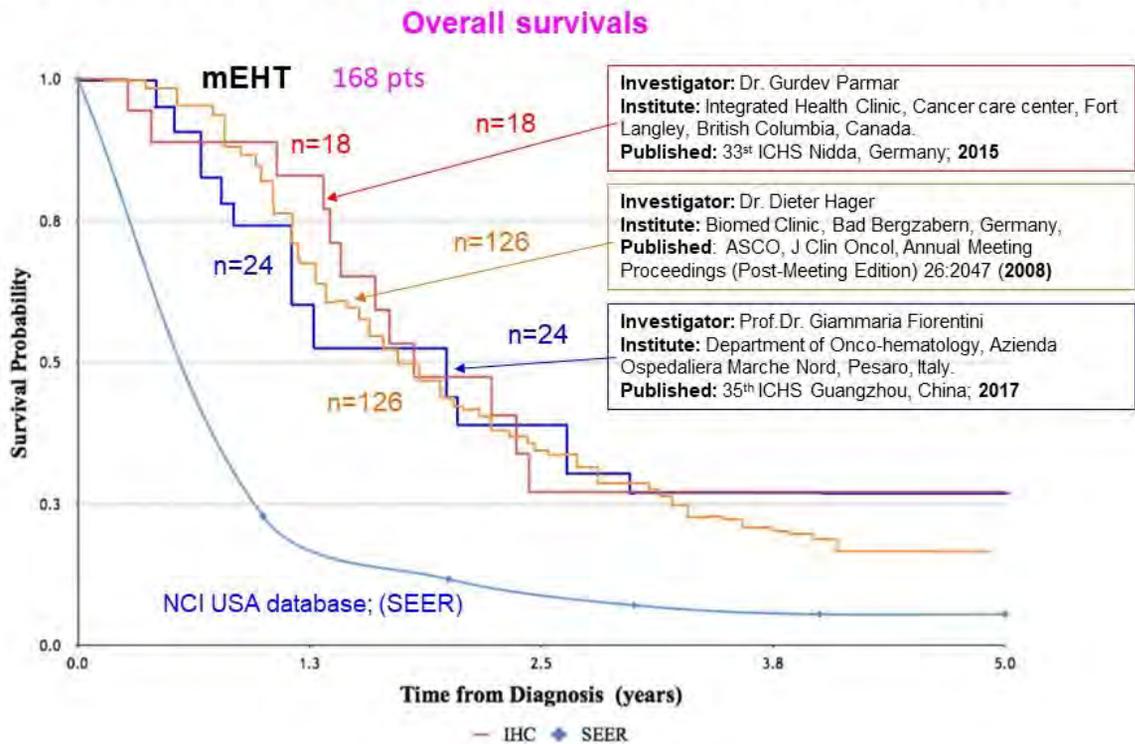
**Investigator:** Dr. Gurdev Parmar

**Institute:** Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

**Published:** 33<sup>rd</sup> ICHS Nidda, Germany; 2015



## Glioblastoma multiform – comparison of three survival results



## Small-cell-lung-cancer (n=9+10) double arm prospective study 2L

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

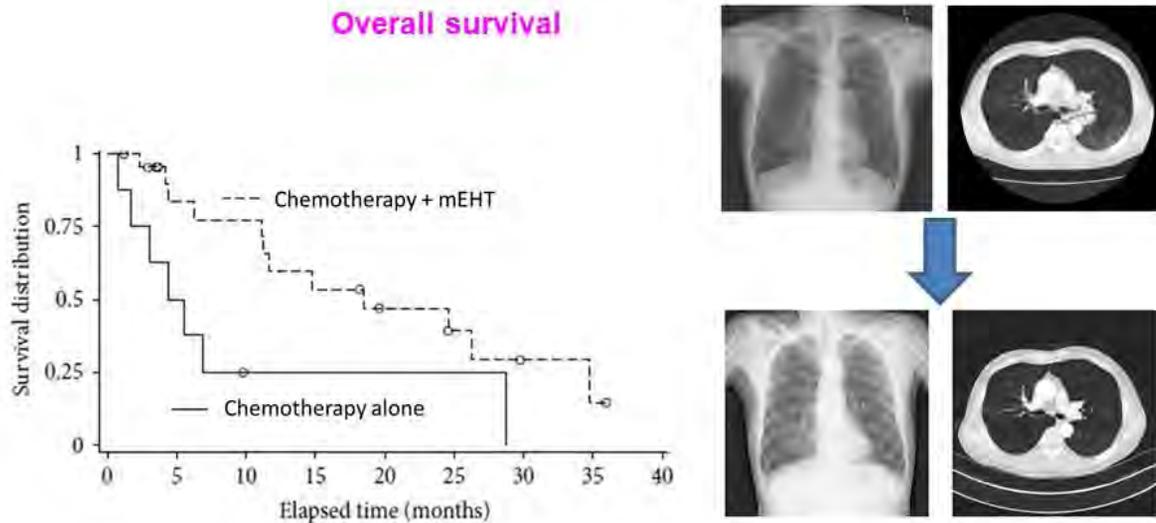
**Published:** Lee DY, et al. (2013) Conference Papers in Medicine, Vol.2013, Article ID 910363, pp.1-7

Prospective, monocenter, cohort double-arm study of chemotherapy with and without complementary oncothermia

**Chemotherapy 1<sup>st</sup> line (n=28):** Irinotecan (60 mg/m<sup>2</sup>), Cisplatin (60 mg/m<sup>2</sup>) three times.

**Chemotherapy 2<sup>nd</sup> line (n=19):** Etoposide, (110 mg/m<sup>2</sup>) Cisplatin (70 mg/m<sup>2</sup>)

**Additional oncothermia in 2<sup>nd</sup> line combination (n=9):** 150 Watt, 1,490.5 kJ, 60 min, every second day, with rise in temperature to 38.5°C–42.5°C. Electrode 30 cm diameter at least 12 sessions were in 1 cycle.

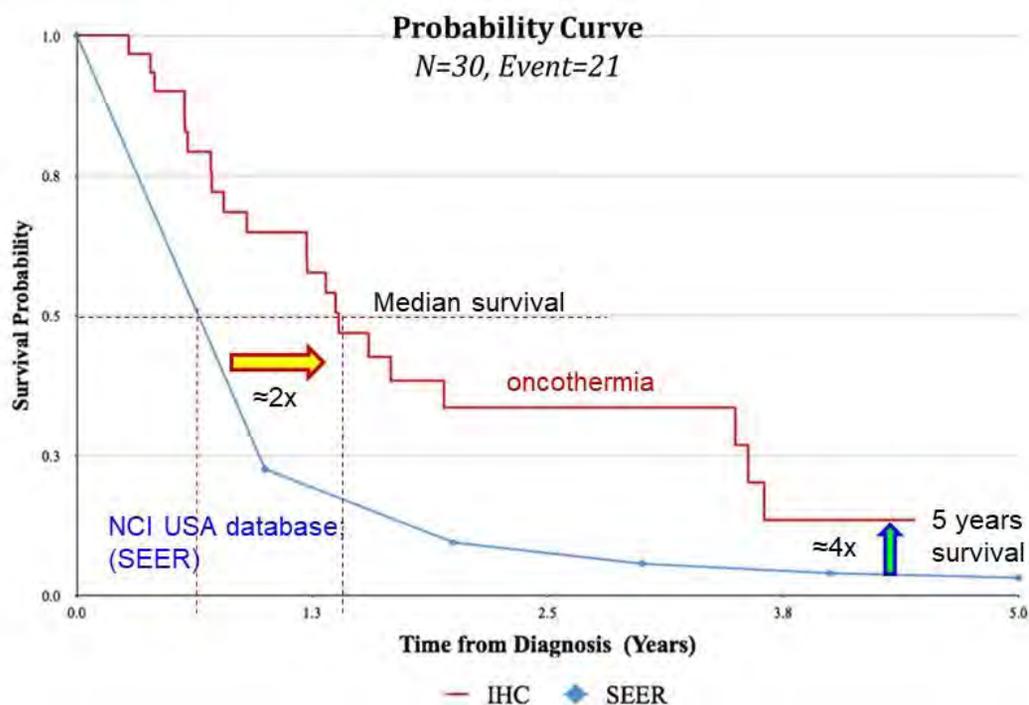


## Metastatic lung

**Investigator:** Dr. Gurdev Parmar

**Institute:** Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

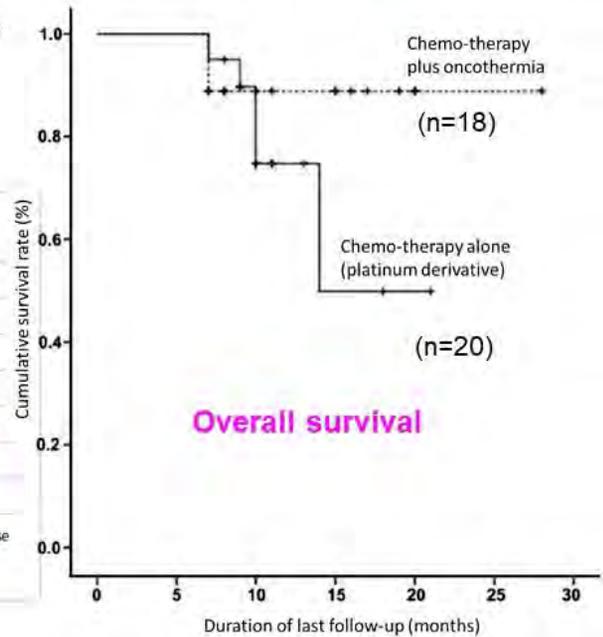
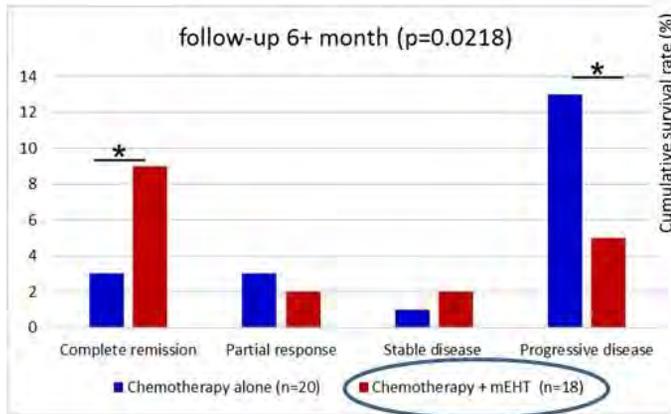
**Published:** 33<sup>rd</sup> ICHS Nidda, Germany; 2015



## Recurrent cervix double arm (n=20+18), randomized study

Lee SY, Lee NR, Cho D-H, Kim JS; Oncology Letters, <https://doi.org/10.3892/ol.2017.6117>, (2017)

Patients received *conventional chemotherapy alone* (n=20) compared to the combination to mEHT (n=18). Every patient had chemotherapy [paclitaxel + cisplatin (n=14), paclitaxel + carboplatin (n=10), cisplatin + 5-fluorouracil (n=12), cisplatin alone (n=2)]. *Radiotherapy was not permitted* in this cohort.



Both the local control and the overall survival are improved

## Phase III randomised cervix trial (n=236) of mEHT with CHRT (interim results (n=160), follow-up is ongoing)

**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 IIB *cervical cancer*

Statistics	n	%
HIV positive	120	51%
Stage III	157	66.6%

**Radiation:** 25x2Gy external and 3x8Gy brachytherapy

**Chemotherapy:** 3x 80mg/m<sup>2</sup> Cisplatin

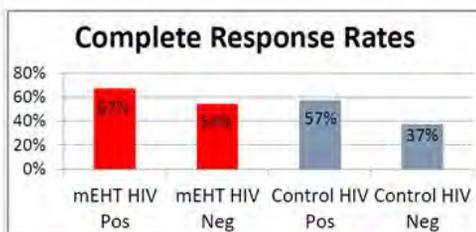
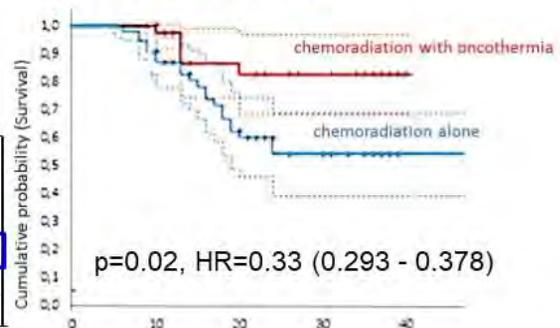
**mEHT (oncothermia):** 2x 55min/week (4 weeks)

### Local control

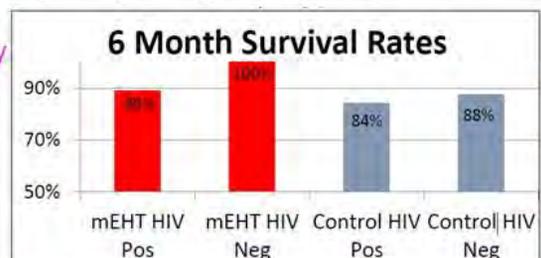
Until now: 6 month Local Disease Control  
160 patients completed 6 month PET scan.

Measured	Radio-chemotherapy				Gain by mEHT (%)
	with mEHT		without mEHT		
	n	%	n	%	
Complete response	33	47%	27	32%	15%
6 months survival (n=160)	70	91%	90	81%	10%
24 months survival (n=114)	55	78%	59	65%	13%

### Survival time control



Interim report by HIV infection (subgroups)



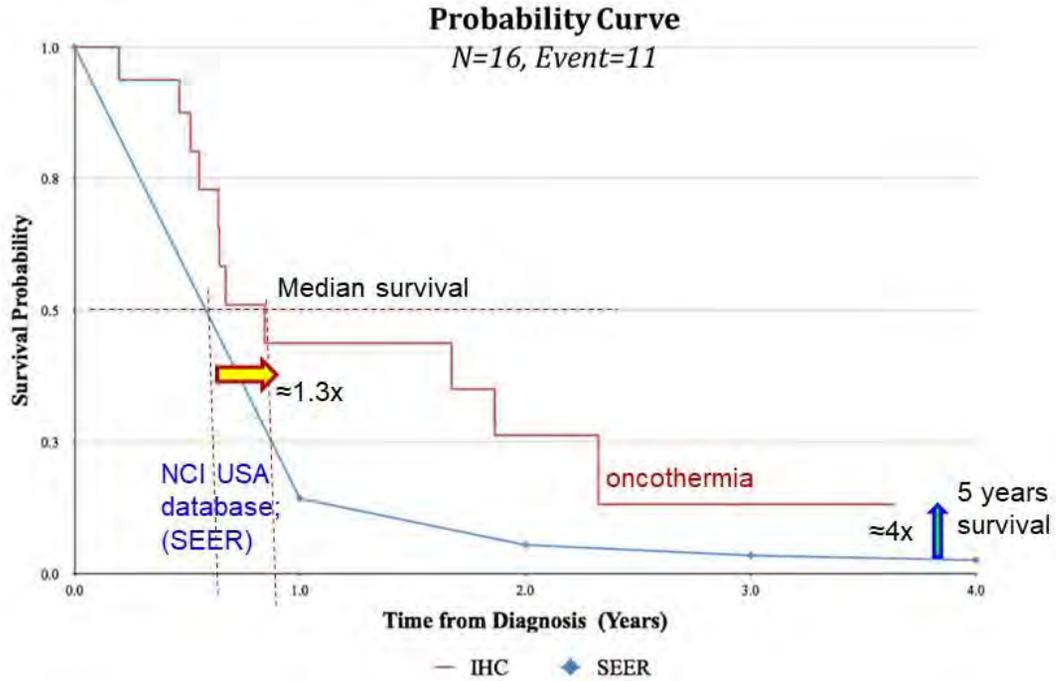
Until now, both the local control and the overall survival are improved

# Non-resectable pancreatic adenocarcinoma

Investigator: Dr. Gurdev Parmar

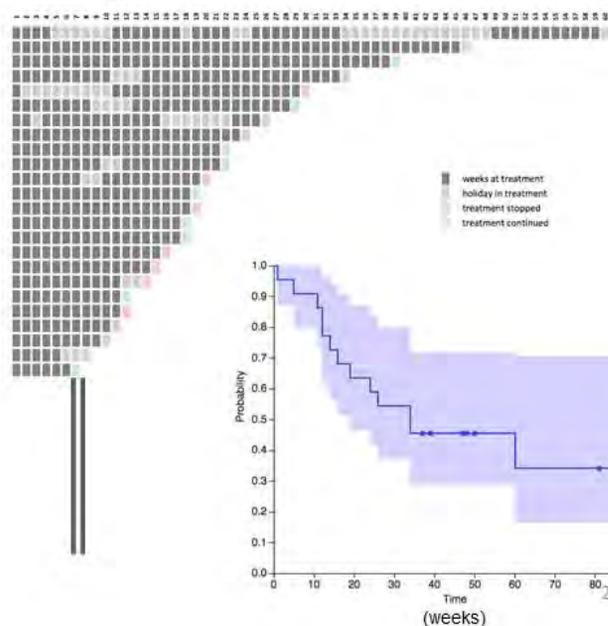
Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

Published: 33<sup>rd</sup> ICHS Nidda, Germany; 2015

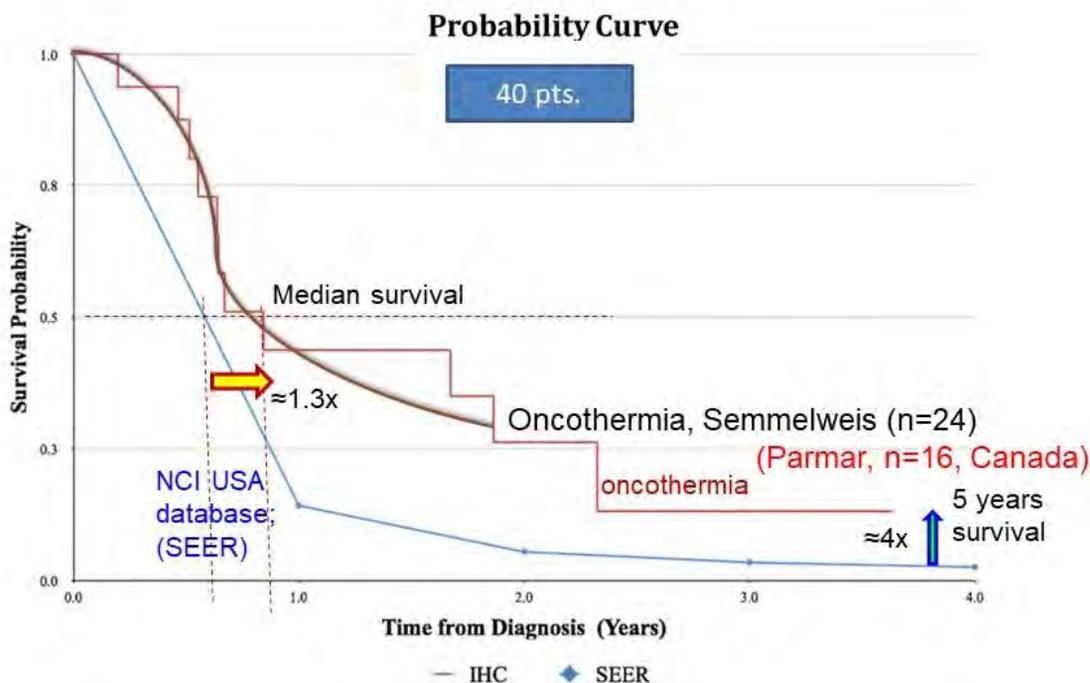


Own study – real life data at Cancer Center,  
Semmelweis University (poster at ESHO 2018)

	gender/age	session	weeks	adjuvant T/A	reason for stopping/break
1					
2	F/68	85	60	GEM/B, Folfirinox	fever
3	M/68	86	46	week Gemzar/B	intolerance
4	M/71	79	39		
5	M/56	82	34	Folfirinox	
6	F/63	22	30	Gemzar/SU+LV	neutropenia
7	M/71	54	29	weekly CDDP+Gemzar	pneumonia
8	M/26	42	26	10x Irad	fever
9	F/69	52	24	CO GEM+CCDP	progression, ileus
10	F/7	41	22	GEM+CCDP	
11	M/64	39	22	GEM-Tax	urticaria
12	F/57	24	20	Gemzar	intolerance
13	F/76	34	19	Tegafur	
14	M/72	8	19	GEM+CCDP	pain
15	M/63	29	18	GEM+CCDP	
16	F/72	33	18	gemzar	
17	M/61	51	16	Folfirinox	progression, ascites
18	F/62	28	15	Folfirinox	cholangitis, jaundice, ascites
19	M/56	30	14	GEM+CCDP	progression, ascites
20	F/66	42	12	GEMox, majd GEM mono	
21	M/68	16	12	Folfirinox	progression
22	M/48	23	11	week Gemzar	jaundice, hyperkalemia
23	F/65	12	10	Folfirinox	
24	M/56	14	8	Folfirinox	pain, ascites
25	F/75	15	7	GEM/B	



## Non-resectable pancreatic adenocarcinoma



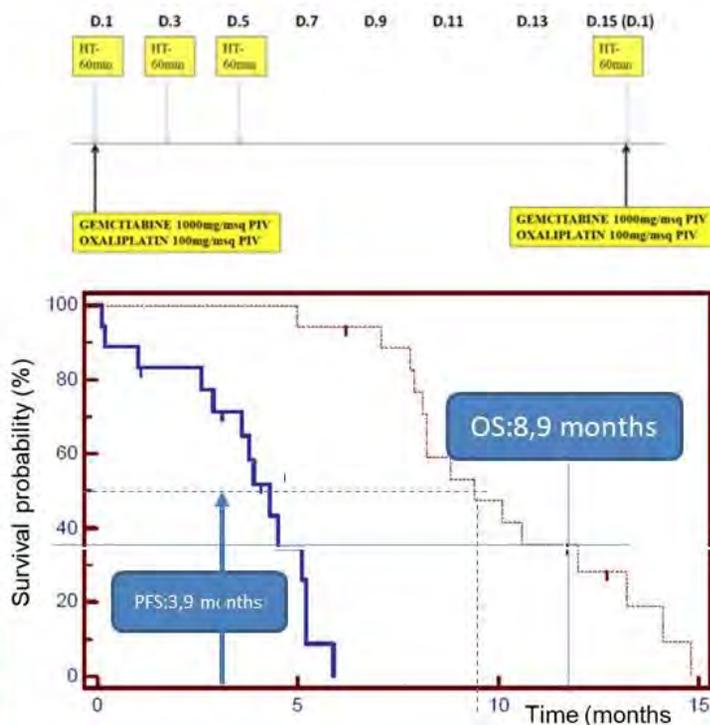
### Preliminary results of an prospective trial with 2L GEMOX+mEHY (n=26)

Metastatic pancreatic cancer after 1L gemcitabine treatment. In the 2<sup>nd</sup> line the patients received gemcitabine 1000mg/m<sup>2</sup> IV and oxaliplatin 100mg/m<sup>2</sup> IV day 1 (GEMOX) combined with mEHT days 1, 3 and 5 all repeated at 14 days

Characteristics	Enrolled (n=17)
Male	9
Female	8
ECOG Performance status	
ECOG 1	5
ECOG 2	12
Stage at study entry	
Liver metastasis	6
Lung metastasis	4
Lymph node metastasis	6
Peritoneal carcinosis	4
Bone metastasis	6
Ascites/pleural effusion	8
Nr. of prior chemotherapy cycles (GEM) - median	5.4
Histopathologic types	
Duct cell carcinoma	11
Acinar cell carcinoma	1
Papillary mucinous carcinoma	2
Signet ring carcinoma	1
Adenosquamous carcinoma	1
Undifferentiated carcinoma	1
Prior regional therapy	
Surgery	6
Radiotherapy	3

Volovat et al.; (2014); Romanian Reports in Physics, 66:166-174

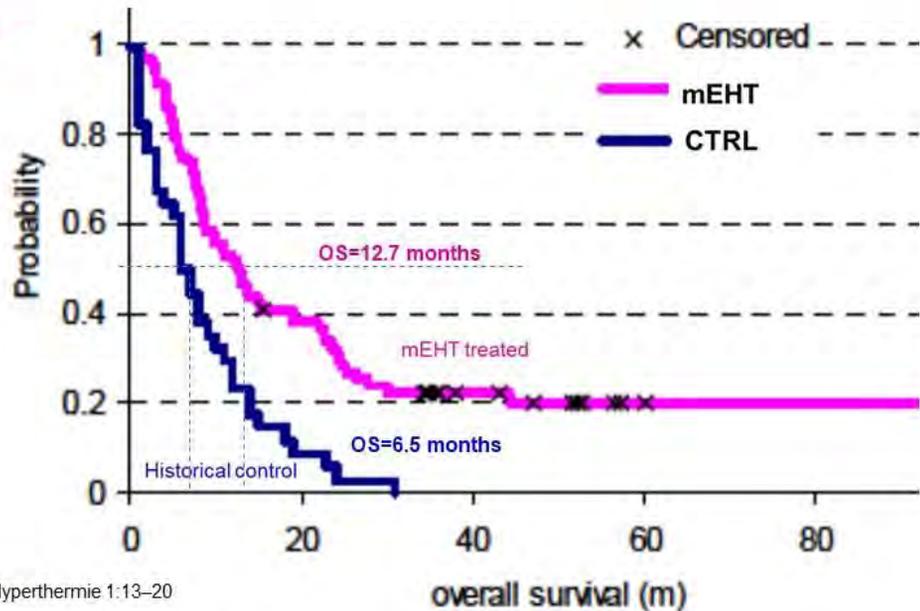
SEER: median survival for all the pancreatic patients is 7.5 months



## Advanced, metastatic pancreas study (n=99)

Retrospective, 2centers (A & B), single-arm clinical trial (n=99) for advanced pancreas cancer treated by oncothermia [1]. Most of the patients had **distant mets** (77, 77.8%; A:23,88.7%, B:54,74%) and more than40% had **multiple mets**. The trial includes a cohort of **heavily pretreated patients** (3+ lines), and due to the refractory or another fail of the conventional therapies, in this study **mEHT was applied as monotherapy**. The first and subsequent year survivals were: 1st:50.5%, 2nd: 27.3%, 3rd:15.2%, 4th:8.1%, 5th:3%. These values are significantly higher than the values from the large databases (SEER and Eurocare). The center B had the historical arm of conventional therapies (and palliation) of the cohort, with **median overall survival 6.5 m**, while the **median in study arm was 12.7 m**.

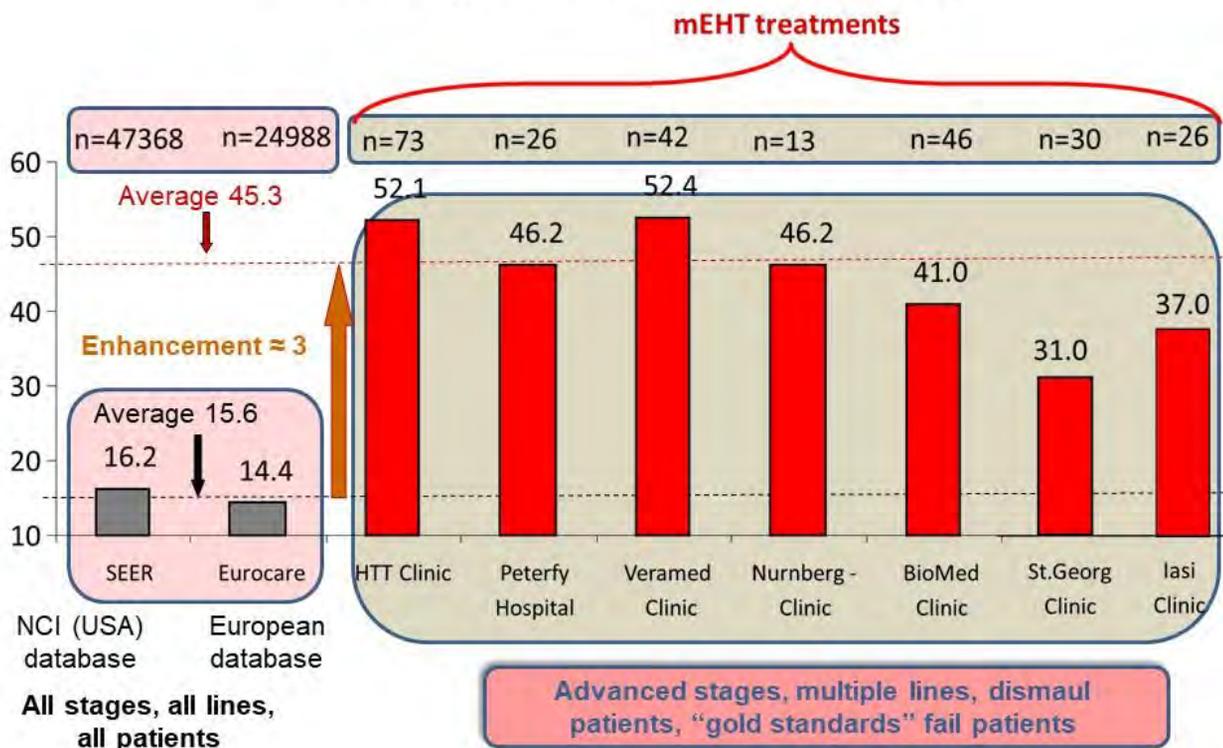
### Overall survival



Dani A, et al. (2008) Forum Hyperthermie 1:13-20

## Comparison of pancreas studies

### Metastatic pancreas CA 1y survival [%]



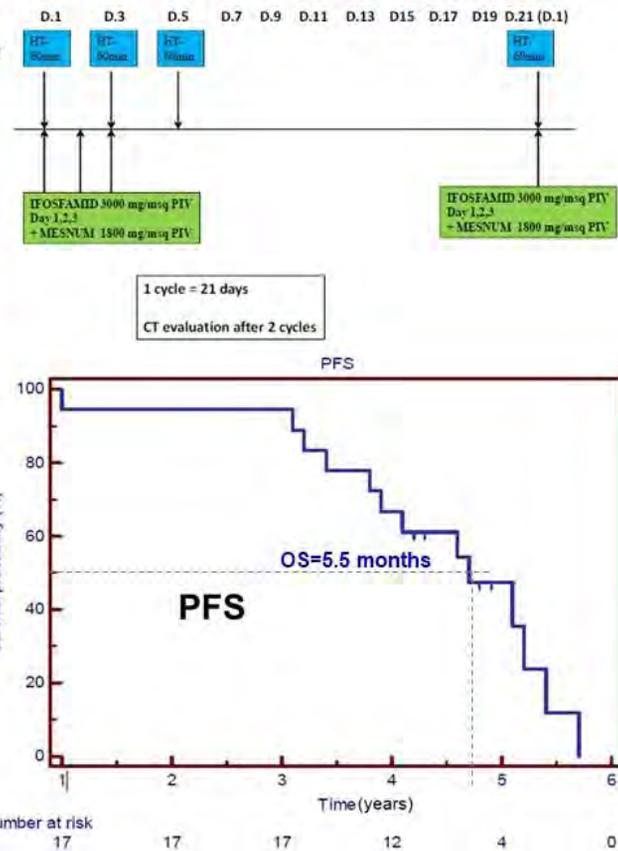
## Advanced, high risk recurrent sarcoma (n=24)

After recurrence of 1L CHT with doxorubicin 2L CHT (ifosfamide 3000mg/m<sup>2</sup>, day 1–3) and mEHT (1 hour application with temperature between 41.5°C and 42°C, 3 days/week).

The response 88% (partial response 44% patients for 4 m; stable disease 44% patients for 4 m and 5% only 1 m).

Characteristic	Nr. of patients
Performance status	
ECOG 2	4
ECOG 3	14
Site of metastasis	
Lung	8
Liver	11
Bone	7
Histopathologic Type	
Fibrosarcoma	5
Mixofibrosarcoma	2
Synovial sarcoma	3
Leiomyosarcoma	3
Epithelioid Sarcoma	2
Angiosarcoma	3

Volovat et al.; (2014) The results of combination of ifosfamide and locoregional hyperthermia (ehy 2000) in patients with advanced abdominal soft-tissue sarcoma after relapse of first line chemotherapy, *Romanian Reports in Physics*, 66:175–181

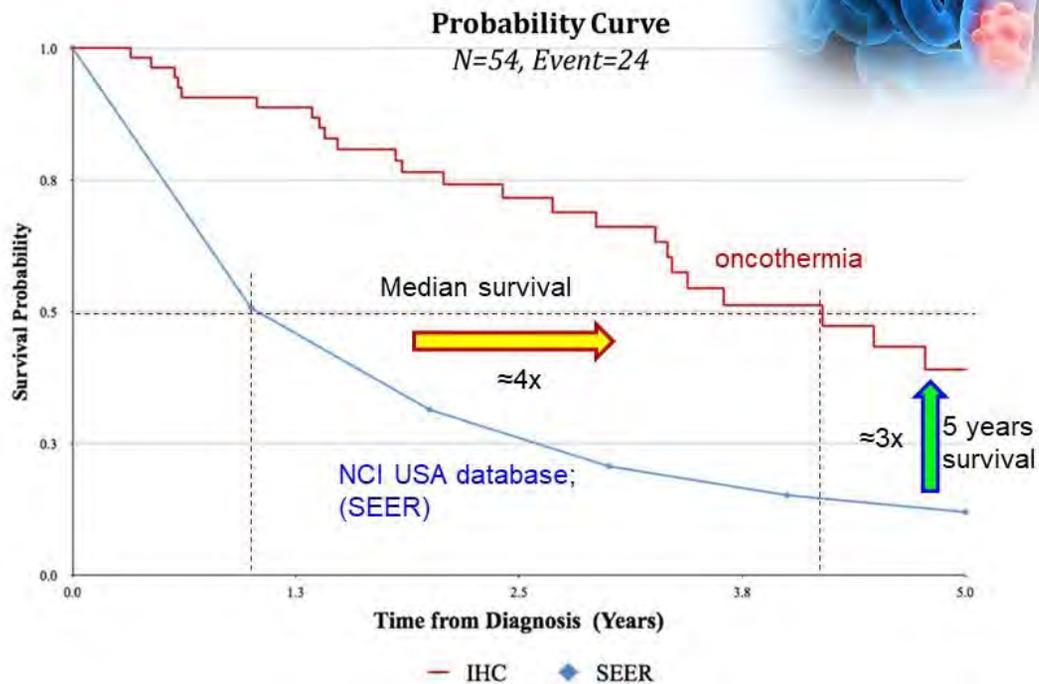


## Metastatic colorectal cancer

Investigator: Dr. Gurdev Parmar

Institute: Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

Published: 33<sup>rd</sup> ICHS Nidda, Germany; 2015

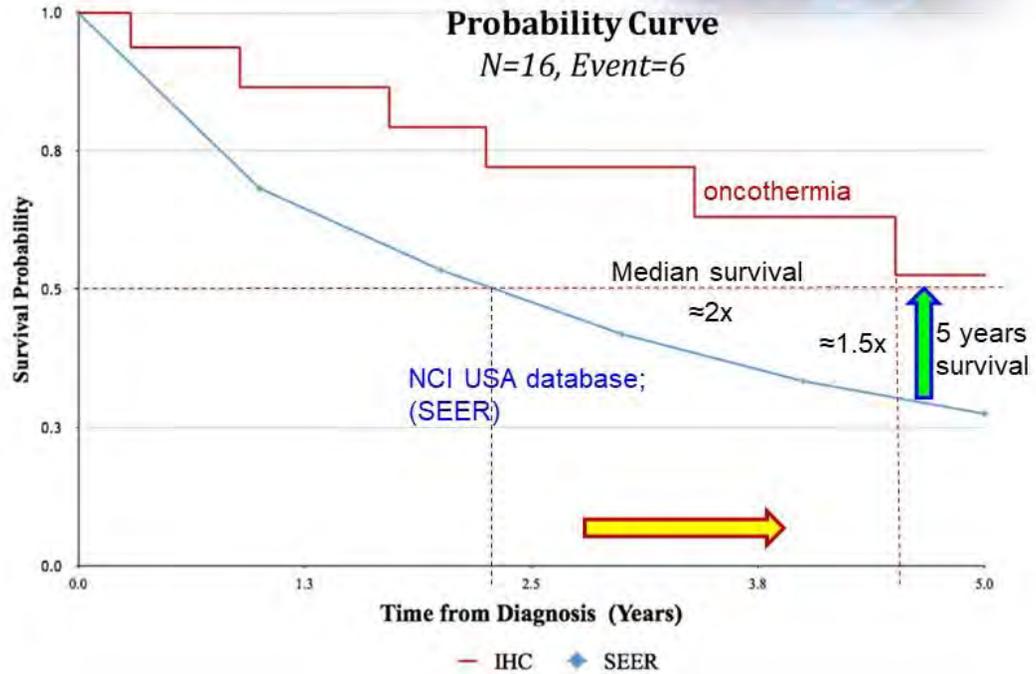


## Advanced ovarian cancer

**Investigator:** Dr. Gurdev Parmar

**Institute:** Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

**Published:** 33<sup>st</sup> ICHS Nidda, Germany; 2015

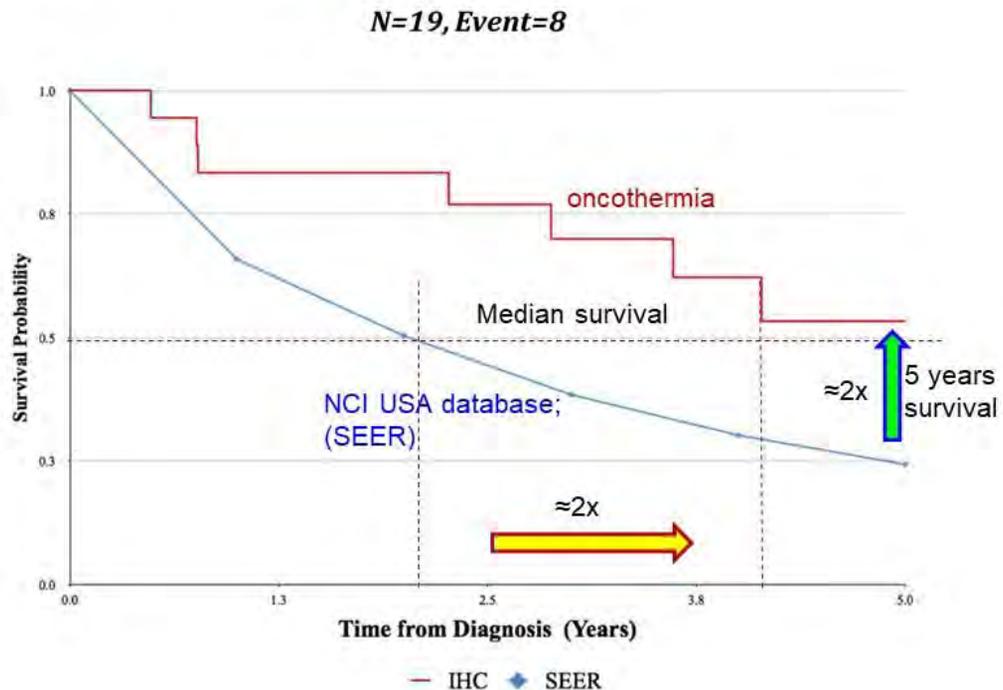


## Metastatic breast cancer

**Investigator:** Dr. Gurdev Parmar

**Institute:** Integrated Health Clinic, Cancer care center, Fort Langley, British Columbia, Canada.

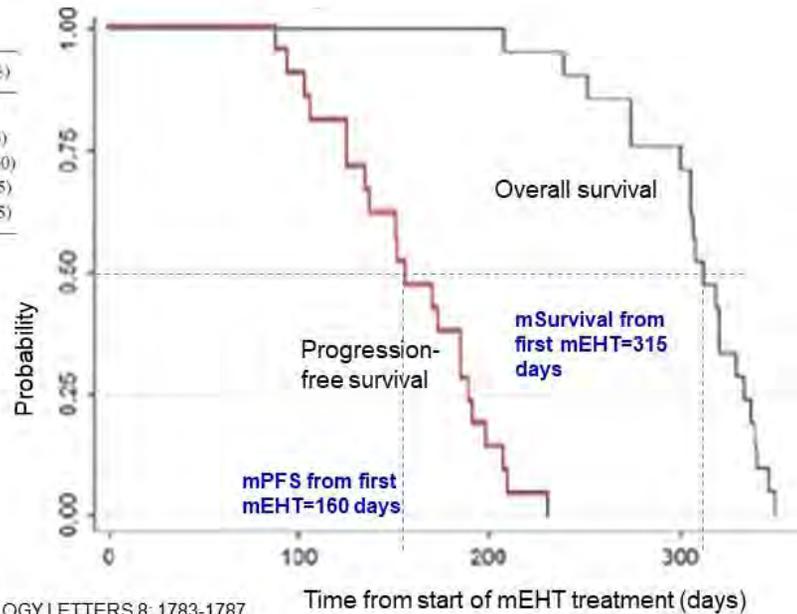
**Published:** 33<sup>st</sup> ICHS Nidda, Germany; 2015



## Hepatocellular carcinoma Phase II study (n=21)

A mono-institutional uncontrolled phase II trial was conducted on advanced HCC patients. Treatment was continued until disease progression (PD) or unacceptable drug-related toxicities. Sorafenib treatment interruptions and dose reductions (initially 200 mg twice daily, then reduced to 200 mg once daily) were allowed for drug-related toxicity.

Response	n (%)
Complete response	0
Partial response	1 (5)
Stable disease	11 (50)
Progressive disease	9 (45)
Disease control rate	9 (45)



Gadaleta-Cardarola G. et al.; (2014); ONCOLOGY LETTERS 8: 1783-1787

## TCM + oncothermia for intraperitoneal chemoinfusion (IPCI)

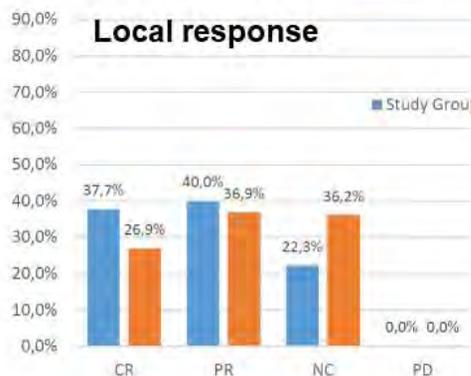
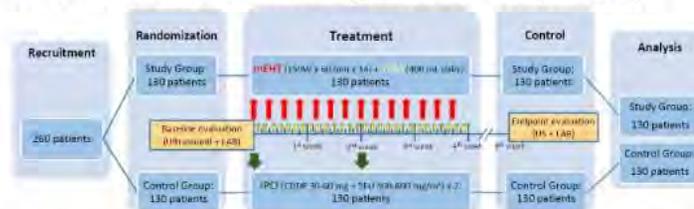
Investigator: Prof. Dr. Clifford LK Pang

Institute: Clifford Hospital, Panyu, Guangzhou, China

Published: CLK Pang et al (2017) Local modulated electro-hyperthermia in combination with traditional Chinese medicine vs. intraperitoneal chemoinfusion for the treatment of peritoneal carcinomatosis with malignant ascites: A phase II randomized trial, MOLECULAR AND CLINICAL ONCOLOGY 6: 723-732, 2017

Patient: 260 patients in two randomized groups: IPCI control and IPCI+TCM+mEHT

Diagnosis: peritoneal carcinomatosis with malignant ascites (PCMA)



# TCM + oncothermia for intraperitoneal chemoinfusion (IPCI)

**Investigator:** Prof. Dr. Clifford LK Pang

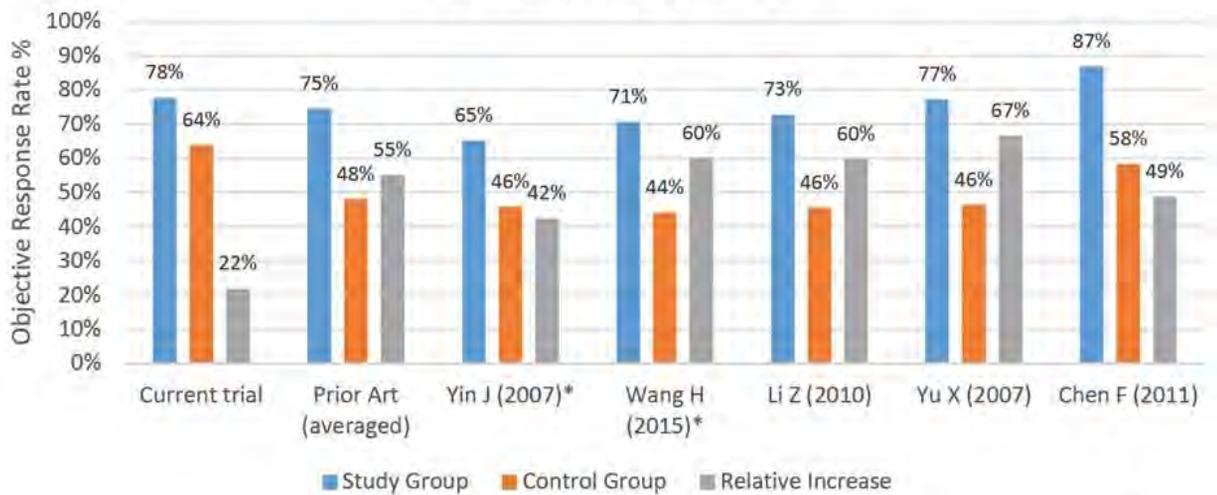
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**Patient:** 260 patients in two randomized groups: IPCI control and IPCI+TCM+mEHT

**Diagnosis:** peritoneal carcinomatosis with malignant ascites (PCMA)

## Comparison of efficacy



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## a penny for your thoughts

Immuncells  
 Imflammation- hot and cold tumours  
 CHT, targeted therapy and RT induces tumor-  
 antigens  
 Neovangiogenesis

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**Antibiotic Augmentes Thermo-Eradication (AAT)  
A new treatment Approach for Cure of chronic Lyme disease  
(LD)**

**Friedrich Douwes**  
Klinik St. Georg, Bad Aibling

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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Journal 24:34-58

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journal.com/journal/2018/Antibiotic\\_augmentes\\_thermo\\_eradication.pdf](http://www.oncothermia-journal.com/journal/2018/Antibiotic_augmentes_thermo_eradication.pdf)

# The Successful Antibiotic Augmented Thermal Eradication of Chronic Lyme Disease

Friedrich Douwes

Klinik St. Georg

## Aim

In my presentation, I explain the effectiveness of the "Antibiotics Augmented Thermoeradication" (AAT) we have developed for the treatment of patients with chronic *Borrelia* infection and its late sequelae.

## Methods

It is scientifically proven that the *Borrelia burgdorferi* bacterium is thermolabile. It is killed at a temperature of 41.6° C (106.8° F). The thermolability is scientifically proven. Systemic whole-body hyperthermia (WBH) not only kills the *Borrelia*, but also activates the body's immune system, especially macrophages and natural killer (NK) cells. This allows the bacteria to be eliminated. In addition, the activity of antibiotics is increased about 16 times by a temperature increase, e.g. per 2 degrees.

## Results

We have successfully treated more than 800 chronic Lyme disease patients with AAT and have seen drastic improvements as AAT kills the *Borrelia* wherever they are in the body, immediately halting the production of neurotoxins. For the elimination of neurotoxins, we have developed our own and individually adapted detoxification programs. The endocrine disorders commonly present in chronic Lyme disease, such as hypothyroidism or adrenal insufficiency must be eliminated, as well as, sexual disorders.

The almost always present intestinal symbiosis (leaky gut) can also be recognized and treated.

## Conclusion

Because the chronic Lyme disease causes multifunctional disturbances and can imitate almost all clinical patterns, the therapy must also be complex.

The focus is on the elimination of *Borrelia* by the SGHT in combination with antibiotics, everything else is then a *cura posterior*, which ensures the success achieved by the whole body hyperthermia and leads the patients back to life after a long history of suffering, to a life without Lyme disease.

## Antibiotic Augmentes Thermo-Eradication (AAT) A new treatment Approach for Cure of chronic Lyme disease (LD)

Dr. med. Friedrich Douwes  
Klinik St. Georg, Bad Aibling



## What am I going to talk about?

1. What is not optimal in conventional medicine for Lyme Disease(LD) and why treatment fails. ?
2. Why do we treat chronic LD differently?
3. What results do we have with:

**“Antibiotic Augmented Thermoeradication” (AAT)  
of chronic LD?**

- St. George Hospital (SGH) was founded 1991 as a specialized Institution for **Cancer**, Immunology, Environmental & Preventative Medicine
- SGH practices an “**Integrative Therapy Concept**” (ITC)
- That is a **combination of conventional medicine with scientifically based complementary treatment modalities**, including :
  - Superficial, Local and Systemic Hyperthermia (Whole Body Hyprthermia(WBH))

## St. George Hospital Bad Aibling, Germany



Dr. med. Friedrich Douwes, MD, Klinik St. Georg, Bad Aibling, Germany

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## Klinik St. Georg in Bavaria



Dr. med. Friedrich Douwes, MD, Klinik St. Georg, Bad Aibling, Germany

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But before I explain you the „Antibiotic Augmented Thermoeradication“ (AAT) & why it works so effectively.

I need to explain why it is so difficult to diagnose Lyme Disease(LD) & why conventional medicine often fails to treat it successfully

- After a tick bite **Borrelia burgdorferi**, can progress from characteristic expanding skin rash, **erythema migrans (EM)**, to a wide variety of **nonspecific systemic symptoms**
- **that can affect any part of the body.**
- Causing physical, cognitive, and psychological disabling manifestations.
- leading to a complex syndrome (**chronic LD**)



### Lyme stage I&II

**Common Symptoms**

- bull's eye rash
- flu-like reactions
- joint pain or inflammation

**Uncommon Symptoms**

- memory loss
- eye inflammation

verywell

### SYMPTOMS OR ILLNESSES ASSOCIATED WITH LYME DISEASE



Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling, Germany

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## Diseases which can hide behind chronic Lyme



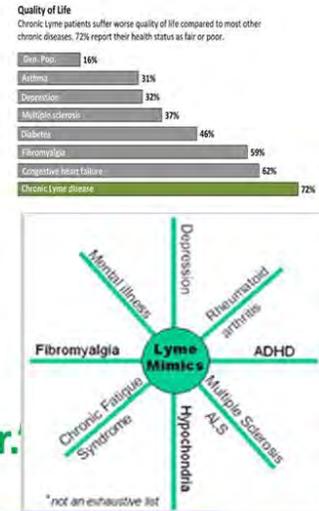
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## The cause for these multiple systemic problems of Lyme disease are:

1. Persisting chronic infection,
2. Production of Biotoxins, Neurotoxins &
3. Inflammatory cytokines
4. **The manifestation in different organs & tissues.**

**Lyme disease is therefore “the great imitator.”**



## What makes Lyme disease so specific and why?

That is the Borrelia itself !!



## Its difficult to cultured Borrelia in labs.



Borrelia has three layers.



The outer coat is composed of lipoproteins.



Spirochetes hide their flagella from the host immune defenses, which are normally antigenic and would trigger an immune response for detection.



Phagozytes and antibodies have difficulties to recognize Borrellias.



Require little oxygen.

- Divide only every 12-24 hours, which reduces the effectiveness of antibiotics.
- Borrelia does not divide in a suitable environment (Persisters).
- Bacteria usually multiply every 20 minutes & can be killed by antibiotics within two weeks.
- To kill Borrelia, one would have to use antibiotics for one and a half year
- Borrellias reside extra- & intracellularly.
- Neurotoxines are mainly extracellularly
- Can penetrate all tissues and cell membranes

- 1. Only in stage I/II LD is successfully treatable with antibiotics.**
- 2. In chronic stage III antibiotic treatment fails often, because of the aforementioned peculiarities of Borrellia and the fact that they are mostly intracellularly**
- 3. Side effects of long term antibiotic treatment are very negative & add negatively into the anyway negative course of the disease**

A maximum of thirty days of antibiotics is the accepted standard of care for LD stage III.

- In the beginning antibiotics can bring some relief.
- **But they never catch all Borrelia**
- Because most of them are located intracellularly or in places with low blood flow.
- Or they are resistance
- Or they divide so slowly that treatment of one and half years are necessary
- So the disease persists and slowly gets worse and worse

1.) Azithromycin,  
2.) Ceftriaxon,  
3.) Amoxicillin,  
4.) Doxycyclin,  
Aber...

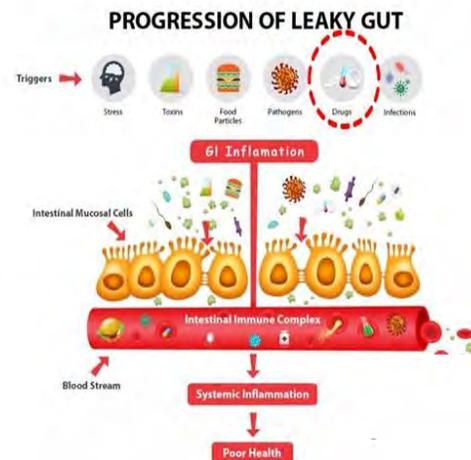


Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling, Germany

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- One of the most serious side effects is the negative action on the microbiom and bowel

***this contributes significantly to the disease***



Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling, Germany

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- The lab- testing for Lyme disease(LD) (ELISA, Westernblot, and LTT) are unreliable
- therefore we often have to rely on history and physical exam to make a diagnosis.
- The limitations of current laboratory methods for Lyme are multifactorial

Advanced late stage LD is therefore  
difficult to diagnose &  
frequently not correctly treated .

- But *Borrelia* has one weak heel!!
- **It is sensitive to heat & can be killed by heat.**

- **“Antibiotic Augmented Thermo-Eradication” (AAT) of chronic LD is a promising alternative.**
- **Why ?**
- **What is the scientific rational ??**

- Treponema pallidum, a spirochaete causing Syphilis is closely related to Borrelia.
  - This germ is thermosensitive and could be successfully treated with **Malariotherapy** in combination with Salvasan & Bismuth?
- **Malario-therapy is a special fever treatment.**

- Patients got infected with malaria & developed severe fever.
- **The fever destroyed the bacteria (syphilis spirochaete)**
- **The disease improved.**
- Prof. Dr. Julius Wagner Jauregg received the Nobel Prize in 1927 for Malariotherapy.
- **Malariotherapy was the treatment of choice for syphilis,** but is forgotten since the introduction of antibiotics.

- **Fact is & scientifically proven that borellias are thermolabile, respectively thermosensitive.**
- In cultures they die off at **41.6°C (106,9°F)** after 2 h.
- **Antibiotics are activated with increasing temperatures**
- **Per 2 °C up to 16 fold.**

[Reisinger et.al. Scandinavian Journal of Infectious Diseases,](#)  
Volume [28, Issue 2 1996](#) , pages 155 - 157

In a study *Borrelia Burgdorferi* was cultured at different temperatures, alone and in combination with antibiotics.

- **The data demonstrate:**
  - growth of the strains PKo and ATCC 35210 (B31) was impaired at temperatures of **37°C (98,6°F)** and
  - inhibited at **39°C (102,2°F)** and **40°C (104°F)**, respectively.
  - Strain ATCC 35211, however, grew well up to **39°C (102,2°F)** but did not multiply at **40°C (104 °F)**
  - **A bactericidal effect was seen at 41°C (105,8 °F) for the strains B31 and PKo and at 41,6°C (106,9 °F) for all strains.**

[Reisinger et al. Scandinavian Journal of Infectious Diseases, Volume 28, Issue 2 1996](#) , pages 155 - 157

**Susceptibility** of all strains to **penicillin and ceftriaxone** was **increased up to 16-fold** by an elevation of temperature from **36°C (96,8 °F)** to **38°C (100,4 °F)**.

[Reisinger et al. Scandinavian Journal of Infectious Diseases, Volume 28, Issue 2 1996 , pages 155 - 157](#)

## What do these data suggest?

- 1. Hyperthermia can kill Borrelia!!!**
2. Elevated body temperature is beneficial for antimicrobial treatment of LD.
3. The combination as we use it in AAT protocol is lethal for all Borrellias.

- **We therefore use a combination of antibiotics with extreme whole body hyperthermia (WBH) at 41,6°C(106,9 °F) in chronic LD.**

The protocol is called:

**“Antibiotic Augmente Thermoeradication”(AAT)**

All our chronic LD patients we treated  
had their LD diagnosis for several years &

- had several courses of long term antibiotics &
- **all more or less where in a desperate situation**
- with no hope of improvement by conventional treatment.
- **Were so called “Lost cases”**

# How is „AAT“ carried out ?

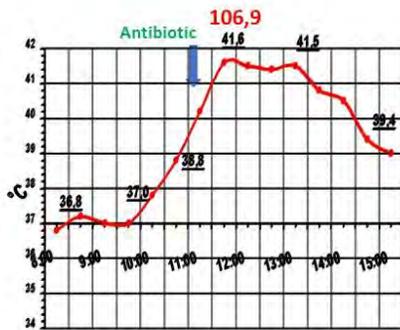
## Whole Body Hyperthermia (WBH)

- Is carried out in special unit
- **Under intensive monitoring**
- Patient is under sedation
- Heat is developed by far-infrared radiation (850 - 1300 nm wavelength)
- **The body temperature is increased up to 41.6 °C & is kept there for 2 hours**
- **In chronic Borreliosis only 2-time whole-body hyperthermia in combination with antibiotic treatment are necessary to eradicate the Borrelia completely**

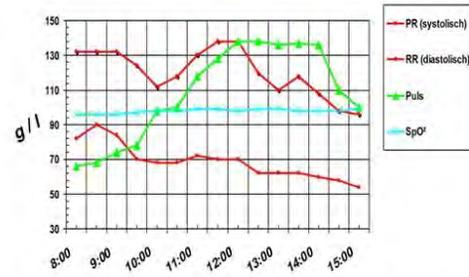




WBH Treatment-Protokoll



WBH Treatment-Protokoll

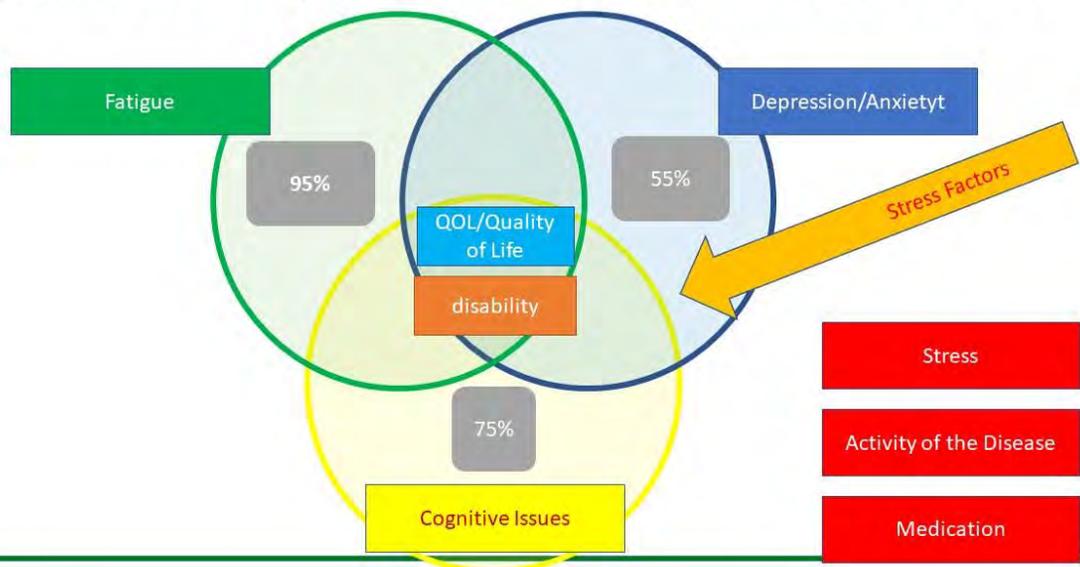


# How does Whole Body Hyperthermia (WBH) work ?

1. **Borrelia spirochetes can not tolerate higher temperature over a longer time, they die at 41.6°C (106,9°F)**
2. Heat leads to failure of important functional systems
3. Cells become more receptive to antibiotics (Rocephin)
4. MDR can be overcome
5. Antibiotics similar to cytostatics are activated massively by heat. Ceftriaxon (Rocephin), for example, per 2°C up to 16 fold
6. **So with our AAT Protocol we create a lethal condition for all Spirochaetes**
7. Elevated temperature activates the immune system

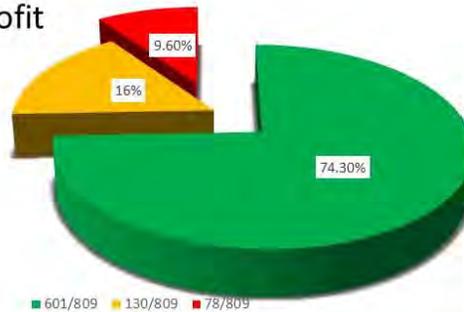
- With this procedure we create a **lethal situation** for all Borrelia
- So, **we can eradicate them**, wherever they are located in the body, intracellularly, in the brain or in biofilms etc.
- **We call this treatment approach**
- **“Antibiotic Augmented Thermo-Eradication” (AAT).**

## Symptoms of 809 patients with chronic LD before AAT



## Results of 809 evaluated patients 6-12 months after AAT

- 601/809 (= 74,3%) had good to very good results
- 130/809 (= 16%) had satisfying results
- 78/809 (= 9,6%) had no profit



### What does it mean ?

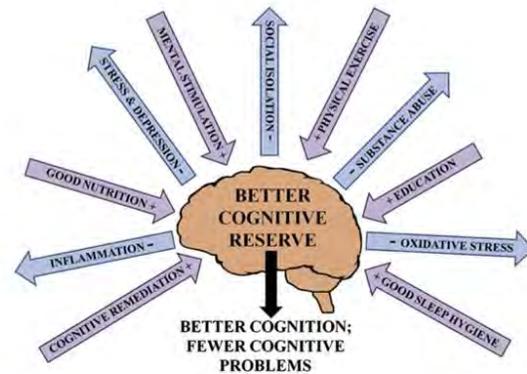
- **Clinical symptoms were reduced or disappeared totally.**
- **Burrascano-Score reduced to 50% of pretreatment score**
- **CD 56/57 numbers increased.**

## Especially the cognitive symptoms improved after AAT within 3-8 weeks

- Forgetfulness
- Memory loss
- Distractibility
- Confusion
- Difficulty thinking
- Difficulty concentrating
- Difficulty with talking, reading, spelling



- some of the bedridden and paralyzed patients could walk again,
- seizures diminished,
- brain fog disappeared
- pain was resolved.
- All this is well documented, testimonial can be found on our website or facebook.



## Please keep in mind:

- All these patients were so called “lost cases,”
- had the disease for several years
- had several courses of antibiotics which did not help.
- **So there was no curative treatment in conventional medicine available for this poor people, except a symptomatic treatment to ease of pain or fatigue etc.,**
- little could be done to help this patients not progressing and worsen every day.
- All of them have been finished their jobs and were reduced in their daily social activity.
- Many patients were also financially exhausted and felt themselves in a desperate and hopeless situation.



Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling,  
Germany

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## Thanks to Dr.Douwes and his team

April 12, 2018

Dr. Douwes/Klinik St. Georg Rosenheimer  
Str. 6-8, 83043 Bad Aibling,  
Germany

Dear Doctor Douwes,

**I cannot begin to thank you and all of your wonderful staff for curing my Lyme disease, and in turn, giving me back my life.** The majority of staff were extremely kind and compassionate during my stay. I traveled alone for my treatment and greatly appreciated those staff members that went out of their way to make me feel comfortable and cared for. Nurses Christoph, Christina, and Berget were especially kind to me. Mariola, Manfred, Heidi and Monica in the dining room, and Diana (massage) **all made me feel welcome and comfortable. The people on the operations side were extremely helpful and prompt in their responses-**Gabi, Verena, and Frederika. The staff members that went far above and beyond to help me emotionally were nurse Traudi, Urs, and Bernd. Doctor Zabel, Doctor Kroiss, and Doctor Pascu **were all very gentle and took their time with my needles (despite my tears).** I very much appreciated the assessment by Doctor Katharin Douwes as well. ...

**...Please know that I am forever grateful for my experience at your clinic. At this time last year I was ready to die; today I am living life to the fullest and prepping my body to full health in order to have a child. I regularly refer people to your clinic and will continue to do am living proof of the miraculous treatment that you offer.**

With Deepest Gratitude, K.B.



Dr. med. Friedrich Douwes, Klinik St. Georg Bad Aibling

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## Thanks to Dr. Douwes and his team

An: [info@st-georg-hospital.de](mailto:info@st-georg-hospital.de)

Betreff: Thank You Dear Dr. Douwes,

**I wanted to thank you and your team of doctors and nurses for giving me my life back.**

After being sick for 6 years and then getting infected again in May of 2016, I was losing hope that I would ever feel normal again. The summer of 2016 was torturous as my brain was so inflamed that I couldn't control my thoughts of despair and the severe panic, anxiety and depression. I was unable to walk for 3-4 months and I was beginning to feel that my kids would be better without me until my 9 year old told me that even though I was sick, he was so happy I was here. I pushed through my first bout with Lyme disease like a warrior but the second infection brought me to my knees. My boys' love and compassion for me during this time helped me push through when I felt like giving up.

I am so thankful for your trip to Boston because after meeting you, your family and Kirstin I felt more comfortable with traveling to a foreign country to receive treatment. I considered canceling my trip a few days before my departure but my aunt wouldn't have it and off we went. Upon arriving at the Klinik I was greeted by Gabi who instantly made me feel at ease and was a huge help throughout our stay. Frederika was also very helpful and accommodating and was always available to answer questions before my trip to Germany. It was so nice to see you before you left for vacation and I appreciate your taking the time to talk to me and check in after my treatments, it meant a lot to me. Thank you.

Dr. Zabel and Dr. Kroiss took good care of me and helped me work through my fear of the hyperthermia treatment. The nurse for my second Hyperthermia treatment (I can't recall her name blonde hair) was one of the kindest people I met at the Klinik. I had a terrible morning... and was not feeling well before treatment and this woman was so calming. I instantly felt more comfortable when I knew she would be taking care of me for the next six hours. I would love to send her a letter to thank her.

I would also like to thank Dr. T and Urs for the compassionate care they provided for all of the patients at the Klinik. They were always so attentive and kind and all of our patients from the Dean Center have spoken so highly of them because of their extensive knowledge and compassion. I wish more physicians followed their approach to patient care....



Dr. med. Friedrich Douwes, Klinik St. Georg Bad Aibling

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....I have just returned from a weekend yoga retreat in the Berkshire mountains in western Massachusetts and am so grateful for my restored health since receiving treatment at your Klinik.

**I am thankful for every day that I wake up without the debilitating fatigue, weakness, anxiety and panic attacks. I am thankful that I'm finally feeling normal and healthy again and for being able to attend my boys' hockey and soccer games that I missed so much last year. More importantly I am thankful for the one doctor who thought "outside the box" 30 years ago (15 for Lyme) and made this treatment possible.**

**Thank you for giving me my life back and doing the same for so many patients from all over the world. Eternally grateful, B.D.**



Dr. med. Friedrich Douwes, Klinik St. Georg Bad Aibling

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## Letter to Dr. Douwes

Dear Dr. Douwes,

I have advised A. B., 12/30/2000, to contact you regarding hyperthermia and plasmapheresis treatment for Neuroborreliosis.

I am aware of your clinic as my colleague N.Z. and I have discussed results she has seen in her patients who have sought treatment for tick borne disease at St. Georg. Recently you saw a patient of mine, M.K., who improved with the treatment he received from St. Georg and is going to matriculate at Baylor University this month. I have been Mr. K.'s doctor since 2012 and observed his great improvement with the hyperthermia and plasmapheresis as well as your integrative approach to his chronic infection with borreliosis.

Mr. A. B. is 17-year-old male who has been ill for 8 years. With this referral is a summary of the patient's history, laboratory values and treatment in our office. Mr. B. and his parents will contact St. Georg regarding their desire to be considered for treatment. Please let me know if any other documentation regarding young Mr. B. would be helpful.

Sincerely,  
Christine Green MD



Dr. med. Friedrich Douwes, Klinik St. Georg Bad Aibling

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## Summary

1. **Hyperthermia kills Borrelia** because they are sensitive to heat (thermolabil).
2. Whole body hyperthermia kills the bacteria **where ever they are located** in the body.
3. The „Killing-Effect“ is supported & augmented by simultaneous antibiotic treatment.
4. The elevated temperature increases the effectivity of the antibiotic massively.



Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling, Germany

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- With the eradication of the bacteria per AAT, the toxin load will be reduced
- The sick making mechanisms are eliminated, which are responsible for the many symptoms of chronic LD.
- The elimination of toxins and the elimination of chronic inflammation leads to fast clinical improvement and finally to a cure even in far advanced cases.
- Organ damages need of course a longer & specific & individual treatment.

**This is the first time since Malariotherapy for Syphilis, that it could be shown that a chronic infectious disease, which otherwise was not treatable can be successfully treated and/or even cured by hyperthermia.**

Thank you  
for your attention.

# **Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)**

**Elisabeth E. Arrojo**

Radiation Oncologist

University Hospital Marqués de Valdecilla, Santander, Spain

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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[www.oncothermia-journal.com/journal/2018/Future\\_position\\_of\\_oncothermia.pdf](http://www.oncothermia-journal.com/journal/2018/Future_position_of_oncothermia.pdf)

# **Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice - Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)**

**Elisabeth E. Arrojo, MD, PhD,**

Radiation Oncologist, University Hospital Marqués de Valdecilla, Santander, Spain

## **Introduction**

Aggressive malignant tumors are known to be usually hypoxic. It's well known that hypoxia decreases tumors' response to radiotherapy (radiosensitivity). At least 2 or 3 times more radiation dose is needed to kill hypoxic cells compared with well oxygenated cells.

Several studies have shown that modulated electro hyperthermia (mEHT) is able to increase tumor oxygenation, and thus alleviate the hypoxia that would lead to greater radioresistance, establishing itself as an optimal moment to apply radiotherapy, about 30 minutes after the treatment of mEHT.

There are also several studies showing the efficacy of mEHT in killing cancer cells when used alone without any other cancer treatments.

These are some of the reasons why the combination of these treatments (mEHT + Radio-chemotherapy) could result on an improvement in tumor control and survival for cancer patients. Despite several studies about mEHT treatment in cancer patients alone or combined with standard radio-chemotherapy have been published with wonderful results, we still do not have enough phase III trials to clarify the role of mEHT on cancer treatment.

## **Purpose**

To perform three different phase III clinical studies to test whether the combination of radio-chemotherapy treatment with mEHT in the 30 minutes prior to the radiotherapy session, or the treatment in monotherapy with mEHT in those cases not susceptible to another oncological treatment, will improve local control (primary objective) and/or survival (secondary objective) in patients with high-grade brain tumors, pancreatic cancer or rectal cancer, without increasing side effects from the standard treatments.

## **Material and methods**

Patients diagnosed with high grade glioma, pancreatic cancer, or rectal cancer will be included in three different phase III clinical studies. These studies will include newly diagnosed cancer patients or patients with recurrent malignant tumors after treatment with standard therapies. The study for patients diagnosed with high grade brain glioma (stages III and IV) will include patients who will receive treatment in an adjuvant setting after surgery combining mEHT with standard chemo-radiotherapy or with mEHT as the only treatment in those cases not candidates to surgery, chemo and/or radiotherapy. The clinical study about pancreatic cancer, will include patients with locally advanced cancer and again, mEHT treatment will be combined with the standard chemo-radiotherapy treatment in a neoadjuvant, radical, palliative or adjuvant setting, or will be the unique treatment in those cases not amenable to be treated with standard therapies. The third study, is for patients diagnosed with rectal cancer who meet the criteria to receive standard treatment with neoadjuvant chemo and radiotherapy, in whom mEHT will be combined with these neoadjuvant treatments. In all the studies, when mEHT is combined with radiotherapy, it will be always delivered around 30

minutes before each radiotherapy session. Patients with history of other cancer in the past 10 years will be excluded.

### **Results**

Three different phase III clinical studies have been already designed to be performed at the radiation oncology department of Valdecilla University Hospital in Santander, Spain. We have already received the approval of the University Hospital Marqués de Valdecilla and the "Idival" research institute, which will be also a collaborator, to begin with the studies, and we also have the necessary insurances to run them. We have also appointed a coordinator to control and check the proper development of these studies.

### **Conclusion**

Modulated electro hyperthermia combined with standard radio and chemotherapy or as a unique treatment in cancer patients not candidate to standard treatment, looks very promising to improve local control and survival in cancer patients. These clinical studies will give us very valuable information about the role of mEHT in cancer treatment, and its contribution as a radiotherapy and chemotherapy sensitizer.



ICHS  
36th Conference of the International  
Clinical Hyperthermia Society

Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)

**Elisabeth E. Arrojo, MD, PhD**

Radiation Oncologist

University Hospital Marqués de Valdecilla, Santander, Spain

Budapest, September 28th 2018



ICHS  
36th Conference of the International  
Clinical Hyperthermia Society

## WHAT I WILL TALK ABOUT?

- Introduction
- Cancer Statistics
- Radiotherapy
- Some of our projects to solve/improve our cancer treatment results
  - **Future position of oncothermia combination with standard chemo and radiotherapy in clinical practice – Highlights of upcoming Phase III clinical studies in Hospital Universitario Marqués de Valdecilla (HUMV)**
- Take home messages - conclusions





# INTRODUCTION...

## University Hospital Marqués de Valdecilla

Santander, Spain



- Main aim is:
  - CURE CANCER
  - Without toxicities

### Pioneer on different successful treatments:

- Brachytherapy in only 1 session for breast cancer.
- Rectal protection with hyaluronic acid for prostate cancer patients who will receive brachytherapy treatment.

### Radiotherapy department:

- Team: 62 people.
  - 11 Radiation oncologists.
- External beam radiotherapy:
  - 3 linear accelerators:
    - Radiosurgery
    - Stereotactic RT (intra and extracranial)
    - Image guided RT
    - Intensity modulated RT
- 2 operating rooms for Brachytherapy
  - HDR and LDR
- Intraoperative radiotherapy



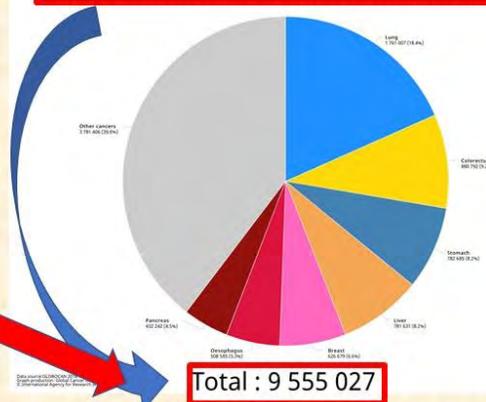
# CANCER STATISTICS

**>18 million** NEW cancer cases in 2018 (Globocan 2018)

**> 45% will die from cancer.**

- Depending on:
  - Country
  - Race
  - Sex
  - Type of cancer
  - Stage
  - Treatment

Estimated number of deaths in 2018, worldwide, all cancers, both sexes, all ages

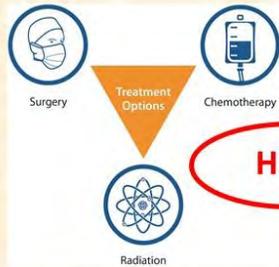




## CANCER STATISTICS

ESTIMATED NUMBER NEW CANCER CASES IN 2018 (ALL AGES, BOTH SEXES) **18,078,957**

ESTIMATED NUMBER OF DEATHS BY CANCER IN 2018 (ALL AGES, BOTH SEXES) **9,555,027**



**HELP**

**> 45% cancer patients will die from cancer.**

- Depending on:
  - Country
  - Race
  - Sex
  - Type of cancer
  - Stage
  - Treatment

**NOT ENOUGH!!!**

**NEW TREATMENTS**



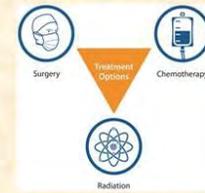
## RADIOTHERAPY

- According to the American Society of Radiation Oncology (ASTRO), **more than 60% of cancer patients will receive radiation therapy** - either alone or in combination with other treatment approaches, such as surgery and chemotherapy.
- Only improving radiation therapy results → we will improve results in more than 60% of cancer patients.





## RADIOTHERAPY



- Very powerful tool → able to kill “anything”
  - Power to kill depends on type of energy...
    - but mainly **dose**

**“We cannot kill all cancer cells with radiation in some tumors, because we cannot give enough dose”**

Tumors can be:

- **Radiosensitive** → dye “easily” with radiation. (With acceptable radiation doses for healthy tissues).
- **Radioresistant** → dye with “higher” radiation doses (Not tolerable for healthy tissues).



## TUMOR RADIORESISTANCE

- Clinically, **a tumor is considered radioresistant when irradiation is unable to reduce its volume or when a recurrence occurs after a possible regression.** Four general characteristics are currently used to predict tumor radiocurability:
  - **The number of clonogenic cells:** the probability of local control depends on the number of clonogenic cells present in the tumor at the beginning of treatment. **When more clonogenic cells are present, the tumor presents a higher risk of radioresistance.**
  - **The kinetics of tumor growth** and tumor cell proliferation: after radiotherapy, a small number of surviving tumor cells can gradually and slowly proliferate and reestablish the tumor (fractionation). **The greater the number of proliferating cells, the higher the likelihood that the tumor will be radiosensitive.**
  - **The number of hypoxic cells:** cells that are hypoxic or anoxic at the time of irradiation suffer less damage from a given radiation dose than do oxygenated cell → poorly vascularized areas within tumors is an important component of tumor radioresistance. **A greater number of hypoxic cells within a tumor makes it more radioresistant.**
  - **The intrinsic radiosensitivity:** intrinsic radiosensitivity is the cell's own response to radiation, that is, its implementation of radioresistant molecular mechanisms. This factor depends primarily on the integrity of the cell's detection and repair of DNA damage, but it is also affected by intercellular communication and the cell's response to growth factors.





## RADIOSENSITIVITY

**Radiosensitivity**

- 17 tumor types were placed in 5 categories.
- Categories A to E with decreasing sensitivity.
- A: Lymphoma, Myeloma, Neuroblastoma.
- B: Medulloblastoma, SCLC
- C: Breast, Bladder, Cervix
- D: Pancreas, Colo-Rectal, Squamous Lung.
- E: Melanoma, Osteosarcoma, Glioblastoma, RCC

32

The radioresponsiveness of human tumours and the initial slope of the cell survival curve. Deacon J, Peckham MJ, Steel GG. Radiother. Oncol. 1984 Dec;2(4):317-23.

**LESS  
RADIORESISTANT**

**MORE  
RADIORESISTANT**



## TUMOR “RADIOCURABILITY”:

- **The number of clonogenic cells:**
  - More cells, more radioresistant
  - We cannot change this (“we have what we have” at diagnosis).
- **The kinetics of tumor growth**
  - More growth, more radiosensitive
  - We might change this
- **The number of hypoxic cells**
  - More hypoxic, more radioresistant
  - We **may** change this up to date
- **The intrinsic radiosensitivity**
  - We might change this



## TUMOR "RADIOCURABILITY"

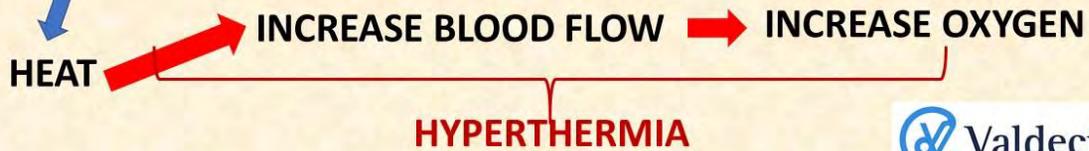
- **The number of hypoxic cells**

- More hypoxic → more radioresistant and **more "chemo-resistant"**

→ We **may** change this up to date

- Great amount of studies with different drugs to decrease hypoxia → radiosensitizers

- Discouraged by the predominantly negative results of the clinical trials (side effects, low efficacy...)



## ARE TUMORS REALLY MORE HYPOXIC?

Comparison of the oxygenation in organs and respective tumors

Tissue/organ	Physoxia (median % O <sub>2</sub> )	Cancer	Hypoxia (median % O <sub>2</sub> )
Brain	4.6	Brain tumor	1.7
Breast	8.5	Breast cancer	1.5
Cervix (nullipara)	5.5	Cervical cancer	1.2
Kidney cortex	9.5	Renal cancer	1.3
Liver	4.0–7.3	Liver cancer	0.8
Lung	5.6	Non-small-cell lung cancer	2.2
Pancreas	7.5	Pancreatic tumor	0.3
Rectal mucosa	3.9	Rectal carcinoma	1.8

**YES THEY ARE!!!**

Muz B, de la Puente P, Azab F, Azab AK. The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia*. 2015;3:63-92.



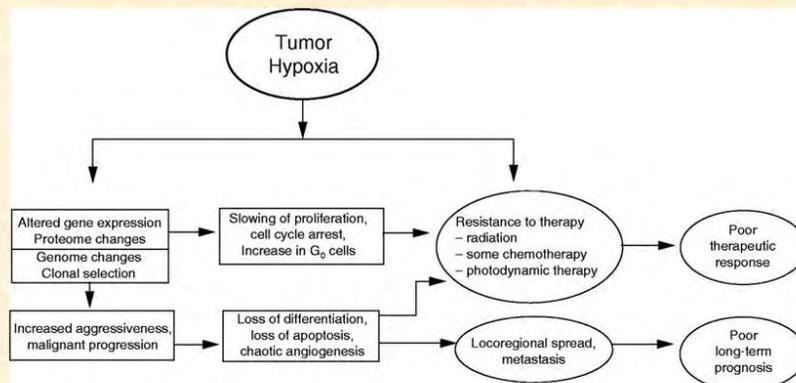


## TUMOR HYPOXIA

- Evidence has shown that **50–60% of locally advanced solid tumors may exhibit hypoxic and/or anoxic tissue** areas that are distributed heterogeneously within the tumor mass.
- Hypoxia arises in tumours through the uncontrolled oncogene-driven proliferation of cancer cells in the **absence of an efficient vascular bed**.
- Data do not suggest a topological distribution of the pO<sub>2</sub> values within a tumor.
- Tumor-to-tumor variability in oxygenation is greater than intratumor variability.
- **Local recurrences have a higher hypoxic fraction than the respective primary tumors**, although there is no clear cut difference between primary and metastatic malignancies.



**Schematic representation of the role of hypoxia in the development of an aggressive tumor cell phenotype and in malignant progression leading to resistance to cancer therapy and poor patient outcome.**



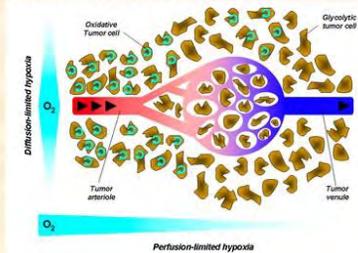
Peter Vaupel, and Louis Harrison *The Oncologist* 2004;9:4-9





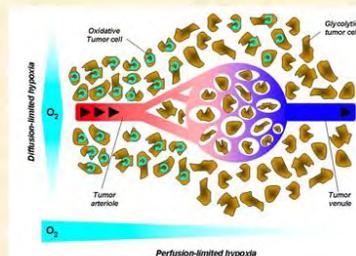
## TUMOR HYPOXIA

- Results from a **mismatch between the oxygen supply by poorly efficient blood vessels and oxygen consumption** by metabolically overactive tumor cells.
- Three main forms of hypoxia:
  - **Diffusion-limited hypoxia:** A gradient of oxygen deprivation from the nearest perfused blood vessels toward tumor cells at increasing distances from this vessel. It originates from high-rate of oxygen extraction through layers of cells within a loosened vascular network.



## TUMOR HYPOXIA

- Three main forms of hypoxia:
  - **Diffusion-limited hypoxia.**
  - **Perfusion-limited hypoxia:** Oxygen deprivation along the vascular tree from the tumor margin toward the tumor core.
    - Poor oxygen delivery has many causes in tumors, including high-rate of oxygen extraction at the tumor margin, decreased red blood cell deformability, and stacking, increased blood viscosity due to water extraction, vascular disorganization, and angiogenesis.
    - Arrows represent the blood flow.





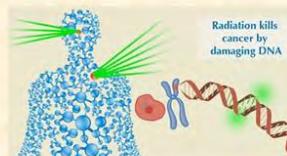
## TUMOR HYPOXIA

- Three main forms of hypoxia:
  - **Diffusion-limited hypoxia.**
  - **Perfusion-limited hypoxia.**
  - **Anemic hypoxia** : reduced O<sub>2</sub> transport capacity of the blood subsequent to tumor-associated or therapy-induced anemia.
    - Experimental studies have shown that the O<sub>2</sub> supply to tumors is greatly reduced and hypoxia is intensified at hemoglobin levels below 10–12 g/dl, especially when low O<sub>2</sub> transport capacity coincides with a low perfusion rate.



## WHY HYPOXIA INCREASES RADIORESISTANCE?

- The lack of oxygen leads to decreased production of reactive oxygen species and consequently to reduced DNA damage after conventional radiotherapy with high energy photons.
- There is a **relationship between decreased oxygen tension and gradual decline of radiation cell killing** changing with different radiation qualities

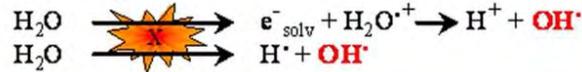




## HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

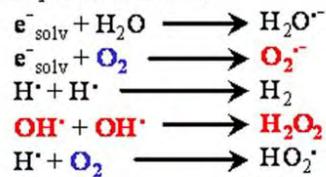
- In biological tissues, irradiation primarily **induces water ionization and destabilization**, leading to the formation of **reactive radical species**.

### A Water radiolysis



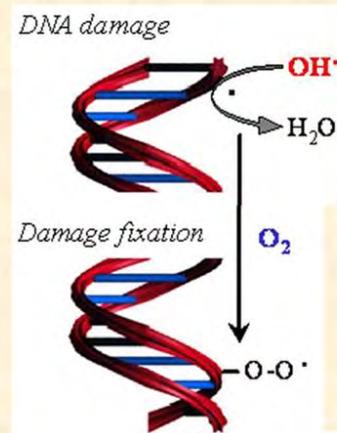
- These species then **react with neighboring molecules to yield reactive oxygen species (ROS)**, among which the **hydroxyl radical** is believed to be the most cytotoxic.

### B Subsequent reactions



## HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

- When generated in the proximity of DNA, hydroxyl radicals and, to a lesser extent, other less energetic species attack DNA. The resulting formation of a **DNA radical** is readily **reversible**.
- However, in the presence of **oxygen, DNA damage can be stabilized** through oxidation of DNA radicals, eventually leading to the formation of DNA peroxides.
- In oncology, oxygen-dependent DNA damage fixation is known as the "oxygen enhancing effect" of radiotherapy.**



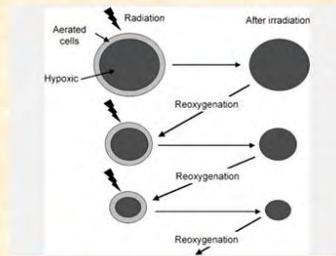


## HIPOXIA: A MAJOR ISSUE IN RADIOTHERAPY

- And the hypoxia does not only determine “radiosensitivity” but also...

- **RT fractionation:**

- For several reasons, RT is normally administered as a fractionated regimen.
- **One of the reasons** is because there is improved targeting of previously hypoxic cells, as **they reoxygenate between fractions.**



Imaging oxygenation of human tumours.  
Padhani AR, Krohn KA, Lewis JS, Alber M - Eur Radiol (2006)

**The proportion of hypoxic cells is lower in radiated vs not radiated tumors.**



## THE ROLE OF “mEHT” IN CANCER TREATMENT

- Several studies have shown that modulated electro hyperthermia (mEHT) is able to **increase tumor oxygenation.**

- → Decrease the hypoxia

- → **Increase radiosensitivity**

- An optimal moment to apply radiotherapy, about 30 minutes after the treatment with mEHT.





## “mEHT AS A RADIO-CHEMOSENSITIZER”

- eMHT improves blood flow → decreases hypoxia

Int J Hyperthermia, 2018 Nov;34(7):953-960. doi: 10.1080/02656736.2018.1423709. Epub 2018 Jan 21.

### The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma.

Lee SY<sup>1,2</sup>, Kim JH<sup>2,3</sup>, Han YH<sup>2,4</sup>, Cho DH<sup>5</sup>.

#### Author information

#### Abstract

**INTRODUCTION:** Mild hyperthermia has been known to enhance the response of tumours to radiotherapy or chemotherapy by increasing tumour blood flow, thereby increasing tumour oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

**METHODS:** The pelvic area of 20 patients with cervical carcinoma was heated with mEHT. The peri-tumour temperature was measured using an internal organ temperature probe. The tumour blood flow was measured using 3D colour Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels.

**RESULTS:** The mean peri-tumour temperature was  $36.7 \pm 0.2$  °C before heating and increased to  $38.5 \pm 0.8$  °C at the end of heating for 60 min. The marked declines in RI and S/D values strongly demonstrated that heating significantly increased tumour blood perfusion.

**CONCLUSIONS:** Regional heating of the pelvic area with mEHT significantly increased the peri-tumour temperature and improved the blood flow in cervical cancer. This is the first demonstration that the blood flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.



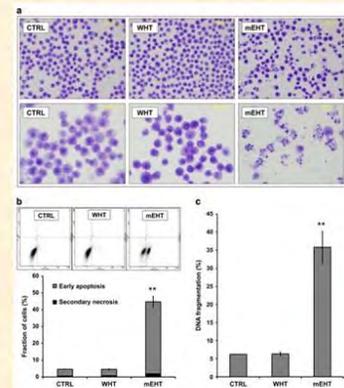
## “mEHT” IN CANCER TREATMENT

- There are also several studies showing the efficacy of mEHT in killing cancer cells when used alone without any other cancer treatments.

- mEHT kills **cancer** cells by **apoptosis**

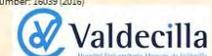
- No necrosis
- Less toxic

Selective



Representative microscopy images of untreated control, WHT-treated and mEHT-treated cells, 3h post-treatment in Giemsa stained cell samples (a). Representative flow cytometric histogram of the Annexin V-FITC and PI staining 3h after treatment. The quantitative analysis shows a significant increase of Annexin V positive-cell fraction only in mEHT samples (b). Quantitative results from DNA fragmentation assay. The mEHT-treated cells showed a significant increase in DNA fragmentation percentage, which is one of the hallmarks of apoptotic cell death (c). The results are presented as the mean±S.D. (n=3). \*\*P<0.01 as compared to WHT treatment.

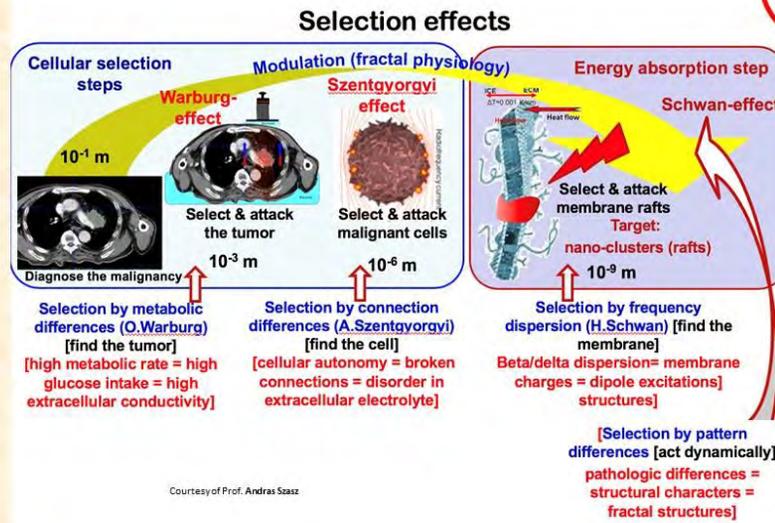
G. Andocs et al. Comparison of biological effects of modulated electro-hyperthermia and conventional heat treatment in human lymphoma U937 cells. *Cell Death Discovery* volume 2, Article number: 16039 (2016)





# "mEHT" IS SELECTIVE

Selective for  
malignant  
cells



# "mEHT" AS A CANCER CELL "KILLER"

Int J Hyperthermia. 2015;31(7):784-92. doi: 10.3109/02656736.2015.1069411. Epub 2015 Sep 14.

## Electro-hyperthermia inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis.

Cha J<sup>1,2</sup>, Jeon TW<sup>1</sup>, Lee CG<sup>1</sup>, Oh ST<sup>1</sup>, Yang HB<sup>1</sup>, Choi KJ<sup>1</sup>, Seo D<sup>3,4</sup>, Yun J<sup>1</sup>, Baik JH<sup>1</sup>, Park KN<sup>5</sup>

Author information

### Abstract

**PURPOSE:** Modulated electro-hyperthermia (mEHT), also known as oncothermia, types of tumours, including glioma. The aim of the present study was to investigate changes in oncothermic cancer cells.

**MATERIALS AND METHODS:** U87-MG and A172 human glioma cells were exposed to mEHT at different intervals and subsequently tested for growth inhibition using MTS, FACS and microarray analysis. In response to mEHT, global changes in gene expression were examined. In mEHT, we used U87-MG glioma xenografts grown in nude mice.

**RESULTS:** mEHT inhibited glioma cell growth through the strong induction of apoptosis. Expression under mEHT showed that the anti-proliferative effects were induced through the up-regulation of E2F1 and p53 and the down-regulation of ADAR and PSAT1. Subsequent Western blotting revealed that mEHT increased the levels of E2F1 and p53 and decreased the level of PARP-1, accelerating apoptotic signalling in glioma cells. mEHT significantly suppressed the growth of human glioma xenografts in nude mice. We also observed that mEHT dramatically reduced the portion of CD133(+) glioma stem cell population and suppressed cancer cell migration and sphere formation.

**CONCLUSIONS:** These findings suggest that mEHT suppresses glioma cell proliferation and mobility through the induction of E2F1-mediated apoptosis and might be an effective treatment for eradicating brain tumours.

## Overexpression of E2F1 in glioma-derived cell lines induces a p53-independent apoptosis that is further enhanced by ionizing radiation<sup>1</sup>

Hui-Kuo G. Shu, Carol M. Jolin, Felix Furman, Garret L. Yount, Daphne Haas-Kogan, and Mark A. Israel<sup>2</sup>

Preuss Laboratory for Molecular Neuro-oncology, Department of Neurological Surgery (H.-K.G.S., C.M.J., F.F., G.L.Y., D.H.-K., M.A.I.) and Department of Radiation Oncology (H.-K.G.S., G.L.Y., D.H.-K.), University of California, San Francisco, CA 94143



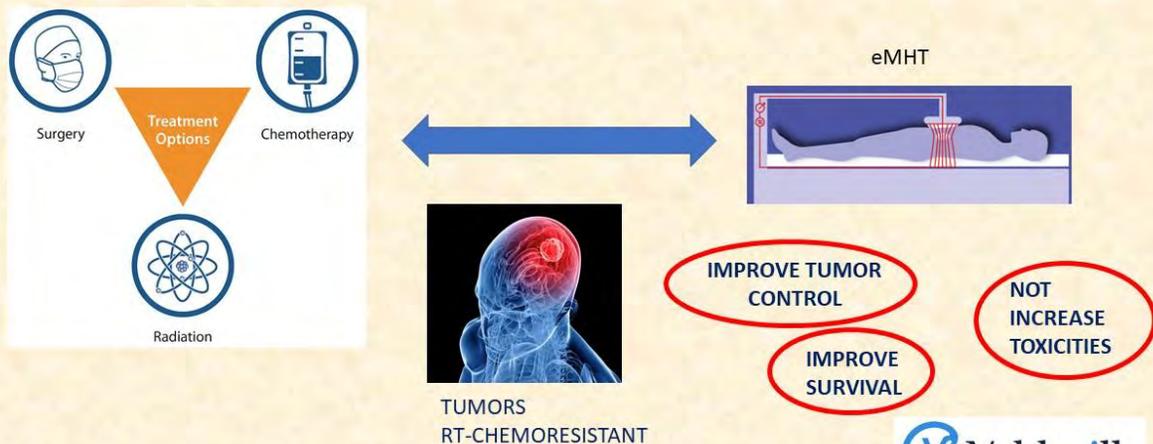


## THE ROLE OF “mEHT” IN CANCER TREATMENT

- **Modulated electro hyperthermia is able to increase tumor oxygenation.**
  - Increase radiosensitivity
  - Increase chemosensitivity
- **Modulated electro hyperthermia is able to kill by apoptosis malignant cells**
- These are some of the reasons why the combination of mEHT + Radio-chemotherapy, could result on an improvement in tumor control and survival for cancer patients.



## ADDING EFFORTS...







## University Hospital Marqués de Valdecilla



- **One of the "top" public hospitals of Spain.**
- **Very soon the first public hospital in Spain to have an mEHT device.**

## Virtual Hospital Valdecilla



- A pioneer center in Europe in the use of clinical simulation for the training of health professionals and the improvement of patient safety.
- Works in collaboration with the Center for Medical Simulation (Boston)

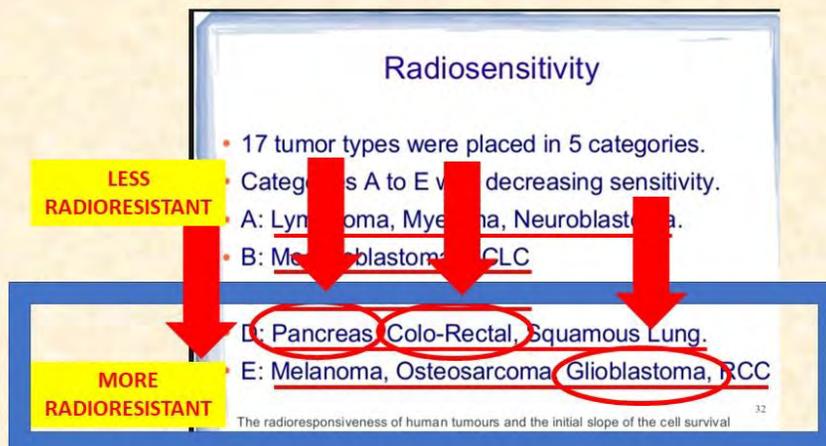
## IDIVAL Research Institute



In March 2015 IDIVAL was awarded by the Spanish Institute of Health Carlos III as **one of the reference Institutes for Health Research in Spain**



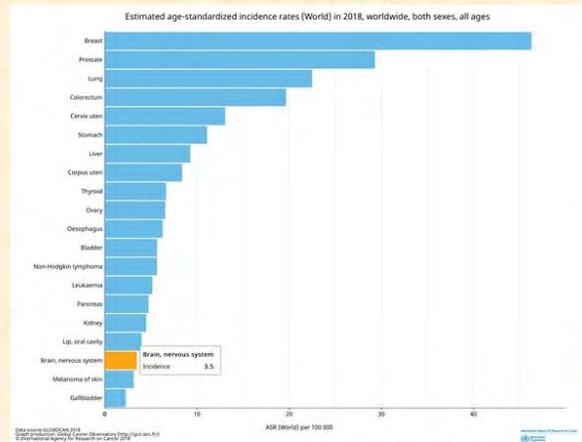
## WHICH TUMORS → THE DIFFICULT!!!



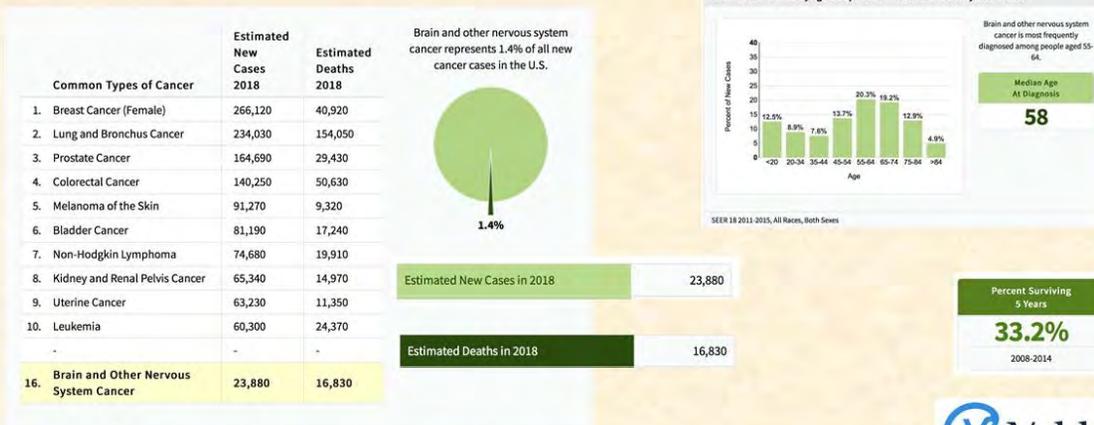


## GLIOBLASTOMA AND GRADE III ASTROCYTOMA

- Glioblastoma multiforme (GBM), a grade IV astrocytoma, is the most common and deadly type of primary malignant brain tumor.



## CENTRAL NERVOUS SYSTEM CANCER





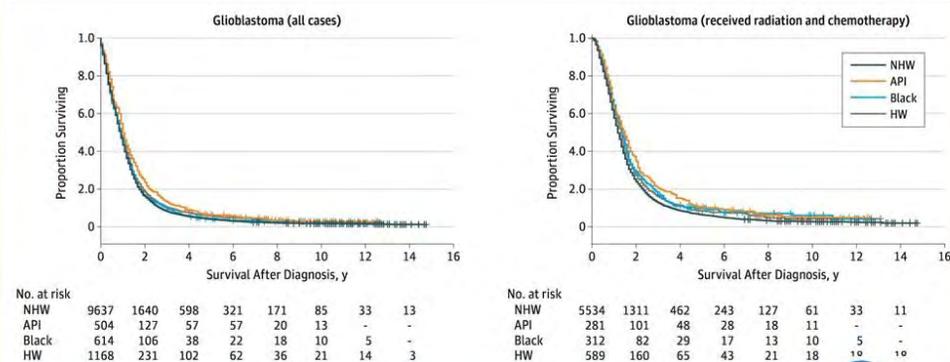
## CENTRAL NERVOUS SYSTEM CANCER

- The current treatment for GBM involves tumor resection surgery based on MRI image analysis, followed by radiotherapy and treatment with temozolomide.
- Radiotherapy alone can significantly increase median survival, although **the most common radiological response is to stabilize** the disease **but ultimately tumor progression** follows.
- Despite treatment, patient's **median survival rate ranges from 15 to 17 months.**



## GLIOBLASTOMA SURVIVAL

Figure 2. Survival Curves by Histologic Subtype for Individuals Who Received Resection by Race or Ethnicity, Adjusted by Age and Extent of Resection (Subtotal vs Gross Total), 2000-2014





## HIGH GRADE GLIOMA TUMORS

- High grade glioma tumors (grade III and IV) are radioresistant.
- Several reasons for radioresistance:
  - **The number of clonogenic cells:**
    - More cells, more radioresistant
  - **The kinetics of tumor growth**
    - More growth, more radiosensitive
  - **The number of hypoxic cells**
    - More hypoxic, more radioresistant
    - The clinical-pathological effects of hypoxia in GBM can be observed by magnetic resonance imaging (MRI) where **significant oxygen diffusion restriction is detected**, consistent with absent or defective blood flow
  - **The intrinsic radiosensitivity**

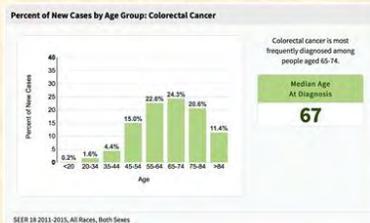
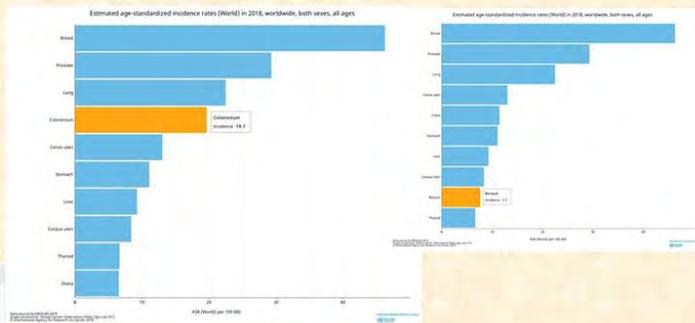
Comparison of the oxygenation in organs and respective tumors

Tissue/organ	Physoxia (median % O <sub>2</sub> )	Cancer	Hypoxia (median % O <sub>2</sub> )
Brain	4.6	Brain tumor	1.7



## RECTAL CANCER

- Colorectal cancer: 4<sup>th</sup> most common cancer diagnosed in both men and women in the world (3rd in USA).
- Rectal cancer: 9<sup>th</sup>





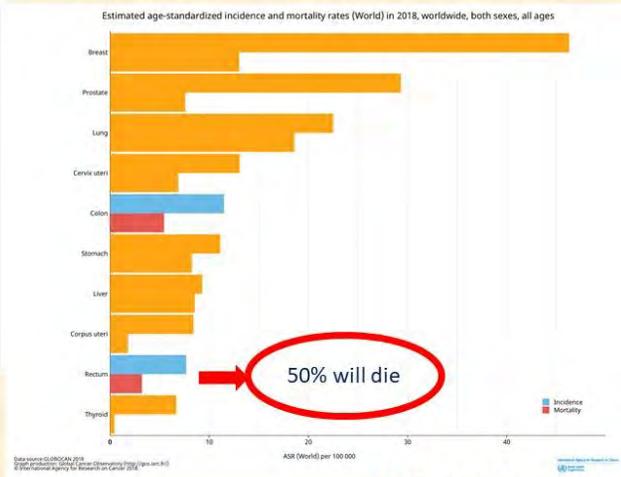
## COLORECTAL CANCER SURVIVAL

Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1. Breast Cancer (Female)	266,120	40,920
2. Lung and Bronchus Cancer	234,030	154,050
3. Prostate Cancer	164,690	29,430
4. Colorectal Cancer	140,250	50,630
5. Melanoma of the Skin	91,270	9,320
6. Bladder Cancer	81,190	17,240
7. Non-Hodgkin Lymphoma	74,680	19,910
8. Kidney and Renal Pelvis Cancer	65,340	14,970
9. Uterine Cancer	63,230	11,350
10. Leukemia	60,300	24,370

Colorectal cancer represents 8.1% of all new cancer cases in the U.S.



SEER 18 2011-2015, All Races, Both Sexes

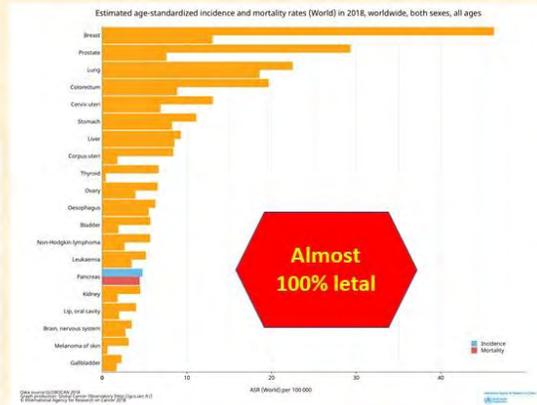
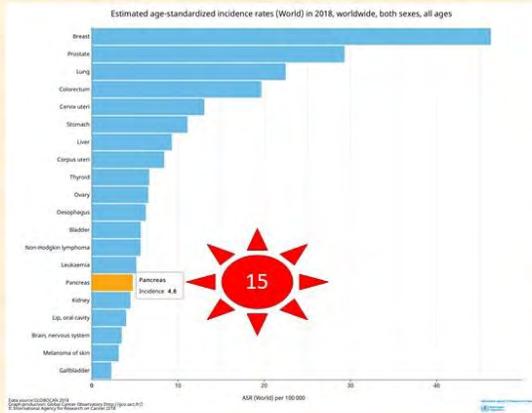


## RECTAL BUT NOT COLON CANCER

- Rectal cancer and not colon cancer → Why?
- Because we don't treat colon cancer with radiotherapy.



# PANCREATIC CANCER



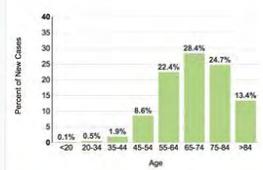
# PANCREATIC CANCER IN THE USA

Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1. Breast Cancer (Female)	266,120	40,920
2. Lung and Bronchus Cancer	234,030	154,050
3. Prostate Cancer	164,690	29,430
4. Colorectal Cancer	140,250	50,630
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7. Non-Hodgkin Lymphoma	74,680	19,910
8. Kidney and Renal Pelvis Cancer	65,340	14,970
9. Uterine Cancer	63,230	11,350
10. Leukemia	60,300	24,370
11. <b>Pancreatic Cancer</b>	<b>55,440</b>	<b>44,330</b>

Pancreatic cancer represents 3.2% of all new cancer cases in the U.S.



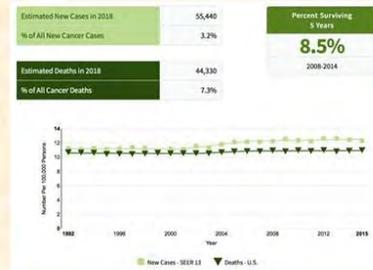
Percent of New Cases by Age Group: Pancreatic Cancer



Pancreatic cancer is most frequently diagnosed among people aged 65-74.

Median Age At Diagnosis  
**70**

SEER 18 2011-2015, All Races, Both Sexes

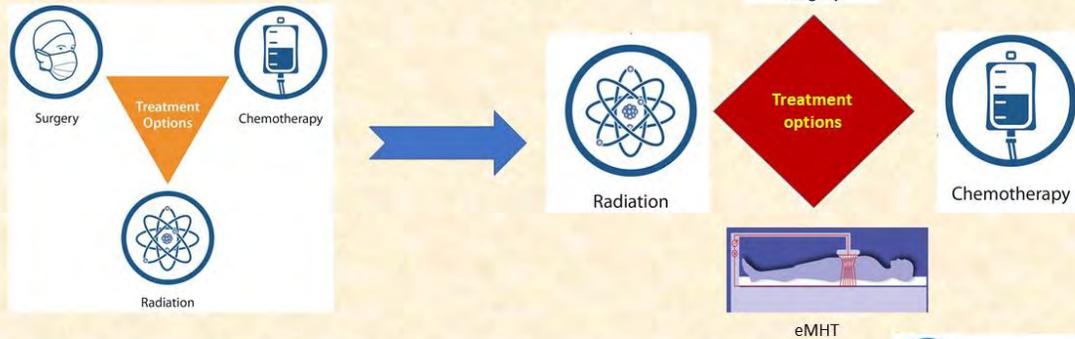




## IMPROVING TREATMENT...

### 3 STUDIES:

- HIGH GRADE GLIOMA
- RECTAL CANCER
- PANCREATIC CANCER



## COMMON POINTS FOR THE 3 STUDIES

### 5. STUDY DESIGN



This is a prospective, randomized study designed to evaluate the possible benefit in terms of better control of the disease, of adding a treatment with modulated electrohyperthermia to standard surgery, radio and chemotherapy treatments or as a single treatment in those cases that meet the inclusion criteria of the study and in which it is not possible to apply any other treatment.

It is hypothesized that treatment with modulated electrohyperthermia, will produce different beneficial effects that will impact on better oncological control such as:

- **Radiosensitivity:** mEHT will increase oxygenation and therefore will decrease hipoxia, improving this way radiosensitivity in those patients who will receive radiotherapy treatment concomitantly with mEHT.
- **Chemosensitivity:** mEHT will increase oxygenation and improve blood flow to improve the "drugs" distribution in the tumor area.
- **Improve cancer cell killing:** mEHT will promote cancer cell destruction through apoptosis by a mechanism of selection and modulation.



## COMMON POINTS FOR THE 3 STUDIES

- **PRETREATMENT DIAGNOSIS:**

- Complete clinical history including toxic habits, oncologic and laboral history.
- Physical examination.
- Complete anatomopathological report.
- Diagnostic imaging tests as indicated in the gold standard guidelines for cáncer treatment.
- Assessment of QoL

- **FOLLOW-UP DURING TREATMENT:**

- Weekly visit with the radiation oncologist to evaluate toxicities from the treatment.



## COMMON POINTS FOR THE 3 STUDIES

- **FOLLOW-UP AFTER TREATMENT:**

- **3 weeks after treatment:**
  - Physical exam (toxicities). No imaging test unless recommended for any special condition.
- **1-3 months after treatment (depending on the tumor).**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.
- **6 months after treatment.**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.
- **From 6th month → visits every 3 months.**
  - Physical exam (toxicities, signs/symptoms relapse/progression).
  - Imaging test (MRI, CT, PET... depending on the tumor).
  - Tumor markers when indicated.





## INCLUSION CRITERIA

HIGH GRADE GLIOMA	RECTAL CANCER	PANCREATIC CANCER
Patients able to understand and sign informed consent		
Age >18 years		
Karnofsky $\geq$ 70		
Confirmed by pathology <b>High Grade Glioma (III and IV)</b> <ul style="list-style-type: none"> <li>Newly diagnosed patients</li> <li>Patients with relapse/progression.</li> </ul>	Confirmed by pathology, imaging, and physical exam, <b>Stage II</b> (T3-4, node-negative disease with tumor penetration through the muscle wall) <b>or stage III</b> (node-positive disease without distant metastasis) <b>rectal cancer</b> . <ul style="list-style-type: none"> <li>Patients who will receive <b>neoadjuvant standard treatment with chemo-RT</b>.</li> </ul>	Confirmed by pathology, imaging, and physical exam <b>pancreatic adenocarcinoma</b> . <ul style="list-style-type: none"> <li>Patients candidates to neoadjuvant chemoradiotherapy.</li> <li>Patients M0 who will receive radiotherapy and/or chemotherapy and no surgery.</li> <li>Patients with relapse M0 not candidates to surgery as the first therapeutic option.</li> </ul>



## EXCLUSION CRITERIA

HIGH GRADE GLIOMA	RECTAL CANCER	PANCREATIC CANCER
<ul style="list-style-type: none"> <li>Dementia/ psychiatric illness.</li> <li>Drug abusers (active in the last 5 years).               <ul style="list-style-type: none"> <li>mEHT treatment contraindicated.                   <ul style="list-style-type: none"> <li>Another sincronic cancer.                       <ul style="list-style-type: none"> <li><b>No macroscopic disease</b></li> </ul> </li> </ul> </li> </ul> </li> <li>Another cancer diagnosed in the last 10 years.</li> </ul>		





## CLINICAL STUDIES

	HIGH GRADE GLIOMA	RECTAL CANCER	PANCREATIC CANCER
<b>EXTERNAL BEAM RT</b>	46Gy + 14 Gy Boost	45 Gy + 5.4Gy Boost	36-54Gy (depending on the case)
<b>CHEMOTHERAPY</b>	Temozolamide	5-Fu / Capecitabine	Folfirinox/Gemcitabine/Platinum
	<p><b>2 STUDIES:</b></p> <p><b>1st study:</b></p> <ul style="list-style-type: none"> <li>• <b>Patient candidates to standard RT-Chemotherapy</b></li> <li>• Randomized</li> <li>• 2 arms <ul style="list-style-type: none"> <li>• <b>Arm 1:</b> Standard adjuvant RT-CT</li> <li>• <b>Arm 2:</b> Standard adjuvant RT-CT + mEHT (30 min before RT Monday-Friday)</li> </ul> </li> </ul> <p><b>2nd study</b></p> <ul style="list-style-type: none"> <li>• Patient <b>not candidate</b> to any other standard oncological treat.</li> <li>• 1 arm: mEHT only (3 times a week)</li> </ul>	<p><b>1 STUDY:</b></p> <ul style="list-style-type: none"> <li>• Randomized</li> <li>• 2 arms <ul style="list-style-type: none"> <li>• <b>Arm 1:</b> Standard neoadjuvant RT-CT</li> <li>• <b>Arm 2:</b> Standard neoadjuvant RT-CT + mEHT (30 min before RT Monday-Friday)</li> </ul> </li> </ul>	<p><b>1 STUDY:</b></p> <p>1 arm, different groups:</p> <ul style="list-style-type: none"> <li>• Patients candidates to standard RT-CT + mEHT (30 min before RT Monday-Friday)</li> <li>• Patients not candidates to any standard treatment → mEHT (3 times a week)</li> </ul>



## COMMON POINTS FOR THE 3 STUDIES

### 6. TREATMENT DESCRIPTION.

#### Treatment with modulated electrohyperthermia:

Patients will receive a treatment with modulated electrohyperthermia following the recommendations of the physician responsible for the study.

- Patients who will receive concomitant radio and chemotherapy treatment:
  - mEHT treatment will be before each radiotherapy session.
  - Timing between the end of mEHT treatment and the beginning of radiotherapy treatment will be approximately 30 minutes. Before this 30 minutes, no patients will be treated with radiotherapy.
- Patients who will receive mEHT treatment as an unique therapy:
  - mEHT treatment will be performed every 48 hours from Monday to Friday.



## COMMON OBJECTIVES FOR 3 STUDIES

- **Main objectives:**

- To evaluate the impact of performing a treatment with modulated electro hyperthermia, on the rates of **local, regional and distant control** in patients treated concomitantly with radio-chemotherapy, or as a unique treatment in those patients not candidates to standard therapies due to lack of efficacy or risk of toxicity as a single therapy.

- **Secondary objectives**

- To analyze the impact of mEHT treatment (used concomitant with radio-chemotherapy or as a unique treatment) in the **cause specific and overall survival** rates, and **acute, subacute and chronic toxicities** from this treatment.
  - \*For rectal cancer cases we will also evaluate:
    - The rates of sphincter preservation → impact in QoL
    - The rates of CR after neoadjuvant treatment.



## HIGH GRADE GLIOMA STUDY: mEHTGlio

1.1 **Title: "Treatment with modulated electro-hyperthermia in high grade gliomas (grade III and IV) as an adjuvant treatment to standard radiotherapy and chemotherapy or as a unique treatment".**

1.2 **Protocol name:** mEHTGlio

1.3 **Date and protocol version:** version 1.0 of May 20th 2018

1.4 **Study|promotor:**

Dra. Elisabeth Estefanía Arrojo Álvarez  
Radiation Oncology department. University Hospital Marqués de Valdecilla  
C/ Avda. Valdecilla s/n 39008 Santander  
Email: [earrojo@hotmail.com](mailto:earrojo@hotmail.com)





## RECTAL CANCER STUDY: mEHTRec

### 1. GENERAL INFORMATION

1.1 **Title: "Treatment with modulated electro-hyperthermia as a radio-chemosensitizer, in rectal cancer patients who will receive neoadjuvant standard long course radio-chemotherapy".**

1.2 **Protocol name:** mEHTRec

1.3 **Date and protocol version:** version 1.0 of May 20th 2018

#### 1.4 Study promotor:

Dra. Elisabeth Estefanía Arrojo Álvarez  
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C/ Avda. Valdecilla s/n 39008 Santander  
Email: [earrojo@hotmail.com](mailto:earrojo@hotmail.com)



## PANCREATIC CANCER STUDY: mEHTPan

### 1. GENERAL INFORMATION

1.1 **Title: "Treatment with modulated electro-hyperthermia in locally advanced pancreatic cancer as radio-chemosensitizer, or as a unique treatment in patient not candidates to standard oncological therapies".**

1.2 **Protocol name:** mEHTPan

1.3 **Date and protocol version:** version 1.0 of May 20th 2018

#### 1.4 Study promotor:

Dra. Elisabeth Estefanía Arrojo Álvarez  
Radiation Oncology department. University Hospital Marqués de Valdecilla  
C/ Avda. Valdecilla s/n 39008 Santander  
Email: [earrojo@hotmail.com](mailto:earrojo@hotmail.com)





## RECRUITMENT AND LENGHT...

- **Expected recruitment:**
  - 60 cases each year for high grade gliomas.
  - 80 cases each year for rectal cancer
  - 30 cases each year for pancreatic cancer
- **Lenght of the studies: 2 years.**
  - Not a lot of time but....
    - **Results soon:**
      - High grade glioma → median survival around 12 months.
      - Rectal cancer → pre-surgery treatment, so response in surgical specimen.
      - Locally advanced pancreatic cancer → poor survival.



## CONCLUSIONS

- The first\* trials to analyze the **role of mEHT applied as a radiosensitizer 30 minutes before each radiotherapy session.**
  - Up to date, in the published studies mEHT applied every 48 hours, not related with an "specific" timing with radiotherapy.
  - **Tumor oxygenation increases after mEHT, but how long do we have that "higher" oxygen levels?**
    - Maybe, if we treat every 48 hours, without a "timing relation" with radiotherapy, we loose that increase in radiosensitivity?





## CONCLUSIONS

- Potential advantages of adding mEHT to conventional oncological treatments.
  - **Increase cancer cell killing**
  - **Increase radio-chemosensitivity** → increase cancer cell killing
  - Not increase toxicities (more than 10.000 patients treated in clinical studies without significant toxicities with mEHT)
    - **A potential to decrease toxicities.**
      - Not curable tumors → cannot decrease current treatment “dose” at the moment.
      - Curable tumors → decrease treatment dose (for RT/chemo) → add mEHT → decrease toxicity → without risk in tumor control???
- **For the future:**
  - Other interesting studies: role of mEHT for microscopic disease.
    - Areas where RT treatment (conventional for this) is not possible. (ie. colon cancer).



# THANK YOU!

earrojo@humv.es

\* All my efforts to all cancer patients, specially those so close to me....



# Therapy of advanced, therapy resistant Pancreas cancer, with local hyperthermia in combination with chemotherapy

**Friedrich Douwes**  
Klinik St. Georg, Bad Aibling

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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[www.oncothermia-journal.com/journal/2018/Therapy\\_of\\_advanced.pdf](http://www.oncothermia-journal.com/journal/2018/Therapy_of_advanced.pdf)

# Therapy of advanced, therapy resistant Pancreas cancer, with local hyperthermia in combination with chemotherapy

Friedrich Douwes

Klinik St. Georg

## Background

The therapy results of pancreas cancer remains disappointing. In nearly all cases the disease progresses, response rates of cytotoxic therapy are low and the 5- year survival rate amounts to 1%. The purpose of our clinical study was to proof if criteria like response rate, time to progression and survival time can be improved by the use of a cytostatic treatment with Mitomycin-C, 5-FU and Folinic Acid in combination with loco-regional hyperthermia respectively by thermo-chemotherapy.

## Methods

In this clinical study 30 patients with advanced pancreas cancer are included and treated with thermo-chemotherapy that is a combination of loco-regional hyperthermia and chemotherapy including Mitomycin C (8mg/m<sup>2</sup>), 5- fluorouracil (5-FU) (500 mg/m<sup>2</sup>) and calcium folinate (200 mg/m<sup>2</sup>) on day 1 and 7. Loco- regional capacitive radiofrequency hyperthermia (13.56 MHz) was applied on day 1,3,5,7,9, 11. The mean temperature achieved in the tumor site was 42°C – 44°C. Treatment was repeated every 4 weeks until progression.

## Results

According to the standard criteria, 1 patient had a complete remission, 10 patients (=33,3%) had a partial remission; 12 (=40%) had a stable disease. 7 patients (=23,3%) did not respond to the therapy and showed progressive disease. Median survival time was 8 months (range 2-53 months), time to progression was 5.5 months (range 1-40 months).

## Conclusion

Thermo-chemotherapy as applied in this clinical study shows a remarkable clinical outcome in advanced pancreas cancer and is well tolerated. Since all chemotherapy studies did not show significant response rates and prolongation of survival time the data obtained with thermo-chemotherapy vers positive and suggest further evaluation in randomized trials.

Key words: Thermo-chemotherapy, pancreas cancer, loco-regional hyperthermia, palliative chemotherapy, improvement of response rate & survival time

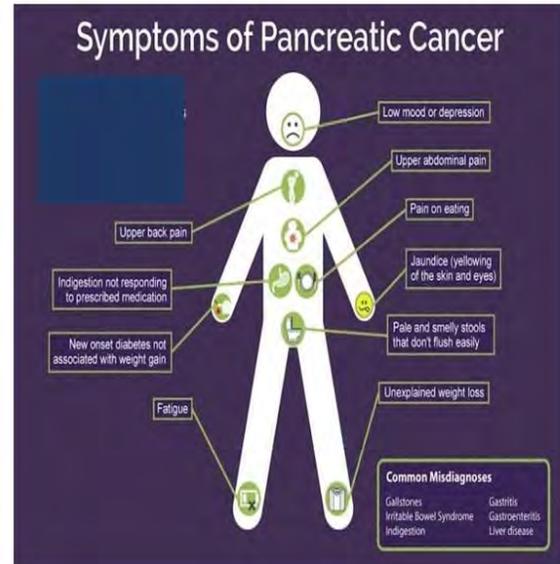
## Therapy of advanced, therapy resistant Pancreas cancer, with local hyperthermia in combination with chemotherapy

Dr. med. Friedrich Douwes  
Klinik St. Georg, Bad Aibling



- Prognosis of exocrine Pancreas cancer is poor.
- In less than 20 % a resection is possible.
- Even after R0-resection the 5y survival rate is less than 10 %.
- **In palliative situation the median survival rate is 6 month & the 1 year survival 1-2%**

- most patients with advanced pancreatic cancer have pain due to tumor-forming symptom.
- This reduces their daily activities & life quality

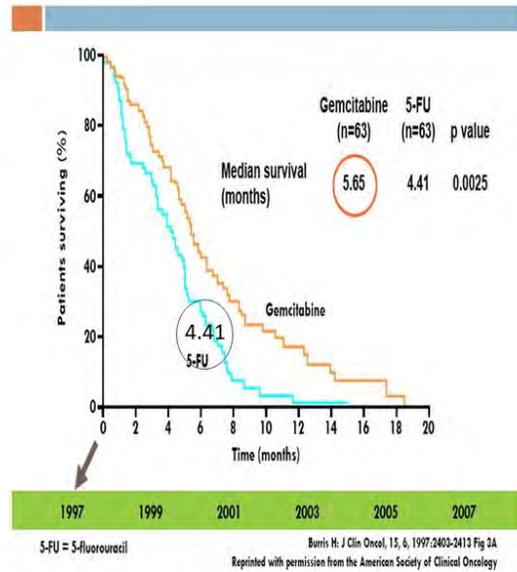


- However, chemotherapy can increase the survival rate and improve clinical symptoms
- Studies with 5-FU, Gemcitabine, Oxaliplatin, Irinotecan, Erlotinib(Tarceva) show marginal improvement in disease-related symptoms & prolonged 1-year survival

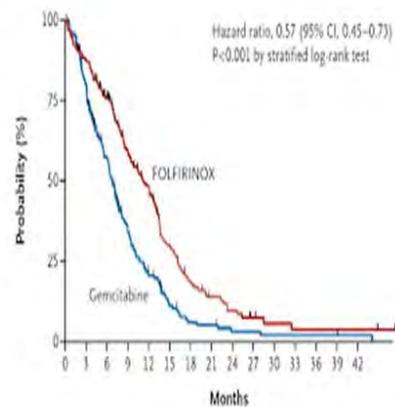
1997 American Society of Clinical Oncology  
**Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial.**

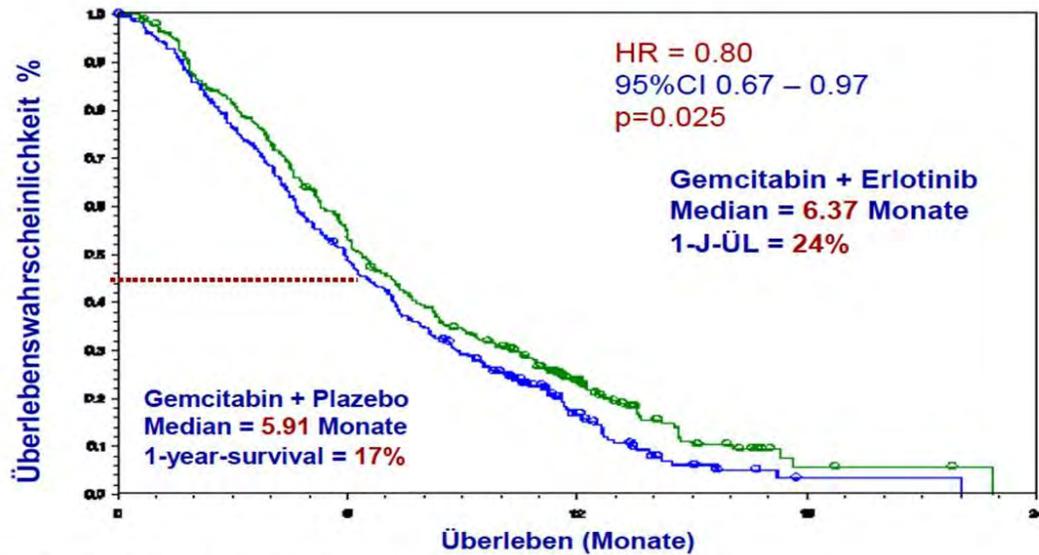
H A Burris 3rd, M J Moore, J Andersen, M R Green, M L Rothenberg, M R Modiano, C D Stephens and D D Von Hoff

- The clinical benefit was 23.8% response in the gemcitabine-treated group, and 4.8% in the 5-FU group (P = .0022).
- Median survival was **5.65** in gemcitabine and **4.41** months in 5-FU group (P = .0025).
- **4.41** months in 5-FU group (P = .0025).
- **The survival rate at 1 year was 18% for gemcitabine patients & 2% for 5-FU patients**



Folfinox Gemcitabine N=171 N=171 p HR
Medianes <b>11.1 mo.</b> <b>6.8 mo.</b> Überleben <0.0001 0.57
1-yr. survival 48.4% 20.6%
18-mo. survival 18.6% 6%

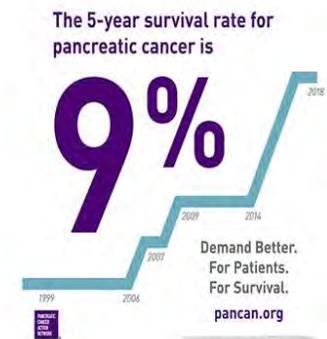




\* Adjusted for PS and extent of disease at baseline

Moore et al. JCO 2007

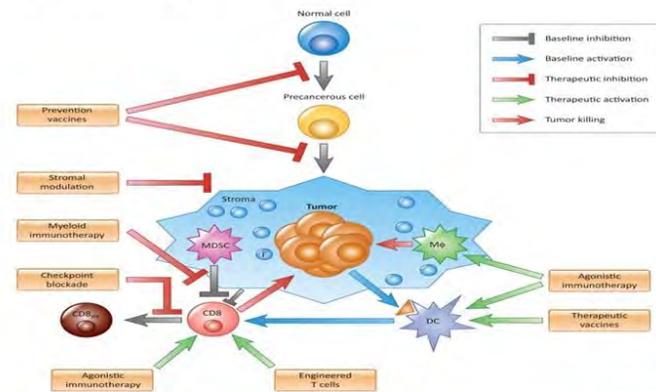
- So even in 2018 the prognosis of pancreas cancer has a poor prognosis.
- Therefore development of new therapeutic agents and/or modalities are necessary to improve the clinical outcome.



