Oncothermia Journal

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Imprint

Editorial

Dear reader, Dear colleagues, Dear hyperthermia experts,

June 1st, 2024 marks a groundbreaking step in the fight against cancer as a Launching event of Oncothermia was held in the vibrant city of Makati, Philippines. Organized in collaboration with Oncotherm, the large-scale event presented the latest clinical results of modulated electro-hyperthermia (mEHT) including a lineup of scientific presentations by Prof. Dr. Pirus Ghadjar (Charité – Universitätsmedizin Berlin, Germany), Dr. Carrie Minnaar (University of the Witwatersrand, Johannesburg, South Africa), Dr. Paul Mulholland (University College London, UK), Prof. Dr. Magdolna Dank (Semmelweis University, Budapest, Hungary), Prof. Dr. Elisabeth Arrojo (University Hospital Marqués de Valdecilla, Santander, Spain), Dr. habil. Marcell Szász (Semmelweis University, Budapest, Hungary) and Prof. András Szász (Hungarian University of Agriculture and Life Sciences, Hungary). The present 35th issue of the Oncothermia Journal publishes the presentations in their original form. The results clearly show the clinical successes of mEHT in relation to the long-term survival time amalgamated with excellent improvement of the quality of life.

Prof. A. Szász summarized the primary principles of mEHT, which was followed by the presentations of the renowned clinical experts. Prof. Dr. Ghadjar presented the first interim results of the clinical trials led by him. The results are very encouraging. Prof. Dr. Dank outlined the results of the clinical trials of mEHT summarizing the excellent improvement of the survival time, compared the multi-university results with the expectations from the large databases. Dr. M. Szász shared the results of the running clinical trial on triple-negative breast cancer, showing longer survival rates compared to the control arm. He presented promising outcomes for inoperable pancreas and highlighted some special proteome profiles that explained mEHT in a molecular level. Dr. P. Mulholland demonstrated the inspiring interim results of his glioblastoma multiforme clinical study. Prof. Dr. E. Arrojo showed excellent case reports from various advanced cancers treated with mEHT and presented interim results from the clinical studies she is leading as a principal investigator. Dr. C. Minnaar demonstrated the excellence of mEHT with her results of 3y follow-up of phase III clinical study of advanced cervix tumors for over two hundred patients. She emphasized the abscopal effects which she documented even at the HIV-infected patients. She also summarized some other mEHT trials and had shown the economic excellence of mEHT.

I am convinced that expert readers will find their expectations in the current issue of Oncothermia Journal and will be able to use this information in their daily medical practice. I am pleased to recognize the overall success of the mEHT method to help for suffering patients to survive the malignant disease with excellent quality of life. The recent clinical data further strengthens the superiority of mEHT verifying the method's promised advantages. I am thankful for the presenters of the successful meeting whose collected presentation are featured in this volume of the Oncothermia Journal. I am sure these info gives further support for the clinicians using mEHT in their everyday practice.

Dr. Andras Szasz
Professor, Chair, Biotechnics Department of St. Istvan University

Liebe Leser, liebe Kollegen, liebe Hyperthermie-Experten,

der 1. Juni 2024 markiert einen bahnbrechenden Schritt im Kampf gegen Krebs, als in der pulsierenden Stadt Makati, Philippinen, eine Auftaktveranstaltung zur Oncothermie stattfand. In Zusammenarbeit mit Oncotherm organisiert, präsentierte die groß angelegte Veranstaltung die neuesten klinischen Ergebnisse der modulierten Elektro-Hyperthermie (mEHT) und bot eine Reihe wissenschaftlicher Präsentationen von Prof. Dr. Pirus Ghadjar (Charité – Universitätsmedizin Berlin, Deutschland), Dr. Carrie Minnaar (University of the Witwatersrand, Johannesburg, Südafrika), Dr. Paul Mulholland (University College London, UK), Prof. Dr. Magdolna Dank (Semmelweis Universität, Budapest, Ungarn), Prof. Dr. Elisabeth Arrojo (Universitätsklinikum Marqués de Valdecilla, Santander, Spanien), Dr. habil. Marcell Szász (Semmelweis Universität, Budapest, Ungarn) und Prof. András Szász (Ungarische Universität für Agrar- und Lebenswissenschaften, Ungarn). Die vorliegende 35. Ausgabe des Oncothermia Journals veröffentlicht die Präsentationen in ihrer Originalform. Die Ergebnisse zeigen eindeutig die klinischen Erfolge der mEHT in Bezug auf die langfristige Überlebenszeit, verbunden mit einer hervorragenden Verbesserung der Lebensqualität.

Prof. A. Szász fasste die grundlegenden Prinzipien der mEHT zusammen, gefolgt von den Präsentationen der renommierten klinischen Experten. Prof. Dr. Ghadjar stellte die ersten Zwischenergebnisse der von ihm geleiteten klinischen Studien vor. Die Ergebnisse sind sehr ermutigend. Prof. Dr. Dank skizzierte die Ergebnisse der klinischen Studien zur mEHT und fasste die hervorragende Verbesserung der Überlebenszeit zusammen, indem sie die Ergebnisse mehrerer Universitäten mit den Erwartungen aus großen Datenbanken verglich. Dr. M. Szász teilte die Ergebnisse der laufenden klinischen Studie zu dreifach negativem Brustkrebs, die längere Überlebensraten im Vergleich zur Kontrollgruppe zeigte. Er präsentierte vielversprechende Ergebnisse für inoperablen Bauchspeicheldrüsenkrebs und hob einige spezielle Proteomprofile hervor, die mEHT auf molekularer Ebene erklärten. Dr. P. Mulholland demonstrierte die inspirierenden Zwischenergebnisse seiner klinischen Studie zu Glioblastoma multiforme. Prof. Dr. E. Arrojo zeigte hervorragende Fallberichte von verschiedenen fortgeschrittenen Krebserkrankungen, die mit mEHT behandelt wurden, und präsentierte Zwischenergebnisse aus den von ihr geleiteten klinischen Studien. Dr. C. Minnaar demonstrierte die Exzellenz der mEHT mit ihren Ergebnissen einer dreijährigen Nachbeobachtung der Phase-III-Studie zu fortgeschrittenen Gebärmutterhalstumoren bei über zweihundert Patienten. Sie betonte die abskopalen Effekte, die sie selbst bei HIV-infizierten Patienten dokumentierte. Außerdem fasste sie weitere mEHT-Studien zusammen und zeigte die wirtschaftliche Exzellenz der mEHT auf.

Ich bin überzeugt, dass die fachkundigen Leser in der aktuellen Ausgabe des Oncothermia Journals ihre Erwartungen finden und diese Informationen in ihrer täglichen medizinischen Praxis nutzen können. Es freut mich, den Gesamterfolg der mEHT-Methode anzuerkennen, die dazu beiträgt, leidenden Patienten zu einem Überleben der bösartigen Erkrankung mit hervorragender Lebensqualität zu verhelfen. Die jüngsten klinischen Daten stärken weiter die Überlegenheit der mEHT und bestätigen die versprochenen Vorteile der Methode. Ich bin den Referenten des erfolgreichen Treffens dankbar, deren gesammelte Präsentationen in diesem Band des Oncothermia Journals enthalten sind. Ich bin sicher, dass diese Informationen den Klinikerinnen und Klinikern, die mEHT in ihrer täglichen Praxis einsetzen, weitere Unterstützung bieten.

Rules of submission

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

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

1. Aims and Scope

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

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

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

Umfang und Ziele

Das Oncothermia Journal ist das offizielle Magazin der Oncotherm Gruppe und soll diejenigen unterstützen, die ihre Ergebnisse der Allgemeinheit zur Verfügung stellen möchten. Das Oncothermia Journal ist neuen Inhalten gegenüber offen, sollte aber vor allem Studienarbeiten, Fallstudien, Hypothesen, Meinungen und alle weiteren informativen Materialien, die für die internationale Oncothermie-Gemeinschaft hilfreich sein könnten, enthalten. Werbung mit Bezug zum Thema ist ebenfalls willkommen.

- Klinische Studien: regionale, lokale oder multilokale Oncothermie oder Electro Cancer Therapy (ECT) Behandlungen, Fallstudien, praktische Erfahrungen in komplexen Behandlungen, klinische Versuche, physiologische Effekte, Oncothermie in Kombination mit anderen Modalitäten und Behandlungsoptimierungen

- Biologische Studien: Mechanismen der Oncothermie, thermale oder temperaturunabhängige Effekte, Ansprechen auf ein elektrischesFeld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
- Oncothermie-Techniken: technische Entwicklungen, neue technische Lösungen
- Hypothesen undMeinungen, wie die Oncothermie- und ECT-Methoden verbessert werden können, um die Behandlung zu unterstützen

Weitere Informationen zum Journal sowie Links zu Online-Beispielen und Inhaltsbeschreibung sind auf der Website zu finden: www.oncothermia-journal.com

2. Submission of Manuscripts

All submissions should be made online via email: info@oncotherm.org

Manuskripte einreichen

Manuskripte können online eingereicht werden: info@oncotherm.org

3. Preparation of Manuscripts

Manuscripts must be written in English, but other languages can be accepted for special reasons, if an English abstract is provided.
Texts should be submitted in a format compatible with Microsoft Word for Windows (PC). Charts and tables are considered textual and should also be submitted in a format compatible with Word. All figures (illustrations, diagrams, photographs) should be provided in JPG format.

Manuscripts may be any length, but must include:

- Title Page: title of the paper, authors and their affiliations, 1-5 keywords, at least one corresponding author should be listed, email address and full contact information must be provided
- Abstracts: Abstracts should include the purpose, materials, methods, results and conclusions.
- Test: unlimited volume
- Tables and Figures: Tables and figures should be referred to in the text (numbered figures and tables). Each table and/or figure must have a legend that explains its purpose without a reference to the text. Figure files will ideally be submitted as a jpg-file (300dpi for photos).
- References: Oncothermia Journal uses the Vancouver (Author-Number) system to indicate references in the text, tables and legends, e.g. [1], [1-3]. The full references should be listed numerically in order of appearance and presented following the text of the manuscript.

Manuskripte vorbereiten

Manuskripte müssen in englischer Sprache vorliegen. Andere Sprachen können in Ausnahmefällen akzeptiert werden, wenn ein englisches Abstract vorliegt.
Texte sollten in einem mit Microsoft Word für Windows (PC) kompatiblen Format eingereicht werden. Tabellen sollten in einem Word-kompatiblen Format eingefügt werden. Alle Graphiken (Illustrationen, Diagramme, Photographien) sollten im jpg Format vorliegen.

Manuskripte können jede Länge haben, müssen aber die folgenden Punkte erfüllen:

- Titelseite: Titel der Arbeit, Autor, Klinikzugehörigkeit, 1-5 Schlüsselworte, mindestens ein Autor muss genannt werden, E-Mail-Adresse und Kontaktdetails des Autors
- Abstracts: Abstracts müssen Zielsetzung, Material und Methoden, Ergebnisse und Fazit enthalten.
- Text: beliebige Länge

- Abbildungen und Tabellen: Abbildungen und Tabellen sollten im Text erläutert werden (nummeriert). Jede Abbildung / Tabelle muss eine erklärende Bildunterschrift haben. Bilder sollten als jpg eingereicht werden (300 dpi).
- Zitate: Das Oncothermia Journal verwendet die Vancouver Methode (Autornummer), um Zitate auszuweisen, z.B. [1], [1-3]. Die Bibliographie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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

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Bewertung

Die Texte für das Oncothermia Journal werden durch die Redaktion kontrolliert. Um Konflikte zu vermeiden, werden die Namen des jeweiligen Korrektors nicht öffentlich genannt. Artikel, die nicht zu den Themen des Journals passen, können abgelehnt werden

Content

Principles of Modulated Electro-Hyperthermia (mEHT)

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Prof. Dr. András Szász

Founder of Oncotherm
Biotechnics Department, Hungarian University of Agriculture and Life Sciences, Gödöllő, Hungary
XAX Consulting LLC. – Lincoln MA 01773, Boston, USA

Citation

Szasz, A. (2024) Principles of Modulated Electro-Hyperthermia (mEHT)
Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/uWPUCgKANcc,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 9-20.
https://oncotherm.com/SzaszA_2024_Principles-of-mEHT_20240601

PHILIPPINES LAUNCHING EVENT
1ST JUNE 2024 | FAIRMONT MAKATI

Oncotherm
HYPERTHERMIC IMMUNO-ONCOLOGY

MATE
HUNGARIAN UNIVERSITY OF AGRICULTURE AND LIFE SCIENCES

Principles of modulated electro-hyperthermia (mEHT)

Brand name:
Oncothermia

Presenter:
Andras Szasz
Ph.D. Professor of Biophysics

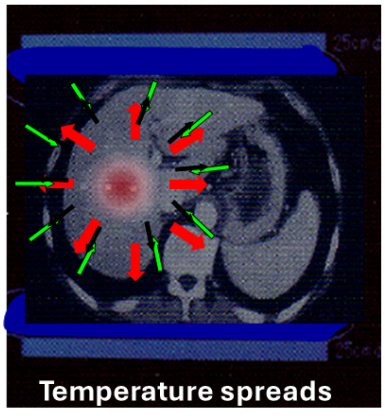
Hyperthermia in oncology was recognized in ancient medicine

Why are doctors skeptical nowadays?
Why is the method not used routinely?
What hinders practical applications?

WHY?

The heating is not controlled enough, the results are contingent.

What is the reason?



The blood flow tries to compensate for the warming

It is useful for complementary therapies

- **radio [reoxygenization]**
- **chemo [drug delivery and reaction activity])**

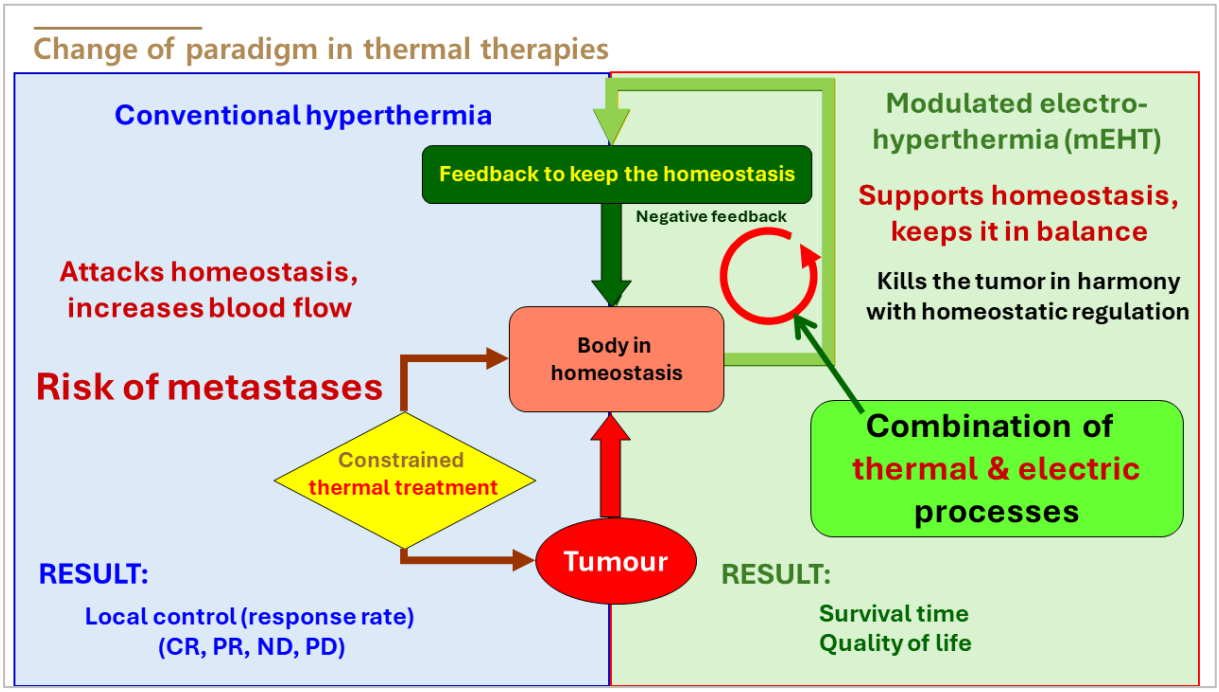
BUT:

It supplies extra nutrients for the tumor!

It risks the intensive dissemination, metastases

Further uncertainty:
the thermal homeostasis is subject-dependent

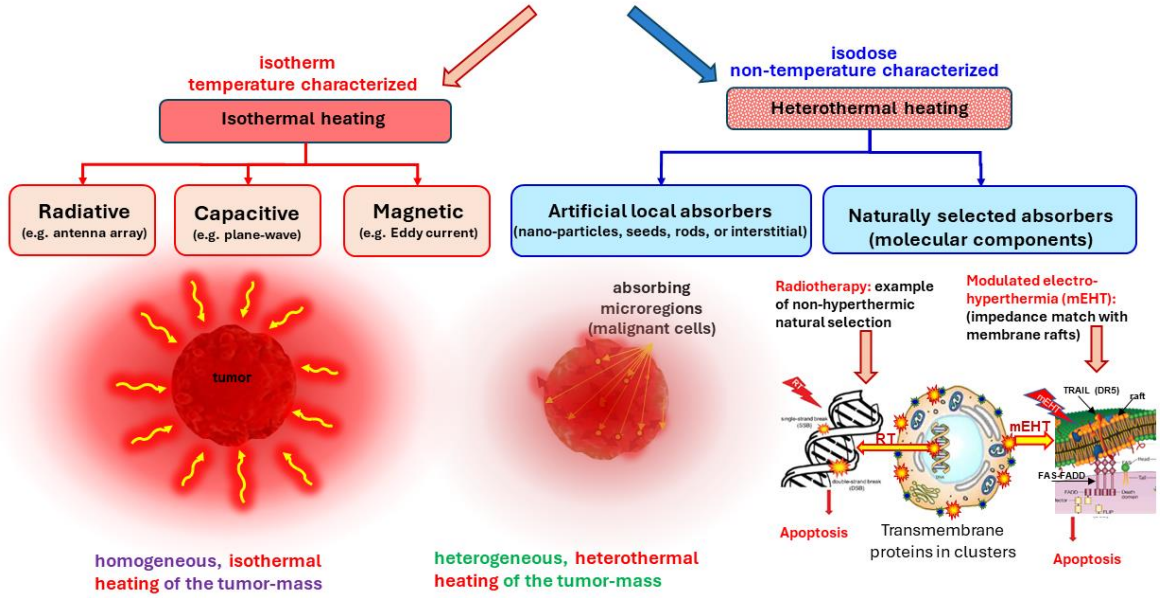
What to do? How to get out of the trap?



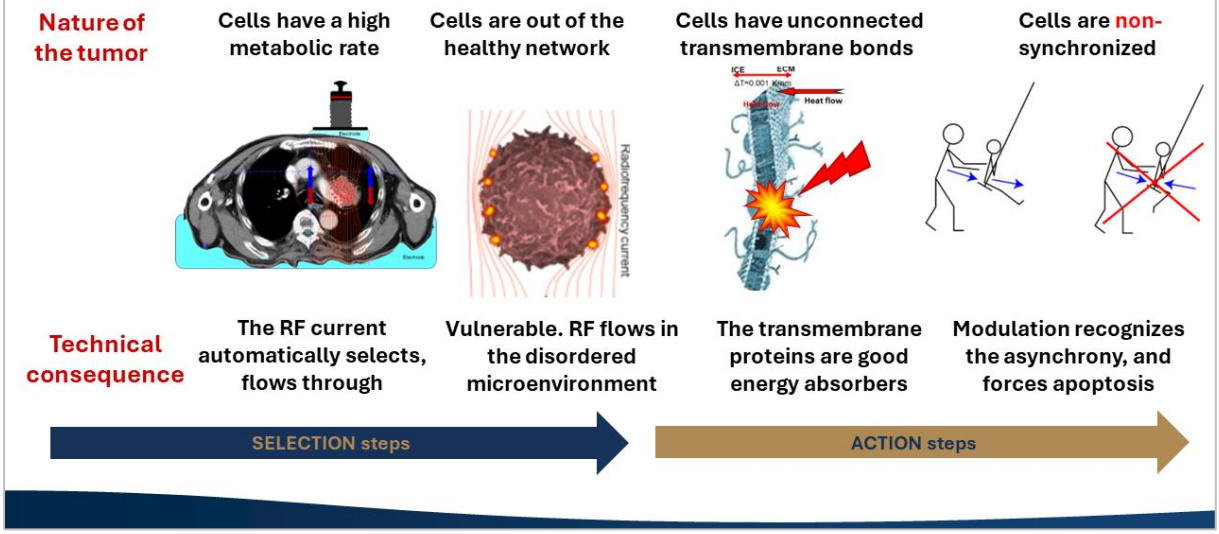
How to do it?

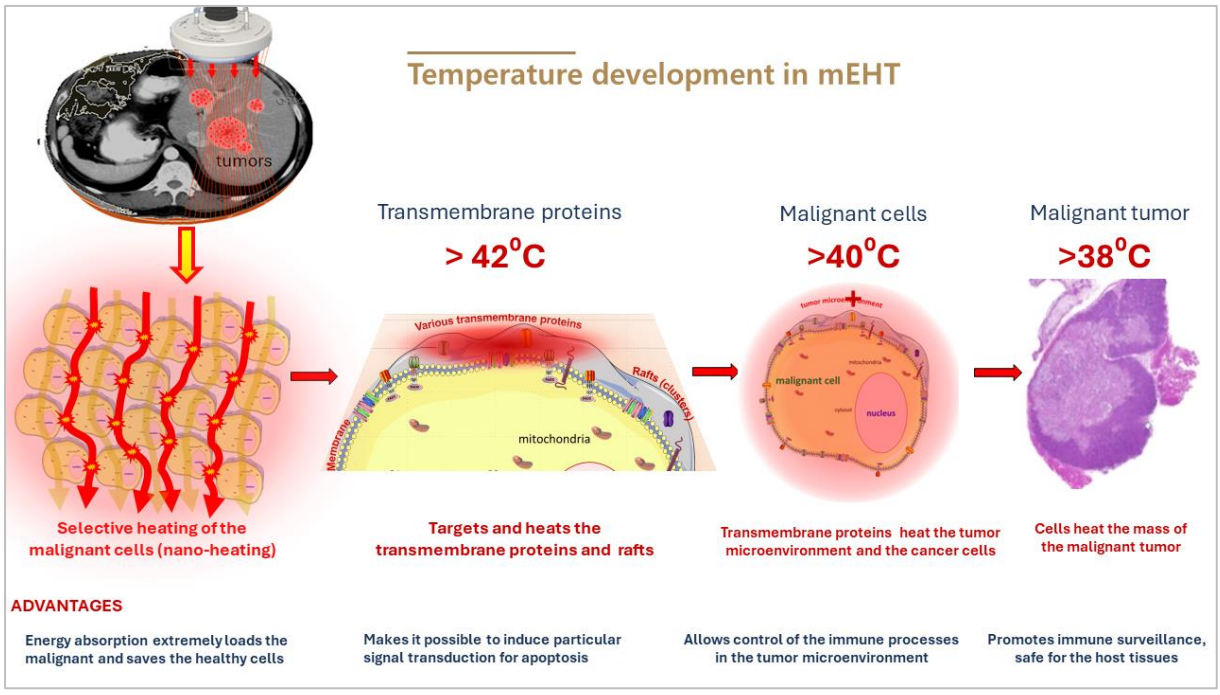
The trick is technical!

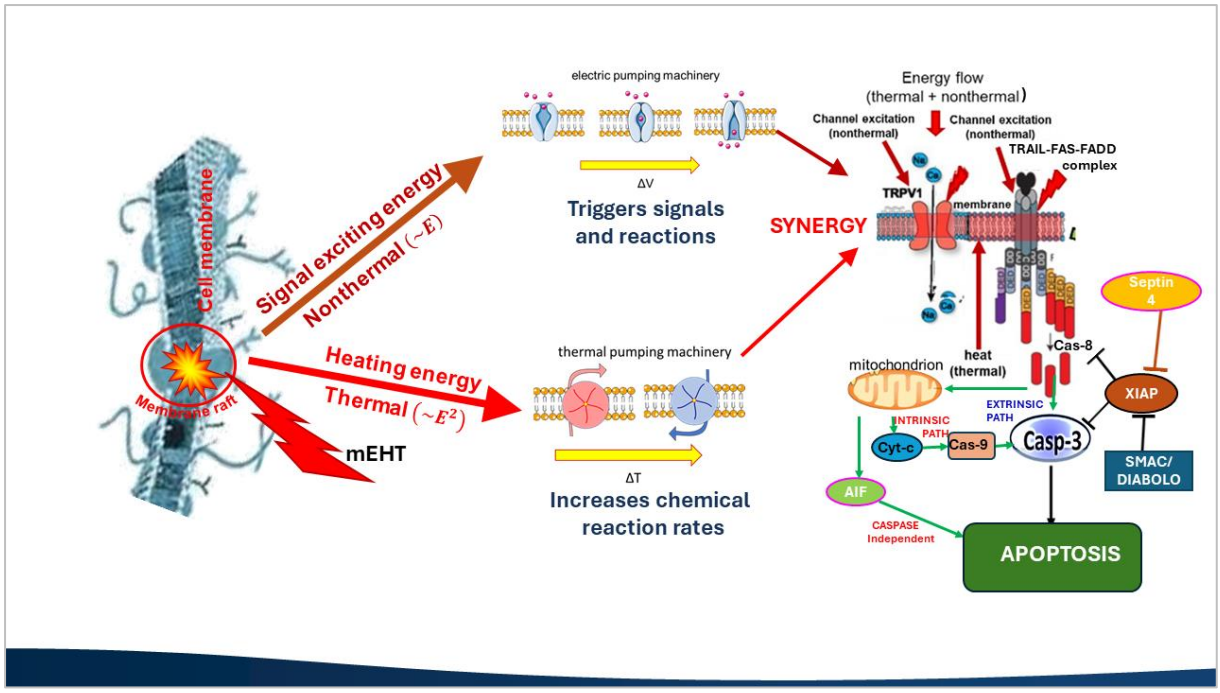
Electromagnetic technics of loco-regional hyperthermia



The tool: modulated electro-hyperthermia (mEHT, oncothermia ®)




Temperature development in mEHT
tumors
Transmembrane proteins
> 42°C
Malignant cells
>40°C
Malignant tumor
>38°C
Various transmembrane proteins
Rafts (clusters)
Membrane
mitochondria
malignant cell
nucleus
Selective heating of the malignant cells (nano-heating)
Targets and heats the transmembrane proteins and rafts
Transmembrane proteins heat the tumor microenvironment and the cancer cells
Cells heat the mass of the malignant tumor
ADVANTAGES
Energy absorption extremely loads the malignant and saves the healthy cells
Makes it possible to induce particular signal transduction for apoptosis
Allows control of the immune processes in the tumor microenvironment
Promotes immune surveillance, safe for the host tissues


Cell membrane
Signal exciting energy
Nonthermal (~E)
Heating energy
Thermal (~E²)
mEHT
Membrane raft
electric pumping machinery
ΔV
Triggers signals and reactions
thermal pumping machinery
ΔT
Increases chemical reaction rates
SYNERGY
Energy flow
(thermal + nonthermal)
Channel excitation (nonthermal)
Channel excitation (nonthermal)
TRAIL-FAS-FADD complex
TRPV1
membrane
Septin 4
Cas-8
mitochondrion
heat (thermal)
XIAP
EXTRINSIC PATH
INTRINSIC PATH
Cyt-c
Cas-9
Casp-3
SMAC/ DIABOLO
AIF
CASPASE Independent
APOPTOSIS

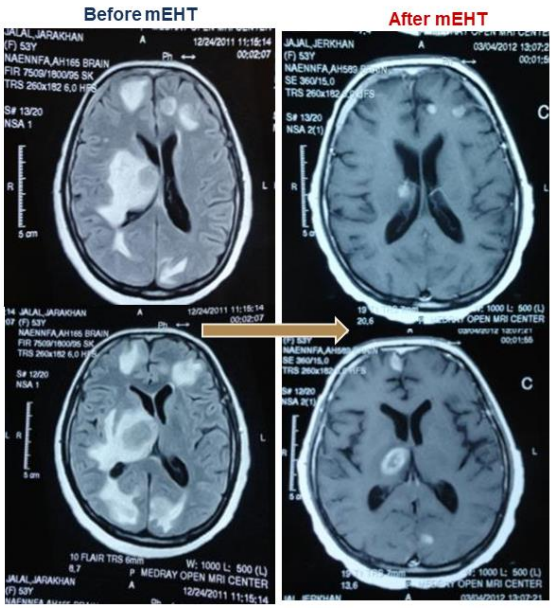
Brain metastasis from breast cancer

Investigator:
Dr. Marwan Akasheh

Institute:
Dar Alshefa' Tumors
Treatment Center,
Amman, Jordan,

Patient:
female 53 y.

mEHT Monotherapy



Mammary carcinoma

Investigator:
Prof.Dr.A.Herzog

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

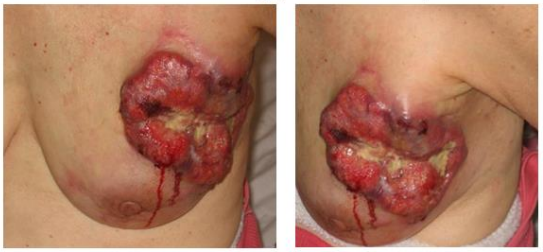
Patient:
60 y, female, (H.S.)

