
# 37th Conference of the International Clinical Hyperthermia Society

Thessaloniki | September 19-21, 2019

Abstracts and program

# WELCOME TO GREECE!

We wish you a pleasant stay in Thessaloniki!

The **ICHS** Organisers

***Dear Colleagues,***

*The 37th conference of ICHS is here! I have the pleasure and honour of welcoming you, the distinguished Hyperthermia experts, in this magnificent up-the-hill suburb of Thessaloniki. The purpose is to exchange our scientific views, get to know us better, socialize, collaborate and have some fun too.*

*There were a few governing ideas behind our effort to organize this conference, that I would like to share with you all:*

***• Hyperthermia within the frame of integrative oncology.***

*Despite the complex nature of malignant disease, the prevailing treatment paradigm is simplistic. Patients are asking for integrative approaches and prestigious institutions have started offering them: A paradigm shift is in order. So, where does hyperthermia stand in the integrative frame?*

***• Consensus on hyperthermia (definitions, practices, technologies etc.).***

*The open discussion started last year must be continued. In Budapest I got the impression that we are divided: Shall we give precedence to the physical aspects or to the clinical ones? In science it has always been like that, and that is how advancement happens; provided we keep on discussing honestly, without letting diversions of opinions become conflicts of interests.*

***• This brings me to another critical matter: Technology.***

*The scientific and clinical aspects of Hyperthermia have been plagued by preferences of research teams in specific hyperthermic technologies. But what are technologies? I view them as imperfect ways Man uses to attack problems; the fate of technologies is that at some point a new technology will make them obsolete. We, as physicians, should focus on clinical results, and let the best tech win.*

*And another point on technologies: It seems that some technologies produce more biological effects than mere heating. It will only be for the benefit of our patients, if we look with an open mind into this fortunate possibility.*

*Our organizing team devoted ourselves to the production of a technology neutral scientific meeting, precisely as we did at a previous congress that we organized 2 years ago. Our success on this is not yet satisfactory, but we will keep trying…*

*The 37th ICHS conference will offer presentations on the latest progress, by an international array of distinguished researchers and clinicians. The interdisciplinary sessions provide excellent opportunities for one to stay informed on the most recent biological, technological and clinical advances in hyperthermia. The organizers hope that you enjoy the scientific presentations, discussions and networking as well as find some free time to experience Thessaloniki with all your senses.*

*As a special treat we have organized the fractal physiology course and the educational visit to the nanoparticle research center of the Aristotelian University, where everyone is invited. On the optional side, the gala dinner and guided city tour will get you acquainted with the "flavors" of this part of the world; last but not least, the half day trip to Vergina, the ancient capital of the Macedonian kingdom of Philip II. The visit to the underground museum will be a breath-taking experience.*

*I wish everyone a pleasant stay in Thessaloniki and a fruitful scientific experience.*

***Aias-Theodoros Papastavrou, MD, PhD***

***Chairman of the conference***

## COMMITTEES

***Conference chairman:*** Dr. Aias-Theodoros Papastavrou [North Macedonia]

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## Platinum sponsor

- ***ONCOTHERM S.A.***

## Other sponsors

- ***BIOMED AID***
- ***ZEN in the City by Loukia***
- ***HLS IKE HEMPRESS***
- ***ONCOHYPERTHERMIA S.A.***

The Meeting is Organized by the **Hellenic Society for Hyperthermic Oncology** and the **Hellenic Society for Integrative Oncology.**

## SATELLITE ACTIVITIES

### Satellite 1 (GALA DINNER and City Tour)

**Departure** from hotel 19:30 -20:30. Sightseeing tour of the City and Monuments.
**Dinner** 20:30 at "HAMODRAKAS"
(http://WWW.HAMODRAKAS.GR)
**Departure** 23-23:30 for the hotel.
**Cost:** 80 Euros per person
**Date:** FRIDAY 20/09/2019
Departure from the hotel 19:30
City - Tour 19:30 - 20:30

### Satellite 2 (Tour of Vergina - Birthplace of Alexander the Great)

**Departure** 09:30 from the hotel
**Arrival** at Vergina 11:00 http://www.aigai.gr/visit/tour guide
**11:30** Vergina tour in english with D Kakagiannis
**12:45** Departure for "Ktima Kalaitzis" for lunch
**13:00** Lunch http://www.ktima-Kalaitzi.gr
**Departure** for SKG-Airport-14:45
**Arrival** SKG airport 15:30
**Cost:** 90 euros per person
**Date:** SUNDAY 22/9/2019

**TRANSPORTATION**

Panorama is a suburban area of Thessaloniki, located in the foothills of Hortiatis Mountain.

The city center is 5.5 km away and it takes about 15 minutes to get to by car. Taxis and public bus to the city are also available.

Macedonia International Airport of Thessaloniki (SKG) is located 9 km away from Hotel Panorama and 12 km away from the city center. It's the third busiest airport in Greece. The estimated time to the airport is approximately 20 minutes. Please ensure you allow extra travel time during rush hour, inclement weather and special events. Directions to the airport will be happily provided by Reception if needed.

**Contact & Address details:**

Airport TELEPHONE CENTER: +30 2310 - 985000 / FAX: +30 2310 - 475555

P.O.BOX 22605

GR-55103, Kalamaria

THESSALONIKI

**BUS**

Public Bus Transport (line 58) is available until midnight and the nearest bus stop is located 500m away from the hotel.

For more detailed information regarding Line 58 & timetable, you can visit: http://oasth.gr/#en/masterinfo/list/63/1/ or contact Reception for assistance.

General information for Public Transportation in Thessaloniki: http://oasth.gr/

## TAXI

Taxis are available 24 hours, standing by just 300 m away from the hotel. The route to the city center costs approximately 10-15€ during the day depending on the traffic. Please note that an additional late-night charge applies after midnight. Depending on where you need to go (e.g. airport), please be advised that there are also some "station fees" applicable.

If you need a taxi to pick you up from the hotel, kindly note that an "appointment" fee applies.

Reception will happily arrange a taxi for you anytime.

We would like to inform you that Panorama Hotel collaborates with the transportation company "TaxiWay", in order to provide privileged prices for you and allow you to calculate with accuracy the transportation costs.

You may find below a price list from "TaxiWay" with the most common routes and the relevant costs.

Please keep in mind that the below rates apply only to the specific routes and provided that you use "TaxiWay" company.

The hotel will not be held responsible for different prices through other transportation companies.

For car rentals, please consult with Reception.

| | FROM HOTEL | TO HOTEL | FROM 00.00-24.00 |
|---|---|---|---|
| **AIRPORT** | 15 € | 20 € | 20 € |
| **RAILSTATION** | 15 € | 15 € | 20 € |
| **BUS STATION** | 20 € | 23 € | 30 € |
| **PORT** | 15 € | 15 € | 20 € |
| **WHITE TOWER** | 15 € | 15 € | 20 € |
| **ARISTOTELOUS SQ.** | 14 € | 15 € | 20 € |
| **LADADIKA** | 15 € | 15 € | 20 € |
| | | | |
| **IKEA** | 15 € | 15 € | 15 € |
| **MEDITERANNEAN COSMOS** | 14 € | 14 € | 14 € |
| | | | |
| **ST. LUCAS CLINIC** | 5,5 € | 5,5 € | 5,5 € |
| **PAPANIKOLAOU HOSPITAL** | 15 € | 15 € | 15 € |
| **GENESIS CLINIC** | 10 € | 10 € | 10 € |
| **AROGI CLINIC** | 10 € | 10 € | 10 € |
| | | | |
| **Mini Van (9 seats)** | 30 € | 30 € | 30 € |
| | | | |
| **HALKIDIKI, VERGINA etc.** | 1 €/Km, standby 10 €/hour | | |
| **Mini Van (9 seats)** | 1,3 €/Km, standby 10 €/hour | | |
| | | | |
| Rates incl. VAT | | | |

## ACTIVITIES AND CITY TOURS

### ACTIVITIES

- Sailing
- Fishing
- Bike riding
- Horse riding
- Floating cafes
- Baseline Canyoning

- Boat tours
- Hiking
- Game & entertainment centers/Escape rooms

**CITY TOURS**

- Thessaloniki Food & Culture tours
- Wine Tours
- Thessaloniki walking tours
- Bike Tours
- Sightseeing buses
- Day Trips

For more detailed information, click on Trip Advisor link below:
https://www.tripadvisor.com/Attractions-g189473-Activities-c42-Thessaloniki_Thessaloniki_Region_Central_Macedonia.html

**CITY'S ATTRACTIONS**

Points of Interest & Landmarks

- White Tower of Thessaloniki
- Monument of Alexander the Great
- Aristotelous Square
- Church of Agia Sofia
- Rotunda church monument
- Agios Demetrius church and catacombs (crypt)
- Arch of Galerius ("Kamara" Paleochristian & Byzantine monument)
- Statue of Aristotle

**MUSEUMS**

- Archaeological Museum of Thessaloniki
- Museum of the Byzantine culture
- Museum of the Macedonian struggle
- War Museum of Thessaloniki
- Noesis Science Center and Technology Museum

- Thessaloniki Olympic Museum
- Ataturk Museum
- Jewish Museum

**OTHER ATTRACTIONS**

- Nea Paralia waterfront walk
- Ladadika district
- OTE Tower
- Heptapyrgion
- Nymphs Stones

**BARS & CAFES**

Panorama has a variety of restaurants, bakeries, fast foods, patisseries, cafeterias and bars.

**HERE ARE THE MOST POPULAR:**

- Kritikos Gallery and restaurants
- Sushija, sushi & cocktails
- Elenidis traditional patisserie
- Plaisir patisserie & bakery
- Goody's Burger House
- Dio con Dio café bar
- Paradosiako café

**SWIMMING**

Panorama has a modern municipal swimming pool that offers swimming lessons and Aqua Aerobic courses for adults and children. Telephone: 2310-340 361-2

**JOGGING**

Panorama is an ideal place for jogging, as it is surrounded by nature and beautiful views over the city. Suggested places for jogging at Panorama:

- "Platanakia" local area (declared "Natura" preserved area)
- Sports Center (route available)

Or anywhere else you prefer!

**SPORTS CENTER**

Panorama has a municipal athletic center that can host various sports, such as:

- Basketball
- Football
- Volleyball
- Tennis
- Indoor Gym
- Weightlifting train center

Telephone: 2310 345194

**37. Conference of International Clinical Hyperthermia Society**
**19-21. September 2019, Thessaloniki**
**Place of the conference:**
**Hotel Panorama ******

***Under the Auspices of Mayor and Municipality of Panorama***

# PROGRAM

**1. Day – September 19, 2019**

| **Starts** | **Ends** | |
|---|---|---|
| 9:00 | 13:00 | Fractal Physiology Course: Complexity in Medicine.<br>**Venue:** Aristotelian Univ-Thessaloniki, dept of Physiology<br>(optional, free of charge) |
| 14:00 | 19:00 | Registration (ongoing) |
| 15:00 | 16:00 | Opening |

- Welcome notes
- Opening remarks by Chairman Dr. Aias-Theodoros Papastavrou
- Frm.Minister Kostas Gioulekas, President of Permanent Committee of Foreign Affairs and Defence of Hellenic Parliament
- Mr. Ignatios Kaitezidis Mayor of Panorama, Pylea, Hortiati,
- Dr. Athanasios Exadaktilos, President Hellenic Med. Association
- Dr. Nikos Nitsas, Pres. Med. Association Thessaloniki, Other Dignitaries
- Prof. Andras Szasz, Hon. president ICHS

**I. Session**
**Chair: Papastavrou TA**

| | | |
|---|---|---|
| 16:00 | 16:10 | Oncological hyperthermia in Greece<br>***(Uzunoglou N)*** |
| 16:15 | 16:45 | Achievements and challenges in oncological hyperthermia<br>***(Datta NR)*** |

| | | |
|---|---|---|
| 16:45 | 17:05 | The role of Oncothermia in Integrative Oncology<br>***(Barich AJ)*** |
| 17:05 | 18:00 | Cocktail Reception |
| 18:00 | 19:00 | Board Meeting |

**2. Day – September 20, 2019**

**II. Session**
**Chair: Herzog A**

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|---|---|---|
| 9:00 | 9:30 | Strengthening evidence for the acceptance of clinical thermoradiotherapy in the oncology community<br>***(Bodis S)*** |
| 9:30 | 9:50 | Modulated electro-hyperthermia, an effective oncological treatment and chemosensitizer<br>***(Arrojo E)*** |
| 9:50 | 10:10 | Clinical Case Report mEHT - Results on CA Esterioneuroblastoma - Brazilian Experience<br>***(Pontes S)*** |
| 10:10 | 10:30 | Multimodal immunotherapy for patients with ovarian cancer<br>***(Van Gool S)*** |
| 10:30 | 10:50 | Modulated electro-hyperthermia, a local treatment with systemic effect<br>***(Arrojo E)*** |
| 10:50 | 11:20 | Coffee break |

**III. Session**
**Chair: Arrojo E**

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|---|---|---|
| 11:20 | 11:40 | Modulated electro-hyperthermia as Palliative treatment for Pancreatic cancer: a retrospective observational study on 106 patients<br>***(Fiorentini G)*** |

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|---|---|---|
| 11:40 | 12:00 | Effectiveness of Hyperthermia in Clinical Stage IV Pancreatic Cancer<br>***(Ono E)*** |
| 12:00 | 12:20 | Final Results on Local Control in Cervical Cancer Patients treated with Chemoradiotherapy with/without Modulated Electro-Hyperthermia as Published in PLoS ONE (2019)<br>***(Minnaar CA)*** |
| 12:20 | 12:40 | Hyperthermia as part of multimodal immunotherapy for patients with GBM<br>***(Van Gool S)*** |
| 12:40 | 13:50 | Lunch |
| | | **IV. Session**<br>**Chair: Minnaar CA** |
| 13:50 | 14:10 | Modulated electro-hyperthermia for the treatment of Relapsed Brain Tumors<br>***(Fiorentini G)*** |
| 14:10 | 14:30 | Modulated electro-hyperthermia in metastatic colorectal cancer: a retrospective cohort study with meta-comparison<br>***(Roussakow S)*** |
| 14:30 | 14:50 | How to set up an individual program of hyperthermia and conventional treatment in heavily pretreated cancer patients<br>***(Herzog A)*** |
| 14:50 | 15:10 | Potential application of neoadjuvant chemotherapy plus modulated electro-hyperthermia (mEHT, trade name: Oncothermia) among patients with advanced cancer: retrospective clinical analysis of single hospital experiences<br>***(Kim JH)*** |
| 15:10 | 15:40 | Coffee break |

**V. Session**
**Chair: Fiorentini G**

| | | |
|---|---|---|
| 15:40 | 16:00 | Modulated electro-hyperthermia in uncommon/aggressive cancers. A safe and promising treatment<br>***(Arrojo E)*** |
| 16:00 | 16:20 | Hyperthermia for the management of cervical cancer: a review of techniques, protocols and outcomes<br>***(Minnaar CA)*** |
| 16:20 | 16:40 | Survival time in cancer patients getting in addition to conventional treatments hyperthermia and complementary treatments in comparison to published data of similar patients. Retrospective study over a period of 12 years. Project of a doctorate thesis<br>***(Herzog A)*** |

**VI. Session**
**Chair: Krenacs T**

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|---|---|---|
| 16:40 | 17:00 | Efficacy and dose of local hyperthermia<br>***(Szasz O)*** |
| 17:00 | 17:20 | Effects of modulated electro-hyperthermia on peripheral white blood cell counts of clinically responding and non-responding patients<br>***(Szasz M)*** |
| 17:20 | 17:40 | Effects of modulated electro-hyperthermia on triple negative mouse breast cancer with differential metastatic potential<br>***(Schvarcz Cs)*** |
| 17:40 | 18:00 | Modulated electro-hyperthermia suppresses H19, a tumor promoting long non coding RNA, in a triple-negative breast cancer model<br>***(Danics L)*** |
| 19:30 | 20:30 | Thessaloniki tour |
| 20:30 | 23:30 | Gala dinner |

**3. Day – September 21, 2019**

**VII. Session**
**Chair: Samaras T**

| | | |
|---|---|---|
| 9:30 | 9:50 | Differential tumor damage by modulated electro-hyperthermia (mEHT)<br>***(Krenacs T)*** |
| 9:50 | 10:10 | Effects of modulated electro-hyperthermia on peripheral white blood cell counts -- a pilot study<br>***(Karaszi A)*** |
| 10:10 | 10:30 | Modulated electro-hyperthermia effectiveness compared with classic chemotherapy and radiotherapy on a pancreas adenocarcinoma cell line<br>***(Forika G)*** |
| 10:30 | 10:50 | Modulated electro-hyperthermia and combined primary, immortalized NK-cell therapy in human A2058 xenograft model<br>***(Vancsik T)*** |
| 10:50 | 11:20 | Coffee break with poster session |

**VIII. Session**
**Chair: Szasz M**

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|---|---|---|
| 11:20 | 11:40 | Thomas-Treatment protocol for studying the effect of modulated electro-hyperthermia on melanoma lung metastasis in a mouse model<br>***(Thomas MJ)*** |
| 11:40 | 12:00 | Evaluation of clinical studies when no reference arm exists<br>***(Szasz A)*** |
| 12:00 | 12:20 | Computational study of simplified numerical phantoms inside capacitive hyperthermia devices<br>***(Alexiou G)*** |
| 12:20 | 13:20 | Lunch |

**IX. Session**
**Chair: Szasz A**

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|---|---|---|
| 13:20 | 13:40 | Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer ***(Bakacs T)*** |
| 13:40 | 14:00 | Electro-Hyperthermia and Immunotherapy Combinations for the Treatment of Cancer ***(Wang YS)*** |
| 14:00 | 14:20 | Numerical Simulation and Evaluation of Magnetic Particle Hyperthermia System and Conditions ***(Maniotis N)*** |
| 14:20 | 14:40 | The Effects of microwave normothermic irradiation on cultured cancer cells ***(Asano M)*** |
| 14:40 | 15:00 | Reduction of magnetic fluid hyperthermia side effects in phantom models and ex vivo tissues using intermittent Alternating Magnetic Field ***(Kalimeri AA)*** |
| 15:00 | 15:30 | Coffee break with poster session |