## The treatment modalities under intensive research are:

- Target & Signal Transduction Therapy
- molecular-genetical & immunological approaches

➤ Or completely other therapy entities such as loco-regional deep hyperthermia.



## Why Hyperthermia ?

- Clinical efficacy of local and regional hyperthermia has been studied and proven in numerous clinical trials.
- Randomized Phase III trials have been successfully completed for the combination of hyperthermia and radiotherapy & chemotherapy.

## Local hyperthermia in conjunction with radiotherapy induced significant therapeutic success

- recurrent malignant **melanoma** (Overgaard et al., 1995),
- In local recurrence of **breast cancer** (Vernon et al., 1996) and
- in advanced lymph node metastases of **head and neck carcinomas** (Valdagni et al., 1994).
- in **advanced pelvic tumors** (significant improvements in survival rates (van der Zee et al., 2000).

### The Rationale for Combining Hyperthermia with Chemotherapy

#### Synergism between cytostatics & hyperthermia, e.g.

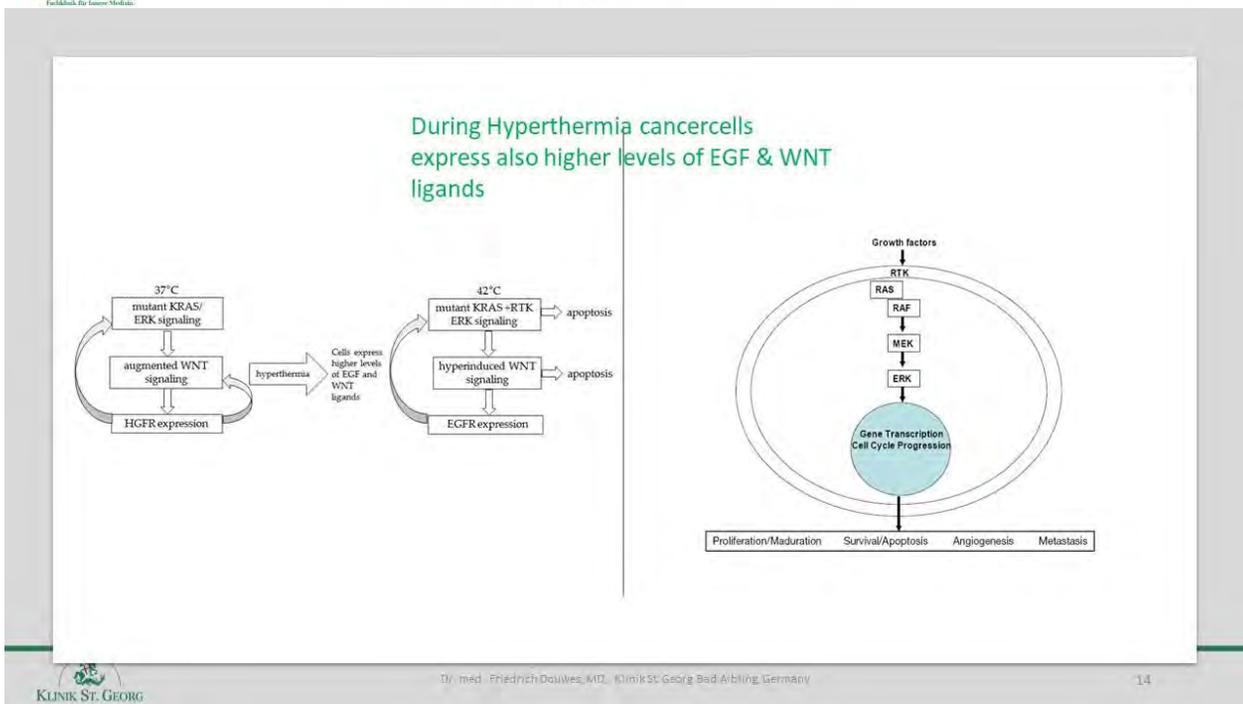
- Cisplatin, Carboplatin, Oxaliplatin
- melphalan,
- cyclophosphamide,
- anthracyclines,
- nitrosurea,
- bleomycin,
- mitomycin C (69).

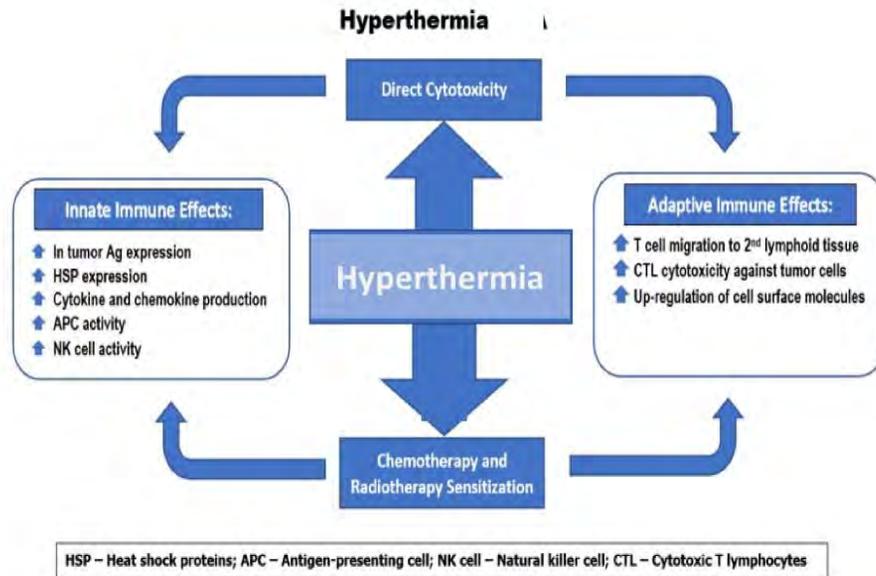


## The mechanism of synergism

### Heat:

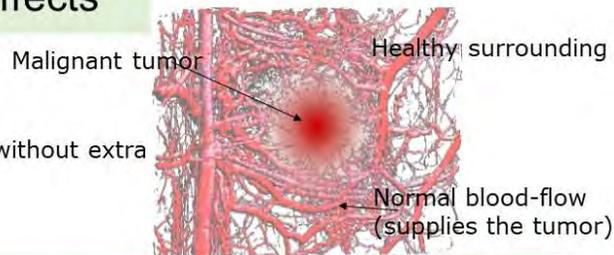
- increases cellular uptake of the drug
- increases oxygen radical production and
- increases DNA damage and
- inhibits DNA repair (28).
- Heat induce hypoxia and pH changes, which are also responsible for the higher therapeutic effect.



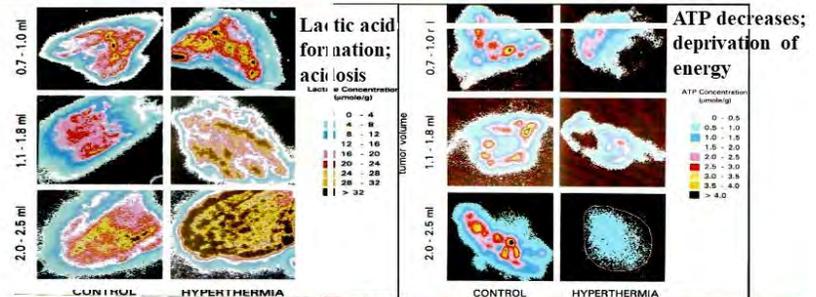
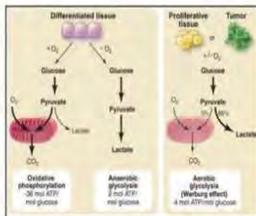


## Classical hyperthermia effects

**Local heating** → intensifies the metabolism, without extra supply → **burning out**



Comparison of Glycolysis between a Normal Tissue and Tumour/Proliferated Tissue



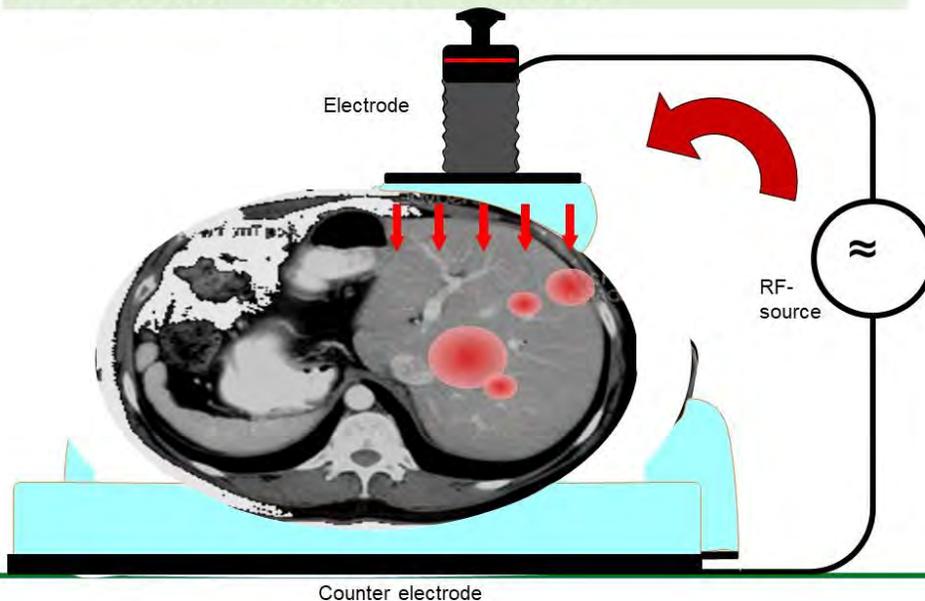
## Hyperthermia alters tumorcell metabolism biology & triggers immunological activity

- From 41 °C degrees, the tumor cell induces heat shock proteins.
- These HSPs serve as immune signals for the immune cells. e.g.
- HSP72 is a specific recognition structure for NK cells
- HSP72 increases sensitivity to the cytotoxicity of IL-2-stimulating NK cells
- Hyperthermia also leads to the activation of various cytokines, e.g. IL-1 $\beta$ , IL-6, IL-8, IL-10, TNF- $\alpha$ , G-CSF.

For our clinical trial in advance chemoresistant pancreas cancer  
we used the Oncotherm device



## Oncotherm – easy to use device



## Our clinical trial in advance chemoresistant pancreas cancer consisted of:

1. Chemotherapy with Mitomycin C (8 mg / m<sup>2</sup>) and 5-Fluorouracil (500 mg / m<sup>2</sup>) and Folinic acid (200 mg / m<sup>2</sup>) on days 1 and 7 and
2. regional electro-hyperthermia (13.56 MHz, EHY 2000) was applied on day 1,3,5, 8,10,12, ...
3. The duration of therapy for hyperthermia was 60 min.
4. The treatment cycle was repeated every 3 weeks until progression occurred



## Why did we do this ?

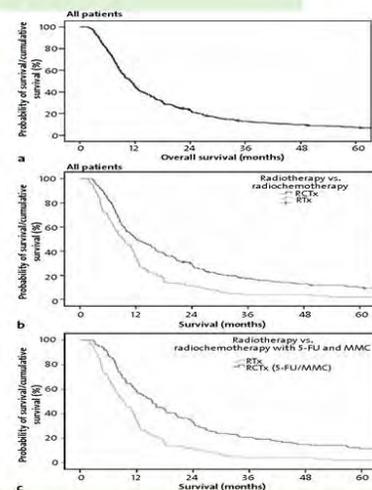
Due to the lack treatment options in such a desperate situation it should be checked:

1. whether the MDR can be overcome and if so, can a response to chemotherapy be achieved.
2. can quality of life be improved
3. can survival time be extended

## Why Mitomycin & 5-FU/ Folinic acid ?

*In a randomized study with inoperable, advanced pancreatic carcinoma, an advantage of combining 5-FU with mitomycin C versus 5-FU monotherapy was demonstrated;*

- The response rate was 17.6% vs. 8.4% (Maisey et al., 2002).
- There were no significant differences in survival time (6.5 months vs. 5.1 months).



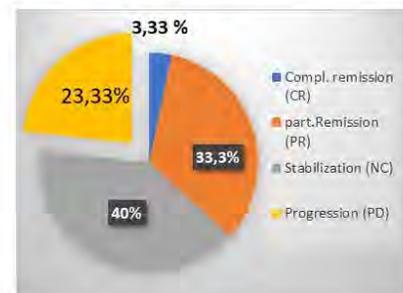
Tab. 1: Patientencharakteristika

Nr.	Ge- schlecht	Alter (a)	Chemotherapie vorher	Ausgangs- stadium (AJCC)	Metastasen	Primär inoperabel
1	m	60,8		IV	hepatisch	x
2	m	71,2		IV	peritoneal	x
3	w	40,1	GEM	IV	hepatisch	
4	w	58		IV	hepatisch	x
5	m	41,1		IV	hepatisch	x
6	m	66,9		IV	hepatisch	x
7	w	37,6		IV	hepatisch	x
8	w	55,8	GEM	IV	hepatisch,	x
9	w	61,3	MITO	III	Lymphknoten	x
10	m	56	GEM	II		x
11	w	64,9		IV	hepatisch	
12	w	78,6		IV	hepatisch, Nebeniere	
13	m	59,5	GEM, CDDP	IV	hepatisch	
14	m	31,5		IV	hepatisch	
15	m	60,5	GEM, 5-FU, CDDP	IV	hepatisch, peritoneal	
16	m	64,8	GEM	IV	hepatisch	
17	w	48	GEM	IV	pulmonal	x
18	w	53,7		II		x
19	w	63,5	GEM, 5-FU,	IV	hepatisch	
20	m	67,2	GEM	IV	peritoneal	x
21	m	53,7	IFO	IV	hepatisch	
22	w	63,9	GEM	IV	hepatisch	
23	m	41,5		IV	hepatisch, pleural, ossär	
24	m	63		IV	cutan	
25	w	73,6		IV	hepatisch	x
26	m	59,2	GEM	IV	peritoneal	x
27	w	60,7	MITO	II	peritoneal	
28	m	36		IV	hepatisch	x
29	w	60,1	GEM	IV	hepatisch	x
30	m	52,8	5-FU	IV	hepatisch, peritoneal	

Abkürzungen: CDDP = Cisplatin; 5-FU = 5- Fluorouracil; GEM = Gemcitabin; MITO = Mitomycin; IFO = Ifosfamid;

- The result of this combination therapy (thermo-chemotherapy) in 30 patients (16 men and 14 women) with inoperable, widely pretreated pancreatic carcinoma was the following:

- Compl. remission (CR) 1/30 = 3.33%
- part.Remission (PR) 10/30 = 33.33%
- Stabilization (NC) 12/30 = 40%
- Progression (PD) 7/30 = 23.33%



Tab. 2: Therapieergebnisse

Nr.	Therapiezyklen	Ergebnis	CA-19-9-Response	Überlebenszeit (M)	Zeit bis zur Progression (M)	Leukopenie (Grad)	Thrombopenie (Grad)	Anämie (Grad)
1	3	PR	x	6,5	2	1	2	0
2	4	PR		11	8	1	3	2
3	4	PR	x	6+	6	2	0	3
4	4	PR	x	18	7	1	0	1
5	7	PR	x	30+	26	0	0	2
6	2	PD		6	2	1	0	1
7	3	NC		15+	7+	1	2	2
8	9	NC		37	12	2	2	2
9	5	PR	x	53	10	0	0	0
10	2	PD		8	2	1	0	1
11	2	NC		4	2	1	0	1
12	3	NC		10	7	1	0	1
13	2	NC		7+	5+	2	2	2
14	5	PR		41	26	1	0	1
15	3	PD		4	3	1	0	2
16	2	NC		5	4	2	1	2
17	2	PD		5	4	0	0	0
18	2	CR		40+	40+	1	0	1
19	5	PR	x	20,5	8	2	1	2
20	5	PR		9+	8	1	0	2
21	1	PD		2	1	0	0	0
22	3	NC		7	4+	2	0	2
23	2	NC		8	6	0	0	1
24	2	NC	x	5	1,5	3	2	2
25	3	PR	x	9+	5,5	0	0	2
26	4	NC	x	8,5	8,5	0	0	3
27	1	NC		5	5	1	0	1
28	1	PD		3		0	0	3
29	3	NC		5	4	3	2	2
30	1	PD		3	2	1	0	1

Abkürzungen: PR = Partielle Remission; NC = No change (Stillstand); PD = Progression



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## Results

- The median survival was 8 months (2-53)
- The 1 years survival 31%
- Even after 2 years still 24 % of the patients are still alive

**Disease control rate“ (DCR)  
All types of response in this study  
CR, PR & SD was 72%**



Dr. med. Friedrich Douwes, MD, Klinik St. Georg Bad Aibling, Germany

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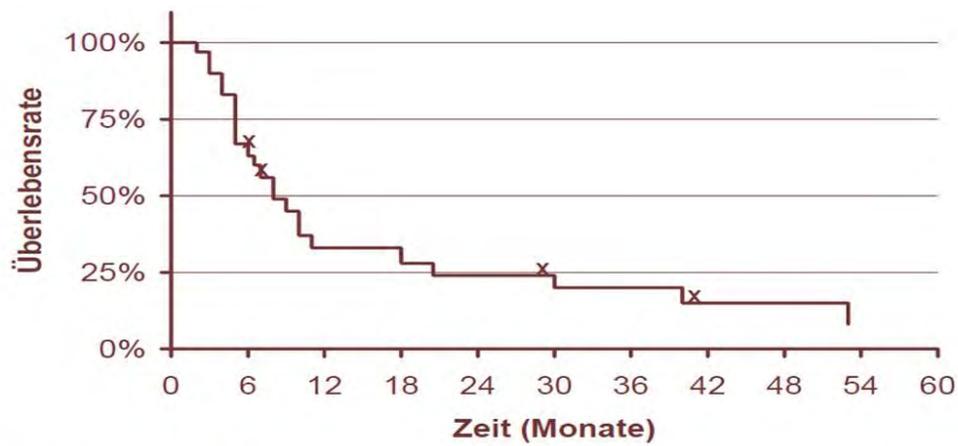
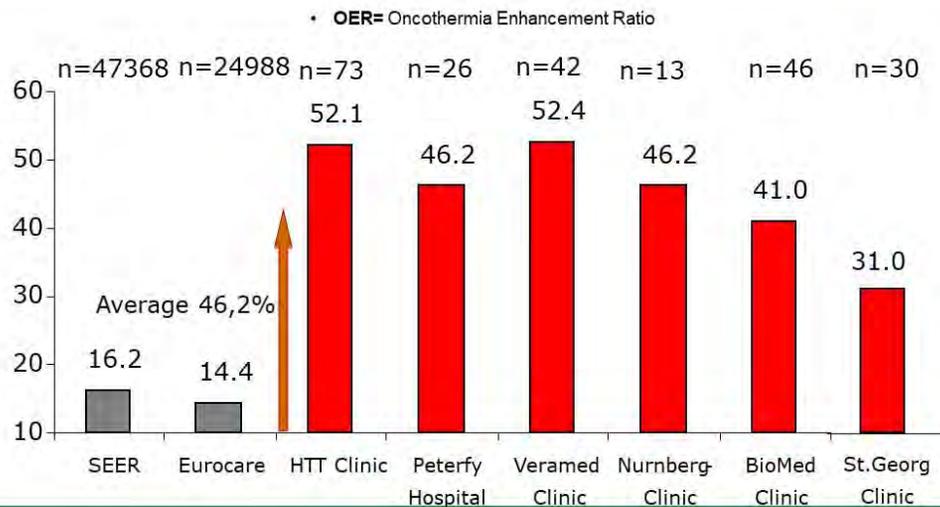


Abb. 2: Verlauf der Überlebensraten (Kaplan-Meier- Diagramm) nach Behandlung des fortgeschrittenen Pankreaskarzinoms mit Chemotherapie und regionaler Hyperthermie Tumoren darstellen (Thermo-Chemotherapie) (n= 30). Die mediane Überlebenszeit betrug 8 Monate, die 1-Jahresüberlebenszeit erstaunliche 31% und stabilisierte sich so, dass auch nach zwei Jahren noch 24% der Patienten lebten.

## Summary in this clinical study,

we were able to show a survival advantage in advanced MDR pancreas cancer by combining electro-hyperthermia (Oncotherm) with chemotherapy (5-FU/Mitomycin C)

## Pancreas Ca 1y survival [%]



## Conclusion: Thermo-chemotherapy advanced heavy pretreated pancreas carcinoma

- Therapy of the exocrine pancreas cancer remains one of the most difficult challenges
- Curative treatment is achieved only in a small number of the cases.
- The patients in our study all had an advanced stage (III or IV) and have been heavy pretreated.
- Our treatment protocol with 5-FU / folinic acid and mitomycin C combined with regional radiofrequency hyperthermia (Chemo-Thermotherapy) was tolerated very well.

Hyperthermia ideally complements:

- conventional therapies,
- increases response rates
- prolongs survival time
- improves quality of life.
- Without increasing the toxicity.



*Thank you for your  
attention!*

## **Breast Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) a single center experience**

**Erika, Borbenyi<sup>1</sup>, Judit Desfalvi<sup>1</sup>, Gyongyver Szentmartoni<sup>1</sup>, Tamas Garay<sup>1,2</sup>, Reka Mohacsi<sup>1</sup>, Mariann Kvensika<sup>1</sup>, Marcell A. Szasz<sup>1</sup>, Magdolna Dank<sup>1</sup>**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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[www.oncothermia-journal.com/journal/2018/Breast\\_cancer\\_series.pdf](http://www.oncothermia-journal.com/journal/2018/Breast_cancer_series.pdf)

# Breast Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) -- a single center experience

Erika, Borbenyi<sup>1</sup>, Judit Desfalvi<sup>1</sup>, Gyongyver Szentmartoni<sup>1</sup>, Tamas Garay<sup>1,2</sup>, Reka Mohacsi<sup>1</sup>,  
Mariann Kvensika<sup>1</sup>, Marcell A. Szasz<sup>1</sup>, Magdolna Dank<sup>1</sup>

<sup>1</sup>Cancer Center, Semmelweis University, Budapest, Hungary

<sup>2</sup>Faculty of Information Technology and Bionics, Pazmany Peter Catholic University,  
Budapest, Hungary

## Background

mEHT is a relatively new kind of hyperthermia in oncology. It is a further development of the conventional heating methods.

## Aim

Our objective in this presentation is to summarize our knowledge about the utilization of mEHT therapy from the practical perspective in breast cancer and summarize our experience in our breast cancer patients treated with mEHT.

## Methods

Thirteen patients with advanced breast cancer (12 invasive ductal carcinoma and 1 postirradiation angiosarcoma) were treated in a 20 months period at the Cancer Center of Semmelweis University, with the instruments EHY-2000 and EHY-2030 (Oncotherm Ltd., Budaörs, Hungary). One patient also developed pancreatic cancer, and one patient only attended one session, thus, these were omitted from further analysis.

## Results

Two patients were treated for locally advanced disease in a neoadjuvant fashion. The rest of patients were node positive and/or metastatic. The most common metastatic sites were lymph nodes (9), bone (5), liver (4) and lung (4) with cutaneous involvement (2). The average time in treatment was 11.2 weeks (range: 2.4-23.2). Various neoadjuvant and first-line chemotherapeutic protocols were applied, mostly platinum and taxane containing regimens, but also capecitabine, tegafur, mitomycin C, gemcitabine, lapatinib were administered. A two-week break in therapy was necessary in five cases due to local discomfort (2), nausea and weakness (2) and hydrothorax (1). The patients with primary systemic therapy continued with surgery and finished treatment, one patient stopped at week 20 due to inflamed port and eight patients progressed in an average 9.7 weeks.

## Discussion

Complementary mEHT treatment of breast cancer patients is feasible and easy to administer. Most durable responses were seen in skin metastases and/or bone and decreasing time with lung and liver involvement. Most important favoring prognostic factors were lower stage and less number of metastases (oligometastatic status with maximally two distant metastatic sites). Younger age was a poor prognostic factor also accompanied with multiorgan metastases (3<).

Grant support: NVKP\_16-1-2016-0042

# Breast Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) a single center experience

Borbényi E<sup>1</sup>, Désfalvi J<sup>1</sup>, Szentmártoni Gy<sup>1</sup>, Garay T<sup>1,2</sup>,  
Mohácsi R<sup>1</sup>, Kvasnika M<sup>1</sup>, Szasz AM<sup>1</sup>, Dank M<sup>1</sup>



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## Disclosures – conflict of interest

# NONE

- M.D./Ph.D., pathologist
- Research funding
  - Hungarian Society of Medical Oncology (indirectly from Roche, Pfizer, GlaxoSmithKline)
  - Bristol-Myers Squibb
  - Hungarian National Research, Development and Innovation Office (NRDI Office), consultant for Oncotherm
- Head of Science - Cancer Center, Semmelweis University, Budapest, Hungary
- Secretary General, Hungarian Society of Senology
- Member of Board of Curators, International Academy of Pathology (IAP), Hungarian Division

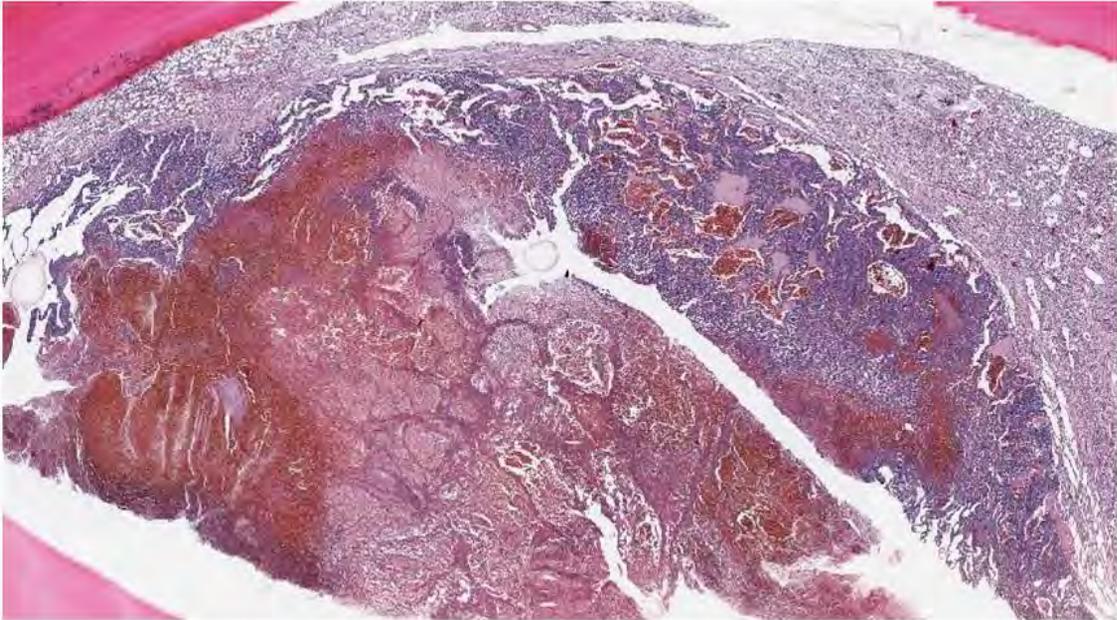
## Background and aim

- mEHT is a relatively new kind of hyperthermia in oncology.
- it is a further development of the conventional heating methods.
- Our objective in this presentation is to summarize our knowledge about the utilization of mEHT therapy from the practical perspective in breast cancer and summarize our experience in our breast cancer patients treated with mEHT.

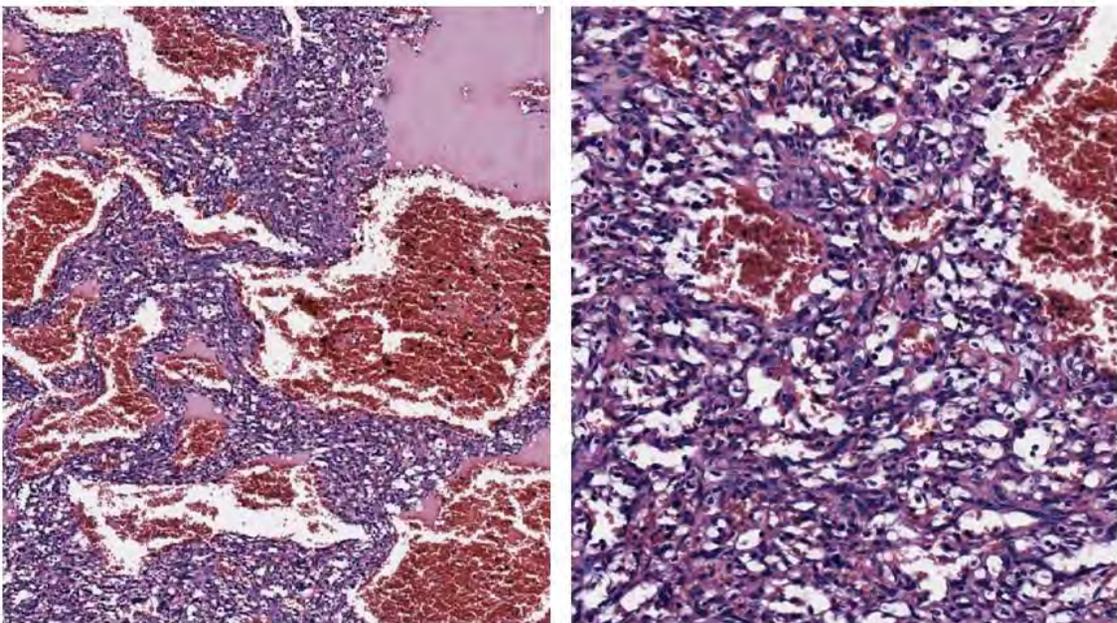
## Patients and methods

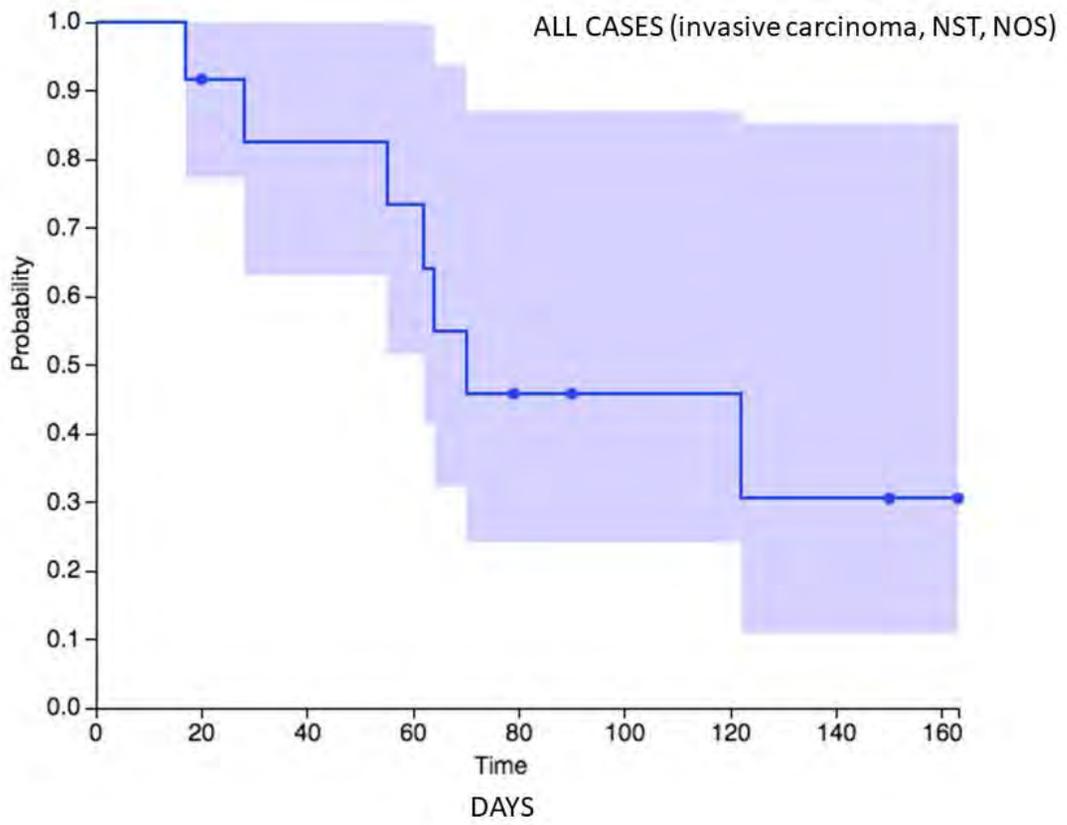
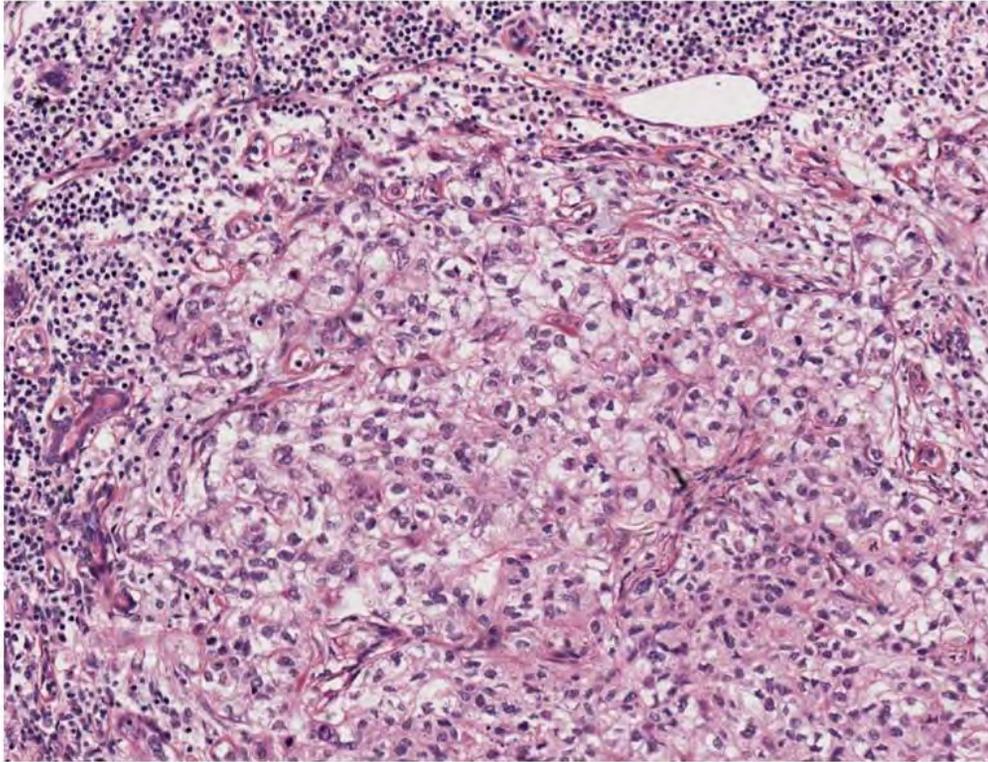
- Thirteen patients with advanced breast cancer
- 12 invasive ductal carcinomas
- 1 postirradiation angiosarcoma
- Pilot study for 20-month period
- instruments EHY-2000 and EHY-2030 (Oncotherm Ltd., Budaörs, Hungary)
- One patient also developed pancreatic cancer, and one patient only attended one session, thus, these were omitted from further analysis.

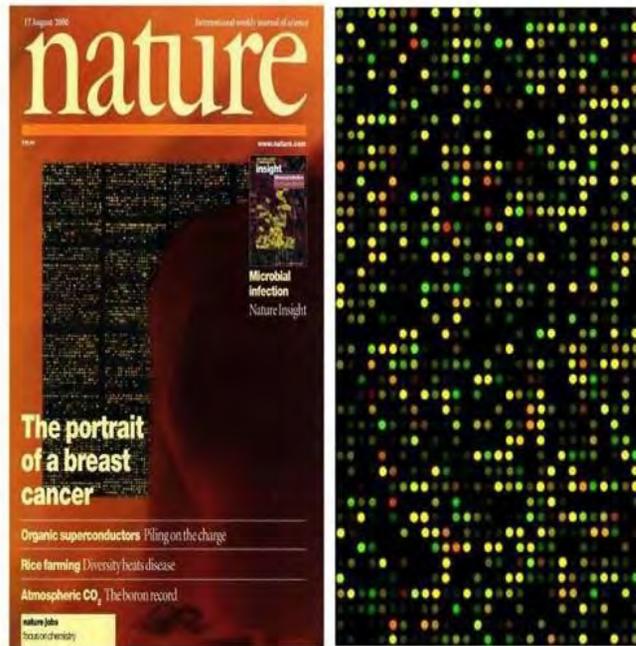
## Postirradiation angiosarcoma



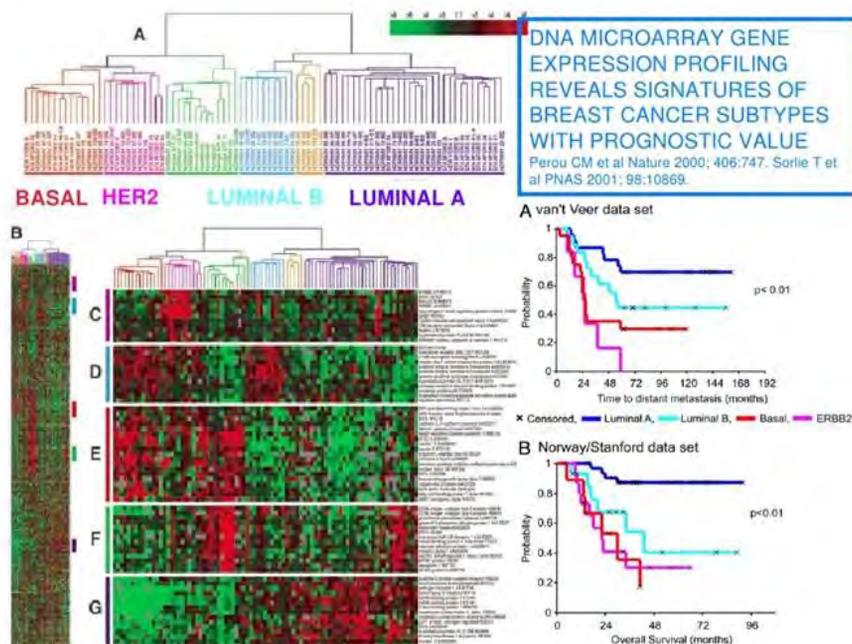
## Postirradiation angiosarcoma





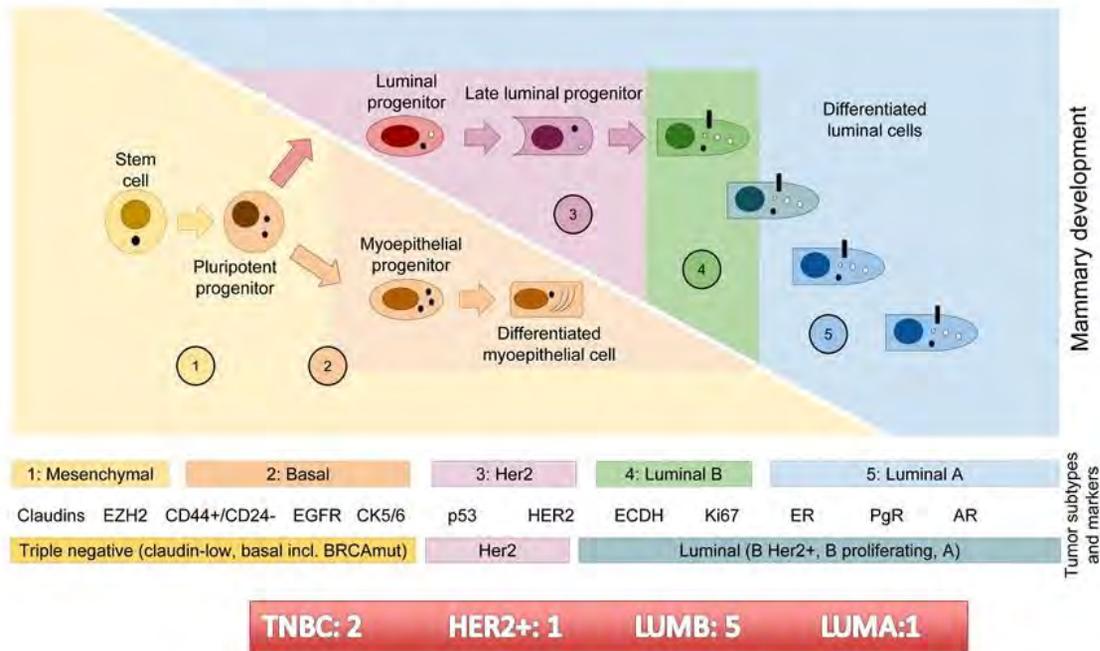


## Breast cancer intrinsic biology and gene/protein expression



Perou, Nature 2000

# Breast cancer intrinsic biology and gene/protein expression

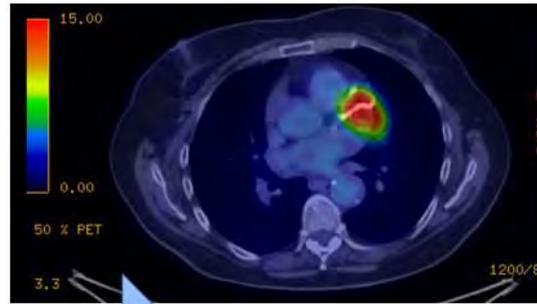
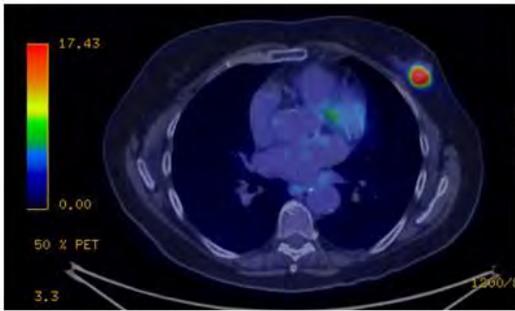
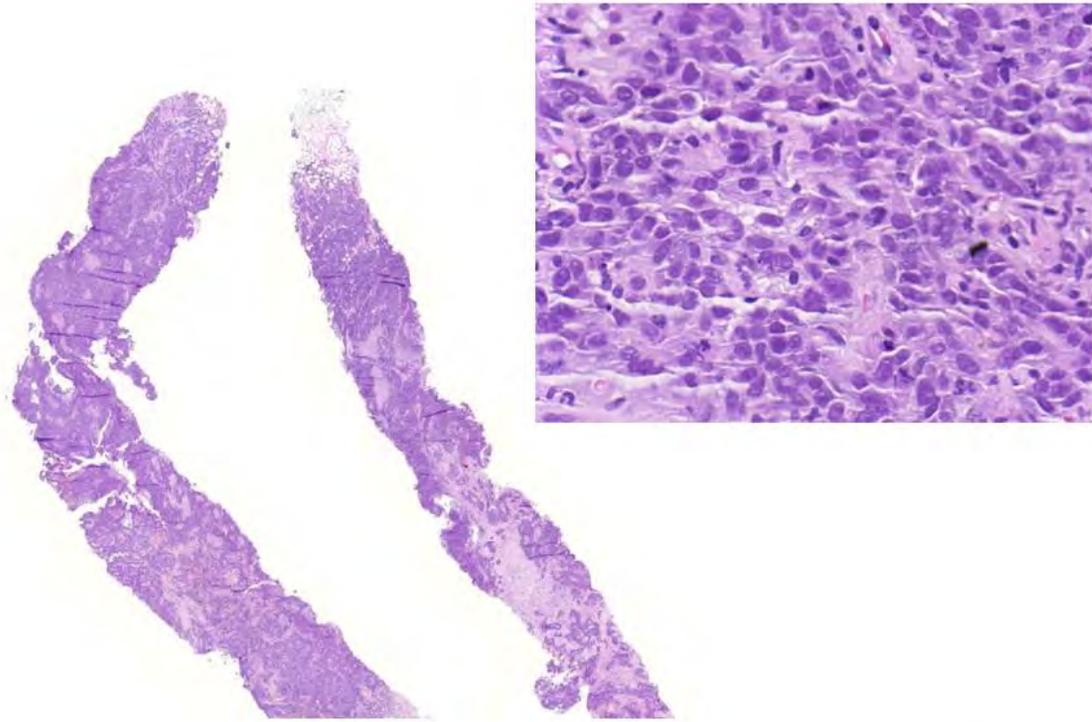


Madaras, Pathobiology 2016

## Results

- Various neoadjuvant and first-line chemotherapeutic protocols were applied, mostly
- platinum and taxane containing regimina,
- but also capecitabine, tegafur, mitomycin C, gemcitabine, lapatinib were administered.
- A two-week break in therapy was necessary in five cases due to local discomfort (2), nausea and weakness (2) and hydrothorax (1).
- Two patients were treated for locally advanced disease in a neoadjuvant fashion.
- The patients with primary systemic therapy continued with surgery and finished treatment.

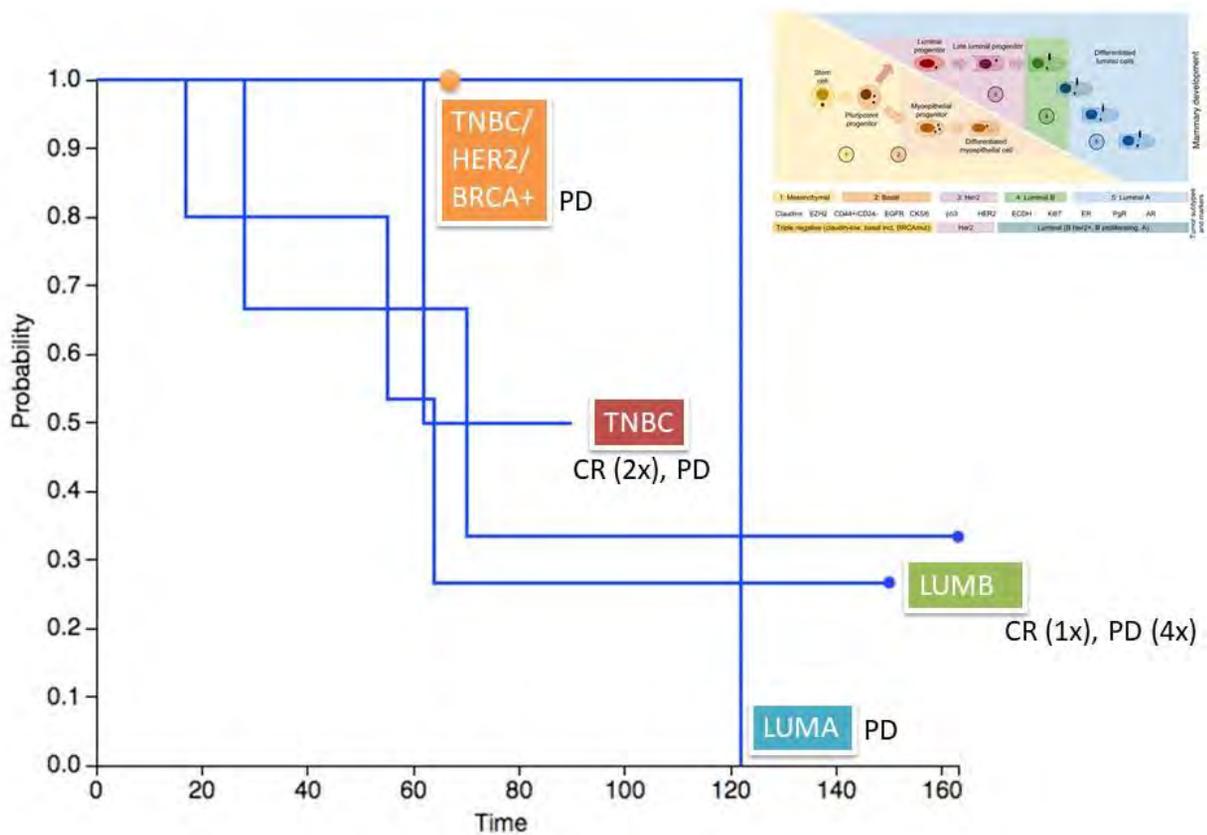
# TNBC, neoadjuvant tx



April --» October







## BRCA case (DOB: 1969)

- **BRCA 1, exon 2, nucleotid 189, insertion 1A → aminoacid 39 STOP codon, ONCOGENIC MUTATION**
- Primary tumor (2014): ER-, PR, HER2-, p53-, Ki67 50% (pT2N1a)
  - TXT-CBP (6x), irradiation
- Supraclavicular metastasis (2015): ER-, PR-, HER2+ by FISH), p53-, KI67 80%
  - AC-trastuzumab (4x)
- Thoracal lesion (2016): ER-,PR-, HER2-, Ki67 60%
  - Lapatinib-capecitabine
- Mediastinal lesion (2017): PET/CT
  - Vinorelbine-mEHT
- Suprarenal and LN metastasis (2018): PET/CT
  - ADM-doxorubicin

## Discussion

- Complementary mEHT treatment of breast cancer patients is feasible and easy to administer.
- Most **durable responses** were seen in skin metastases and/or bone, and decreasing time with lung and liver involvement.
- **Instinsic subtype** reflected by routine immunoprofiling is conserved in mEHY treated breast cancer.
- Most important favoring prognostic factors were lower stage and less number of metastases (oligometastatic status with maximally two distant metastatic sites).
- Younger age was a poor prognostic factor also accompanied with multiorgan metastases (3<).

## Conclusion and directions

- Heterogeneity in the breast cancer population
- Survival improved greatly in the past 20 years
- Tumor biology is reflected
- Patients have more opportunities to get into clinical trials
- Heavily pretreated cases emerge
- Dismal prognosis when recruited to mEHY

surgery

radiation

chemotherapy

hyperthermia



Grant support: NVKP\_16-1-2016-0042

# **Possible potentiation of the abscopal effect of ionising radiation by modulated electro-hyperthermia in locally advanced cervical cancer patients**

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[journal.com/journal/2018/Possible\\_potentiation\\_of\\_the\\_abscopal\\_effect.pdf](http://journal.com/journal/2018/Possible_potentiation_of_the_abscopal_effect.pdf)

# Possible potentiation of the abscopal effect of ionising radiation by modulated electro-hyperthermia in locally advanced cervical cancer patients

Carrie Anne Minnaar<sup>1</sup>, Jeffrey A. Kotzen<sup>2</sup>, Ans Baeyens<sup>3</sup>

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## Introduction

Literature has shown that the local application of ionising radiation is able to induce a response at distant sites of disease. This effect, known as the abscopal effect, is generally accepted to be mediated by the triggering of an immune response by ionising radiation. The application of hyperthermia has also been suggested to enhance the abscopal effect. Our ongoing phase III randomised clinical study investigates the effects of the addition of modulated electro-hyperthermia (mEHT) on chemoradiotherapy in locally advanced cervical patients. We assess the response of the tumour and lymph nodes inside and outside of the radiation treatment field based on PET/CT images and report on the potential abscopal effect mediated by mEHT.

## Methods

Participants enrolled in the study had FIGO stage IIb (distal parametrium involvement) to IIIb (bilateral hydronephrosis excluded) cervical cancer. HIV positive participants were included if their CD4 count was >200cells/mL or they had been on antiretroviral therapy for more than 6 months. Participants were randomised into a mEHT arm or a control arm. All participants were prescribed 50Gy external beam radiation to the pelvis in 25 fractions, plus 3 fractions of 8Gy High Dose Rate (HDR) Brachytherapy. Participants in the mEHT arm were prescribed 2 mEHT treatments per week during external beam radiation using modulated 13.56MHz capacitive heating (55 minutes; 130W). 155 pre-treatment and 155 post-treatment 18F-FDG PET/CT scans were analysed. Each region (head and neck; thorax; abdomen; pelvis) was scored according to the nodes visualised on 18F-FDG PET/CT: no change in the number of visualised nodes; resolution of all nodes; new nodes; no nodes in either pre- or post-treatment scans. Tumour response was reported based on PERCIST version 1.0 criteria.

## Results

56% and 62% of the participants in the mEHT and control arm respectively had nodes with an 18F-FDG Standard Uptake Value of more than 2.5 visualised on PET/CT before treatment. A complete metabolic response of the tumour was significantly higher in the participants in the mEHT group than in the participants in the control group (58% versus 37% respectively). The number of participants with a complete metabolic response of the tumour and extra-pelvic nodes was also significantly higher in the mEHT group versus in the control group (27.7% vs 6.8%; Chi2: p=0.009).

## Conclusion

In our study, the addition of mEHT may be contributing to an enhanced abscopal effect with a significantly higher increase in the complete metabolic response of nodal disease outside of the treated area observed in the mEHT group.



# Possible potentiation of the abscopal effect of ionising radiation by modulated electro- hyperthermia in locally advanced cervical cancer patients

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## Disclosures

The authors are not aware of any circumstances which may lead to a conflict of interest.



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# Introduction

IR can trigger regression of metastases outside of the treated radiation field.

## *Abscopal effect*

- ▶ Believed to be due to a systemic immune reaction towards targeted malignant cells elicited by IR.
- ▶ *IR is able to trigger the immune response towards metastatic disease.*

Only a handful of cases are reported annually in the literature.



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# Introduction

First described in 1979 by Slone *et al.*, who showed that the degree of integrity of the immune system had an effect on the radiosensitivity of the tumour.

In murine fibrosarcoma models, the RT dose needed to control tumour growth in T-cell competent mice was compared to the dose needed to control the tumour growth in T cell-deficient mice.

The average RT dose required was lower and the likelihood of developing metastases was lower in T cell-competent mice.



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# Introduction

Systemic immunotherapies added to RT =

- Increase in the number of abscopal effects

- Increased interest in the field

The abscopal effect has also been described after the application of hyperthermia combined with RT

HT may therefore enhance the abscopal effect...



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# Objective

Ongoing phase III, randomised trial in South Africa investigating the effects of the addition of modulated electro-hyperthermia (mEHT) on chemoradiotherapy in locally advanced cervical patients – with particular interest in HIV-positive patients.

We assess the response of the tumour and lymph nodes inside and outside of the radiation treatment field on PET/CT images and report on the potential abscopal effect mediated by mEHT.



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# Methodology

- ▶ FIGO stage IIb to IIIb cervical cancer
- ▶ HIV-positive and -negative
- ▶ CD4 count >200cells/mL OR on ARVs > 6 months
- ▶ Bilateral hydronephrosis excluded

Randomised: mEHT /Control (stratum: HIV; Age; Stage)

Treatment:

50Gy EBRT (25 fractions) + 3 fractions of 8Gy HDR Brachytherapy  
Cisplatin (planned 2 doses of 80mg/m<sup>2</sup>)

mEHT group received 2 mEHT / week (55 minutes; 130W)

LDC measured at 6 months post treatment using <sup>18</sup>F-FDG PET/CT images.



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# Methodology

155 pre-treatment and matching post-treatment <sup>18</sup>F-FDG PET/CT scans were analysed;

Pre-treatment scans with extra-pelvic nodes were compared to post treatment scans of the same participants.

Each region (head and neck; thorax; abdomen; pelvis) was scored according to the nodes visualised on <sup>18</sup>F-FDG PET/CT:

1. no change in the number of visualised nodes;
2. resolution of all nodes;
3. new nodes;
4. no nodes in either pre- or post-treatment scans.

Tumour response was reported based on PERCIST version 1.0 criteria.



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## Results

54 Participants from each treatment group had nodes visualised on the pre-treatment  $^{18}\text{F}$ -FDG PET/CT scans outside the radiation field.

Of which: 26 of the mEHT Group participants (25%) and 29 of the Control Group participants (28%) had para-aortic nodes.



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## Results

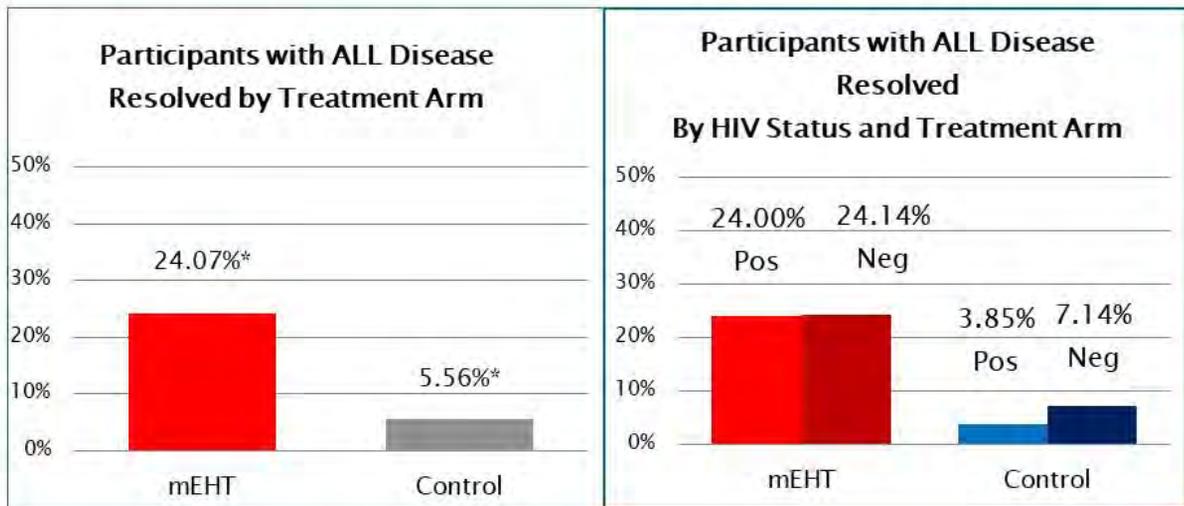
- Complete Metabolic Response of the Tumour:  
58% (mEHT) versus 37% (control)  
*Pearson's Chi2:  $p=0.006$ .*
- Complete Metabolic Response of the Tumour and extra-pelvic nodes:  
28% (mEHT) versus 7% (control)  
*Pearson's Chi2:  $p=0.009$ .*
- Complete Metabolic Response of the Tumour, pelvic and extra-pelvic nodes:  
24.1% (mEHT) versus 5.6% (control)  
*Pearson's Chi2:  $p=0.007$ .*



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# Results



Pearson's Chi2: p=0.007



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# Results

One Participant had neck and thorax nodes, bone, and lung metastases on pre-treatment scan.

- ▶ HIV negative
- ▶ Stage IIIB
- ▶ Age 34 years
- ▶ 2 Chemotherapy doses

*Post treatment scan showed complete response of all disease*



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# Results

## Characteristics of abscopal participants

	<i>n</i>	mEHT		Control
HIV Positive	13		3	
	6	46%	1	33%
0 Cisplatin	1	8%	1	33%
1 Cisplatin	4	31%	0	0%
2 Cisplatin	8	62%	2	67%
Stage IIB	6	46%	2	67%
Stage IIIA	0	0%	0	0%
Stage IIIB	7	54%	1	33%
Min Age	30		28	
Max Age	64		66	
Mean Age	50.4		53.0	



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## Conclusion

In our study, the addition of mEHT may be contributing to an enhanced abscopal effect with a significantly higher increase in the complete metabolic response of nodal disease outside of the treated area observed in the mEHT group.

*A detailed analysis of the results is in process*



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# Discussion

1. Resolution of extra-pelvic nodal disease + pelvic disease = Abscopal effect
2. Significantly higher rate in the mEHT group:  
Abscopal effect potentiated by the addition of mEHT?
3. The addition of immunotherapy drugs to mEHT + RT may potentiate systemic anti-tumour effects of IR
4. Future Research:
  - a) Investigations into biomarkers predicting/indicating the presence of the abscopal effect
  - b) Studies investigating this combination of treatment are warranted.

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# Acknowledgements

- ▶ Trial funded by the South African National Research Foundation (NRF)
- ▶ Device supplied by Oncotherm GmbH
- ▶ <sup>18</sup>F-FDG isotopes supplied at research costs by NTP (Pty)Ltd

Thank you to my colleagues, supervisors and mentors, and to all of the participants without whom this trial would not have been possible.

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# Thank You



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# **Concurrent Chemo-Hyperthermia for recurrent cervix cancer after previous CCRT**

**Sun Young Lee**

Chonbuk National University Hospital  
Department of Radiation Oncology

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

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[www.oncothermia-journal.com/journal/2018/Concurrent\\_chemo\\_hyperthermia.pdf](http://www.oncothermia-journal.com/journal/2018/Concurrent_chemo_hyperthermia.pdf)

# Concurrent Chemo-Hyperthermia for recurrent cervix cancer after previous CCRT

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<sup>2</sup>Division of Hematology/Oncology, Department of Internal Medicine Chonbuk National University Hospital-Chonbuk National University Medical School, Jeonju, Republic of Korea

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## Introduction

Survival in patients with recurrent cervical cancer after irradiation remains very poor. Chemotherapy combined with hyperthermia has been shown to improve the response rate. This study was performed to evaluate the effect of electro-modulated hyperthermia combined with conventional chemotherapy vs. chemotherapy alone on recurrent cervical cancer previously treated with irradiation.

## Methods

Twenty patients were treated with chemotherapy alone, and 18 were treated with chemotherapy combined with electro-modulated hyperthermia. One patient was treated with chemo-radiotherapy as a primary treatment and then relapsed; the tumor was inoperable and radio-refractory after recurrence. Nearby metastases were included, such as metastasis of the para-aortic lymph nodes (PANs) and adjacent pelvic lymph nodes (PLNs), but distant metastases were excluded. Electro-modulated hyperthermia was performed three times per week beginning at chemotherapy initiation; patients underwent a total of 36 sessions.

## Results

The overall response (CR+PR+SD/PD) to treatment was significantly greater in the group of patients who underwent chemotherapy combined with electro-modulated hyperthermia ( $p=0.0461$ ), and at the evaluation conducted at the last follow-up examination, the reaction results were significantly greater in this group ( $p=0.0218$ ). Additionally, severe complications were not reported.

## Conclusion

In this study, for patients with recurring cervical cancer previously treated with irradiation, the overall response rate for patients treated with chemotherapy combined with electro-modulated hyperthermia was significantly greater than that for the group of patients who were treated with chemotherapy alone.

**Keywords:** concurrent chemo-modulated electro-hyperthermia, chemotherapy alone, recurrent cervix cancer, treatment outcome

# Concurrent Chemo–Hyperthermia for recurrent cervix cancer after previous CCRT

Chonbuk National University Hospital  
Department of Radiation Oncology

Sun Young Lee

 대한민국 의료의 또 하나의 중심

## Introduction

Survival in patients with recurrent cervix cancer in previously irradiation remains very poor. Chemotherapy combined hyperthermia has been shown to improve response rate, occasionally.

This study is devoted to evaluate the effect of electro–modulated hyperthermia with conventional chemotherapies on recurrent cervical cancer previously irradiation; analyzing of chemotherapy alone vs chemotherapy combined electro–modulated hyperthermia.

## Materials and Methods

### Materials

#### Inclusion Indications

1. para-aortic lymph node alone or pelvic lymph node and or cervix bed recurrent.
2. No distance metastasis (exclude PAN).
3. Not possible radiotherapy
  - because previous RT field recurrent.
4. above 6 months follow up periods

## Materials and Methods

### Materials

Chemotherapy alone (n=20)

Chemotherapy combined hyperthermia (n=18)

Age(year)	CTx	CTx + HT
Range	36~71	36~71
Mean	53	50.8
FIGO stage	CTx	CTx + HT
Ib	2	3
IIa	3	3
IIb	3	3
IIIa	5	2
IIIb	4	4
IVb	3	3

## Materials and Methods

### Materials

Pathology	CTx	CTx+HT
Squamous cell carcinoma	15	15
adenocarcinoma	5	3

## Materials and Methods

### Materials

### Recurrent lesions

Recurrent lesions	CTx	CTx + HT
Cervix bed alone	4	6
PAN alone	4	4
Iliac LN alone	4	5
Iliac LN+cervix bed	8	3

## Materials and Methods

### Materials

#### Chemotherapy agents

Agent	CTx		CTx+HT	
	1st	2nd	1st	2nd
Cisplatin	12	0	11	2
Cisplatin+5-FU	1	6	1	6
Cisplatin+adriamycin	3	0	3	0
Cisplatin+paclitaxel	4	8	0	6
Cisplatin+paclitaxel	0	6	0	4

## Materials and Methods

### Materials

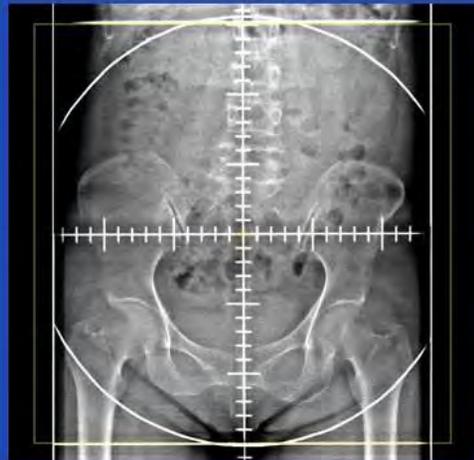
#### Chemotherapy cycles

Chemotherapy cycles	CTx		CTx+HT	
	1st	2nd	1st	2nd
3	0	0	0	1
4	0	3	0	3
5	1	4	1	3
6	15	11	14	10
7	0	1	0	0
9	4	1	3	1

## Materials and Methods

### Methods (Hyperthermia)

1. All patients performed 2-dimensional simulation. → Treatment field encompassed the mass over 3 cm margin from X, Y, Z dimension.



## Materials and Methods

### Methods (Hyperthermia)

2. The hyperthermia was performed for 60 min.

3. The hyperthermia was performed three times a week, starting at the same time as chemotherapy and performed 36 sessions.

## Materials and Methods

### Methods (Hyperthermia)

4. The power output was 80 W for the first 10 min, 120 W over the next 10 min and 150 W for the remaining treatment time.

5. The body and skin temperature, blood pressure, and pulse rate of each subject were measured before, during and after the experiment.

## Materials and Methods

### Methods (Hyperthermia)

6. Body temperature was measured using an infrared ear thermometer (Infrared Thermometer IRT 4020, Braun, Germany), and temperature of the abdominal skin surface below the circular upper electrode probe was measured using a non-contact infrared thermometer transmitter (Thermo Checker DT-060, Easytem, Republic of Korea).

## Materials and Methods

### Statistics

The time to event variable was estimated using Kaplan–Meier analysis.

P-values less than 0.05 were considered significant.

Statistical analysis was conducted using SAS software (version 9.3, SAS Institute Inc., Cary, NC, USA).

## Results

### Response Rate

#### Follow up periods

Periods (month)	CTx	CTx+HT
Range	7~21	7~28
Mean	11	13.5

The overall response rate (CR+PR+SD/PD) to treatment

	Complete remission	Partial response	Stable disease	Progressive disease	P-value
chemotherapy alone (n=20)	4	3	1	12	0.0461
chemotherapy combined hyperthermia (n=18)	9	2	2	5	

## Results

### Response Rate

The last follow up response rate (CR+PR+SD/PD) to treatment

	Complete remission	Partial response	Stable disease	Progressive disease	P-value
chemotherapy alone (n=20)	3	3	1	13	0.0218
chemotherapy combined hyperthermia (n=18)	9	2	2	5	

## Results

### Chemotherapy alone

only to recur when the cervix bed is therapeutic response was statistically significant (p=0.0456)

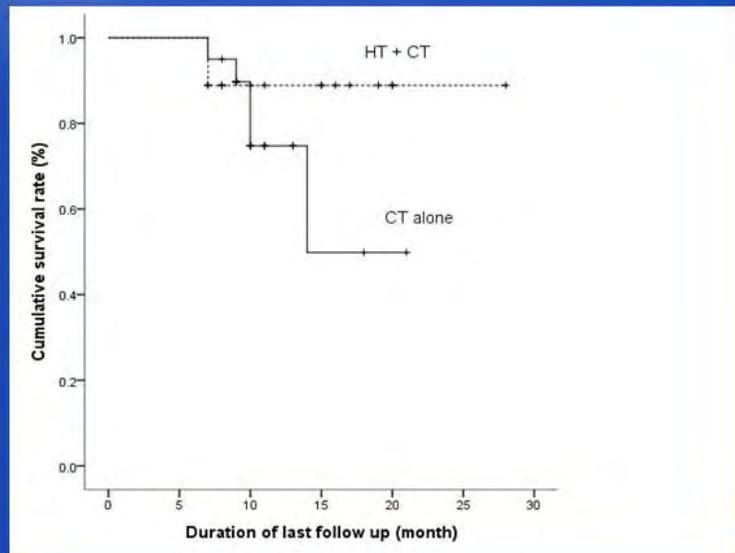
### Chemotherapy combined hyperthermia

not observed any significant differences in abdominal lymph nodes and cervix bed recurrence (0.6199)

## Results

Overall survival Kaplan–Meier plot

Chemotherapy combined hyperthermia was not significantly increased overall survival ( $p=0.235$ ).



## Results

Body temperature

before : 36.4~36.9°C (mean 36.5 °C)

after : 36.9~38.2 °C (mean 37.6 °C)

Abdominal skin temperature

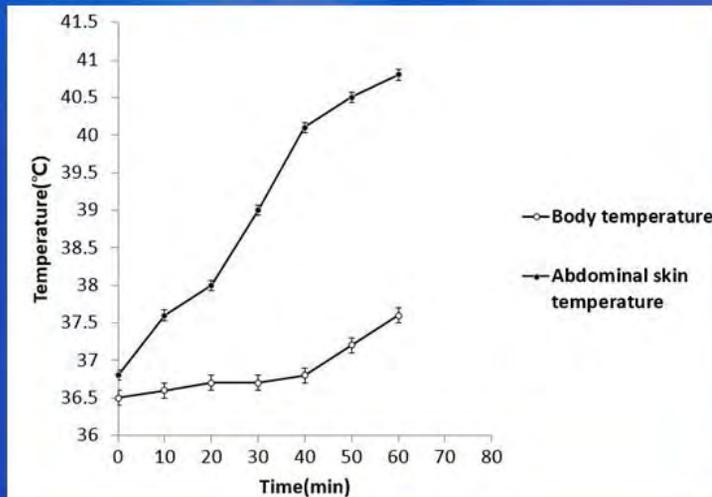
before: 36.4~37.3 °C (mean 36.8 °C)

after: 39.8 ~41.9 °C (mean 40.8 °C)

## Results

Body temperature

Abdominal skin temperature



## Results

Pathological characteristics

chemotherapeutic regimens, cycles, dosages  
age

There were no statistically significant difference  
at treatment response.

## Results

### Complications

Chemotherapy alone : nausea, vomiting, pancytopenia, and peripheral neuropathy

Chemotherapy combined hyperthermia : hot-sensation and abdominal discomfort at 8/18 (44%) patients, no other side effects (burn or blisters) were observed

## Conclusion

In this study, the overall response rate (CR+PR+SD/PD) to treatment was significantly greater in the group of patients who underwent chemotherapy combined with electro-modulated hyperthermia ( $p = 0.0461$ ).

For the evaluation conducted at the last follow-up examination, the results were significantly greater in the group who underwent chemotherapy combined with electro-modulated hyperthermia ( $p = 0.0218$ ).

## Conclusion

Specifically, in the case of chemotherapy alone, significant recurrence was observed only when the cervix was the target of the therapeutic response ( $p = 0.0456$ ), but in the chemotherapy combined with electro-modulated hyperthermia group, no significant differences in abdominal lymph node and cervical recurrence were observed ( $p = 0.6199$ ).

Hyperthermia may be slightly more effective for the treatment of abdominal lymph node metastasis.

## Conclusion

This study clearly demonstrates the feasibility and advantages of chemotherapy combined with hyperthermia, concurrent with the application of platinum derivatives, for recurrent cervical cancer patients who specifically have regional lymph node metastasis.

Additionally, longer-term follow-up is needed to compare the disease-free survival rates of patients.

*Thanks for attention!*

# **Hyperthermia in the treatment of soft tissue sarcoma: state of the art**

**Sergey Roussakow**  
Galenic Research Institute  
Moscow, Russia

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

Roussakow S. (2018): Hyperthermia in the treatment of soft tissue sarcoma: state of the art; *Oncothermia Journal* 24:148-195

[www.oncothermia-journal.com/journal/2018/Hyperthermia\\_in\\_the\\_treatment.pdf](http://www.oncothermia-journal.com/journal/2018/Hyperthermia_in_the_treatment.pdf)

# Hyperthermia in the treatment of soft tissue sarcoma: state of the art

**Sergey V. Roussakow, MD, PhD**

Galenic Research Institute, 127051, Moscow, Russian Federation

## **Background**

Soft tissue sarcomas (STS) is a heterogeneous group of mesenchymal tumours accounting less than 1% of solid tumours in adults. Preparing a randomized trial (RCT) on the modulated electro-hyperthermia (mEHT) in the treatment of STS, we have performed a systematic review (SR) of conventional hyperthermia (HT) and mEHT in the treatment of STS.

## **Methods**

The SR was performed according to PRISMA statement with qualitative and semi-quantitative analysis of the results and comprehensive bias analysis

## **Results**

A level 1 evidence on HT in STS is scarce. Actually, it is limited to phase III RCT of RTOG/ESHO of 2010, where regional HT combined with chemotherapy (ChT) was studied versus the ChT alone. The bias analysis shows that the trial is severely biased, including performance bias (the control group is undertreated; infringement of inclusion criteria by inclusion of unmeasurable tumours); information bias (exclusion of unmeasurable tumours (34.6% of the sample) from assessment of primary endpoints, so that these endpoints refer to a subgroup with measurable tumors and are not a valid result of the RCT); statistical bias (informative censoring); selection bias; and reporting bias, since these flaws were concealed and the study was presented as unequivocally successful. Thus, the study is corrupted and not subject to evaluation. Actually, the available evidence did not show an advantage of HT in the treatment of STS. mEHT as a new evolving type of HT is still doesn't have level I evidence. Its evidence is limited to a single phase II study, multiple case reports and a case series. Nevertheless, the promising results of these level II-IV evidence are sufficient for initiation of RCT.

## **Conclusion**

This SR hasn't confirmed an efficacy of conventional HT in the treatment of STS. mEHT shows a potential of an effective co-treatment of STS that requires a confirmation in RCT.

This work was supported by the Hungarian Competitiveness and Excellence Programme grant (NVKP 16-1-2016-0042)

# HYPERTHERMIA IN THE TREATMENT OF SOFT TISSUE SARCOMA: STATE OF THE ART

SERGEY ROUSSAKOW, MD, PHD  
GALENIC RESEARCH INSTITUTE  
MOSCOW, RUSSIA

36<sup>TH</sup> INTERNATIONAL CLINICAL HYPERTHERMIA SOCIETY  
SEPTEMBER 28TH-29TH 2018 BUDAPEST, HUNGARY

## THE TYPICAL DELUSION OF HYPERTHERMIA BELIEVERS

“Hyperthermia, i.e. heating of tumors to temperatures of 41-45°C for 1h, is a proven radiosensitizer and chemosensitizer.”

*Kok HP, Crezee J. A comparison of the heating characteristics of capacitive and radiative superficial hyperthermia. Int J Hyperthermia. 2017 Jan 8:1-9.*

**FALSE**

# THE TYPICAL DELUSION OF

Conference Papers in Science

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- About this Journal
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Conference Papers in Medicine  
Volume 2013, Article ID 428027, 40 pages  
<http://dx.doi.org/10.1155/2013/428027>

**Conference Paper**  
**The History of Hyperthermia Rise and Decline**  
Sergey Roussakow  
Galenic Research Institute, Moscow, Russia  
Received 13 February 2013; Accepted 17 April 2013  
Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz  
This Conference Paper is based on a presentation given by Sergey Roussakow at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.  
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# THE TYPICAL DELUSION OF

Conference Papers in Science

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Conference Papers in Medicine  
Volume 2013, Article ID 412186, 31 pages  
<http://dx.doi.org/10.1155/2013/412186>

**Conference Paper**  
**Critical Analysis of Electromagnetic Hyperthermia Randomized Trials: Dubious Effect and Multiple Biases**  
Sergey Roussakow  
Galenic Research Institute, Moscow, Russia  
Received 20 January 2013; Accepted 18 April 2013  
Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz  
This Conference Paper is based on a presentation given by Sergey Roussakow at

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- Citations to this Article
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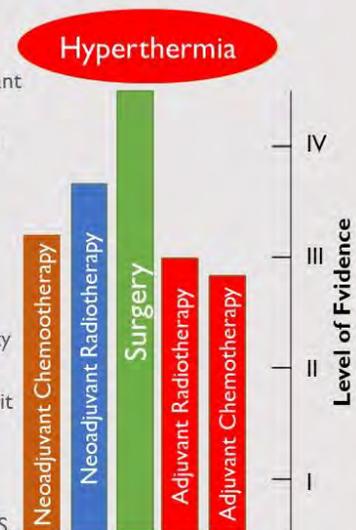
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Citations	2
ePub	23

# STUDY QUESTION

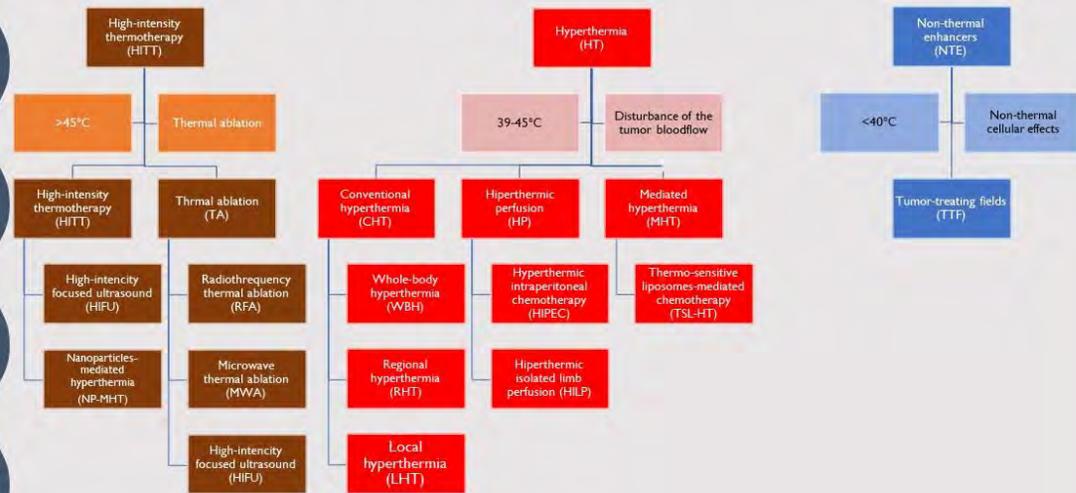
Is hyperthermia *per se* effective in the treatment of soft-tissue sarcoma?

## HYPERTHERMIA IN SOFT-TISSUE SARCOMA: THE PROBLEM

- Soft tissue sarcoma is a rare tumor that accounts for less than 1% of all malignant tumors,
- Nevertheless, these tumors are very polymorphic, show aggressive growth and resistance to treatment, and lead to high level of disability due to amputation.
- Radical surgery is the standard treatment of STS.
- Efficacy of neoadjuvant and adjuvant treatment is still controversial since randomized trials mainly failed to show their significant advantage.
- There is a consensus that neoadjuvant radiotherapy is rather beneficial.
- The benefit of neoadjuvant chemotherapy is marginal. Nevertheless, the majority of experts consider it justified.
- The benefit of adjuvant treatment is doubtful. The majority of experts consider it unjustified.
- Any method enhancing the efficacy of the available treatments gains attention.
- Hyperthermia which is considered to be an enhancer of chemotherapy and radiotherapy has an extensive and long-term application in the treatment of STS.



# HYPERTHERMIA: THE SUBJECT



## METHOD

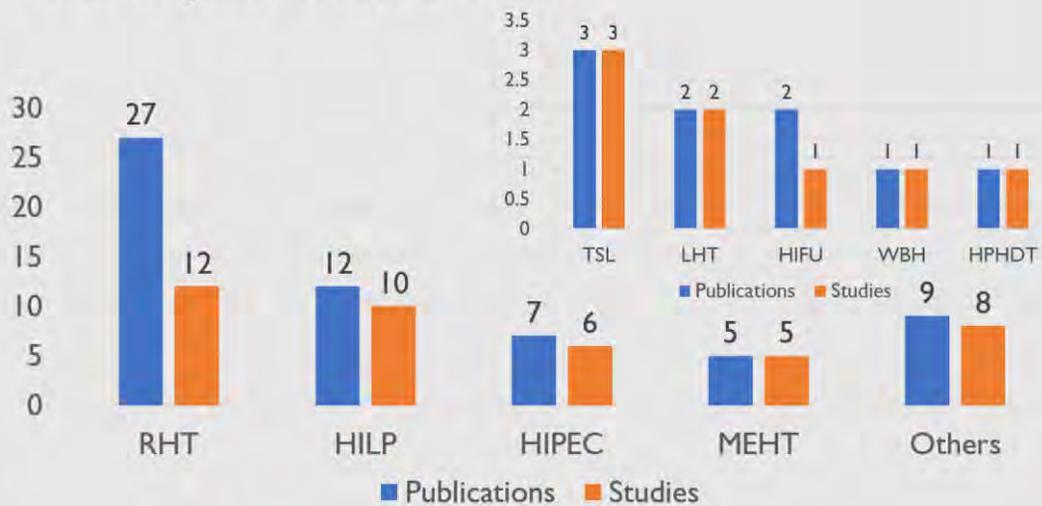
- Systematic review of hyperthermia evidence at soft-tissue sarcoma.
- Literature search based on PRISMA statement:
  - Pubmed
  - Since 2010
- Comprehensive bias analysis.
- Translation.
- Estimation of level of evidence.
- Synthesis of evidence.

# EVIDENCE LEVELS (CEBM-WCF)

WCF	
	Level
Convincing	I
Probable	II
Possible	III
Insufficient	IV

# LITERATURE SEARCH RESULTS

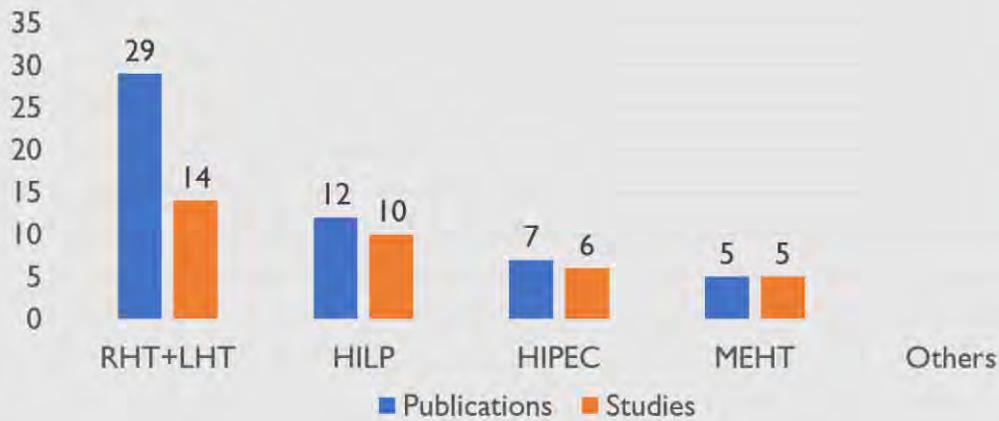
Found: 60 publications; 42 studies.



# LITERATURE SEARCH RESULTS

Found: 60 publications; 42 studies.

Included: 52 publications; 36 studies.



## REGIONAL HYPERTHERMIA EVIDENCE IN SOFT-TISSUE SARCOMA

No	Study name	Country	Type	NOP
1	Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study	International	Phase III RCT	341
2	Effect of concurrent chemotherapy and hyperthermia on outcome of preoperative radiotherapy of high-risk soft tissue sarcomas	Germany	Retrospective	28
3	Reirradiation and hyperthermia for radiation-associated sarcoma	Netherlands	Retrospective	16
4	Concomitant trimodality therapy of re-irradiation, chemotherapy and regional hyperthermia for a pretreated inoperable sarcoma recurrence	Germany	Case report	1
5	Preoperative evaluation of the efficacy of radio-hyperthermo-chemotherapy for soft tissue sarcoma in Japan: a case series	Japan	Case series	20
6	Clinical outcomes of radio-hyperthermo-chemotherapy for soft tissue sarcoma compared to a soft tissue sarcoma registry in Japan: a retrospective matched-pair cohort study	Japan	Retrospective analysis.	60
7	Radiotherapy and hyperthermia with curative intent in recurrent high risk soft tissue sarcomas	Germany	Cohort	42
8	[A case of synovial sarcoma of the mediastinum]	Japan	Case report	1
9	Palliation of recurrent myxofibrosarcoma with radiotherapy and hyperthermia	Japan	Case report	1
10	Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall	Netherlands	Retrospective	23
11	Complete pathological response to neoadjuvant pemetrexed/cisplatin in combination with regional hyperthermia in a patient with sarcomatoid peritoneal mesothelioma	Germany	Case report	1
12	Salvage method for unplanned excision of soft tissue sarcoma: long-term results of second-look surgery following radio-hyperthermo-chemotherapy	Japan	Retrospective	6
13	PET response criteria in solid tumors predicts progression-free survival and time to local or distant progression after chemotherapy with regional hyperthermia for soft-tissue sarcoma	Germany	Cohort	73
14	Enhanced tumour regression in a patient of liposarcoma treated with radiotherapy and hyperthermia: Hint for dynamic immunomodulation by hyperthermia	Switzerland	Case report	1

## REGIONAL HYPERTHERMIA EVIDENCE IN SOFT-TISSUE SARCOMA

No	Study name	Country	Type	NOP	Effect	LOE
1	Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study	International	Phase III RCT	341	NEG	I
2	Effect of concurrent chemotherapy and hyperthermia on outcome of preoperative radiotherapy of high-risk soft tissue sarcomas	Germany	Retrospective	28	Pos	IV
3	Reirradiation and hyperthermia for radiation-associated sarcoma	Netherlands	Retrospective	16	Pos	IV
4	Concomitant trimodality therapy of re-irradiation, chemotherapy and regional hyperthermia for a pretreated inoperable sarcoma recurrence	Germany	Case-report	1	Pos	IV
5	Preoperative evaluation of the efficacy of radio-hyperthermo-chemotherapy for soft-tissue sarcoma in a case series	Japan	Case-series	20	Neg	IV
6	Clinical outcomes of radio-hyperthermo-chemotherapy for soft tissue sarcoma compared to a soft-tissue sarcoma registry in Japan: a retrospective matched-pair cohort study	Japan	Retrospective analysis	60	Neg	IV
7	Radiotherapy and hyperthermia with curative intent in recurrent high risk soft-tissue sarcomas	Germany	Cohort	42	Pos	IV
8	[A case of synovial sarcoma of the mediastinum]	Japan	Case-report	1	Neg	IV
9	Palliation of recurrent myxofibrosarcoma with radiotherapy and hyperthermia	Japan	Case-report	1	Pos	IV
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13	PET response criteria in solid tumors predicts progression-free survival and time to local or distant progression after chemotherapy with regional hyperthermia for soft-tissue sarcoma	Germany	Cohort	73	NA	IV
14	Enhanced tumour regression in a patient of liposarcoma treated with radiotherapy and hyperthermia: Hint for dynamic immunomodulation by hyperthermia	Switzerland	Case-report	1	Pos	IV

## NEO-ADJUVANT CHEMOTHERAPY ALONE OR WITH REGIONAL HYPERTHERMIA FOR LOCALISED HIGH-RISK SOFT-TISSUE SARCOMA: A RANDOMISED PHASE 3 MULTICENTRE STUDY

- Type: Phase III Randomized Controlled Trial.
- Institutions: 9 leading cancer centers from Europe and USA, EORTC, ESHO
- Number of patients: 341.
- Design: Efficacy of Thermo-Chemotherapy (TCT) vs. Chemotherapy (CT) in the complex treatment of high-risk soft-tissue sarcoma (341 patients):  
Neoadjuvant TCT/CT => Neoadjuvant RT => Definitive Surgery => Adjuvant TCT/CT
- Result: **NEGATIVE** – no advantage in overall survival, local progression-free survival and progression-free survival.
- Level of evidence: I (convincing evidence).

## Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study

Rolf D Issels\*, Lars H Lindner\*, Jaap Verweij, Peter Wust, Peter Reichardt, Baard-Christian Schem, Sultan Abdel-Rahman, Soeren Daugaard, Christoph Salat, Clemens-Martin Wendtner, Zeljko Vujaskovic, Rüdiger Wessalowski, Karl-Walter Jauch, Hans Roland Dürr, Ferdinand Ploner, Andrea Baur-Melnyk, Ulrich Mansmann, Wolfgang Hiddemann, Jean-Yves Blay, Peter Hohenberger, for the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG) and the European Society for Hyperthermic Oncology (ESHO)

### Summary

**Background** The optimum treatment for high-risk soft-tissue sarcoma (STS) in adults is unclear. Regional hyperthermia concentrates the action of chemotherapy within the heated tumour region. Phase 2 studies have shown that chemotherapy with regional hyperthermia improves local control compared with chemotherapy alone. We designed a parallel-group randomised controlled trial to assess the safety and efficacy of regional hyperthermia with chemotherapy.

**Methods** Patients were recruited to the trial between July 21, 1997, and November 30, 2006, at nine centres in Europe and North America. Patients with localised high-risk STS ( $\geq 5$  cm, Fédération Nationale des Centres de Lutte Contre le Cancer [FNCLCC] grade 2 or 3, deep to the fascia) were randomly assigned to receive either neo-adjuvant chemotherapy consisting of etoposide, ifosfamide, and doxorubicin (EIA) alone, or combined with regional hyperthermia (EIA plus regional hyperthermia) in addition to local therapy. Local progression-free survival (LPFS) was the primary endpoint. Efficacy analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT 00003052.

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### REPORTED RESULTS

- ▶ Significantly better 4-year LPFS ( $p = 0.003$ ) and DFS ( $p = 0.011$ ) in the thermochemotherapy group.
- ▶ No effect to OS ( $p = 0.43$ )

**JAMA Oncology** | Original Investigation

### Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma: The EORTC 62961-ESHO 95 Randomized Clinical Trial

**IMPORTANCE** Patients with soft tissue sarcoma are at risk for local recurrence and distant metastases despite optimal local treatment. Preoperative anthracycline plus fluorouracil chemotherapy improves outcome in common histological subtypes.

**OBJECTIVE** To analyze whether the previously reported improvement in local progression-free survival by adding regional hyperthermia to neoadjuvant chemotherapy translates into improved survival.

**DESIGN, SETTING, AND PARTICIPANTS** Open-label, phase 3 randomized clinical trial to evaluate the efficacy and toxic effects of neoadjuvant chemotherapy plus regional hyperthermia. Adult patients (age  $\geq 18$  years) with localized soft tissue sarcoma (tumor  $\geq 5$  cm, French Federation Nationale des Centres de Lutte contre le Cancer [FNCLCC] grade 2 or 3, deep) were accrued across 9 centers (6, Germany; 1, Norway; 1, Austria; 1, United States) from July 1997 to November 2006. Follow-up ended December 2014.

**INTERVENTIONS** After stratification for tumor presentation and site, patients were randomly assigned to either neoadjuvant chemotherapy consisting of doxorubicin, ifosfamide, and etoposide alone, or combined with regional hyperthermia.

**MAIN RESULTS AND MEASUREMENTS** The primary end point was local progression-free survival. Secondary end points included treatment safety and survival, with survival defined from date of randomization to death due to disease or treatment. Patients lost to follow-up were censored at the date of their last follow-up.

**RESULTS** A total of 341 patients were randomized, and 329 (median [range] age, 51 [18-70] years; 147 women, 82 men) were eligible for the intention-to-treat analysis. By December 2014, 220 patients (67%, 95% CI, 62%-72%) had experienced disease relapse, and 188 (57%, 95% CI, 52%-62%) had died. Median follow-up was 11.3 years. Compared with neoadjuvant chemotherapy alone, adding regional hyperthermia improved local progression-free survival (hazard ratio [HR], 0.65; 95% CI, 0.49-0.86,  $P = .002$ ). Patients randomized to chemotherapy plus hyperthermia had prolonged survival rates compared with those randomized to neoadjuvant chemotherapy alone (HR, 0.73; 95% CI, 0.54-0.98,  $P = .04$ ) with 5-year survival of 63.7% (95% CI, 55.2%-70.7%) vs 51.3% (95% CI, 43.7%-59.0%), respectively, and 10-year survival of 52.6% (95% CI, 44.7%-60.6%) vs 42.7% (95% CI, 35.0%-50.4%).

**CONCLUSIONS AND RELEVANCE** Among patients with localized high-risk soft tissue sarcoma, the addition of regional hyperthermia to neoadjuvant chemotherapy resulted in increased survival, as well as local progression-free survival. For patients who are candidates for neoadjuvant treatment, adding regional hyperthermia may be warranted.

**TRIAL REGISTRATION** clinicaltrials.gov Identifier: NCT00003092

JAMA Oncol. doi:10.1001/jamaoncol.2018.4996  
Published online February 15, 2018.

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**JAMA Oncology** | Original Investigation

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JAMA Oncol. doi:10.1001/jamaoncol.2018.4996  
Published online February 15, 2018.

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**REPORTED RESULTS**

Significantly better survival ( $p = 0.04$ )

**ROUSSAKOW S.  
NEO-ADJUVANT  
CHEMOTHERAPY ALONE  
OR WITH REGIONAL  
HYPERTHERMIA FOR  
LOCALIZED HIGH-RISK  
SOFT-TISSUE SARCOMA.  
LANCET ONCOL. VOL. 18,  
OCTOBER 2017.**

Diagnosis, Analysis and Interpretation  
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Correspondence

**Neo-adjuvant  
chemotherapy alone or  
with regional  
hyperthermia for  
soft-tissue sarcoma**

A randomised, controlled, phase 3 trial by Ruff, Baskin and colleagues on neo-adjuvant chemotherapy alone or with regional hyperthermia for localized, high-risk, soft-tissue sarcoma published in 2010 in *The Lancet Oncology* is currently the only trial to evidence in favour of regional hyperthermia for the treatment of soft-tissue sarcoma. I believe a bias is present in this analysis because the combined treatment group received more chemotherapy than the chemotherapy alone group (median 9.0 cycles vs 5.0 cycles). Transformation of the median into means by the Hozo algorithm returns the mean values of 6.0 (SD 2.6) for the combined treatment group versus 4.5 (2.3) for the chemotherapy alone group with a relative increase of 1.33 (95% CI 1.20-1.45;  $p=0.0001$ ) in the combination treatment group, with a power of 95%. There was also a significant difference between the groups in post-adjuvant treatment (53% for the combined treatment group vs 41% for the chemotherapy alone group who completed chemotherapy;  $p=0.027$ ). Therefore, one cannot conclude that chemotherapy plus hyperthermia is superior to chemotherapy alone, because the difference in chemotherapy received obfuscates the effect of the addition of hyperthermia.

Moreover, I believe there is also information bias, because the reported advantage of chemotherapy plus hyperthermia versus chemotherapy alone regarding the endpoints of tumour response, local progression-free survival, and disease-free survival is based on the analysis of a subgroup of measurable

tumours ( $n=244$  [22%]) but not the total randomised sample ( $n=311$ ). 118 (38%) patients were excluded from evaluation of the primary endpoint (local progression-free survival), including 21 patients with measurable tumours, because the number of patients with a complete or partial response was different between the groups (14 in the combined treatment group vs 16 in the chemotherapy alone group), the progression-free survival difference is unreliable. Additionally, the external validation of tumour response did not include the possibility of misclassification, because it was applied only to patients who were locally assessed as responders. The validity of the trial is arguable since its overall results are substantially worse than those reported by the Sarcoma Meta-analysis Collaboration.<sup>1</sup> Because I believe that these potential biases are concealed by understatement, I am concerned about the results of this trial highlighting these issues to prevent the ongoing misinterpretation of this trial and to avoid unproven treatments being used in clinical practice.

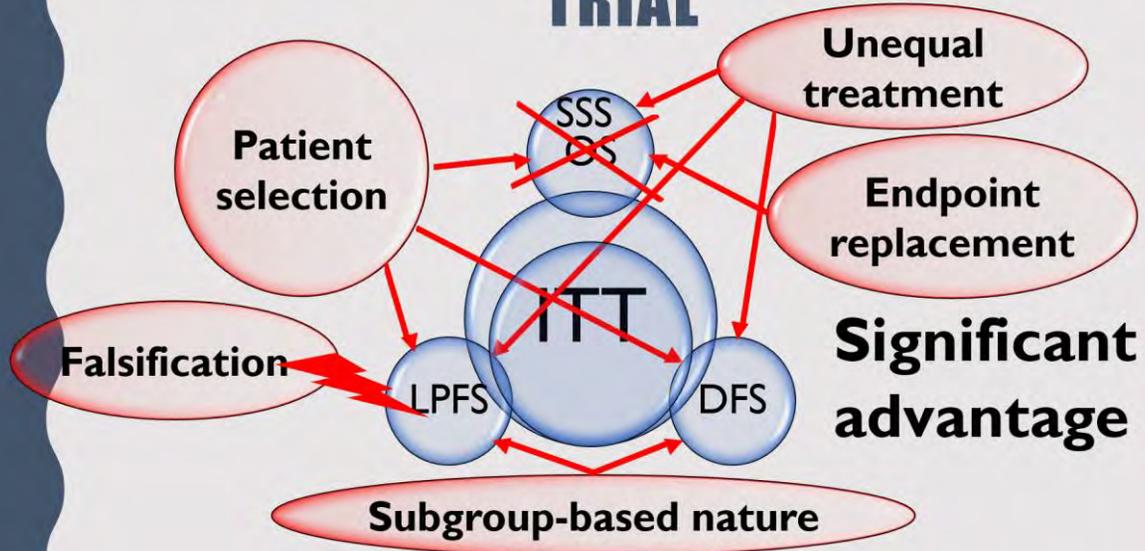
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1 Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for localized resectable soft-tissue sarcoma of adults: meta-analysis of randomised trials. *Lancet Oncol* 2002; 3: 1120-30.  
2 Hozo SP, Sijda D, Djavlikhanov S, Vatanaditkul W. Meta-analysis of survival in randomized trials. *Stat Med* 2005; 24: 1595-610.  
3 Sarcoma Meta-analysis Collaboration. Adjuvant chemotherapy for the treatment of resectable soft-tissue sarcoma of adults: meta-analysis of randomised trials. *Lancet Oncol* 2002; 3: 1120-30.

**ROUSSAKOW S.  
"EFFECT OF  
NEOADJUVANT  
CHEMOTHERAPY PLUS  
REGIONAL  
HYPERTHERMIA ON  
LONG-TERM OUTCOMES  
AMONG PATIENTS WITH  
LOCALIZED HIGH-RISK  
SOFT TISSUE  
SARCOMA:" A CRITICAL  
BIAS AND NO  
ADVANTAGE OF  
HYPERTHERMIA.  
JAMA ONCOLOGY 2018  
(SUBMITTED)**

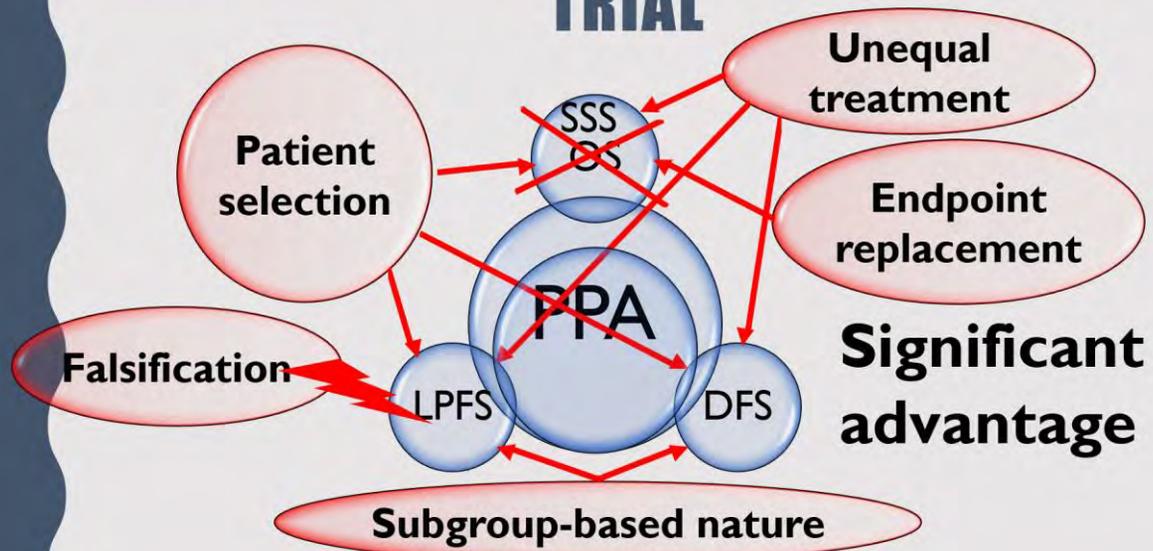
Dear Editor,

The report of Issels et al on long-term survival in the randomized clinical trial of regional hyperthermia (RHT) plus neoadjuvant chemotherapy vs neoadjuvant chemotherapy alone in the complex treatment of soft-tissue sarcoma is misleading. This is a post-hoc analysis of the initial study results that did not show an advantage of RHT in overall survival (OS, hazard ratio [HR] 0.88, 95% CI 0.64-1.21;  $P=0.43$ ). The authors reported the result of a competing risks analysis that found that the specific risk of death from sarcoma was significantly lower after RHT (HR 0.73, 95% CI 0.54-0.98;  $P=0.042$ ), though the reported number of not sarcoma-related deaths suggests that this risk was significantly higher after RHT (15 vs. 6 deaths, odds ratio 2.76, 95% CI 1.04-7.29;  $p=0.035-0.041$  by two-tailed chi-square test), so in general there is no gain. Instead of appropriately reporting the result of this secondary analysis, the authors presented it as the initial result of the study. They did not mention that there was no actual advantage in OS, presented the competing risks-based sarcoma-specific survival (SSS) as the initial study endpoint, and omitted the significant increase in the not sarcoma-related mortality. Moreover, there is a risk for selection bias because the authors excluded 12 patients apparently due to withdrawal of consent or metastatic disease, though this was not included in the previous report after 3 years of follow-up. Interesting, in the supplement the authors stated additional reason for the exclusion, that these patients did not start their allocated treatment after randomization. This is confusing as it appears that seven patients were excluded from the RHT arm, whereas only 4 did not start treatment. The study result is presented as a robust intention-to-treat analysis, though after the exclusions, this is a less reliable per-protocol analysis. Furthermore, the SSS is confounded by fewer cycles of chemotherapy in the control arm (median 5 cycles) than in the RHT arm (median 8 cycles), and apparently no adjustment for the confounding was applied. These possible confounders – endpoint substitution, competing risks-based nature of the endpoint, selection bias resulting from excluded patients – were not properly addressed and as a result the conclusion that the advantage in SSS is due to the longer follow-up may not be justified. In my opinion, this report does not show an advantage of RHT plus neoadjuvant chemotherapy vs neoadjuvant chemotherapy alone. I highlight these issues to prevent possible misinterpretation of this trial as positive and to avoid unproven treatments being used in clinical practice.

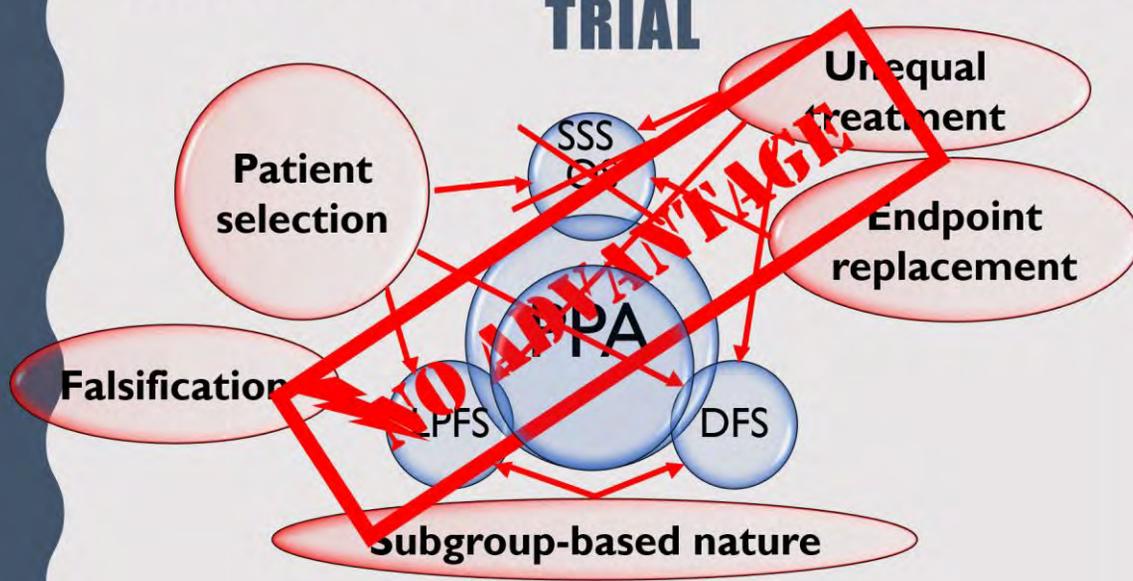
# ANALYSING BIAS IN THE EORTC-ESHO TRIAL



# ANALYSING BIAS IN THE EORTC-ESHO TRIAL



# ANALYSING BIAS IN THE EORTC-ESHO TRIAL



## THE LIST OF BIASES OF THE RTOG-ESHO TRIAL

1. Violation of the study protocol:
  - Inclusion of unmeasurable tumors.
  - Treatment until progression instead of treatment until completion.
2. Replacement of endpoint: sarcoma-specific survival instead of overall survival.
3. Replacement of analysis type: per protocol analysis instead of ITT.
4. Concealment of the replacements.
5. Concealment of the subgroup nature of the LPFS and DFS.
6. Fabrication of the progression endpoints (LPFS and DFS).
7. Falsification of LPFS.
8. Selection of patients.
9. Concealment of the unequal treatment confounding.
10. Fabrication of the TSS outcome.
11. Concealment of the limiting toxicity of the studied application.
12. Concealment of increase of death rate from toxicity and other reasons.

## REGIONAL HYPERTHERMIA EVIDENCE IN SOFT-TISSUE SARCOMA

No	Study name	Country	Type	NOP	Effect	LOE
1	Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study	International	Phase III RCT	341	NEG	I
2	Effect of concurrent chemotherapy and hyperthermia on outcome of preoperative radiotherapy of high-risk soft tissue sarcomas	Germany	Retrospective	28	Pos	IV
3	Reirradiation and hyperthermia for radiation-associated sarcoma	Netherlands	Retrospective	16	Pos	IV
4	Clinical outcomes of radio-hyperthermo-chemotherapy for soft tissue sarcoma compared to a soft tissue sarcoma registry in Japan: a retrospective matched-pair cohort study	Japan	Retrospective analysis,	60	Neg	IV
5	Radiotherapy and hyperthermia with curative intent in recurrent high risk soft tissue sarcomas	Germany	Cohort	42	Pos	IV
6	Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall	Netherlands	Retrospective	23	Pos	IV
7	Salvage method for unplanned excision of soft tissue sarcoma: long-term results of second-look surgery following radio-hyperthermo-chemotherapy	Japan	Retrospective	6	Pos	IV

**“Clinical outcomes of radio-hyperthermo-chemotherapy for soft tissue sarcoma compared to a soft tissue sarcoma registry in Japan: a retrospective matched-pair cohort study.”**  
**a severe bias and no advantage of radio-hyperthermo-chemotherapy**

Revised: 31 July 2018

Dear Editor,

In my opinion, the report of H.Aiba et al. on clinical outcomes of radio-hyperthermo-chemotherapy (RHC) for soft tissue sarcoma (STS) compared to the Bone and Soft Tissue Tumor Registry of Japan (BSTT) is misleading. In the abstract, a significant improvement in local control (LC) versus the matched BSTT group ( $P=0.037$ ) is reported. This comparison is biased due to critical inequality of the groups: in the matched BSTT group ( $n=270$ ), only 31.5% of patients received neoadjuvant chemotherapy (NAC) and only 8.1% received NA radiotherapy (NART), whereas all patients (100%) received both in the RHC group ( $n=60$ ) ( $P<0.001$  for both). Thus, this results rather refers to the comparison RHC + NAC + NART + surgery vs. surgery alone, so it is obviously incorrect in the context of the intended comparison of RHC with conventional treatment vs. the conventional treatment without RHC (*ceteris paribus*).

Meanwhile, the authors made a more correct comparison with subgroup of BSTT who received NAC ( $n=395$ ). This comparison did not reveal a significant difference in LC both versus the total group ( $p=0.074$ ) and the matched group ( $n=180$ ,  $P=0.058$ ). Unfortunately, this result didn't come into the abstract and conclusions. The remaining confounding by insufficient NART in the BSTT arm was not addressed. The authors performed a multivariate analysis to detect a risk factors, so there was not a problem to perform a multivariate log-rank adjustment for NACT. True, this should make the difference in LC even more inconclusive.

Moreover, the risk of selection bias is very high. Although it is explicitly stated in the "Patients" section, that totally 150 patients with grade 2-3 STS of extremities were enrolled, 30 of them (20%) were then excluded due to "non-STs", 4 (2.7%) due to "trunk location" and 11 (7.3%) due to "other reasons" (not explained). Thus, 30% of patients (or 45 out of 90 (50%) excluded patients) seems to be excluded due to doubtful reasons. The authors themselves recognize the possibility of the selection bias when discussing the difference in amputations.

Finally, as it follows from the first phrase of the abstract, the true interest of the authors is a regional hyperthermia (RHT) but the trial studies the RHC (RHT plus intra-arterial chemotherapy (IAC)) instead of the RHT. Thus, any comparison of RHC refers to the RHC but not to the RHT *per se*, so the question "would the result differ after removing HT or IAC from the combination?" remains open. This means the misleading trial design: the authors use an unproven intervention (RHT) in combination with the proven intervention (IAC) and try substantiating the combined intervention, avoiding the evidence of the unproven part and not answering the question, is RHT necessary in this combination at all?

So, in my opinion, actually the trial did not reveal an advantage of RHC in both overall survival (OS) and LC. The reporting of the biased favorable outcomes in the abstract while concealing the more correct unfavorable outcomes means obvious reporting bias in violation of CONSORT statement.

I highlight these issues to prevent a possible misinterpretation of this trial as positive and to avoid unproven treatments being used in clinical practice.

## REGIONAL HYPERTHERMIA EVIDENCE IN SOFT-TISSUE SARCOMA

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## REGIONAL HYPERTHERMIA EVIDENCE IN SOFT-TISSUE SARCOMA

No	Study name	Country	Type	NOP	Effect	LOE
1	Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study	International	Phase III RCT	341	NEG	I
2	Hyperthermia + radiotherapy + chemotherapy;no control vs. control: outcome of preoperative radiotherapy of high-risk soft tissue sarcomas	Germany	Retrospective	28	Pos	IV
3	Hyperthermia + radiotherapy;no control vs. control: radiation-associated sarcoma	Netherlands	Retrospective	16	Pos	IV
4	Hyperthermia + radiotherapy + chemotherapy;no control vs. control: soft tissue sarcoma compared to a soft tissue sarcoma registry in Japan: a retrospective matched-pair cohort study	Japan	Retrospective analysis,	60	Neg	IV
5	Hyperthermia + radiotherapy;no control vs. control: curative intent in recurrent high risk soft tissue sarcomas	Germany	Cohort	42	Pos	IV
6	Effect of a combined surgery, re-irradiation and hyperthermia therapy on local control rate in radio-induced angiosarcoma of the chest wall	Netherlands	Retrospective	23	Pos	IV
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## RESUME ON REGIONAL HYPERTHERMIA IN SOFT-TISSUE SARCOMA

**NO ADVANTAGE  
LEVEL I EVIDENCE**

## EVIDENCE OF HYPERTHERMIC ISOLATED LIMB PERFUSION

No	Name	Country	Type	NOP
1	Hyperthermic isolated limb perfusion, preoperative radiotherapy, and surgery (PRS) a new limb saving treatment strategy for locally advanced sarcomas	Germany	Retrospective	11
2	Hyperthermic isolated limb perfusion. The switch from Steinmann pins to Omni-tract assisted isolation.	Greece	Retrospective	40
3	Laparoscopic hyperthermic isolated limb perfusion a new minimally invasive approach for HILP	Italy	Case report	1
4	Hyperthermic isolated limb perfusion for recurrent melanomas and soft tissue sarcomas: feasibility and reproducibility in a multi-institutional Hellenic collaborative study	Greece	Retrospective	6
5	Hyperthermic isolated limb perfusion for unresectable extremity sarcoma with TNF and melphalan	USA	Cohort trial	17
6	[Cytostatic hyperthermic isolated limb perfusion (HILP) in VFN (General Faculty Hospital in Prague)]	Czechia	Retrospective	10
7	[Tumor necrosis factor $\alpha$ and melfalan-based hyperthermic isolated limb perfusion in locally advanced extremity soft tissue sarcomas and melanomas]	Spain	Retrospective	30
8	Impact of hyperthermic isolated limb perfusion on tumour oxygenation in soft tissue sarcoma	Germany	Mechanism	34
9	Isolated limb infusion with hyperthermia and chemotherapy for advanced limb malignancy: factors influencing toxicity	Brazil	Retrospective	31
10	The pathologic response of resected synovial sarcomas to hyperthermic isolated limb perfusion with melphalan and TNF- $\alpha$ : a comparison with the whole group of resected soft tissue sarcomas	Germany	Retrospective	125

## EVIDENCE OF HYPERTHERMIC ISOLATED LIMB PERFUSION

No	Name	Country	Type	NOP
1	Hyperthermic isolated limb perfusion, preoperative radiotherapy, and surgery (PRS) a new limb saving treatment strategy for locally advanced sarcomas	Germany	Retrospective	11
2	Hyperthermic isolated limb perfusion. The switch from Steinmann pins to Omni-tract assisted isolation.	Greece	Retrospective	40
3	<b>Laparoscopic hyperthermic isolated limb perfusion a new minimally invasive approach for HILP</b>	<b>Italy</b>	<b>Case report</b>	<b>1</b>
4	Hyperthermic isolated limb perfusion for recurrent melanomas and soft tissue sarcomas: feasibility and reproducibility in a multi-institutional Hellenic collaborative study	Greece	Retrospective	6
5	Hyperthermic isolated limb perfusion for unresectable extremity sarcoma with TNF and melphalan	USA	Cohort trial	17
6	[Cytostatic hyperthermic isolated limb perfusion (HILP) in VFN (General Faculty Hospital in Prague)]	Czechia	Retrospective	10
7	[Tumor necrosis factor $\alpha$ and melfalan-based hyperthermic isolated limb perfusion in locally advanced extremity soft tissue sarcomas and melanomas]	Spain	Retrospective	30
8	<b>Impact of hyperthermic isolated limb perfusion on tumour oxygenation in soft tissue sarcoma</b>	<b>Germany</b>	<b>Mechanism</b>	<b>34</b>
9	Isolated limb infusion with hyperthermia and chemotherapy for advanced limb malignancy: factors influencing toxicity	Brazil	Retrospective	31
10	The pathologic response of resected synovial sarcomas to hyperthermic isolated limb perfusion with melphalan and TNF- $\alpha$ : a comparison with the whole group of resected soft tissue sarcomas	Germany	Retrospective	125

## EVIDENCE OF HYPERTHERMIC ISOLATED LIMB PERFUSION

No	Name	Country	Type	NOP	LOE
1	Hyperthermic isolated limb perfusion, preoperative radiotherapy, and surgery (PRS) a new limb saving treatment strategy for locally advanced sarcomas	Germany	Retrospective	11	IV
2	Hyperthermic isolated limb perfusion. The switch from Steinmann pins to Omni tract assisted isolation.	Greece	Retrospective	40	IV
3	<b>HYPERTHERMIA + CHEMOTHERAPY ± RADIO THERAPY;</b>				
4	<b>NO CONTROL</b>				
	with TNF and melphalan				
5	{Cytostatic hyperthermic isolated limb perfusion (HILP) in VFN (General Faculty Hospital in Prague)}	Czechia	Retrospective	10	IV
6	{Tumor necrosis factor α and melphalan based hyperthermic isolated limb perfusion in locally advanced extremity soft tissue sarcomas and melanomas}	Spain	Retrospective	30	IV
7	Isolated limb infusion with hyperthermia and chemotherapy for advanced limb malignancy: factors influencing toxicity	Brazil	Retrospective	31	IV
8	The pathologic response of resected synovial sarcomas to hyperthermic isolated limb perfusion with melphalan and TNF-α: a comparison with the whole group of resected soft tissue sarcomas	Germany	Retrospective	125	IV

## HYPERTHERMIC ISOLATED LIMB PERFUSION: THE CONSENSUS

### MEDICAL POLICY



<b>SUBJECT:</b> ISOLATED LIMB PERFUSION and INFUSION	<b>EFFECTIVE DATE:</b> 01/17/02 <b>REVISED DATE:</b> 09/19/02, 11/20/03, 11/18/04, 09/15/05, 07/20/06, 09/20/07, 08/21/08, 07/16/09, 08/19/10
<b>POLICY NUMBER:</b> 741.52	<b>ARCHIVED DATE:</b> 08/18/11
<b>CATEGORY:</b> Technology Assessment	<b>EDITED DATE:</b> 09/20/12, 09/19/13, 09/18/14, 09/17/15, 09/15/16, 09/21/17
<b>PAGE:</b> 1 OF 8	

• If a product excludes coverage for a service, it is not covered, and medical policy criteria do not apply.  
• If a commercial product, including an Essential Plan product, covers a specific service, medical policy criteria apply to the benefit.  
• If a Medicare product covers a specific service, and there is no national or local Medicare coverage decision for the service, medical policy criteria apply to the benefit.

#### POLICY STATEMENT:

- Based upon our criteria and assessment of peer-reviewed literature:
- I. Isolated Limb Perfusion/Infusion has been medically proven to be effective and therefore **medically appropriate** in the treatment of patients with local recurrence of unresectable melanoma.
  - II. Isolated Limb Perfusion/Infusion as an adjuvant treatment in patients with resectable primary melanoma who have no other clinical evidence of the disease does not improve patient outcomes and is considered **not medically necessary**.
  - III. Hyperthermia in conjunction with isolated limb perfusion/infusion does not improve patient outcomes and is considered **not medically necessary**.
  - IV. Isolated Limb Perfusion/Infusion has not been medically proven to be effective and is therefore considered **investigational** under the following conditions:
    - A. as an adjuvant treatment of surgically treated recurrent melanoma with no other evidence of disease; or
    - B. as a primary or adjuvant treatment for any other malignant diagnosis (e.g., soft tissue or bone sarcoma).
  - V. Tumor Necrosis Factor in conjunction with isolated limb perfusion/infusion has not been medically proven to be effective and is therefore considered **investigational**.

#### POLICY GUIDELINES:

- I. Patients typically undergo one treatment with ILP/ILI. Some patients with incomplete responses after the first procedure may undergo a second course of treatment.
- II. The Federal Employees Health Benefit Program (FEHBP/FEPP) requires that procedures, devices or laboratory tests approved by the U.S. Food and Drug Administration (FDA) may not be considered investigational and thus these procedures, devices or laboratory tests may be assessed only on the basis of their medical necessity.

#### DESCRIPTION:

Isolated Limb Perfusion (ILP) is a surgical procedure in which an artery and vein to an extremity are exposed and cannulated with catheters to circulate blood and drugs. Surgeons occlude the proximal artery and vein and maintain circulation to the limb by using a pump-oxygenator similar to that used for cardiopulmonary bypass in cardiac surgery. Collateral branches of the proximal vein and artery are also ligated and a tourniquet is applied at the root of the extremity to complete the vascular isolation of the limb. Chemotherapeutic drugs are then circulated or perfused for up to 90 minutes and then flushed out of the extremity prior to reestablishing circulation. The major advantage of this procedure is the ability to dose escalate the drugs to levels that cannot be achieved with systemic circulation. The amount of the drug used in ILP would otherwise be toxic if given systemically. The goal of ILP is to effect control of tumor load in an extremity, prevent local recurrences from progressing to unacceptably marked tumor masses and salvage limbs from amputation.

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Excellus BlueCross  
BlueShield Association (US)

## **HYPERTHERMIC ISOLATED LIMB PERFUSION: THE CONSENSUS**

*Hyperthermia in conjunction with isolated limb perfusion or infusion does not improve patient outcomes and is considered not medically necessary.*

Isolated limb perfusion and infusion:  
Medical Policy, Nr. 7.01.52, 2002  
(Last Revised: 19.08.2010).  
Excellus Health Plan, Inc.

Isolated Limb Perfusion (ILP) is a surgical procedure in which an artery and vein to an extremity are exposed and cannulated with catheters to circulate blood and drugs. Surgeons occlude the proximal artery and vein and maintain circulation to the limb by using a pump-extractor similar to that used for cardiopulmonary bypass in cardiac surgery. Collateral branches of the proximal vein and artery are also ligated and a tourniquet is applied at the root of the extremity to complete the vascular isolation of the limb. Chemotherapeutic drugs are then circulated or perfused for up to 90 minutes and then flushed out of the extremity prior to reestablishing circulation. The major advantage of this procedure is the ability to dose escalate the drugs to levels that cannot be achieved with systemic circulation. The amount of the drug used in ILP would otherwise be toxic if given systemically. The goal of ILP is to effect control of tumor load in an extremity, prevent local recurrences from progressing to unacceptably sized tumor masses and salvage limbs from amputation.

Proprietary Information of Excellus Health Plan, Inc.

**KLAASE JM, KROON BB, EGGERMONT AM, VAN GEEL AN, SCHRAFFORDT KOOPS H, OLDHOFF J, LIÉNARD D, LEJEUNE FJ, BERKEL R, FRANKLIN HR, ET AL.  
A RETROSPECTIVE COMPARATIVE STUDY EVALUATING THE RESULTS OF MILD HYPERTHERMIC VERSUS CONTROLLED NORMOTHERMIC PERFUSION FOR RECURRENT MELANOMA OF THE EXTREMITIES.  
EUR J CANCER. 1995;31A(1):58-63.**

- 218 patients treated with hyperthermic isolated limb perfusion with cytostatics (39-40 degrees C) were compared retrospectively to 166 patients perfused under normothermic conditions (37-38 degrees C).
- Only patients whose lesions had been excised before or at the moment of perfusion were eligible for this study.
- A variety of prognostic factors was controlled for in a Cox proportional hazards analysis.
- The application of mild hyperthermia did not influence limb recurrence-free interval nor survival (corrected P values 0.46 and 0.18, respectively).
- **No benefit for mild hyperthermia in regional isolated perfusion could be identified.**

# RESUME ON HYPERTHERMIC ISOLATED LIMB PERFUSION

**NO ADVANTAGE  
LEVEL II EVIDENCE**

## EVIDENCE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

No	Name	Country	Type	NOP
1	Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery?	France	Retrospective, cohort	107
2	Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy	International	Retrospective, cohort	36
3	Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor	USA	Retrospective, cohort	26
4	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in sarcomatosis from gastrointestinal stromal tumor	USA	Retrospective, cohort	18
5	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal sarcomatosis: long-term outcome from a single institution experience	Italy	Retrospective, cohort	15
6	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal sarcomatosis	USA	Retrospective, cohort	7

## EVIDENCE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

No	Name	Country	Type	NOP	Effect	LOE
1	Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery?	France	Retrospective, cohort	107	NEG	II
2	Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.	International	Retrospective, cohort	36	Pos	IV
3	Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor.	USA	Retrospective, cohort	26	Pos	IV
4	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in sarcomatosis from gastrointestinal stromal tumor.	USA	Retrospective, cohort	18	NA	IV
5	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal sarcomatosis: long-term outcome from a single institution experience.	Italy	Retrospective, cohort	15	NEG	III
6	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal sarcomatosis.	USA	Retrospective, cohort	7	NEG	III

## EVIDENCE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

No	Name	Country	Type	NOP	Effect	LOE
	<ul style="list-style-type: none"> <li>Large retrospective nation-wide France survey</li> <li>conducted by crossing the databases of                             <ul style="list-style-type: none"> <li>French Network for Rare Peritoneal Malignancies,</li> <li>French Reference Network in Sarcoma Pathology,</li> <li>French Sarcoma Clinical Network and</li> <li>French Pediatric Cancer Society.</li> </ul> </li> <li><b>RESULT: The influence of HIPEC/EPIC on OS and DFS was not statistically conclusive.</b></li> <li><b>CONCLUSION: The benefit of HIPEC is still unknown.</b></li> </ul>				NEG	II
					Pos	IV
					Pos	IV
					NA	IV
5	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal sarcomatosis: long-term outcome from a single institution experience.	Italy	Retrospective, cohort	15	NEG	III
6	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal sarcomatosis.	USA	Retrospective, cohort	7	NEG	III

## EVIDENCE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

No	Name	Country	Type	NOP	Effect	LOE
1	Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery?	France	Retrospective, cohort	107	NEG	II
	<ul style="list-style-type: none"> <li>Studies the efficacy of CRS+HIPEC</li> <li>The effect of HIPEC is not evaluable</li> </ul>				Pos	IV
	<ul style="list-style-type: none"> <li>The study proved the dependence of CRS/HIPEC of the quality of CRS</li> <li>The effect of HIPEC is not evaluable</li> </ul>				Pos	IV
	<ul style="list-style-type: none"> <li>Studies the role of resistance to tyrosine kinase inhibitor tumor.</li> <li>The effect of HIPEC is not evaluable</li> </ul>				NA	IV
5	Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in patients with peritoneal sarcomatosis: long-term outcome from a single institution experience.	Italy	Retrospective, cohort	15	NEG	III
6	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in peritoneal sarcomatosis.	USA	Retrospective, cohort	7	NEG	III

## EVIDENCE OF HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

No	Name	Country	Type	NOP	Effect	LOE
1	Abdominal desmoplastic small round cell tumor without extraperitoneal metastases: Is there a benefit for HIPEC after macroscopically complete cytoreductive surgery?	France	Retrospective, cohort	107	NEG	II
2	Multi-institutional study of peritoneal sarcomatosis from uterine sarcoma treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.	International	Retrospective, cohort	36	Pos	IV
3	Complete cytoreduction and HIPEC improves survival in desmoplastic small round cell tumor.	USA	Retrospective, cohort	26	Pos	IV
4	Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in sarcomatosis from gastrointestinal stromal tumor.	USA	Retrospective, cohort	18	NA	IV
	<ul style="list-style-type: none"> <li>The impact of HIPEC after radical surgery for PS remains questionable and still has to be further evaluated in large cooperative multi-institutional studies.</li> </ul>				NEG	III
	<ul style="list-style-type: none"> <li>Median survival for patients with peritoneal sarcomatosis treated with CRS-HIPEC is similar with the historical reported survival before introducing chemoperfusion.</li> <li>Although a complete cytoreduction is related to improved survival, the role of HIPEC in these patients is unknown.</li> </ul>				NEG	III

## RESUME ON HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC)

**NO ADVANTAGE  
LEVEL II EVIDENCE**

## RESUME ON HYPERTHERMIA IN THE TREATMENT OF SOFT-TISSUE SARCOMA

Type of hyperthermia	Conclusion	Level of evidence
Regional hyperthermia	No advantage	I (conclusive)
Hyperthermic intraperitoneal chemotherapy (HIPEC)	No advantage	II (probable)
Hyperthermic isolated limb perfusion	No advantage	II (probable)

**NO ADVANTAGE**



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Conference Papers in Medicine  
 Volume 2013, Article ID 428027, 40 pages  
<http://dx.doi.org/10.1155/2013/428027>

**Conference Paper**  
**The History of Hyperthermia Rise and Decline**

Sergey Roussakow

Galenic Research Institute, Moscow, Russia

Received 13 February 2013; Accepted 17 April 2013

Academic Editors: G. F. Baronzio, M. Jackson, and A. Szasz

This Conference Paper is based on a presentation given by Sergey Roussakow at "Conference of the International Clinical Hyperthermia Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hungary.