Diagnosis:
Mammary carcinoma, (March 2007)

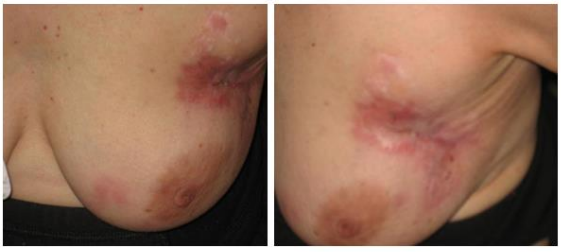
Treatment:
(started December 2008) Chemotherapy
Vinorelbine + Mitomycine C, accompanied by
several sessions of oncothermia;

Result: complete remission (CR)

Before oncothermia therapy; 12. December, 2008



After oncothermia therapy, 20. March 2009



Esophagus carcinoma

Investigator:
Prof.D.Gronemeyer & Dr.H.Sahinbas

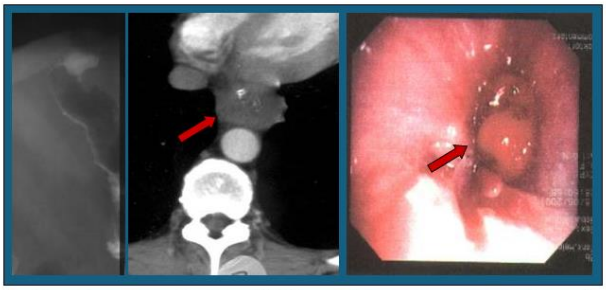
Department:
Department of Radiology and Microtherapy,
University of Witten-Herdecke, Bochum, Germany

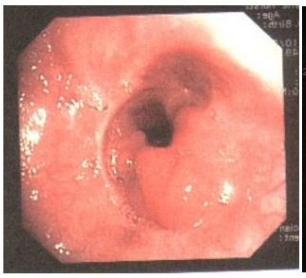
Patient:
M, 46 y, male

Diagnosis:
Esophagus-Ca.

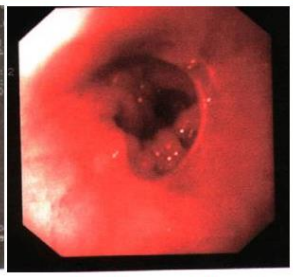
Therapies:
Surgery: +
Chemotherapy: Multiple CxT
Radiotherapy: (50 Gy) from
Relapse: Anastomose, Full block of food-passage in esophagus,
Oncothermia: monotherapy
Result: Complete remission (CR) Free-food passage

Follow-up: Censored





after 6x oncothermia



after 12x oncothermia

Stomach Carcinoma, WHO IV

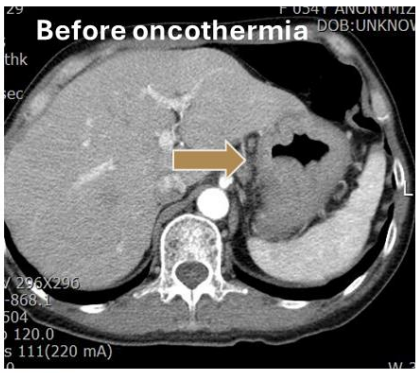
Investigator: Prof.Dr. Taesing Jeung

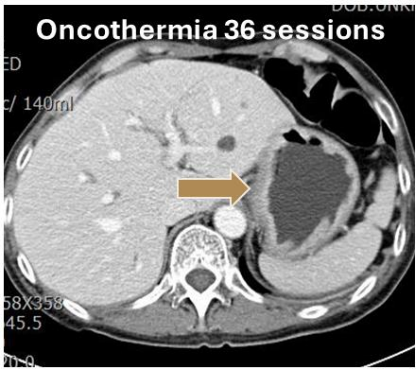
Institute: Department of Radiation Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital.

Patient: (54y/F)

Published: 31st ICHO Oct. Budapest; 2012

Stomach Ca in Jan/2012
No chemoTx, oncothermia monotherapy
HT 36 times: Mar/2012~Sept/2012





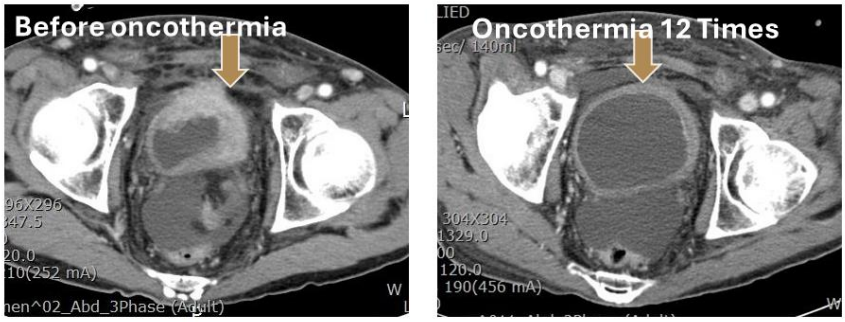
Pancreatic Ca and Metastatic Bladder Cancer (49y/M)

Investigator: Prof.Dr.Taesing Jeung

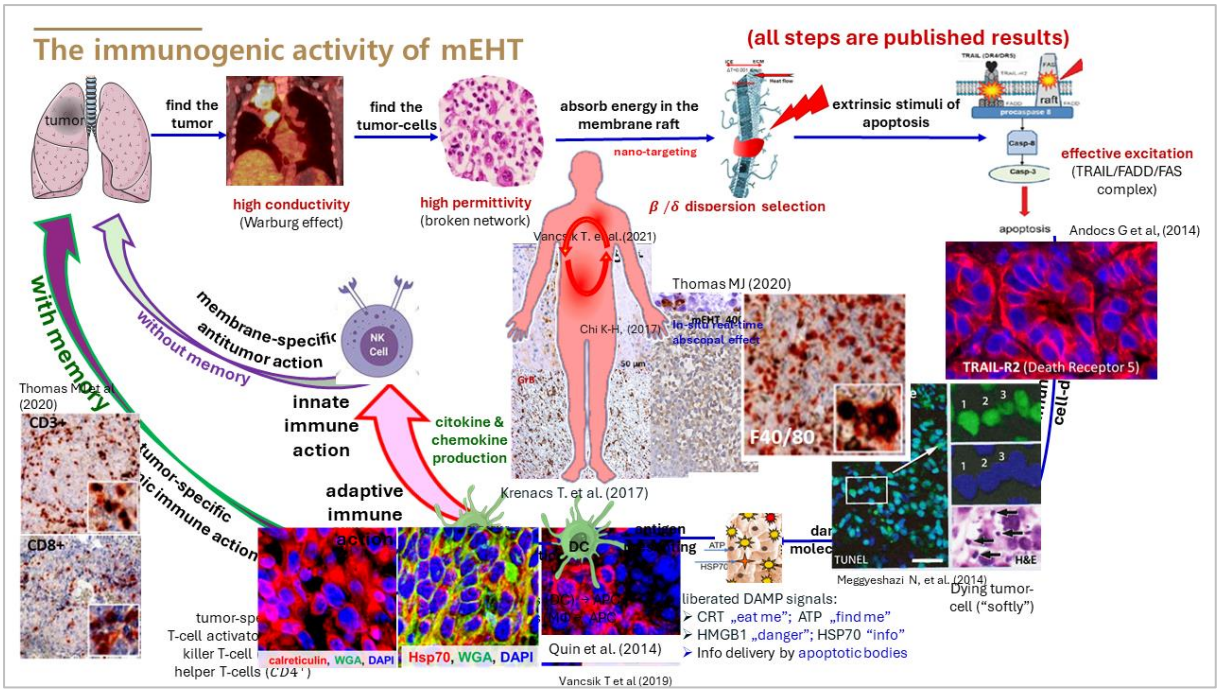
Institute: Department of Radiotion Oncology, Kosin University, College of Medicine & Kosin University Gospel Hospital.

Oncothermia applied as monotherapy

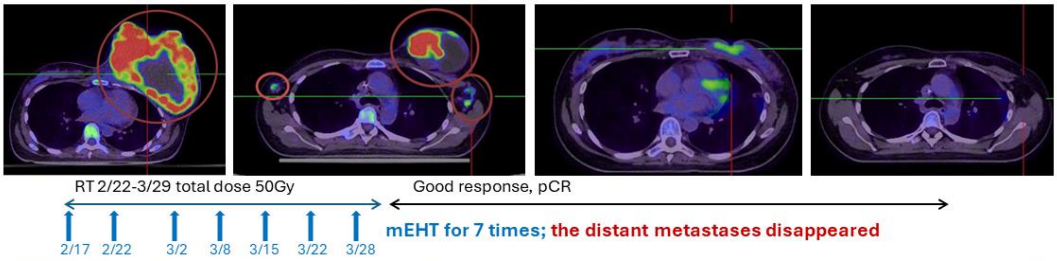
Published: 31st ICHO Oct. Budapest; 2012



The immunogenic activity of mEHT

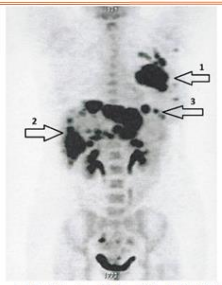


Marked local and distant response (immunogenic action)

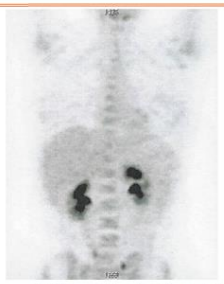


Chi M-S. et.al. (2021) Marked local and distant response of heavily treated breast cancer with cardiac metastases treated by combined low dose radiotherapy, low dose immunotherapy and hyperthermia, Ther Radiol Oncol 2021;5:17

Before therapy



After therapy



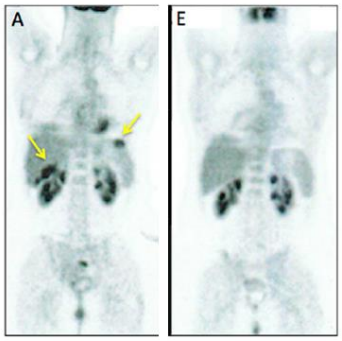
Whole body (18F)-FDG-PET-CT scan showing a 77 mm x 55 mm primary tumor in the left breast (arrow 1), multiple widespread liver masses (arrow 2), and an upper left nodular abdominal lesion (arrow 3). The metastases are so widespread, the use of arrows is nearly insufficient.

İyikesici MS, Slocum AK, Slocum A, Berkarda FB, Kalamian M, Sey\\fried TN; (2017) Efficacy of Metabolically Supported Chemotherapy Combined with Ketogenic Diet, Hyperthermia, and Hyperbaric Oxygen Therapy for Stage IV Triple-Negative Breast Cancer; Cureus 9(7): e1445. DOI 10.7759/cureus.1445

Ovarian cancer with liver and spleen metastasis

Ranieri G et al.; (2017) Bevacizumab-Based Chemotherapy Combined with Regional Deep Capacitive Hyperthermia in Metastatic Cancer Patients: A Pilot Study;, Int. J. Mol. Sci. 18: 1458;

Before therapy | After therapy



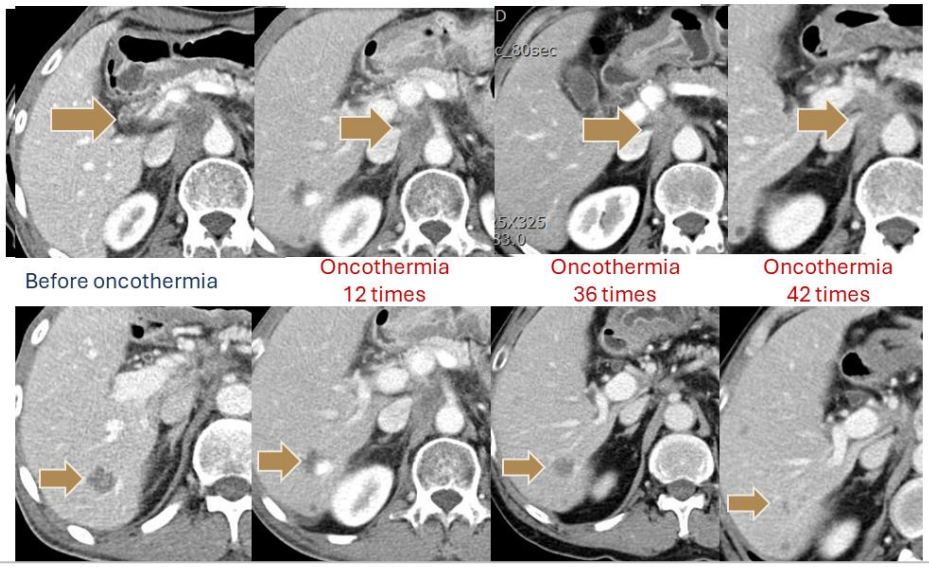
A 56-year-old female affected by ovarian cancer with liver and spleen metastasis, already treated with 12 cycles of Bevacizumab-based chemotherapy and 24 hyperthermia sessions

Metastatic esophageal cancer

Chi K-W et al.; (2018) Tumor-directed immunotherapy: combined radiotherapy and oncothermia, Conference of International Clinical Hyperthermia Society, Budapest, published in Oncothermia Journal, 2019.

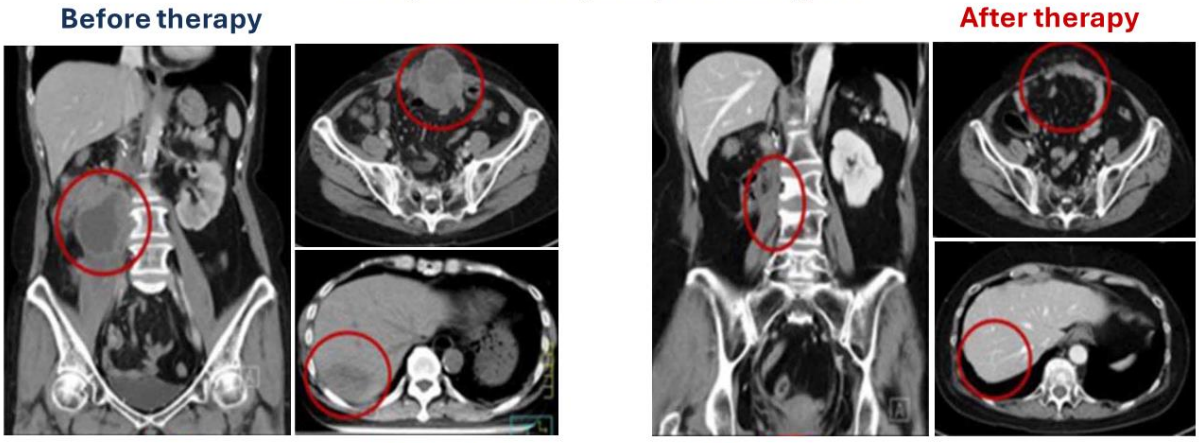
Pancreatic cancer and liver metastasis

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



Metastatic urothelial carcinoma with abscopal tumor effect on liver metastases

Chi et al. (2020) Putative abscopal effect in three patients treated by combined radiotherapy and modulated electrohyperthermia, Frontiers in Oncology, 10:254



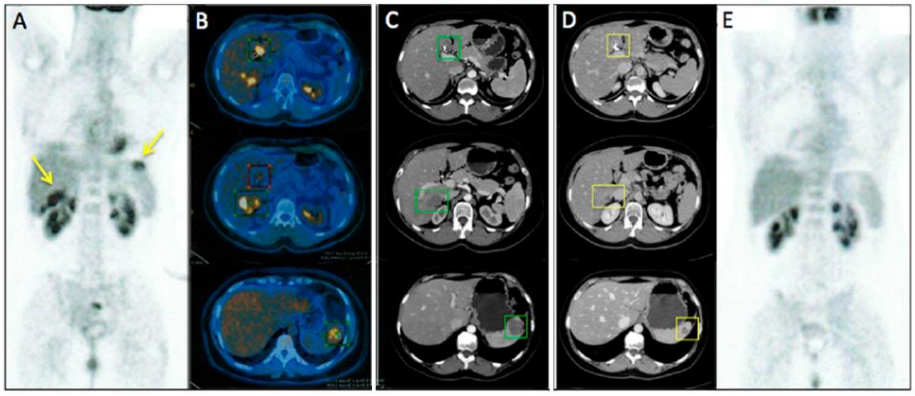
RT to abdomen mass 40Gy

+ 6 x Oncothermia

Abscopal effect

Ovarian cancer → liver + spleen metastasis
(Bevacizumab + mEHT)

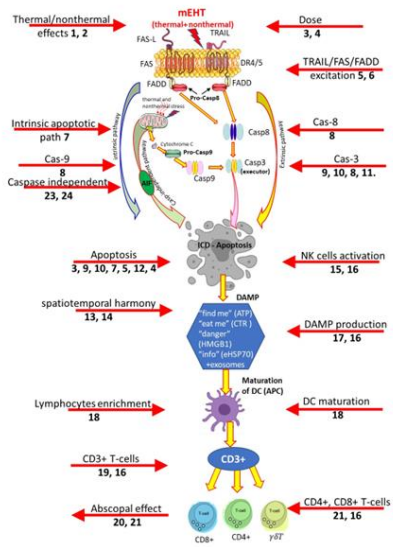
Before treatments (A,B) During therapy (C) After therapy (D,E)



Ranieri G et al.; (2017) Int. J. Mol. Sci. 18: 1458; doi:10.3390/ijms18071458

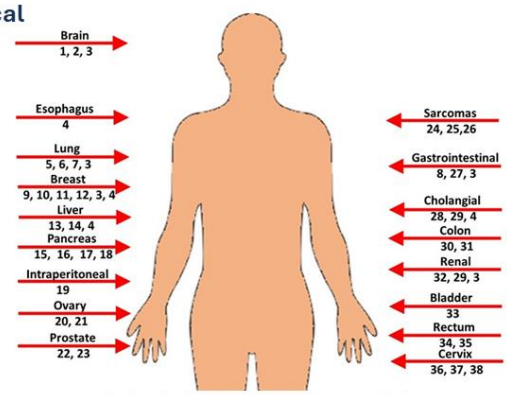
Publications

Basic molecular, preclinical



Some preclinical experiments with mEHT method. The numbers refer on the references: 1.= [42], 2.= [237], 3.= [238], 4.= [94], 5.= [202], 6.= [198], 7.= [239], 8.= [65], 9.= [207], 10.= [203], 11.= [240], 12.= [64], 13.= [207], 14.= [206], 15.= [204], 16.= [32], 17.= [205], 18.= [66], 19.= [241], 20.= [200], 21.= [33], 23.= [205].

Clinical



The clinical studies with mEHT. It contains various level of evidences including case reports and phase II/III trials. The **Oncotherm PubList** numbers denoting on the references.

1.= [243], **2.**= [244], **3.**= [245], **4.**= [246], **5.**= [247], **6.**= [248], **7.**= [249], **8.**= [250], **9.**= [251], **10.**= [252], **11.**= [253], **12.**= [254] **13.**= [255], **14.**= [256], **15.**= [257], **16.**= [258], **17.**= [259], **18.**= [260], **19.**= [261], **20.**= [262], **21.**= [263], **22.**= [264], **23.**= [265] **24.**= [266], **25.**= [267], **26.**= [268], **27.**= [269], **28.**= [270], **29.**= [254], **30.**= [271], **31.**= [272], **32.**= [273], **33.**= [274], **34.**= [275] **35.**= [276], **36.**= [277], **37.**= [278], **38.**= [20],


PHILIPPINES LAUNCHING EVENT
1ST JUNE 2024 | FAIRMONT MAKATI
Oncotherm
HYPERTHERMIC IMMUNO-ONCOLOGY
MATE
HUNGARIAN UNIVERSITY OF AGRICULTURE AND LIFE SCIENCES
Thanks for your kind attention
Prof.Szasz@gmail.com

Use of Radiofrequency Hyperthermia to improve cancer therapy

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Prof. Dr. Pirus Ghadjar

Senior Physician
Head of Hyperthermia Department, Charité – Universitätsmedizin Berlin, Berlin, Germany

Citation

Ghadjar, P. (2024) Use of Radiofrequency Hyperthermia to improve cancer therapy, Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/NiBrjACZnQc,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 21-36.
https://oncotherm.com/GhadjarP_2024_Use-of-radifrequency-hyperthermia_20240601

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Use of radiofrequency hyperthermia to improve cancer therapy

Department of Radiation Oncology | Charité – Campus Virchow Klinikum

Pirus Ghadjar | June 2024 | Manila

Charité at a glance

23,479 employees*	from 125 countries	**4** campuses	>100 departments and institutes
47 EU projects; of which, 28 ERC Grantees	137,825 inpatients and day case patients; **787,757** outpatients	5,671 researchers and physicians; 6,188 nurses; 321 professors	
3,293 beds**	4,985 births, **5,131** children born	12 times No. 1 Germany's best hospital	295 million euros in external funding
9,879 students	in **15** degree programs	871 trainees in **23** professions	**31** DFG collaborative research centers; 4 Clusters of Excellence

* Average annual number of employees across the Charité group of companies
** As per the State of Berlin's "Krankenhausplan 2020" (Health Care Plan 2020) of September 14, 2021 and of December 20, 2022

Last updated 12/31/2023

Rankings

- Newsweek — **One of the world's best hospitals**
- Focus — **Germany's best hospital**
- Times Higher Education — **Leading position among international hospital**
- Universum — **Most attractive employer for students**

2

Agenda/Contents

1. Completed randomized trials to improve radiation therapy
2. Potential of hyperthermia
3. Recent preclinical results of modulated electrohyperthermia
4. Running clinical trials at Charité
5. Future developments

- 1.3 million people die yearly due to cancer within the EU
- Treatment related toxicity worsens quality of life

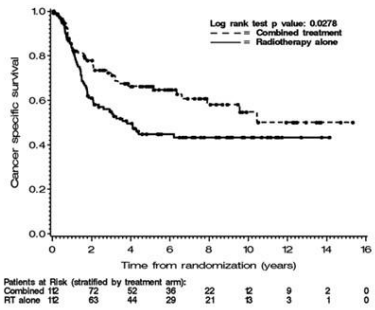
1

Completed randomized trials to improve radiation therapy

Addition of chemotherapy to radiation therapy

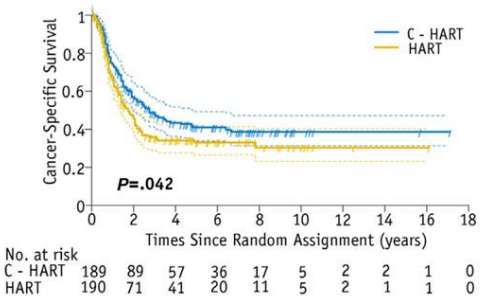
Two clinical trials in advanced head and neck cancer

SAKK 10/94 Trial



Ghadjar 2011

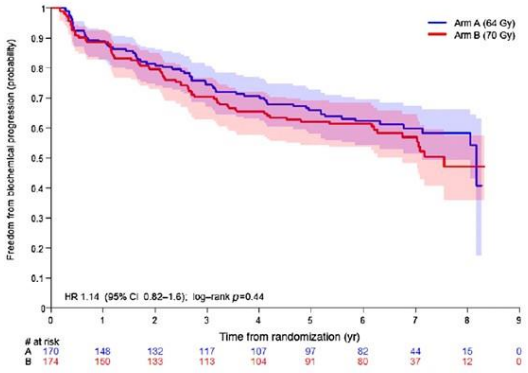
ARO 95/06 Trial



Budach & Ghadjar 2015

Dose intensified postprostatectomy salvage radiation therapy for prostate cancer

The SAKK 09/10 trial

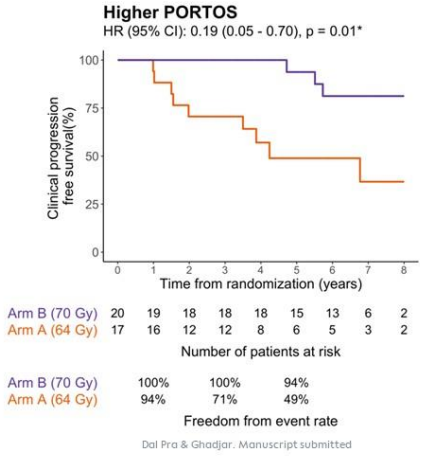


Ghadjar 2021

- Salvage RT 64 vs. 70 Gy
- No difference in FFBP
- Late rectal toxicity increased after 70 Gy

Personalized therapy

Translational analysis of the SAKK 09/10 trial



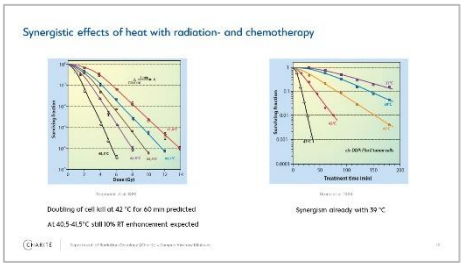
Dal Pra & Ghadjar. Manuscript submitted

- Gene signature PORTOS validated as biomarker for radiation therapy response
- Patients with higher PORTOS benefited from 70 Gy

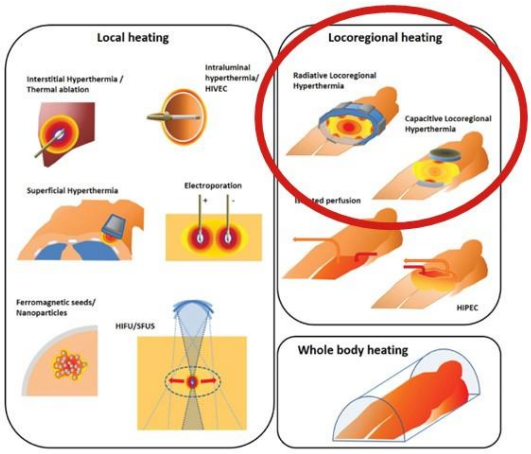
2

Potential of hyperthermia

CHARITÉ | Department of Radiation Oncology | Charité – Campus Virchow Klinikum 9



Available locoregional heating technology to treat advanced solid tumors



Kok et al. 2020

- Radiative and capacitive hyperthermia can be used for locoregional therapy of advanced solid tumors
- Oncotherm main vendor for capacitive hyperthermia (modulated electrohyperthermia, mEHT)

Hyperthermia is an effective Radiosensitizer

38 clinical trials including almost 3500 patients

different cancer entities, including breast, cervix, head and neck, rectum, bladder, esophagus, lung, melanoma, anal cancer

+ 15% increased complete response rate

Cancer Treatment Reviews 41 (2015) 742–753

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Anti-Tumour Treatment

Local hyperthermia combined with radiotherapy and-/or chemotherapy: Recent advances and promises for the future

N.R. Datta [a,*], S. Gómez Ordóñez [a], U.S. Gaipl [b], M.M. Paulides [c], H. Crezee [d], J. Gellermann [e], D. Marder [a], E. Puric [a], S. Bodis [a,f]

[a] Centre of Radiation Oncology, KSA-KSB, Kantonsspital Aarau, Aarau, Switzerland
[b] Department of Radiation Oncology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany
[c] Department of Radiation Oncology, Hyperthermia Unit, Erasmus MC Cancer Institute, Rotterdam, The Netherlands
[d] Department of Radiation Oncology, Academic Medical Centre, University of Amsterdam, The Netherlands
[e] Praxis/Zentrum für Strahlentherapie und Radioonkologie, Janusz-Korczak-Str. 12, 12627 Berlin, Germany
[f] Department of Radiation Oncology, University Hospital Zurich, Switzerland

Datta et al. 2015

Hyperthermia + RT improves survival in RCTs

Head and neck

● *Hyperthermia Original Contribution*

REPORT OF LONG-TERM FOLLOW-UP IN A RANDOMIZED TRIAL COMPARING RADIATION THERAPY AND RADIATION THERAPY METASTATIC LYMPHNODES IN STAGE IV HEA

RICCARDO VALDAGNI, M.D.*† AND MAURIZIO

Glioblastoma

● *Clinical Investigation*

SURVIVAL BENEFIT OF HYPERTHERMIA IN A PROSPECTIVE TRIAL OF BRACHYTHERAPY BOOST ± HYPERTHERMIA FOR GLIOBLASTOMA MULTIFORME

Sneed et al. 1998

Rectal cancer

Thermoradiotherapy of patients with locally advanced carcinoma of the rectum

Berdov et al. 1990

Cervical cancer

CLINICAL INVESTIGATION — Cervix

LONG-TERM IMPROVEMENT IN TREATMENT OUTCOME AFTER RADIOTHERAPY AND HYPERTHERMIA IN LOCOREGIONALLY ADVANCED CERVIX CANCER: AN EPHATE OF THE DUTCH DEEP HYPERTHERMIA TRIAL