**X. Session**
**Chair: Szasz O**

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|---|---|---|
| 15:30 | 15:50 | Examination of the optimum anticancer agent with a thermal effect for non-small cell lung cancer ***(Masato S)*** |
| 15:50 | 16:10 | Combined magnetic hyperthermia and magnetomechanical treatment on breast cancer and non-cancerous cells ***(Tsiapla AR)*** |
| 16:10 | 16:50 | Computational Study of Capacitive Hyperthermia with Realistic Models ***(Samaras T)*** Adjournment & Closing Remarks and Awards ***Chair Prof. V. Koulilias and Co-Chair Dr. A.J. Barich*** |

| | | |
|---|---|---|
| 16:50 | 17:20 | Visit to KEDEK: Presentation of ongoing multi-disciplinary research programs at the Aristotelian University |

**4. Day – September 22, 2019**

| | | |
|---|---|---|
| 9:30 | 12:45 | Half day tour of Vergina |
| 13:00 | 14:45 | Lunch |
| 14:45 | 15:30 | Arrival SKG Airport |

## POSTER PRESENTATIONS

*Poster session will be on 21 September, during the coffee breaks*

1. **Combined magnetic hyperthermia and magneto mechanical treatment on breast cancer and non-cancerous cells** (Tsiapla, Aikaterini-Rafailia, Department of Physics, Aristotle University of Thessaloniki)
2. **Reduction of magnetic fluid hyperthermia side effects in phantom models and ex vivo tissues using intermittent Alternating Magnetic Field** (Kalimeri Antonia Areti- Department of Physics, Aristotle University of Thessaloniki)
3. **Malignant retroperitoneal HISTIOSARCOMA and ONCOTHERMIA** (Marangos, Michael- 424 General Military Hospital of Thessaloniki)
4. **Oncothermia for lung cancer with brain metastases and extended hypermetabolic lymphadenopathy (PET CT)** (Marangos, Michael- 424 General Military Hospital of Thessaloniki)
5. **Palliative oncothermia in patient with metastatic breast cancer and significant comorbidities. our experience in thessaloniki oncothermia center** (Marangos, Michael- 424 General Military Hospital of Thessaloniki)
6. **Increasing the quality of life with hyperthermia in oncological patients** (Badzgaradze, Sophie- Medical center "SAROV")
7. **iTRAQ-based proteomics analysis reveals the differentially expressed proteins related to radiosensitivity induced by hyperthermia in highly invasive human non-small cell lung cancer cells** (Zhang Shiron- 1Department of Translational Medicine Centre, Hangzhou First People's Hospital, Zhejiang Medical University, Hangzhou, China)
8. **Microwave hyperthermia increases sensitivity to radiation in highly invasive human non-small cell lung cancer cells** (Zhao Yanyan- 1Department of Translational Medicine Centre, Hangzhou First People's Hospital, Zhejiang Medical University, Hangzhou, China)

# ABSTRACTS

The abstracts are listed in alphabetic order by surnames of the authors.

# Computational study of simplified numerical phantoms inside capacitive hyperthermia devices

**Alexiou, Georgios; Samaras, Theodoros**
Department of Physics, Aristotle University, Greece
E-mail: gealexio@physics.auth.gr

## Introduction

Capacitive hyperthermia is often used in conjunction with radiotherapy and chemotherapy for the treatment cancer. It is applied by the use of electrodes, which can be either changeable or fixed. The main frequencies used for this electromagnetic heating modality are 8 and 13.56 MHz. In order to achieve better coupling of the electromagnetic energy to the body and, at the same time, cool the surface tissues, all devices use a water bolus between the application electrode and the body, commonly with a cooled circulating liquid. However, not much work has been performed until now on the treatment planning with such devices [1, 2].

## Objectives

The objective of the current study was to investigate the distributions of the electric field, the specific absorption rate (SAR) and the temperature inside a simplified numerical phantom of the human torso with an embedded spherical tumor, when the number, shape and positioning of electrodes was changed to achieve an optimized treatment. Finally, we also aimed at examining the effect of optimal positioning derived with the simplified model on a numerical phantom of realistic anatomy.

## Material/Methods

The software platform we used for performing the numerical simulations was Sim4Life Version 4.4.2 (Zurich Med Tech, Zurich, Switzerland), which implements the Finite Element Method (FEM). A homogenous numerical phantom of the torso (cylindrical with elliptical cross-section) was created. The phantom comprised two tissues: an internal cylinder with small and large diameters of 40 cm and 72 cm, respectively, which was assigned the electric conductivity of muscle, and a cylindrical shell of 2 cm thickness on top, which was assigned the properties of fat. The realistic model of 'Ella' from the Virtual Population (IT'IS Foundation, Zurich, Switzerland) was also used and studied; this model represents a 26-year-old female with height 1.63 m and 57 kg. The circular electrodes simulated were of 25 cm in diameter.

## Results

It was confirmed that the number and size of the electrodes induce differences in electric field (SAR) distribution. At first, we used two

electrodes with different dimensions (circular and rectangular). A different geometry was applied with two electrodes with different dimensions (circular and square) with which we achieved the maximum local SAR per 100W of absorbed power in the tumor region and lower total deposited power in healthy muscle and fat tissue. Using the most efficient model we performed the thermal simulation. Through the thermal simulations we confirmed that temperature distribution changes in proportion with the applied power and boundary settings. After studying the homogenous models, we confirmed the results with the realistic model of 'Ella'.

**Conclusion**

We have shown that, starting with a simplified numerical model of the torso, it is possible to achieve an electrode configuration, which can be used with realistic patient models to improve power deposition inside the tumor while sparing healthy tissues.

**References**

1. V. D'Ambrosio, F. Dughiero. Numerical model for RF capacitive regional deep hyperthermia in pelvic tumors. Medical & Biological Engineering & Computing 45:459, 2007
2. H. P. Kok, A. N. T. J. Kotte, J. Crezee. Planning, optimisation and evaluation of hyperthermia treatments. International Journal of Hyperthermia 33(6):593-607, 2017

# Modulated electro-hyperthermia in uncommon/aggressive cancers. A safe and promising treatment

**Arrojo, Elisabeth[1,2]; Miguel, Christina [3,4]; Suarez, Beatriz[5]; Cuesta, Natalia[6]; Resines, Felipe Javier[7]; Leal, Begona[8]**
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[2]Medical institute of advanced oncology – INMOA, Madrid, Spain
[3]Medical institute of advanced oncology – INMOA, Madrid, Spain
[4]MD Anderson Cancer Center Hospital, Madrid, Spain
[5]University Hospital Central de Asturias, Oviedo, Spain
[6]Medical institute of advanced oncology – INMOA, Madrid, Spain
[7]Clínica Mompía, Cantabria, Spain
[8]Medical institute of advanced oncology – INMOA, Madrid, Spain
E-mail: dra.arrojo@oncothermia-madrid.com

## Introduction

Modulated electro-hyperthermia (mEHT), is a type of selective hyperthermia against malignant cells which has several advantages over "conventional hyperthermia". The best evidence of mEHT effectiveness is in cervical cancer but seems to be also a very promising treatment in uncommon and/or aggressive cancers where standard care does not achieve a good cancer control.

## Objectives

To present results of mEHT treatment on monotherapy or as a concomitant treatment with chemotherapy, in patients with uncommon and/or aggressive cancers.

## Material/Methods

Patients with aggressive/uncommon cancers treated with mEHT were selected. All patients were treated with mEHT only or with concomitant chemotherapy which was not responding over the last months. Patients could have received other complementary treatments as high dose vitamin C. Tumor response was determined by reduction on tumor size and/or decrease on tumor markers.

## Results

Five cases with different aggressive/uncommon histologies were reviewed. The mEHT prescription for all patients was 3 treatments a week, with at least 48 hours between treatments, for 12 to 24 sessions.

• Male, 50-year-old. Diagnosed with right leg Ewing Sarcoma, without distant metastases. Tumor size by MRI before any treatment was 6x5x4cm. MRI after 6 mEHT treatments, just before beginning chemotherapy,

showed a 20% reduction on tumor size. The patient began then, concomitant chemotherapy with ciclofosfamide, doxorrubicin, vincristine,
ifosfamide and etoposide, every 3 weeks. Three weeks after 1 chemotherapy cycle, and 12 mEHT treatments, tumor reduced another 20%. Patient has already recovered 100% of leg movements. The patient goes on now under chemotherapy concomitant with mEHT.

• Female, 51-year-old. Diagnosed with metastatic left uveal melanoma (bulky liver and bone metastases). Before mEHT treatment, tumor markers and liver enzymes were: LDH: 16798 UI/L, GOT: 281 UI/ml, GPT: 54 UI/ml. Patient was not candidate for chemotherapy. After 8 mEHT treatments on monotherapy, tumor markers and liver enzymes markedly decreased to: LDH: 4981 UI/L, GOT: 112 UI/ml, GPT: 41 UI/ml. A 25% reduction of liver metastases size was also confirmed by echography.

• Male, 56-year-old. Diagnosed with inoperable peritoneal mesothelioma with carcinomatosis. Tension ascites at diagnosis. Treatment with carboplatino-Alimta for 3 months before mEHT without significant response. Drainage of 13 liters of ascites in 4 weeks just before mEHT treatment. Patient went on under chemotherapy concomitant with mEHT. Tumor markers under chemotherapy (before mEHT): CA-125 II: 126 UI/ml. After 6 and 12 mEHT treatments, tumor markers decreased to 95.7 UI/ml, and 84.5 UI/ml
respectively. Ascites after mEHT treatment decreased to a drainage of 6 liters in 4 weeks. CT 4 weeks after mEHT treatment showed partial response, with a decreased of around 1 cm in all peritoneal implants.

• Female, 63-year-old. Diagnosed with gastric adenocarcinoma with multiple bone metastases. The importance of this case is that the treatment was for bone metastases, which is not a commonly published location for mEHT treatment. Tumor marker (CA19.9) under taxol-ramocifupan treatment progressively increased from 4030 UI/ml in may 2019 to 21400 UI/ml just before beginning mEHT treatment in June 2019. After 6 mEHT treatments, tumoral markers have decreased for the first time in the last 6 months to 19100 UI/ml.

• Female, 72-year-old. Diagnosed with locally advanced ductal infiltrating carcinoma. Right breast mass of 6cm of maximum diameter with ipsilateral bulky axillary nodes. After 24 mEHT treatments, breast mass reduced to a maximum size of 4 cm, and 80% of axillary nodes disappeared. She did not receive any chemotherapy treatment. None of the cases had any significant toxicities related to mEHT treatment.

**Conclusion**

Aggressive and/or uncommon malignant tumors are a very important health problem as "conventional" oncological treatments do not usually achieve good control rates. On the other hand, patients with advanced tumors are frequently not candidates for chemotherapy or radiotherapy

treatments because of their poor general status. mEHT is a very promising treatment for patients with aggressive/advanced tumors as it can improve tumor control, without increasing toxicities for the patients, as its selective against malignant cells. This makes mEHT a good option for concomitant treatment in patients with aggressive cancers, or in monotherapy for patients not candidates for any other oncological treatments, as it can improve their cancer control without significant toxicities.

# Modulated electro-hyperthermia, an effective oncological treatment and chemosensitizer

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## Introduction

Oncothermia, also known as modulated electro-hyperthermia (mEHT), is a selective hyperthermia therapy against malignant cells. This selectivity gives mEHT the advantage of increasing temperature inside malignant cells, while keeping healthy cells' temperature without significant changes. This have some advantages as: no toxicity for healthy tissues inhomogeneous heat with vasodilatation of intratumoral vessels only, avoiding the risk of migration of malignant cells secondary to a massive vasodilatation in healthy and malignant tissues, as it happens with conventional hyperthermia. Selective vasodilatation of intratumoral vessels, has also the advantage of increasing intratumoral chemotherapy distribution, and this way, its efficacy.

## Objectives

To present results of a dissociated response to oncological treatments in a cancer patient treated with mEHT and concomitant chemotherapy, showing the benefit of adding mEHTto improve chemotherapy sensitivity and cancer control.

## Material/Methods

The case of a 34-year-old pre-menopausal female was reviewed. She was diagnosed with an infiltrating squamous cell cervical carcinoma, G2, T3b, N1, M1 (multiple bone metastases: cervical, thoracic, lumbar, scapular and costal bones). The patient at diagnosis hadcervical cord compression with pain and motor disfunction associated, so she was treated with palliative radiotherapy (24Gy in 6 fractions) at that level. She had anuria secondary to bilateral ureter compression by tumor, so nephrostomy bilateral catheters were placed at diagnosis also. FDG18-PET-CT at diagnosis showed pathologic metabolic disease at the multiple metastases described and pelvis, external and internal bilateral iliac nodes, paraaortic and retroperitoneal nodes with a SUVmax of 15.38 and retrocrural right region with a SUVmax of 3.35.

**Results**

The patient began chemotherapy treatment every 21 days with cisplatin, paclitaxel and bevacizumab, concomitantly with mEHT 3 times a week for 12 treatments. mEHT treatment was applied to the abdomen-pelvis area in order to treat cervix, parametrium, low-abdominal and pelvic pathologic nodes. Two weeks after 1 chemotherapy cycle and 6 mEHT treatments, patient progressively began to urinate by the urethra. Tumor markers (CEA) at diagnosis were: 35,7 ng/ml and decreased to 6 ng/ml after 2 chemotherapy cycles and 12 mEHT treatments. FDG18-PET-CT after 3 chemotherapy cycles and 6 weeks after mEHT treatment, showed completed metabolic response in the gynecological area and abdominal-pelvic nodes. **(Figures 1 and 2).**

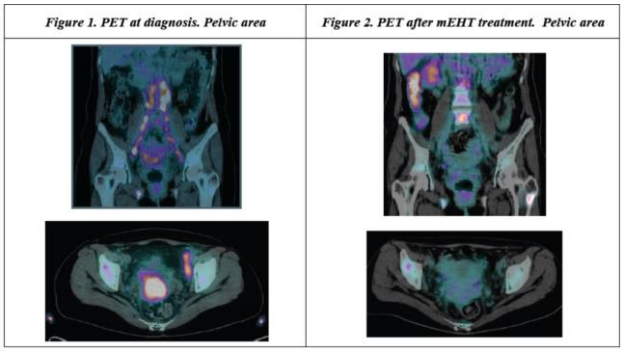

*Figure 1. PET at diagnosis. Pelvic area*



*Figure 2. PET after mEHT treatment. Pelvic area*

On the other hand, high metabolic pathologic activity persisted in all bone metastatic locations (except cervical metastases which had been treated with radiotherapy) and disease progressed at lumbar bones with fracture of T2 (with spinal canal invasion), T8 and L3 vertebras **(Figures 3 and 4).**

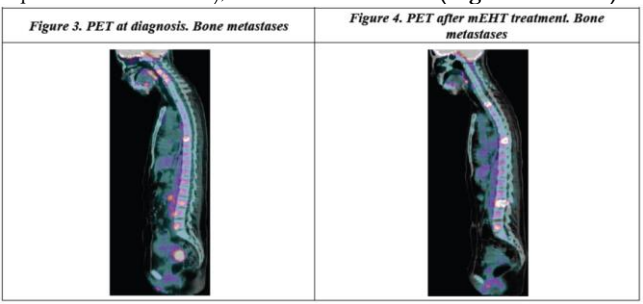

*Figure 3. PET at diagnosis. Bone metastases*

*Figure 4. PET after mEHT treatment. Bone metastases*

**Conclusion**

Modulated electro-hyperthermia improves cancer control and chemotherapy distribution, increasing chemo-sensitivity, especially in the most aggressive tumors which are usually the most hypoxic also, due to its aberrant vessels which difficult chemotherapy distribution. This case shows how tumor response was excellent at the level where mEHT was applied with complete metabolic response and was poor at other distant sites where cancer progressed. mEHT should be considered as an oncological treatment and chemosensitizer specially in aggressive, advanced tumors.

# Modulated electro-hyperthermia, a local treatment with systemic effect

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**Introduction**
Modulated electro-hyperthermia (mEHT), is an oncological hyperthermia therapy with some differential advantages over "conventional" hyperthermia. Some of these are that mEHT is selective against malignant cells and kills cancer cells by apoptosis (immunogenic death) and not necrosis. This apoptotic cell death stimulates immune system to kill malignant cells not only where mEHT is applied, but also at distant locations. This is called the "abscopal effect", also described with radiotherapy.

**Objectives**
To present results of abscopal effect in a patient with an aggressive malignant inflammatory breast cancer treated with mEHT.

**Material/Methods**
We reviewed the case of a 49-year-old pre-menopausal female, diagnosed with a triple negative, multicentric, right breast infiltrating carcinoma, who underwent a right mastectomy with ipsilateral axillary node dissection in May 2018 with immediate reconstruction with an expander. The pathology report showed metaplastic infiltrating multicentric carcinoma, triple negative, with negative margins, and 7 axillar nodes of 8 resected with macroscopic disease, extracapsular and vascular invasion. The patient was treated also with adjuvant radiotherapy, and chemotherapy with capecitabine. The patient developed local relapse (skin) and distant metastases (lung and bone) during adjuvant chemotherapy, which progressed to different chemotherapy and immunotherapy treatments. Right breast skin lesions were biopsied with pathology results of inflammatory carcinoma. Patient was evaluated for mEHT treatment. She was at that moment, under Eribulin treatment without improvement in cancer control. At the first mEHT consult,

the patient presented with right breast bleeding ulcerative, raised, skin lesions all over the breast. Right breast skin, including right axillary skin was indurated, swollen and clearly affected by tumor. She was anemic in probably relation with significant breast bleeding. As the patient had open wounds on the right breast skin
and a metallic expander, she was not considered candidate for mEHT treatment at that location. She was on the other hand, considered candidate for left lung metastases treatment with mEHT. The patient continued on Eribulin during mEHT treatment.