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# IS THIS THE END?



## EVIDENCE OF MODULATED ELECTROHYPERTHERMIA (MEHT, ONCOTHERMIA®)

No	Name	Country	Type	NOP
1	The Results of Combination of Ifosfamid and Locoregional Hyperthermia (EHY 2000) in Patients with advanced Abdominal Soft-Tissue Sarcoma after Relapse of First Line Chemotherapy	Romania	Prospective, cohort	18
2	Positive response of a primary leiomyosarcoma of the breast following salvage hyperthermia and pazopanib	Korea	Case report	1
3	[Best results of Oncothermia (electrical hyperthermia) in the therapy of carcinomas and sarcomas in combination with other conventional medical treatment without significant side effects]	Germany	Case series	5
4	Results of Oncothermia Combined with Operation, Chemotherapy and Radiation Therapy for Primary, Recurrent and Metastatic Sarcoma	Korea	Case series	13
5	Cases That Respond to Oncothermia Monotherapy	Korea	Case series	1

## EVIDENCE OF MODULATED ELECTROHYPERTHERMIA (MEHT, ONCOTHERMIA®)

No	Name	Country	Type	NOP	Effect	LOE
1	The Results of Combination of Ifosfamid and Locoregional Hyperthermia (EHY 2000) in Patients with advanced Abdominal Soft-Tissue Sarcoma after Relapse of First Line Chemotherapy	Romania	Prospective, cohort	18	Pos	II



# EVIDENCE OF MODULATED ELECTROHYPERThERMIA (MEHT, ONCOTHERMIA®)

No	Name	Country	Type	NOP	Effect	LOE
1	The Results of Combination of Ifosfamid and Locoregional Hyperthermia (EHY 2000) in Patients with advanced Abdominal Soft-Tissue Sarcoma after Relapse of First Line Chemotherapy	Romania	Prospective, cohort	18	Pos	II
2	Positive response of a primary leiomyosarcoma of the breast following salvage hyperthermia and pazopanib	Korea	Case report	1	Pos	IV
3	[Best results of Oncothermia (electrical hyperthermia) in the therapy of carcinomas and sarcomas in combination with other conventional medical treatment without significant side effects]	Germany	Case series	5	Pos	IV
4	Results of Oncothermia Combined with Operation, Chemotherapy and Radiation Therapy for Primary, Recurrent and Metastatic Sarcoma	Korea	Case series	13	Pos	III
5	Cases That Respond to Oncothermia Monotherapy	Korea	Case series	1	Pos	III



**NATIONAL CANCER INSTITUTE**  
DCTD Division of Cancer Treatment & Diagnosis

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## OCCAM Office of Cancer Complementary and Alternative Medicine

Home CAM at the NCI Research Health Info International Activities Identifying CAM Therapies News & Events About Us

Overview Identifying Novel CAM Therapies Last Updated: 05/30/13

NIH **National Cancer Institute** Best Case Series Program

The National Cancer Institute (NCI) is committed to finding innovative, promising treatments for people with cancer. As part of the Division of Cancer Treatment and Diagnosis (DCTD), the NCI's **Office of Cancer Complementary and Alternative Medicine (OCCAM)** coordinates the Institute's research program in complementary and alternative medicine (CAM). Since its inception in 1991, the NCI Best Case Series Program has had a process for evaluating patient data from CAM practitioners around the world. Through OCCAM's Case Review and Intramural Science Program (CRISP), the process involves the same rigorous scientific methods employed in evaluating treatment responses with conventional medicine and provides an independent retrospective review of medical records and medical imaging from patients treated with alternative cancer therapies.

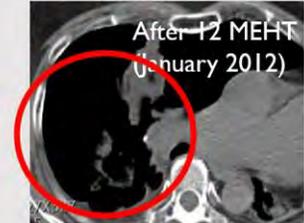
For more information of the NCI Best Case Series Program visit the web page below:  
[NCI BCS Protocol](#)

# NCI BEST CASE SERIES PROTOCOL

1. Definitive diagnosis of cancer.
2. Documentation of Disease Response.
3. Absence of Confounders.
  - a. The patient should not have received concurrent treatments with known therapeutic potential (e.g. chemotherapy or radiation therapy).
  - b. There should be sufficient time between the end of any conventional anticancer therapy and the beginning of an alternative therapy to minimize the probability that a response was due to the conventional therapy.
4. Documented Treatment History.

## NCI BCS CASE REPORT SYNOVIAL SARCOMA

- Patient: 55-year old Korean female (lost the left lung by tuberculosis when she was young).
- Primary diagnosis: Synovial sarcoma of right thigh in 2004 (48-year old).
- Primary treatment: Surgery in 2004, complete remission.
- Relapse: local relapse with massive metastasis in the right lung in September, 2011.
- Metastasis treatment: IGRT 45 Gy /15 fractions/3 weeks in September, 2011.
- Response: immediate partial response with following progression (November 2011)
- 2<sup>nd</sup> line treatment: MEHT monotherapy, 39 sessions from November 2011 to April 2012
- Response: Good partial response



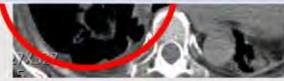
# NCI BCS CASE REPORT SYNOVIAL SARCOMA

- **Patient:** 55-year old Korean female (lost the left lung by tuberculosis when she was young).



Case report	Confirmed diagnosis	No confounding treatment	Detectable disease	Objective response	Adequate documentation	Compliance
Synovial sarcoma	Yes	Yes (RT ended 8 weeks before MEHT)	Yes	Yes Partial response	Yes Radiographic (CT)	Compliant

- **Metastasis treatment:** IGRT 45 Gy / 15 fractions/3 weeks in September, 2011.
- **Response:** immediate partial response with following progression (November 2011)
- **2<sup>nd</sup> line treatment:** MEHT monotherapy, 39 sessions from November 2011 to April 2012
- **Response:** Good partial response
- **Abstract:** a case of good partial response of the radioresistant metastasis of the relapsed synovial sarcoma in the right lung, after 2<sup>nd</sup> line MEHT monotherapy (39 sessions for 5 months); BCS-compliant.
- **Source:** Jeung TS, Ma SY, Yu J, Lim S. Cases That Respond to Oncothermia Monotherapy. Conference Papers in Medicine. 2013; 2013: Article ID 392480, 12 p.

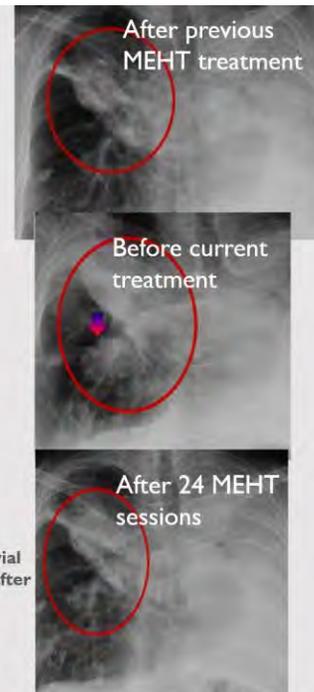


# NCI BCS CASE REPORT SYNOVIAL SARCOMA

- **Patient:** The same 57-year old Korean female.
- **Pre-history:**
  - Synovial sarcoma of right thigh in 2004 (48-year old);
  - Surgery in 2004, complete remission;
  - local relapse with massive metastasis in the right lung in September, 2011
  - IGRT 45 Gy / 15 fractions/3 weeks in September, 2011;
  - immediate partial response with following progression (November 2011)
  - MEHT monotherapy, 48 sessions from November 2011;
  - Good partial response

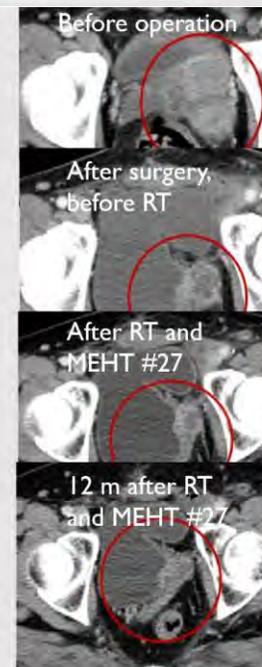
## NCI BCS CASE REPORT SYNOVIAL SARCOMA

- **Patient:** The same 57-year old Korean female.
- **Pre-history:**
  - Synovial sarcoma of right thigh in 2004 (48-year old);
  - Surgery in 2004, complete remission;
  - local relapse with massive metastasis in the right lung in September, 2011
  - IGRT 45 Gy /15 fractions/3 weeks in September, 2011;
  - immediate partial response with following progression (November 2011)
  - MEHT monotherapy, 48 sessions from November 2011;
  - Good partial response
- **Progression:** the tumor progressed in 2 months from stopping MEHT.
- **Treatment:** MEHT monotherapy, 24 sessions in 3 months.
- **Response:** Partial response.
- **Abstract:** a case of partial response of the radioresistant metastasis of the relapsed synovial sarcoma in the right lung, after 3<sup>rd</sup> line MEHT monotherapy (24 sessions for 3 months), after progression after the 2<sup>nd</sup> line MEHT; BCS-compliant.
- **Source:** Jeung TS, Ma SY, Choi JH, Yu J, Lee SY, Lim S. Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. *Case Reports in Clinical Medicine*. 2015; 4: 157-68 .



## NCI BCS CASE REPORT FIBROUS HISTIOCYTOMA

- **Patient:** A 32-year-old Korean male.
- **Diagnosis:** malignant fibrous histiocytoma in left pelvis in March 2012.
- **1<sup>st</sup>-2<sup>nd</sup> line treatment:** Sigmoidectomy & partial cystectomy in March 2012. Post-operative radiation therapy of 50.4 Gy in 28 fractions in April-June 2012.
- **Response:** Minor response (inconclusive).
- **3<sup>rd</sup> line treatment:** MEHT monotherapy, 27 sessions in 3 months.
- **Response:** Nearly complete response in 12 months after the treatment.
- **Abstract:** a case of nearly complete response of the post-operative primary malignant fibrous histiocytoma in left pelvis, after 3<sup>rd</sup> line MEHT monotherapy (27 sessions for 3 months), after inconclusive response after the 2<sup>nd</sup> line adjuvant radiotherapy (50.4 Gy); partially BCS-compliant.
- **Source:** Jeung TS, Ma SY, Choi JH, Yu J, Lee SY, Lim S. Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. *Case Reports in Clinical Medicine*. 2015; 4: 157-68 .



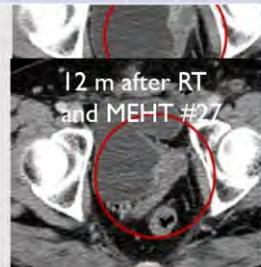
# NCI BCS CASE REPORT FIBROUS HISTIOCYTOMA

- **Patient:** A 32-year-old Korean male.



Case report	Confirmed diagnosis	No confounding treatment	Detectable disease	Objective response	Adequate documentation	Compliance
Malignant fibrous histiocytoma	Yes	Confounding is possible (RT just before MEHT)	Yes	Yes Nearly complete response	Yes Radiographic (CT)	Partially compliant

- **Response:** Nearly complete response in 12 months after the treatment.
- **Abstract:** a case of nearly complete response of the post-operative primary malignant fibrous histiocytoma in left pelvis, after 3<sup>rd</sup> line MEHT monotherapy (27 sessions for 3 months), after inconclusive response after the 2<sup>nd</sup> line adjuvant radiotherapy (50.4 Gy); partially BCS-compliant.
- **Source:** Jeung TS, Ma SY, Choi JH, Yu J, Lee SY, Lim S. Results of oncothermia combined with operation, chemotherapy and radiation therapy for primary, recurrent and metastatic sarcoma. *Case Reports in Clinical Medicine*. 2015; 4: 157-68 .



## EVIDENCE OF MODULATED ELECTROHYPERTHERMIA (MEHT, ONCOTHERMIA®)

No	Name	Country	Type	NOP	Effect	LOE
1	The Results of Combination of Ifosfamid and Locoregional Hyperthermia (EHY 2000) in Patients with advanced Abdominal Soft-Tissue Sarcoma after Relapse of First Line Chemotherapy	Romania	Prospective , cohort	18	Pos	II
2	Positive response of a primary leiomyosarcoma of the breast following salvage hyperthermia and pazopanib	Korea	Case report	1	Pos	IV
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# RESUME ON ELECTRO-HYPERTHERMIA IN THE TREATMENT OF SOFT-TISSUE SARCOMA

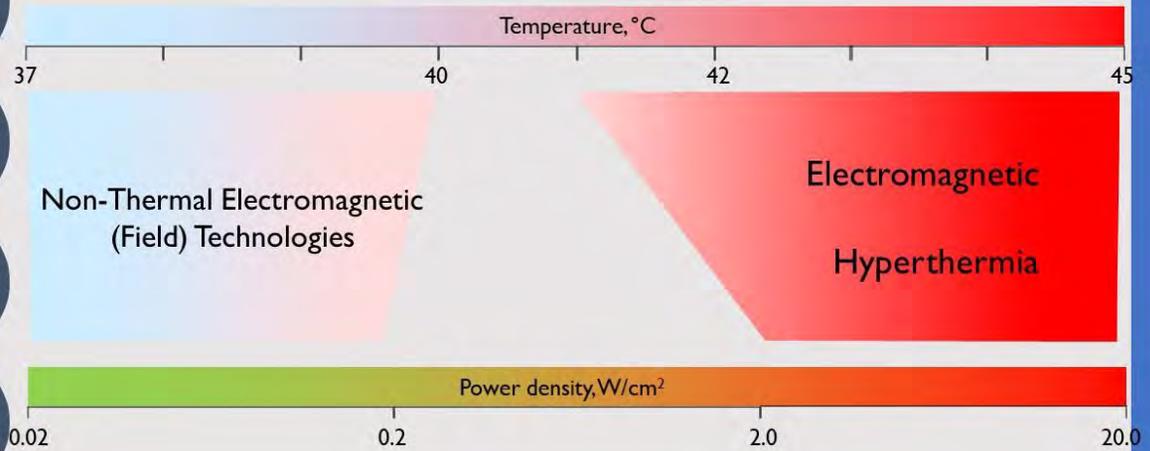
Type of hyperthermia	Conclusion	Level of evidence
Modulated electro-hyperthermia (MEHT, Oncothermia®)	Advantage	II (probable)

## ELECTROHYPERTHERMIA: WHAT IS THIS?

The screenshot shows the FDA's 'Recently-Approved Devices' page for the NovoTTF-100A System - P100034. The page includes the FDA logo, navigation tabs for various product categories, and a search bar. The main content area features a 'Recently-Approved Devices' sidebar with links for 2015 and 2016 approvals. The main article for the NovoTTF-100A System includes social media sharing options, a brief overview of the product, and key details: 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](http://www.accessdata.fda.gov/cdrh_docs/pdf10/p100034a.pdf). A small image of the device is also visible.



# HYPERTHERMIA – NON-THERMAL – ONCOTHERMIA



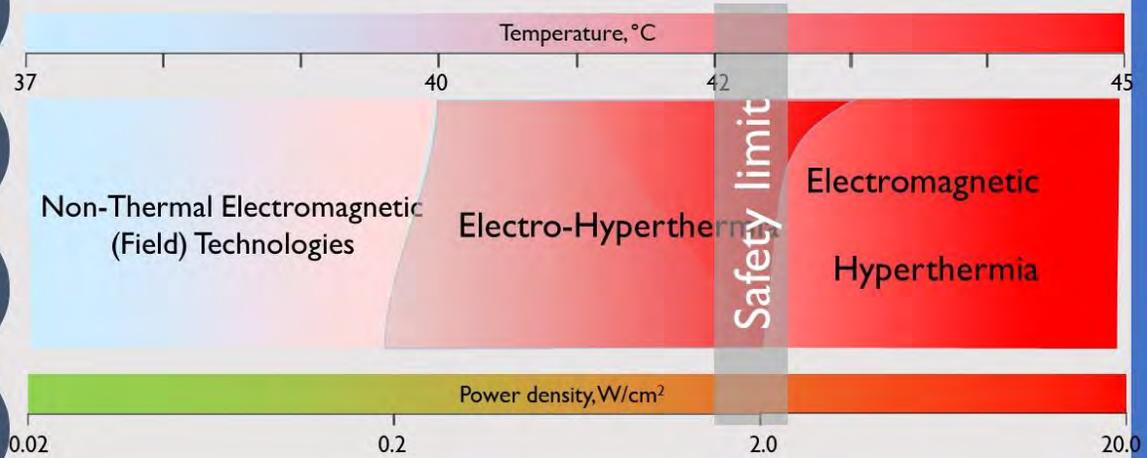
## THE FRONTLINE OF XX CENTURY



“In fact in our opinion the burden of proof still lies on those who claim any biological effects of high frequency currents other than heat production”

*Christie, Loomis, 1930*

# HYPERTHERMIA – NON-THERMAL – ONCOTHERMIA

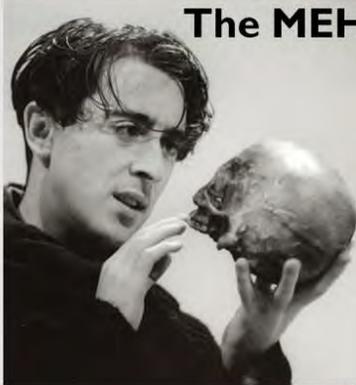


## THERMAL OR NON-THERMAL?



# NEW FRONTLINE OF XXI CENTURY

The MEHT or TTF?



Athermic  
(TTF)  
Non-thermal

Hyperthermic  
(MEHT)

Thermally-induced  
not temperature-dependent



Thank you for  
attention.

To be continued ...

# WHERE IS THE BIAS?



intensity STS in the combined treatment group had better surgical outcomes than those in the EIA-alone group, largely because a greater proportion of them underwent R0 (67.7% vs 56.0%; 36/53 vs 29/58) resections including amputation and a lower proportion underwent R1 and R2 resections (38.4% vs 41.1%; 14/15 vs 25/58). These patients in the combined treatment group and 4 patients in EIA-alone group had no resection (5.7% vs 6.9%; 3/51 vs 4/58). In patients with non-extremity STS, the proportion of patients who underwent R0 (combined treatment 36.9% vs 47.9% in the EIA-alone group; 24/65 vs 22/58) resection including amputation and R1 or R2 resections (combined treatment 46.2% vs 41.1% in the EIA-alone group; 50/65 vs 25/58) were similar in both treatment groups. Eleven patients in the combined treatment group and 11 patients in EIA-alone group had no resection (16.9% vs 19.0%; 11/65 vs 11/58). Six patients in the combined treatment group and 52 in the EIA-alone group had previous inadequate surgery where a re-resection was not possible. 14 patients in the combined treatment group and 15 in EIA-alone group had no resection, primarily because of non-resectability. The median interval between induction therapy and surgery was 5.9 weeks (range 4.9-7.7 weeks) in the combined treatment group and 5.7 weeks in the EIA-alone group (range 4.5-7.9 weeks).

38 patients in the combined treatment group and 38 in the EIA-alone group received radiotherapy with a mean dose of 51.2 Gy (SD 8.9) and 52.7 Gy (SD 9.4), respectively. The median interval between surgery and radiotherapy was 6.3 weeks (range 4.7-8.9 weeks) in the combined treatment group and 5.9 weeks (range 4.1-8.9 weeks) in the EIA-alone group. 41 patients in the combined treatment group and 64 in the EIA-alone group did not receive radiotherapy. The main reasons for not receiving radiotherapy was an abdominal or retroperitoneal tumor location.

Most patients in the combined treatment group completed full post-induction chemotherapy compared with the EIA-alone group (89 [52.7%] vs 71 [40.3%];  $p=0.02$ ). Similar numbers of patients did not receive post-induction therapy (41 in the combined treatment group vs 47 in the EIA-alone group) due to non-compliance, whereas the number of patients showing early progression including death, before the start of post-induction therapy was significantly lower in the combined treatment group than in the EIA-alone group (3 vs 17;  $p=0.003$ ). In the combined treatment group, only 60 patients (35.5%) received 7-8 regional hyperthermia treatments, 28 patients (16.6%) 1-6 regional hyperthermia treatments, and 66 patients (39.6%) received none (figure 2). Reasons for not receiving regional hyperthermia were related to side-effects (eg, distal wound healing, infection, acute reactions due to radiation therapy) or intolerance to further local treatment (eg, pain due to tumor pressure on heart) after local therapy (surgery or radiation).

The overall duration of study treatment was 32.4 weeks (range 24.9-40.3 weeks) for the combined treatment

	All-patients (n=103)	EIA (n=58)	Combined (n=45)	p-value*
Median follow-up time (months) (IQR)	36 (22-60)	33 (18-60)	33 (18-60)	0.18
Local progression-free survival				
Median duration (months)	25 (4.0-42.0)	25	0.53 (95% CI 0.43-0.66)	0.8483
Proportion (%) at 2 years	70 (68.0)	64 (52.0)	64 (52.0)	
Proportion (%) at 4 years	34 (32.7)	35 (48.6)	35 (48.6)	
Overall survival				
Median duration (months)	32 (4.0-60)	38 (14-78)	35 (19-58)	0.001
Proportion (%) at 2 years	58 (52.4)	44 (52.0)	44 (52.0)	
Proportion (%) at 4 years	40 (35.0)	40 (48.3)	40 (48.3)	
Overall survival				
Number of deaths	74	38	0.0004 (95% CI 0.0001-0.002)	
Median duration (months)	29 (4.0-52.0)	24 (4.0-42.0)	24 (4.0-42.0)	
Proportion (%) at 2 years	38 (32.0)	30 (38.0)	30 (38.0)	
Proportion (%) at 4 years	18 (15.0)	17 (48.0)	17 (48.0)	
Response to induction therapy				
No resectable disease	13 (10.0)	18 (24.0)	18 (24.0)	0.001
Resectable disease	118 (90)	118 (97)	118 (97)	
Complete response (%)	1 (0.8)	1 (0.8)	1 (0.8)	
Partial response (%)	11 (8.0)	11 (11.0)	11 (11.0)	
Stable disease (%)	44 (33.0)	29 (32.0)	29 (32.0)	
Progression disease (%)	6 (4.0)	10 (14.0)	10 (14.0)	
Death not resectable (%)	31 (23.0)	19 (21.0)	19 (21.0)	
Overall response (%)	18 (13.0)	18 (21.0)	18 (21.0)	

Table 2. Response to treatment and survival in all patients assigned to treatment

group versus 35.1 weeks (range 20.3-58.4 weeks) in the EIA-alone group. The median number of cycles of chemotherapy was 8.9 in the combined treatment group versus 5.9 in the EIA-alone group (IQR 6.8 cycles for both treatment groups). Dose reductions (29% vs 23%; 41/65 vs 35/60) and cycles delayed more than 7 days (18.5% vs 22.4%; 59/65 vs 37/60) were mainly due to haematological toxicity. Within the combined treatment group, maximum temperature measurements were done in 71.9% (116/162) of patients. For  $T_{re}$ , the median intratumoural temperature was 41.8°C (IQR 41.1-42.2). The median time-averaged temperature was 40.9°C for the  $T_{re}$  (IQR 40.1-42.1), 40.7°C for the  $T_{sk}$  (IQR 39.5-39.8°C).

56 patients in the combined treatment group had local progression compared with 78 in the EIA-alone group. Response to treatment and survival is shown in table 2. The relative hazard for local progression or death between patients receiving combined therapy or EIA alone was 0.58 (95% CI 0.41-0.84,  $p=0.003$ ), with a median duration of greater than 120 months (ie, the median is not yet reached) versus 75 months and an absolute difference

	EIA plus RHT	EIA	Hazard ratio	p value*
<b>Response to induction therapy†</b>				0.002
No measurable disease	51 (30.2)	46 (26.7)	..	..
<u>Measurable disease</u>	118 (69.8)	126 (73.3)	..	..
Complete response (n [%])	3 (2.5)	1 (0.8)	<b>3/0.025 = 120</b>	..
Partial response (n [%])	31 (26.3)	15 (11.9)	<b>31/0.263 = 118</b>	..
Stable disease (n [%])	66 (55.9)	73 (57.9)	<b>66/0.559 = 118</b>	..
Progressive disease (n [%])	8 (6.8)	26 (20.6)	<b>8/0.068 = 118</b>	..
Could not be evaluated (n [%])	10 (8.5)	11 (8.7)	<b>10/0.085 = 118</b>	..
Overall response (%)	34 (28.8)	16 (12.7)	<b>34/0.288 = 118</b>	..

EIA=etoposide+ifosfamide+doxorubicin. RHT=regional hyperthermia. \*Calculated by log-rank test. †Response according to WHO criteria was assessed in patients with measurable disease at the time of randomisation. Responses (complete response and partial response) have been confirmed by external review (independent review committee) in 48 of 50 patients.

**Table 2: Response to treatment and survival in all patients assigned to treatment**

	EIA plus RHT	EIA	Hazard ratio	p value*
<b>Response to induction therapy†</b>				0.002
No measurable disease	51 (30.2)	46 (26.7)	..	..
<u>Measurable disease</u>	118 (69.8)	126 (73.3)	..	..
Complete response (n [%])	3 (2.5)	1 (0.8)	<b>3/0.025 = 120</b>	..
Partial response (n [%])	31 (26.3)	15 (11.9)	<b>31/0.263 = 118</b>	..
Stable disease (n [%])	66 (55.9)	73 (57.9)	<b>66/0.559 = 118</b>	..
Progressive disease (n [%])	8 (6.8)	26 (20.6)	<b>8/0.068 = 118</b>	..
Could not be evaluated (n [%])	10 (8.5)	11 (8.7)	<b>10/0.085 = 118</b>	..
Overall response (%)	34 (28.8)	16 (12.7)	<b>34/0.288 = 118</b>	..

The treatment response rate in the group that received regional hyperthermia was 28.8%, compared with 12.7% in the group who received chemotherapy alone (p=0.002).

(complete response and partial response) have been confirmed by external review (independent review committee) in 48 of 50 patients.

**Table 2: Response to treatment and survival in all patients assigned to treatment**

The treatment response rate in the group that received regional hyperthermia was 28.8%, compared with 12.7% in the group who received chemotherapy alone (p=0.002).

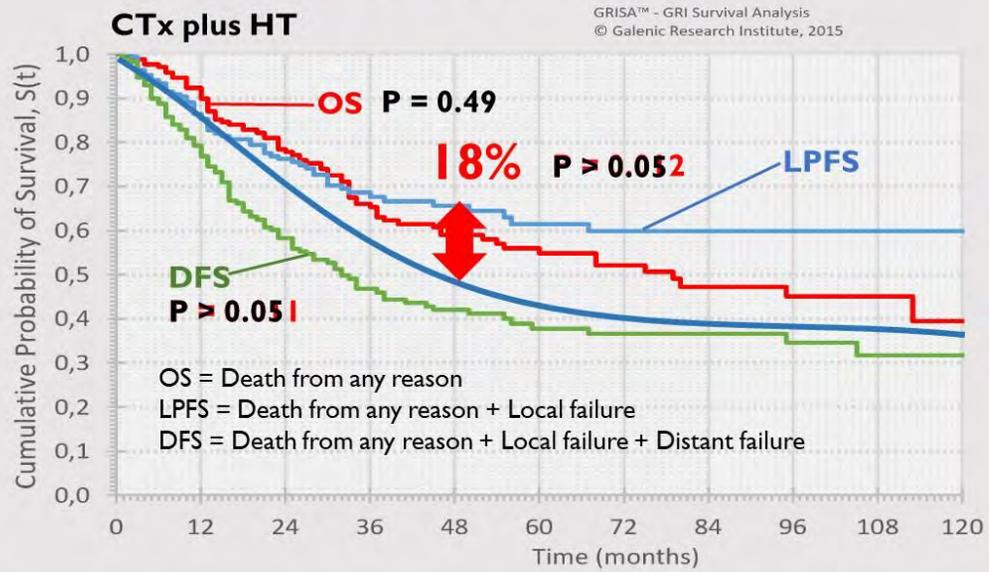
Table 2: Response to treatment and survival in all patients assigned to treatment

Response to induction therapy†				0.002	
No measurable disease	51 (30.2)	46 (26.7)	<b>61 (38.7)</b>	<b>57 (35.4)</b>	
Measurable disease	118 (69.8)	126 (73.3)			
Complete response (n [%])	3 (2.5)	1 (0.8)	<b>118 (34.6)</b>		118
Partial response (n [%])	31 (26.3)	15 (11.9)	..	..	
Stable disease (n [%])	66 (55.9)	73 (57.9)	..	..	341
Progressive disease (n [%])	8 (6.8)	26 (20.6)	..	..	
Could not be evaluated (n [%])	10 (8.5)	11 (8.7)	<b>22 - 16 = 6</b>		
<b>Overall response (%)</b>	<b>34 (28.8)</b>	<b>16 (12.7)</b>	<b>34 - 22 = 12</b>	<b>P = 0.068</b>	
			<b>34 - 16 = 18</b>	<b>P = 0.005</b>	

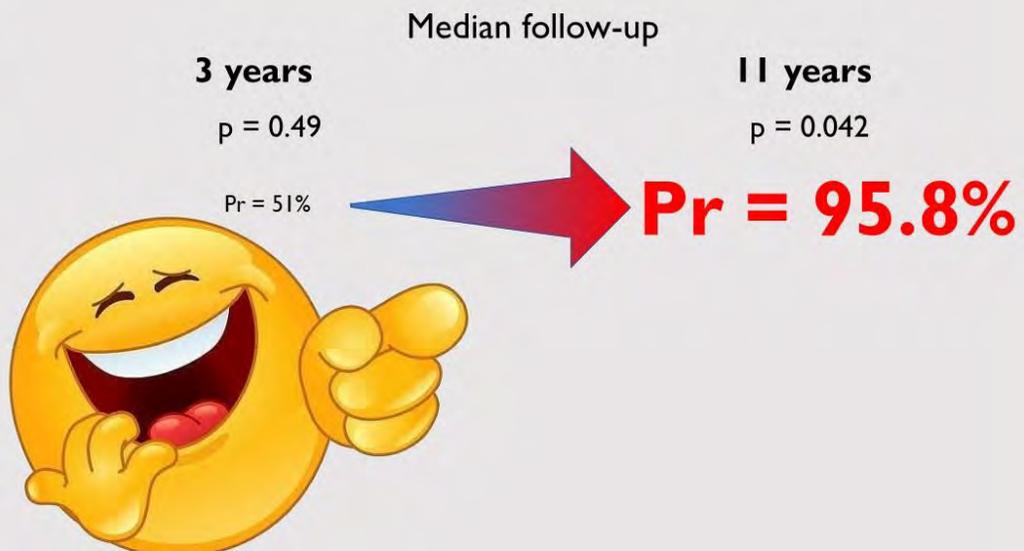
EIA=etoposide+ifosfamide+doxorubicin. RHT=regional hyperthermia. \*Calculated by log-rank test. †Response according to WHO criteria was assessed in patients with measurable disease at the time of randomisation. Responses (complete response and partial response) have been confirmed by external review (independent review committee) in 48 of 50 patients.

Table 2: Response to treatment and survival in all patients assigned to treatment

# WHERE IS THE BIAS?



# WHERE IS THE BIAS?



## WHERE IS A BIAS?

**OS** = Death from any reason =  
sarcoma-related death + death from treatment toxicity  
+ death from other tumors + death from other reason

**Sarcoma-specific survival** =  
sarcoma-relates death + death from treatment toxicity

“Among secondary endpoints, tumor response to induction therapy, disease-free survival, and **survival** were included ... **Survival** was defined as the time to death due to sarcoma or its treatment ... Deaths from other causes were not considered events and censored at the time of death.”

-14

315

-12

## WHERE IS A BIAS?

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sarcoma-related death + death from treatment toxicity  
+ death from other tumors + death from other reason

**Sarcoma-specific survival** =  
sarcoma-relates death + death from treatment toxicity

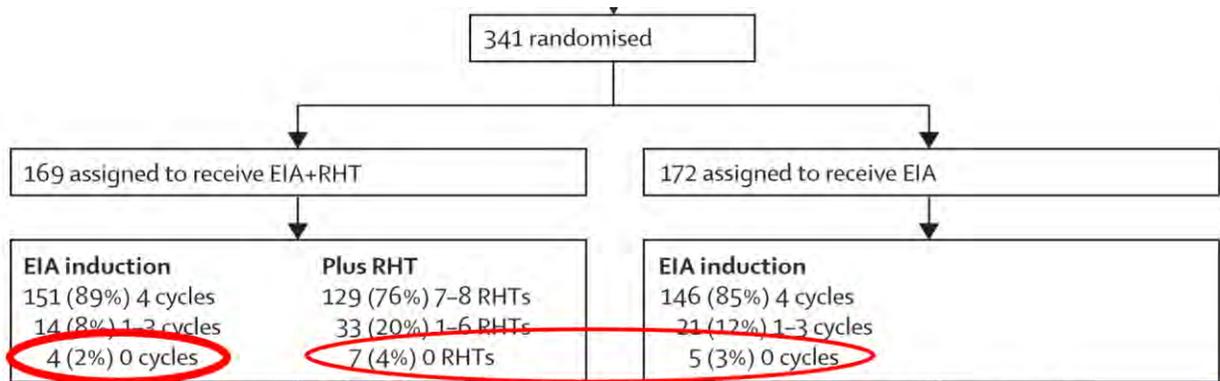
“Seven patients of the NACT-RHT group (6 withdrew of consent, 1 metastatic disease), and 5 patients of the NACT-alone group (4 withdrew of consent, 1 metastatic disease) were excluded.”

“Those patients never started their allocated treatment after randomization.”

-14

315

-12

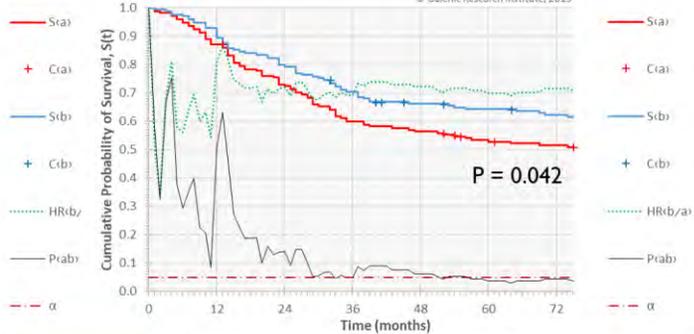
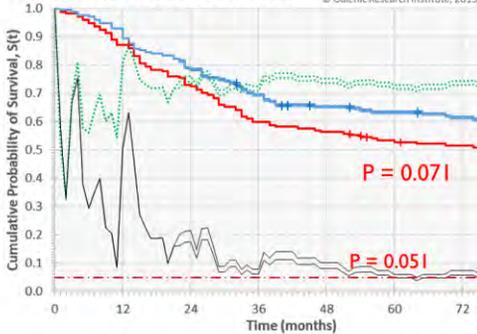


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“Those patients never started their allocated treatment after randomization.”

-14      315      -12

+ 2 events in the TCT arm

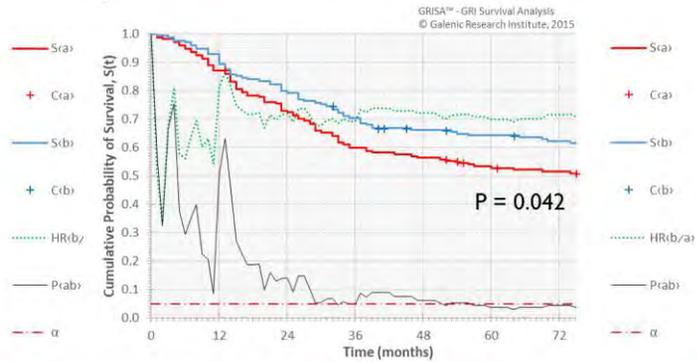
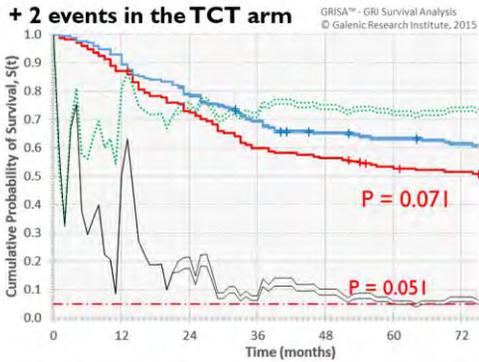


“Seven patients of the NACT-RHT group (6 withdrew of consent, 1 metastatic disease), and 5 patients of the NACT-alone group (4 withdrew of consent, 1 metastatic disease) were excluded.”

“Those patients never started their allocated treatment after randomization.”

-14      315 ~~+26 (7.6%)~~      -12  
-10      -7

**ITT**



“The survival-type analyses presented were based on the intention-to-treat population, which includes all eligible patients in the study who started their allocated treatment.”



## WHERE IS A BIAS?

**Sarcoma-specific survival (SSS) =**

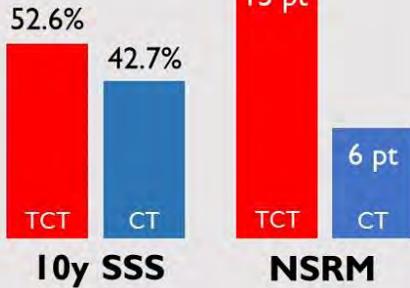
sarcoma-relates death + death from treatment toxicity

**Not sarcoma-related survival (NSRS) =** death from

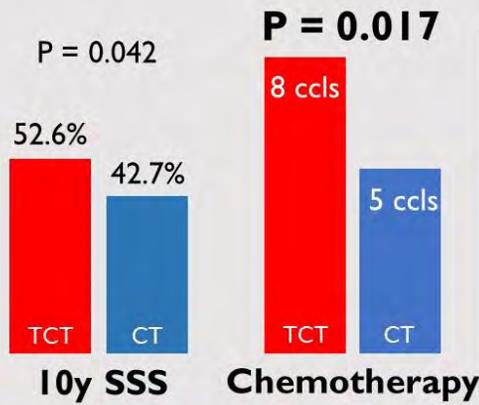
treatment toxicity + from other tumors + from other reason

P = 0.042

P = 0.039



# WHERE IS A BIAS?

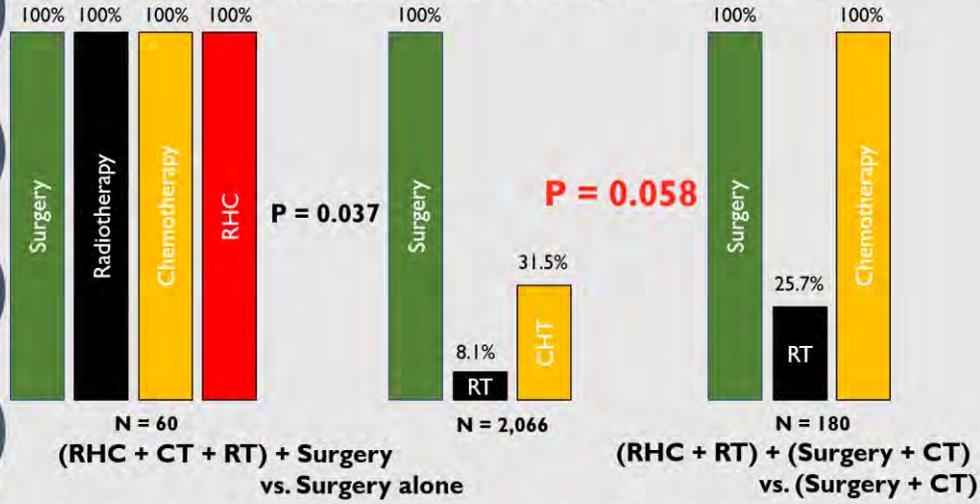


## CLINICAL OUTCOMES OF RADIO-HYPERTHERMO-CHEMOTHERAPY FOR SOFT TISSUE SARCOMA COMPARED TO A SOFT TISSUE SARCOMA REGISTRY IN JAPAN: A RETROSPECTIVE MATCHED-PAIR COHORT STUDY

- Institution: Departments of Orthopaedic Surgery of Graduate Schools of Medical Sciences of Nagoya City University and Kanazawa Universities, Japan; Department of Musculoskeletal Oncology, National Cancer Center Hospital, Tokyo, Japan
- Type: Retrospective analysis with matched control.
- Number of patients: 60
- Design: Efficacy of Neoadjuvant Radio-hyperthermo-chemotherapy (RHC) in 60 STS patients (of 150 treated with RHC) vs. propensity scores-matched group from 11,031 patients in the Bone and Soft Tissue Tumor Registry in Japan (BSTT).
- Result: **NEGATIVE** – no advantage in overall survival and local control.

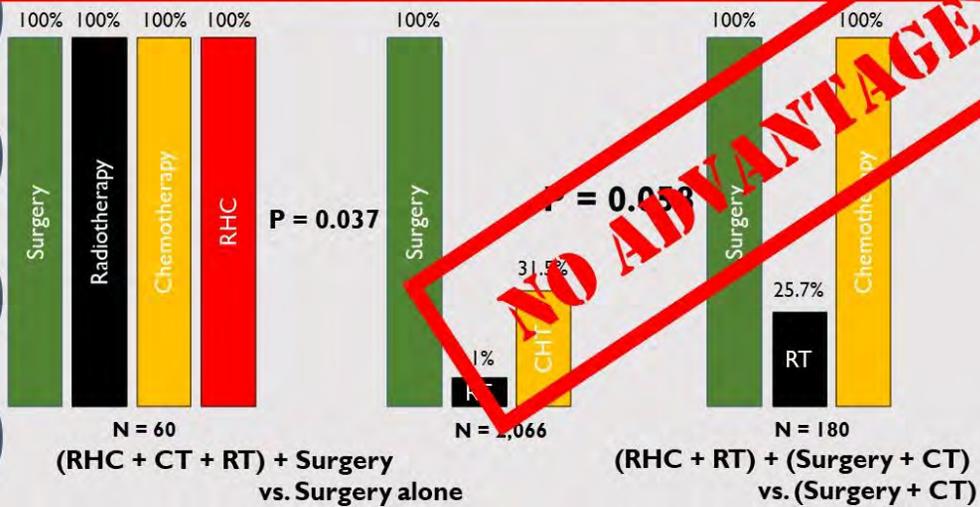
**CLINICAL OUTCOMES OF RADIO-HYPERTHERMO-CHEMOTHERAPY FOR SOFT TISSUE SARCOMA COMPARED TO A SOFT TISSUE SARCOMA REGISTRY IN JAPAN: A RETROSPECTIVE MATCHED-PAIR COHORT STUDY**

After adjustment, the difference in OS was not significant between groups (HR = 1.26, P = 0.532); however, a statistically significant difference in LC was observed (HR = 4.82, P = 0.037).



**INSUFFICIENT EVIDENCE**

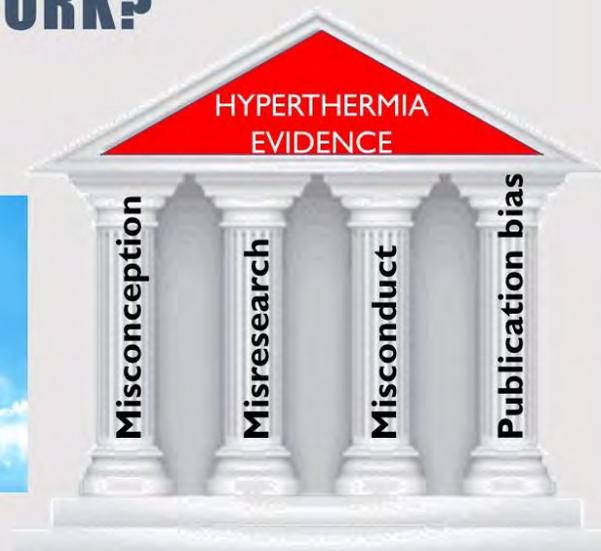
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- **Result:** NEGATIVE – no advantage in overall survival and local control.
- **Assessment:** the study relates to RHC but not hyperthermia.
- **Level of evidence:** IV (insufficient evidence).

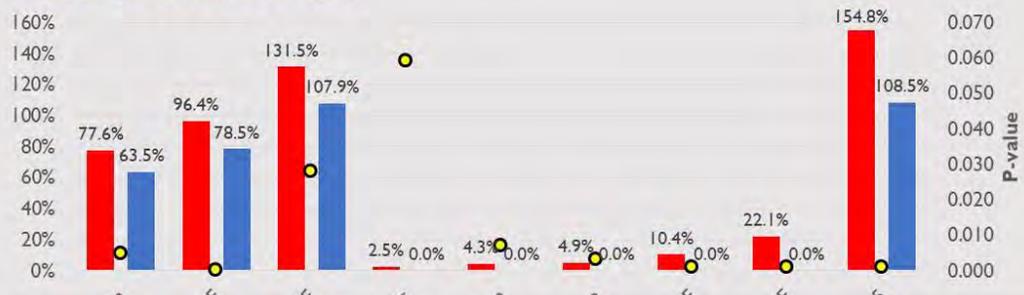
## HYPERTHERMIA EVIDENCE: HOW DOES IT WORK?





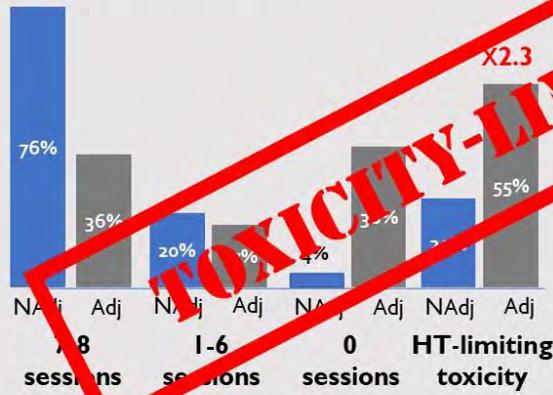
# WHY HYPERTHERMIA FAILED?

## HYPERTHERMIA: A TOXICITY-LIMITED TECHNOLOGY



*Our results indicate that regional hyperthermia combined with the three-drug-regimen EIA can be given **safely with moderate toxicity.***

# HYPERTHERMIA: A TOXICITY-LIMITED TECHNOLOGY



Other results indicate that regional hyperthermia combined with the three-drug-regimen EIA can be given **safely with moderate toxicity**.

# **Tumor-directed immunotherapy: combined radiotherapy and oncothermia**

**Kwan-Hwa Chi**

Professor, National Yang-Ming Medical University  
Chairman, Department of Radiation Therapy & Oncology, Shin-Kong Memorial Hospital, Taipei

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

Chi KH. (2018): Tumor-directed immunotherapy: combined radiotherapy and oncothermia; *Oncothermia Journal* 24:196-235  
[www.oncothermia-journal.com/journal/2018/Tumor\\_directed\\_immunotherapy.pdf](http://www.oncothermia-journal.com/journal/2018/Tumor_directed_immunotherapy.pdf)

# Tumor-directed immunotherapy: combined radiotherapy and oncothermia

**Kwan-Hwa Chi**

Chairman, Department of Radiation Therapy & Oncology, Shin Kong Wu Ho-Su Memorial Hospital

Professor, National Yang-Ming University

## Objective

Radiotherapy is an important part of cancer treatment. Hyperthermia has long been regarded as one of the best radiosensitization method. Oncothermia is a new kind of hyperthermia machine emphasizing energy absorbed on tumor cell membrane instead of nonspecific temperature rising around the treatment region. We proposed that oncothermia may have immune potentiation effect besides its radio(chemo)-sensitization effect

## Methods

We aimed to examine, how real the abscopal events and what is the therapeutic effect of combined oncothermia and RT. Patients treated with combined RT and oncothermia since January 2017 till December 2017 at Shin-Kong Hospital, Taipei were retrospectively reviewed. We analyzed those who have measurable disease, performance status  $\leq 2$ , a minimal RT dose of 30Gy and at least 4 times of oncothermia treatments. The primary prostate cancers were excluded.

## Results

There were 60 patients evaluable, 27 patients with localized disease, in whom RT were the main treatment. Among them the CR rate was 22.2%, PR rate was 55.5%, SD with 14.8%. Two patients (one phylloid tumor of breast and one pancreatic cancer) were progressive disease after treatment. Most patients had acceptable local control for a median follow-up time of 9 months. Thirty-three patients with metastatic disease received palliative RT for a total of 38 sites, with a median dose of 44Gy/22fx to major disease sites. Patients with CR/PR has much longer survival than those not (SD+PD) ( $P < 0.001$ ). Shallower tumor ( $< 5\text{cm}$  below skin) seemed to have better effect than deeper tumor, but not significant ( $P > 0.1$ ). The objective response (CR+PR) in treated area is 60.7%. Most strikingly, there were obvious abscopal response in 3 patients. All of them had autoimmune reaction from treatment. One patient had autoimmune hepatitis the other one had dermatitis hapefiforms, and one patient had severe myasthenia gravis. They all had long duration of response without systemic treatment.

## Conclusion

We reported that the combination of RT and oncothermia is effective and well tolerated. Oncothermia seems to have efficient radiosensitization effect in combined with RT or CCRT. Only randomized trial can answer the real clinical benefit of combined RT+HT on advanced cancer. However, a connection of autoimmune response is an evidence of immune boosting from oncothermia. Oncothermia activates lymphocyte in situ and provoked abscopal effect with RT. How oncothermia treatment provokes autoimmune reaction can pave the way antitumor immunity is underway

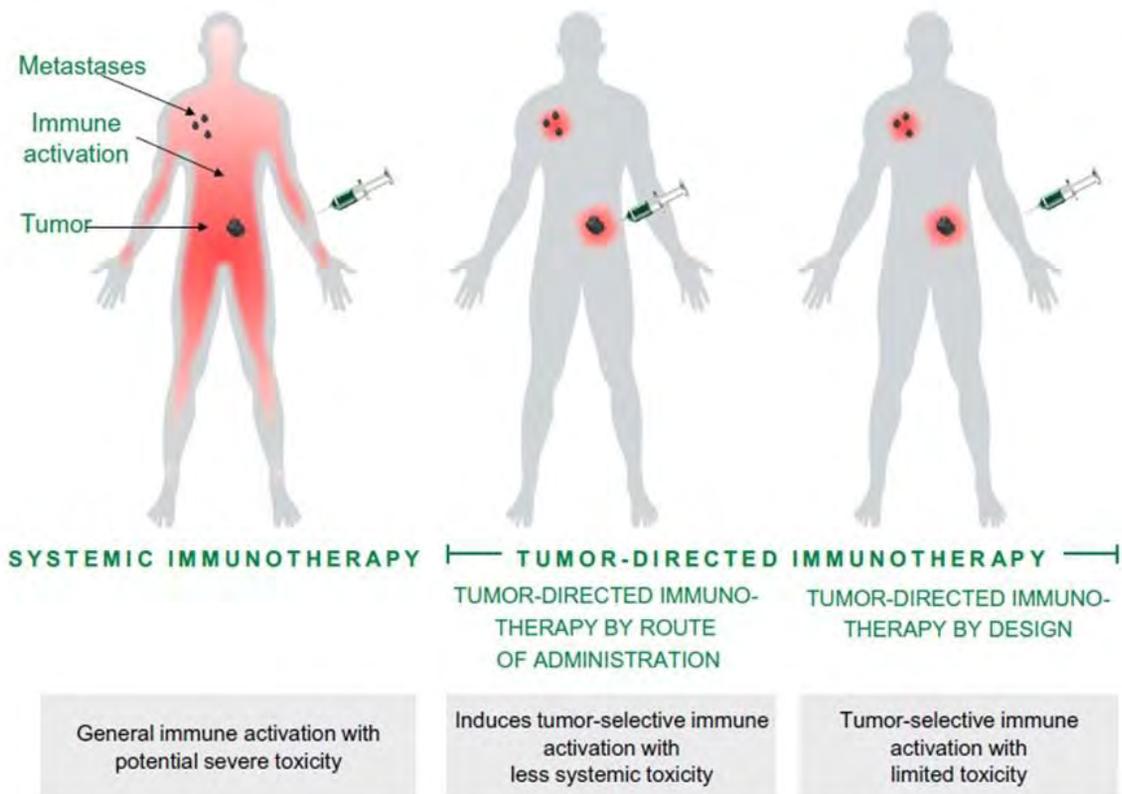
# Tumor-directed immunotherapy: combined radiotherapy and oncothermia

Kwan-Hwa Chi, MD

Professor , National Yang-Ming Medical University  
Chairman, Department of Radiation Therapy& Oncology,  
Shin-Kong Memorial Hospital, Taipei

## Tumor-directed immunotherapy

- Produce specific immune cells that did not exist.
- Activate immune cells that have already home to the tumor/ local LN where tumor antigen present.
- Minimizing irrelevant activation of the rest of immune system.



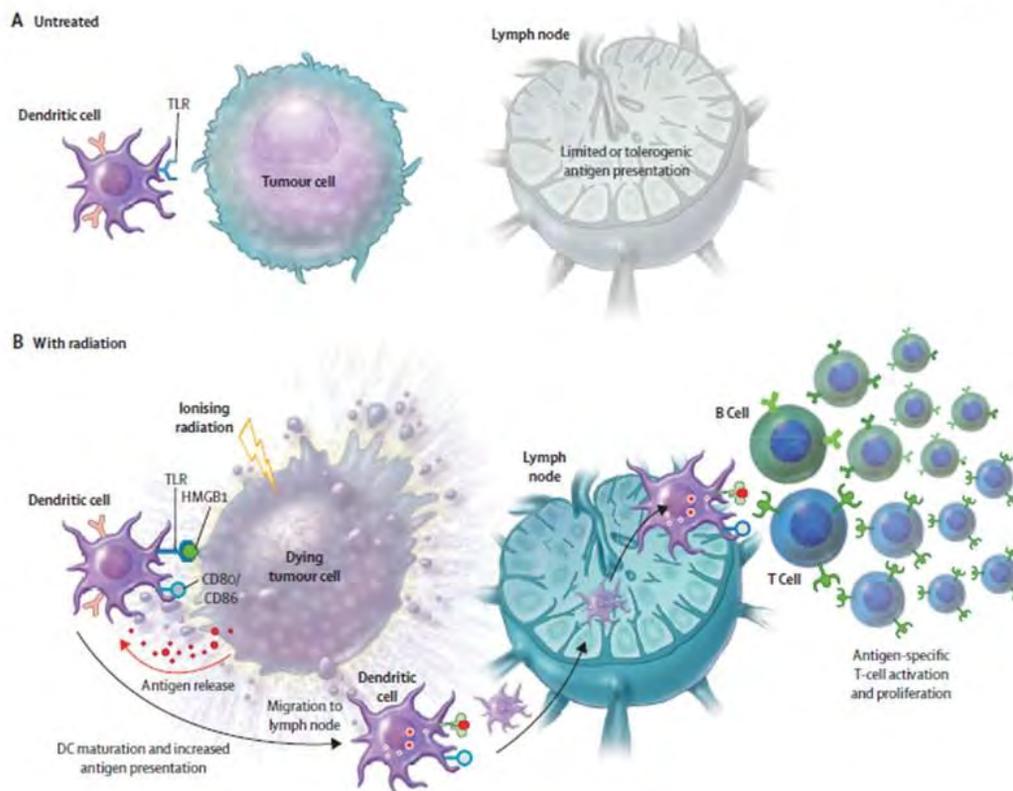
## Goal of in situ vaccination

- Stimulate local anti-tumor immune response
- Generate systemic anti-tumor immune response
- Local control + systemic control

- Immune system is inherently systemic, Not local!
- But local inflammation is much safer than systemic inflammation, if the inflammation should be strong enough.

## Methods of in situ vaccination

- Cell death + immune adjuvant (local)
- Tumor targeted immunotherapy
- The role of RT
- The role of HT



7

## STING

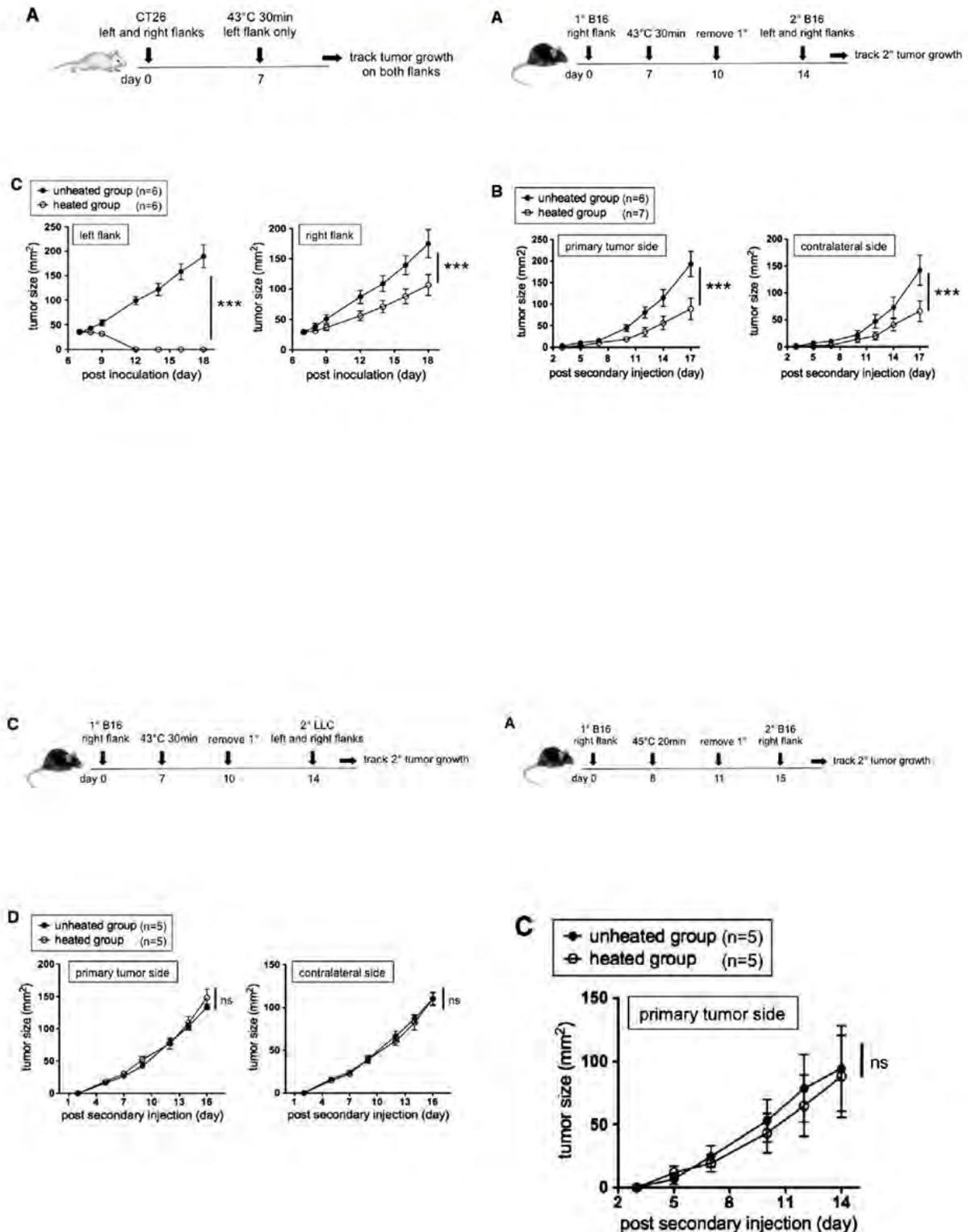
- The most important source of STING is endothelial cells.
- The principle controlling source is cyclic GMP-AMP synthase (cGAS)-the cytosolic DNA sensor for STING.
- cGAS STING-IFN is required for DCs cross-priming.
- DNA delivery in a cell contact – dependent manner to DC-tumor interaction.
- Exogenous cGAMP could improve RT effect effectively.

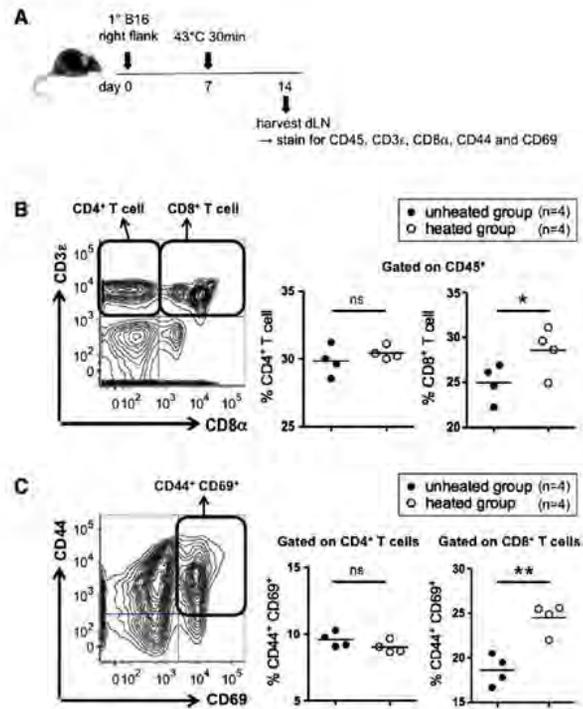
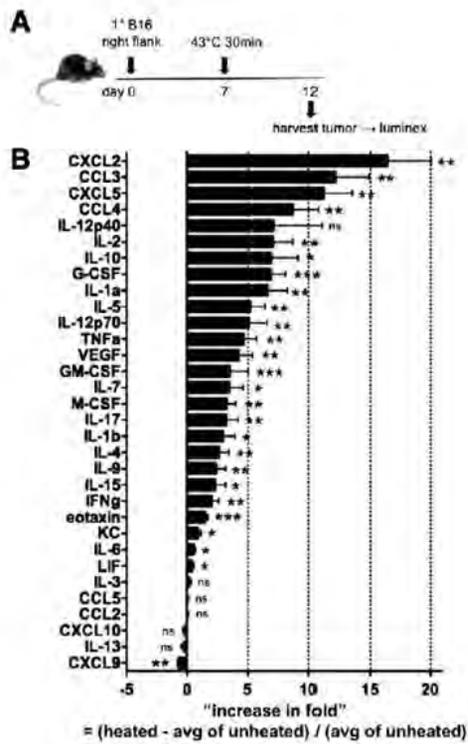
8

# Local hyperthermia treatment of tumors induces CD8<sup>+</sup> T cell-mediated resistance against distal and secondary tumors

Seiko Toraya-Brown, PhD<sup>a,1</sup>, Mee Rie Sheen, MS<sup>a,1</sup>, Peisheng Zhang, MD<sup>a</sup>, Lei Chen, BS<sup>a</sup>,

Nanomedicine: Nanotechnology, Biology, and Medicine  
10 (2014) 1273–1285





## SKH-Hyperthermia Center

Oncothermia EHY-2000



Yamamoto RF-8



# Thermatron RF-8 vs Oncothermia

- Both are RF hyperthermia (8MHz vs 13.56 MHz), but different in electrode (capacitive vs radiative capacitive)
- RF-8 maximizing the power to heat, Oncothermia maximizing current (minimizing voltage) with fixed power.
- Oncothermia uses SAR, based on Joule energy absorption for dose; RF-8 uses CEM43Tx, based on temperature.
- The goal of RF-8 is the homogeneous heating of tumor mass, while oncothermia goal is the heterogeneous heating of the membrane rafts of malignant cells.

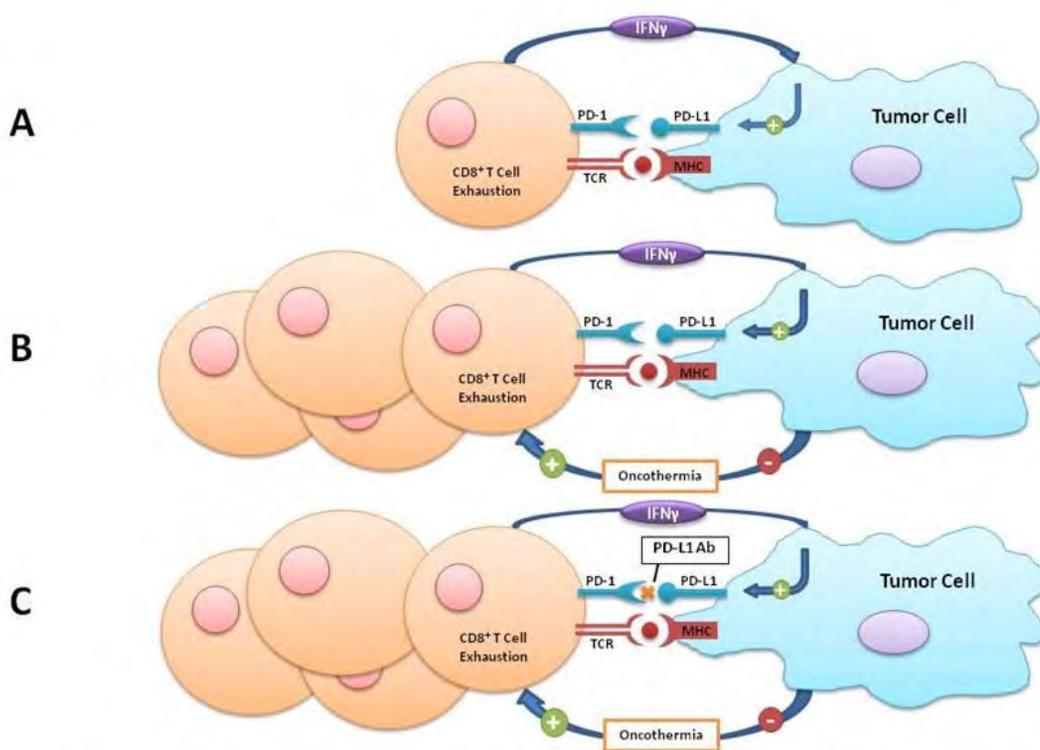


**RF-8 is a more reliable temperature dependent radio(chemo)sensitization machine, but Oncothermia has more Immune sensitization effect.**

**Why? Really?**

# Oncothermia is a hyperthermia machine with stronger excitability than heat

1. Cancer cells were excited but exhausted with ATP depletion.
2. Immune cells were excited and activated

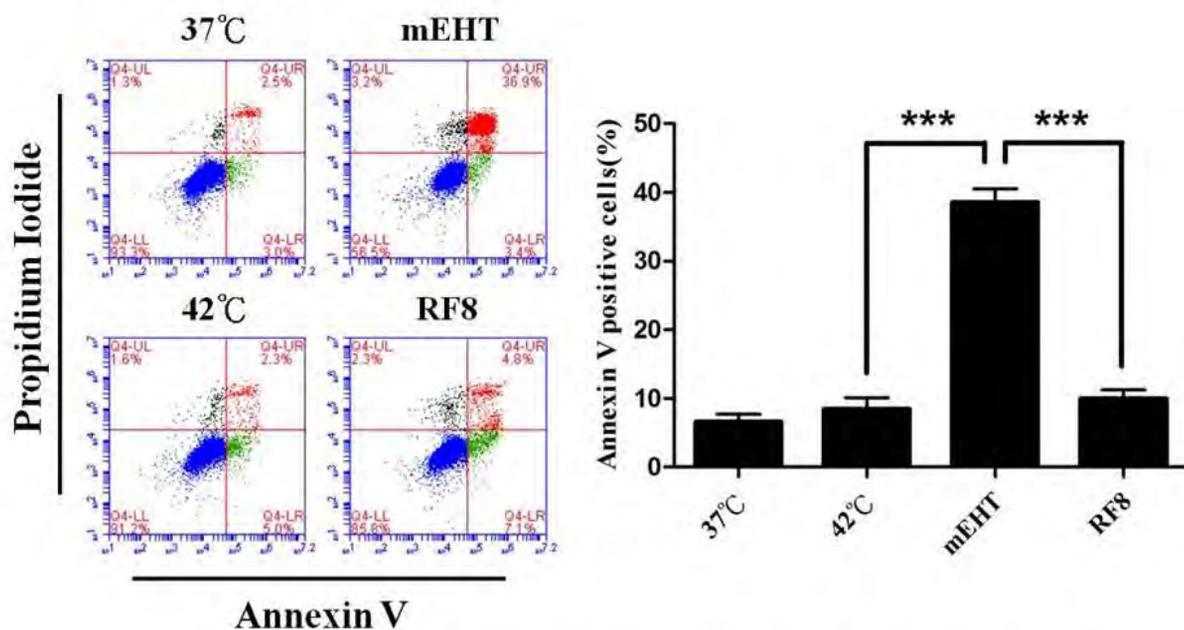


The rationale for adding Anti PD-L1 monoclonal antibody to Oncothermia

# Oncothermia as immunotherapy machine ?

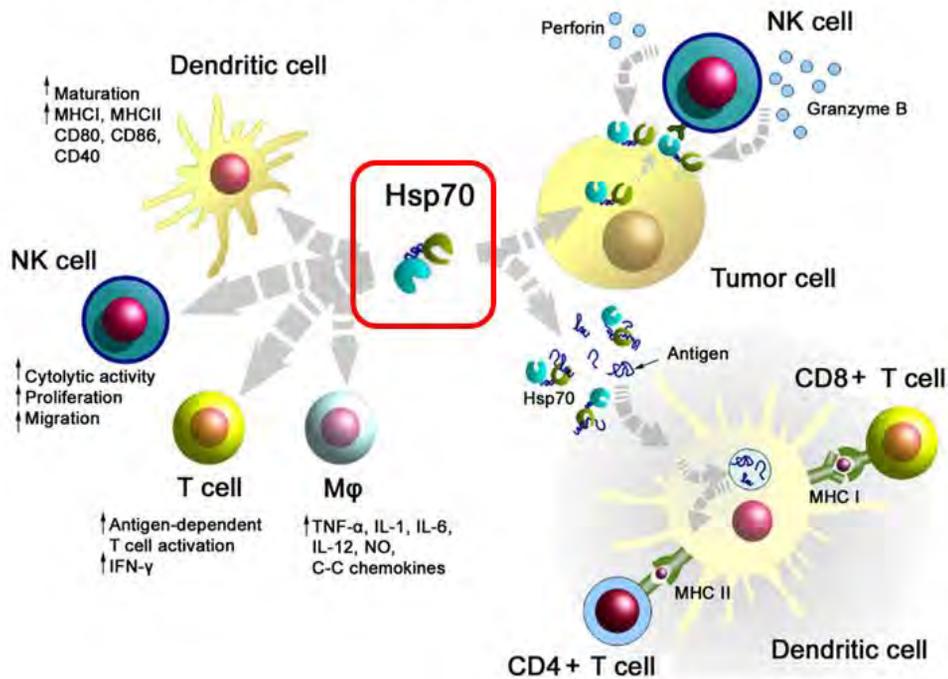
- Will oncothermia change tumor microenvironment ?
- Will oncothermia activate immune cells ?
- Will oncothermia intensify the effect of immune checkpoint inhibitors ?
- Will oncothermia increase abscopal effect ?
- Will oncothermia increase autoimmune reaction ?
- Will oncothermia produce tumor hyperprogression ?

## Significant Elevation of Apoptosis After Oncothermia Treatment



Yang KL et al, Oncotarget. 2016 Dec 20;7(51):84082-84092.

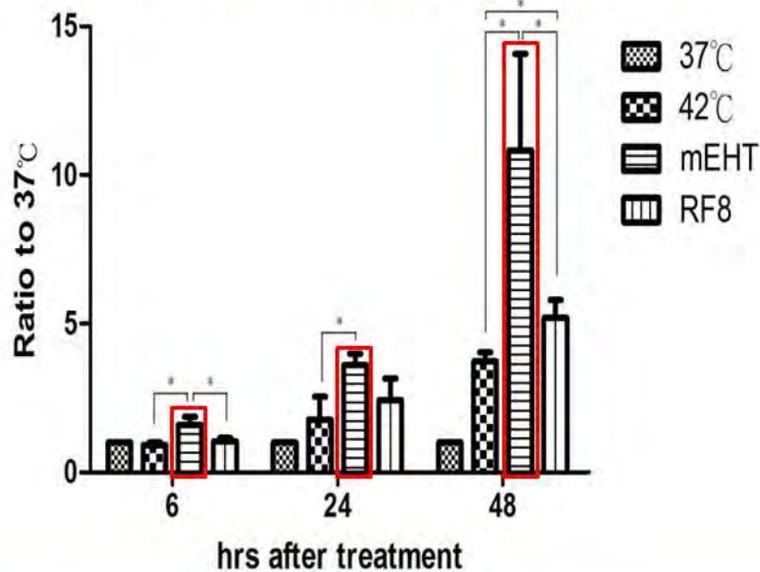
# Major immune modulatory functions of heat shock protein 70 (Hsp70)



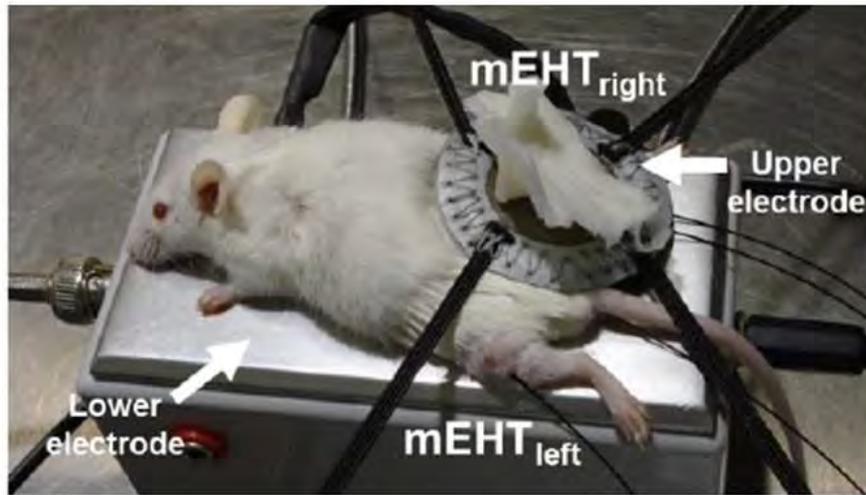
Shevtsov M and Multhoff G (2016) *Front. Immunol.* 7:171.

## Stress protein analysis

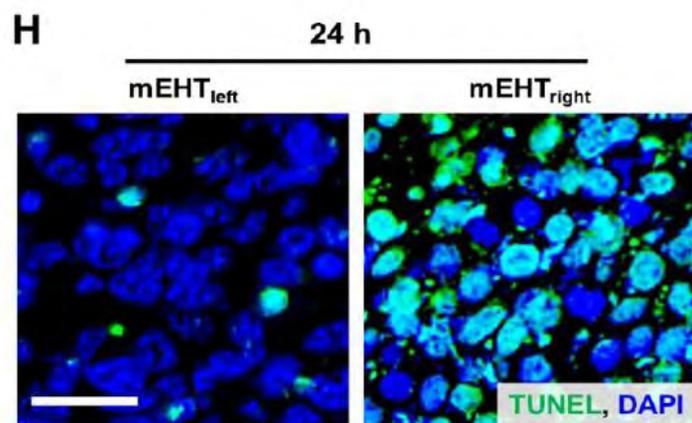
### The release of HSP70 expression



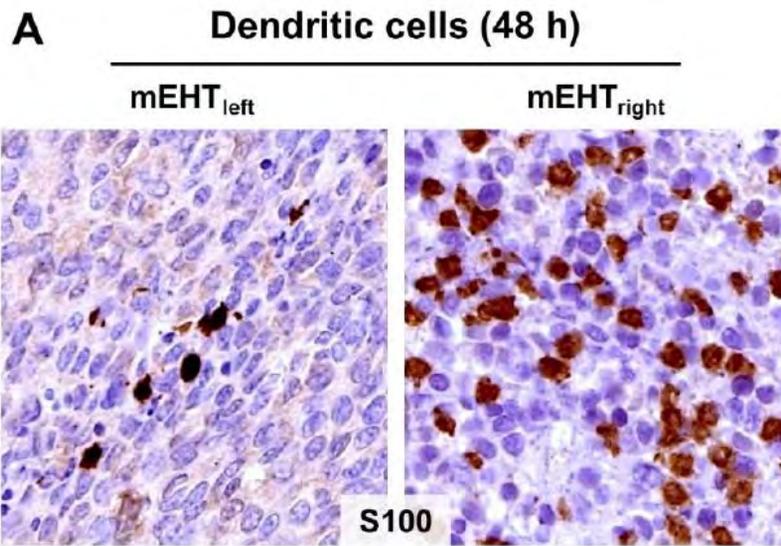
Oncothermia triggered a significantly secretion of HSP70 from cancer cells.



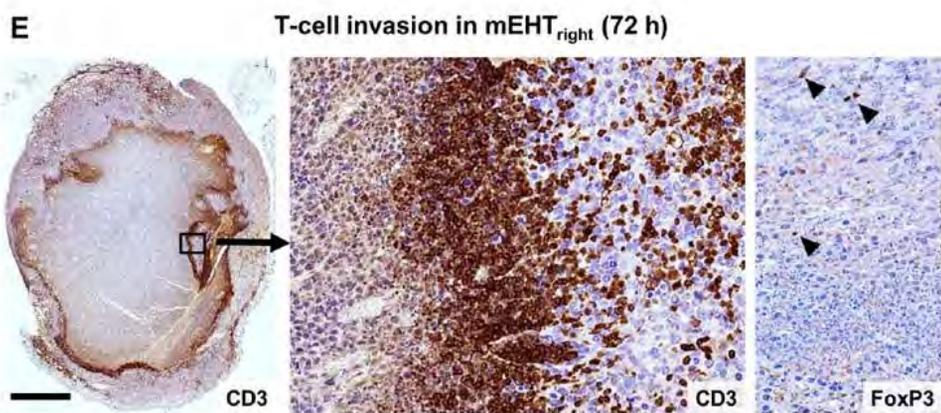
Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts  
 Vancsik T, Krenacs T, et al. 2018



Vancsik T, Krenacs T, et al. 2018

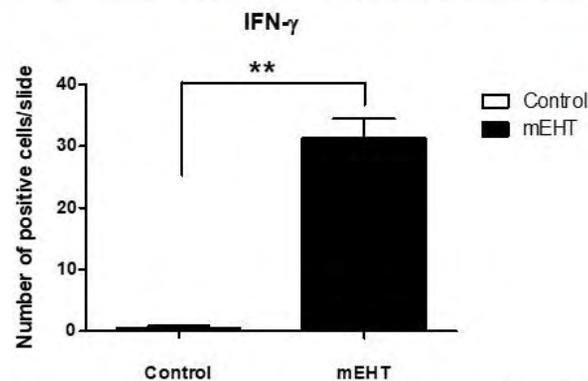
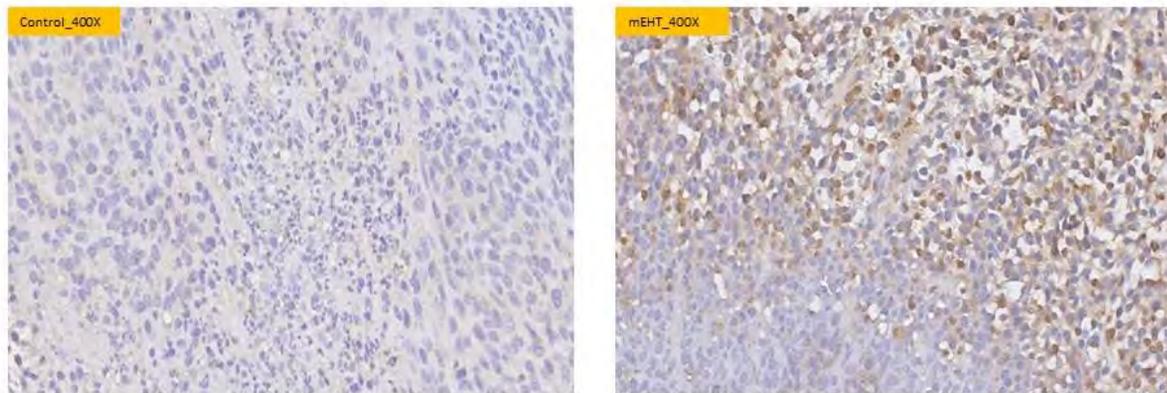


Vancsik T, Krenacs T, et al. 2018



Vancsik T, Krenacs T, et al. 2018

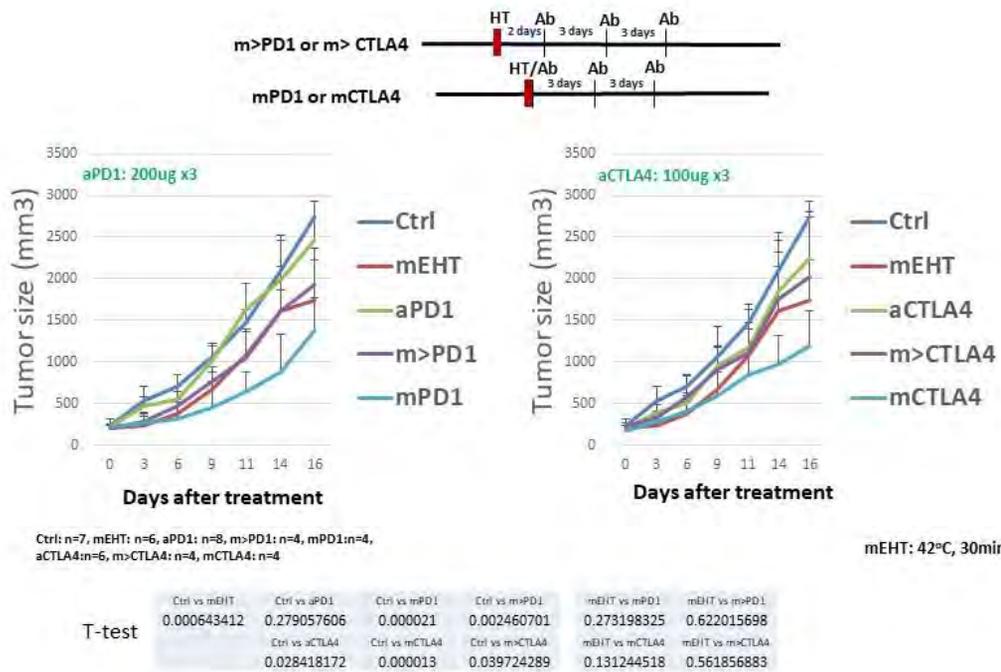
## Oncothermia Induced IFN- $\gamma$ Production in Tumor



Wang YS et al, Unpublished data

## Oncothermia as immunotherapy machine ?

- Will oncothermia change tumor microenvironment ?
- Will oncothermia activate immune cells ?
- **Will oncothermia intensify the effect of immune checkpoint inhibitors ?**
- Will oncothermia increase abscopal effect ?
- Will oncothermia increase autoimmune reaction ?
- Will oncothermia produce tumor hyperprogression ?



## Retrospective review of our Oncothermia experience:

- Treatment period: 2017/1- 2017/11.
- All patients were treated with combined radiotherapy and oncothermia with or without other systemic therapy.
- Response was evaluated on irradiated site

## Patient characteristics

Characteristics	No	%
Sex		
Female	26	43.3
Male	34	56.7
Age, median, range	59.5	36-89
WHO Performance status		
0	1	1.7
1	54	90.0
2	5	8.3
Localized disease	27	
RT	27	100
CT	17	63.0
IO	1	3.7
CT+IO	2	7.4
Metastatic/ Recurrent disease	33	
RT	33	100
CT	12	36.4
IO	8	24.2
CT+IO	8	24.2

## Cancer Type

Primary cancer site	Localized(N=27)	(%)	Metastatic/ Recurrent(N=33)	(%)
Breast ca	6	22.2	7	21.2
Lung ca	5	18.5	5	15.2
HCC	4	14.8	3	9.1
Head & Neck ca	2	7.4	2	6.1
Pancreas ca	2	7.4	1	3.0
Cholangiocarcinoma	1	3.7	3	9.1
Bladder ca	1	3.7	2	6.1
Colon ca	1	3.7	2	6.1
Esophageal ca	1	3.7	1	3.0
GBM	1	3.7	0	0
Thyroid ca	1	3.7	0	0
Spine tumor	1	3.7	0	0
Gallbladder ca	1	3.7	0	0
Prostate ca	0	0	1	3.0
Gastric ca	0	0	1	3.0
Cervix cancer	0	0	1	3.0
Ovary ca	0	0	1	3.0
Rectal ca	0	0	1	3.0
Urothelic cancer	0	0	1	3.0
Uterine sarcoma	0	0	1	3.0

## Response rate on the irradiated sites

Response	Localized(N=27)	Metastatic/ Recurrent(N=33)
CR	6 (22.2%)	2 (6.1%)
VGPR*	5 (18.5%)	5 (15.2%)
PR	10 (37.0%)	13 (39.4%)
SD	4 (14.8%)	9 (27.3%)
PD	2 (7.4%)	4 (12.1%)

\*VGPR = Very good CR , mean >90% shrinkage

## Response rate according to tumor size analysis for all patients

Tumor volume	CR/PR (%)	SD/PD(%)
GTV $\geq 500\text{cm}^3$ (N=12)	11 (91.7)	1 (8.3)
GTV $< 500\text{cm}^3$ (N=48)	30 (62.5)	18 (37.5)

P=0.049\*

## Treatment toxicity (CTCAE v4.0)

Toxicity	Case number (N)	Grade
Skin toxicity	1*	1
Hepatic toxicity	1*	3
Myelotoxicity	0	0
Neurotoxicity	1*	3
Renal toxicity	0	0
Pneumonitis	0	0
Soft tissue damage	0	0
Fatigue	0	0
Fever	0	0
Fat induration	0	0

\*auto-immune reaction

### 許\*毓 Hepatoma



2016/10/16 治療前CT

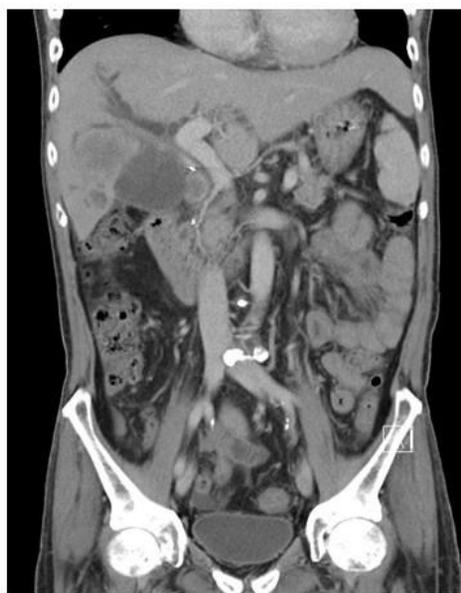


20170525治療後CT

## 王\*豪 Cholangiocarcinoma



20170608治療前CT



20170731治療中CT

## 曾\*耀 Hepatoma



20161201治療前CT

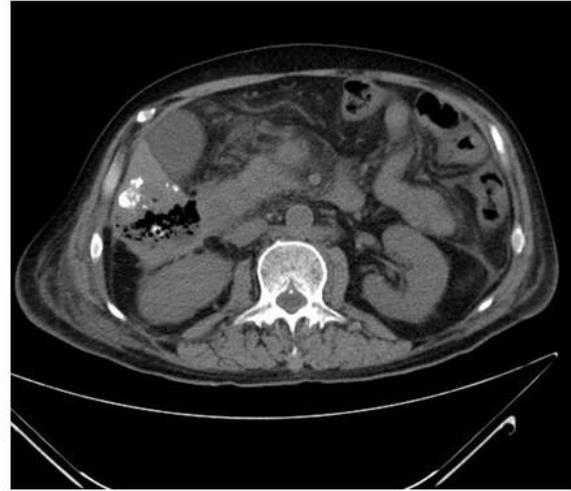


20170216最後一天治療完CT

## 郭\*豪 14530953



20170425治療前CT



20170707 治療第一階段完CT

## 許\*欣 Hepatoma



20171009治療前CT



20180403治療後CT

鄭\*玲 05537437

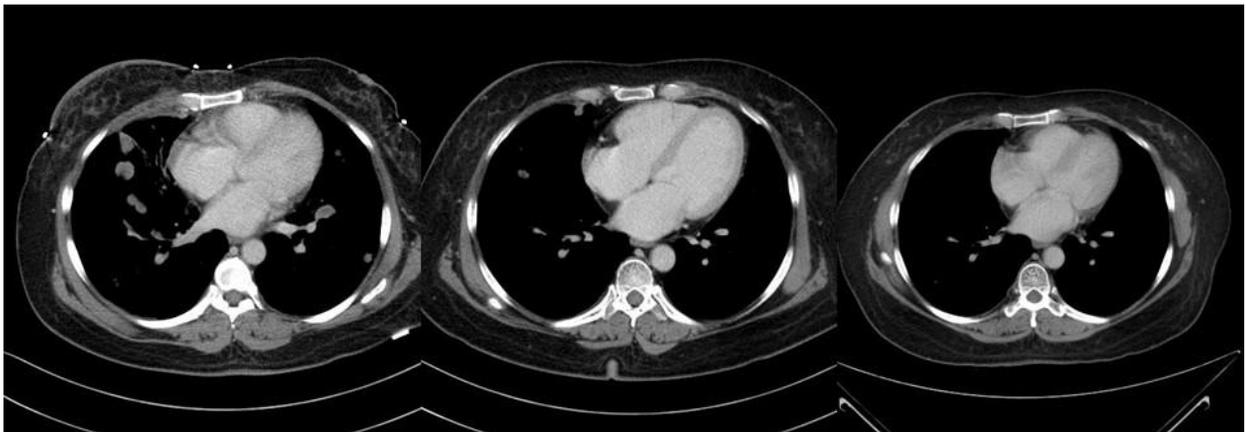


治療前



治療後

陳\*鳳 20067028



20170328治療前CT

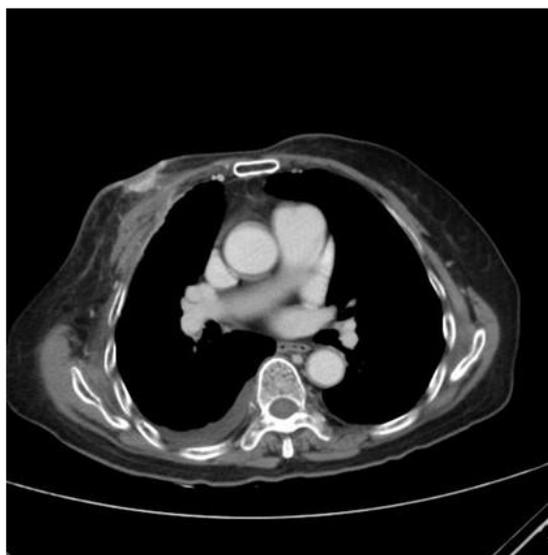
20171024治療後CT

20171226治療後 追蹤CT

## 簡\*妙子 Breast ca

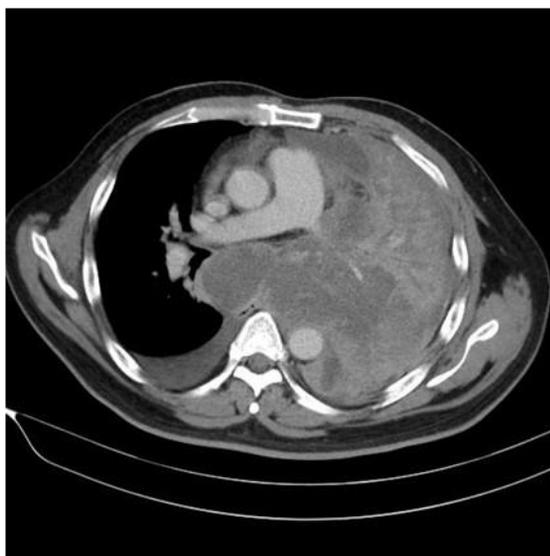


20161206治療前



20171017治療後

## 陳\*達 Small cell lung cancer

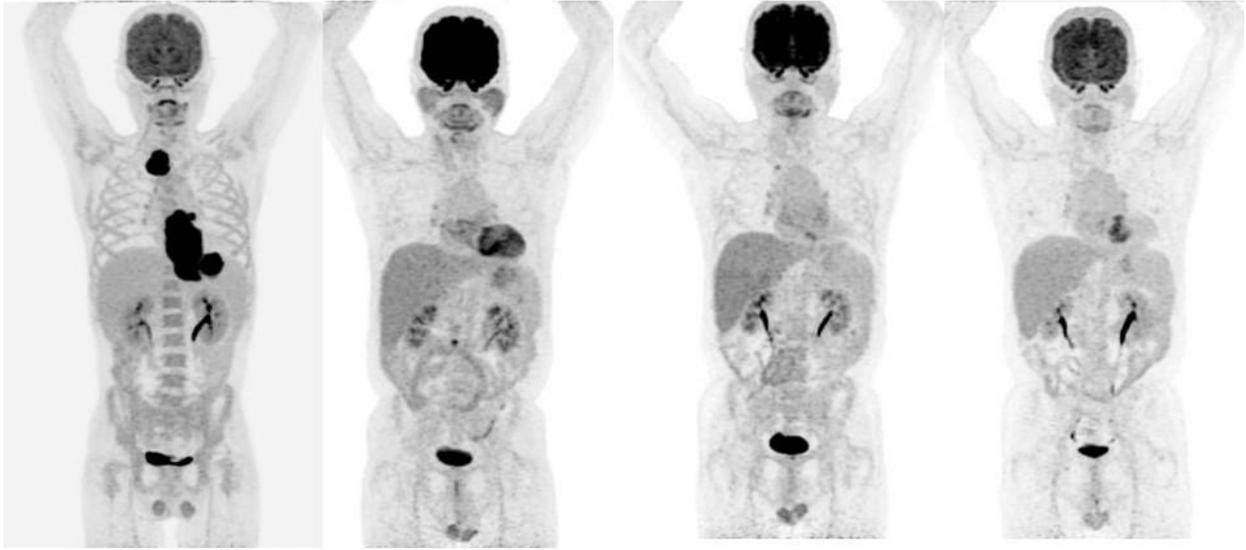


20170509 治療前CT



20171003 治療後CT

# 葉\*宏 Esophageal cancer



20170322 治療前  
PET-CT

20170913 治療後  
PET-CT

20171229 治療後  
持續追蹤PET-CT

20180419 治療後  
持續追蹤PET-CT

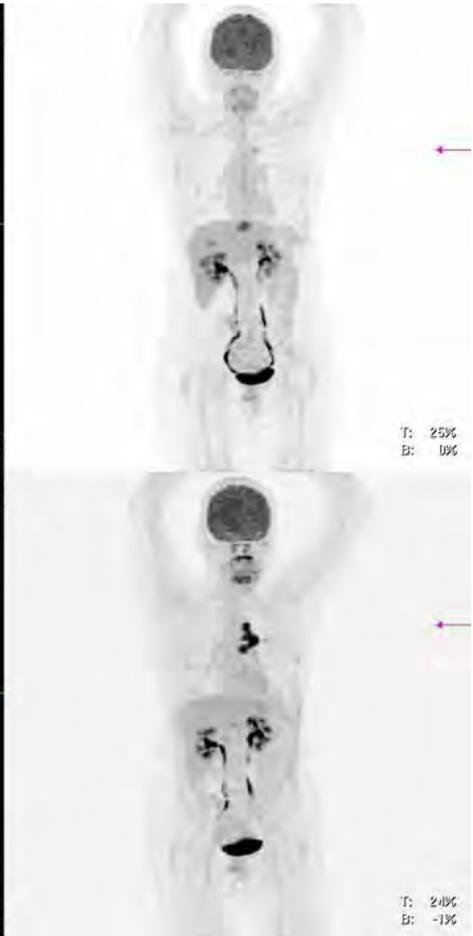
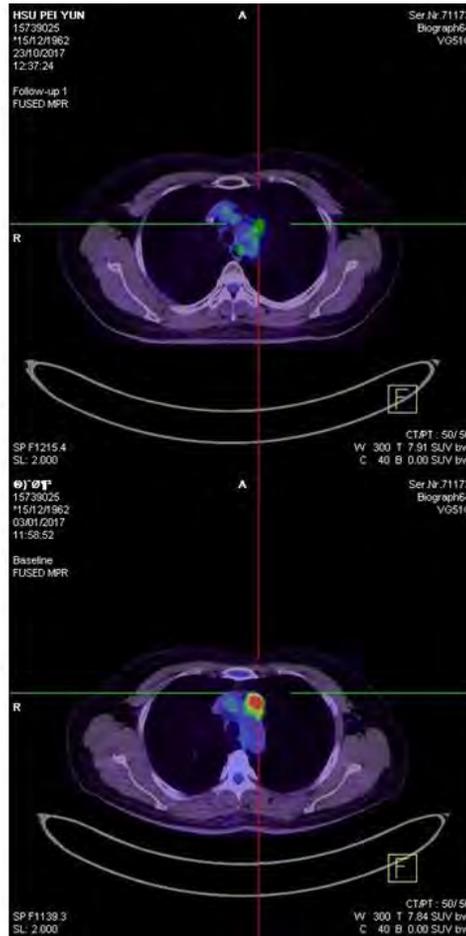
徐\*雲

15739025

Lung

20171026  
治療後PET-CT

20170103  
治療前PET-CT



## 余\*\*雲 Cervix cancer lung mets



20170705 治療前CT



20170926 治療中PET-CT

T:  
B

## 張\*正 Stomach cancer peritoneal seedings



20170323 治療前CT



20170609 治療後CT

## Oncothermia as immunotherapy machine ?

- Will oncothermia change tumor microenvironment ?
- Will oncothermia activate immune cells ?
- **Will oncothermia increase abscopal effect ?**
- **Will oncothermia increase autoimmune reaction ?**
- Will oncothermia produce tumor hyperprogression ?
- Will oncothermia intensify the effect of immune checkpoint inhibitors ?

There were 3 patients out of 33 patients developed autoimmune disease, all of them had more than 8 month of treatment-free interval.

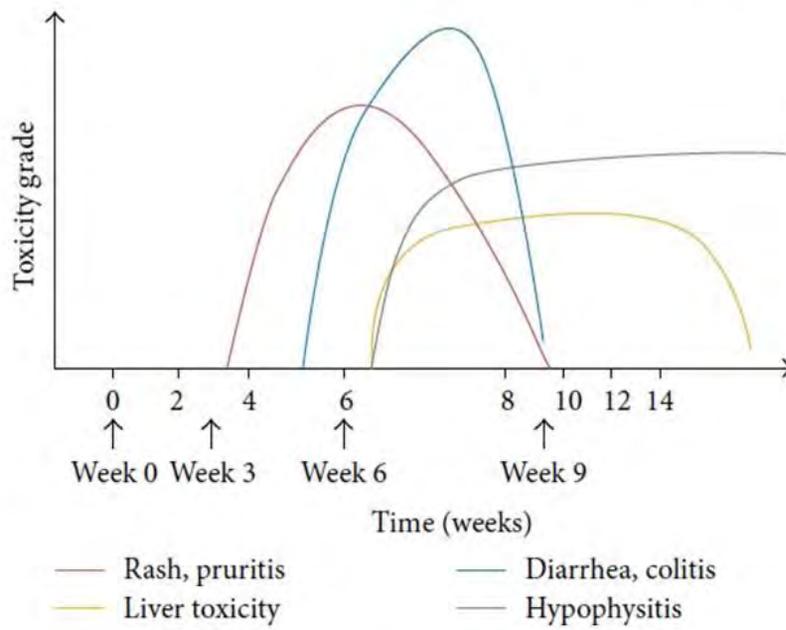
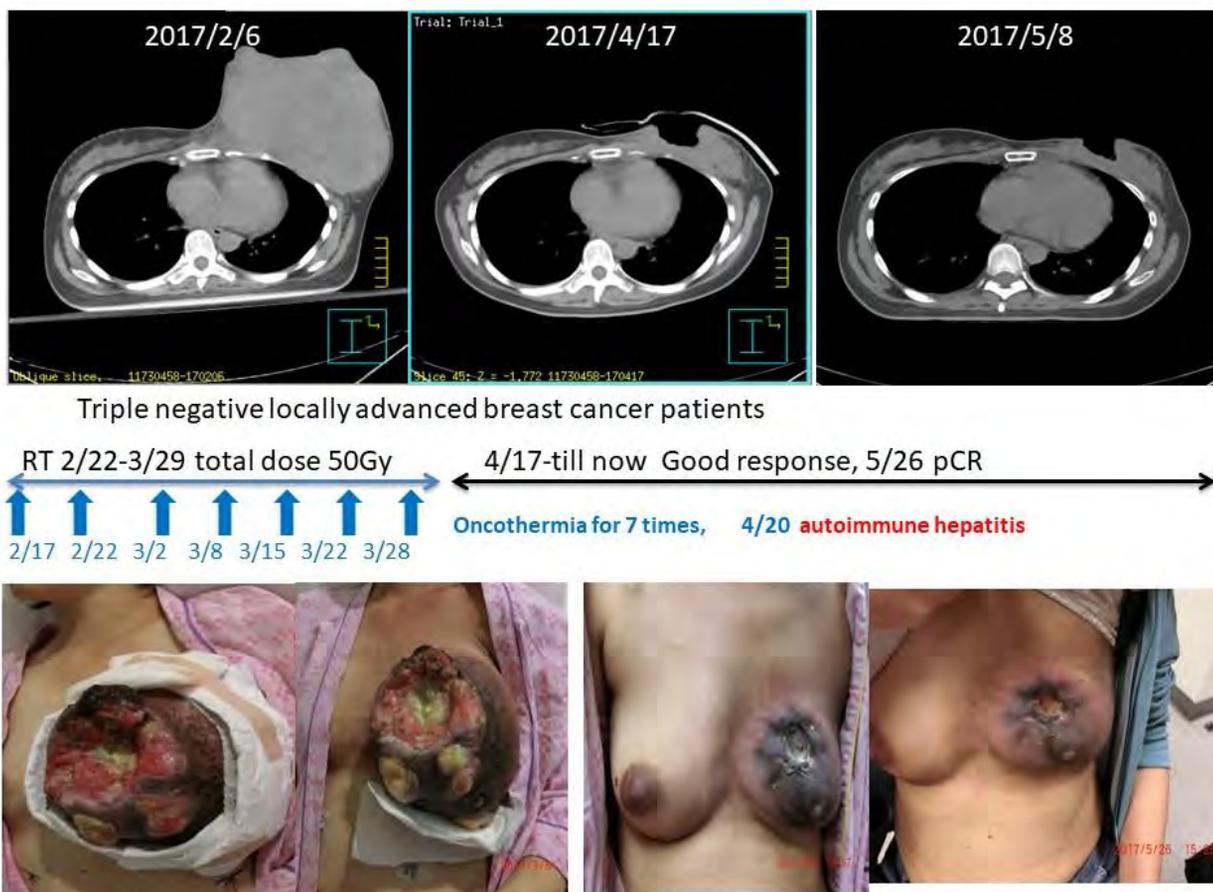
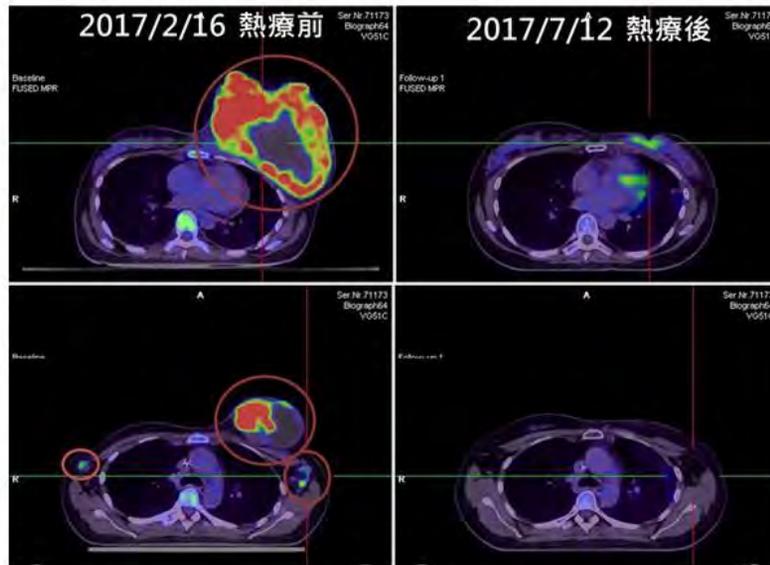


FIGURE 2: Kinetics of appearance of irAEs according to organ system involved [11]; adapted with permission from Weber et al. 2012 [11].





謝\*真 11730458  
**Breast ca with Lung Metastasis**



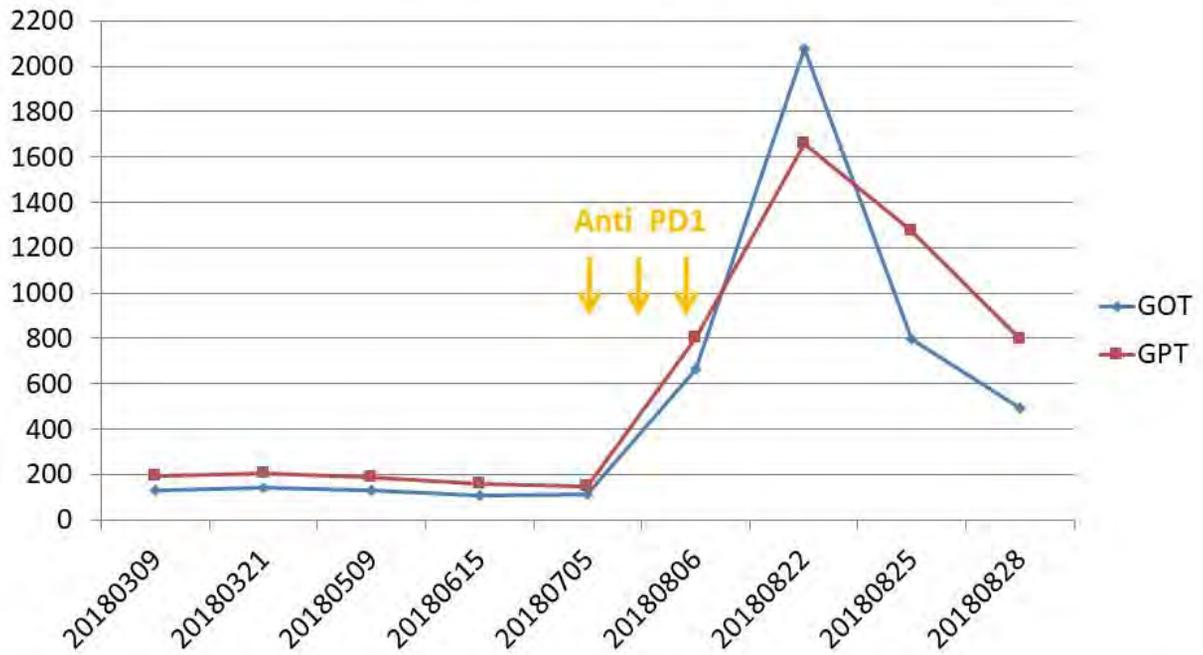
20180328 CT

20180628 CT

20180730 CT

Chi KH et al, Unpublished data

# 謝\*真 11730458



Chi KH et al, Unpublished data

Rt. UCC of renal pelvis with abdomen and liver meta.  
RT to abdomen mass 40Gy +OT x 6



20170521治療前CT



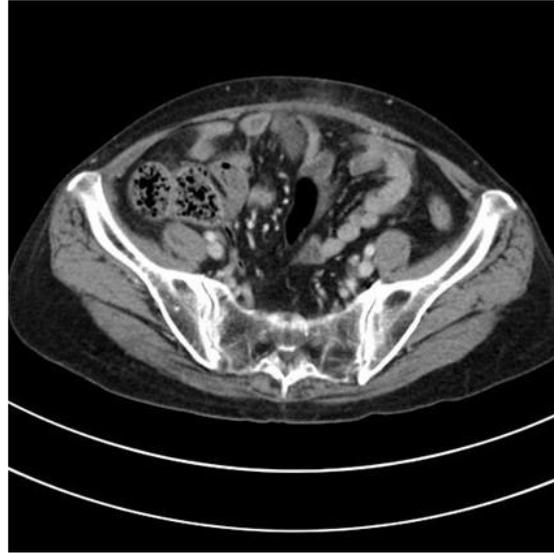
20170821治療第一階段完CT

Rt. UCC of renal pelvis with abdomen and liver meta.

RT to abdomen mass 40Gy +OT x 6

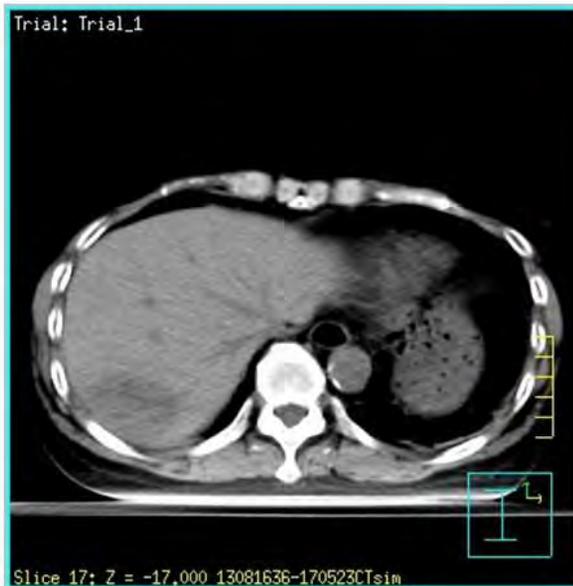


20170521治療前CT



20170821治療第一階段完CT

Abscopal Effect on Liver mass  
(no liver irradiation)



Slice 17; Z = -17,000 13081636-170523CTsim



Oblique slice, 13081636-170626-MVCT

# 葉\*華 130xx636



20170521治療前CT



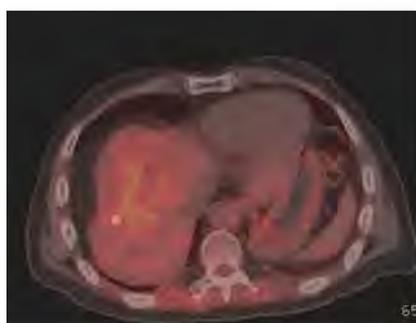
20170821治療完CT



20171120治療後CT

# 劉\*秋 20311631

## Cholangiocarcinoma with Liver Metastasis



治療前 PET-CT



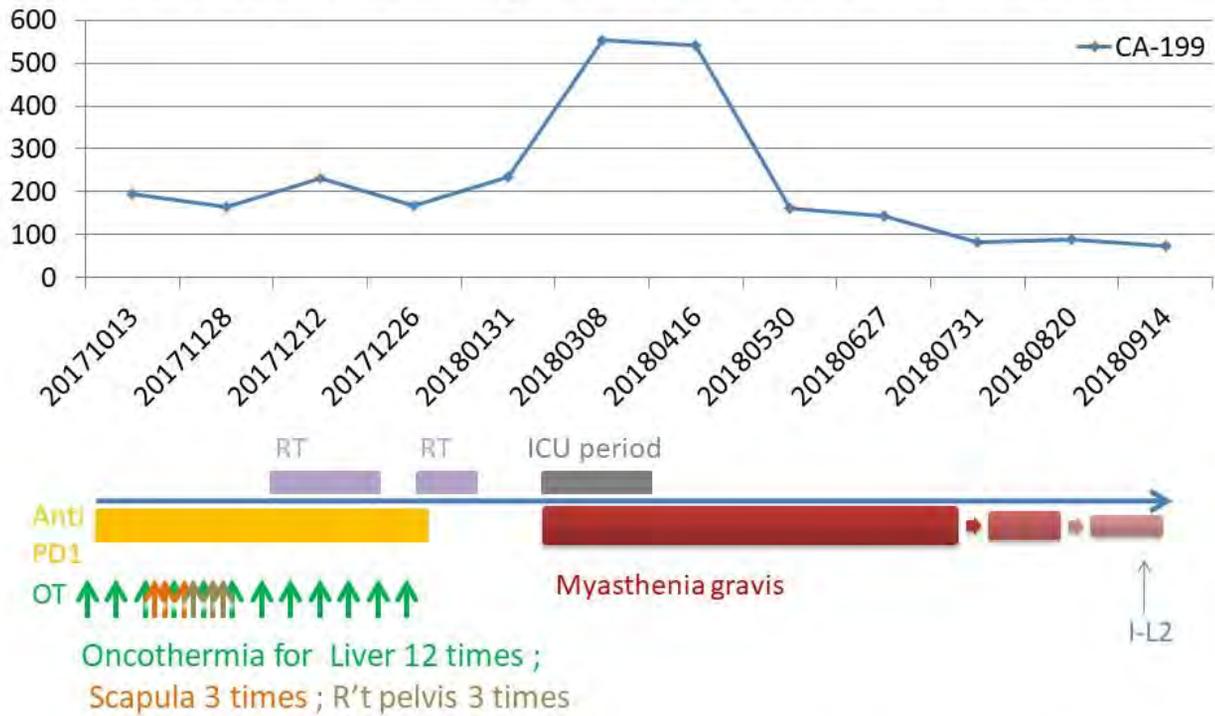
治療中 CT



治療後 CT

Chi KH et al, Unpublished data

## 劉\*秋 cholangiocarcinoma CA-199



Chi KH et al, Unpublished data

## Oncothermia as immunotherapy machine ?

- Will oncothermia change tumor microenvironment ?
- Will oncothermia activate immune cells ?
- Will oncothermia increase abscopal effect ?
- Will oncothermia increase autoimmune reaction ?
- **Will oncothermia produce tumor hyperprogression ?**
- Will oncothermia intensify the effect of immune checkpoint inhibitors ?

## 林\*珍 Phyllodes tumor

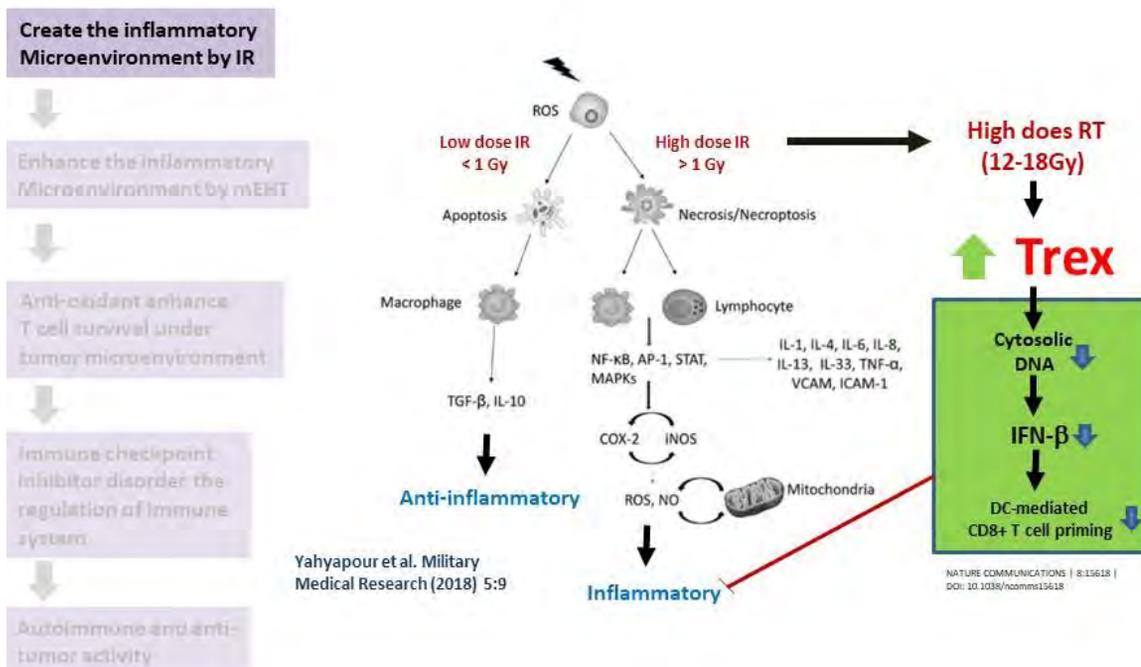


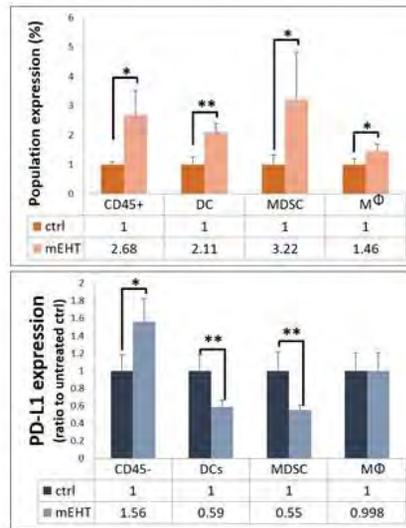
### What we have learned ?

- OT must have some radio-sensitization effect.
- Long lasting response only comes with autoimmune reaction. The incidence is 3 out of 33 (9.1%). The incidence of combined GM-CSF +RT is 2/41 (4.9%) if only >90% shrinkage of tumor were counted.
- Large and non-deep seated tumors seemed to have better response by RT + OT.
- Checkpoint inhibitors did not increase the response rates from RT + OT. But severe autoimmune response may be resulted.

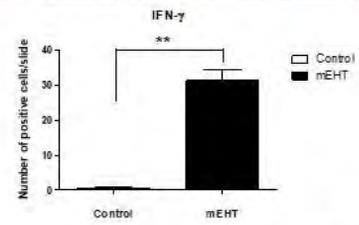
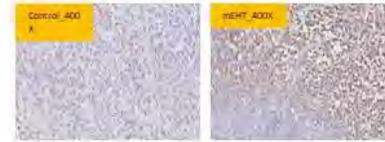
# How to increase autoimmune response by radiotherapy + oncothermia?

- Anti-CTLA 4 / Anti-PD1 ?
- GM-CSF
- By detecting pathogens to induce autoimmunity ?
- Harness innate immunity cells to adaptive immunity ?
- $\gamma\delta$  T cells ?
- Anti-oxidant ?

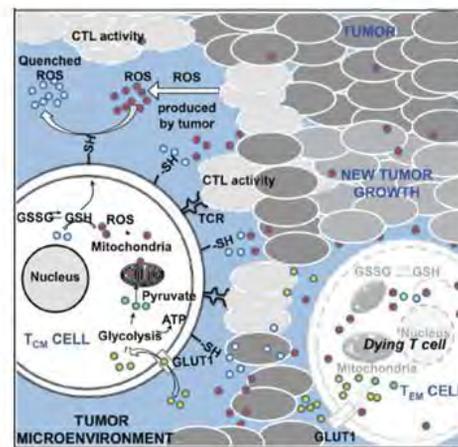
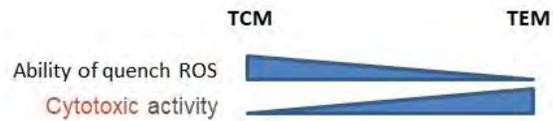
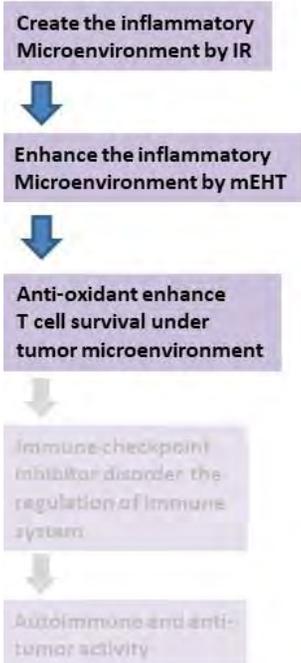




48h after treatment  
\* p<0.05, \*\*p<0.01, \*\*\*p<0.001



Wang YS et al, Unpublished data



Oncimmunology 4:1, e985942; January 1, 2015;

Create the inflammatory Microenvironment by IR



Enhance the inflammatory Microenvironment by mEHT



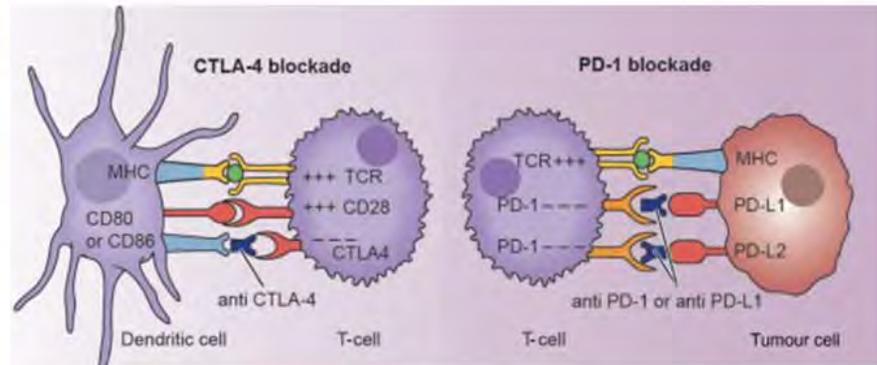
Anti-oxidant enhance T cell survival under tumor microenvironment



Immune checkpoint inhibitor disorder the regulation of immune system



Autoimmune and anti-tumor activity



rheumjc@rheumjc.com

Create the inflammatory Microenvironment by IR



Enhance the inflammatory Microenvironment by mEHT



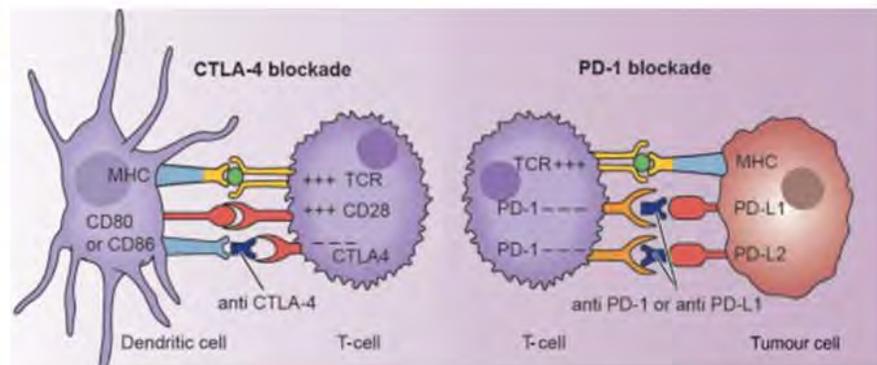
Anti-oxidant enhance T cell survival under tumor microenvironment



Immune checkpoint inhibitor disorder the regulation of immune system

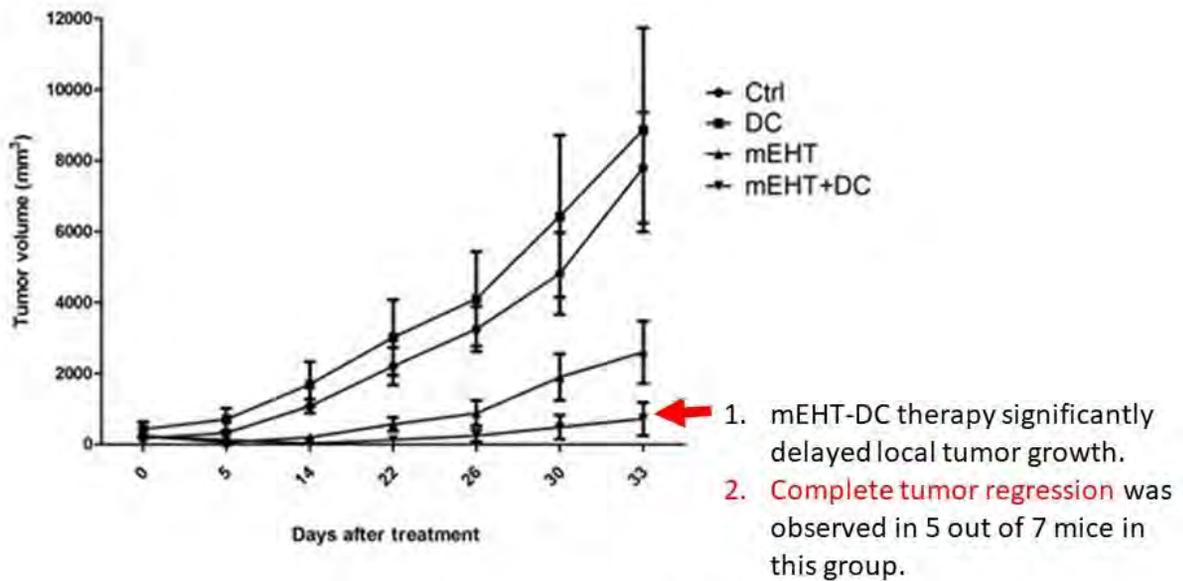


Autoimmune and anti-tumor activity



rheumjc@rheumjc.com

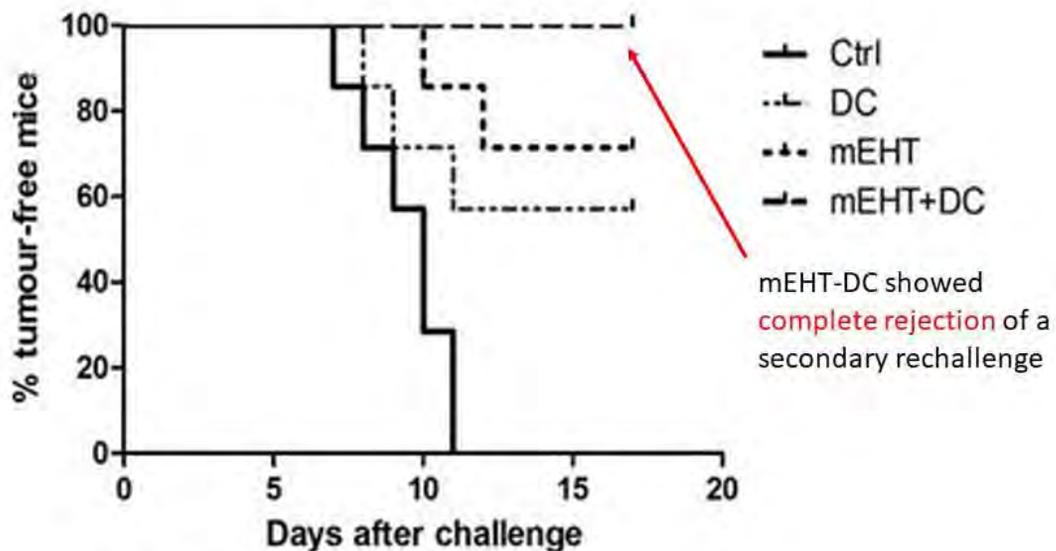
## Combination of mEHT induced local anti-tumor effect of DC therapy in vivo



Tsang et al. BMC Cancer 2015; 15:708

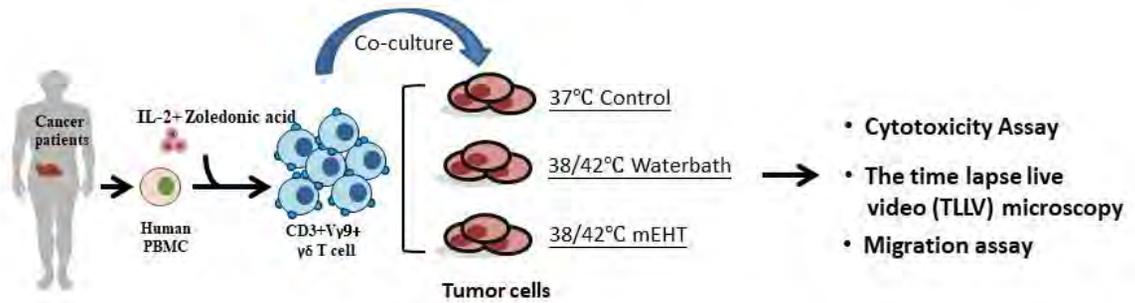
## Combination of mEHT induced systemic anti-tumor effect of DC therapy in vivo

Rechallenge a secondary tumor one month later

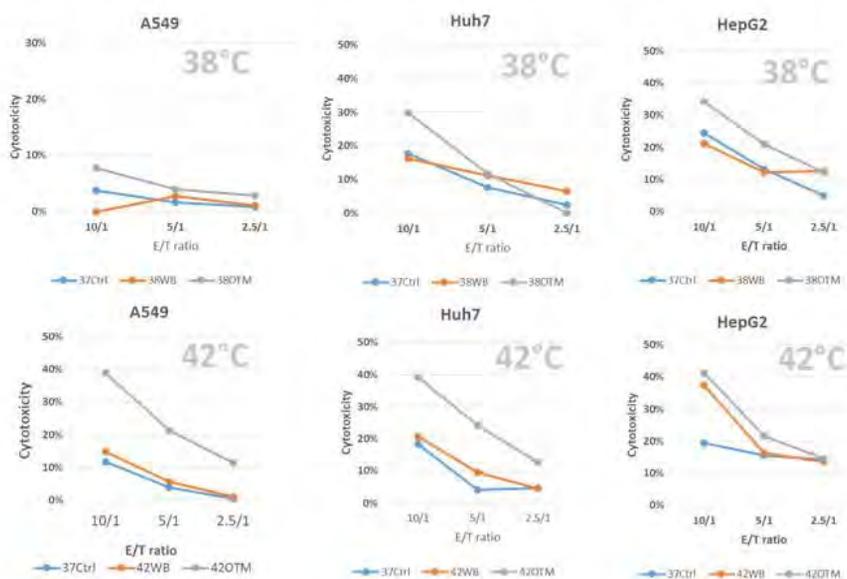


Tsang et al. BMC Cancer 2015; 15:708

## To assess the cytotoxicity of $\gamma\delta$ T cells on mEHT treated tumor cells

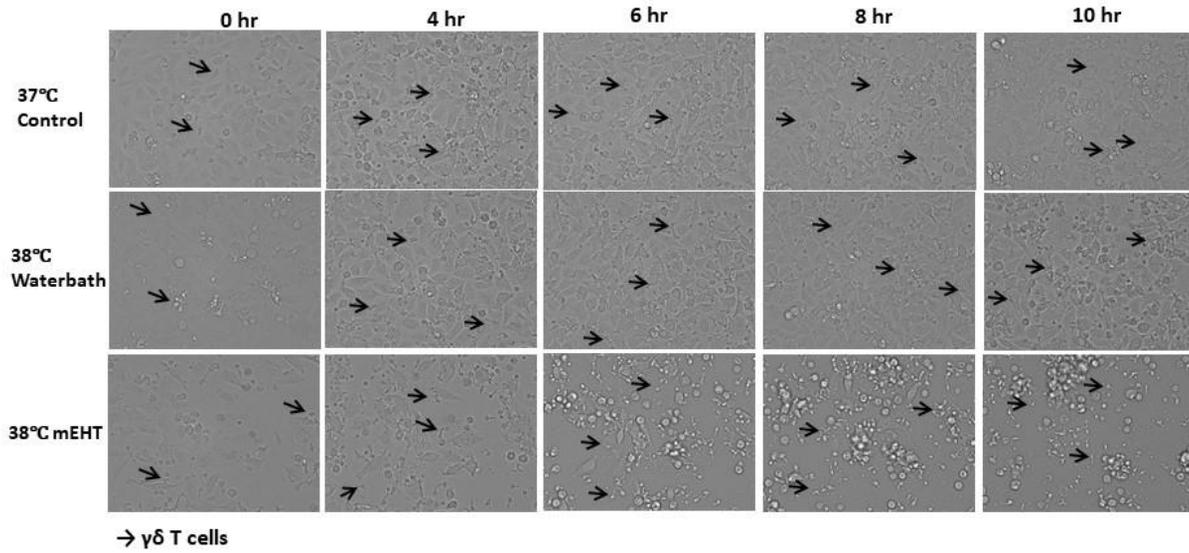


## To assess the cytotoxicity of $\gamma\delta$ T cells on mEHT treated tumor cells



**To assess the cytotoxicity of  $\gamma\delta$ T cells on mEHT treated tumor cells**

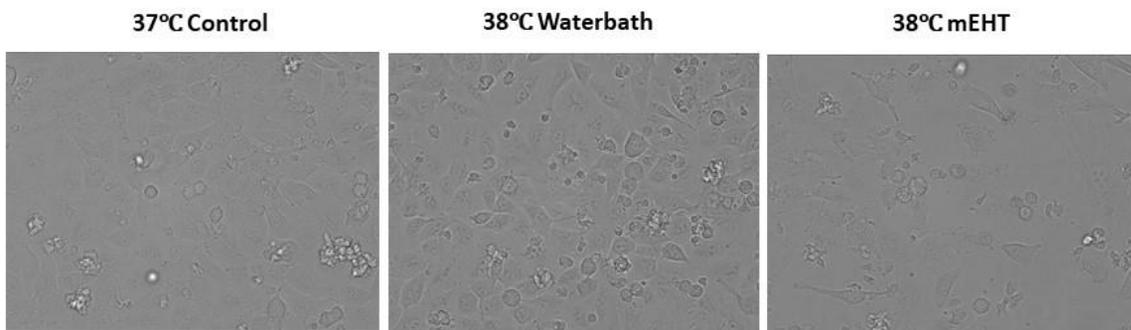
A549 with  $\gamma\delta$ T during 16hr coculture



73

**To assess the cytotoxicity of  $\gamma\delta$ T cells with or without mEHT treated tumor cells**

A549 with  $\gamma\delta$ T during 16hr coculture

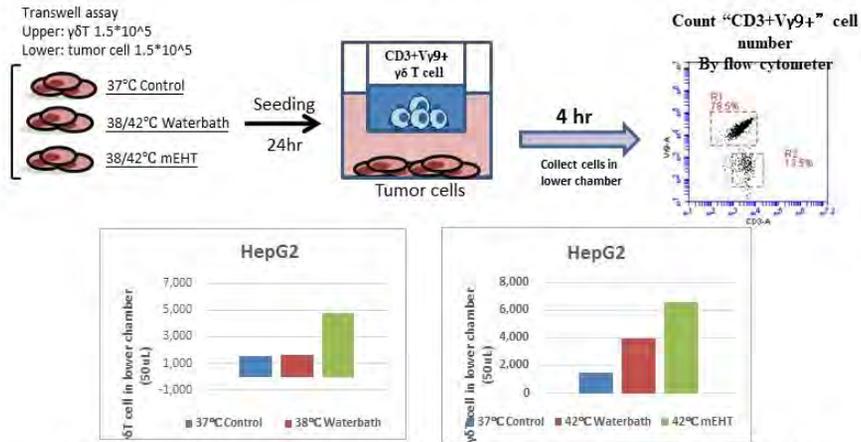


25min/second

- mEHT treatment can enhance  $\gamma\delta$ T cell cytotoxicity

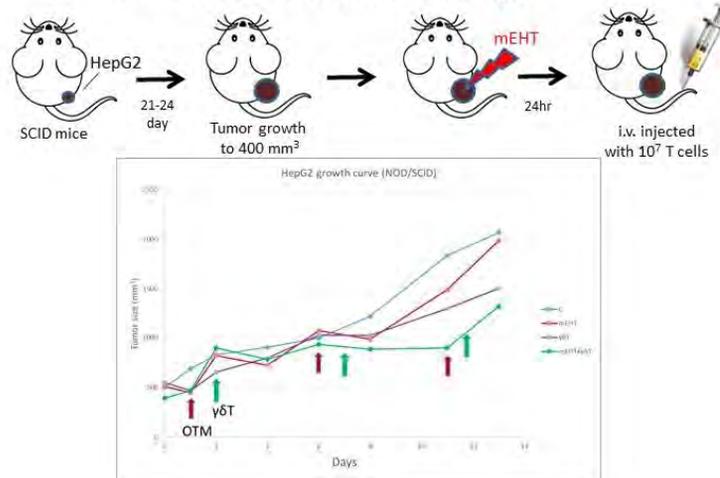
74

**To assess the migration ability of  $\gamma\delta$ T cells  
After mEHT treatment**



• mEHT treatment can enhance  $\gamma\delta$ T cell migration towards tumor cells

**To assess the anti-tumor effect of  $\gamma\delta$ T cells  
on mEHT-treated tumor bearing mice**



**Thank you for your attention!**

# **Exploiting autoimmunity to treat advanced cancer Using off-label low-dose immune checkpoint blockade in combination with hyperthermia and IL-2**

**Tibor Bakacs<sup>1</sup>, Ralph W Moss<sup>2</sup>, Marcell A. Szasz<sup>3</sup>, Colin C Anderson<sup>4</sup>**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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hyperthermia and IL-2; *Oncothermia Journal* 24:236-247

[www.oncothermia-  
journal.com/journal/2018/Exploiting\\_autoimmunity\\_to\\_treat\\_advanced\\_cancer.pdf](http://www.oncothermia-journal.com/journal/2018/Exploiting_autoimmunity_to_treat_advanced_cancer.pdf)

# Exploiting autoimmunity unleashed by an off-label-dose immune checkpoint blockade in combination with hyperthermia and interleukin-2

**Tibor Bakacs<sup>1\*</sup>, M.D., Ph.D., D.Sc., Ralph W Moss<sup>2</sup>, Ph.D., A. Marcell Szasz<sup>3</sup>, M.D., Ph.D., Colin C Anderson<sup>4</sup>, Ph.D.**

<sup>1</sup>PRET Therapeutics Ltd., 1124 Budapest, Hungary; Phone: +36 30 7265122;  
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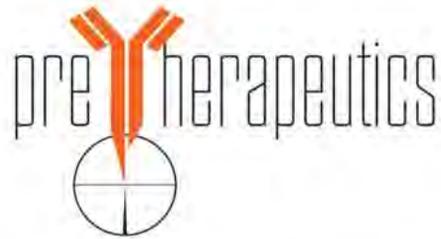
<sup>2</sup>Cancer Communications, Inc., PO Box 1076 Lemont, PA 16851 USA; Phone: 814-238-4064;  
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## Abstract

Checkpoint inhibitors achieved regression of cancer in a minority of patients, while the majority suffered immune-related adverse events (irAEs). irAEs could affect any tissue, their incidence may reach up to 90% of patients and toxicity is dose-dependent. Cancer regression can only be achieved by tolerance breakdown. Since autoimmunity is emerging as the nemesis of immunotherapy, a therapeutic paradigm shift is required. Based on the hypothesis that the anti-CTLA-4 therapy has similar mechanism to that occurring in inherited human CTLA4 haplo-insufficiency, it was predicted that autoimmune T cells can be harnessed by a low-dose combined checkpoint blockade. The proof-of-principle was first demonstrated in a heavily pre-treated triple negative breast cancer (TNBC) patient with far advanced pulmonary metastases and severe shortness of breath, who had exhausted all conventional treatment. The patient was treated with immune checkpoint blockade including ipilimumab (0.3 mg/kg) combined with nivolumab (0.5 mg/kg). This was complemented with interleukin-2 treatment and loco regional- and whole body hyperthermia without classical chemotherapy. The patient went into complete remission of her lung metastases and all cancer related symptoms vanished with transient WHO I-II diarrhea and skin rash. The patient remained alive for 27 months after the start of treatment. Previous NCI director and Nobel laureate Harold Varmus stated that we can really learn from such "exceptional responders". Since this protocol consists only of approved drugs and treatments, our prediction that autoimmune T-cells induced by a low-dose immune checkpoint blockade are powerful therapeutic tools can be confirmed or refuted in prospective controlled clinical trials.