Franckena et al. 2008

Hyperthermia enhances effectiveness of Chemotherapy

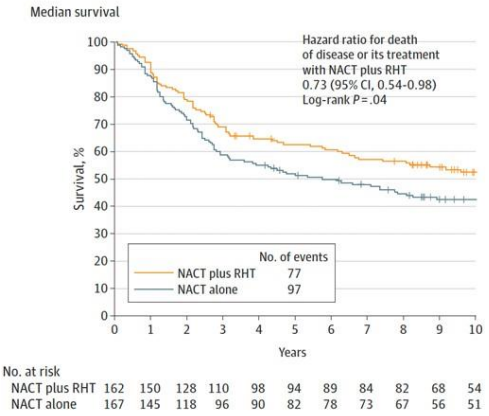
JAMA Oncology | Original Investigation

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

Rolf D. Issels, MD, PhD; Lars H. Lindner, MD; Jaap Verweij, MD; Rüdiger Wessalowski, MD; Peter Reichardt, MD; Peter Wust, MD; Pirus Ghadjar, MD; Peter Hohenberger, MD; Martin Angele, MD; Christoph Salat, MD; Zeljko Vujaskovic, MD; Soeren Daugaard, MD; Olav Mella, MD; Ulrich Mansmann, MD; Hans Roland Dürr, MD; Thomas Knösel, MD; Sultan Abdel-Rahman, PhSc; Michael Schmidt, MD; Wolfgang Heldemann, MD; Karl-Walter Jauch, MD; Claus Belka, MD; Alessandro Gronchi, MD; for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

Issels et al. 2018



No. at risk

NACT plus RHT	162	150	128	110	98	94	89	84	82	68	54
NACT alone	167	145	118	96	90	82	78	73	67	56	51

European Society of Hyperthermic Oncology (ESHO)

"To promote for the public benefit, fundamental and applied research in physics, engineering, biological and clinical sciences relating to the use of hyperthermia in cancer therapy"

Hans Crezee – President

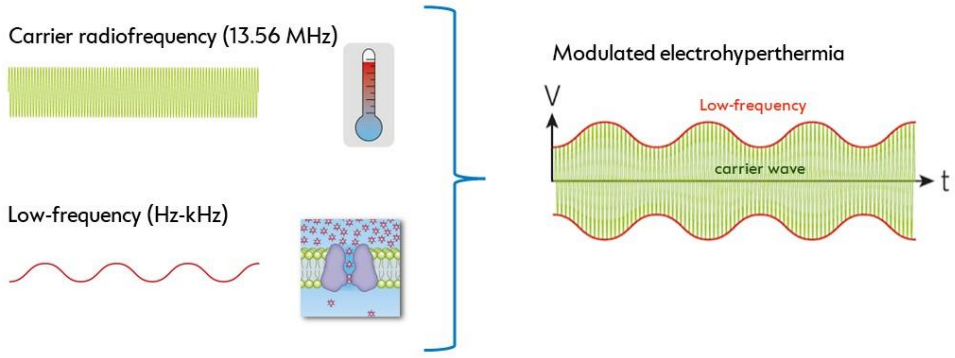
Pirus Ghadjar – Vice President

Lars Lindner – Vice President

3

Recent preclinical results of modulated electrohyperthermia

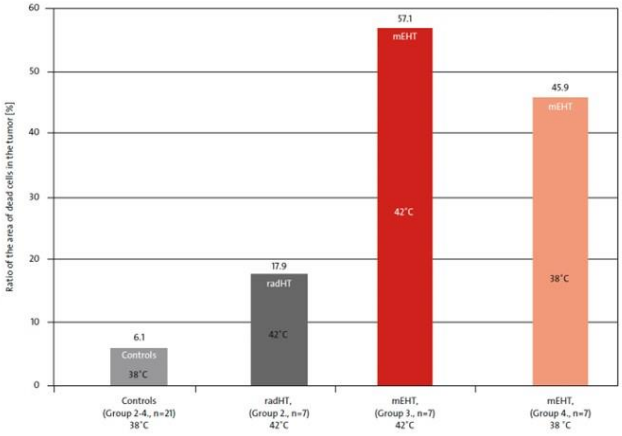
Modulated electrohyperthermia (mEHT)



Wust et al. 2022

Modulated electrohyperthermia (mEHT)

Evidence of "cellular anticancer effects"



Andocs et al. 2009

- *In vivo* xenograft mouse model (HT-29 cells)
- 30 min treatment
- Histological analysis of tumors
- Anticancer effects beyond direct temperature effects
- Temperature may not be the single target parameter but an important covariable in radiofrequency hyperthermia

Mode of action of mEHT

A decade of preclinical research

International Journal of Molecular Sciences

MDPI

Review

Modified Electro-Hyperthermia-Induced Tumor Damage Mechanisms Revealed in Cancer Models

Tibor Krenacs [1,*], Nora Meggyeshazi [1], Gertrud Forika [1], Eva Kiss [2], Peter Hamar [3], Tamas Szekely [1] and Tamas Vancsik [3]

[1] Department of Pathology and Experimental Cancer Research, Semmelweis University, H-1085 Budapest, Hungary; meggyeshazinora@gmail.com (N.M.); forika.gertrud@med.semmelweis-univ.hu (G.F.); szekely.tamas1@med.semmelweis-univ.hu (T.S.)
[2] Institute of Oncology at 1st Department of Internal Medicine, Semmelweis University, H-1083 Budapest, Hungary; kiss.eva@med.semmelweis-univ.hu
[3] Institute of Translational Medicine, Semmelweis University, H-1094 Budapest, Hungary; hamar.peter@med.semmelweis-univ.hu (P.H.); vancsik.tamas@med.semmelweis-univ.hu (T.V.)
* Correspondence: krenacs.tibor@med.semmelweis-univ.hu; Tel.: +36-208-259-700

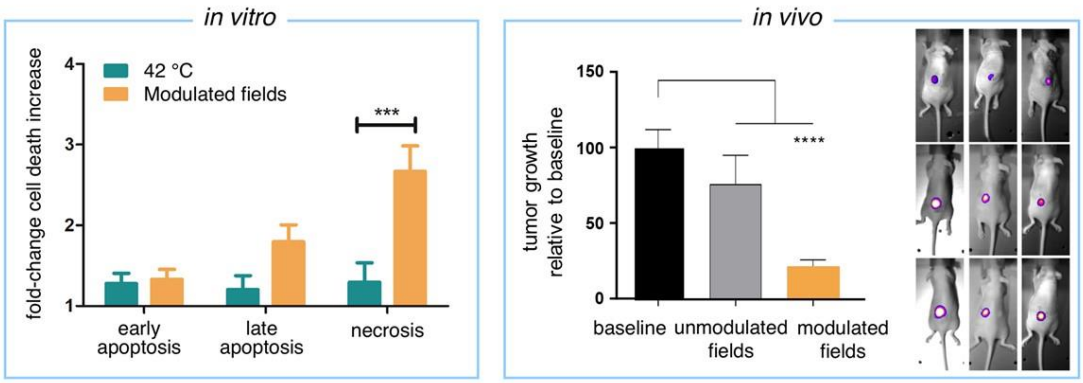
Received: 15 July 2020; Accepted: 24 August 2020; Published: 29 August 2020

- Induction of ion fluxes and ion disequilibrium
- Induction of DNA double-strand breaks
- Induction of immunogenic cell death
- Increased chemotherapy drug uptake
- Radiosensitizing by reduction of hypoxia

Krenacs et al. 2020

Benefit due to the use of amplitude modulation

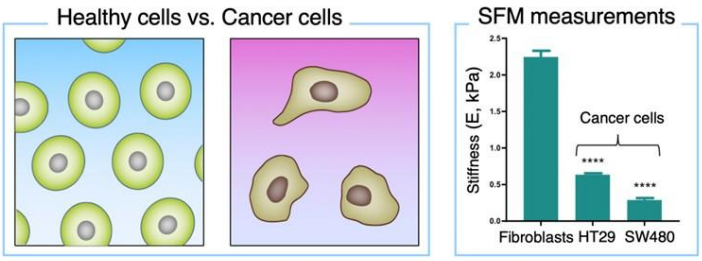
In vitro and *in vivo* evidence



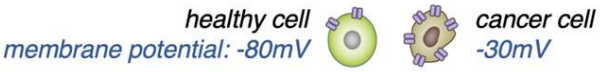
Wust et al. 2022

Potential for cancer cell specific therapy

Based on cell mechanics and ion channel expression



- Cancer cells are less stiff
- Elasticity of cancer cells increases with aggressiveness
- Ion channel expression is different in cancer cells resulting in a different membrane potential



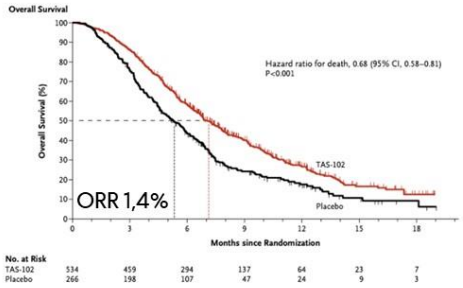
Wust et al. 2022

4 Running clinical trials at Charité

Live-RF Phase II trial

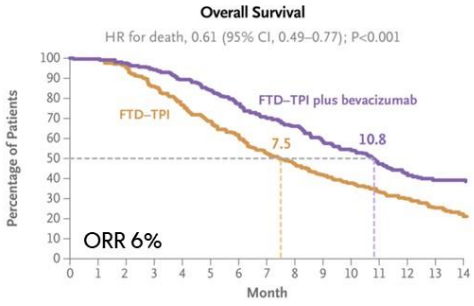
mEHT + chemotherapy in colorectal cancer patients with liver metastasis

Lonsurf (TAS-102)



Mayer et al. 2015

Lonsurf (TAS-102) + Bevacizumab



Prager et al. 2023

Live-RF Phase II trial

mEHT + chemotherapy in colorectal cancer patients with liver metastasis

- Null-Hypothesis: ORR 6% ; Alternative Hypothesis: 3 / 12 patients respond
- Primary endpoint: ORR
- Secondary endpoints: PFS, OS, Toxicity, QoL
- Sample size: 12 evaluable patients

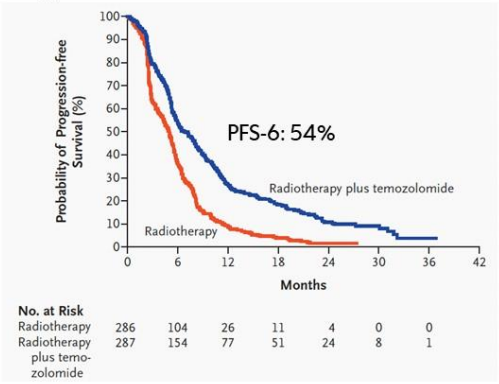
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
TAS-102																												
Bevacizumab																												
Recovery																												
mEHT		*		*					*		*					*		*					*		*			

ClinicalTrials.gov ID NCT05991102

Brain-RF Phase II trial

mEHT + radiochemotherapy in newly diagnosed glioblastoma

"Stupp" Protocol



Brain-RF Phase II trial

mEHT + radiochemotherapy in newly diagnosed glioblastoma

- Null-Hypothesis: PFS-6 is 54% ; Alternative Hypothesis: PFS-6 is 80%
- Primary endpoint: PFS
- Secondary endpoints: OS, Toxicity, QoL
- Sample size: 26 evaluable patients

Radiochemotherapy schedule:

Treatment week	1	2	3	4	5	6
Radiation therapy	■■■■■	■■■■■	■■■■■	■■■■■	■■■■■	■■■■■
Temozolomide	■■■■■■■	■■■■■■■	■■■■■■■	■■■■■■■	■■■■■■■	■■■■■■■
mEHT	■■■■■	■■■■■	■■■■■	■■■■■	■■■■■	■■■■■

Adjuvant Chemotherapy schedule:

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Temozolomide	■	■	■	■	■																							
Recovery						■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■
mEHT		■		■																								

ClinicalTrials.gov ID NCT06140875

5

Future developments

Future developments

1. Further pre-clinical research including RNA sequencing to further explore mode of action
2. Further preparatory trials (hepatocellular cancer among others)
3. Multicentric confirming Phase III trials


Let us improve the lives of patients with cancer

Clinical Evidences and Trials in Modulated Electro-Hyperthermia: Establishing Proof of Efficacy in Medical Oncology

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Prof. Dr. Magdolna Dank

Director
Cancer Center of Semmelweis University, Budapest, Hungary

Citation

Dank, M. (2024) Clinical Evidences and Trials in Modulated Electro-Hyperthermia: Establishing Proof of Efficacy in Medical Oncology, Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Oncothermia Journal 35, July 2024: 38-40.
https://oncotherm.com/DankM_2024_Clinical-evidences-and-trials-in-mEHT_20240601

Lifetime Probability of Developing Cancer and Cancer-Related Mortality

In Hungary, the lifetime probability of developing cancer has reached significant levels, with men having a 56.9% probability and women having a 51.9% probability. The cancer-related mortality rates are similarly high, at 27.6% for men and 21.7% for women. These rates are expected to rise due to demographic shifts, with an anticipated 18% increase in the population aged 60 and above by 2030. This demographic change will likely lead to a 35% increase in cancer incidence and a 30% rise in cancer deaths among individuals aged 65-85 years. These statistics underscore the urgent need for effective and accessible cancer treatments to manage the growing cancer burden.

Patient-Centric Clinical Trials

The shift towards patient-centric clinical trials emphasizes the importance of involving patients as active collaborators in their treatment processes. Key priorities in this approach include increasing the transparency of clinical trials, utilizing communication and wearable technologies for real-time monitoring, ensuring cybersecurity, automating clinical trial supplies, and supporting patient reintegration. These approaches leverage self-reported and real-world data to enhance the relevance and impact of clinical research.

Optimal Treatment for Various Cancers

Modulated electro-hyperthermia (mEHT) offers a promising treatment alternative for patients unable to undergo conventional therapies due to comorbidities, limitations of conventional curative procedures, or severe metastatic activity. The presentation discusses the effectiveness of mEHT in treating various cancers, including cervix cancer, glioblastoma, non-small cell lung cancer (NSCLC), breast cancer, castration-resistant prostate cancer (CRPC), Wilms tumor, sarcomas, gynecologic tumors, hepatobiliary cancers, and astrocytoma. For instance, in NSCLC, mEHT has demonstrated improved disease control rates and overall survival compared to traditional treatments.

Clinical and Economic Evaluation in Glioblastoma Multiforme (GBM)

A retrospective cohort study evaluated 54 patients with recurrent glioblastoma multiforme (GBM) treated with dose-dense temozolomide (ddTMZ) and mEHT, comparing them with five pooled cohorts (114 patients) treated with ddTMZ alone. The analysis demonstrated that ddTMZ combined with mEHT is cost-effective, yielding significant budget savings and a favorable cost-benefit profile over eight years. This combination significantly improved survival outcomes, suggesting that mEHT enhances the cost-benefit profile of ddTMZ regimens for recurrent GBM.

Prospective Randomized Clinical Trials

Future directions include conducting prospective randomized clinical trials to validate the efficacy of mEHT in early-stage adjuvant or neoadjuvant settings. One notable trial is the

Neoadjuvant Concomitant Modulated Electro-hyperthermia in HER2-negative Breast Cancer trial (NeoHTerMa). This trial investigates the benefits of integrating mEHT with standard neoadjuvant chemotherapy in HER2-negative breast cancer. The study is a randomized, open-label trial involving female patients aged 18 years or older with locally advanced, unilaterally localized HER2-negative breast cancer. The trial compares the effectiveness of a standard neoadjuvant chemotherapy regimen (wTAX +/- P + AC) with and without the addition of mEHT. The primary outcome measure is the percentage of tumor size reduction, while secondary outcomes include complete pathological response rates, treatment response patterns, and quality of life assessments. The study aims to enroll 120 patients and spans over 27 months. Details about this trial can be found online at ClinicalTrials.gov (NCT05889390).

Quality of Life (QoL) Data

Quality of life (QoL) is a crucial consideration in cancer treatment, and the presentation highlights various studies that demonstrate the positive impact of modulated electro-hyperthermia (mEHT) on QoL for patients with different types of cancer.

1. Glioblastoma Multiforme (GBM): In patients with recurrent GBM, the combination of dose-dense temozolomide (ddTMZ) and mEHT significantly improved survival outcomes compared to ddTMZ alone. This combination was not only effective in extending overall survival but also proved to be cost-effective, highlighting the dual benefit of mEHT in enhancing patient outcomes while reducing healthcare costs.
2. Non-Small Cell Lung Cancer (NSCLC): Studies in NSCLC patients have shown that mEHT enhances disease control rates and overall survival. Patients undergoing mEHT reported improved QoL, with significant relief from symptoms such as fatigue, dyspnea, and pain. These improvements underline the potential of mEHT to enhance both clinical outcomes and the daily lives of patients battling this aggressive cancer.
3. Breast Cancer: The ongoing Neoadjuvant Concomitant Modulated Electro-hyperthermia in HER2-negative Breast Cancer trial (NeoHTerMa) is particularly noteworthy. This trial explores the integration of mEHT with standard neoadjuvant chemotherapy in HER2-negative breast cancer patients. By comparing tumor size reduction and pathological response rates, the study aims to establish the efficacy of mEHT in improving treatment outcomes and QoL for breast cancer patients. The NeoHTerMa trial represents a significant step towards validating mEHT's role in breast cancer treatment and could pave the way for broader adoption of this therapy.

Take Home Messages

Modulated electro-hyperthermia (mEHT) is emerging as a powerful adjunct treatment for various types of cancer, offering several key benefits that make it a valuable addition to current oncology practices.

1. Cost-Effectiveness: mEHT is a cost-effective treatment option compared to traditional oncological treatments. Its ability to enhance the efficacy of existing therapies, such as chemotherapy and radiotherapy, without significantly increasing costs makes it an attractive option for healthcare systems looking to optimize resources while providing effective care.

2. Safety: mEHT has an excellent safety profile, with minimal adverse effects reported in clinical studies. This makes it a suitable option for patients who might not tolerate conventional treatments due to comorbidities or other health issues.

3. Versatility: mEHT can be used in combination with other cancer therapies or as a standalone treatment. Its versatility allows it to be integrated into various treatment regimens, providing flexibility for oncologists in tailoring personalized treatment plans for their patients.

4. Enhanced Outcomes: Clinical studies have shown that mEHT increases local response rates, extends overall survival, and improves the quality of life for patients. These outcomes are particularly significant for patients with aggressive or advanced cancers, where traditional treatments alone may not be sufficient.

- The NeoHTerMa trial, a breast neoadjuvant hyperthermia prospective randomized investigator-initiated non-sponsored audited trial, is another milestone for mEHT. This trial aims to validate the efficacy of mEHT in combination with standard neoadjuvant chemotherapy for HER2-negative breast cancer. The trial's results are expected to provide robust evidence supporting the integration of mEHT into mainstream cancer treatment protocols, further solidifying its role in oncology.

By integrating the latest clinical findings and practical experiences, this presentation underscores the significant benefits of mEHT in oncology. It advocates for the broader adoption of mEHT in clinical practice to improve patient outcomes and quality of life, offering hope and improved care for cancer patients worldwide.

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3. https://pubmed.ncbi.nlm.nih.gov/31216321/

4. https://pubmed.ncbi.nlm.nih.gov/29102988/

Advancements in Modulated Electro-Hyperthermia (mEHT): Applications in Translational Oncology and Future Perspectives

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Dr. habil. A. Marcell Szász

Head of Science
Division of Oncology, 1st Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

Citation

Szasz, A.M. (2024) Advancements in Modulated Electro-Hyperthermia (mEHT): Applications in Translational Oncology and Future Perspectives,
Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/riUp3wr-qGw,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 41-44.
https://oncotherm.com/SzaszAM_2024_Advancements-in-mEHT_20240601

Median Overall Survival and Disease Control Rate

Hyperthermia, when combined with traditional cancer treatments such as chemotherapy and radiation therapy, has been shown to improve median overall survival (OS) and disease control rates (DCR). Clinical studies have demonstrated that hyperthermia enhances the efficacy of these treatments by increasing tumor cell sensitivity to radiation and chemotherapy, improving drug delivery, and boosting the body's immune response against cancer cells. For instance, in breast cancer, hyperthermia combined with radiation therapy resulted in significantly higher response rates compared to radiation alone (Loboda et al., 2018). Similarly, in lung cancer, the combination of hyperthermia and chemotherapy improved progression-free survival and overall survival compared to chemotherapy alone (Ou et al., 2020). These findings highlight the potential of hyperthermia to significantly impact patient outcomes positively (Cleveland Clinic, 2024; Szasz AM, 2024).

Pancreatic Cancer and mEHT Studies

Pancreatic cancer, known for its poor prognosis, has seen promising results with the use of modulated electro-hyperthermia (mEHT). Clinical trials at the Semmelweis Cancer Center, including the NeoHTerMa trial, have shown that mEHT can improve median overall survival and progression-free survival in patients. These studies reported positive trends in overall survival, with Kaplan-Meier analysis indicating significant benefits for patients treated with mEHT. The research underscores mEHT's potential as a valuable adjunct therapy in managing pancreatic cancer, a notoriously difficult-to-treat malignancy (Dank Magy Onkol, 2023; Szasz AM, 2024).

Propensity Score Matching

Propensity score matching (PSM) is a statistical technique used to reduce bias in observational studies by ensuring that the groups being compared are similar in key characteristics. In the context of mEHT studies, PSM helps ensure that patients receiving hyperthermia treatment are comparable to those who do not, based on factors like age, sex, and concurrent treatments. This method improves the reliability of findings by isolating the effect of mEHT, providing more robust evidence of its efficacy in enhancing cancer treatment outcomes (Shen et al., 2019; Szasz AM, 2024).

Proteomic Analysis in Pancreatic Cancer

Proteomic analysis, which studies protein expressions in cells and tissues, provides crucial insights into the molecular mechanisms affected by treatments like mEHT. In pancreatic cancer, proteomic studies have shown that hyperthermia can significantly modulate protein expression involved in inflammatory responses, immune function, and cell adhesion. Treatment with mEHT can restore dysregulated pathways to normal levels, contributing to its therapeutic effects. These analyses are essential for understanding how hyperthermia impacts cancer biology at a molecular level and for identifying biomarkers that can predict treatment response, thus aiding in the personalization of cancer therapy (Pinto de Almeida et al., 2023; Szasz AM, 2024).

Quality of Life (QoL) Data

Quality of life is a critical measure in cancer treatment, reflecting the overall well-being of patients. Studies on mEHT have consistently shown significant improvements in QoL across various cancer types:

1. High-Mortality Cancers: mEHT enhances QoL for brain, pancreas, lung, and liver cancers.
2. Phase I Safety Study in NSCLC: In a study involving 35 patients with stage IV non-small cell lung cancer, mEHT combined with chemotherapy led to rare temporary adverse effects (fatigue, nausea, vomiting, diarrhea, headache), significant physical status improvement after four weeks, and significant symptom relief (fatigue, dyspnea, insomnia, appetite loss, diarrhea) (Lee et al., 2023; Szasz AM, 2024).
3. Phase II Study in Peritoneal Carcinomatosis: This study reported significant QoL improvements in all functional and symptom categories compared to the control group. mEHT was favored over intraperitoneal chemoinfusion for overall QoL improvement (32.3% vs. 49.2%) (Lee et al., 2023; Szasz AM, 2024).
4. Pain Relief in Lung Cancer: Pain initially increased post-mEHT but decreased significantly over time, with a 90% improvement (Lee et al., 2023; Szasz AM, 2024).
5. Combination with Lower Radiation Doses in Rectal Cancer: Fewer adverse effects and higher QoL were observed with this combination (Lee et al., 2023; Szasz AM, 2024).
6. Phase III Randomized Controlled Study in Cervical Cancer: This study showed decreased toxicity, improved QoL, significant cognitive function improvement at six weeks post-treatment, increased social and emotional functions at three months, and significant reduction in fatigue and pain (Minnaar et al., 2020; Szasz AM, 2024).

Take Home Messages

Modulated electro-hyperthermia (mEHT) is an effective and safe adjunct treatment for various cancers, offering several key benefits:

- Cost-Effectiveness: mEHT is cheaper compared to traditional medical oncological treatments.
- Safety: It has an excellent safety profile with minimal adverse effects.
- Versatility: mEHT can be used in combination with other therapies or as a standalone treatment.
- Enhanced Outcomes: It increases local response rates, extends overall survival, and improves the quality of life for patients.

By integrating the latest clinical findings and experiences, this presentation highlights the significant benefits of mEHT in oncology, advocating for its broader adoption in clinical practice to improve patient outcomes and quality of life (Szasz AM, 2024).

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5. Minnaar, C. A., et al. (2020). Randomized Controlled Study in Cervical Cancer. Int J Hyperther.
6. Ou, Y., et al. (2020). mEHT and vitamin C in lung cancer. World J Clin Oncol.
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Clinical trials in Glioblastoma

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Dr. Paul Mulholland

Consultant in Medical Oncology and Honorary Associate Professor
National Hospital for Neurology and Neurosurgery, University College London, United Kingdom

Citation

Mulholland, P. (2024) Clinical trials in Glioblastoma,
Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/asHdJtezmjc,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 45-54.
https://oncotherm.com/MulhollandP_2024_Clinical-trials-in-Glioblastoma_20240601

Clinical Trials in Glioblastoma

Professor Paul Mulholland PhD, FRCP(UK)
Honorary UCL Associate Professor
Consultant in medical oncology

UCL and UCLH

1

1

2

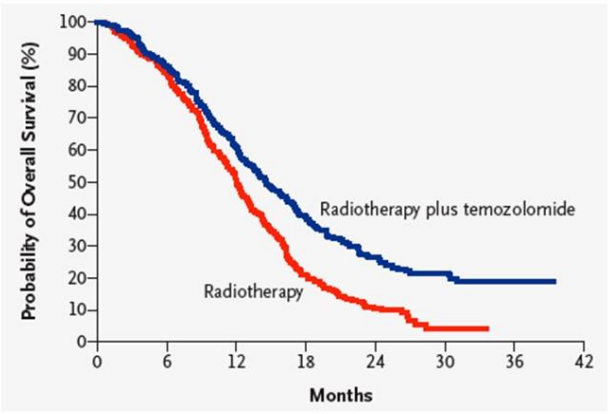
1 UCLH
2 UCH Macmillan Cancer Centre
3 University College London, Cancer Institute

3

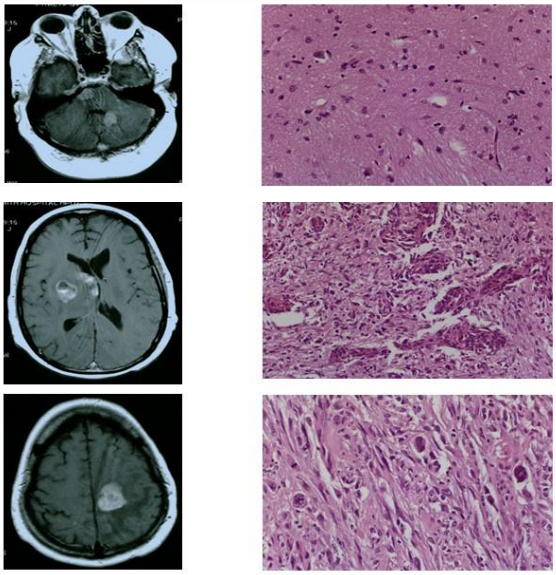
Research Overview

- Perspective on glioblastoma
- Past clinical trials
- Clinical trials in development
- Research group field of activity

MRI diagnosis → Surgery → Chemo-radiation → Adjuvant treatment → Recurrent disease

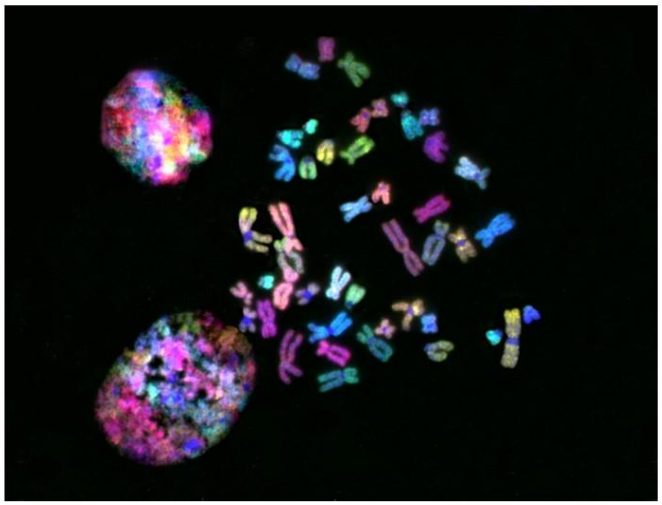


Glioblastoma Treatment Pathway and Clinical Trials



Tumour heterogeneity

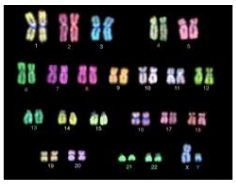
Chromosomal Architecture



Tania Jones
Prof Sheer's Laboratory

Considerations when Treating Glioblastoma

Normal Male

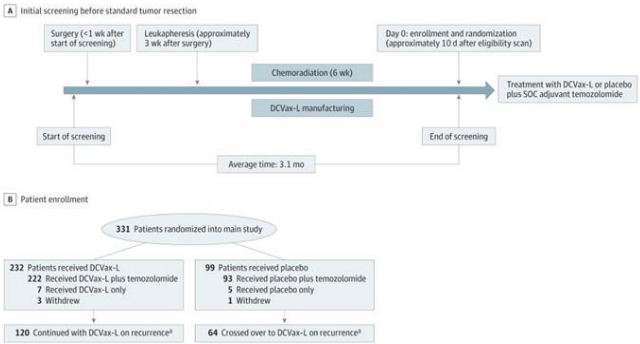


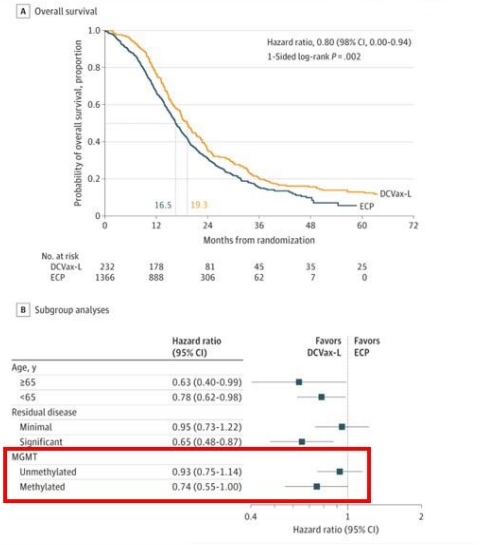
Glioblastoma

Mulholland et al. Cell Cycle 2005

- Resistant to most conventional treatment options, including chemotherapy, radiotherapy and molecularly targeted therapy.
- 'Promising' phase II results failing to be translated into encouraging phase III.
- Poor trial design, for example using historical data and not appropriate controls.
- The biology of glioblastoma is still not well understood.
- Improving our understanding of the molecular mechanisms driving this aggressive disease will allow development of more effective treatment.

