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Editorial

Dear Readers, Dear Fellow Researchers, Dear Colleagues,

Our Journal's recent volume gives you a complete summary about the 38th Conference of the International Clinical Hyperthermia Society (ICHS), held on the 5th of November 2020. The organization of the conference was unusual due to the nonconventional conditions. After careful consideration of the pandemic's difficult circumstances, we arranged the conference online on Zoom platform.

The online discussions were more successful than expected. Despite the time zone differences, we were happy to see that 90 participants were able to attend, representing the following 28 countries: Australia, Brazil, Colombia, Ecuador, Georgia, Germany, Greece, Hungary, Italy, Mexico, Mumbai, North Macedonia, Norway, Pakistan, Peru, Portugal, Russia, Saudi Arabia, South Africa, South Korea, Spain, Switzerland, Syria, Taiwan, the Netherlands, the UK, the USA and Vietnam. The presenters were from the Universities of Germany, Hungary, South Africa, Spain, Switzerland, and Taiwan. In the first session of the conference new clinical results were discussed. The second session focused on preclinical information of the experimental research. A keynote speech by Professor Stephan Bodis (Switzerland) opened the clinical session. He summarized the strengths and threats of hyperthermic oncology, showing our achieved status in the medical processes giving a general overview of the particular challenges and results. The presentations that followed the keynote speech showed clinical results on painful bone metastases, sarcomas, inoperable pancreas cancers, and pediatric application of hyperthermia. In the second session, the keynote presentation was biophysical, presented by Professor Peter Wust (Charité, Berlin). It was followed by immune-related experimental topics. The perspectives were discussed at the end of the session. The successful meeting was summarized and closed by the president of ICHS, Doctor Elisabeth Arrojo (Valdecilla University, Spain).

Enjoy the present volume of the Oncothermia Journal informing you about this particularly successful and informative event. In case of interest, visit our YouTube Channel to see the online video-recordings of any chosen topic. With this, you may be a virtual participant of the event. Doctor Arrojo and the organizers of ICHS would be happy to read your comments and notes. In case you have any, please contact Ms. Ilka Schulz, the managing editor, via her email address schulz@oncotherm.de.

I do hope this volume also offers relevant and up to date information for your everyday practice.

I am thankful for your attention.

Prof. Andras Szasz
Editor of the Oncothermia Journal
Biotechnics Department of St. Istvan University

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

der aktuelle Band unseres Journals enthält die vollständige Zusammenfassung der 38. Konferenz der International Clinical Hyperthermia Society (ICHS), die am 5. November 2020 stattfand. Die Organisation war aufgrund der aktuellen Bedingungen anders als sonst und nach sorgfältiger Abwägung der durch die Pandemie verursachten Umstände wurde die Konferenz online auf Zoom organisiert.

Die Online-Diskussionen waren erfolgreicher als zunächst erwartet. Wir haben uns sehr gefreut, dass trotz der verschiedenen Zeitzonen 90 Teilnehmer aus den folgenden 28 Ländern teilnehmen konnten: Australien, Brasilien, Deutschland, Ecuador, Georgien, Griechenland, Großbritannien, Italien, Kolumbien, Mexiko, Mumbai, Niederlande, Nordmazedonien, Norwegen, Pakistan, Peru, Portugal, Russland, Saudi-Arabien, Schweiz, Spanien, Südafrika, Südkorea, Syrien, Taiwan, Ungarn, USA und Vietnam. Die Referenten selbst waren Angehörige von Universitäten in Deutschland, Ungarn, Südafrika, Spanien, der Schweiz und Taiwan. Während des ersten Teils der Konferenz wurden neue klinische Ergebnisse diskutiert. Der Zweite konzentrierte sich auf präklinische Informationen der experimentellen Forschung. Eine Grundsatzrede von Professor Stephan Bodis (Schweiz) stellte den Auftakt des klinischen Teils dar. Er fasste die Stärken und Schwächen der hyperthermischen Onkologie zusammen und zeigte mithilfe eines allgemeinen Überblicks über die besonderen Herausforderungen und Ergebnisse den Status der medizinischen Prozesse. Die Präsentationen, die auf die Grundsatzrede folgten, zeigten klinische Ergebnisse zu Knochenmetastasen, Sarkomen, inoperablen Pankreaskarzinomen und zur pädiatrischen Anwendung von Hyperthermie. Der zweite Teil wurde durch die biophysikalische Keynote-Präsentation von Professor Peter Wust (Charité, Berlin) eingeleitet. Es folgten immunbezogene experimentelle Themen. Zudem wurden am Ende die Standpunkte diskutiert. Abschließend wurde das gelungene Meeting von der Präsidentin der ICHS, Doktor Elisabeth Arrojo (Valdecilla Universität, Spanien), zusammengefasst.

Erfreuen Sie sich an dem vorliegenden Band des Oncothermia Journals, der Sie über diese besonders erfolgreiche und aufschlussreiche Veranstaltung informiert. Besuchen Sie bei Interesse gerne unseren YouTube-Kanal, um sich die Videoaufnahme zu ausgesuchten Themen anzusehen und so ein virtueller Teilnehmer der Veranstaltung zu werden. Doktor Arrojo und die Organisatoren der ICHS freuen sich, Ihre Kommentare und Anmerkungen zu lesen. Bitte wenden Sie sich dazu per E-Mail an die Chefredakteurin Ilka Schulz (schulz@oncotherm.de).

Ich hoffe, dieser Band bietet Ihnen relevante und aktuelle Informationen für Ihre tägliche Praxis.

Ich bin dankbar für Ihre Aufmerksamkeit.

Prof. Andras Szasz
Herausgeber des Oncothermia Journals
Lehrstuhl für Biotechnik, St. Istvan Universität

Letter from the President of ICHS

"Difficulties are the only thing that have the power to make us grow in skills ..."

In these current times when we believed we were so advanced as to think that pandemics were a thing of the past, or of underdeveloped countries; where the great world powers, a few months ago, even showed a certain pride, believing themselves invincible to what was devastating their neighbors ... Times that force us to rethink our priorities as a society. Times in which we prove how the rich and the poor are equal in their condition of finite humans ... Times, as Darwin would say, of evolution for survival, we should stop to reflect upon such a strong impact like the one we are suffering.

Stephen Hawking said that "The worst enemy of knowledge is not ignorance; it is the illusion of knowledge." Unfortunately, we have seen and are seeing, how the illusion of knowledge in the global measures in the face of the COVID-19 pandemic, which have been affirmed as safe, with subsequent disastrous results, have caused dramatic consequences. And this shows, how without investigation, without real knowledge, we will not get the weapons we need to protect our physical and mental integrity. We cannot suppose, we need "to know".

I hope that this pandemic situation improves and disappears as soon as possible, although very tough months are still ahead. But my greatest wish after this, is that this terrible situation, at least helps us to grow as human beings with values. May all this serve to put on the table what really matters. That once and for all, the scientific world can be supported in its research to improve and protect our being, our health. Research will always have an important component of personal and professional sacrifice of the researchers, but at least, that it stops being a heroic task, in which getting involved makes those people who put all their talent and effort in their great investigations ending many times exhausted, desolated, ruined, and even despised.

All my respects to all the brilliant people that exist in our world in various disciplines. But hopefully one day, we will see mass celebratory meetings with society in the street, each time we win a great "scientific match", each time a researcher finds something great which will improve our lives.

Having said that, and as human beings have great resilience, I am sure that all of this will make us stronger. In fact, we are already getting stronger. As highly adaptable beings, we are making an immense effort to carry on with our lives in the middle of the chaos. The scientific world continues to fight even harder against difficulties. We have seen our research suspended or delayed, but here we are, at this 38th Conference of the International Clinical Hyperthermia Society, to continue blazing a trail on the hard and thorny path of cancer, opening new paths that will lead us to a better destination. I do not know if one day humanity will be able to eradicate cancer, but I do know that it will cease to be one of the main causes of death, thanks to the efforts of so many researchers. Thanks to all the people who hold out your hand, sharing your experience, knowledge and dedication on the hard path of scientific knowledge.

And one last thought, this time addressed to our world leaders. People with COVID-19 without treatment may die. People with cancer, without treatment, will die for sure. Let us not try to fix a problem creating a bigger one ... "Difficulties often prepare an ordinary person for an extraordinary destiny" (C.S. Lewis).

Elisabeth Arrojo, MD
PhD Radiation oncologist
President of the ICHS

„Schwierigkeiten sind das Einzige, was uns dazu bringt, unsere Fähigkeiten zu verbessern ..."

In den heutigen Zeiten, in denen wir geglaubt haben, dass Pandemien der Vergangenheit angehörten; in denen vor einigen Monaten die Weltmächte sogar mit einem gewissen Stolz zeigten, dass sie sich für unangreifbar gegenüber dem hielten, was bereits verheerende Folgen für ihre Nachbarn hatte ... Zeiten, die uns zwingen, unsere Prioritäten als Gesellschaft zu überdenken. Zeiten, in denen sich zeigt, dass sowohl die Reichen als auch die Armen nur Menschen sind ... Zeiten der Evolution, um zu überleben, wie Darwin sagen würde, in denen wir innehalten sollten, um über die gegenwärtigen Auswirkungen nachzudenken.

Stephen Hawking sagte: „Der schlimmste Feind des Wissens ist nicht Unwissenheit, sondern die Illusion von Wissen." Leider sehen wir auch weiterhin die dramatischen Folgen der als sicher bestätigten Maßnahmen im Angesicht der COVID-19-Pandemie, verursacht durch eine Illusion von Wissen. Und dies zeigt, wie wir ohne Forschung und ohne wirkliches Wissen nicht die nötigen Werkzeuge erschaffen können, die wir brauchen, um unsere körperliche und geistige Unversehrtheit zu bewahren. Wir können nicht annehmen, wir müssen "wissen".

Ich hoffe, dass die Pandemiesituation so schnell wie möglich bewältigt werden kann. Aber mein größter Wunsch ist es, dass uns diese furchtbare Situation zumindest hilft, als Menschen zu wachsen. Möge all dies dazu dienen, das zu fördern, was wirklich wichtig ist. Dass die wissenschaftliche Welt in ihrer Forschung unterstützt wird, um unsere Gesundheit zu verbessern und zu schützen. Persönliche und berufliche Opfer der Forscher werden immer Teil der Forschung sein, doch zumindest die Forschung selbst sollte aufhören als heldenhafte Aufgabe angesehen zu werden, deren Erfüllung die Menschen, die all ihr Talent und ihre Energie in sie legen, oft entkräftet und ruiniert.

Mein Respekt gilt all den brillanten Menschen aus den unterschiedlichsten Bereichen der Wissenschaft. Hoffentlich werden die Menschen in Zukunft feiern, wenn ein bedeutender wissenschaftlicher „Wettkampf" gewonnen wurde oder ein Forscher etwas findet, dass unser Leben verbessern wird.

Ich bin mir sicher, dass all dies uns stärker machen wird, da wir Menschen mit genug Widerstandskraft ausgestattet sind. Tatsächlich wachsen wir bereits daran. Als sehr anpassungsfähige Wesen sind wir immer bestrebt, unser alltägliches Leben inmitten des Chaos weiterzuleben. Die wissenschaftliche Welt kämpft noch härter gegen Hindernisse. Wir haben gesehen, dass unsere Forschungen ausgesetzt oder verzögert wurde, aber dennoch haben wir uns auf dieser 38. Konferenz der International Clinical Hyperthermia Society getroffen, um weiterhin gegen den Krebs zu kämpfen und neue Wege zu finden, die uns an einen besseren Ort führen. Ich weiß nicht, ob die Menschheit eines Tages in der Lage sein wird, den Krebs auszurotten, aber ich weiß, dass er dank der Bemühungen so vieler Forscher keine der Haupttodesursachen mehr sein wird. Vielen Dank an alle Menschen, die Ihre Erfahrungen und Ihr Wissen teilen.

Ein letzter Gedanke, der an die Regierungen dieser Welt gerichtet ist. Menschen, die an COVID-19 erkranken und nicht behandelt werden, können sterben. Menschen, die an Krebs erkranken und nicht behandelt werden, sterben bestimmt. Lassen Sie uns also nicht versuchen, ein Problem mit einem noch größeren zu lösen ... „Schwierigkeiten bereiten einen gewöhnlichen Menschen oft auf ein außergewöhnliches Schicksal vor" (C.S. Lewis).

Dr. Elisabeth Arrojo
Strahlenonkologin
Präsidentin der ICHS

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 höchstmöglichen 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 elektrisches Feld, bioelektromagnetische Anwendungen bei Tumoren, Kombination von Oncothermie und anderen Modalitäten, Effekte auf normale und maligne Zellen und Gewebe, immunologische Effekte, physiologische Effekte etc.
   - Oncothermie-Techniken: technische Entwicklungen, neue technische Lösungen
   - Hypothesen und Meinungen, 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 Bibliografie erfolgt numerisch in Reihenfolge der Erwähnung im Text.

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Wenn die Korrekturfahnen fertig gestellt sind, werden die Autoren per E-Mail informiert. Gedruckte Kopien werden nicht per Post versandt. Um Verzögerungen in der Produktion zu verhindern, müssen die korrigierten Texte innerhalb von 48 Stunden per E-Mail oder Fax zurückgesandt werden.

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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.

8. **Legal responsibility**

   Authors of any publications in the Oncothermia Journal are fully responsible for the material which is published. The Oncothermia Journal has no responsibility for legal conflicts due to any publications. The editorial board has the right to reject any publication if its validity has not been verified enough or the board is not convinced by the authors.

   Haftung

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

9. **Reviewing**

   The Oncothermia Journal has a special peer-reviewing process, represented by the editorial board members and specialists, to whom they are connected. To avoid personal conflicts the opinion of the reviewer will not be released and her/his name will be handled confidentially. Papers which are not connected to the topics of the journal could be rejected without reviewing.

   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.

Contents

Integrating loco-regional hyperthermia into the current oncology practice: A SWOT and TOWS analysis

Niloy R. Datta[1], H. Petra Kok[2], Hans Crezee[2], Udo Gaipl[3], Stephan Bodis[1]

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www.oncotherm.com/sites/oncotherm/files/2021-02/Datta_Integrating

Abstract

Moderate hyperthermia at temperatures between 39 and 45°C is a multifaceted therapeutic modality. It is a potent radiosensitizer, interacts favorably with a host of chemotherapeutic agents and with RT enforces immunomodulation akin to "in situ tumor vaccination." By sensitizing hypoxic tumor cells and inhibiting repair of radiotherapy-induced DNA damage, the properties of hyperthermia delivered with photons provides a tumor-selective therapeutic advantage analogous to high LET neutrons, but without normal tissue toxicity. Furthermore, the high LET attributes of hyperthermia thermoradiobiologically enhance low LET protons; thus, proton thermoradiotherapy mimics 12C ion therapy. Hyperthermia with radiotherapy and/or chemotherapy substantially improves therapeutic outcomes without enhancing normal tissue morbidities yielding level I evidence as reported in several randomized clinical trials, systematic reviews and meta-analyses for various tumor sites. Further, hyperthermia along with immune check point inhibitors and DNA damage repair inhibitors could further augment the therapeutic efficacy resulting in synthetic lethality. Besides technological advancements in hyperthermia delivery, complemented by hyperthermia treatment planning, its integration with radiotherapy treatment plans, online thermometry and adherence to quality assurance guidelines have all ensured safe and effective delivery of hyperthermia to the target region. Additionally, hyperthermia induced by magnetic nanoparticles coupled to selective payloads provides a comprehensive tumor-specific theranostic modality akin to "magic (nano)bullets." To get a realistic overview of the strength (S), weakness (W), opportunities (O) and threats (T) of hyperthermia, a SWOT analysis has been undertaken. Additionally, a TOWS analysis categorizes future strategies to facilitate further integration of hyperthermia with the current treatment modalities. These could gainfully accomplish a safe, versatile and cost-effective enhancement of the existing therapeutic armamentarium to improve outcomes in clinical oncology.

Keywords: hyperthermia, radiation therapy, chemotherapy, immunotherapy, radiosensitizer, hyperthermia treatment planning, SWOT analysis, clinical trials

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

38. ICHS Meeting (Online!)

Integrating loco-regional hyperthermia into current oncology practice: A SWOT and TOWS analysis

2020 update of oncologic thermotherapy activities in EU/CH

Stephan Bodis on behalf of the Swiss Hyperthermia Network (SHN)
5.11.2020

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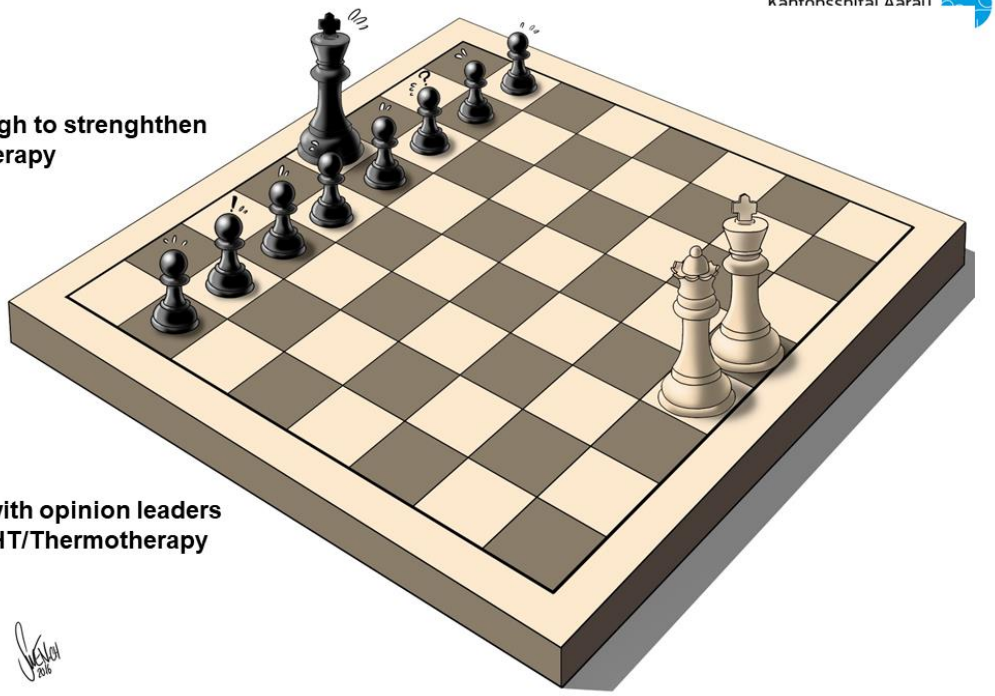
SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

1 strong partner is enough to strenghthen oncologic HT/Thermotherapy



Use meeting debates with opinion leaders to promote oncologic HT/Thermotherapy

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

The future of Oncologic Thermotherapy is Technology

Niels Kuster

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SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

Niels Kuster

Prof. Niels Kuster is the founder and Director of the Foundation for Research on Information Technologies in Society (IT'IS Foundation) in Zurich, Switzerland, and Associate Professor of the Department of Information Technology and Electrical Engineering at ETH Zurich.

His research covers many aspects of electromagnetics and computational life sciences, and focus, in particular, on the modeling of both internal and external physical factors that affect human physiology. These include electromagnetic fields (e.g. MR safety assessments), tissue heating and cooling (e.g. hyperthermia and ablation), acoustics in biology (e.g. focused ultrasound/pressure waves), biofluid dynamics (e.g. blood flow and aneurysm), biomechanics (e.g. bone, ligaments, and arterial walls), and dynamic tissue models (e.g. nerve models and tumor growth).

Prof. Kuster has published over 700 publications in books, journals, and proceedings on measurement techniques, computational electromagnetics, dosimetry, exposure assessments, and bioexperimentation. He is a long-time member of several standardization bodies and serves as a consultant on exposure safety assessment for governmental agencies around the globe.

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SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

The future of Oncologic Thermotherapy is Biology

Jean Bourhis

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SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

Jean Bourhis

Prof. Bourhis has been Chairman of the Radiation Oncology at the Institute Gustave Roussy (Villejuif, France), one of the most prominent Cancer Center in Europe, and moved in 2012 to the CHUV as Head of Radiation Oncology.

His clinical activity is focused on Radiation Oncology Head and Neck cancers, he is chairman of the GORTEC, a cooperative group dedicated to Head and Neck Oncology.

Prof. Bourhis has been for 15 years also Director of a laboratory dedicated to Translational Research in Radiation Oncology. He authored more than 300 scientific papers.

Prof. Bourhis is also Past President of the European Society for Radiotherapy and Oncology (ESTRO), Past President of the ESTRO Cancer Foundation and currently serves as SASRO President."

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frontiers in Oncology

Datta et al.
June 2020

Integrating Loco-Regional Hyperthermia Into the Current Oncology Practice: SWOT and TOWS Analyses

Niloy R. Datta[1*], H. Petra Kok[2], Hans Crezee[2], Udo S. Gaipl[3] and Stephan Bodis[1]

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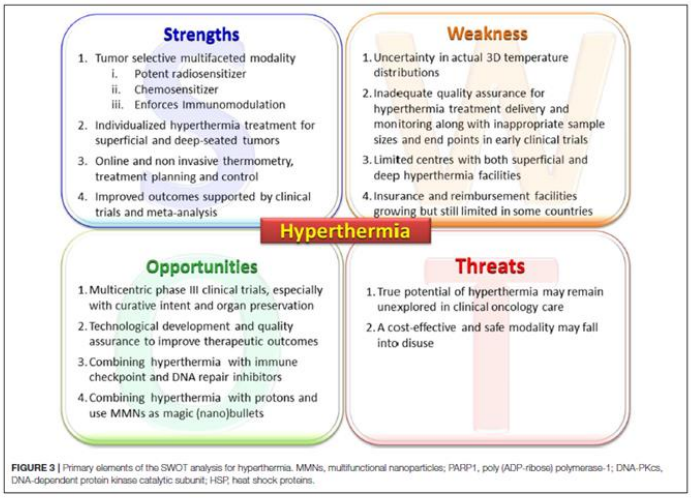
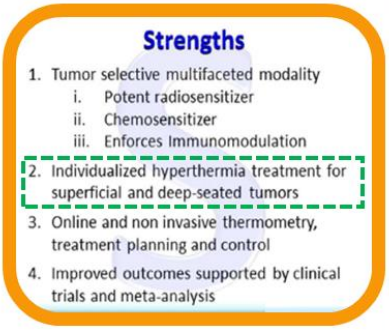
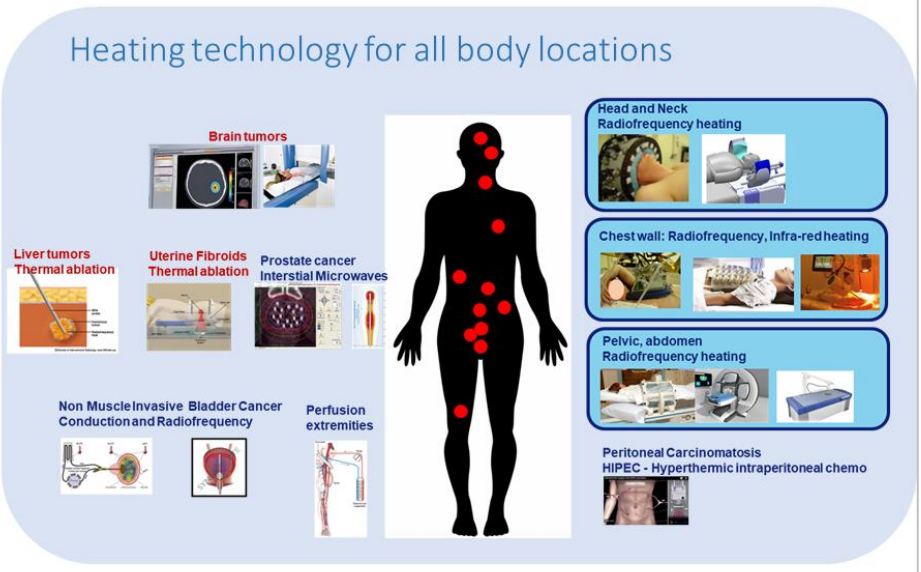


FIGURE 3 | Primary elements of the SWOT analysis for hyperthermia. MMNs, multifunctional nanoparticles; PARP1, poly (ADP-ribose) polymerase-1; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; HSP, heat shock proteins.