**Results**

Patient began mEHT treatment for left lung metastases, with the prescription of 3 treatments per week with at least 48 hours between treatments. Treatment electrode was placed over the left chest, out of the area of right breast skins lesions. After 9 mEHT treatments applied over the contralateral chest, all right breast skin lesions stopped bleeding and almost all of the ulcers disappeared. Still remained right breast skin changes, with raised lesions and induration in relation with tumor, but right breast skin tumor significantly decreased. Table 1 shows some pictures of the right breast skin lesions evolution along mEHT treatment. Patient is still under mEHT treatment, so CT studies for lung control have not been done yet. 3 mEHT treatments 7 mEHT treatments 9 mEHT treatments 11 mEHT treatments.

| 3 mEHT treatments | 7 mEHT treatments | 9 mEHT treatments | 11 mEHT treatments |
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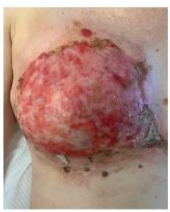
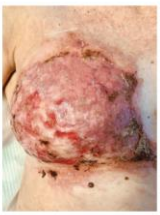
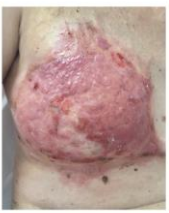
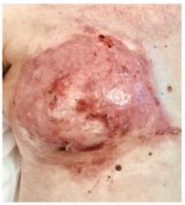
|  |  |  |  |

**Table 1**. Right breast skin lesions evolution along mEHT treatment over the contralateral chest (abscopal effect).

**Conclusion**

A significant number of cancer patients have distant metastases at diagnosis or develop them at some point over the years, so cancer is very frequently not a local disease, but a systemic disease. Modulated electro-hyperthermia despite being a local treatment, kills cancer

cells by an immunogenic death which stimulates immune system to kill malignant cells not only locally, but also systemically (abscopal effect). mEHT should be considered as a treatment option not only in localized malignant tumors, but also in cancer patients with systemic disease.

# The effects of microwave normothermic irradiation on cultured cancer cells

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## Introduction

Microwaves (frequency: 0.3–300 GHz) have long been used in cancer therapies such as microwave coagulation therapy and hyperthermia therapy. In these therapies, microwave irradiation is used to kill tumor cells by raising cellular temperature. These therapies have been used for treatment of various cancers for a long time. In recent years, microwave irradiation technology has been developed further, and it has been reported that the yield and reaction rate of many chemical reactions can be increased by microwave irradiation at a much lower temperature as compared to a conventional heating method such as water bath heating1. Therefore, we hypothesized that microwave normothermic irradiation might affect biological phenomena in cells.

## Objectives

We previously developed a microwave irradiation system that could irradate cells under normothermic conditions by controlling the outputs and frequency precisely2. We then investigated the cell death pathways in HL-60 cells, induced during microwave irradiation under normothermic conditions. After being exposed to our microwave irradiation system, the cells were killed through "caspase-independent apoptosis"3. In this study, we investigated the cell death of other cultured cancer cells by microwave irradiation such as T98G (for human glioblastoma cells), MDA-MB-231 (for human breast cancer cells), and KATO III (for human gastric cancer cells).

## Material/Methods

T98G, MDA-MB-231, and KATO III cells were seeded in 35 mm culture dishes containing 2.5 mL of media, at a density of $1 \times 105$ cells/mL. Microwave irradiation (2.45 GHz) was applied for 1 h, and the temperature of cells was maintained at 37 °C. However, the temperature inside the applicator, during these experiments, was set at 10 °C. Following irradiation, the cells were moved to a CO2 incubator, where they were incubated for 6 h before use in the following assays; Caspase 3/7 assay carried out by using Caspase-3/7 Assay Kit (AnaSpec, San Jose, CA, USA) and Annexin V-PI assay performed by using an Annexin V-FITC Apoptosis Detection Kit (Nacalai Tesque).

**Results**

According to the microscopic observations, the number of late stage apoptotic cells (both Annexin V and PI positive) had increased in all cell types, while early apoptotic cells (Annexin V positive, PI negative) were not observed. The adherent cell types, T98G and MDA-MB-231, were cast off by microwave irradiation, further indicating that cells were near death. Moreover, after microwave irradiation, the activity of caspase 3/7 did not increase significantly in any of the cell types.

**Conclusion**

The results indicate that cell death pathways activated by microwave irradiation in the examined cells may be similar. However, further investigations should be performed to better understand the effects of irradiation on each cell type in detail.

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# Increasing the quality of life with hyperthermia in oncological patients

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## Topicality

Treatment of oncological patients and getting clinical remission is an unfortunate topic even for the 21st century; despite the correctly selected therapy, which gives minimal risks of complications because of the chemo sensitive tests, there are important problems connected with the quality of life of patients and naturally we ask questions to ourselves: How could we manage to increase the quality of life in oncological patients on the 3rd and 4th levels and decrease the number of the side effects that accompany Ch/therapy and R/therapy procedures.

## Aim

The aim of the study was the patient with a 32-year diagnosis: Hodgkin's lymphoma, nodular sclerosis; Thigh bone MTS, 3rd stage; 3rd class group; R /therapy and CH /therapy; ECOG-2; pancytopenia with pain syndrome R-CHOP and 4 courses conducted by BEACOPP schemes; Clinical remission was not achieved; Symptoms of progression of the hip fracture were strengthened, and the institution was addressed with the aforementioned history.

## Methods and Materials

For the patient was selected CH/course; the GEMOX scheme and recommended to strengthen the course effectiveness, weaken toxicity and to improve the quality of life recommended for the treatment CH/therapy with hyperthermia and hypoglycemia; For this procedure, a hyperthermic camera was installed, where the procedure is carried out at 43-48 degrees Celsius, and we have a sugar content of 25-30000 per one 40-45 mm / l in the bloodstream with the following doses: -1500 mg, Oxalipltin-150mg.
Results: Only 2 courses were conducted with the patient with a CH/therapy hyperthermia. During the treatment the patient did not have any clinical remission was only reached in 2 courses, the patient was active and ECOG-4.

## Conclusion

So, we managed to get maximal results through high-tech hyper thermic chemotherapy, patient's clinical remission and this was without any side effects. Increased the quality of life; From ECOG-2 to ECOG-4;We

recommend giving a hyper thermic chemotherapy in oncological patients at 3rd and 4th stage, which is a firm guarantee of increasing their quality of life.

# Exploiting autoimmunity unleashed by an off-label low-dose immune checkpoint blockade to treat advanced cancer

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To the memory of Melvin Cohn, founding fellow and professor emeritus of the Salk Institute for Biological Studies

## Introduction

As a result of the cancer immunotherapy revolution more than 2,000 immuno-oncology agents are currently being tested or in use to improve responses. Not unexpectedly, the 2018 Nobel Prize in Physiology or Medicine was awarded to James P. Allison and Tasuku Honjo for their development of cancer therapy by blockade of co-inhibitory signals. While success stories of terminal cancer patients achieving complete remissions are accumulating, not enough research has been done into the risks of the new therapies. Since the use of immunotherapy is becoming more common, and is beginning to develop into first- and second-line treatments, autoimmunity is emerging as the nemesis of immunotherapy. Immune-related adverse events (irAEs) could affect any tissue; their incidence may reach up to 96% of patients; and toxicity is dose-dependent. While the combination of two immune checkpoint inhibitors (ICIs) increases efficacy, the incidence of severe adverse events is also increased. Apparently, ICIs cannot be restricted to the targeted anti-tumor T cell population. The long lasting objective of cancer regression can only be achieved by paying a price: tolerance to healthy self tissues is compromised.

## Objectives, Material/Methods

In the face of an ipilimumab-induced pan-lymphocytic activation, a therapeutic paradigm shift is required. The task is not to desperately put the genie back in the bottle by immune suppressive treatments, but instead harnessing the autoimmune forces by an off label low-dose combined anti-CTLA-4 and anti-PD1 antibody blockade, which is supplemented with conventional interleukin-2 (IL-2) stimulation and hyperthermia.

**Results**

The proof-of-principle of the low-dose-combination therapy was 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. Her pulmonary metastases went into complete remission with transient WHO I-II diarrhea and skin rash. She lived for 27 months after starting the low-dose-combination therapy. Since then, 111 stage IV cancer patients with a variety of cancer types have been treated. A retrospective analysis of these single cases demonstrated that the overall response (OR) rate was 48% with an objective response (ORR) of 33%, while irAEs of WHO grade I, II, III and IV were observed in 21%, 14%, 7% and 2% of patients, respectively.

**Conclusion**

Since the low-dose-combination protocol consists only of approved drugs and treatments, these single patient responses can be confirmed or refuted in prospective controlled clinical trials.

# The role of oncothermia in integrative oncology- exploring unchartered waters

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Chairman Scientific Advisory Board to Hellenic Society for Hyperthermic Oncology
AHEPA University Hospital/Euromedica/Thessaloniki Oncothermia Center

Multiple Phase III studies have been published establishing the significance of Hyperthermia, and its indisputable synergy with the Conventional modalities of Cancer treatment (Surgery-HIPEC, Chemotherapy and Radiation therapy). Its autonomous effect on cancer cells has also been established. The appearance of mEHT has created ripples in the pond of the Hyperthermia Community. Its modulated capacitive coupling function is focused on the same target, but delivers results in a different way. This comes to augment the growing Global focus on Integrative Medicine and more so, on Integrative Oncology.

Many questions arise from the growing experience of Institutions that use Hyperthermia in their Therapeutic Strategies against cancer. Clashes are resulted, in the attempt to clarify the best mode of Hyperthermia for treating patients. What the Hyperthermia Community forgets, is that we haven't yet resolved basic questions on the Role of Hyperthermia in the Arsenal against cancer. We have established it synergy with chemotherapy and Radiation therapy. What about Immunotherapy, what about Biologicals, what about Small Molecular Agents (Sunitinib, Imatinib etc.), Monoclonal Antibodies, what about its possible interactions with Dendritic Cell therapy and Anti-Sense Oligonucleotide therapy? These are emerging strategies that may be potentiated by Hyperthermia. Multicentric studies are urgently needed to clarify the full extent of these potential synergies. We have moved onward and gained experiences that have put us well beyond the 2004 Kadota Consensus, and a great necessity for an updated Consensus is imperative.

Integrative Oncology is focused on these synergies, and only through consensus on the essential issues (impact on patients), can we formulate successful Therapeutic Strategies for our patients.

Recent studies have indicated that mEHT may have an impact on cancer microenvironment. Our experience with mEHT and parallel Integrative therapeutic strategies indicate that focusing on increasing Oxygen perfusion to cancer tissues and simultaneously inducing tissue Alkalynization may significantly enhance tumor destruction by not only thermal induced damage and potential Apoptotic induction, but also by disrupting the tumor microenvironment.

These are issues that require urgent consideration for multicentric trials. Each of our Institutions has its own experiences that gives us the incentive to further explore into unchartered waters. This is a necessity. This is a journey we should take together, like Magellan before us. It is up to us to discover a pass into the Pacific. Our focus on researching this area may set a new precedent in the therapy of Cancer.

# Strengthening evidence for the acceptance of clinical thermoradiotherapy in the oncology community

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**Background**
Hyperthermia/Thermotherapy (HT/TT) as a therapeutic option in the multimodality approach for cancers has yet to gain widespread acceptance in clinical oncology. At 39-43°C, hyperthermia is one of the most potent radiosensitizer and is also synergistic to a number of chemotherapeutic agents. Furthermore, recent evidence also indicates a favorable immunomodulatory effect at moderately raised body/tumor-temperatures. Despite this progress, enthusiasm among academically oriented clinical oncologists remains far below for broad acceptance in clinical practice.

**Current status and next steps**
Biology and Immunology: In vitro and in vivo data imply a strong synergistic activity using HT/TT combined with radio-and or chemotherapy. However, we currently have little data about tumor/patient specific molecular mechanisms and pathways for this synergistic activity of HT/TT with RT and/or CT. Furthermore, an increasing amount of data implies that moderate regional/whole body hyperthermia has a direct immunomodulatory tumor effect. Little is known so far about optimizing this immunomodulatory effect within a multimodal anticancer therapy for specific tumor entities and individual patients.

**Physics and Technology**
Impressive progress has been realized over the last 10 years for HT/TT treatment planning, temperature monitoring, QA, patient comfort and safety. However, with nowadays available technology high precision planning and high precision temperature monitoring is feasible. This might only be clinically relevant for a small (-er) number of treated patients. However, this potential for better local tumor control, the increase of patient comfort during HT/TT sessions and the decrease of treatment related side effects needs to be determined in properly conducted clinical trials. Workflow optimization and further workflow automatization (e.g. with the synchronous planning and applications of locoregional RT and HT/TT) is mandatory to increase the efficiency of HT.

**Evidence based multimodal oncology therapies including locoregional HT/TT**

In the absence of a critical number of published multi-centric, randomized phase III trials (CT-and or RT +/- HT/TT) with long term follow up 4 steps are mandatory to integrate hyperthermia in routine multidisciplinary cancer care:

- Proper patient selection and mandatory discussion in a multidisciplinary (national) hyperthermia tumor board via web link respecting published guidelines and the relevant clinical data.
- Have a local patient registry with follow up data.
- Have a national indication list for loco-regional HT indications (combined with RT and or CT), accepted by the natl. oncology community and reimbursed by the natl. health care insurances
- Mandatory participation in phase I-II local/national and phase III national/international multi-centric clinical trials

# Modulated electro-hyperthermia suppresses H19, a tumor promoting long noncoding RNA, in a triple-negative breast cancer model

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## Introduction

Modulated electro-hyperthermia (mEHT) is a complementary antitumor therapy, based on selective tumor cell killing by a 13.56 MHz radiofrequency induced electric field. The H19 long non coding RNA (lncRNA) is involved in tumor progression and metastasis. Its overexpression is associated with poor prognosis in breast cancer. We observed previously significant tumor inhibitory effects of mEHT.

## Aims

Our aim was to investigate the hypothesis, that mEHT effects are related to H19 lncRNA inhibition in a triple negative breast cancer (TNBC) bearing mouse model.

## Method

TNBC cells (highly aggressive 4T1 or less aggressive 4T07) were inoculated orthotopically in female BALB/c mice. Tumor growth was monitored in vivo by digital caliper and ultrasound (Phillips Sonos 5500), mice were randomized into two groups based on tumor size. Mice were treated with mEHT in monotherapy or in combination with methotrexate (MTX) 2 or 3 times for 30 minutes with 1.0±0.5W power to achieve 40°C skin temperature above the tumor. At the end of the experiments mice were euthanized, the tumors were dissected and processed for molecular biologic techniques. H19 expression was measured with real-time PCR, results were normalized to GAPDH. Five representative samples from each group were deep-sequenced by Illumina NextSeq system (Illumina Inc. San Diego, CA, USA).

## Results

There was a significant decrease in H19 expression of 4T1 tumors after two (sham: 0.068±0.044, mEHT: 0.033±0.024, $p<0.05$) and three mEHT treatments (sham: 0.097±0.059 vs mEHT: 0.050±0.030, $p<0.05$) compared to the sham group. In case of combination treatments H19 expression was significantly lower in the mEHT+MTX group compared to MTX only (MTX: 0.104±0,038 vs mEHT+MTX: 0.056±0.025, $p<0.01$). The basic expression of H19 was significantly lower in 4T07 tumors compared to the

more aggressive 4T1 tumors (4T07: 0.006±0.004 vs 4T1: 0.399±0.071, p<0.0001). In 4T07 tumors H19 expression did not change after three mEHT treatments (sham: 0.404±0.334 vs mEHT: 1.391±1.840, p>0.10) compared to the sham group. Preliminary results of the total transcriptome analysis indicated 150 differentially expressed genes (109 upregulated and 43 downregulated). Significant changes were detected in the following KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways: neuroactive ligand-receptor interaction, peroxisome proliferator-activated receptor (PPAR) signaling, cell adhesion, drug metabolism – other enzymes and type I diabetes mellitus. We analyze the rank of H19 targets in the transcriptome analysis.

**Conclusion**

Our results demonstrate, that repeated modulated electro-hyperthermia can reduce the expression of tumor promoting H19 lncRNA in vivo both in monotherapy and in combination with chemotherapy. Our findings suggest, that mEHT as an alternative complementary treatment could promote antitumor therapy by inhibiting the tumor progression mediating H19 lncRNA expression. More effective therapy against the more aggressive 4T1 line may be related to higher baseline expression and more significant effect on H19. Transcriptomic analysis should shed further light on the role of H19 in breast cancer progression.

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

# Modulated electro-hyperthermia as palliative treatment for pancreatic cancer: a retrospective observational study on 106 patients

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**Background**
Pancreatic adenocarcinoma is one of the cancers with the poorest prognosis, resulting in a <10% survival rate at 5-years. Modulated electro-hyperthermia (mEHT) combines the heat-therapy with an electric field and has been increasingly used for cancer therapy alone or in combination with radiotherapy and chemotherapy. Clinical researchers show that hyperthermia is feasible not only for palliative care but has also therapeutic effects in pancreatic cancer.

**Purpose**
To monitor the efficacy and safety of mEHT for the treatment of pancreatic cancer.

**Methods**
We collected data retrospectively on 170 patients affected by stage III-IV pancreatic adenocarcinoma, and 106 were considered for this study. The sample was divided in two groups: patients that did not receive mEHT (no-MEHT) and patients that were treated with mEHT.
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 (40-90 minutes). The applied power was 60-150 Watts. mEHT was

performed in association with chemotherapy in 32 (82%) of patients whereas 7 (18%) received mEHT alone.
The majority (54%) of no-mEHT group received a second line chemotherapy, whereas 31 (46%) did not receive any further treatment.

**Results**
106 consecutive patients were enrolled in this study, median age of the sample was 65 (range 31-80) years.
After three months of therapy, tumor response in mEHT group was: partial response (PR) in 22 (56%) patients, stable disease (SD) in 15 (38%) patients and progression disease (PD) in 2 (5%) patients. Tumor response in no-mEHT group was: partial response (PR) in 4 (11%) patients, stable disease (SD) in 11 (31%) patients and progression disease (PD) in 21 (58%) patients.
The median overall survival (OS) of mEHT group was 17.23 (range 2.6-30.4) and 11,33 months (range 0.4-56.25) for non-mEHT group.