## Exploiting autoimmunity to treat advanced cancer\*

Using off-label low-dose immune checkpoint blockade in combination with hyperthermia and IL-2

Tibor Bakacs, M.D.(1), Ph.D., D.Sc., Ralph W Moss, Ph.D. (2),  
Marcell Szasz, M.D., Ph.D. (3), Colin C Anderson, Ph.D. (4)

(1) PRET Therapeutics Ltd., 1124 Budapest, Hungary

(2) Cancer Communications, Inc., PO Box 1076 Lemont, PA 16851 USA;

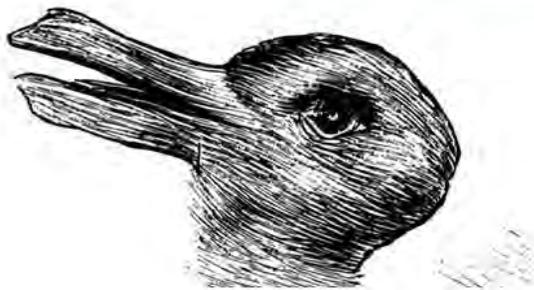
(3) Cancer Center, Semmelweis University, 1083 Budapest, Hungary;

(4) Departments of Surgery and Medical Microbiology & Immunology, University of Alberta; Canada;

\*Based on: Bakacs et al, [Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer](#) (under review)

## Checkpoint inhibitors: paradigm shift is required (elevator talk)

---



- ✓ Regression in a minority of patients
  - ✓ Majority suffered immune-related adverse events (irAEs)
  - ✓ Regression was achieved by tolerance breakdown
- 
- ✓ “Autoimmunity is the Achilles' heel of immunotherapy”
  - ✓ Autoimmune T cells can be harnessed by a low-dose checkpoint blockade combined with hyperthermia and IL-2
  - ✓ “We might only be at the tip of the iceberg” of immunotherapy

## “Seismic shift in cancer”

---

Improved survival with ipilimumab in patients with metastatic melanoma  
Hodi et al, N Engl J Med, 2010

**“Abrogation of the function of CTLA-4 would permit CD28 to function unopposed and might swing the balance in favor of immune stimulation, tolerance breakdown and tumor eradication...”**

This prediction proved to be entirely correct:

- Response rate of 10.9 % in 676 patients; CR 0.2%; in one patient out of 403
- Tolerance to self was broken in ~70% of the patients
- 38.7% of the patients experienced severe irAEs
- There were 14 deaths related to the study drugs

We have considered the very same published evidence of the NEJM paper

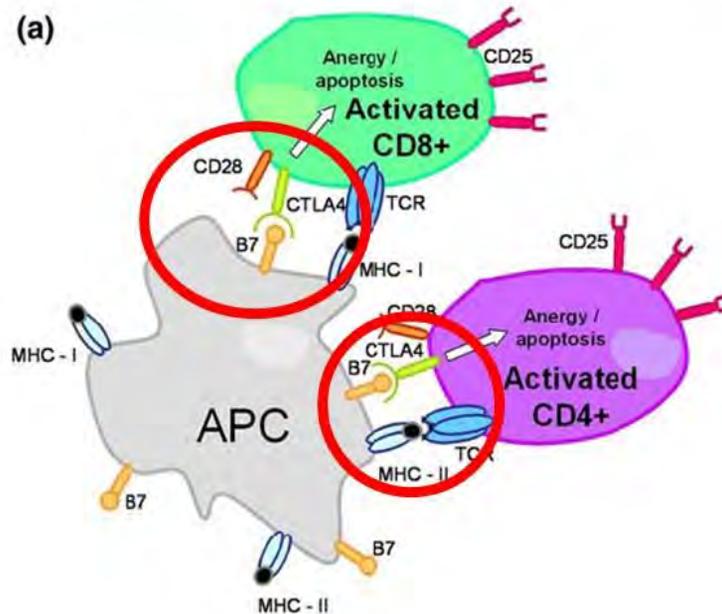
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- Ipilimumab (Yervoy) and the TGN1412 catastrophe, Bakacs et al, Immunobiology, 2012
- As if looking at a painting of Escher: others saw only the white picture, while we saw also the black one



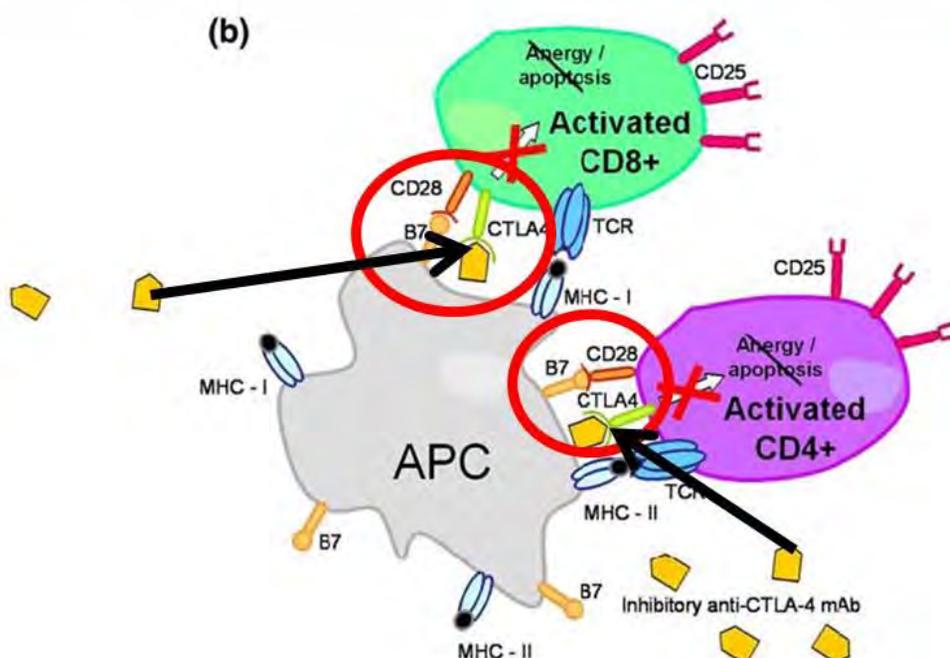
The B7-CD28 co-stimulatory and B7-CTLA-4 co-inhibitory pathways of T cells are pivotal in maintaining health

---



“Anti-CTLA-4 selectively extends the functional longevity of activated T-cells”

---



## Lessons from the anti-CD28 mAb (TGN1412) trial catastrophe in London

---

Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412

Suntharalingam et al, N Engl J Med, 2006

- Cytokine storm: life-threatening organ failures in volunteers
- anti-CD28 (TGN1412) mAb “preferentially” activated Treg but also activated all CD28 positive T cells
- **Common Ags on targeted as well as non-targeted T cells**
- With increasing dose the kinetics shifts from specific toward non-specific T cell expansion

## irAEs of anti-CTLA-4 (ipilimumab) explained by a new theory: all T cells possess self reactivity

---

T cells survey the stability of the self: a testable hypothesis on the homeostatic role of TCR-MHC interactions

Bakacs et al, Int Arch Allergy Immunol, 2007

- Short-lasting ‘tonic’ TCR signal 1 promotes survival of T cells
- T cells temporarily expressing CTLA-4 can be targeted by ipilimumab
- Ipilimumab blockade causes T cell activity to spill over onto healthy cells or tumor cells

## The mechanism of anti-CD28 (TGN1412) and anti-CTLA-4 (ipilimumab) therapies are similar

---

- PubMed search in **2011**:  
ipilimumab/ 144; TGN1412/ 120 papers  
**ipilimumab and TGN1412: 0 paper**
- PubMed search in **2018**:  
ipilimumab/ 2483; TGN1412/ 167 papers  
**ipilimumab and TGN1412: 1 paper**

Medical community is still unmindful of the anti-CD28 (TGN1412) trial catastrophe insisting that anti-CTLA-4 (ipilimumab) targets only tumor specific T cells

Dogma: immunity is as protective against isogenic cancer as against xenogeneic infections

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### The Fallacy of Tumor Immunology

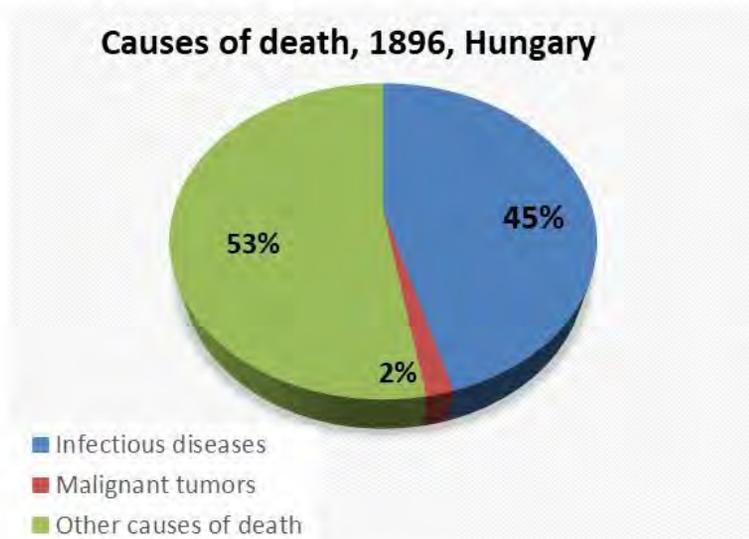
[Bakacs et al, Arxiv Cornell University Library, 2016](#)

- Cancer immunotherapy trials resulted in anecdotal responses
- Evolutionary origin of adaptive immunity is not related to defense against pathogenic microorganisms (Burnet)
- Why invertebrates (more than two million species; 20 phyla) use only innate immunity?
- Why vertebrates reject any allogeneic or xenogeneic transplanted tissue?

„Prior to modern medicine people were long consumed by tuberculosis, dropsy, cholera, smallpox, leprosy, plague, or pneumonia before cancer developed.”

---

Mukherjee, *The Emperor of All Maladies; A biography of cancer*, 2011



- The immune system evolved for purging nascent selfish cells
- Defense against pathogens (xenogeneic aliens) appeared later in evolution

Insisting that ipilimumab is tumor specific is ignoring the obvious

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Managing toxicities associated with immune checkpoint inhibitors Puzanov et al, *Journal for Immunotherapy of Cancer*, 2017

- irAEs affect any tissue, incidence up to 90%
- Overall incidence <75% with ipilimumab monotherapy; ≤30% anti-PD-1/PD-L1 agents
- IrAEs of ≥ grade 3 up to 43% with ipilimumab and ≤20% with PD-1/PD-L1 agents
- Combination of ipilimumab with nivolumab: 55% of grade 3/4 irAEs; discontinuation rate 30%
- irAEs with ipilimumab and pembrolizumab is dose-dependent
- Death due to irAEs occurred in up to 2% of patients

Patients often deny their symptoms when they fear their treatment will be stopped due to irAEs

### IMMUNOTHERAPY WALLET CARD

NAME: \_\_\_\_\_

CANCER DX: \_\_\_\_\_

I-O AGENTS RCVD:  CHECKPOINT INHIBITOR(S)

CAR-T  VACCINES  ONCOLYTIC VIRAL THERAPY

MONOCLONAL ANTIBODIES

DRUG NAME(S): \_\_\_\_\_

IMMUNOTHERAPY TX START DATE: \_\_\_\_\_

OTHER CANCER MEDICATIONS: \_\_\_\_\_

NOTE: IMMUNOTHERAPY AGENTS ARE NOT CHEMOTHERAPY AND SIDE EFFECTS MUST BE MANAGED DIFFERENTLY (SEE BACK)

### IMMUNOTHERAPY CARD

IMMUNE-RELATED SIDE EFFECTS\*, COMMON WITH CHECKPOINT INHIBITORS VARY IN SEVERITY AND MAY REQUIRE REFERRAL AND STEROIDS. PATIENTS HAVE A LIFETIME RISK OF IMMUNE-RELATED SIDE EFFECTS.

\*MAY PRESENT AS RASH, DIARRHEA, ABDOMINAL PAIN, COUGH, FATIGUE, HEADACHES, VISION CHANGES, ETC.—CONFER WITH ONCOLOGY TEAM BEFORE CHANGING I-O REGIMEN OR STARTING SIDE EFFECT TREATMENT.

ONCOLOGY PROVIDER NAME \_\_\_\_\_

ONCOLOGY PROVIDER NO. \_\_\_\_\_

EMERGENCY CONTACT \_\_\_\_\_

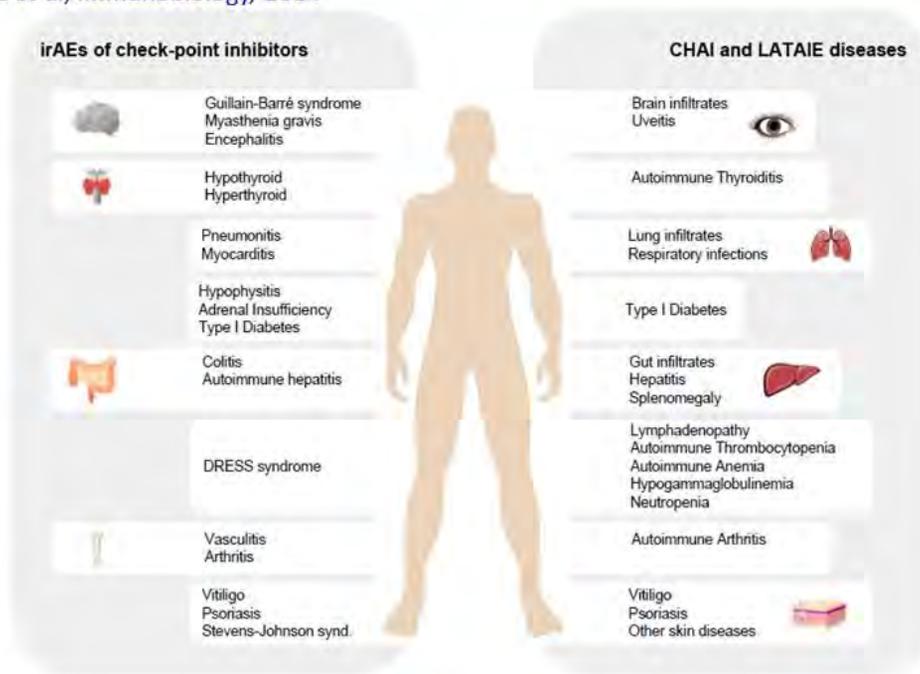
CONTACT PHONE NO. \_\_\_\_\_

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Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy, Brahmer et al, J Clin Oncol, 2018

Anti-CTLA-4 therapy may have mechanisms similar to those occurring in inherited human CTLA4 haploinsufficiency

Bakacs et al, Immunobiology, 2014



## Paradigm shift: exploiting Graft-Versus-Tumor (GVT) effect

The same GVT effect could be achieved by ipilimumab as by donor lymphocyte infusion but without severe GVHD

- 3 mg/kg ipilimumab reversed relapse without worsening GVHD after allogeneic HSCT ([Bashey et al, Blood, 2009](#))
- Ipilimumab 0.3 mg/kg mild-to-moderate irAEs suggests a biological effect ([Wolchok et al, Lancet Oncol, 2010](#))
- Low-dose adjuvant ipilimumab (0.3 mg/kg) could induce auto-GVHD at the stage of minimal residual disease (MRD) ([Slavin et al, Pharmacol Res, 2013](#))
- High-dose (10 mg/kg) adjuvant ipilimumab gained FDA approval (33.3 times higher dose than that of suggested by Slavin) ([Eggermont et al, N Engl J Med, 2016](#))

## Complete remission of lung metastases in TNBC

Transient WHO I-II diarrhea and skin rash, patient alive for 27 months



**ipilimumab** (0.3 mg/kg) **nivolumab** (0.5 mg/kg)  
**interleukin-2** (54 Mio/m<sup>2</sup> as decrescendo regimen)  
loco regional- and whole body **hyperthermia**

[Kleef et al Integrative Cancer Therapies, 2018](#)  
DOI: [10.1177/1534735418794867](https://doi.org/10.1177/1534735418794867)

## Autoimmunity is the Achilles' heel of cancer immunotherapy

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- Incidence of irAEs is underestimated
  - ✓ most cancer trials follow patients for only a brief time
  - ✓ patients who died from their cancer are not included
- Incidence of irAEs will rise as these therapies become more widely used
- The risks of the ICIs is „a massively understudied area“

**Since our low-dose ICI protocol consists only of approved drugs and treatments it can be confirmed or refuted in controlled clinical trials**

„As I go around the country, I talk about the tragedy of cancer to remind people that the tragedy is not our inability to prevent the inevitable or to do the impossible; tragedy is when a person, a group or a society fails to achieve the possible.“



Remark  Free Access

**Cancer, minorities & the medically underserved\***

The role of the National Cancer Institute

Richard D. Klausner M.D.

First published: 09 November 2000

## Thank you for your attention

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Dr. Tibor BAKACS, Chief Scientific Officer [tiborbakacs@gmail.com](mailto:tiborbakacs@gmail.com)



# **Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors**

**Stefaan W. Van Gool, Jennifer Makalowski, Wilfried Stuecker**  
Immun-Onkologisches Zentrum Köln

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

**Cite this article as:**

Van Gool S. (2018): Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors; *Oncothermia Journal* 248: -269

[www.oncothermia-journal.com/journal/2018/Modulated\\_electrohyperthermia\\_\(mEHT\)\\_as\\_part\\_of.pdf](http://www.oncothermia-journal.com/journal/2018/Modulated_electrohyperthermia_(mEHT)_as_part_of.pdf)

## **Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors**

**Stefaan W. Van Gool, Jennifer Makalowski, Wilfried Stuecker**

Immun Onkologische Zentrurn Köln, Germany

### **Abstract**

Immunotherapy has become a fourth pillar of anticancer treatment. Modern immunotherapy consists of multiple strategies all aimed to induce an antitumoral immune response including immunologic memory. Antibody therapy is considered as passive immunotherapy. Immunogenic cell death induction with oncolytic viruses like Newcastle disease virus (NDV), and techniques like local modulated electrohyperthermia (mEHT) aim to induce immunogenic cell death (ICD) of tumor cells thereby creating the necessary danger signals in tumors and a subsequent active immunization. Autologous mature dendritic cells (DC) loaded with tumor antigens are considered as active specific immunotherapy aimed directly to stimulate tumor-reacting T cells. Actual tumor antigens can be derived from NDV/mEHT-induced serum-derived antigenic extracellular microvesicles. Total body hyperthermia in order to stimulate the innate immune system, ATRA in order to deplete myeloid derived suppressor cells, low dose cyclophosphamide to deplete regulatory T cells, checkpoint blockers to release the immune system all are considered as immunomodulatory strategies. In the presentation, data will be discussed on a group of patients with glioblastoma multiforme and a group of children with diffuse intrinsic pontine glioma, for whom multimodal immunotherapy was part of the multi-treatment strategy including radiochemotherapy and chemotherapy. The data suggest that mEHT can contribute as direct anti-tumor treatment, as immune stimulator via ICD and as tool for yielding actual tumor antigens.

# Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors

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Immun-Onkologisches Zentrum Köln  
 www.iozk.de

Liau et al. *J Transl Med* (2018) 16:142  
<https://doi.org/10.1186/s12967-018-1507-6>

Journal of  
 Translational Medicine

## RESEARCH

## Open Access



# First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma

Linda M. Liou<sup>1\*</sup>, Keyoumars Ashkan<sup>2</sup>, David D. Tran<sup>3</sup>, Jian L. Campian<sup>4</sup>, John E. Trusheim<sup>5</sup>, Charles S. Cobbs<sup>6</sup>, Jason A. Heth<sup>7</sup>, Michael Salacz<sup>8</sup>, Sarah Taylor<sup>8</sup>, Stacy D. D'Andre<sup>9</sup>, Fabio M. Iwamoto<sup>10</sup>, Edward J. Dropcho<sup>11</sup>, Yaron A. Moshel<sup>12</sup>, Kevin A. Walter<sup>13</sup>, Clement P. Pillainayagam<sup>14</sup>, Robert Aiken<sup>15</sup>, Rekha Chaudhary<sup>16</sup>, Samuel A. Goldlust<sup>17</sup>, Daniela A. Bota<sup>18</sup>, Paul Duic<sup>19</sup>, Jai Grewal<sup>59</sup>, Heinrich Elinzano<sup>20</sup>, Steven A. Toms<sup>20</sup>, Kevin O. Lillehei<sup>21</sup>, Tom Mikkelsen<sup>22</sup>, Tobias Walpert<sup>22</sup>, Steven R. Abram<sup>23</sup>, Andrew J. Brenner<sup>24</sup>, Steven Brem<sup>25</sup>, Matthew G. Ewend<sup>26</sup>, Simon Khagi<sup>26</sup>, Jana Portnow<sup>27</sup>, Lyndon J. Kim<sup>28</sup>, William G. Loudon<sup>29</sup>, Reid C. Thompson<sup>30</sup>, David E. Avigan<sup>31</sup>, Karen L. Fink<sup>32</sup>, Francois J. Geoffroy<sup>33</sup>, Scott Lindhorst<sup>34</sup>, Jose Lutzky<sup>35</sup>, Andrew E. Sloan<sup>36</sup>, Gabriele Schackert<sup>37</sup>, Dietmar Krex<sup>37</sup>, Hans-Jorg Meisel<sup>38</sup>, Julian Wu<sup>39</sup>, Raphael P. Davis<sup>40</sup>, Christopher Duma<sup>41</sup>, Arnold B. Etame<sup>42</sup>, David Mathieu<sup>43</sup>, Santosh Kesari<sup>44</sup>, David Piccioni<sup>44</sup>, Manfred Westphal<sup>45</sup>, David S. Baskin<sup>46</sup>, Pamela Z. New<sup>46</sup>, Michel Lacroix<sup>47</sup>, Sven-Axel May<sup>48</sup>, Timothy J. Pluard<sup>49</sup>, Victor Tse<sup>50</sup>, Richard M. Green<sup>51</sup>, John L. Villano<sup>52</sup>, Michael Pearlman<sup>53</sup>, Kevin Petrecca<sup>54</sup>, Michael Schulder<sup>55</sup>, Lynne P. Taylor<sup>56</sup>, Anthony E. Maida<sup>58</sup>, Robert M. Prins<sup>1</sup>, Timothy F. Cloughesy<sup>1</sup>, Paul Mulholland<sup>57</sup> and Marnix L. Bosch<sup>58\*</sup> 

• Humanarzneimittel  
• Prüfpräparate zur Anwendung am Menschen der Phasen I, II, III

• Human Medicinal Products  
• Human Investigational Medicinal Products for phase I,II,III

**UMFANG DER ERLAUBNIS**

Name und Anschrift der Betriebsstätte:  
IOZK Laboratorium GmbH, Mauritiuswall 48, 50676 Köln

Anlage 1

**1 HERSTELLUNGSTÄTIGKEITEN**

- Die erlaubten Herstellungstätigkeiten umfassen vollständige und teilweise Herstellung (einschließlich verschiedener Prozesse wie Umfüllen, Abpacken oder Kennzeichnen), Chargenfreigabe und -zertifizierung, Lagerung und Vertrieb der genannten Darreichungsformen sofern nicht anders angegeben;

- Die Qualitätskontrolle und/oder Freigabe und/oder Chargenzertifizierung ohne Herstellungsschritte sollten unter den entsprechenden Punkten spezifiziert werden;

- 1.1 Sterile Produkte
  - 1.1.1 Aseptisch hergestellt
    - 1.1.1.4 Kleinvolumige flüssige Darreichungsformen
- 1.3 Biologische Arzneimittel
  - 1.3.1 Biologische Arzneimittel
    - 1.3.1.2 Immunologische Produkte
- 1.6 Qualitätskontrolle
  - 1.6.4 Biologisch

Einschränkungen oder Klarstellungen Anmerkungen betreffend den Umfang des Zertifikats:  
Anmerkungen: zu 1.3.1.2 Spezifische, autologe Anti-Tumor-Dendritenzell-Vakzine zur intrakutanen Anwendung: - aus Patienten-eigenen Monozyten gezüchtete dendritische Zellen, die mit Tumorantigenen aus einem Lysat patienteneigener Tumorzellen mit immunologisch wirksamen Gefahrensignalen ausgehend aus dem New Castle Disease Virus (NDV) beladen werden

**1 MANUFACTURING OPERATIONS**

- authorized manufacturing operations include total and partial manufacturing (including various processes of dividing up, packaging or presentation), batch release and certification, storage and distribution of specified dosage forms unless intended to the contrary;

- quality control testing and/or release and batch certification activities without manufacturing operations should be specified under the relevant items;

- If the company is engaged in manufacture of products with special requirements e.g. radiopharmaceuticals or products containing penicillin, sulphoramides, cytotoxics, cephalosporins, substances with hormonal activity or other or potentially hazardous active ingredients this should be stated under the relevant product type and dosage form (applicable to all sections of Part 1 apart from sections 1.5.2 and 1.6)

- 1.1 Sterile Products
  - 1.1.1 Aseptically prepared
    - 1.1.1.4 Small volume liquids
- 1.3 Biological medicinal products
  - 1.3.1 Biological medicinal products
    - 1.3.1.2 Immunological products
- 1.6 Quality control testing
  - 1.6.4 Biological

Any restrictions or clarifying remarks related to the scope of this certificate:  
Comments: To 1.3.1.2 Specific, autologous anti-tumor directed dendritic cell vaccine for intracutaneous application: from patient-derived blood monocytes generated dendritic cells which are loaded with tumor antigens from a lysate of patient-derived tumor cells together with immunologic danger signals from Newcastle disease virus (NDV).

Humanarzneimittel

ERLAUBTE TÄTIGKEITEN  
Herstellungstätigkeiten (gemäß Teil 1)

**Teil 1 - HERSTELLUNGSTÄTIGKEITEN**

- Die erlaubten Herstellungstätigkeiten umfassen vollständige und teilweise Herstellung (einschließlich verschiedener Prozesse wie Umfüllen, Abpacken oder Kennzeichnen), Chargenfreigabe und -zertifizierung, Lagerung und Vertrieb der genannten Darreichungsformen sofern nicht anders angegeben;

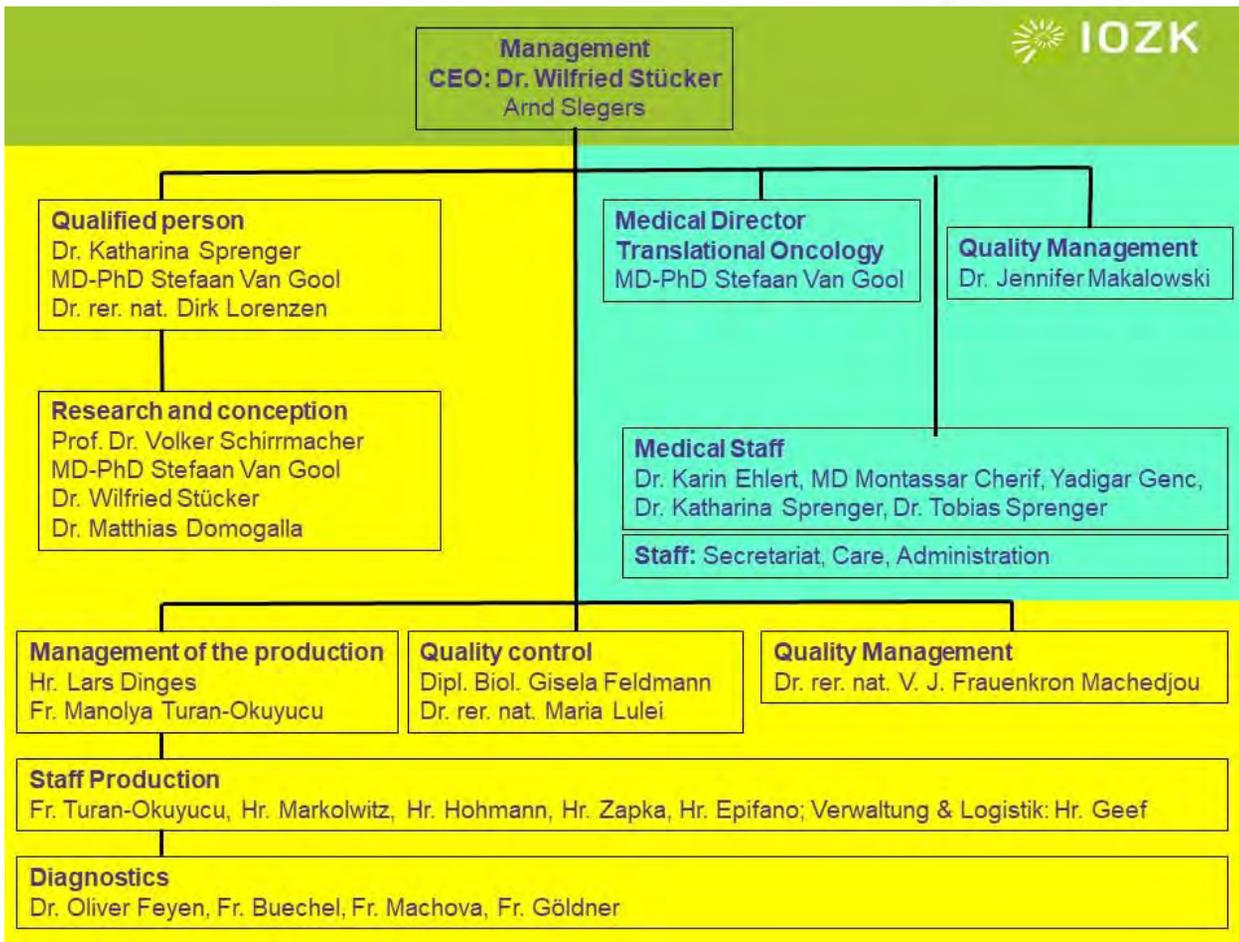
- Die Qualitätskontrolle und/oder Freigabe und/oder Chargenzertifizierung ohne Herstellungsschritte sollten unter den entsprechenden Punkten spezifiziert werden;

- Unter der relevanten Produktart und Darreichungsform sollte auch angegeben werden, wenn der Hersteller Produkte mit speziellen Anforderungen herstellt, z.B. radioaktive Arzneimittel oder Arzneimittel, die Penicilline, Sulfonamide, Zytostatika, Cephalosporine, Stoffe mit hormoneller Wirkung oder andere potenziell gefährliche Wirkstoffe enthalten (anwendbar für alle Bereiche des Teils 1 mit Ausnahme 1.5.2 und 1.6).

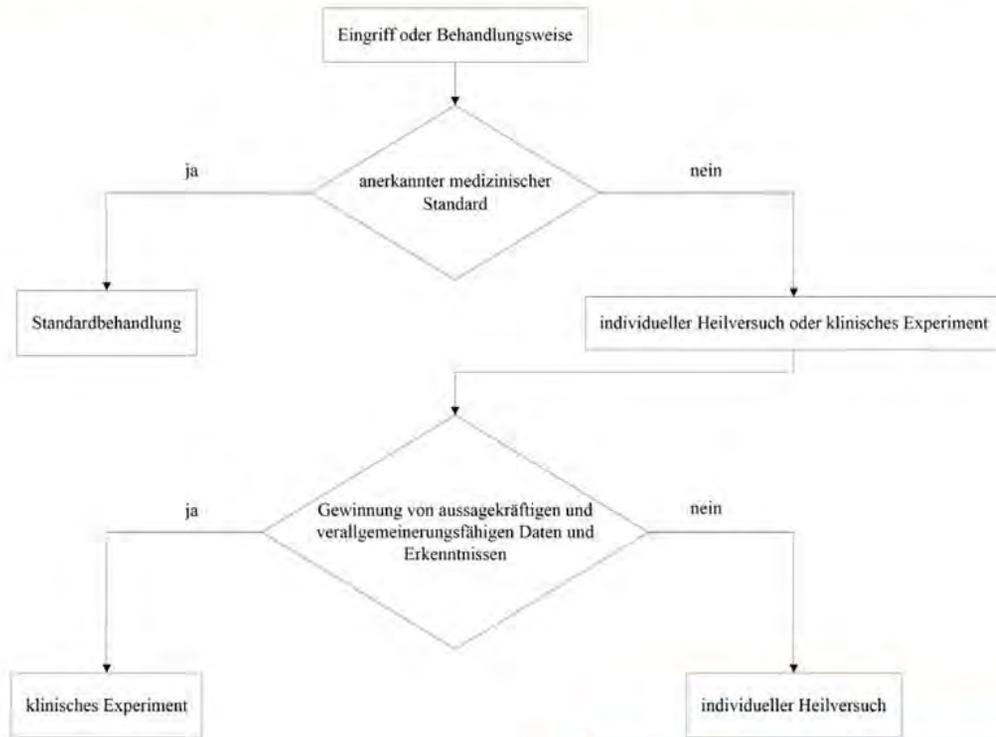
<b>1.1 Sterile Produkte</b>
1.1.1 Aseptisch hergestellt
1.1.1.4 Kleinvolumige flüssige Darreichungsformen
<b>1.3 Biologische Arzneimittel</b>
1.3.1 Biologische Arzneimittel
1.3.1.2 Immunologische Produkte
<b>1.6 Qualitätskontrolle</b>
1.6.4 Biologisch

**Einschränkungen oder Klarstellungen bezüglich der Herstellungstätigkeiten**

zu 1.3.1.2 Spezifische, autologe Anti-Tumor-Dendritenzell-Vakzine zur intrakutanen Anwendung: aus Patienten-eigenen Monozyten gezüchtete dendritische Zellen, die mit Tumorantigenen aus einem Lysat patienteneigener Tumorzellen mit immunologisch wirksamen Gefahrensignalen ausgehend aus dem New Castle Disease Virus (NDV) beladen werden.



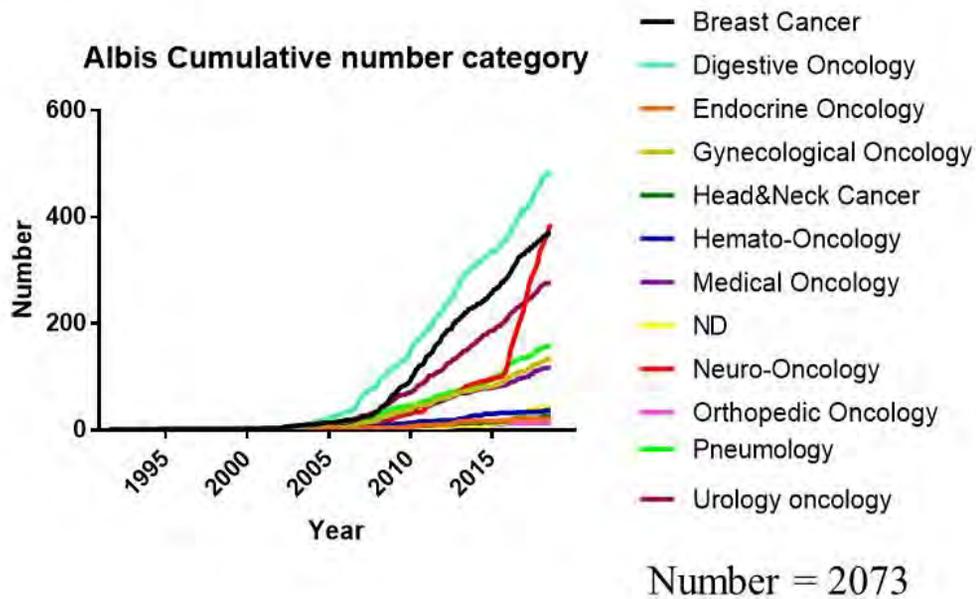
Prüfungsschema praktische Abgrenzung zwischen individuellem Heilversuch und klinischem Experiment



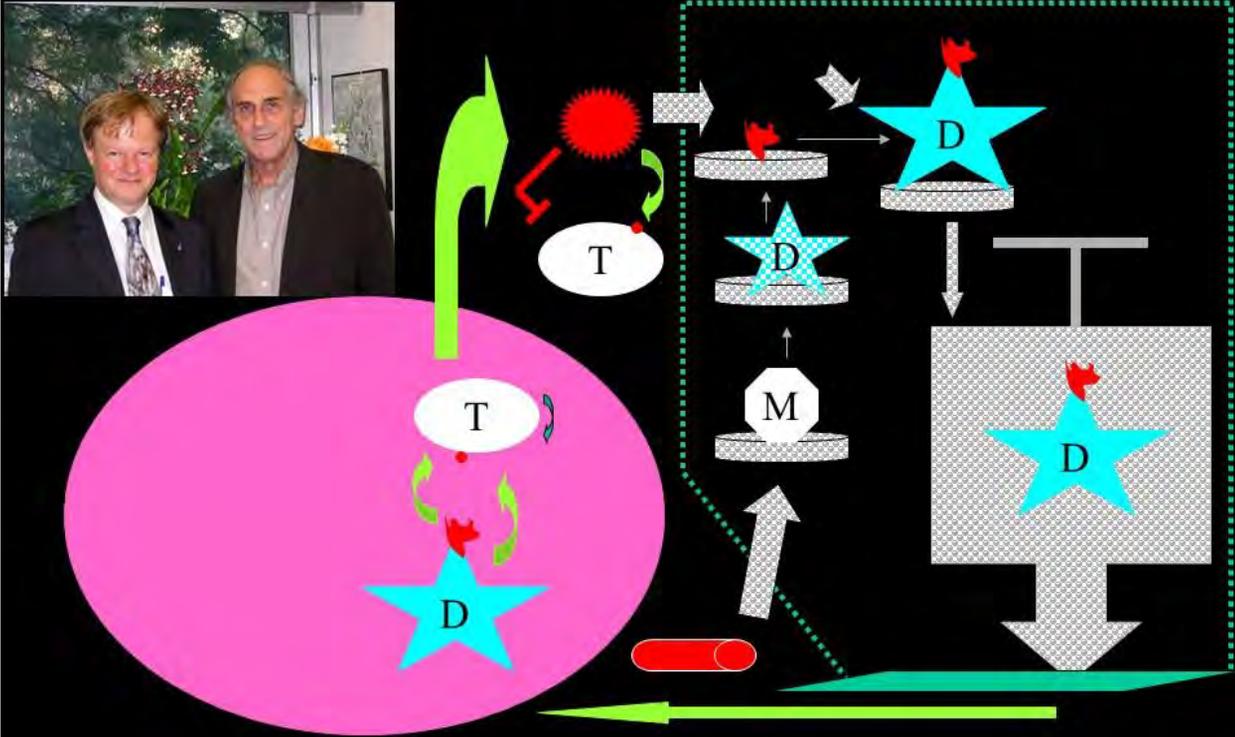
*Fabian Huber, August 2014*

[www.iozk.de](http://www.iozk.de)

Diagnostic categories total group < September 2018

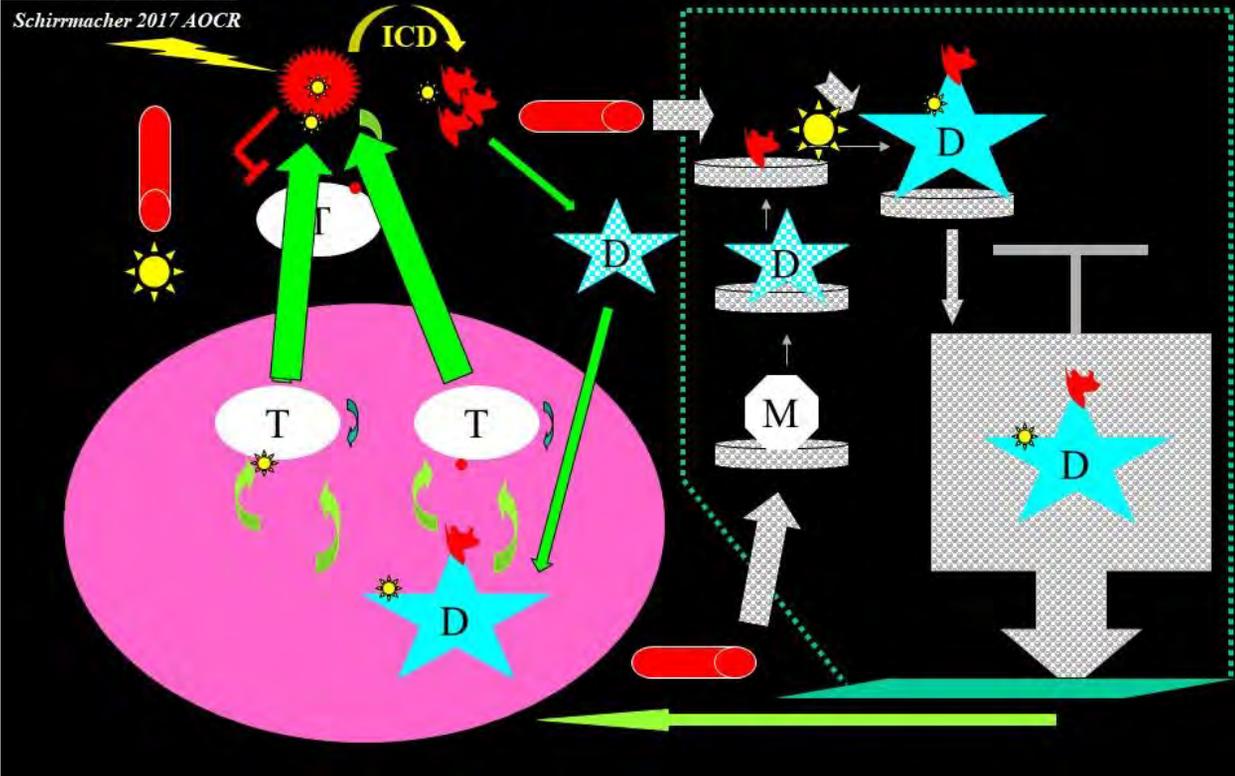


# Principle of tumor vaccination

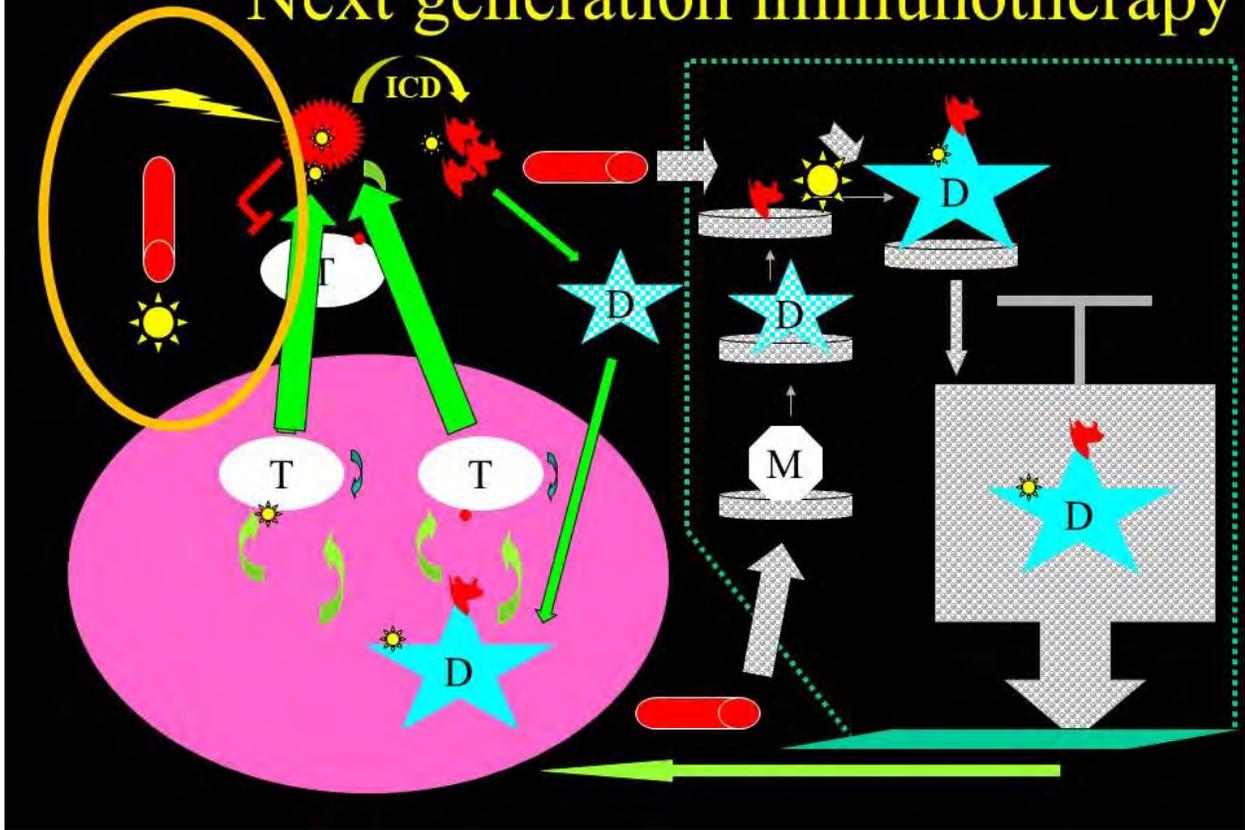


Neuer Anti-Tumor-Impfstoff zur Sekundärprophylaxe  
 Dr. Wolfgang Hübner Prof. Dr. Ulfrich Schumacher Prof. Dr. Stefan Schreiber  
 Aktuelle Gesundheits-Nachrichten 2016;20:38-43

# Next generation immunotherapy



# Next generation immunotherapy



Cell Death & Differentiation  
<https://doi.org/10.1038/s41418-017-0012-4>

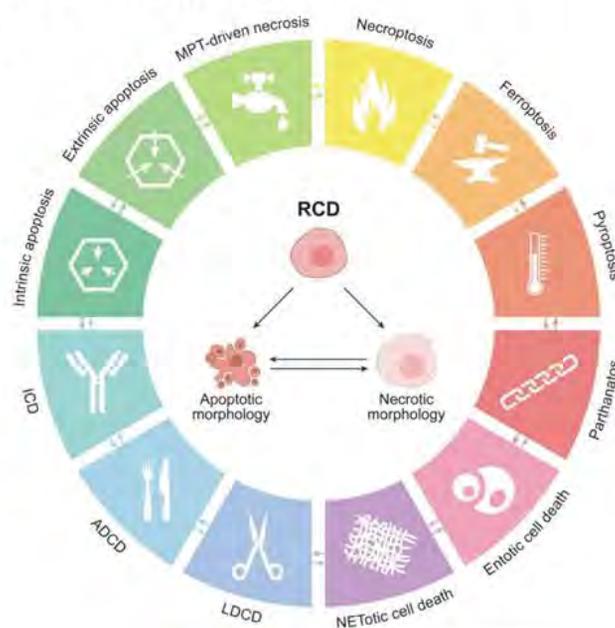
Cell Death & Differentiation

REVIEW



## Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi<sup>1,2,3</sup> · Ilio Vitale<sup>4,5</sup> et al.





Research Paper

## Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts

Tamas Vancsik<sup>1</sup>, Csaba Kovago<sup>2</sup>, Eva Kiss<sup>1</sup>, Edina Papp<sup>3</sup>, Gertrud Forika<sup>1</sup>, Zoltan Benyo<sup>4</sup>, Nora Meggyeshazi<sup>1\*</sup>, Tibor Krenacs<sup>1\*</sup>

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2. Department of Pharmacology and Toxicology, Faculty of Veterinary Science, St. Istvan University, Budapest, Hungary;
3. Faculty of Bionics, Pazmany Peter Catholic University, Budapest, Hungary;
4. Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary.

\* These authors equally contributed to this paper

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IJC  
International Journal of Cancer

## Newcastle disease virotherapy induces long-term survival and tumor-specific immune memory in orthotopic glioma through the induction of immunogenic cell death

Carolien A. Koks<sup>1</sup>, Abhishek D. Garg<sup>2</sup>, Michael Ehrhardt<sup>3</sup>, Matteo Riva<sup>1</sup>, Lien Vandenberg<sup>1</sup>, Louis Boon<sup>4</sup>, Steven De Vleeschouwer<sup>5,6</sup>, Patrizia Agostinis<sup>2</sup>, Norbert Graf<sup>3</sup> and Stefaan W. Van Gool<sup>1,7</sup>

<sup>1</sup> Pediatric Immunology, Department of Microbiology and Immunology, KU Leuven, Herestraat 49, Leuven, Belgium

<sup>2</sup> Department of Cellular and Molecular Medicine, KU Leuven, Herestraat 49, Leuven, Belgium

<sup>3</sup> Department for Pediatric Oncology, University of Saarland Medical School, Kirberger Straße, Homburg, Germany

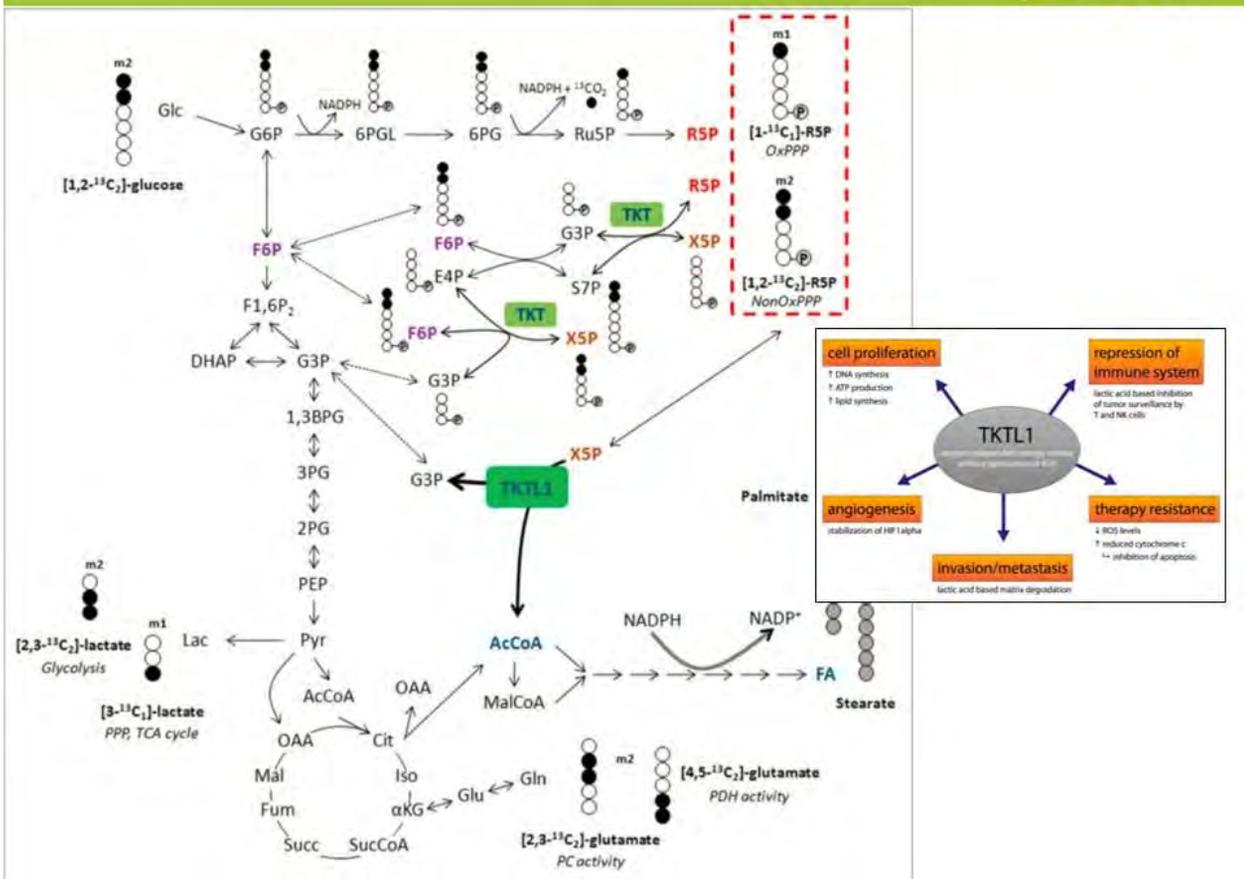
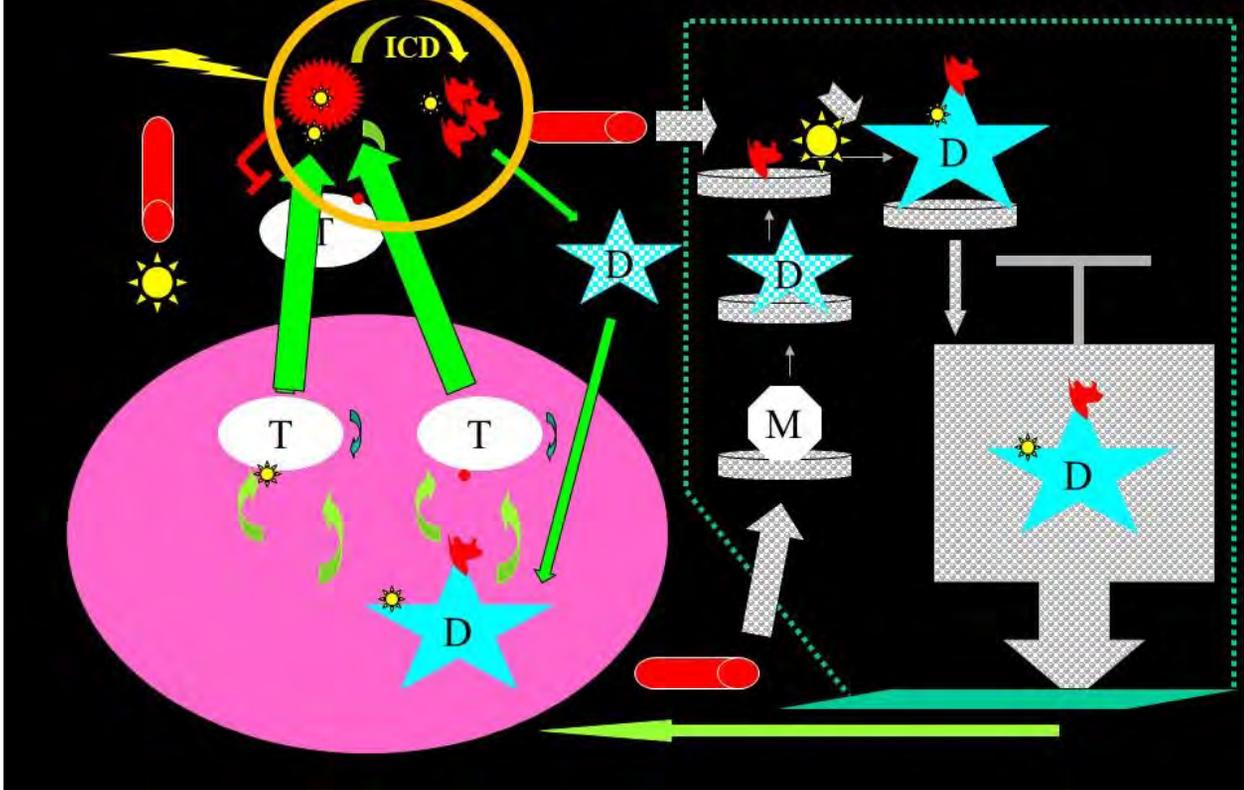
<sup>4</sup> Bioceros BV, Yalelaan 46, 3584 CM Utrecht, The Netherlands

<sup>5</sup> Department of Neurosciences, KU Leuven, Herestraat 49, Leuven, Belgium

<sup>6</sup> Department of Neurosurgery, University Hospitals Leuven, Herestraat 49, Leuven, Belgium

<sup>7</sup> Department of Pediatric Neuro-oncology, University Hospitals Leuven, Herestraat 49, Leuven, Belgium

# Next generation immunotherapy



Cell Death Differ. 1996 Apr;3(2):199-206

### Isolation, differential splicing and protein expression of a DNase on the human X chromosome.

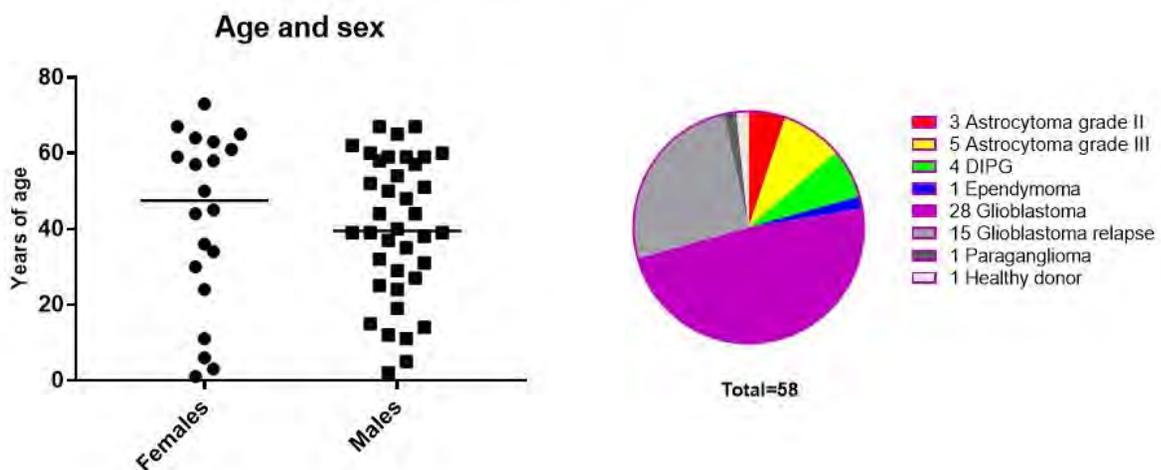
Coy JF<sup>1</sup>, Velhagen I, Himmele R, Delius H, Poustka A, Zentgraf H.

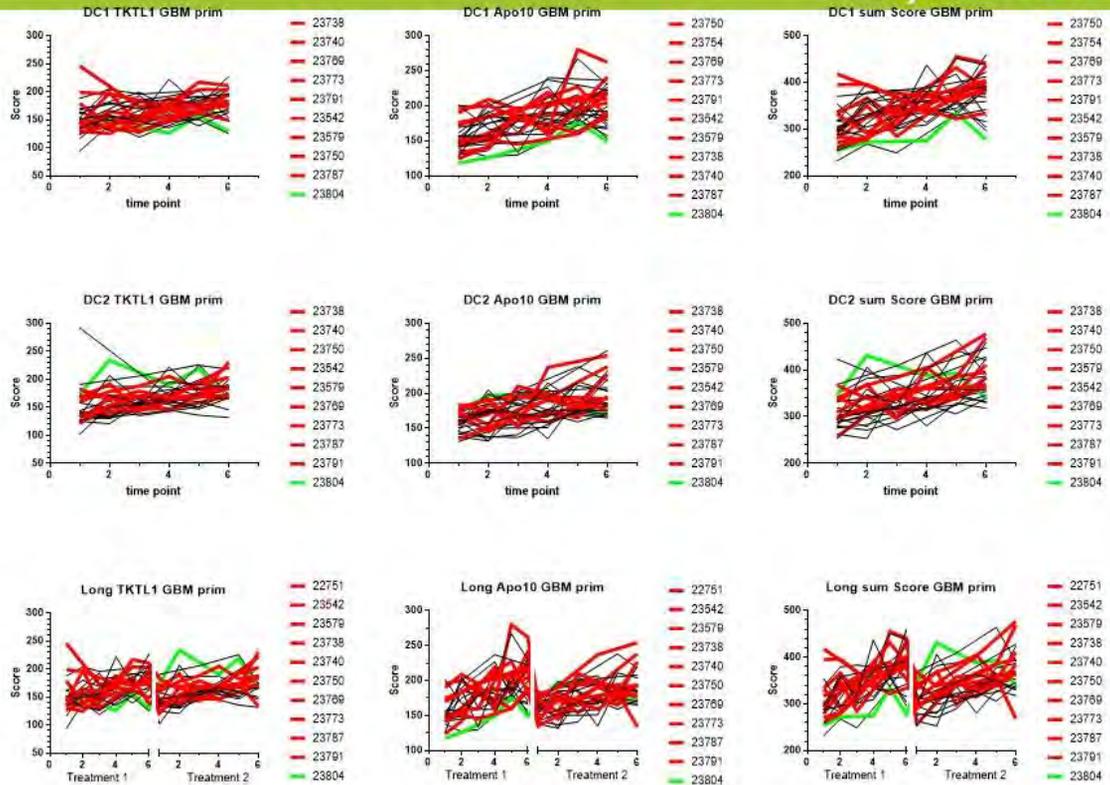
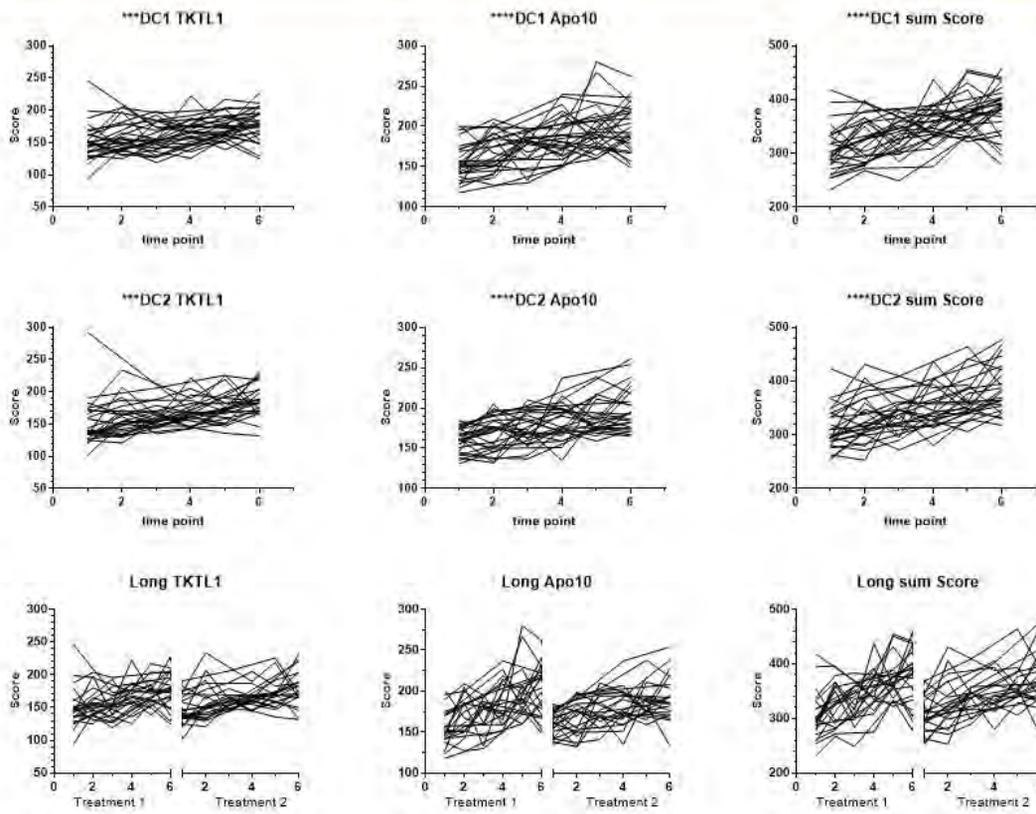
#### Author information

#### Abstract

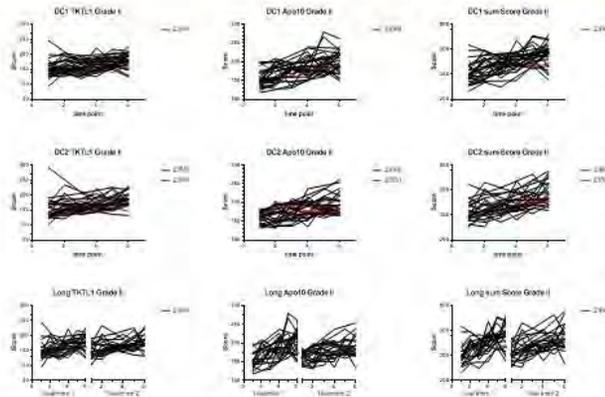
A systematic search for genes differentially expressed in human tissues resulted in the isolation of a gene encoding a protein with high homology to DNase I. In addition to the recently described cDNA sequence (Parrish et al., 1995) we have isolated a transcript, alternatively spliced in the 5' noncoding region. The gene is located between the QM and the XAP-2 gene in Xq28 and encodes a 302 amino acid protein with 39% identity to human DNase I. Besides a high homology at the nucleotide and amino acid level, most exon-intron boundaries of DNase I and DNase X are identical, indicating that both genes may have evolved from a common ancestor. The predicted function was verified by expression of a recombinant protein in an inducible bacterial system and detection of DNase activity. In contrast to DNase I a 18 kdal amino terminal fragment of the full length 35 kdal protein exhibited DNase activity.

## PanTum Tests using the EDIM platform During treatment

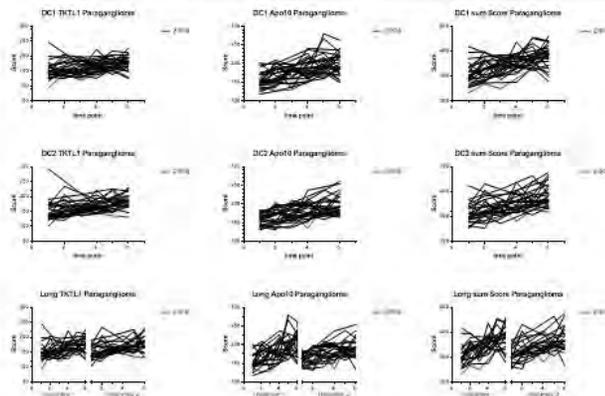




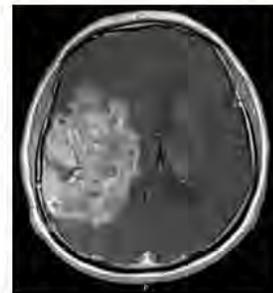
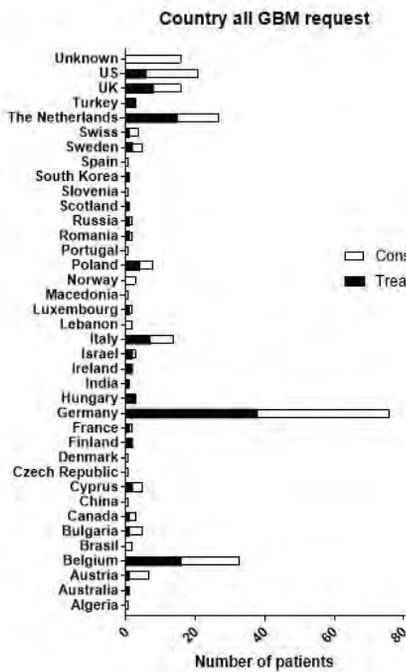
Grade II glioma



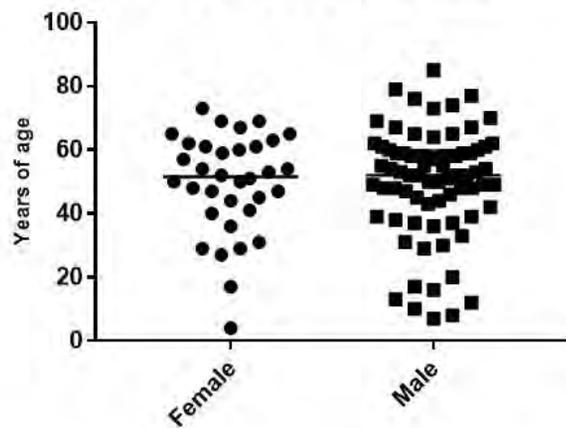
Metastasized Paraganglioma



01/01/2018



Sex and age at diagnosis



Retrospective summary of patients treated as „Individueller Heilversuch“

**Database 20180101**

Database. 2347 records  
 GBM label. 282 records  
 GBM label + Albis number. 198 records  
 GBM label + Albis number + treatment. 122 records

Now we classified in the **classification** system the entities 1 to 3

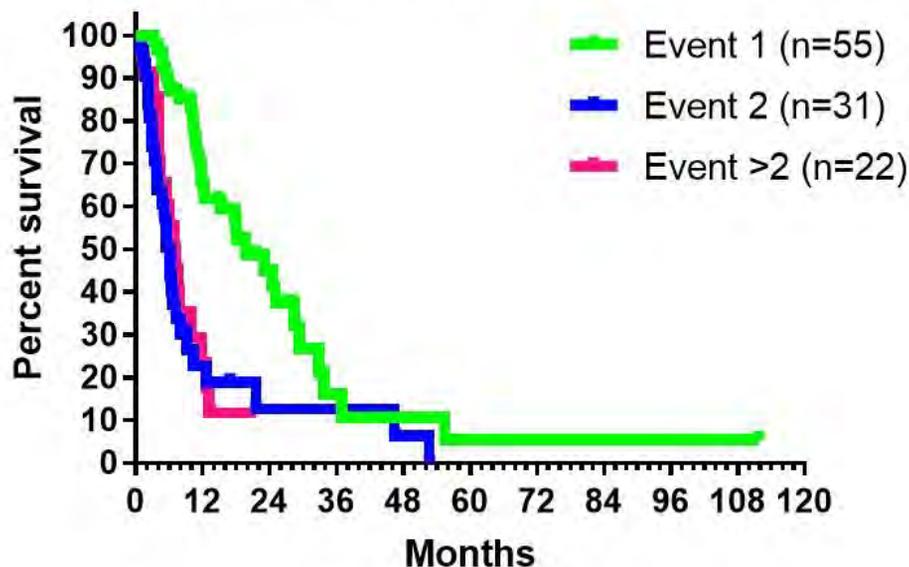
- Classification 1: 109 primary GBM, 1 patient loss of follow up for OS.
- Classification 2: 12 secondary GBM (IDHmut or LGG mentioned)
- Classification 3: 1 GBM DMG

We classified further towards event number

	Primary (or unknown) GBM	Secondary GBM	GBM DMG
Event 1	56	2	1
Event 2	31	1	
Event 3	18		
Event 4	3	5	
Event 5	1	3	
Event 6			
Event 7		1	

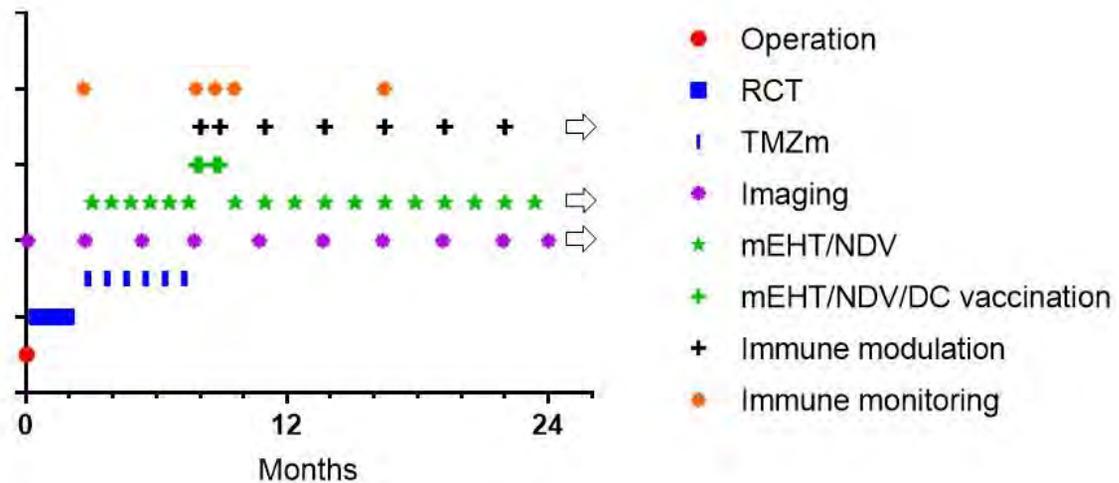
Retrospective summary of patients treated as „*Individueller Heilversuch*“

**\*\*\*\*OS since event total group, event before IT**



Retrospective summary of patients treated as „*Individueller Heilversuch*“

**Standard therapy supplemented with immunogenic cell death therapy during and subsequent multimodal immunotherapy for GBM**



15/03/2018

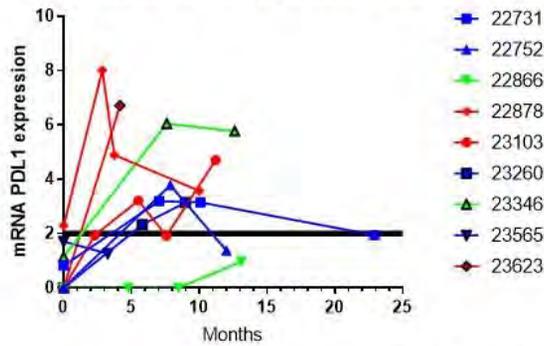
Table 1: Patient characteristics

Number	Sex	Age	Karnofsky	Location	Methylation	Extent of resection	TMZm <sup>2</sup>
22731	M	54	100	Temporal left	Methylated	R1	0
22752	F	61	70	Temporoparietal right	Methylated	R0	0
22866	F	44	70	Occipital right	Methylated	R0	0
22878	M	67	70	Occipital links	Not methylated	R0	0
23103	M	42	100	Parietal right	Not methylated	S nd <sup>1</sup>	0
23260	F	62	70	Parietal left	Methylated	R0	0
23346	M	37	70	Frontal right	Methylated	R1	0
23565	M	57	100	Occipital right	Methylated	R0	5
23579	M	59	80	Frontal right	Not available	R1	0
23623	F	61	100	Frontal right	Not available	S nd	3
23696	M	65	90	Temporal left	Not methylated	S nd	0
23769	M	67	100	Frontal right	Not available	R0	2
23806	M	60	100	Temporal right	Methylated	R1	0
23834	M	60	60	Frontal left	Not available	B	2
23877	M	44	100	Parietal right	Not methylated	R0	0

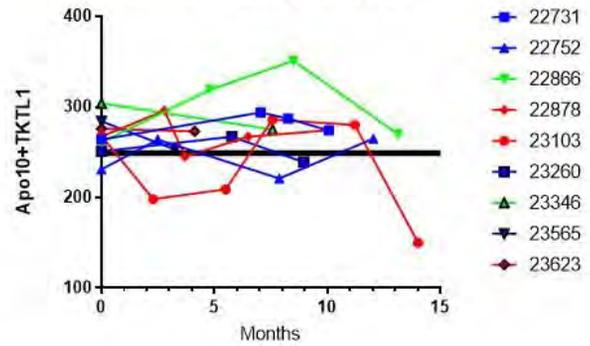
1 S nd: extent of resection not documented.

2 Number of maintenance TMZ courses prior to combining TMZ + NDV/mEHT

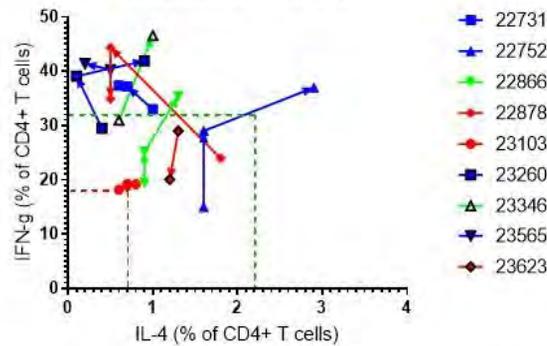
Evolution PDL1 mRNA expression in CTC



Evolution of Apo10+TKTL1



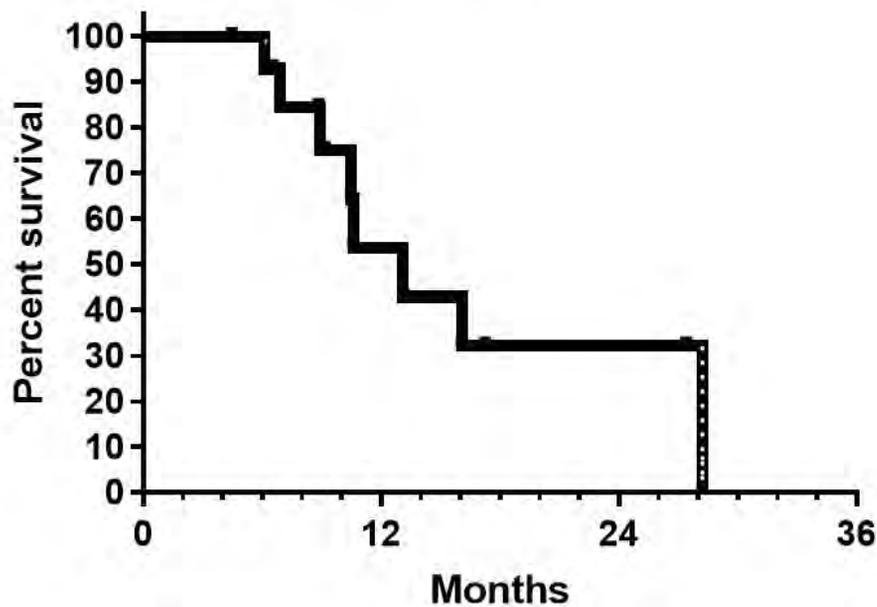
Evolution of IL-4/IFN-g



Van Gool SW, et al. AOCR 2018

Retrospective summary of patients treated as „Individueller Heilversuch“

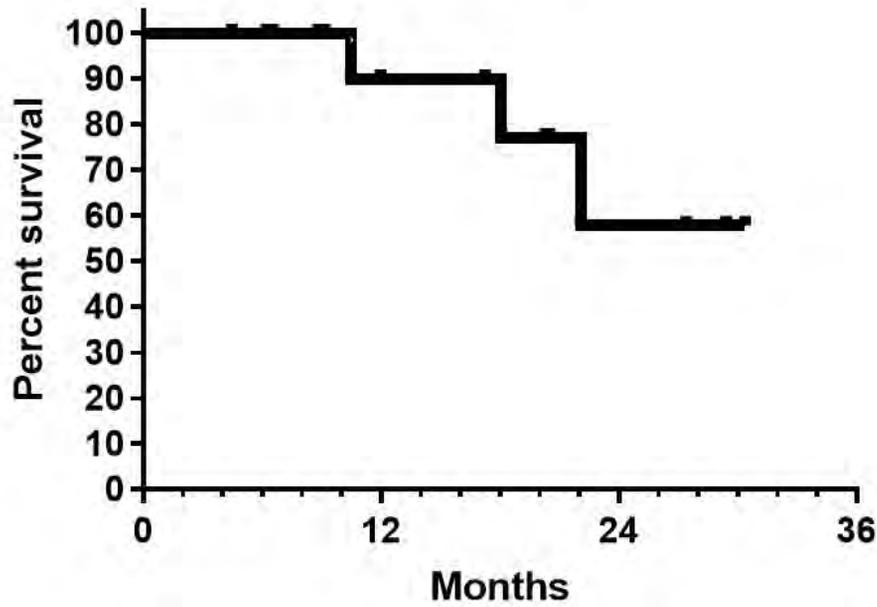
PFS 5d3d



Van Gool SW, et al. AOCR 2018

Retrospective summary of patients treated as „Individueller Heilversuch“

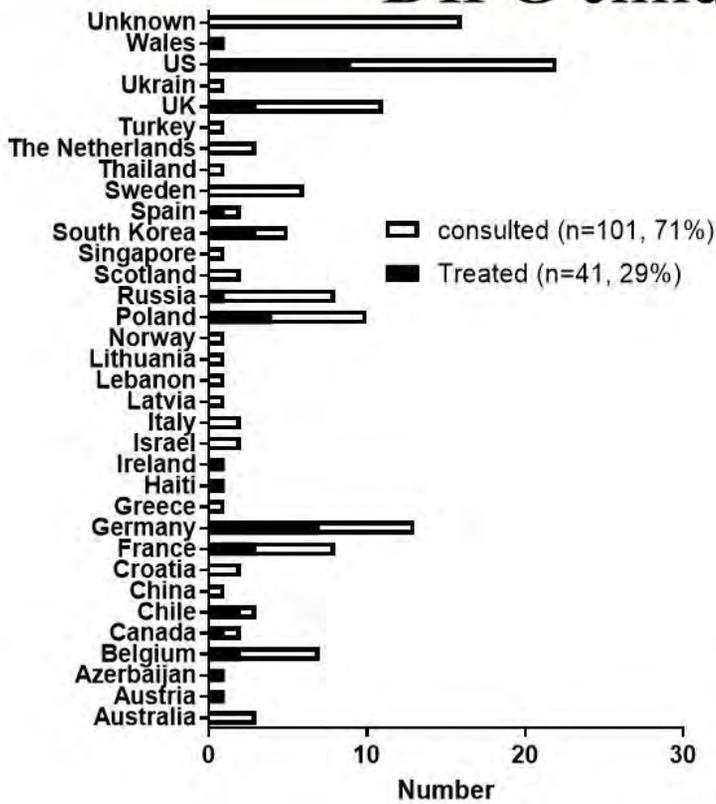
### OS 5d3d



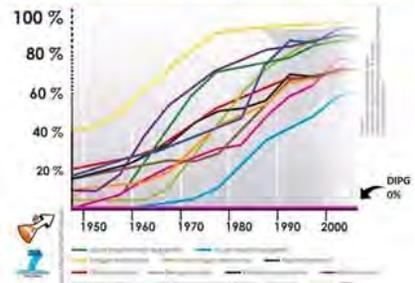
Van Gool SW, et al. AOCR 2018

Retrospective summary of patients treated as „Individueller Heilversuch“

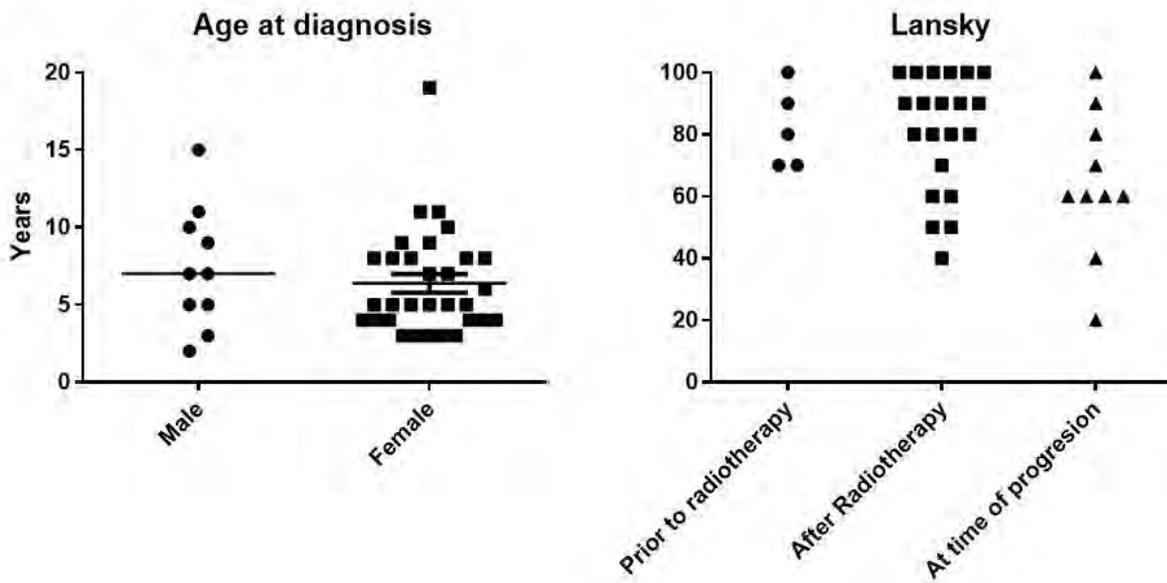
### DIPG children



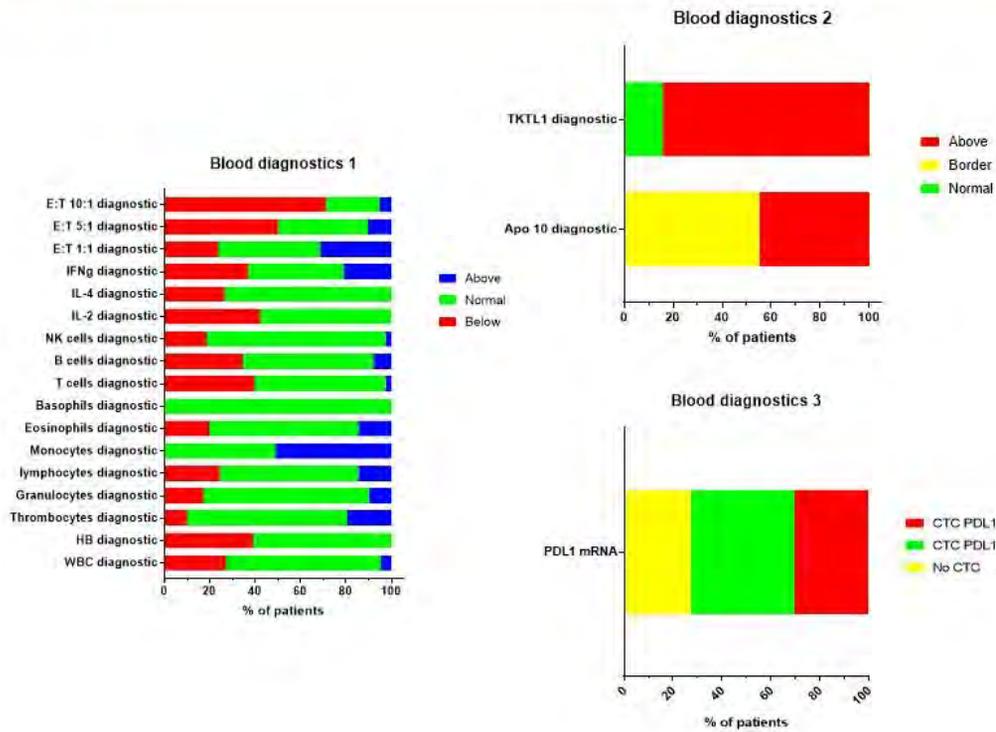
General Status of Children and Young Adults Suffering from Cancer



Retrospective summary of Children treated as „Individueller Heilversuch“



Retrospective summary of Children treated as „Individueller Heilver such“

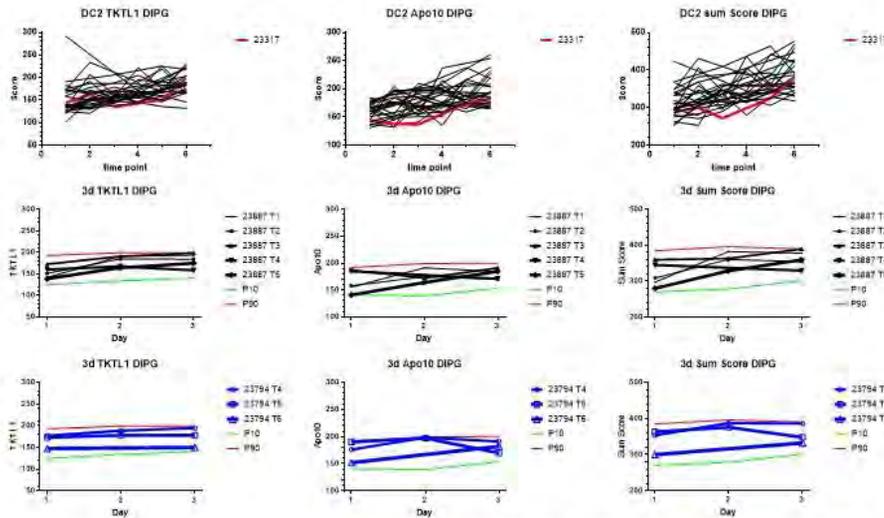


Retrospective summary of Children treated as „Individueller Heilver such“

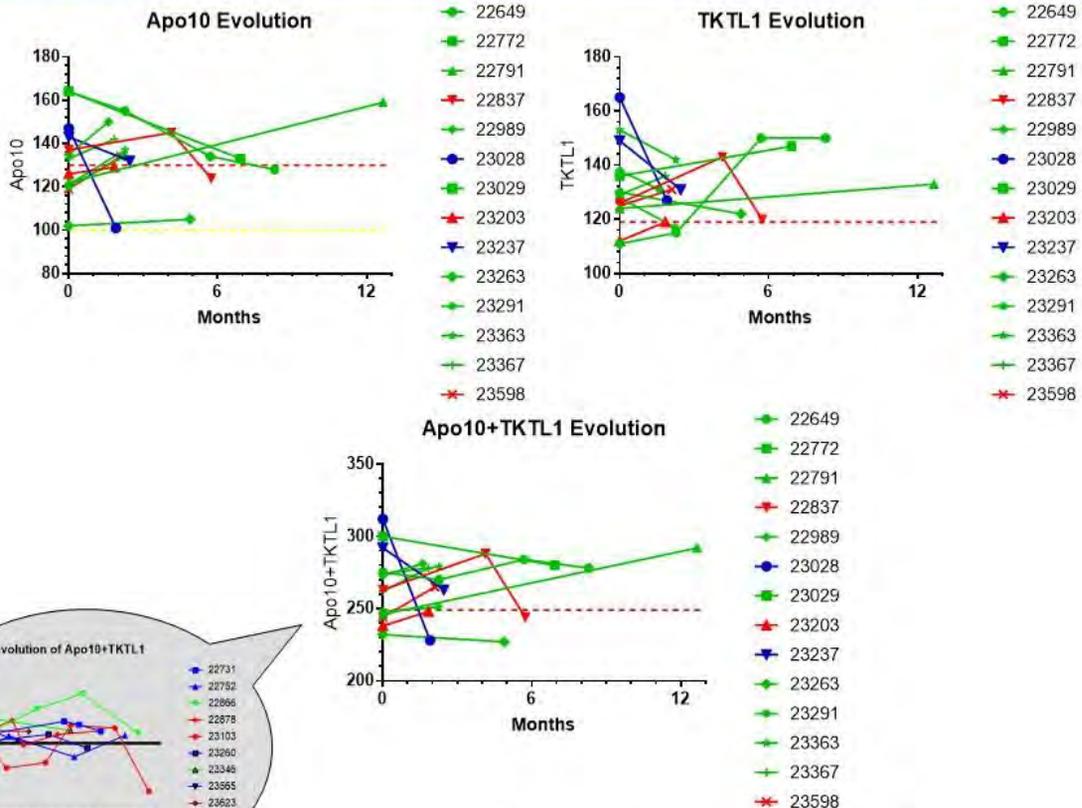
Phase I read-out: feasibility, no major toxicity

- \* NDV infusions
- \* modulated Electrohyperthermia
- \* DC vaccination

Phase IIa read-out: response to treatment

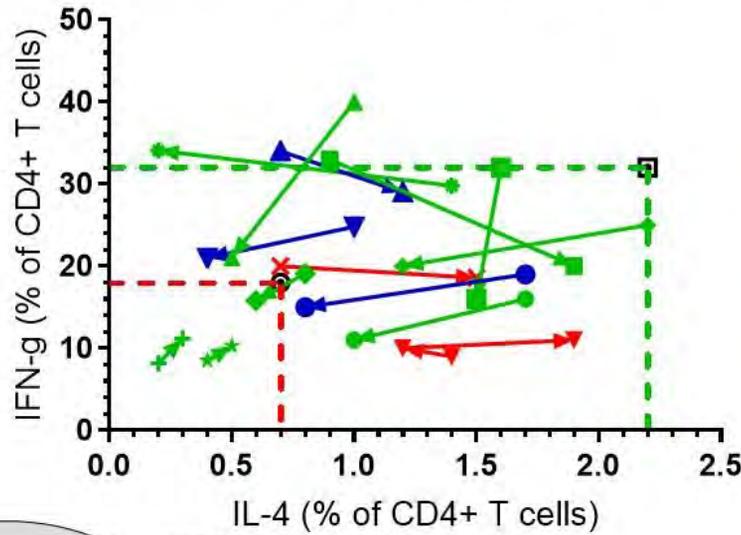


Retrospective summary of Children treated as „Individueller Heilversuch“

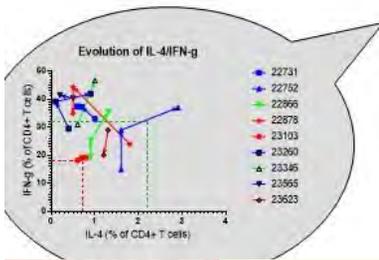


Retrospective summary of Children treated as „Individueller Heilversuch“

IL-4/IFN-g evolution

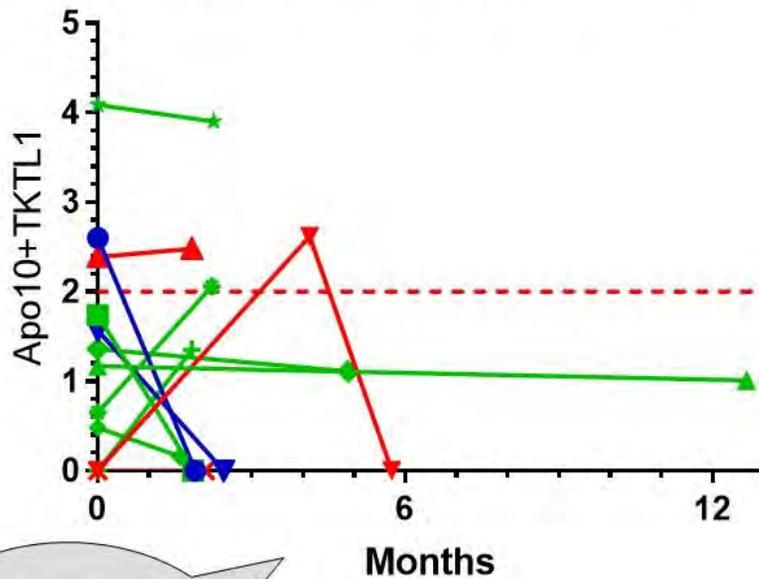


- 22649
- 22772
- 22791
- 22837
- 22989
- 23028
- 23029
- 23203
- 23237
- 23263
- 23291
- 23363
- 23367
- 23598

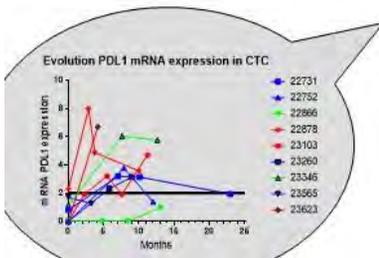


Retrospective summary of Children treated as „Individueller Heilversuch“

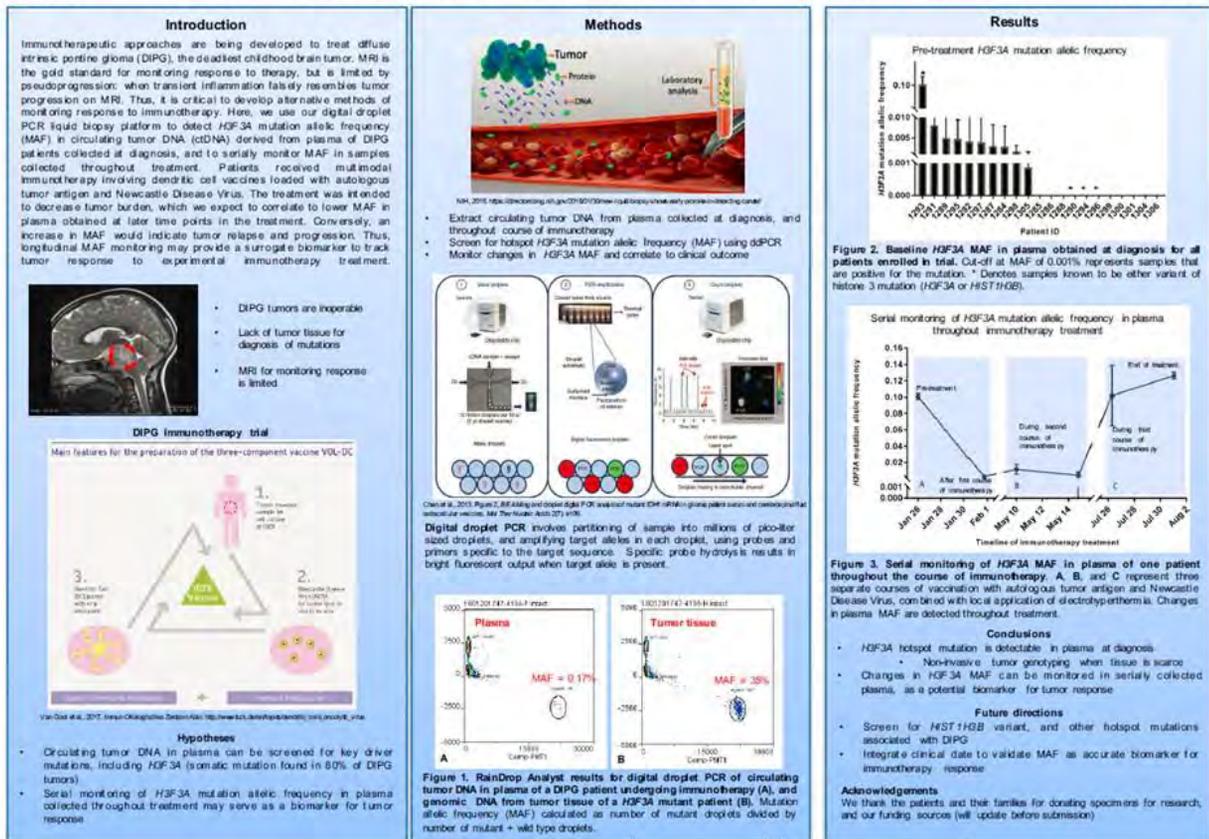
PDL1 mRNA Evolution



- 22649
- 22772
- 22791
- 22837
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- 23029
- 23203
- 23237
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- 23598

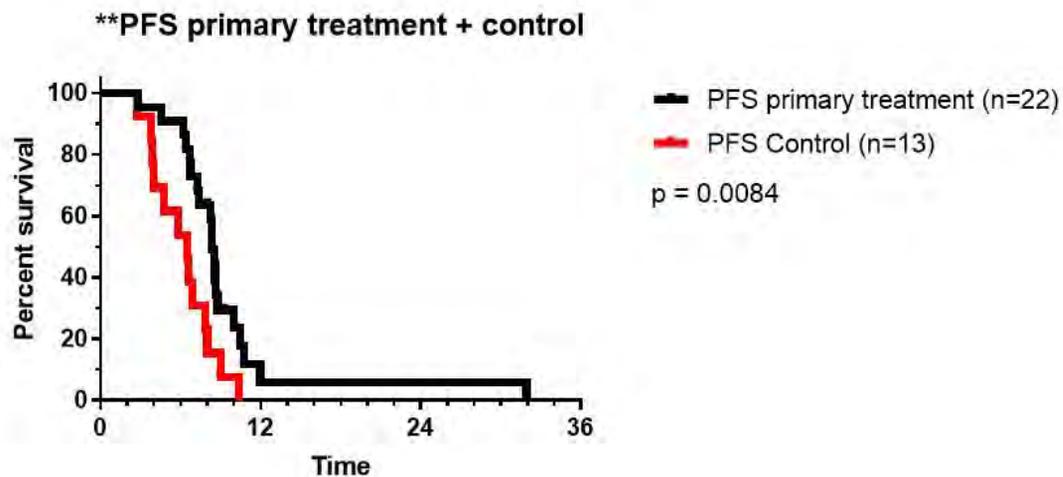


Retrospective summary of Children treated as „Individueller Heilversuch“



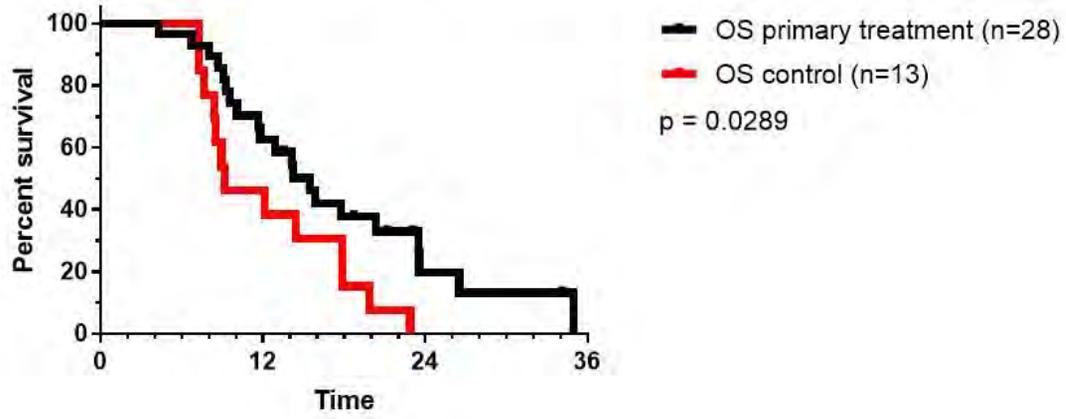
15/07/2018

IOZK



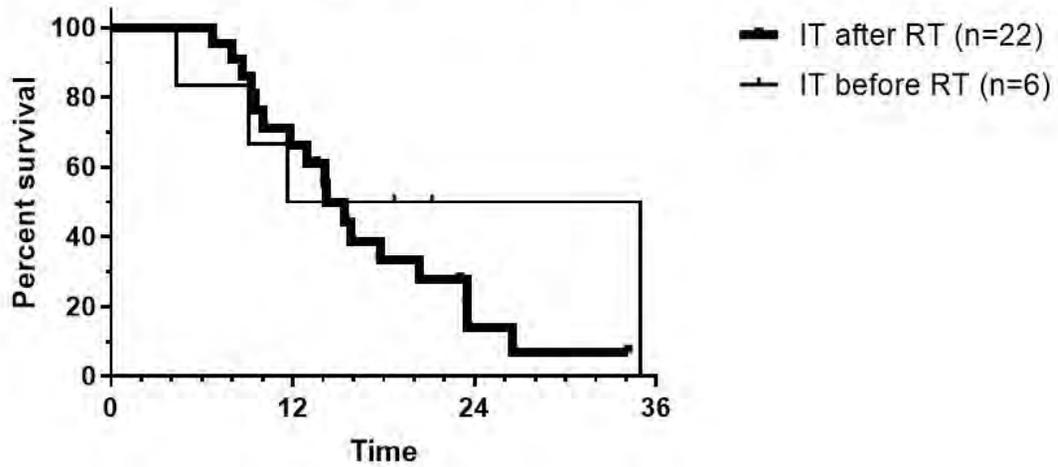
Retrospective summary of Children treated as „Individueller Heilversuch“

**\*OS primary treatment + control**



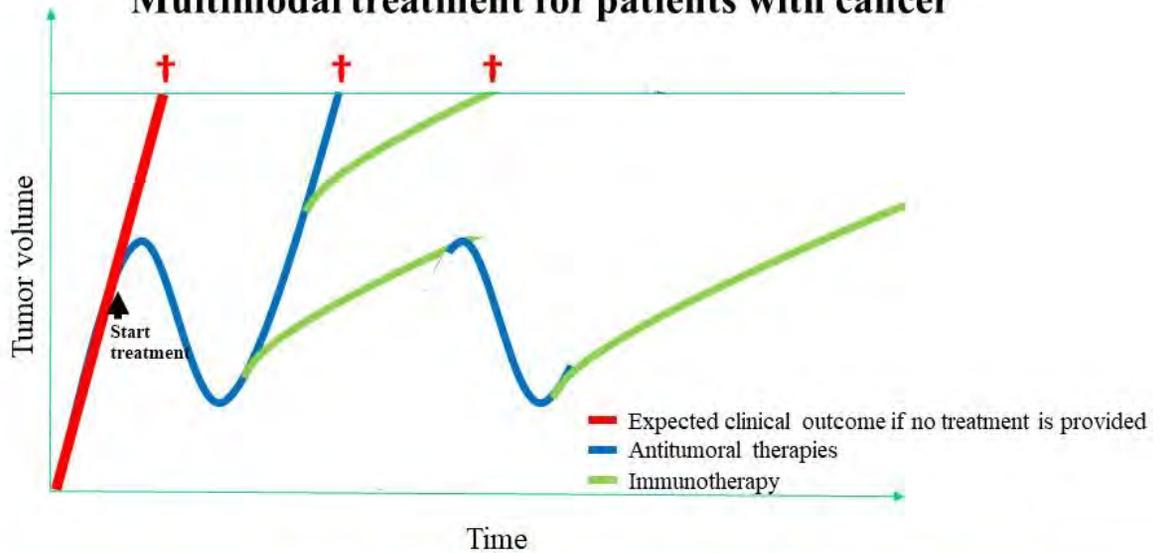
Retrospective summary of Children treated as „Individueller Heilversuch“

**OS primary treatment -+ RT**



Retrospective summary of Children treated as „Individueller Heilversuch“

### Multimodal immunotherapy as part of Multimodal treatment for patients with cancer



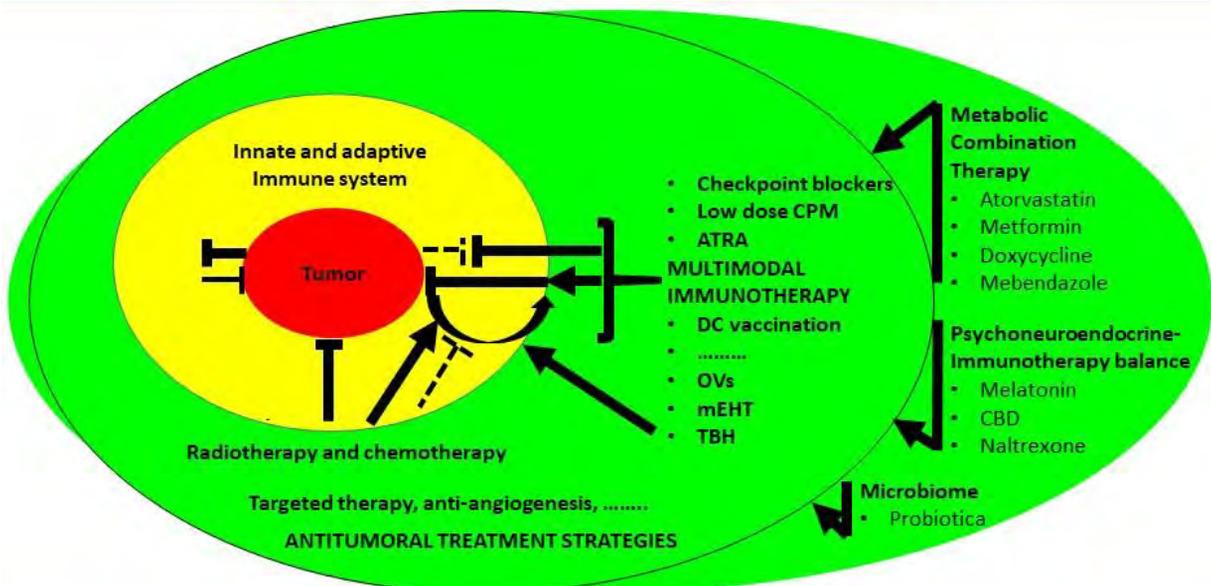
*Ideal scenario = early start with multimodal immunotherapy*

Antitumor strategy

Surgery (-> R(C)T + CT)

Multimodal immunotherapy

Personalized medicine for cancer patients  
 „Personalized“ in three Dimensions !



1. Tumor antigens

2. Immune system

3. Combination therapy

Tumor and host and their interaction are dynamic processes

## **Hyperthermic Immunotherapy**

**Ralf Kleef**

Dr. Kleef Hyperthermia, Vienna, Austria

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

**Cite this article as:**

Kleef R. (2018):Hyperthermic Oncology; Oncothermia Journal 24:270-302

[www.oncothermia-journal.com/journal/2018/Complete\\_clinical\\_remission\\_of\\_stage\\_IV\\_breast\\_cancer.pdf](http://www.oncothermia-journal.com/journal/2018/Complete_clinical_remission_of_stage_IV_breast_cancer.pdf)

# Complete clinical remission of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

**Ralf Kleef, Robert Nagy, Viktor Bacher, Hans Bojar, Ralph Moss, Dwight McKee**

Immunology & Integrative Oncology; Auhofstraße 1, A-1130 Vienna, Austria;

[ralf.kleef@dr-kleef.at](mailto:ralf.kleef@dr-kleef.at)

Advanced stage inoperable breast cancer has a poor prognosis and patients rarely enjoy durable complete response to treatment; progression free survival often is limited.

## Methods

We previously reported complete remission of far advanced lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and complete remission of inoperable esophageal Cancer ITOC4 (Prague) 2017; here we report a similar successful treatment concept.

FD: 09/2016 in our clinic; the 65-y female patient noticed the tumor about 10 years ago. She had always refused treatment. When she first presented in September 2016 she was diagnosed with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, cT4 N1 M1 (bone), ER 100% and PR 40% positive, Ki-67 19%, HER-2/NEU (c- cerbB-2) neg. confirmed by FISH score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA-4 overexpressed, TM CA 15-3 was elevated at 42 kU/L.

Additionally, soft tissue nodule upper lobe right lung suspicious for lung metastasis. Atelectasis changes in the lingula and lower lobes of the left lung, bilateral pulmonary embolism. Patient was on anticoagulants Tinzaparin 10.000 IE. When she was seen initially she presented with hemoglobin of

3.3 (!) and received 4 units of packed red blood cells. Karnofsky Index was 80%, moderate pain right chest, stable weight of 60 kg.

Social history: married, mother of 5 children; negative family history for cancer.

The patient initially presented with a very far advanced massive right sided breast cancer cT4 N1 M1 (bone) which was bleeding heavily upon slightest touch. The patient therefore underwent emergency palliative radiation 5 times between November 10 and November 17, 2016 with 25 Gy TD at 5 Gy single dose; additionally, she underwent immunotherapy as described previously combining low-dose checkpoint inhibitor ipilimumab-nivolumab in combination with low dose interleukin (IL-2) treatment parallel to local regional and whole-body hyperthermia. Additionally, low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m<sup>2</sup>) and vinorelbine (30mg/m<sup>2</sup>).

## Results

Unexpectedly, restaging at the end of January 2017 performed with clinical examination, bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers. Telephone up in 07/2018 confirms Karnofsky score of 100%, pain or any other cancer related symptoms have vanished. Current (08/2018) follow-up time 22 months.

**Conclusion**

The unexpected remission of far advanced inoperable and metastatic breast cancer following a complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemo-radiation therapy warrants further clinical studies. The presentation would include description of more cases and an overview of all treated patients.



## Complete clinical remission of stage IV breast cancer with bone and lymph node metastasis combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

Ralf Kleef<sup>a\*</sup>, Robert Nagy<sup>a</sup>, Viktor Bacher<sup>a</sup>, Hans Bojar<sup>b</sup>, Dwight McKee<sup>c</sup>, Ralph Moss<sup>d</sup>

### INTRODUCTION

We previously reported complete remission of far advanced massive right sided lung metastasis in triple negative breast cancer at ITOC3 (Munich) 2016 and complete remission of inoperable esophageal Cancer ITOC4 (Prague) 2017; here we report a similar successful treatment concept.

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Unexpectedly, restaging at the end of January 2017 performed with clinical examination, bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers. Telephone up in 07/2018 confirms Karnofsky score of 100%, pain or any other cancer related symptoms have vanished. Current (08/2018) follow-up time 22 months.

### STAGING



10/2016 before treatment



11/2016



03/2017



09/2017

### CONCLUSION

The unexpected remission of far advanced inoperable and metastatic breast cancer following a complex immunotherapy treatment including low-dose checkpoint inhibitors, hyperthermia and metronomic chemo-radiation therapy warrants further clinical studies.

### MATERIALS & METHODS

FD: 09/2016 in our clinic; the 65-y female patient noticed the tumor about 10 years ago. She had always refused treatment. When she first presented in September 2016 she was diagnosed with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, cT4 N1 M1 (bone), ER 100% and PR 40% positive, Ki-67 19%, HER-2/NEU (c-erbB-2) neg. confirmed by FISH score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA-4 overexpressed, TM CA 15-3 was elevated at 42 KU/l. Additionally, soft tissue nodule upper lobe right lung suspicious for lung metastasis. Atelectasis changes in the lingula and lower lobes of the left lung, bilateral pulmonary embolism. Patient was on anticoagulants Tinzaparin 10.000 IE. When she was seen initially she presented with hemoglobin of 3.3 (l) and received 4 units of packed red blood cells. Karnofsky Index was 80%, moderate pain right chest, stable weight of 60 kg.

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 \* Corresponding author: Ralf Kleef, M.D., ralf.kleef@dr-kleef.at  
 Declaration of conflict of interest: RK has a patent pending.



Immunotherapy. Integrative Oncology.

# Hyperthermic Immunotherapy

Ralf Kleef, Vienna, Austria



36. Conference of the International Clinical Hyperthermia Society  
28th- 29th September 2018, Budapest, Hungary

## Hyperthermic Immunotherapy Learning objectives

- **Fever and cancer**
- **Loco-regional versus whole-body hyperthermia**
- **Hyperthermic Immunotherapy in oncology**

Epidemiology

**In clear words:**

**Fever protects!**

Fever– Harmful or beneficial?

4 Hypotheses

# Fever– Harmful or beneficial?

## 1. Hypothesis: Evolution Studies [1].

**Even cold-blooded animals can get fever, as a result they are looking for warmer waters or areas**

[1] Kluger et al 2001. Fever and Immunity. In: Ader R et al (eds) Psychoneuroimmunology, 3rd edn. Academic Press, San Diego, pp 687-701

# Fever– Harmful or beneficial?

- 2. Hypothesis: Correlational Studies[2].
  - **Comparing the extent of the reaction fever temperature relative to morbidity and mortality.**
- All "fever"-Studies in humans and animals demonstrate the protective function of the fever**

[2] Kluger et al 2001. Fever and Immunity. In: Ader R et al (eds) Psychoneuroimmunology, 3rd edn. Academic Press, San Diego, pp 687-701

## Fever– Harmful or beneficial?

- 3. Hypothesis: Antipyresis [3,4].
- **Reduction of fever increases morbidity and mortality.**

[3] Bernheim et al 1977. Fever: effect of drug-induced antipyresis on survival. *Science* 193: 237-239  
[4] Covert et Reynolds 1976. Survival value of fever in fish. *Nature*. 1977 May 5;267(5606):43-5

## Fever– Harmful or beneficial?

- 4. Hypothesis: Hyperthermia [5-8].

**Hyperthermia reduces morbidity and mortality and improves immunological functions**

[5] Kluger et al 1975. Fever and survival. *Science* 188: 166-168  
[6] Reynolds et al 1976. Behavioral fever in teleost fish. *Nature*. 259: 41-42  
[7] Jiang et al 2000. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. *Infect Immun* 68: 1265-1270  
[8] Zellner et al 2002. Human monocyte stimulation by experimental whole body hyperthermia. *Wien Klin Wochenschr* 114: 102-107



*" I would cure all diseases if only I could produce fever*

Parmenides, Grec physician , 4. century BC



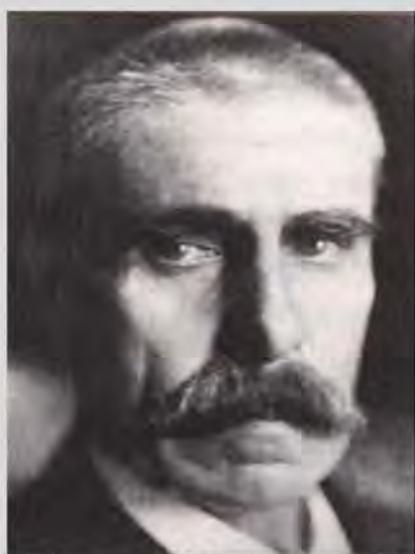
***" Fever is „Body-Buildung“ for the Immune systeme,,***

Kleef, German physician, 21 century AC

## William B. Coley (um 1888)



## Julius Wagner-Jauregg



- 1927 the Austrian Julius Wagner-Jauregg was awarded the Nobel Prize for his fever therapy until then hardly curable syphilis in the final stage. He infected patients with malaria control to trigger the healing fevers.
- **Hyperthermia by the means of the 19. century**



**Were the ancient physicians better?**



**Fever and cancer are inversley related**

**Kleef R et al. Fever, cancer incidence and spontaneous remissions.  
Neuroimmunomodulation 2001;9(2):55-64.**



**Spontaneous remissions were frequently associated with concurrent febrile infections**

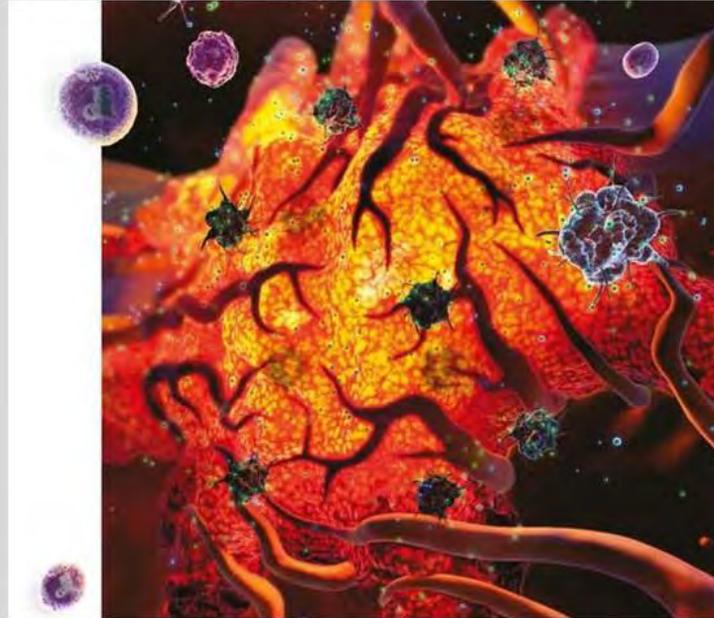
**Kleef R et al. Fever, cancer incidence and spontaneous remissions. Neuroimmunomodulation 2001;9(2):55-64.**

## Chronic Infection or Inflammation and Cancer

- Chronic infection/inflammation engages leukocytes' pro-inflammatory 'tissue repair' mode, resulting in 'vicious cycle' that:
  - (1) Promotes cancer initiation and development
  - (2) Suppresses immune function, including suppression of immune function of:
    - Macrophages
    - Neutrophils
    - Cytotoxic T cells
    - Natural Killer cells
    - B cells

## Malignant inflammation

G. Stix



Following this brief introduction into fever and immunology we will now jump into clinical hyperthermia

# Loco-regional hyperthermia



Issels R et al.



JAMA Oncology

[View Article](#)

JAMA Oncol. 2018 Apr; 4(4): 483–492.