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020





Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

Strengths

1. Tumor selective multifaceted modality
   i. Potent radiosensitizer
   ii. Chemosensitizer
   iii. Enforces Immunomodulation
2. Individualized hyperthermia treatment for superficial and deep-seated tumors
3. Online and non invasive thermometry, treatment planning and control
4. Improved outcomes supported by clinical trials and meta-analysis

Clinical evidence hyperthermia

> 27 positive randomized trails RT or CT ± HT

Reference	Treatment	Tumor	Endpoint	Lesions	RT/CT	RT/CT+HT
Van Driel (2018)	CT (hipec)	Ovarian	med Surv.	245	33.9m	45.7m
Issels (2018)	CT	Soft tissue sarcoma	med. Surv.	329	6.2yrs	15.4yrs
Chi (20018)	RT	Painful Bony mets	Time2pain prog	57	55d	>168d
Zhao (2014)	RT	Nasopharynx	3yr OS	83	54%	73%
Kang (2013)	RT+CT	Nasopharynx	5yr OS	154	50%	68%
Hua (2011)	RT+CT	Nasopharynx	5yr PFS	180	63%	73%
Huilgol (2010)	RT	Head and Neck	CR	54	42%	79%
Jones (2005)	RT	Various	CR	109	42%	64%
		previously irradiated		39	24%	68%
Colombo (2003)	CT	Bladder	2yr OS	75	40%	83%
Verwaal (2003)	CT (hipec)	Colorectal peri. car.	med. Surv.	105	12.6m	22.3m
Harima (2001)	RT	Cervix	CR	40	50%	85%
Van der Zee (2000)	RT	Blad., Cerv., Rect.	3yr OS	358	24%	30%
Sneed (1998)	RT	Glioblas.	2yr S	112	15%	31%
Vernon (1996)	RT	Breast	CR	308	41%	59%
		previously irradiated		39	39%	79%
Wang (1996)	RT	Oesophagus	3yr S	125	24%	42%
Overgaard (1995)	RT	Melanoma	2 yr NED	134	28%	48%
Kitamura (1995)	RT,CT	Oesophagus	CR	66	6%	25%
You (1993)	RT, surg.	Rectum	pCR	122	5%	23%
Sugimachi (1992)	RT, CT, surg.	Oesophagus	Palliation	53	8%	70%
Strotsky (1991)	RT, surg.	Bladder	3yr S	102	67%	94%
Berdow (1990)	RT, surg.	Rectum	5yr S	115	7%	36%
Kakehi (1990)	RT	Rectum	Response	14	20%	100%
Engelhardt (1989)	CT	Lung	Response	44	36%	60%
Egawa (1989)	RT	Various	Response	92	63%	82%
Valdagni (1988)	RT	Hoofd-hals	CR	44	41%	83%
Datta (1987)	RT	Cervix	CR	64	31%	55%
Kohno (1984)	CT	Vulva/vagina	Response	65	19%	59%

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

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> 27 positive randomized trails RT or CT ± HT

All clinical studies report no relevant increase of side effects

re-RT+HT Standard of care for recurrent tumors in several European Countries

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

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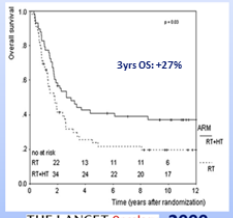
Clinical evidence hyperthermia >27 positive randomised trials RT or CT ± HT

Radiotherapy

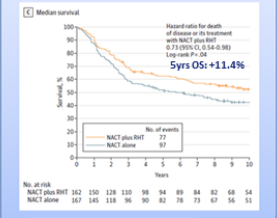
vd Zee et al. Franckena et al. Dutch Deep Hyperthermia Trial RT±HT in LACC: long term follow-up



THE LANCET Oncology 2000
Radiation Oncology ASTRO 2008

Chemotherapy

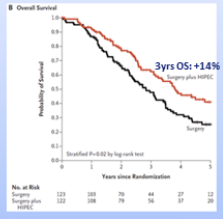
Issels et al. NAC+RHT: Long-term Outcomes Localized High-Risk Soft Tissue Sarcoma



JAMA Oncology 2018

Chemotherapy

Van Driel et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer



The NEW ENGLAND JOURNAL of MEDICINE 2018

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

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Chemotherapy

Issels et al. NAC+RHT: Long-term Outcomes Localized High-Risk Soft Tissue Sarcoma

Chemotherapy

Van Driel et al. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer

RT+HT regular care in NL, CH for patients with locally advanced cervical cancer refractory for chemo-radiation

July 2018 Every German Sarcoma cancer centre must provide access to hyperthermia

Jan 2018 Reimbursed in NL for abdominal metastasized Ovarian ca.

Review Hyperthermia, Datta et al

Strengths

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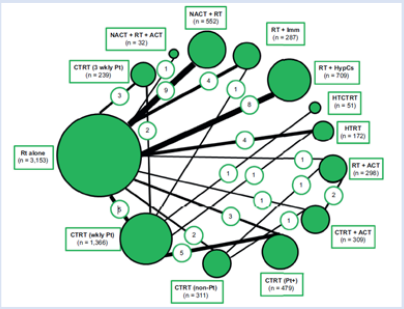
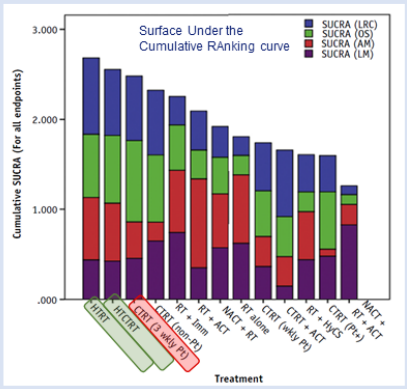
Systematic Review and Network Meta-Analysis of Randomized Clinical Trials
Locally Advanced Cervical Cancer



59 RCTs in LACC
9894 patients evaluated



Datta et al., Int. J. Radiation Oncology Biology Physics, 2019

Review Hyperthermia, Datta et al

Adding hyperthermia gives the best results

Strengths

trials and meta-analysis

Systematic Review and Network Meta-Analysis of Randomized Clinical Trials
Locally Advanced Cervical Cancer

59 RCTs in LACC
9894 patients evaluated

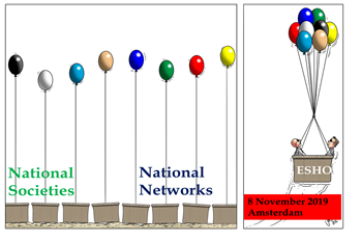
Datta et al., Int. J. Radiation Oncology Biology Physics, 2019

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

Opportunities

1. Multicentric phase III clinical trials, especially with curative intent and organ preservation
2. Technological development and quality assurance to improve therapeutic outcomes
3. Combining hyperthermia with immune checkpoint and DNA repair inhibitors
4. Combining hyperthermia with protons and use MMNs as magic (nano)bullets



ESHO and Atzelsberg Circle combine efforts for CT-RT trials including hyperthermia (HT). Kick- off in Amsterdam 11-2019

Evaluating
- **Natl. phase II study RT+HT in rectum cancer Germany**
- **Int. study CT+HT: HEAT trial in pancreatic tumors Germany, Poland**

Running
- **Int. study RT+HT in anal cancer Germany, Italy, CH**
- **Natl. phase II study CRT+HT inop Rectum Ca. Germany**
- **Natl. study HyperThermia Enhanced Trabectedin for STS**

Initiatives
- **Int. study proton+HT in sacral chordoma patients CH, Netherlands, USA**
- **Intl. study RT/CT-HT for muscle invasive bladder cancer**
- **Natl. RTCT-HT for local advanced non metastastic pancreatic cancer (HEATPAC)**

Exclusive company initiated clinical trials.

Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

Opportunities

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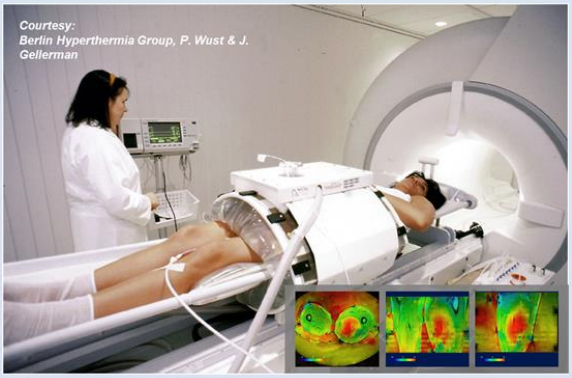
Non-invasive thermometry by MRI research



- Munich
- Rotterdam
- Dusseldorf
- Tubingen
- Erlangen

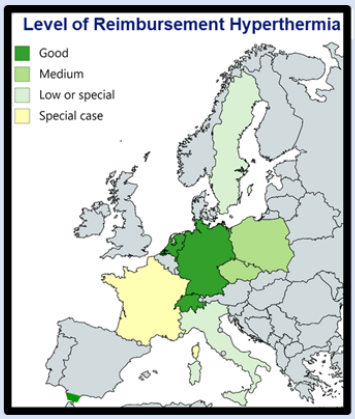
Review Hyperthermia, Datta et al

Frontiers in Oncology 2020

Weakness

1. Uncertainty in actual 3D temperature distributions
2. Inadequate quality assurance for hyperthermia treatment delivery and monitoring along with inappropriate sample sizes and end points in early clinical trials
3. Limited centres with both superficial and deep hyperthermia facilities
4. Insurance and reimbursement facilities growing but still limited in some countries

Reimbursement hyperthermia



Netherlands: HT reimbursed with radiotherapy. Regional deep and superficial hyperthermia, from January 1st 2010 onwards:

- **Locally advanced cervical cancer for patients that are refusing or refractory for chemoradiation**

Any recurrent tumor in previously irradiated areas:

- **breast ca.**
- **lymph node metastasis of Head & Neck ca.**
- **tumors causing local complaints as palliation**
- **Rectum ca.**
- **Superficial local recurrence of mesothelioma**
- **Lymph node met's or recurrent malig. melanoma**

Hyperthermic Intraperitoneal Chemotherapy:

- **Peritoneal metastasis colon ca, mesothelioma**
- **Since 2019: ovarian ca.**

Summary

1. Recent **Phase III trials** confirm the potential of Hyperthermia to boost effectiveness of Radiotherapy and Chemotherapy
2. **New multicentric intl. phase III trials are mandatory to keep up to momentum**. Sites could be stratified for technology used. Central QA mandatory.
3. **Reimbursement** of hyperthermia is improving. A long way to go…
4. **Innovation** is needed to improve workflow for all staff (patients, physicians, physicist, RTT) and to therapy algorhythms (prescription, planning, execution, QA) for HT combined with RT/CT
5. **Quality assurance** is essential for good clinical practice of all devices

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

Oncologic Thermotherapy/Hyperthermia 2020

Selected Swiss Activities

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

Reimbursement of Oncologic Hyperthermia (HT combined with RT) in CH

2020: 4 indications for superf. HT approved 2016, 7 for deep HT final approval pending

Massnahmen	Leistungs-pflicht	Voraussetzungen	gültig ab
		Die Behandlungen erfolgen im Rahmen einer Klinik, die dem Swiss Hyperthermia Network angeschlossen ist. Indikationsstellung durch dessen Tumorboard.	
Regionäre Tiefen-hyperthermie zwecks Tumortherapie in Kombination mit externer Strahlen therapie oder Brachytherapie	Ja	Bei folgenden Indikationen: – Cervix-Karzinom, bei Kontraindikation für Chemotherapie oder lokal vorbestrahlt – Blasen-Karzinom (Funktionserhalt), bei Kontraindikation für Chemotherapie oder lokal vorbestrahlt – Rektum-Karzinom (Funktionserhalt), bei Kontraindikation für Chemotherapie oder Lokalrezidiv in vorbestrahltem Areal – Weichteil-Sarkom (Funktionserhalt), bei Kontraindikation für Chemotherapie – Pankreas-Karzinom, lokal fortgeschrittener, primär inoperabler Tumor Die Behandlungen erfolgen im Rahmen einer Klinik, die dem Swiss Hyperthermia Network angeschlossen ist. Indikationsstellung durch dessen Tumorboard.	1.1.2017 bis 31.12.2018

Diese Änderung tritt am 1. Januar 2017 in Kraft. Bitte beachten Sie, dass die Leistungspflicht für die regionäre Tiefenhyperthermie erst provisorisch mit einer Befristung bis Ende 2018 gilt. Wir bitten Sie, dem BAG bis spätestens Ende März 2017 ein vollständig dokumentiertes Antragsdossier zur erneuten Beurteilung der Wirksamkeit, Zweckmässigkeit und Wirtschaftlichkeit dieser Leistung durch die ELGK einzureichen.

Freundliche Grüsse

Abteilung Leistungen
Sektion Medizinische Leistungen

F. Gu

Felix Gurtner

Von: felix.gurtner@bag.admin.ch <felix.gurtner@bag.admin.ch>
Gesendet: Dienstag, 18. August 2020 10:51
An: Bodis Stephan <stephan.bodis@ksa.ch>
Betreff: Tiefen-Hyperthermie

Sehr geehrter Herr Prof. Bodis

Wegen Überlastung unseres Teams konnten nicht alle ursprünglich vorgesehenen Themen für die Beratung in der Eidg. Leistungs- und Grundsatzkommission (ELGK) vorbereitet bzw. in der ELGK beraten werden. Da in Zusammenhang mit der Tiefen-Hyperthermie keine hohe medizinische oder gesundheitspolitische Dringlichkeit besteht, wurde die Beratung dieses Themas auf die ELGK-Sitzung im November vertagt. Damit keine Leistungslücke entsteht, werden wir dem Eidg. Departement des Innern (EDI) empfehlen, die aktuell gültige, befristete Leistungspflicht für die Tiefenhyperthermie vorerst bis Mitte 2021 zu verlängern und erst auf dieses Datum hin anhand der Empfehlung der ELGK die Leistungspflicht definitiv zu regeln.

Wir werden Sie orientieren, sobald die ELGK das Thema beraten hat und sobald das Departement über die Verlängerung der Leistungspflicht entschieden hat.

Freundliche Grüsse

Felix Gurtner

Dr. med. Felix Gurtner, MSc
Facharzt für Prävention und Gesundheitswesen
Wissenschaftlicher Mitarbeiter

Eidgenössisches Departement des Innern EDI
Bundesamt für Gesundheit BAG
Direktionsbereich Kranken- und Unfallversicherung
Abteilung Leistungen Krankenversicherung
Sektion Medizinische Leistungen

Schwarzenburgstrasse 157, CH-3003 Bern
Tel. +41 58 46 32804
Fax +41 58 46 29020
felix.gurtner@bag.admin.ch
www.bag.admin.ch

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

ISO-Certification DIN EN ISO 9001:2015 of our Hyperthermia Unit in 2020 (Radiation Oncology Center Aarau and Baden) Increased acceptance of HT at least by hospital administrators and QA management

CLARCERT

ZERTIFIKAT

Auf Grundlage der Zertifizierungsentscheidung vom 01.07.2020 bescheinigt die ClarCert GmbH, dass das

Kantonsspital Aarau

Tellstrasse 25, CH-5001 Aarau

für das

Radio-Onkologie-Zentrum KSA-KSB

für den Geltungsbereich

Anwendung der Hyperthermie

ein Qualitätsmanagementsystem nach

DIN EN ISO 9001:2015

erfolgreich eingeführt hat und anwendet.

Gültigkeitsdauer: 10.06.2021
Registrier-Nummer: ISO-091-3
Datum der Ausstellung: 30.07.2020
Neu-Ulm, den 30.07.2020

DAkkS Deutsche Akkreditierungsstelle D-ZM-16034-01-01

Dieses Zertifikat ist ein Unterzertifikat und nur in Verbindung mit dem Hauptzertifikat mit der Registriernummer ISO-091-3 gültig.

Jürgen Fischer
Geschäftsführer ClarCert GmbH

ClarCert GmbH · Gartenstraße 24 · D-89231 Neu-Ulm

SWISS HYPERTHERMIA NETWORK

SHN/SHRN activities with partners in intl. networks

Kantonsspital Aarau

Workshop ESHO 2019 : Strengthen the ESHO clinical trial committee
Intl. clinical study projects development for Hyperthermia combined with Radiotherapy

- F/u meeting in Amsterdam 11/2019 with a voting on presented clinical protocols (active, finalised not yet activated, in development) for phase I/II/III clinical trials
- Joint ESHO/Atzelsberg effort: Launch/conduct intl. multicentric trials in oncologic HT combined with RT and/or CT

EU Horizon 2020 Grant H2020-MSCA-ITN-2020-955625
Research and Innovation Framework Programme
Hyperthermia boosting the effect of radiotherapy
Swiss members: RAO KSA-KSB and ZHAW

ESTRO 2021
Scientific session: Current status of hyperthermia in radiation oncology
Interdisciplinary Symposium on Oncologic Hyperthermia as plenary session jointly with opinion leaders from Japan and USA

ESTRO 2021: ESTRO - JASTRO Hyperthermia Symposium

Biological rational for combining heat and radiation
Jens Overgaard DK

Clinical heating techniques, thermometry and quality assurance
Hans Creeze NL

Status of clincial Hyperthermia in Japan
Hideyuki Sakurai Jp

Thermoradiotherapy: Clinical evidence and potential indications
Zeljko Vujaskovic USA

Conclusions
Ben Slotman NL

Chairs: Naojuki Shimegatsu Jp and Stephan Bodis CH

SHN | SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

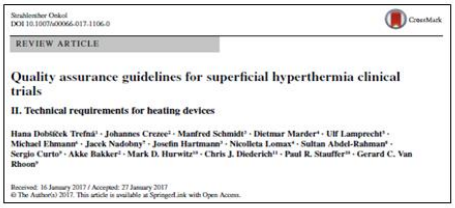
ESHO technical committee guidelines

Superficial HT - Current guideline 2017


International Journal of Hyperthermia

Quality assurance guidelines for superficial hyperthermia clinical trials: I. Clinical requirements

Hana Dobsicek Trefna, Hans Crezee, Manfred Schmidt Diplom-Physiker, Dietmar Marder, Ulf Lamprecht, Michael Ehmann, Josefin Hartmann, Jacek Nadobny, Johanna Gellermann PhD, Netseke van Holthe, Pirus Ghadjar MD, Nicoletta Lomax, Sultan Abdel-Rahman, Christoph Bert, Akke Bakker, Mark Hurwitz, Chris J Diederich, Paul R. Stauffer & Gerard C van Rhoon


REVIEW ARTICLE

Quality assurance guidelines for superficial hyperthermia clinical trials

II. Technical requirements for heating devices

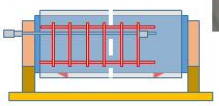
Hana Dobšíček Trefná[1] · Johannes Crezee[2] · Manfred Schmidt[3] · Dietmar Marder[4] · Ulf Lamprecht[5] · Michael Ehmann[6] · Jacek Nadobny[7] · Josefin Hartmann[7] · Nicolleta Lomax[8] · Sultan Abdel-Rahman[9] · Sergio Curto[10] · Akke Bakker[11] · Mark D. Hurwitz[12] · Chris J. Diederich[13] · Paul R. Stauffer[14] · Gerard C. Van Rhoon[15]

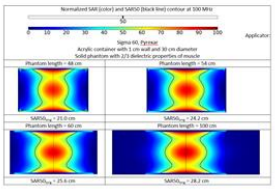
Deep HT - Current guideline 2012


Guideline for the clinical application, documentation and analysis of clinical studies for regional deep hyperthermia

Quality management in regional deep hyperthermia

Currently under revision – new release 2021 planned





HYPERBOOST

Hyperthermia boosting the effect of Radiotherapy

H2020-MSCA-ITN-2020-955625

6 countries
11 beneficiaries
14 PhD students
Budget: € 3,761,881.56

Project coordination:
Hans Crezee
Amsterdam UMC

SWISS HYPERTHERMIA NETWORK

Kantonsspital Aarau

EU Horizon 2020 Programme

Grant approved for Hyperthermia

Associated with document Ref. Ares(2020)2474290 - 11/05/2020

Proposal Evaluation Form

EUROPEAN COMMISSION

Horizon 2020 - Research and Innovation Framework Programme

Evaluation Summary Report

Call: H2020-MSCA-ITN-2020
Type of action: MSCA-ITN-ETN
Proposal number: 955625
Proposal acronym: HYPERBOOST
Duration (months): 48
Proposal title: Creation of advanced cancer treatment planning to boost the effect of Radiotherapy by combining with hyperthermia, heating the tumor.
Activity: MSCA-ITN-ETN: LIF

N.	Proposer name	Country	Total Cost	%	Grant Requested	%
1	ACADEMISCH MEDISCH CENTRUM BIJ DE UNIVERSITEIT VAN AMSTERDAM	NL	531,239.76	14.12%	531,239.76	14.12%
2	AARHUS UNIVERSITETSHOSPITAL	DK	595,044	15.82%	595,044	15.82%
3	Kantonsspital Aarau AG	CH	281,276.64	7.48%	281,276.64	7.48%
4	UNIVERSITAETSKLINIKUM ERLANGEN	DE	505,576.8	13.44%	505,576.8	13.44%
5	ZURCHER HOCHSCHULE FUR ANGEWANDTE WISSENSCHAFTEN	CH	281,276.64	7.48%	281,276.64	7.48%
6	Dr. Sennewald Medizintechnik GmbH	DE	252,788.4	6.72%	252,788.4	6.72%
7	Medlogix srl	IT	261,499.68	6.95%	261,499.68	6.95%
8	CHARITE - UNIVERSITAETSMEDIZIN BERLIN	DE	252,788.4	6.72%	252,788.4	6.72%
9	CHALMERS TEKNISKA HOEGSKOLA AB	SE	281,982.96	7.50%	281,982.96	7.50%
10	ERASMUS UNIVERSITAIR MEDISCH CENTRUM ROTTERDAM	NL	265,619.88	7.06%	265,619.88	7.06%
11	MAX DELBRUECK CENTRUM FUER MOLEKULARE MEDIZIN IN DER HELMHOLTZ-GEMEINSCHAFT (MDC)	DE	252,788.4	6.72%	252,788.4	6.72%
	Total:		3,761,881.56		3,761,881.56	

Abstract:
Hyperthermia (HT), heating tumors to temperatures of 40-44 °C, is an oncological treatment used in combination with radiotherapy (RT) and chemotherapy to enhance their efficacy. Clinical effectiveness of HT has been demonstrated in randomised studies and HT is currently applied for many clinical indications, like cervical cancer and recurrent breast cancer. Clinical results can be further improved as application of HT with well-controlled tumor temperatures and optimal timing and sequence realising full synergy of RT+HT is challenging. Optimal HT delivery requires accurate planning, moreover preclinical research has shown that many mechanisms are responsible for the therapeutic effect of HT, all presumably with a different temperature-effect relationship and with different optimal timing between RT and HT. Optimisation of clinical RT+HT treatments therefore requires a quantum leap in understanding and in clinical application.
Scientific objective of this multidisciplinary project with contributions from all sectors and disciplines (biology, physics and oncology) is to combine training and research into the synergistic molecular mechanisms responsible for the therapeutic effect of HT on RT with the development of a versatile and innovative planning platform which utilises biological knowledge to achieve optimal patient-specific treatment delivery and ultimately application in a clinical registration study in a network of European centres implementing this treatment planning software to ensure optimal treatment delivery.
This ground-breaking and multidisciplinary project with contributions from biology, physics and oncology will create a versatile and innovative planning platform, enhance fundamental knowledge and create practical tools to achieve personalised treatment, thereby augmenting treatment delivery and clinical results. The projects will also educate 15 highly skilled professionals capable of addressing and solving complex oncological issues.