**Conclusions**
mEHT may improve tumor response and survival of pancreatic cancer patients.

| | n | % |
|---|---|---|
| **males** | 59 | 56 |
| **females** | 47 | 44 |
| **mEHT** | 39 | 37 |
| **no-mEHT** | 67 | 63 |
| **non-metastatic** | 45 | 42 |
| **metastatic** | 61 | 58 |
| | | |
| **site of metastases** | | |
| **liver** | 49 | 46 |
| **lung** | 6 | 6 |
| **lymphnodes** | 5 | 5 |
| **peritoneum** | 4 | 4 |
| **bones** | 2 | 2 |
| **pelvis** | 1 | 1 |
| | | |
| **type of first line CHT** | | |
| **gemox** | 47 | 44 |
| **gemcitabine** | 31 | 29 |
| **gemcitabine abraxane** | 12 | 11 |
| **gemcitabine FU** | 4 | 4 |
| **gemcitabile platimun** | 2 | 2 |
| **other** | 10 | 9 |
| | | |
| **previous surgery** | 21 | 20 |
| **previous radio** | 11 | 10 |

**Table 1.** The sample

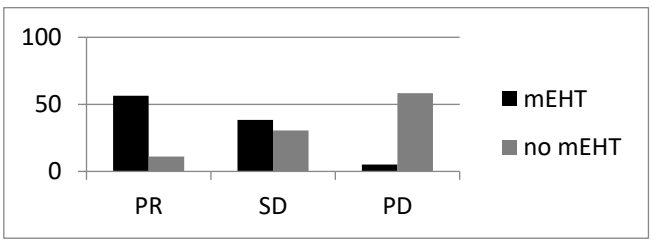


**Figure 1.** Tumor response at three months

| | n | % |
|---|---|---|
| m | 42 | 58 |
| f | 37 | 51 |
| mEHT | 35 | 49 |
| no-mEHT | 35 | 49 |
| non-metastatic | 31 | 43 |
| metastatic | 41 | 57 |
| site of metastases | | |
| liver | 34 | 47 |
| lung | 4 | 6 |
| peritoneum | 3 | 4 |
| lymphnodes | 2 | 3 |
| bones | 1 | 1 |
| pelvis | 1 | 1 |
| type of first line CHT | | |
| gemox | 26 | 36 |
| gemcitabine | 24 | 33 |
| gemcitabine abraxane | 9 | 13 |
| gemcitabine FU | 4 | 6 |
| gemcitabile platimun | 2 | 3 |
| folfirinox | 1 | 1 |
| other chemotherapy lines | 59 | 82 |
| previous surgery | 11 | 15 |
| previous radio | 5 | 7 |

**Table 2.** Characteristics of the sample

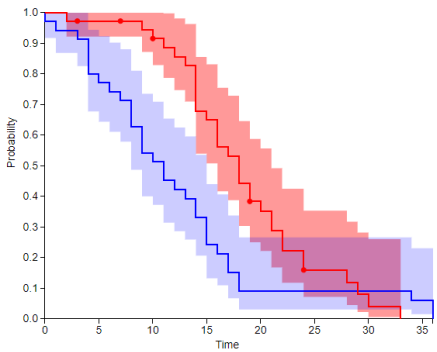


**Figure 2.** Survival no mEHT (blue) versus mEHT (red ) group

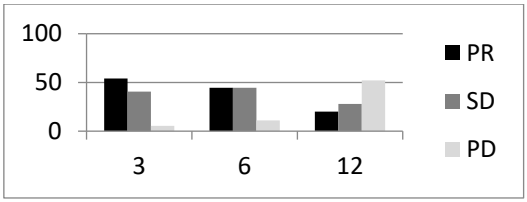


**Figure 3.** Tumor response after mEHT

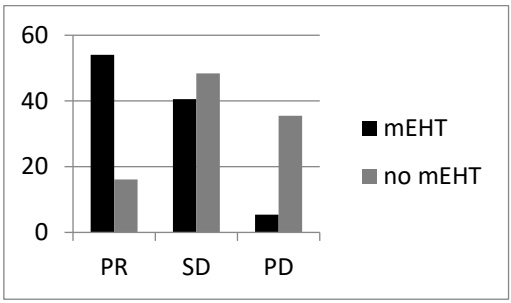


**Figure 4.** Tumor response after 3 months of the two groups mEHT and no-mEHT

# Modulated electro-hyperthermia for the treatment of relapsed brain tumors

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**Aim**

To motor the efficacy and safety of modulated electro-hyperthermia (mEHT) for the treatment of relapsed brain tumors.

**Methods**

We collected data retrospectively on 164 patients that were affected by recurrent malignant brain tumors: glioma and astrocytoma. Patients were included in the study if: informed consent signed, >18 years old, histological diagnosis of malignant glioma or astrocytoma, failure of previous temozolamide-based chemotherapy and radiotherapy, indication for treatment with mEHT as palliative setting.

mEHT was performed using a capacitive coupling technique that allowed to keep the skin surface at 26 C° and to reach 40-42.5 C° inside the tumor for > 90% of treatment duration (20-60 minutes) by applying a power of 40-150 Watts.

**Results**

The study sample included 164 patients with brain tumor, 115 of these (70%) had glioblastoma multiforme (GBM) and 50 (30%) had astrocytoma. mEHT was performed to 29 (25%) GBM and 28 (56%) of astrocytoma, whereas the remaining patients received the best supportive care (BSC).

Three months after mEHT, tumor response rate was 24% for GBM and 43% for astrocytoma, whereas it was 4% for GBM and 37% for astrocytoma for the BSC group. The median overall survival (OS) was 12 months (range 5-108) for GBM, and 17 months (6-156) for astrocytoma group. We observed 2 long-term survivors in the AST and 1 in the GBM group that were treated with mEHT.

**Conclusions**

mEHT may have promising efficacy for the treatment of relapsed malignant glioma and astrocytoma and can be a useful integrative therapy.

# Modulated electro-hyperthermia effectiveness compared with classic chemotherapy and radiotherapy on a pancreas adenocarcinoma cell line

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## Objectives

Malignant tumors of the pancreas responds poorly to oncotherapy. The most critical factor is the capacity of the tumor cells to develop resistance to the available chemo- or radiotherapies.
Modulated electro-hyperthermia (mEHT) is a non-invasive therapy form using impedance-coupled radiofrequency and generate 42°C heat in malignant tissues.
The aim of our study was to test the efficacy of mEHT on pancreatic adenocarcinoma cells both alone and in combination with radio- or chemotherapy

## Material and method

Panc1 pancreas adenocarcinoma cell line was grown on coverslips. The following groups were made: untreated control (C); mEHT treated for 60 min (mEHT); irradiated with 2 Gy using 137Cs (R), gemcitabine-treated with 10μM/ml (G); irradiated followed by mEHT (mEHT+R) or gemcitabine during mEHT (mEHT+G). Morphological changes, apoptotic ratio, cell stress, DNA double-strand breaks and tumor progenitor cell (CSC) amount was measured.
For quantification the differences flow cytometry and immunocytochemistry were used. The measurements were analyzed digitally and statistically evaluated.

## Results

24 hours post-mEHT treatment significant tumor destruction was observed with nuclear shrinkage, chromatin condensation and apoptotic bodies. The apoptotic ratio was the highest in groups receiving combined treatments. The ALDH1+ tumor progenitor cell number reduced significantly in mEHT, gemcitabine, mEHT+G and mEHT+R treated groups. Furthermore, H2Axγ and cleaved caspase 3 positive nuclei were also increased in the mEHT, G, mEHT+G and mEHT+R treated groups.

**Conclusion**
Our study is based on in vitro experiments, where the molecular changes clearly showed the tumor destruction capacity of mEHT. Cell stress and DNA damage involved the CSCs population. Single mEHT treatment was as effective as gemcitabine treatment. Though irradiation alone had no major effect on Panc1 cells including CSCs, its combination with mEHT resolved the irradiation resistance.

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

# How to set up an individual program of hyperthermia and conventional treatment in heavily pretreated cancer patients

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How to set up an individual program of hyperthermia and conventional treatment in heavily pretreated cancer patients Hyperthermia is not sufficient as sole treatment. Even though there are experimental studies on cancer cells and in animals showing that hyperthermia may kill cancer cells, in patients up to now the results are not satisfactory. But hyperthermia may serve as an important tool to improve the efficacy of conventional treatments like chemotherapy or radiation. This has been shown in numerous studies in particular in advanced, recurrent or metastatic disease. But to achieve good results it is not just enough to perform hyperthermia. A skilful setting of hyperthermia and conventional treatments is crucial.
There are not only different types of hyperthermia (superficial, deep-regional, whole-body hyperthermia), there are also several different drugs of chemotherapy and different techniques of radiation which have to be put together in a correct order to achieve best possible success.
For first or second line treatment there are in general guidelines clearly showing possible success rates of certain treatments whereas in heavily pretreated patients there are no guidelines anymore. So individual treatment concepts have to be set up.
In three exemplary still alive patients (pancreatic cancer with peritoneal carcinosis, recurrent synovial sarcoma and non-small-cell lung cancer) treatment strategies are explained and the outcome discussed.

**Patient 1:**

**Diagnosis:** Pancreatic cancer with peritoneal metastases

**Oncological history:**

| | |
|---|---|
| 11/15 | Advanced cancer of pancreatic tail. Distal pancreatectomy, splenectomy, left colectomy. |
| 01/16 | FOLFIRINOX 12 cycles. |
| 03/17 | Carcinosis of gall bladder. Cholecystectomy. Pembrolizumab for 10 cycles. Progressive peritoneal carcinosis. |
| 10/17 | T-cell immunotherapy, PD. |
| 12/17 | Ileus and jaundice. Parts of small intestine removed. Ileostomy. Bile duct metal stent |

02/18 Subileus, nasogastric tube, parenteral nutrition

**Problem:** The patient was heavily pretreated with chemotherapy (Folfirinox), immuno- therapies and several surgeries He came to us in a terminal situation, was not able to eat anymore and had a nasogastric tube because of continuous vomiting. The tumor marker CA19-9 was >5.000. The patient was extremely weak and in pain. No treatment options anymore. No likelyhood of response to chemotherapy anymore

**Solution:**

03/18 Local and whole body hyperthermia (Oncotherm EHY 2000, lratherm 2000) In combination with Gemcitabine. Parenteral nutrition and complementary treatments.

**Result:** Decrease of tumor markers. Normal food uptake and bowl function, good quality of life again.

10/18 Maintenance therapy with Capecitabine and hyperthermia.

04/19 Cholangitis and stenosis of bile duct stent. Placement of 2 plastic stents into the metal stent. Continuation of Capecitabine and hyperthermia.

06/19 Lasting PR, Ca19-9 at 73,6ng/ml, good quality of life.

**Comment:** Given the situation of this patient in the beginning a survival beyond a few weeks was not likely. Now 1 Y, years after first admission the patient is still alive and in a good condition. Only the combined treatment adding hyperthermia to chemotherapy can explain this outcome. After Gemcitabine alone in his condition such a result never would have been expected.

**Patient 2:**

**Diagnosis:** Synovial sarcoma of left knee

**Oncological history:**

01/16 Lump at left knee, at biopsy synovial sarcoma

03/16 Resection, stage pT2RO

04/16 Radiation of the distal right femur

12/16 Local recurrence above the field of radiation

01/17 Resection of recurrence, Radiatio and brachytherapy

06/17 Grossly swollen left leg, thrombosis of the vena femoralis caused by large tumor metastases in the left groin.

08/17 Chemo-immunotherapy with Doxorobicin and Olaratumab, PD
10/17 Carboplatin and Gemcitabine, PD
12/17 Pazopanib, PD
02/18 One cycle of Ifosfamide high dose, not tolerated (encepalopathy).

**Problem:** Progression of the disease resulting in a tumor of more than 11 em diameter in the left groin reaching into the pelvis, compressing bladder and ureter and growing around the blood vessels and nerves of the left leg. 3 more large masses along and around the arteria femoralis down the left thigh, the lowest mass a few centimeters above the inner left knee. Metastatic sarcoma of the left knee spreading into the lymphatic tissues along the left thigh up to the pelvis. Progression after 3 lines of chemotherapy and immuno-therapy. The last chemotherapy with Ifosfamid in high dose he almost had not survived. No other treatment options now as left hemipelvectomy and amputation of the left leg.

**Solution:** Continuation of Ifosfamide but in lower doses combined with local hyperthermia (Oncotherm EHY 2000) to the metastatic sites at pelvis and left thigh.

**Result:** Very good partial remission. The patient was free of pain, could walk again without crutches, the swelling of the leg had come down.

**Comment:** Because of the good response amputation was not necessary anymore. This result can only be explained by the additional treatment with hyperthermia. The plan was now to perform limb saving surgery, but the patient was reluctant because he was afraid of the risk of nerve damage. Hyperthermia was continued as sole maintenance treatment but did not control the disease. But the lesions were now in a dimension which allowed proton radiation therapy which was performed in January 2019. After this again a very good and lasting remission. Now 1 %years after starting hyperthermia the patient is still in remission without new activity of the disease, he is walking on both legs, exercising regularly and has a good quality of life.

**Patient 3:**

**Diagnosis:** NSCL (adenocarcinoma) with metastases to the brain (EGFR pas.)

**Oncological history:**

| | |
|---|---|
| 01/11 | Adenocarcinoma of the left lung with brain metastases (T3, M1), surgery of the brain metastases, chemotherapy with Carboplatin and Vinorelbine, radiation of the lung tumour and the brain. |
| 07/11 | Progression of the brain metastases, treatment with Gammaknife. |
| 10/11 | Progression in the lung, Pemetrexed |
| 02/12 | Progression in the brain and the lung, treatment with Gammaknife for the brain. Treatment with Tarceva for the lungs, progressive disease. |

**Problem:** Progressive disease after multiple chemotherapies and targeted therapy. He suffered from caugh and chest pain. No treatment options anymore, the tumor was considered as resistant to further chemotherapy.

**Solution:** Whole body and local hyperthermia in combination with Taxotere in moderate doses.

**Result:** Partial remission of the pulmonary disease, no new activity in the brain

| | |
|---|---|
| 03/15 | Stereotactic radiation of the remaining lung tumor |
| Since 10/15 | normalization of tumor markers, no evidence of active disease. |

**Comment:** In this patient the likelyhood of response to further chemotherapy was very little and if at all only for a short time. Hyperthermia in this case very likely helped to overcome resistancies and enabled long term survival. The patient has now been free of disease for more than 4 years (since March 2015), he is in a good quality of life. He comes every 6 months for check up.

**Conclusion:** Even in heavily pretreated patients there is a chance to achieve a good and long lasting treatment success. Hyperthermia in these cases seems to be the crucial tool. The setting in each situation has to be a specific combination with adapted programs of conventional treatments like chemotherapy and radiation.

# Survival time in cancer patients getting in addition to conventional treatments hyperthermia and complementary treatments in comparison to published data of similar patients. Retrospective study over a period of 12 years. Project of a doctorate thesis

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**Introduction**
Up to now approval of hyperthermia treatment to any kind of cancer depends on studies examining specific chemotherapy or radiation with or without hyperthermia. But if the guidelines change hyperthermia has to be examined again in new randomized studies.

But is this really necessary? Hyperthermia already has shown to improve the efficacy of chemotherapy and radiation in multiple randomized studies. So why not just compare survival times of patients getting hyperthermia plus chemotherapy with patients getting chemotherapy alone?

**Methods**
In published "control" groups patients got chemotherapy according to guidelines. In the hyperthermia group patients got the chemotherapy substances in combination with hyperthermia (often even in lower doses as hyperthermia improves the efficacy of chemotherapy). The endpoint survival time was chosen as this is the most important endpoint.

**Discussion**
The results will be interesting: If survival times are shorter hyperthermia in the future should not be any more integrated in treatment protocols outside of studies as specific subgroups have to be found in which hyperthermia may work.
If the survival rates are the same patients should be treated with hyperthermia plus chemotherapy if chemotherapy doses in certain groups were less compared to guidelines doses. These patients would have the advantage of less toxic treatments.
If the survival times in the hyperthermia groups are longer the question will be raised why in these groups of patients hyperthermia is not used as standard treatment.
Preliminary results show already now prolonged survival for patients with pancreatic cancer, the results of other groups are still collected (breast, colon, lung cancer)

# Reduction of magnetic fluid hyperthermia side effects in phantom models and ex vivo tissues using intermittent alternating magnetic field

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## Introduction

Magnetic hyperthermia is a promising type of cancer treatment, where magnetic nanoparticles (MNPs) are exposed to Alternating Magnetic Fields (AMF), resulting in the heating and eventual apoptosis of cancerous cells. However, one of the restrictions in the use of hyperthermia is the appearance of eddy currents on healthy human tissues, causing adverse side effects in patients, like heating and peripheral nerve stimulation.

## Objectives

The purpose of this work is to minimize the heating rate of healthy tissues while maintaining satisfactory heat release from MNPs at the tumor, using intermittently instead of continuously applied AMF with multiple on-off cycles [1,2]. The reduction of heating due to the induced eddy currents was examined in phantom models composed of agarose, resembling healthy tissues, while the heating caused by magnetic losses was examined on phantoms combined with MNPs, resembling the tumor.

## Material/Methods

MNPs of 9nm in diameter were prepared by aqueous coprecipitation of ferric and ferrous salts at alkaline conditions at 70°C. The MNPs were injected into hot agarose gel with NaCl (1:1) at 84°C (phantom) mimicking human tissue. Then they were exposed to hyperthermia treatment with and without MNPs. For the *ex vivo* experiments performed at optimized experimental conditions (field amplitude 45 mT, f = 375 kHz), minced beef with and without MNPs (8 mg/ml) was also treated.