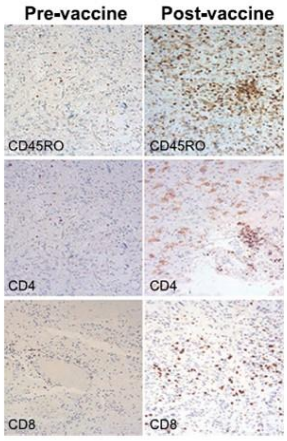
Immunotheray: DCVax-L





- DC vaccine added to SOC after chemoradiation
- Compared to matched historical controls
- Signal of activity in the MGMT methylated subgroup
- Licencing application submitted in the UK

Liau et al. JAMA Oncol, 2022



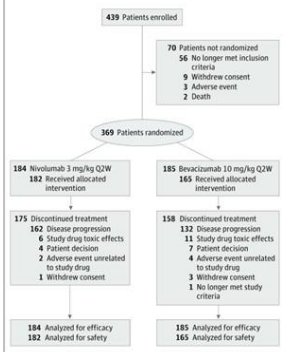
Infiltration of T cells into Glioblastoma tumors is observed in patients treated with DCVax®-L

Both CD4 and CD8 T cells are seen

T Cells Can Cross the Blood Brain Barrier; T Cells Infiltrate Glioblastoma Tumors After DCVax-L

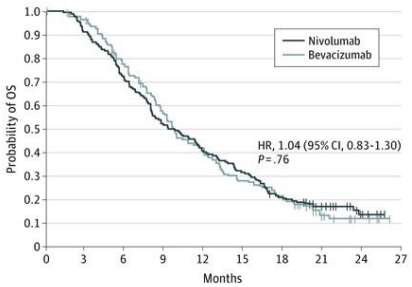
L. Liau et al.

Immunotherapy CheckMate 143



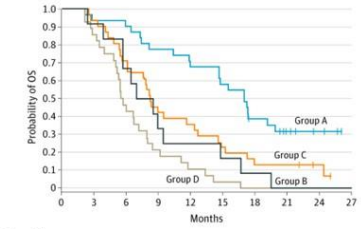
A Probability of OS by intervention

Intervention	Events, No.	Median OS (95% CI), months	OS Rate (95% CI), %		
			6 Months	12 Months	18 Months
Nivolumab	154	9.8 (8.2-11.8)	72.3 (65.2-78.2)	41.8 (34.7-48.8)	21.7 (16.1-27.9)
Bevacizumab	147	10.0 (9.0-11.8)	78.2 (71.2-83.6)	42.0 (34.6-49.3)	21.6 (15.8-28.0)



B Nivolumab

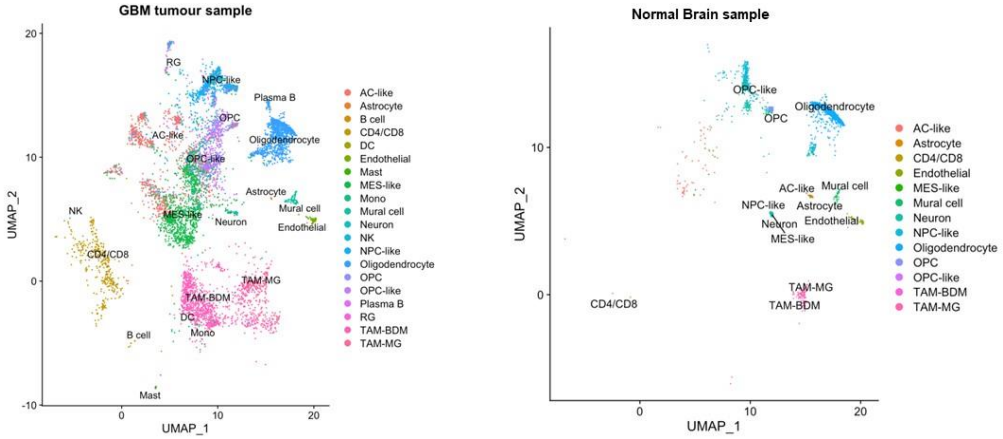
Group A: *MGMT* methylated; no baseline corticosteroid use	21/31	17.0 (11.9-19.8)



- Anti-PD-1 monotherapy compared to Bevacizumab
- Signal of activity in MGMT methylated with no baseline corticosteroid

Reardon et al. JAMA Oncol, 2020

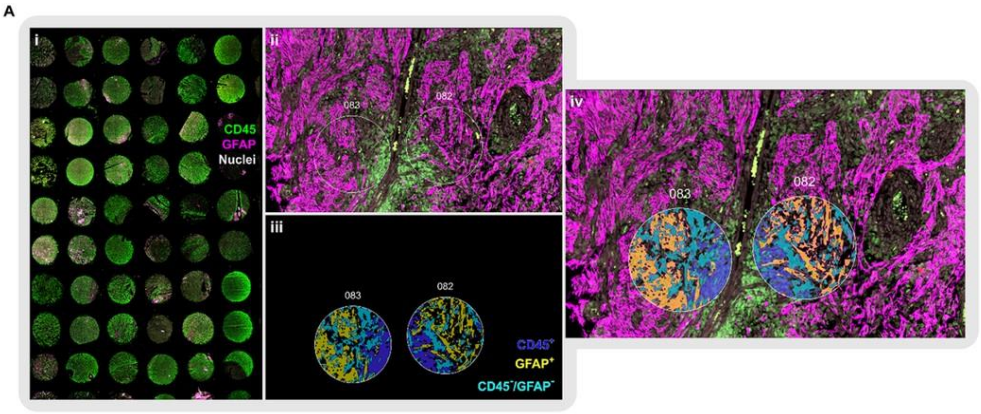
Lab – Correlative studies



- Single-cell analysis allows to characterize the tumour cells and surrounding cells complexity
- UMAP artificially plots the composition of identified cell subtype

Unpublished, Wang et al.,Cancer Cell, 2021; Ruiz-Moreno et al., bioRxiv, 2022

Lab – Correlative studies



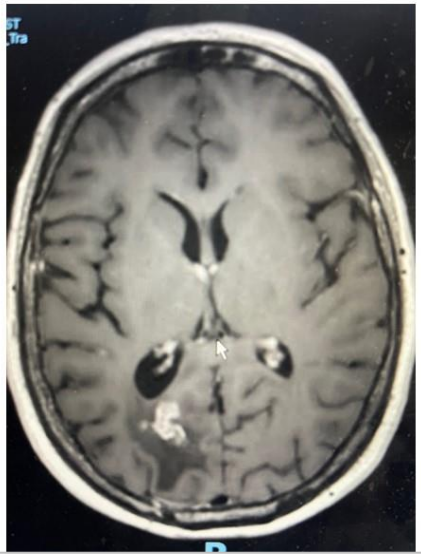
- Spatial-transcriptomics allows the same analysis genomic analysis while preserving the tissue architecture
- Enables to identify location-specific cell subtype interactions

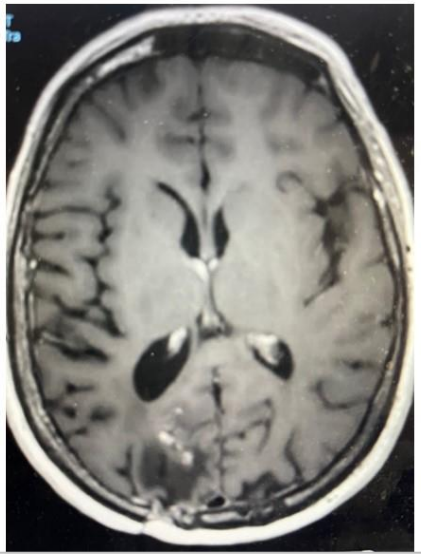
Bonnett et al., Cancer Res Commun, 2023

Modulated electro-hyperthermia: My experience

Started using the device in January 2023
Treated 27 patients so far

Seeing reductions in tumour volume





CITADEL-123

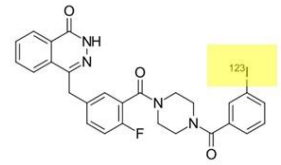
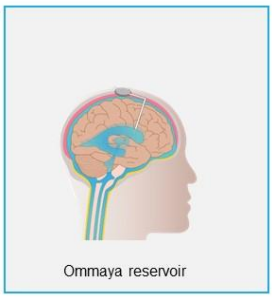


Figure 1 **Chemical structure of ^{123}I-ATT001**



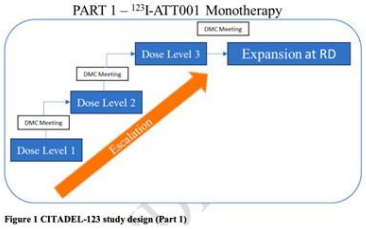


Figure 1 CITADEL-123 study design (Part 1)

A Phase I clinical trial to assess the activity of I-123 Poly Adenosine Diphosphate Ribose Polymerase I inhibitor (123I-ATT001) directly administered in subjects with relapsed glioblastoma.

Clinical Trials in Glioblastoma

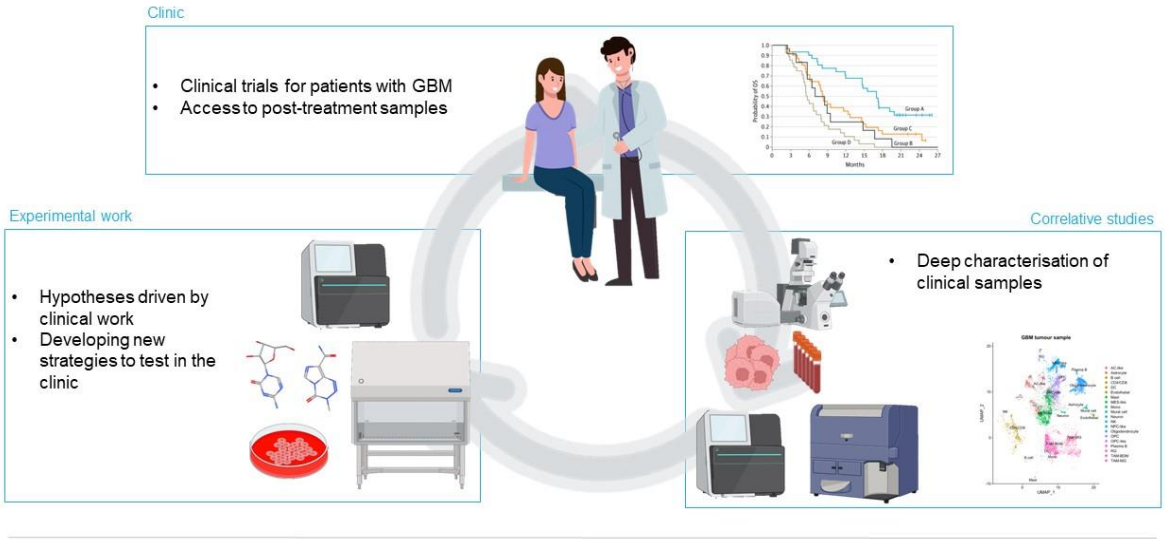
1. Feasibility Phase II study of Standard of Electro-hyperthermia plus Standard of Care

2. Feasibility Phase II study Checkpoint inhibitor prior to Standard of Care in Glioblastoma

3. Following the feasibility studies: Phase II study of Checkpoint inhibitor plus Electro-hyperthermia

4. Citadel -123 Plus Electro-hyperthermia

UCL Glioblastoma Research Group



Thank you for your time

Glioblastoma is very challenging to treat
Targeted therapies not been effective
There has been benefit seen with immunotherapy

We need to systematically test agents in clinical trials and we need to explore the full potential of electro-hyperthermia

Hyperthermia as an immune system activator

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Prof. Dr. Elisabeth Arrojo

Radiation Oncologist
University Hospital Marqués de Valdecilla, Santander, Spain

Medical Director
Medical Institute of Advanced Oncology, Madrid, Spain

Citation

Arrojo, E. (2024) Hyperthermia as an immune system activator,
Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/qEYuvFuFpzA,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 55-99.
https://oncotherm.com/ArrojoE_2024_Hyperthermia-as-an-immune-system-activator_20240601

Philippines, June 1st 2024

Hyperthermia and immune system

Prof. Elisabeth Arrojo Álvarez, MD, PhD

Radiation oncologist

Founder & Medical director of INMOA (Medical Institute of advanced oncology, Madrid and Bilbao, Spain)

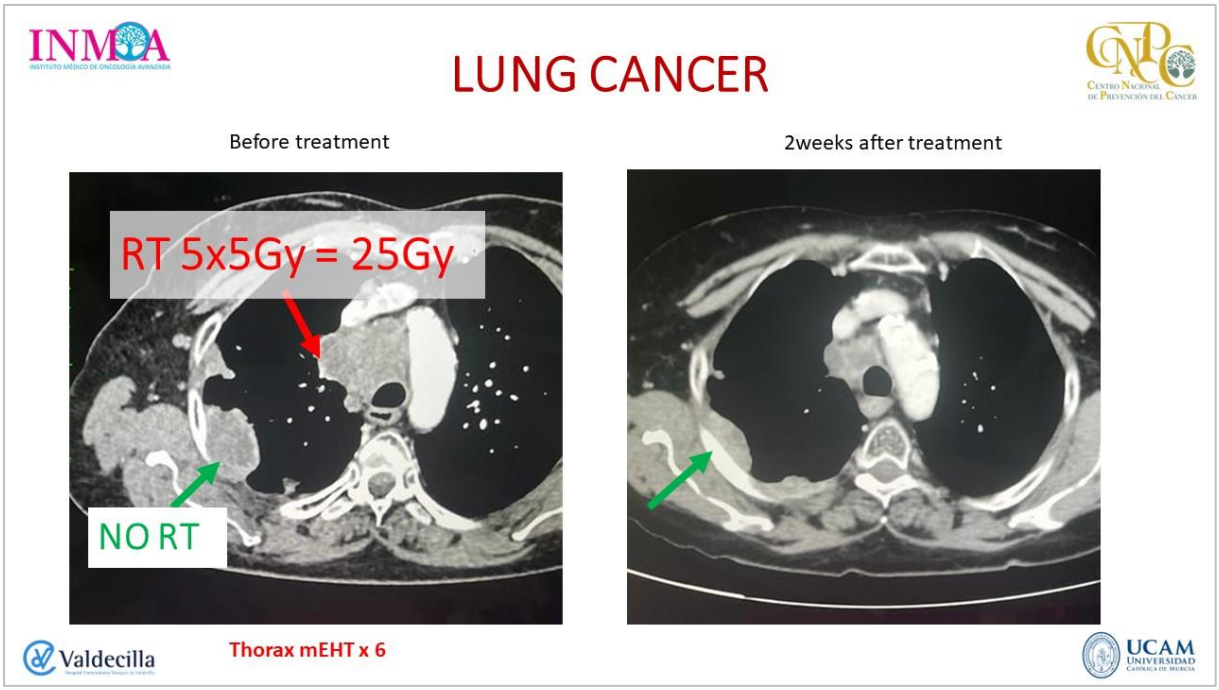
Founder & Director of the National Cancer Prevention Center (Spain)

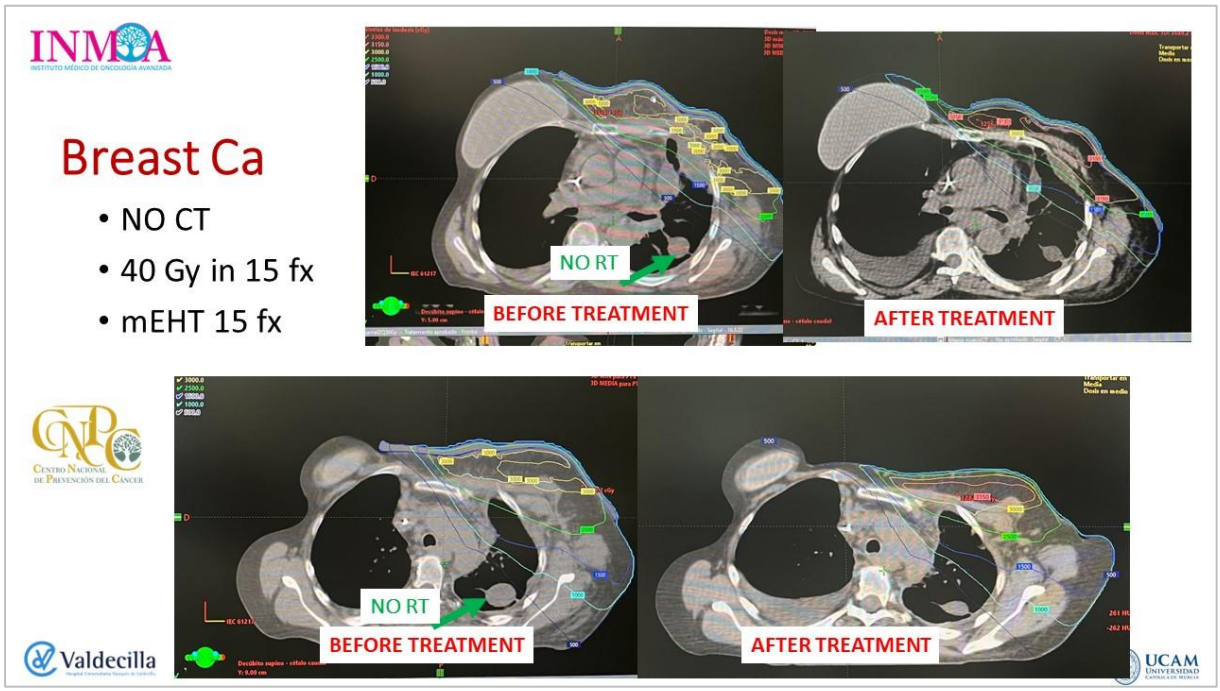
Chair professor in Oncological hyperterhmia at Catholic University of Murcia (UCAM)

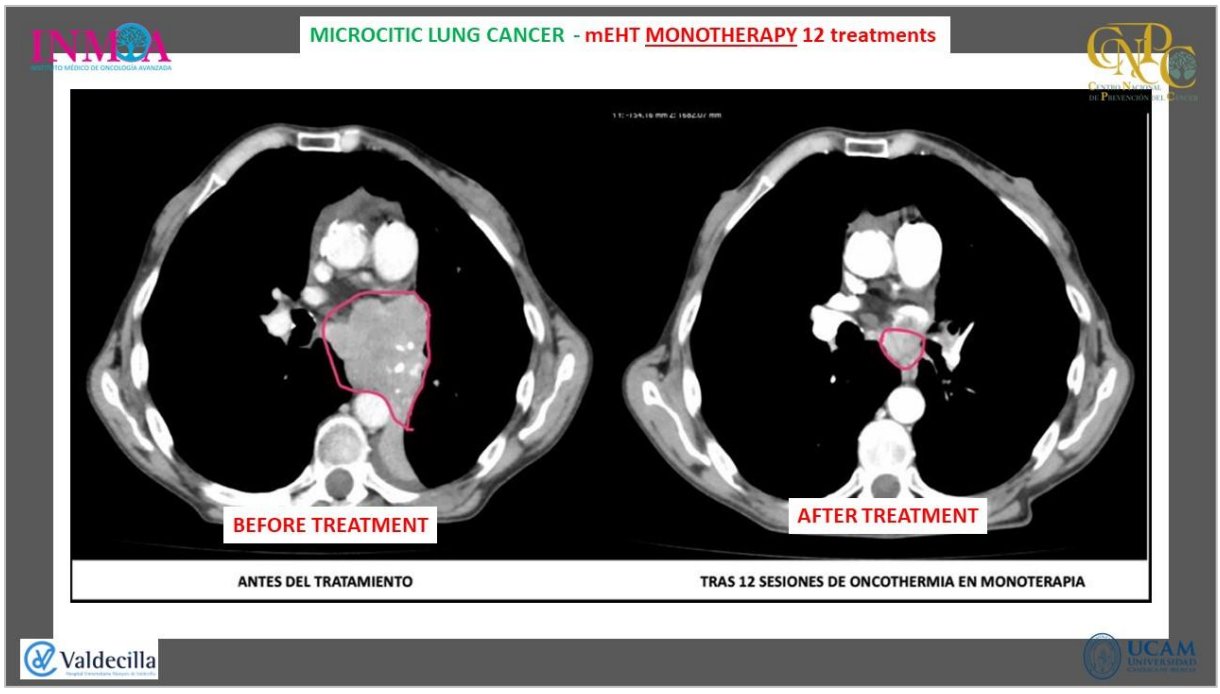
Radiation oncologist at University Hospital Marqués de Valdecilla, Santander, Spain

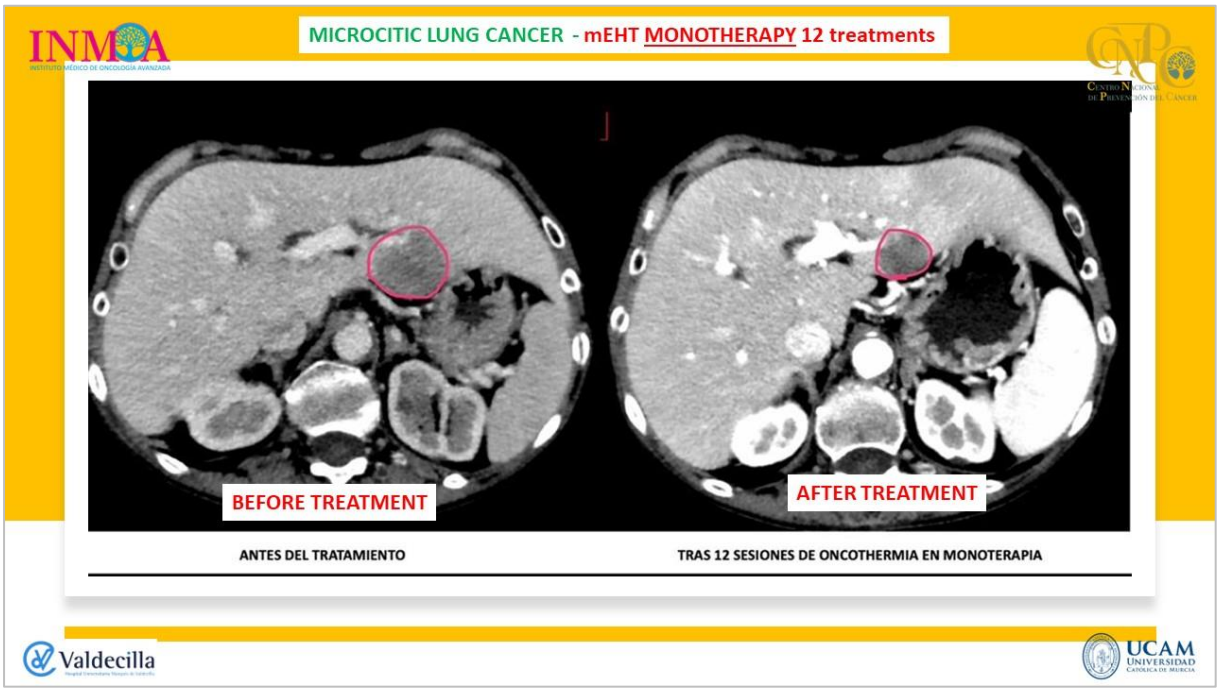
(responsable for the hyperthermia research)

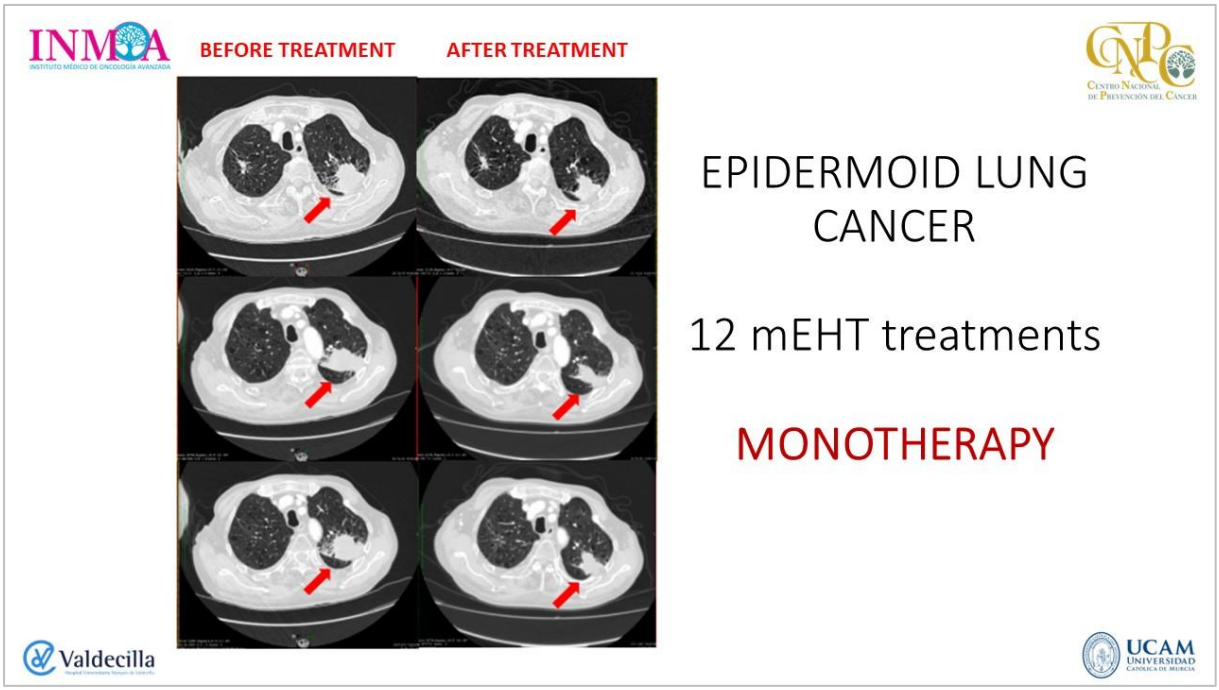

INMOA
Experiences to think about...
Valdecilla
UCAM


INMOA
LUNG CANCER
Before treatment
2weeks after treatment
RT 5x5Gy = 25Gy
NO RT
Thorax mEHT x 6
Valdecilla
UCAM


Breast Ca
• NO CT
• 40 Gy in 15 fx
• mEHT 15 fx
NO RT
BEFORE TREATMENT
AFTER TREATMENT
NO RT
BEFORE TREATMENT
AFTER TREATMENT