Evaluation Summary Report

Evaluation Result

Total score: 96.00% (Threshold: 70/100.00)

HYPERBOOST

Hyperthermia boosting the effect of Radiotherapy

H2020-MSCA-ITN-2020-955625

Key objectives "*HYPERBOOST*"

- Train and equip early stage researchers with transferable, multi-disciplinary skills essential in high-end biomedical engineering, clinical hyperthermia and translational oncology (**WP2**)
- Obtain and validate new insights into clinical working mechanisms of hyperthermia (**WP3**)
- Translate preclinical and clinical results (**WP3**, **WP5**) into mathematical relations and treatment planning models (**WP4**)
- Apply novel treatment planning models for personalised treatment (**WP4**) clinically to improve the efficacy of clinical treatments (**WP5**)
- Initiate, stimulate and profit from **multidisciplinary cross-pollination** between the disciplines involved in hyperthermic oncology (**WP3-5**)
- Consolidate and expand the **European infrastructure** and industry for hyperthermia research and clinical application (**WP 2-6**)

Pediatric application of modulated electro-hyperthermia (mEHT)

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Citation: Lee S.Y. (2020): Pediatric application of modulated electro-hyperthermia (mEHT), Oncothermia Journal 29: 25 – 59,
www.oncotherm.com/sites/oncotherm/files/2021-02/Lee_Pediatric

Abstract

Introduction: Pediatric oncology has numerous tasks that are difficult to handle with conventional therapies. Most of the cancers that are common in adults differ from those seen in children and adolescents. In the last three decades, mortality from pediatric cancers has been cut in half, which is a remarkable result, but many cases are difficult and challenging and often do not have conventional protocols.

Method: I will show several cases successfully treated with a new treatment modality: modulated electro-hyperthermia (mEHT, trade name of oncothermia). When conventional therapies were not effective enough, mEHT was applied as a complementary treatment to existing protocols. We followed the case through various imaging facilities (CT, MRI, PET) as well as laboratory controls and measurement of tumor markers.

Results: I have collected 8 characteristic cases, 5 boys and 3 girls, with severe neoplasms. The age of the children ranged from 1 to 16 years. Treated tumors cover a wide spectrum of cases, including neuroblastoma, brain stem cell tumor, germ cell tumor, B cell lymphoma, Hodgkin lymphoma, and desmoplastic small cell tumor. The children received intensive pretreatments, underwent surgery when possible, and were given appropriate adjuvant chemotherapy and radiation therapy. At the end of a long follow-up (various periods of time), three children have no evidence of disease, one has stable disease, and one died. Two children were transferred to another hospital, with no data available on their current condition. The children tolerated the treatments well, no notable adverse effects were observed.

Discussion: I will show the details of the cases in my presentation. The main guide we followed in therapy was to focus on the child rather than looking at the tumors only. This complex approach was in harmony with our general philosophy: change from tumor-oriented to patient-oriented methods.

Conclusion: These case reports show the feasibility of applying mEHT to pediatric tumors in the cases studied, of children from 1 year up to 16 years.

ICHS 38.

38th Conference of the International Clinical Hyperthermia Society

November 5, 2020

전북대학교병원 CHONBUK NATIONAL UNIVERSITY HOSPITAL

Hyperthermia for pediatric cancer

Department of Radiation Oncology

Chonbuk National University Hospital

LEE SUN YOUNG

Another No.1 대한민국 의료의 또 하나의 중심

Another No.1 전북대학교병원 CHONBUK NATIONAL UNIVERSITY HOSPITAL

Introduction

1. Treatment of pediatric cancer
2. Palliative aim hyperthermia
   - 4 patients
     brain stem tumor, germ cell tumor,
     neuroblastoma
     dermoplastic small cell tumor,
3. Definitive aim hyperthermia
   - 4 patients
     neuroblastoma, lymphoma (3)
4. Conclusions

Pediatric cancer

- Pediatric oncology has numerous tasks that are difficult to handle with conventional therapies.
- Most of the cancers that are common in adults differ from those seen in children and adolescents.
- In the last three decades, mortality from pediatric cancers has been cut in half, which is a remarkable result, but many cases are difficult and challenging and often do not have conventional protocols.

Pediatric cancer

- treatment methods
  : surgery, chemotherapy, radiotherapy so on
- In particular, in the case of radiation therapy for symptom relief purposes, it is difficult to perform if the patient is in poor condition.
  : Reduce patient compliance
  : If the child does not cooperate with the treatment at each treatment, he should sleep with a sleeping drug.
  : Radiation treatment side effects were also not negligible.

Pediatric cancer

- Hyperthermia
  : Treatment that does not need to sedation the patient
  : The patient's emotions are stabilized during treatment as it can be accompanied by a parient.
  : It is an optimized treatment that can be used for pain control purposes without side effects.

No. 1

-4/M
-brain stem tumor (pontine glioma)
-previous treatment
 : CTx (CCG9991A)
   RTx (50Gy)
-general status before hyperthermia
 : progressive disease
-symptoms
 : severe headache, nausea, vomiting, anorexia

No. 1

-MRI (3/14/2013) before hyperthermia

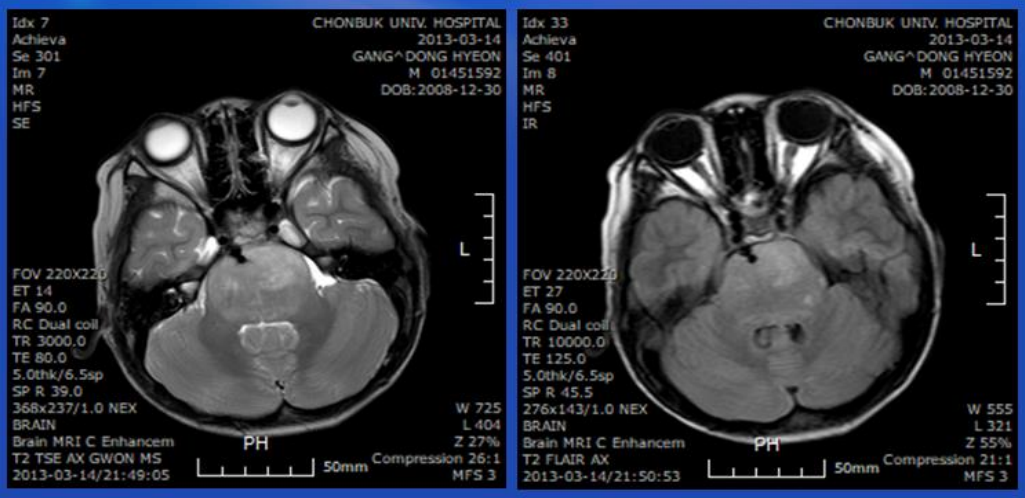
:**Pons show a high signal at T2WI, and a mass that does not enhance contrast is still observed,**

and is still extended to prepontine.

:**Compared to the 2013-January image, there was no significant change in the size, and compared to the 2012-October image, both obstructive hydrocephalus and basilar artery encasement were improved.**

No. 1

-MRI (3/14/2013) before hyperthermia



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No. 1

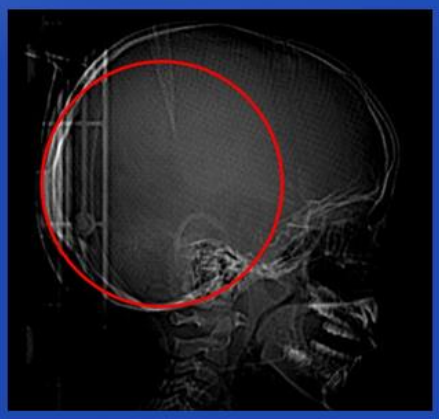
-hyperthermia

: decubitus position

: brain (electrode 20x20 cm)

: no sedation

: 36 sessions



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No. 1

-MRI, after HT (16/7/2013)

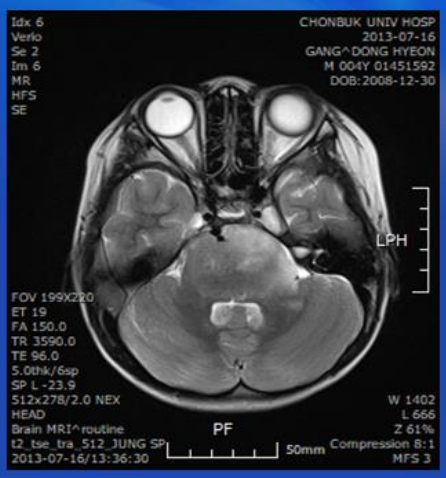
:The overall size of the expansile tumor mass lesion on the pons is slightly reduced.

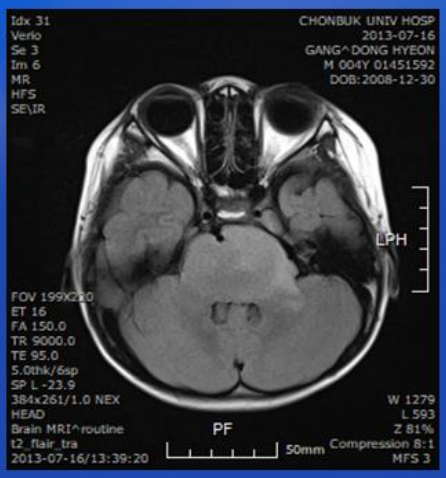
: However, microhemorrhage is newly observed inside the mass in the SWI image, and microhemorrhage is also observed in the Rt posterior temporal lobe.

: No mass enhancement and no hydrocephalus findings.

No. 1

-MRI, after HT (16/7/2013)





No. 1

: decreased tumor volume
  decreased symptoms (> 50%)
  decreased pain killer drugs
: no complications related hyperthermia
: last follow up status
  death
: survival periods
  62 months

No. 2

-2/F

-germ cell tumor (york cell tumor - coccyx)

-previous treatment

: CTx (CCG8882/Cis VAB/POG-ICE/ VELP/T-ICE/Taxo-VBL+IRT+Oxel so on)

RTx (5040Gy at coccyx)

surgical excision

-general status before hyperthermia

: progressive disease

-symptoms

: severe pelvic pain, nausea, vomiting, anorexia

No. 2

-MRI (28/6/2010) before hyperthermia

: Pelvic cavity mass: Probably malignant tumor, most likely

: The main lesion is in the presacral area, pushing the rectum forward

: The boundary with Rectum is relatively clear.

: The mass destroys and encases parts of lower sacrum and coccyx bone

: Some masses infiltrate from the sacrum level to the central spinal canal and surround the sacrum and coccyx.

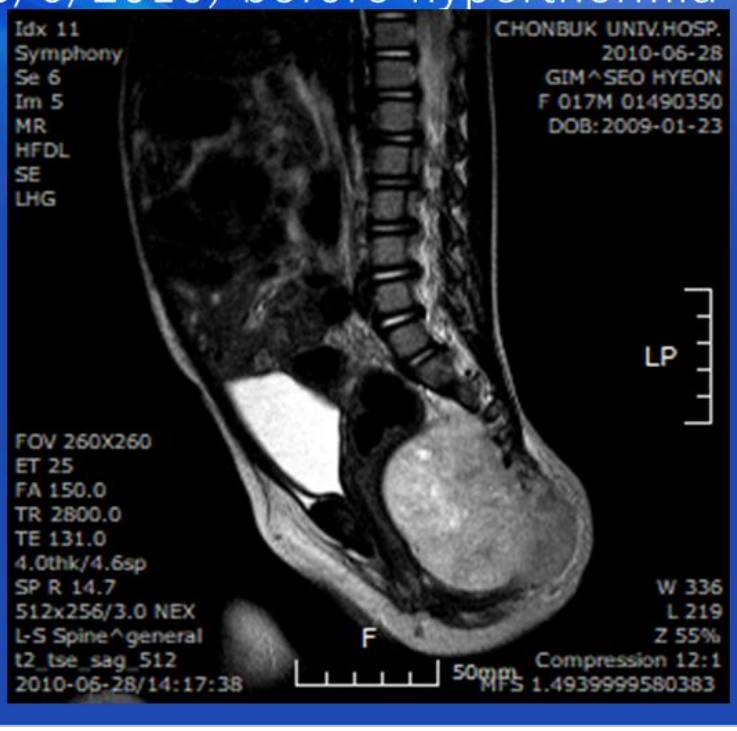
: Plain radiography also shows bone destruction

: When a contrast agent is given, it enhances the contrast and contains several cystic spaces inside, and some bleeding is also accompanied.

: Some masses in the Rt side are infiltrated toward the gluteus muscle.

No. 2

-MRI (28/6/2010) before hyperthermia



No. 2

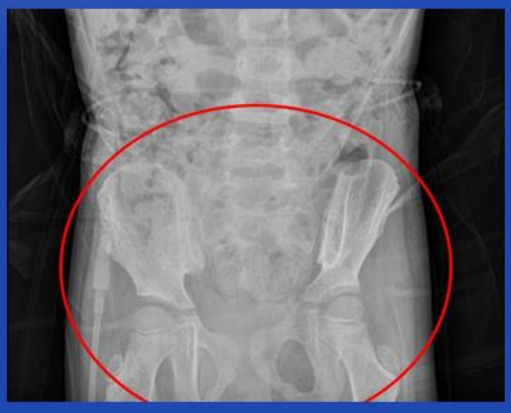
-hyperthermia

: prone position

: pelvis (electrode 20x20 cm)

: no sedation

: 9 sessions



No. 2

-treatment results

: could not perform image examination because very poor general condition and could not sedation.

: decreased symptoms (> 30%)
decreased pain killer drugs

: no complications related hyperthermia

: last follow up status
death

: survival periods
40 months

No. 3

-2/M

-neuroblastoma (Rt adrenal neurobastoma)

-previous treatment

: CTx (Cytoxan, Topotecan, VP-16, Ifosfamide, carboplatin)
surgical resection
palliative radiotherapy at Lt lower leg (22Gy)

-general status before hyperthermia

: progressive disease (Lt tibia/fibula/Lt inguinal area)

-symptoms

: severe pain, anorexia

No. 3

-leg MRI, before HT (31/12/2012)

: Compared to the October 2012 MR image,

tumors grew much more in the bone marrow space and in the subperiosteal space.

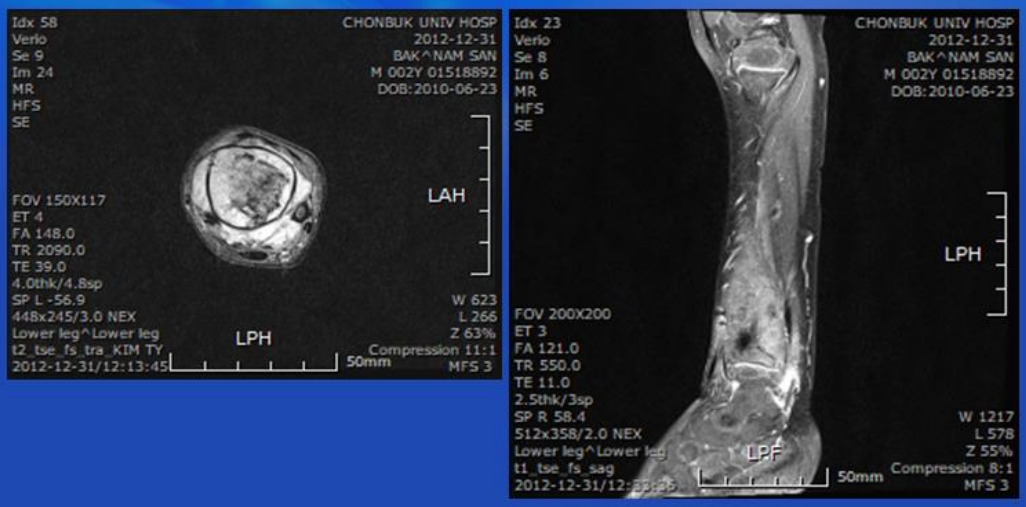
: The lesion is spread upward from the distal tibia plafond level to about 9cm, and the periosteum is generally lifted

and the mass is filled.

: Signal intensity of the mass is the same as that of normal tumor

No. 3

-leg MRI, before HT (31/12/2012)



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No. 3

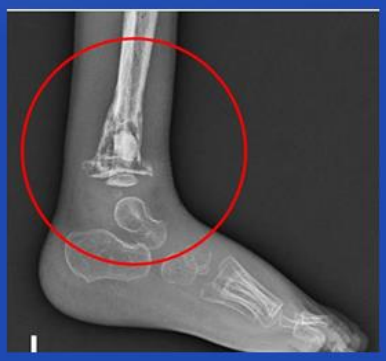
-hyperthermia

: **sitting position**

: **Lt lower leg (electrode 20x20 cm)**

: **no sedation**

: **28 sessions**



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No. 3

-treatment results

: could not perform image examination because very poor general condition and could not sedation.

: decreased symptoms (> 60%)
decreased pain killer drugs

: no complications related hyperthermia

: last follow up status
death

: survival periods
36 months

No. 4

-15/M

-desmoplastic small cell tumor (abdomen)

-previous treatment

: CTx (ICE/IE/VDC/VAC/irinotecan+TMZ so on)
palliative colostomy

-general status before hyperthermia

: progressive disease

-symptoms

: severe abdomen/pelvic pain, nausea,
vomiting, anorexia

No. 4

- abdomen CT (14/08/2018) before HT

: Clinical information: Known Desmoplastic small round cell tumor,

2016-11 Colostomy state Due to bowel strangulation

: Scalloping masses are observed around Liver, periportal hilum, and

CBD, accompanied by diffuse biliary dilatation.

: Several low attenuated lymph nodes are enlarged in the periportal,

portocaval, aortocaval, and paraaortic areas.

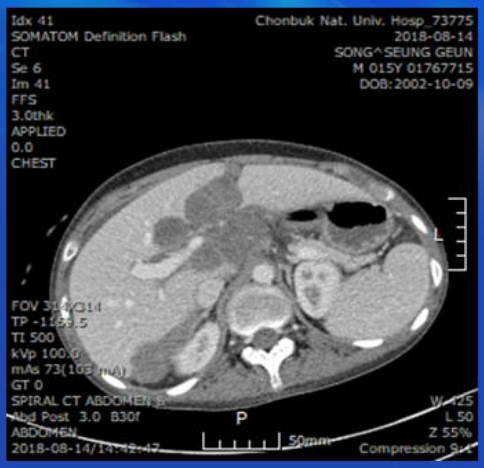
: Masses within 4cm with nodularity are scattered throughout the peritoneum, and peritoneal fluid collection is observed.

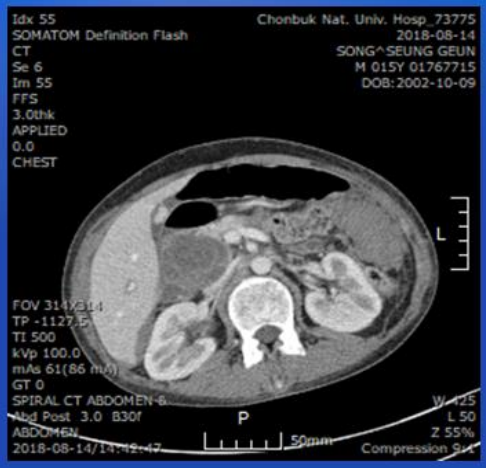
: There is no mass that distinguishes pancreas, adrenal gland, kidney, spleen itself.

: There is a dominant fluid collection in the Rt subpleural space.

No. 4

- abdomen CT (14/08/2018) before HT





No. 4

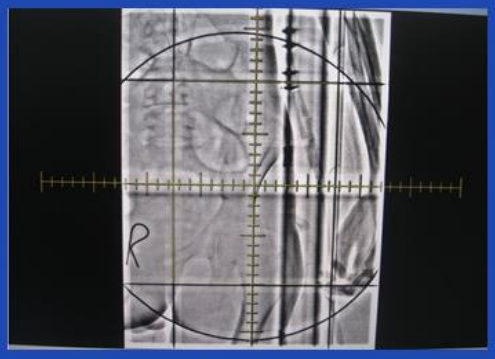
-hyperthermia

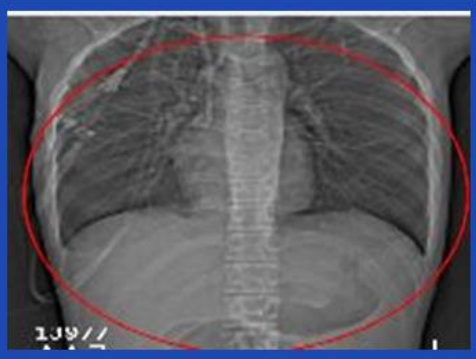
: supine position

: chest/ abdomen (electrode 30x30 cm)

: no sedation

: 29 sessions





No. 4

-abdomen CT (16/4/2019) after HT

: Clinical information: Known Desmoplastic small round cell tumor, 2016-11 Colostomy state Due to bowel strangulation

: Metastatic lesions up to 2.7cm in size are scattered inside the Liver, and some of them are conglomerated.

: Around the periportal hilum and CBD, scalloping masses with a size of up to 6 cm or less are observed, and both sizes and numbers are increased compared to previous tests.

: Several low attenuated lymph nodes are enlarged in the periportal, portocaval, aortocaval, and paraaortic areas.

: There is nodularity throughout the peritoneum, and the size and extent increase compared to the previous one.