## Results

Temperature increase was reduced in the reference phantom from $\Delta T = 9.1$ for the conventional continuously applied AMF to 2.9°C for the intermittently applied AMF. In the case of agarose with MNPs, $\Delta T$ increase was reduced from 17.0 to 7.2°C for the continuously and the intermittently applied AMF, respectively. Such a drop in the temperature increase inside the tumor area is acceptable, as it is still within the clinical hyperthermia

window ($\Delta T$ = 4-8°C, i.e., from 37 to 41-45°C) while the drop of $\Delta T$ in the healthy tissues would likely reduce the adverse side effects caused by eddy currents. Pulse mode hyperthermia was applied in *ex-vivo* experiments (with and without MNPs). The increase in temperature in the reference tissue sample was reduced from $\Delta T$ = 12.5 to 3.0°C, for the continuously and the intermittently applied AMF, respectively. For the tissue sample with MNPs, the increase in temperature was reduced from $\Delta T$ = 15.6 to 5.1°C accordingly; this $\Delta T$ still resides within the hyperthermia window and is adequate to cause apoptosis of cancerous cells. Computational models were developed to study the experimental procedure, in the form of an algorithm that predicts the increase in temperature caused by the application of an intermittently applied AMF. The computationally predicted results are in good agreement with the experimental results.

**Conclusion**

The use of multiple pulse mode hyperthermia has a direct impact on heating reduction by minimizing the duration of eddy currents flow, while a high enough temperature increase due to MNPs is maintained, to secure effective treatment. These results are encouraging for the prospect of effectively applying magnetic hyperthermia in cancer treatment and protecting the patient from adverse side effects.

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# Effects of modulated electro-hyperthermia on peripheral white blood cell counts -- a pilot study

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## Background

Modulated electro-hyperthermia (mEHT) is considered also as an immunomodulant, which is based on growing body of evidence in preclinical and clinical models and strengthened by valid observation of abscopal effect. We are performing a study treating patients with advanced stage and inoperable tumors of the pancreato-hepatobiliary system: every 3 months radiologic imaging, quality of life and peripheral white blood cell analysis is investigated.

## Patients and methods

In 7 pancreatic carcinoma patients undergoing mEHT treatment we have performed regular blood draws and investigated the number of peripheral white blood cells with a Beckman-Coulter CytoFLEX flow cytometer. The investigated markers were: CD3, CD4, CD8, CD19, CD56 besides morphology. B-lymphocytes were CD19+, T-lymphocytes were CD3+, and subpopulations were identified as CD4+ or CD8+. Natural Killer (NK) cells were CD3-/CD56+, while NKT cells were CD3+CD56+.

## Results

In 3 months, leukocyte ratio on average increased from 85,8% (absolute count: 76674) 95,3% (68622). Monocytes went from 8,3% (6381) to 10.2% (7368). Lymphocyte ratios were stable: 25,9% (19912) to 30,7% (18844). Of lymphocytes, number of B-cells decreased from 8,7% (1755) to 6,6% (1248). Of lymphocytes, T cells increased from 76% (15133) to 78,6% (14906). Of T cells, CD4+ cells were stable 73,4% (11151) vs. 71,9% (10791), while CD8+ cells increased from 18,4% (2955) to 21,1% (3161). Of lymphocytes, NK cells went from 10,7% (2148) to 9,19% (1624). Of lymphocytes, NKT cells' number slightly increased from 12,3% (2458) to 13,3% (2778).

## Discussion

In a period of 3 months, those patients who managed to attend the mEHT treatment series, white blood cell counts stay at least stable if not increase. Here we observed that leukocytes increase in numbers, so are monocytes and T cells, while B cells decrease. CD8+ cells increase in comparison to CD4+ cells. Similarly, NKT cells display an increasing tendency as compared to NK cells.

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# Potential application of neoadjuvant chemotherapy plus modulated electro-hyperthermia (mEHT, trade name: Oncothermia) among patients with advanced cancer: Retrospective clinical analysis of single hospital experiences

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## Introduction

Despite aggressive local therapy, patients with locally advanced cancer are at significant risk for local recurrences and systemic metastases. The risk of local recurrence after operation is largely dependent on clinical stage. The predominant cause of metastatic recurrence is occult micro metastases. More effective treatment methods are therefore needed for local and systemic controls. For these purposes, hyperthermia is limitedly applied to locally advanced sarcoma or high risk peritoneal carcinomatosis patients with perioperative chemotherapy. But because of some side effects and low patient compliance neoadjuvant chemotherapy with classic hyperthermia has limitations. In preclinical and clinical data modulated electro-hyperthermia (mEHT) not only suppress local tumour growth but also demonstrate immunologic effects at distant sites with negligible side effects. For this reason, there is interest in combining locoregional mEHT and systemic chemotherapy before definitive surgical treatment.

## Objectives

The primary objective is whether the neoadjuvant chemotherapy plus mEHT in patients with various locally advanced cancer is feasible. The secondary objective is evaluation of safety and side effects of this treatment.

## Material/Methods

This is a single hospital, observational and retrospective clinical study. We reviewed the medical records of all patients who underwent mEHT at Oasis Cancer Hyperthermia Research Center between January 2017 and July 2019. The feasibility of patients treated with neoadjuvant chemotherapy plus mEHT as well as safety and side effects were investigated. The chemotherapy regimens differed from cancer types and the university hospitals they treated.

## Results

Data from 203 eligible patients were collected. The number of patients by cancer types were 101 breast, 26 stomach, 13 thyroid, 12 colon, 10 rectum, 9 lung, 8 ovary, 6 liver, 5 cervix, 5 sarcoma, 5 pancreas and 3 oesophageal cancer patients respectively. Among them 21 patients showed receiving

neoadjuvant chemotherapy with mEHT treatment. The majority of these patients had stage III or IV disease at diagnosis. The number of patients by cancer types were 11 breast, 4 rectum, 3 stomach, 2 ovary and 1 colon cancer patients. No patients showed progressive disease during this treatment and all of them could done operation. Two breast cancer patients showed complete response. The side effects were tolerable and compatible with the type of chemotherapy regimen they received. No additional side effects related to the treatment of mEHT was noted.

**Conclusion**

There is no clinical trial whether neoadjuvant mEHT with chemotherapy treatment of localized advanced cancer feasible. Our retrospective analysis demonstrates that this treatment method can be given safely before operation to patients with locally advanced cancers. Although patient numbers were small all 21 patients could receive operation without disease progression. We believe that this neoadjuvant hyperthermic chemotherapy can be offered to patients with locally advanced cancers. Further studies are needed to evaluate the patient survival.

# Differential tumor damage by modulated electro-hyperthermia (mEHT)

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## Introduction

Modulated electro-hyperthermia (mEHT) controlled at ~42°C can directly induce programmed tumor cells death and may contribute to a secondary immune mediated cancer death (ICD). However, the same treatment protocol may provoke differential death pathways and different extents of tumor damage, depending on the inherent genetic and epigenetic make up of the treated tumors. In this presentation we are going to overview briefly the major effects of mEHT revealed in our studies using *in vitro* and *in vivo* models of colorectal (CRC) and pancreas adenocarcinoma, and melanoma.

## Materials, Methods & Results

As a common feature, either a single or repeated shot of mEHT can provoke significant heat and cell stress signalled by early upregulation of heat shock proteins (hsp70 in particular), and other chaperone proteins i.e. calreticulin. H2Ax overexpression and phosphorylation (H2Axγ) indicating DNA double-strand breaks are also general signs after treatment. These are followed by tumor destruction of different ranges, dominantly through activation of programmed cell death pathways. In TP53 wild-type tumors upregulation, nuclear translocation and occasionally stabilization by acetylation of p53 protein can activate caspase dependent apoptosis, usually through both the extrinsic (casp8+) and the intrinsic (cytochrome C+) pathways leading to the phosphorylation/activation of caspase-3 protein that can induce endonucleases to fragment DNA. Usually, p53 related overexpression of the cyclin dependent kinase inhibitor $p21^{waf1}$ can also be detected in parallel, which may mediate tumor senescence. In TP53 mutant CRC, mEHT elicits caspase independent, apoptosis inducing factor (AIF)-associated cell death, while in melanoma, growth inhibition is manifested mainly through $p21^{waf1}$ activity, and less intense apoptosis.
Elevated damage (DAMP) signalling shown by the translocation and release of hsp70, calreticulin and HMGB1 (and ATP) is observed in all mEHT treated tumor types. This may potentiate tumor immunogenicity leading to the accumulation and activation of cytotoxic T-cell (CTL), antigen presenting dendritic cells (APC), natural killer cells (NK) and macrophages

(M). However, in the mEHT treated melanoma, reduced MHC-I and melan A levels might explain why the number of CTLs is moderately reduced, the amount of NK cells remains unchanged and only macrophages gather at increased amount in the tumor. The resulting lack of secondary immune mediated tumor cell death (ICD) can also be the reason for the moderate apoptosis in melanoma compared to those seen in our other mEHT treated models. **Figure 1.** summarizes the potential primary and secondary tumor damaging effect of mEHT.
Inhibition of tumor progentior cell fractions seen in colony forming assays and through reduced ALDH1+ cell fractions can also be observed after mEHT treatment both in colorectal and pancreas cancers. Furthermore, mEHT treatment in combinations shows additive tumor inhibition when used with doxorubicin in CRC, and with gentamycin in pancreas cancer, besides resolving radioresistance of Panc1 pancreas adenocarcinoma.

**Conclusions**
Predictive markers of mEHT (and hyperthermia in general) are still needed. These could be the epi-/genetic predispositions particularly related to elements involved in stress response, apoptosis, immune escape and oncogenic pathways. In mEHT, additional predictors such as the oncometabolit and metabolic enzyme levels linked to glycolysis and electric permittivity in the tumors may also be relevant.

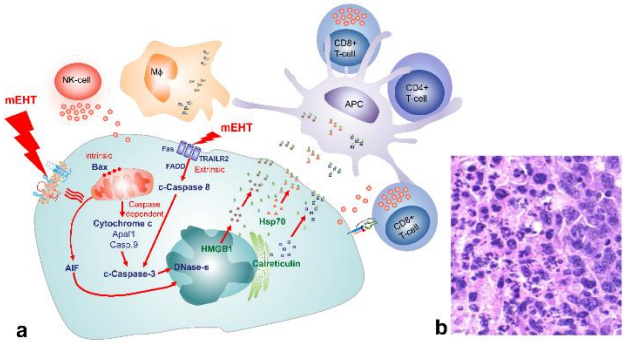


**Figure 1.** Modulated electro-hyperthermia (mEHT) induced primary effect involves heat and cell stress which activate apoptotic pathways, while the secondary immune mediated cell death (ICD) may be related to the upregulation and release of DAMP signalling molecules which support the uptake, processing and presentation of tumor antigens to activate immune cells (a). Treatment induced massive apoptosis indicated by apoptotic bodies in a colorectal cancer allograft (b).

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# Numerical simulation and evaluation of magnetic particle hyperthermia system and conditions

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## Introduction

Magnetic particle hyperthermia (MPH) is a novel, minimally invasive, therapeutic modality, used as a cancer treatment, that employs a magnetic fluid (also termed ferrofluid) as the heating source. A magnetic fluid is a stable colloidal suspension of magnetic nanoparticles (MNPs) that can be injected directly into the tumor or delivered to the tumor via passive or active targeting upon intravenous administration. Once accumulated to the tumor area, MNPs are exposed to an external alternating magnetic field (AMF) that causes reversal of their magnetic moments, activating mechanisms of energy deposition in the form of heat [1].
Objectives The main objective of the present work is the development and evaluation of numerical models for the description of the phenomena that take place in a MPH in vitro system. In particular, we aim at the estimation of the spatial distribution of the magnetic field and the spatiotemporal temperature distribution by taking into account all the appropriate field and heat transfer boundary conditions.

## Material/Methods

In order to simulate the physical phenomena, two numerical models were developed in COMSOL Multiphysics. In the first model the "Azimuthal Induction Currents" interface provided in "AC/DC" Module, was used in order to obtain the magnetic field distribution corresponding to a 2-turn circular and 8-turn squared coil geometries, while in the second model the transient analysis of the "General Heat Transfer" interface provided in "Heat Transfer" Module was employed to calculate the MNPs volumetric power dissipation (by importing Rosensweig's model [2]) and obtain the time-dependent heating curves. The ferrofluid concentration used was 4 mg/ml for an aqueous solution of 10 nm magnetite MNPs, dispersed in 1 ml of water, while the AMF amplitude and frequency were 30 mT and 765 kHz, respectively, for the 2-turn coil, and 60 mT and 365 kHz, respectively, for the 8-turn coil.

## Results

The solution of the electromagnetic problem provides the magnetic field distribution for the experimentally applied current amplitude and frequency. The role of coils geometry is also presented since COMSOL takes into account the coil geometrical characteristics, ignored in the analytical

expressions. Moreover, the solution of the Heat Transfer problem gives the spatial distribution of temperature in the various subdomains of the MPH system like the ferrofluid, the vial, the coil and the surrounding air while the time-dependent heating curves are obtained after 30 minutes of treatment and are compared to the corresponding experimental ones observed under the same conditions. The spatiotemporal distribution of the MNPs volumetric power dissipation is also estimated for the non-adiabatic conditions, studied in the present work, validating Rosensweig's model [2].

**Conclusion**

Proper use of simulations can lead to better understanding of complex physical processes, further progress in the development of novel MPH equipment designs, replacement of invasive temperature measurements and establishment of updated hyperthermia treatment protocols. In silico testing and evaluation of material properties and innovative methods can substantially accelerate their approval for clinical use and result in better treatment quality.

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# Malignant retroperitoneal HISTIOSARCOMA and ONCOTHERMIA

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## Introduction

Histiosarcoma or undifferentiated pleomorphic sarcoma belongs to mesenchymal malignancies. It is often found in the extremities, but a form, which presents intense inflammatory components, frequently occurs in retroperitoneal "space". Clinically, retroperitoneal sarcoma variety presents with general symptoms (fever, malaise, weight loss), whereby the mass enclosed in this confined area, already of large size, and displacemes abdominal organs. Sometimes it can coexist with lymphoma, multiple myeloma or malignant histiocytosis. Histologically the retroperitoneal tumors are diverse, with , necrosis and calcification, often infiltrating the abdominal muscle wall, but not the renal and central vasculature. Therapeutic surgery, can be applied to smaller retroperitoneal Histiosarcomas, but the larger ones are only treatable with debulking surgical techniques. The chemo- and radiotherapy, which are suitable for peripheral sarcomas generally not applicable to intra- and retroperitoneal because the toxicity is too great and these modalities are not enough to deal with such bulky disease. The prognosis is generally the worst.

## Purpose

Undifferentiated retroperitoneal sarcoma in a patient 62 years from 11/05/2013 to was immediately operated with debulking surgery and chemotherapy in our neighboring country.). After about 11 months, during which the patient was with a low Performance Status and treated at home for symptomatic relief. Upon restaging with CT (10/02/14), recurrence of disease was established. Initial dimensions (diameter ~ 103 mm) .
We report of our experience after multidimensional and targeted treatment approach to controll pain. Metastases, sensory and neuropsychological disturbances.Prevention of worsening, by application of Oncothermia and the prospect of conversion of fatal desease to chronic, with better Quality of Life.

**Material and Method**

Between October 2014 and November 2015 the patient presented to our center for one hour local Oncothermia application, twice a week, with complementary High Dose vitamin C intravenously(22.5)g to a, and selenium. He also received ozone therapy IV ( auto-transfusion) twice weeklywith 35μg/ml concentration, and 40μg/ml hyperbaric infusion, with total volume 60mlX8. We also proceeded to tissue Alkalynization with Bicarbonate IV.

***Restaging***

CT-scan (2/10/2014):

Recurrence of disease, the initial dimensions (diameter ~ 103 mm).

***Principal symptom:*** Fever, malaise, weight loss, depression

***Treatment of choice:*** Completely targeted therapeutic strategy based on culturing of circulating tumor cells and the sensitivity test to chemotherapeutics and Biologicals *(RGCC Onconomics plus test)*. SC Immunostimulation with HelixorP(Viscum Alba) whose administration began because the patient refused chemotherapy . The patient underwent local Oncothermia (a one-hour session twice a week to prevent thermoresistance).It was the classic 12 sessions of local Oncothermia. Implemented a vertical abdominal field concurrent to the SC application of Viscum Alba locally. We coadministered to the patient injections of IV vit.C (22,5 gr) since he refused targeted chemotherapy ,and selenium. Along with ozone therapy (IV auto-transfusion) twice weekly.

**Results**

The patient experienced a reduction in the and size of the primary site and the numerous metastases by ~ 14 mm but mainly by tumor necrosis especially in its center, remission of fever, feeling of malaise and mood and generally spectacular improvement of mobility and neuropsychological status, returning gradually to the daily tasks.The patient was happy about the result and decided to continued Oncothermia once a week by choice, despite our recommendations that should continue the same treatment that demonstrably improved his status.

**Conclusion**

The application of palliative Oncothermia,to the patient was a safe therapeutic approach, which the secured with minimal side effects, the ability of a better quality of life. The concurrent application of Oncothermia, co-administration of HelixorP, Vitamin C and selenium , and IV ozone transfusion, improved his psychology and general Quality of Life. It seems that Oncothermia can potentiate not only Chemotherapy and Radiation therapy, but also Biological therapies. Another interesting finding is the duration of stable disease with improved QOL. Is it possible that

Oncothermia creates an equilibrium between Organism and Tumor, creating a symbiotic complex?

# Oncothermia for lung cancer with brain metastases and extended hypermetabolic lymphadenopathy (PET CT)

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**Introduction**
Pneumonectomy is a heavy operation.It is performed in centralized or extensive disease It is peformed with extensive lymphnode dissection. Prerequisite: Good breathing study of the patient preoperatively to assess the quality of life with one lung. It demands highly specialized treatment. The patient presented for treatment in 2017, 4 years after pneumonectomy already with Left mediastinal displacement, brain metastases and poor psychological state.