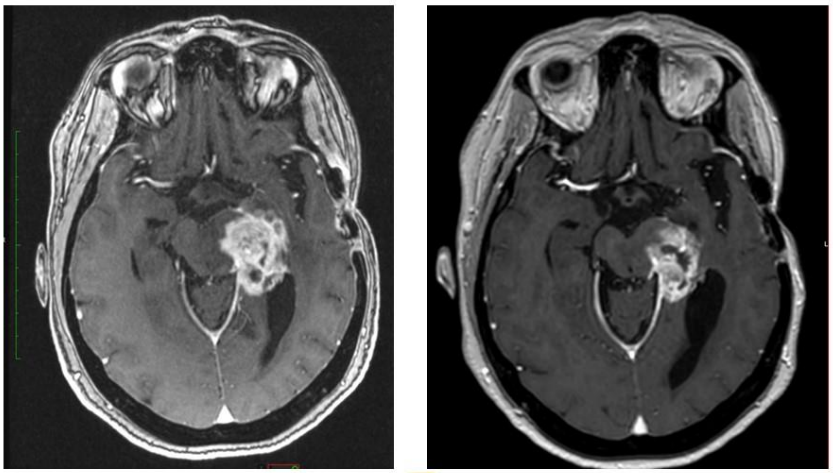

MICROCITIC LUNG CANCER - mEHT MONOTHERAPY 12 treatments
BEFORE TREATMENT
AFTER TREATMENT
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA


MICROCITIC LUNG CANCER - mEHT MONOTHERAPY 12 treatments
BEFORE TREATMENT
AFTER TREATMENT
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA
Valdecilla
UCAM


BEFORE TREATMENT
AFTER TREATMENT
EPIDERMOID LUNG CANCER
12 mEHT treatments
MONOTHERAPY
Valdecilla
UCAM

mEHT MONOTHERAPY

43 yo Female with "IDH –" GBM

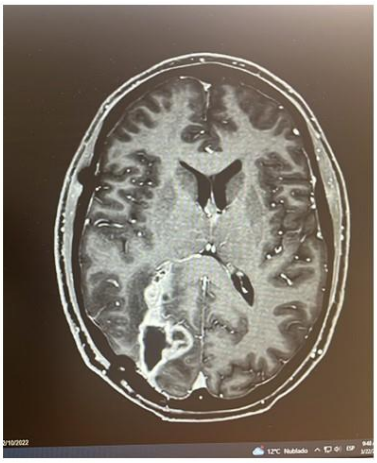


MRI 1 month after mEHT treatment

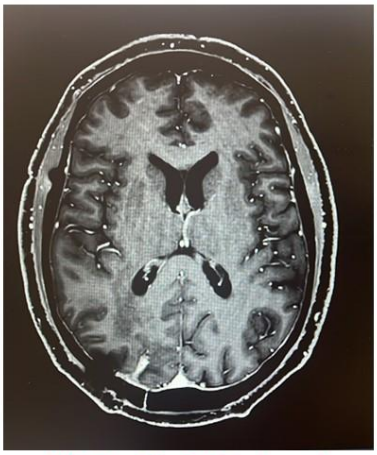
mEHT MONOTHERAPY

52 yo male, GBM IDH negative

Progressed 1 month after standard CT-RT



MRI after progression



MRI after 18 mEHT treatments

frontiers in Oncology

ORIGINAL RESEARCH
published: 24 March 2020
doi: 10.3389/fonc.2020.00376

Potentiation of the Abscopal Effect by Modulated Electro-Hyperthermia in Locally Advanced Cervical Cancer Patients

*Carrie Anne Minnaar[1], Jeffrey Allan Kotzen[2], Olusegun Akinwale Ayeni[3], Mboyo-Di-Tamba Vangu[3] and Ans Baeyens[1,4]**

[1] Radiobiology, Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa, [2] Radiation Oncology, Wits Donald Gordon Medical Centre, Johannesburg, South Africa, [3] Nuclear Medicine, Department of Radiation Sciences, University of the Witwatersrand, Johannesburg, South Africa, [4] Radiobiology, Department of Human Structure and Repair, Ghent University, Ghent, Belgium

OPEN ACCESS

Edited by:
Mary Helen Barcellos-Hoff, University of California, San Francisco, United States

Reviewed by:

Background: A Phase III randomized controlled trial investigating the addition of modulated electro-hyperthermia (mEHT) to chemoradiotherapy for locally advanced cervical cancer patients is being conducted in South Africa (Human Research Ethics Committee approval: M1704133; ClincialTrials.gov ID: NCT03332069). Two hundred and ten participants were randomized and 202 participants were eligible for six month local disease control evaluation. Screening ^{18}F-FDG PET/CT scans were conducted and

randomised controlled Phase III trial involving 210 participants evaluating chemoradiotherapy (CRT)

- **Abscopal effect**: **systemic response to RT** in which **non-irradiated lesions respond after irradiation of the primary** treatment site.
  - Immune system activation by radiotherapy.
  - Very low frequency.

Cervical Cancer - Phase III trial

- **Results:**
  - **Abscopal response mEHT group 24.1%** (13 of 54) **vs 5.6%** (3 of 54) control group (p=0.013).
  - No significant difference between VIH + and -.
  - Multivariant analysis not significant:
    - Age
    - Cispatin
    - Days to PET-CT
    - Total RT

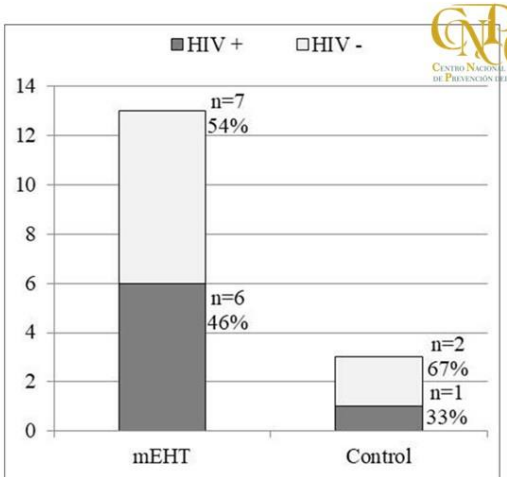
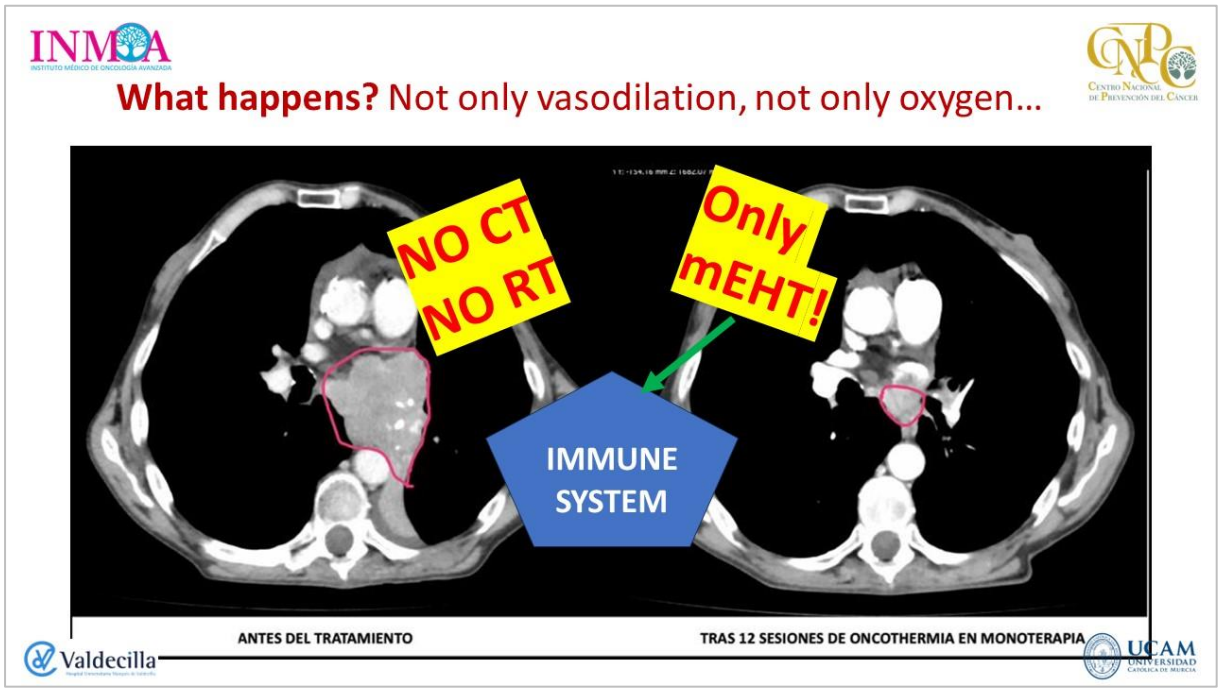
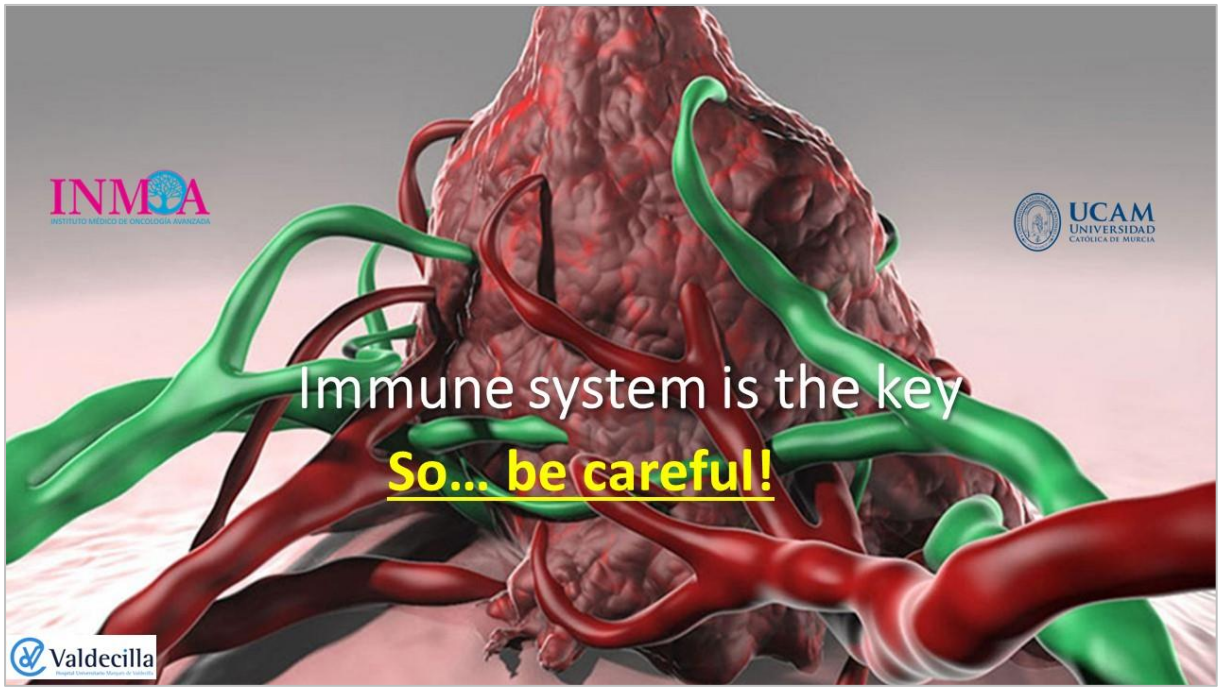
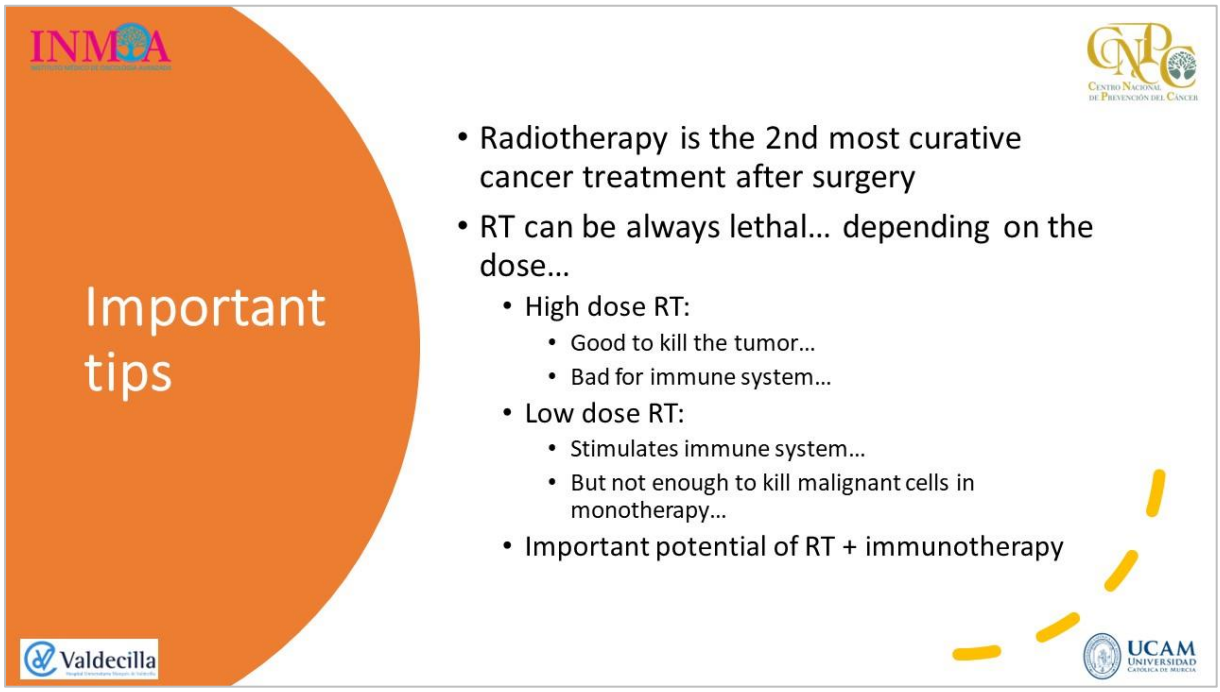
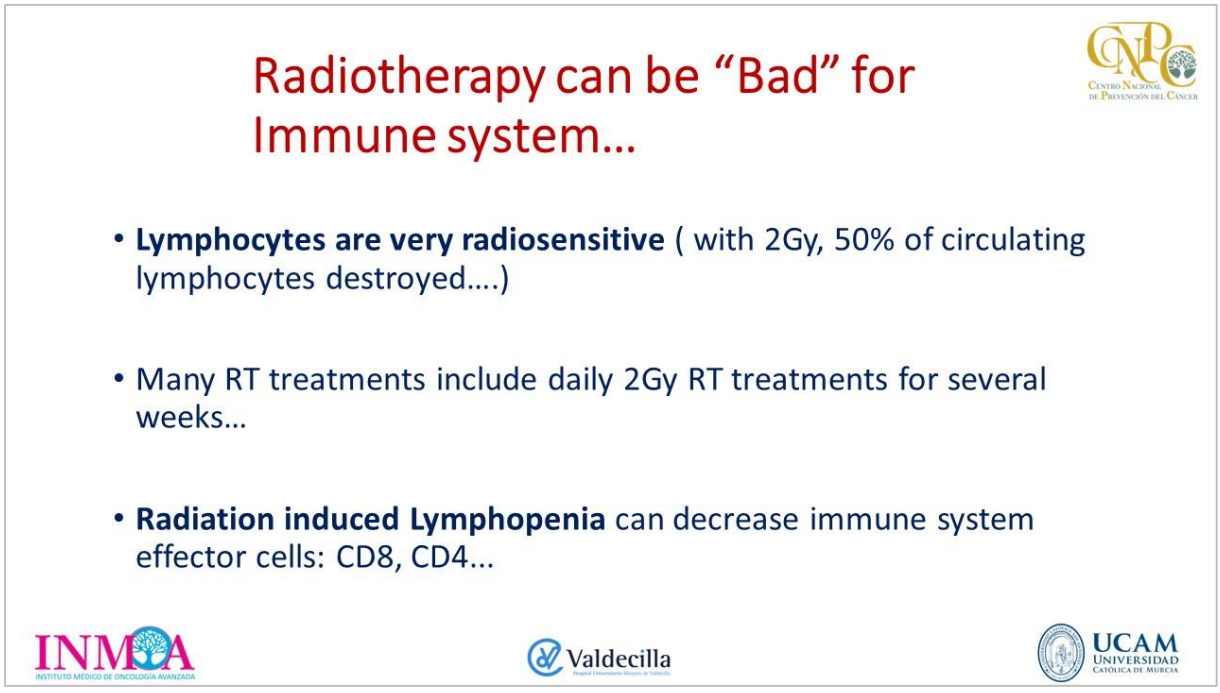


FIGURE 2 | Frequency of observed abscopal effect in HIV-positive and HIV-negative participants in each treatment group. A significant difference between the frequency of abscopal effect was noted between the mEHT Group (13 out of 54[24.1%]) and the Control Group (3 out of 54 [5.6%]) (p = 0.013). There was no significant difference in frequency of the observed abscopal between the HIV-positive and HIV-negative participants. mEHT, Modulated Electro-Hyperthermia; HIV, Human Immunodeficiency Virus.

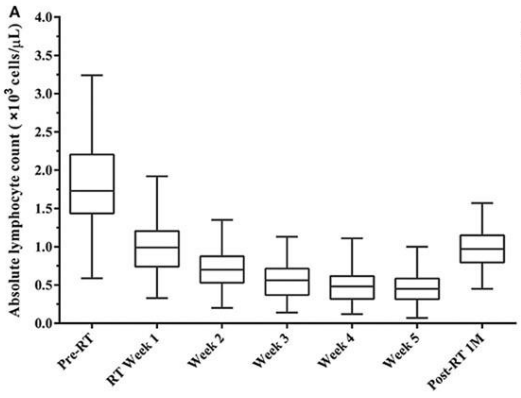

What happens? Not only vasodilation, not only oxygen…
NO CT
NO RT
Only
mEHT!
IMMUNE
SYSTEM
ANTES DEL TRATAMIENTO
TRAS 12 SESIONES DE ONCOTHERMIA EN MONOTERAPIA


Immune system is the key
So… be careful!


INMOA
Important tips
• Radiotherapy is the 2nd most curative cancer treatment after surgery
• RT can be always lethal… depending on the dose…
• High dose RT:
• Good to kill the tumor…
• Bad for immune system…
• Low dose RT:
• Stimulates immune system…
• But not enough to kill malignant cells in monotherapy…
• Important potential of RT + immunotherapy
Valdecilla
UCAM

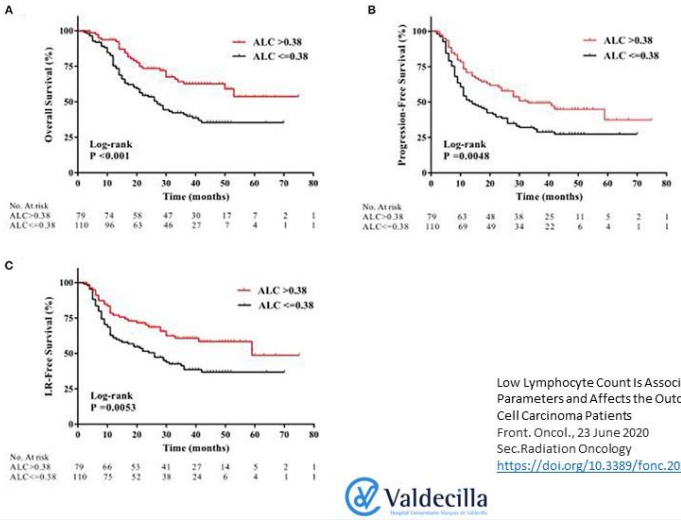

Radiotherapy can be "Bad" for Immune system…
• **Lymphocytes are very radiosensitive** (with 2Gy, 50% of circulating lymphocytes destroyed….)
• Many RT treatments include daily 2Gy RT treatments for several weeks…
• **Radiation induced Lymphopenia** can decrease immune system effector cells: CD8, CD4…
INMOA
Valdecilla
UCAM

Long treatments… (2Gy/fx)



Low Lymphocyte Count Is Associated With Radiotherapy Parameters and Affects the Outcomes of Esophageal Squamous Cell Carcinoma Patients
Front. Oncol., 23 June 2020
Sec.Radiation Oncology

Destroying lymphocytes negatively impacts survival…



Low Lymphocyte Count Is Associated With Radiotherapy Parameters and Affects the Outcomes of Esophageal Squamous Cell Carcinoma Patients
Front. Oncol., 23 June 2020
Sec.Radiation Oncology
https://doi.org/10.3389/fonc.2020.00997

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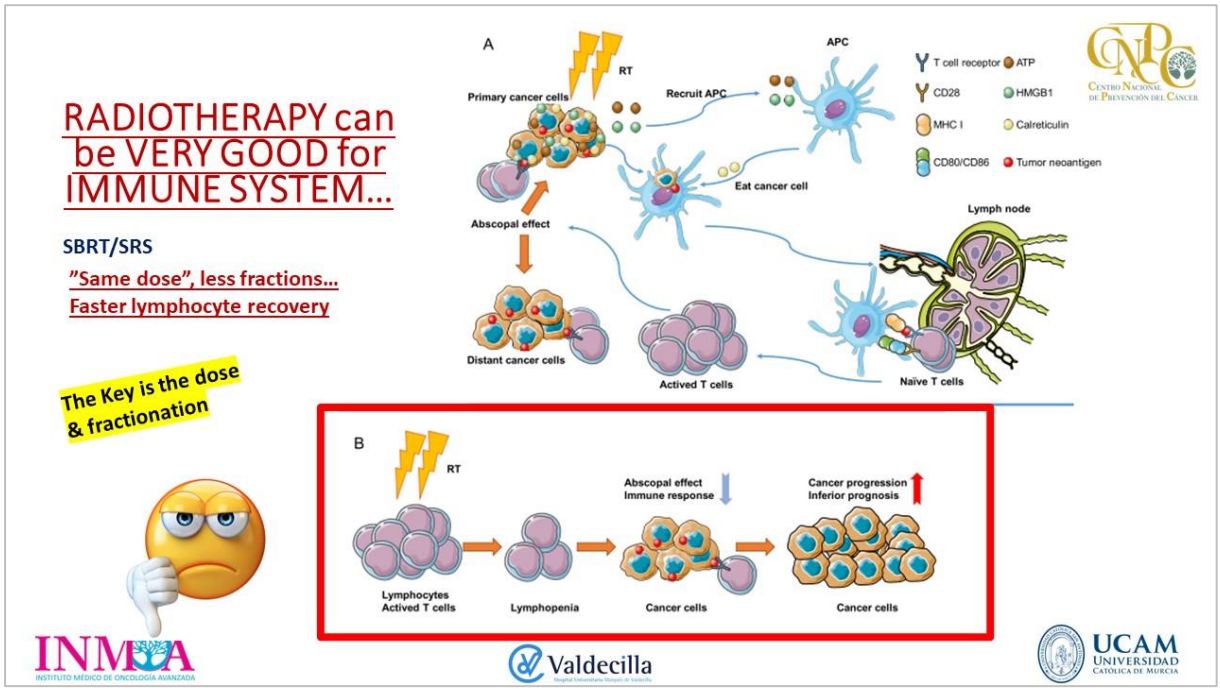

RADIOTHERAPY can be VERY GOOD for IMMUNE SYSTEM...
SBRT/SRS
"Same dose", less fractions...
Faster lymphocyte recovery
The Key is the dose & fractionation
A
RT
Primary cancer cells
Recruit APC
APC
Eat cancer cell
Abscopal effect
Distant cancer cells
Actived T cells
Lymph node
Naive T cells
T cell receptor
ATP
CD28
HMGB1
MHC I
Calreticulin
CD80/CD86
Tumor neoantigen
B
RT
Abscopal effect
Immune response
Cancer progression
Inferior prognosis
Lymphocytes
Actived T cells
Lymphopenia
Cancer cells
Cancer cells
INMOA
Valdecilla
UCAM
UNIVERSIDAD CATÓLICA DE MURCIA


INMOA
High and low dose RT combination?
Let's try!
Valdecilla
UCAM

Radiotherapy and Oncology 162 (2021) 60–67

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial

Roshal R. Patel [a,i,1], Kewen He [a,j,1], Hampartsoum B. Barsoumian [a], Joe Y. Chang [a], Chad Tang [a], Vivek Verma [a], Nathan Comeaux [a], Stephen G. Chun [a], Saumil Gandhi [a], Mylene T. Truong [b], Jeremy J. Erasmus [b], David S. Hong [e], Percy P. Lee [a], Matthew S. Ning [a], Quynh-Nhu Nguyen [a], John V. Heymach [d], Mehmet Altan [d], George Blumenschein [d], Frank V. Fossella [d], Duygu Sezen [a,k], Dawei Chen [a,i], Brett W. Carter [b], Michael A. Davies [c], Isabella C. Glitza [d], Adi Diab [c], Renata Ferrarotto [d], Maria E. Cabanillas [f], Ying Yuan [g], Shalin J. Shah [a], Edwin R. Parra [h], Baohua Sun [h], Maria Angelica Cortez [a], James W. Welsh [a,*]

[a] Departments of Radiation Oncology, The University of Texas MD Anderson Cancer Center; [b] Departments of Thoracic Imaging, The University of Texas MD Anderson Cancer Center; [c] Departments of Melanoma Medical Oncology, The University of Texas MD Anderson Cancer Center; [d] Departments of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center; [e] Departments of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center; [f] Departments of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center; [g] Biostatistics, The University of Texas MD Anderson Cancer Center; [h] Translational Molecular Pathology, The University of Texas MD Anderson Cancer Center, Houston; [i] Albany Medical College, Albany, USA; [j] Departments of Radiation Oncology, Shandong Cancer Hospital Affiliated to Shandong University, Jinan, China; [k] Department of Radiation Oncology, School of Medicine, Koc University, Istanbul, Turkey

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial.

- Pathological confirmed M1, at least one metastatic lesion amenable to RT and progression of disease on immunotherapy.
- 74 patients (NSCLC, n = 38; melanoma n = 21)
  - **39 received HD-RT (20–70 Gy total; 3–12.5 Gy/f)**
  - **35 received HD-RT + LD-RT (0.5–2 Gy/f up to 1–10 Gy total)**
  - **Went on with same immunotherapy they had progressed to.**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **Patients received IT for a median of 7.1 months before RT.**
- **No significant differences in patients' characteristics between groups.**
- **88% of the evaluable patients received at least 1 cycle of immunotherapy after RT** (29/34 in the HD-RT + LD-RT and 34/38 in the HD-RT cohort).
- **Of patients continuing to immunotherapy after RT, most patients 95%, continued on the same regimen and 54% continued to receive the same agent at 4 months.**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

Table 1
Clinical response by treatment group.

	High + Low Dose No. (%)	High-Dose-Only No. (%)	
CR	2 (6%)	1 (3%)	
PR	7 (21%)	4 (10%)	
SD	14 (41%)	16 (42%)	
PD	11 (32%)	17 (45%)	
			P value
DCR[a]	16 (47%)	14 (37%)	0.38
ORR[b]	9 (26%)	5 (13%)	0.27

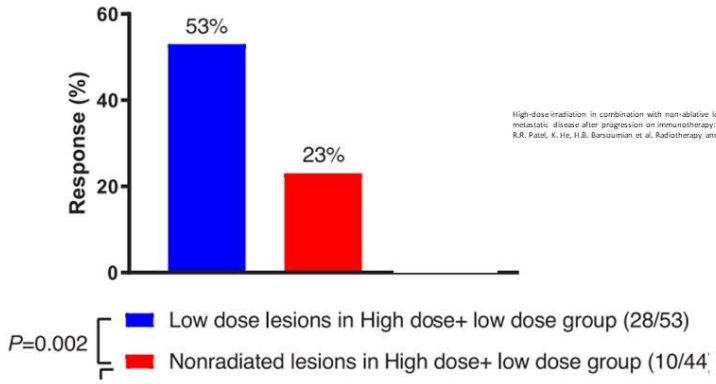
[a]Disease control rate: CR/PR/SD at 4 months.
[b]Overall response rate: CR/PR at any time.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **HDRT + LD-RT**

HD-RT: high-dose radiotherapy;
LD-RT: low-dose radiotherapy.