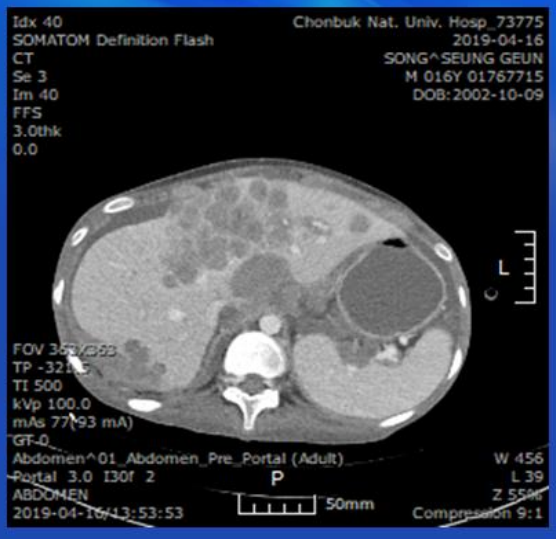
: It is judged that these masses in the mesentery are aggregated and pressed or adhered to the surrounding structures.

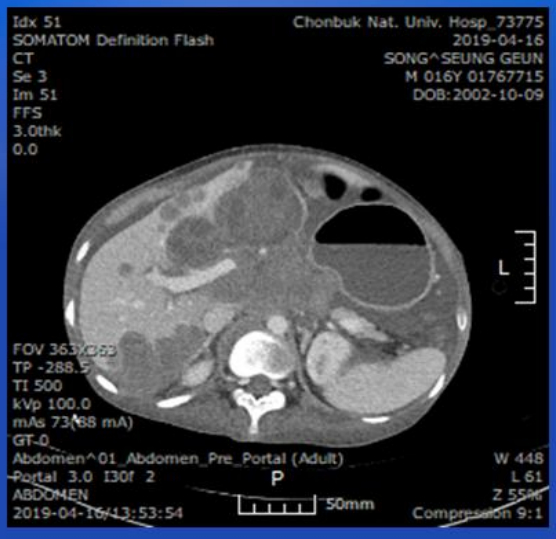
: Due to this, the jejunum and duodenum showed diffuse dilatation from the upper part of the ileostomy.

: Large amount of fluid collection in the Lt pleural space

No. 4

-abdomen CT (16/4/2019) after HT





No. 4

-treatment results

: more aggravation tumor

: decreased symptoms (> 30%)
decreased pain killer drugs

: no complications related hyperthermia

: last follow up status
death

: survival periods
36 months

Palliative aim hyperthermia

1. Can be usefully used for treatment in the absence of other alternative treatment.

2. In the case of treatment that requires sedation, it is a treatment that can be performed when the patient does not sedate.

3. Improves the quality of life of the patient by reducing pain.

4. No obvious side effects.

5. Helps to stabilize the patients mind and body as treatment can be carried out with a parient.

Pediatric cancer

- definitive aim
  : surgery/chemotherapy/radiotherapy so on

- In particular, in the case of lymphatic cancer, radiation therapy is often performed after chemotherapy.
- At this time, since the children are in the growing stage, chronic side effects such as growth retardation, metabolic disease due to hormonal imbalance, and bone growth delay occur depending on the irradiated area.
- As the average survival periods of patients increases, various treatments are being tried to reduce chronic side effects.

No. 5

-1/M
-neuroblastoma (ganglioblastoma – chest)
-previous treatment
: CTx (CEDE+ICE/Cis-retinoic acid)
surgical excision
-general status before hyperthermia
: stable disease
-symptoms
: nausea, vomiting, anorexia

No. 5

-chest CT, (20/05/2015), at first diagnosis

: Both thyroid gland and both neck showed no abnormal findings.

: A homogenous enhancing mass like lesion of about 5 cm in size on the anterior mediastinum was judged as thymus and as reactive hyperplasia. There is an enhnancing mass of about 4cm in Superoposteiror mediastinum, and it is judged as a neurogenic tumor such as neuroblastoma.

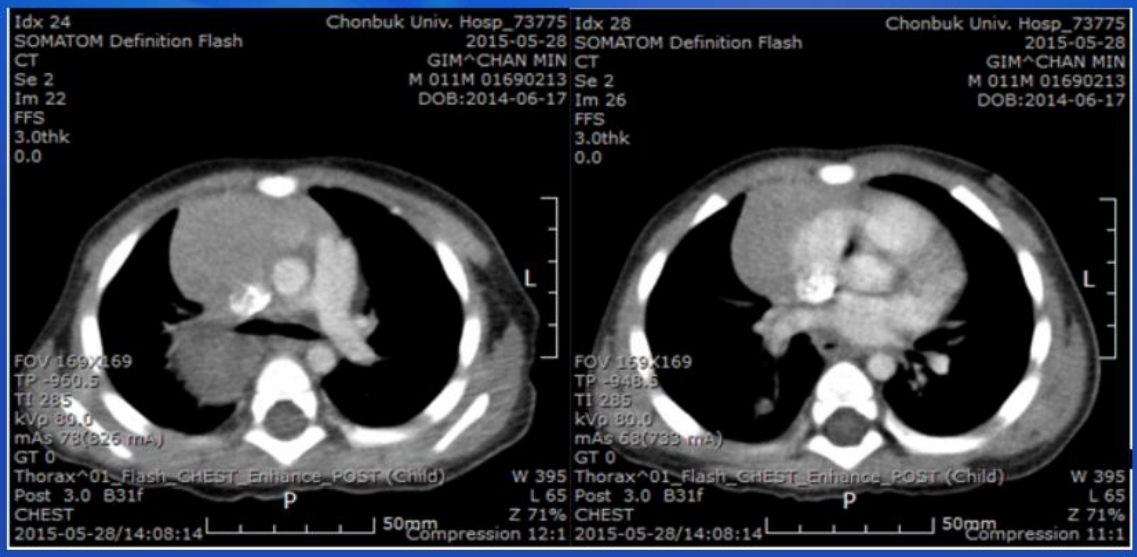
: No evidence of tracheal mass or stenosis.

: There is a nodular consolidation of about 8mm in the RUL posterior segment, and there is GGO around it.

: There were no abnormal findings in both pleural space and bony thorax.

No. 5

-chest CT, (20/05/2015), at first diagnosis



No. 5

-chest CT, (20/10/2015), before hyperthermia

: **Both thyroid gland and both neck showed no abnormal findings.**

: **Thymus reactive hyperplasia approximately 3 cm in size in the anterior mediastinum currently shows a reduction in size to 2.5 cm. Known neuroblastoma of about 3.5*2cm in Superoposteiror mediastinum is currently showing a decrease in size to 3.3*1.8cm.**

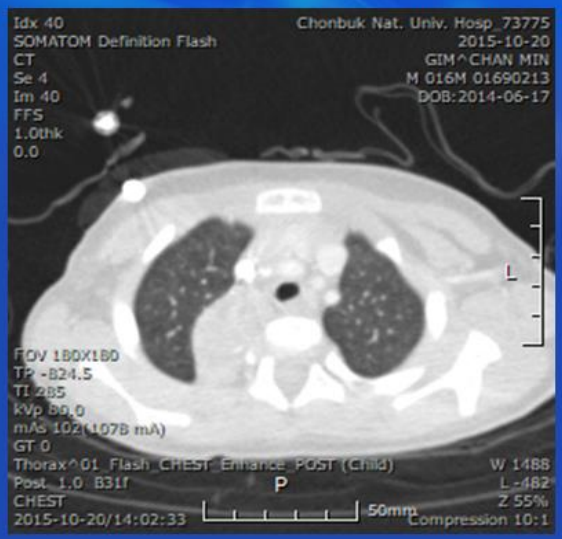
: **No evidence of tracheal mass or stenosis.**

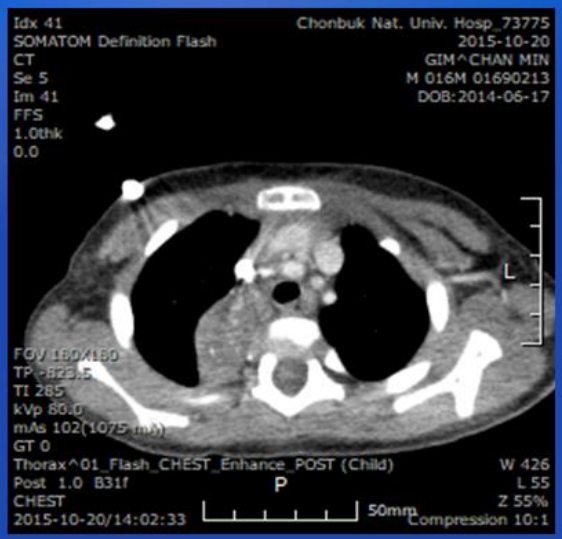
: **Nodular consolidation(2015-05-28) of about 8mm in the RUL posterior segment is not clearly visible.**

: **No abnormal findings in both pleural space and bony thorax**

No. 5

-chest CT, (20/10/2015), before hyperthermia





No. 5

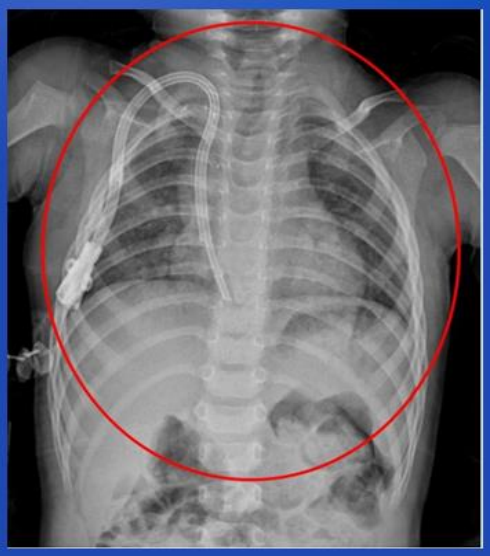
-hyperthermia

: **supine position**

: **chest (electrode 20x20 cm)**

: **no sedation**

: **12 sessions**



No. 5

-chest CT, (19/03/2016), after hyperthermia

: **Thymus reactive hyperplasia with a size of about 2.5 cm in the anterior mediastinum showed an increase in size to 3.5 cm, but it was judged as a normal range for the age of the patient.**

: **In Superoposteiror mediastinum, known neuroblastoma of about 3.5*2cm in size was markedly reduced and not seen.**

: **No evidence of tracheal mass or stenosis.**

: **Nodular consolidation(2015-05-28) of about 8mm in the RUL posterior segment is currently not clearly visible.**

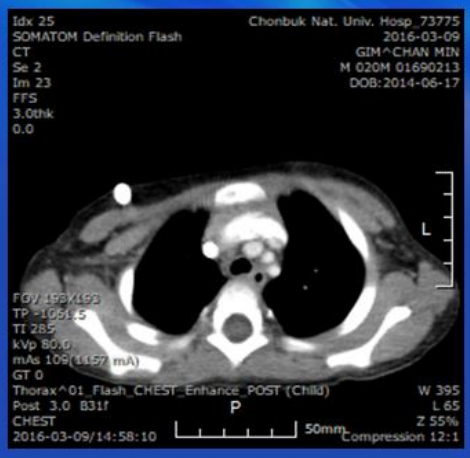
: **No abnormal findings in both pleural space and bony thorax**

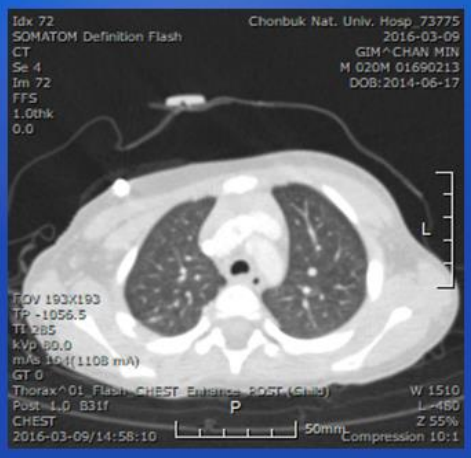
[CONCLUSION]

1. Known neuroblastoma - Complete remission compared with 2015-05-28

No. 5

-chest CT, (19/03/2016), after hyperthermia





No. 5

-treatment results

: complete remission after hyperthermia

: no complications related hyperthermia

: last follow up status

alive

no evidence without disease

: survival periods

60 months

No. 6

-11/F

-Hodgkin's lymphoma (diffuse large B cell lymphoma, tonsil/both neck LN)

-previous treatment

: CTx (R-CHOP)

surgical excision (tonsileectomy)

-general status before hyperthermia

: stable disease

-symptoms

: nausea, vomiting, anorexia

No. 6

-PET/CT (08/12/2016, at diagnosis)

<Head & Neck>

:Both palatine tonsillectomy state, showing increased intake of intense FDG (Rt<Lt) in both tonsillar beds. Soft tissue thickening suspected in Lt tonsillar bed.

: There are enlarged LNs with mild FDG intake at both cervical level II. F/U required.

: Both thyroid gland observed small.

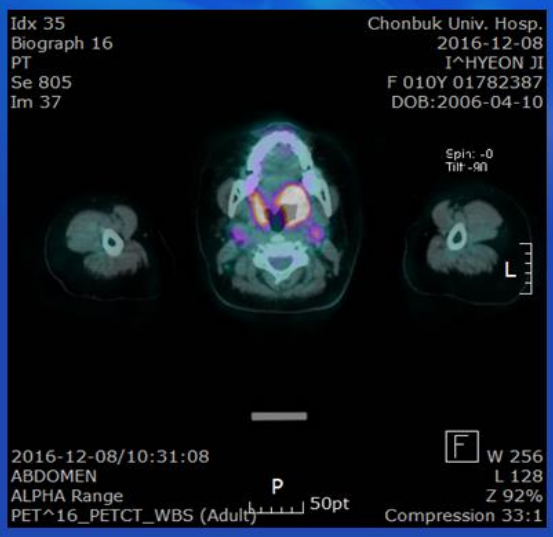
<Chest> No significant increase in FDG intake was observed in lung parenchyme or mediastinum.

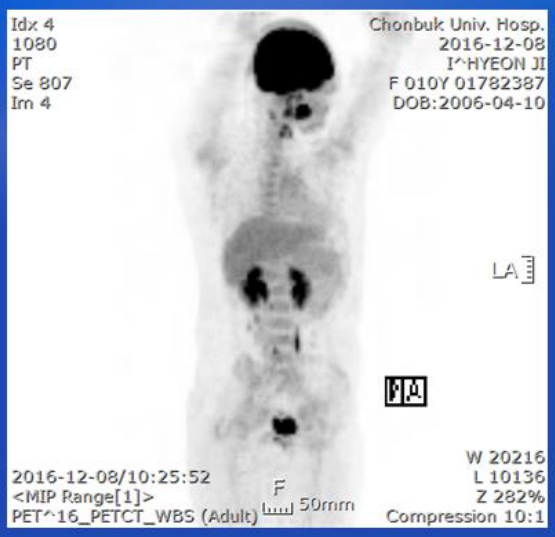
<Abdomen & pelvis> - Nonspecific finding

<Bone, Joint & Soft tissue> - Nonspecific finding

No. 6

-PET/CT (08/12/2016, at diagnosis)





No. 6

-PET/CT (25/04/2017, before hyperthermia)

<Head & Neck>

: Both palatine tonsillectomy state, no significant FDG intake. Compared with the previous FDG PET/CT (2016.12.08), the size and metabolism were significantly reduced.

: Hyper-metabolism in the postcricoid portion and vocal cord seems to have a high possibility of physiologic uptake by vocalization.

: Both thyroid gland observed small.

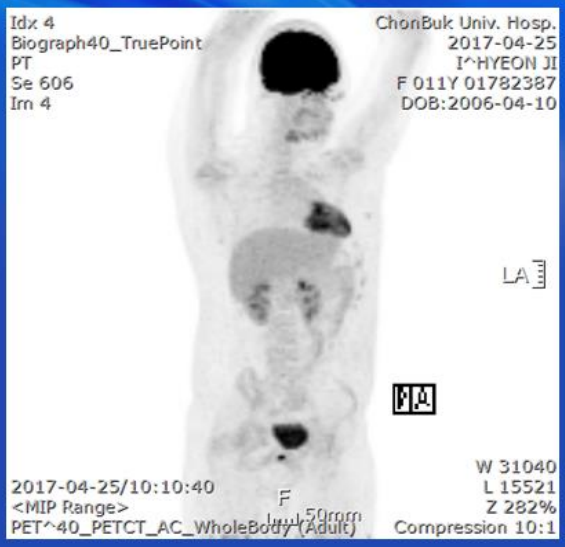
<Chest> No significant increase in FDG intake was observed in lung parenchyme or mediastinum.

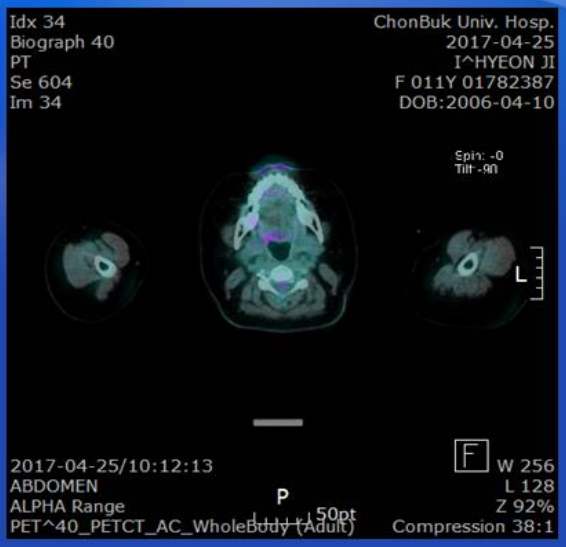
<Abdomen & pelvis> - Nonspecific finding

<Bone, Joint & Soft tissue> - Nonspecific finding

No. 6

-PET/CT (25/04/2017, before hyperthermia)





No. 6

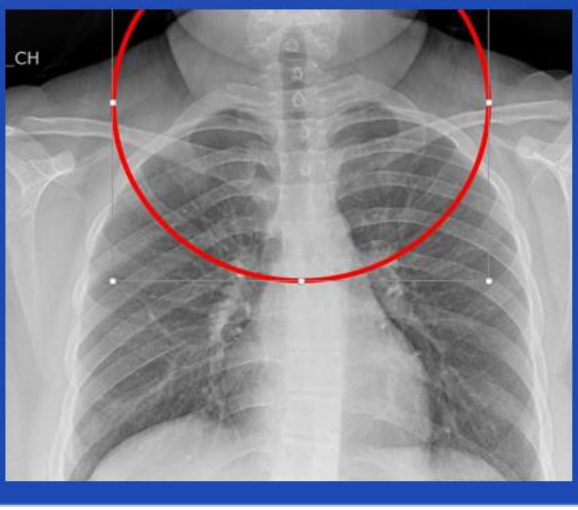
-hyperthermia

: supine position

: neck(electrode 20x20 cm)

: no sedation

: 24 sessions

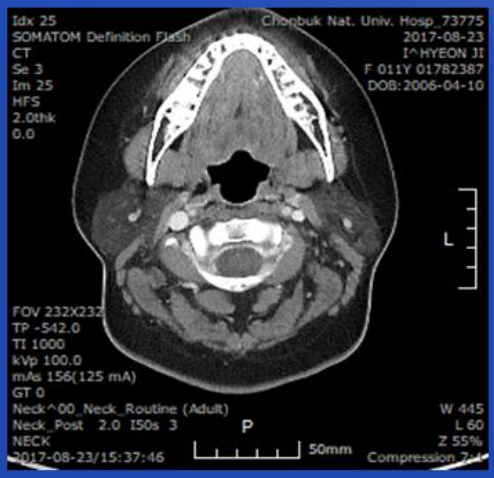


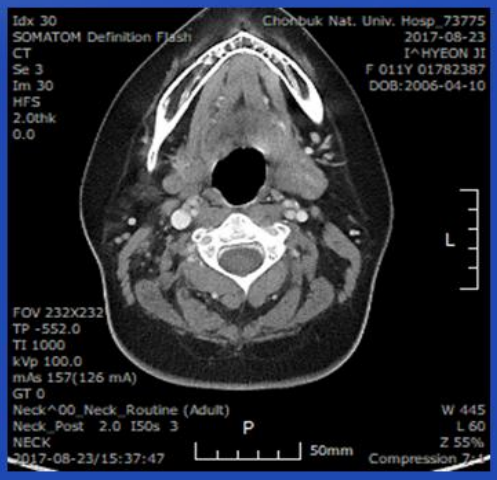
No. 6

-neck CT (23/08/2017), after HT

: Lymph node enlargement not visible

: Other than that, no abnormality was found on the neck.





No. 6

-treatment results

: complete remission after hyperthermia

: no complications related hyperthermia

: last follow up status

alive

no evidence without disease

: survival periods

42 months

No. 7

-16/M

-Hodgkin's lymphoma (mixed cellularity, neck/axillary/mediastinum/spleen)

-previous treatment

: CTx (OEPA-CDPDAC)

-general status before hyperthermia

: stable disease

-symptoms

: nausea, vomiting, anorexia

No. 7

PET/CT (05/02/2018), at diagnosis,

<Lymph node>

There are multiple FDG-avid enlarged LNs in Rt supraclavicular, Rt axilla, and mediastinum, and FDG-avid lesions in subcarina~posterior mediastinum extend to T9 level.

<Head & Neck> Nonspecific finding

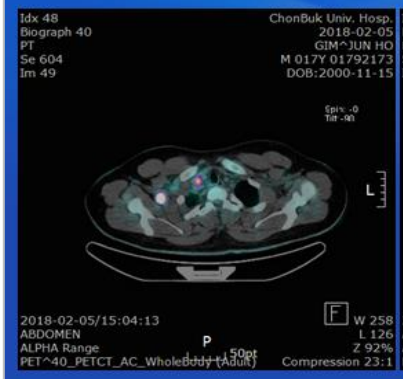
<Chest> Nonspecific finding

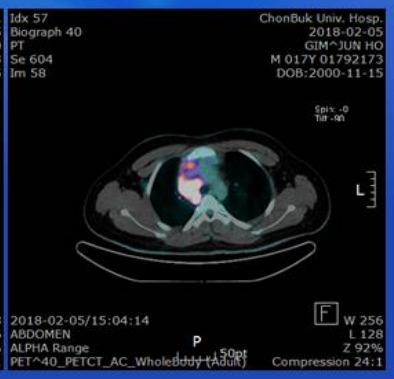
<Abdomen & pelvis> Spleen has multifocal FDG-avidities.

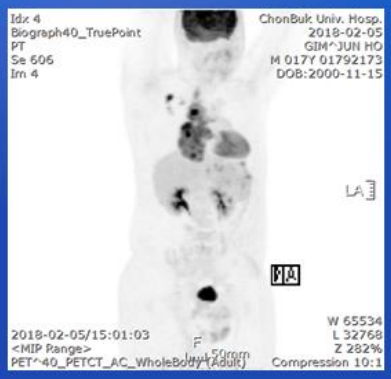
<Bone, Joint & Soft tissue> Nonspecific finding

No. 7

PET/CT (05/02/2018), at diagnosis,







No. 7

PET/CT (05/04/2018), before HT

<Lymph node>

Multiple FDG-avid LNs of Rt supraclavicular, Rt axilla, and mediastinum, which were previously observed in FDG PET/CT (2018.02.05), significantly decreased in size and metabolism. Most are not observed and remain tiny to small LNs showing some minimal metabolism.