**Purpose**
Our Experience at Oncothermia center, treating lung and brain metastases, and methodology in treating the pain and dyspnea,as well as the psychological state, to achieve sustained relief and quality of life.
Proposal for establishment of Oncothermia as palliative treatment in such severe cases.

**Material and Method**
AdenoCarcinoma of the lung in woman 48 years old. Left pneumonectomy lung since 2013 metastases on right lung and mild emphysematous lesions in the right lung, multiple metastases in the brain, incipient radiation-induced leukoencephalopathy and extensive lymphadenopathy, hypermetabolic (PET CT) from 2016, having undergone chemotherapy and radiation therapy previously.
Between 10/07/2017 to 05/09/2018, the patient presented to our center for local Oncothermia: two fields a lung and brain for 90' and 60' respectively.

**PET / CT (29/4/2013):**
1. Positive solitary lesion in the field of previous pneumonectomy
2. Extensive hypermetabolic lymphadenopathy throughout the body

**BIOPSY (06.05.2013):**
'Primary invasive adenocarcinoma good-moderate differentiation lung TNM stage Pt1AN0 »
**BIOPSY (05.15.2017):**
"Stereotactic biopsy Brain lesion: Finds compatible with metastasis with Lung Ca as in her lung adenocarcinoma history"
**Lung CT (05/15/2017):**
"Small 4mm nodule in RLL

**Treatment of choice**
From 07.10.2017 the patient was treated with Local Oncothermia , two fields a pulmonary (covering both lungs) and a brain field , for 90' and 60' respectively, twice a week to prevent the thermoresistance. 12 sessions of local Oncothermia were Performed with Large Module for affected areas in the Thorax and Medium Module for the brain. The patient received parallel to Oncothermia IV infusions of Ozonated blood (autotransfusion), 8.4% Bicarbonate for tissue Alkalynization, and High dose Vitamin C (22.5gr).

**Results**
**CT (17/8/2017)** "We have at our disposal the prior CT 5/15/2017 and PET / CT 25-5-2017 benchmarking the findings"
**Brain:** "A clear improvement of the radiological image of the brain in terms of size and extent of perifocal edema of the metastatic sites"
**Chest:** "In the rear portion RUL we recognize fibrotic lesions and area like blurred glass max IU = 2,1 cm without clear imaging of any solid lesion, a finding suggesting improved radiological image of the right lung.No evidence of other invasive or focal lesion in the right lung parenchyma outside known emphysema.
**CT (14/12/2017)**
**Brain:**"Further improvement of the radiological image of the brain: Reduction dmax of larger lesion left temporal lobe from 6,3 mm to 5,5 mm, and the only lesion that has radiopaque uptake.the rest of the lesions have no uptake and there is considerably reduced edema. "
**Chest:** "In the rear portion of the RUL lesion (tumor right lung) rechecked without appreciable change. The fibrotic lesions and known area "blurred glass" dmax = 2,1 cm without clear imaging of any other lesions.

**Conclusion**
The focus on Palliative treatment with Oncothermia in conjunction with Integrative therapeutic strategy, targeting the cancer and its microenvironment ,definitely improves the quality of life ( Self-assessment of symptoms and functionality based (QLQ-C30 VER 1.0):
Wellness: 5 vs 3

Quality of life: 5 vs 3) and seems to have an objective response in known lesions, while suppressing disease progression.

# Palliative Oncothermia in patient with metastatic breast cancer and significant comorbidities. our experience in Thessaloniki Oncothermia center

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**Introduction**
A significant number of patients with breast cancer relapse despite initial therapy.10% of patients initially appear with Metastatic disease. Verified median survival in the case of localization in the CNS is lower than 6months.Only 20% of women with metastatic cancer survive more than five years, while in general the median survival is 2-3 years. The goal of treatment is to improve the quality of life and its prolongation. Chemotherapeutic and monoclonal antibodies are considered until now a one-way street.

**Purpose**
We relay our experience, regarding application of Oncothermia for improving quality of life in this patient 84 years old, with discontinued hormone therapy for breast Ca, multiple metastases in lungs, bones for three years.
Comorbidities: heart disease, insulin dependent diabetes mellitus and Hysteria and Depression (under treatment).
The role of Oncothermia in controlling generalized metastases, pain and psychological Disturbances.

**Material and Method**
Between 10/05/2019 to 06/18/2019, the patient presented to our Center for palliative Oncothermia under the optimum use of supportive care possible for treatment of metastatic breast Ca disease after suspended hormonotherapy.

**Immunohistochemical Status:**
ER (+) 80%
PR (-)
c-erb-B2: negative
Ki 67 (+) 20%

Bone-scan (3/5/2019):
Scattered foci of increased radiopharmaceutical concentration uptake in most of the skeleton.
**CT (24-4-2019)**
Thoracic: Numerous lesions in the pulmonary parenchyma bilaterally. All lesions exhibit somewhat increased dimensions compared to the previous examination.
**CT (24-7-2019)**
Thoracic: Multiple secondary sites in the pulmonary parenchyma bilaterally controlled and stable, unchanged in number, and for most of them, a small reduction in their dimensions. Indicatively, the lesion localized in the left lower lobe having a maximum diameter 37mm as compared to 45mm in previous examination. Another lesion at right pulmonary base i has a maximum diameter of 25 mm vs 29mm in previous CT.,and another on the top portion of the right lower lobe has a diameter of 17mm vs. 20 mm in the previous examination.

**Principal symptoms:** Breathing difficulties, insulin dependent diabetes and Cardiopathy, Depression and generally a very low performance status.

**Treatment of choice:** 12 local Oncothermia sessions for lungs and 12 abdominal field due to metastasis in the adrenal glands. The patient additionally received IV infusions of Vitamin C (22,5 gr) autotransfusion of Ozonated blood and IV Blood Alkalynization with 8.4% Bicarbonate.

**Results**
Artial remission, with considerable improvement in her dyspnea.Her pain improved considerably, and her energy levels as well. She declares herself to be happy,and has returned to daily her daily habits and continues today with new series of Oncothermia sessions.
**Self-assessment of quality of life and symptom functionality based (QLQ-C30 VER 3.0):**
Physical well-being: 6
Quality of life: 5

**Conclusion**
The application of palliative Oncothermia in the patient by co-administration of vitamin C and IV bicarbonate, in conjunction with autotransfusion of Ozonated blood was a safe therapeutic approach, which the secured possibility of a better quality of life with negligible side effects.

# Examination of the optimum anticancer agent with a thermal effect for non-small cell lung cancer

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## Introduction

It is often difficult to control pleural dissemination or pleural effusion due to pleuritis carcinomatosa during the course of treatment of advanced non-small cell lung cancer (NSCLC). For these patients in our institution, we have performed intrapleural hyperthermic perfusion with chemotherapy (IPHC) for malignant pleural effusion and pleural dissemination of non-small cell lung cancer. At present, CDDP is used as an anticancer agent that has a thermal sensitization effect. Therefore, we examined whether there is any anticancer drug that can be used to have a thermal effect other than CDDP in non-small cell lung cancer.

## Objectives

We designed a thermal warming experiment to search for effective drugs other drugs than cisplatin (CDDP) that can be usually used for this therapy using the anticancer drug sensitivity test (HDRA method). The aim was to find an effective drug (7agents) with thermal sensitization rather than CDDP.

## Material/Methods

The specimens were obtained the tissues resected non-small cell lung cancer in the operation. As a subject, a surgical excision sample of a non-small cell lung cancer curatively resected case having a tumor diameter of 2 cm or more was used. The growth inhibition rate was compared between the anticancer agent group of the normal culture group of 37 degrees C (control) and 1-hour thermal stimulation (41 degrees C or 43 degrees C) after the anticancer agent (7 agents) additional group. We compared by the ratio of the number of cases in which the inhibition rate was clearly increased by 10%.

## Results

At 41 degrees C, thermal effects were more pronounced in CBDCA, Docetaxel, and Gemcitabine than in CDDP, and at 43 degrees C, thermal effects were more pronounced in CBDCA, Gemcitabine, and Vinorelbine than CDDP (table 1).

**Conclusion**

A HDRA method using an exposure temperature of 41 or 43degrees C can be used to predict the anti-tumor effect of thermo-chemotherapy for NSCLC. We will continue experimenting with multiple drugs and plan to consider more effective drug combinations for IPHC.

| drugs | 41℃ 60mins | | | 43℃ 60mins | | |
|---|---|---|---|---|---|---|
| | Cases Number (A) | Inhibition rate 10%UP Number (B) | (B)/(A) x 100 | Cases (A) | Inhibition rate 10%UP (B) | (B)/(A) x 100 |
| CBDCA | 19 | 7 | 37 | 47 | 18 | 38 |
| CDDP | 20 | 3 | 15 | 41 | 10 | 24 |
| Docetaxel | 16 | 6 | 38 | 44 | 10 | 23 |
| Paclitaxel | 16 | 3 | 19 | 39 | 6 | 15 |
| 5-FU | 18 | 5 | 28 | 42 | 9 | 21 |
| Gemcitabine | 14 | 5 | 36 | 22 | 10 | 45 |
| Vinorelbine | 9 | 1 | 11 | 11 | 6 | 55 |

# Final Results on Local Control in Cervical Cancer Patients treated with Chemoradiotherapy with/without Modulated Electro-Hyperthermia as *Published in PLoS ONE (2019)*

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## Introduction

A Phase III randomised controlled trial has been conducted in South Africa, investigating the effect of the addition of modulated electro-hyperthermia (mEHT) to chemoradiotherapy (CRT) protocols for the treatment of locally advanced cervical cancer (LACC). The final results on local disease control (LDC) at six months post-treatment have been published and are reported on in this presentation as well as preliminary three year survival rates.

## Methods

Participant recruitment began in January 2014 and closed in November 2017. The final participant was treated in January 2018 and collection of LDC data was completed in August 2018. Inclusion criteria: FIGO stage IIb to IIIb (bilateral hydronephrosis excluded) cervical cancer staged clinically by physical examination, abdomino-pelvic ultrasound, and chest radiography; creatinine clearance >60ml/min; eligible for CRT with radical intent; HIV positive participants were included provided the CD4 count was >200cells/mL or they had been on antiretroviral therapy for >6 months. Randomisation (using REDCap online randomisation tool) accounted for Age and Stage of disease. All participants were planned for 50Gy external beam radiation to the pelvis, three fractions of 8Gy Brachytherapy, and two doses of cisplatin (80mg/mm2) three weeks apart. Participants in the mEHT Group were prescribed two mEHT treatments/week (55 minutes at 42.5°C; max power output of 130W). Local disease control was considered a failure if there was any disease confirmed in the pelvic field on PET/CT, CT, examination, cytology, or fine need aspiration of palpable lymph nodes.

## Results

Two hundred and two participants were available for analysis at six months post-treatment (mEHT: n=101; Control: n=101). LDC (censored for survival) was significantly higher in the mEHT Group (n=40⌈45.5%⌉) than the Control Group (n=20⌈24.1%⌉); (p=0.003). Local disease-free survival at six months post treatment was significantly better in the mEHT Group (n=39⌈38.6%⌉), than in the Control Group (n=20⌈19.8%⌉); (p=0.003) (Minnaar et al, 2019). In the participants who have reached three years post-treatment (mEHT: n=31; Control: n=46), three-year disease-free survival is

significantly higher in the mEHT group: 18[58%] versus 16[35%], (HR: 1.97; p=0.042).

**Conclusions**
mEHT has demonstrated efficacy as a radiosensitiser when added to CRT protocols for the management of high risk LACC patients and the addition of mEHT is associated with improved local control at six months. Early results indicate the benefits extend to three years post treatment with an improvement in three-year disease-free survival.

Minnaar CA, Kotzen JA, Ayeni OA, Naidoo T, Tunmer M, Sharma V, et al. (2019) The effect of modulated electro-hyperthermia on local disease control in HIV-positive and -negative cervical cancer women in South Africa: Early results from a phase III randomised controlled trial. PLoS ONE 14(6): e0217894. https://doi.org/10.1371/journal.pone.0217894

# Hyperthermia for the management of cervical cancer: a review of techniques, protocols and outcomes

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## Introduction

There are a variety of hyperthermia (HT) techniques available on the current market. Various techniques with various protocols have been investigated for the management of cervical cancer. In this report we review the trials published on hyperthermia for cervical cancer and we report on outcomes, protocols, and techniques used to treat cervical cancer. Recommendations for protocols based on patient samples, techniques and results are formulated.

## Methods

Trials were grouped according to treatment regimens investigated: HT + radiotherapy (RT)(n=7); HT + chemoradiotherapy (CRT)(n=4); and HT + chemotherapy (ChT)(n=4). The HT protocols, techniques, patient sample, and outcomes were tabulated.

## Results

Two heating techniques are used: Capacitive coupling heating using either 8MHz radio-frequency (RF) at (800-1500W) (n=3), 13.56MHz RF amplitude modulated (mEHT, Maximum 150W) (n=1), or 27MHz (n=3); And Inductive heating using either annular phased array heating (n=5), 4-waveguide applicator system (n=2), or a coaxial TEM applicator (n=1). Differences in protocols, technical specifications, and administration exist between various techniques. Inductive heating requires shielding and requires patients to be sedated.

One trial using each technique have demonstrated a local control benefit when added to RT: Capacitive heating: 80% versus 50% (p=0.048)[1], inductive heating: 83% versus 57% in the control arm (p=0.003)[2]; and survival benefit: Inductive heating: 51% versus 27% (p=0.015) [2], however two studies on capacitive heating showed an improvement in tumour control, but the sample was too small to show significance[3,4] and one study showed no difference between groups.[5] One study on interstitial hyperthermia showed no improvement when added to RT.[6] Triple therapy has only shown a significant local control and survival benefit when mEHT is used with CRT twice per week[7], with no difference seen in HT applied weekly with inductive or capacitive heating.[8,9] Inductive and mEHT have shown benefit in recurrent or residual disease combined with ChT.[10,11]

## Conclusion

The heating technique used is an important factor in the prediction of outcomes. HT is an effective radiosensitiser for cervical cancer patients who cannot receive chemotherapy, regardless of technique. When applied twice a week to CRT protocols, mEHT improves local disease response and may improve three-year disease-free survival. Both mEHT and inductive heating improve local control in patients with recurrent / residual disease in a previously irradiated region where treatment options are limited.

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# Effectiveness of hyperthermia in clinical stage IV pancreatic cancer

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## Introduction

Although recent progress of chemotherapy for the pancreatic cancer patients provide improvement of the patients' prognosis, the advanced pancreatic cancer in clinical stage IV with local recurrence, distant metastasis or peritoneal dissemination are still quite difficult to increase the survival rate. Hyperthermia is expected as an effective treatment for such patients in combination with chemotherapy. During 3 years and 5 months since 2016, 41 pancreatic cancer patients in various situation treated in our hospital by the hyperthermia using Thermotron RF-8. In this study, we evaluated the result of 28 patients treated more than 5 times by this therapy.

## Objectives

In order to investigate the effectiveness of the hyperthermia using Thermotron RF-8 combined with chemotherapy for the patients in clinical Stage IV, including tumor recurrence after surgery. We examined the outcomes of the patients in the periods until two years after beginning of this therapy. The results were compared to the registered data of the multi-center of Japan of the pancreas cancer patients in Stage IV treated with chemotherapy alone. The aim of this study is to investigate whether hyperthermia contribute to improve the prognosis of the pancreatic cancer patients in clinical stage IV.

## Material/Methods

28 patients (from 40 to 79 years of age) with advanced pancreatic cancer in clinical stage IV treated by more than 5 times of hyperthermia combined with chemotherapy were examined. These patients had distant metastasis or peritoneal dissemination, and were treated with the several types of combination chemotherapy, FOLFIRINOX, Gemsitabin plus nab-Pacritaxel or S-1. Among them,9 patients had the history of surgery for the primary tumor and 21 had no surgery. Hyperthermia using heating device Thermotron RF-8 was administrated for 50 min in each times just after chemotherapy 3 or 4 times in a month. Evaluation of outcomes of the patients was expressed as complete remission (CR), partial response (PR),

stable disease (SD), progress disease (PD) and survival rate. This evaluation was done at 3,6,12,18 and 24 months after the beginning of this therapy.

**Results**

In the response to the treatment at 3 months, CR was 0 %, PR was 18%, SD was 39% and PD was 42%. Survival rate was 97%. At 6 months, CR was 0 %, PR was 21%, SD was 24% and PD was 28%. Survival rate was 71%. At 12 months, CR was 6%, PR was 0%, SD was 6% and PD was 59%. Survival rate was 41%. At 18 months, CR was 6%, PR was 0%, SD was 0% and PD was 19%. Survival rate was 25%. The survivors more than 2 years were 2 patients. Among 12 patients observed for these two years, two patients were alive, and one of them is still maintaining the situation of CR. The survival rate in 2 years was 17%. According to the registered data in 2010 of Japanese Association of Clinical Cancer Centers, 1-year survival rate and 2 years survival rate of the stage IV pancreas cancer patients treated with chemotherapy alone, is 20% and 8% respectively. Even though the number of the patients in our study is small, the outcomes of the patients were superior to that of the registered patients in Japanese Association of Clinical Cancer Centers, who were treated without hyperthermia.

**Conclusion**

These results in this study indicate that the treatment of hyperthermia combined with chemotherapy have a strong possibility to contribute to prolong the survival of the patients even if in the clinical stage IV.

# Clinical case report- mEHT - Results on CA - Esterioneuroblastoma - Brazilian experience

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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**
Our 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.

**Development**
The patient is a white skin, 47 years old male, 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 times a week, a 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), ozone therapy rectal 2 X week, reduced intake of simple

carbohydrates, Joanna Budwig diet, homeopathic support, and "a more healthy lifestyle".

**Results**

On PETscan dated 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% strabism recuction. The clinical impressions show significant improvement of energy and quality of life, and great improvement of vision. Still remains a slight strabismus, to be analyzed by the ophthalmologist. The patient continues with a low carb diet. He is able to drive safely and returned to normal work activities. Suggested oncological follow-up every six months.