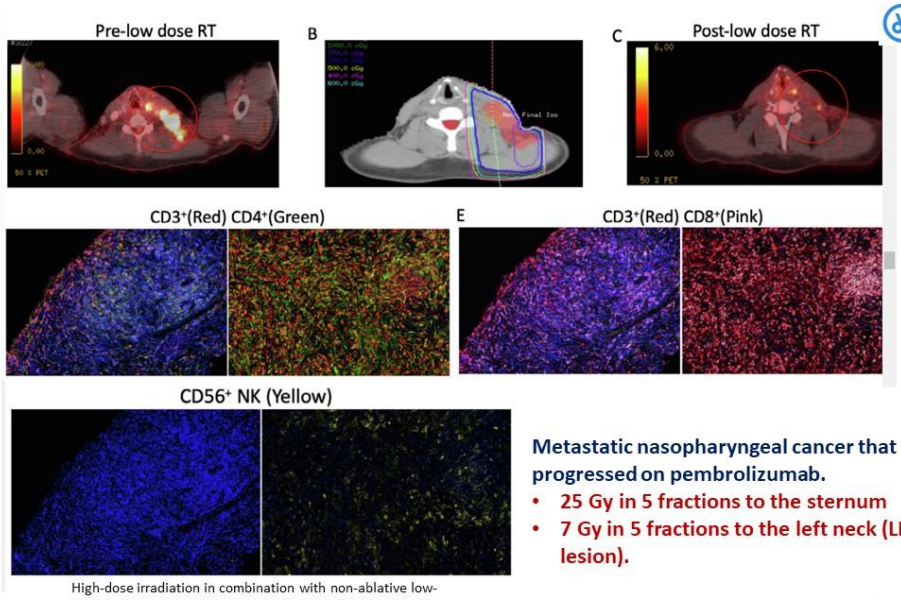


High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **Patients with PD after more than 6 months of immunotherapy were more likely to achieve an objective response** (CR/PR, i.e., met the primary endpoint) **in both** the overall cohort (54% vs. 26%, **P = 0.02**) and the high-/low-dose RT cohort alone (69% versus 30%, **P = 0.03**).

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67



Metastatic nasopharyngeal cancer that progressed on pembrolizumab.

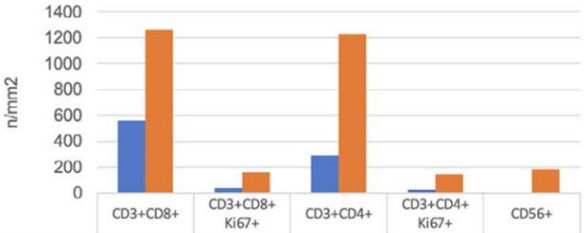
- **25 Gy in 5 fractions to the sternum**
- **7 Gy in 5 fractions to the left neck (LD-RT lesion).**

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

RESULTS

- **LD-RT induced a remarkable increase in immune cell infiltration into the irradiated lesions:**
  - **300% increase in CD4+ T cells**
  - **187% increase and NK cells.**

G

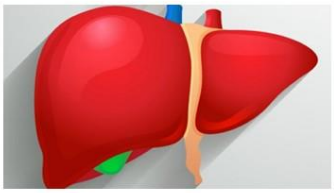


	CD3+CD8+	CD3+CD8+ Ki67+	CD3+CD4+	CD3+CD4+ Ki67+	CD56+
pre L-XRT	558.02	41.35	287.81	26.20	0.00
post L-XRT	1261.51	158.77	1233.01	144.51	187.60
% change	126 %	284%	300%	452%	-

High-dose irradiation in combination with non-ablative low-dose radiation to treat metastatic disease after progression on immunotherapy: Results of a phase II trial. R.R. Patel, K. He, H.B. Barsoumian et al. Radiotherapy and Oncology 162 (2021) 60–67

- **HD-RT starts movement: Activates Ag release and presentation.**
- **LD-RT: "modulates" and power response.**

- **Liver, an "special " organ…**



frontiers in Immunology

MINI REVIEW
published: 15 December 2021
doi: 10.3389/fimmu.2021.812210

Novel Use of Low-Dose Radiotherapy to Modulate the Tumor Microenvironment of Liver Metastases

*Kewen He[1,2,3], Hampartsoum B. Barsoumian[3], Genevieve Bertolet[3], Vivek Verma[4], Carola Leuschner[3], Eugene J. Koay[5], Ethan B. Ludmir[6], Ethan Hsu[3], Esha Pisipati[3], Tiffany A. Voss[3], Nahum Puebla-Osorio[3], María Angelica Cortez[3] and James W. Welsh[3]**

[1] Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China, [2] Cheeloo College of Medicine, Shandong University, Jinan, China, [3] Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [4] Department of Radiation Oncology, Allegheny General Hospital, Pittsburgh, PA, United States, [5] Department of Gastrointestinal Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, [6] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX, United States

OPEN ACCESS

Edited by:
Anil Shanker,
Meharry Medical College,

Despite multiple therapeutic approaches, the presence of liver metastases carries a guarded prognosis, urgently necessitating further clinical and scientific research to develop curative interventions. The liver is an immunoprivileged organ that suppresses

- Although immunotherapies have shown significant clinical benefit in patients with extrahepatic tumors, **patients with metastases to the liver had been historically identified to respond poorly to immunotherapy.**

ESMO

Annals of Oncology 29: 959–965, 2018
doi:10.1093/annonc/mdy041
Published online 21 February 2018

ORIGINAL ARTICLE

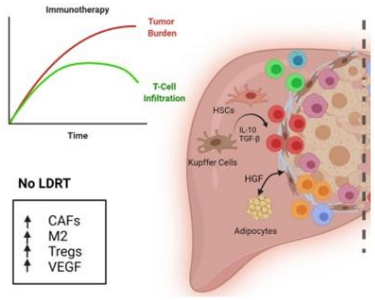
Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases

E. E. Vokes[1*], N. Ready[2], E. Felip[3], L. Horn[4], M. A. Burgio[5], S. J. Antonia[6], O. Arén Frontera[7], S. Gettinger[8], E. Holgado[9], D. Spigel[10,11], D. Waterhouse[12,13], M. Domine[14], M. Garassino[15], L. Q. M. Chow[16], G. Blumenschein Jr[17], F. Barlesi[18], B. Coudert[19], J. Gainor[20], O. Arrieta[21], J. Brahmer[22], C. Butts[23], M. Steins[24], W. J. Geese[25], A. Li[25], D. Healey[25] & L. Crinò[5]

For example, a subanalysis of two phase-III trials, demonstrated **decreased overall survival** (OS) in **non-small cell lung cancer (NSCLC)** patients **with liver metastases treated with nivolumab compared to the overall pooled population treated with nivolumab** (3-year OS: 17% vs. 8%; median OS: 11.1 vs. 6.8 months, respectively)

IT efficacy in liver is limited by the unfavourable conditions of the liver: dense estroma, low rate macrophages M1/M2, increase TGF-b, VEGF and cancer associated fibroblasts (CAFs)

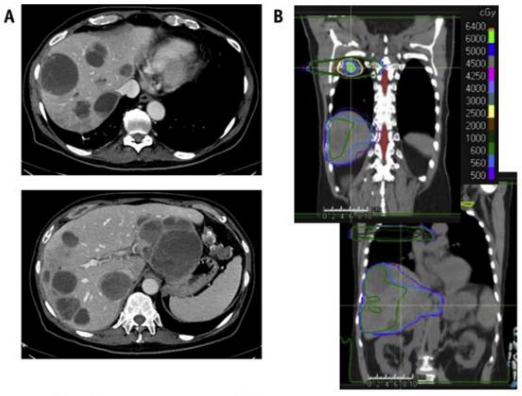
LDRT: repolarize macrophages, decrease CAFs, TGF-b and VEGF. Facilites T and NK cells infiltration and macrophages M1 stimulation.



- **LDRT Reprograms tumor microenvironment, making more easy immune system cells to go inside the tumor.**

RESULTS

- Low-dose RT to large areas of tumor burden can be safe and achieve significant responses.
- CASE:
  - Patient with **melanoma metastases in the liver, lung, bone, and brain** that **progressed during the course of 4 years on numerous chemo, targeted, and immune therapies**, yttrium-90 radioablation to 2 liver lobes, and T cell therapy presented to our clinic. Three months after T cell infusion and 1 month after resuming combined ipilimumab with nivolumab the patient continued to progress.



Four-months later, the patient achieved a partial response in liver.
No changes in liver function or hepatic/pulmonary toxicity were noted.

Fig. 3. Low-dose radiation therapy (RT) to nearly the whole liver. (A) Computed tomography with contrast before RT. (B) Low-dose RT treatment plan (coronal).

50 Gy in 4 fractions to a lung lesion and 5.6 Gy in 4 fractions to nearly the entire liver (Fig. 3B). Given the extent of disease burden (largest liver lesion measuring 9.5 cm) and the risk for radiation-induced hepatopathy, a small portion of the inferior liver was spared.

Two years after liver radiation treatment, the patient has no evidence of disease, with a durable and complete response for the liver metastases (Figure 2C).

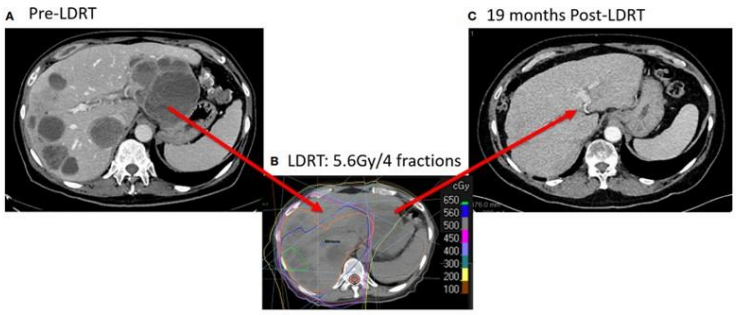


FIGURE 2 | Complete Response with LDRT to Liver metastases. **(A)** CT scanning (9/4/2019) before LDRT showed multiple liver metastases. **(B)** The patient received 50 Gy/4 fractions to a lung lesion and 5.6 Gy/4 fractions to nearly the entire liver from 10/8/2019 to 10/11/2019. **(C)** 19 months after LDRT, CT scans (4/19/2020) showed a complete response in the liver.

Hyperthermia

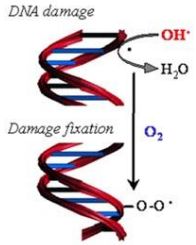
What we can do to improve?

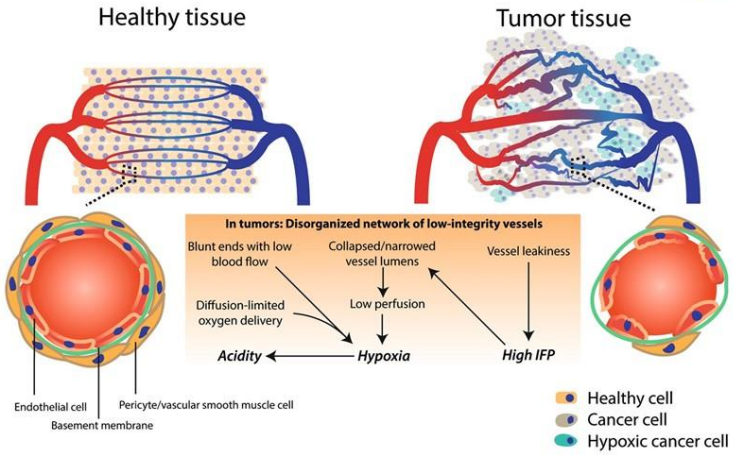
- Having a high dose to kill the tumor without damaging the patient
- Having immune system estimulation and systemic response (abscopal response)

HYPOXIA

- **90% of tumor have high grade hypoxia… specially the most agressive.**

"Oxygen enhancing effect" of RT





Cell Death & Disease (*Cell Death Dis*) ISSN 2041-4889 (online)

Hypertermia & alfa-beta

Table 1
Summary of the randomized studies of RT vs HTRT, complete responders in each arm, corresponding BED of the RT schedule and the estimated α/β with HTRT for each study.

Author	Site	RT/HTRT		Hyperthermia				RT		HTRT		BED (RT) (Gy_{10})	$\%CR_{HTRT}/\%CR_{RT}$ (X)	BED_{HTRT} (Gy)	Estimated α/β for HTRT (Gy)
		Dose (Gy)	Dose/fr (Gy)	T (°C)	Time (mins)	Per week	Total sessions	Total	CR	Total	CR				
Wahl et al. [35]	RcBC	48.0	2.0	NA	NA	NA	NA	18	7	36	24	57.6	1.71	98.7	1.89
Vernon et al. (MRC) [36]	RcBC	28.8	3.6	43.0	60.0	1	3	59	17	90	51	39.2	1.97	77.0	2.15
Vernon et al. (ESHO) [36]	RcBC	32.0	4.0	43.0	60.0	2	8	29	11	27	21	44.8	2.05	91.9	2.14
Wen et al. [37]	LAHNC	70.0	2.0	44.4	60.0	2	6	49	23	49	34	84.0	1.48	124.2	2.58
Huilgol et al. [38]	LAHNC	70.0	2.0	42.3	30.0	1	7	26	11	28	22	84.0	1.86	156.0	1.63
Valdagni et al. [39]	LAHNC	68.0	2.0	42.5	30.0	2	12	22	9	18	15	81.6	2.04	165.0	1.38
Datta et al. [40]	LAHNC	64.0	2.0	42.5	50.0	2	12	32	10	33	18	76.8	1.75	134.1	1.83
Arcangeli et al. [41]	LAHNC	60.0	1.5	42.5	45.0	3	7	43	18	38	30	69.0	1.89	130.1	1.28
Harima et al. [42]	LACC	52.2	1.8	40.6	60.0	1	3	20	10	20	16	61.6	1.60	98.6	2.03
Franckena et al. [43]	LACC	48.3	2.0	42.0	60.0	1	5	56	32	58	48	58.0	1.45	83.9	2.71
Chen et al. [44]	LACC	40.0	2.0	42.0	45.0	2	8	30	14	30	18	48.0	1.29	61.7	3.68
Datta et al. [45]	LACC	60.0	2.0	42.5	45.0	2	12	26	15	27	20	72.0	1.28	92.4	3.70

Abbreviations: RT: Radiotherapy; HTRT: Thermoradiotherapy; T: Temperature; RcBC: Recurrent breast cancer; LAHNC: Locally advanced head and neck cancer; LACC: Locally advanced cancer cervix; BED: Biologically effective dose; $\%CR_{HTRT}$: % complete response with HTRT; $\%CR_{RT}$: % complete response with RT.
BED_{HTRT} and α/β_{HTRT} are estimated as described in text.
*Average dose to RT group: 68 Gy whilst to HTRT 67.5 Gy.
†Only patients with neck nodes were considered, treated with 1.5 Gy–2 Gy per fraction, 3 fractions/day.
For all LACC studies, only external RT doses were considered.

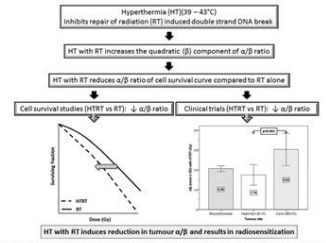


Fig. 4. Hyperthermia results in reduction in α/β values. This was evident in cell survival studies reported by Franken et al. [31] and corroborates the estimated α/β values from clinical trials of radiotherapy (RT) vs thermoradiotherapy (HTRT) in recurrent breast cancers, locally advanced head & neck cancer and locally advanced cancer cervix in the present study.

BED

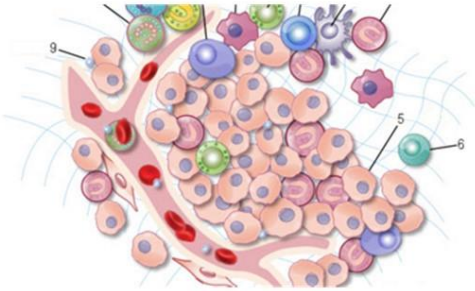
Tumor type	BED RT	BED RT + HT
Recurrent Breast	47.2Gy (39.2-57.6)	**89.2 Gy** (77.0-98.7)
LA H&N	79.1Gy (69-84)	**141.9Gy** (124.2–165.0)
LA Cervical ca	59.9Gy (48-72)	**84.2Gy** (61.7–98.5)

a/b

Tumor type	a/b RT	a/b RT+HT
Recurrent Breast	10	**1.89 a 2.15** (mean: 2.05, 95% CI: 1.90–2.22).
LA H&N	10	**1.28 a 2.58 Gy** (mean: 1.74, 95% CI: 1.29–2.19)
LA Cervical ca	10	**2.03 a 3.70 Gy** (mean: 3.03, 95% CI: 2.24–3.82)

Tumor microenvironment…

- Different cells, including immune cells inside and around tumor.
- **Has been demonstrated to have a role in tumor progression.**



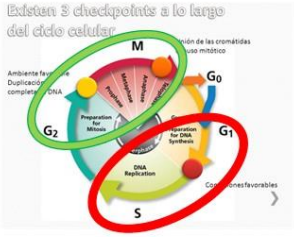
"Tumor microenvironment" is hostile to radiotherapy

- Lack of oxygen…
- **Acidity…**
- **And..**

RADIOTHERAPY AND CELL CYCLE

- **Late G2 phase** and **M** the most **radiosensitive**
- **G1 phase** and **late S** the most **radioresistant**.

How much & **when** we treat with RT matters!



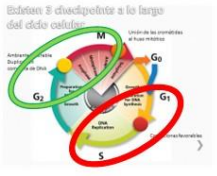
MICROENVIRONMENT also MATTERS!

HeonJoo Park, John C. Lyons, Robert J. Griffin, Byung U. Lim, and Chang W. Song "Apoptosis and Cell Cycle Progression in an Acidic Environment after Irradiation," *Radiation Research* 153(3), 295-304, (1 March 2000). https://doi.org/10.1667/0033-7587(2000)153[0295:AACCPI]2.0.CO;2

- **Relation: Apoptosis/cell cycle phase/RT dose/microenvironment in irradiation cels**
- **Different RT doses**
  - **4Gy: Apoptoses after G_2/M.**
  - **12 Gy: Some apoptosis in G_1 y S . Most apoptosis G_2/M.**

Acid pH (<7,1) apoptosis at 4 & 12 Gy supressed (difficulties in cell cycle progression towards G2/M).

- **20 Gy apoptosis in all phases.**
  - **Fast at neutral pH, low at acid pH**

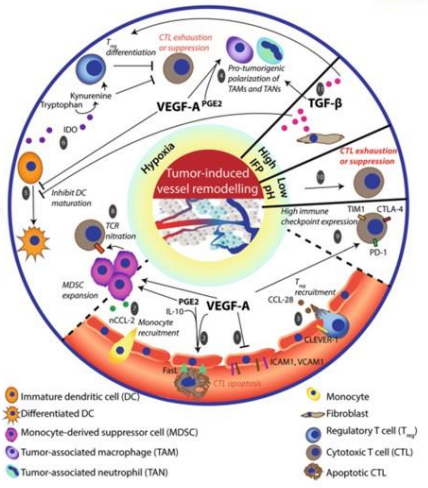


"Tumor microenvironment" is hostile to radiotherapy

- Lack of oxygen…
- **Acidity…**
- **And..**

HYPOXIA IMPORTANCE…

Dendritic cells and vaccine therapy!!!



Schaaf et al. Cell Death and Disease 20189:115

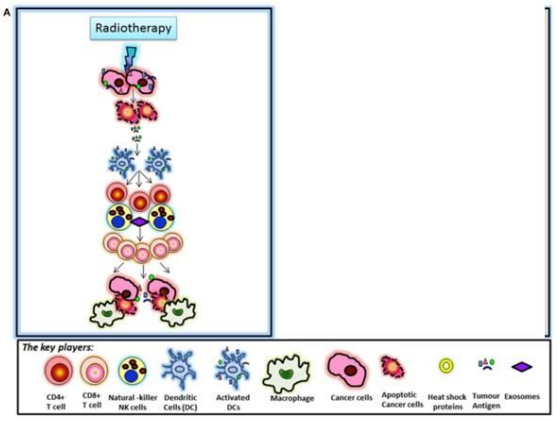
Hyperthermia

What we can do to improve?

- Having a high dose to kill the tumor without damaging the patient
- Having immune system estimulation and systemic response (abscopal response)
- Increasing oxygen
- Decreasing acidity
- "Unblocking immune system"

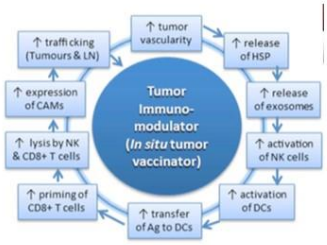
RT, HT & Immune system activation...

- **RT:**
  - Activate DC → Ag presentation → activate T cell → estimulates TCD8+ → citokines → malignant cells death → macrophages. (ABSCOPAL)



Datta NR, Kok HP, Crezee H, Gaipl US and Bodis S (2020) Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses. Front. Oncol. 10:819. doi: 10.3389/fonc.2020.00819

- **HT:**



HSP: Heat shock proteins; NK: Natural killer; DC: Dendritic cells; Ag: Antigens; CAM: Cell adhesive molecule; LN: Lymph nodes

Lymphocytes infiltration rate determines immune response

Radiotherapy/**Hyperthermia** & Immunotherapy combination

Radiotherapy & hyperthermia can convert "COLD" tumors that don't respond to immunotherapy, in "HOT" tumors with high T lymphocytes infitration more responders

Demaria, Journal of Immunotherapy of Cancer, 2022

What we need is to adapt our treatments to what we want to achieve…

- Local lethal effect.
- Systemic effect.

JAMA Oncology | Original Investigation

Effect of Neoadjuvant Chemotherapy Plus Regional Hyperthermia on Long-term Outcomes Among Patients With Localized High-Risk Soft Tissue Sarcoma

The EORTC 62961-ESHO 95 Randomized Clinical Trial

Rolf D. Issels, MD, PhD; Lars H. Lindner, MD; Jaap Verweij, MD; Rüdiger Wessalowski, MD; Peter Reichardt, MD; Peter Wust, MD; Pirus Ghadjar, MD; Peter Hohenberger, MD; Martin Angele, MD; Christoph Salat, MD; Zeljko Vujaskovic, MD; Soeren Daugaard, MD; Olav Mella, MD; Ulrich Mansmann, MD; Hans Roland Dürr, MD; Thomas Knösel, MD; Sultan Abdel-Rahman, PhSc; Michael Schmidt, MD; Wolfgang Hiddemann, MD; Karl-Walter Jauch, MD; Claus Belka, MD; Alessandro Gronchi, MD; for the European Organization for the Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group and the European Society for Hyperthermic Oncology

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00003052

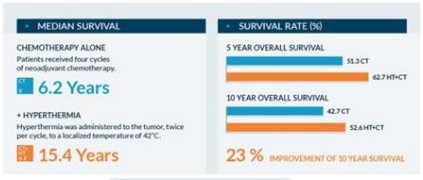
JAMA Oncol. 2018;4(4):483-492. doi:10.1001/jamaoncol.2017.4996
Published online February 15, 2018. Last corrected on April 12, 2018.

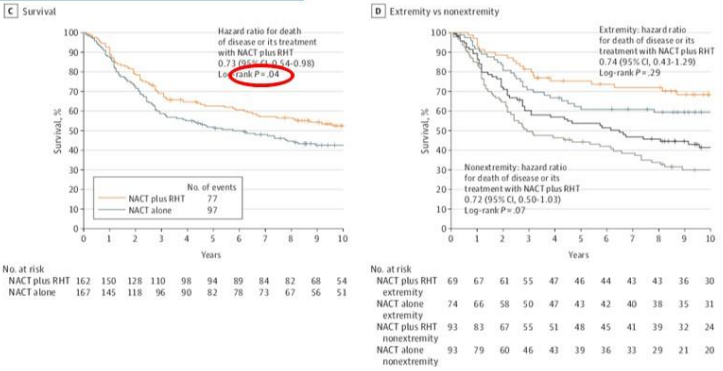
JAMA Oncology | Original Investigation

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

OS HT+CT vs CT:

- 5 years:
  62.7% vs 51.3%, (**p = 0.04**)





A, Median local progression free survival was 5.6 years (95% CI, 2.9-8.7) in the NACT plus RHT group compared with 2.4 years (95% CI, 1.7-4.2) in the NACT-alone group. B, Median disease-free survival was 2.8 years (95% CI, 2.0-4.9) in the NACT plus RHT group compared with 1.5 years (95% CI, 1.1-2.1) in the NACT-alone group. C, Median survival was 15.4 years (95% CI, 6.6 to >17.0 [the upper confidence limit cannot be estimated and represents the lower bound for the value to be expected]) in the NACT plus RHT group compared with 6.2 years (95% CI, 3.2-10.3) in the NACT-alone group. D, Extremity tumor-survival rates at 5 and 10 years were 75.2% and 68.3% in the NACT plus RHT group compared with 60.8% and 59.2% in the NACT-alone group. The absolute difference at 5 years was 14.4% (95% CI, 0%-29.5%) and was 9.1% (95% CI, 0%-24.7%) at 10 years. Nonextremity tumor-survival rates at 5 years and 10 years were 53.5% and 41.3% in the NACT plus RHT group compared with 44.0% and 29.9% in the NACT-alone group. The absolute difference at 5 years was 9.5% (95% CI, 0%-23.8%) and was 11.4% (95% CI, 0%-25.1%) at 10 years. NACT indicates neoadjuvant chemotherapy consisting of doxorubicin, ifosfamide, and etoposide; RHT, regional hyperthermia.

European Journal of Cancer 158 (2021) 123–132

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journal homepage: www.ejcancer.com

Original Research

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

Rolf D. Issels [a,*,1], Elfriede Noessner [b,1], Lars H. Lindner [a], Michael Schmidt [c], Markus Albertsmeier [d], Jean-Yves Blay [e], Emanuel Stutz [f], Yujun Xu [g], Veit Buecklein [a], Annelore Altendorf-Hofmann [h], Sultan Abdel-Rahman [a], Ulrich Mansmann [g], Michael von Bergwelt-Baildon [i], Thomas Knoesel [j]

[a] Department of Medicine III, University Hospital, LMU, Marchioninistr.15, Munich, 81377, Germany
[b] Helmholtz Zentrum München, German Research Center for Environmental Health, Germany
[c] Munich Cancer Registry, Institute of Medical Information Processing, Biometry and Epidemiology, LMU, Munich, Germany
[d] Department of General, Visceral and Transplantation Surgery, LMU Munich, Munich, Germany
[e] Department of Medicine, Centre Leon Berard, 28 Rue Laennec1, Lyon, 69373, France
[f] Dept. of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Bern Freiburgstr.18, Switzerland
[g] Institute of Medical Informatics, Biometry and Epidemiology (IBE), LMU Munich, Germany
[h] Department of General, Visceral and Vascular Surgery, University Hospital Jena, Germany
[i] Deutsches Konsortium für Translationale Krebsforschung, Bayrisches Zentrum für Krebsforschung, and Comprehensive Cancer Center LMU, Munich, Germany
[j] Institute of Pathology, LMU, Thalkirchner Str.36, Munich, 80337, Germany

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Available online 16 October 2021

- The study protocol included an optional accompanying **translational program, to determine immune cells of tumour tissue.**

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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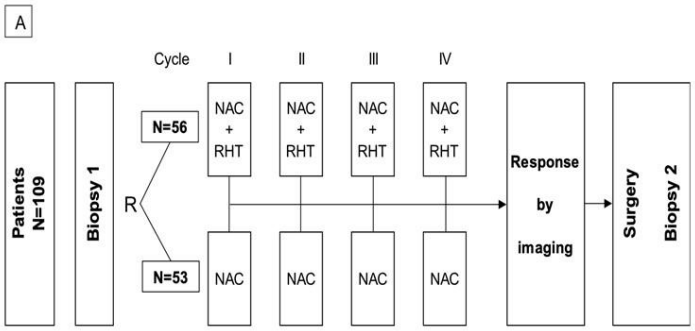

- **28 patients had paired samples** (only available for patients who had been biopsied and finally operated at the Munich Centre).
  - NAC-RHT: 13
  - NAC: 15

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

European Journal of Cancer 158 (2021) 123–132

- Examined for **TILs (Infiltrating tumor lymphocytes)** and immune biomarker expression, including **CD8, PD-1, PD-L1, and FOXP3.**
  - The TIL score was assigned as high (>5 cells per HPF) or low (5 cells per HPF).
  - The CD8 cell score was defined by anti-CD8 antibody immunoreactivity as high (>10 cells per HPF) or low (<10 cells per HPF)

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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- Compared the tumour-associated immune infiltrate between **NAC-RHT and NAC treatment at baseline (biopsy 1) and after pre-operative therapy (biopsy 2)**
- As seen in paired samples, **the immune infiltrate** in post- treatment biopsies of the NAC-RHT and the NAC groups **showed comparable distributions of**:
  - high TIL tumours (46.2%; 6/13 versus 53.3%; 8/15)
  - high CD8 tumours (33.3%; 4/12 versus 45.5%; 5/11)
  - tumours with PD-1pos cells (33.3%; 4/12 versus 38.5%; 5/13),
  - FOXP3pos cells (0%; 0/13 versus 6.7%; 1/15)
  - PD-L1pos tumour cells (0%; 0/13 versus 6.7%; 1/15).