<Head & Neck> - Nonspecific finding

<Chest> - Nonspecific finding

<Abdomen & pelvis> Spleen's multifocal FDG-avid lesions were no longer observed. Colon has diffuse physiologic uptake.

<Bone, Joint & Soft tissue> - Nonspecific finding

No. 7

PET/CT (05/04/2018), before HT

No. 7

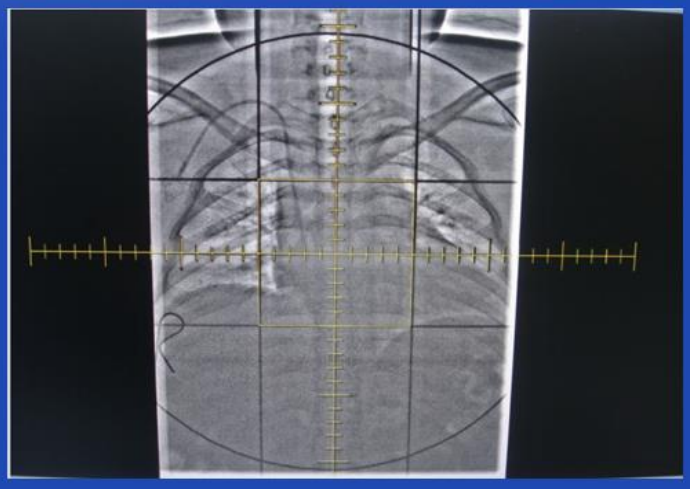
-hyperthermia

: supine position

: neck and mediastinum (electrode 30x30 cm)

: no sedation

: 24 sessions



No. 7

PET/CT (19/11/2018), after HT

<Lymph node> Significant FDG-avid LN in Rt supraclavicular, Rt axilla, and mediastinum, which were the lymphoma involvement sites, were no longer observed. There are some tiny to small LN and no significant FDG intake.

<Head & Neck> - Nonspecific finding

<Chest> - Nonspecific finding

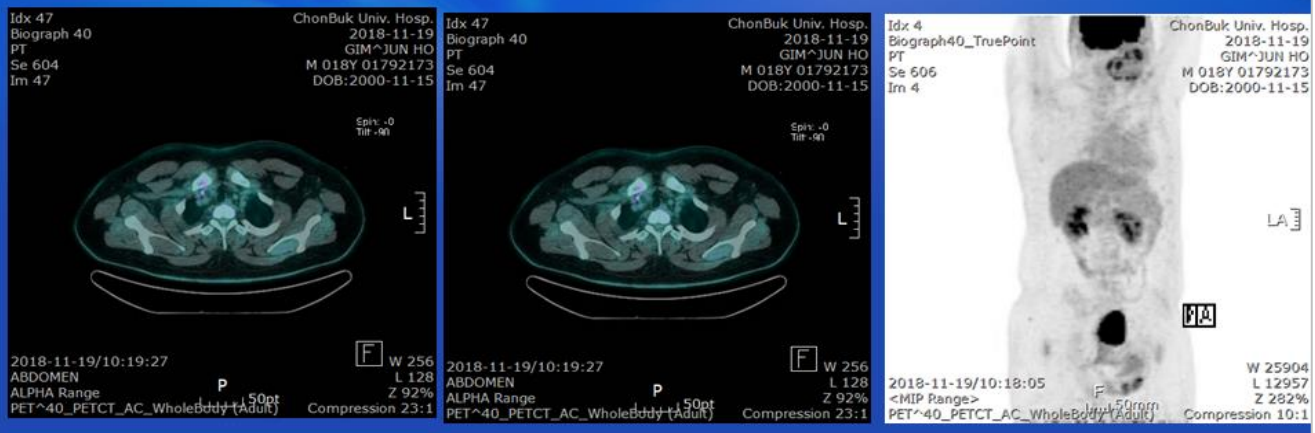
<Abdomen & pelvis> Spleen multifocal FDG-avid lesions were no longer observed.

<Bone, Joint & Soft tissue> - Nonspecific finding

[CONCLUSION] No demonstrable FDG-avid lesion

No. 7

PET/CT (19/11/2018), after HT



No. 7

-treatment results

: complete remission after hyperthermia

: no complications related hyperthermia

: last follow up status

alive

no evidence without disease

: survival periods

27 months

No. 8

-15/F

-Hodgkin's lymphoma (lymphocyte rich classic, neck)

-previous treatment

: CTx (OEPA-CDPDAC)

-general status before hyperthermia

: stable disease

-symptoms

: nausea, vomiting, anorexia

No. 8

PET/CT (04/01/2020), at diagnosis,

<Head & Neck> FDG-avid enlarged LNs in Lt cervical level II~V, Rt cervical level II, & Lt supraclavicular area

<Chest> No significant increase in FDG intake was observed in lung parenchyme or mediastinum.

<Abdomen & pelvis> - nonspecific finding

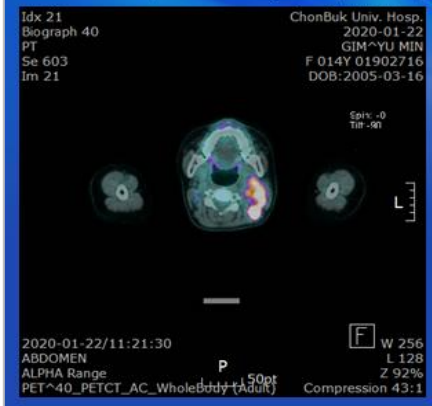
<Bone, Joint & Soft tissue> - nonspecific finding

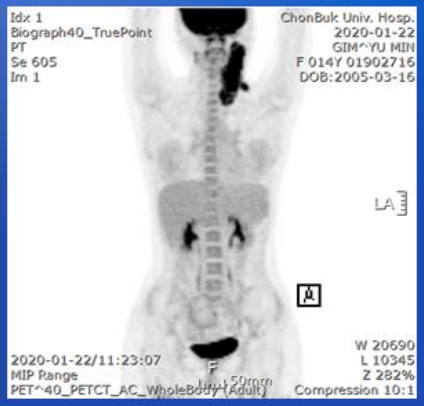
[CONCLUSION]

FDG-avid lymphoma involving LNs in Lt cervical level II~V, Rt cervical level II, & Lt supraclavicular areas

No. 8

PET/CT (04/01/2020), at diagnosis





No. 8

PET/CT (08/07/2020), before HT

<Head & Neck> Compared to the previous FDG PET/CT (2020.03.23), LNs in Lt cervical level II~V, Rt cervical level II, & Lt supraclavicular area were further reduced in size, resulting in tiny to small LNs suspected of some minimal metabolism.

<Chest> No significant increase in FDG intake was observed in lung parenchyme or mediastinum.

<Abdomen & pelvis> nonspecific finding

<Bone, Joint & Soft tissue> nonspecific finding

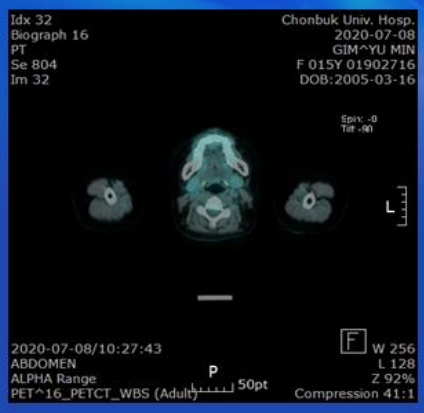
[CONCLUSION]

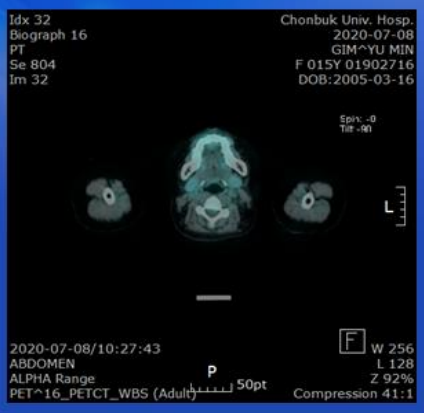
Known lymphoma involving LNs in Lt cervical level II~V, Rt cervical level II, & Lt supraclavicular areas

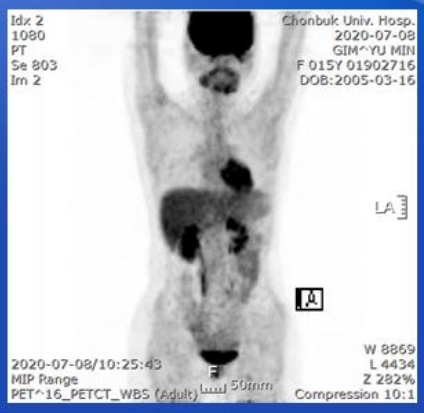
=> decreased size, compared with previous FDG PET/CT(2020.03.23)

No. 8

PET/CT (08/07/2020), before HT







No. 8

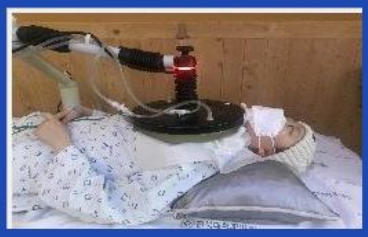
-hyperthermia

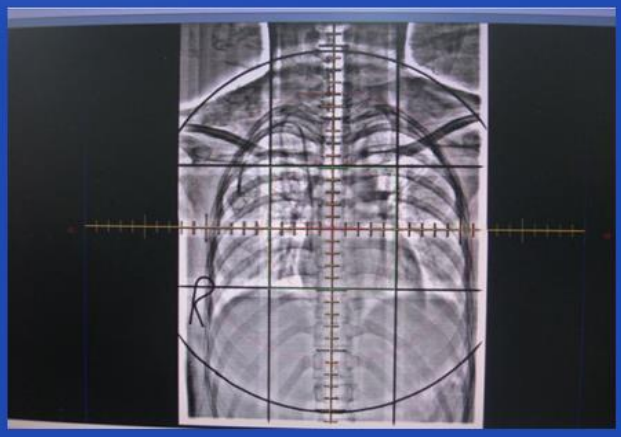
: **supine position**

: **neck and mediastinum (electrode 30x30 cm)**

: **no sedation**

: **24 sessions**





No. 8

-treatment results

: not evaluate radiologic examination

: no complications related hyperthermia

: last follow up status
alive

: survival periods
10 months

Conclusions

1. With the development of anticancer chemicals these days, the average survival time of childhood cancer patients is also increasing.

2. Previously, the purpose of treatment was to remove the mass, but the recent treatment focuses not only on the removal of the mass, but also on the reduction of acute and chronic side effects.

Conclusions

3. In the case of pain relief purposes, if it is difficult to calm the patient or cooperation is difficult, an alternative to radiation therapy can be tried.

4. Can be used for pain control-Helps improve quality of life.

5. Since there is no specific side effect, it can be tried if the existing treatment is refused due to concerns of chronic side effects.

Modulated electro-hyperthermia (mEHT) in monotherapy for painful bone metastases. A new promising indication?

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Madrid, Spain

Citation: Arrojo E. et al. (2020): Modulated electro-hyperthermia (mEHT) in monotherapy for painful bone metastases. A new promising indication?, Oncothermia Journal 29: 60 – 73,
www.oncotherm.com/sites/oncotherm/files/2021-02/Arrojo_Painfulbone

Abstract

Introduction: Painful bone metastases (PBM) have a great negative impact in patient's quality of life. Pain drugs for PBM are usually not enough and have serious side effects. Up to date, radiotherapy is the most effective treatment for PBM, but has some important limitations (toxicity, dose limits…).

Material and methods: We prospectively included 10 patients with different types of primary active tumors with PBM and tested mEHT as an "analgesic" treatment for PBM. 9 patients had solid tumors and 1 had a multiple myeloma with only one vertebral body affected. All patients had pain which was not responding to systemic and/or analgesic treatment.

Table 1. Patient characteristics and results

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone / Progression		mEHT Bone / Pain Response	
1	F	GYN	YES	UTEROUS	YES	FEMUR	**YES**
2	F	BREAST	YES	BREAST	NO	VERTEBRA	**YES**
3	M	MYELOMA	NO	NO	-	VERTEBRA	**YES**
4	F	BREAST	YES	LIVER	YES	HIP	**YES**
5	F	BREAST	YES	BRAIN	YES	VERTEBRA	NO
6	F	BREAST	NO	NO	-	VERTEBRA	NO
7	F	LUNG	YES	NO	-	RIBS	**YES**
8	F	SARCOMA	YES	NO	-	HIP	**YES**
9	F	BREAST	NO	NO	-	HIP	**YES**
10	F	BREAST	YES	NO	-	VERTEBRA	**YES**

**SEX: F: Female, M: Male.*

***Patients treated with mEHT at other "no bone" sites with tumor and evidence of progression at those sites after mEHT treatment.*

Results: All patients with solid tumors had stage IV (AJCC) and the patient with myeloma had stage III (ISS). All patients received between 5 and 12 mEHT treatments at PBM sites. Seven patients were under systemic treatment. 80% of the patients had significant pain response to mEHT treatment.

Three patients had radiotherapy scheduled and after mEHT treatment, did not need to receive it. Patient's pain response to mEHT was not related to systemic tumor response. Despite tumor progression at other sites treated with mEHT, mEHT was very effective on pain control for treated PBM. It's remarkable, that the patient with the no solid tumor (myeloma), had a significant pain response after mEHT treatment in monotherapy.

Conclusions: mEHT can be a very safe and effective treatment for PBM as a combined treatment, but also in monotherapy. Contrary to the common belief that mEHT does not works in hematological tumors, mEHT may have a role also in no solid tumors as multiple myeloma. These findings open a very interesting path of research.

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November 5, 2020

Modulated electro-hyperthermia (mEHT) in monotherapy for painful bone mestastases. A new promising indication?

Elisabeth Arrojo, MD, PhD
Radiation oncologist at HUMV
Medical director of INMOA
President of ICHS 2020

BONE METASTASES

- Bone is **the most frequent site of metastasis of the most common cancers** in men and women.
- Although bone metastases are sometimes asymptomatic, their **consequences are most often devastating, impairing both life quality and expectancy**, due to the occurrence of the skeletal-related events, including bone fractures, hypercalcemia and spinal cord compression.

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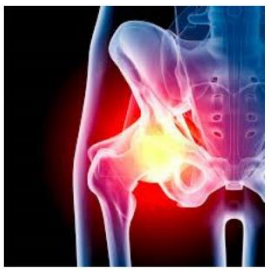
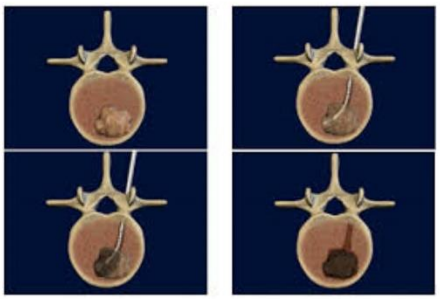
MAIN TREATMENTS FOR PAINFUL BONE METASTASES

- **Analgesics:** usually opioids → important side effects.
- **Bisphosphonates, calcitonin**
- **Systemic treatment** (chemotherapy, immunotherapy…) → very frequently not enough…
- **Radiotherapy**
  - Very effective
  - Dose limit
    - Organs at risk
    - Only once, twice…



MAIN TREATMENTS FOR PAINFUL BONE METASTASES



- **Radiofrequency (*"Agressive heat…"*)**
  - If live tissue is heated **beyond the threshold for protein denaturation (57–60°C) for a few seconds, coagulation necrosis occurs.**
  - Because heating above these critical levels **is not selective** and kills both normal and neoplastic cells, thermal ablations are limited among other things, by risk of side effects.

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MAIN TREATMENTS FOR PAINFUL BONE METASTASES

- **Hyperthermia**:
  - Studies mainly combined with radiotherapy.
    - **Good side**: usually more effective than radiotherapy alone.
    - **Bad side:** Radiotherapy limitations.
- **Hyperthermia alone**?
  - Almost nothing published…

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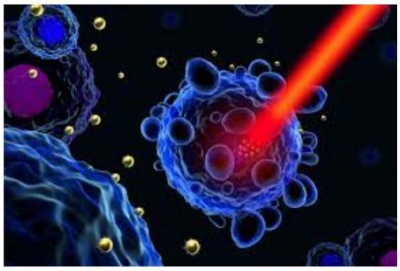

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We have some comments in different studies about metastatic bone pain and mEHT but not a specific study for this….

Hindawi Publishing Corporation
Conference Papers in Medicine
Volume 2013, Article ID 392480, 12 pages
http://dx.doi.org/10.1155/2013/392480

Conference Paper

Cases That Respond to Oncothermia Monotherapy

Tae Sig Jeung, Sun Young Ma, Jesang Yu, and Sangwoo

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Received 17 January 2013; Accepted 29 April 2013

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

This Conference Paper is based on a presentation given by Tae Sig Jeung at "C Society 2012" held from 12 October 2012 to 14 October 2012 in Budapest, Hur

Tumor mass was regressed at the right lung and spine. However, tumors progressed in the left lung because oncothermia was not given at the left lung.

Back pain to the right chest was subsided after oncothermia. Many cases showed the reduction of the metastatic bone pain with oncothermia.

It is possible to apply oncothermia to reduce metastatic bone pain with a variety of cancers.

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MOLECULAR PLAYERS IN CANCER-INDUCED BONE PAIN

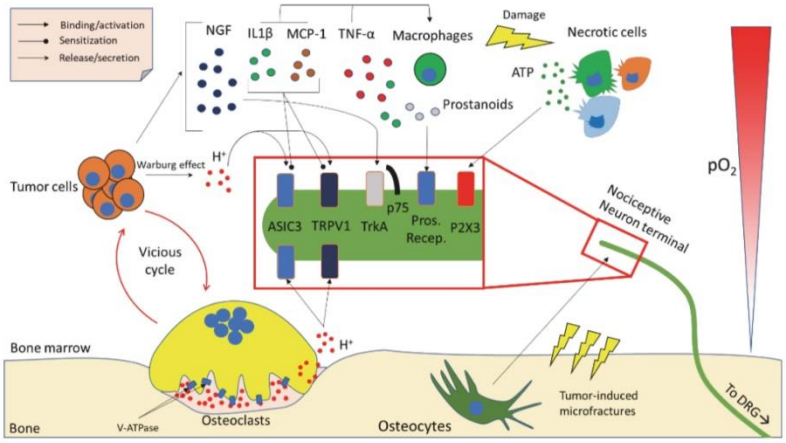

Figure 2. Cartoon representing the main cellular and molecular players in cancer-induced bone pain (CIBP).

Int. J. Mol. Sci. **2019**, *20*, 280

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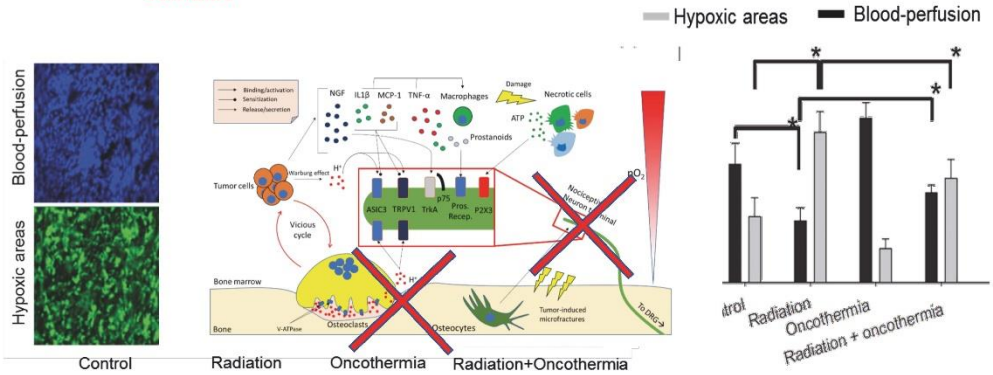
MODULATED ELECTRO-HYPERTHERMIA (mEHT) + RT

Heat → vasodilatation → decrease hypoxia → decrease H+ release and nociceptive stimulus



Five fields in each of the three tissue sections per tumor were studied and the % positive area calculated. Means of five tumors ±1 SE are shown. _indicates p<0.05.

Wonwoo Kim, Mi-Sook Kim, Hee-jong Kim, Eunjin Lee, Jae-hoon Jeong, Inhwan Park, Youn Kyoung Jeong & Won Il Jang (2017): Role of HIF-1α in response of tumors to a combination of hyperthermia and radiation in vivo, International Journal of Hyperthermia, DOI: 10.1080/02656736.2017.1335440; https://doi.org/10.1080/02656736.2017.1335440

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mEHT FOR PAINFUL BONE METASTASES

- We **prospectively** included **10 patients** with different types of primary active tumors with PBM and tested mEHT as an "analgesic" treatment for PBM.
- **All patients had pain which was not responding** to systemic and/or analgesic treatment. (No new treatments besides mEHT which could impact on PBM relief).
- All patients were under **high dose of opioids** and other analgesics.
- **All treatments at PBM sites were prescribed for pain relief as main objective** (not for tumor control).

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PATIENT FEATURES

	*Sex	Primary Tumor
1	F	GYN
2	F	BREAST
3	M	MYELOMA
4	F	BREAST
5	F	BREAST
6	F	BREAST
7	F	LUNG
8	F	SARCOMA
9	F	BREAST
10	F	BREAST

**SEX: F: Female, M: Male.*

- **9 patients had solid tumors** and **1 had a multiple myeloma** with only one vertebral body affected.
- All patients with solid tumors had stage IV (AJCC) and the patient with myeloma had stage III (ISS).

PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment
1	F	GYN	YES
2	F	BREAST	YES
3	M	MYELOMA	NO
4	F	BREAST	YES
5	F	BREAST	YES
6	F	BREAST	NO
7	F	LUNG	YES
8	F	SARCOMA	YES
9	F	BREAST	NO
10	F	BREAST	YES

7 patients were under systemic treatment.

PATIENT FEATURES

- **Unable to walk because of pain: 3 (Myeloma, sarcoma and breast)**
- **Able to walk with help: 1**

- **Able to move on his/her own but limited by pain: 6**

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PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone
1	F	GYN	YES	UTEROUS
2	F	BREAST	YES	BREAST
3	M	MYELOMA	NO	NO
4	F	BREAST	YES	LIVER
5	F	BREAST	YES	BRAIN
6	F	BREAST	NO	NO
7	F	LUNG	YES	NO
8	F	SARCOMA	YES	NO
9	F	BREAST	NO	NO
10	F	BREAST	YES	NO

- ***4 patients*** *received* ***mEHT*** *treatment at other* ***no bone sites*** *(cervix, breast, liver, brain).*

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PATIENT FEATURES

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone	mEHT Bone
1	F	GYN	YES	UTEROUS	FEMUR
2	F	BREAST	YES	BREAST	VERTEBRAE
3	M	MYELOMA	NO	NO	VERTEBRAE
4	F	BREAST	YES	LIVER	HIP
5	F	BREAST	YES	BRAIN	VERTEBRAE
6	F	BREAST	NO	NO	VERTEBRAE
7	F	LUNG	YES	NO	RIBS
8	F	SARCOMA	YES	NO	HIP
9	F	BREAST	NO	NO	HIP
10	F	BREAST	YES	NO	VERTEBRAE

- *5 patients vertebrae*
- *1 patient femur*
- *3 patients hip*
- *1 patient rib*

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RESULTS:

- All patients received **between 5 and 12 mEHT treatments** at painful bone metastases (PBM) sites.
- **80% of the patients had significant pain response** to mEHT treatment.