Published online 2018 Feb 15. doi: [10.1001/jamaoncol.2017.4996](https://doi.org/10.1001/jamaoncol.2017.4996)

PMCID: PMC5885262

PMID: [29450452](https://pubmed.ncbi.nlm.nih.gov/29450452/)

## Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

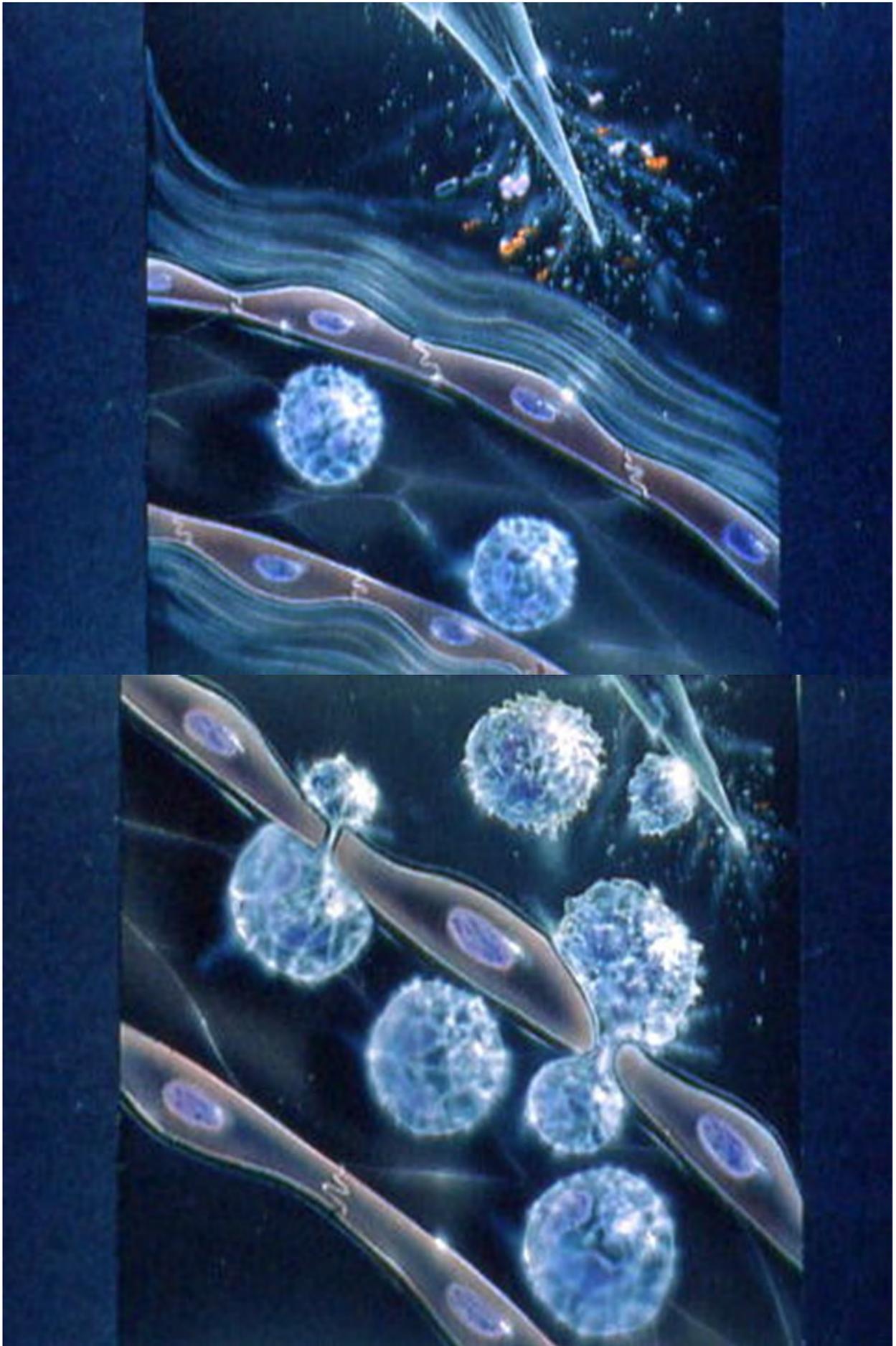
Rolf D. Issels, MD, PhD,<sup>1</sup> Lars H. Lindner, MD,<sup>1</sup> Jaap Verweij, MD,<sup>2</sup> Rüdiger Wesselowski, MD,<sup>3</sup> Peter Reichardt, MD,<sup>4</sup> Peter Wust, MD,<sup>5</sup> Pirus Ghadjjar, MD,<sup>5</sup> Peter Hohenberger, MD,<sup>6</sup> Martin Angele, MD,<sup>7</sup> Christoph Salat, MD,<sup>1</sup> Zeljko Vujaskovic, MD,<sup>8</sup> Soeren Daugaard, MD,<sup>9</sup> Olav Mella, MD,<sup>10</sup> Ulrich Mansmann, MD,<sup>11</sup> Hans Roland Dürr, MD,<sup>12</sup> Thomas Knösel, MD,<sup>13</sup> Sultan Abdel-Rahman, PhD,<sup>1</sup> Michael Schmidt, MD,<sup>14</sup> Wolfgang Hiddemann, MD,<sup>1</sup> Karl-Walter Jauch, MD,<sup>7</sup> Claus Belka, MD,<sup>15</sup> and Alessandro Gronchi, MD<sup>16</sup>, for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

## WBH – Heckel HT 3000

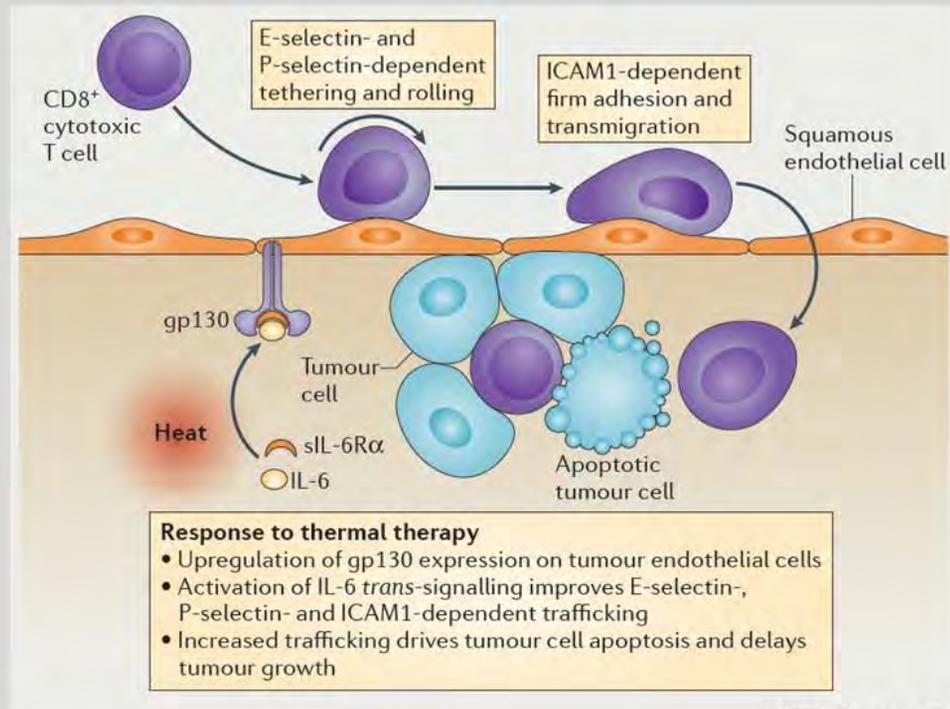


## WBH – Ardenne Iratherm 1000





## Cell adhesion molecule mediated extravasation of immune cells following hyperthermia



Evans, Repasky, Fisher (2015)

Proposed mechanism of action:

## ICD – Immunogenic Cell Death induced by chemotherapy

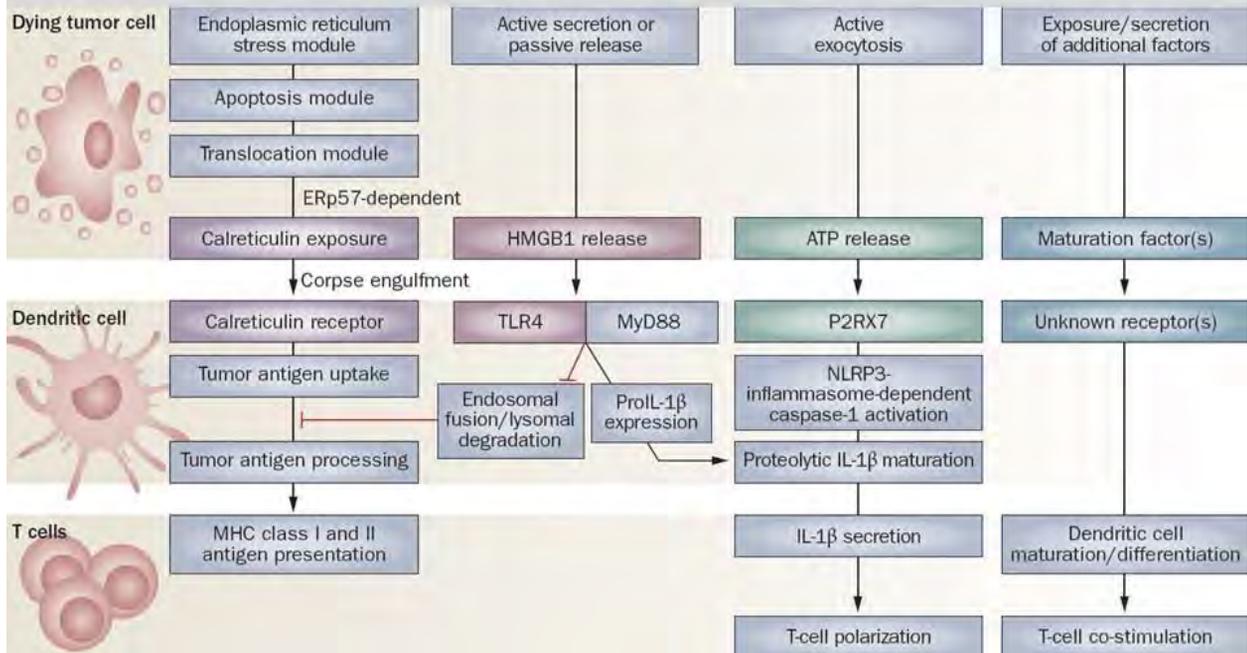
A series of immunogenic signals delivered by tumor cells undergoing ICD stimulates DCs to take up antigens from dying tumor cells.

“Cancer cells succumbing to ICD are de facto converted into an anticancer vaccine and as such elicit an adaptive immune response.”

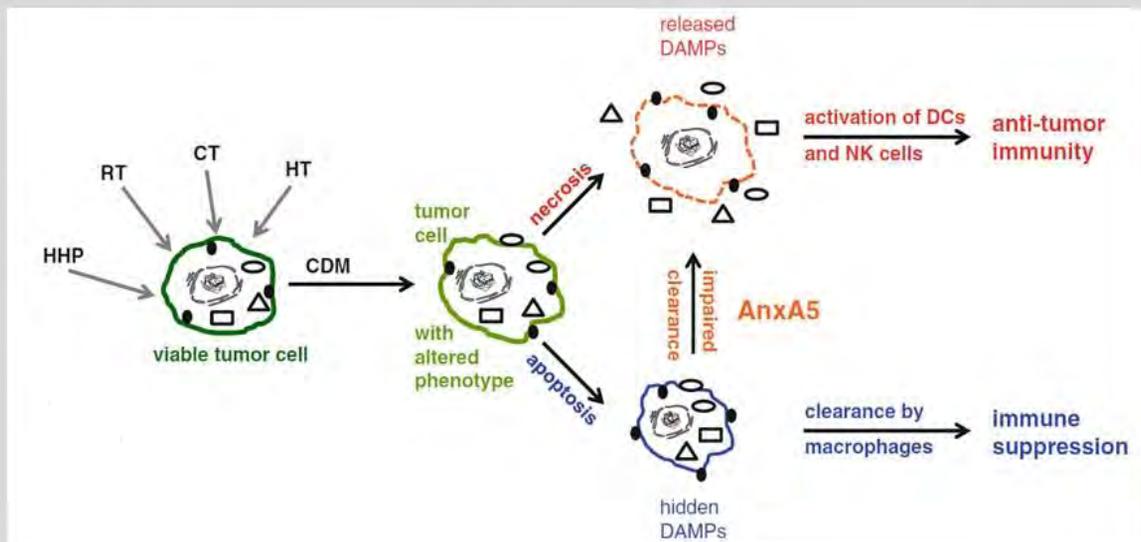
But:

This specific immune effect is considerably counteracted by the general immune-suppressive effect of chemotherapy.

# ICD – Immunogenic cell death

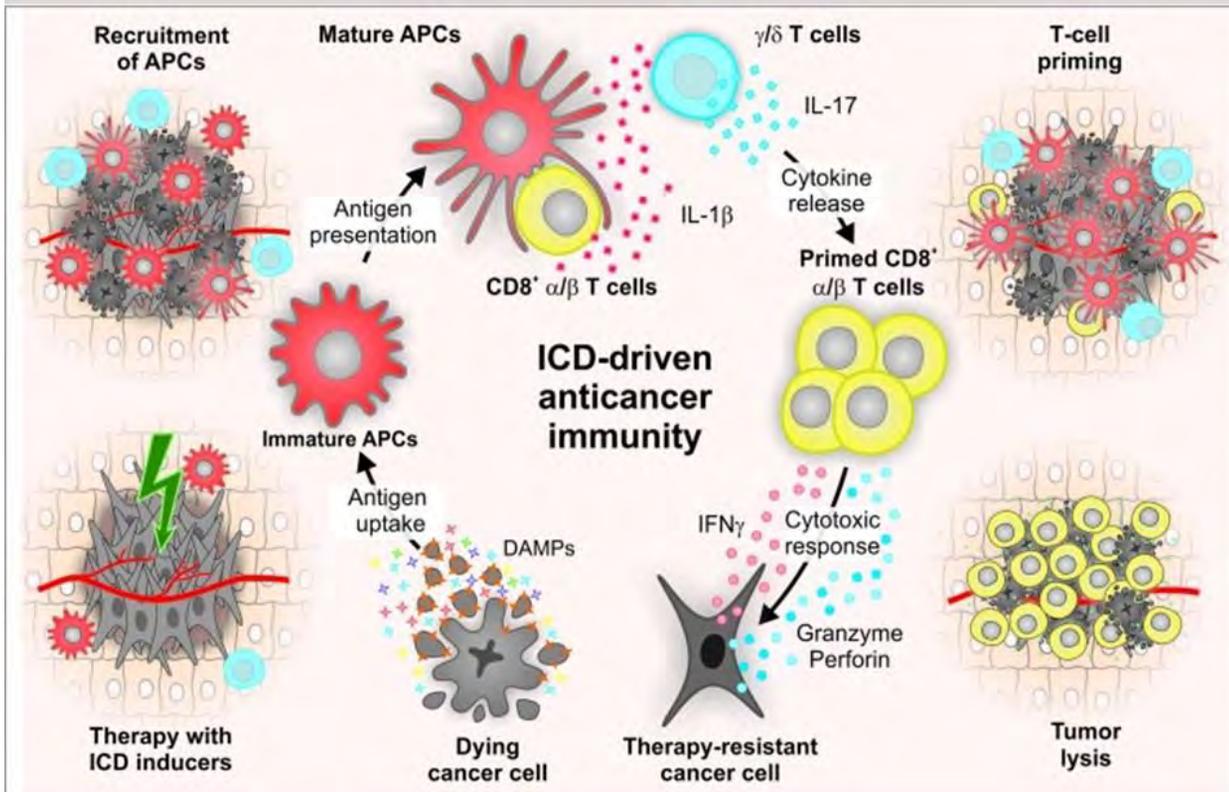


## Hyperthermia releases Damage Associated Molecular patterns (DAMPs)



Gaipl (2011)

## Hyperthermia releases Damage Associated Molecular patterns (DAMPs)



## Rational for Immune therapy in Cancer Patients

- **Disturbed immune system**
- **Inadequate immune reactions**
- **Immune cells are unable to detect tumor cells**

## Disclosures

RK has European and International patent pending



Low-dose checkpoint inhibitor therapy with interleukin-2 (IL-2) and fever range hyperthermia in stage IV cancer: a retrospective analysis with single case presentations

**Ralf Kleef, Vienna, Austria**



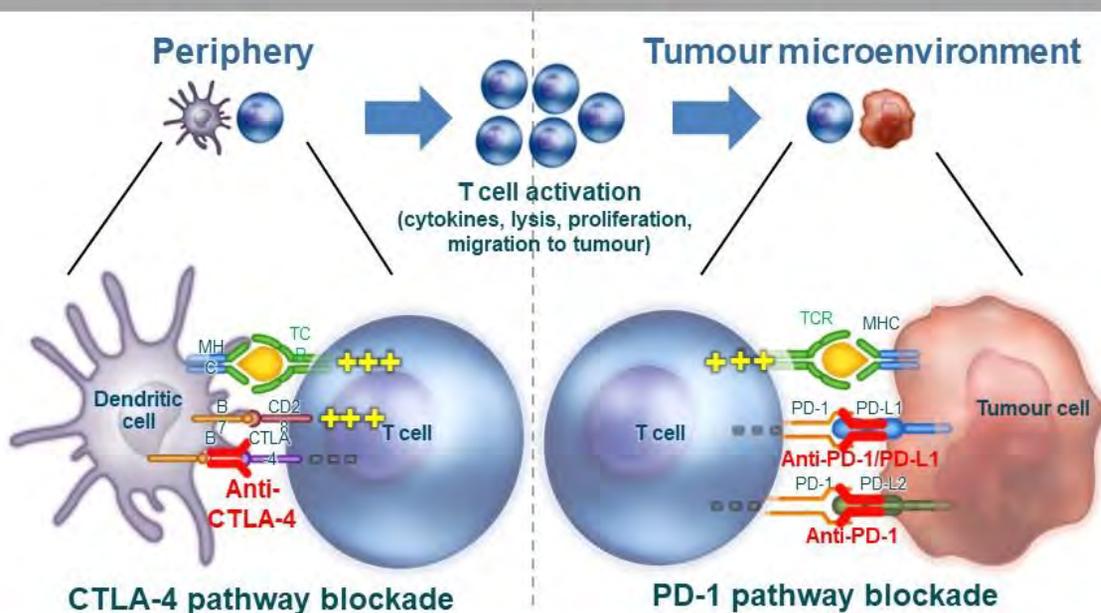
**Presentation to 36. Conference of the International Clinical Hyperthermia Society  
28th- 29th September 2018, Budapest, Hungary**

## OUR TREATMENT CONCEPT

- ❖ Every year 8.2 million deaths occur due to metastatic (**stage IV**) cancer worldwide
- ❖ Management of metastatic cancer is palliative by intent; even combination therapies with checkpoint inhibitors results in only a small minority (with the exception of metastatic melanoma) of durable responses, often at the cost of long lasting grade 3 and 4 autoimmune side effects.
- ❖ Our team combines the following immunotherapies (with 52% clinical benefit rate in 98/119 evaluable patients; 38% Objective response rate):
  - 1) Low-dose immune checkpoint blockade (LD-IC; ipilimumab plus nivolumab)
  - 2) Individually titrated interleukin 2 (IL-2) treatment under Taurolidine protection
  - 3) Loco regional – and whole body hyperthermia without classical chemotherapy
  - 4) If Chemotherapy: only after Chemo sensitivity testing and metronomic low dose chemotherapy

## IMMUNO-ONCOLOGY:

Blocking CTLA-4 and PD-1 pathways with monoclonal antibodies



CTLA-4 = cytotoxic T-lymphocyte antigen-4; PD-1 = programmed cell death 1; PD-L1/2 = PD ligand 1/2; TCR = T cell receptor.

Adapted from Wolchok J, et al. Oral presentation at ASCO 2013 (Abstract 9012).

## IMMUNE-CHECKPOINT BLOCKADE

**Immune-checkpoint blockade:** antibodies targeting the negative regulatory molecules CTLA-4 and PD-1 to release the brakes on natural T cells responsive to tumor

### Disadvantages

- ❖ **Tolerance breakdown** resulting in a high incidence of immune-related adverse events (irAEs)
- ❖ A meta-analysis in 1265 patients from 22 clinical trials found a respective incidence of **72 % for all-grade immune-related adverse effects irAEs and 24 % for high-grade irAEs** leading to hospitalization or intravenous treatment.
- ❖ The risk of developing irAEs in many clinical trials was **dependent of dosage**, with incidence of all-grade irAEs of 61 % for ipilimumab 3 mg/kg and 79 % for ipilimumab 10 mg/kg. Death due to irAEs occurred in 0.86 % of patients.
- ❖ **Tumor regression is frequently associated with the development of autoimmunity**

## THERAPEUTIC PARADIGM SHIFT:

The autoimmune effect of T cells should be exploited for the treatment of advanced cancer

- ❖ Breakthrough concept since irAEs associated with checkpoint inhibitors are considered primarily as severe safety issue (1, 2)
- ❖ *low-dose immune checkpoint inhibitor (LD-IC) combination immune therapy demonstrated partial to complete remission in stage IV cancer patients (triple negative and hormone rec. pos. breast cancer, melanoma, bladder cancer and prostate cancer, (among others)*
- ❖ LD-IC needs the Synergy of hyperthermia and fever

1 June CG et al. Is autoimmunity the Achilles' heel of cancer immunotherapy. Nature Medicine 23; 540-548, 2017

2 Boutros C, et al. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nature Reviews Clinical Oncology. 13, 473-486, 2016.

## Proof-of-Principle retrospective analysis

Five best cases out of 119 intend-to-treat patients

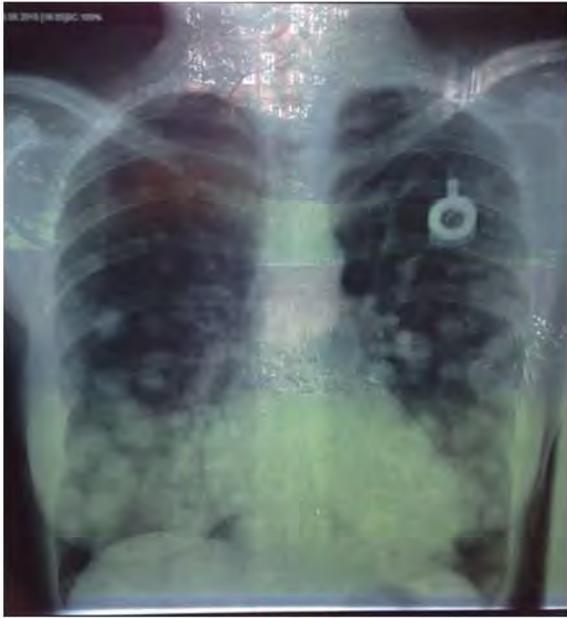
- ❖ We report five cases of stage IV patients with solid carcinomas with far advanced metastases
- ❖ They had exhausted all conventional treatments
- ❖ They went into complete remission with *low-dose* IC (LD-IC) blockade in combination with individualized doses of IL-2 (ID-IL-2) treatment under Taurolidine protection and loco-regional and whole body hyperthermia but without classical chemotherapy.

### Case 1.: COMPLETE CLINICAL REMISSION

of Lung Metastases of Stage IV Triple Negative Breast Cancer  
Administering Low-Dose Immune Checkpoint Blockade in  
Combination with Hyperthermia and Interleukin-2

- 51 y.o. female with TNBC [ICD10: C50.9]
- Disseminated lung metastases [ICD10: C78.6]
- Malignant Lymphadenopathy [ICD10: R59.1]
  
- Karnofsky score of 70% (ECOG = 1)
- During inspiration severe pain in the left lateral chest wall
- Extreme Pain during sneezing
- Severe dyspnoea on exertion (DOE)
- Lack of appetite, insomnia, and exhaustion
- No more conventional treatments offered

## Case 1.: RESULTS



**06/2015**



**08/2016**

Accepted for Publication: J. Integrative Cancer Therapies 08/2017;  
presented at ASCO Chicago 2016 and ITOC3 Munich, 2016

## TNBC Pulmonary metastasis

---



**06/2015**



**08/2015**



**10/2015**



**12/2015**

Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR)  
of stage IIIB oesophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

The patient was a 56-year-old male newly diagnosed with:

- Advanced uT4, N2, M0 inoperable adenocarcinoma of the distal esophagus [ICD10:C15.9]
- with disseminated mediastinal, sub/infradiaphragmal lymphadenopathy [ICD10: R59.1].
- MSI-low, Her-2-neu positive. He refused neoadjuvant chemotherapy, radiotherapy and chemo-radiotherapy

Presented at ITOC4, Prague, March 2017

Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR)  
of stage IIIB oesophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia



08/2016



10/2016



Case 2.: COMPLETE PATHOLOGICAL RESPONSE (pCR)  
of stage IIIB esophageal cancer combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

pCR was documented by 8 biopsies when re-endoscoped in 10/2016 after 8 weeks of primary combined immunotherapy

Case 3.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer chest wall recurrence combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia

51y female, Local (chest wall) recurrence of her-2 neu pos.  
Breast cancer [C50.9]

- FD 11/2015 neoadjuvant chemotherapy Taxotere/Cytosan with Herceptin and Perjeta followed by right-sided mastectomy in May 2015.
- 08/2016 Chest wall recurrence, biopsied and proven to be recurrence of Her2-neu+ breast cancer, unresectable.
- Histology of recurrence was invasive ductal carcinoma grade 3 extending to the anterior inferior margin; also DCIS solid type nuclear grade 3 with microcalcification.
- Unfavorable high Ki-67 expression, p53 75% positive.
- Second opinion of radiation department: no radiation possible

Case 3.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer chest wall recurrence combining low-dose  
checkpoint inhibitors with interleukin-2 (IL-2) and fever range  
hyperthermia



02.12.2016



08.03.2017

Case 4.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer with bone and lymph node metastasis  
combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and  
fever range hyperthermia

- ❖ The 65 y female first presented in September 2016 with a massive fungating exulcerating right breast carcinoma deeply infiltrating the anterior right chest wall with metastatic right axillary lymph adenopathy and metastasis to the right iliac bone and vertebral body L5 and T8. She underwent Tru-Cut biopsy which revealed invasive ductal carcinoma of no special type, G3, cT4 N1 M1 (bone), ER 100% and PR 40% positive, Ki-67 19%, HER-2/NEU (erbB-2) neg. confirmed by FISH, Score 2+; the cancer was luminal A, EGFR neg., Tp53 neg., AR neg., PD-L1 and CTLA-4 overexpressed, CA 15-3 was elevated at 42 kU/l. When she was seen initially she presented with hemoglobin of 3.3 g/dl .
- ❖ Patient underwent emergency palliative radiation 4 times (5Gy Per fraction) between November 10 and November 18, 2016. Additionally to our immunotherapy low-dose metronomic chemotherapy was performed only twice combining gemcitabine (800mg/m<sup>2</sup>) and vinorelbine (30mg/m<sup>2</sup>).
- ❖ Unexpectedly, restaging at the end of January 2017 performed with bone scintigram, and CT thorax/abdomen and full laboratory workup proved complete remission of the primary large fungating breast cancer, complete remission of bone metastasis and massive shrinkage of lymphadenopathy with normal tumour markers

Case 4.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer with bone and lymph node metastasis  
combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and  
fever range hyperthermia



21.10.2016



22.09.2017

Late breaking abstract accepted for ESGO Vienna Nov. 2017

Case 4.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer with bone and lymph node metastasis  
combining low-dose checkpoint inhibitors with interleukin-2 (IL-2) and  
fever range hyperthermia



10/2016 before  
treatment



11/2016



03/2017



05/2017



09/2017

Late breaking abstract accepted for ESGO Vienna Nov. 2017

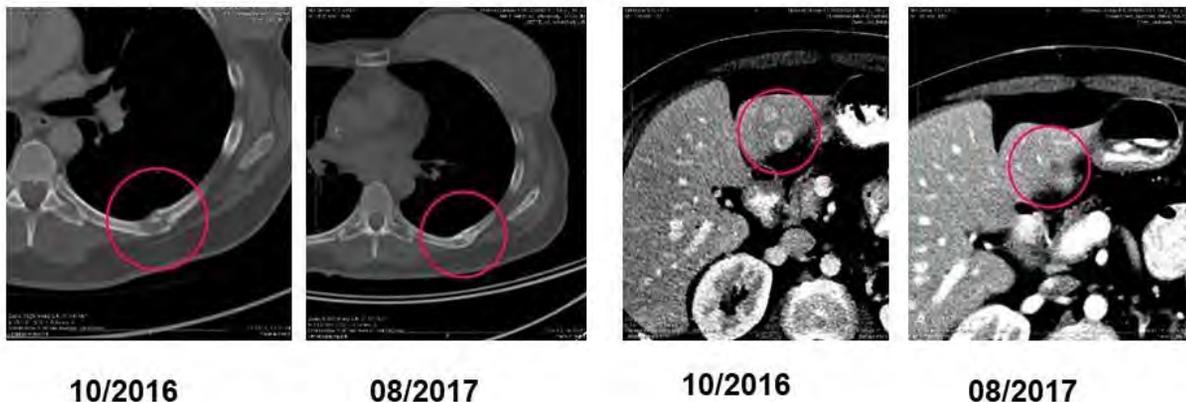
Case 5.: COMPLETE CLINICAL REMISSION  
of stage IV breast cancer with bone, liver and lung metastasis  
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever  
range hyperthermia

09/2014 grade 3 invasive ductal adenocarcinoma of the left breast, ER 100% percent positive, PR neg., Her2-neu neg. Patient underwent initial resection (02/2015) and neoadjuvant chemo radiation ACT, followed by aromatase inhibitor  
07/2016 very large bone metastasis left skull, infiltrating to her dura mater; the patient underwent initial radiation; also new pulmonary metastasis.  
08/2016 patient was started on Ibrance and aromatase inhibitor: PD.  
09/2016 radiation of the cervical spine and T2.

10/2016 restaging with CT of the thorax and abdomen: stable lung metastasis but increasing pleural nodules; disseminated liver metastasis with index lesions between 2.1, 3.1 and 1.3 cm; new lytic osseous lesions are present; restaging of the skull with MRI indicated PD of the previously radiated left sphenoid lesion as well as PD of further lesions in the skull base and mandible. Bone scan indicates PD of all innumerable bony lesions.

11/2016-02/2017 – immune-thermotherapy two times following each other, and 3 cycles of topotecan chemotherapy.  
03/2017 restaging with CT of Abdomen, pelvis and thorax demonstrated overall PR  
06/2017 tumor markers decreased to the normal range.  
05/2017 Restaging, MRI: overall stabilization and PR of the previously demonstrated disseminated metastasis in the skull and head.  
08/2017 PET indicates CR

Case 5.: COMPLETE CLINICAL REMISSION  
of stage IV Breast cancer with bone, liver and lung metastasis  
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever  
range hyperthermia



10/2016

08/2017

10/2016

08/2017

Case 5.: COMPLETE CLINICAL REMISSION  
of stage IV Breast cancer with bone, liver and lung metastasis  
With low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever  
range hyperthermia



**11/2016**



**02/2017**

Side effect profile  
Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and  
fever range hyperthermia in advanced cancer

Number of patients treated: n=119

**WHO I: 30%**      diarrhea, skin rash, nausea, headache

**WHO II: 15%**     diarrhea, skin rash, pneumonitis, elevated liver enzymes

**WHO III: 7%**

2 patients developed ulcerative colitis after 2 months controlled with corticosteroids

2 patients developed autoimmune thyroiditis controlled with hormone suppl.

2 patients developed autoimmune hepatitis controlled with corticosteroids

2 patients with pre-existing atrial fibrillation developed heart rhythm disturbances  
controlled with standard medical treatment (SMT)

**WHO IV: 3 %**

2 patients developed Diabetes mell. I treated with Insulin

1 patient developed AKI after 1 week and had to be transferred to dialysis

### SUMMARY

Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

#### Staging with iRECIST

**Objective response rate - ORR      38%**

**Overall response – OR      52%**

**n=      98 of 119 evaluable**

### SUMMARY

Low-dose checkpoint inhibitors with interleukin-2 (IL-2) and fever range hyperthermia in advanced cancer

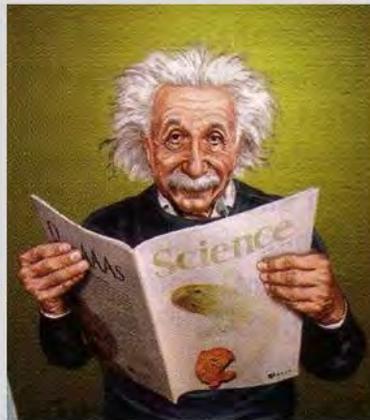
#### Staging with iRECIST

**Objective response number pat.    n=37**

**TTP: not calculated      n=4**

**Median Follow up:      14 month (3-33)**

**Great potential but...  
more experience is needed**



***“The only way to increase the success rate is to double the rate of failures”***





Thank you for your attention



[www.dr-kleef.at](http://www.dr-kleef.at)

## **Modulated electro-hyperthermia as a monotherapy: A potential for further research?**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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# Modulated electro-hyperthermia as a monotherapy: A potential for further research?

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## Introduction

The benefits of hyperthermia (HT) combined with chemotherapy or radiotherapy in oncology are widely documented, with several Phase III studies and reviews published demonstrating improved local control and survival. The history of HT and its progression from a monotherapy to a complimentary treatment are discussed. We address the question of whether there is still a place for monotherapy studies with a special focus on the modulated electro-hyperthermia (mEHT) technique. Our objective in this paper is to explore the potential for mEHT to be applied as a monotherapy for palliative intent, in cases where conventional therapies have failed and no further options are available for the patients (e.g. due to recurrent disease, organ failure, treatment toxicity or disease progression).

## Methods

Modulated electro-hyperthermia (mEHT, trade name oncothermia) is a complementary hyperthermia treatment that is used in combination with conventional oncology treatments. The protocol used in the studies discussed on mEHT in this paper is the step-down method, not the standard step-up heating protocol used when mEHT is combined with radiation therapy (RT) or chemotherapy (CT). The application of mEHT as a monotherapy would be for palliative intent only: for disease stabilisation and the management of symptoms.

## Results

We discuss animal models showing potential for disease stabilisation and human cases which show that mEHT as a monotherapy is safe with limited and acceptable adverse events. Four phase I/II studies on mEHT as a monotherapy are discussed which also showed a potential for disease stabilisation and symptomatic management: 1) Colorectal liver metastases n=50, median survival 16 months. 2) Malignant glioma, n=12, 25% response rate, 1 complete response, 25% 1-year survival, 42% improved performance. 3) Hepatocellular carcinoma, n=8, improved quality of life and disease stabilisation. 4) Gastric carcinoma, n=25, symptomatic and performance improvement, reduction in tumour volume. The effect of mEHT as a monotherapy on disease stabilisation, and occasionally even regression, may be potentiated by the immune responses elicited by mEHT.

## Conclusion

Randomized studies and evidence-based statistics on mEHT as a monotherapy are not available. However, the available literature provides enough motivation for the development

of future trials on the topic and investigations into the future use of mEHT as a monotherapy for disease stabilisation and palliation, when there are no further treatment options available.

**Keywords:** mEHT, monotherapy, palliation, complementary therapy, step-up heating, step-down heating



# Modulated electro–hyperthermia as a monotherapy: A potential for further research?

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## Disclosures

The authors are not aware of any circumstances which may lead to a conflict of interest



# Introduction

*HT Progressed from a monotherapy to a complimentary treatment ...*

*Is still a place for monotherapy studies?*

Specific interest in modulated electro-hyperthermia (mEHT):

- ▶ mEHT is a complementary hyperthermia treatment
- ▶ Used in combination with conventional oncology treatments
- ▶ Step-up heating protocol used when mEHT is combined RT / CT



# History

- ▶ Historically, absence of other options, HT applied as a monotherapy.
- ▶ Tumour thermosensitivity investigations date back to as early as 1903
- ▶ Tumours showed signs of destruction after high temperatures ( $>44^{\circ}\text{C}$ ) administered for short periods ( $\leq 30$  min)
- ▶ 1920s: heat sensitivity of different tumours – Malignant cells more heat sensitive



# History

RF techniques in hyperthermia has been discussed in literature since the 1930s

1927, RF was shown to have a special selectivity for malignant tissue; destroying the tumour without damaging their healthy tissue in rat models

Results were promising but healthy tissue damage was a problem.

- ▶ *HT was applied as a monotherapy, using RF or microwave, 60 superficial recurrences in 57 patients after treatment failure.*
  - 10% CR
  - 23.4% PR



# History

Some suggested heating tumours (increases blood flow) may increase risk of dissemination

- ▶ Two laboratory studies: HT (monotherapy) = increased rate of metastases from mammary carcinomas of C3H mice and on rat's sarcoma.

Why is HT not widely accepted as a monotherapy?

- ▶ Better outcomes in combined treatments
- ▶ When combined with other treatment modalities, the risk of distant metastases appears to be reduced.



# Objective

To explore the potential for mEHT to be applied as a monotherapy

- For palliative intent;
- When conventional therapies have failed;
- No further options are available;
  - Recurrent disease,
  - Organ failure,
  - Treatment toxicity or
  - Disease progression.



# Methodology

- ▶ **Technology:** Modulated Capacitive coupling, RF:13.56MHz (Oncotherm GmbH, Driosderf, Germany)
- ▶ Studies using the step-down protocol are reviewed
- ▶ The application of mEHT as a monotherapy would be for palliative intent only: for disease stabilisation and the management of symptoms



## Results: Animal Models

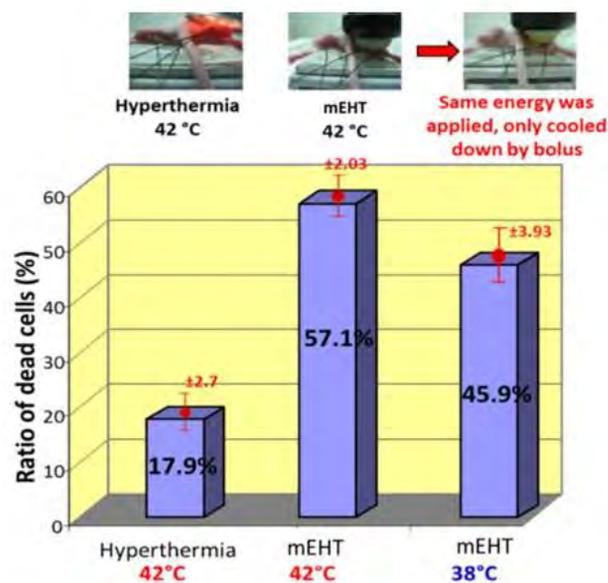
- ▶ Potential for disease stabilisation
- ▶ Almost all *in vitro* and *in vivo* (murine) experimental studies were performed using monotherapy protocols with success.

Andocs G. *et al*(2009):

- ▶ Synergy of the electric field and thermal effects of mEHT *in vivo*
- ▶ HT29 (humancolorectal tumour) cell line derived xenograft in nude BALB/c (nu/nu) mice



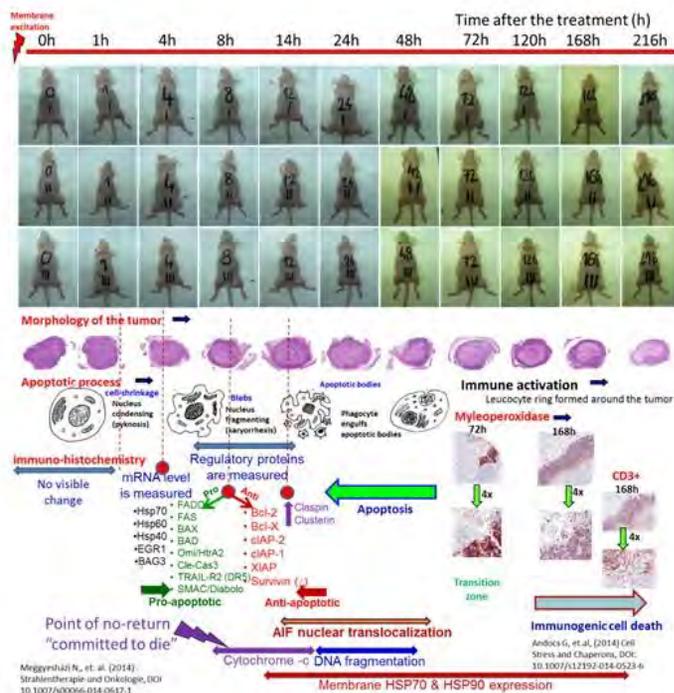
## Results: Animal Models



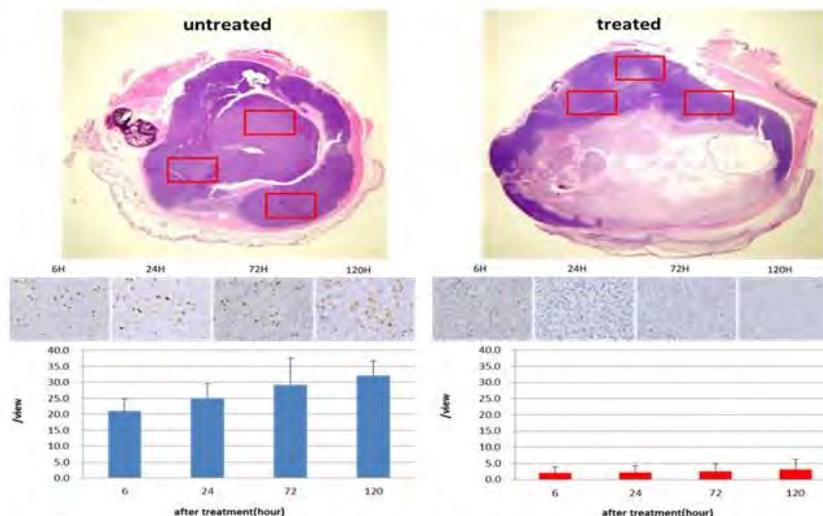
# Results

Follow up study:  
Same HT29 cell line  
Time-course monotherapy experiment  
To describe molecular mechanisms of mEHT induced cell death

Apoptotic process is shown:  
At 72 hours post treatment the apoptotic processes have slowed and a non-specific antitumor immune reaction was observed.



# Results: Animal models



Result of the measurement of Ki-67 proliferation marker protein. Samples were taken from both the untreated (a) and treated (b) tumors, and from their vivid part containing dividing cells. (Shown with red rectangular shapes on the tumor cross sections.)

## Results: Human studies

- ▶ Several mEHT monotherapy cases have been published after failure of the gold standards of treatments.
- ▶ mEHT as a monotherapy is safe with limited and acceptable adverse events.
- ▶ Is there high level evidence?
- ▶ Four phase I/II studies on mEHT as a monotherapy are discussed which also showed a potential for disease stabilisation and symptomatic management



## Results: Colorectal Liver Metastases

Location: Germany

Methods: Prospective trial, n=80; Palliative intent

The results were compared to a historic arm

Pts all failed the previously administered (with curative intent) cytotoxic therapies.

- ▶ 37.5% of patients (n=30) were eligible for palliative CHT + mEHT.
- ▶ 62.5% (n=50) received only mEHT

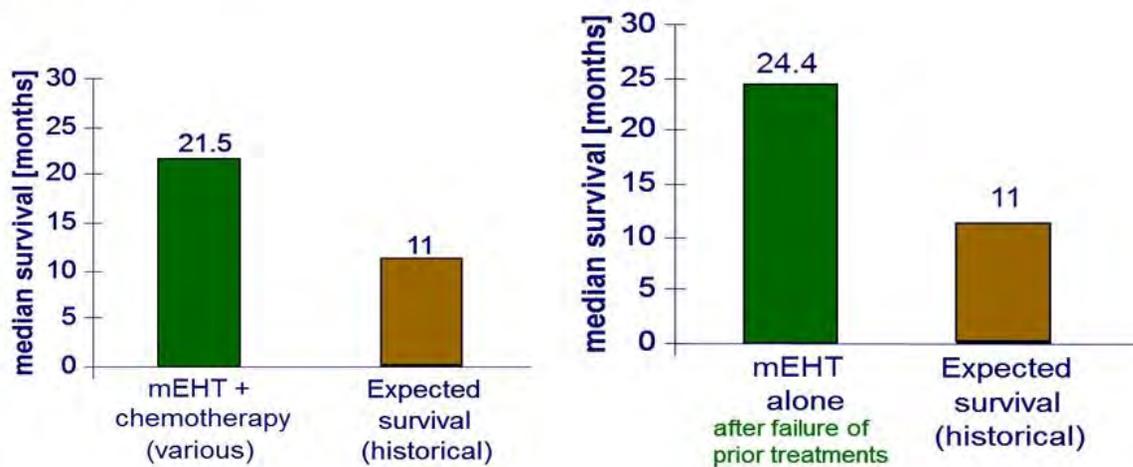
Results: Median Survival 16 months.

Both groups showed more than double the survival time, compared to the historical data.

(mEHT alone had highest higher survival time)



# Results



Clinical study for colorectal liver metastases (Bad Chemotherapy + mEHT: (left), mEHT alone: (right).



## Results: Brain

Location: Italy

Methods: Malignant glioma patients. n:12; Histologically diagnosed malignant glioma (8 pts GBM; 2: astrocytoma gr III; 2 anaplastic Oligodendroglioma).

- ▶ Pre-treated with Temozolamide-based CHT + RT
- ▶ mEHT: 40–150 Watts

Results: 1 CR; 2 PR

Overall response rate of 25%

Median duration of response: 10 months (range 4–32).

Median survival was 9 months, (with 25% at 1 year)



## Results: Brain

**Location:** Italy

**Methods:** 24 consecutive patients:

19 (79%) GBM 13 Gr <4; 6 Gr 4,

5 (21%) Astrocytoma

Tumor response 2 after mEHT

**Results:** 2 (8%) CR (astrocytomas) and  
5 (21%) PR (2 astrocytoma; 3 GBM)

- ▶ Overall Response rate: 29%
- ▶ The median duration of response was 16 months (range 6–120).
- ▶ The median survival: 19.5 months (range 2–156), 55% survival rate at 1 year, and 15 % at two years. We observed 3 long survivors at 156, 60, 62 months in astrocytomas.



## Results: Hepatocellular carcinoma (Poster)

**Location:** Italy

**Methods:** A prospective study; n=22; Hepatocellular carcinoma (Stage C: BCLC classification) patients who failed treatment.

- ▶ Non-operable: 68%.
- ▶ Portal vein-thrombosis: 70%.
- ▶ Distant metastasis: 9%.

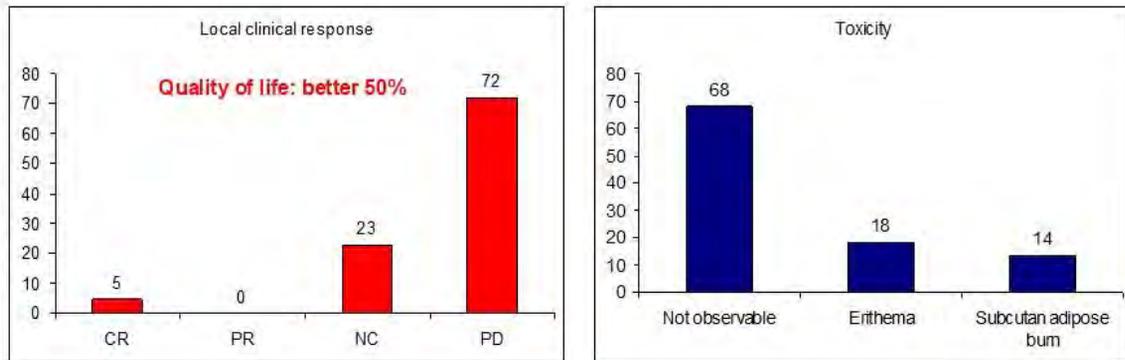
Patients eligible for further CHT (n=14, 64%) received mEHT + oxaliplatin reduced from 85 to 50 mg/m<sup>2</sup> (42% dose reduction).

Patients not eligible for CHT (n=8, 36%), received only mEHT.

- ▶ 80–140 W, 60 min/session, 2 sessions/week.
- ▶ 10 sessions/cycle, Median of 1.5 cycles (1–4



## Results: HCC phase II study (n=22)



**Results:** Improved quality of life in 50% of pts (LEFT)

Acceptable toxicity (RIGHT) Erythema (18%); subcutaneous adipose burns (14%).

- ▶ Disease stabilisation: 1 CR; 5 SD; 16 PD
- ▶ Median survival was 20.5 weeks (5-81+)



## Results: Gastric carcinoma

**Location:** Japan

**Methods:** mEHT for unresectable /recurrent gastric ca, treated 3/week for 60 minutes; n=25;

**Results:** Improved symptoms + performance  
Reduced tumour volume

9 pts had distant metastases: Survival time was significantly better ( $p < 0.01$ ) than 42 historical control patients who also had peritoneal dissemination.



## Results: Traditional Chinese Medicine

- ▶ **Location:** China (several studies show mEHT has + TCM = a strong synergy with in colorectal malignancies)
- ▶ **Methods:** Prospective randomized; n=156; TCM = control arm and mEHT = study arm.
- ▶ **Results:** mEHT could be applied as a stand-alone treatment in refractory and non-refractory cases with promising outcomes.



## Conclusion

- ▶ Randomized studies and evidence-based statistics on mEHT as a monotherapy are not available.
- ▶ We hypothesise that the effect of mEHT as a monotherapy on disease stabilisation, and occasionally even regression, may be due to immune responses elicited by mEHT.
- ▶ Protocols must be developed to test this hypothesis.



# Discussion

- ▶ Available literature provides sufficient motivation for the development of trials and investigations into the use of mEHT as a monotherapy for:
  - disease stabilisation,
  - palliation,
  - no further available treatment options.
- ▶ Understanding how mEHT works as a monotherapy may improve the development of protocols for combined therapies.



# Thank You



# **Time-fractal modulation of modulated electro-hyperthermia (mEHT)**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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# Time-fractal modulation of modulated electrohyperthermia (mEHT)

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<sup>1</sup> Founder and Chief Scientific Officer of Oncotherm & Biotechnics Department, St. Istvan University, Hungary

<sup>2</sup> Chief Executive Officer of Oncotherm & Biotechnics Department, St. Istvan University, Hungary

## Introduction

Local hyperthermia in oncology is well-known from the ancient time. Unfortunately, oncological hyperthermia has no wide acceptance in the modern oncotherapies, it is much rarely applied than would be optimal. Contrary to its remarkable results and its opportunity applying complementary to almost any state-of-art oncological methods, it is suffering much of the negligence, it had no breakthrough in clinical practices. According to my opinion, one of the major factors of the missing applications is the thinking about hyperthermia as simple heating, like a "kitchen" method considering the devices as the hear-providing oven where the patients are "cooked". Indeed, the thinking about its control is also kitchen like: for how long and on what temperature it is applied, just like when we make a cake or biscuit at home. Our objective would genuinely like to break with the kitchen category and take into account the living physiology in the oncologic hyperthermia.

## Methods

The complexity is one of the central properties of the living organisms. The self-organized and consequently self-similar structure [1] characterizes the complexity in its complete form. The study of biological complexity raised a new discipline: the fractal physiology (FP) [2]. FP is rigorously based on natural sciences, like physics, chemistry and of course mathematics, [3]. The dynamism, how the parts interact and change in time, is an important character of FP. The dynamism of the bio-systems can be described in spatio-temporal frame, having the bio-structure with the bio-processes in complex unity [4], [5]. The method applying FP in oncological hyperthermia is the modulated electro-hyperthermia (mEHT, oncothermia) [6], as a renewal of the historical heating methods, applying the synergy of the bio-electromagnetism with FP. The basic physiological and biophysical differences of malignant cells from their healthy counterpart make the mEHT method special: (1) the accurate selection of the tumor, [7]; (2) control the homeostatic correction feedbacks [8]; (3) select the malignant cells [9]; (4) the electromagnetic excitation of the clusters of transmembrane proteins by the beta/delta dispersion [10] (5) induce apoptosis by excitation with electromagnetic field [11]; (6) activate the immune system recognizing the tumor [12]. The homeostasis of the organism is a well-defined equilibrium, where the energy dissipation is well balanced with the metabolic energy controlling the dynamic fluctuations in a certain fractal range [13]. The fluctuations have a correlation in time, following the chemical and structural changes in dynamical equilibrium. The correct electromagnetic signal correlates with the healthy changes, act in time repeatedly which is in correlation with the steps of metabolic activity (autocorrelation of the signal). This signal follows a time-fractal fluctuation, which selectively supports or blocks the preferred (healthy) or avoidable (malignant) processes at the cellular membrane, respectively. This signal is taken by the amplitude

modulation of the carrier frequency (13.56MHZ), and is demodulated by the rectification of the membrane potential. This dynamical effect well expands the above selection mechanisms, which are mostly structure connected.

## Results

Morphological difference of modulated (mEHT) and unmodulated (EHT) treatments were measured in vivo for HT29 (human colorectal carcinoma, xenograft) and C26 (murine colorectal carcinoma, allograft) models, and analyzed 48h after treatment. Results favor the mEHT by 66.4% and 17.4%, for H29 and C26 in vivo measurements, respectively. In case of 4T1 breast cancer cell-line in balb/c mice the result 96h after treatment was 83.6% gain in mEHT case compared to the same treatment with EHT. The immune-response differs too. The CD3 T cell marker distribution in the living part of the treated tumor was higher in the modulated cases relative to untreated references 91.4% at EHT 104.6% in mEHT compared to their individual untreated sham samples. It is even more important that the Ki67 proliferation marker was significantly suppressed by modulation compared to the unmodulated treatment, [14]. The massive domains of sample patterns show better reaction on the modulation than on the mixed formations. This supports the noise-selection facilities of cancerous and non-cancerous tissue [15]. The destruction of the malignant cells is dominantly apoptotic, [16], preparing antigen recognition cells to produce helper and killer T-cells. This allows direct systemic effect to kill the malignant cells over the body, finding the disseminated cells and distant metastases, (abscopal effect) [17]. The results clearly show the additional effects of the fractal modulated EMF to the other heating methods [18].

## Conclusion

mEHT is a new hyperthermia method using fractal modulation to improve the effective selection and killing the malignant cells. It is a controlled, reproducible and reliable treatment: it treats locally and acts systemically, (abscopal effect) [19].

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## **Time-fractal modulation of modulated electro-hyperthermia (mEHT)**

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### **Objective**

**Most local hyperthermia devices in oncology use bio-  
electromagnetic effects with various frequencies.**

**The chosen frequency may optimize the energy-absorption and  
the consequent changes in the malignant cell.**

### **Outline**

- Specialties of modulated electro-hyperthermia**

---
- Concept of spatio-temporal fractals**
- Modulated carrier frequency and its effects**

## Success of modulated electro-hyperthermia

### Selection by

**1** **Electric conductivity**  
(Metabolic differences, Warburg effect)

Due to high metabolic rate, the tumor ionic concentration is high and consequently its **conductivity selects**

**2** **Dielectric permittivity**  
(autonomy of malignant cells; Szentgyorgyi effect)

Due to missing cellular network, extracellular matrix of malignant cells have high dielectric **permittivity selects**

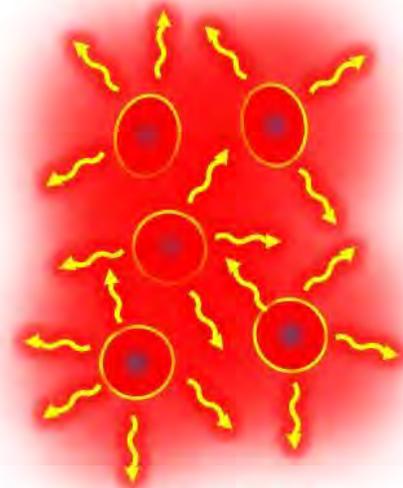
**3**  **$\beta/\delta$  frequency dispersion**  
(lipid resonance absorption; Schwan effect)

Due to large number of clusters of transmembrane proteins the protein-lipid complex attacked, **frequency dispersion selects**

**4** **Time-fractal modulation**  
(lipid resonance absorption; Schwan effect)

Produce damage associated molecular pattern (DAMP) and immunogenic cell death (ICD), **synchronization selects**

**Selective, heterogenous heating**  
(targeted molecules of selected cells)



**mEHT solution**

The heating is heterogenic, only the malignant cells are selected

← **Objective of my presentation**

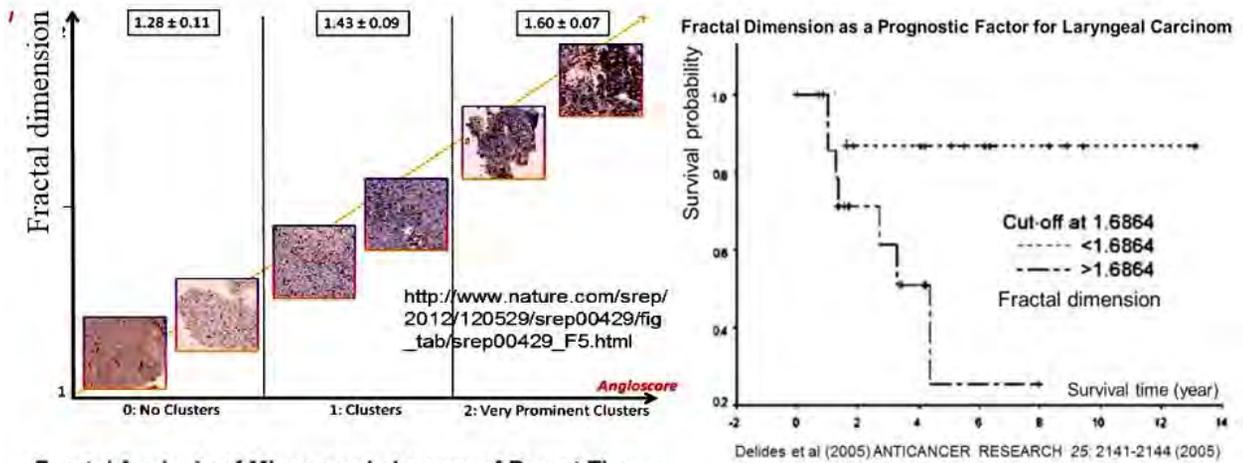
### Outline

Specialties of modulated electro-hyperthermia

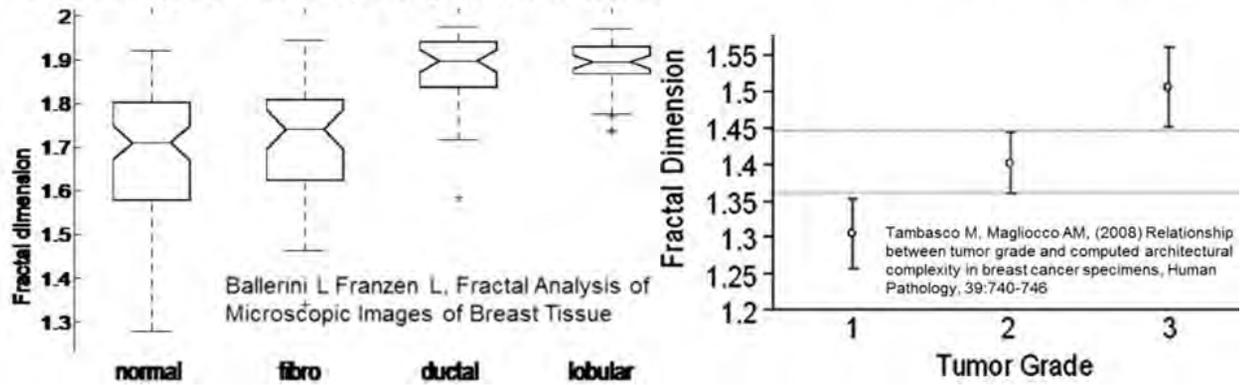
Concept of spatio-temporal fractals

Modulated carrier frequency and its effects

## Structural fractals

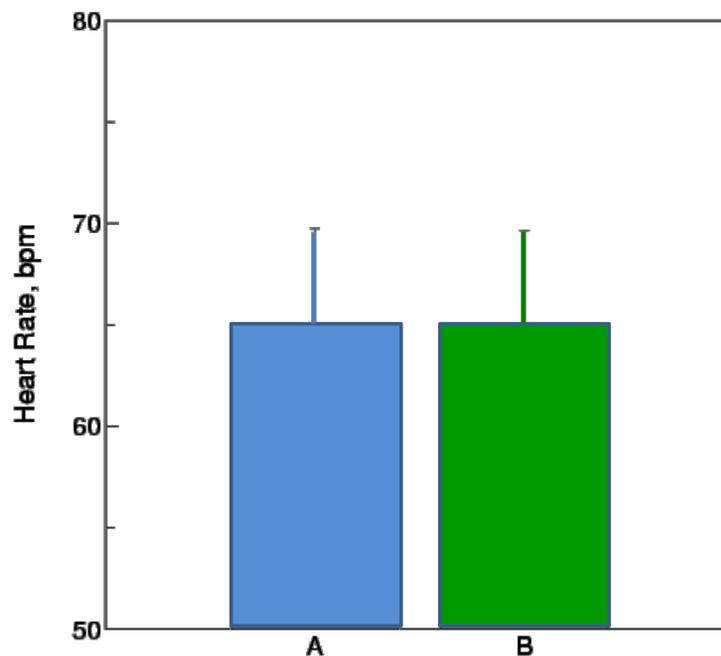


### Fractal Analysis of Microscopic Images of Breast Tissue

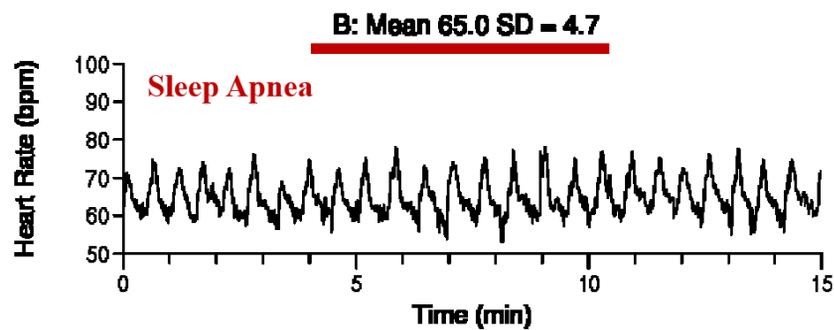
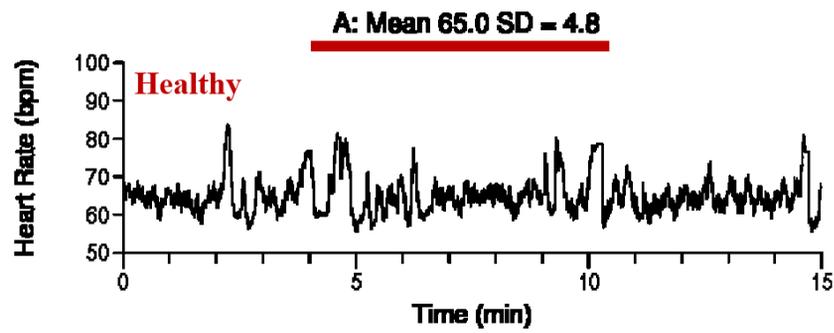


## Quiz

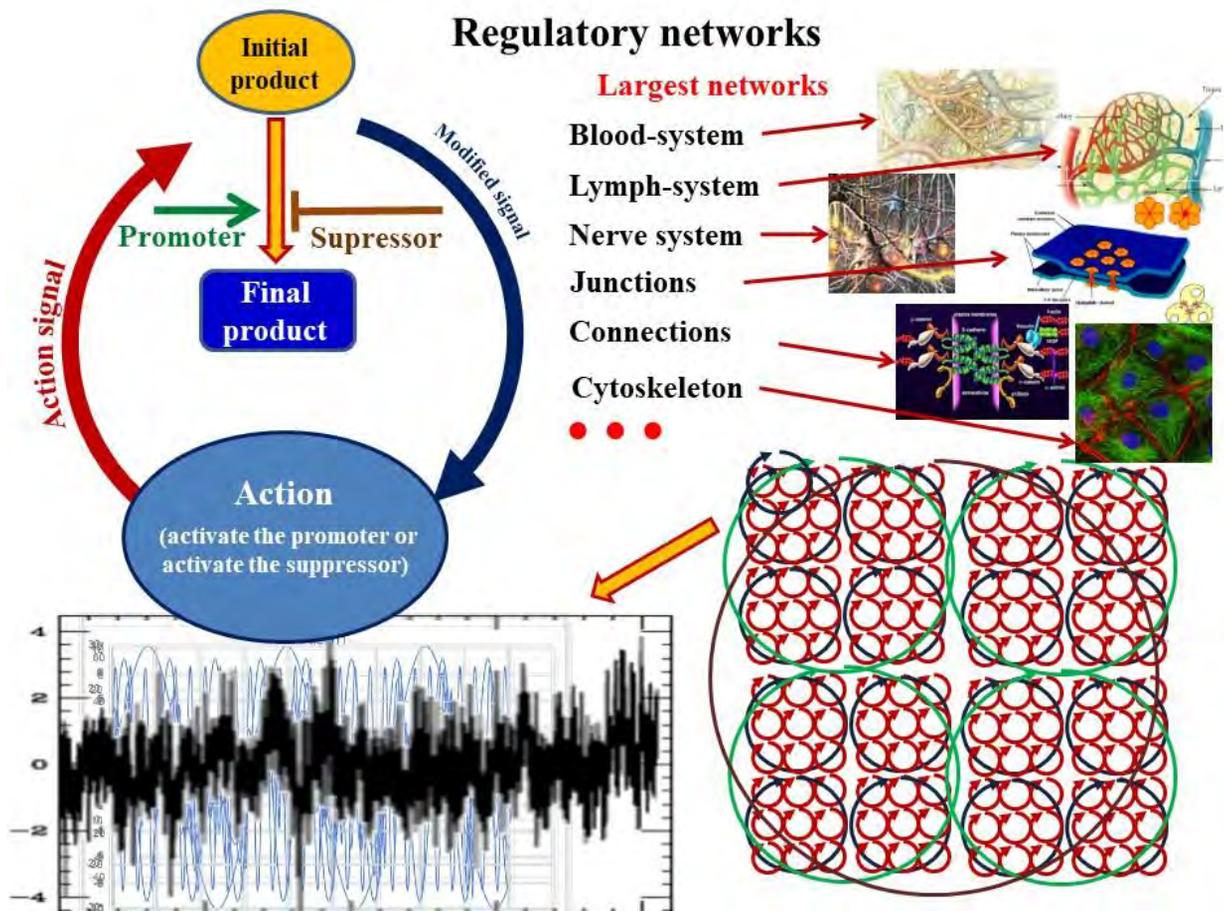
Which subject is healthier?



# Quiz



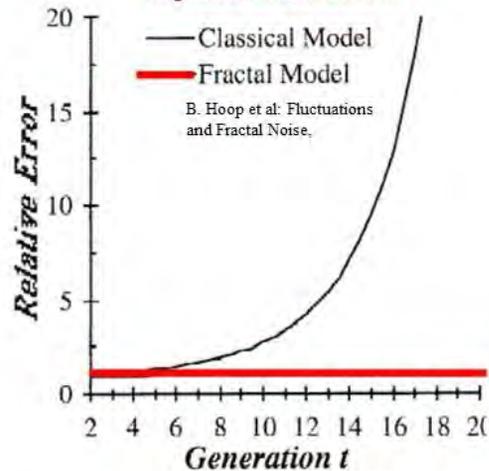
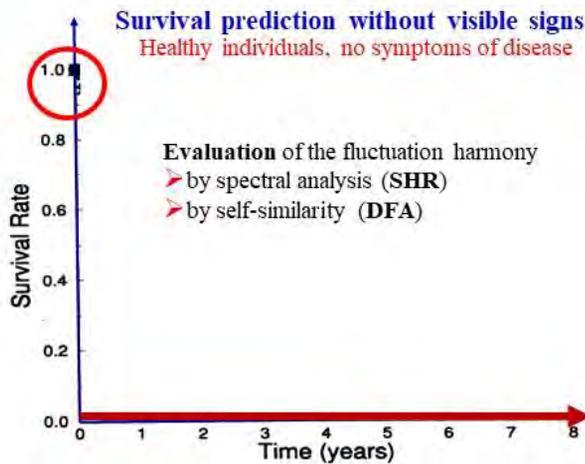
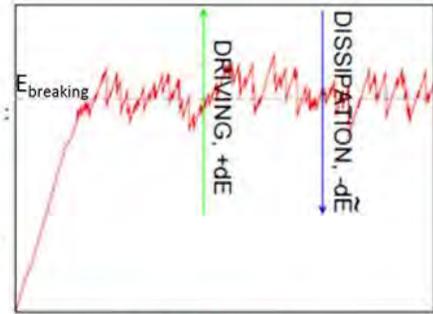
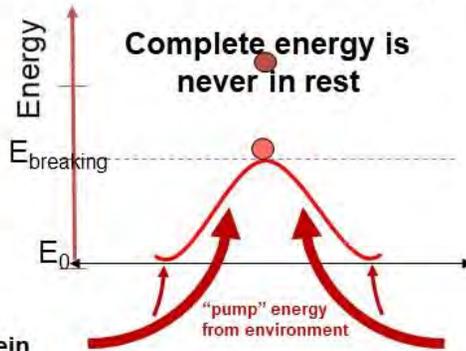
The variability of the signal has a role, not only the averages



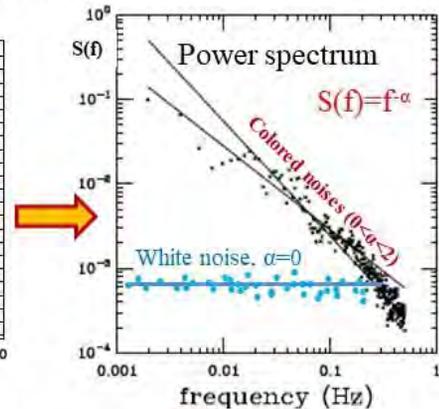
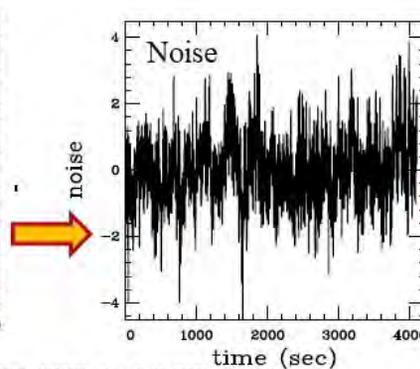
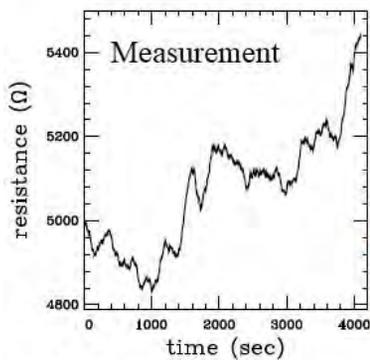
# Homeostasis in fractal physiology



"Life is like riding a bicycle. To keep your balance, you must keep moving" **A. Einstein**

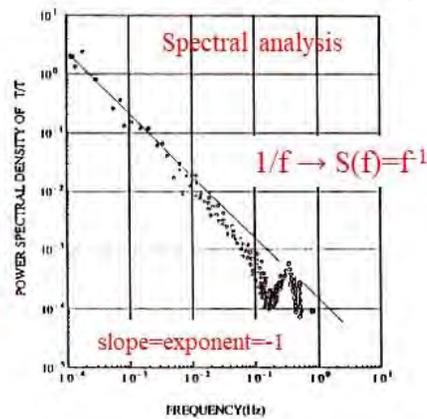


# Dynamism of fractal structures



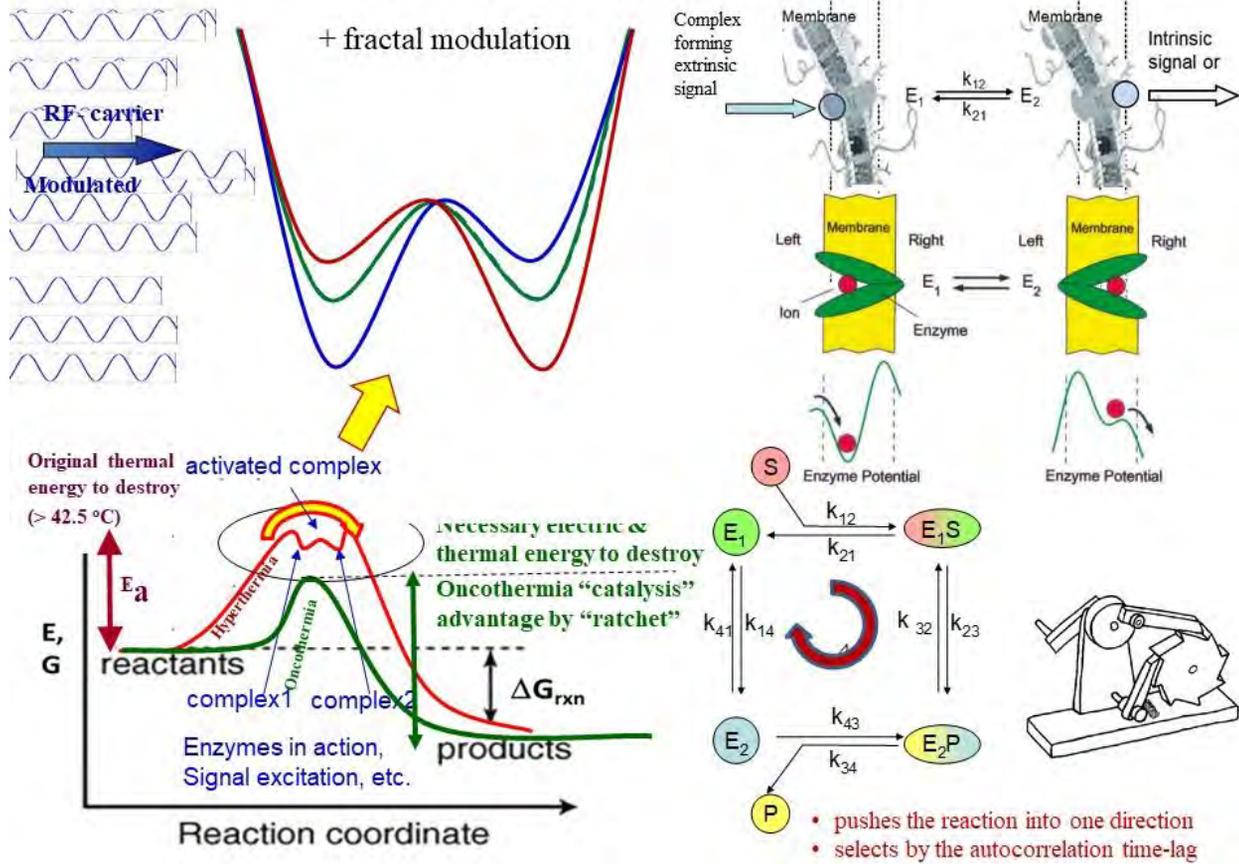
Modified from : Lovelady et. al Phys.Rev. E 76 (2007), 041908. Rev. E 76 (2007), 041908.

## Example: fluctuation of R-R interval of heart-beat

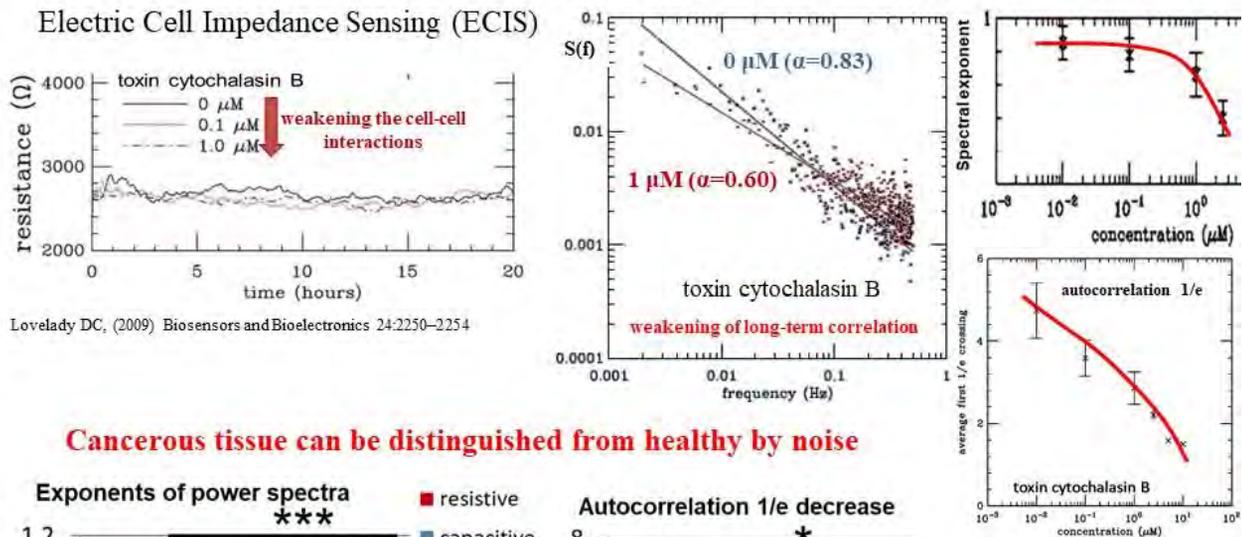


Musha & Sawada: Physics of Living systems, 1994

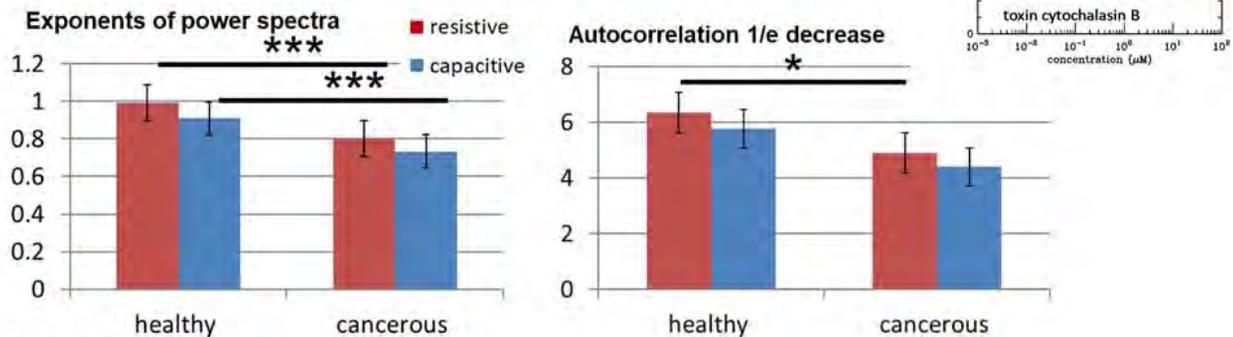
## Stochastic resonant "ratchet"



## The fluctuations (noise) defines the cellular interactions



## Cancerous tissue can be distinguished from healthy by noise

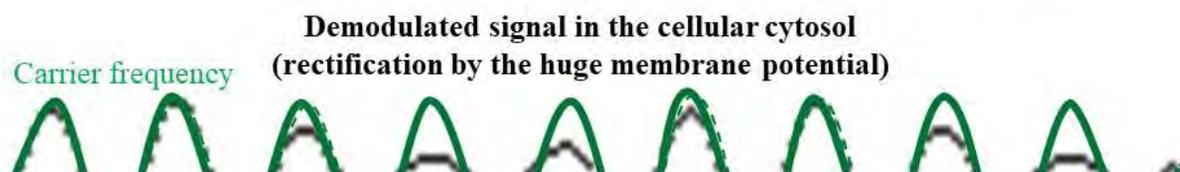
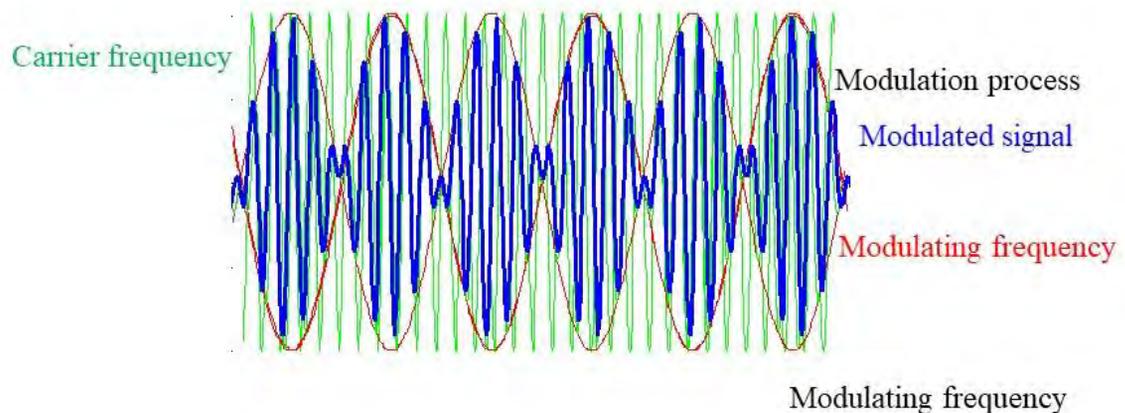


Lovelady et. al. Rev. E 76 (2007), 041908.

## Outline

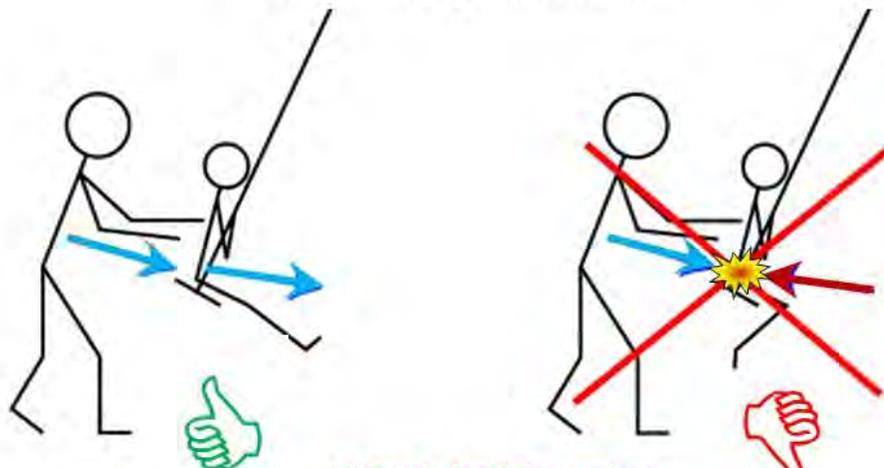
- ❑ Specialties of modulated electrohyperthermia
- ❑ Concept of spatio-temporal fractals
- ❑ Modulated carrier frequency and its effects

### Modulation process



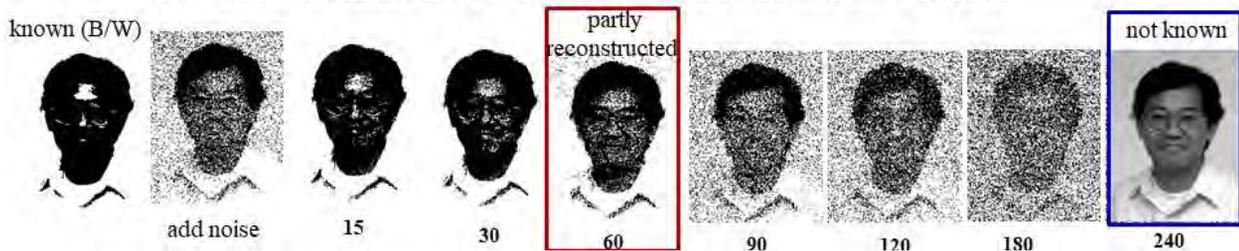
**This excites the missing apoptotic pathways in sequences of the autocorrelation of the demodulated signal**

## Selection by modulation



**What is bad for swing  
is good for exciting special receptors and signal pathways**

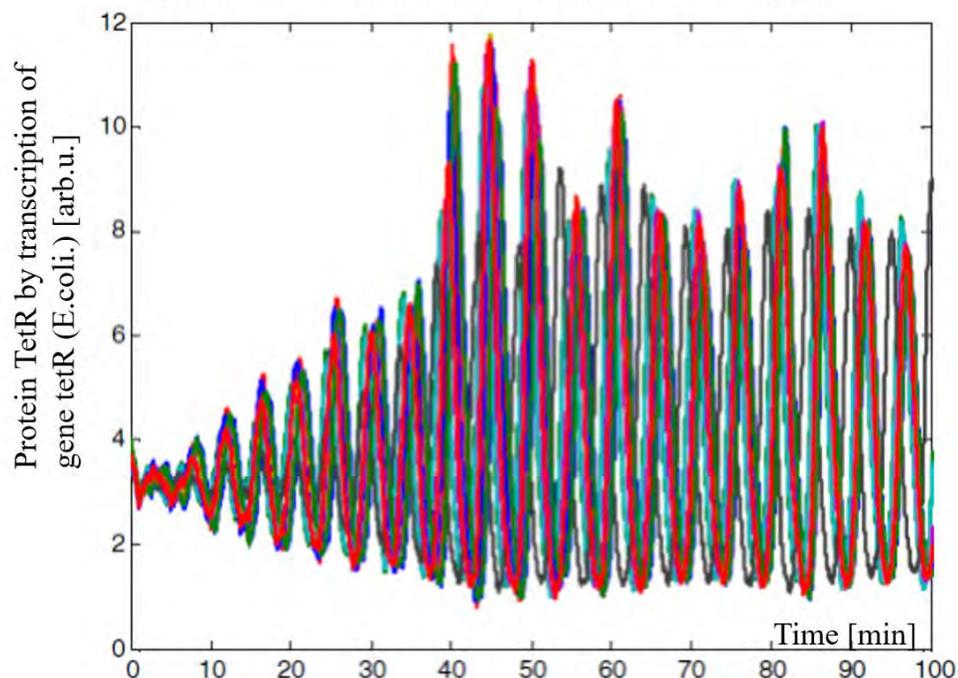
It is stochastic process like for example the photo-reconstruction by noise



## Example: genetic synchronization by extrinsic noise

### Ten coupled genetic oscillators

**Synchronization cannot be achieved** under intrinsic kinetic parameter fluctuations and extrinsic molecular noise.

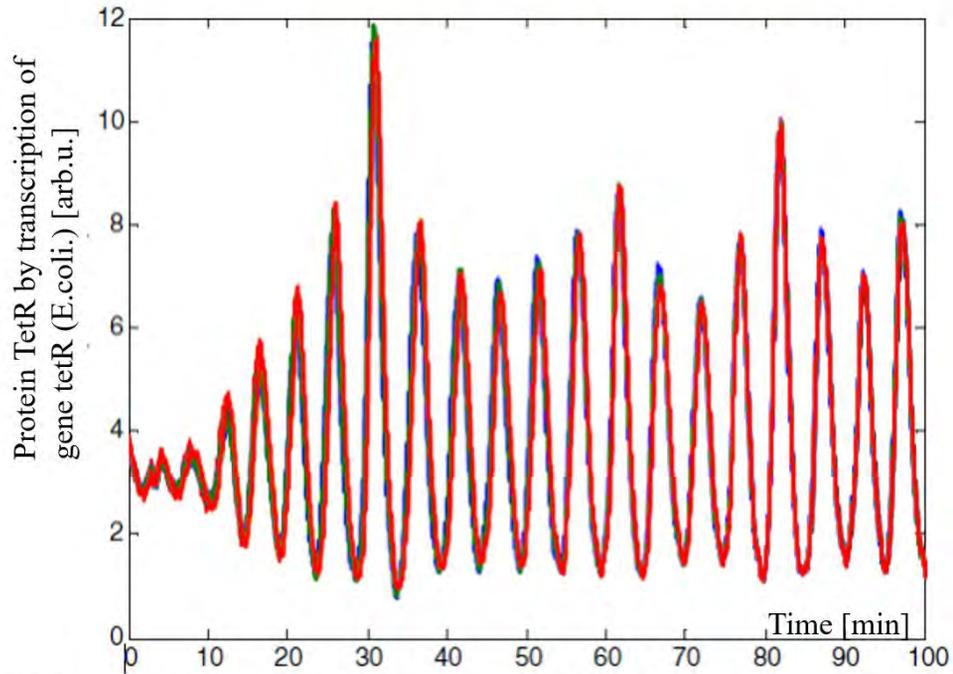


Chen B-S, Hsu C-Y; Robust synchronization control scheme of a population of nonlinear stochastic synthetic genetic oscillators under intrinsic and extrinsic molecular noise via quorum sensing; BMC Systems Biology 2012, 6:136

## Example: genetic synchronization by extrinsic noise

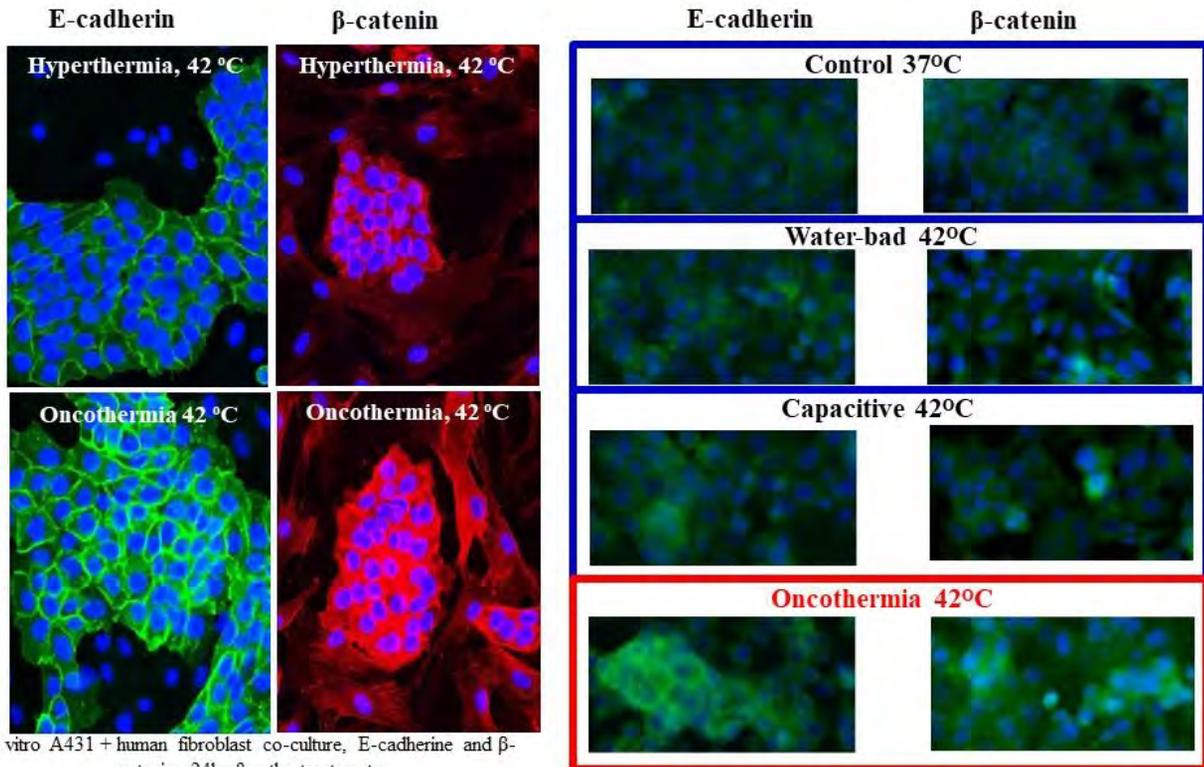
### Ten coupled genetic oscillators

The robust synchronization result by extrinsic noise.



Chen B-S, Hsu C-Y; Robust synchronization control scheme of a population of nonlinear stochastic synthetic genetic oscillators under intrinsic and extrinsic molecular noise via quorum sensing; BMC Systems Biology 2012, 6:136

## Block the invasion and dissemination



Andocs G, Szasz O, Szasz A (2009) Oncothermia treatment of cancer: from the laboratory to clinic. Electromagn Biol Med 28(2):148-165

Yang K-L, Huang C-C, Chi M-S, Chiang H-C, Wang Y-S, Andocs G, et al. (2016) In vitro comparison of conventional hyperthermia and modulated electro-hyperthermia, Oncotarget, doi: 10.18632/oncotarget.11444

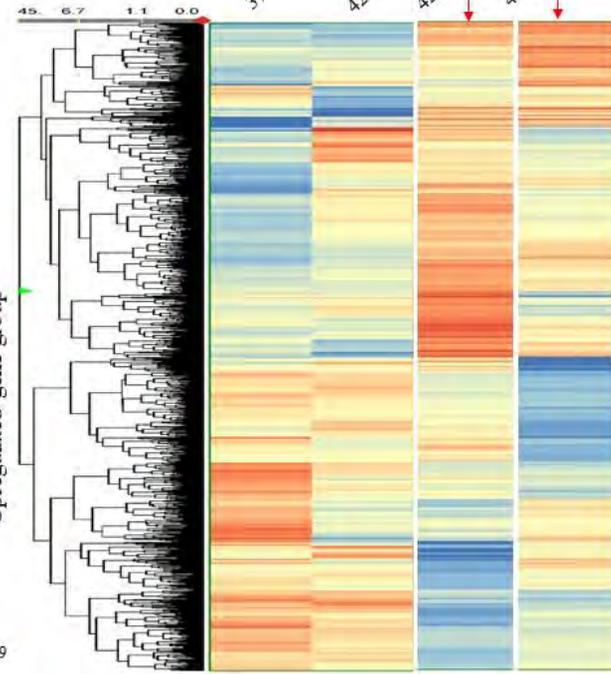
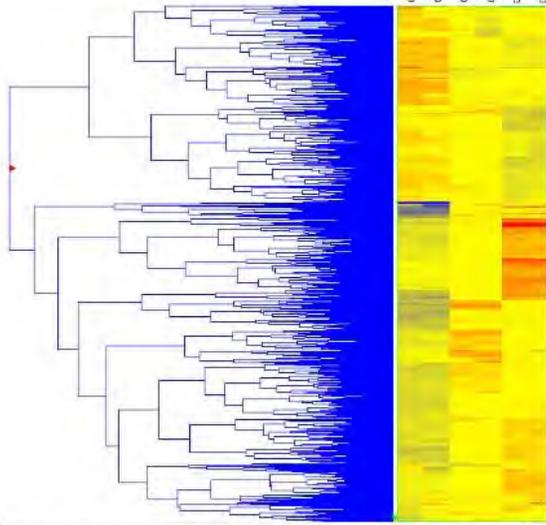
# Oncothermia heats differently (mRNA-based info)

Human lymphoma U937 cell (in-vitro)

C26 allograft (in-vivo)

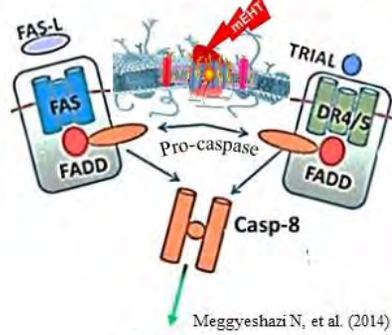
Andocs G, Kondo T, Toyama University, Japan, (2018)

1. Control (37°C)
2. Water-bath (42°C)
3. mEHT (42°C)

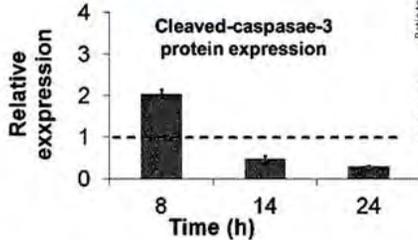


Andocs G, et al. (2016) Cell Death Discovery (Nature Publishing Group), 2, 16039

## Excite membrane rafts: extrinsic pathways of apoptosis

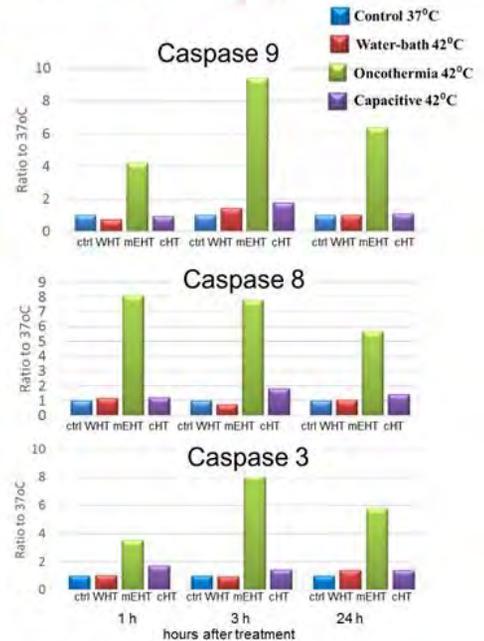
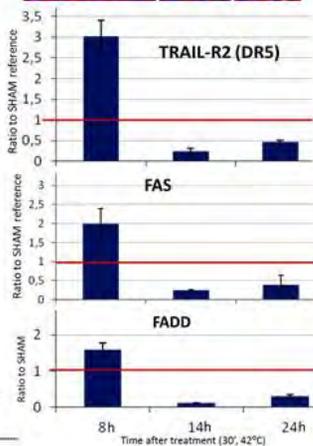
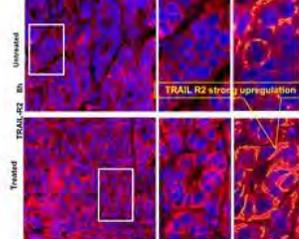


Meggyeshazi N, et al. (2014)



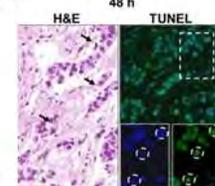
HT29 cell-line, mEHT (42°C)

Oncothermia induced ICD-TRAIL R2 (DR5)



Yang K-L, et al., Oncotarget, doi: 10.18632/oncotarget.11444,

DNA fragmentation  
Meggyeshazi N, et al. (2014)



# Challenge of tumor-specific immune support (abscopal)

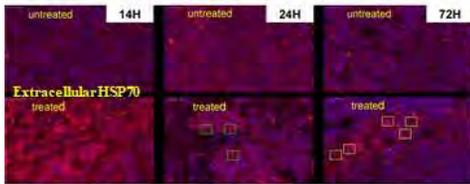
**Malignancy is a systemic disease !!**

Produce DAMP and ICD  
tumor-specific immune reaction, like vaccination

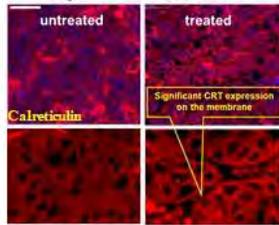
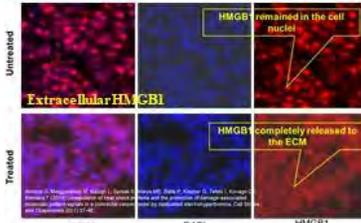
Andocs G, et al. (2014) Cell Stress and Chaperones 20(1):37-46



HT29 cell-line, mEHT (42°C)



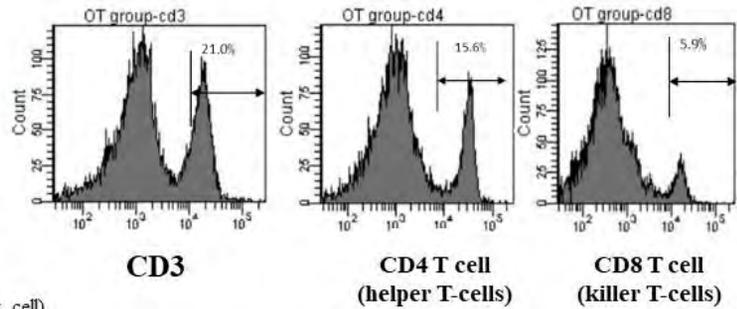
- CRT „eat me” signal
- ATP „find me” signal
- HMGB1 „danger” signal
- HSP70 “info” signal



**DC maturation**

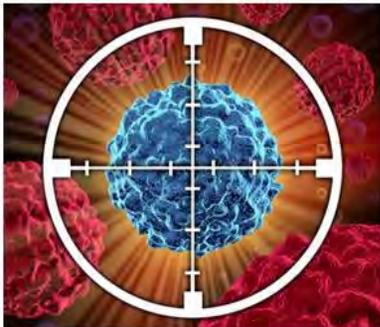


APC (antigen presenting cell)

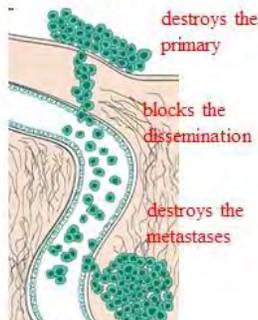


## mEHT fits well to the modern oncology

**Targeted therapy to malignant cells**

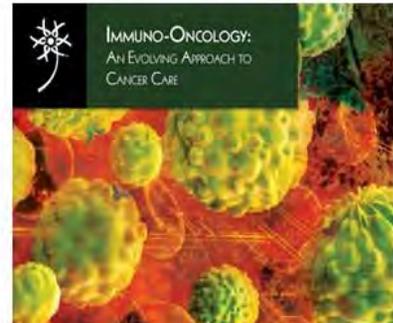


**Complex therapy to system**



ACTS SYSTEMICALLY

**Direct and effective way to immuno-oncology**



**mEHT is a new kind of hyperthermia**

- Heats selectively
- Physiology compatible
- It has applicable dose

# Thank you for your attention

[Szasz.Andras@gek.szie.hu](mailto:Szasz.Andras@gek.szie.hu)

Grant support: NVKP\_16-1-2016-0042

# **Performance comparison of electro-hyperthermia devices: EHY-2000plus and EHY-2030**

**Benedek Orczy-Timko**

Oncotherm Kft. Hungary

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

Orczy- Timko B. (2018): Performance comparison of electro-hyperthermia devices:  
EHY-2000plus and EHY-2030; Oncothermia Journal 24:333-343

[www.oncothermia-journal.com/journal/2018/Performance\\_comparison.pdf](http://www.oncothermia-journal.com/journal/2018/Performance_comparison.pdf)

## Performance comparison of Electro-hyperthermia Devices: EHY2000plus and EHY-2030

**Benedek Orczy- Timko**

Oncotherm Kft.

### **Abstract**

To assess to the effect of a medical device on the patients is critical for clinical users and device developers. The effect of the device on the patient, the physical characteristics that generate it and the way in which these features are regulated are of decisive importance when evaluate the performance of a medical device.

The aim of our study we would like to introduce was to determine the magnitude of energy transmitted via electromagnetic field to the patient at EHY-2000plus and EHY-2030 types of Oncotherm electro-hyperthermia devices by using experimental methods, investigate the depth distribution of the absorption in order to compare the essential characteristic of the two devices and describe a technically relevant dose measurement device for hyperthermia. As the first step of the study, we identified the variable set (outputs) whose representative to the performance of the devices (TS1 ... TS12) then the environmental conditions that could have a significant effect on these monitored outputs (Tamb, ctarget, Ztarget) . In order to mimic the intended use and the human anatomy as well as possible during the measurements we have developed and utilized an artificial target which can be a valid replacement of the average patient from electromagnetic, thermal and macrostructural point of view (thermally well isolated DIA200mm, 200mm high polymer tube filled with mixed pork tissue) even though the vascular system and the inhomogeneity of the human body where not taken into account.

During measurements we utilized the most commonly used applied parts (electrodes) which are at the same size (DIA200mm) but structurally significantly different on the two evaluated device. We selected the maximum output power (Set Power: 150W) allowed for the DIA200mm electrodes. To continuously monitor temperature TM-300 series thermometers where chosen which has comprehensive immunity to the frequency used by the evaluated devices (13.56MHz) and a recent development of the Oncotherm Kft. Our study pointed out that both of the evaluated devices transmit energy to the tissues in a highly effective way even in larger depths (minimum 0.15°C/minute thermal gradient) and the method which was elaborated is able to measure output parameters in a consistent and reproducible manner. It was clearly demonstrated that the new developments had a positive effect on the quality of the application of the technology, both the average temperature gradient and the temperature distribution as a function of anatomic depth, including skin surface temperature control have been improved significantly.

This study was supported by the NVKP 16-1- 2016-0042 grant.

## > Performance comparison of electro-hyperthermia devices: EHY-2000plus and EHY-2030

Benedek Orczy-Timkó

Head of Engineering, Oncotherm Kft., HUNGARY

2018.09.29.



## > General description of the devicesre

*EHY-2000plus electro-hyperthermyia device*



### EHY-2000plus

#### Main features

- 150W rated output power
- 13.56MHz output carrier frequency
- 0-5 kHz modulating frequency
- D100, D200 and D300 size applicators
- Water bed with active temperature control



## > General description of the devicesre

*EHY-2030 electro-hyperthermia device*

### **EHY-2030**

#### Improvements

- New smart electrode design, flexible, conductive material
- 250W rated output power
- 0-10 kHz modulating frequency
- Easy to use graphic interface
- Compact design



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## > Challenge identification

*Evaluation of effective energy through temperature measurement*

#### Parameters have influence

- Electrical properties of the target and surrounding tissues
- Thermal properties of the target and surrounding tissues
- Anatomic dimensions
- Vascularization
- Homogeneity / inhomogeneity



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## > Study design

*Control of input parameters*

- |   |   |   |
|---|---|---|
| <ul style="list-style-type: none"> <li>• Electrical properties of the target and surrounding tissues</li> </ul> |  | <ul style="list-style-type: none"> <li>• Utilization of tissues from animal source to match impedance</li> </ul>                          |
| <ul style="list-style-type: none"> <li>• Thermal properties of the target and surrounding tissues</li> </ul>    |  | <ul style="list-style-type: none"> <li>• Utilization of tissues from animal source and measure /calculate thermal coefficients</li> </ul> |
| <ul style="list-style-type: none"> <li>• Anatomic dimensions</li> </ul>   |  | <ul style="list-style-type: none"> <li>• Mimic the human body cross-section lay between the two electrodes</li> </ul>                     |
| <ul style="list-style-type: none"> <li>• Homogeneity / inhomogeneity</li> </ul>                                 |  | <ul style="list-style-type: none"> <li>• Simplification the system and test in homogenous system</li> </ul>                               |

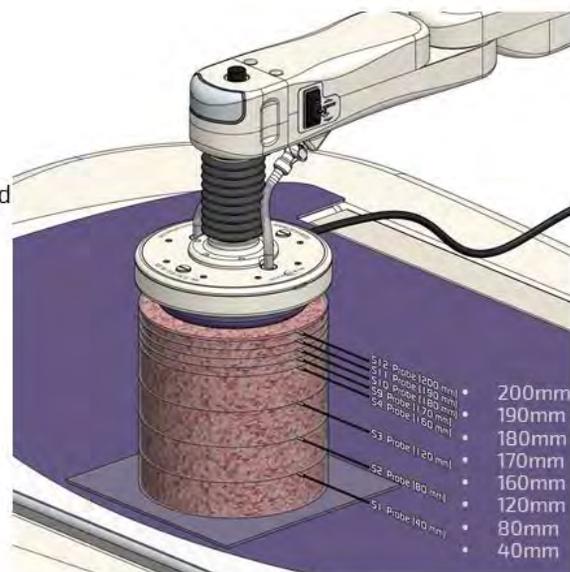


## > Study design

*Test setup*

### INPUTS

- Applicator size: 200mm diameter electrode
- Impedance of the test analogue
- Set power: 150W
- Height of the test analogue: 200mm
- Tissue type: pork ribs
- Weight of tissue: 6.6kg

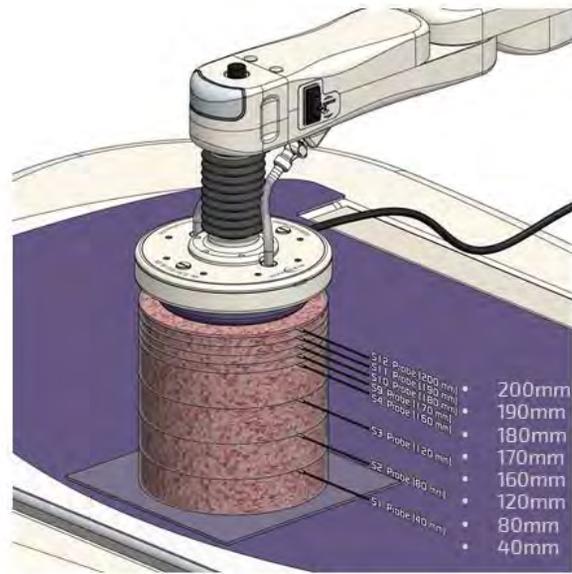


## > Study design

Test setup

### OUTPUTS

Thermal probes in 8 different heights of the tissue column. The thermal probes were introduced through side holes. The probes were placed in the middle of the tissue column **40 mm, 80 mm, 120 mm, 160mm, 170mm, 180mm, 190mm and 200mm** away from the bottom plate of the test analogue.

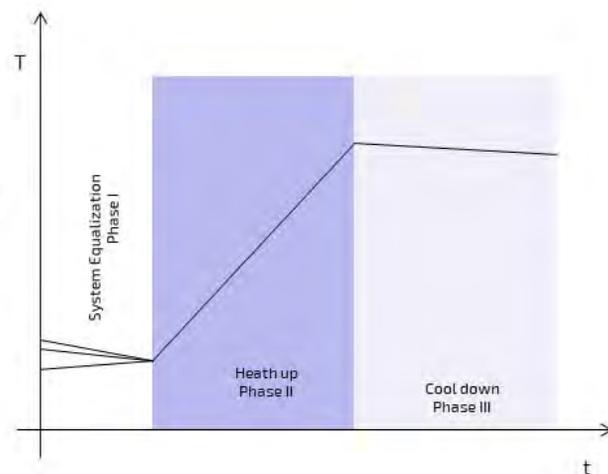


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## > Study design

Methodology

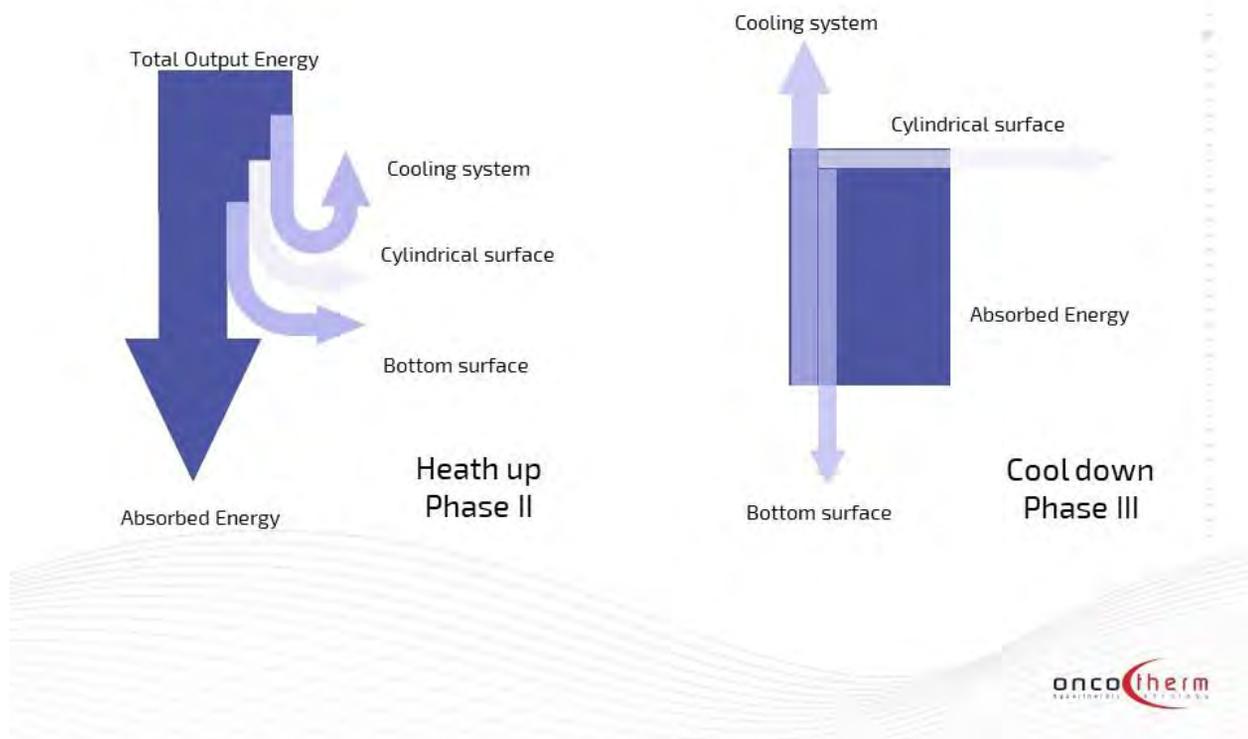
- Test analogue placement to device
- Equalisation of the system (Phase I)
- Treatment initiation using 150W set power
- Treatment, energy transfer for about an hour (Phase II)
- Treatment ends but maintains electrode cooling
- Cools down in about an hour (Phase III)



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## > Study design

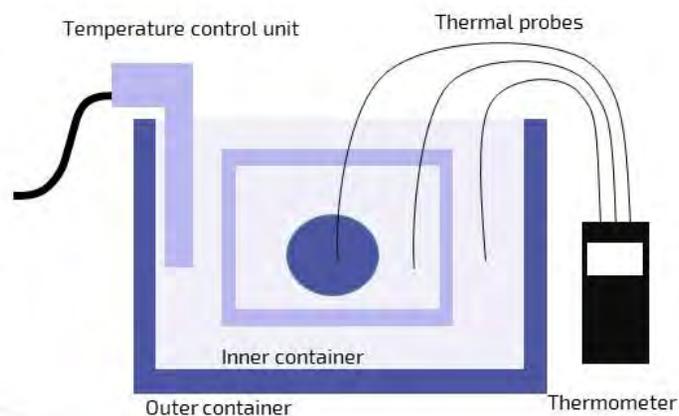
Methodology



## > Specific heat capacity

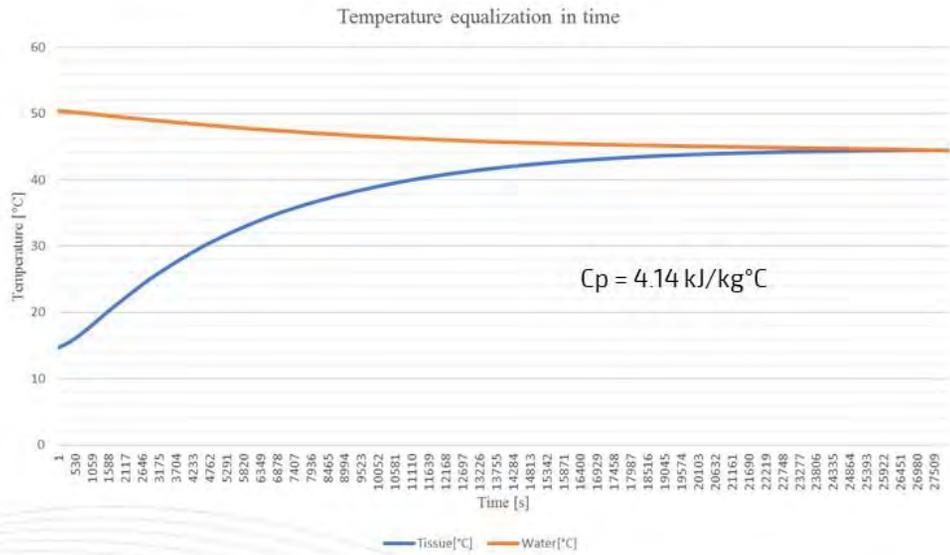
Experimental evaluation

- Environmental control for test volume
- Cold pork rib tissue
- Hot water
- Temperature monitoring until the equalization
- $C_p$  calculation using initial and final temperatures



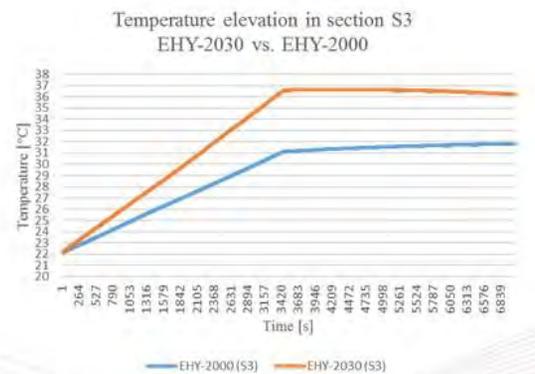
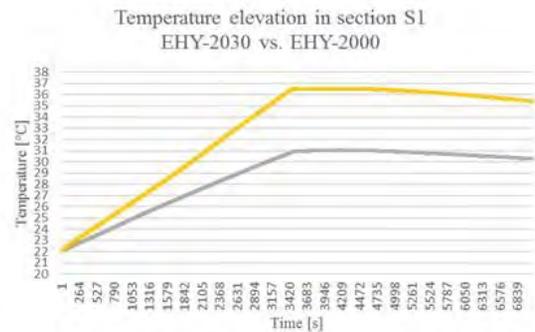
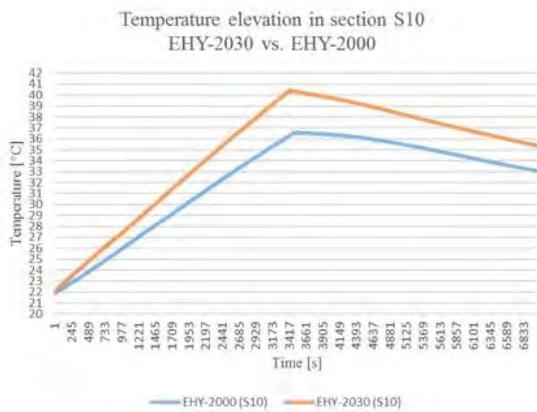
## > Specific heat capacity

Experimental evaluation



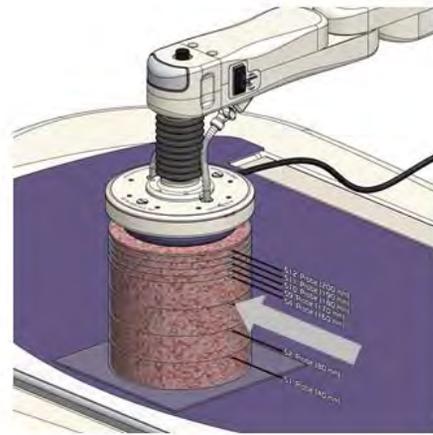
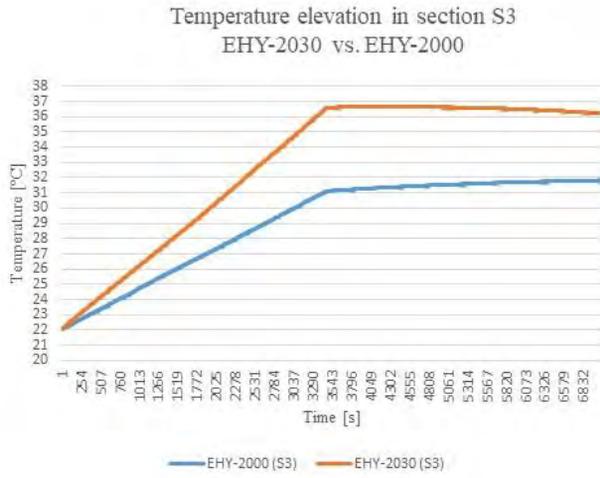
## > Results

Temperature data from sections



## > Results

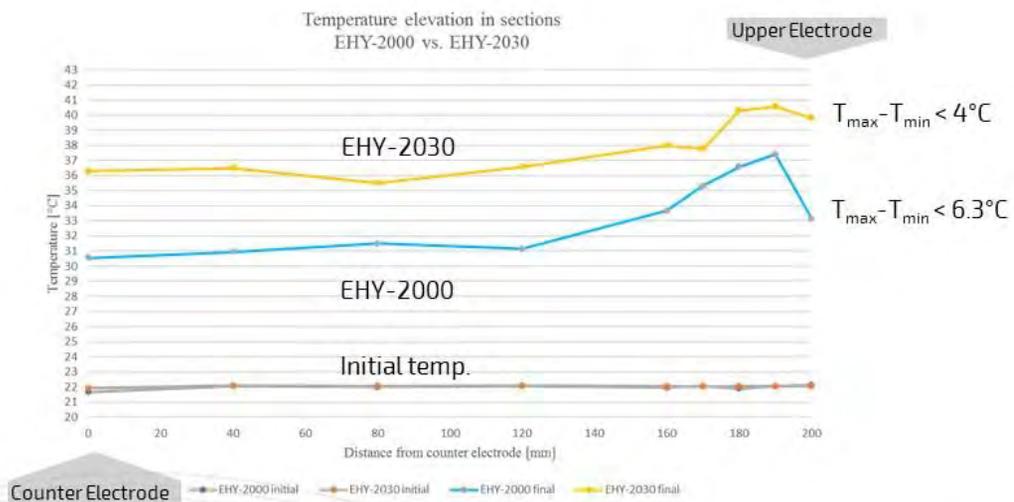
Temperature elevation in section S3



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## > Results

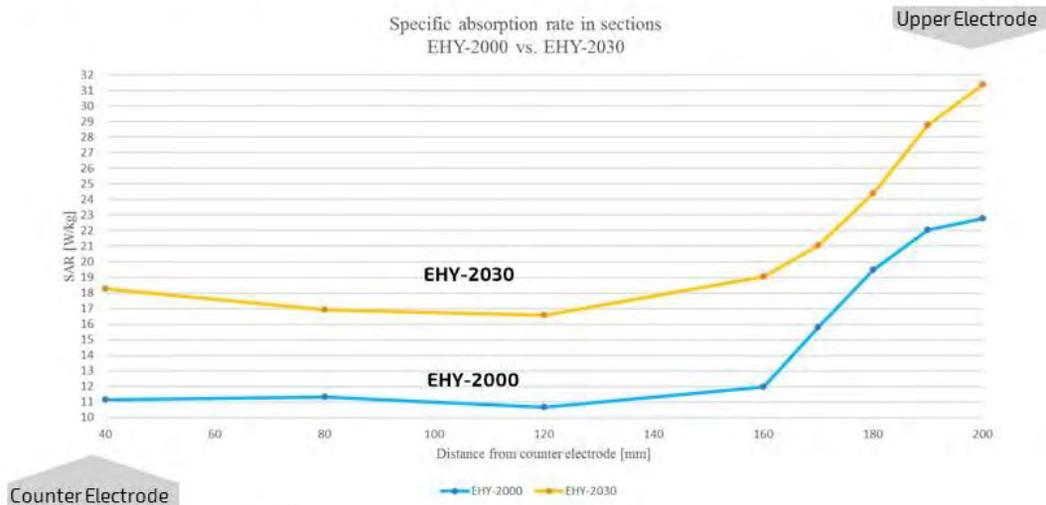
Temperature elevation in sections



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## > SAR in sections

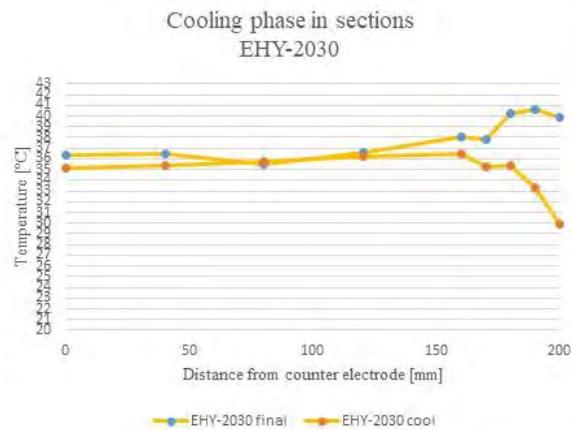
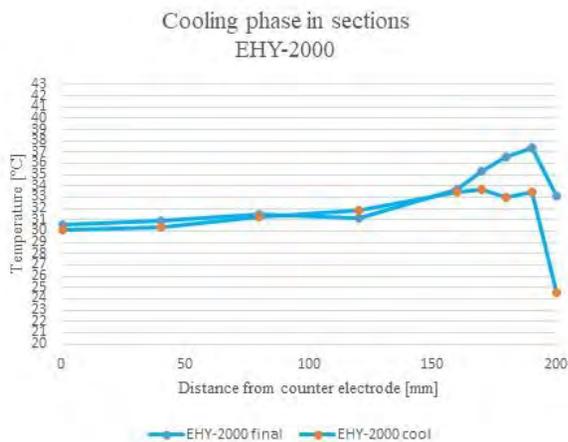
Specific absorption rate calculation



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## > Results

Heat conduction



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## > **Conclusions**

*Improvements at EHY-2030*

- Better energy distribution
- Higher Specific Absorption Rate
- Intuitive user interface
- Compact design
- Intelligent features



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## > **THANK YOU!**

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HYPERTHERMIA TREATMENT

# Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol

István Portoro<sup>1</sup>, Lea Danics<sup>1</sup>, Daniel Veres<sup>2</sup>, Tamas Kaucsar<sup>1</sup>, Ildiko Horvath<sup>2</sup>, Jeremiah Thomas<sup>1</sup>, Csaba Schvarcz<sup>1</sup>, Krisztian Szigeti<sup>2</sup>, Domokos Mathe<sup>2</sup>, Peter Hamar<sup>1</sup>, Zoltan Benyo<sup>1</sup>

<sup>1</sup> Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

<sup>2</sup> Department of Biophysics and Radiation Biophysics, Semmelweis University, Budapest, Hungary

Presented at 36<sup>th</sup> ICHS, Budapest, 2018

## Cite this article as:

Portoro I. (2018): Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol; *Oncothermia Journal* 24:344-356

[www.oncothermia-journal.com/journal/2018/Increased\\_efficacy\\_in\\_treatment.pdf](http://www.oncothermia-journal.com/journal/2018/Increased_efficacy_in_treatment.pdf)

# Increased efficacy in treatment of glioma by a new modulated electro-hyperthermia (mEHT) protocol

István Portoro<sup>1</sup>, Lea Danics<sup>1</sup>, Daniel Veres<sup>2</sup>, Tamas Kaucsar<sup>1</sup>, Ildiko Horvath<sup>2</sup>, Jeremiah Thomas<sup>1</sup>, Csaba Schvarcz<sup>1</sup>, Krisztian Szigeti<sup>2</sup>, Domokos Mathe<sup>2</sup>, Peter Hamar<sup>1</sup>, Zoltan Benyo<sup>1</sup>

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## Introduction

Modulated electro-hyperthermia (mEHT) is an effective and widespread supplemental therapy in cancer treatment using the radiofrequency (RF) of 13.56 MHz and a fractalphysiology-based modulation frequency based on selective heating of the tumors. From the Pennes equation... We used an animal model to demonstrate the hypothesis in vivo.

## Methods

RG2 [D74] (ATCC®, CRL 2433™) glioma cell line was inoculated into the parietal lobe of syngeneic Fischer 344 rats. This model mimics the human malignant astrocytoma by having incompetent BBB. A gadolinium-based MRI contrast agent (MAGNEVIST®, 0.5 mmol/mL, 0.2 mL/kg bdw) was used to detect lesions associated with altered blood-brain barrier and the volume of the tumor was quantificated at the 8th and 15th days after inoculations (AMIDE® software). The animals was divided randomly in 4 groups: sham (3), treated with classical mEHT protocol (3), treated with new mEHT protocol (3), treated with classical mEHT protocol and with the temozolamide (30 mg/kg bdw for 5 days), an oral chemotherapy drug used as a second-line treatment for astrocytoma and a first-line treatment for glioblastoma multiforme (1). We applied the mEHT treatment at 6th, 9th, 11th and 13th days after inoculations.

## Results

As a result of a technological improvement we used a new cooling system wich was able to prevent the overheating of the skin below the RF electrode and above the skull with high electrical impedance. Consequently based on a stepwise protocol we could apply extremely high energies (even 10 W) to reach as soon as possible the requested temperature into the brain. The brain temperature was evaluated indirectly by the measurement of the temperature in the middle ear and by using a correlation curve set up in an earlier experiment. The tumor growing rate between the 8th and 15th days after inoculations was in the case of sham animals:  $23.73 \pm 12.15$ , treated with classical mEHT protocol:  $19.08 \pm 0.49$ , treated with new mEHT protocol:  $6.83 \pm 2.02$ , treated with classical mEHT protocol and with the temozolamide: 7.99.

## Conclusion

Text The application of the new cooling system allowed us to set up in the case of glioma a new mEHT protocol which is based on that principle to reach a very high specific absorption rate in the treated tissue. This new protocol was more efficient as the classical one and

surprisingly looks like more efficient/similarly efficient than the classical one combined with chemotherapy.