# Modulated electro-hyperthermia in metastatic colorectal cancer: a retrospective cohort study with meta-comparison

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## Introduction

Colorectal cancer (CRC, C18-C21) ranks third in the world in prevalence (9.4% in men and 10.1% in women) and fourth in causes of cancer mortality. The 5-year survival rate for CRC is 65.1% in the United States and 56.6% in Europe. Metastasis dramatically worsens the prognosis: 5-year survival decreases to 13.5% in the USA and to 7.6% in the UK. Modulated electro-hyperthermia (MEHT) is a promising complementary treatment of CRC, which efficacy is shown in at least eight studies.

## Objectives

To study the efficacy of MEHT in the combined treatment of metastatic CRC.

## Material/Methods

The survival results of a retrospective, cohort, two-center Hungarian study of MEHT in complex treatment of CRC were compared with data from SEER, Eurocare and the results of a meta-analysis on CRC.

## Results

218 patients with CRC (C18-C21), median 58 years old (27 - 85), were recruited for 63 months. The average follow-up time was 14.6 ± 1.0 months. (median 8 (0 - 64)), the overall time of the study is 76 months. 116 patients (57.7%) had metastatic CRC at the diagnosis. The 5-year overall survival was 25.2% (18.8 - 31.6%), median survival time was 29.7 months (26.3 - 34.9 months.) The 5-year overall survival in patients with primary metastatic cancer was 18% with the median survival time of 21 months. The clinical response was evaluated in only one group (n = 175): 49.7% of these patients showed improvement, 47.4% showed no changes, and 2.9% worsened. Comparison with other studies with a comparable sample structure shows a significant superiority of this study in 5-year survival.

**Conclusion**

The results of the study suggest that the inclusion of MEHT in the complex treatment of CRC improves the clinical response and 5-year survival.

# Effects of modulated electro-hyperthermia on triple negative mouse breast cancer with differential metastatic potential

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## Introduction

Breast cancer is the most common malignancy among women. In triple negative breast cancer (TNBC) the lack of receptors excludes the possibilities of hormone- and targeted-therapies. Modulated electro-hyperthermia (mEHT) is a possible complementary treatment. We investigated two distinctly progressing isogenic mouse TNBC clones.

## Methods

4T1 (more aggressive) and 4T07 (less aggressive) cells were inoculated orthotopically into female BALB/c mice. Tumor growth was monitored by digital caliper and ultrasound (Phillips Sonos 5500). Animals were randomized into sham (n=10) and mEHT (n=11) treated groups 6 days after inoculation. Animals received mEHT treatment 3 times in every 48 hours with Labehy 200 (Oncotherm Ltd.). On day 12, animals were euthanized, tumors were dissected, weighed and processed. Histology slides were digitalized and evaluated with HistoQuant of Caseviewer (3DHistech Ltd.) Tumor Destrucion Ratio (TDR) was evaluated on cleaved caspase 3 and H&E stained slides. Heat-shock protein (HSP70) and Ki67 proliferation marker were evaluated (relative mask area %). Immune-related markers (T-lymphocyte: CD4, CD8; macrophage: F4/80) and immune-checkpoint molecules (CTLA4, PD-1, PD-L1) were measured by quantitative PCR normalized to GAPDH.

## Results

mEHT treatment reduced the size of 4T1 but not 4T07 tumors. mEHT increased TDR and HSP70 in all treated mice. Ki67 strong positive nuclei were not different from sham mice in either model.

| | 4T07 | | | 4T1 | | |
|---|---|---|---|---|---|---|
| | sham | mEHT | Significance | sham | mEHT | Significance |
| caliper | 77.78± 31.92 | 110.7± 49.52 | ns | 172.4± 28.92 | 138.2± 42.65 | p<0.05 |
| ultrasound | 79.68± 37.06 | 118.0± 53.28 | ns | 196.5± 36.36 | 147.2± 52.08 | p<0.05 |
| weight | 91.40± 33.14 | 102.3± 39.77 | ns | 199.7± 17.35 | 139.6 ± 12.07 | p<0.001 |
| TDR (%) | 43.46± 23.60 | 82.39± 22.25 | p<0.001 | 29.84± 16.02 | 67.71± 24.70 | p<0.001 |
| HSP70 (%) | 0.016± 0.017 | 2.334± 1.501 | p<0.0001 | 0.065± 0.066 | 2.585± 1.995 | p<0.01 |

Markers of immune infiltration (CD4, CD8 and F4/80) as well as immune checkpoint inhibitor molecules (CTLA4, PD-1, PDL-1) had an order of magnitude lower expression in the 4T1 model.

| | Sham | | | mEHT | | |
|---|---|---|---|---|---|---|
| | 4T07 | 4T1 | Significance | 4T07 | 4T1 | Significance |
| CD4 | 0.2479± 0.2189 | 1.104e-003± 5.916e-004 | p<0.01 | 0.1441± 0.1244 | 6.108e-004± 5.101e-004 | p<0.001 |
| CD8 | 0.2687± 0.1996 | 3.486e-004± 1.613e-004 | p<0.01 | 0.1718± 0.1003 | 1.576e-004± 8.980e-005 | pp<0.0001 |
| F4/80 | 0.9670± 0.8811 | 1.324e-002± 6.623e-003 | p<0.01 | 1.405± 1.062 | 1.583e-002± 1.342e-002 | p<0.001 |
| CTLA4 | 0.2000± 0.1168 | 2.716e-003± 1.372e-003 | p<0.01 | 0.1407± 0.08599 | 9.301e-004± 8.069e-004 | p<0.0001 |
| PD-1 | 0.2255± 0.1792 | 1.343e-003± 6.709e-003 | p<0.05 | 0.1334± 0.07477 | 3.186e-004± 3.079e-004 | p<0.0001 |
| PDL-1 | 1.983± 1.035 | 7.395e-003± 2.893e-003 | p<0.05 | 2.092± 0.7377 | 5.118e-003± 1.334e-003 | p<0.0001 |

24 hours after the last treatment mEHT reduced both tumor cell- and infiltrating lymphocyte-count. However, both infiltrating immune cells and checkpoint molecules increased vs sham if tumors were removed 96 hours after the last treatment suggesting a possible immune-stimulatory role of mEHT.

| | ΔExpr(mEHT-Sham) | | |
|---|---|---|---|
| | 24 h after treatment | 96 h after treatment | Significance |
| CD4 | -1.267e-003± 1.401e-003 | 5.544e-004± 4.392e-004 | p<0.01 |
| CD8 | -5.223e-004± 2.033e-004 | 2.235e-004± 1.938e-004 | p<0.01 |
| F4/80 | -4.959e-003± 1.124e-003 | 3.331e-003± 5.058e-003 | p<0.01 |
| CTLA4 | -1.357e-003± 5.013e-004 | 3.947e-004± 1.596e-004 | p<0.01 |
| PD-1 | -2.786e-004± 4.712e-005 | 1.081e-004± 9.568e-005 | p<0.01 |
| PDL-1 | -1.100e-002± 1.194e-003 | 1.082e-003 ± 9.750e-004 | p<0.01 |

**Conclusion**

4T07 tumors grew slower supporting that they have a less aggressive phenotype. The effect of mEHT treatment on TNBC was related to heat – shock response and was more effective against the more aggressive 4T1 type TNBC.

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# Computational study of capacitive hyperthermia with realistic models

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## Introduction

In radiofrequency (RF) capacitive hyperthermia the dielectric properties of tissues induce variation in the temperature distribution [1], since they vary not only from one tissue to another, but also within the same tissue depending on whether it is healthy or cancerous. Moreover, the presence of water boluses between electrodes and the human body is essential not only for the prevention of skin burns, but also for a better coupling of the electromagnetic energy to the body, also depending on the dielectric properties of the water contained within the boluses.

## Objective

The objective of the current study was to investigate the effect of tissue and water-bolus electric conductivity on the deposited power distribution in realistic numerical models of patients.

## Material/Methods

For the requirements of this study, two models were used. The first one was a model of realistic anatomy, constructed from medical images of a female patient who had undergone radical double mastectomy, following the development of breast cancer; thereafter multiple metastatic tumors occurred in the liver and lungs. The second female model was 'Ella', a numerical model of detailed anatomy obtained from the Virtual Population (IT'IS Foundation, Switzerland) [2]. Liver was chosen as the treatment target and the electric conductivity of liver, liver cancer and breast cancer at the frequency of 13.56 MHz were retrieved from a literature search. The properties of deionized water and saline were used for the bolus. The treatment simulations were performed in the software package Sim4Life (ZMT, Switzerland). An electrode of 30 cm was positioned on the model, which was lying on top of a full-body return electrode. The results were evaluated in terms of the Specific Absorption Rate (SAR) resulting in the tissues.

## Results

Variation in the electric conductivity of tissues induces, as expected, variations in the energy absorbed by the tissues. In particular, we noticed that when the liver tumor had higher conductivity than the surrounding

liver tissue the energy absorbed was also higher. The composition of the bolus filling resulted in differences of the absorbed energy, as well. As its conductivity increased, the energy absorbed by the tissues was also higher, since the more current is allowed to flow through the boluses and reach the tissues. Finally, it was clear that the position of the electrode on the body of the patient's model plays an important role for the energy delivered to treatment target; by moving the top electrode to the side, we noticed that the value of energy absorbed in the liver was increased, whereas the energy absorbed by the liver tumor decreased, as a result of their relative anatomical position.

**Conclusion**

We conclude that basics parameters that need to be considered in the treatment of hyperthermia are the tumor origin in order to be aware of the electric conductivity of the tumor and the healthy tissue surrounding it, as well as the anatomy of the tissue, in order to adjust the placement of the electrode. Moreover, the composition of the water contained within the water boluses, should be carefully chosen in order to achieve better coupling of the electromagnetic energy from the electrodes to the tissues.

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# Evaluation of clinical studies when no reference arm exists

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In the advanced metastatic stages of the malignant diseases the standard curative therapies usually fail, and the patient receive palliative care only. In the case of modulated electro-hyperthermia (mEHT, tradename oncothermia) this situation is common. The patients come to mEHT when no other curative therapy is available, and mEHT tries to turn the simple palliation to the curative therapeutic approach again. This could be with resensitization of the standard conventional therapies or applied mEHT in monotherapy regime together with the best supportive care. The treatment setup in these cases is very individual, it depends on the previous treatments and their results, the reason of the inapplicability of conventional methods (like organ failure, hemato-complications, refractory status, intolerable side effects, comorbidities, etc.). Due to the broad spectra of the patients and the missing availability of other active treatment for comparison form randomized, the double arm is impossible.

Furthermore, sometimes highly personalized therapies combined with mEHT block the collection of the homogeneous group and limit its double-arm randomization. Due to the above problems, many clinical trials have prospective or retrospective data-sets without comparison to the control-group formed by the same cohort as the active one. The measured single arm naturally contains the relevant information; however, in most of the cases, it is impossible to obtain it from the complex survival curve without a reference. Our objective is to discuss the situations of the single arm evaluation. We give a method for the mining of information from single arm study to increase the level of evidence of the measured dataset. The basic idea of the data-separation is the appropriate parameterization of the non-parametric Kaplan-Meier survival pattern by the psychometric poly-Weibull fit. With the Weibull decomposition of the survival curve, we can fit at least two subgroups of patients. The weighted sum of the decomposed fractions could be optimized analytically and determining the best parameters of the components and the best composition ratio of the weighted sum is also possible. We will show how the method works in a real clinical environment through mEHT as a complementary method, applied curatively when no other conventional curative therapies are available. The decomposed function of the non-responding group provides an excellent agreement with

the historical controls in the investigated group of patients with pancreatic cancer and non-small-cell-lung-cancer studies.

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

# Effects of modulated electro-hyperthermia on peripheral white blood cell counts of clinically responding and non-responding patients

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## Background

Modulated electro-hyperthermia (mEHT) is considered also as an immunomodulant, which is based on growing body of evidence in preclinical and clinical models and strengthened by valid observation of abscopal effect. We are performing a study treating patients with advanced stage and inoperable tumors of the pancreato-hepatobiliary (PHB) system. Here we analysed the peripheral white blood cell counts of clinically responding and non-responding patients.

## Patients and methods

In 37 PHB carcinoma patients who are candidates for mEHT treatment we have investigated the number of peripheral white blood cells with a Beckman-Coulter CytoFLEX flow cytometer. The investigated markers were: CD3, CD4, CD8, CD19, CD56 besides morphology. B-lymphocytes were CD19+, T-lymphocytes were CD3+, and subpopulations were identified as CD4+ or CD8+. Natural Killer (NK) cells were CD3-/CD56+, while NKT cells were CD3+CD56+.

## Results and discussion

Those patients who managed to attend the mEHT treatment series, white blood cell counts stayed at least stable if not increased. Those who were not responding or had poor prognosis, the cell counts initially were also lower.

## Grant support

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# Efficacy and dose of local hyperthermia

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Hyperthermia in oncology is based on energy-absorption from electromagnetic or mechanical sources. The specific absorption rate (SAR) measures the absorbed power (W/kg), and its multiplication by the duration of application in seconds gives the absorbed energy (J/kg). The dose is directly the absorbed energy, but in most of the applications, it is not a measurable parameter, due to the low efficacy of the absorption. The efficacy depends on the technical solution of the coupling of energy-source to the target, the surface cooling, and energy losses by the transmission, including the reflected power. The temperature is a consequence of the energy-absorption, and it depends on the thermal homeostatic activity of the targeted tissue.

Consequently, the inaccuracy of the SAR is mostly a technical problem, while the inaccuracy of the temperature is mainly physiological. The SAR is the source of the desired changes in the target, so it must be measured or at least estimated for dosing the local hyperthermia. The measured temperature is only an orienting parameter about the absorbed energy, and from that, we may calculate the SAR when otherwise it is not measurable. The planning is more straightforward; the SAR calculation with planning is a direct task, it is not necessary to transform it to the temperature of the target. This way the clue of dosing of local hyperthermia is the efficacy of the energy-targeting, making it possible to measure the applied dose with eligible accuracy. This approach needs well designed and controlled coupling for energy transfer to the tissue. My objective is to discuss the conditions of this request.

This study has been supported by the Hungarian National Research, Development and Innovation Office (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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## 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. In the present study we aimed to optimize the protocol 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 as well as interfere with respiration. Here, we demonstrate a strong correlation between the intrapulmonary and the laryngopharyngeal temperature of mice enabling an indirect evaluation of the treated lung temperature.

Electrode Design for Lung Treatment

Pilot studies with conventional electrode covering the thorax revealed scarring of skin tissue underlying the 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 adverse effect was the observed scarring. Furthermore, in some cases we have experienced liver damage as another unwanted side effect. We therefore went on to design an electrode specific for lung treatment and capable of preventing these adverse effects.

Treatment setup and protocol

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 customized electrode that covers the thorax. Mice were sacrificed on day 18 and metastatic nodules were counted. Immunohistochemical analysis was performed on obtained lung samples.

**Results and Discussion**

Our results demonstrate that a strong temperature correlation exist between the main bronchi and the laryngopharynx in mice with an average laryngopharyngeal-bronchial temperature difference of 1.44 ± 0.46 °C. When mice induced with B16-F10 melanoma in the lungs were treated with mEHT, a significant reduction in the number of metastatic nodules was observed as compared to the control group indicating a therapeutic value of the intervention. A reduction of the tumor burden was also detectable by histochemical analysis of lung sections. In addition, our redesigned electrode, customized for the lung treatment could avoid skin or liver damage.

**Conclusion**

Taken together, we have demonstrated that a temperature correlation exist between the main bronchi and the laryngopharynx in mice which proved useful in estimating lung temperature during treatment by measuring the laryngopharyngeal temperature which is less invasive. Our studies have also indicated that mEHT treatment has a beneficial effect in reducing the number of melanoma metastasis in the lung.

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

# Combined magnetic hyperthermia and magneto mechanical treatment on breast cancer and non-cancerous cells

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## Introduction

The exertion of magnetomechanical forces is a powerful tool for handling magnetic nanoparticles (MNPs) in biological environments by converting electromagnetic to mechanical energy, causing stress on malignant cells. [1]. Magnetic hyperthermia is a potential cancer treatment aiming to increase the temperature of the body's cancerous tissues to 41-45°C, causing cell apoptosis [2].

## Objectives

MNPs were used to study the cumulative effect of consecutively magnetomechanical and magnetic hyperthermia treatment on breast cancer cells (MCF-7) and non-transformed cells (MCF-10A).

## Material/Methods

MNPs (Ø = 200 nm, Chemicell, fluidMAG-D) were investigated inside a pulsed magnetic field to induce mechanical effects (field amplitude 200 mT, f = 2 Hz, exposure duration 30 min) and/or in combination with hyperthermia (field amplitude 60 mT, f = 375 kHz, exposure duration 15 min). MCF-7 and MCF-10A cell lines were purchased from ATCC (American Type Culture Collection). MCF-10A and MCF-7 cells were seeded with density of 2x105 cells/dish and 3x105 cells/dish, respectively. Directly to the cells MNPs were added at 0.25 mg/ml and cells were incubated for 24h at 37oC and 5% CO2. The next day the cells in the presence of MNPs were exposed to magnetic-mechanical treatment and/or to hyperthermia. MTT data were collected at 0, 24 and 120 hours to measure cell viability.

**Results**

MNPs exhibited excellent biocompatibility and allowed cell proliferation. MTT data showed high cell viability (between 80-100%) of non-cancerous cells after the following treatments: Pulsed+MNPs, Hyperthermia+MNPs and Hyperthermia+Pulsed+MNPs. MCF-7 showed higher sensitivity after treatment with Pulsed+MNPs, Hyperthermia+MNPs and Hyperthermia+Pulsed+MNPs. Pulsed+MNPs induced a time-dependent reduction of viable cells and after 5 days of incubation viability decreased to 50%. The greatest effect on cell viability suppression was observed after treatment with Hyperthermia+Pulsed in presence of MNPs, were the cell viability was <50%. No morphological changes were observed in non-cancerous cells after treatments. MCF-7 cells showed more rounded cell morphology especially after 5 days treatment with Hyperthermia+Pulsed+MNPs.