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone / Progression		mEHT Bone / Pain Response	
1	F	GYN	YES	UTEROUS	YES	FEMUR	YES
2	F	BREAST	YES	BREAST	NO	VERTEBRA	YES
3	M	MYELOMA	NO	NO	-	VERTEBRA	YES
4	F	BREAST	YES	LIVER	YES	HIP	YES
5	F	BREAST	YES	BRAIN	YES	VERTEBRA	NO
6	F	BREAST	NO	NO	-	VERTEBRA	NO
7	F	LUNG	YES	NO	-	RIBS	YES
8	F	SARCOMA	YES	NO	-	HIP	YES
9	F	BREAST	NO	NO	-	HIP	YES
10	F	BREAST	YES	NO	-	VERTEBRA	YES

- All patients with good response **felt improvement since de first mEHT** treatment.

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RESULTS:

	*Sex	Primary Tumor	Systemic Treatment	**mEHT NO bone	mEHT Bone
1	F	GYN	YES	UTEROUS	FEMUR
2	F	BREAST	YES	BREAST	VERTEBRA
3	M	MYELOMA	NO	NO	VERTEBRA
4	F	BREAST	YES	LIVER	HIP
5	F	BREAST	YES	BRAIN	VERTEBRA
6	F	BREAST	NO	NO	VERTEBRA
7	F	LUNG	YES	NO	RIBS
8	F	SARCOMA	YES	NO	HIP
9	F	BREAST	NO	NO	HIP
10	F	BREAST	YES	NO	VERTEBRA

- **3 patients had radiotherapy scheduled** and after mEHT treatment, **did not need to receive it**.

Unable to walk because of pain: 3 (Myeloma, sarcoma and breast)

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RESULTS:

- **4 patients were treated with mETH at other no bone sites**. All these 4 were receiving systemic treatment.
  - **1 mEHT at cervix (cervical cancer) –> progression**
    - Bone mets femur → significant pain response with mEHT
  - **1 mEHT at breast (breast cancer) –> tumor response**
    - Bone mets vertebrae → significant pain response with mEHT
  - **1 mEHT at liver (breast cancer) –> progression**
    - Hip mets → significant pain response with mEHT
  - **1 mEHT at brain (breast cancer) –> progression**
    - Vertebral mets → NO pain response with mEHT

- **Despite tumor progression** at other sites treated with mEHT, mEHT **was very effective on pain control for treated PBM in 2 patients.**

- **mEHT can relief pain despite tumor progression**

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INTERESTING...

- **The patient with the no solid tumor (myeloma), had a significant pain response after mEHT treatment in monotherapy.**

FACTS about Oncothermia

Oncothermia is active in all solid tumors.

No side effects, rare contraindications.

Combined energy absorption with modulated electric field.

Oncologists or other medical specialists treat with the method worldwide.

Tumour tissue is selectively treated, the malignance is destroyed.

Healthy tissue is unaffected.

Efficacy of chemotherapy and radiotherapy is improved by the treatment.

Reestablishes the intercellular junctions, supresses the dissemination.

Modulated electro-hyperthermia induces immunogenic cell-death.

Improves the quality of life, reduces the side-effects of other treatments.

A proven method since 30 years with more than 200.000 treatments yearly.

Myeloma is cancer of the plasma cells → Is considered a hematologic tumor...

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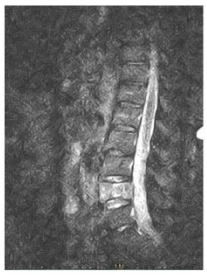
MYELOMA CASE



- Male 59 year old.
- Dx: **Multiple myeloma** IgG kappa IIA, **mets and fracture L4** and light hypercalcemia.
  - **VAS (Visual analogic scale): 9 with movement, 3 relaxed.**
  - **Wheel chair → could not stand on his own.**
  - **High dose Opioids**
  - **High dose Corticoids**
- Scheduled for bone marrow transplation after induction chemotherapy.
- **Proposed for vertebroplasty + radiotherapy** before beginning CT.

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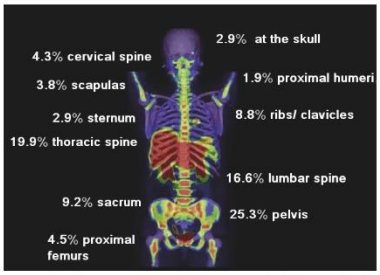
MYELOMA CASE

- **Suggest try with mEHT.**
  - Patient received **6 mEHT treatments** every other day.
    - After 1st treatment → was able to stand on his own.
    - After 3 treatments decreased 50% analgesics and was able to walk with crutches.
    - After 5 treatments stopped opioids, and decrease corticoids 75%.
  - **1 week after 6th treatment**:
    - **No analgesic nor corticoids.**
    - **Able to walk on his own and climbing stairs.**
  - He was treated on february 2020.
    - **Up to date**, he already received bone marrow transplation and **no evidence of disease and no pain.**

WHY?

- **We don't find a pattern related to:**
  - **Histology.**
  - **Tumor systemic or local response.**
  - **Type of bone.**
    - Of course → not enough patients to rise conclusions.



Distribution of Proliferating Bone Marrow in Adult Cancer Patients Determined Using FLT-PET Imaging ijrobp.2009.11.040

HOW LONG?

Length of response

- 1 patient died 1 month after treatment.
- All the other 7 patients still have pain controlled:
  - Follow Up:
    - 4 patients 6 months.
    - 3 patients 9 months.
    - 2 patients 12 months.

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CONCLUSIONS

- **mEHT can be a very safe and effective treatment for PBM as a combined treatment, but also in monotherapy.**
- **Contrary to the common belief that mEHT does not works in hematological tumors, mEHT may have a role also in no solid tumors as multiple myeloma.**
- **These findings open a very interesting path of research.**
  - We need more studies to know:
    - Indications
    - Number of sessions.
    - Length of response.

Four case reports on complex high risk sarcoma cases treated with modulated electro-hyperthermia

Carrie Anne Minnaar[1,2], Jeffrey Kotzen[1,2]

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Johannesburg, South Africa
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Johannesburg, South Africa

Citation: Minnaar C.A., Kotzen J. (2020): Four case reports on complex high risk sarcoma cases treated with modulated electro-hyperthermia, Oncothermia Journal 29: 74 – 88
www.oncotherm.com/sites/oncotherm/files/2021-02/Minnaar_Highrisksarcoma

Abstract

Introduction: Radiative hyperthermia (HT) for the treatment of sarcomas has been applied in combination with chemotherapy, showing improved local control and survival [1,2]. Only two small studies have assessed HT plus radiotherapy (RT) [3,4] and few have assessed mEHT for the management of sarcomas.

Objectives: To determine if there is sufficient motivation for the addition of mEHT, as a more affordable and practical HT solution, in the management of sarcomas, in the absence of any further options.
Material and methods: We present four interesting and complex cases of local recurrences in a previously irradiated region treated with modulated electro-hyperthermia (mEHT) locally, combined with chemotherapy or RT, at our facility.

Results
Patient 1: 42yr old female with a synovial sarcoma of the heart valve treated with a heart transplant and chronic immunosuppressant medication; mediastinum and pulmonary nodules developed 5yrs later. Treatment: 30x2Gy fractions + mEHT to the mediastinum. Inactive pacemaker present, outside the treatment field. Patient is stable at 18months post treatment and is enjoying an excellent quality of life.
Patient 2: 68yr old male with a local recurrence of a myxoid liposarcoma in the right thigh (30cm) 1yr after excision and RT. Treatment mEHT twice weekly for 19mnths (12 of which chemotherapy was administered 3wkly). Tumour shrunk significantly and remained stable until the patient died of septicaemia from a wound infection on his foot.
Patient 3: 52yr old woman with an RAS 5yrs after treatment for a SCC of the left maxilla sinus. Prescribed RT+mEHT. Treatment was tolerated well but the tumour did not respond.
Patient 4: Male patient with a sarcoma in the right shoulder, treated initially with surgery, followed by several local recurrences treated with either surgery, external beam radiation, or brachytherapy, over five years. Prescribed external beam radiation combined with mEH
Conclusions: mEHT could be considered when no further options are available as a safe adjunct to treatments. There is motivation for the design of a trial investigating RT+mEHT for the management of high-risk sarcomas, especially in cases in which patients have been previously irradiated.

[1] Issels RD et al, Lancet Oncol [Internet]. 2010.11(6):561–70
[2] Issels RD et al, JAMA Oncology. 2018;4(4):483-492
[3] Leopold A et al, Int J Radiat Oncol Biol Phys. 1989.16(1):107–15
[4] de Jong MAA et al, Cancer. 2012;118(1):180-187

Four case reports on complex high risk sarcoma cases treated with modulated electro-hyperthermia

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38th Conference of the International Clinical Hyperthermia Society
November 5, 2020

Sarcomas

- Sarcomas are rare (<1% of all cancers) and heterogenous tumours
- More than 100 unique sarcoma subtypes
- Metastatic and refractory tumors have poor outcomes
- Management involves a multidisciplinary approach
  - Surgery
  - Radiation
  - Chemotherapy
  - Rehabilitation
- Management guidelines have been developed in high-income countries, but their applicability in low-income countries, where resources may be limited, remains a challenge.

DOI: 10.1200/EDBK_200589 American Society of Clinical Oncology Educational Book 38 (May 23, 2018) 916-924.

Sarcomas and Hyperthermia

ESMO guidelines mention Hyperthermia (HT) for the management of high risk soft tissue sarcomas.

HT combined with radiotherapy or chemotherapy indicated for:

- Irresectable, locally advanced deep high-risk soft tissue sarcomas (>5 cm) grade 2 or 3,
- Limb-preserving surgery – isolated limb perfusion/regional;
- Metastatic or recurrent tumours that have been previously exposed to treatment and require re-treatment.

Including Liposarcoma, leiomyosarcoma, synovial sarcoma

Based on a Phase III clinical trial with a 10 year follow

Casali P, Bbecassis N, Bauer S, et al. Soft tissue and visceral sarcomas : ESMO – EURACAN Clinical Practice
Guidelines for diagnosis , treatment Clinical Practice Guidelines. ESMO Clinical Practice Guidelines. 2018;29

Sarcomas and Hyperthermia

- Randomised controlled multicentre Phase III, multicentre
- 329 participants with grade 2 or 3 STS >5cm (deep)
- Neoadjuvant chemotherapy: EIA x 8 cycles 3 wks apart
- 16 HT (administered on day 1 and 4 of each cycle)

Outcome	HT+ChT	ChT	*p*
Progression free at 2yr	30%	19%	*p*=0.035
Median PFS	120mnths	75mnths	*p*=0.003
Median DFS	18mnths	32mnths	*p*=0.011
5yr Survival	63%	51%	*p*=0.04
10yr Survival	53%	43%	
Median time to local progression	67.3mnths	29.2mnths	*p*=0.002
Median survival	15.4yrs	6.2yrs	*p*=0.04

[1] Issels RD *et al*, *Lancet Oncol*. 2010.11(6):561–70.
[2] Issels RD *et al*, *JAMA Oncology*. 2018;4(4):483-492.

Sarcomas and Hyperthermia

Only two small studies have assessed HT plus radiotherapy (RT) for the management of sarcomas:

1. Phase II study investigating neoadjuvant RT+HT (n=17):
   Showed Significantly higher histopathological regression when HT applied 2/wk vs 1/wk [1]

2. Retrospective study of RAS of the thorax (n=16):
   Treated with RT (AMC/BVI protocol*) +HT
   7 CR; 2 PR and a median survival of 15.5 months [2]

*AMC protocol: 8x4Gy (twice per week) + HT once a week
BVI protocol: 12x3Gy (4 per week) + HT twice a week

[1] Leopold A *et al*, *Int J Radiat Oncol Biol Phys.* 1989.16(1):107–15
[2] de Jong MAA *et al*, *Cancer.* 2012;118(1):180-187

Sarcomas and Hyperthermia

Triple modality Study

- CRT+HT (8MHz RF capacitive) was administered to 60 STS patients in Japan and compared to retrospectively to the bone and soft tissue tumour registry
- OS was not significant between groups (HR=1.26, p=0.532);
- LC was significantly improved with HT (HR=4.82, p=0.037).
- Higher 5 year LC rate with HT and amputation was averted despite wider resection margins in the retrospective group.

Aiba et al, (2018) Cancer Original Research. doi: 10.1002/cam4.1366

Modulated Electro-Hyperthermia (mEHT)

- Capacitive heating technology
- Transmits amplitude modulated radiofrequency (RF) waves 13.56MHz, between two electrodes.
- Small electrode is covered by a water bolus in an adjustable arm,
- Large electrode is in the bed and is covered by a water mattress.
- Amplitude modulation is the main difference between mEHT and other capacitive devices
- Modulation is a key component of the enhanced efficiency of mEHT, allowing for a lower power output and increased safety

Minnaar et al (2020) Int J HT, VOL. 37, NO. 1, 263–272

mEHT and Sarcomas

Case Study:

Case report on Synovial Sarcoma, published in 2013 [1]:

- 48-year-old female with synovial sarcoma in the right thigh
- Treated surgically in 2004
- Lung metastasis diagnosed in 2011
- Treated with RT (10x3Gy) - Partial regression
- mEHT administered as a monotherapy: (39 treatments over 6 months) – Partial response

[1] Jeung et al, Conference Papers in Science, vol. 2013, Article ID 392480, 12 pages, 2013.

mEHT and Sarcomas

Report on 13 Cases:

Patients between 18 to 73 years old, 6 male and 7 female, primary and recurrent. Histologic type:

- 2 rhabdomyosarcomas,
- 2 synovial sarcomas,
- 3 leiomyosarcomas,
- 1 malignant peripheral nerve sheath tumor,
- 1 spindle sell sarcoma
- 1 malignant fibrous histiocytoma,
- 2 chondrosarcomas,
- 1 osteosarcoma.

Treatments involved RT+mEHT post-op or primary treatment
mEHT applied twice a week, for a median of 18 treatments (2-108)
1 case received ChT as well
All patients showed stable disease or partial regression

Jeung et al (2015) Case Reports in Clinical Medicine, 4, 157-168

Objectives

To determine if there is sufficient motivation for the addition of mEHT (an affordable option), as a unique therapeutic approach, in the management of sarcomas, in the absence of any further options.

Materials and Methods

We present four interesting and complex cases of local recurrences treated with mEHT locally, combined with chemotherapy or RT, at our facility.
All patients provided consent for the use of their data for this report

Patient 1

42yr old female

2014:

- Diagnosed with a synovial sarcoma of the heart valve
- Heart transplant, pace maker inserted; prescribed chronic immunosuppressant medication (Satican).
- 6 months later the pacemaker was deactivated as heart was functioning normally.

2015 recurrence:

- Multiple pulmonary nodules
- Treated with radio-ablation

2018:

- CT scan revealed progressive disease and multiple pulmonary nodules: Right upper, middle and lower lobe (largest 9.6mm); Left upper, and lower lobe (largest 19.2mm); and Subcarinal and Mediastinal lymphadenopathy.
- Histopathology confirmed monophasic synovial sarcoma
- Gene sequencing showed no relevant mutations
- PDL-1 negative, MLH-1; MSH-2; MSH-6 positive

Patient 1

Treatment:

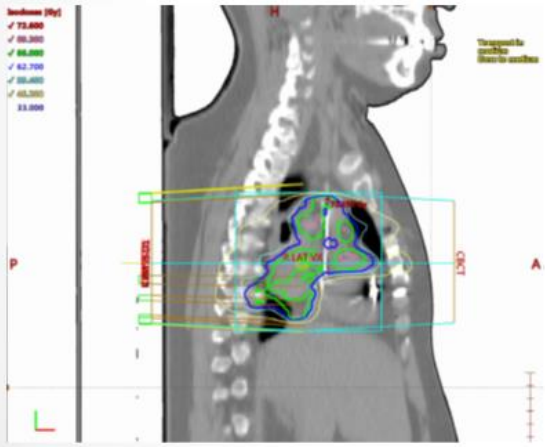
- Not eligible for chemotherapy.
- Prescribed EBRT to the mediastinum: 33x2Gy fractions
- mEHT:
  - 20cm electrode used, modulation on from 3rd session
  - Progressed from 45W to 90W over 5 sessions.
  - Inactive pacemaker was outside the treatment field.

Follow up scan revealed stable disease.

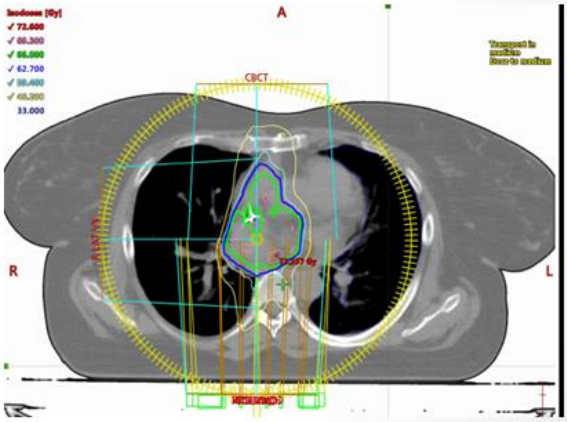
Patient is still stable at 18months post treatment and is enjoying an excellent quality of life.

Patient 1

Axial Plan

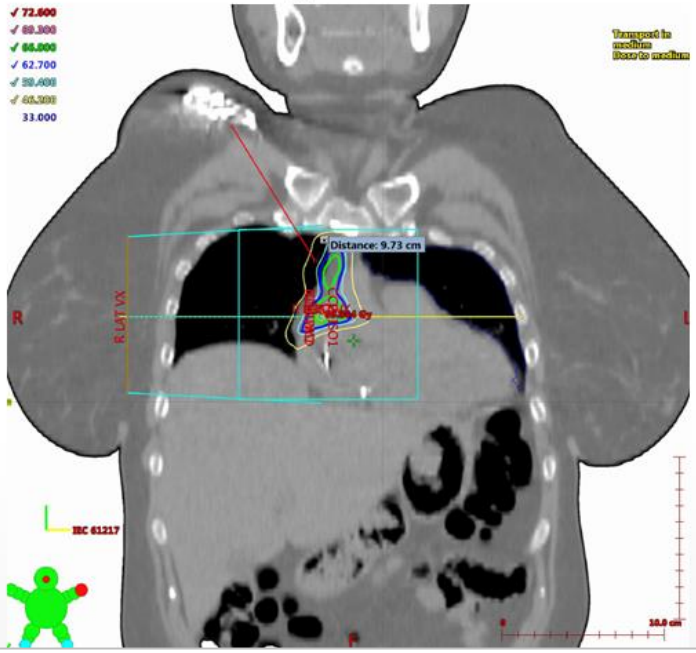


Coronal Plan



Patient 1

Sagittal Plan



Patient 2

68yr old male

2015

- Diagnosed with Myxoid Sarcoma in the right thigh
- 21x15x10cm
- Surgically excised
- Treated with EBRT (2Gy x 33 treatments) in early 2016
- Followed by another surgically

2018

Inoperable local residual myxoid liposarcoma in the right thigh (30cmx25cm)
Tumour extended from the pelvis, into the anterior thigh and right scrotum, with bladder and rectal compression and displacement, and bilateral hydronephrosis (not eligible for chemotherapy or further RT).

Patient 2

Treatment.

mEHT twice weekly for 3 months (150W for one hour using the 30cm electrode)
CT scan revealed stable disease and improved renal function which allowed for the addition of Caelyx (6 cycles administered 3 weekly) combined with mEHT twice weekly

November 2019 CT showed:

- Resolution of bilateral hydronephrosis,
- Significant decrease in the pelvic portion of the tumour,
- Resolved bowel and bladder obstruction.
- Patient reported normal bowel and urinary function.

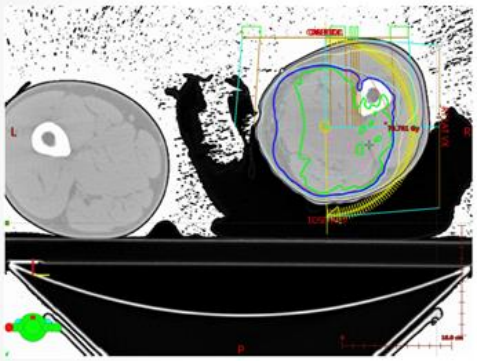
A further 6 cycles of chemotherapy + mEHT were prescribed

CT in May 2020 revealed stable disease, with the tumour remaining predominantly in the anterior portion of the right thigh.

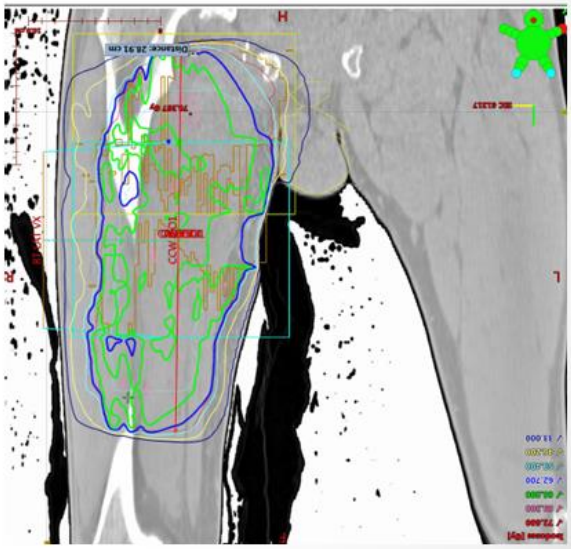
Disease remained stable until the patient died of septicaemia at 19 months from a wound infection on his foot.