This study was supported by the Hungarian National Research, Development and Innovation Office (NVKP\_16-1-2016-0042)

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Jeremiah Thomas<sup>1</sup>, Csaba Schvarcz<sup>1</sup>, Krisztián Szigeti<sup>2</sup>,  
Domokos Máthé<sup>2</sup>, Péter Hamar<sup>1</sup>, Zoltán Benyó<sup>1</sup>**

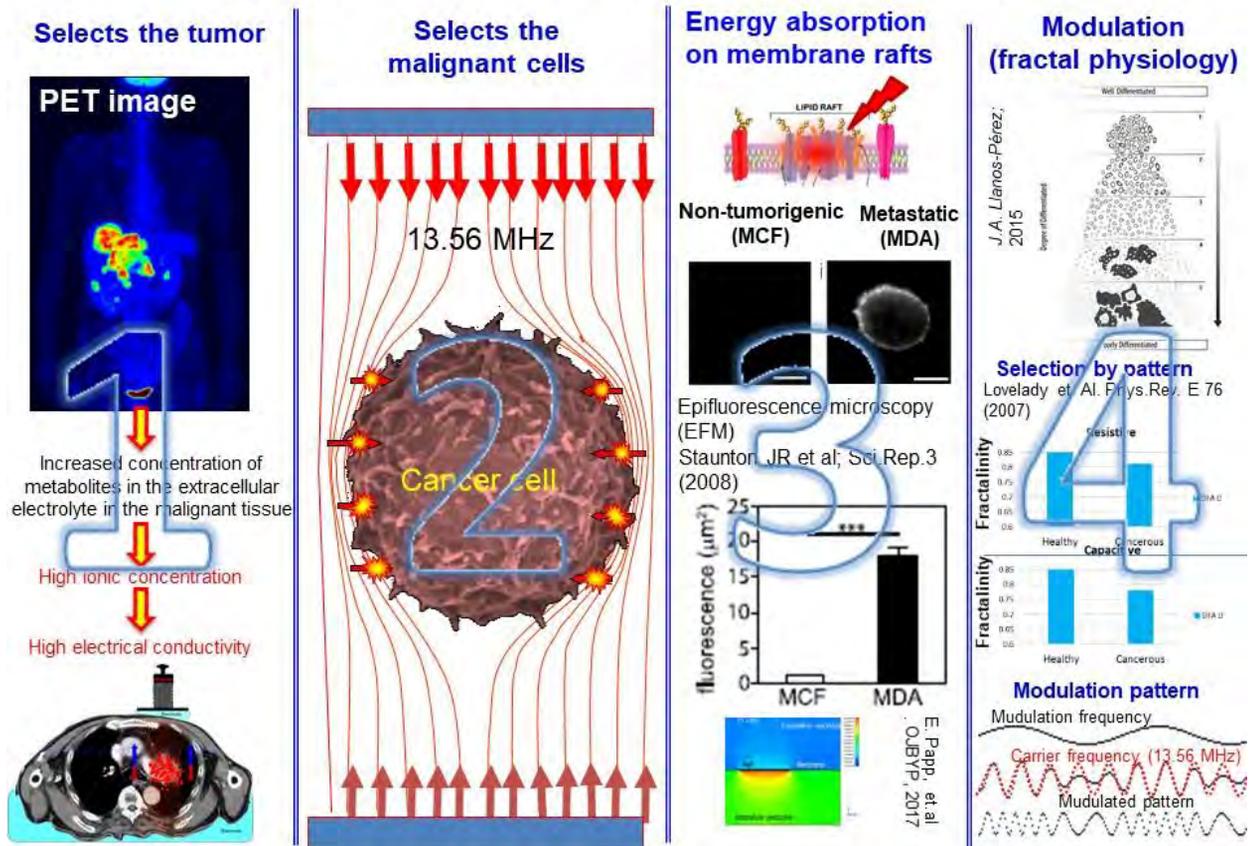
<sup>1</sup> Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

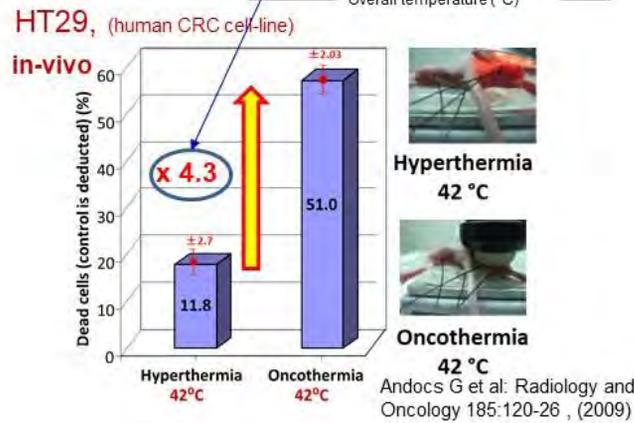
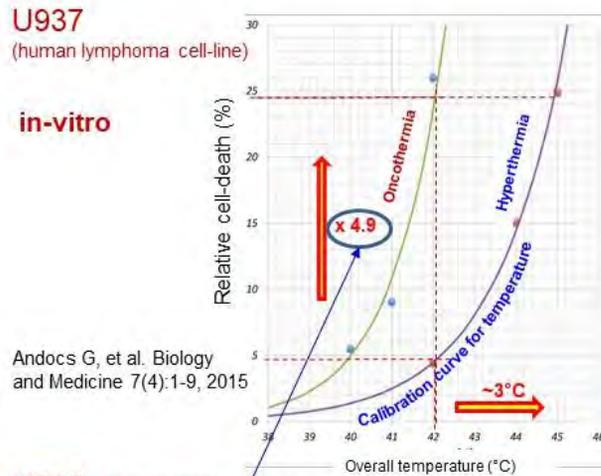
<sup>2</sup> Department of Biophysics and Radiation Biophysics, Semmelweis University, Budapest, Hungary

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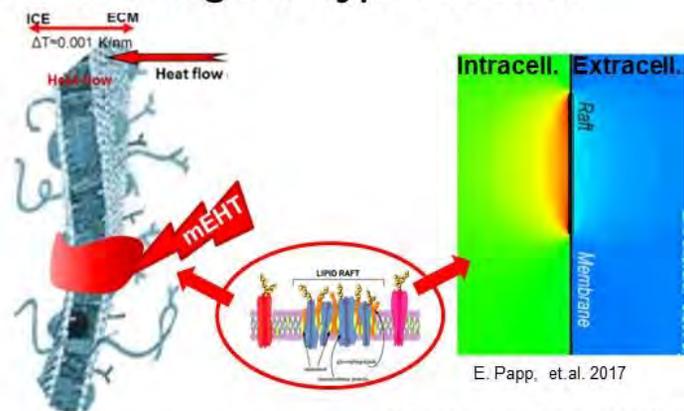
### Selection of the malignant cells by biophysical differences



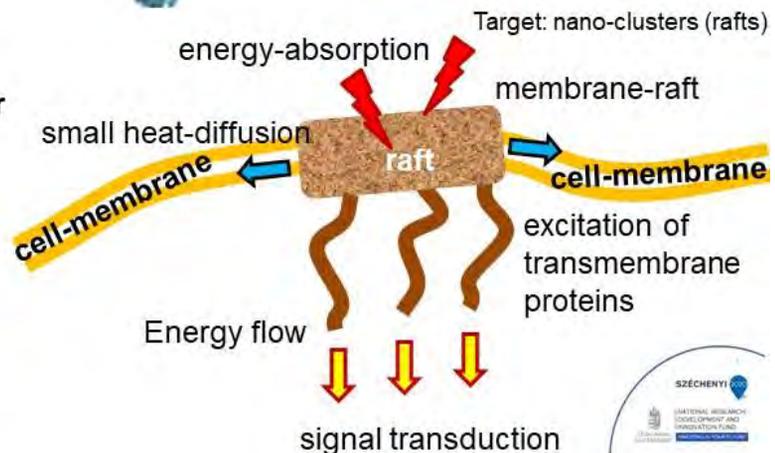
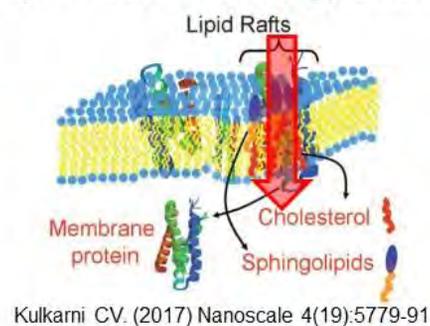


## Challenge of the dose of oncological hyperthermia

mEHT heats the cell-membrane rafts



quasi adiabatic energy transfer



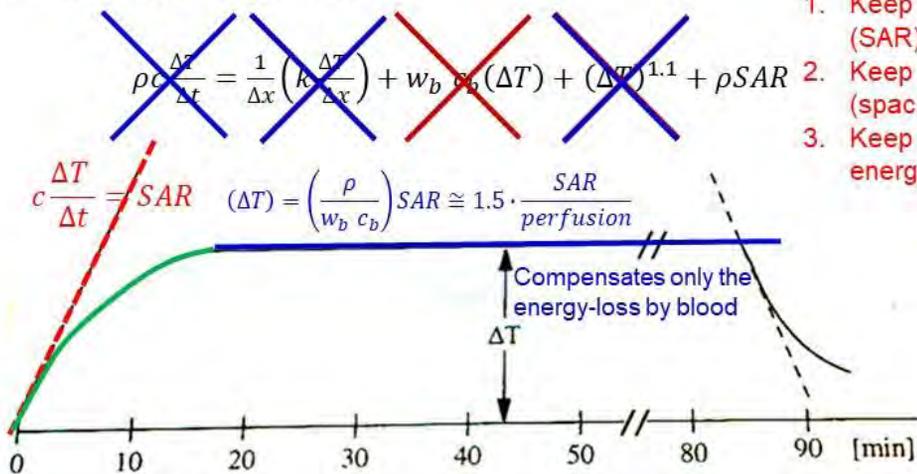
## Power equation (Pennes equation)

$$\rho c \frac{\partial T}{\partial t} = \nabla(k \nabla T) + w_b c_b (T_a - T) + q_m + \rho SAR$$

Change by time      Change by space      Change by blood      Change by metabolism      **Hyperthermia Pumped-in power**

where  $\rho$ ,  $c$ , and  $k$  are the density ( $\text{kg/m}^3$ ), the specific heat ( $\text{J/(kgK)}$ ), and the tissue thermal conductivity ( $\text{W/(m.K)}$ ), respectively;  $w_b$  is the mass flow rate of blood per unit volume of tissue ( $\text{kg/(sm}^3\text{)}$ );  $c_b$  is the blood specific heat;  $q_m$  is the metabolic heat generation per unit volume ( $\text{W/m}^3$ );  $T_a$  represents the temperature of arterial blood (K);  $T$  is the actual temperature risen above the ambient level;  $\partial T/\partial t$  is the rate of temperature rise. (**SAR (Specific Absorption Rate) – (W/kg)**)

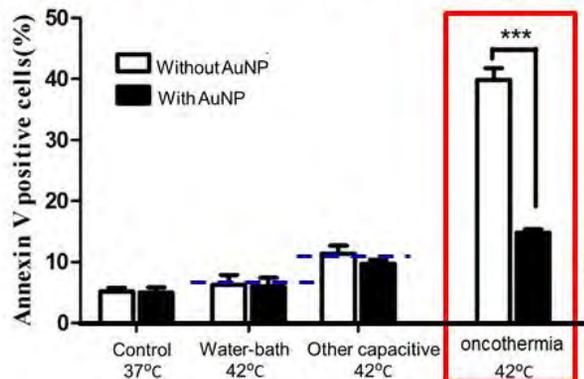
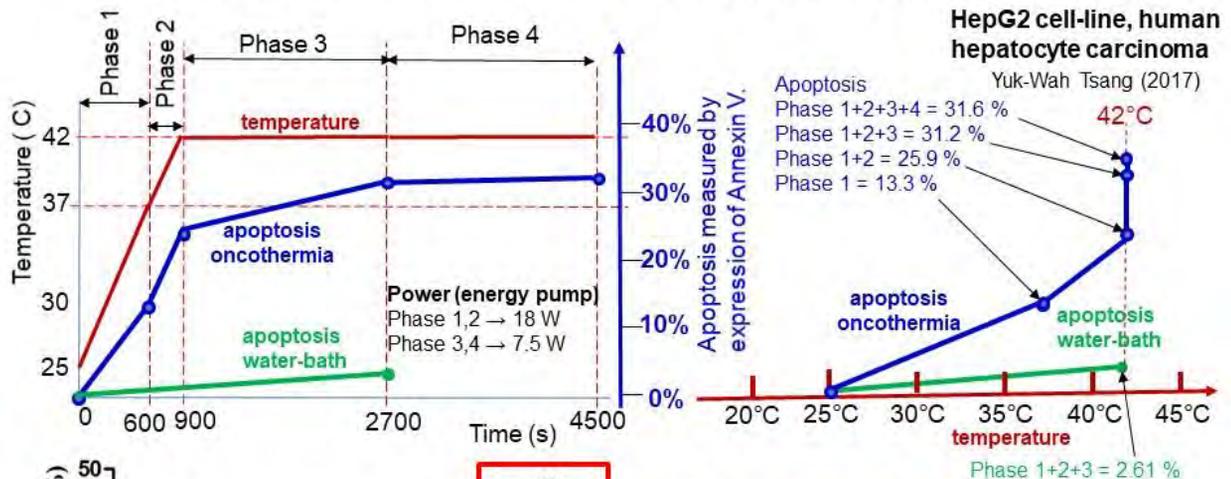
Simplified (no derivatives)



**Our tasks:**

1. Keep the time-dependent part (SAR) large
2. Keep the environmental (space-dependent) part small
3. Keep the compensating energy small

## Challenge of the dose of oncological hyperthermia

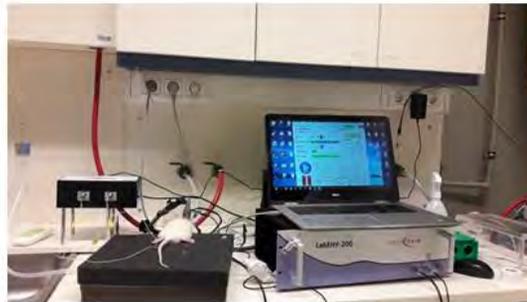
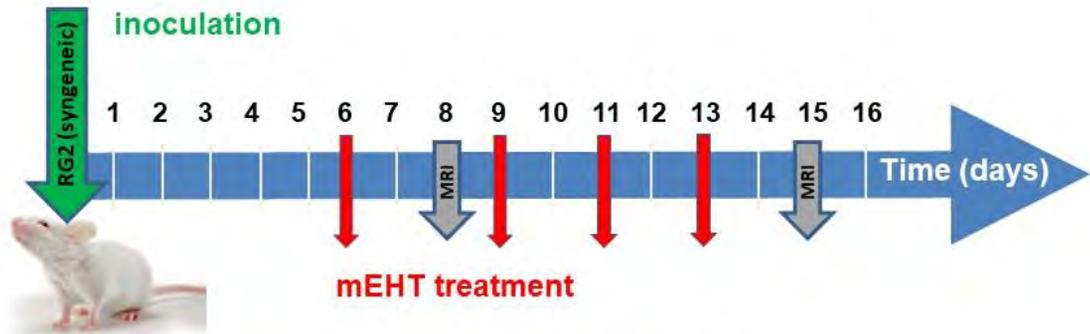
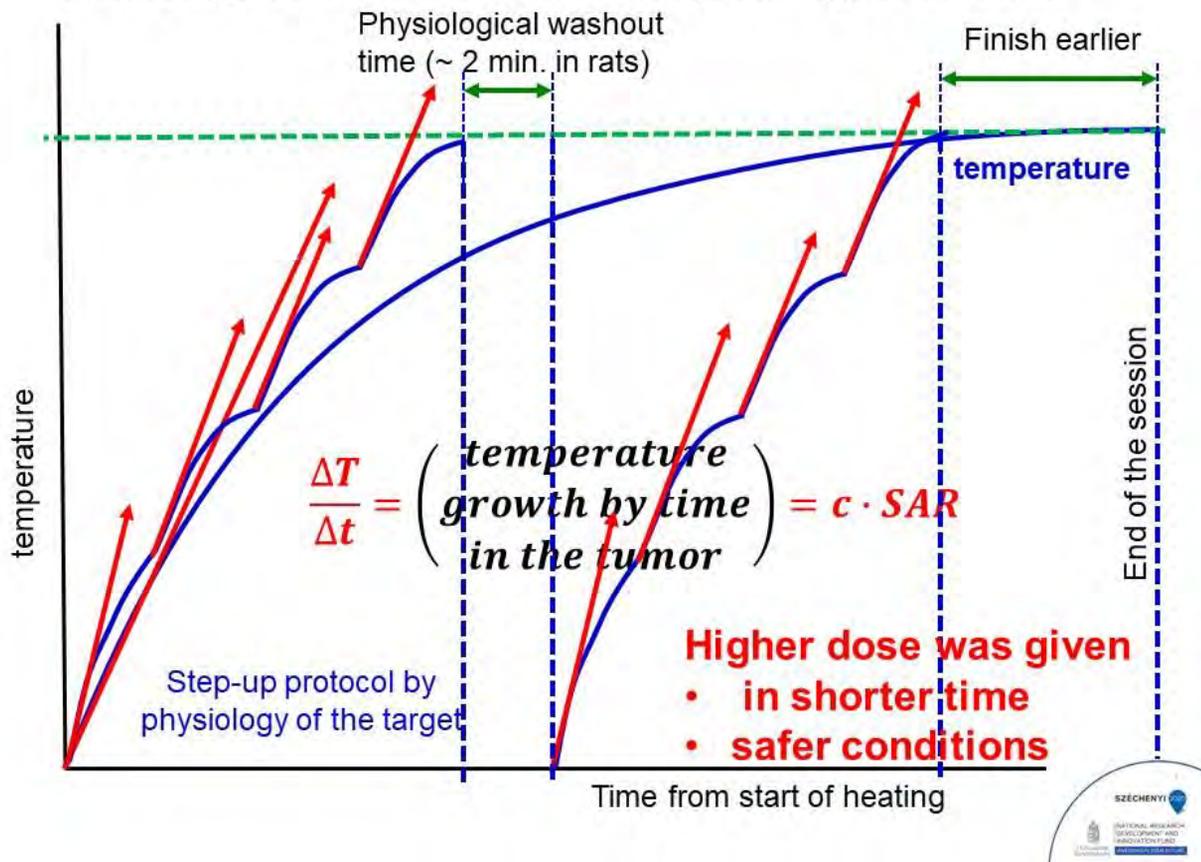


AuNP heats conventionally, produces the same apoptotic rate than without when heated to the same temperature

but

AuNP heated with oncothermia the effect of apoptosis decreases, because less energy is given to the malignant cells directly when AuNP is also heated

## Challenge of the dose of oncological hyperthermia



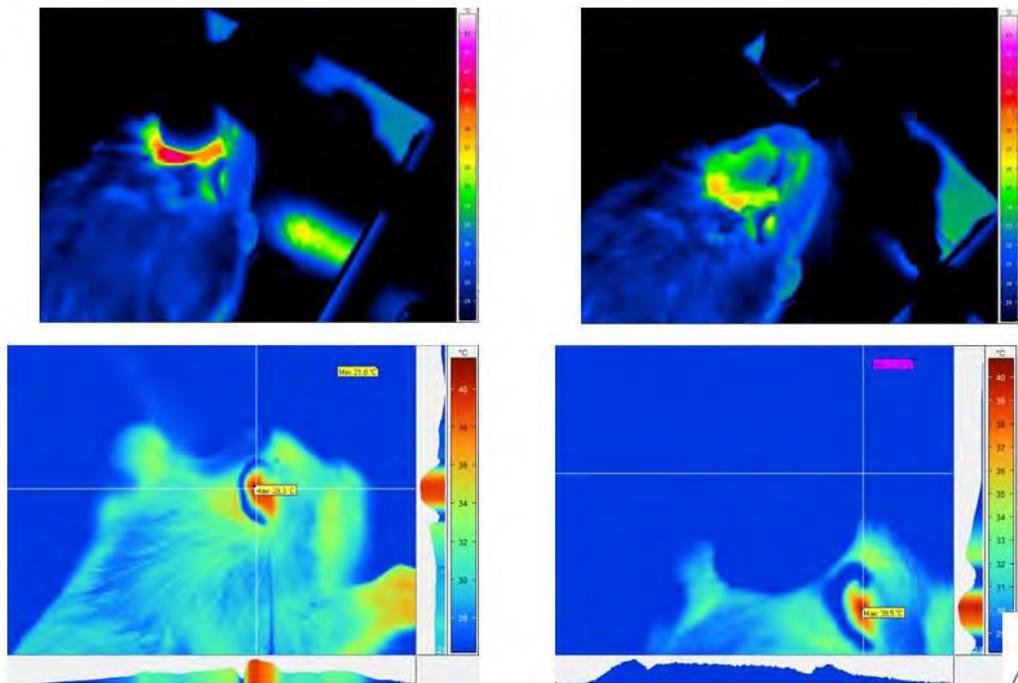
## Development on an evaporation-based cooling system

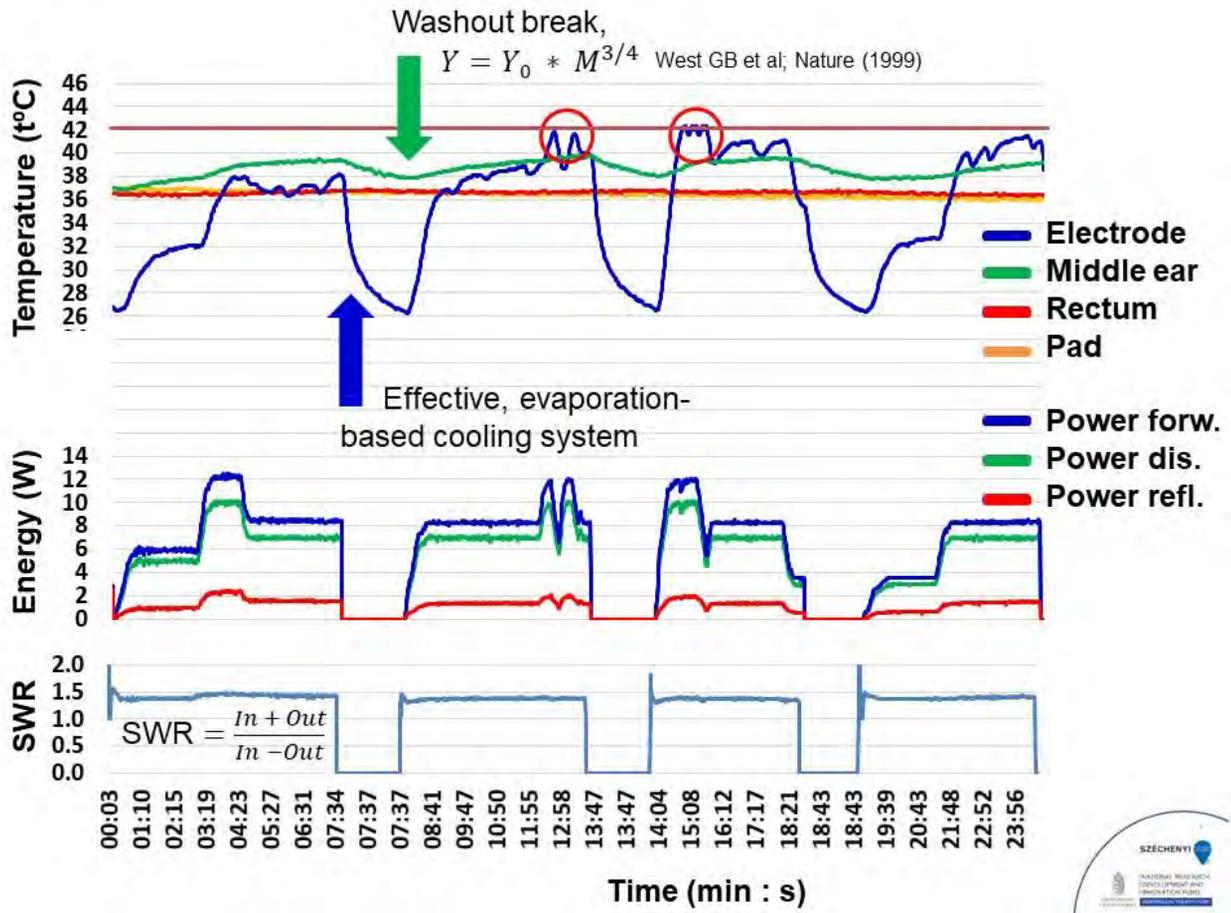


Calibration curve:  
The temperature in the brain area  
under the electrode is 1,78 C higher  
than in the middle ear

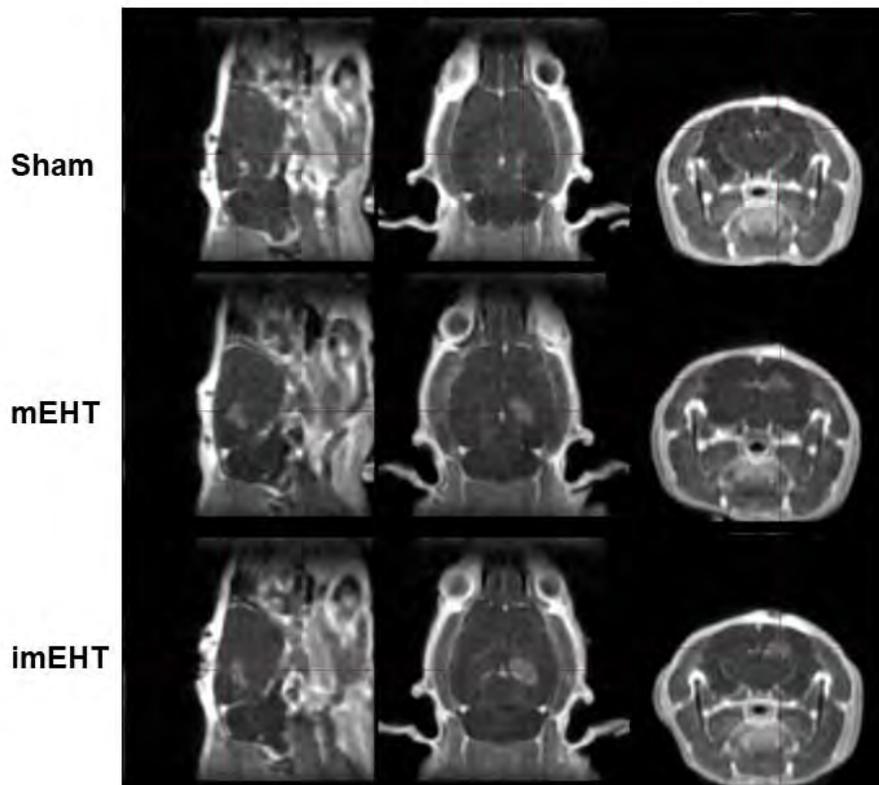


The application of the new cooling system allowed us to achieve a very high quasi adiabatic specific absorption rate in the treated tissue.





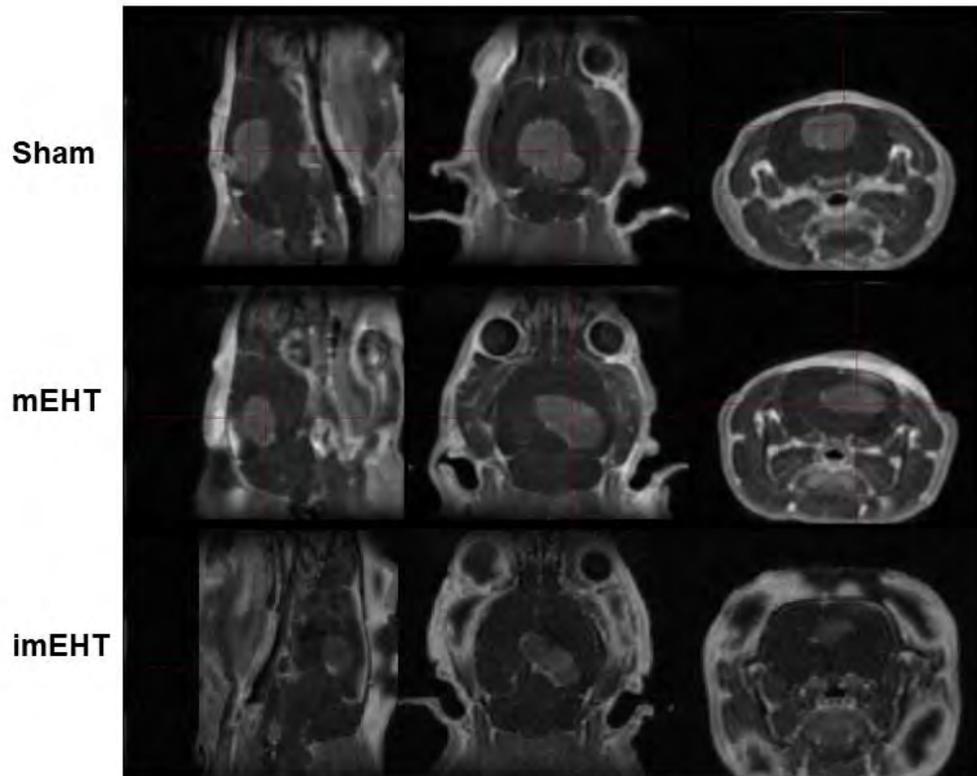
**Mediso nanoScan 1T small animal MRI system  
 and a 3D image acquisition sequence**



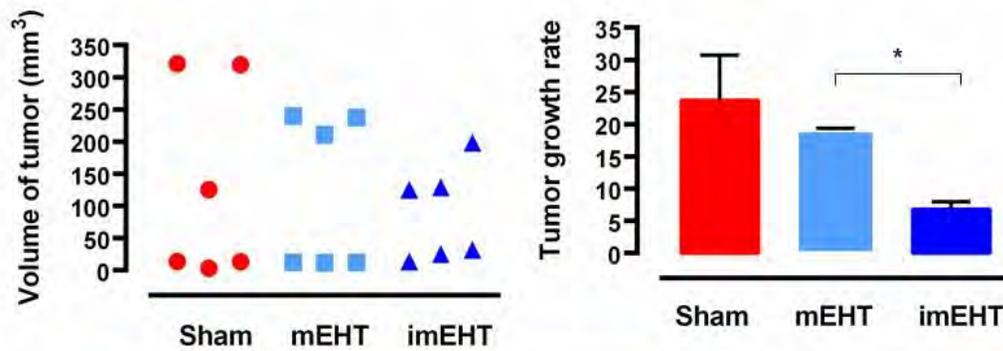
MAGNEVIST®,  
 0.5 mmol/mL,  
 0.2 mL/kg bdw



## Tumor size after the treatment (15<sup>th</sup> day)



## Quantification of the MRI results



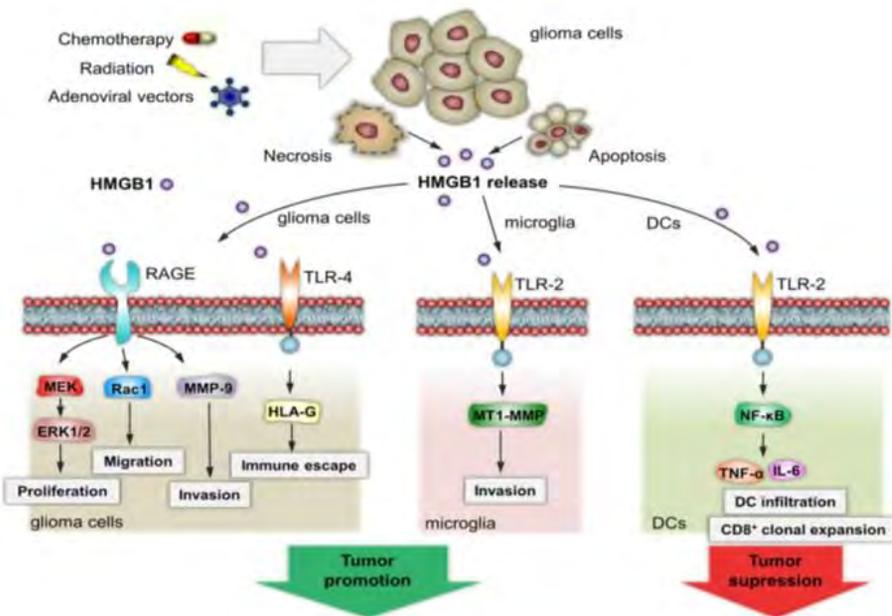
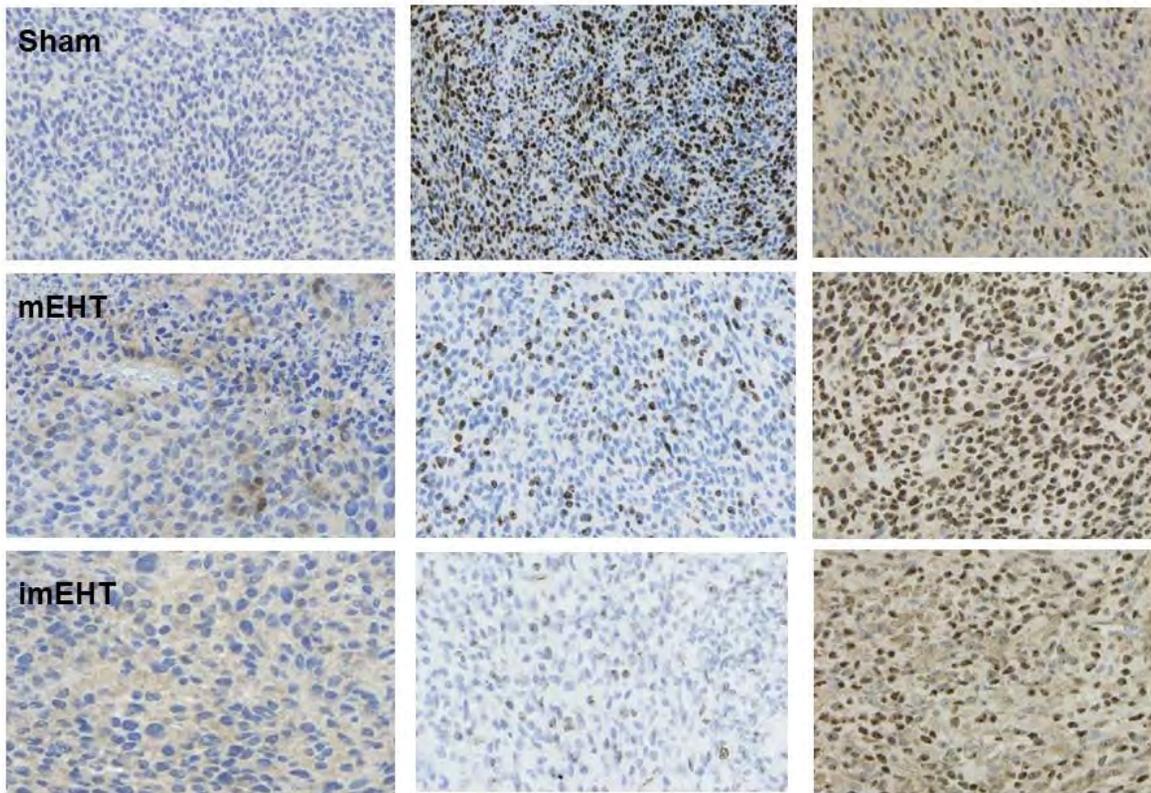
	Sham		mEHT		imEHT	
(volume, mm <sup>3</sup> )	8 <sup>th</sup> day MRI	15 <sup>th</sup> day MRI	8 <sup>th</sup> day MRI	15 <sup>th</sup> day MRI	8 <sup>th</sup> day MRI	15 <sup>th</sup> day MRI
	13,76342773	321,4416504	12,35961914	239,6240234	13,79394531	125,213623
	3,479003906	125,5187988	11,35253906	210,3271484	24,99389648	128,7231445
	13,58032227	319,6105957	12,23754883	236,9689941	31,58569336	198,2116699
<b>Mean</b>	10,2742513	255,5237	11,98324	228,9734	23,45785	150,7161
<b>SD</b>	5,885568985	112,5913	0,549599	16,20259	8,994785	41,16974



HSP70

Ki67

HMGB1



Angelopoulou et al; J Mol Med (2016)





Thank you for your attention!



# International Guideline Proposal for Hyperthermia based Oncological Treatments -- an Initiative from Hungary

**Marcell A. Szasz<sup>1</sup>, Gyongyver Szentmartoni<sup>1</sup>, Peter Arkosy<sup>2</sup>, Tibor Csozsi<sup>3</sup>, Zsolia Dankovics<sup>4</sup>, Gabor Rubovszky<sup>5</sup>, Andras Csejtei<sup>4</sup>, Gabor Pajkos<sup>6</sup>, Bela Piko<sup>7</sup>, Erika Borbenyi<sup>1</sup>, Magdolna Dank<sup>1</sup>**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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# International Guideline Proposal for Hyperthermia based Oncological Treatments -- an Initiative from Hungary

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## Background

Hyperthermia is composed of a wide variety of treatment methods which ranges from physiotherapy to oncology and can have various physical and technical background. Even the definition needs careful consideration and is subject to discussion. Dosing may vary between the equipments of individual vendors. There was substantial development in this field, thus, the previously proposed guidelines and protocols do not fully apply to all approaches and devices.

## Aims

Our objective in this presentation is to summarize our knowledge about the utilization of hyperthermic therapy from the practical perspective and propose a guideline which seems timely and necessary. In line with this, definition, dosing will be discussed, and the objective is to provide a recommendation for the implementation of the hyperthermia and also take into consideration data analysis and comparability.

## Methods

We would like to collect the experience of the centers which utilize hyperthermia in any oncological treatment fashion, gather a collective wisdom on best practices, filter and organize the procedures into an adaptable recommendation, and establish standards and quality control.

## Results

The literature for hyperthermia guidelines will be reviewed, clinical evidences will be referenced, discussion and credentials on recommendations will be collected and a guideline will be developed, drafted into a manuscript with all national and international contributors.

Grant support: NVKP\_16-1-2016-0042

# International Guideline Proposal for Hyperthermia based Oncological Treatments -- an Initiative from Hungary

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Rubovszky Gábor<sup>5</sup>, Csejtei András<sup>4</sup>, Pajkos Gábor<sup>6</sup>,  
Pikó Béla<sup>7</sup>, Borbényi Erika<sup>1</sup>, Dank Magdolna<sup>1</sup>**

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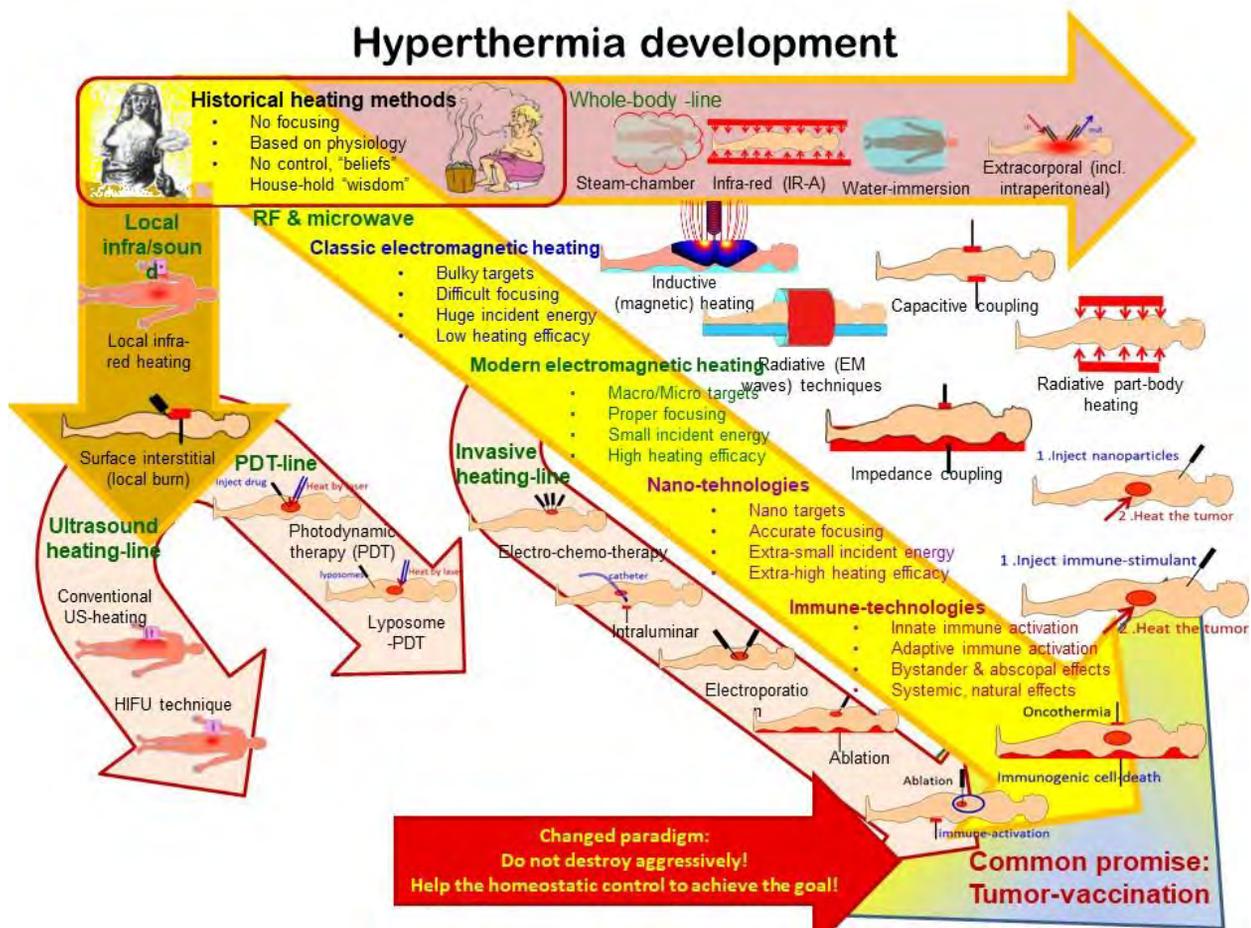
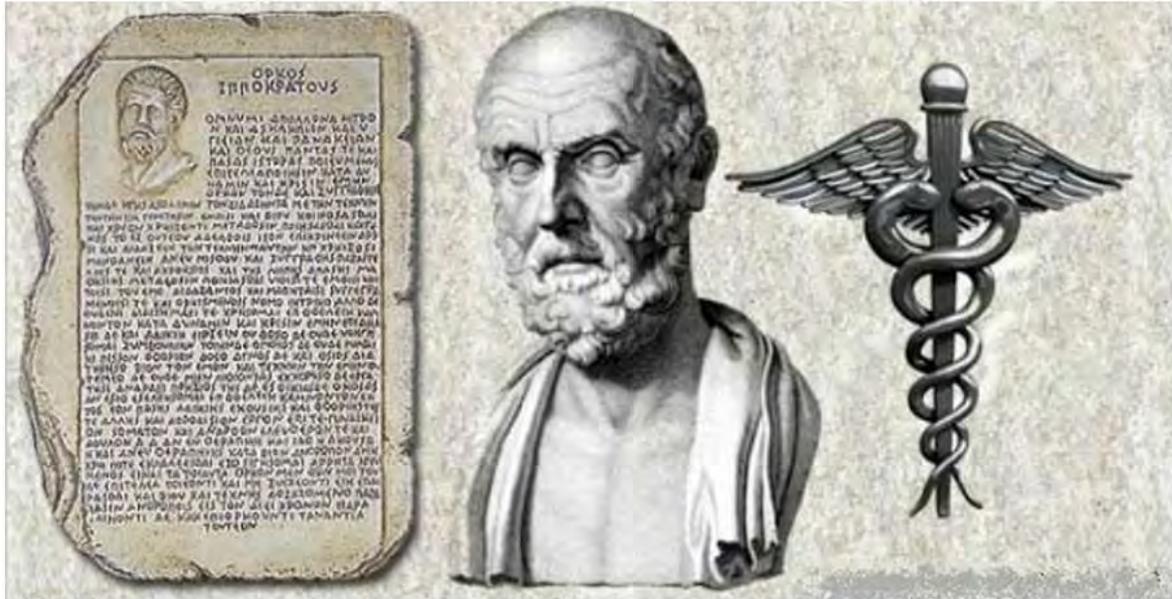
(6) Department of Oncology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary

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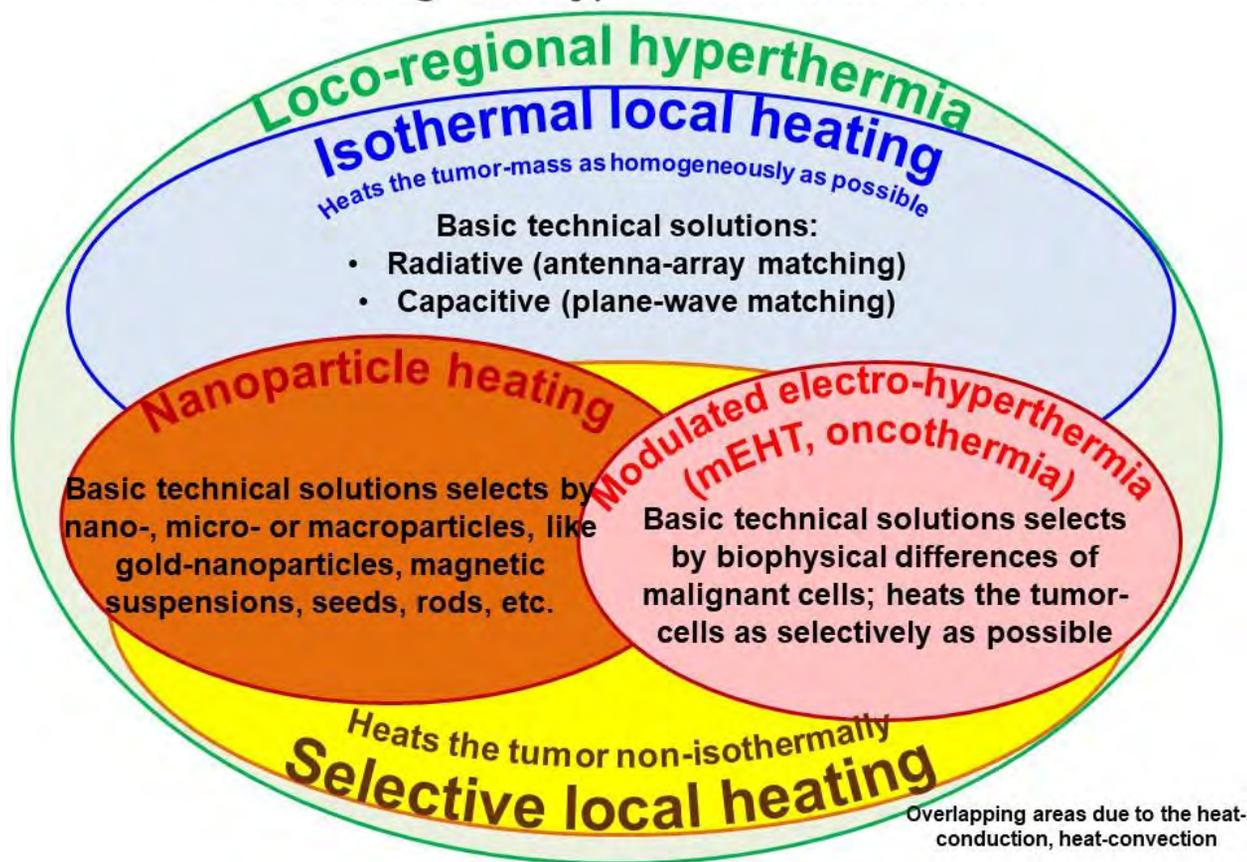
## Disclosures – conflict of interest (NONE)

- Physics student at Eötvös Loránt University (TTK)
- M.D./Ph.D. Ast. Professor - 2nd Department of Pathology, Semmelweis University, Budapest, Hungary
- Senior scientist - "Lendület" Cancer Biomarker Research Group, Hungarian Academy of Sciences, Budapest, Hungary
- Consultant Pathologist - Clinical Pathology/Cytology, Karolinska University Hospital, Stockholm, Sweden
- Chief of Pathology - Centre of Excellence in Biological and Medical Mass Spectrometry, Biomedical Centre, Lund University, Lund, Sweden
- Consultant – LoDoCo Ltd.
- Consultant, patent pending – CiC Therapeutics Ltd.
- Developer – Treat4Life AB, Malmö, Sweden
- Research funding – Hungarian Society of Medical Oncology (indirectly from Roche, Pfizer, GlaxoSmithKline), Bristol-Myers Squibb, Hungarian National Research, Development and Innovation Office (NRDI Office), consultant for Oncotherm
- Head of Science - Cancer Center, Semmelweis University, Budapest, Hungary
- Research Fellow - Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
- Secretary General, Hungarian Society of Senology
- Member of Board of Curators, International Academy of Pathology, Hungarian Division

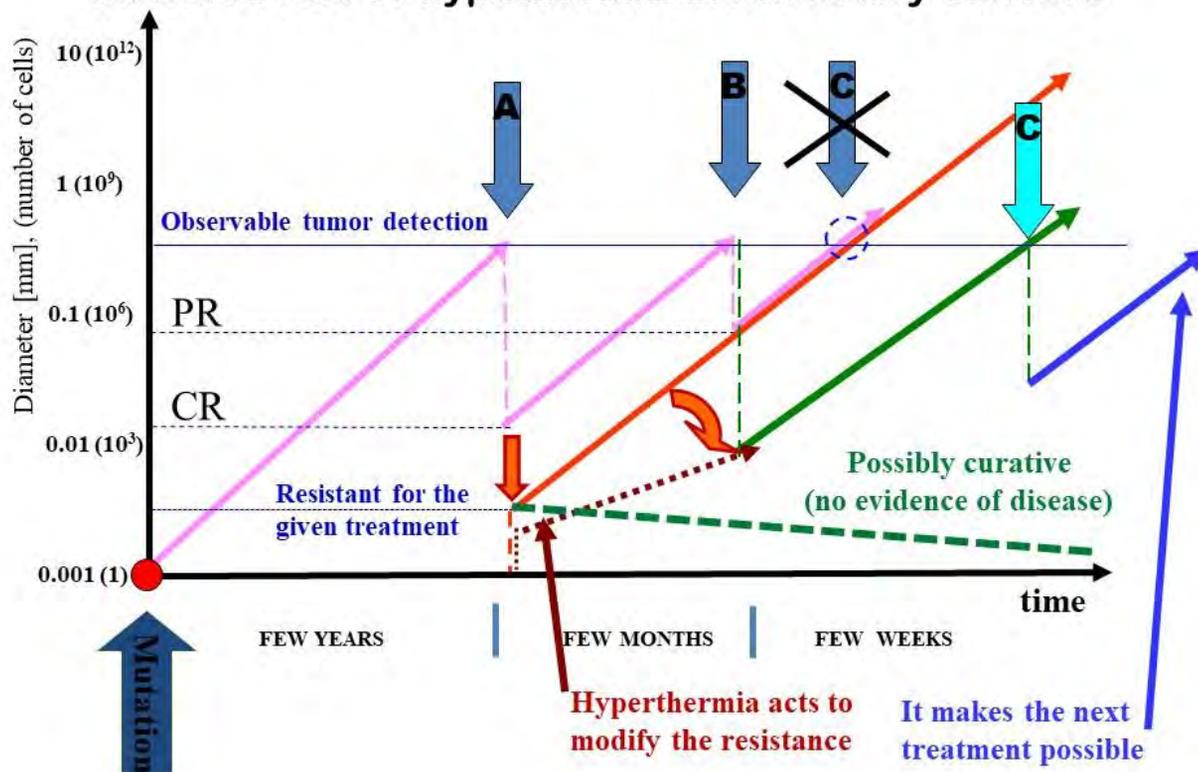
# Hippocrates



## Local/regional hyperthermia methods



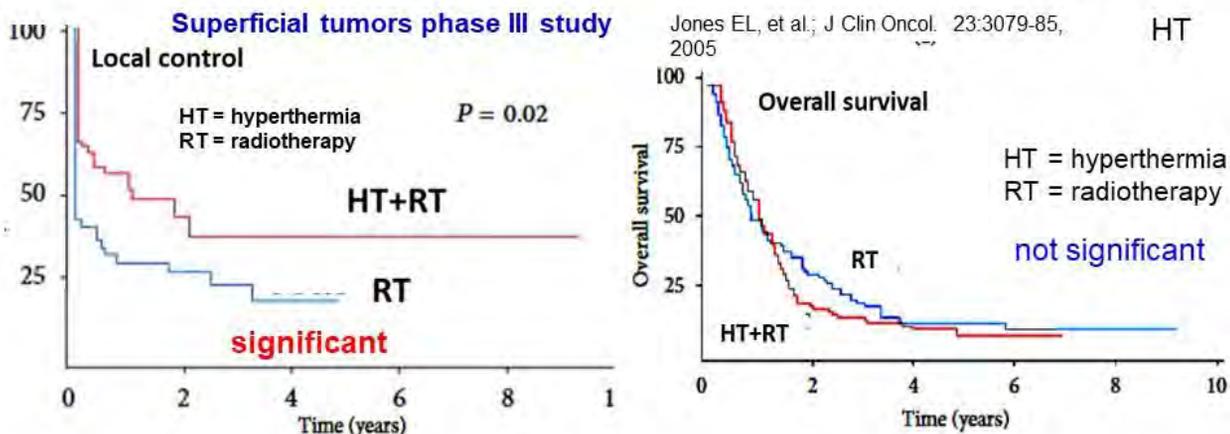
## Intended role of hypethermia in refractory cancers



## Hyperthermia has controversies between the

**local response and control** ↔ **overall survival**

### Local control and survival time are not in harmony



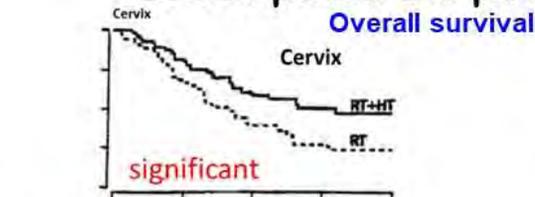
### Non-small-cell lung cancer Initial site of disease progression after treatment

	RT (n = 40)	RT + HT (n = 40)	P-value
No recurrence	3	4	
Primary tumor and/or regional lymph nodes	15	7	
Distant metastasis	2	10	0.07
Both locoregional and distant*	3	4	
Unknown/missing	17	15	

\*Patients in whom the interval between locoregional disease progression and distant metastasis was less than or equal to 1 month

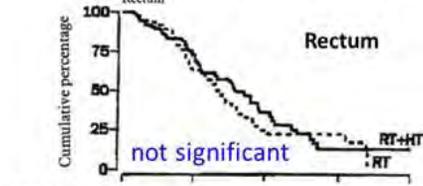
Michihide Mitsumori, Zeng Zhi-Fan Praskovya Oliynychenko Jeong Ho Park, Ihl Bohng Choi Hideo Tatsuzaki - Yoshiaki Tanaka, Masahiro Hiraoka; (2007) Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency, Int J Clin Oncol (2007) 12:192-198

# Break-point: the pelvic tumors – Lancet publication



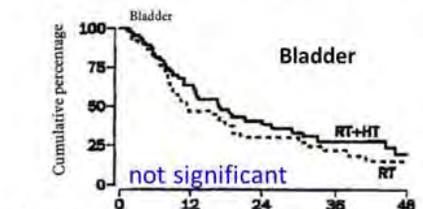
Number at risk

	58	43	26	17	13
RT+HT					
RT	56	36	17	9	6



Number at risk

	72	41	13	4	2
RT+HT					
RT	71	40	13	5	0



Number at risk

	52	28	16	9	5
RT+HT					
RT	49	21	11	8	5

## Overall survival

	Complete response/patients	Statistics	Odds ratio	Mean decrease
	Radiotherapy plus	Cancer hyperthermia Radiotherapy (O-E) Variance	(95% CI)	in odds (SD)
Rectal	52/72	44/71	3.8	23.2
Cervical	26/58	38/56	-10.3	15.3
Bladder	37/52	39/49	-4.0	18.2
Total	115/182 (63%)	121/176 (69%)	-10.6	56.7

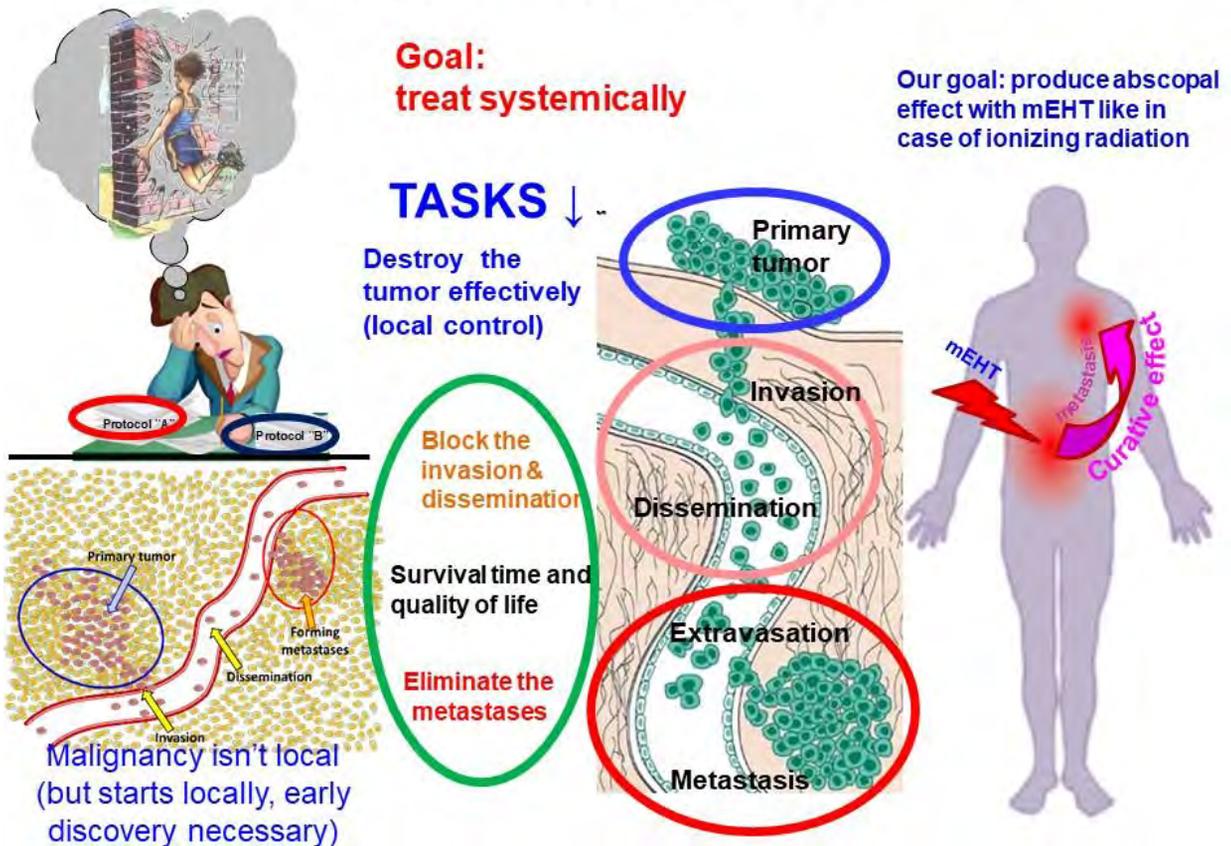
17% (11) reduction  
p=0.16

0 0.5 1.0 1.5 2

Radiotherapy plus hyperthermia better | Radiotherapy better

**IMPROVEMENT is necessary which is the direction of immuno-oncology**

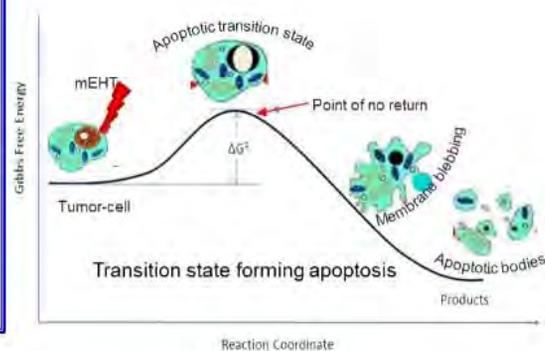
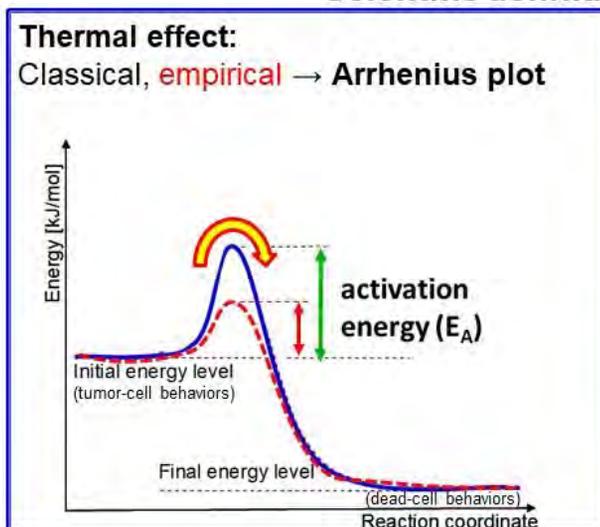
Challenge in oncology – malignancy is systemic



**Unfortunately presently  
we have no correct definition.  
We have no convenient  
dose-definition either.**

**When we have no correct definitions  
about our topic why we expect, that  
other disciplines accept us**

### Scientific definition of thermal effect

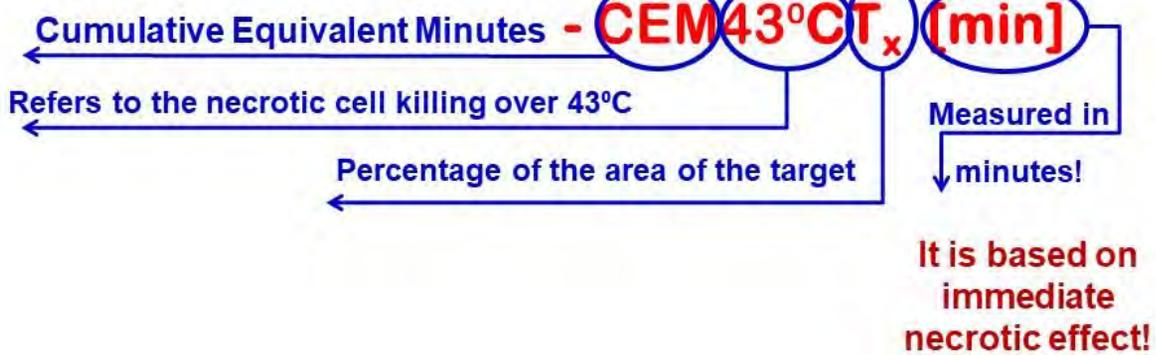


## Dosing, safety and reproducibility

### Conventional tumor-therapies

- ✓ **Concept** is to apply the largest tolerable dose [mg/m<sup>2</sup>], [J/kg]
- ✓ **Efficacy** is measured by off-situ diagnostics
- ✓ **Safety** is measured by toxicity limit (dose-escalation studies) [mg/m<sup>2</sup>], [J/kg]

### Hyperthermia dose in guidelines (Sapareto & Dewey 1984)



Sapareto and Dewey, CEM43, dose model (Sapareto SA, Dewey WC; (1984) THERMAL DOSE DETERMINATION IN CANCER THERAPY Int.J.Rad. Oncol. Biol. Phys. 10:787-800)

## Challenge of dose of hyperthermia

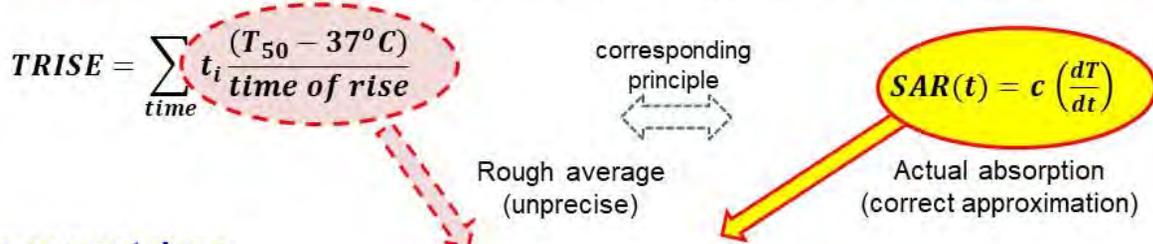
### CEM43°C T<sub>x</sub> Calibrated in vitro

Sapareto and Dewey, CEM43, dose model (Sapareto SA, Dewey WC; (1984) THERMAL DOSE DETERMINATION IN CANCER THERAPY Int.J.Rad. Oncol. Biol. Phys. 10:787-800)

$$CEM43^{\circ}CT_x = \sum_{time} t_i R^{(43^{\circ}C - T_x)}$$

### Fits to the clinical data

Francena M, et al: Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur. J. Cancer, 45:1969-1978 (2009)



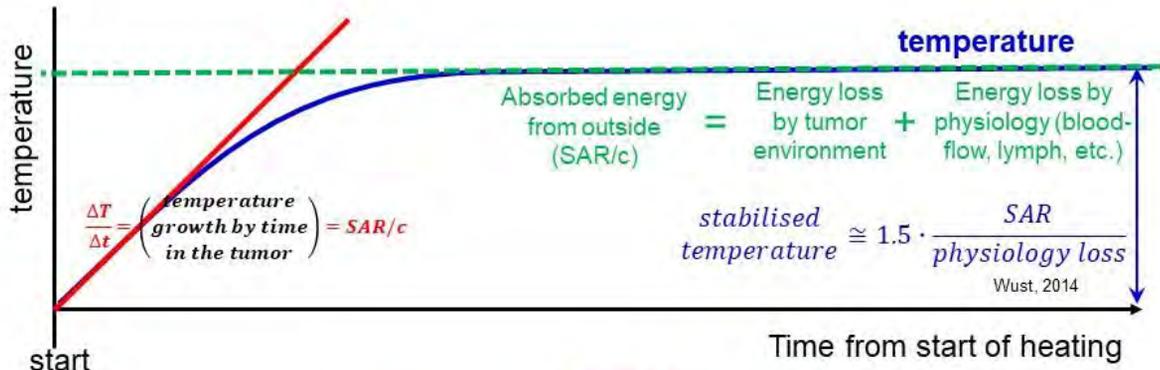
### The correct dose

$$Absorbed\ energy = \sum_{time} t_i (SAR(t))$$

↑  
measured in Gy (J/kg)  
(like in ionizing radiation)

**Technical requirement:  
high efficacy of energy absorption**

## Challenge of the dose of oncological hyperthermia



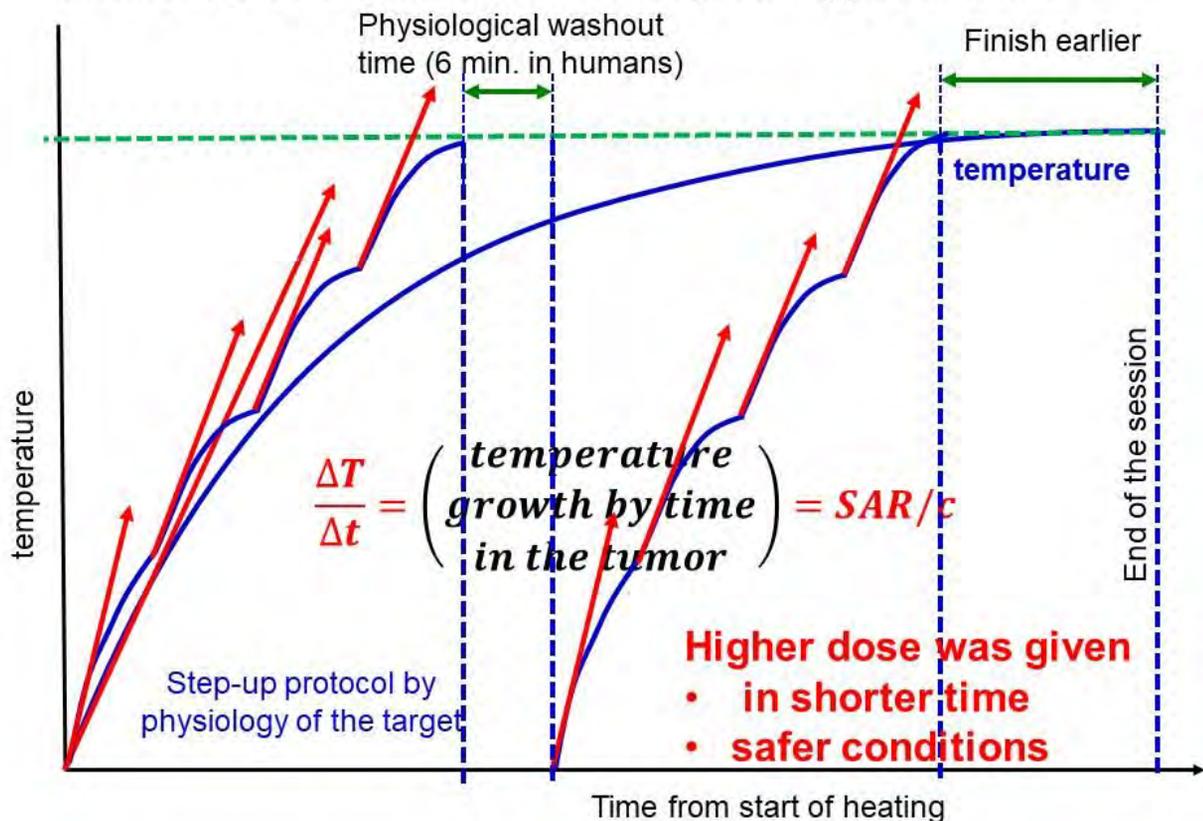
### Our tasks:

1. Keep the time-dependent part (SAR) large
2. Keep the environmental and physiology part small
3. Measure the dose as absorbed energy:

measured in Gy (J/kg) (like in ionizing radiation)

$$AE = \sum_{\substack{\{i\} \\ \text{steady} \\ \text{-state}}} c \frac{\Delta T}{\Delta t}$$

## Challenge of the dose of oncological hyperthermia



## General challenge

How to raise the prestige of hyperthermia again to the top of oncotherapies, like it was at its start?

### Challenge of definition of oncological hyperthermia

No clear definition of oncological hyperthermia is declared

### Present convention on definition

**Oncology encyclopaedia** – hyperthermia is **therapeutic heat**

**Medicine.net** – overheating of the **body**

**National Cancer Institute** – body **tissue** is exposed to high temperatures (up to 45°C)

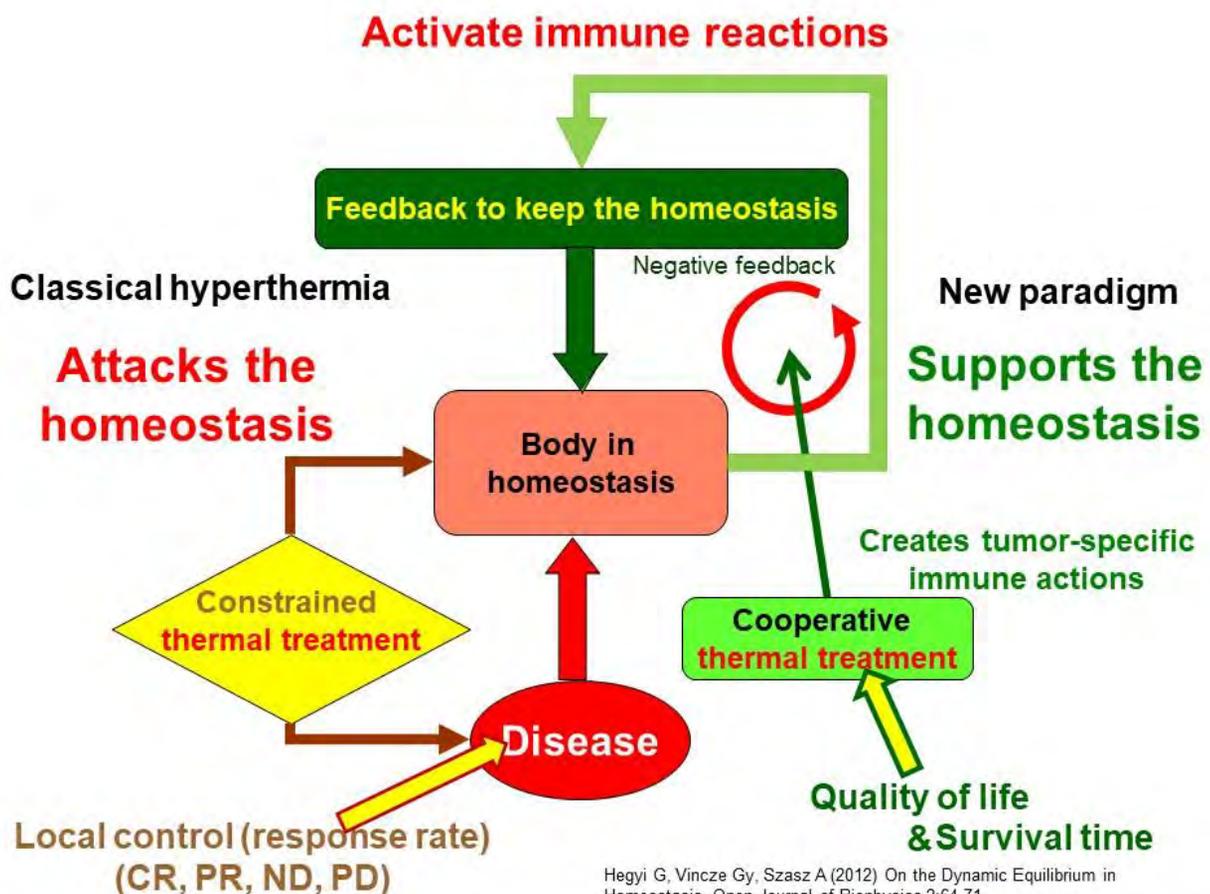
**Wikipedia** – body **tissue** is exposed to **slightly higher** temperatures to damage and **kill** cancer cells or to make cancer cells more **sensitive** to the effects of radiation and certain anti-cancer drugs

**Medical Dictionary** – **much higher** than normal body temperature induced therapeutically or iatrogenically

**The Am.Canc.Soc.** – **body** is exposed to **higher than normal** temperatures, changes take place inside the cells

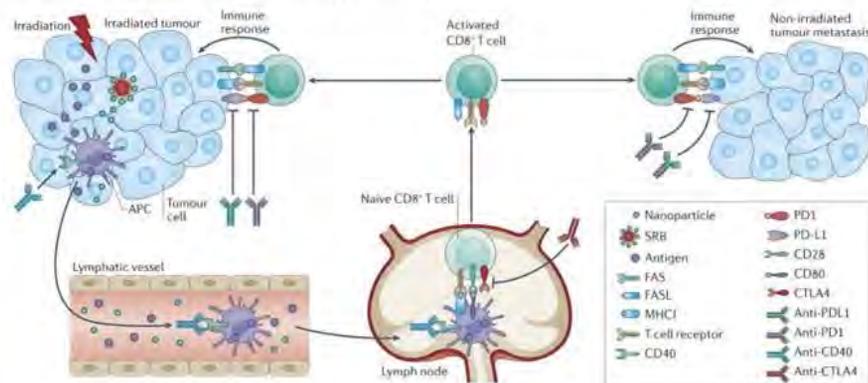
### Oncothermia definition

Oncological hyperthermia is a method to kill **malignant cells** by **heat-inducing absorbed** energy and/or **sensitize** certain complementary therapies



## Local absorbance, systemic effects

- DAMP (damage associated molecular pattern)
  - Heat-shock proteins
- ICD (immunogenic cell death)
  - Apoptosis
  - Dendritic cells, T cell response
- Abscopal effect (mediated by the immune system)



Ngwa, Nature Rev Cancer 2018

## Clinics in practice

- INDICATION
  - NOT only locally advanced but palliative as well by curative intent
  - Treatment decision in hand of certified and accredited physician and tumor board
  - According to local law and ethics
- PERSONEL
  - physician on duty
  - Nurses
  - Planning (by the decision of the tumor board)
  - others upon need

## Practical measures - endpoints

- DEMAND
  - localization dependent applicator,
  - starting and ending energy,
  - intervals

Survival time and quality of life in the same time

- Disease-free survival
  - Progression-free survival
  - Time to progression
- 
- Overall survival and quality of life

### Treatment indications

- ❖ Any solid tumor, primer, metastatic or recurrent
- ❖ Patient is treatable with any TNM and stage
- ❖ Combined treatment:
  - Applied to **increase treatment efficacy**
  - and for the **resensitisation of tumours**
  - to standard treatment protocols.
- ❖ Complementary applications:
  - Curative goal:
    - Increase the efficacy of the applied concomitant treatment
    - Resensitize the tumor even in refractory state.
  - Palliative goal:
    - Pain reduction
    - Increase the quality of life

- ❖ **Monotherapy:**

Only when other conventional therapy is non-applicable, (organ failure, labor-results, refractory state, no result expected by conventional therapies, psycho-resistance, other reasons not considering conventional therapies).

## Basic treatment conditions

- ❖ First conventional therapy must be applied if possible
- ❖ Personal adjustment
- ❖ No daily hyperthermia treatment, except potentiation
- ❖ Oncothermia is complementary therapy with well-known others
- ❖ Step-up heating is necessary for combined therapies. (The rate of growth is decided by the tolerance of patients.)
- ❖ Step-down heating is necessary for monotherapy. (The rate of decrease decided by the tolerance of the patient.)
- ❖ Modulation adaptation is necessary for sensitive (brain) treatments.
- ❖ Relaxed conditions have to be formed around the patient
- ❖ Not too long, not too short effective treatment time (45-90 mins)
- ❖ Give information to the patient and relatives about the dose (energy) only at the end of the treatment. No temperature or other parameters are open for them during the session.

## Oncothermia synergy with radio-therapies

Oncothermia has to be carefully fitted to the blood-perfusion and neo-vascularization of the actually treated tumor. It could be applied before or after the radio treatment.

**Oncothermia is applied as potentiation before radiotherapy** when the blood-flow is not satisfactory. Low dose (also fraction) of **oncothermia is given before** every radiotherapy fractions.

Example (fractional radiotherapy):

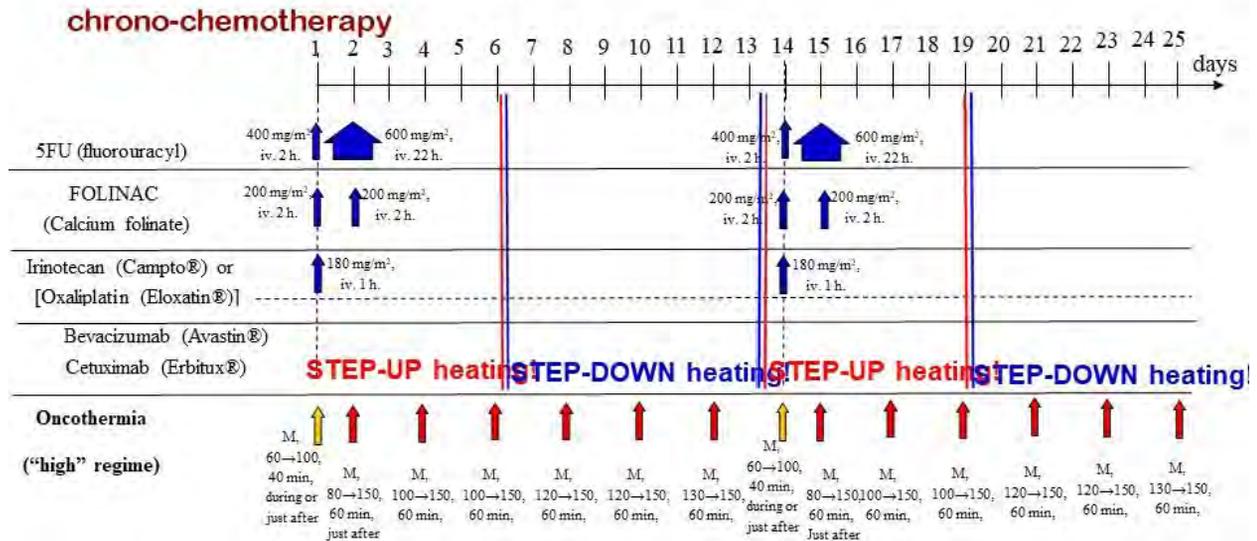
Day	1   2   3   4   5   6   7   8   9   10   11   12   13   14   15   16   17   18   19   20   21   22   23   24   25   26   27   28   29   30   31   32   33   TOTAL:																																			
	Oncothermia before fractional radiotherapy																								<b>STEP-UP heating!</b>											
Electrode	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	80→140W
D <sub>01</sub> , kJ	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	180	4500 kJ
T, min	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	750 min
	Fractional radiotherapy as soon as possible, but <b>not more than 30 min</b>																																			
D <sub>01</sub> , Gy	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	50 Gy

**After the fractional potentiation** oncothermia **can be applied** in its complete protocol every second day (**rarely done**).

	<b>STEP-DOWN heating!</b>																				
Electrode	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	↑	80→140W
D <sub>01</sub> , kJ	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	380	5700 kJ
T, min	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	60	900 min

## Chrono-chemotherapy (e.g. DeGramont protocol)

“(applied in the National Institute of Oncology, Budapest, Hungary)”



## Contraindications

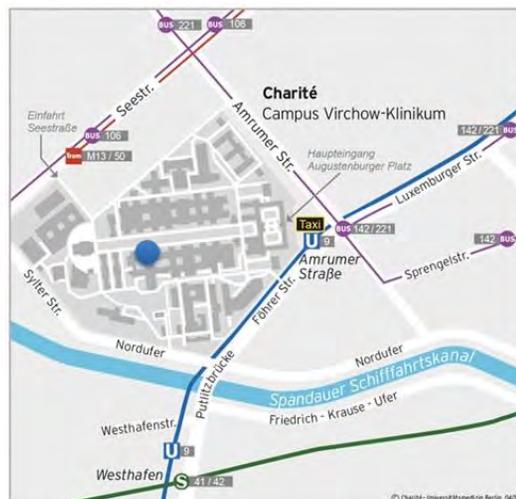
- **Pacemakers / field sensitive devices**  
(depends on the actual ESM standard and the position of the treatment)
- Patients who are **unable to communicate the complains**
- Conditions, e.g. **epilepsy**, sensitive to electromagnetic fields
- Patient has immune-suppression due to organ-transplant
- When the patient is not able to form the position for the treatment
- **DON'T** treat **pregnant** women.

## Precautions BE CAREFUL!

- The applicator should not be applied over **open wounds**.
- Tumors close to **large metallic implants** should be treated with caution.
- Treatment is prohibited through any **implantation** by plastic surgery (like breast implant)
- Patients with acute systemic or localised **infections or inflammatory** processes.
- **Elderly** patients have a higher pain under the heavy applicator.
- Areas in which there is a large amount of **fat** must be closely monitored for surface burns and subcutaneous fibrosis.
- Thick **hair** in the treated area (hair, pubic hair, etc.).
- **Fluid** may affect the energy distribution (e.g. urine or ascites).
- The applicator has to be fixed **correctly**
- When the applicator is over a volume having **low blood-flow**.

## OPEN DISCUSSION AND CONTRIBUTION

szaszam@gmail.com



THANK YOU

# **Oncothermia and the paradigm shift in integrative oncology**

**Alfred J. Barich<sup>1</sup>, Lazaros Daniilidis<sup>2</sup>, Michael Marangos<sup>3</sup>, Aias Papastavrou<sup>4</sup>, John Vakalis<sup>5</sup>,  
Petros Kouridakis<sup>6</sup>, Valentini Natsouki<sup>7</sup>**

<sup>1</sup>President Hellenic Society for Integrative Oncology/AHEPA University Hospital/Oncothermia Center Thessaloniki

<sup>2</sup>Oncothermia Center Thessaloniki

<sup>3</sup>Radiation Oncologist/ Oncothermia Center Thessaloniki

<sup>4</sup>Oncothermia Center Athens

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<sup>6</sup>Oncothermia Center Thessaloniki /424 Military Hospital

<sup>7</sup>Oncothermia Center Thessaloniki

**Presented at 36<sup>th</sup> ICOS, Budapest, 2018**

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[www.oncothermia-](http://www.oncothermia-)

[journal.com/journal/2018/Oncothermia\\_and\\_the\\_paradigm\\_shift.pdf](http://journal.com/journal/2018/Oncothermia_and_the_paradigm_shift.pdf)

## **Oncothermia and the paradigm shift in integrative oncology**

**Dr. Alfred J. Barich<sup>1</sup>, Dr. Lazaros Daniilidis<sup>2</sup>, Dr. Michael Marangos<sup>3</sup>, Dr. Aias Papastavrou<sup>4</sup>,  
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### **Abstract**

We are all aware of the Phase III trials with chemotherapy and Hyperthermia vs chemotherapy alone and radiation therapy with Hyperthermia vs radiation therapy alone. All the trials indicated statistically significant differences (almost doubling of the response rates) in favor of the combination arm. The difference with Conventional vs Integrative approach to cancer treatment is similar to the differences of Conventional Hyperthermia and Oncothermia. What do we expect to see when we combine Integrative Oncology with Oncothermia? This is an analysis of the results of an Integrative Oncology Center, using an Oncothermia flagship in conjunction with a quantitative molecular/genetic analysis of the patients' cancer cells. Integrative Oncology is forcing a paradigm shift in the treatment of cancer. When Oncothermia is included in the therapeutic strategy as a flagship for the integrative therapeutic strategy, the shift is intense. Patients are demanding more from their Oncologists beyond the Triad of Surgery, Radiation therapy and Chemotherapy. This is true for the other fields of Medicine as well, and this led to the creation of CAHCIM (Consortium of Academic Health Centers for Integrative Medicine). The demand of not only patients, but Medical Students as well, led to the formation of this Organization which has enlisted High profile institutions such as Harvard Univ., Dukes Univ., Mayo Clinic, Stanford University and many more. The establishment of CTCA (Cancer Treatment Centers of America) all across the USA, is proof of this Paradigm Shift). The combination of modulated electro Hyperthermia (Oncothermia) with a targeted approach to cancer cell kill based on molecular/genetic sensitivities, as well as targeting the cancer cell microenvironment by oxygen perfusion of the tissues (autologous ozonated blood transfusion) and tissue alkalinization (IV bicarbonate infusion) in conjunction with high doses of IV vitamin C has led to unprecedented increase of response rates and TTP. Herein we analyze these findings and propose multicentric randomized trials in centers that use mEHT.

36<sup>th</sup> ICHS CONGRESS  
BUDAPEST  
September 28-29 2018



HELLENIC SOCIETY FOR INTEGRATIVE  
ONCOLOGY

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HELLENIC SOCIETY FOR  
INTEGRATIVE ONCOLOGY  
**H.E.I.S.O.**

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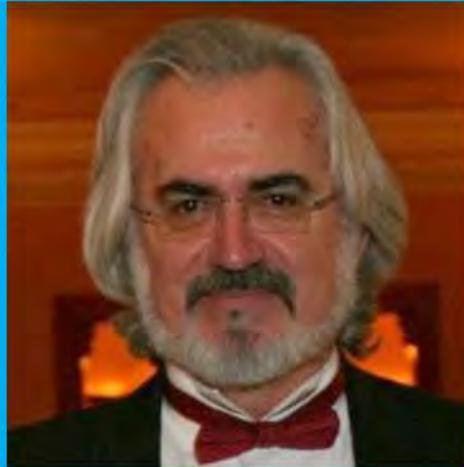


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ΕΛΛΗΝΙΚΗ ΕΤΑΙΡΙΑ  
ΕΣΑΤΟΜΙΚΕΥΜΕΝΗΣ ΟΓΚΟΛΟΓΙΑΣ  
**ΕΛ.ΕΤ.ΕΣ.Ο**

---

Dr. Alfred J. Barich  
President Hellenic Society for Integrative Oncology  
Chairman of Scientific Advisory Board for Hellenic Society for  
Hyperthermic Oncology



## **ONCOTHERMIA AND THE PARADIGM SHIFT IN INTEGRATIVE ONCOLOGY**

**Dr. Alfred J. Barich** (President Hellenic Society for  
Integrative Oncology/AHEPA University  
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## CONFLICT OF INTEREST

THE AUTHORS HAVE CONFLICT OF INTEREST WITH THE PREVAILING MENTALITY OF CANCER TREATMENT

# WHAT IS INTEGRATIVE ONCOLOGY AND HOW DOES ONCOTHERMIA CONTRIBUTE TO PATIENT RESPONSE

DR. ALFRED J. BARICH

Surgeon – Integrative Oncologist

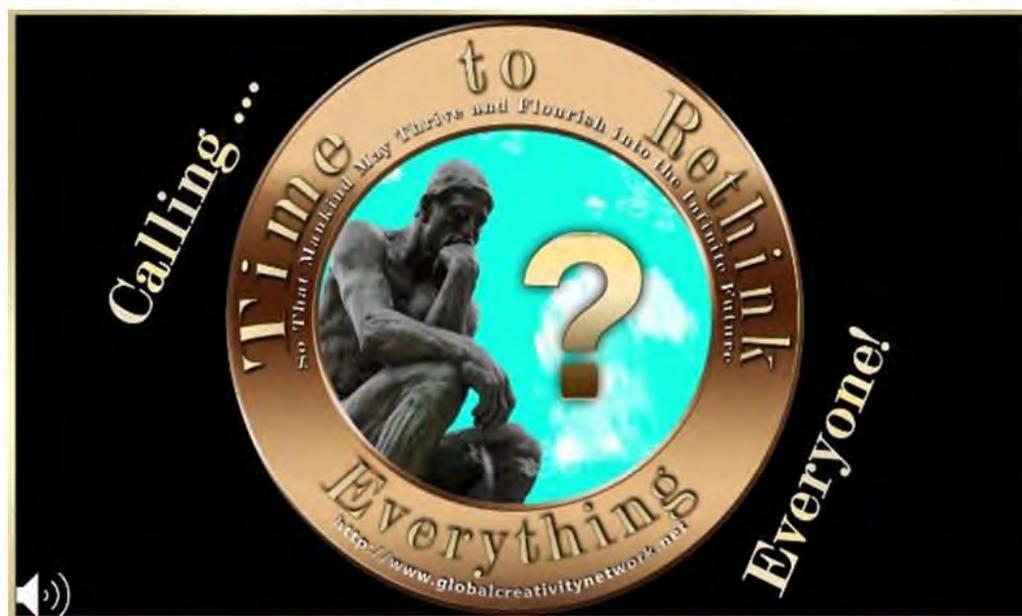
President Hellenic Society for Integrative Oncology

Member of New York Academy of Sciences

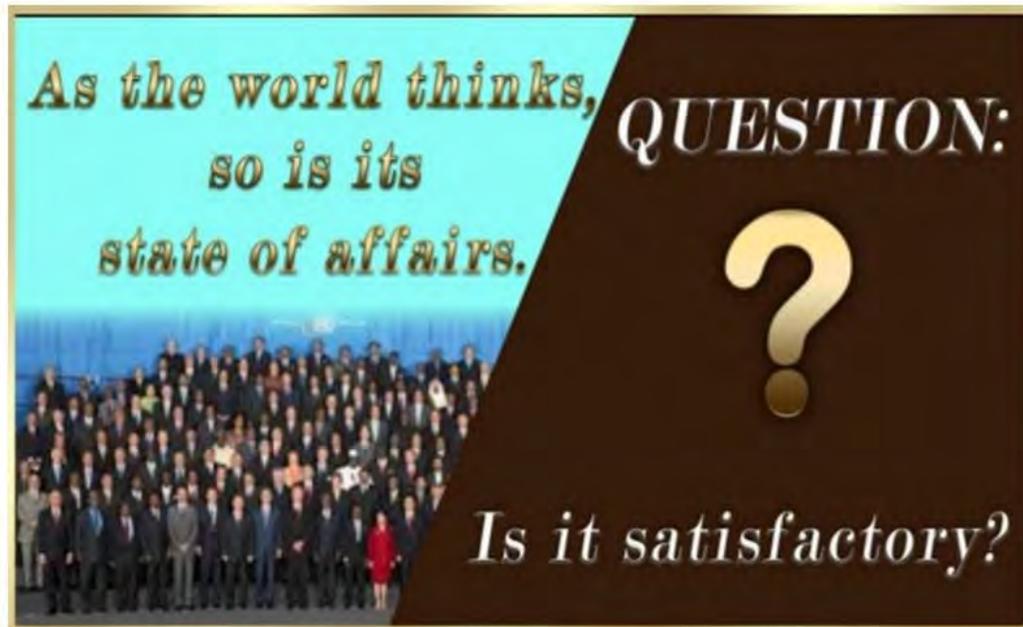
Member of European Association for Cancer

Research

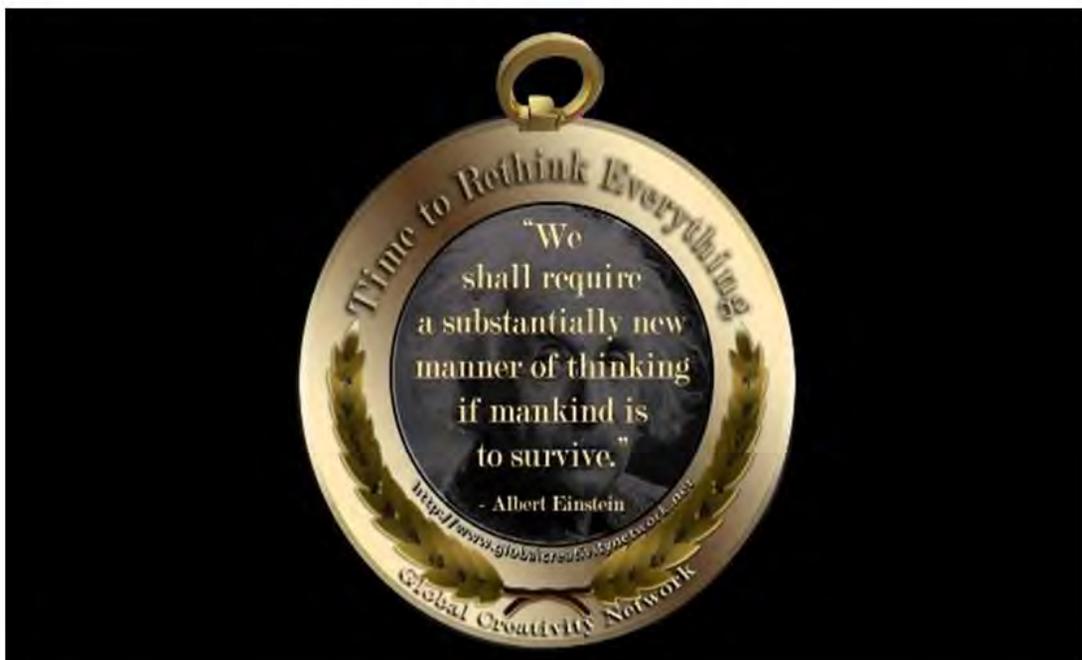
A NEW START WITH A NEW PHILOSOPHY  
AND A NEW PARADIGM WILL PREVAIL



PROGRESS COMES FROM THINKING OUT  
OF THE BOX



CURRENT MEDICINE FAVORS PROTOCOLS  
AND NOT PATIENTS



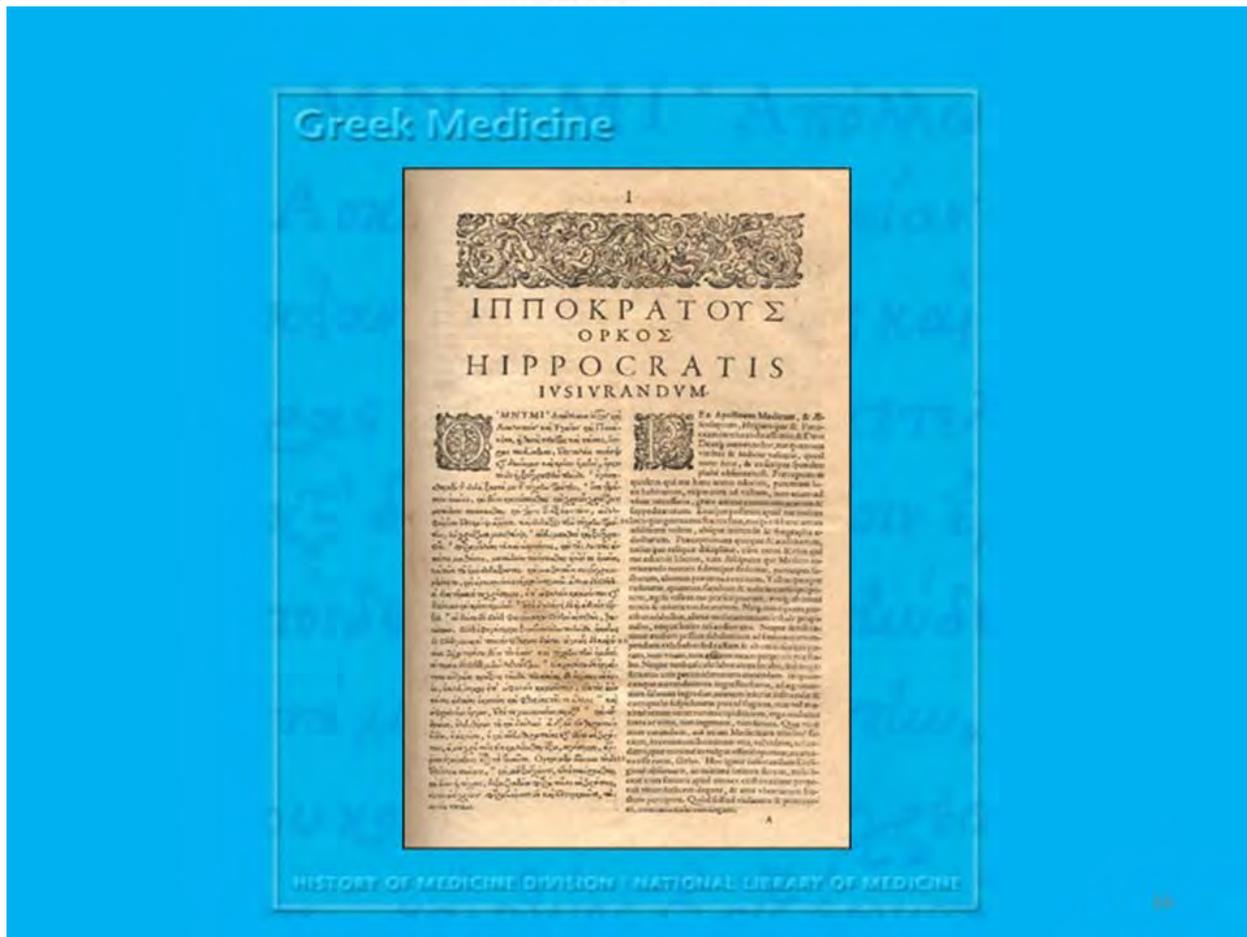
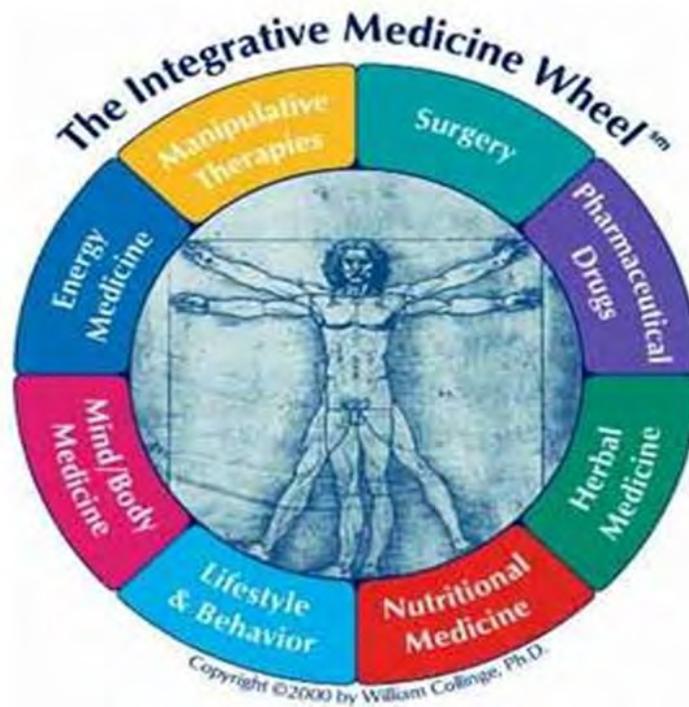
## THINKING GLOBALLY AND ACTING LOCALLY



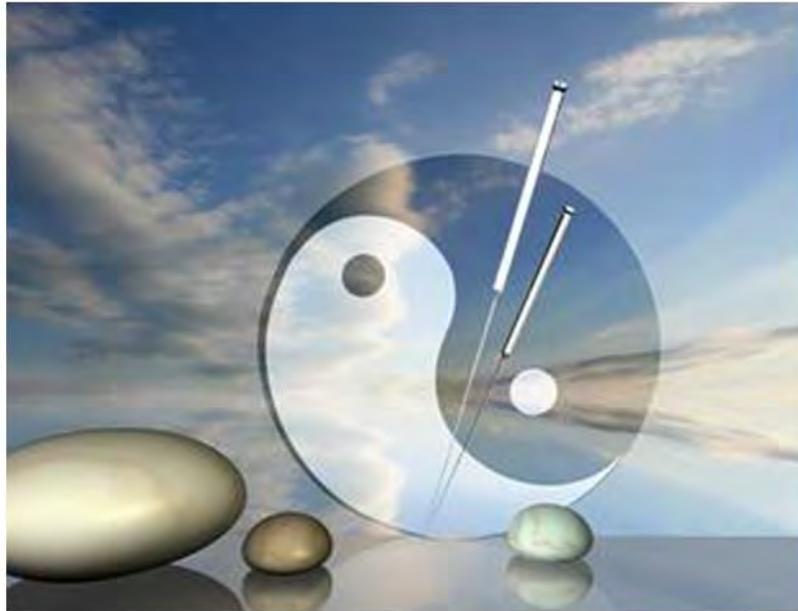
## WE MUST LEARN FROM OUR MISTAKES



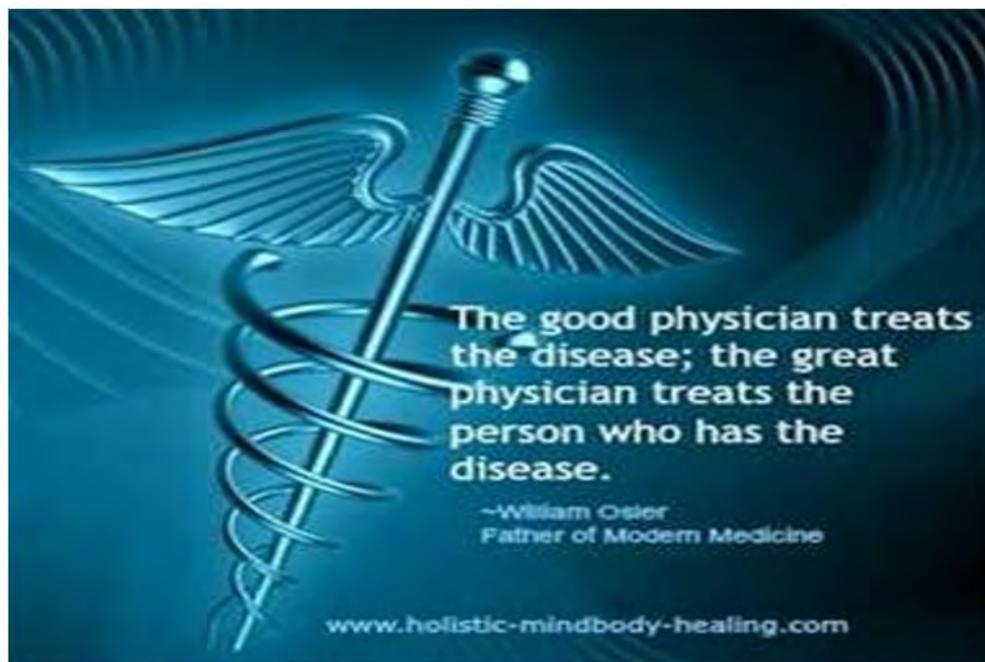
# MEDICINE MUST BE INCLUSIVE AND NOT EXCLUSIVE



WE MUST COMPLEMENT NATURE AND  
NOT FIGHT IT



THE PATIENT MUST BE AT THE CENTER OF  
OUR FOCUS



## A TOAST TO HEALTH

### BOWL OF HYGEIA

The bowl with a snake coiled around it is called the bowl of Hygeia with the serpent of Epidaurus, and is a variant on the above. Hygeia was Aesculapius's daughter and a Greek Goddess of health. Her symbol was a serpent drinking from a bowl. The vessel is usually depicted with a long stem and a shallow, wide bowl as seen here. It also is considered suitable for pharmacy. The bowl of Hygeia with serpent of Epidaurus shown here is the symbol for Hungarian pharmacists.



## Integrative Medicine

Integrative medicine combines biomedical care with appropriate complementary therapies, to heal and preserve the health of the patient's body, mind, and spirit.

It emphasizes the individual's capacity for self-healing and offers an approach to care that is personalized, collaborative, and comprehensive. This approach is interdisciplinary and utilizes the skills of other health care disciplines and professionals through referral and consultation.

***Consortium of Academic Health Centers for Integrative Medicine***



## CAHCIM Members

- **Albert Einstein/Beth Israel**
- **Columbia University**
- **Duke University**
- **George Washington**
- **Georgetown**
- **Harvard**
- **Laval University**
- **Mayo Clinic**
- **OHSU**
- **Stanford University**
- **Yale University**
- **Wake Forest University**
- **University of Alberta**
- **University of CA/Irvine**
- **Thomas Jefferson**
- **UMDNJ**
- **University of Arizona**
- **University of Calgary**
- **University of Hawaii**
- **University of Washington**
- **University of California/LA**
- **University of California/SF**
- **University of Colorado**
- **University of Connecticut**
- **University of Kansas**
- **University of Maryland**
- **University of Massachusetts**
- **University of New Jersey**
- **University of New Mexico**
- **University of North Carolina-Chapel Hill**
- **University of Michigan**
- **University of Minnesota**
- **University of Pennsylvania**
- **University of Pittsburgh**
- **University of Texas-Galveston**
- **University of Vermont**
- **University of Wisconsin**

## INTEGRATIVE ONCOLOGY



.. Because humans are different!

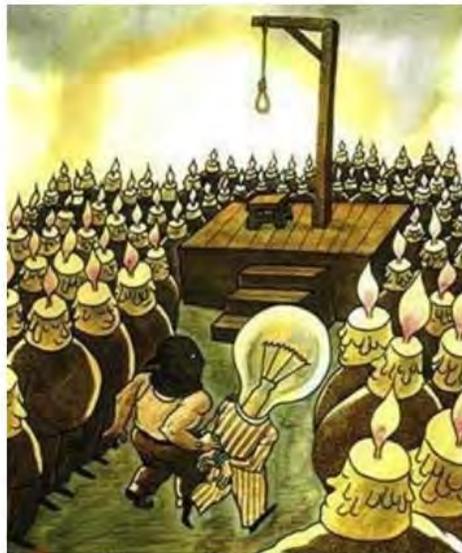
## The Phases of Integrative Oncology



**THE STRUGGLE TO INTRODUCE NEW  
IDEAS AND APPROACHES IS OFTEN  
UNEVEN**



**TRYING TO INTRODUCE NEW IDEAS IS OFTEN  
MET WITH HOSTILITY**



YOU CAN FIGHT PROGRESS AND CHANGE ...BUT YOU  
CAN'T STOP THEM !!  
TODAY, BASTIONS OF CONSERVATISM ARE SLOWLY  
INCLUDING DEPARTMENTS OF INTEGRATIVE  
ONCOLOGY IN THEIR HOSPITALS...  
THE PARAGIGM SHIFT HAS BEGUN

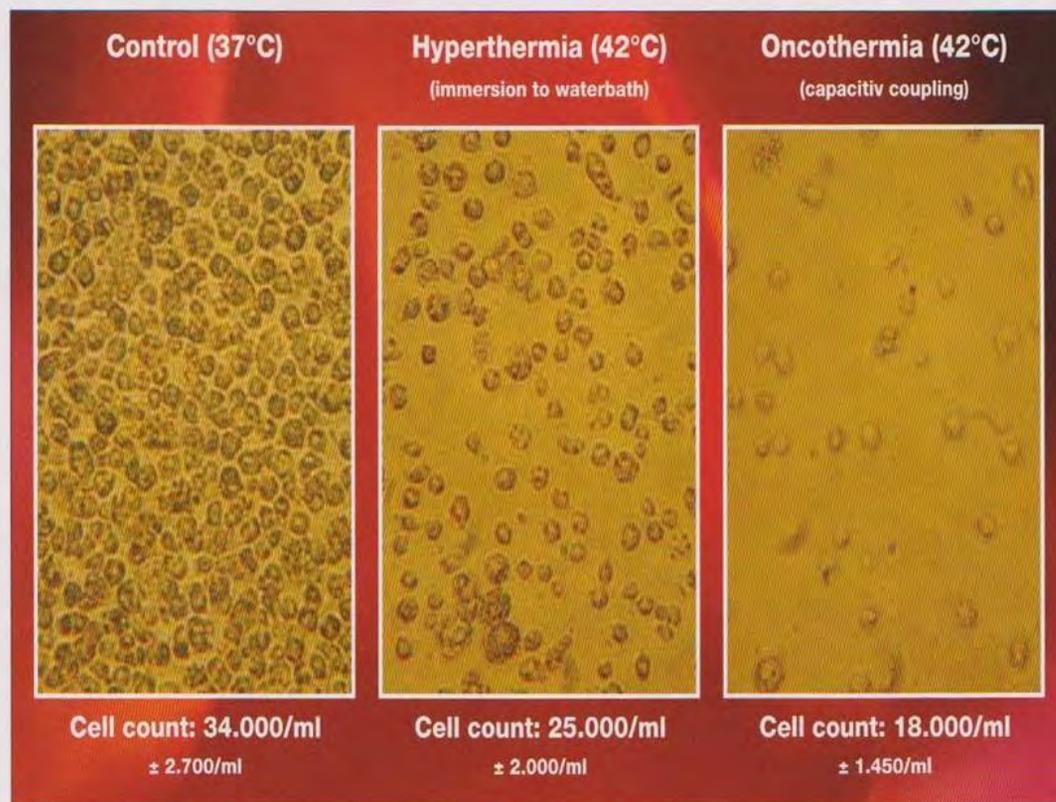


## **COMPLEMENTARY AND ALTERNATIVE MEDICINE... LEADING TO INTEGRATIVE ONCOLOGY**

- “Complementary and Alternative Medicine is a Group of Diverse Medical and Health Care Systems, Practices, and Products That are Not Presently Considered Part of Conventional Medicine”

National Center for Complementary and Alternative Medicine

# ONCOTHERMIA – A STRATEGICAL ADDITION TO THE ARSENAL AGAINST CANCER



## R.G.C.C GROUP

Meeting and delivering the highest standards of excellence to the clinical, R&D and Pharmaceutical sectors across the globe.

# Individual Cancer Treatment Based On Liquid Biopsy



HP Florian Schilling

[www.sanomni.eu](http://www.sanomni.eu)

## Circulating Tumor Cells: Liquid Biopsy of Cancer

Catherine Alix-Panabières; Klaus Pantel

 **Clinical Chemistry**, Volume 59 (1): 110 – Jan 1, 2013

Overall, there is increasing evidence that CTCs reflect cancer progression in real time and that this information may be particularly helpful in the context of systemic therapies. In the future, CTC characterization is expected to contribute to guiding specific targeted therapies to a defined population of cancer patients within a certain therapeutic window—which is the hallmark of personalized medicine.

## COMPARATIVE METHODS

	Beads Based Method	PCR Based Method	R.G.C.C.	Microscopy Based Method	Gradient
<b>Method of Isolation</b>	Magnetic Beads (antibodies with iron particles)	PCR based method which need to destroy the cells in order to identify one marker (mainly panCK or Epcam)	Flow cytometric sorting with interrogation in droplets in ratio of droplet per cell (1:1)	Immobilizing cells on a slide and staining	The cells are isolated based on size
<b>Purity of CTCs</b>	Enrichment method and not isolation method	There are no cells any more	<b>Purity is higher than 97-99% (isolation method)</b>	The CTCs are simply stained not isolated	It is an enrichment method
<b>Viability of the Isolated cells</b>	70-85%	No cells	<b>Viability &gt;99%</b>	NO viable cells remain	Questionable
<b>Quality of CTCs for further analysis</b>	Inappropriate for further molecular analysis due to lymphocyte contamination	Limited for further molecular analysis	Appropriate for further molecular analysis since there is no noise	The CTCs are no longer viable	Not recommended for further studies
<b>Selection of CTCs</b>	Based mainly in positive selection of CTCs in a few number of markers	Based on positive selection	Based on negative and positive selection in order to identify and secondly immunophenotyping CTCs	Possible selection method	Based on size
<b>Further abilities</b>			Identification of heterogeneity of CTCs	The identification of heterogeneity depends of the selected markers	Identification of heterogeneity of CTCs
<b>Additional features</b>	Method only to enumerate CTCs	Method to enumerate CTCs and identify only very limited features of CTCs	Method which allows to perform gene expression assays and determine features vital for therapy scheduling	A method for detection and enumeration only	

R.G.C.C. International GmbH  
Headquarters  
Baarstrasse 95, Zug 6301

ASSESSMENT REPORT

1 / 2



### R.G.C.C.-RESEARCH GENETIC CANCER CENTRE LTD

#### Assessment of the results:

<b>Patient Name:</b> Ms Janja Cotar	<b>Type of cancer:</b> breast
<b>Physician:</b> Dr Schilling Florian	<b>Stage:</b> N/A

**Risk of relapse:**

CTC concentration  
Measured: isolated 9.3cells/7.5ml, SD +/- 0.3cells  
Cut off point <= 5cells/7.5ml

**Resistance markers:**

MDR1: 65%  
MRP: 55%  
LRP: 2%  
GST: 25%

**Metastases/angiogenesis risk related markers**

FUNCTION	CLINICAL RISK	MARKERS	RESULTS	OUTCOME
Migration-invasion	HIGH RISK	MMPs	35%	HIGH RISK
		KISS-1-r	normal	LOW RISK
		Nm23	-25%	HIGH RISK
Angiogenesis	HIGH RISK	VEGFr	35%	HIGH RISK
		FGFr	40%	HIGH RISK
		PDGFr	35%	HIGH RISK

**Proliferation related markers:**

MECHANISM	CLINICAL RISK	MARKERS	RESULTS	OUTCOME
Signal transduction pathways	HIGH PROLIFERATIVE SIGNAL	Ras/raf/MEK/Erk1-2	30%	HIGH RISK
		mTOR	35%	HIGH RISK
		EGFr	40%	HIGH RISK
Growth factor receptors	HIGH PROLIFERATIVE SIGNAL	TGF-β1/2	55%	HIGH RISK
		c-erb-B2	normal	LOW RISK
		Progesterone Receptor	normal	LOW RISK
Hormone receptors	HORMONE INDEPENDENT	Estrogen Receptor	normal	LOW RISK
		NC3R4-A	normal	LOW RISK
		NC3R4-B	normal	LOW RISK
Cell cycle rate	RAPID	P27	20%	LOW RISK
		P16	35%	HIGH RISK
		P53	35%	HIGH RISK

**Resistance phenotype markers:**

MARKERS	RESULTS	OUTCOME	PHENOTYPE
Dnmt1	normal	LOW RISK	NON RESISTANT
06-methyl-DNA-tran.	normal	LOW RISK	
HAT	normal	LOW RISK	
Histone deacetylase	normal	LOW RISK	

**Radiotherapy/Hyperthermia sensitivity:**

Marker	Result (%)	Clinical outcome per marker	Clinical outcome
HSP90	-35%	SENSITIVE	SENSITIVE
HSP72	-10%	SENSITIVE	
HSP27	-25%	SENSITIVE	

**Follow-up options:**

YES	✓
NO	

**Time interval (when)**

After 3 months	After 6 months	After 12 months
✓		

## Steps of therapy

1. Bring down resistance
2. Introduce cytotoxic procedures
3. Take care of the immune system

## RESISTANCE

Antisense  
Metabolic inhibitors  
KD  
HDS  
Quercetin  
Piperin

## CYTOTOXIC PROCEDURES

IPT  
TACE  
TACP  
Biological substances

## IMMUNOTHERAPY

DC  
MOAB  
GcMAF

# RGCC/ BIOMED AID

RGCC technology enables the application of Integrative Oncology to our patients, giving them completely Targeted Therapeutic Strategy Options

Integrative Oncology without RGCC molecular profile places us in the position of Conventional Oncology (giving our patients therapeutic options based solely on STATISTICS but never knowing before hand on which side of the statistics they will be...).



RGCC technology is revolutionizing the practice of Oncology and BIOMED AID enables application of advanced Biotechnology.

## CONCLUSIONS

THERE IS A PARADIGM SHIFT IN CANCER RESEARCH  
EMPHASIS IS BEING PLACED ON TARGETED THERAPIES  
HYPERTHERMIA IS GAINING GROUND IN THE MAJORITY OF  
PUBLISHED STUDIES AS WELL AS CELL THERAPIES WITH  
DENDRITIC CELLS

ONGOING STUDIES FOCUS ON COMBINED MODALITY  
TREATMENTS INCLUDING COMBINATIONS OF  
CONVENTIONAL RT WITH HT AND CT WITH HT

LIQUID BIOPSIES GIVING US FULL MOLECULAR  
PROFILES OF CANCER CELLS AND EXPOSING THEIR  
RESISTANCE MECHANISMS AS WELL AS THEIR  
SENSITIVITIES HAVE MADE THE FLEETING IMAGE OF  
COMPLETELY TARGETED THERAPIES A REALITY. MORE AND  
MORE RESEARCH INTO BIOLOGICAL AND NATURAL  
AGENTS HAVE ENABLED LESS TOXIC APPROACHES.



## Vitamin C and Hyperthermia

**Enhancement of radical intensity and  
cytotoxic activity of ascorbate by  
hyperthermia.**

The combination of hyperthermia and ascorbate  
treatment might produce higher antitumor  
activity.



Satoh K, Sakagami H, Nakamura K  
Anticancer Res; 16(5A):2987-91 1996

## Oncological Studies at Universities II

### Phase I/II studies at Roswell Park Cancer Institute Buffalo, E Repasky, W Kraybill

Phase 1- Study of Fever-Range Whole-Body Hyperthermia in Patients  
with Advanced Solid Tumours

⇒ Int J Hyperthermia, 2002, VOL.18, NO.3

Phase 1- Study of Doxil with Long Term Low Level WBH

⇒ Abstract STM 2007

### Phase I/II studies at Univ. of Texas, Medical School at Houston, JM Bull

FR-WBH + Cisplatin (CIS) + Gemcitabine (GEM) + Metronomic, Low-Dose Interferon-  
alpha

CIS 24h before FR WBH/GEM

Running protocol with various tumor entities, mainly pancreatic cancer

⇒ Int J Hyperthermia, Dec 2008

⇒ <http://www.uth.tmc.edu/thermalthrapy/>

## **Breast CA (Jones et al 2007 + 2005 Duke Univ.)** randomised Phase III and Phase I Trials

2007

109 Patients with breast CA close to skinsurface

**Comprehensive response rate of 68,1 % (radiation + HT)  
vs. 42,3% (radiation alone)**

**Most significant difference with patients previously radiated :  
68,2% in radiation+ HT  
vs. 23,5 % radiation alone**

*( Jones et. al., Journal of Clinical Oncology Vol. 23, No 13, May 1, 2005.)*

In an extension using thermo-sensitive Liposomen as carrier of Doxorubicin running as phase I trial, the authors came to a cautious conclusion, that here as well hyperthermia with a liposomal-thermosensitive chemotherapy seems to enhance „anti-tumor-effects“ . (Jones et al, June 2007, 24th Annual Meeting of ESHO, Prag, Abstracts S. 11)

## Cervix Tumor (Van der Zee, Franckena et al)

2007

(randomised Phase III trial incl. Follow-Up)

Follow-Up : long time survival after 12 years

58 Patients (Rad.+HT) vs. 56 Patients (Rad. alone)

- \* Better lokal Control: **36 % (radiation alone)**  
**vs. 56 % (radiation + HT)**
- \* overall Survival after 12 years: **20 % (radiation alone)**  
**vs. 37 % (radiation + HT)**  
(at p= 0,02)

(Franckena et al, June 2007, 24th Annual Meeting of ESHO, Prag, Abstracts S. 18)

Bezug auf: Van der Zee J, Gonzalez Gonzalez D, van Rhoon GC, van Dijk JD, van Putten WL, Hart AA. Comparison of radiotherapy alone with radiotherapy plus hyperthermia in locally advanced pelvic tumors: a prospective randomized multicentric trial. *Lancet* 200; 335: S.1119-1125

## Hyperthermia successes:

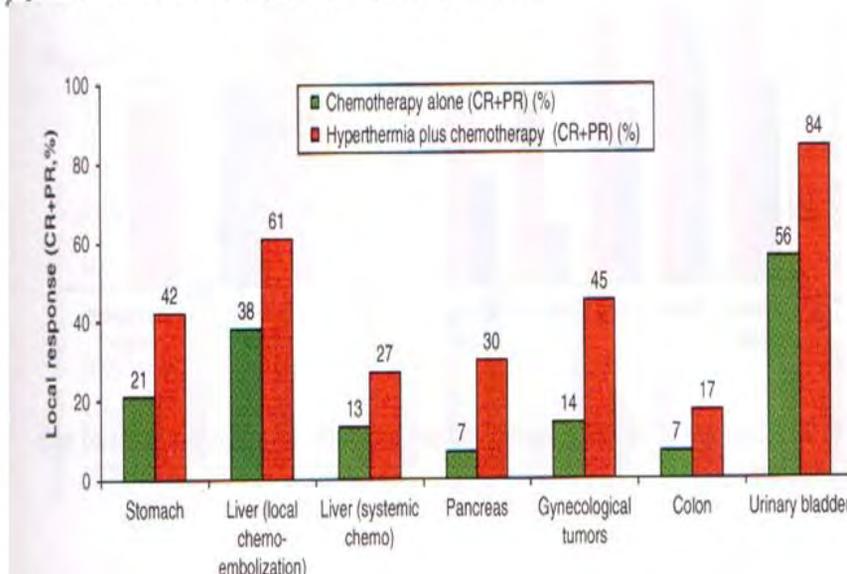
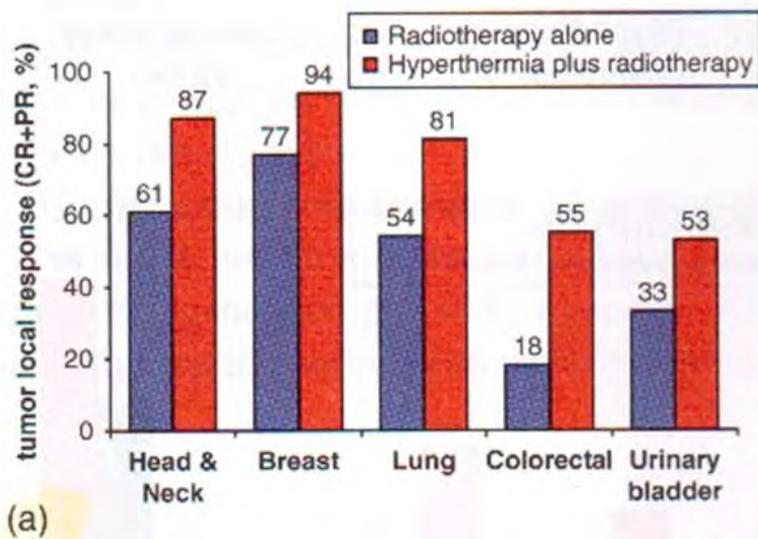
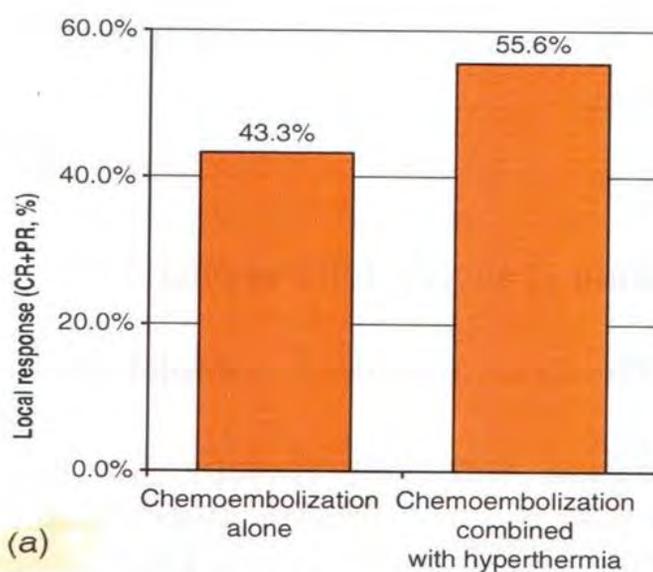


Fig. 2.20 Local response of hyperthermia plus chemotherapy compared to chemotherapy alone. (Chemotherapy is mostly Adriamycin, Bleomycin, Cisplatin, Mitomycin, and 5FU), (Hyperthermia 40–60 min, capacitive, 8 MHz, 4–16 lesions)



Summary of the results obtained in Japan by capacitive hyperthermia combined with radiotherapy.

Hepatocellular carcinoma and metastatic tumors of the liver.



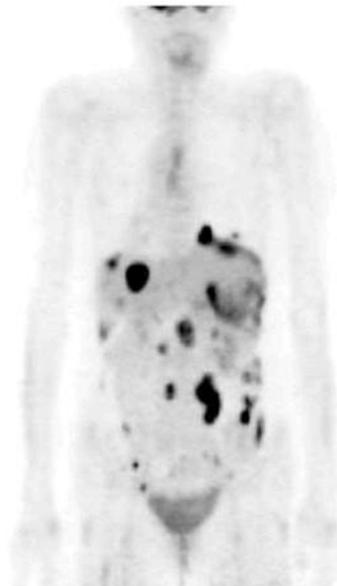
# Trials in combination with radiation therapy

Tumorart	Anzahl der Studien.	Anzahl Patienten /Regionen	Strahlentherapie allein (%)	Strahlentherapie + Hyperthermie (%)	Odds ratio (95% CI) (CI-Confidence ratio)
Breast	2	143	67	68	1.06 (0.52–2.14)
Chest Wall	4	276	38	59	2.37 (1.46–3.86)
Cervix	4	248	52	77	3.05 (1.77–5.27)
Rectum	2	258	9	19	2.27 (1.08–4.76)
Bladder	1	101	51	73	2.61 (1.14–5.98)
Prostata	1	49	79	81	1.16 (0.28–4.77)
Melanom	1	70/128	31	56	2.81 (1.36–5.80)
Head & Neck	5	274	33	51	2.08 (1.28–3.39)
Diverse	3	442	34	39	1.24 (0.84–1.82)
All Studies	23	1861	38	52	1.80 (1.50–2.16)

Journal of Clinical  
Oncology 19: 2007  
Horseman/Overgaard

Meta-Analysis  
on radiation alone  
versus radiation  
plus hyperthermia

The authors concluding: if taken all these clinical results (1861 Patienten from 23 Studies) it shows a highly significant benefit ( $P < 0.0001$ ) that confirms the rationell of a combined efficacy of radiation with hyperthermia. That result stands besides the fact that there were quite different treatment protocols in the various tumor entities (dito p.423).



**Figure 1**

SM's PET-Scan taken in January 2007  
The PET-Scan shows a massive infiltration in the peritoneum, the lymph nodes, liver, and spleen. The patient was at this time untreatable because of multidrug resistance.

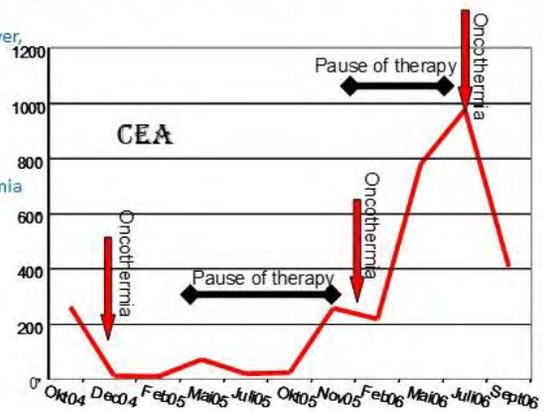


**Figure 2**

SM after treatment at St. George Hospital with two whole body hyperthermias, local hyperthermia, and a complementary nontoxic cancer treatment program. No hot spots are visible; patient is in a complete remission. See also Figure 3.

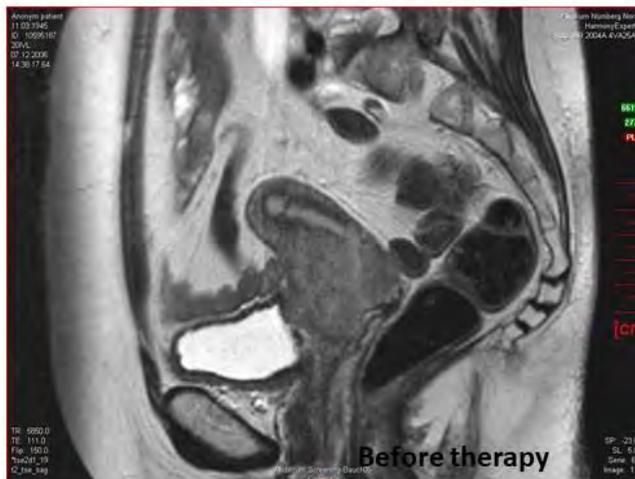
# Colon (transversum) carcinoma

**Investigator:** Prof.H.Kirchner  
**Department:** Department of Hematology & Oncology, Hospital Siloah, Hannover, Germany  
**Patient:** B.Z. 61 y, male  
**Diagnosis:** Colon transversum carcinoma, Sep.2004,  
**Surgery:** Hemicolektomie,  
**Tumor classification:** pT4, pN2, M1 (Liver);  
**Therapy (1):** Oxalyplatine, Leukovorine, 5-FU (Oct.2004-Apr.2005),+ oncothermia on liver Dec.2004.  
**Therapy (2):** Erbitux, Campto (Mar.2006) + oncothermia on liver  
**Result (1):** Good partial remission (PR) (May.2005-Mar.2006)  
**Therapy-pause**  
**Result (2):** Progressive disease (PD)  
**Therapy (3):** Erbitux, Campto (Jul.2006-Oct.2006) + oncothermia (liver)  
**Result (3):** Good partial remission (PR) tumor and tumor marker regression, became normal



# 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:** 12/06-01/07 bimodality therapy, Radiotherapy: 50.4 Gy; (5x1.8 Gy/weeks); oncothermia: 6 sessions.  
**Control:** 3 months later hysterectomy (Wertheim).  
**Result:** pathologically complete remission ypT0ypN0



# Intrahepatic bile-duct carcinoma

**Investigator:** Dr. A.Csejtey & Mr.P.Lorentz

**Institution:** Markusovsky Hospital, Szombathely, Hungary,

**Diagnosis:** Intrahepatic bile-duct carcinoma, inoperable

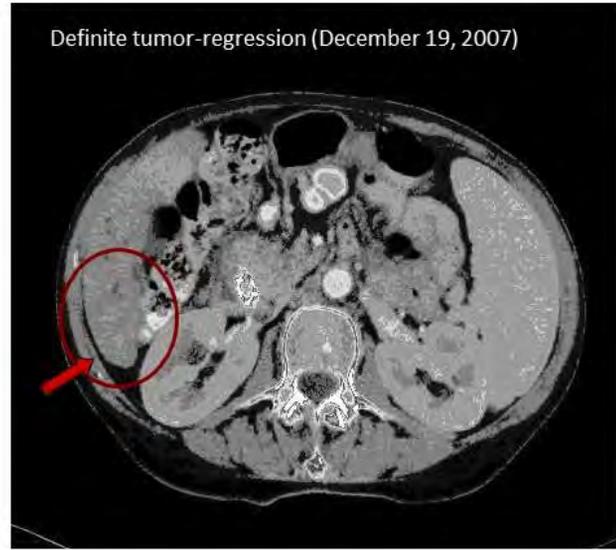
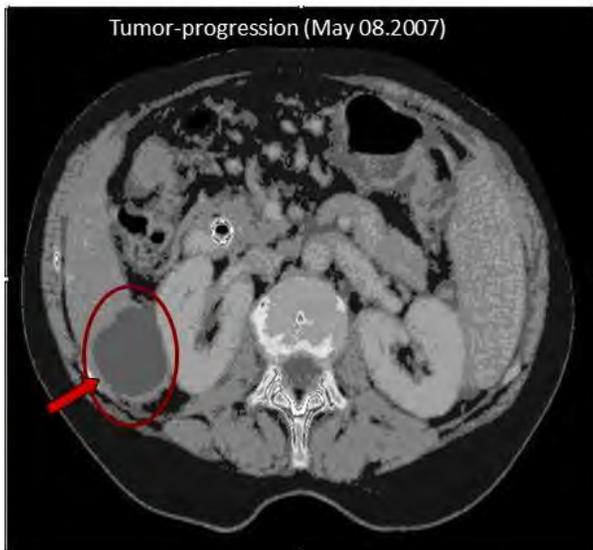
**Therapy:** Oncothermia as monotherapy with concomitant supportive vitamins only.