Immune infiltrates in patients with localised high-risk soft tissue sarcoma treated with neoadjuvant chemotherapy without or with regional hyperthermia: A translational research program of the EORTC 62961-ESHO 95 randomised clinical trial

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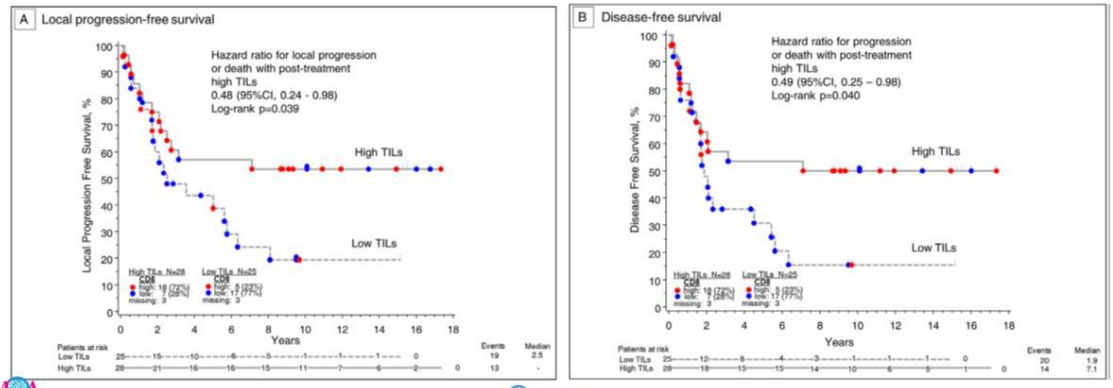
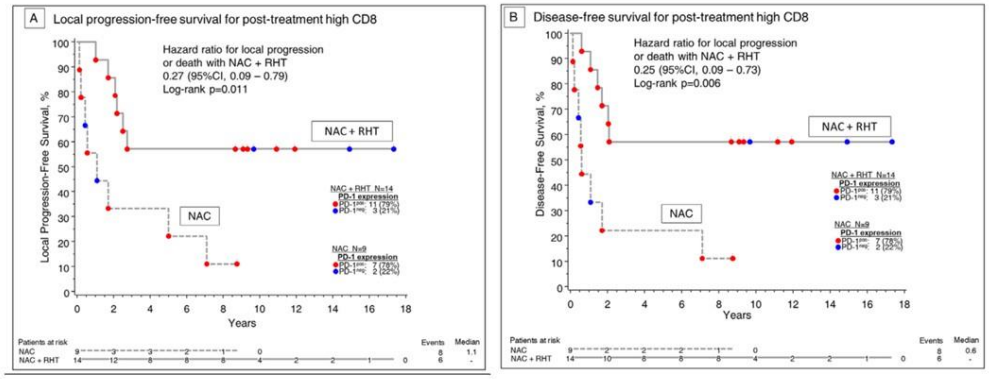
- In post-treatment samples (biopsy 2): **53%** (28/53) tumours **high TIL infiltrate** *vs* 47% (25/53) with low TIL infiltrate.
- **High TILs significantly associated with prolonged LPFS (p 0.039) and DFS (0.040)**

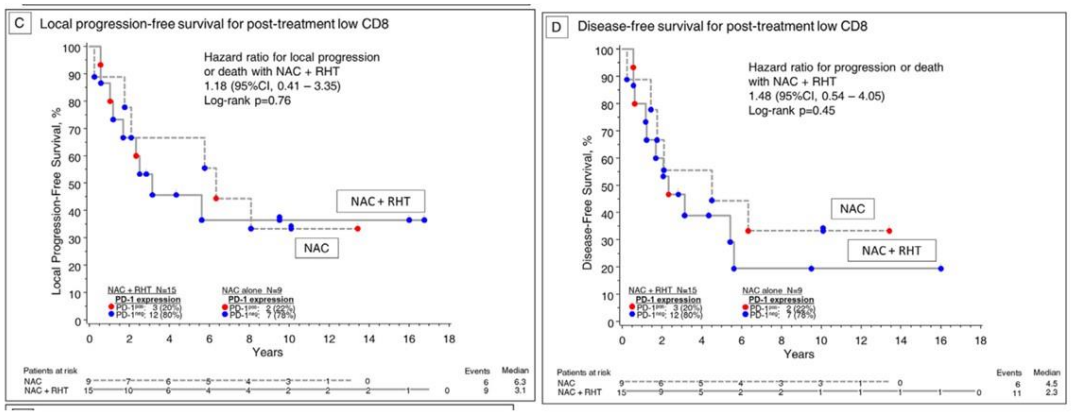


High CD8 by groups



Patients of the NAC-RHT group, whose tumours exhibited high CD8 counts, had significantly longer LPFS (p=0.011) and DFS (p =0.006) compared to the NAC group.

Low CD8 by groups



CONCLUSIONS

- **Preoperative chemotherapy +/- concomitant Hyperthermia turned the state of a cold, non-immunogenic sarcoma into a more immunogenic tumour** with high TILs, a decrease of immune-suppressive FOXP3 regulatory Tcells, and absence of PD-L1 expression.
- In patients with **high increase in CD8, the addition of hyperthermia significantly increased local progression free survival and disease free survival.**

Immune effect of hyperthermia

We need to increase CD8 and then… hyperthermia
How we increase CD8?

QT, RT, IMMUNOTHERAPY, HYPERTHERMIA

> Oral Oncol. 2012 Jul;48(7):594-601. doi: 10.1016/j.oraloncology.2012.01.024. Epub 2012 Feb 21.

Radiochemotherapy induces a favourable tumour infiltrating inflammatory cell profile in head and neck cancer

M Tabachnyk [1], L V R Distel, M Büttner, G G Grabenbauer, E Nkenke, R Fietkau, D Lubgan

Affiliations + expand

PMID: 22356894 DOI: 10.1016/j.oraloncology.2012.01.024

> Ann Surg. 2018 Dec;268(6):992-999. doi: 10.1097/SLA.0000000000002410.

The Dynamic and Transient Immune Microenvironment in Locally Advanced Esophageal Adenocarcinoma Post Chemoradiation

Ronan J Kelly [1], Ali H Zaidi [2], Matthew A Smith [3], Ashten N Omstead [2], Juliann E Kosovec [2], Daisuke Matsui [2], Samantha A Martin [2], Christina DiCarlo [3], E Day Werts [4], Jan F Silverman [3], David H Wang [5], Blair A Jobe [2]

Clinical Trial > Br J Cancer. 2019 Sep;121(6):490-496. doi: 10.1038/s41416-019-0541-3. Epub 2019 Aug 7.

Alteration in tumoural PD-L1 expression and stromal CD8-positive tumour-infiltrating lymphocytes after concurrent chemo-radiotherapy for non-small cell lung cancer

Kazue Yoneda [1], Taiji Kuwata [1], Masatoshi Kanayama [1], Masataka Mori [1], Toshinori Kawanami [2], Kazuhiro Yatera [2], Takayuki Obuuri [3], Masanori Hisaoka [4], Toshiyuki Nakayama [5], Fumihiro

Observational Study > Int J Radiat Oncol Biol Phys. 2018 Nov 1;102(3):593-600. doi: 10.1016/j.ijrobp.2018.06.404. Epub 2018 Jul 12.

Kinetics of Intratumoral Immune Cell Activation During Chemoradiation for Cervical Cancer

Stephanie Dorta-Estremera [1], Lauren E Colbert [2], Sita S Nookala [1], Ananta V Yanamandra [1], Guojun Yang [1], Andrea Delgado [2], Megan Mikkelson [2], Patricia Eifel [2], Anuja Jhingran [2], Lin L Lille [2], James Welsh [2], Kathleen Schmeler [3], Jagannadha K Sastry [1], Ann Klopp [4]

Randomized Controlled Trial > Anticancer Res. 2014 Nov;34(11):6505-13.

Effect of neoadjuvant chemoradiation on tumor-infiltrating/associated lymphocytes in locally advanced rectal cancers

Stephanie H Lim [1], Wei Chua [2], Christina Cheng [3], Joseph Descallar [4], Weng Ng [2], Michael Solomon [5], Les Bokey [6], Karen Wong [7], Mark T Lee [8], Paul de Souza [9], Joo-Shik Shin [10], Cheok Soon Lee [11]

Breast cancer with multiple brain metastases – Hypofractionated RT

- **30Gy in 5 fx RT concomitant with 3 fx Hyperthermia**
- **3 Hyperthermia fx in monotherapy**

Red – Only RT
Red and green – RT + HT
Green – Only RT

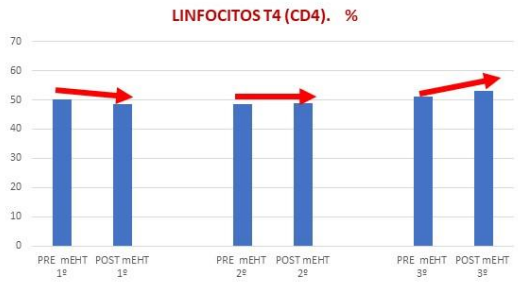
enero

L	M	X	J	V	S	D
26	27	28	29	30	31	1
2	3	4	5	6	7	8
9	10	11	12	13	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30	31	1	2	3	4	5

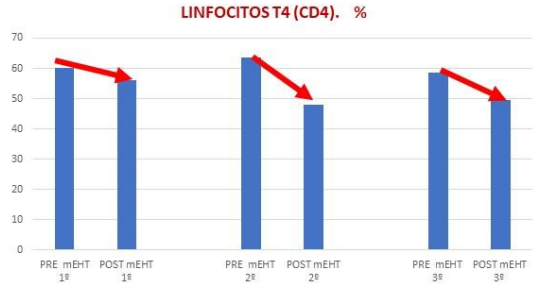
- **Analyze peripheral blood level of lymphocytes just before & after each hyperthermia treatment**

Breast cancer with multiple brain metastases–Hypofractionated RT

- RT + Hyperthermia



Hyperthermia in monotherapy

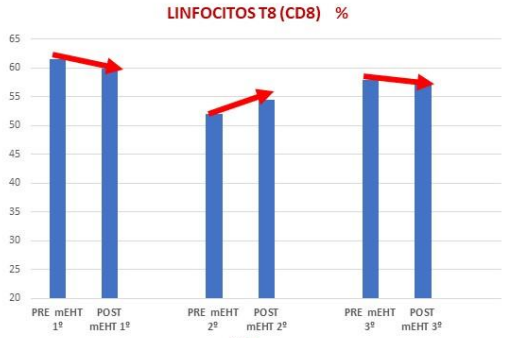


Red – Only RT
Red and green – RT + HT
Green – Only RT

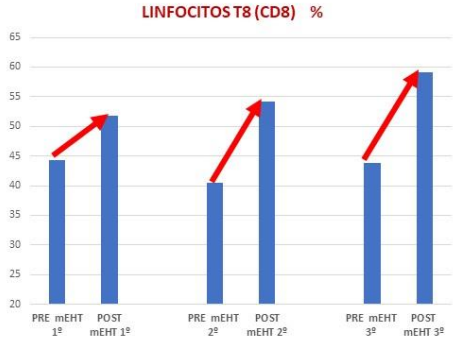
T CD4⁺ decrease → favorable prognosis

Breast cancer with multiple brain metastases – Hypofractionated RT

- RT + HT



Hyperthermia in monotherapy



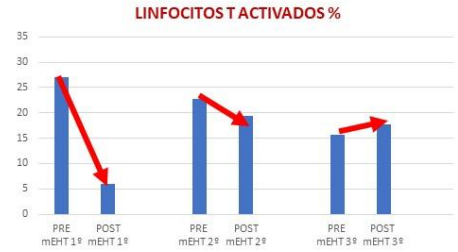
Red – Only RT
Red and green – RT + HT
Green – Only RT

NK, activated T lymphocythes & TCD8⁺ increase-> improves prognosis

Breast cancer with multiple brain metastases – Hypofractionated RT

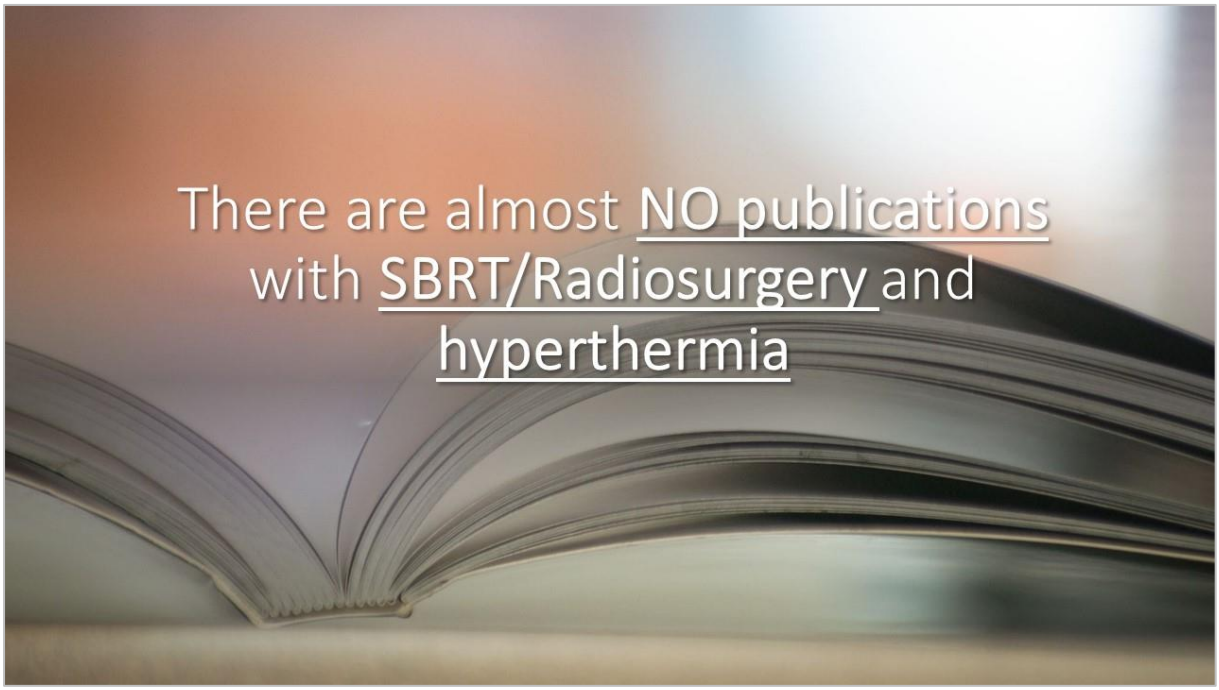
- RT + HT

Hyperthermia in monotherapy



Red – Only RT
Red and green – RT + HT
Green – Only RT

NK, activated T lymphocythes & TCD8⁺ increase-> improves prognosis



We have published the ”first abstract” combining Radiosurgery/SBRT + mEHT…

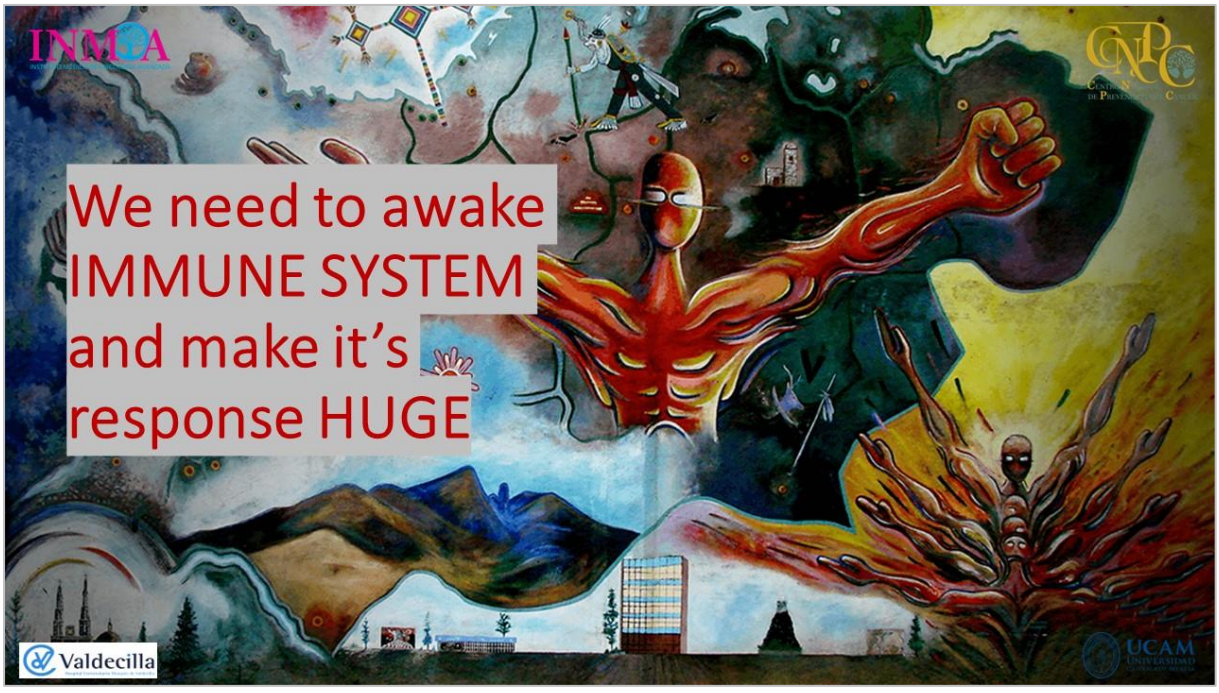
Increase Radiosentivity

Increase Abscopal

International Radiosurgery Congress NY 2024

Reirradiation High Grade Glioma with RS+mEHT (No options...)

- **8 patients with 14 lesions that received GRS and mEHT between** April 2023 and November 2023 were prospectively included.
- Median age of 48 years (range 30-62 years)
- Median of 2 lesions (range 1-3) underwent GRS and mEHT during the study period.
- Tumor progression after standard Stupp protocol and 3 patients had a previous second course of radiation.
- The median time from previous radiation was 11 months (range 21 – 6 months).
- The median (2.8cm³), minimum (0.2cm³), and maximum PTV volume (51cm³). 57% (n = 8) of the lesions were treated in 1 fraction, 29% (n = 4) in 5 fractions and 14% (n = 2) in 3 fractions. **Median dose in 1 fraction was 15 Gy** (range 15 - 18 Gy). Lesions treated in **5 fractions received 25 Gy or 30 Gy** and lesions treated in **3 fractions received 24 Gy.**
- **Overall survival at 6 months was 67%.** Acute and subacute treatment tolerance was acceptable, all patients needed ambulatory steroid medication adjustment.
- **Conclusion**: **High grade glioma reirradiation with GRS in combination with mEHT showed a favourable impact in local control and overall survival with low toxicity**. Longer follow-up and larger series is needed to validate these results.



SBRT in polimetastases

Advances in Radiation Oncology (2021) 00, 100734

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Can Polymetastatic Disease Be ARRESTed Using SABR? A Dosimetric Feasibility Study to Inform Development of a Phase 1 Trial

Mark T. Corkum, MD, MSc,[a] Hatim Fakir, PhD,[b] David A. Palma, MD, PhD,[a] Timothy Nguyen, MD,[a] and Glenn S. Bauman, MD[b,c]

[a]Division of Radiation Oncology, Department of Oncology; [b]Department of Medical Biophysics, London Health Sciences Centre, London, Ontario, Canada

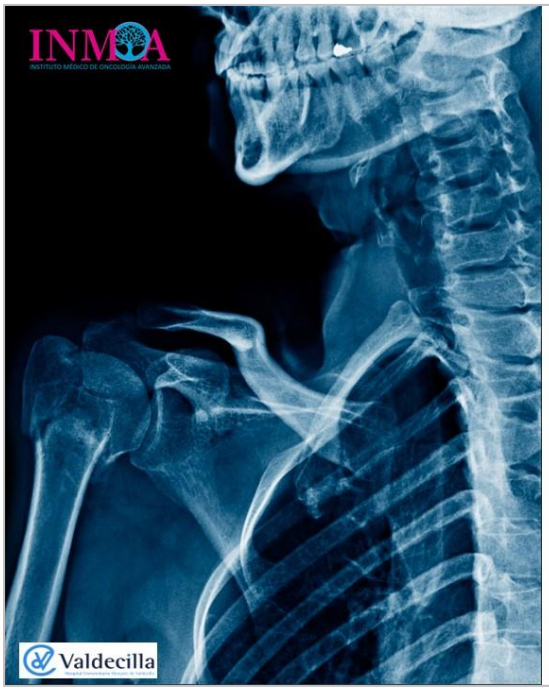
Received December 14, 2020; accepted May 21, 2021

Phase I ARREST trial
- Patients with > 10 metastases
- No available systemic treatment option

De-escalation dose level
- Dose level 0: 6Gy × 1 fraction to all sites in 1 week.

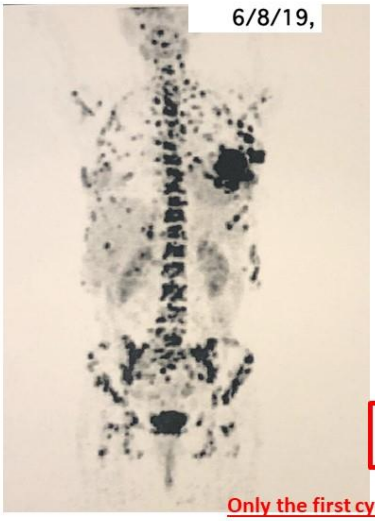
Escalation dose levels
- Dose level 1: 6Gy × 2 fractions to all sites in 2 weeks.
- Dose level 2: 6Gy × 3 fractions to all sites in 3 weeks.
- Dose level 3: 6Gy × 4 fractions to all sites in 4 weeks.
- Dose level 4: 6Gy × 5 fractions to all sites in 5 weeks.

Valdecilla *orkum, Advances in Radiation Oncology ,2021*



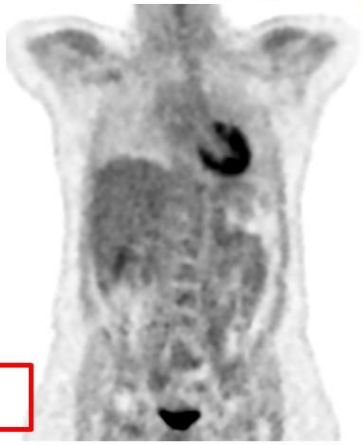
One of our cases…

- 48yo man
- Primary tumor: colon cancer
- **15 lung metastases & 2 liver metastases**
- No options for more chemotherapy
- IK 90%
- **Treatment:**
  - **SBRT to each of the lung metastases**
  - **SBRT to each of the liver metastases**
  - **+ mEHT to both locations.**
- **18 months later stable disease.**
- **No significant toxicities**



6/8/19,

28/10/19,



Breast cancer

4* CT cycles
29 mEHT treatments

2.5 months later
COMPLETE RESPONSE

Only the first cycle with paclitaxel + pertuzumab + trastuzumab.

The other ones only pertuzumab + trastuzumab (patient desirees)

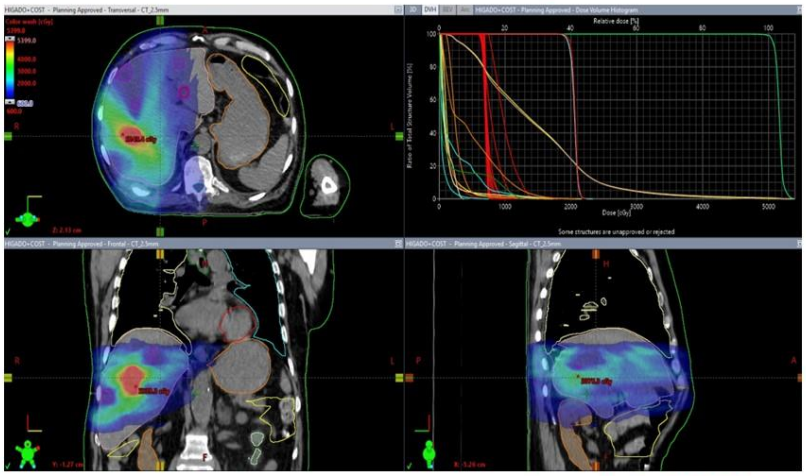
CLINICAL CASE

Male, 62yo
Stage IV prostate cancer, Gleason 9 (4+5) diagnosed in 2013.
Multiple treatments: radiotherapy, Abiraterone, Enzalutamide, Docetaxel...)

On february 2022:

Multiple bone metastases (skull, spine, pelvis, escapula, ribs...)
14 liver metastases on MRI
No options for systemic treatment

RT + HYPERTHERMIA as a “local-systemic” treatment.

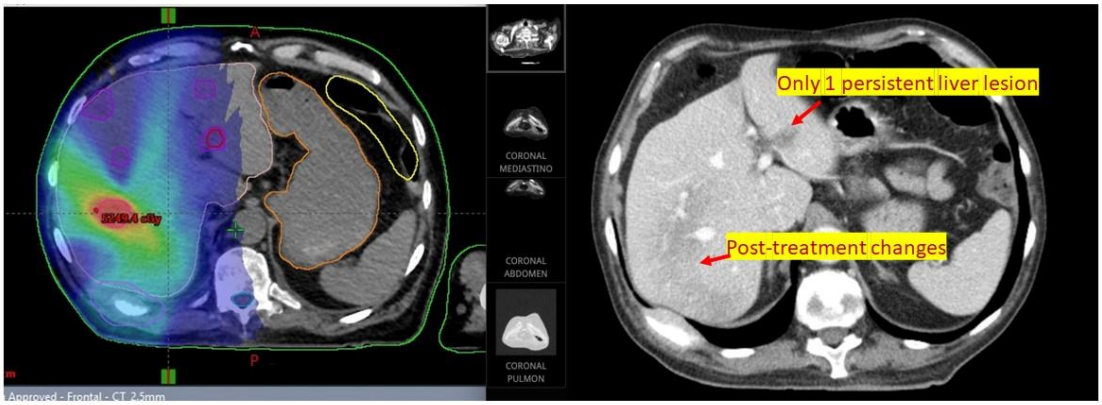


- 13 liver metastases treated with 5 fractions of 1.4Gy
- 1 liver metastases treated with 5 fractions of 10 Gy

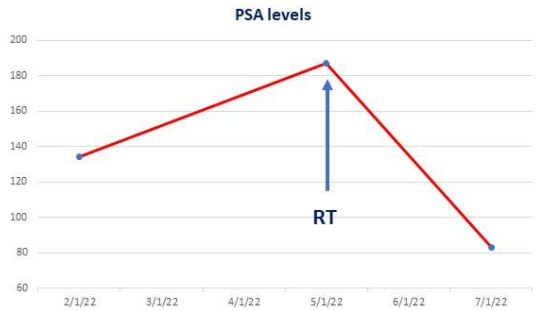
Concomitant mEHT (3 times a week, 60 minutes per treatment)

RESULTS

2 months after RT + mEHT treatment



RESULTS



No toxicities from treatment

Patient lived without systemic treatment for 15 months more with Good QoL...

CLINICAL CASE

Male, 42 yo
Local Adenocarcinoma of pancreas in 2019

→ Surgery
→ Relapse → Folfirinox
→ Progression → Gemcitabine-Abraxane
→ Radiofrequency of 3 liver metastases
→ Progression → Clinical Trial immunotherapy
→ Progresion → Folfirinox → Partial response but persistent disease.

CLINICAL CASE

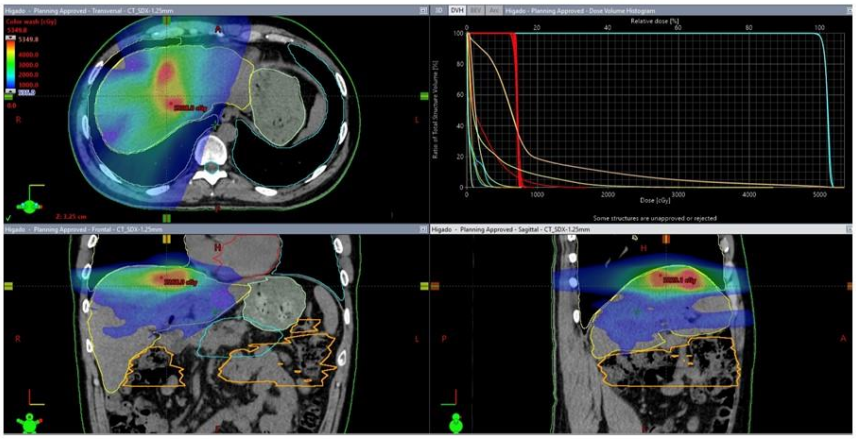
Male, 42 yo
Local Adenocarcinoma of pancreas in 2019

→ Surgery
→ Relapse → Folfirinox
→ Progression → Gemcitabine-Abraxane
→ Radiofrequency of 3 liver metastases
→ Progression → Clinical Trial immunotherapy
→ Progresion → Folfirinox → Partial response but persistent disease.