Patient 2

Sagittal Plan



Coronal Plan



Patient 3

52yr old woman

2013

SCC of the left maxilla (T4a No Mo)
Left maxillectomy in September 2013
Completed adjuvant EBRT in January 2014

2018

Presented with an enhancing necrotic mass in left maxillary sinus.
Histopathology confirmed a pleomorphic soft tissue sarcoma
In a previously irradiated region
No possibility of surgical resection
Not eligible for chemotherapy

Treatment

IMRT: 2Gy x 25 (large field), then 2Gy x 5 (gross tumor volume boost)
mEHT weekly up to 100W

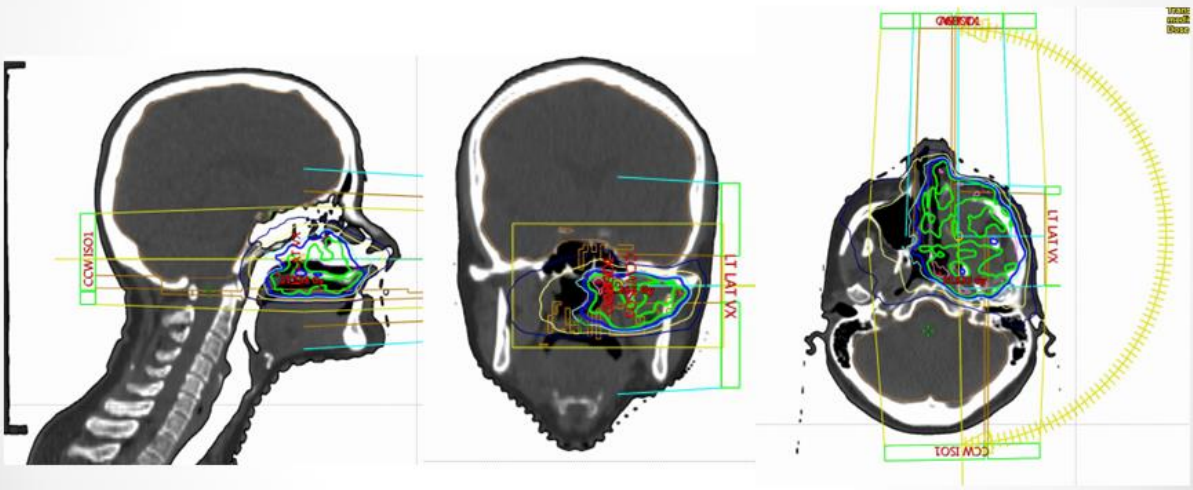
Patient 3

Outcome

- Radiation Associated Sarcomas are notoriously difficult to manage.
- Post-treatment CT showed progressive disease.
- mEHT did not result in any additional RT related toxicity
- No AEs resulted form mEHT

Patient 3

Sagittal Plan Coronal Plan Axial Plan



Patient 4

57 year old male

2013
Diagnosed with dermatofibrosarcoma of the right clavicle
Treated with EBRT

2015
Local recurrence,
Surgically resected and treated with brachytherapy

2017; 2018; and 2019:
Local recurrence treated with surgical resection and brachytherapy

2020
Local recurrence: 1.6x11x14mm, at the remaining stump of the clavicle

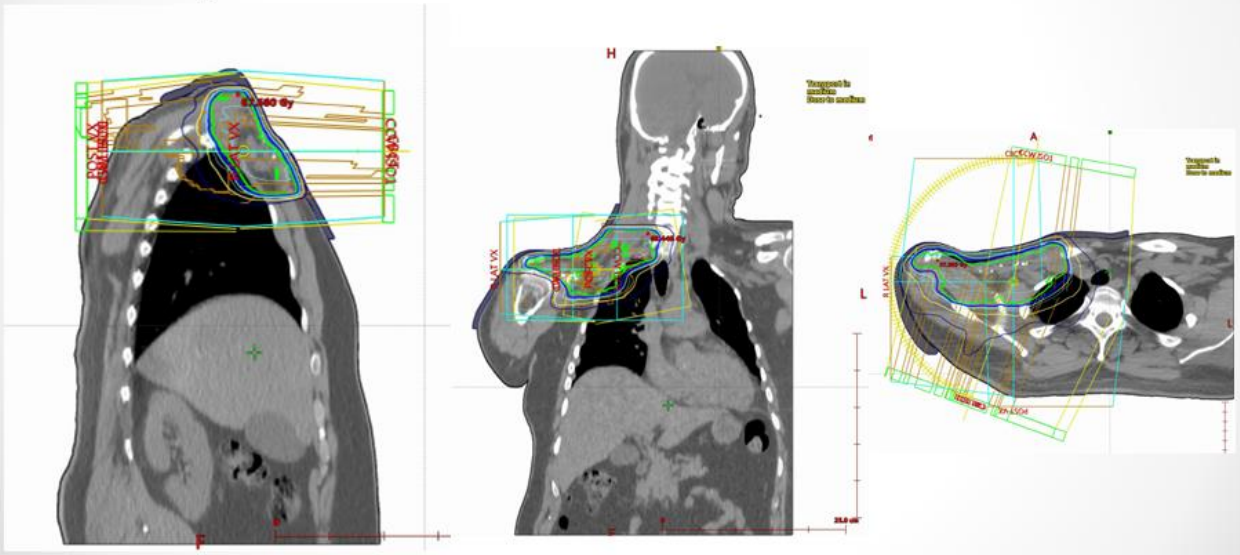
Patient 4

Treatment:
Resection
Followed by EBRT (2Gy x 32)
mEHT twice weekly at 100W using a 20cm electrode

Patient has completed treatment, with changes in pigmentation being the only adverse event noted.

Patient 4

Sagittal Plan | Coronal Plan | Axial Plan



Discussion

These four cases represent interesting situations in which predicted **outcomes were poor** and further **treatment options were limited**.

- No adverse events were reported when administering mEHT to a patient with a **deactivated pacemaker outside the treatment field**.
- No adverse events have been reported after administering mEHT to the mediastinum with a portion of a **transplanted heart** in the treatment field
- mEHT plus RT in a **previously irradiated region** was **not associate with additional toxicity** in the head region and the shoulder region
- **Chronic management** of a residual, previously irradiated sarcoma in the thigh afforded the patient an additional 19 months of **improved quality of life**

Conclusion

The addition of mEHT to improve the chance of a positive outcome in these cases was safe, practical and affordable in comparison to other treatments

mEHT could be considered when no further options are available as a safe adjunct to treatments, both chemotherapy and radiotherapy, for complex, inoperable sarcoma cases.

There is motivation for the design of a trial investigating RT+mEHT for the management of high risk sarcomas, especially in cases in which patients have been previously irradiated.

Acknowledgements

We would like to acknowledge Theo Nair and Tamryn Patrick from the planning department at the Wits Donald Gordon Radiation Centre for arranging the images, and Dr Richard Kyte, the referring surgeon on the cases.

We would also like to thank the patients for allowing us to present their data.

Modulated electro-hyperthermic treatment in the therapy of inoperable pancreatic cancer patients - a single center case-control study

Petényi, Flóra Gréta[1]; Mühl, Dorottya[2]; Izsó, Blanka[1]; Tóth, Simon[2]; Garay Tamás [1,2]; Erika Borbényi[2]; Dank, Magdolna[2]; Szász A Marcell[2]

[1]Faculty of Information Technology and Bionics, Pázmány Péter Catholic University, Budapest, Hungary
[2]1st Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary

Citation: Petényi F.G. et al. (2020): Modulated electro-hyperthermic treatment in the therapy of inoperable pancreatic cancer patients - a single center case control study, Oncothermia Journal 29: 89 – 102, www.oncotherm.com/sites/oncotherm/files/2021-02/Petenyi_Inoperablepancreas

Abstract

Introduction: Inoperable pancreatic cancer poses a challenge as it is often a therapy resistant tumor which bears a poor prognosis. Hyperthermic treatments aim to break this resistance and facilitate oncotherapies.

Objective: To analyze the benefit of concomitant mEHT for inoperable pancreatic cancer patients to form basis for further investigation.

Materials and methods: We present a retrospective single-center case-control study including 78 inoperable pancreatic cancer patients. The case group comprised 39 patients receiving first mEHT treatment at Semmelweis University Cancer Centre between 2016 September and 2019 November and underwent at least 19 mEHT treatment sessions. All pancreatic cancer diagnosis was confirmed during routine diagnostic protocol by histological examination between 2014.12.26 and 2019.10.17. Data collection was closed on 2020.01.31. The time elapsed between the date of diagnosis and death was as overall survival (OS).

Results: In first step each case-patient was individually matched to a control-patient by age, sex and chemotherapy administration during mEHT treatment. To reach higher similarity in overall status of the case and control patients also presence or absence of distal metastases and emerging ascites were taken in count as matching criteria by generating case-control pairs.
Of note, a trend in difference was found in overall survival of patients in case-control pairs matched for age, sex and chemotherapy receiving during mEHT treatment favoring mEHT ($p=0.0704$). Overall survival of inoperable pancreatic cancer patients with or without distant metastasis in both case and control groups was analyzed, metastatic disease resulting in significantly higher OS ($p=0.022$). Overall survival with or without the presence of ascites in both case and control showed a trend favoring mEHT treatment as well ($p=0.0611$). Elapsed time between diagnosis and start of mEHT treatment did not significantly influence overall survival.

Discussion: In our series of inoperable pancreatic cancer patients treated with mEHT applied as concomitant therapy, we have detected a significant improvement in overall survival, especially in metastatic setting. To further analyze the biological background for this treatment response, we have concluded analyses investigating the tumor-host immunological interface and quality of life, and we have developed the protocol for a randomized clinical trial for this patient group.

Modulated electro-hyperthermic treatment in the therapy of inoperable pancreatic cancer patients - a single center case-control study

Szász, A. Marcell

Cancer Center,

Department of Internal Medicine and Oncology

38th Conference of International Clinical Hyperthermia Society

5th November 2020

250 years of EXCELLENCE in medical education, research & innovation and healthcare

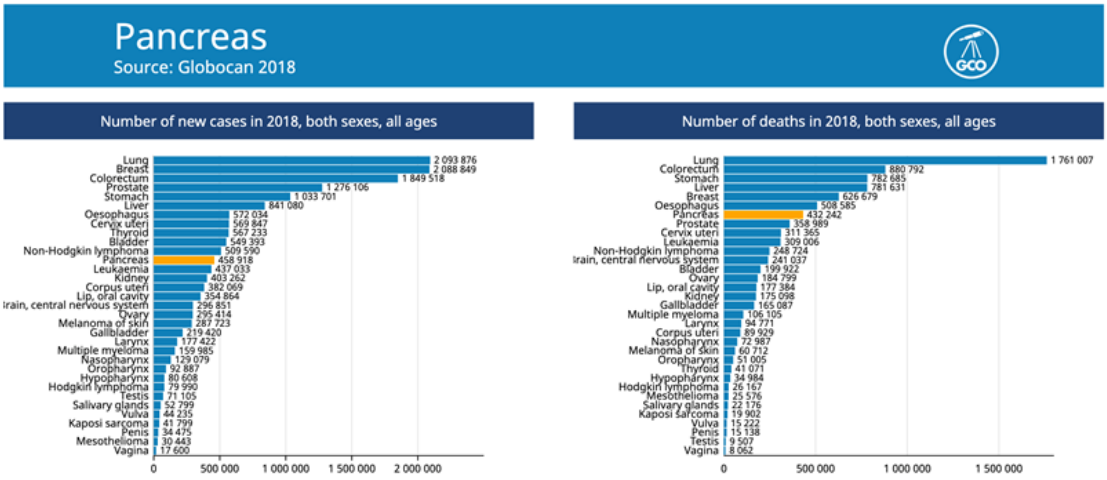
Semmelweis University
http://semmelweis.hu/

Cancer Center
Department of Internal Medicine and Oncology

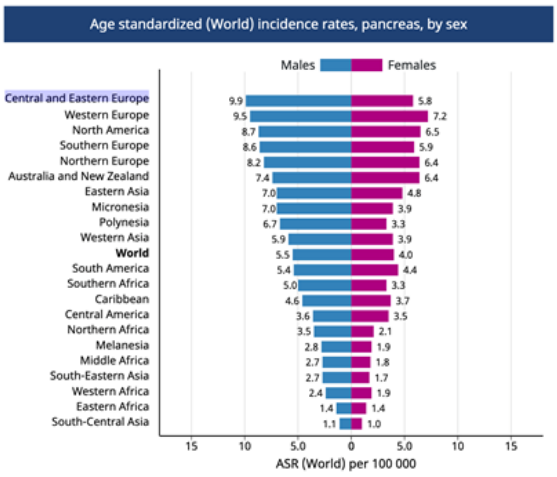
New cases and deaths worldwide

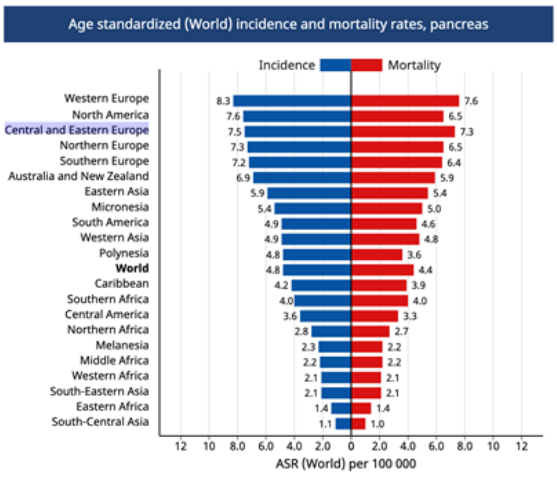
Pancreas

Source: Globocan 2018

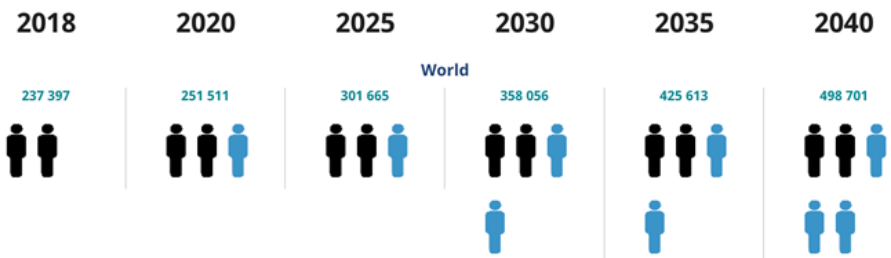


Incidence and mortality regionally



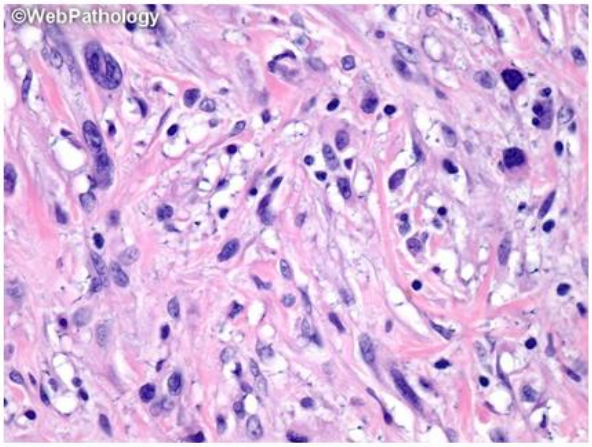


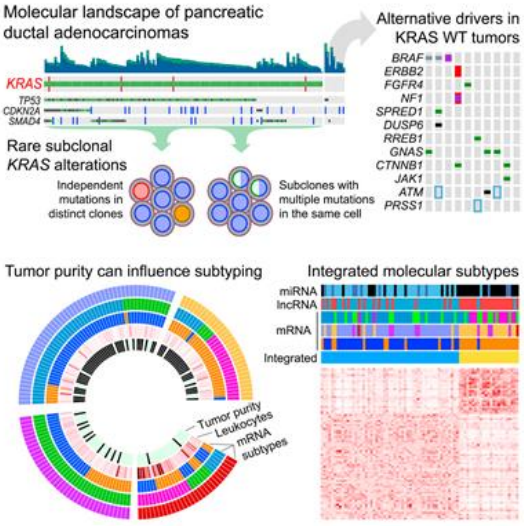
From 2018 to 2040



		2018	2040			
		Number	Number	Demographic change	Change in risk	Overall change
World	Males (APC 0%)	243 033	426 284	183 251 (+75.4%)	0	183 251 (+75.4%)
World	Females (APC 0%)	215 885	388 992	173 107 (+80.2%)	0	173 107 (+80.2%)
World	Both sexes	458 918	815 276	356 358 (+77.7%)	0	356 358 (+77.7%)

Morphology and underlying genetics



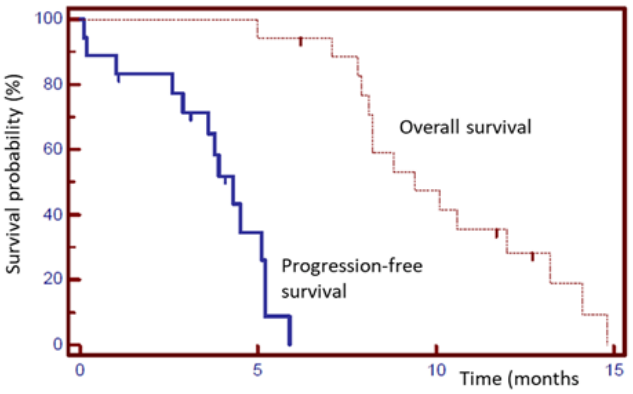


Pancreatic studies

Metastatic Pancreas; Phase II study (n=26)

Second-line chemotherapy in combination with Oncothermia for patients with refractory metastatic (progressive in liver) pancreatic cancer.
The treatment protocol was intravenous chemotherapy (gemcitabine, 1000 mg/m2 IV and oxaliplatin 100 mg/m2 [GEMOX]) on day one combined with mEHT (days1, 3 and 5); and the protocol repeated by every two weeks.

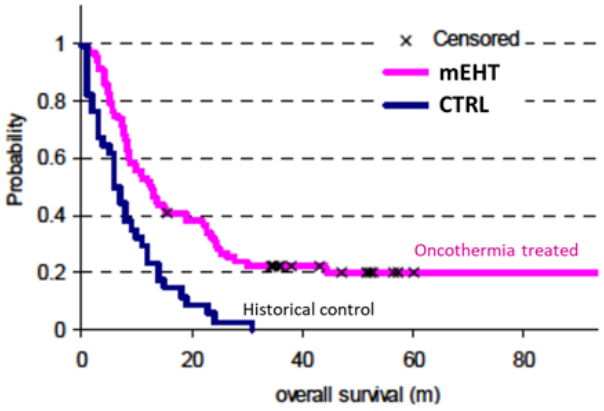
Volovat et al.; (2014); *Romanian Reports in Physics, 66:166–174*



Pancreatic studies

Phase II study of advanced, metastatic pancreas cancer (n=99) Dani A, et al. (2008) Forum Hyperthermie 1:13–20

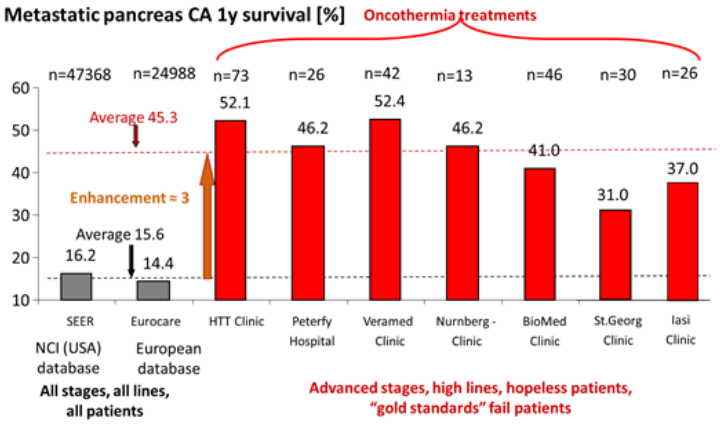
Phase II clinical trial, double center (A & B), single-arm in comparison to historical control from the same hospital, same doctors. 40+% of patients had multiple metastases. The trial includes a cohort of heavily pretreated patients (3+ lines), and due to the refractory or another fail of the conventional therapies oncothermia was applied as monotherapy. The first and subsequent year survivals were: 1st:50.5%, 2nd: 27.3%, 3rd:15.2%, 4th:8.1%, 5th:3%. These values are significantly higher than the values from the large databases (SEER and Eurocare).



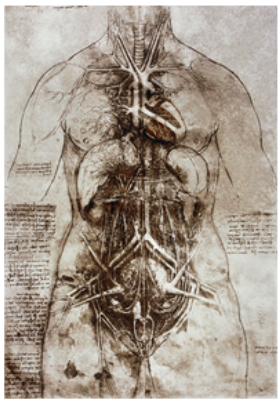
Pancreatic studies

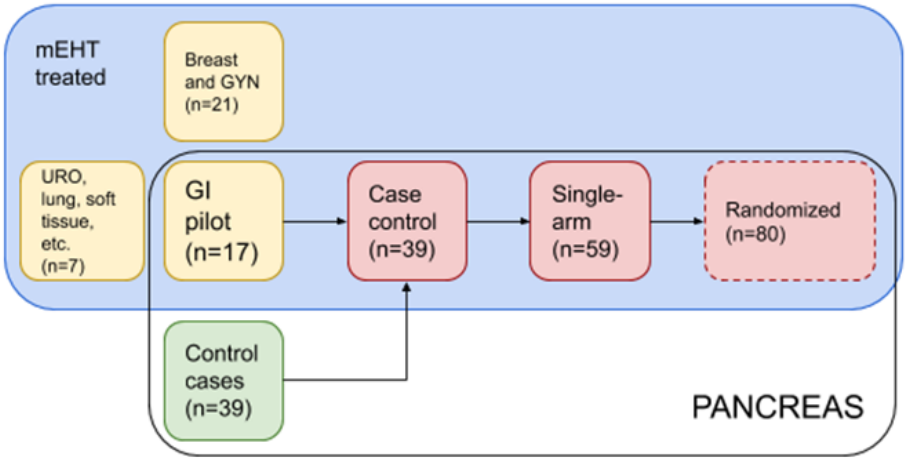
1st year survival comparison of pancreas studies in different hospitals using oncothermia protocol

The achieved results of 1st year survival is compared to the same time achieved results in USA and EU, according to the relevant databases; SEER and EuroCare. The weighted average is nearly 3 times higher for oncothermia treated patients than the general expectation. This result is despite the fact, that the general statistics contain all the patients, while patients treated with oncothermia are all in high-line treatment advance stages, where the "gold standards" fail.



mEHT studies at Semmelweis Cancer Center





Study Design and Patient Selection

- retrospective single-center case-control study
- 78 pancreatic cancer patients (ductal adenocarcinoma)
- all pancreatic cancer diagnosis was set during routine diagnostic protocol by histological examination between 2014.12.26 and 2019.10.17.
- case group comprised of 39 inoperable pancreatic cancer patients
- data collection was closed on 2020.01.31.
- each case-patient was individually matched to a control-patient by age (±5 years), sex and chemotherapy received during mEHT treatment.
- presence or absence of distal metastases and emerging ascites. (However, this led to the exclusion of some case-patient as no suitable control was found.)