Due to the patient's status, no any other therapies was possible. Oncothermia started (June14.2007)

**Prognosis:** overall median survival 6 months

**Results:** Complete remission (CR)

**Follow up:** last checkup Sept. 2009, symptom-free, tumor-free



A PATIENT OF OURS WITH MULTIPLE PULMONARY METASTASES WHO HAD A COMPLETE REMISSION IN 6 MONTHS WITH INTEGRATIVE TREATMENT AND mEHT



## 6 MONTHS LATER



### **HIV-positive patient with multiple myeloma and Lymphoma from 2016. The role of mEHT.**

Patient with multiple myeloma and Lymphoma that started from the palate, with a history of immunosuppression(, AIDS). After 3 sessions of mEHT in June 2018, parallel to his chemotherapy, a remission of the disease was observed. At that point, he decides to interrupt mEHT and continue solely with chemotherapy. In the duration of stops in the middle of sessions and continue with chemotherapy. Results: The disease relapses and the extension of the disease into adjacent tissues. The patient returned in mid-August in the center of personalized Oncology and began anew his therapy with mEHT sessions. Today significant remission of the disease with mEHT as monotherapy, depicting extensive liquification of the previous tumors.

04/10/2017 status: (CT Visceral Cranium): "Invasive soft tissue CT 68 x 45 mm, with erosion of adjacent bone jaw citizens and lower parts of the sinuses. 12/02/2018 status: (CT Visceral Cranium): "Invasive CT soft tissue X22 44 mm, with erosion of adjacent maxillary bone and the lower parts of the sinuses. Multiple osteolytic masses in the bones of the skull and infiltration of soft tissue (meta-disease), the greater lesion is frontal right 29Ch28 mm.

Sensitivity to mEHT. Documented through measurement of levels of HSP'S (27, 72 and 90)

**CONCLUSION**-An Integrative Oncology Centre with hyperthermia should have very specific characteristics in order to meet the difficult challenges of the times. The ability to evaluate the molecular and genetic profile of individual cancer cells, creates a definite advantage and doubles the response rates of patients who have failed conventional treatment modalities. On the basis of our patients profiles it seems that 85% of the patients have sensitivity to Hyperthermia (as expressed by measuring HSP levels). Even patients undergoing chemotherapy (non targeted) continue to respond even when chemo is interrupted.

**SUBJECT:** the combination of ozone with mEHT in combination with blood alkalinization and high dose Vitamin C, in multiple metastatic bone disease from prostate Ca for control of disease symptoms and avoidance of the risk of further damage to the maxillary bone of Osteoradionecrosis due to RT (radiation therapy) in very extensive metastatic focus in the left mandible

**INTRODUCTION:** In prostate cancer of this stage it is common to see the presence of distant metastases. The situation becomes much more difficult when metastatic foci are identified in bones of the jaw. In the stage VI of prostate Ca, therapy must be highly personalized with the best supportive care of the patient to relieve symptoms of pain and avoiding automatic fractures and should include Hormonal manipulations, the use of bisphosphonate, Surgery, Chemotherapy and or radiotherapy. But we should not ignore and use hyperbaric oxygen (or ozone) where necessary to maintain as far as possible the quality of life in patients' daily lives as is in this case the mastication function.

Presentation incident: Patient 65 years with meta-disease of Prostate Biopsy 20/12/2014 Ca: AdenoCa 4 + 3 = 7/10 by Gleason 4/5/2018 State (CT-scanning): multiple bone lesions scattered the bones of the skeleton especially in the vertebrae and the pelvis and strong fixation of radiolabeled Tc on the left upper jaw, attributed to metastatic disease. Hormonal manipulations with the X-120 Geva formulations mg and 80 mg Firmagon Condition 8/8/2018 gave no response and added considerable morbidity (Medical radiological diagnosis) area #37, 38 teeth molars until the angle of the mandible and with the extended subperiosteal reaction (2.9 cm) with irregularly shaped core osteolytic imagery indicative metastatic flare. 8/8/2018 status: (CT of lumbar Spine): extensive osteoblastic and mixed lesions.

**METHODS:** the sensitivity to mEHT. Documented through measurement of levels HSP'S (27, 72, and 90).

Results: Date Value Comments 16/12/2014 100.20 PSA ng/ml ng/ml 05/01/2015 15.92 21/01/2015 2.18 ng/ml ng/ml 0.81 18/02/2015 18/12/2015 0.55 15/01/2016 0.27 ng/ml ng/ml ng/ml 11/03/2016 0.14 0.12 ng/ml 16/01/2017 07/04/2017 0.90 ng/ml ng/ml 27/04/2017 0.75 Total testosterone: 0.11 ng/ml ng/ml 09/02/2018 27.71 07/05/2018 281 ng/ml ng/ml 05/06/2018 176.5 Introduction the Oncothermia Center and starting with 2 y fields mEHT (abdominal covering prostate and lumbar areas, and the left mandible with extensive osteolytic disease) with O3 autotransfusion of Ozonated blood and Vitamin C and hormone therapy (LHRH analogue) with Bisphosphonates, in 6 weeks and impressive drop to 28 ng/ml PSA CT-scan "04/08/2018 significant improvement. Bone Scan also indicates clear response of osteolytic lesions. CURRENT PERFORMANCE STATUS: 85-95% (Karnofsky) vs 50% previously.

**CONCLUSIONS:** Even stage IV disease with very poor performance status can be treated with an Integrative approach using Oncothermia as a pivot point for therapeutic strategy.

## KEEPING BALANCES, FOR THE GOOD OF OUR PATIENTS IS OFTEN VERY DIFFICULT



**We are still sailing in uncharted waters and making new maps**



**IT'S JUST A MATTER OF TIME...**



**BEFORE WE SEE HAPPY PATIENTS!!**



**ALL WE HAVE TO DO IS TAKE THE LEAP!!**





## **INTEGRATIVE ONCOLOGY...THE DIFFICULT BUT RIGHT PATH**

“Two roads diverged in a wood, and I—  
I took the one less traveled by,  
And that has made all the difference”

Robert Frost, New England Wisdom

ALWAYS KEEPING OUR GOALS SKY-HIGH AND STRIVING TO  
ACHIEVE THEM

# **KÖSZÖNÖMA FIGYELMET**



# **Naturopathic Anti-Tumoral Treatment & 8 Year Survival Benefit Statistics: A Single-Centre Experience**

**Gurdev Parmar**

Integrated Health Clinic  
Fort Langley BC Canada

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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[www.oncothermia-journal.com/journal/2018/Naturopathic\\_anti\\_tumoral\\_treatment.pdf](http://www.oncothermia-journal.com/journal/2018/Naturopathic_anti_tumoral_treatment.pdf)

# **Naturopathic Anti-Tumoral Treatment & 8 Year Survival Benefit Statistics: A Single-Centre Experience”**

**Gurdev Parmar**

Integrated Health Clinic, Cancer Care Center, Fort Langley, B.C. Canada

## **Background**

There is a considerable amount of research supporting the use of hyperthermia as an adjuvant treatment in oncology. Both modulated electrohyperthermia (mEHT) and fever-range whole body hyperthermia (FR-WBHT) have been added to our adjuvant treatment of various cancer types. This study will present the findings of these treatments over the past 8 years in our integrative naturopathic oncology setting. There will also be a presentation of several exceptional case studies from this dataset, which will help illustrate the process by which these treatments are incorporated into an integrative treatment approach.

## **Methods**

mEHT was administered using the Oncotherm EHY-2000+, and FR-WBHT using the Heckel HT-2000.

## **Results**

An examination of the data from the past 8 years will be provided. mEHT has been administered to hundreds of patients with over 35 cancer types. Data elements include patient statistics, cancer group & type, treatment(s) used, adverse events, overall survival (OS), diagnostic imaging & blood test results. We have also now provided FR-WBHT to hundreds of patients and we have collected similar data in the evaluation of this treatment's benefit. An initial analysis of this data will be provided. A Best Case Series of several exceptional case reports will also be presented.

## **Conclusion**

mEHT and FR-WBHT are safe treatments with very few adverse events or side effects, allowing patients to maintain a high quality of life. Moreover, our initial data indicates that the addition of these therapies into an integrative oncology setting provides benefits to PFS and OS, as well as to QOL.

# Integrated Health Clinic Cancer Care Center

BRINGING HOPE TO CANCER CARE

## Naturopathic Anti-Tumoral Treatment & 8 Year Survival Benefit Statistics: A Single-Centre Experience

Fort Langley BC Canada



**INTEGRATIVE THERAPIES**

Exceptional Technology...The Right People...Uncompromising Care



IHC Cancer Care

## OUR MODEL

Integrative Cancer Care

### Integrative Cancer Care

Treating the Whole Patient



#### Primary Cancer Therapies

Cytotoxic treatments that also work with standard treatments improving efficacy & reduce SE's

#### Immune System Therapies

Therapies that improve immune management of cancer

#### Supportive Protocols

Managing the unique issues faced by each patient maximizing quality of life throughout their care

#### Prevention & Survivorship

Personalizing cutting edge survivorship, surveillance and prevention strategies



## Primary Cancer Therapies

Killing Cancer Cells



### **Loco-Regional Hyperthermia**

Using heat and EMF to kill cancer cells & enhance CT/RT

### **I.V. Therapy**

Direct infusion of high dose vitamins & other medicines

### **Injection Therapy**

Direct introduction of focused cancer fighting agents

### **Targeted Supplementation**

Addressing known molecular targets of each patient's cancer

### **Prescriptive Medications**

Repurposed drugs used to manage known targets of cancers

### **Conventional Therapy Sensitization**

Maximizing conventional treatment efficacy

### **Sonodynamic Therapy**

Ultrasound induced activation of cancer fighting agents

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## Immune System Therapies

Boosting Natural Systems



### **I.V. Therapy**

Infusions of immunologic medicines such as Vitamin C

### **Injection Therapy**

Focused immune support such as mistletoe therapy

### **Targeted Supplementation**

Oral meds to support the branches of the immune system

### **Biological Therapy**

Biological agents to stimulate immune activity

### **Immunotherapy Sensitization**

Supporting PD-1/PD-L1, CTL-4 and other approaches

### **Body Warming Therapy**

Fever response activation

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## Supportive Protocols

Achieving Wellness



### **Detoxification / Chelation**

Removes toxins, heavy metals and other waste materials

### **Vital Organ Support**

Targeted support for the liver, kidneys, skin and bowels/biome

### **Laboratory Testing**

Use laboratories worldwide to provide best practices

### **Dietary Counselling**

Understanding the best foods for your specific body/disease

### **Lifestyle Counselling**

Harnessing the benefits of exercise, stress management, mindfulness, etc.

### **Acupuncture & TCM**

Using acupuncture & herbs to support healthy Qi



## Prevention & Survivorship

Life Without Cancer



### **I.V. Therapy**

Infusions to optimize nutrition and tissue health

### **Injection Therapy**

To support a healthy immune system

### **Targeted Supplementation**

Addressing each patients specific need for support.

### **Dietary Counselling**

Eating foods with known anti-cancer benefits

### **Lifestyle Counselling**

Harnessing the benefits of exercise, stress management, mindfulness and other cancer prevention strategies

### **Detoxification / Chelation**

Remove toxins, heavy metals and other waste materials known to interfere with proper body function



Dr. Gurdev Parmar, BSc, ND, FABNO

**Integrated Health Clinic**

Fort Langley BC Canada

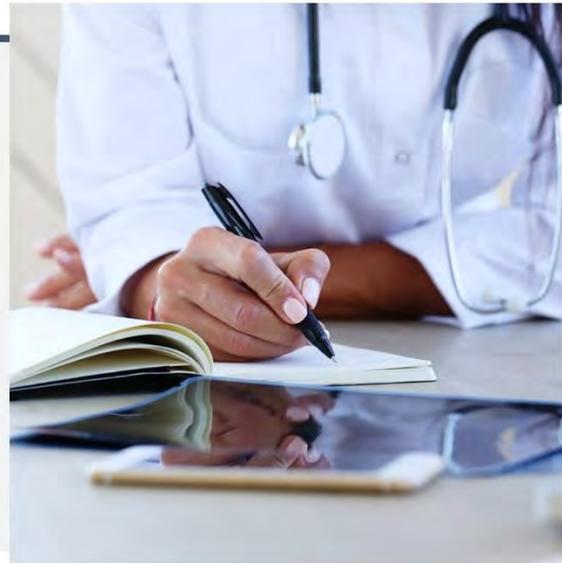
Naturopathic Anti-Tumoral  
Treatment & 8 Year Survival  
Benefit Statistics: A Single-  
Centre Experience



## Disclosure

Owner Integrated Health Clinic, which offers Hyperthermia Treatment

Ownership interests in Teneovita Medical Innovations, Inc., an international distributor of hyperthermia devices



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## Research & Ethics

The CCNM Research and ethics board (REB) has provided review and oversight for this research project, in order to assure that it meets all scientific and ethical principles, and that it complies with all applicable regulations and standards pertaining to human participant protection.



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## Background

The benefit of hyperthermia as an integrated cancer therapy is well established in many parts of the world <sup>1,2,3,4</sup>

The application of heat (locally or as a whole body treatment) is not widely administered in North America, partly due to limited available research in this geographic location.

The compelling evidence supporting its safety and use as an adjunct to standard of care in Europe and Asia highlights the need for further hyperthermia research in North America <sup>5,6</sup>

## Background

In June 2010 Integrated Health Clinic successfully applied for a Special Access License & then a Class 3 Medical Device License to import and use an Oncotherm modulated electro-hyperthermia device, a first in Canada & the USA.

As a naturopathic oncologist, I have a 100% oncology practice having seen over 10,000 patients over the past 18 years with a team of associates, management, assistants, nurses and medical lab assistants.

In 2012 we brought in a whole body hyperthermia (WBHT) device to provide outpatient fever-range WBHT targeting between 38.5 - 40.5 degrees Celsius.

## PURPOSE

- To describe baseline characteristics on the use of hyperthermia as part of an integrative naturopathic treatment protocol at IHC, from **June 2010 -> July 2018**.
- To assess the safety profile for **fever-range WBHT and LRHT**.
- To assess **5 year survival patterns** for IHC's top ten treated cancer types including glioblastoma multiforme (GBM), stage 4 colorectal cancer, and non-resectable pancreatic adenocarcinoma.

## METHOD

- A retrospective study was conducted on all **785** patients who received hyperthermia at IHC from **June 2010 to July 2018**.
- Patient **Inclusion criteria**:
  - Only distant metastatic disease (**stage IV**) for all 10 cancer types.
  - Received a minimum of **6 LRHT** treatments.
- **Evaluation** measures included:
  - Baseline Measures: date of diagnosis, stage at diagnosis, stage at new patient visit, concurrent treatments, and previously tried therapies.
  - Overall survival was assessed over 5 years using Kaplan-Meier plots.

# RESULTS

- As of July 2018, the IHC has treated **1289** and **327** patients using LRHT and WBHT respectively.
- **785** of these patients met all the criteria to be included in our dataset.
- **16,752 LRHT** and **1082 WBHT** treatments have been administered between June 2010 & June 2018.
- 66% of patients had metastatic cancers at their initial IHC visit, compared to 49% at initial diagnosis.

## Global Cancer Group Population Frequency Data.

For top All Cancer Groups at IHC (for 785 patients)



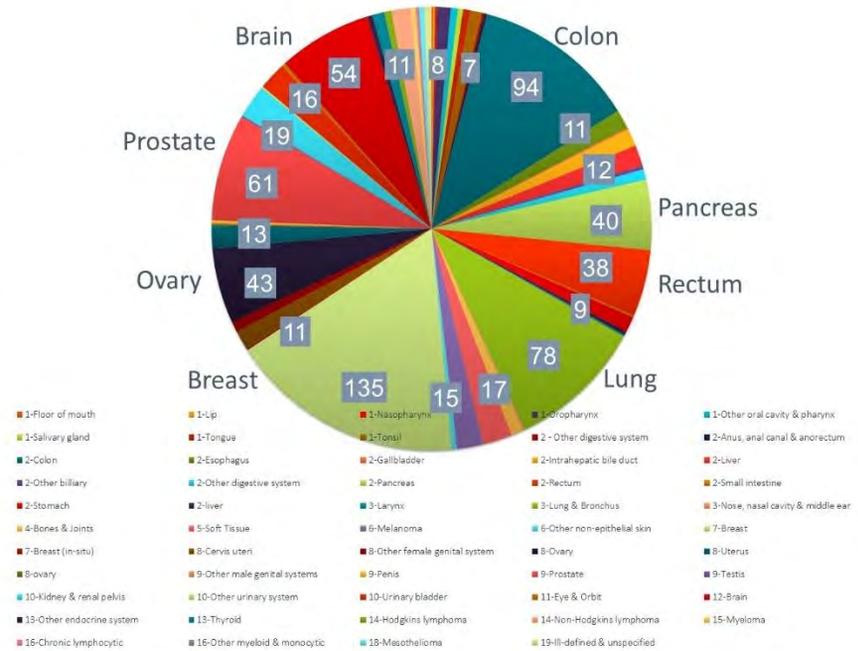
Cancer_Group	Frequency	Percent
Digestive System	228	29.08
Breast	136	17.35
Respiratory System	80	10.2
Female Genital System	74	9.44
Male Genital System	64	8.16
Brain & Nervous System	54	6.89
Urinary System	36	4.59
Oral Cavity & Pharynx	28	3.57
Skin	19	2.42
Soft Tissue	18	2.3

**Cancer Group & Frequency Data.**

For top 10 Cancer Groups (for 737 patients)

**Global Cancer Types Population Frequency Data.**

For top All Cancer Groups at IHC (for 785 patients)



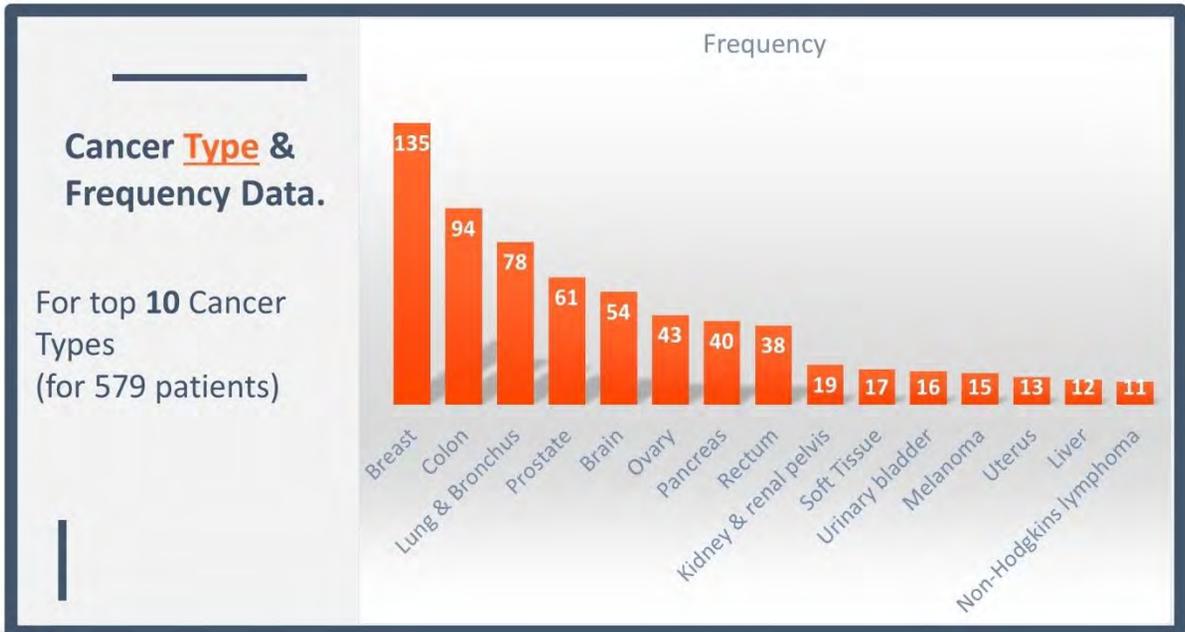
**Cancer Type & Frequency Data.**

For top 10 Cancer Types (for 579 patients)

Cancer_Type	Frequency	Percent
Breast	135	29.08
Colon	94	17.35
Lung & Bronchus	78	10.2
Prostate	61	9.44
Brain	54	8.16
Ovary	43	6.89
Pancreas	40	4.59
Rectum	48	3.57
Kidney & Renal Pelvis	19	2.42
Soft Tissue	17	2.3

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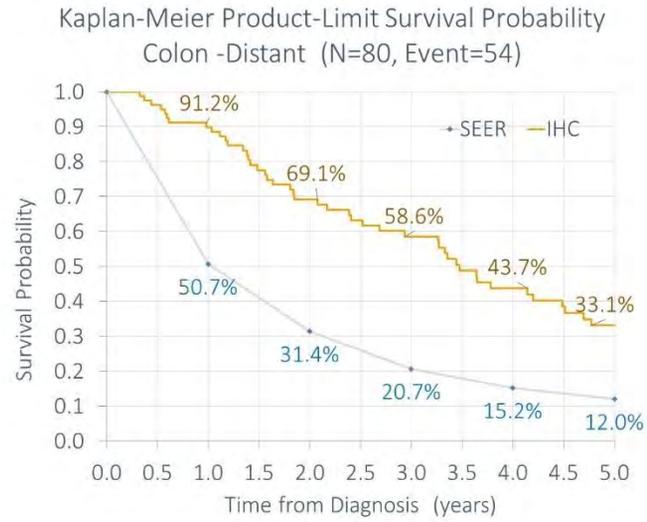
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For top 7 Cancer Types

### Kaplan-Meier by Cancer Type

#### Colon – Stage IV



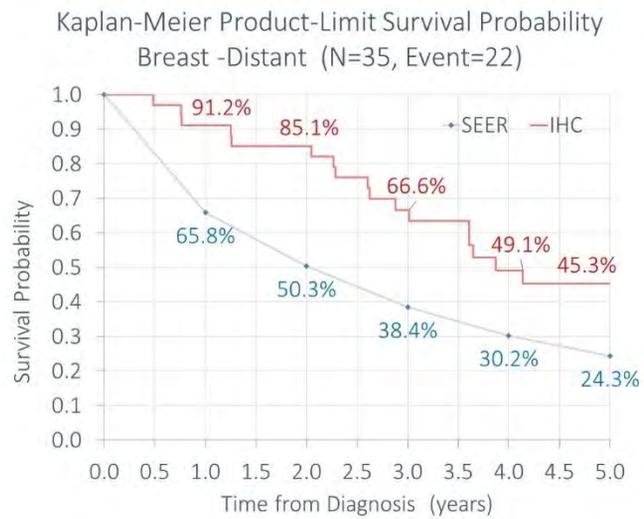
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For top 7 Cancer Types

### Kaplan-Meier by Cancer Type

#### Breast – Stage IV



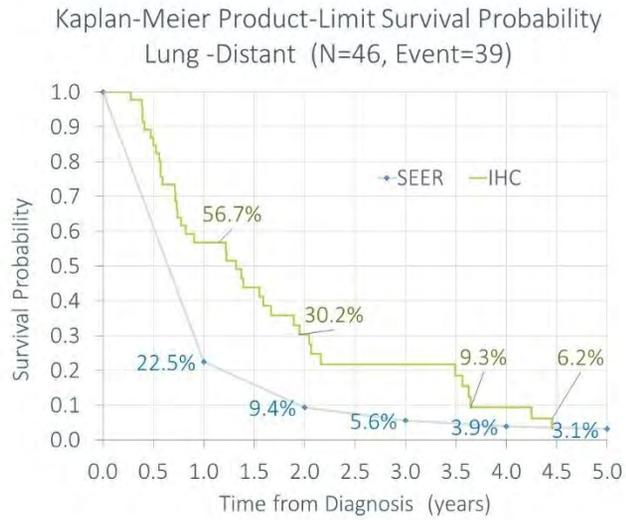
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For top 7 Cancer Types

**Kaplan-Meier by  
Cancer Type**

**Lung – Stage IV**



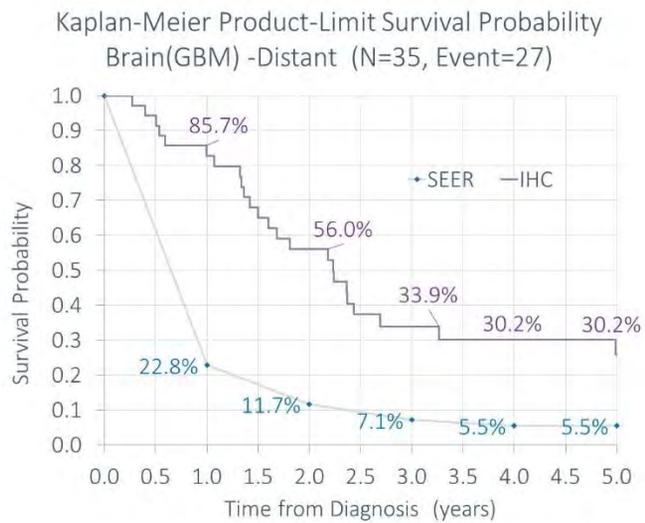
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For top 7 Cancer Types

**Kaplan-Meier by  
Cancer Type**

**Brain (GBM) – Stage IV**



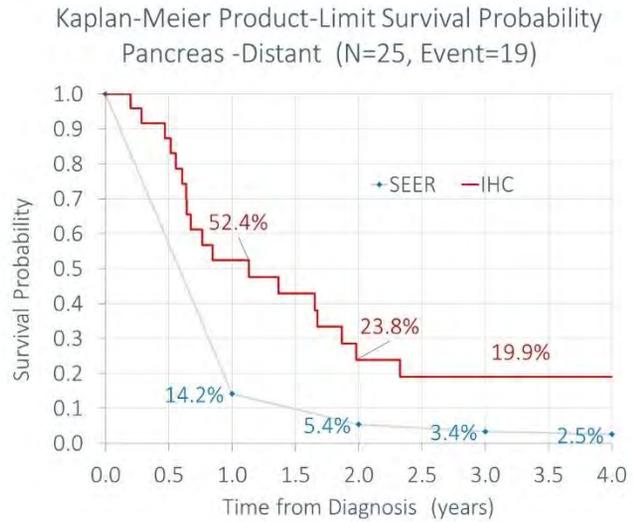
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For top 7 Cancer Types

Kaplan-Meier by  
Cancer Type

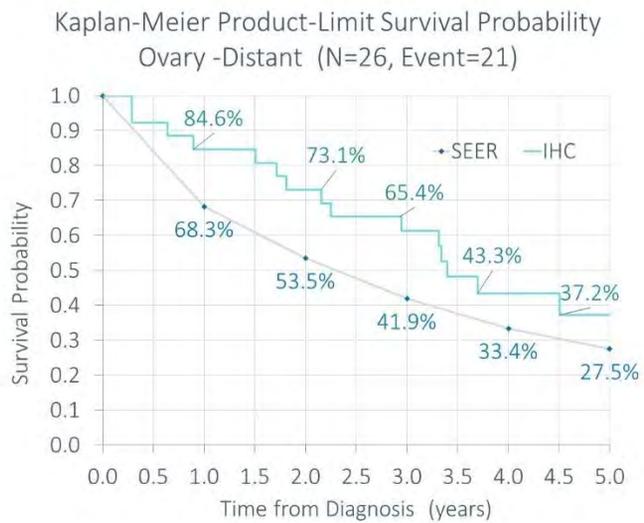
**Pancreas – Stage IV**



For top 7 Cancer Types

Kaplan-Meier by  
Cancer Type

**Ovary – Stage IV**

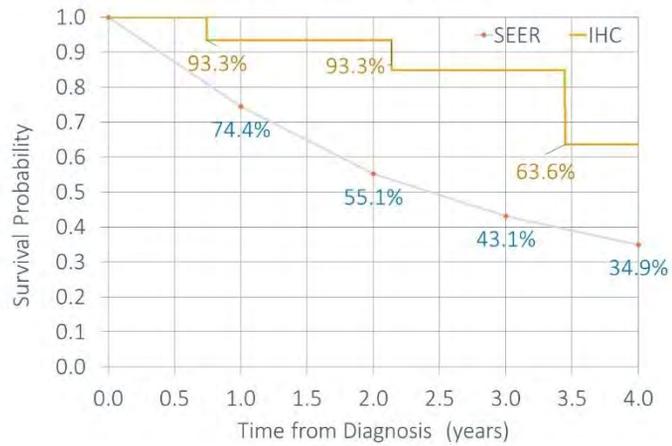


For top 7 Cancer Types

## Kaplan-Meier by Cancer Type

Prostate – Stage IV

Kaplan-Meier Product-Limit Survival Probability  
Prostate-Distant (N=16, Event=4)



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## Adverse Effects.

- LRHT – Superficial Skin Blisters - 7
- LRHT - Subcutaneous Fibrosis - 5
- FR-WBHT - Superficial Skin Blisters - 3
- FR-WBHT – Urethral Catheter Bleed - 1



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## Conclusions.

- Preliminary results show **promising survival trajectories** for all ten most commonly treated cancer types we have reviewed in this retrospective data analysis
- Hyperthermia proves to be **a safe adjunctive treatment** in integrative oncology care.
- Further research is necessary to assess the effectiveness of hyperthermia using a larger sample population and over a longer period of time.



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## Future Plans.

- A **prospective study** is now underway at the IHC to further assess the impact of our naturopathic integrative protocols on OS.
- A **'best case series'** will be published to disseminate knowledge on the use of our protocols as an adjunct treatment.
- We are one of **7 clinics in North America** chosen to participate in the CUSIOS Trial to assess the benefits of advanced integrative naturopathic oncology with standard of care in several stage 3-4 cancers



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- Statistician

### **Erin Rurak, BSc, ND**

- Synthesis

### **Mark Elderfield, MSc**

- Co-ordinator

### **Sarah Soles, ND**

- Data

### **Emma Lee, BSc**

- Data



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# Integrated Health Clinic Cancer Care Center

THANK YOU

Fort Langley BC Canada

# **Molecular mechanisms of modulated electrohyperthermia (mEHT) induced tumor damage**

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Semmelweis University, Budapest, Hungary

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

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# Molecular mechanisms of modulated electrohyperthermia (mEHT) induced tumor damage

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<sup>2</sup>Department of Radiological Sciences, Graduate School of Medicine and Pharmaceutical Sciences, University of Toyama, Toyama, Japan

## Abstract

Modulated electro-hyperthermia (mEHT), a non-invasive, loco-regional complementary of radio- or chemotherapy, can by itself induce selective heat shock and cell stress in malignant tumors at ~42°C. Based on the published results we briefly summarize what has been revealed on the molecular background of tumor damage caused by mEHT treatment.

A single mEHT shot of 30-60 min provoked significant upregulation of  $\gamma$ -H2Ax (indicating DNA double strand breaks) and tumor destruction in colorectal cancer models, both in vitro and in vivo, dominantly following programmed tumor cell death mechanisms. Apoptotic response was diverse based on the (epi) genetic makeup of treated tumors and following both extrinsic (casp-8+) and intrinsic (translocated Bax & Cytochrome C) caspase-dependent (casp-3+; in C26), or AIF-mediated (in p53 mutant HT29) caspase-independent pathways. Treatment response in C26 in vitro involved the upregulation of Ser15 phospho-p53 (indicating escape from Mdm2 control) and p21waf1 (the mediator of cell senescence), accompanied by the elevation of the pro-apoptotic PUMA, Bax and Bak-1 and the downregulation of the antiapoptotic XIAP, Bcl-2 and Bclx. Furthermore, mEHT treatment synergized with Doxorubicine chemotherapy. In histiocytic lymphoma (U937) both extrinsic and intrinsic caspase-dependent apoptosis was driven by phosphorylation of the c-Jun N-terminal kinases (JNK).

In vivo, early apoptosis was supplemented by complete cell cycle arrest shown by Ki67 negativity, and the occurrence and release of DAMP (damage associated molecular pattern) signals including chaperons such as calreticulin, Hsp70 and Hsp90 and the high mobility group1 (HMGB1) protein. After single treatment, the progressive tumor damage and accumulation of CD3 positive T-cells, including granzyme B+/CD8+ cytotoxic cells (granzyme B+/CD8- NK cells) as well as S100+ antigen presenting dendritic cells (APC), were consistent with a secondary, immunogenic cell death (ICD) mechanism added to the primary effect of mEHT. Furthermore, treatment response could be associated with elevated levels of glycolytic enzymes in vivo, and with increased lactate production and reduced buffer capacity (and pH) in cultures. mEHT treatment also supported antitumor immune response when combined with tumor-specific, intratumoral dendritic cell delivery involving tumor sites distant from the treated focuses (Abscopal effect).

In summary, radio- or chemotherapy can be supported by the inherent antitumor effects of mEHT, which can induce diverse, tumor-specific apoptosis pathways and antitumor immune response too. Besides direct heat induction in the extracellular space due to elevated glycolysis (Warburg-effect) and ion-concentration in cancer, mEHT may also act directly on cell membrane rafts (where local electric loss/absorption peaks), which concentrate ion

channels and transmembrane receptors. These features may explain the higher efficiency of mEHT compared to traditional hyperthermia under the same temperature.

This study has been supported by the Hungarian National Research, Development and Innovation Office (NVKP\_16-1-2016-0042).



# Molecular mechanisms of modulated electrohyperthermia (mEHT) induced tumor damage

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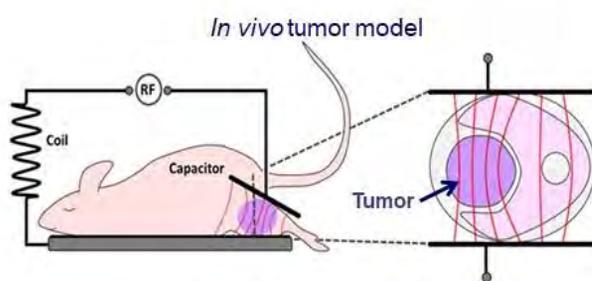


ICHS Congress, Budapest  
September 28-29, 2018

## mEHT of 13.65 MHz – selective tumor targeting

### Enrichment of electric field in malignant tumors

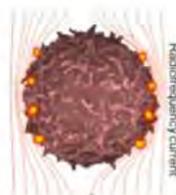
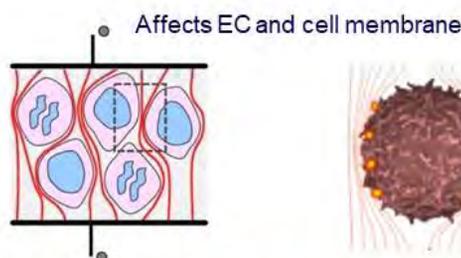
- **Elevated:** glucose uptake, aerobic glycolysis (Warburg-effect) lactate<sup>-</sup> H<sup>+</sup> & other ion concentration & permittivity



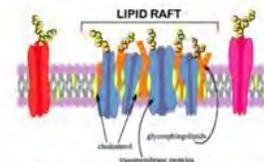
Lung cc liver metastasis



GLUT1



Radiofrequency current

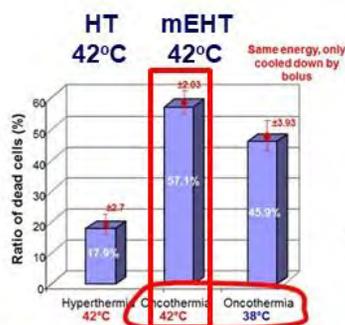
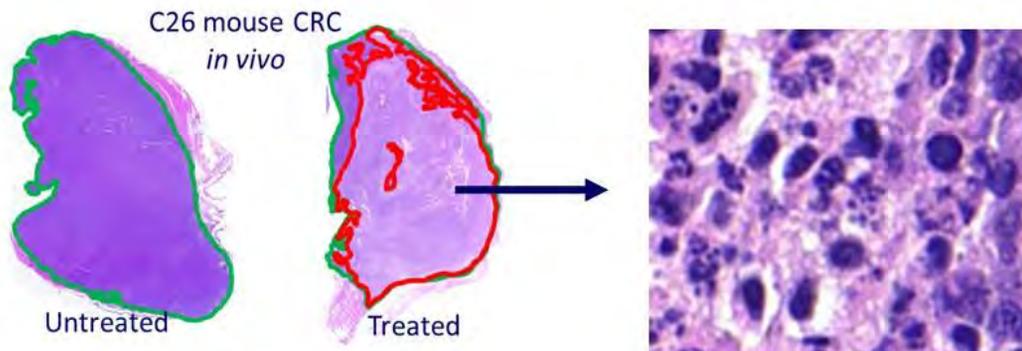


High dielectric potential in lipid rafts concentrating transmembrane receptors

- Dielectric polarization/rotational friction – heat

# mEHT of 13.65 MHz – Significant tumor destruction

- Mechanism: Programmed tumor cell death



Synergy  
Heat stress  
+  
Direct effect of EF

Additional effects  
compared to  
conventional heating

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

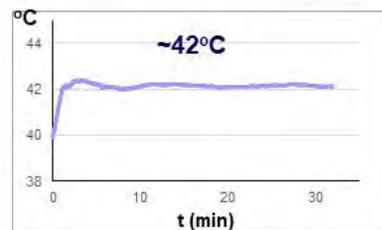
## mEHT effects: *in vivo* & *in vitro* tumor models

### Mouse: allo-, xenografts



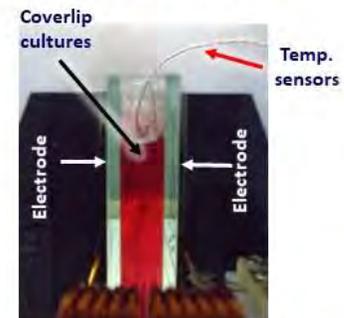
- Symmetrical tumors
- right leg - mEHT treated
  - left leg - control

### Temperature control



mEHT: single/repeated 30 or 60 min  
42 ± 0.5°C (Lab EHY 100)

### Tumor cell cultures



mEHT: mono-, or combined with  
chemo- or radio- or DC therapy

### Tumor cell lines

- Colorectal ADC: C26, C38 CRC, HT29,
- Lung ADC: LLT-H,
- Hepatoc. ADC: HepG2, Huh7
- Head-neck SCC: CCVII
- Glioma: U87-MG, A172
- Hist. lymphoma: U937
- Fibrosarcoma: FSall

### Published results from:

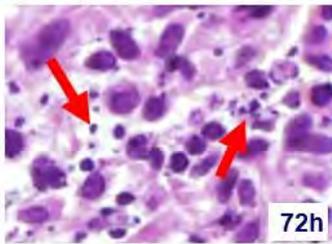
- Yonsei University College of Medicine Seoul, South Korea
- National University, Seoul, South Korea
- Tottori University, Japan
- Chiba University, Japan
- Toyama University, Japan
- Memorial Hospital, Taipei, Taiwan, ROC
- Chung Yuan Christian University, Taoyuan City, Taiwan, ROC
- Semmelweis University, Budapest, Hungary

# mEHT induced programmed cell death (42°C)

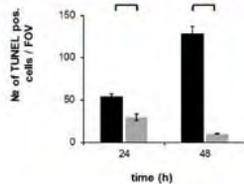
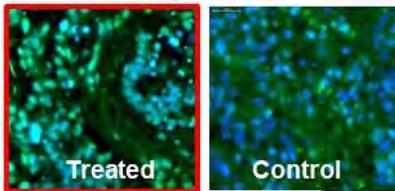
Colorectal cancer (CRC) cell lines: HT29 human (TP53 mutant); C26 mouse

hHT29  
CRC

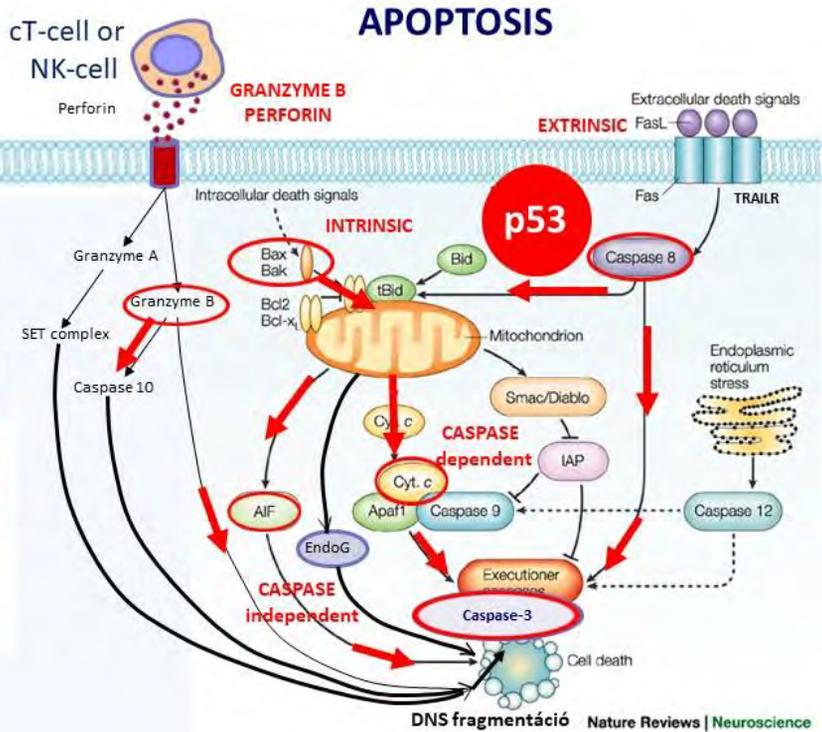
Apoptotic bodies



DNA fragmentation



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



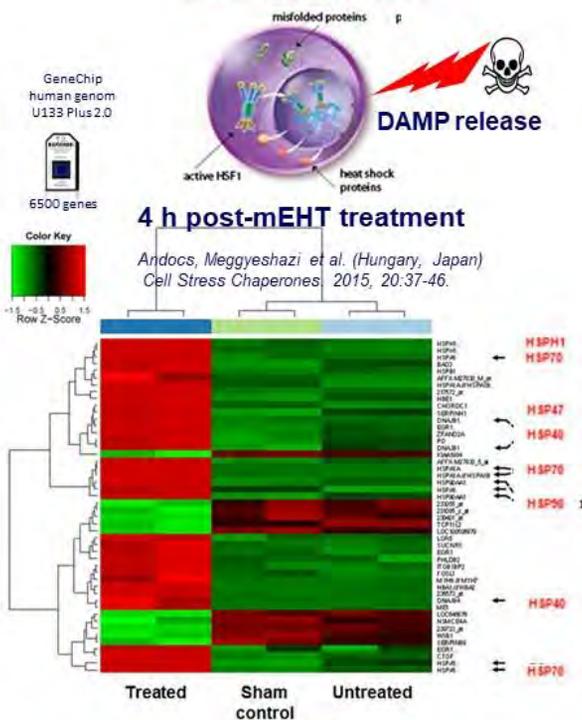
DNS fragmentáció Nature Reviews | Neuroscience  
Vila-Przedborski: Apoptosis-Nature Reviews  
Neuroscience 2003, 4:365-375.

# Early heat shock/cell stress & apoptosis response

hHT29  
CRC

Upregulation of Hsp-s

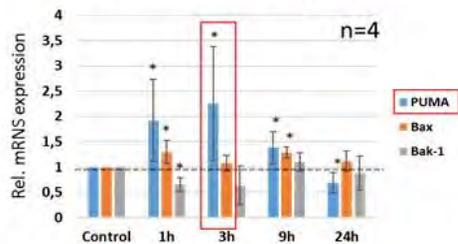
HEAT SHOCK + CELL STRESS



mC26  
CRC

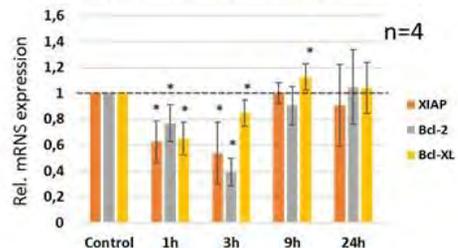
Pro-apoptotic (mRNA levels):

- PUMA (p53 upregulated modulator of apoptosis)
- Bax (Bcl-2-associated X)
- Bak-1 (Bcl-2 homologous antagonist/killer)



Anti-apoptotic (mRNA levels):

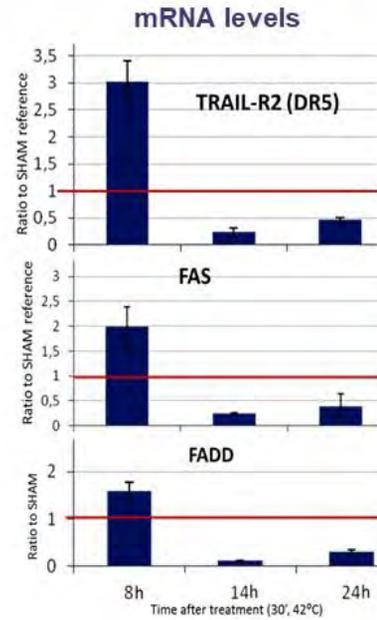
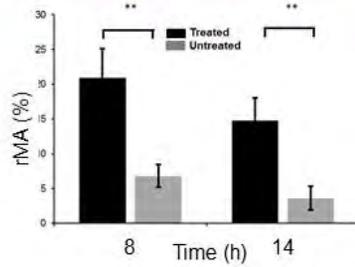
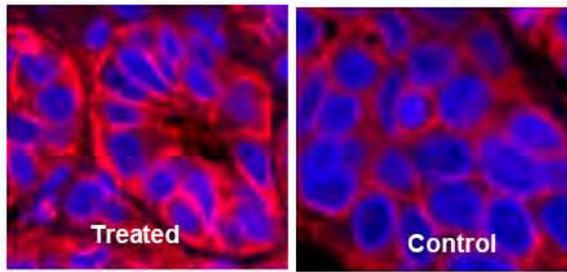
- XIAP (X-linked inhibitor of apoptosis)
- Bcl-2 (B-cell lymphoma type-2 protein)
- Bcl-XL (B-cell lymphoma-extra large)



# mEHT induced death receptor mediated extrinsic pathway

hHT29 (TP53 mutant) CRC xenograft

TRAIL-R2 (Death Receptor 5)



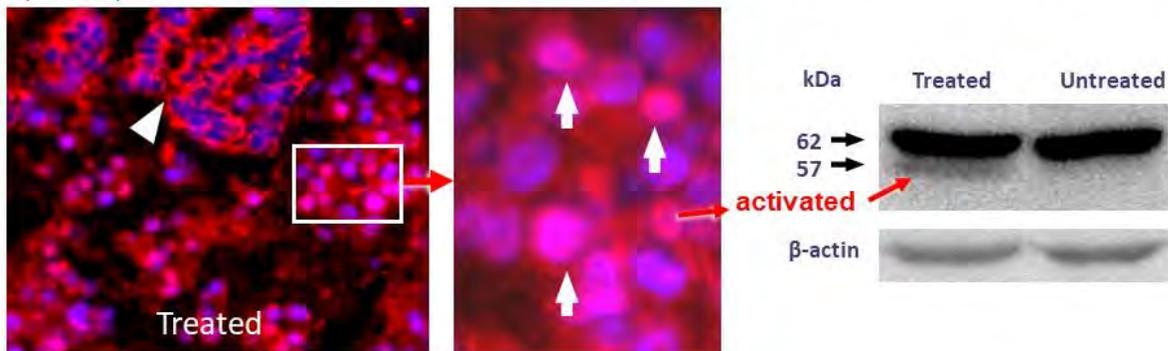
**Targeted therapy:** rh-Apo2L/TRAIL and MAbs (*HGS ETR2/lexatumumab*) - agonist

- Supported cytotoxic chemo- and radiation therapy in breast cancer & CRC
- Phase-I-II trials have been running *De Miguel et al. Cell Death and Differentiation 2016, 23:733-747*

# mEHT induced Caspase independent & dependent apoptosis

mHT29 CRC (mTP53)

AIF (apoptosis inducing factor) translocation (24h)



mC26 CRC (wTP53)

Extrinsic Caspase dependent  
Cleaved-Caspase 8

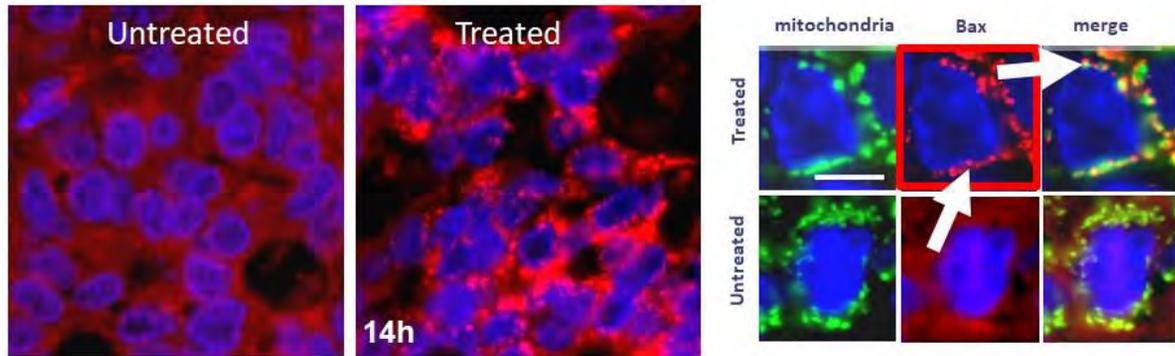
Cleaved-Caspase 3



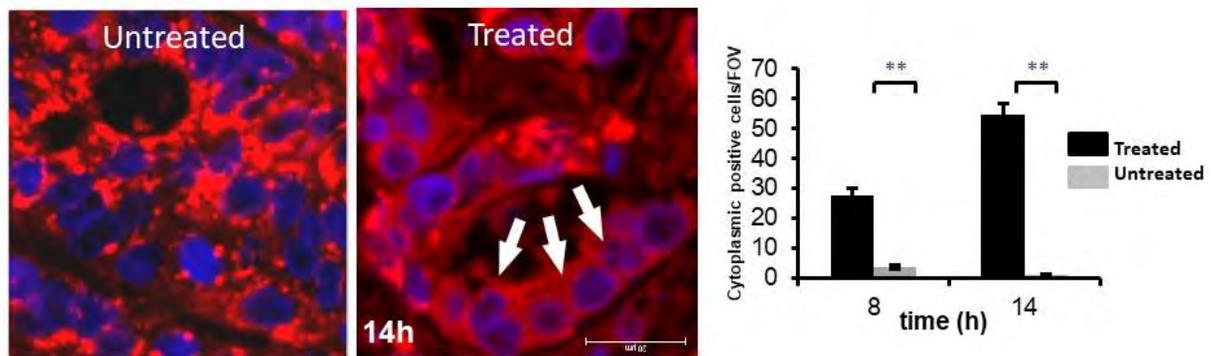
24h post-treatment

## mEHT induced Caspase-dependent intrinsic pathway

### Bax - mitochondrial translocation

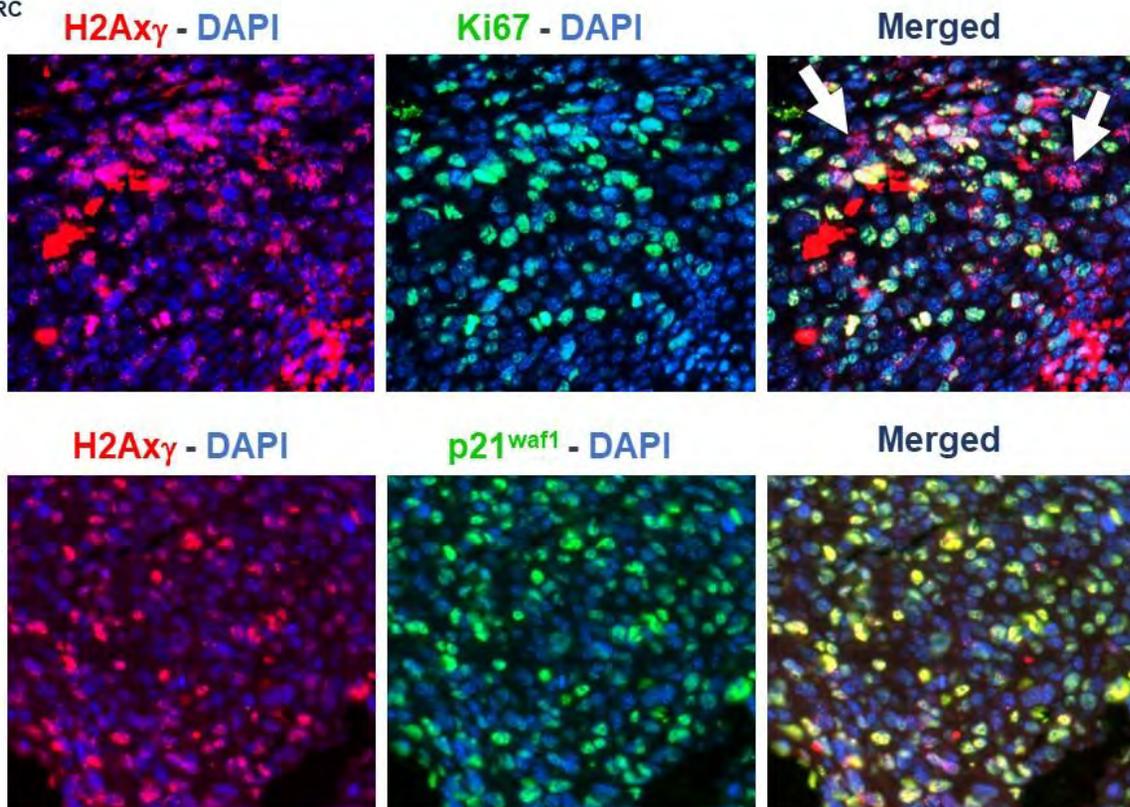


### Cytochrome C - cytoplasmic release



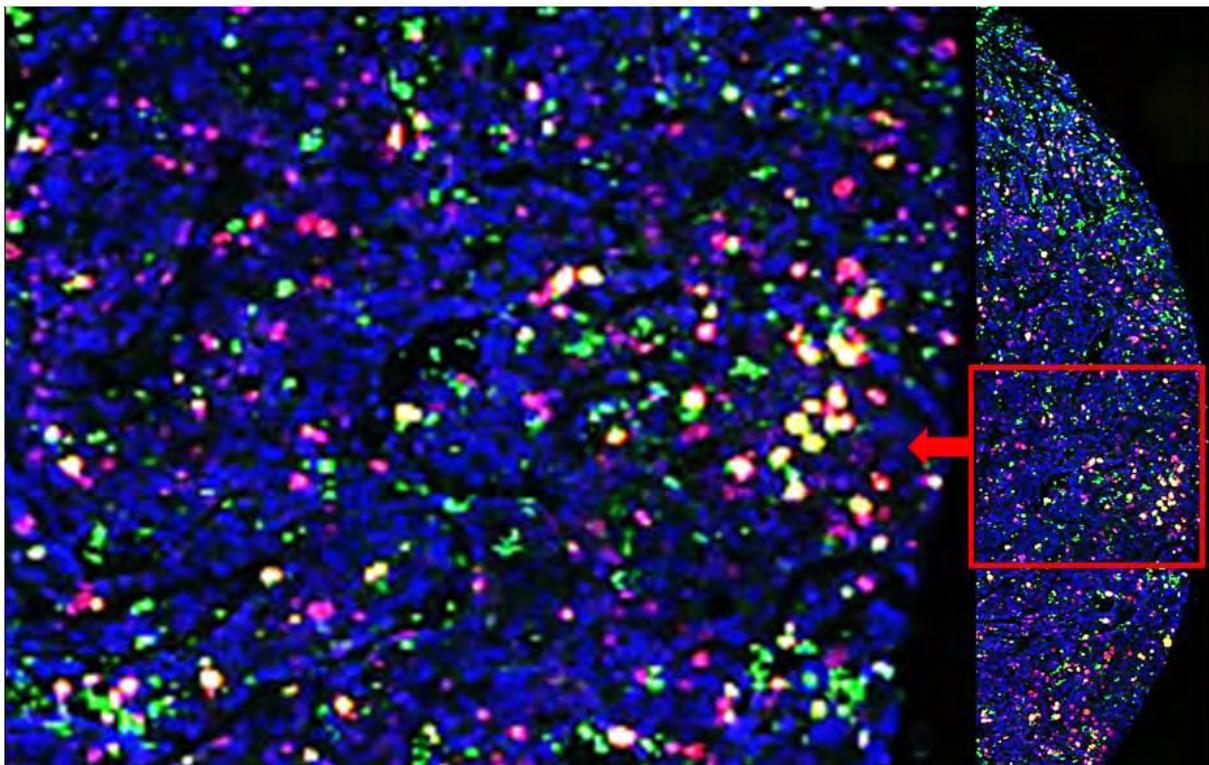
## mEHT-induced DNA double strand breaks

mC26  
CRC



# mEHT-induced DNA damage - apoptosis

H2A $\gamma$  c-Caspase 3 DAPI

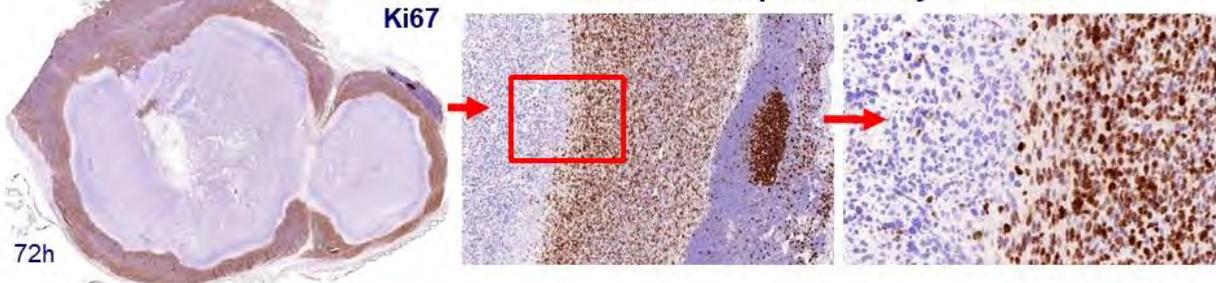


## mEHT induced apoptosis and cell cycle arrest

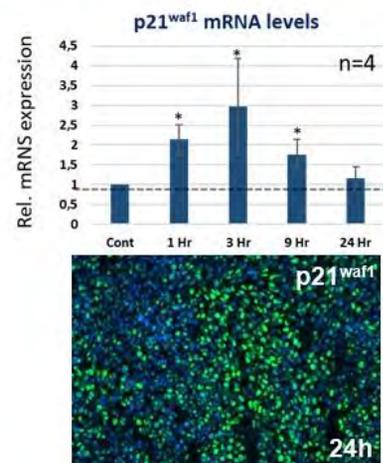
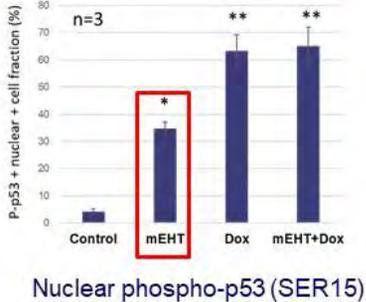
mC26  
CRC

Proliferation rate >90%

mEHT - Complete cell cycle arrest

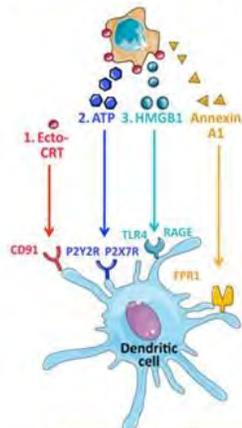


24h



## Spatiotemporal „danger” signaling – systemic effect

### Damage associated molecular patterns (DAMP)



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

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

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



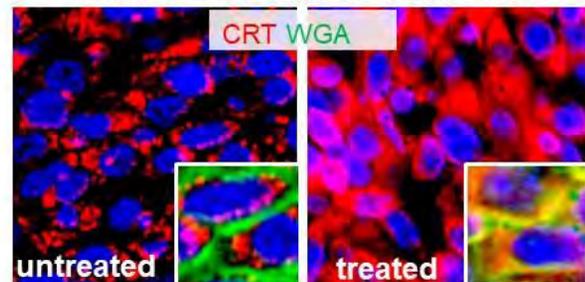
- Antitumor immune response
- Immunogenic cell death (ICD)

- **Antracyclins**  
Doxorubicin
- **UV or  $\gamma$ -irradiation**
- **EGFR immunotherapy**
- **Capsaicin**

C26 CRC allograft

### Calreticulin membrane translocation

Vancsik et al. (Hungary) *J Cancer*. 2018, 9:41-53.



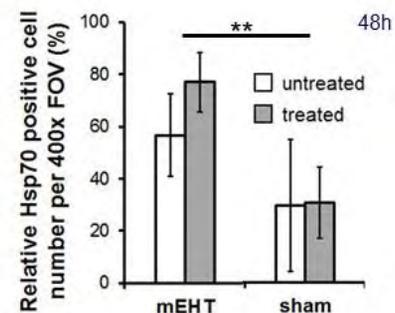
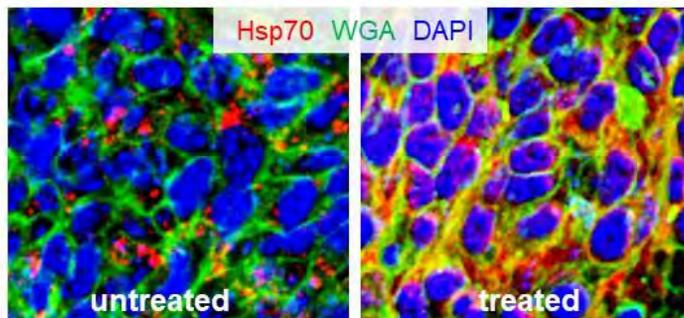
mEHT mC26: CRT *in vitro*



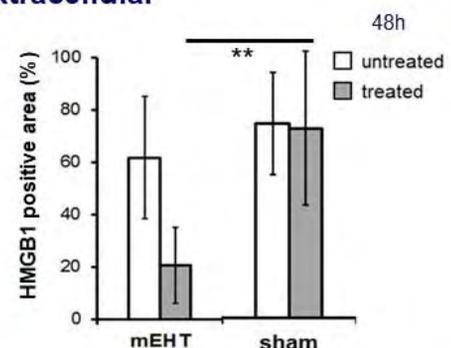
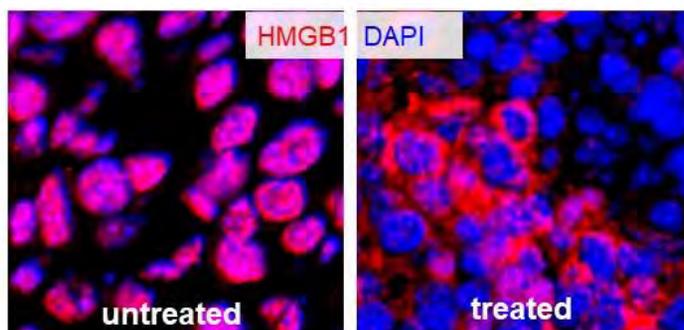
## Spatiotemporal DAMP signaling – systemic effect

C26 CRC allograft

### Hsp70 membrane translocation



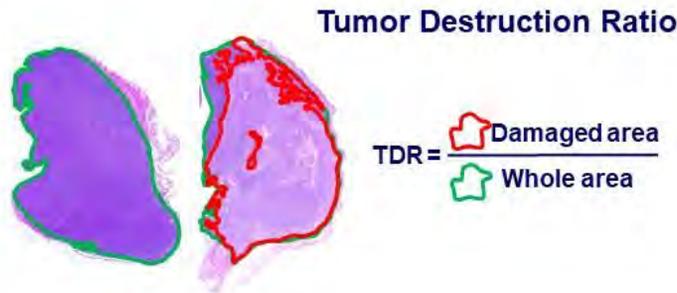
### HMGB1 release – cytoplasmic & extracellular



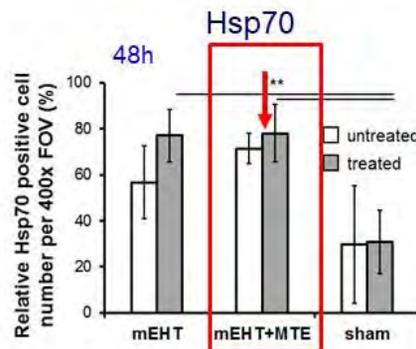
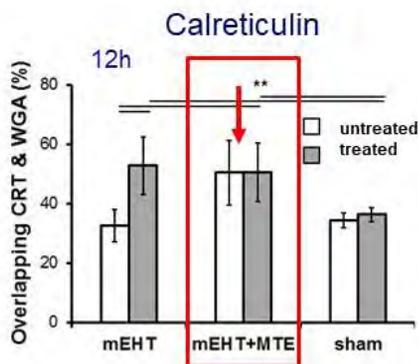
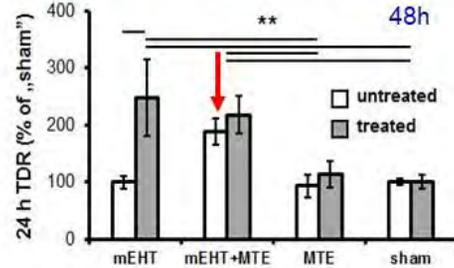
# mEHT combined with MTE (T-cell promoter)

## Systemic (abscopal) effect

Kang et al. J Anal Methods Chem. 2013;2013:617243.  
MTE: Direct antitumor effect + T-cell promotion



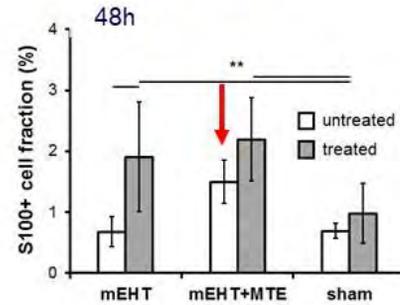
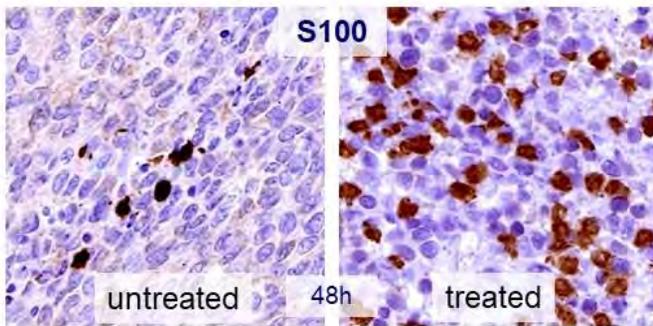
In mEHT treated & mEHT+MTE treated  
& in mEHT+MTE treated opposite site



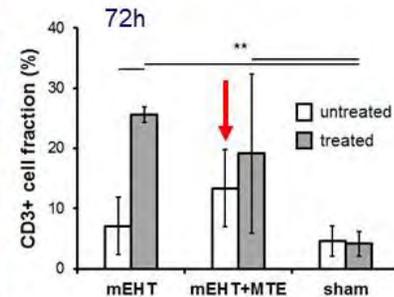
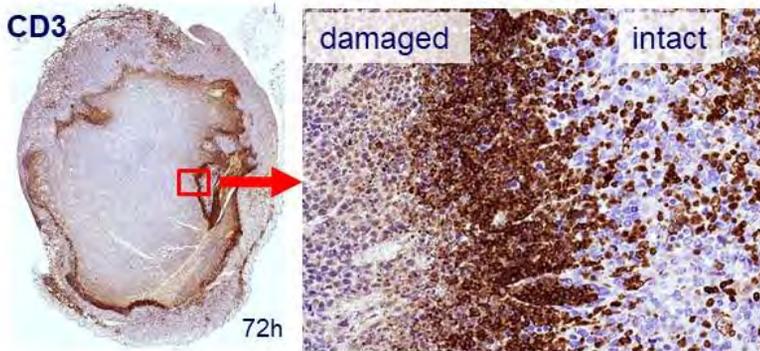
## Antitumor immune response - local and systemic

C26 CRC allograft

### Elevated number of antigen presenting DC (APC)



### Massive T-cell infiltration

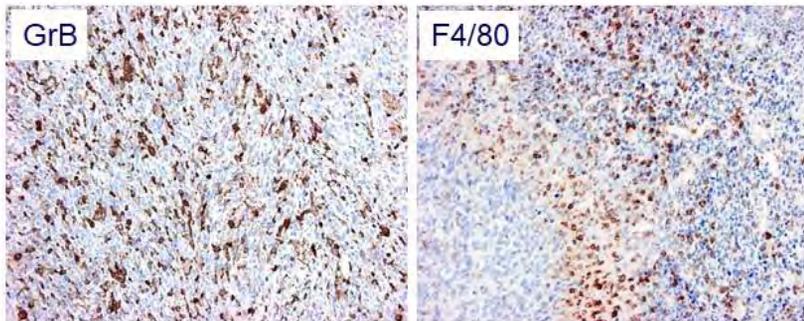
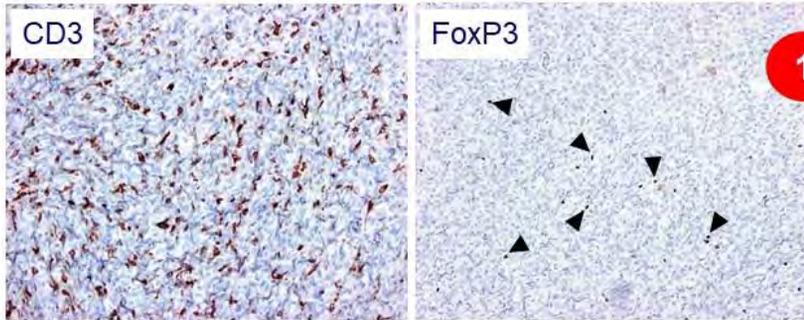


# Antitumor immune response – immunogenic cell death

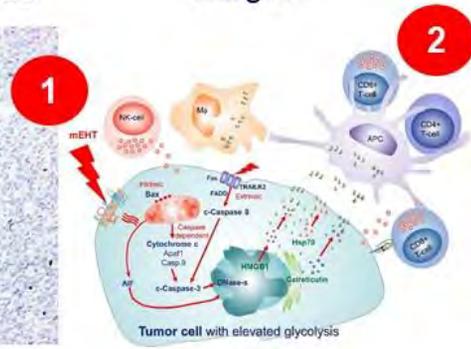
48 h post-mEHT

**T-cell infiltration, negligible regulatory T-cells**

**C26 CRC allograft**



**Cytotoxic T-cells & NK cells + Macrophages**



**Single mEHT shot**

Progressive

- accumulation of immune cells &
- tumor damage

**Immunogenic cell death ICD**

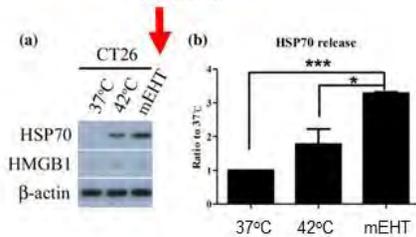
## Combination of mEHT + DC therapy

mC26 *in vitro* & allografts

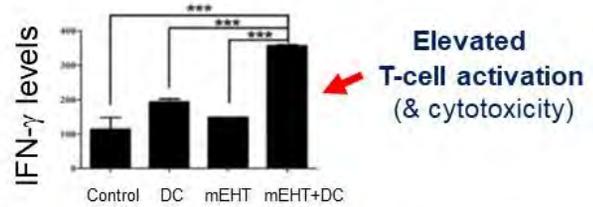
**Enhanced immune response**

*Tsang et al. (Taiwan) BMC Cancer, 2015, 15:708*

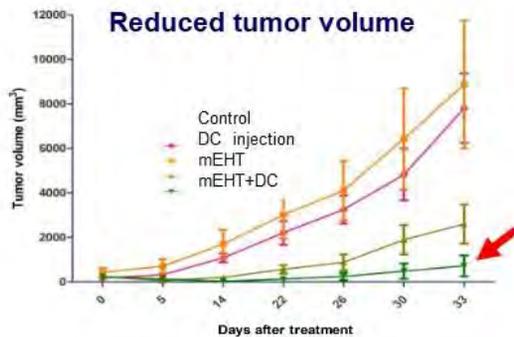
**Elevated Hsp70 release *in vitro***



**Tumor antigen+Hsp70 activated DC**

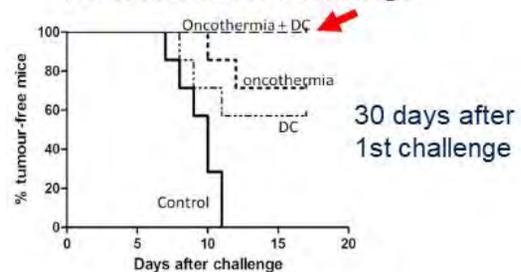


**Elevated T-cell activation (& cytotoxicity)**



**Reduced tumor volume**

**No tumor after rechallenge**



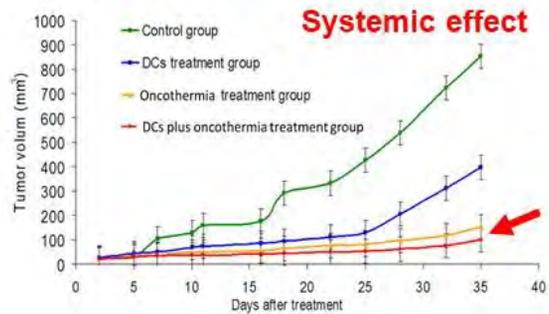
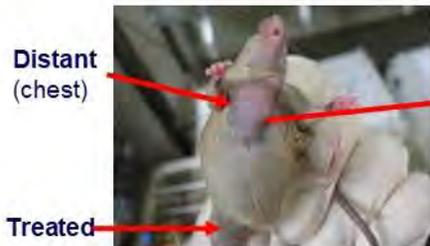
**30 days after 1st challenge**

# mEHT + DC therapy – systemic „abscopal” effect

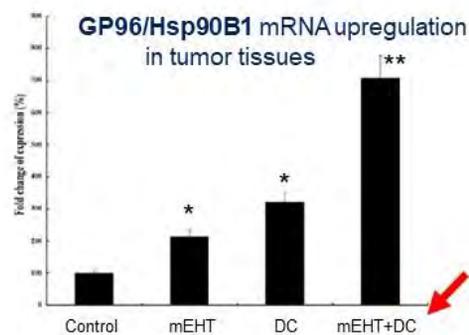
## Reduced tumor sizes distant from the mEHT treatment site

H&N SCCVII allograft

Quin et al. (Japan) *Oncology Reports* 2014, 32:2373-2379.



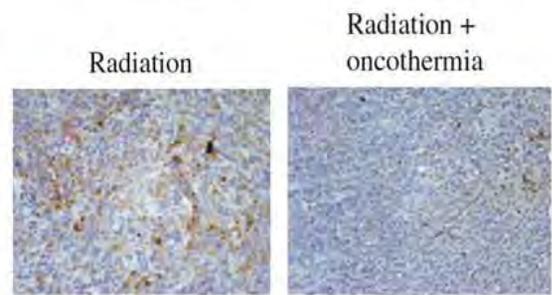
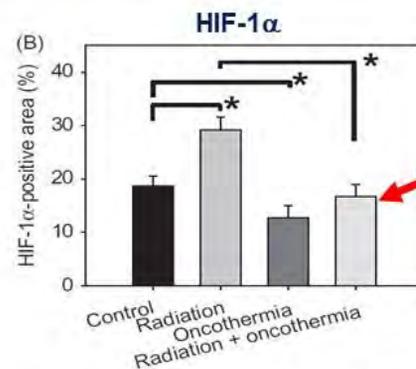
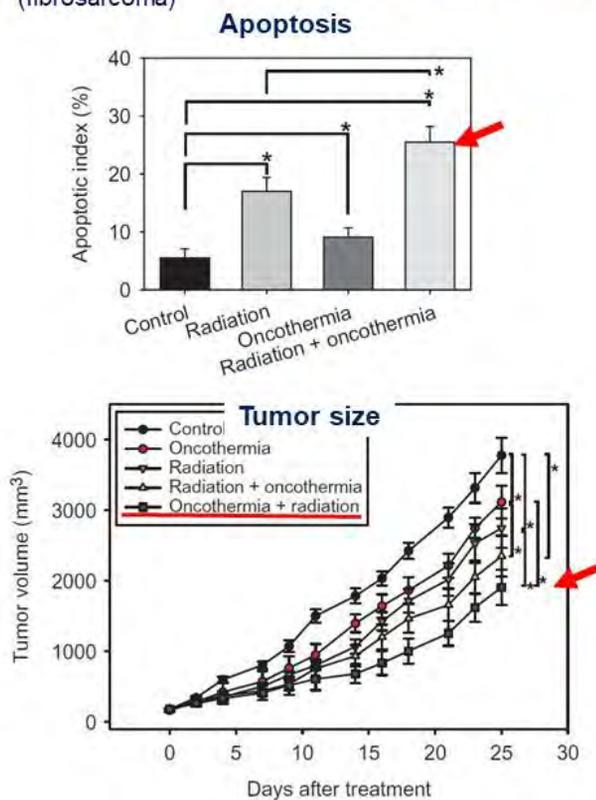
- Elevated CD3+ and CD8+ T-cells & S100+ antigen presenting DCs
- Reduced FoxP3+ regulatory T-cells



# mEHT promoted radiation damage by inhibiting HIF1 $\alpha$

FSa11 allograft (fibrosarcoma)

Kim et al. (Korea) *Int J Hyperthermia*. 2018, 34:276-283.

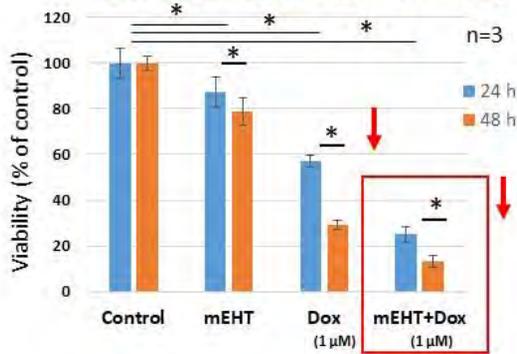


# Combination of 2x30' mEHT + Doxorubicin

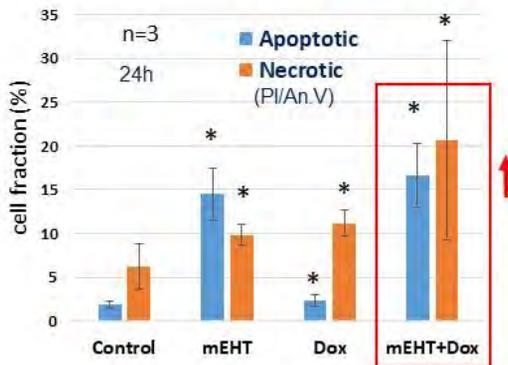
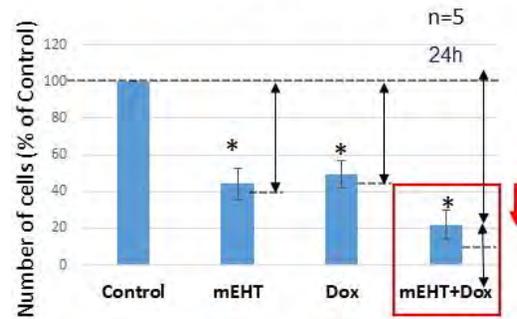
mc26 CRC  
in vitro

Own group at Semmelweis University (under publication)

## Cell viability: Resazurin assay



## Cell loss



mEHT - dominantly apoptosis  
Doxo - dominantly necrosis

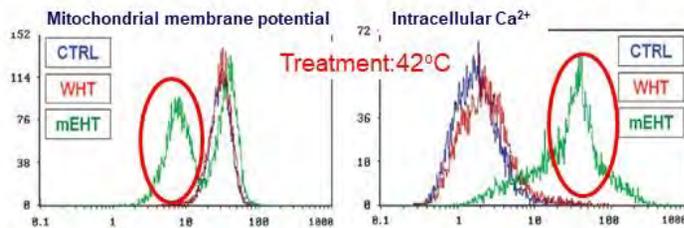
Additive effect in reducing viability & enhancing cell death by the combination therapy

## Comparison of mEHT with conventional HT or cRF therapy

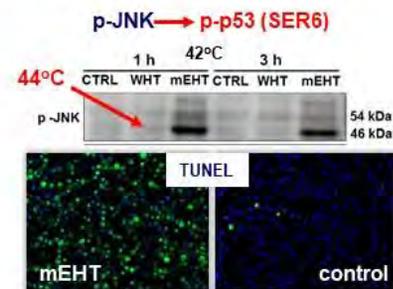
hU937  
histiocytic  
lymphoma

Andocs et al. (Japan) Cell Death Discov. 2016 Jun 13;2:16039.

### Upregulation of Fas, Casp-8 and Casp-3 & phosphorylation of JNK



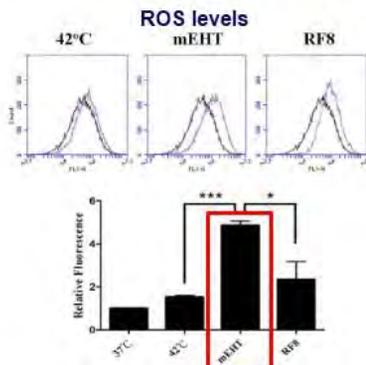
mRNA expression array



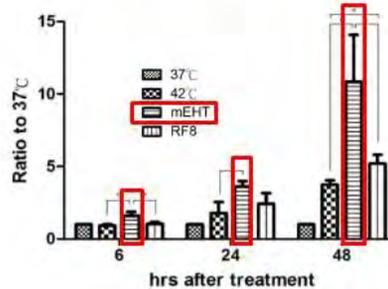
hHepG2  
HCC

Yang et al. (Taiwan & Japan) Oncotarget. 2016, 7:84082-84092.

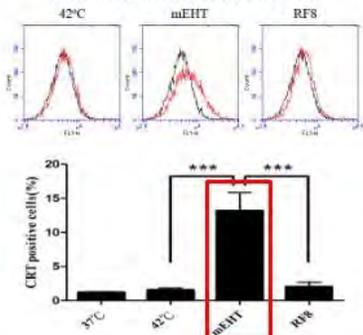
### Upregulation of ROS, ex.Hsp70 & CRT; Casp-8 and Casp-3



### Extracellular Hsp70



### Cell membrane Calreticulin



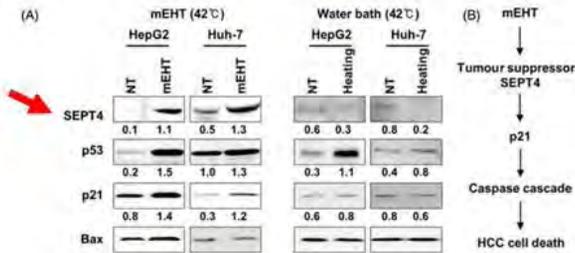
# mEHT upregulated Septin-4 promoted p53 functions

HepG2 & Huh7 HCC  
in vitro & in vivo xenograft

Jeon et al. (Korea) *Int J Hyperthermia*. 2016, 32:648-56.

Transcriptomic analysis of gene expression by RNA sequencing

## Upregulation of Septin-4

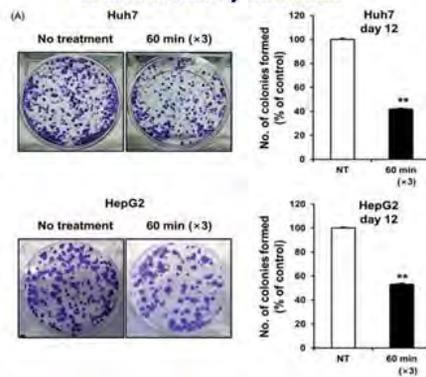


SEPT4 gene, encodes the inhibitor of apoptosis proteins (IAP) antagonist ARTS

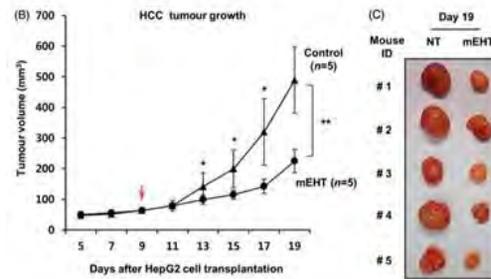
Sept4/ARTS is required for stem cell apoptosis and tumor suppression.

Upregulation of p53

## Reduced colony formation

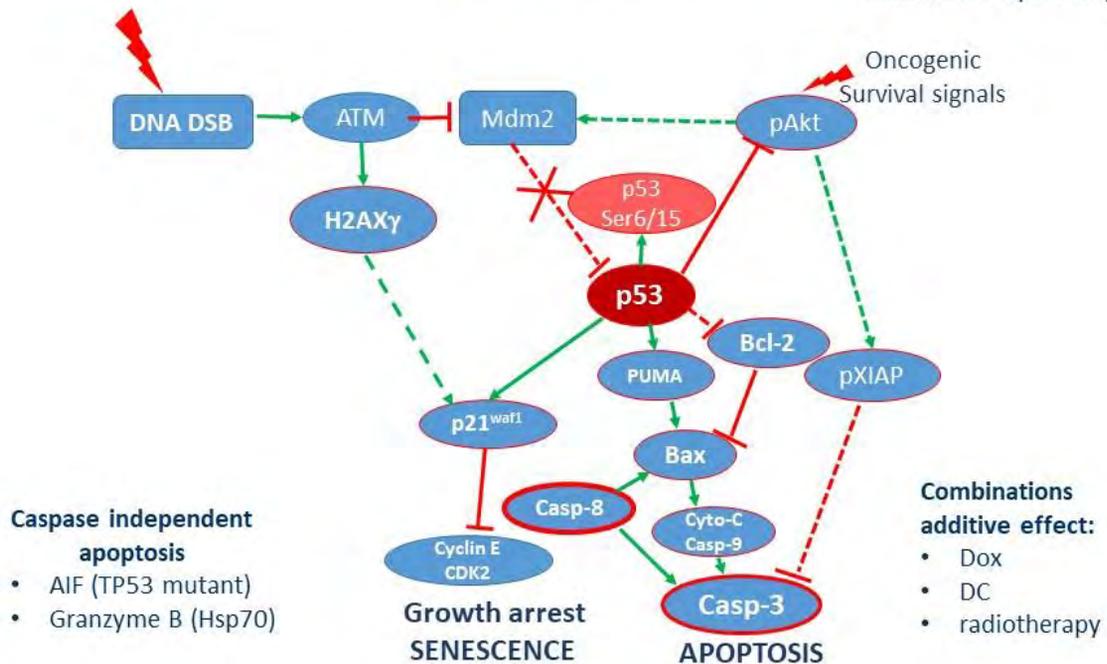


## Reduced HepG2 tumor size



# Molecular pathways involved in EHT effects

PRIMARY effect: mEHT induced heat/cell stress → Upregulation, translocation and release of DAMPS → SECONDARY effect: Support of antitumor immune response (ICD)



## Common features of mEHT & Prediction

### COMMON

- The extrinsic apoptosis pathway was involved: cell membrane effect
- P53<sup>wt</sup> activation was frequent: caspase-dependent apoptosis + senescence

### DIFFERENT

- Extent of tumor damage & the preferred damage signaling pathway(s) are tumor (type) dependent

& determined by inherent epi-/genetic make up

*(the same molecular events in the endogenously damaged areas in controls)*

## mEHT

### PREDICTIVE BIOMAKERS

- Epi-/genetic predisposition
  - Oncometabolit
  - Metabolic enzyme
- } levels
- others ???

## Acknowledgements



Thank you!

Nora Meggyeshazi

Tamas Vancsik

Edit Parsch<sup>†</sup>

Eva Balogh Matraine

Gabor Andocs

Peter Balla

Eva Kiss, Gertrud Forika

Renata Kiss, Zsibai Zsófi

This study has been supported by the Hungarian National Research Development and Innovation Office (NVKP\_16-1-2016-0042).

# **Modulated electro hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model**

**Lea Danics<sup>1</sup>, Csaba Schvarcz<sup>1</sup>, Zita Zolcsak<sup>1</sup>, Zoltan Benyo<sup>1</sup>, Tamas Kaucsar<sup>1</sup>, Peter Hamar<sup>1</sup>**

<sup>1</sup> Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

Danics L. (2018): Modulated electro hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model; *Oncothermia Journal* 24: 442-454

[www.oncothermia-journal.com/journal/2018/Modulated\\_electro\\_hyperthermia\\_inhibits\\_tumor.pdf](http://www.oncothermia-journal.com/journal/2018/Modulated_electro_hyperthermia_inhibits_tumor.pdf)

# Modulated electro hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model

Lea Danics<sup>1</sup>, Csaba Schvarcz<sup>1</sup>, Zita Zolcsak<sup>1</sup>, Zoltan Benyo<sup>1</sup>, Tamás Kaucsar<sup>1</sup>, Peter Hamar<sup>1</sup>

<sup>1</sup> Institute of Clinical Experimental Research, Semmelweis University, Budapest

## Introduction

The effective therapy of triple-negative breast cancer (TNBC) has not yet been achieved. Modulated electro-hyperthermia (mEHT) is a novel adjuvant antitumor therapy, based on the highly selective heating of the tumor tissue by a 13.56 MHz radiofrequency current induced electric field.

## Aims

Our aim was to investigate the effects of repeated mEHT treatment in a triple-negative mammary carcinoma bearing mouse model.

## Methods

4T07 cells were inoculated orthotopically in female BALB/c mice. Tumor growth was monitored in vivo by digital caliper and ultrasound (Phillips Sonos 5500). The mEHT (n=8) or sham (n=9) treatments started 7 days after inoculation and were repeated 5 times, on every other day. Mice were euthanized 1 day after the fifth treatment and the tumors were dissected, weighed and processed for histology and molecular biology techniques. The ratio of the damaged area compared to the whole tumor area (Tissue Destruction Ratio, TDR) was evaluated on H&E and cleaved caspase-3 stained sections, while HSP70, a common damage-associated molecular signal, Ki67, a proliferation marker and p21, a tumor suppressor protein expression were analyzed on immunohistochemical staining with the HistoQuant module of the CaseViewer Software (3DHistech).

## Results

There was a significant decrease in tumor growth (sham: 5.7x, mEHT: 2.4x relative to pre-treatment (day 6) size,  $p < 0.0001$ ) and weight (sham:  $288.3 \pm 58.1$  mg vs mEHT:  $85.3 \pm 21.3$  mg,  $p < 0.05$ ) in the mEHT treated group, compared to the sham group. The HSP70 stained area in the non-destructed tumor tissue was 5.2 fold higher in the mEHT treated group, compared to the sham group ( $p < 0.05$ ). Moreover, the Ki67 positive nucleus / mm<sup>2</sup> count was significantly lower (sham:  $2823.4 \pm 211.9$  pcs/mm<sup>2</sup> vs mEHT:  $1736.7 \pm 315.3$  pcs/mm<sup>2</sup>,  $p < 0.05$ ) and the p21 positive nucleus / mm<sup>2</sup> count showed increasing tendency (sham:  $127.0 \pm 25.3$  pcs/mm<sup>2</sup> vs mEHT:  $242.2 \pm 78.2$  pcs/mm<sup>2</sup>,  $p = 0,073$ ) in the mEHT treated group, compared to the sham group.

## Conclusion

Our findings suggest, that repeated mEHT could lower tumor cell proliferation by promoting cell cycle arrest in vivo. Thus, mEHT could be a possible alternative adjuvant therapeutic strategy for TNBC cancer patients. We plan next generation sequencing to elucidate the biological mechanism behind the effects of mEHT.

NVKP\_16-1-2016-0042



SZÉCHENYI 2020

NEMZETI KUTATÁSI  
FELSORTELÉS ÉS  
INNOVÁCIÓS ALAP  
ELLENŐRZÉS ÉS  
ELÉRTETÉS ÉS JÖVŐJE

# Modulated electro hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model

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<sup>1</sup> Institute of Clinical Experimental Research

36th Conference of the International Clinical Hyperthermia Society  
2018. Budapest, September 28-29.

NVKP-16-1-2016-0042 project

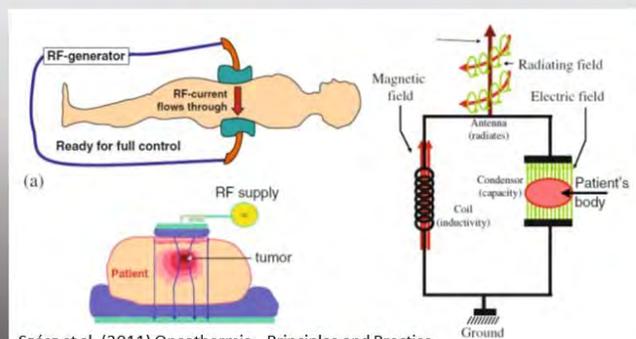


## Modulated electrohyperthermia

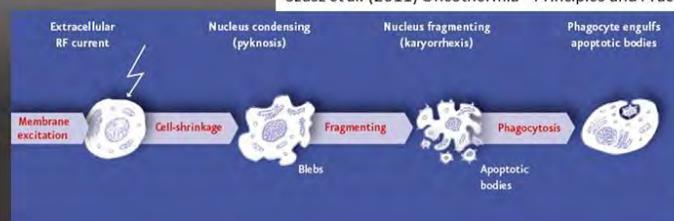
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INNOVÁCIÓS ALAP  
ELLENŐRZÉS ÉS  
ELÉRTETÉS ÉS JÖVŐJE

**Highly-selective  
heating of the  
tumor**

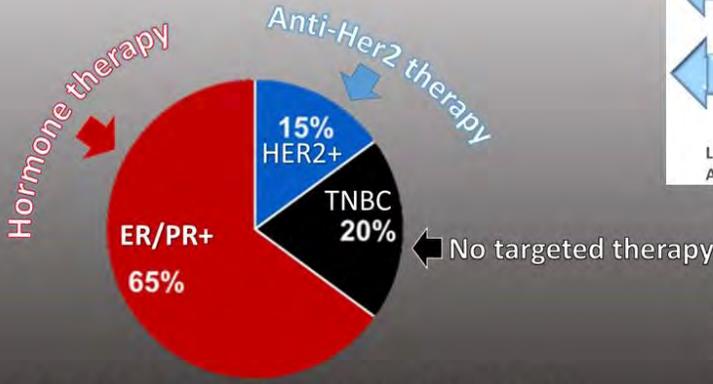


Szász et al. (2011) Oncothermia – Principles and Practice



www.oncotherm.org

# TRIPLE-NEGATIVE BREAST CANCER (TNBC)



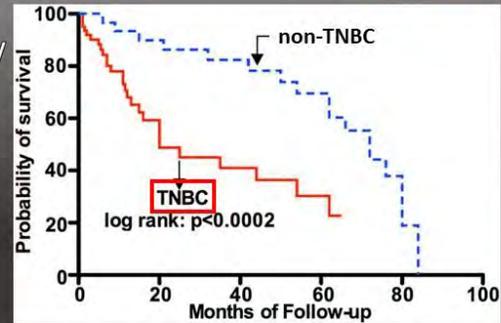
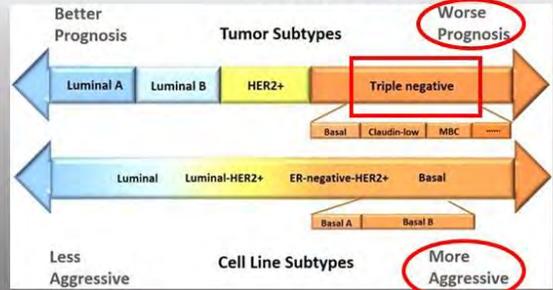
## MOLECULAR SUBTYPES OF BREAST CANCER

Berrocal et al. (2017) *AJHO*, 13(6):16-19

ER/PR – Estrogen/Progesterone receptor

Her2 – Human Epidermal growth factor Receptor

Li et al. *JC* 2017; 8(16):3131-3141



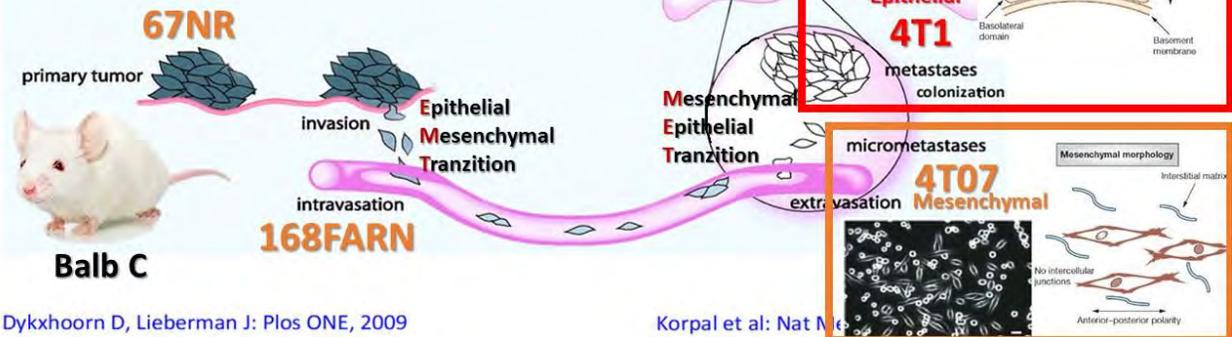
Islam et al. (2016) *SciRep*, 18830(6):7

Turley EA et al. (2008) *Nat Clin Pract Oncol*

## Isogenic clones of a spontaneous mouse triple-negative breast cancer

- Different metastatic potential

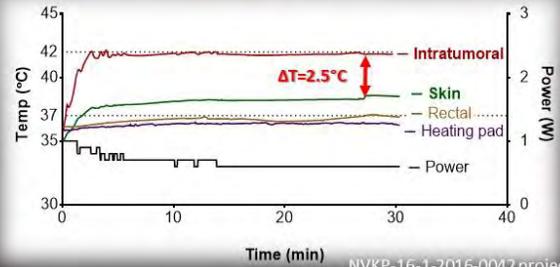
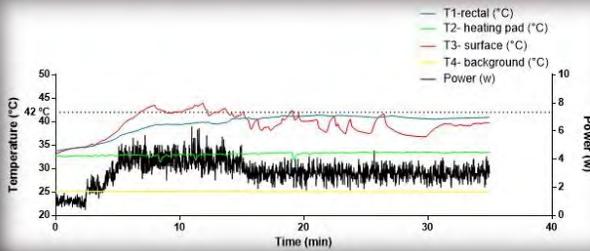
67NR < 168FARN < 4T07 < 4T1



Dykxhoorn D, Lieberman J: *Plos ONE*, 2009

Korpal et al: *Nat Med*

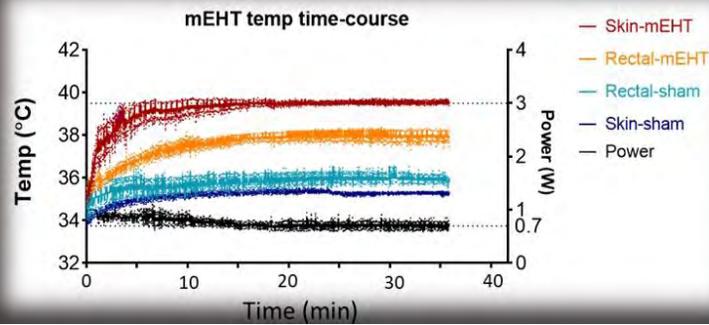
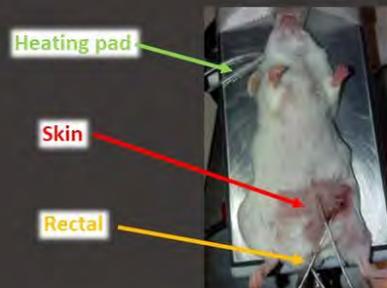
# TREATMENT OPTIMIZATION



NVKP-16-1-2016-0042 project

## Treatment settings:

Heating pad temperature	37-38 °C
Skin temperature	40 °C
Rectal temperature	37-38 °C
Power	0.7±0.3 W
Time	35 min

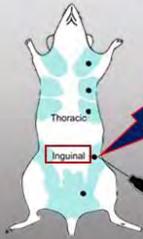




# ONE-TREATMENT PROTOCOL



Female Balb/C mice (N = 14)



**1X modulated electrohyperthermia**

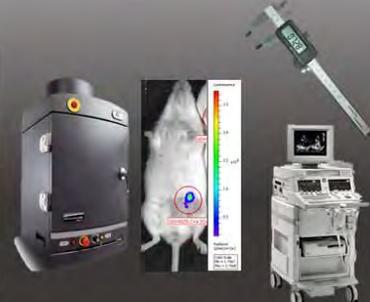
LabEHY-200

40°C 30min



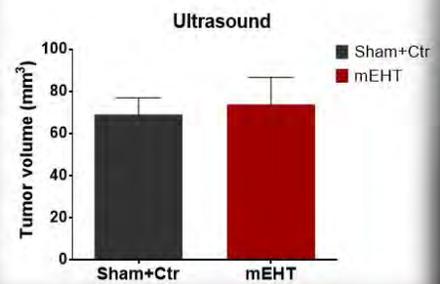
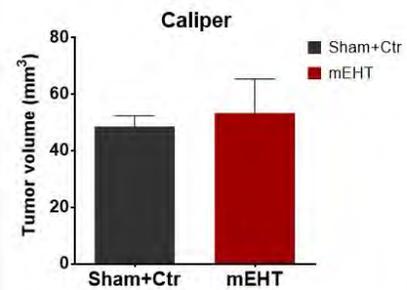
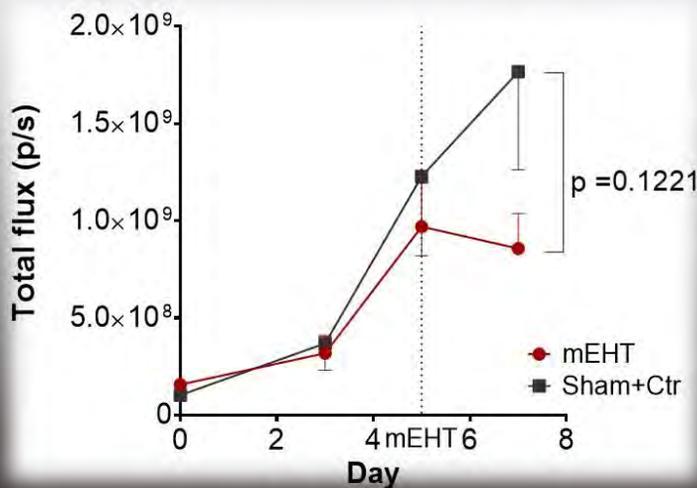
$10^6$  **4T1-GFP-mCherry-Luciferase**  
TNBC cells / 100  $\mu$ l **PBS:Matrigel**

Day after inoculation	0	1	2	3	4	5	6	7
4T1 cell inoculation	x							
IVIS				x		x		x
Ultrasound				x		x		x
Caliper				x	x	x	x	x
mEHT						x		
Harvest								x



NVKP-16-1-2016-0042 project

## RESULTS – one treatment

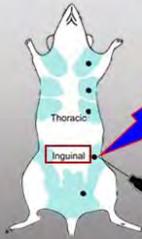




# TWO-TREATMENT PROTOCOL



Female Balb/C mice (N = 12)



**2X modulated electrohyperthermia**

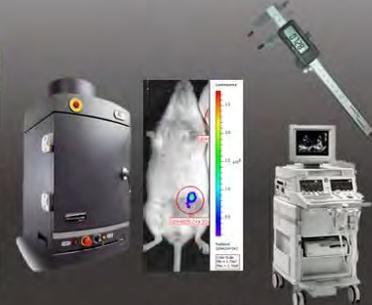
LabEHY-200

40°C 30min



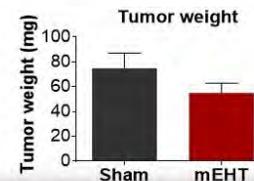
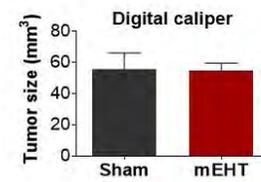
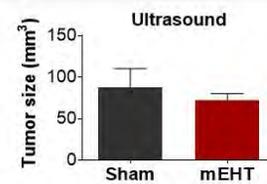
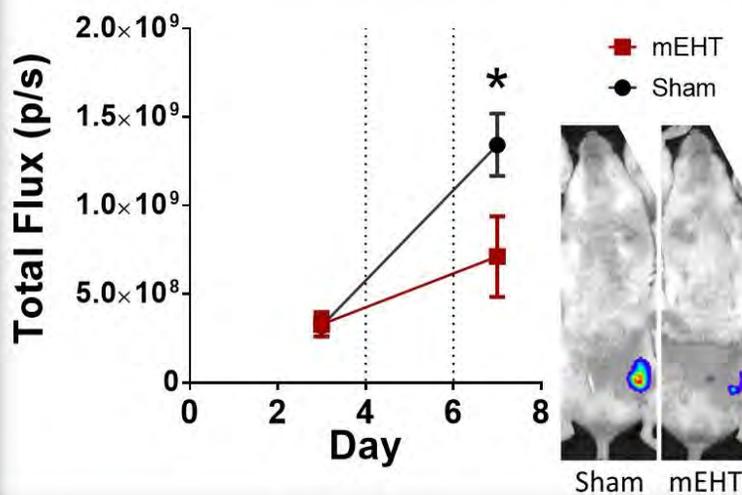
$10^6$  **4T1-GFP-mCherry-Luciferase**  
TNBC cells / 50  $\mu$ l **PBS:Matrigel**

Day after inoculation	0	1	2	3	4	5	6	7
4T1 cell inoculation	X							
IVIS				X				X
Ultrasound								X
Caliper								X
mEHT					X		X	
Harvest								X



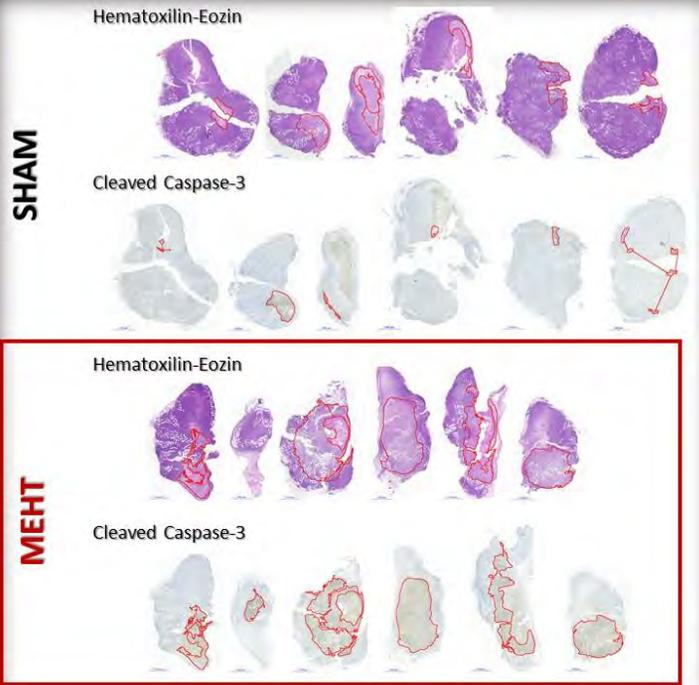
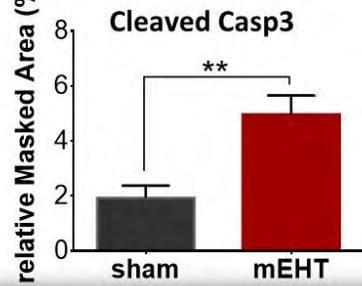
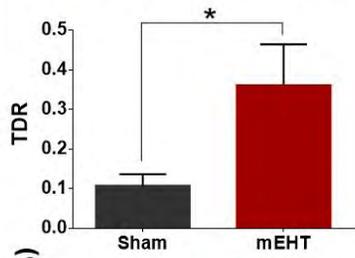
NVKP-16-1-2016-0042 project

## RESULTS – two treatments



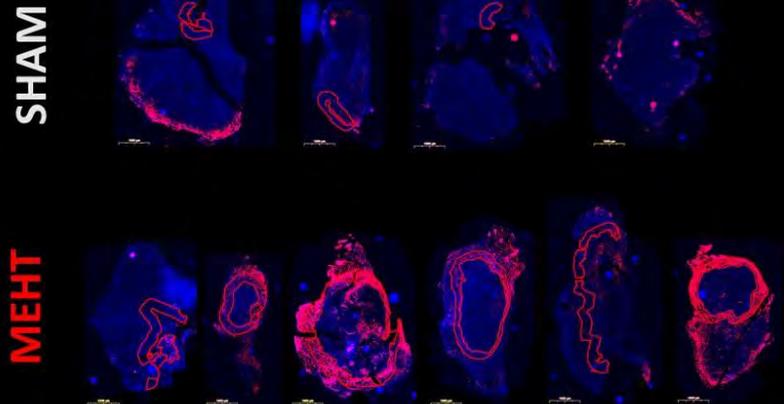
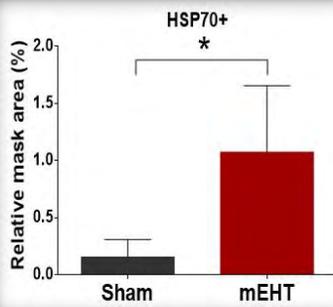
## RESULTS – two treatments

### Tissue destruction ratio

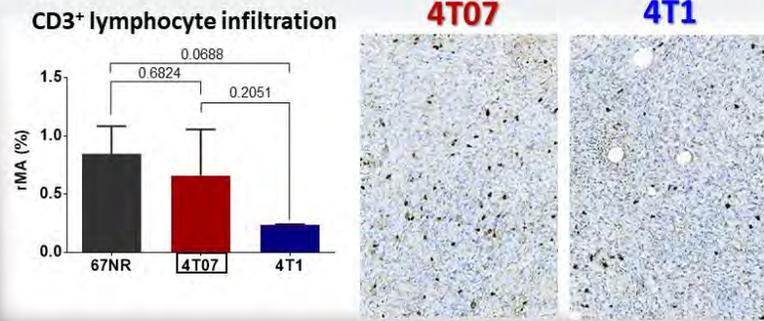


## RESULTS two treatments

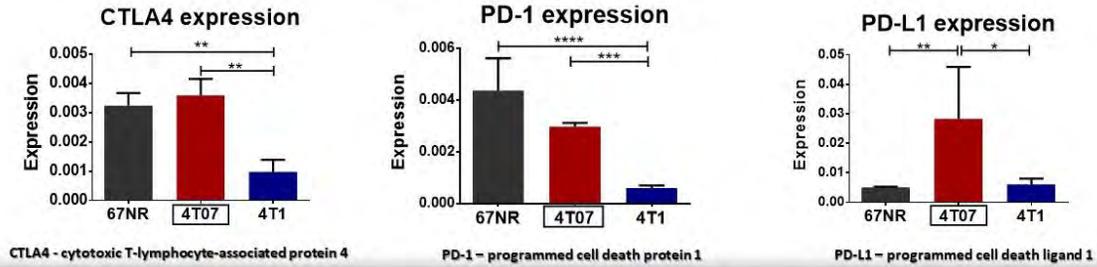
### HSP70 – damage associated molecular marker



# Immune profile of TNBC isografts

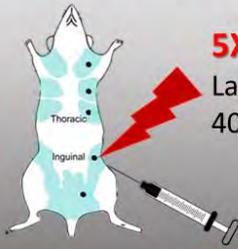


## Expression of checkpoint inhibitors



# FIVE-TREATMENT PROTOCOL

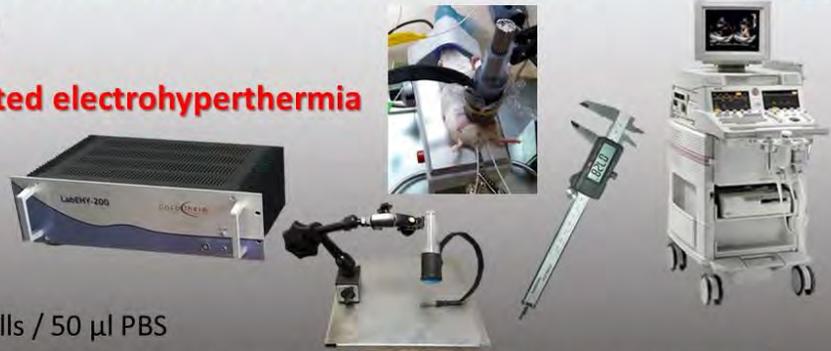
Female Balb/C mice (N = 18)



**5X modulated electrohyperthermia**

LabEHY-200  
40°C 30min

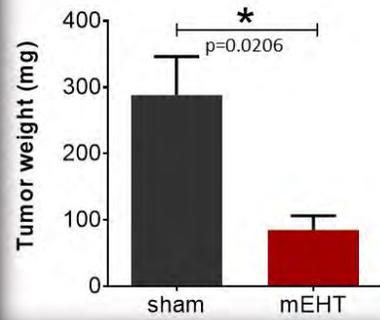
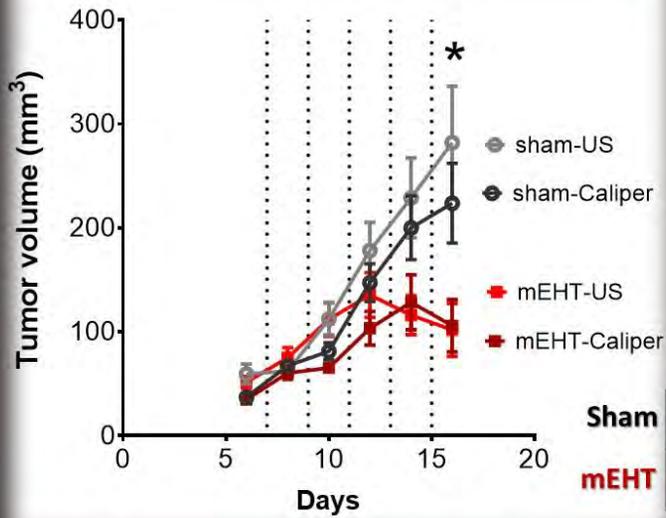
10<sup>6</sup> **4T07** TNBC cells / 50 µl PBS



Day after inoculation	-1	0	6	7	8	9	10	11	12	13	14	15	16
4T07 cell inoculation		X											
Tumor size (US, caliper)			X		X		X		X		X		X
mEHT				X		X		X		X		X	
Harvest													X

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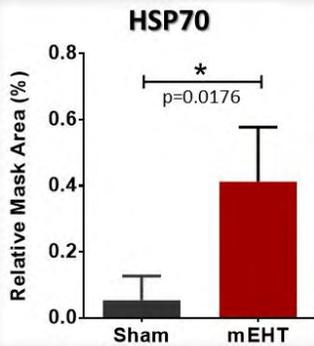
## RESULTS – five treatments



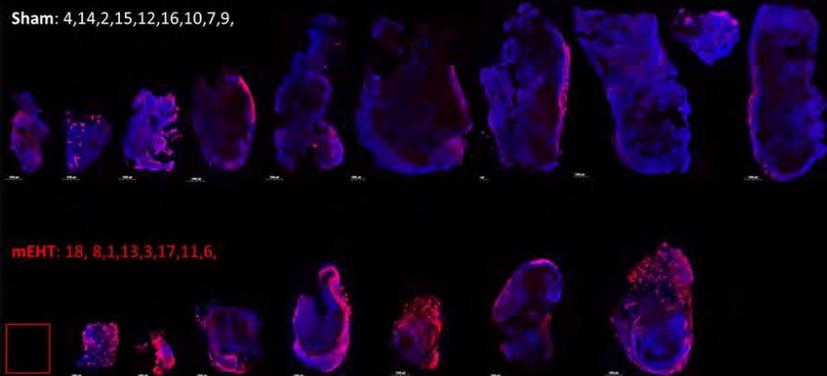
NVKP-16-1-2016-0042 project

## RESULTS five treatments

### HSP70 – damage associated molecular marker



Sham: 4,14,2,15,12,16,10,7,9,



mEHT: 18, 8,1,13,3,17,11,6,

NVKP-16-1-2016-0042 project

## HSP70 – damage associated molecular marker

after two treatments

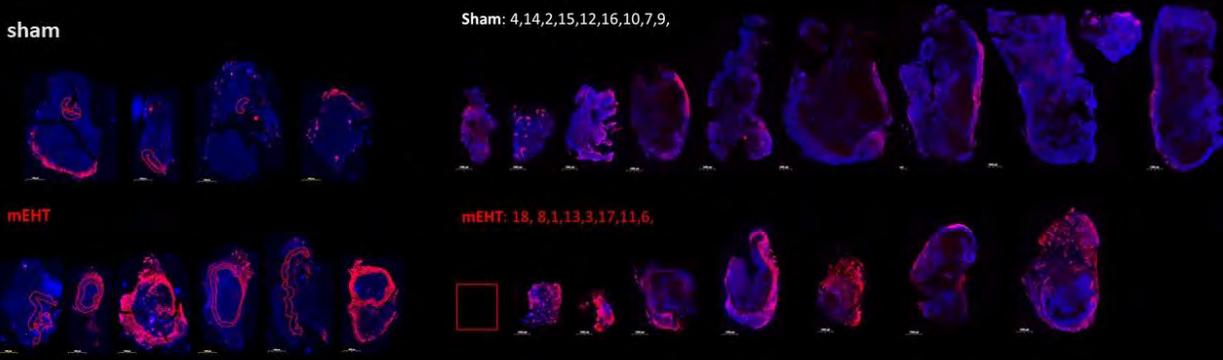
after five treatments

sham

Sham: 4,14,2,15,12,16,10,7,9,

mEHT

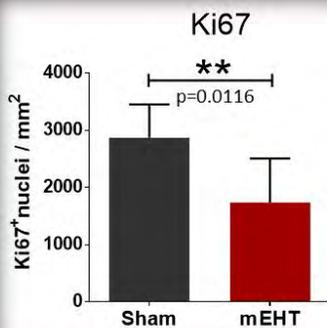
mEHT: 18, 8,1,13,3,17,11,6,



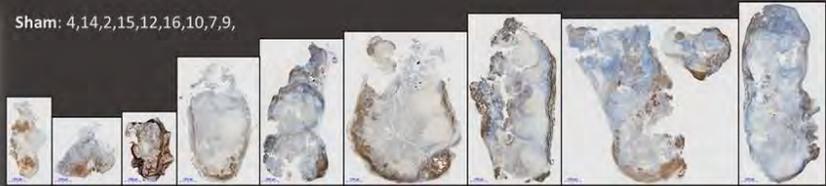
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## RESULTS five treatments

## Ki67 – proliferation marker



Sham: 4,14,2,15,12,16,10,7,9,



mEHT: 18,8,1,13,3,17,11,6,20

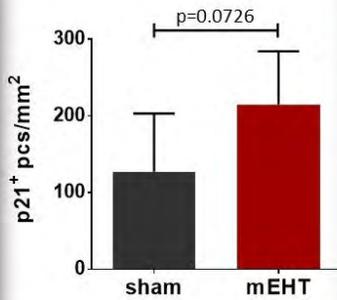


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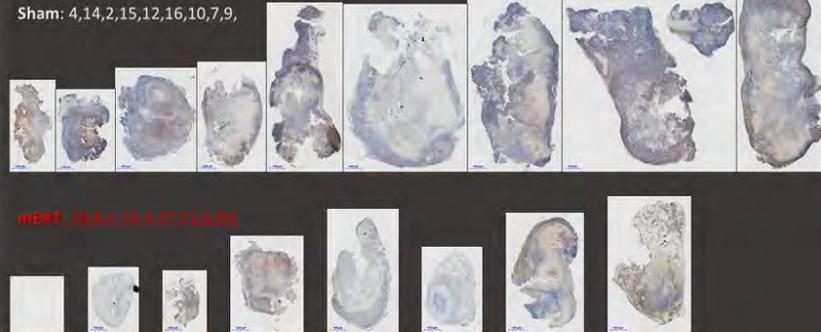
# RESULTS

five treatments

## p21 - common cyclin-dependent kinase inhibitor



Sham: 4,14,2,15,12,16,10,7,9,



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## Summary



### Short-term effects

### Long-term effects

👉 **heat-shock** (Hsp70) 👉

- 👉 **tissue damage** (TDR, cCasp3)
- 👉 tumor **cell death** (IVIS)
- 👉 **no reduction in tumor size** with traditional methods (US, caliper) but with IVIS and TDR (weight and volume)

- 👉 **decrease tumor cell proliferation** (Ki67)
- 👉 **Inhibit tumor growth** (weight and volume)

NVKP-16-1-2016-0042 project



SZÉCHENYI 2020

NEMZETI KUTATÁSI,  
FEJLESZÉSI ÉS  
INNOVÁCIÓS ALAP  
EFOP-1-2016-0008

Thank you for your kind attention!



Péter Hamar  
MD, PhD, Dsc



Tamás Kaucsár  
MD, PhD, postdoc



Csaba Schvarcz  
MD, PhD student



Zita Zolcsák  
MD, resident



Bettina Farkas  
Pharm. student  
TDK



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NVKP-6-1-2016-0042 project

# **Radiotherapy and modulated electro-hyperthermia effect on Panc1 and Capan1 pancreas adenocarcinoma cell lines**

**Forika Gertrud**

1<sup>st</sup> Department of Pathology and Experimental Cancer Research  
Semmelweis University, Budapest, Hungary

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

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# Radiotherapy and modulated electro-hyperthermia effect on Panc1 and Capan1 pancreas adenocarcinoma cell lines

Gertrud Forika<sup>1</sup>, Andrea Balogh<sup>2</sup>, Tamás Vancsik<sup>1</sup>, Zoltán Benyo<sup>2</sup>, Tibor Krenacs<sup>1</sup>

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## Background & Objective

The majority of pancreas malignancies are adenocarcinomas, which show poor outcome. Despite of sophisticated chemotherapy guidelines, those tumor types react very poorly to any treatment regimens, thus new combinations and treatment approaches are intensively searched for. Modulated electro-hyperthermia (mEHT) is a complementary non-invasive cancer treatment modality which uses impedance-coupled radiofrequency to generate selective cell stress and destruction at <42°C in malignant tissue. Here we studied the mechanism of action of mEHT treatment alone and in combination with radiotherapy in Panc-1 and Capan-1, two aggressive pancreas adenocarcinoma cell lines.

## Methods

Panc-1 and Capan-1 cells grown on coverslips were treated with mEHT using LabEHY100 (Oncotherm™) for 60 minutes, irradiated with 2 Gy using <sup>137</sup>Cs source or exposed to combined therapy. To evaluate the effect of treatment on cell death morphological changes were analyzed, apoptosis was measured using Annexin V/7-AAD staining, the ALDH+ cancer stem cell fraction (CSC) and also the presence of phosphorylated gamma histone H2AX (using both immunocytochemistry and flow cytometry).

## Results

Morphological changes (apoptotic bodies, dead cell residues) were observed in both cell lines treated with mEHT. The late apoptotic cell fraction (Annexin V+/7-AAD+) was significantly higher in mEHT alone or 2 Gy + mEHT treated samples than in the irradiated or control groups. The CSC fraction decreased both after mEHT or combined mEHT-radiotherapy treatments, while radiotherapy alone had no remarkable effect on CSC population. The  $\gamma$ -H2AX was upregulated in all treated samples detected by both immunocytochemistry and flow cytometry.

## Conclusion

mEHT induced massive apoptosis in both cell lines tested and sensitized cells to radiation. Elevated levels of the double DNA-strand break marker  $\gamma$ -H2AX in mEHT treated samples suggest that the primary mechanism of tumor destruction by mEHT is the induction of DNA lesions, which ultimately lead to apoptosis. Furthermore, mEHT alone or combined with radiation significantly reduced the ALDH+ CSC population.

This study was founded by the NKFIH-NVKP\_16-1-2016-0042 grant.

# Radiotherapy and modulated electro-hyperthermia effect on Panc1 and Capan1 pancreas adenocarcinoma cell lines

Fórika Gertrúd

1st Department of Pathology and Experimental Cancer Research

## Pancreas malignancies

### Statistics:

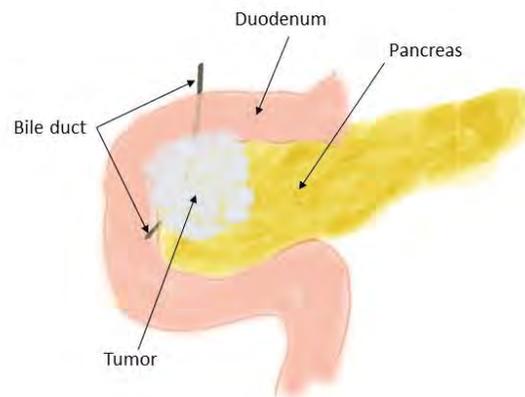
8,2% survival rate for 5 years

Mortality/incidency index: 98%

### Actual treatments:

Surgical

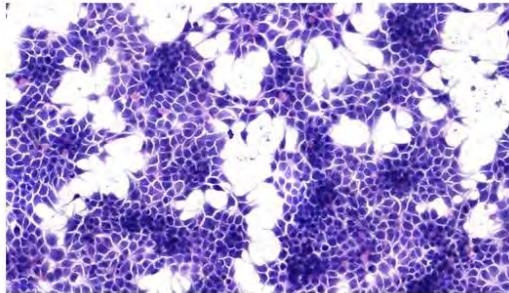
Gemcitabine, Erlotinib, FOLFIRINOX



# Pancreas adenocarcinoma cell lines

## Panc1:

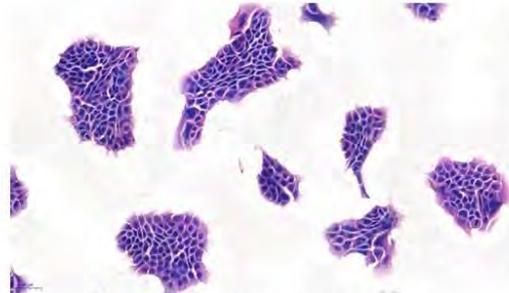
1975 isolated from a ductal adenocarcinoma  
 Good model for radio-chemoresistivity  
 Numerous metastases *in vivo*  
 High tumor stem cell rate



Haematoxylin eosin staining, Ob:20x

## Capan1:

Isolated from a liver metastasis of pancreatic adenocarcinoma  
 Good model for radio-chemoresistivity

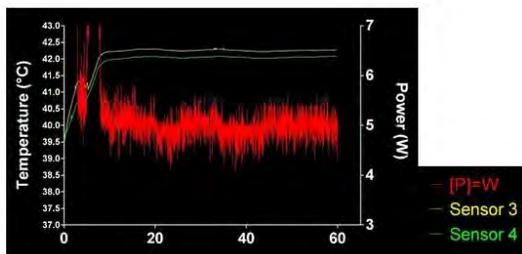


Haematoxylin eosin staining, Ob:20x

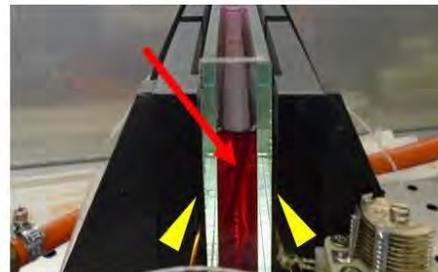
## mEHT treatment *in vitro*

### Modulated electro-hipertermia (mEHT):

- Complementer therapy to radio- or chemotherapy
- Non invasive
- 13.56 MHz radiofrequency -> electric field => 42°C heat
- Selective: elevated glycolysis, ion concentration and conductivity

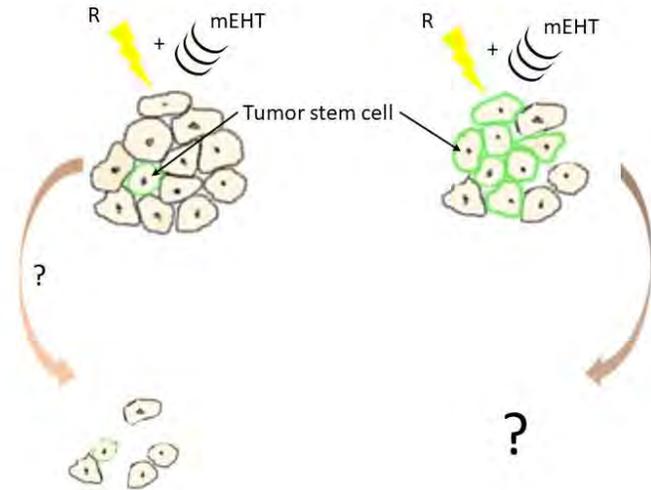


Heat control with power adjustment



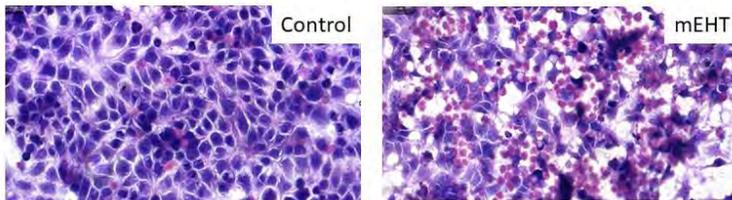
# Aim of the work

- Is mEHT treatment effective on Panc1 and Capan1 cell lines?
- Can mEHT treatment support radiotherapy on tumor cell destruction?
- Combination therapy is effective on tumor stem cells too?