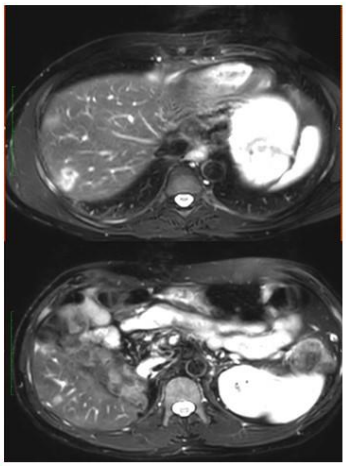
TREATMENT

RT:
- **Pancreas: 45Gy in 25 fractions**
- **Liver metastases:**
  - **2 treated with 5 fractions of 10Gy (50Gy)**
  - **9 treated with 5 fractions of 1.4Gy (7Gy)**

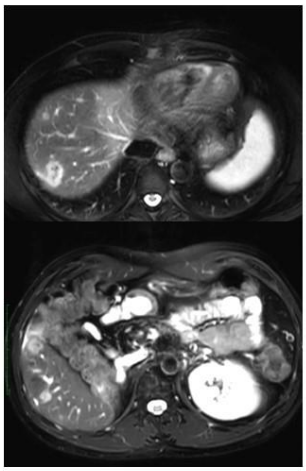
HYPERTHERMIA to liver and pancreas: three times a week during RT. 60 minutes treatment



- MRI 9 weeks after treatment:
  - Complete response of pancreatic tumor.
  - Stable disease of most of liver lesions. Minimum increase in two.



MRI before treatment



MRI 9 weeks after treatment

Lived for 12 months more without systemic treatment and Good QoL

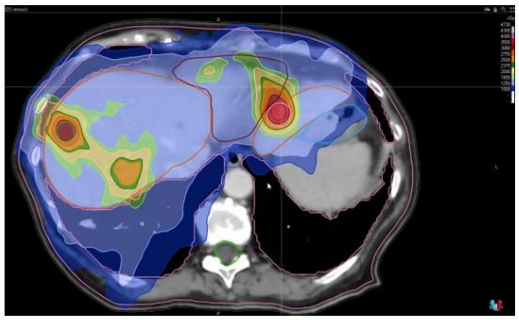
Died from peritoneal infection

Metastatic melanoma

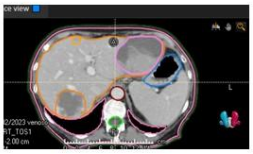
Progresion after immunotherapy

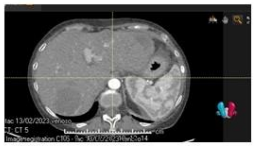
No options for treatment

PTV liver= 10 Gy (5 x 2 Gy)
PTV left lobe metastases= 25 Gy (5 x 5 Gy)
Boost Lattice lef lobe= 18 Gy
Boost to >10 metastases: 18 Gy



February 2023 April 2023

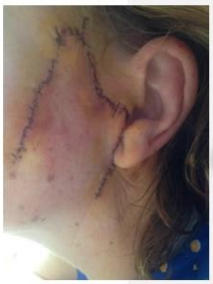


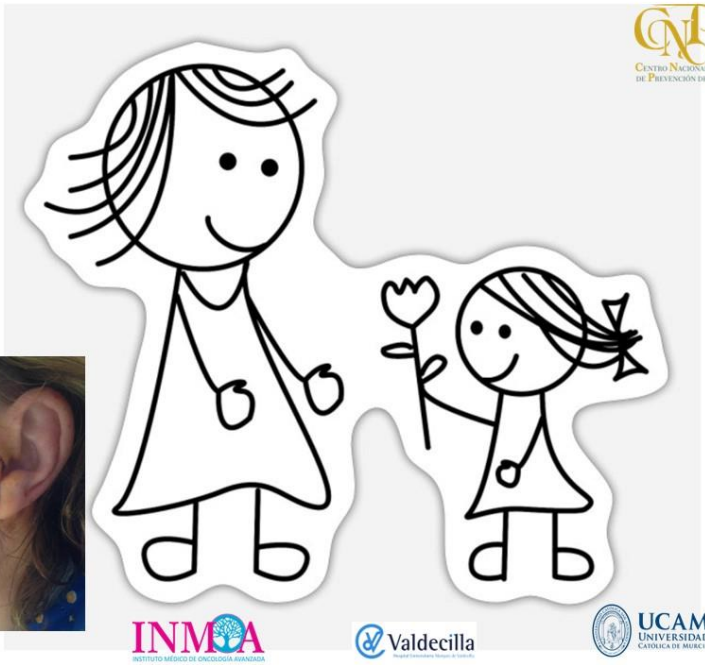


Stable disesease
Still alive
Now with Nivolumab

My mum

55yo Melanoma in cheek
T3N0M0
No adjuvant treatment
December 2015





My mum

June 2018 brain metastases
Surgery
Radiosurgery

September 2018: 4 more metastases
4 types of immunotherapy
Almost death for side effects

March 2019 no options for treatment

What I did?

RT to every lesion in single dose + mEHT

My mum now...

- More than 12 distant metastases...
- Some >7cm
- Free of disease

Muchas gracias

More than 2500m2...
2 clinics (Madrid and Bilbao)

First Cancer Prevention Center in Europe

CONCLUSIONS

- The key of cancer cure is immune system
- Radiotherapy is a very powerful tool to kill malignant cells locally but also to stimulate immune system (abscopal effect).
- Hyperthermia is a very powerful tool to increase radiotherapy, chemotherapy and immunotherapy effect not only locally, but also sistemically as it also stimulates immune system (abscopal effect).
- Oncological treatment combination is the key to have a Good tumor control and survival without significant side effects.
- More research is needed...

Valdecilla Cantabria, España

CNPC Centro Nacional de Prevención del Cáncer

INMOA Instituto Médico de Oncología Avanzada

Madrid
Bilbao

UCAM Universidad Católica de Murcia

Thank you!!! earrojo@inmoa.es

Modulated electro-hyperthermia more than doubles five year disease free survival rates in advanced cervical cancer patients in South Africa

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

Dr. Carrie A. Minnaar

Oncologic Hyperthermia Specialist
Wits Donald Gordon Medical Centre, Johannesburg, South Africa

Citation

Minnaar, C.A. (2024) Modulated electro-hyperthermia more than doubles five year disease free survival rates in advanced cervical cancer patients in South Africa,
Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.
https://youtu.be/qXK_iHG37nk,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

Oncothermia Journal 35, July 2024: 100-112.
https://oncotherm.com/MinnarCA_2024_mEHT-more-than-doubles-5-year-disease-free-survival_20240601

Modulated electro-hyperthermia more than doubles five-year disease-free survival rates in advanced cervical cancer patients in South Africa

Minnaar C.A.[1,2]

[1] University of Witwatersrand, South Africa
[2] Wits Donald Gordon Academic Hospital, South Africa

Oncotherm

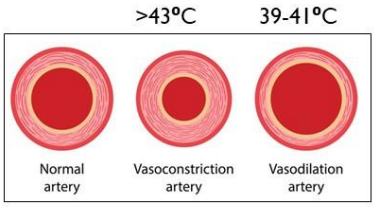
Wits University Donald Gordon Medical Centre
Patient-centred. Independent. Academic.

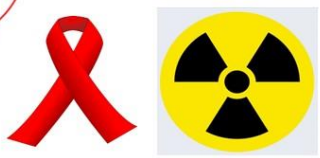
MEDICLINIC

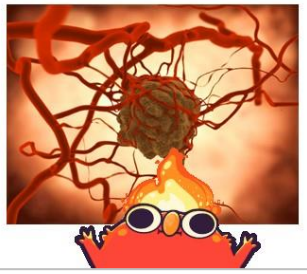
Outline:

- ✓ Introduction
- ✓ Methodology
- ✓ Safety
- ✓ Local Disease Control
- ✓ Long Term Control
- ✓ Systemic Control
- ✓ Future Perspectives

Introduction: Heat as a radio-sensitiser







Introduction: Heat as a radio-sensitiser

39-41°C = vasodilation

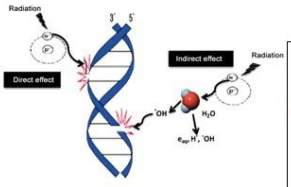
↑↑↑ Blood =

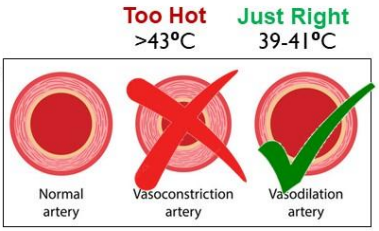
↑↑↑ Oxygen:

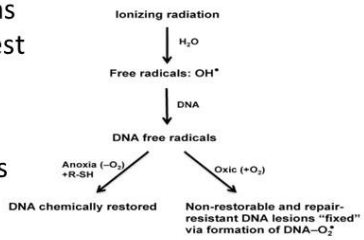
✓ increases ROS formation

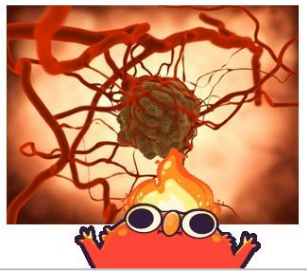
✓ inhibits repair from DSBs as the repair processes work best in an anoxic environment

✓ Heat slows down protein function, which further slows repair processes



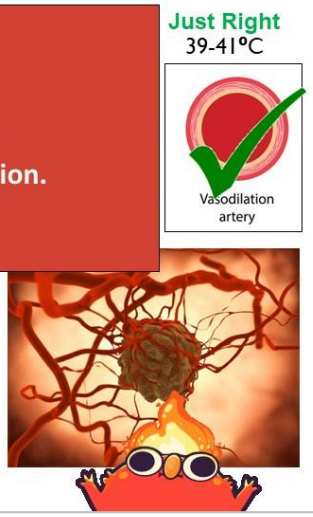






Introduction: Heat as a radio-sensitiser

Mild Heat = excellent radiosensitiser:
increasing the indirect cell kill effect for RT
and inhibiting the repair processes post irradiation.



Introduction: Heat as a radio-sensitiser

20 patients with cervical cancer were treated with mEHT

Measurements

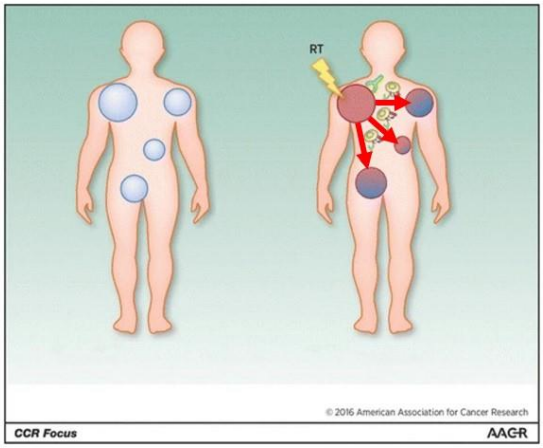
- **Temp**: Peri-tumour using an internal organ temperature probe
- **Blood flow**: 3D colour Doppler ultrasound used to determine peak systolic velocity end diastolic velocity ratio *(SID* ratio) and the resistance index (RI) within blood vessels.

Results:

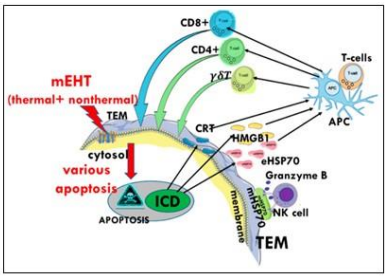
- **Temp:** mean peri-tumour temperature
  - Baseline: 36.7 ± 0.2 °C
  - 30 minutes: 37.5 ± 0.5 °C
  - 60 minutes: 38.5 ± 0.8 °C
- **Blood flow**:
  - *mEHT = significant increase in tumour blood flow*

Lee S-Y, *et al*, **The effect of modulated electro-hyperthermia on temperature and blood flow in human cervical carcinoma.** *International Journal of Hyperthermia*. 2018;34(7):953-960.

Introduction: Immuno-modulation



Abscopal effect:
Immune mediated response to RT resulting in resolution of lesions outside the treatment field



Introduction: Immuno-modulation

mEHT damages cell membranes

Promotes ICD and DAMP

= apoptosis and release of apoptotic bodies

= release of mHSPs into the extra cellular matrix

→ transport intracellular antigenic peptides to DCs

= maturation of DCs into APCs

→ produce antigen-specific cytotoxic T-lymphocytes and activated NK cells

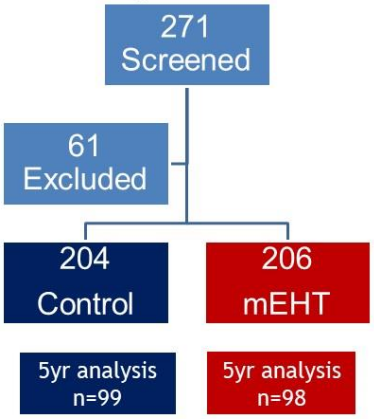
Potentially = adaptive immune response

Immunogenic Hyperthermia = mild heat + immune-modulation

Minnaar CA, Szasz A. Forcing the Antitumor Effects of HSPs Using a Modulated Electric Field. Cells. 2022 Jun 4;11(11):1838. doi: 10.3390/cells11111838. PMID: 35681533;

Methodology:

Phase III RCT 2014-2023
HR Ethics Committee : M1704133
ClincialTrials.gov ID: NCT03332069



Methodology:

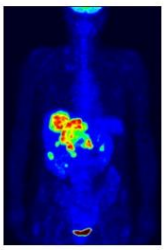
Sample:
Stage IIB-IIIB
Staged clinically: exam, chest x-ray; abdominal/pelvic ultrasound.

Control Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m^2
cisplatin

Randomised using an online tool (RedCap)
Stratum: stage; age; HIV status

Intervention Group
50Gy EBRT
3x8Gy HDR
BT, 80mg/m^2
cisplatin
+ mEHT

HIV-positive participants were included provided their CD4 count was >200cells/mm^3 /they had been on ART for >6m.



LDC:
PET/CT pre-treatment & 6m post-treatment.

Survival:
Last known disease status used for LTFU

QoL:
EORTC CX24 forms

Statistics:
Kaplan-Meier charts; Log rank tests; frequency tables; Markov model

Clinicians conducting follow ups were blinded to the group

Methodology:

mEHT

- 2 x per week
- Immediately before external bean RT

Results: Safety

6 months post treatment

- No dose-limiting toxicities
- High Compliance (97% completed ≥8 treatments)
- No significant differences in CRT-related toxicity between treatment groups
- Toxicity:
  - grade 1–2 adipose burns: 9.5%
  - grade 1 surface burns: 2%
  - pain during mEHT: 8.6%

IJH INTERNATIONAL JOURNAL OF HYPERTHERMIA and thermal therapies

Late Toxicity

At three years still no difference in late toxicities between the groups

cancers

No effect on late toxicity at 5 years

ESTRO 2024

Results: Local Disease Control

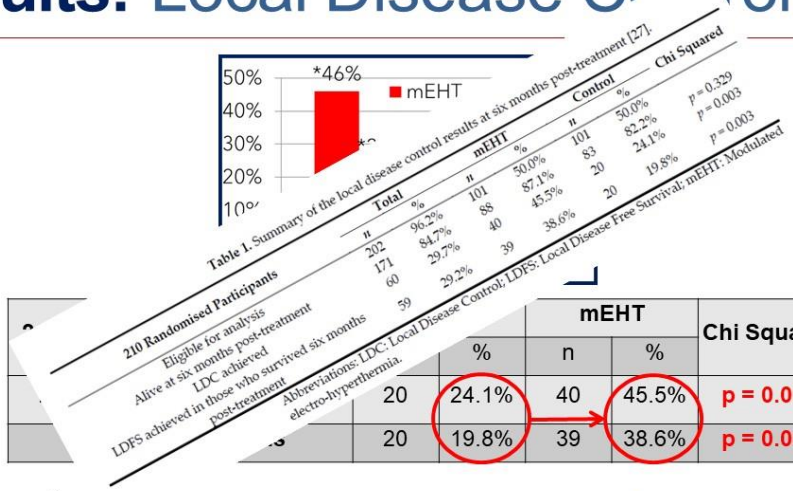


Table 1. Summary of the local disease control results at six months post-treatment [27].

	Total		mEHT		Control		Chi Squared
210 Randomised Participants	n	%	n	%	n	%	
Eligible for analysis	202	96.2%	101	50.0%	101	50.0%	$p = 0.329$
Alive at six months post-treatment	171	84.7%	88	87.1%	83	82.2%	$p = 0.003$
LDC achieved	60	29.7%	40	45.5%	20	24.1%	$p = 0.003$
LDFS achieved in those who survived six months post-treatment	59	29.2%	39	38.6%	20	19.8%	

Abbreviations: LDC: Local Disease Control; LDFS: Local Disease Free Survival; mEHT: Modulated electro-hyperthermia.

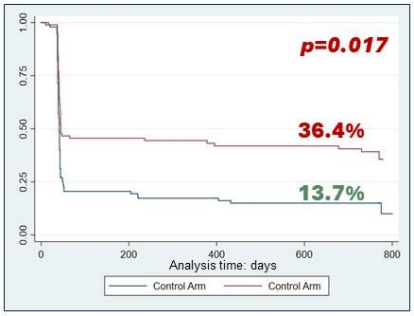
			mEHT		Chi Squared
	n	%	n	%	
	20	24.1%	40	45.5%	p = 0.003
	20	19.8%	39	38.6%	p = 0.003

PLOS ONE

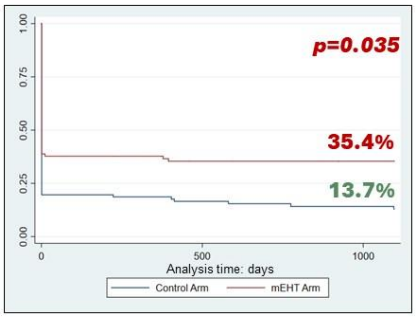
ESTRO 2024

Results: Three-year Survival

2 Year Disease Free



3 Year Disease Free



	OR	p=value	[95%CI]
2 year	3.59	*0.001*	1.79-7.21
3 year	3.4	*0.001*	1.71-6.91

cancers

Results: Quality of Life

Table 9. Mean change in scores from baseline to 24 months in the mEHT and Control Group.

	mEHT				Control			
	Mean	SD	95%CI	*p*-Value	Mean	SD	95%CI	*p*-Value
Visual Analogue	25.1	21.5	16.6 to 33.6	$p < 0.0001$	15.6	31.9	2.9 to 28.2	$p = 0.0176$
Global Health	23.2	31.7	11.7 to 35.6	$p = 0.0002$	17.3	29.1	6.0 to 28.6	$p = 0.0041$
Financial Burden	−26.1	60.9	−48.0 to 4.1	$p = 0.0216$	−16.7	46.7	−34.8 to 1.4	$p = 0.0698$
Symptom Scales								
Pain Reduction	−34.4	32.8	−46.2 to −22.6	$p = 0.0001$	−15.5	35.7	−29.3 to −16	$p = 0.0298$
Nausea/Vomiting	−13.0	27.7	−23.0 to −3.0	$p = 0.0122$	−1.2	18.7	−8.4 to 6.1	$p = 0.7383$
Fatigue reduction	−18.4	27.9	−28.5 to −8.4	$p = 0.0008$	−10.7	34.0	−23.9 to 2.4	$p = 0.1071$
Functional Scales								
Social	12.0	31.2	0.7 to 23.2	$p = 0.0375$	17.3	41.7	1.1 to 33.4	$p = 0.0373$
Cognitive	19.8	33.2	7.8 to 31.6	$p = 0.0020$	−4.2	28.9	−15.4 to 7.0	$p = 0.4523$
Emotional	27.3	30.3	16.4 to 38.3	$p < 0.0001$	17.9	34.2	4.6 to 31.1	$p = 0.0101$
Role Function	9.4	35.1	−3.3 to 22.1	$p = 0.1415$	7.1	35.0	6.4 to 20.7	$p = 0.2893$
Physical	11.7	21.2	4.0 to `9.3	$p = 0.0040$	2.6	27.2	−7.9 to 13.2	$p = 0.6150$

Abbreviations: FIGO: CI: Confidence Interval, mEHT: Modulated Electro-Hyperthermia; SD: Standard Deviation.

Overall significant improvement in 10 out of 11 scores in the mEHT group at 2 years

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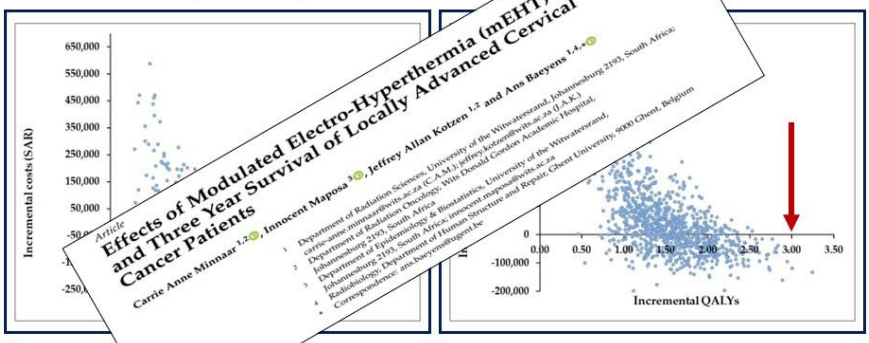
Results: Cost Effectiveness Analysis

Government model
82.2% probability



Article

Effects of Modulated Electro-Hyperthermia (mEHT) on Two and Three Year Survival of Locally Advanced Cervical Cancer Patients

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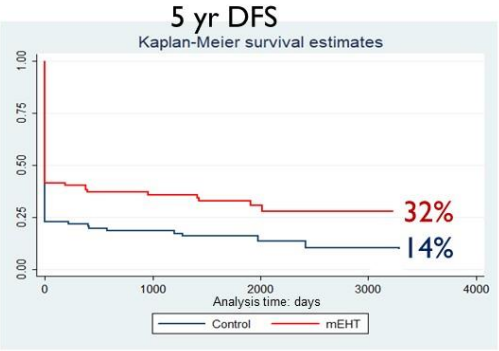
- mEHT + [illegible]nated the model
- mEHT + CR[illegible] less costly and more effective

cancers

Results: Five-year Survival

5yr OS	mEHT	Control	
All	33% [33/99]	26% [25/98]	HR:0.74; 95%CI:0.53-1.03; p=0.083
Stage III	**34% [21/61]**	**23% [15/65]**	HR:0.65; 95%CI:0.43-0.99; p=0.046



OR:3.00; 95%CI:1.49-6.07; ***p=0.002;***
HR:0.73; 95%CI:0.53-1.00; ***p=0.049;***
Chi2: ***p=0.002***

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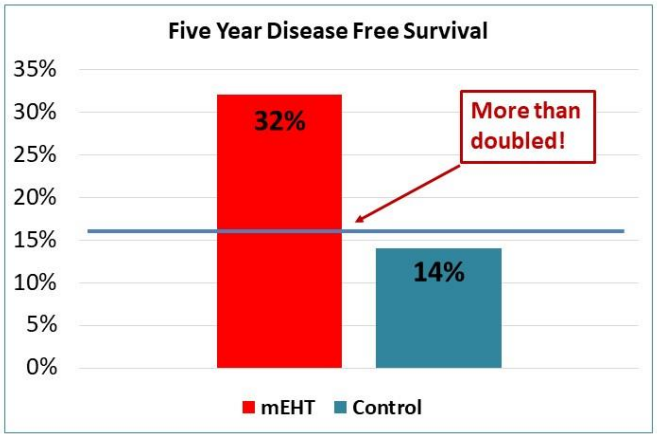
Results: Five-year Survival



32%[32/99] of hyperthermia participants

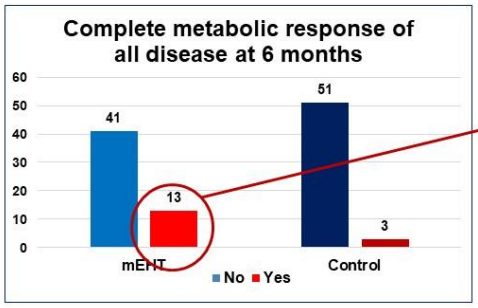
14%[14/102] of control participants

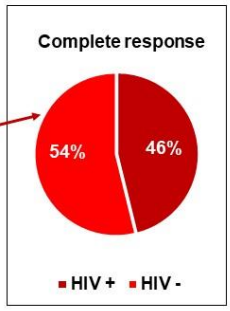
Achieved 5 years DFS

Odds were increased by 3x!

Results: Abscopal Response

- 108 Participants had extra pelvic disease on the pre-treatment PET/CT
- 54 participants in each group





In a multivariate analysis:
- Age,
- Number of cisplatin doses,
- Total RT dose,
- Days between last RT and PET/CT,

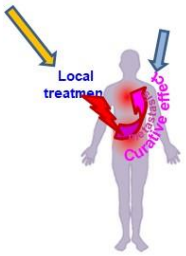
were not associated with an abscopal effect

In a univariate analysis, CD4 count was also not predictive of an abscopal effect

frontiers in Medicine

Results: Systemic Immune Response

SYSTEMIC RESPONSE
- Participants with stage IVB disease outside the pelvis,
- who showed an abscopal response at 6 months,
- remained disease free at 5 years
- With the exception of 2 participants who died of non-cancer related causes



Ladies with stage IV disease outside the pelvis were cured with the addition of a simple local treatment!

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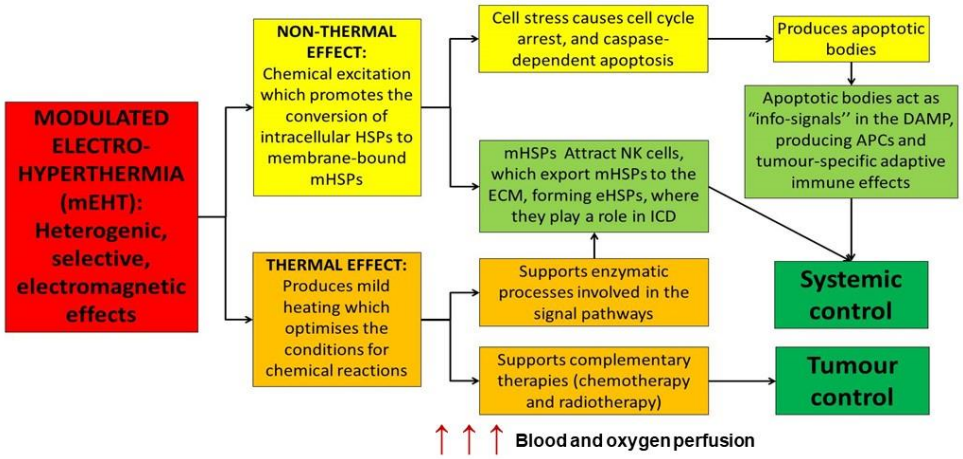
Results: Immunogenic Response



Minnaar CA, Szasz A. Forcing the Antitumor Effects of HSPs Using a Modulated Electric Field. *Cells*. 2022 Jun 4;11(11):1838

Conclusion:

Oncothermia added to CRT for LACC

- ✓ Significantly increases 5y DFS rates,
- ✓ Safely,
- ✓ While lowering treatment costs,
- ✓ And improving Quality of Life.

- ✓ Promotes a sustained long-term, immune-mediated, systemic response to the disease.

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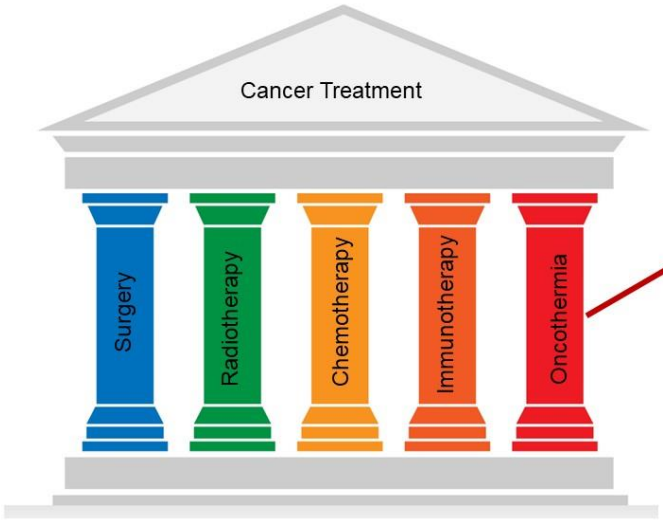
Future Perspectives:



ONCOTHERMIA: Synergistically working with available treatments to promote an immune-mediated, sustained response to cancer.

Thank you

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Oncotherm
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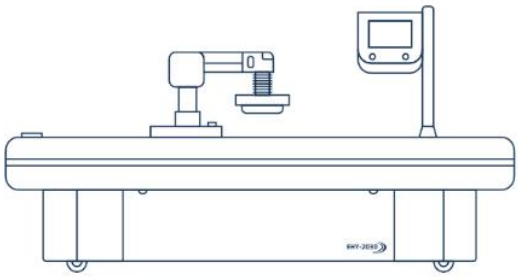
EHY-2030

Loco-regional modulated electro-hyperthermia (mEHT) device

The EHY-2030 is Oncotherm's latest development for the loco-regional treatment of tumors. The newly designed device includes the Smart Electrode system and the integrated Patient Management System (PMS) and a user-friendly touch screen display with full system control. The new RF generator with impulse mode increased peak power has been developed with a new intelligently controlled step motor tuning system for rapid impedance matching to achieve shorter tuning-time.

The EHY-2030 device is a CE-marked medical device, and is intended for professional use.



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