**Conclusion**

This study highlights the differences obtained in sensitivity of breast cancer cells and non-cancerous cells to combined treatment of hyperthermia and pulsed magnetic field in presence of MNPs (mainly iron oxide). Although the above combined treatment caused decreased viability of breast cell cells, the non-cancerous cells retained high cell viability after treatment. So, the present results reveal the potential use of the above combined treatment in anti-tumor therapy with low side effects on normal cells.

**Acknowledgements**

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# Hyperthermia as part of multimodal immunotherapy for patients with GBM

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## Introduction

The prognosis for patients with glioblastoma multiforme (GBM) remains poor in spite of modern neurosurgery, radiotherapy and addition of chemotherapy. Results from the use of checkpoint blockers are disappointing. There is need for active immunization strategies in order to create an anti-tumor immune effector function and an immune memory against GBM for the installation of long-term protection.

## Objectives

We integrated 5-day treatments with injections of Newcastle Disease Virus (NDV) and moderate modulated electro-hyperthermia (mEHT, 50 min, 40-55 Watt) into the maintenance chemotherapy with 5 days temozolomide (TMZ), after which we continued with full vaccination cycles including NDV injections, mEHT sessions, autologous DC vaccinations with IO-VAC® and immunomodulatory strategies. The objective of this study is to report on the results obtained from patients receiving such complex individualized combination treatment.

## Material/Methods

We found in our database (01/05/2019) 71 adults with primary GBM treated with multimodal immunotherapy as part of the first line treatment. For 34 adults, NDV and hyperthermia was administered during TMZ maintenance chemotherapy.

## Results

There were 10 females and 24 males with median age of 58 years (range 20-67). Median Karnofsky performance scale was 75 (range 60-100). Six patients are still under treatment. In median, 2 (range 0-13) DC vaccines, 25 (range 0-117) hyperthermia treatments and 28 (range 7-115) NDV injections were administered. Five from 28 patients who finished immunotherapy did not reach DC vaccination due to progressive disease. Median PFS was 10.46 months. Median OS was 23.44 months with 2-year

OS of 48% (CI95%: +18,-20). There were no major treatment-related toxicities.

**Conclusion**

Multimodal immunotherapy including moderate modulated electro-hyperthermia is feasible for patients with first diagnosis of primary GBM. The treatment can be integrated in the standard therapy and continues thereafter. Median PFS and OS, and more importantly the % long-term OS seem to be improved. The data can form a basis for a prospective controlled clinical trial.

# Multimodal immunotherapy for patients with ovarian cancer

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## Introduction

Ovarian cancer remains a serious disease with bad prognosis, mainly due to spreading disease before diagnosis. Surgery, chemotherapy, and anti-angiogenesis are essential for first line treatment. At time of relapse or metastasis, only palliative treatments can be performed. Active specific immunotherapy, however, give some glimpse of hope.
Objectives. The objective of this study is to report on our experiences obtained from ovarian cancer patients receiving multimodal immunotherapy as individualized treatment approach.

## Material/Methods

Since the approval in May 2015 for GMP production of autologous Dendritic cell vaccines loaded with autologous tumor antigens (IO-VAC®), patients with ovarian cancer were treated with multimodal immunotherapy, consisting of injections with Newcastle Disease Virus (NDV), modulated electro-hyperthermia (mEHT), IO-VAC® and immunomodulatory strategies like ATRA, low dose cyclophosphamide or checkpoint blockers.

## Results

We found in our database (01/05/2019) 9 females with ovarian cancer (5 serous, 2 mixed, 2 not documented). Median age at diagnosis was 39y (range 29-64y). Two patients included immunotherapy at time of first event, while the others presented at later events (1, 2 and 4 patients resp. at event 2, 3, 4). All except 2 patients presented with FIGOIIIB or higher. In median 2 (range 0-4) vaccination cycles with IO-VAC® were administered, 17 (range 7-43) sessions of NDV injections and mEHT treatments, and 1 (range 0-5) total body hyperthermia sessions. One patient received high dose ATRA to block myeloid-derived suppressor cells. At time of analysis, 5 patients were still alive and OS data were calculated from first diagnosis and from start IO-VAC®: Patient 1 (FIGO IV, Event 1): +44m, +40m; patient 2 (FIGO IIIC, Event 4): +133m, +20m; Patient 3 (FIGO IIIB, Event 3): +58m, +18m; Patient 4 (FIGO IIIC, Event 2): +29m, +7m; Patient 5 (FIGO IV, Event 4): +49m, +3m. Other 4 patients died: Patient 6 (FIGO IA, Event4): 37m, 4m;

Patient 7 (FIGO IV, Event 1): 12m, 7m; Patient 8 (FIGO IIIC, Event 4): 69m, 2m; Patient 9 (FIGO IIB, Event 3): 75m; 11m. All treatments were performed in an ambulant setting. Treatment was feasible and safe. There were no toxicities.

**Conclusion**

Multimodal immunotherapy can contribute to improved OS. Further studies on larger groups of patients with longer follow up are needed to demonstrate the efficacy of multimodal immunotherapy in ovarian cancer.

# Modulated electro-hyperthermia and combined primary, immortalized NK-cell therapy in human A2058 xenograft model

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Modulated electro-hyperthermia (mEHT), as a complementary intervention of radio-, chemo- and targeted therapies can induce tumor apoptosis and contribute to a secondary immune mediated cell death. Earlier we showed that mEHT treatment repeated three times resulted in significant tumor size reduction and major stress response indicated by the upregulated cell membrane hsp70 levels in B16F10 melanoma allografts. Though, mEHT promoted the release of damage associated molecular pattern proteins (hsp70, HMGB1 and ATP) which can potentiate tumor immunogenicity, it reduced MHC-I and melan-A levels in tumor cells. The number of cytotoxic T cells were moderately reduced, the amount of NK cells was mainly unchanged. NK cells could effectively recognize and kill cells which lack MHC-I. Here we tested the effect of single and repeated mEHT treatment on tumor growth and tumor microenvironment with respect to infiltration and cytotoxicity of NK cells in the human A2058 melanoma xenograft model in vivo.

A2058 melanoma cells were inoculated into both flanks of BALB/C NOD/SCID immunocompromised mice. After two weeks, 30-min 42°C mEHT treatment was applied locally on the right-side tumors (posttreatment day 0; D0). Tumor damaging effect of mEHT was tested both after a single shot and three times repeated treatments based on morphology, immunohistochemistry and tumor-size measurements. The single-shot protocol proved to be already efficient, thus it was combined with NK-cell therapy. The primary human NK cells (CD56+, granzyme B+) isolated from a healthy donor, were tested functionally in vitro. One day after mEHT treatment (D1), primary human NK-cells or an NK92MI NK-cell line labelled with fluorescent dye were injected subcutaneously above the lumbar region of the spine. Fluorescent in vivo imaging of tumorous mice was performed right before and after the NK-cell injection on D1, D2, D3 and

D4. Changes in tumor size were measured using ultrasonic caliper on D0, D2 and D4 post-treatment.

Both after a single- and three-times repeated treatments mEHT induced significant tumor growth inhibition measured by ultrasonic caliper. Apoptotic tumor cell death was proven morphologically and by measuring the relative dead tumor area, and the significant elevation of the cleaved caspase-3 and γH2AX positive areas. The number of tumor infiltrating F4/80 positive macrophages also showed strong tendency of increase. Significant tumor killing efficiency of both NK-cell types (primary and NK92MI) was pretested and proven in vitro by live cell imaging. In vivo, the injected primary NK-cells and NK92MI cells accumulated in the mEHT-treated and significantly damaged tumors but no such NK-cell migration was observed into the contralateral, untreated tumors.

In conclusion, our result show that mEHT can induce DNA double-strand breaks and caspase-dependent apoptosis in a xenograft model of A2058 melanoma. Furthermore, mEHT treatment may provide a favourable micro-environment for promoting the migration and attraction of NK-cells into the treated tumors. In vitro NK-cell activity in tumor destruction and its accumulation in the mEHT-treated and damaged xenografts suggest the involvement of NK-cells in melanoma destruction. Further testing of tumor stress e.g. hsp70 upregulation and tumor immunogenicity, including MHC-I levels are under way for explaining NK-cell involvement in this model and the potential contribution of mEHT in the success of NK-cell immunotherapy.

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# Electro-Hyperthermia and Immunotherapy Combinations for the Treatment of Cancer

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## Introduction

Cancer Immunotherapy frequently fails due to the non-immunogenic tumor microenvironment (TME). Modulated Electro-hyperthermia (mEHT, tradename: oncothermia) is a significant technological advancement in the cancer hyperthermia treatment, using nano-scale heating to target the cell membrane to create massive apoptosis. On our previous study, we found that mEHT could create a favourable tumor microenvironment for an immunological chain reaction to enhance the successful rate of intratumoral DC immunotherapy.

## Objectives

Various kind of immunotherapy including immunocheckpoint blockage, adoptive T cell therapy and allogenic NK cell therapy to combine with mEHT was evaluated in this study.

## Material/Methods

The in vitro killing effect of immune cells to cancer cells with or without mEHT was evaluated. The growth inhibition of the tumor after combination treatment was measured. The tumor was heated to a core temperature of 42 °C for 30 minutes. The immunotherapy were treated 24 hours after mEHT.

## Results

mEHT significantly enhanced the killing effect of immune cells to cancer cells when cancer cells pretreated with mEHT. mEHT-immunotherapy treatment resulted in significant inhibition of tumor growth compared to immunotherapy alone or mEHT alone. Moreover, the secondary tumor protection effect upon rechallenging was observed in mice treated with the mEHT-immunotherapy group.

**Conclusion**

In this study, we demonstrated that the combination of mEHT and immunotherapy is very effective. mEHT has efficient immune boosting effect for immunotherapy. A connection of the secondary tumor protection effect is an evidence of immune boosting from combined mEHT and immunotherapy. The combination of mEHT and immunotherapy has great potential for the treatment of cancer.

# iTRAQ-based proteomics analysis reveals the differentially expressed proteins related to radiosensitivity induced by hyperthermia in highly invasive human non-small cell lung cancer cells

**Zhang, Shirong[1]; Zhao, Yanyan[1]; Ma, Shinglin[1,2]**
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## Introduction

Postoperative microwave (MW) hyperthermia has been applied as an important adjuvant therapy to enhance the efficacy of traditional cancer treatment. A better understanding of the molecular mechanisms of MW hyperthermia will provide guide information on clinical hyperthermia treatment.

## Objectives

In this study, we investigated the differentially expressed proteins related to radiosensitivity induce by hyperthermia on NSCLC cells in vitro.

## Material/Methods

In previous study, we established highly invasive human non-small cell lung cancer cells (NSCLC), H460-INV, from parental H460 cell lines previously. In order to mimic the clinical treatment, we developed special MW heating equipment for this study. H460-INV cells were exposed to combined MW hyperthermia and irradiation, or alone. Using iTRAQ quantitative proteomics technique we investigated the differentially expressed proteins related to radiosensitivity induced by hyperthermia with or without radiation. The differentially expressed proteins were defined based on the following criteria: the iTRAQ ratio being $> 1.2$ or $< 0.833$ with a P-value $< 0.05$. For bioinformatics analyses, the differentially expressed proteins were annotated using the Gene Ontology (GO) database. Pathway analysis of the differentially expressed proteins was performed by the Kyoto Encyclopedia of Genes and Genomes (KEGG) database.

## Results

In total, 6,565 protein groups were identified, among which 5,225 proteins were quantified. Among the quantified proteins, 8 proteins are up-regulated and 48 proteins are down-regulated in group RT vs control, 10 proteins are

up-regulated and 46 proteins are down-regulated in group HT vs control, 47 proteins are up-regulated and 92 proteins are down-regulated in group HT+RT vs control, 29 proteins are up-regulated and 21 proteins are down-regulated in group HT+RT vs RT. The enriched analysis of GO terms and KEGG pathway on the altered proteins showed that both enriched main GO terms and KEGG pathways appear to be different between the two kinds of treatments: radiation (RT)and combined treatment (RT+HT).

**Conclusion**

These identified proteins might participate in the regulation of a wide range of biological processes, such as immune system process, immune response, metabolic process, response to unfolded proteins, immune effector process, innate immune response. These results from this study provide a new way to gain insight into the mechanisms of hyperthermia on radiosensitivity in NSCLC.

# Microwave hyperthermia increases sensitivity to radiation in highly invasive human non-small cell lung cancer cells

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## Introduction

Hyperthermia as one modality of anticancer therapies can damage the cancer cells and enhance the radiosensitivity by expose the body tissue to the higher temperature. However, the molecular mechanism under the therapeutic effects of hyperthermia combining with radiation is not well understood.

## Objectives

Exploring the molecular mechanism under the therapeutic effects of hyperthermia combining with radiation.

## Material/Methods

In previous study, we established highly invasive human non-small cell lung cancer cells (NSCLC), H460-INV, from parental H460 cell lines previously. In order to mimic the clinical treatment, we developed special MW heating equipment for this study. H460-INV cells were exposed to combined MW hyperthermia and irradiation, or alone. Cell survival was determined by an in vitro clonogenic assay and MTS assay. Immunohistochemical staining was performed to detect the expression of Ki67. Cell apoptosis was determined by flow cytometry. Cell-scratches and transwell assays were performed to detect the ability of cell migration and invasion. Western blot was used to detect molecular changes in EMT pathway. Further, we investigated the down-regulated proteins related to metastasis induced by radiation with or without hyperthermia using iTRAQ quantitative proteomics technique.

## Results

H460-INV presented obvious phenotype of cancer stem cell and increased ability of DNA damage repair, which is relatively resistant to radiation treatment. Hyperthermia can significantly enhance cell killing effect by radiation with radiation sensitivity enhancement ratio rearching1.823. Hyperthermia also led to increased apoptosis and enhanced tumor growth inhibition when combined with radiation in H460-INV cells. Compared with

the control group, hyperthermia significantly reduced the abilities of migration and invasion in H460-INV cell, and down-regulated the expression of N-cadherin and vimentin. Quantitative Analysis of Global Proteome indicated that a total of 56 proteins were significantly changed by the radiation treatment, of which, 8 proteins were up-regulated and 48 proteins were down-regulated. Whereas, 139 proteins were significantly changed by the combined treatment of radiation and hyperthermia, of which 47 proteins were up-regulated and 92 proteins were down-regulated. It was confirmed that the expression of 5 proteins by qPCR and westernblot technique: KRT1, KRT10, MAPT, CTSS and CXCL-5 were agreement with the findings in iTRAQ-Based quantitative analysis.

**Conclusion**

Our findings suggest a potential therapeutic impact of hyperthermia combined with radiation in high invasive lung cancer cells with cancer stem cell phenotype. Inhibition of EMT pathway by microwave hyperthermia may play the important role on enhancing the efficacy of radiation treatment. This study suggests a beneficial clinical impact of microwave thermal therapy as a radiosensitizer for benefiting highly invasive lung cancer patients.

# INDEX OF INVITED SPEAKERS, CHAIRS AND ABSTRACT AUTHORS

## S



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## V



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## Y



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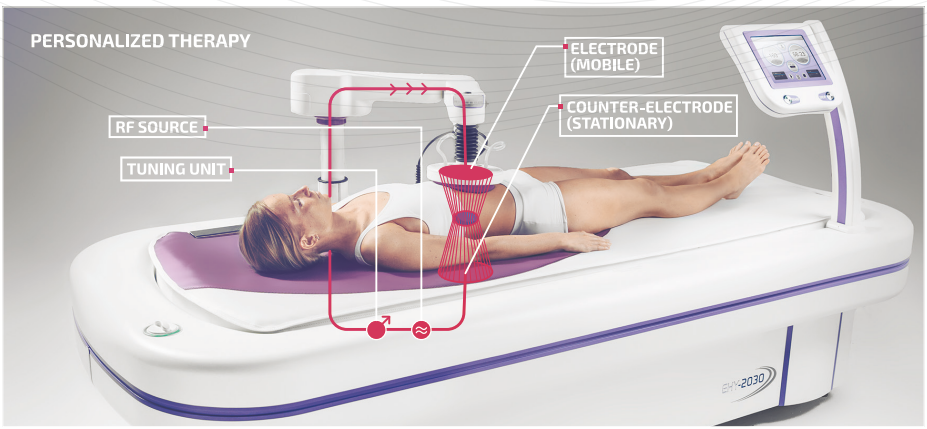
## NOTES


## A revolutionary loco-regional electro-hyperthermia device




**Oncotherm**'s primary goal is to create a treatment modality that can be combined with other therapies and is capable of increasing the survival time and the QoL of the patient at the same time. This is achieved by creating a method that is capable of selectively targeting tumor cells (on cellular level), and supporting multiple immune reactions like apoptosis, DAMP generation, abscopal effects and many other effects. This therapy can be combined with most of the commonly used gold standard therapies or applied as a monotherapy without significant side effects.

oncotherm
hyperthermic oncology

NATIONAL RESEARCH, DEVELOPMENT AND INNOVATION OFFICE
HUNGARY

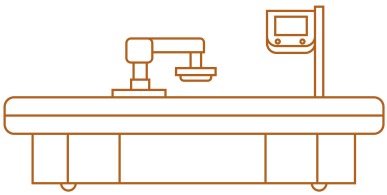
PROJECT FINANCED FROM THE NRDI FUND
*MOMENTUM OF INNOVATION*

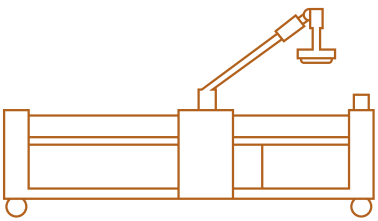
# THE ONCOTHERMIA METHOD & DEVICES

**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 Seystem (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.



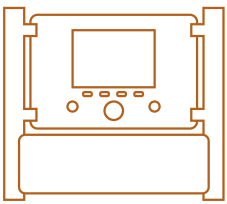


## EHY-2000plus

The EHY-2000plus 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-2000plus 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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