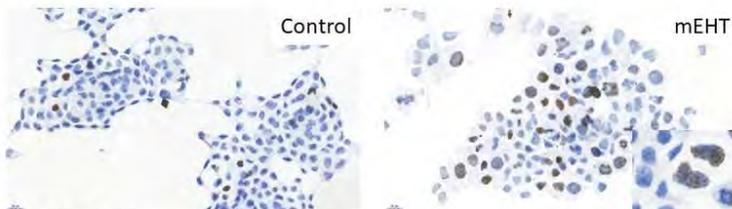


## 60 min mEHT treatment – Panc1

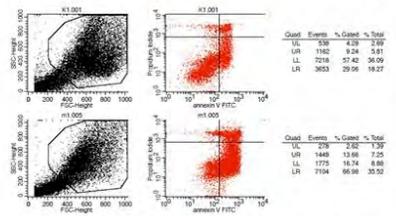
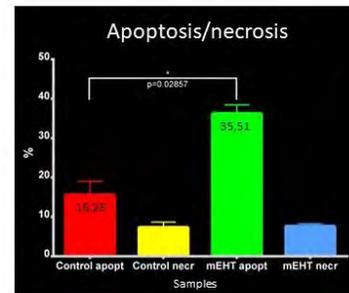
Cell destruction after 24 hours



HE - 24 H

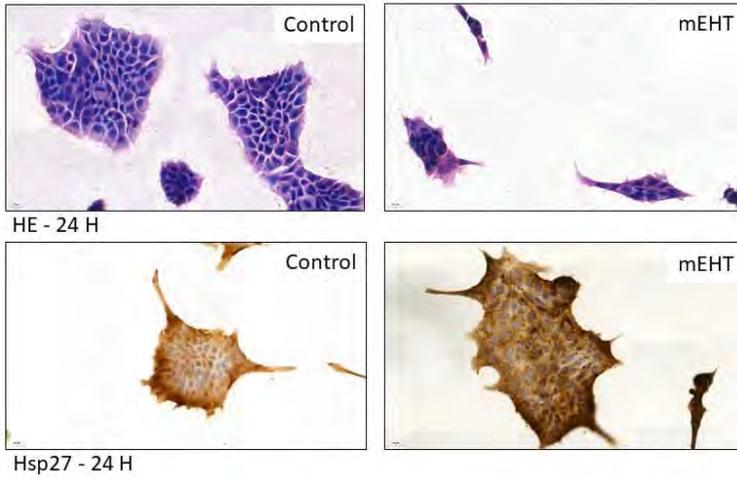


γH2Ax - 24 H

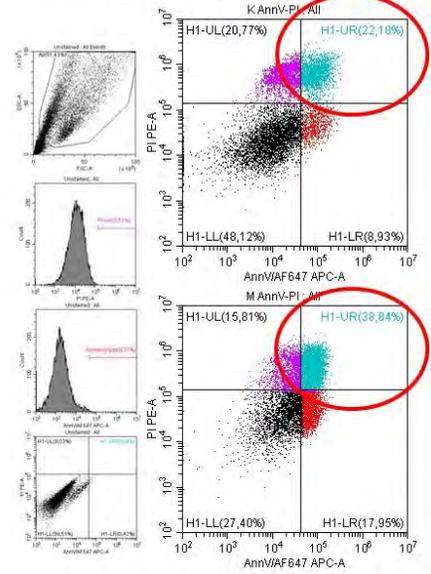


# 60 min mEHT treatment – Capan1

Cell destruction and cell stress after 24 hours

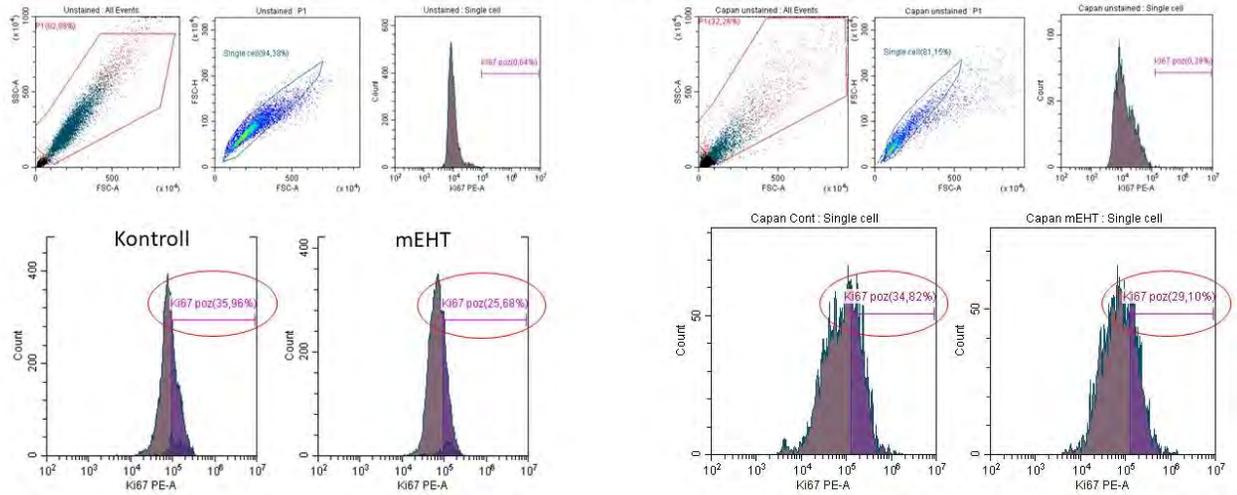


Annexin V and Propidium iodide staining

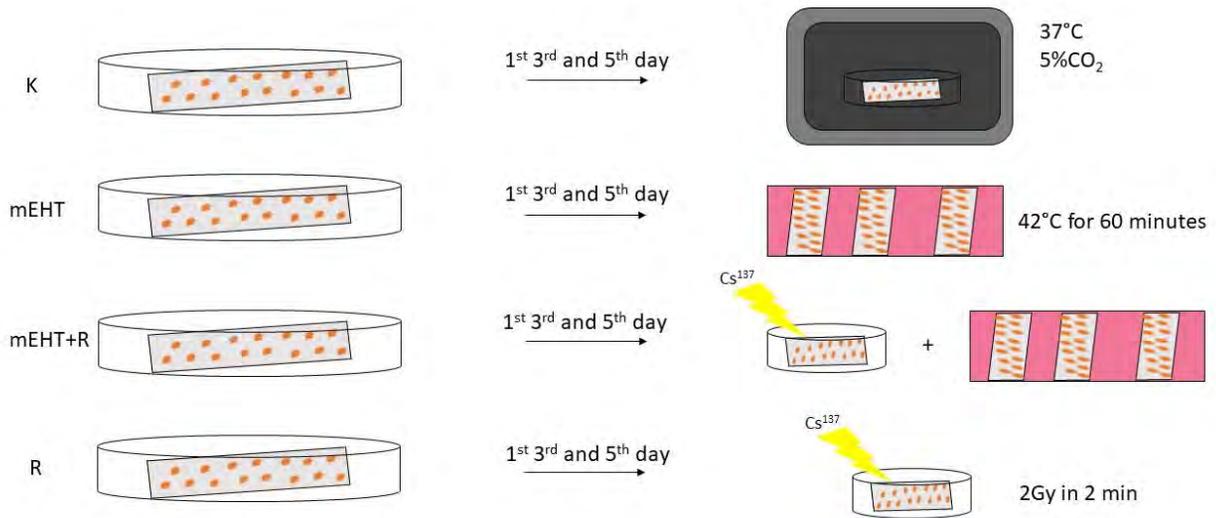


# 60 min mEHT treatment – Ki67 Panc1 Capan1

Ki67: proliferation marker – present in active cell cycle

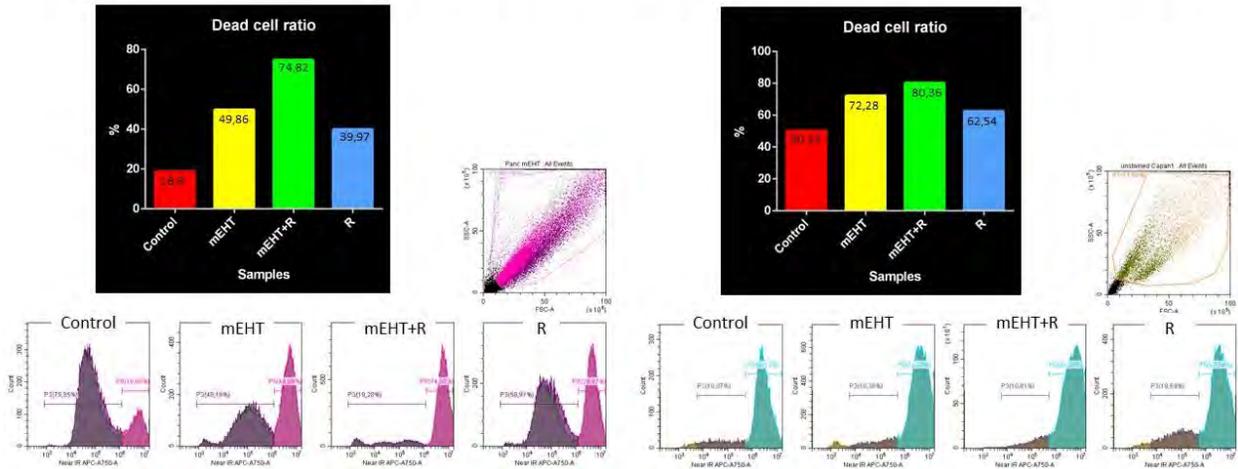


# Combination treatment: 60 min mEHT + 2Gy radiotherapy 3x



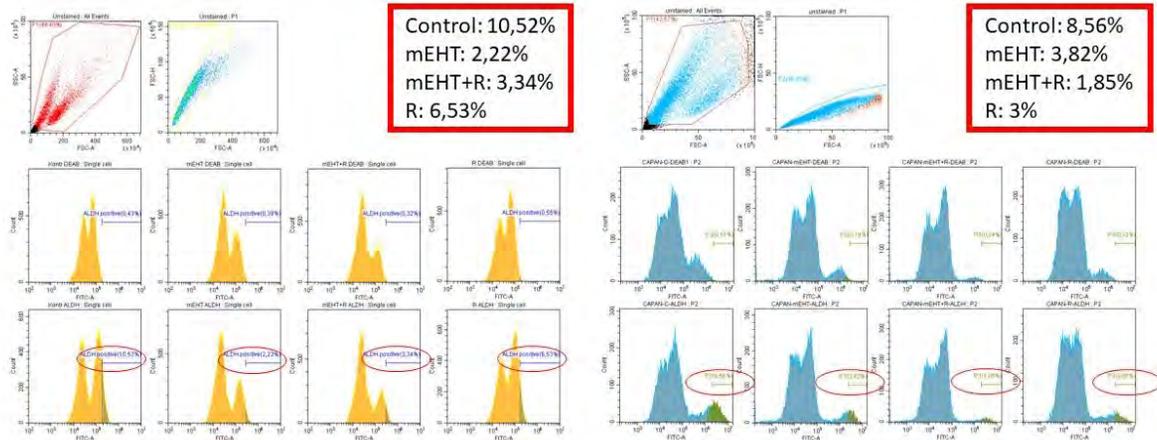
## Combined treatment: Live/dead cell rate Panc1 Capan1

LIVE/DEAD™ Fixable Near-IR Dead Cell Stain Kit - two population: weak signal = living cells, strong signal = dead cells



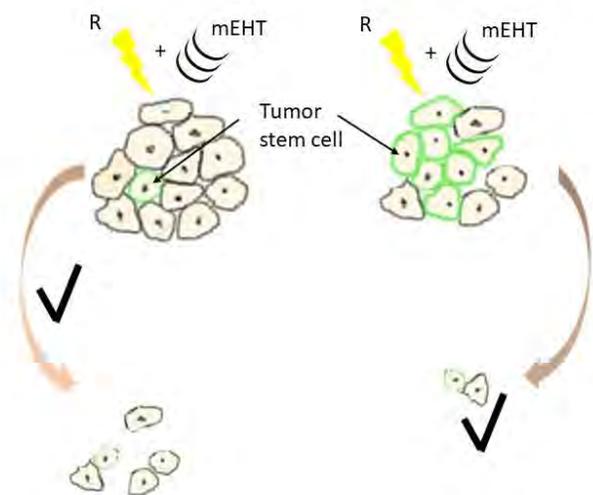
# Combined treatment: Stem cell ratio Panc1 Capan1

ALDH – aldehyde dehydrogenase – highly expressed by tumor stem cells  
ALDEFLUOR Kit – using to detect the ALDH expressing cell amount by flow cytometry



## Conclusions

- Both cell lines (Panc1, Capan1) are suitable for mEHT treatment study
- 1X60 minutes mEHT can lead to a massive apoptosis and cell stress
- Combined with radiotherapy, mEHT potentiate the effectivity of the treatment
- Tumor stem cells are sensitive for mEHT or for combined treatment despite of their resistance for the radiotherapy alone





Thank you for your attention

Special thanks to:

- Balogh Andrea
- Mátrainé Balogh Éva
- Vancsik Tamás

*This study was founded by the NKFIH-NVKP\_16-1-2016-0042 grant*

# **Modulated Electro-Hyperthermia (mEHT) in Intergrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: a retrospective multicenter controlled study**

**Giammaria Fiorentini, Virginia Casadei**  
Onco-Hematology Department, Azienda Ospedaliera  
„Ospedali Riuniti Marche Nord”, 61122 Pesaro, Italy

**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

## **Cite this article as:**

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[www.oncothermiajournal.com/journal/2018/Modulated\\_electro\\_hyperthermia\\_\(mEHT\)\\_in\\_integrative\\_cancer\\_treatment.pdf](http://www.oncothermiajournal.com/journal/2018/Modulated_electro_hyperthermia_(mEHT)_in_integrative_cancer_treatment.pdf)

# **Modulated Electro-Hyperthermia (mEHT) in Intergrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: a retrospective multicenter controlled study**

**Giammaria Fiorentini<sup>1</sup>, Donatella Sarti<sup>1</sup>, Carlo Milandri<sup>2</sup>, Patrizia Dentico<sup>2</sup>, Andrea Mambrini<sup>3</sup>, Caterina Fiorentini<sup>4</sup>, Gianmaria Mattioli<sup>5</sup>, Stefano Guadagni<sup>6</sup>**

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<sup>6</sup>Department of Applied Clinical Sciences and Biotechnology, Section of General Surgery, University of L'Aquila, 67100 L'Aquila, Italy

## **Background**

Brain tumor therapy with hyperthermia and with an electric field is approved by the United States Food and Drug Administration (FDA). There are interesting studies on glioma therapy with modulated electro-hyperthermia (mEHT), which combines the heat-therapy with an electric field. Clinical researchers had found the mEHT method feasible for not only palliative but reported also evidence of therapeutic response.

## **Purpose**

To monitor the efficacy and safety of modulated electro-hyperthermia (mEHT) for the treatment of relapsed malignant glioma and astrocytoma.

## **Methods**

We collected data retrospectively on 150 patients that were affected by malignant glioma and astrocytoma. Inclusion criteria were: informed consent signed, >18 years old, histological diagnosis of malignant glioma or astrocytoma, failure of previous temozolomide-based chemotherapy and radiotherapy, indication for treatment with mEHT as the palliative setting. mEHT was performed using a capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes). The applied power was 40-150 Watts. Results of mEHT were compared to those of the best supportive care (BSC).

## **Results**

150 consecutive patients were enrolled in the study, 111 (74%) had glioblastoma multiforme (GBM), and 39 (26%) had astrocytoma (AST). mEHT was performed to 28 (25%) of GBM and 25 (64%) of AST.

Tumor response analysis three months after mEHT was 29% for GBM and 48% for astrocytoma, whereas it was 4% for GBM and 10% for AST for the group that did not receive mEHT.

The median overall survival (OS) of the whole study population was 9 months (range 5-108) for GBM and 16 months (6-156) for AST group. We observed 3 long survivors at 156, 60, 62 months in AST group.



# **Modulated Electro-Hyperthermia (mEHT) in Integrative Cancer Treatment for Relapsed Malignant Glioblastoma and Astrocytoma: a retrospective multicenter controlled study**

Giammaria Fiorentini, M.D.

Virginia Casadei, M.D.

Onco-Hematology Department, Azienda Ospedaliera  
"Ospedali Riuniti Marche Nord", 61122 Pesaro, Italy

## **Background**

Malignant Gliomas Therapy (MGlioT) with an electric field is approved by the Food and Drug Administration (FDA).

Studies on MGlioT with mEHT, which combines the heat-therapy with an electric field, suggest a new way for research.

Experts had found the mEHT method is feasible for not only palliative but reported also evidence of therapeutic response.

### **Hypothesis: HT may be effective in HG gliomas (I)**

- Radiofrequency hyperthermia is useful for malignant brain tumors (Tanaka R, 1987)
- Thermotherapy of recurrent malignant brain tumors is useful (Sneed 1992)
- Favourable effects of antineoplastic agents and hyperthermia on cytotoxicity toward chronically hypoxic glioma cells . ( Watanabe M, 1992)
- Survival benefit of hyperthermia in a prospective randomized trial of brachytherapy boost +/-hyperthermia for HG gliomas : improves mOS with  $p = 0.008$ ; hazard ratio 0.51 ( Sneed, 1998)

### **Hypothesis: HT may be effective in HG gliomas (II)**

- Application of hyperthermia induced by superparamagnetic iron oxide nanoparticles in glioma treatment contribute toward establishing magnetic hyperthermia as a promising tool in the treatment of malignant gliomas (Silva AC, 2011).
- Treatment of malignant glioma using hyperthermia has beneficial effects (Sun J, 2013)
- Concurrent hyperthermia and re-irradiation for recurrent high-grade gliomas suggested that is a safe and well-tolerated. (Heo J , Neoplasma, 2017)
- Hyperthermia induces translocation of apoptosis-inducing factor (AIF) and apoptosis in human glioma cell lines (Fukami T, 2004)
- Improving efficiency of adriamycin crossing blood brain barrier by combination of thermosensitive liposomes and hyperthermia (Gong W,2011)
- Efficacy and safety of intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with radiotherapy on patients with recurrent HG glioma (Mair-Hauff K, 2011)

### **Hypothesis: HT may be effective in HG gliomas (III)**

- Treatment of malignant glioma using hyperthermia (Sun J, 2013)
- Thermotherapy-induced reduction in glioma invasiveness is mediated by tumor necrosis factor-alpha. (Qin LJ, 2015)
- Stereotactic Laser Interstitial Thermal Therapy for Recurrent High-Grade Gliomas. (Lee I, 2016).
- Enhanced Energy Localization in Hyperthermia Treatment Based on Hybrid Electromagnetic and Ultrasonic System: Proof of Concept with Numerical Simulations.(Nizam-Uddin N, 2017).
- Pulsed-wave low-dose ultrasound hyperthermia selectively enhances nanodrug delivery and improves antitumor efficacy for brain metastasis of breast cancer.(Wu SK, 2017)

### **Hypothesis: mEHT may be effective in HG gliomas**

- Non invasive intracranial hyperthermia with capacitive transference ECT intratumoral and cerebral thermometry gives favourable results (Ley-Valle, 2003) .
- Regional EHT in combination with chemotherapy induces a mOS of 44,2 and 23,2 months in relapsed HG gliomas (Sahinbas, 2005) .
- Phase II clinical study on relapsed HG gliomas treated with EHT reported a RR of 25% (Fiorentini, 2006).
- EHT combined with alkylating drugs in relapsed HG gliomas reported that is tolerable and feasible ( Wismeth ,2010).
- EHT inhibits glioma tumorigenicity through the induction of E2F1-mediated apoptosis. Int J Hyperthermia (Cha J, 2015).

**Hypothesis: mEHT may be effective in HG gliomas**

- Clinical and economic evaluation of modulated EHT concurrent to dose-dense temozolomide regimen in the treatment of recurrent glioblastoma: a retrospective analysis of a two-center German cohort trial with systematic comparison and effect-to-treatment analysis (Roussakov SV, 2017).
- Energy Absorption by the Membrane Rafts in the Modulated Electro-Hyperthermia (Papp E, 2017)
- Retrospective observational Clinical Study on Relapsed Malignant Gliomas Treated with Electro-Hyperthermia (Fiorentini, 2017)

**Purpose**

to study efficacy and safety of mEHT for the treatment of relapsed malignant glioma (GBM and AST) versus the best supportive care (BSC).

## Methods 1

we collected data retrospectively on 149 patients affected by GBM and AST.

Inclusion criteria were: informed consent signed, >18 years old, histological diagnosis of malignant glioma, relapsed after surgery, adjuvant temozolomide-based chemotherapy and radiotherapy, indication for treatment with mEHT as the palliative setting.

**Table 1. Description of AST patient's group.**

Parameters (AST)	#	%
Males	20	52.6
Females	18	47.4
mEHT treated	22	58
MGMT methylated	11	28.9
MGMT non methylated	11	28.9
MGMT ND	16	42.2
IDH1 mutated	13	34.2
IDH1 wild type	11	28.9
IDH1 ND	14	36.9
age (range)	22 - 80	-
survival (range)	3 - 156	-

**Table 2. Description of GBM patient's group**

Parameters (GBM)	#	%
Males	68	61.3
Females	43	38.7
mEHT treated	28	25.2
MGMT methylated	25	22.5
MGMT non methylated	27	24.3
MGMT ND	59	53.2
IDH1 mutated	13	11.7
IDH1 wild type	19	17.1
IDH1 ND	79	71.2
age (range)	27 - 86	-
survival (range)	2 - 108	-

## **Methods 2**

mEHT was performed with capacitive coupling technique keeping the skin surface at 26 C° and 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes). The applied power was 40-150 Watts step-up heating protocol. Results of mEHT were compared to those of the Best Supportive Care. BSC included further chemotherapy and radiotherapy, immunotherapy, CBD and holistic therapy

### Premedications of patients receiving mEHT on the Brain

Generally every patient received surgery and radiotherapy before mEHT, for this reason they had already an anti-seizures therapy.

If the patient suffered from seizures, 250 ml of glicerol 18% solution was administered in 30 minutes before mEHT and also 12 mg of dexamethasone in drops were given to the patient.

Omeprazole (proton pump inhibitor) was administered for the whole cycle therapy at the dosage of 40mg/day.

**Table 3. Treatment parameters**

Practical parameters	value
step-up power (from-to [W])	40-150
average energy-dose (kJ)	540
Therapeutic temperature (°C)	40-42.5
treatment time /session	60
treatment frequency (weakly)	3
treatment cycle (weeks)	8
follow-up time (months)	16

# ELECTRO HYPERTHERMIA



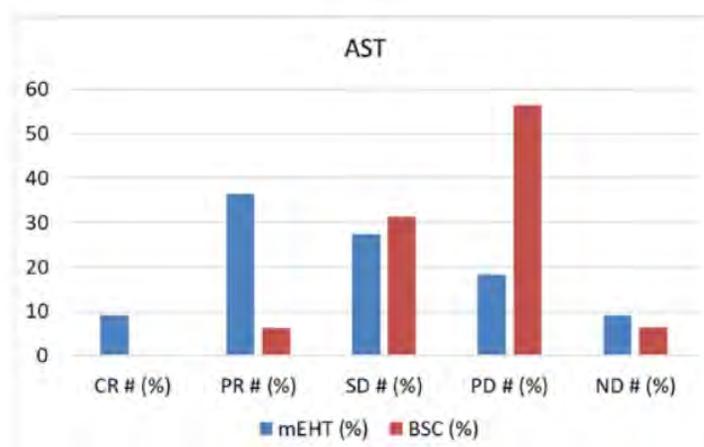
Treating area: **Brain tumor (Pons site)**

Invasivity: **NON-INVASIVE**

**Results 1:** 149 consecutive patients were enrolled, 111 (74%) had GBM and 38 (26%) had astrocytoma (AST). mEHT was performed to 28 (25%) of GBM and 24 (63%) of AST.

Tumor response was observed in 29% and 48% of GBM and astrocytoma in mEHT group respectively, whereas it was observed in 4% and 10% of GBM and AST in BSC group respectively, at the three months follow up.

Response rates of AST



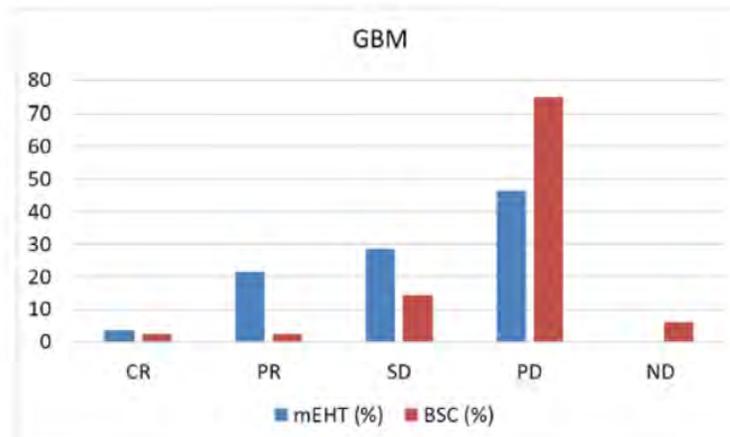
**Table 4. Tumor response and survival of AST group**

Results (AST)	mEHT (#)	mEHT (%)	BSC (#)	BSC (%)
CR # (%)	2	9	0	0
PR # (%)	8	36	1	6
SD # (%)	6	27	5	31
PD # (%)	4	18	9	56
ND # (%)	2	9	1	6
OS median [months] (range)	16	(3-156)	16.5	(3-120)

**Table 5. Tumor response and survival of GBM group**

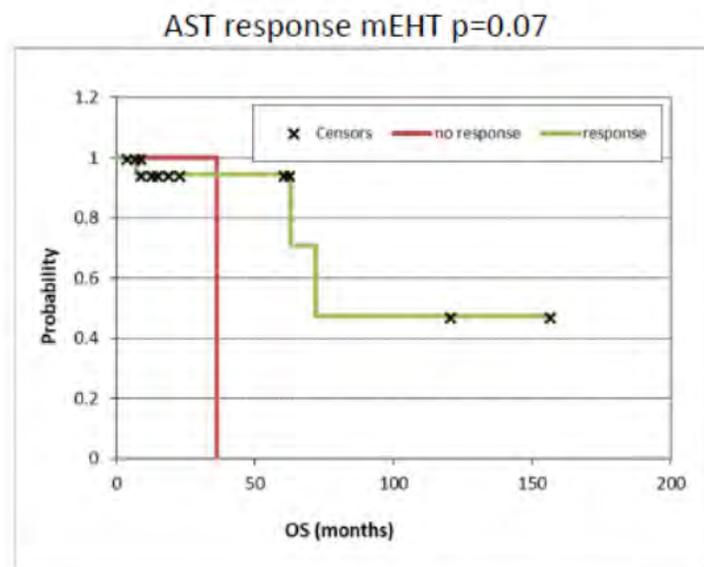
Results (GBM)	mEHT (#)	mEHT (%)	BSC (#)	BSC (%)
CR # (%)	1	4	2	2
PR # (%)	6	21	2	2
SD # (%)	8	29	12	14
PD # (%)	13	46	62	75
ND # (%)	0	0	5	6
OS median [months] (range)	14	(2-108)	9	(2-84)

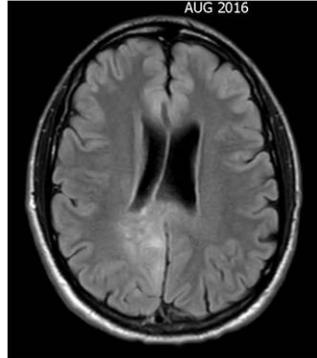
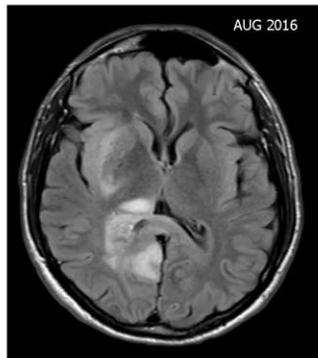
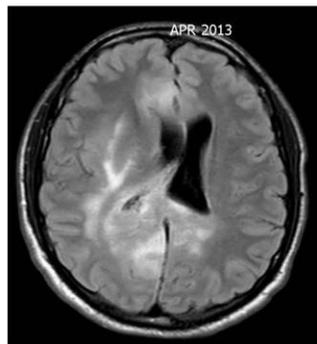
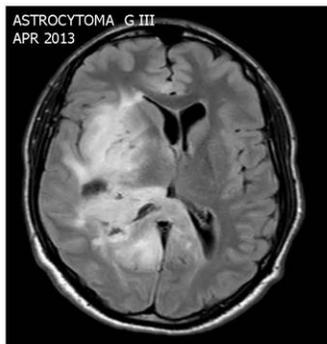
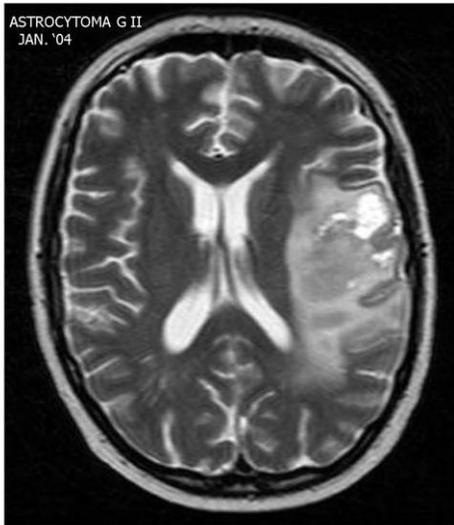
Response rates of GBM



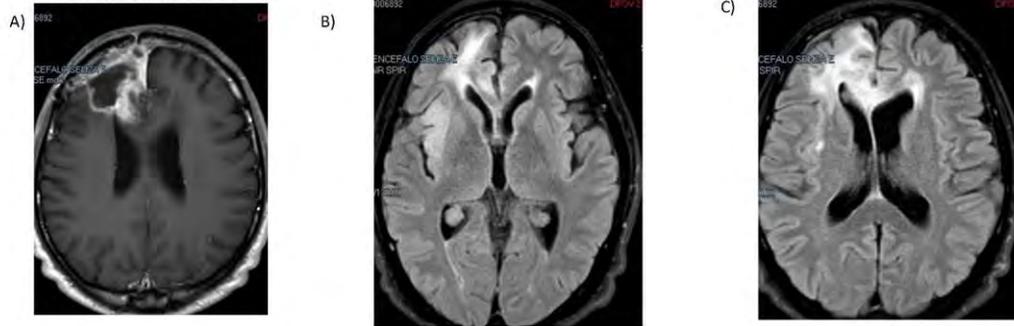
**Results 2:** Survival rate at 1st and 2nd year in the mEHT group was 77.3% and 40.9%, respectively for AST. The 5-year OS of AST was 83% after mEHT vs. 25% after BSC.

The median overall survival (OS) was 10 months (2-108) for GBM and 16.5 months (3-156) for AST group. We observed 4 long survivors in AST and 2 in GBM group. Two of the long survivors in AST the one in GBM group were treated by mEHT.

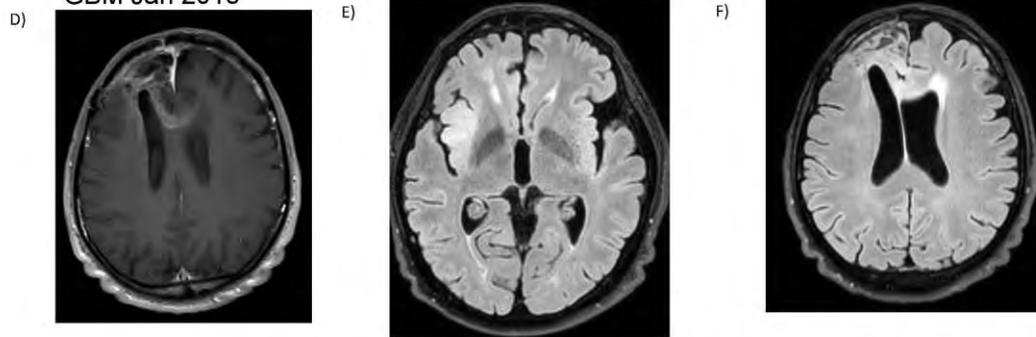




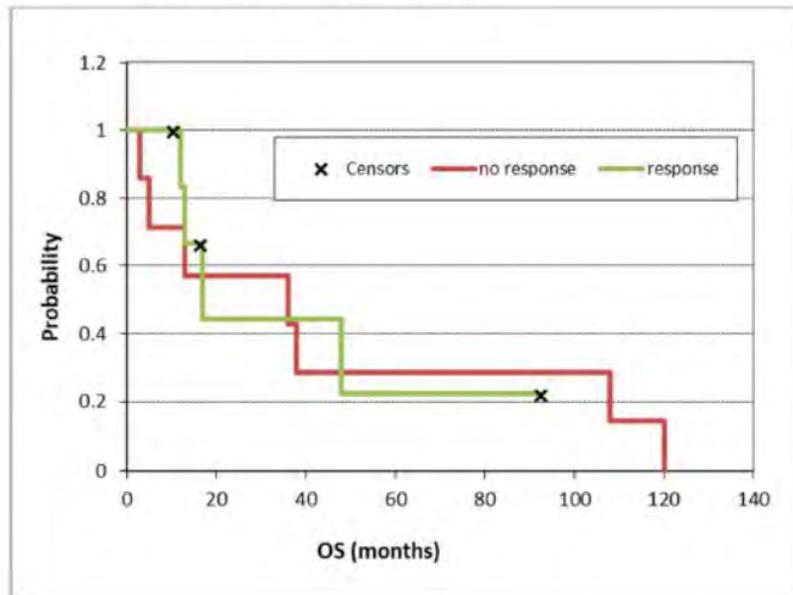
GBM Dec 2017



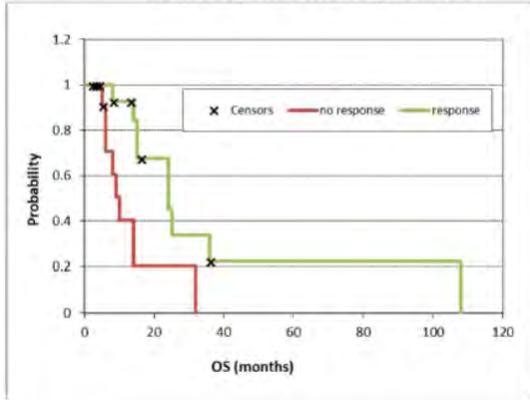
GBM Jan 2018



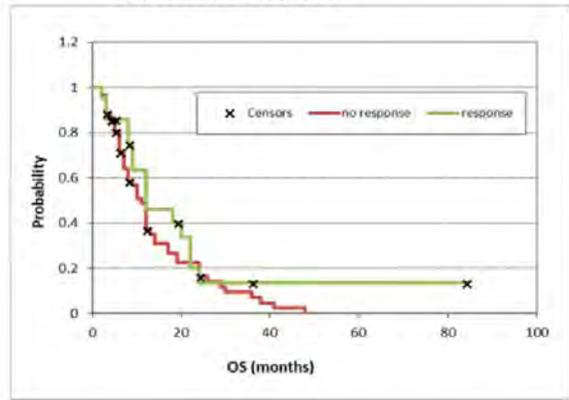
AST response BSC p=0.87



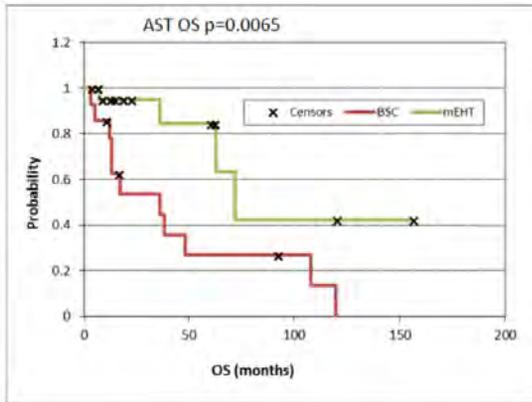
GBM response mEHT p=0.0085



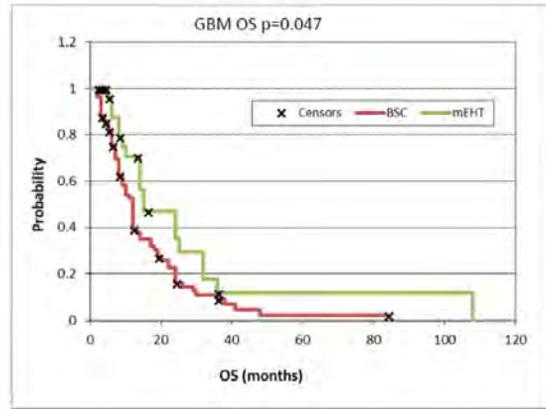
GBM response BSC p=0.23



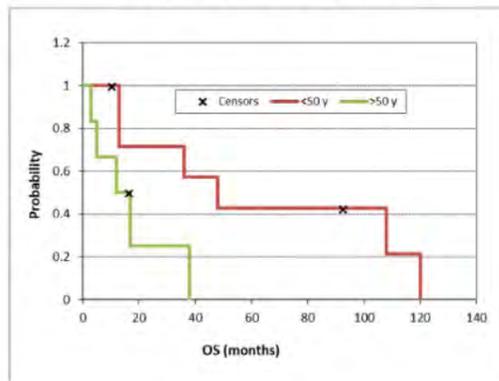
AST OS p=0.0065



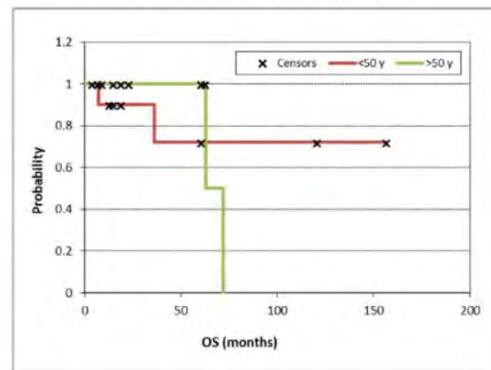
GBM OS p=0.047



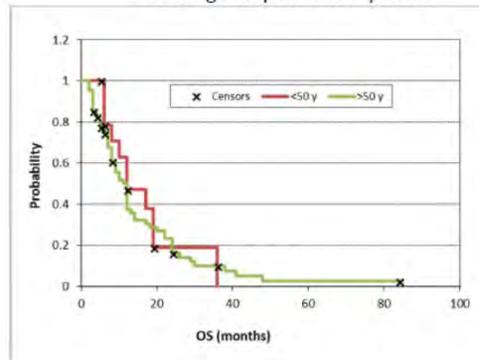
AST age response BSC p=0.04



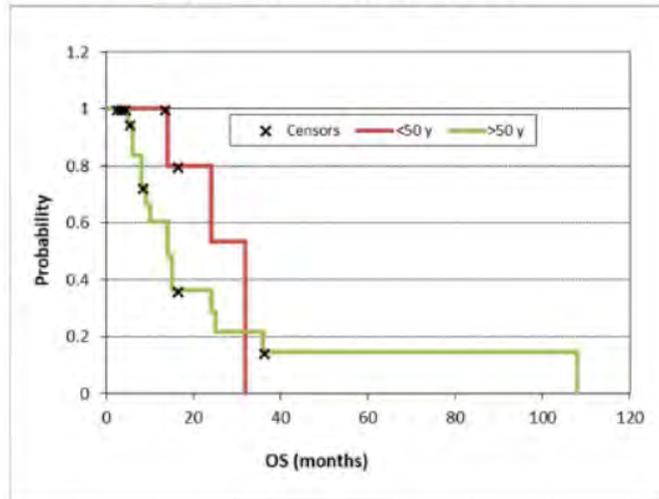
AST age response mEHT p=0.82



GBM age response BSC p=0.75



GMB age response mEHT p=0.39



**Conclusions:** mEHT in integrative therapy may have promising efficacy for the treatment and palliation of relapsed GBM and AST.

# The effect of modulated electro-hyperthermia on temperature and blood-flow in human cervical carcinoma

**Sun-Young Lee<sup>1,2\*</sup>, Jong-Hun Kim<sup>3,2\*</sup>, Yeon-Hee Han<sup>4,2</sup>, Dong-Hyu Cho**

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# The effect of modulated electro-hyperthermia on temperature and blood-flow in human cervical carcinoma

Sun-Young Lee<sup>1,2\*</sup>, Jong-Hun Kim<sup>3,2\*</sup>, Yeon-Hee Han<sup>4,2</sup>, Dong-Hyu Cho<sup>5</sup>

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## Introduction

Mild hyperthermia has been known to enhance the response of tumors to radiotherapy or chemotherapy by increasing tumor blood flow, thereby increasing tumor oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

## Methods

The pelvic area of 20 patients with cervical carcinoma was heated with mEHT. The peri-tumor temperature was measured using an internal organ temperature probe. The tumor blood flow was measured using 3D color Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels.

## Results

The mean peri-tumor temperature was  $36.7 \pm 0.2^\circ\text{C}$  before heating and increased to  $38.5 \pm 0.8^\circ\text{C}$  at the end of heating for 60 min. upon heating for 30 and 60 min, respectively, and was  $37.1 \pm 0.3^\circ\text{C}$  at 30 min after heating. The S/D ratio was  $1.65 \pm 0.20$  at baseline,  $1.40 \pm 0.13$  and  $1.22 \pm 0.09$  upon heating for 30 and 60 min, respectively, and  $1.40 \pm 0.16$  at 30 min after heating. The RI was  $0.40 \pm 0.12$  before heating,  $0.29 \pm 0.11$  and  $0.19 \pm 0.06$  upon heating for 30 and 60 min, respectively, and  $0.30 \pm 0.10$  at 30 min after heating. The marked declines in RI and S/D values strongly demonstrated that heating significantly increased tumor blood perfusion.

## Conclusion

Regional heating of the pelvic area with mEHT significantly increased the peri-tumor temperature and improved the blood flow in cervical cancer. This is the first demonstration that the blood flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.

**Keywords:** intra-tumor blood flow, peri-tumor temperature, electro modulated-hyperthermia

# The effect of modulated electro-hyperthermia on temperature and blood-flow in human cervical carcinoma

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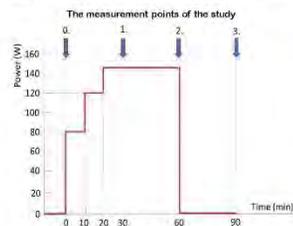
## INTRODUCTION

Mild hyperthermia has been known to enhance the response of tumors to radiotherapy or chemotherapy by increasing tumor blood-flow, thereby increasing tumor oxygenation or drug delivery. The purpose of this study was to assess the changes in temperature and blood-flow in human cervical cancer in response to regional heating with modulated electro-hyperthermia (mEHT).

## METHOD

The pelvic area of 20 patients with cervical carcinoma was heated with mEHT. The peri-tumour temperature was measured using an internal organ temperature probe. The tumor blood-flow was measured using transvaginal 3D color Doppler ultrasound by determining the peak systolic velocity/end-diastolic velocity ratio (S/D ratio) and the resistance index (RI) within blood vessels.

Regional hyperthermia was performed using an mEHT device (EHY-2000, Oncotherm GmbH, Troisdorf, Germany). We have previously used this device to elucidate the effect of regional heating on the pharmacokinetics of an orally administered drug. Patients were placed in a supine position on a couch, and a 30-cm diameter circular electrode was lightly coupled to the pelvic area. All patients underwent two-dimensional simulation to measure the size of the tumour. The pelvic area was heated at 80 W for the first 10 min, 120 W over the next 10 min and 150 W for the remaining treatment time (40 min).



Baseline characteristics of patients (N=20) assigned to treatment

Characteristics	Number of patients (N=20)
Age (years)	30-81
Range	50.5
Median	50.5
ECOG performance status	
1	12 (60%)
2	8 (40%)
Presentation of tumour	
Ectopytic	14 (70%)
Endopytic	6 (30%)
Size of tumour (cm)	
Horizontal x	
Range	2.4-10.0
Median	5.05
Vertical y	
Range	2.0-8.0
Median	4.15
Depth z	
Range	2.9-8.0
Median	4.50
Stage	
Ib	10 (50%)
IIa	2 (10%)
IIb	6 (30%)
IVa	1 (5%)
IVb	1 (5%)
Pathology	
Adenocarcinoma	6 (30%)
Squamous cell carcinoma	13 (65%)
Carcinosarcoma	1 (5%)
Haemoglobin (g/dl)	
Range	6.4-13.2
Median	10.41
Mild anaemia <sup>a</sup> (11.0-12.9)	6 (30%)
Moderate anaemia <sup>a</sup> (8.0-10.9)	10 (50%)
Severe anaemia <sup>a</sup> (<8)	2 (10%)
Non-anaemia (≥13)	2 (10%)
Haematocrit (%)	
Range	19.0-38.0
Median	31.35
CA 19-9 (U/ml)	
Range	1.1-33.8
Median	7.89
CA 125 (U/ml)	
Range	5.5-111.6
Median	45.45

<sup>a</sup>WHO classification.

## RESULTS

The mean peri-tumour temperature was 36.7 ± 0.2°C before heating and increased to 38.5 ± 0.8°C at the end of heating for 60 min upon heating for 30 and 60 min, respectively, and was 37.1 ± 0.3°C at 30 min after heating. The S/D ratio was 1.65 ± 0.20 at baseline, 1.40 ± 0.13 and 1.22 ± 0.09 upon heating for 30 and 60 min, respectively, and 1.40 ± 0.16 at 30 min after heating. The RI was 0.40 ± 0.12 before heating, 0.29 ± 0.11 and 0.19 ± 0.06 upon heating for 30 and 60 min, respectively, and 0.30 ± 0.10 at 30 min after heating. The marked declines in RI and S/D values strongly demonstrated that heating significantly increased tumor blood perfusion.

The main values of starting characteristics divided into subgroups to show the cohort properties of the treated population.

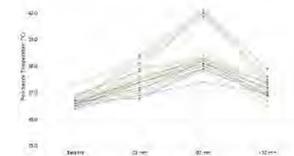
A	Mass size <5 cm (n=11)	Mass size >5 cm (n=9)	p value
RI index	0.39 ± 0.07	0.42 ± 0.05	0.85
S/D ratio	1.34 ± 0.17	1.65 ± 0.21	0.68
Peri tumour temperature (°C)	36.38 ± 0.16	36.57 ± 0.24	0.21
S/Dmax	10.36 ± 2.53	15.32 ± 5.32	0.27
Haemoglobin (g/dl)	11.4 ± 1.4	9.7 ± 1.1	0.007
Haematocrit (%)	33.2 ± 3.9	27.6 ± 3.5	0.0021
CA 125 (U/ml)	37.1 ± 16.6	45.9 ± 31.5	0.88
CA 19-9 (U/ml)	7.5 ± 6.4	13.8 ± 8.1	0.94
B	S/Dmax <10 (n=14)	S/Dmax ≥10 (n=6)	p value
RI index	0.35 ± 0.069	0.42 ± 0.13	0.12
S/D ratio	1.57 ± 0.201	1.68 ± 0.19	0.35
Peri tumour temperature (°C)	36.57 ± 0.16	36.71 ± 0.24	0.2
S/Dmax	8.33 ± 1.02	14.52 ± 4.72	-
Haemoglobin (g/dl)	9.9 ± 1.6	11.5 ± 1.7	0.047
Haematocrit (%)	29.8 ± 4.1	33.8 ± 5.6	0.07
CA 125 (U/ml)	45.2 ± 28.6	32.2 ± 19.4	0.45
CA 19-9 (U/ml)	10.1 ± 7.9	8.0 ± 6.5	0.11
C	Tumour nature Endopytic (n=6)	Tumour nature Ectopytic (n=14)	p value
RI index	0.39 ± 0.063	0.40 ± 0.13	0.91
S/D ratio	1.63 ± 0.21	1.66 ± 0.20	0.49
Peri tumour temperature (°C)	36.4 ± 0.15	36.71 ± 0.24	0.071
S/Dmax	10.81 ± 2.49	13.49 ± 5.39	0.015
Haemoglobin (g/dl)	11.0 ± 1.8	10.7 ± 1.8	0.32
Haematocrit (%)	32.6 ± 5.3	29.9 ± 4.5	0.19
CA 125 (U/ml)	42.9 ± 21.2	40.3 ± 26.9	0.62
CA 19-9 (U/ml)	9.4 ± 8.2	9.5 ± 8.1	0.93
D	Squamous cell carcinoma (n=13)	Non-squamous cell carcinoma (n=7)	p value
RI index	0.37 ± 0.07	0.45 ± 0.17	0.32
S/D ratio	1.64 ± 0.20	1.67 ± 0.20	0.72
Peri tumour temperature (°C)	36.71 ± 0.24	36.6 ± 0.27	0.87
S/Dmax	12.18 ± 2.0	13.61 ± 7.5	0.84
Haemoglobin (g/dl)	10.7 ± 1.4	9.9 ± 1.4	0.32
Haematocrit (%)	31.2 ± 4.18	28.7 ± 4.8	0.45
CA 125 (U/ml)	37.2 ± 21.8	49.7 ± 32.3	0.58
CA 19-9 (U/ml)	6.9 ± 4.8	14.2 ± 10.6	0.13

Significant deviations were observed only in haemoglobin and haematocrit concentrations by mass and by S/Dmax subgroups.

High-resolution Doppler measurements of a representation patient at baseline (A), 30 min into the heating procedure (B), 60 min into the heating procedure (C), and at 30 min after the heating procedure (D).



Peri-tumour temperatures were measured at 30 min before hyperthermia (baseline), at 30 min and 60 min during the hyperthermia procedure, and at 30 min after hyperthermia. The peri-tumour temperatures of all patients are shown.



Changes in the peri-tumour temperature, S/D ratio and RI index in cervical tumours

	Baseline	30 min	60 min	+30 min	p value <sup>a</sup>
Peri-tumour temperature (°C) (n=20)	36.67 ± 0.22	37.47 ± 0.45*** (2.20 ± 1.10%)	38.46 ± 0.84*** (4.91 ± 2.01%)	37.13 ± 0.33* (1.26 ± 0.86%)	<0.0001
S/D ratio (n=20)	1.65 ± 0.20	1.40 ± 0.13*** (-1.495 ± 5.21%)	1.22 ± 0.09*** (-25.09 ± 8.11%)	1.40 ± 0.16*** (-14.75 ± 8.32%)	<0.0001
RI index (n=20)	0.40 ± 0.12	0.29 ± 0.11** (-27.67 ± 19.00%)	0.19 ± 0.06*** (-51.84 ± 13.14%)	0.30 ± 0.10* (-24.81 ± 10.58%)	<0.0001

All changes measured in the study were significant and the values are characteristic of the heating process.

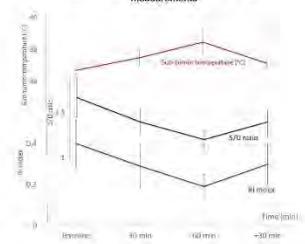
Mean ± SD.  
<sup>a</sup>Repeated measures ANOVA.  
 Comparison with baseline: \*p < 0.05, \*\*p < 0.01 and \*\*\*p < 0.001 (Bonferroni-corrected p values).

The peri-tumour temperatures, S/D ratios and RI indexes in squamous cell carcinoma (sqcc) and non-squamous cell carcinoma (non-sqcc)

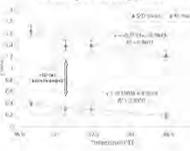
Parameter/time point	Pathology		p value <sup>a</sup>
	Sqcc (n=13)	Non-sqcc (n=7)	
Peri-tumour temperature (°C)			
Baseline	36.67 ± 0.24	36.66 ± 0.20	0.429
30	37.53 ± 0.44	37.36 ± 0.47	
60	38.39 ± 0.79	38.60 ± 0.97	
+30	37.15 ± 0.31	37.07 ± 0.38	
S/D ratio			
Baseline	1.64 ± 0.20	1.67 ± 0.20	0.5327
30	1.39 ± 0.13	1.41 ± 0.15	
60	1.24 ± 0.08	1.20 ± 0.10	
+30	1.38 ± 0.15	1.43 ± 0.19	
RI index			
Baseline	0.37 ± 0.07	0.45 ± 0.17	0.0439
30	0.29 ± 0.07	0.29 ± 0.17	
60	0.19 ± 0.05	0.19 ± 0.08	
+30	0.28 ± 0.06	0.33 ± 0.15	

Mean ± SD.  
<sup>a</sup>Repeated measures ANOVA (pathology = parameter interaction p values).

Average results in the various points of the measurements



The measured values of the temperature including the cooling period



The increase in peri-tumour temperature, excluding the cooling period, was negatively related to the RI and S/D by R2: 0.898 (A) and R2: 0.872 (B), respectively, and positively related to blood flow



## Conclusion

Regional heating of the pelvic area with mEHT significantly increased the peri-tumour temperature and improved the blood-flow in cervical cancer. This is the first demonstration that the blood-flow in cervical cancer is increased by regional hyperthermia. Such increases in temperature and blood-flow may account for the clinical observations that hyperthermia improves the response of cervical cancer to radiotherapy or chemotherapy.

# **Treatment protocol for studying the effect of modulated electro-hyperthermia on melanoma lung metastasis in a mouse model**

**Jeremiah Thomas<sup>1</sup>, Eniko Major<sup>1</sup>, Istvan Dombi<sup>1</sup>, Erno Papanek<sup>1</sup>, Zoltan Benyo<sup>1</sup>, Andrea Balogh<sup>1</sup>**

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**Presented at 36<sup>th</sup> ICHS, Budapest, 2018**

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Jeremiah Thomas<sup>1</sup>, Eniko Major<sup>1</sup>, Istvan Dombi<sup>1</sup>, Erno Papanek<sup>1</sup>, Zoltan Benyo<sup>1</sup>, Andrea Balogh<sup>1</sup>

<sup>1</sup>Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

## Introduction

Modulated electro-hyperthermia (mEHT) is a non-invasive method for locally targeting tumor cells by applying radiofrequency (RF) of 13.56 MHz. Tumors have elevated glycolysis due to the Warburg effect. As a result, there is increased lactate production and reduced electric impedance in tumor cells, leading to increased permittivity and conductivity, which support mEHT to selectively induce apoptosis in malignant tumor cells. Here we look at the protocol, optimized for treating melanoma lung metastasis using mEHT in a mouse model.

## Methods

### Lung vs laryngopharyngeal temperature correlation setup

Measuring lung temperature is crucial to ensure that the target temperature of 41-42 °C is reached and maintained during treatment. Direct measurement of lung temperature during treatment, however, is highly invasive and could result in extensive damage to the treated lungs. Here, we sort out to establish a method of measuring lung temperature indirectly by demonstrating that a strong correlation exist between the main bronchi and laryngopharyngeal temperature.

### Treatment setup and protocol – pilot studies

Lung metastasis was induced by tail vein injection of B16-F10 melanoma cells into C57Bl/6 mice. The following day mice were treated with mEHT (n=6). mEHT treatment of the lungs was performed every third day for a total of 6 times with LabEhy200 (Oncotherm TM) with a treatment protocol set up to maintain 41-42 °C inside the lungs. Treatment was done with a regular round electrode that covers the thorax. Mice were sacrificed on day 18 and metastatic nodules were counted.

### Electrode re-design

Pilot studies with regular round electrode covering the thorax revealed extensive burning on the skin underlying the upper treatment electrode. This may have been caused by the relative high impedance of structures (sternum, ribs, air in lungs) in the thoracic region causing a higher power concentration on the overlying skin. Although the target temperature range of 41-42 °C in the lungs was achievable, an unavoidable side effect was the observed burning. We therefore aimed to redesign a customized electrode for lung treatment, capable of preventing this burning.

## Results and discussion

Text Our results demonstrate that a temperature correlation exist between the main bronchi and the laryngopharynx in mice with an average laryngopharyngeal-bronchial temperature difference of  $1.44 \pm 0.46$  °C (n = 4). Pilot studies also demonstrated that, when mice induced with B16-F10 melanoma in the lungs were treated with mEHT, a relative reduction in the number of metastatic nodules was observed compared to the control group. In addition, our redesigned electrode, customized for the lung treatment showed markedly reduced skin damage.

**Conclusion**

Taken together, our results demonstrate that a temperature correlation exist between the main bronchi and the laryngopharynx in mice which proved useful in estimating the lung temperature during treatment by only measuring the laryngopharyngeal temperature non-invasively. Our pilot studies indicated that mEHT treatment may have a beneficial effect in reducing the number of melanoma metastasis in the lung.

Supporting Grant: NVKP 16-1-2016-0042.



# Treatment protocol for studying the effect of modulated electro-hyperthermia on melanoma lung metastasis in a mouse model

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<sup>1</sup>Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

## Introduction

Modulated electro-hyperthermia (mEHT) is a non-invasive method of locally targeting tumor cells for destruction applying a radiofrequency (RF) of 13.56-MHz. Tumors have elevated glycolysis due to Warburg effect. As a result, there is increase lactate production and reduced electric impedance in tumor cells, leading to increase permittivity and conductivity, which support mEHT to selectively induce apoptosis in malignant tumor cells. Here we look at the effect of mEHT on B16F10 melanoma metastasis in a mouse lung model.

## MATERIALS AND METHODS

### Treatment setup and protocol

Lung metastasis was induced by tail vein injection of B16F10 melanoma cells into C57BL/6 mice. The following day mice were treated with mEHT alone, with mEHT and aspirin (ASA, 11.1 mmol/L) administered in drinking water during the entire experiment or left untreated. 30 min mEHT treatment of the lungs was performed every third day for a total of 6 times with LabEh200 (Oncotherm TM) with a treatment protocol set up to maintain 41-42 °C inside the mice lung.

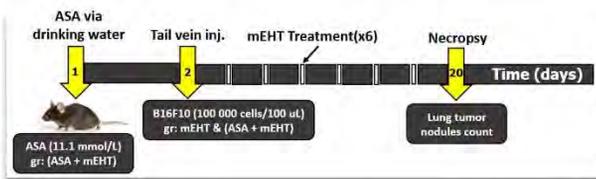


Figure 1 Experimental timeline for lung treatment with mEHT

### Lung temperature correlation setup

Measuring lung temperature is crucial to ensuring that the target temperature of 41-42 °C is reached and maintained during treatment. Direct measurement of lung temperature during treatment however is highly invasive. Here, we sort out to establish a method of measuring lung temperature indirectly by demonstrating that a correlation exist between the lung and laryngopharyngeal temperature.

	Mice 1	Mice 2	Mice 3	Mice 4
Average temp. diff. (°C)	1.16	1.76	0.95	1.89
SD	0.1114	0.1515	0.1075	0.2365

Table showing correlation between lung and laryngopharyngeal temperature in mice (n = 4). Average temperature difference was calculated from time 10 min to 30 min of mEHT treatment across all animals. Average difference across all animals was 1.44 ± 0.4559 °C. Based on this, a laryngopharyngeal temperature of approx. 40 °C was decided optimal to ensure a temp. range of 41–42 °C in the lungs for all subsequent treatments.

### Electrode design for lung treatment

Pilot studies with regular round electrode covering the thorax revealed extensive burning on the skin underlying the upper treatment electrode. This may have been caused by the relative high impedance of structures (sternum, ribs, air in lungs) in the thoracic region causing a higher power concentration on the overlying skin. Although the target temperature range of 41-42 °C in the lungs was achieved, an unavoidable side effect was the observed burning. We therefore aimed to redesign a customized electrode for lung treatment, capable of preventing or reducing the extent of burning.

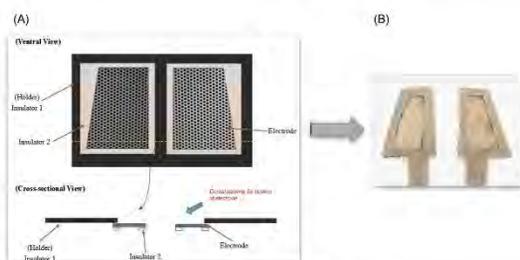
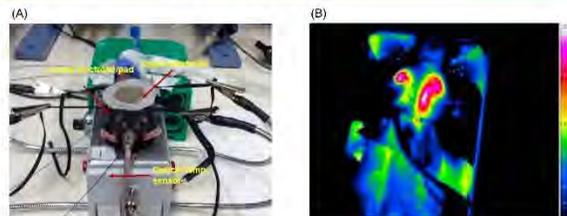


Figure 2 Customized electrode for lung treatment

(A) Schematics of customized electrode designed for lung treatment (B) Lung treatment electrode designed based on schematics. Silicon material was used as insulator. Significant reduction in burning relative to regular round electrode was observed when used in treatment of mice with B16F10 melanoma primary nodules in the lungs.

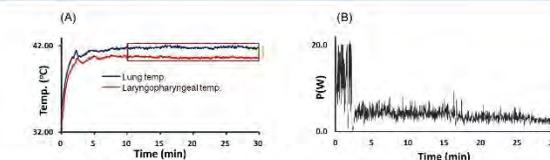
Email: thomas\_jeremiah.mbuotidem\_ex@med.semmelweis-univ.hu

## MATERIALS AND METHODS

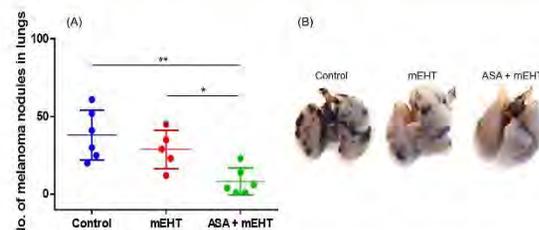


(A) Experimental setup showing positioning of mouse, treatment electrodes and optical temperature sensors. Optical temperature sensors were positioned in laryngopharynx, skin beneath electrode, rectum and pad. (B) Thermal camera imaging showing localized increased temperature in lung region.

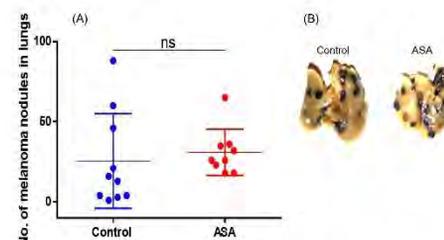
## RESULTS



(A) Representative plot showing correlation between lung and laryngopharyngeal temperature in mouse under treatment with mEHT. Lung temp. was maintained at 41–42 °C during course of treatment for all animals. (B) Representative plot showing power variation during course of mEHT treatment.



(A) Plot of number of B16F10 melanoma metastatic lung nodules in control, mEHT and (ASA + mEHT) experimental groups. mEHT treatment alone showed some reduction in number of metastatic nodules, although this was not significant. mEHT when combined with aspirin (ASA) however showed a significant reduction in the number of metastatic nodules (\*p < 0.05; \*\*p < 0.01, one-way ANOVA). (B) Representative lungs in each experimental groups showing B16F10 melanoma metastatic lung nodules. Significant reduction in nodules was observed when ASA was combined with mEHT treatment.



(A) Plot of number of B16F10 melanoma metastatic lung nodules in control and ASA groups. (B) Representative lungs with metastatic nodules for control and ASA given experimental groups. No significant difference in number of metastatic nodules was observed between both groups.

## CONCLUSIONS

Our results demonstrate that a temperature correlation exist between the main bronchi and the laryngopharynx in mice which proved useful in estimating lung temperature during treatment by only measuring the laryngopharyngeal temperature non-invasively. Pilot studies indicated that aspirin (ASA) when combined with mEHT treatment resulted in a significant reduction in the number of B16F10 melanoma metastatic nodules in the lungs. Aspirin alone, under the concentration used in this experiment did not seem to inhibit the growth of B16F10 melanoma nodules in the lungs. This suggests that this inhibitory effect may only exist when ASA and mEHT are combined together and not separately.

This study was supported by the Hungarian National Research, Development and Innovation Office (NVKP\_16-1-2016-0042)

## **Clinical Case Report**

### **mEHT - Results on CA - Esthesioneuroblastoma- Brazilian Experience**

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# Clinical Case Report

## mEHT - Results on CA - Esterioneuroblastoma - Brazilian Experience

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### Abstract

Cancer incidence in Brazil is as high as in developed countries. The Brazilian Unified Health System (SUS), which provides health care to the majority of the population, offers conventional oncology treatments such as chemotherapy, radiotherapy, hormonal suppressors and surgery. The possibility to offer modulated electro-hyperthermia (mEHT) is not yet being considered by the Government. There is, nevertheless, a growing number of cancer patients interested in the benefits of mEHT. Some of them, after being treated with traditional methods, see new hope in mEHT. Others see it as a complementary treatment. This report does not intend to provide scientific data, but rather a clinical contribution. Its aim is to present a case study, showing a brief patient history, the evolution of malignancy despite conventional treatments (chemotherapy, radiotherapy and immunotherapy) and the results with mEHT as well as support therapies. Conventional treatments were undertaken from 2015 to 2017, but were interrupted at the end of 2017 due to high toxicity. The treatment with mEHT and support therapies were provided from January to April 2018. The patient is male, white skin, 47 years old, diagnosed in 2014 by biopsy with Esthesioneuroblastoma (CID 10 C30). The clinical assessment at the beginning of the treatment with mEHT was: important edema on the left side of the face, severe convergent strabismus in the left eye, duplicated vision; patient reporting sedentary lifestyle, unrestricted feeding, insomnia, feeling depressive, discouraged, unable to work and drive, suffering sequel from previous and recent treatments, and weight loss of 20 kilos. PROTOCOL: mEHT -130 W/ 60min 3 X week total of 36 sessions; no chemotherapy or radiotherapy; oxygen therapy by Manfred Von Ardenne, galvanic micro-current, pulsed magnetotherapy field, Rife frequency therapy (36 session - 20 min), endovenous supplementation of minerals, vitamins, amino acids (500 ml X 12 session) and curcumin supplementation (SC 24 X 200 mcg, 2 ml), ozonotherapy rectal twice a week, reduced intake of simple carbohydrates, Joanna Budwig diet, homeopathic support, and "a more healthy lifestyle". The RESULTS on PETscan dated of April 2018 and the oncological evaluation confirms the total remission of the Esthesioneuroblastoma and cervical lymph nodes, total remission of the facial edema, and 90% strabismus reduction. The clinical impressions show significant improvement of energy and quality of life, and great improvement of vision. A slight strabismus still remains to be analyzed by the ophthalmologist. The patient continues with a low carb diet. The patient is able to safely drive and returned to normal work activities. Suggested oncological follow-up every six months.

## Clinical Case Report

### mEHT - Results on CA - Esthesioneuroblastoma- Brazilian Experience

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#### INTRODUCTION

Cancer incidence in Brazil is as high as in developed countries. The Brazilian Unified Health System (SUS), which provides health care to the majority of the population, offers conventional oncology treatments such as chemotherapy, radiotherapy, hormonal suppressors and surgery. The possibility to offer modulated electro-hyperthermia (mEHT) is not yet being considered by the Government. There is, nevertheless, a growing number of cancer patients interested in the benefits of mEHT. Some of them, after being treated with traditional methods, see new hope in mEHT. Others see it as a complementary treatment. This report does not intend to provide scientific data, but rather a clinical contribution.

#### AIM

Its aim is to present a case study, showing a brief patient history, the evolution of malignancy despite conventional treatments (chemotherapy, radiotherapy and immunotherapy) and the results with mEHT as well as support therapies.

#### DEVELOPMENT

The patient is male, white skin, 47 years old, diagnosed in 2014 by biopsy with Esthesioneuroblastoma (CID 10 C30). Conventional treatments were undertaken from 2015 to 2017, but were interrupted at the end of 2017 due to high toxicity. The treatment with mEHT and support therapies were provided from January to April/2018.

The clinical assessment at the beginning of the treatment with mEHT was: Important edema on the left side of the face, severe convergent strabismus in the left eye, duplicated vision; patient reporting sedentary lifestyle, unrestricted feeding, insomnia, feeling depressive, discouraged, unable to work and drive, suffering sequel from previous and recent treatments, and weight loss of 20 kg.

Polytreated by Chemotherapy, Radiotherapy, Immunotherapy - 2015, 2016, 2017.



**PET SCAN 2015**  
 Paciente began treatment with Chemo and Radiotherapy



**PET SCAN 2016**  
 Identified the expansion of malignant cells to neck lymph nodes. Continued protocol Chemo and Radio



**PET SCAN 2017**  
 Expansion of lesion. Stronger Chemo was used which has caused rejection. Patient had 3 immunotherapy sessions.

The results show recurrence and increased lesion. In 2017 the medical team appealed to Immunotherapy as the last possibility- on the 3rd session they chose to discontinue due to prohibitive toxicity.

**Clinical impression:** The patient had important edema on the left side of the face, severe convergent strabismus in the left eye, vision duplicated, patient confirms insomnia, sedentary, unrestricted feeding. Depressive, discouraged, unable to work and drive, suffering sequel from previous treatments. Weight loss of 20 kilos.

#### 2018 - mEHT - Protocol used from January to April 2018.

Protocol description: Follows the basic propositions of mEHT: Using the medium bolus electrode size applied on the face. 12 sessions/month. No chemotherapy or radiotherapy was used.

- mEHT 3 X week 130 W/ 60min. Total 36 session.
- Reduced intake of simple carbohydrates, Dra. Joana Budwig diet, Homeopatic support, and "Health life style" suggested.
- As complementary therapy used Oxygen therapy + galvanic micro current + magneto therapy + Rife frequency (36 session - 20 min), endovenous supplementation of minerals, vitamins, amino acids (500 ml X 12 session ) and curcumin (SC 24 X 200 mcg, 2 ml), Ozonioterapia Retal 2 X week.

#### RESULTS

From Jan to April/18 the patient has done 36 session of mEHT protocol+ support therapies. The patient shows clinical aspects improvements and 100% reduction of facial edema, 80% reduction of strabismus. On PETscan May /18 – compared to previous images, confirm great remission:



**"Resolution of hypermetabolism on nasopharyngeal lesion in the inferior turbinate medial wall of the left maxillary sinus and bilateral cervical lymphonodes."** PETscan May2018

#### FINAL CONSIDERATIONS

From Jan to April 2018 with the mEHT protocol + support therapies, notice the total reduction of facial edema and according to images + reports, the oncological evaluation confirms an unequivocal remission of the CA – Esthesioneuroblastoma and cervical lymphonodes.

The clinical assessments show improvement of energy and quality of life, great improvement of vision. Still remains a slight strabismus, and the suggestion of the ophthalmologist is to perform a surgical correction in near future.

Since then, the patient continues with low carb diet, supplementation. He returns to normal work activities. And we suggested an oncological follow-up every six months.

Submitted to  
**36<sup>th</sup> ICHS Conference**  
 Budapest Hungary - Sept/2018

## Challenges and proposals in local oncological hyperthermia

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# Challenges and proposals in local oncological hyperthermia

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Hungary ([biotech@gek.szie.hu](mailto:biotech@gek.szie.hu))

## Introduction

Local hyperthermia in oncology has numerous challenges which must be solved for further development of this excellent method. We have to clearly recognize what are the drawbacks and find the way to eliminate them using the latest technical and medical knowledge. Application of hyperthermia apparently looks (but only looks!) very simple, so various "household" or technically underdeveloped solutions are applied widely, which tends to charlatanism and has a danger about the complete negative opinion from the medical experts.

## Methods

There are multiple approaches to heat up the tumor homogeneously as much as possible satisfying the necrotic cell-killing, how CEM43 dose definition requests it. This dose has some basic problems: (1) scientifically the formal fit to the data of the measurements is incorrect by its dimensionality due to the difference of the temperature is used without its actual physical dimension, (2) technically it requests solving the deep selective heating with its proper temperature control; (4) further technical challenge is the proper measurement of the heating homogeneity of the anyway heterogenic tumor; (3) experimentally it is based on necrosis (in vitro reference) which is far away from the medical reality; (4) medically it does not consider the physiological data (blood-flow, invasion, dissemination, non-necrotic cellular changes, etc. The proper dose definition is a crucial request build acceptance of the oncological hyperthermia worldwide [1].

## Results

The attempts by artificial focusing of the electromagnetic waves have partial solution considering only the properly heated portion of the tumor (Tx percent of CEM43Tx). Furthermore, escaping from the medical encounter, only local control is chosen like the endpoints of the trials or only locally advanced tumors (metastases do not exist) are included in the trial protocols. This limits the applicability of oncological hyperthermia to the less life-threatening stages, while its application is usually applied after when the low-line conventional treatments offer unsatisfactory results. Additional drawback of hyperthermia is the rapid development of non-hyperthermia therapies, like the targeted therapies, personalized therapies and immune-oncology. Our primary task is to avoid the declining prestige of oncologic hyperthermia. As a result of the direct facing of the problems we have to answer to special questions:

1. What is the optimal deep hyperthermic temperature and how homogeneously does it have to be provided?

2. How to solve the selection between the healthy and cancerous cells, keeping the healthy cells unharmed, when recognizing the emphasized heterogeneity of the tumor?
3. What is the dose which is accurate, reproducible and safe to control an optimal treatment?
4. How the systemic malignancy (micro and macrometastases) could be blocked by local action of heating?

There are numerous solutions proposed [2], [3], [4].

### **Conclusion**

Answers to the above questions and solutions for the challenges exist [5]. We have to conclude that our task is to reestablish the prestige of oncological hyperthermia that had shown so many good results as well as had produced multiple disappointing controversies until now.

### **References**

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- 2 Hegyi G, Szigeti GP, Szasz A (2013) Hyperthermia versus oncothermia: Cellular effects in complementary cancer therapy. *Evid Based Complement Alternat Med* 2013:672873
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# Challenges and proposals in local oncological hyperthermia

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Local hyperthermia in oncology has numerous challenges which must be solved for further development of this excellent method. We have to clearly recognize what are the drawbacks and find the way to eliminate them using the latest technical and medical knowledge. Application of hyperthermia apparently looks (but only looks!) very simple, so various "household" or technically underdeveloped solutions are applied widely, which tend to charlatanism and has a danger about the complete negative opinion from the medical experts.

**General challenge:** how to raise the prestige of hyperthermia again to the top of oncotherapies, as it was at its start?

**1 Challenge of definition of oncological hyperthermia:** no clear definition of oncological hyperthermia is declared

**Present convention** **Oncology encyclopaedia** – hyperthermia is **therapeutic heat**

**Medicine.net** – overheating of the **body**

**National Cancer Institute** – body **tissue** is exposed to high temperatures (**up to 45°C**)

**Wikipedia** – body **tissue** is exposed to **slightly higher** temperatures to damage and **kill** cancer cells or to make cancer cells more **sensitive** to the effects of radiation and certain drugs

**Medical Dictionary** – **much higher** than normal body temperature induced therapeutically or iatrogenically

**The Am. Canc. Soc.** – **body** is exposed to **higher than normal** temperatures, changes take place inside the **cells**

**Oncothermia definition** Oncological hyperthermia is a method to **kill malignant cells** by heat-inducing absorbed **energy and/or sensitize** certain complementary therapies

**2 Challenge of safety of the radiation of hyperthermia** The safety needs low level electromagnetic radiation to keep the health standards, and make no disturbances on the nearby medical equipments.

**Present conventions**

**1. using frequencies out of medical standards** Complete shielding of the treatment room is necessary (huge extra cost and complications)

**2. applying huge energy with low efficacy** Not known how much is the absorbed energy at the radiative one, so we have to measure the temperature to have an idea about the absorbed energy, ensure the safety

**Oncothermia solution** **1. strict impedance coupling** by application of the frequency according to the medical standards

**2. application of high absorption efficacy (a)** to reduce the radiation near the treatment-bed (b) to measure the absorbed energy without temperature control

**3 Challenge by other therapies** New challenger therapies intensively developed recently by targeted therapies and immune-oncology, solving the above problems by the non-hyperthermic way.

**Present complementary & competitive therapies** **Surgery** minimally invasive (robotic, endoscopic, laparoscopic, etc.)

**Radiotherapy** proton and heavy ion therapies, tomotherapy, radiative seed-therapies, etc.

**Chemotherapy** oral drugs, antibody therapies, immune-effects, check-point inhibitors, etc.

**New diagnostics** circulation tumor cells (CTC), free DNA, microRNA, proteomics, exosomes, etc.

**Theranostics** a combination of diagnostics and therapy

**Oncothermia solution for competence** Local, selective heat-therapy directly targets the tumor-cells by their biophysical characters **It is a modern theranostics that detects the tumor and treats it**

**4 Challenge of selection (focusing)** Selection of the malignant parts in the targeted volume (focusing)

**Present convention** Focusing the electromagnetic waves, similarly to ionizing radiation

**1. The dipole antenna** wave needs high frequency for focusing, where the penetration depth rapidly decreases, most of the energy is absorbed by the coupling bolus, lost control on the absorbed energy

**2. In plane-wave** the focus is roughly approximated by the size of electrodes. The rough size variation loses the control on the real absorbed energy in the targeted tumor.

**Oncothermia solution** Select cellularly by the biophysical differences of malignant cells from their healthy counterparts. The RF-current actively selects the malignancy on cellular level.

**5 Challenge of the dose of oncological hyperthermia**

**Present conventions** **CEM43°C**, Calibrated in vitro Superficial Dose, Thermal Dose Determination (Lancet Oncology, 2014) (DOI: 10.1016/S1473-3099(14)70279-1)

$$CEM43^{\circ}C = \sum_{(t)} t_i R^{(T_c - T_i)} \quad T_c = 43^{\circ}C$$

$$R = \begin{cases} 0.25 & T < 43^{\circ}C \\ 0.5 & T \geq 43^{\circ}C \end{cases}$$

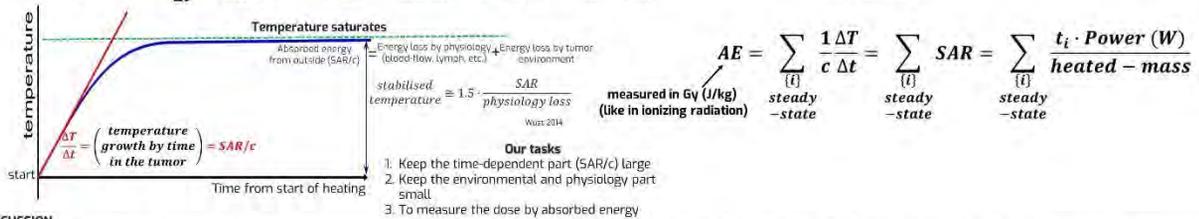
a. scientifically incorrect:  $R^{(T-43^{\circ}C)}$  has no unit  
 b. thermal necrosis concept  
 c. calibrated in vitro  
 d. estimation of heterogeneities ( $T_i$ )  
 e. Arrhenius link depends on chemotherapies  
 f. Eyring reaction-kinetics is not used

**T<sub>RISE</sub>** Fit to the clinical data. Troisdorf, M. et al. Hyperthermia dose-effect relationship in 422 patients with unresectable cancer treated with concurrent radiotherapy and hyperthermia. *Radiotherapy and Oncology* 2014; 112: 543-549 (2014)

$$T_{Rise} = \sum_{(t)} t_i \frac{(T_{50} - 37^{\circ}C)}{treat. time}$$
 Rough average in time and space (unprecise, incorrect)

**Oncothermia solution**  $\frac{\Delta T}{\Delta t} = \frac{\text{Temperature growth by time in the tumor}}{\Delta t} = \frac{\text{Absorbed energy from outside (SAR/c)}}{\Delta t} = \frac{\text{Energy loss by tumor environment}}{\Delta t} - \frac{\text{Energy loss by physiology (blood-flow, lymph, etc.)}}{\Delta t}$  (Pennes' equation)  $SAR = \frac{Power}{mass}$  (W/kg)

The correct dose



## DISCUSSION

There are multiple approaches to heat up the tumor homogeneously as much as possible satisfying the necrotic cell-killing, how CEM43 dose definition requests it. This dose has some basic problems: (1) scientifically the formal fit to the data of the measurements is incorrect by its dimensionality due to the difference of the temperature is used without its actual physical dimension, (2) technically it requests solving the deep selective heating with its proper temperature control; (4) further technical challenge is the proper measurement of the heating homogeneity of the anyway heterogeneous tumor; (3) experimentally it is based on necrosis (in vitro reference) which is far away from the medical reality; (4) medically it does not consider the physiological data (blood-flow, invasion, dissemination, non-necrotic cellular changes, etc). The proper dose definition is a crucial request to have acceptance of the oncological hyperthermia worldwide [1].

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## CONCLUSION

**Temperature measurement is necessary in conventional hyperthermia having idea about the absorbed energy in the tumor-mass**

Answers to the above questions and solutions for the challenges exist [5]. We have to conclude that our task is to reestablish the prestige of oncological hyperthermia that had shown so many good results as well as had produced multiple disappointing controversies until now.

## For oncothermia:

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

1 Don't be isothermal (no homogeneous heating)

2 Heat the malignant cells selectively

3 Use high heating efficacy, less energy-loss

**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

## **Local treatment with systemic effect**

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# Local treatment with systemic effect

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## Objective

Most of the radiation therapies are local. The local control of the tumor in advanced cases is not enough for effective improvement of survival time, due to the systemic malignant spread forming macro and micro metastases which are the main life-threatening factor of cancerous diseases. The local treatment has to be extended by systemic (abscopal) effect. The appropriate immune-stimuli could extend the local method to systemic and acts disseminated cells in distant metastases, too. Our objective is to present the abscopal effect of modulated electro-hyperthermia (mEHT, oncothermia).

## Methods

Non-ionizing radiofrequency (RF) electric current amplitude modulated by the time-fractal technique of relative low carrier frequency (13.56 MHz) is used [1]. The E-class RF-source and the impedance controlled capacitive coupling allows high efficacy targeting selectively the membrane rafts of the malignant cells [2]. The applied nano-selection makes certain deviations of cellular metabolic-processes of malignant cells. The cell-killing mechanism is connected to the nano-range energy absorption. The special process makes it available to present the genetic information of malignant cells to the antigen-presenting cells (APCs). There were various in-vitro and in-vivo immune-histochemical studies proving the selection and its effects.

## Results

The method of mEHT causes significant apoptotic tumor-cell death. Mitochondrial Bax and release of Cytochrome C and nuclear translocation of apoptosis inducing factor AIF are measured [3], showing caspase independent and also excited caspase dependent pathways of the signal processes. Immunohistochemistry and apoptosis protein array proved elevated hsp70 and hsp90 expression and release them from the cell. The process forms damage associated molecular pattern (DAMP) concluding to immunogenic cell-death (ICD). The abscopal effect is proven by the in-vivo experiment using an intratumoral dendritic cell (DC) injection together with the mEHT for C3H/He mice inoculated with tumor in femoral region. The non-treated tumor in the abdomen was measured. The whole body antitumor effects are proven, [4]. Furthermore, mEHT plus DC administration significantly inhibits the CT26 tumor growth in BALB/c mice, while even the re-challenging of the tumor inoculation became impossible, [5]. In this case the abscopal effect works like vaccination. The combined mEHT-DC treatment increases the myeloperoxidase concentration and CD3+ cells organizing specific T-cell response, [6].

## Conclusion

Text 1mEHT induces abscopal effect by immune involving processes. Unlike conventional homogeneous heating of the tumor, this local treatment becomes systemic in consequence of the selective excitation of membrane rafts inducing DAMP and ICD. This way mEHT can

create a favorable tumor microenvironment for an immunological chain reaction which improves the success rate of intratumoral dendritic cell immunotherapy

## **References**

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# Local treatment with systemic effect

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## Objective

Most of the hyperthermia methods use bioelectrodynamics for energy-absorption

Use the bioelectrodynamics differences of malignant and healthy cells

Controlled bioelectromagnetic interactions produce systemic tumor-specific immune action

## INTRODUCTION (malignancy is systemic)

Most of the radiation therapies are local. The local control of the tumor in advanced cases is not enough for effective improvement of survival time due to the systemic malignant spread forming macro and micro metastases, which are the main life-threatening factors of cancerous diseases. **The local treatment has to be extended by systemic (abscopal) effect.** The appropriate immune-stimuli could extend the local method to systemic and acts disseminated cells in distant metastases, too. Our objective is to present the abscopal effect of modulated electro-hyperthermia (mEHT, oncothermia).

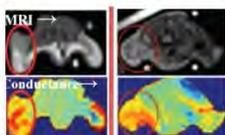
## METHOD (precise selection of targets)

Non-ionizing radiofrequency (RF) electric current amplitude modulated by the time-fractal technique of relative low carrier frequency (13.56MHz) is used [1].

### Selection by

#### 1 Electric conductivity (Metabolic differences, Warburg effect)

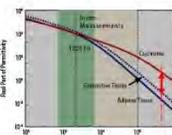
Due to high metabolic rate, the tumor ionic concentration is high and consequently its conductivity selects



Muller (2009)

#### 2 Dielectric permittivity (autonomy of malignant cells; Szentgyorgyi effect)

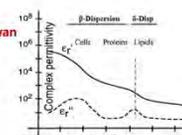
Due to missing cellular network, extracellular matrix of malignant cells have high dielectric permittivity selection



Scholz, 2000

#### 3 β/δ frequency dispersion (lipid resonance absorption; Schwan effect)

Due to large number of clusters of transmembrane proteins the protein-lipid complex is attacked



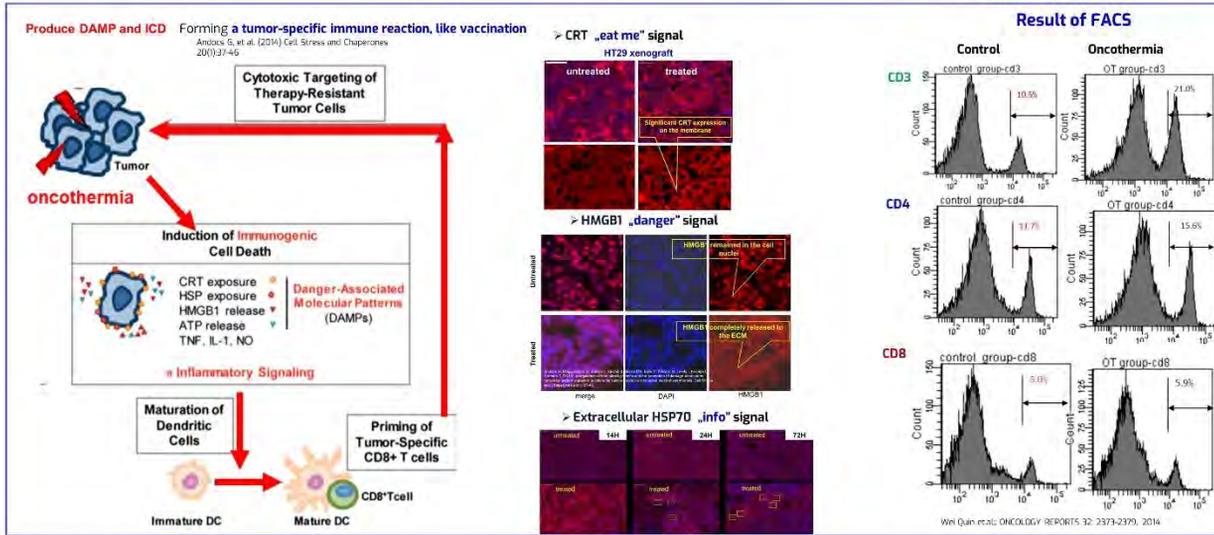
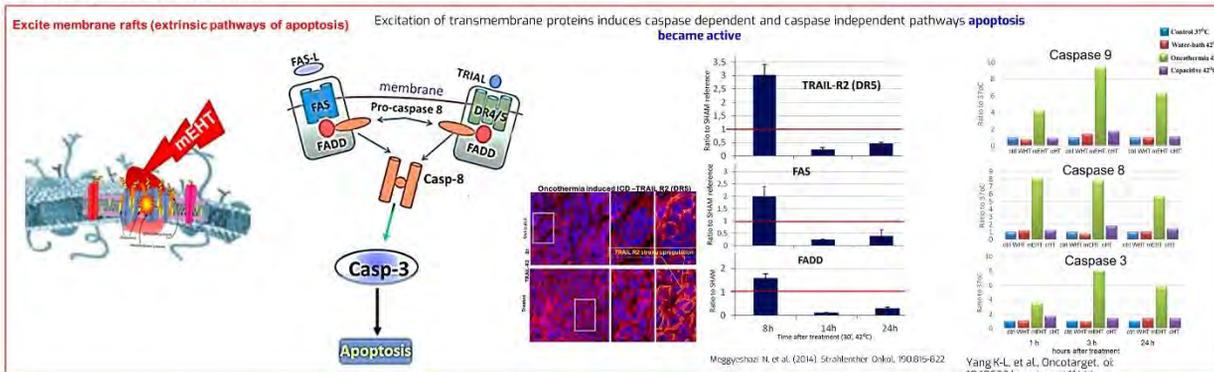
Gaduff, 2010

## Technical

The high-efficacy (E-class) RF-source and the impedance controlled capacitive coupling with a precise control allows to use electric current instead of plain wave radiation allowing high efficacy targeting selectively the membrane rafts of the malignant cells [2]. The precise and automatic tuning makes high efficacy impedance matching and energy absorption, using only 150W maximal power and max. 1-2W reflected one. Due to the step-up heating protocol the average power is 100W/ treatments.

## RESULTS

The method of mEHT causes significant apoptotic tumor-cell death. Mitochondrial Bax and release of Cytochrome C and nuclear translocation of apoptosis inducing factor AIF are measured [3], showing caspase independent and also excited caspase dependent pathways of the signal processes. Immunohistochemistry and apoptosis protein array proved elevated hsp70 and hsp90 expression and release them from the cell. **The process forms damage associated molecular pattern (DAMP)** concluding to immunogenic cell-death (ICD). The abscopal effect is proven by the in-vivo experiment using an intratumoral dendritic cell (DC) injection together with the mEHT for C3H/He mice inoculated with tumor in femoral region. The non-treated tumor in the abdomen was measured. The whole body antitumor effects are proven, [4]. Furthermore, mEHT plus DC administration significantly inhibits the CT26 tumor growth in BALB/c mice, while even the re-challenging of the tumor inoculation became impossible, [5]. In this case the abscopal effect works like vaccination. The combined mEHT-DC treatment increases the **myeloperoxidase concentration** and CD3+ cells organizing specific T-cell response, [6]. The time-fractal modulation chooses special processes for immunogenic reactions. The applied nano-selection makes certain deviations of cellular metabolic-processes of malignant cells. The cell-killing mechanism is connected to the nano-range energy absorption. The special process makes it available to present the genetic information of malignant cells to the antigen-presenting cells (APCs). There were various in-vitro and in-vivo immunohistochemical studies proving the selection and its effects.



## CONCLUSION

mEHT induces abscopal effect by immune involving processes. Unlike conventional homogeneous heating of the tumor, this local treatment becomes systemic in consequence of the selective excitation of membrane rafts inducing DAMP and ICD. On this way mEHT can create a favorable tumor microenvironment for an immunological chain reaction which improves the success rate of intratumoral dendritic cell immunotherapy. Research for the role of exosomes and other small vesicles in the abscopal effect and the crosstalk between the primary and metastatic lesions is in progress.

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## **Gastrointestinal Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) -- a single center experience**

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# Gastrointestinal Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) -- a single center experience

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## Background

mEHT is a relatively new kind of hyperthermia in oncology. It is a further development of the conventional heating methods.

## Aim

Our objective in this presentation is to summarize our knowledge about the utilization of mEHT therapy from the practical perspective in gastrointestinal (GI) cancers and summarize our experience in our GI cancer patients treated with mEHT.

## Methods

Thirty-four patients with advanced GI cancer (23 pancreatic, 7 colorectal, 3 hepato-biliary, 1 esophagus, 1 neuroendocrine carcinoma) were treated in a 20-month period at the Cancer Center of Semmelweis University, with the instruments EHY-2000 and EHY-2030 (Oncotherm Ltd., Budaörs, Hungary). One patient also developed breast cancer, and one patient (with esophageal cancer) only attended one session, thus, these were omitted from further analysis.

## Results

All patients had inoperable and metastatic disease. The most common metastatic sites were lymph nodes (15), liver (12), peritoneum (8), lung (4), bone (1) and the kidney (1). The average time in treatment was 32.8 weeks (range: 1.0-95.0). Various chemotherapeutic protocols were applied, mostly gemcitabine alone or in combination and FOLFIRINOX containing regimens, but also platinum, tegafur, mitomycin C were administered. A two-week break in therapy was necessary in seventeen cases due to fever (8) and local discomfort or pain (6), pneumonia (2), and intolerance (1). Fifteen patients are still under treatment: 11 pancreas, 2 hepatic, 1 neuroendocrine, 1 rectal cancer patient. Those, who finished treatment were mostly due to progression with fluid formation in the cavities or thromboembolism.

## Conclusion

Complementary mEHT treatment of GI cancer patients is feasible and easy to administer. Most durable responses were seen in oligometastatic pancreatic cancers. Prognostic factors were not apparent based on analysis of clinicopathological properties.

Grant support: NVKP\_16-1-2016-0042

# Gastrointestinal Cancer Series Treated with Modulated Electro-Hyperthermia (mEHT) -- a single center experience



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## Introduction

mEHT is a relatively new kind of hyperthermia in oncology. It is a further development of the conventional heating methods. It has shown improved local control and prolonged survival in advanced pelvic cancers and selected regions in the body, e.g. brain tumors, pancreatic carcinomas. Here we analyzed our cases from the gastrointestinal system.

## Patients and methods

Thirty-four patients with gastrointestinal cancer (23 pancreatic, 7 colorectal, 3 hepato-biliary, 1 esophageal and 1 neuroendocrine carcinoma) were treated in a 20-month period at the Cancer Center of Semmelweis University, with the instruments EHY-2000 and EHY-2030 (Oncotherm Ltd., Budaörs, Hungary).

One patient also developed breast cancer, and one patient (with esophageal cancer) only attended one session, thus, these were omitted from further analysis. All cases were locally advanced or metastatic at time of presentation and recruitment into our pilot study. The inclusion criteria was declared by a tumor board in all cases, and the patients then underwent mEHT therapy twice or three times per week until further progression or discontinuation of treatment.

## Results

All patients had inoperable and metastatic disease. The most common metastatic sites were lymph nodes (15), liver (12), peritoneum (8), lung (4), bone (1) and the kidney (1).

The average time in treatment was 32.8 weeks (range: 1.0-95.0). Various chemotherapeutic protocols were applied, mostly gemcitabine alone or in combination and FOLFIRINOX containing regimina, but also platinum, tegafur, mitomycin C were administered.

A two-week break in therapy was necessary in seventeen cases due to fever (8) and local discomfort or pain (6), pneumonia (2), and intolerance (1). Fifteen patients are still under treatment: 11 pancreas, 2 hepatic, 1 neuroendocrine, 1 rectal cancer patient. Those, who finished treatment were mostly due to progression with fluid formation in the cavities or thromboembolism.

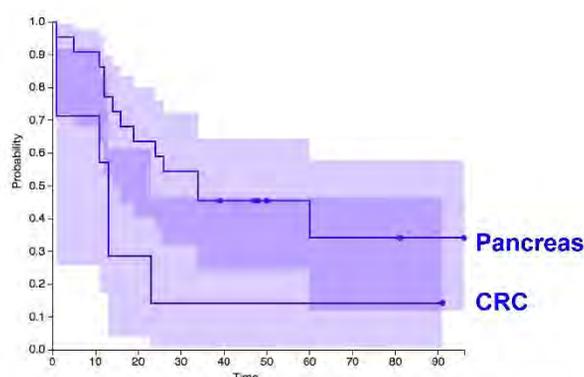


Figure 1. Kaplan-Meier curves of the patient groups with most frequent tumors, pancreatic and colorectal carcinomas included in the study; with 95%CI.

## Discussion and future directions

The treatment of locally advanced pancreatic cancer is currently investigated in the HEAT trial (NCT01077427): gemcitabine+cisplatin+regional hyperthermia, comparator arm gemcitabine+capecitabine but the outcomes are not yet available. Another study in pancreatic cancer is the HEATPAC study (NCT02439593), a phase II randomized study of concurrent thermochemoradiotherapy versus chemoradiotherapy alone. Both studies recruiting patients suffering from locally advanced cancer.

The German Study II, a retrospective study, included 25 patients with locally advanced or metastatic adenocarcinoma of the pancreas. All patients received gemcitabine-based standard chemotherapy combined with a loco-regional hyperthermia of 1 h duration twice a week. The median overall survival showed 12.2 months (versus expected 6–7 months). Cancer control (CR + PR + SD) was 65 % and 1-year survival was 51 % (versus expected 25 %). Negative side effects due to adding hyperthermia have not been found. Though not systematically documented, pain reduction in some patients was observed.

We initiate a single center, open label, randomized phase 2/3 clinical study (MEHYPOP at clinicaltrials.gov) based on our pilot and observational studies in pancreatic carcinoma. The study protocol was developed and audited, IRB approval is in place.

ClinicalTrials.gov PRS  
Protocol Registration and Results System

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## Acknowledgements

## **Local tumor-cell stress induced by modulated electro-hyperthermia could lead to an abscopal effect by immune-promotion in C26 mouse colorectal carcinoma allografts**

**Tamas Vancsik<sup>1</sup>, Eva Kiss<sup>1</sup>, Csaba Kovago<sup>2</sup>, Gertrud Forika<sup>1</sup>, Nora Meggyeshazi<sup>1</sup>, Zoltan Benyo<sup>3</sup>, Tibor Krenacs<sup>1</sup>**

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[www.oncothermia-journal.com/journal/2018/Local\\_tumor\\_cell\\_stress.pdf](http://www.oncothermia-journal.com/journal/2018/Local_tumor_cell_stress.pdf)

# Local tumor-cell stress induced by modulated electro-hyperthermia could lead to an abscopal effect by immune-promotion in C26 mouse colorectal carcinoma allografts

Tamas Vancsik<sup>1</sup>, Eva Kiss<sup>1</sup>, Dr. Csaba Kovago<sup>2</sup>, Gertrud Forika<sup>1</sup>, Nora Meggyeshazi<sup>1</sup>, Zoltan Benyo<sup>3</sup>, Tibor Krenacs<sup>1</sup>

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## Objective

Malignant tissues have elevated glycolytic activity (Warburg-effect) which causes higher lactic acid and ion content in the extracellular space, thus selective energy absorption can be applied by specific electric fields. Modulated electro-hyperthermia (mEHT, tradename; oncothermia) is a non-invasive complementary to chemo- and radiotherapy, which uses 13.56 MHz amplitude modulated field to induce cell stress (at 42°C) and damage. We showed that mEHT caused significant caspase-independent apoptosis and damage associated molecular pattern (DAMP) signal sequence in HT29 colorectal cancer xenografts of immunocompromised mice. Here we tested the mEHT following potential immune-response and tumor-damage in a mice allograft tumor model using immunocompetent animals.

## Methods

Both femoral regions of Balb/C mice were subcutaneously inoculated with C26 colorectal cancer allografts were into. Right side tumors were treated with ~42°C mEHT for 30 minutes. The expression of heat shock, growth-, damage signaling and immune response associated proteins was tested in situ immunohistochemistry.

## Results

mEHT treatment induced significant and progressive tumor damage in treated right-side tumors. Significant increase of cleaved/activated caspase-3 levels indicated caspase-dependent apoptosis, which was proved by the elevated cytochrome-c release from the mitochondria and the significant increase in TUNEL positive tumor cell nuclei as well. There were no such members of the intrinsic programmed cell death pathway as the translocation of apoptosis-inducing factor (AIF) from the mitochondria into cell nuclei, or displacement of Bcl-2-associated X protein (Bax) from cytosol to mitochondria. Significant release of hsp70, HMGB1 and calreticulin which are known participants of DAMP signaling was also showed in mEHT treated tumors. Furthermore the number of S100+ dendritic cells and CD3+ T cells was significantly increased in the treated tumors, while the number of FoxP3+ regulatory T-cells remained unchanged. In addition, mEHT combined with the i.p. administration of a CD8+ T-cell promoting chlorogenic-acid rich herbal seemed to initiate a significant tumor destruction in the untreated distant tumor site too.

## **Conclusion**

The C26 colorectal adenocarcinoma allografts have high proliferation index and lead to cancer cachexia in mice, which partly due to the impaired immune-response. In this study, a single shot mEHT treatment could induce a primary caspase-dependent programmed cell death and the release of stress associated DAMP signals. These were followed by a progressive accumulation of antigen presenting dendritic cells and CD3+ T-cells referring to an immunogenic cell death (ICD) mechanism, which could be extended to systemic anti-tumor response by a T-cell promoting agent.

This study was fund by: NVKP 16-1- 2016-0042 grant.

# Local tumor-cell stress induced by modulated electro-hyperthermia could lead to an abscopal effect by immune-promotion in C26 mouse colorectal carcinoma allografts

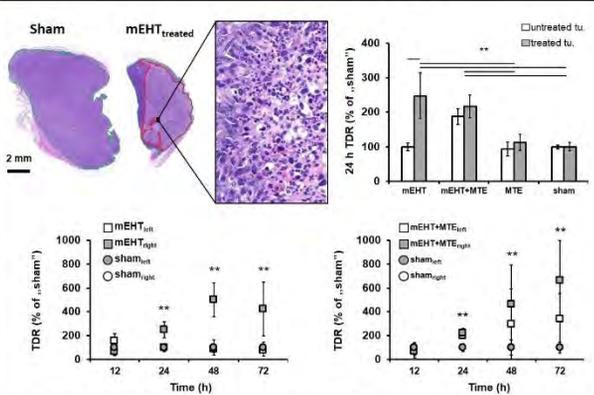
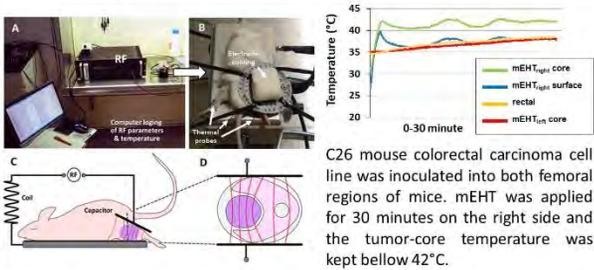


Tamas Vancsik<sup>1</sup>, Eva Kiss<sup>1</sup>, Csaba Kovago<sup>2</sup>, Gertrud Forika<sup>1</sup>, Nora Meggyeshazi<sup>1</sup>, Zoltan Benyo<sup>3</sup>, Tibor Krenacs<sup>1</sup>

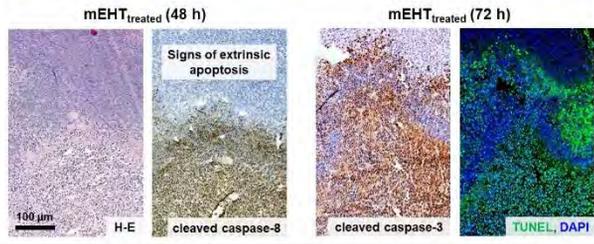
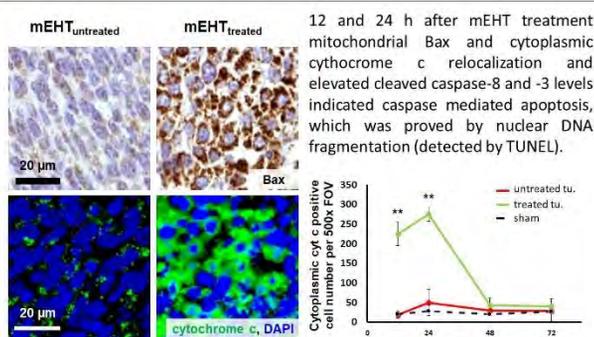
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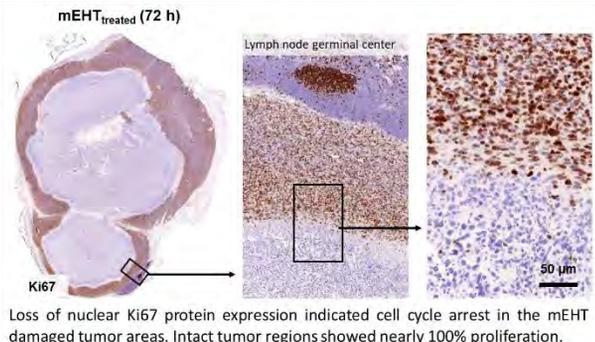
Malignant tissues have elevated glycolytic activity (Warburg-effect) which causes higher lactic acid and ion content in the extracellular space, thus selective energy absorption can be applied by specific electric fields. Modulated electro-hyperthermia (mEHT; oncothermia) is a non-invasive complementary to chemo- and radiotherapy, which uses 13.56 MHz amplitude modulated field to induce cell stress (at 42°C) and damage. We showed that mEHT caused significant caspase-independent apoptosis and damage associated molecular pattern (DAMP) signal sequence in HT29 colorectal cancer xenografts of immunocompromised mice. Here we tested the mEHT following potential immune-response and tumor-damage in a mice allograft tumor model using immunocompetent animals.



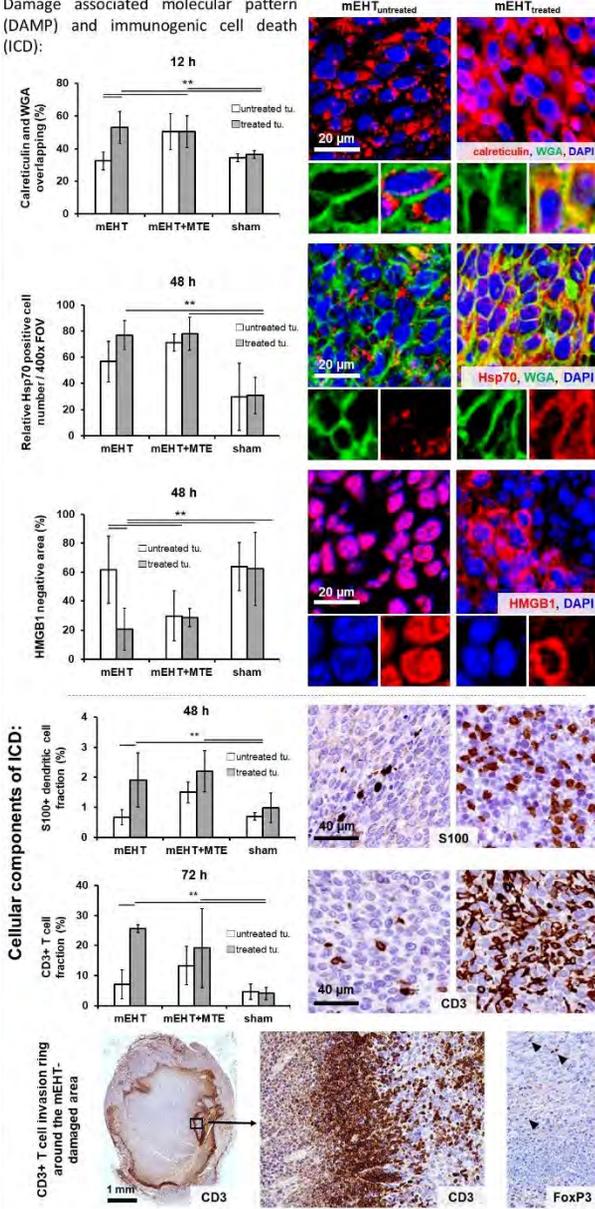
mEHT caused significant and progressive tumor destruction, which was measured by the ratio of damaged tissue to living area.



**Conclusion:** The progressive tumor destruction after a single shot mEHT probable caused by an ICD mechanism, which can be extended to systemic response by immune promotion.



Loss of nuclear Ki67 protein expression indicated cell cycle arrest in the mEHT damaged tumor areas. Intact tumor regions showed nearly 100% proliferation.



This study was funded by: NVKP 16-1-2016-0042 grant.

## Treatment of a locally advanced triple negative breast cancer with oncothermia

Tamas Garay<sup>1,2</sup>, Erika Borbenyi<sup>1</sup>, Marcell A Szász<sup>1</sup>, Janina Kulka<sup>3</sup>, Lilla Madaras<sup>3</sup>, Adam Somorác<sup>3</sup>, Gergo Lóránt<sup>1</sup>, Bela Akos Molnar<sup>4</sup>, Tamas Gyorke<sup>5</sup>, Hajna Galgoczy<sup>5</sup>, Janos Gyebnar<sup>5</sup>, Zsolt Varga<sup>5</sup>, Gyonygver Szentmartoni<sup>1</sup>, Zsuzsanna Nemeth<sup>1</sup>, Magdolna Dank<sup>1</sup>

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# Treatment of a locally advanced triple negative breast cancer with oncothermia

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## Background

Oncothermia (also known as modulated electro-hyperthermia, mEHT) is a current development among the conventional heating methods applied in oncology. mEHT can be considered as curative or palliative treatment for advanced stage, or elderly cancer patients with poor performance status and and/or multiple co-morbidities that otherwise limit the treatment options.

## Aim

Here we report the case of 73-year-old patient diagnosed with grade III triple negative breast cancer (TNBC) with 10% TILs who was successfully treated with mEHT and went into complete remission.

Patient presentation: Diagnosis was set up following PET/CT scan that showed breast tumor (18mm) with lymph node involvement (20mm) in left breast and axilla, that followed a core biopsy revealing grade III, triple negative breast cancer with 10% TILs in April and May 2017, respectively. Neoadjuvant platinum- and taxane-based chemotherapy was administered concomitantly with 24 sessions of mEHT at the Cancer Center of Semmelweis University with the instrument EHY-2000 (Oncotherm Ltd., Budaörs, Hungary). mEHT treatment was performed with power starting at 30-60 Watt with 5-Watt steps every 6 minutes to 50-105 Watt. In two sessions lower maximum power was achieved as the patient's skin showed signs for light burning. Effect of the treatment was clearly demonstrated first in June 2017 with tumor size shrinkage of 11mm and 16mm measured with ultrasound and mammography, respectively. A second ultrasound examination in October 2017 showed 10 mm tumor and the following PET/CT identified 8×3 mm lesion. In November, same year, pathological complete response (pCR) was achieved as no visible tumor was seen via mammography and after sector resection and axillary dissection as no tumor cells were detected by microscopic examination. Patient recovered well from chemotherapy side effects and operation.

Discussion: Complete pathological response was observed in a grade III, triple negative breast cancer after neoadjuvant platinum- and taxane-based chemotherapy and concomitant mEHT treatment. The highest proportion of breast cancer cases reaching pCR following neoadjuvant chemotherapy is in the TNBC subset. Relatively high amount of tumor infiltrating lymphocytes at time of core biopsy and lack of specific immune stimulating treatment might be a sign of the immune-involvement in the molecular mechanism underlying the positive effect of mEHT treatment. Further research is needed to make effects and mechanisms of mEHT treatment deeper understood and its application more accepted.

Grant support: NVKP\_16-1-2016-0042



## **Efficacy of Modulated Electro-Hyperthermia (mEHT) in cancer patients: experiences on 110 patients**

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## **Background and aims:**

There has been a significant improvement in the development and application of hyperthermia treatment and there is a continuous interest and ongoing clinical research in the field of hyperthermia. This study aim to evaluate the efficacy in terms of tumor response, pain reduction and improvement of quality of life due to modulated electro- hyperthermia (mEHT), for the treatment of cancer.

## **Methods**

This was a retrospective observational clinical study. Patients were included in the study if they had >18 years, informed consent signed, indication for treatment with mEHT.

Hyperthermia was performed with short radiofrequency waves of 13.56 MHz using a capacitive coupling technique keeping the skin surface at 26 C°. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumors was above 41,5 C° for more than 90% of the treatment duration (20-60 minutes gradually).

## **Results**

110 consecutive patients were enrolled in the study, tumor distribution was: 11 (10%) colon, 11 (10%), ovary, 10 (9%) central nervous system, 10 (9%) breast, 10 (9%) liver (cholangiocarcinoma and HCC), 10 (9%) lung, 9 (8%) pancreas, 8 (7%) prostate, 5 (5%) pseudo mixoma peritoneii, 5 (5%) stomach, 4 (5%) melanoma, 2(2%) mesothelioma, 3(3%) bladder, 3 (3%) liposarcome and 11 (10%) other type of tumor. Other characteristics of the sample were: 50% presence of metastasis, 70% received concomitant radio or chemotherapy and median number of mEHT cycles was 8 (range 1-37).

Tumor response analysis three months after mEHT showed 3% complete remission and 41% partial remission, 31 % of stable disease and 25% of progression. Median pain intensity and quality of life improved in 85% of the sample. mEHT toxicity was mostly mild (G1). The small total number of adverse events (5%) in this study supports the strong safety profile of mEHT. No complications were observed during the treatments. Cardiac evaluation was performed for all patients with EKG and echocardiography before and after the last cycle of mEHT. No significant variations were observed.

## **Conclusion**

mEHT appears to have promising efficacy in adults with several types of tumor and it can be considered as a highly indicated palliative therapy.

**Keywords:** modulated electro-hyperthermia, survival, tumor response, quality of life, pain

# Efficacy of Modulated Electro-Hyperthermia (mEHT) in cancer patients: experiences on 110 patients

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## Background and aims:

There has been a significant improvement in the development and application of hyperthermia treatment and there is a continuous interest and ongoing clinical research in the field of hyperthermia. This study aims to evaluate the efficacy in terms of tumor response, pain reduction and improvement of quality of life due to modulated electro- hyperthermia (mEHT), for the treatment of cancer.

## Results:

110 consecutive patients were enrolled in the study, tumor distribution was: 11 (10%) colon, 11 (10%), ovary, 10 (9%) central nervous system, 10 (9%) breast, 10 (9%) liver (cholangiocarcinoma and HCC), 10 (9%) lung, 9 (8%) pancreas, 8 (7%) prostate, 5 (5%) pseudo mixoma peritoneii, 5 (5%) stomach, 4 (5%) melanoma, 2 (2%) mesothelioma, 3 (3%) bladder, 3 (3%) liposarcome and 16 (15%) other types of tumor. Other characteristics of the sample were: 50% presence of metastasis, 70% received concomitant radio or chemotherapy and median number of mEHT cycles was 8 (range 1-37). Tumor response analysis three months after mEHT showed 3% complete remission and 41% partial remission, 31 % of stable disease and 25% of progression. Median pain intensity and quality of life improved in 85% of the sample. mEHT toxicity was mostly mild (G1). The small total number of adverse events (5%) in this study supports the strong safety profile of mEHT. No complications were observed during the treatments. Cardiac evaluation was performed for all patients with EKG and echocardiography before and after the last cycle of mEHT. No significant variations were observed.

Table 1) Baseline patient characteristics

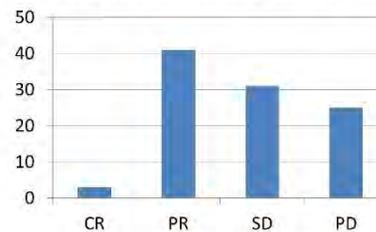
Sex	n	%
females	57	52
males	53	48
Median Age years (range)	64	(27-92)
Type of primary tumor		
colon	10	9
ovary	10	9
central nervous system	10	9
breast	10	9
liver	10	9
lung	9	8
pancreas	8	7
prostate	7	6
pseudomixoma peritoneii	5	5
stomach	5	5
melanoma	3	3
mesothelioma	2	2
bladder	2	2
liposarcoma	3	3
other	16	15
Metastatic	55	50
Concomitant radio- chemotherapy	77	70
Median mEHT cycles (range)	8	(1-37)

## Methods:

This was a retrospective observational clinical study. Patients were included in the study if they were >18 years, informed consent signed, indication for treatment with mEHT.

Hyperthermia was performed with short radiofrequency waves of 13.56 MHz using a capacitive coupling technique keeping the skin surface at 26°C. The applied power ranged between 40-150 Watts and the calculated average equivalent temperature in the tumors was above 41,5°C for more than 90% of the treatment duration (20-60 minutes gradually).

Figure 1) Tumor response (3 months)



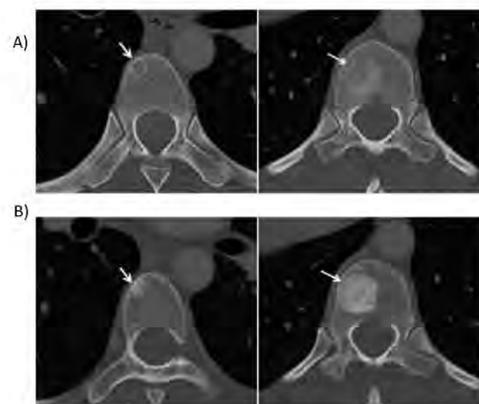
## Conclusions:

mEHT appears to have promising efficacy in adults with several types of tumor and it can be considered as a highly indicated palliative therapy.

Figure 2) Patient with squamous cellular intraoral tumor. a) baseline, b) one and c) three months after mEHT. The tumor arises from the gum and perforates the cheek



Figure 3) Patient, 49yrs with breast cancer and bone metastases. A) CT scans at baseline showed partial osteolytic metastases (arrow) in thoracic vertebrae. B) Three months after mEHT, osseous lesions did not change in size, but showed osteoblastic reaction (arrows in B), representing good response, and disappearance of the back pain.



## **Comparing the Effectiveness of Pain Therapy (PT) and Modulated Electro-Hyperthermia (mEHT) Versus Pain Therapy Alone in Treating Patients With Painful Bony Metastases: an observational trial**

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# Comparing the Effectiveness of Pain Therapy (PT) and Hyperthermia Versus Pain Therapy Alone in Treating Patients With Painful Bony Metastases: an observational trial.

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## Aim

To compare the response, duration of pain relief, and time to achieve pain relief after pain therapy (PT) with or without hyperthermia (HT) in patients with painful bony metastases.

## Methods

Cancer patients with bony metastases and VAS score  $\geq 5$  on a 0-10 scale were treated with fentanyl patches (100  $\mu$ g every three days) and zoledronic acid (4mg every 28 days) combined with HT (PT + HT) versus PT alone. Hyperthermia was performed using the Oncotherm 2000 plus, with maintenance of the target temperature for 60 minutes /twice weekly for 2 weeks. The primary endpoint was VAS = 0-2 after treatment, and ECOG performance status reduction of at least one point from baseline evaluation.

## Results

The study included 19 patients: 10 in the PT + HT group and 9 patients in the PT-alone group. Average age of the sample was 57 years (range 40-86). Median VAS for PT +HT group was 8 at baseline and decreased to 3, 1 and 2 at 1, 3, 6 months after the start of HT respectively. Median VAS for PT-alone group was 8 at baseline and did not change at following time points. Median ECOG of PT +HT group was 2 at baseline and decreased to 1, 1 and 0 at 1, 3, 6 months after the start of HT respectively. Median ECOG for PT-alone group was 2 at baseline and did not change at following time points.

## Conclusion

The addition of HT to PT significantly increases the pain control rate and ECOG compared with RT alone for painful bony metastases.

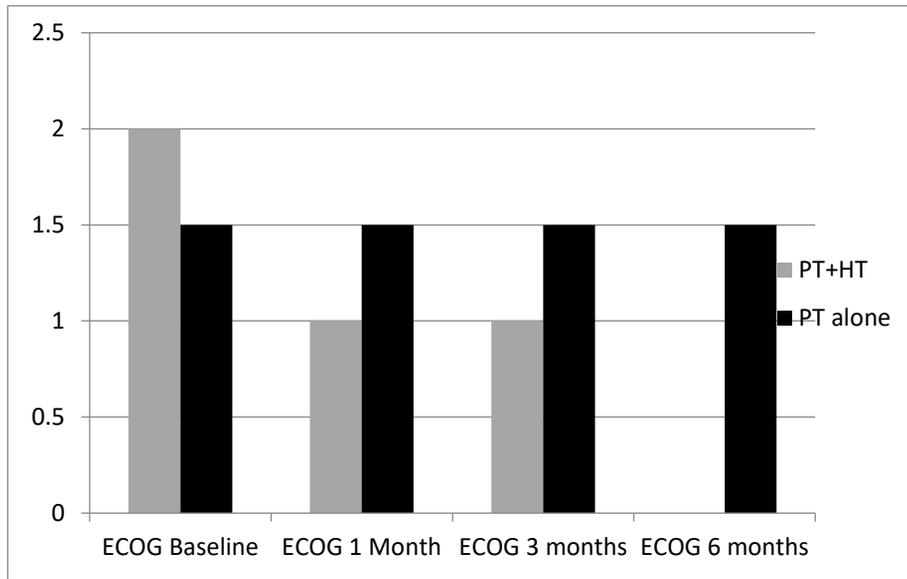


Figure 1) ECOG evaluation

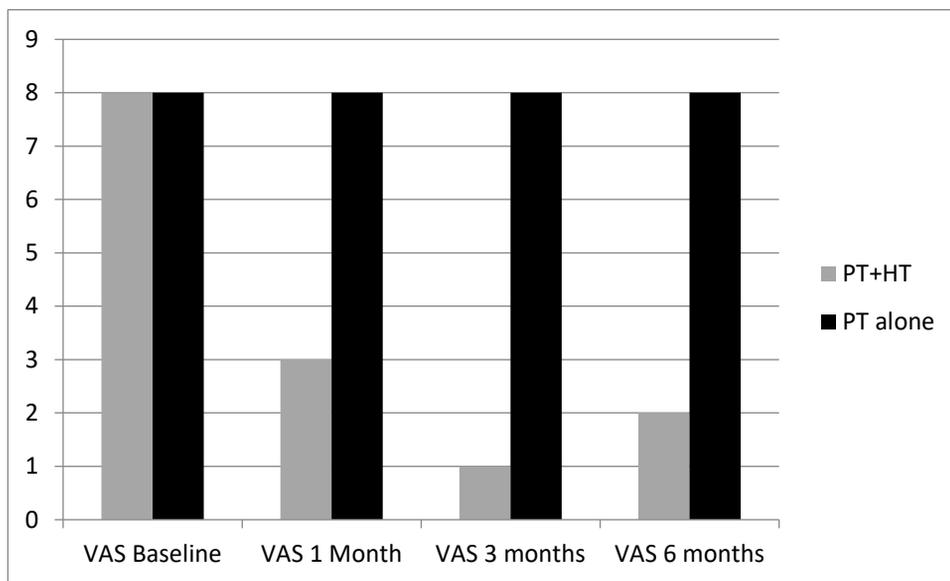


Figure 2) VAS evaluation

# Comparing the Effectiveness of Pain Therapy (PT) and Modulated Electro-Hyperthermia (mEHT) Versus Pain Therapy Alone in Treating Patients With Painful Bony Metastases: an observational trial

AUTHORS: Virginia Casadei 1, Donatella Sarti1, Carlo Milandri2, Patrizia Dentico2, Stefano Guadagni3, Giammaria Fiorentini1

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## AIM:

To compare the response, duration of pain relief, and time to achieve pain relief after pain therapy (PT) with or without hyperthermia (mEHT) in patients with painful bony metastases.

Table 1) Baseline patient characteristics

Sex	n	%
Male	10	53
Female	9	47
Median age years (range)	57	(40-86)
Type of primary tumor		
BREAST	6	32
LUNG	4	21
PROSTATE	4	21
MESOTHELIOMA	1	5
COLON	1	5
OROPHARYNX	1	5
OVARY	1	5
PANCREAS	1	5
Site of pain		
Lumbar/Pelvis	10	53
Ribs	3	16
Pelvis	2	11
Pelvis, ribs	2	11
Sternum	1	5
Sternum, collarbone, ribs	1	5

## METHODS AND MATERIALS:

Cancer patients with bony metastases and VAS score  $\geq 5$  on a 0-10 scale were treated with fentanyl patches (100  $\mu\text{g}$  every three days) and zoledronic acid (4mg every 28 days) combined with mEHT (PT + mEHT) versus PT alone. The PT alone group included patients that were followed by our center but could not come twice a week for the mEHT because they lived too far away. Hyperthermia was performed using the Oncotherm EHY-2000 plus, with maintenance of the target temperature for 60 minutes /twice weekly for 2 weeks. The primary endpoint was VAS = 0-2 after treatment, and ECOG performance status reduction of at least one point from baseline evaluation.

## RESULTS:

The study included 19 patients: 10 in the PT + mEHT group and 9 patients in the PT-alone group. Average age of the sample was 57 years (range 40-86). Median VAS for PT +mEHT group was 8 at baseline and decreased to 3, 1 and 2 at 1, 3, 6 months after the start of mEHT respectively. Median VAS for PT-alone group was 8 at baseline and did not change at following time points. Median ECOG of PT +mEHT group was 2 at baseline and decreased to 1, 1 and 0 at 1, 3, 6 months after the start of mEHT respectively. Median ECOG for PT-alone group was 2 at baseline and did not change at following time points.

## CONCLUSIONS:

The addition of mEHT to PT significantly increases the pain control rate and ECOG compared with PT alone for painful bony metastases.

Figure 1) ECOG evaluation

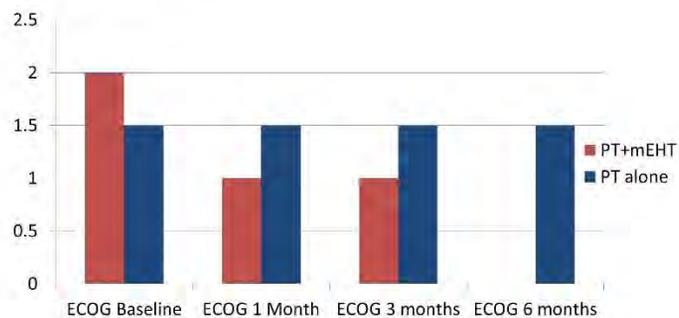
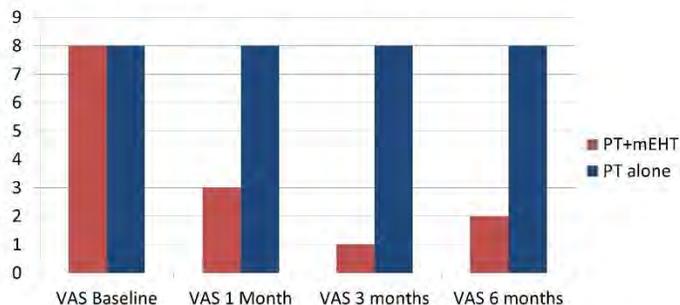


Figure 2) VAS evaluation



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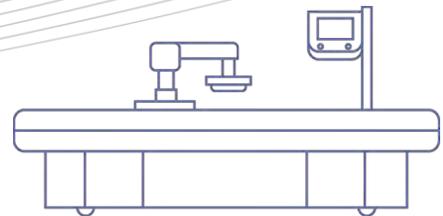


# THE ONCOTHERMIA METHOD & DEVICES ▾

▪ 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, which is generated by two active electrodes.

## > EHY-2030

The EHY-2030 is our latest development in the treatment of loco-regional (including deep and surface) 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 intelligently controlled step motor tuning system for rapid impedance matching to achieve faster tuning times.

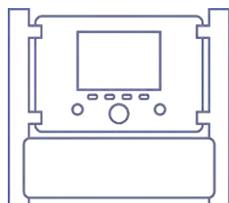
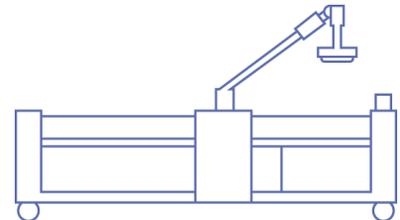


## EHY-3010 <

The EHY-3010 is designed for the simultaneous multi-local treatment of advanced, metastatically disseminated, malignant, 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 better adjust to the treatment area.

## > EHY-2000<sub>plus</sub>

The EHY-2000<sub>plus</sub> is a widely accepted system for loco-regional deep mEHT applications. This model has been used for treatment worldwide for more than 20 years. Popular, versatile device, applicable for a range of solid tumors and improved over the years through feedback from our doctors and experts and the requirements of patients and the people treating them. The EHY-2000<sub>plus</sub> is an easy to use and highly reliable device.



## EHY-1020 <

The EHY-1020 is specifically designed to treat prostate diseases. Both malignant and benign tumors (BPH) can be treated using this system. It uses 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 since 2010 with high success rates and minimal side effect.

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