Treatment

- first mEHT treatment at Semmelweis University Cancer Center between 2016 September and 2019 November
- Instruments: mEHY-2000, mEHY-2030
- at least 19 mEHT treatment sessions

median number of mEHT sessions (range)	49 (19-154)
elapsed time from diagnosis to mEHT treatment (days from pathological diagnosis)	41 (0-717)

- Power from 50W to 100W, then 100W to 150W in an hour session
- (2 or 3 times per week, as long as tolerated)
- systemic treatment: FOLFIRINOX and gemcitabine-based protocols (± platinum / 5FU)

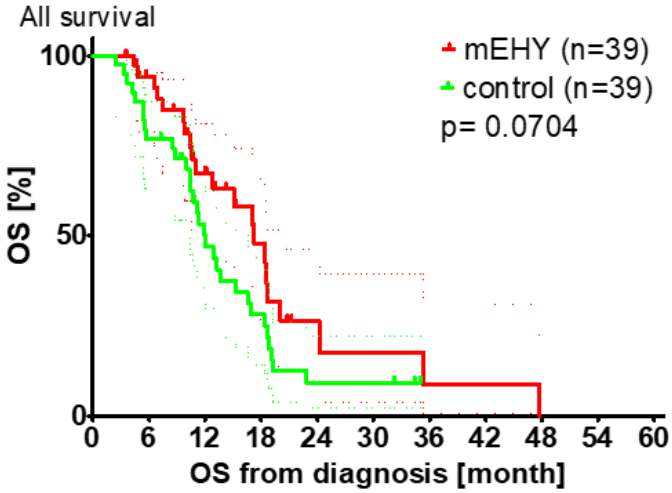
Statistical analysis

- The time elapsed between the date of diagnosis and death from any cause was as overall survival (OS).
- Follow-up of the patients were closed at 2020.01.31. Patients alive at this time point were censored.
- Survival rates were estimated using Kaplan-Meier analysis supported by log-rank tests, and comparison of other parameters between case and control group were investigated using t-test or Fisher exact test for continuous and categorical variables.
- Two-sided p values < 0.05 were considered as significant.

Basic demographic and clinical characteristics

		mEHT treated	Control	p=	
median age (range)		66 (45-84)	68 (45-77)	0.8801	t-test
male gender		18 (46.1)	18 (46.1)	matched	
chemotherapy	GEM/B	24 (61.5)	24 (61.5)	matched	
	Folfirinox	8 (20.5)	8 (20.5)	matched	
	GEM+CDDP	5 (12.8)	5 (12.8)	matched	
	GEM+5FU+LV	1 (2.6)	1 (2.6)	matched	
	Gem+oxaliplatine	1 (2.6)	1 (2.6)	matched	
without pathological ascites		23 (58.9)	21 (53.8)	1.000	Fisher exact test
without distatnt metastasis		16 (41.0)	12 (30.7)	0.3585	Fisher exact test
not-operable		39	39	matched; enrollment criteria	
median overall survival [month]		10.77 (3.5-47.7)	10.83 (2.5-35.0)	0.9059	t-test
1 year survival		18 (46.2)	16 (41.0)	0.6566	Fisher exact test
2 year survival		3 (6.8)	3 (6.8)	1.000	Fisher exact test
3 year survuval		1 (2.6)	0 (0.0)	1.000	Fisher exact test

trend in difference was found in overall survival in case-control pairs (matched for age, sex and chemotherapy receiving during mEHT treatment)



Dotted line represents asymmetrical 95% confidence interval calculated in the Kaplan-Meier analysis

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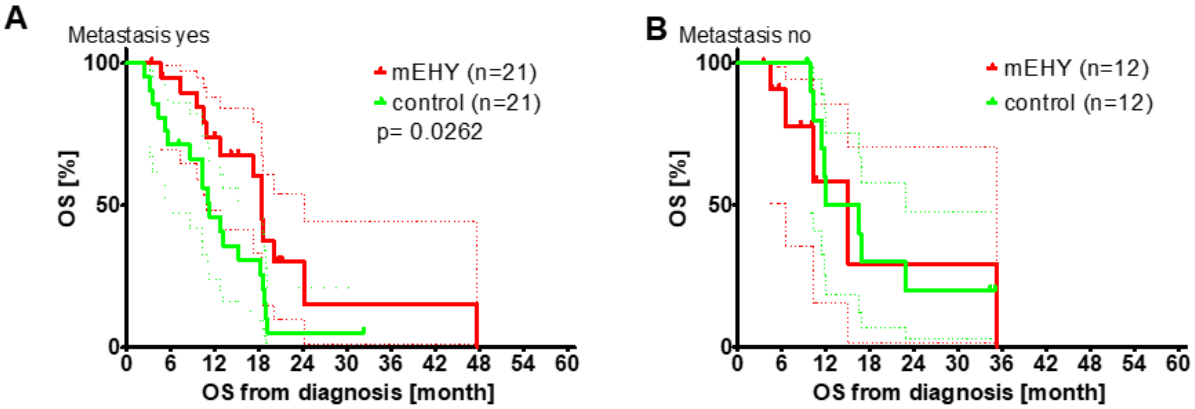
emerging **distant metastasis** or ascites in the patients' history was used as additional matching criteria by making case-control pairs



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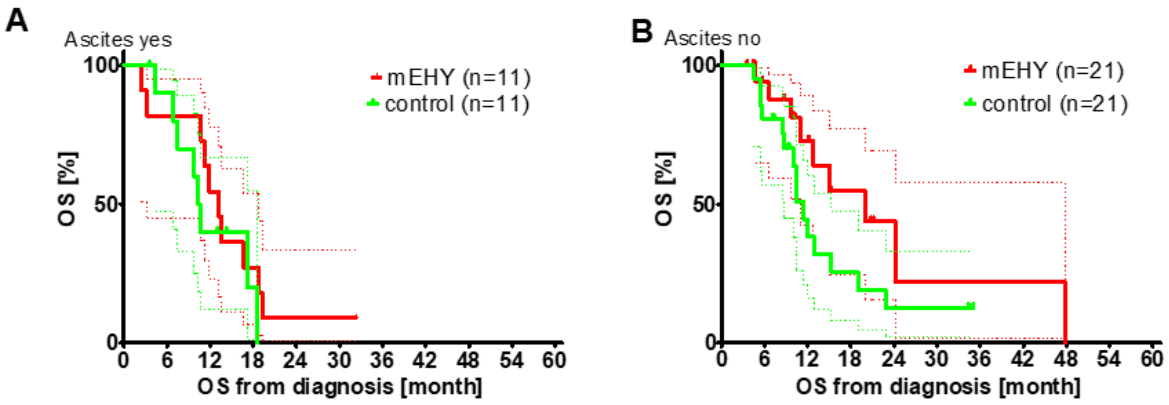
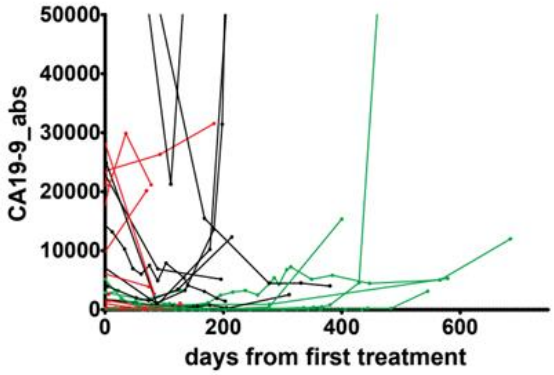
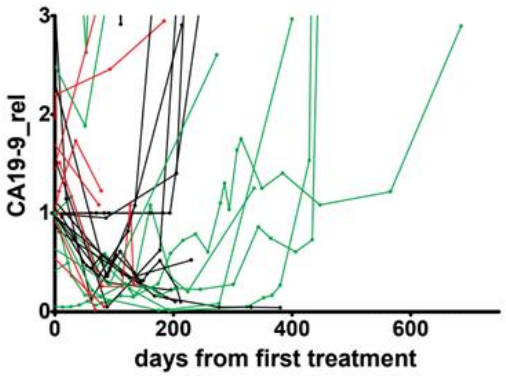
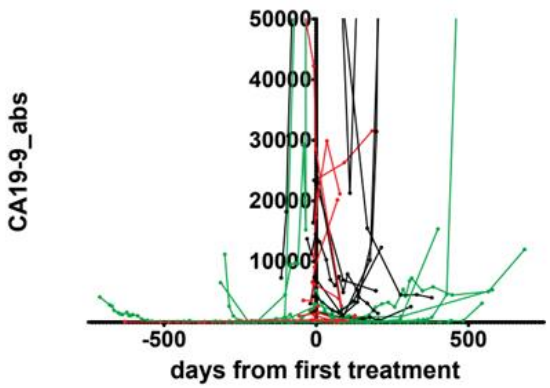


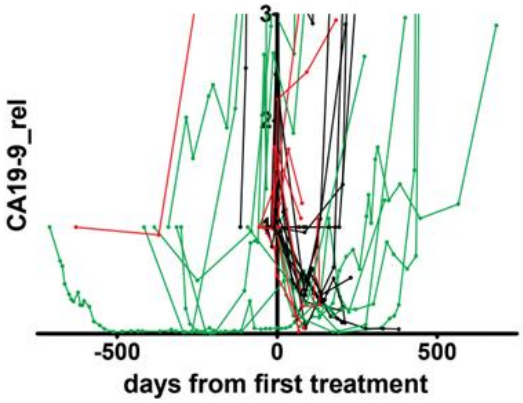
Tumor markers – CA19-9



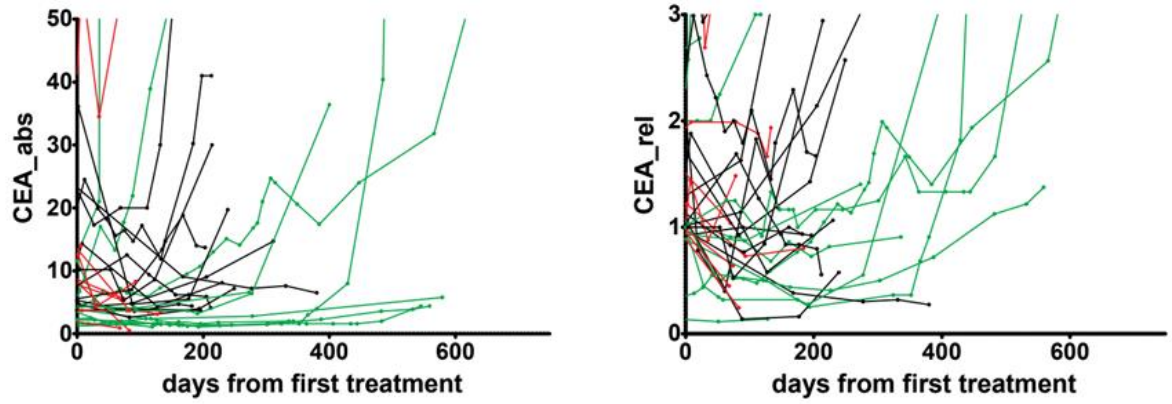


Predicting response with CA19-9





Tumor markers - CEA



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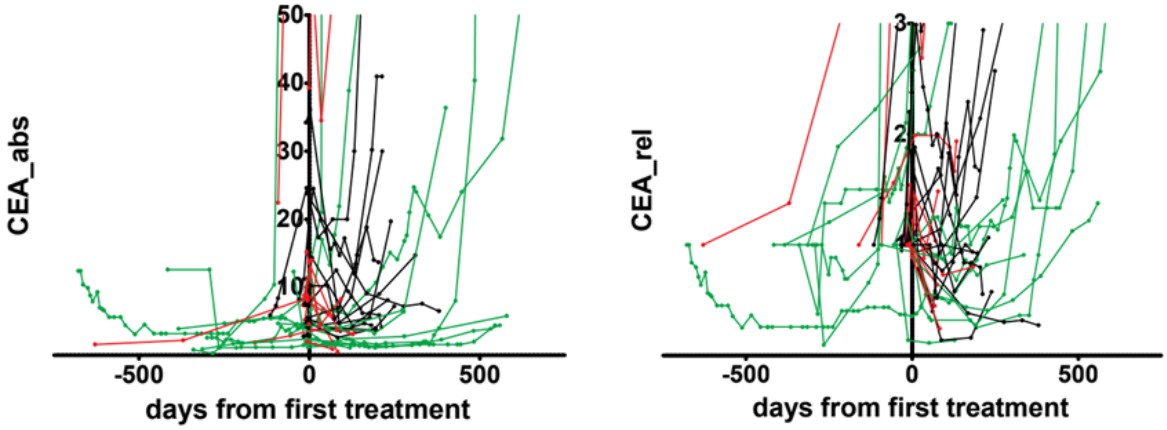
Predicting response with CEA



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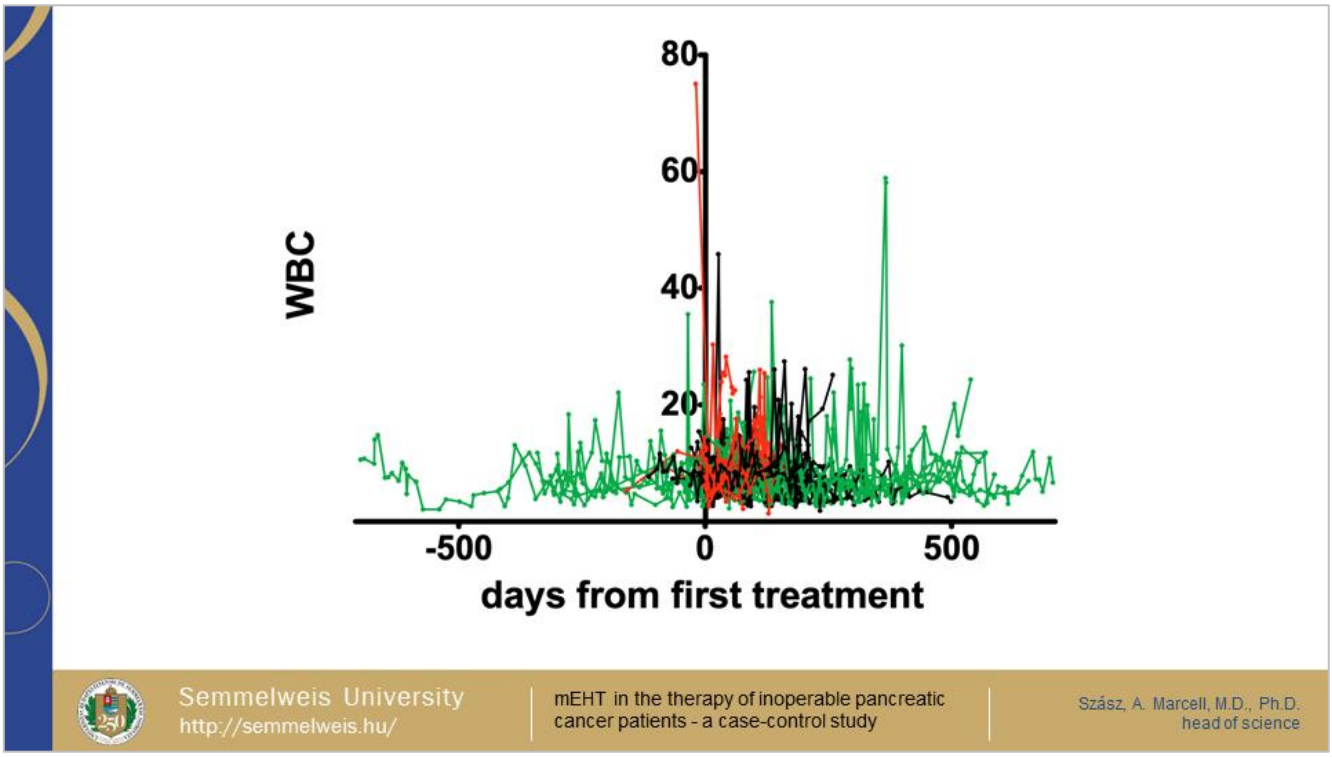
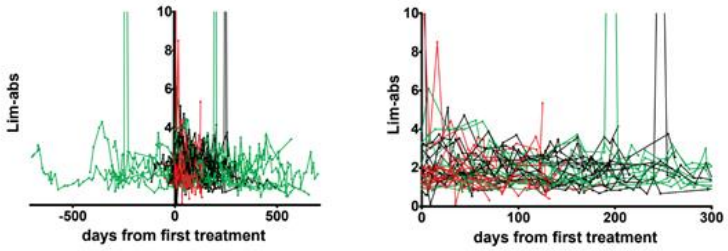
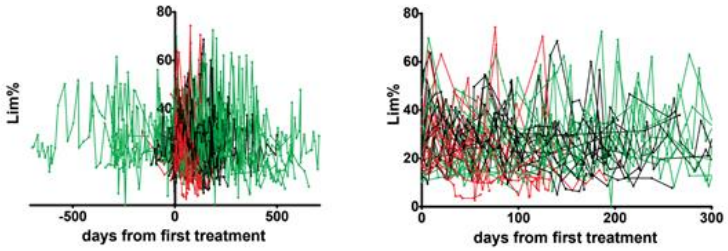


Lymphocyte counts



Intra-patient variation



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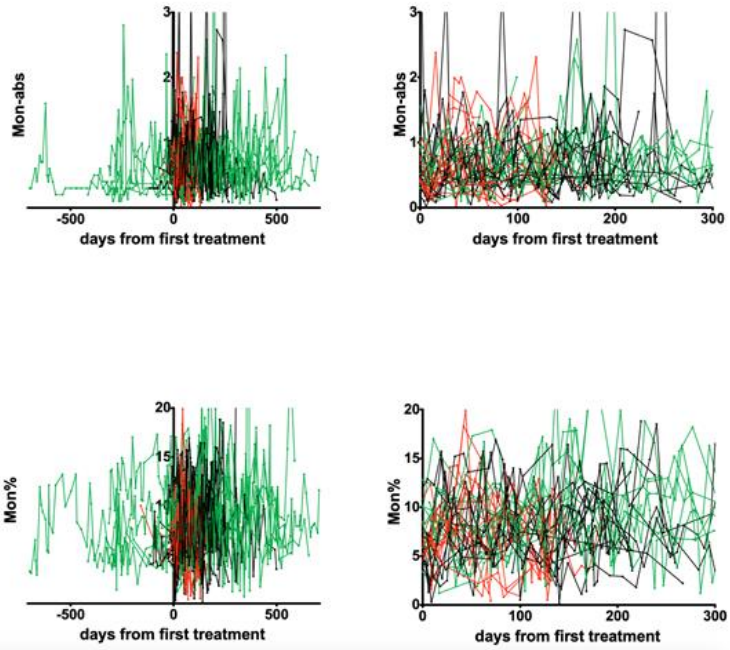
Monocytes



Conclusion

- Modulated electro-hyperthermia is improving overall survival in inoperable pancreastic cancer, especially in the metastatic setting
- Mechanism and prediction of response has to elaborated further
- Randomized clinical trial in metastatic pancreatic cancer to be performed
- AI based evaluation under progress

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Apoptotic response and DNA damage of the radioresistant Panc1 pancreas adenocarcinoma to combined modulated electro-hyperthermia and radiotherapy

Gertrud Forika[1], Andrea Balogh[2], Tamás Vancsik[2], Zoltán Benyó[2], Tibor Krenács[1]

[1]Semmelweis University, 1st Department of Pathology and Experimental Cancer Research, Budapest, Hungary
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Citation: Forika G. et al. (2020): Apoptotic response and DNA damage of the radioresistant Panc1 pancreas adenocarcinoma to combined modulated electro hyperthermia and radiotherapy, Oncothermia Journal 29: 103 – 109,
www.oncotherm.com/sites/oncotherm/files/2021-02/Forika_Apoptoticresponse

Abstract

The pancreas ductal adenocarcinomas (PDAC) have a poor prognosis, due to the high resistance to standard therapies. Modulated electro-hyperthermia (mEHT) generated by 13.56 MHz capacitive radiofrequency can induce direct tumor damage and promote chemo- and radiotherapy. In this study, we tested the effect of mEHT either alone or in combination with radiotherapy using an in vitro model of Panc1, radioresistant PDAC cell line. A single mEHT shot of 60 min induced ~50% loss of viable cells and morphological signs of apoptosis including chromatin condensation, nuclear shrinkage and apoptotic bodies. The mEHT treatment related effects were more expressive when the cells were pretreated with 2Gy radiotherapy. Treatment related apoptosis was confirmed by a significantly elevated number of annexin V single-positive and cleaved/activated caspase-3 positive tumor cells, as well as sub-G1-phase tumor cell fractions. mEHT and mEHT+radioterapy caused the moderate accumulation of H2AX positive nuclear foci, indicating DNA double-strand breaks and upregulation of the cyclin dependent kinase inhibitor p21waf1 besides the downregulation of Akt signaling. A clonogenic assay revealed a tumor progenitor/stem cell loss too. In conclusion, mEHT treatment can contribute to tumor growth inhibition and apoptosis induction and resolves radioresistance of Panc1 PDAC cells.

This research was funded by Hungarian National Research, Development and Innovation Office (NVKP_16-1-2016-0042 and K-125174)

The radioresistant Panc1 pancreas adenocarcinoma answers with apoptosis and DNA damage to modulated electro-hyperthermia treatment

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Hungary had the highest rate of **pancreatic cancer** in 2018 age-standardized rate per 100,000. Just 10% of diagnosed pancreas ductal adenocarcinomas are suitable for surgical resection. For unresecable tumors chemo- and/or the radiotherapy are used as treatment possibility, unfortunately with poor outcome due to **therapy resistance**.

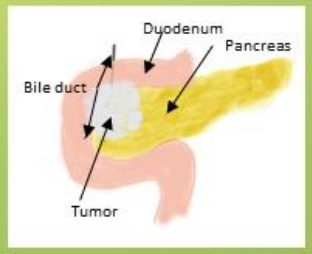
Pancreatic cancer rates: both sexes

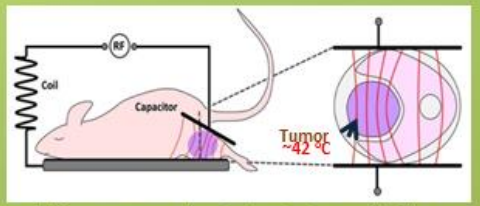
Hungary had the highest rate of pancreatic cancer in 2018, followed by Uruguay.

Rank	Country	Age-standardised rate per 100,000
1	Hungary	10.8
2	Uruguay	10.7
3	Moldova	10.5
3	Latvia	10.3
5	Japan	9.7

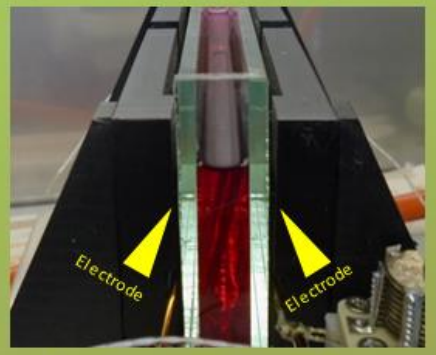
Source: https://www.wcrf.org/dietandcancer/cancer-trends/pancreatic-cancer-statistics

Modulated electro-hyperthermia delivers loco-regional deep hyperthermia by using 13.56 MHz radiofrequency. The generated electric field can be accumulated in malignant tumors to induce selective temperature increase (around 42°C), as a result of elevated glycolysis, lactate concentration and electric conductivity there compared to the adjacent tissues.

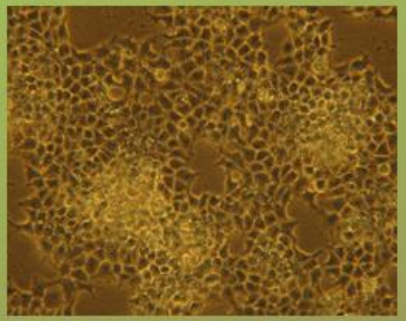




mEHT treatment mechanism in an in vivo model. The elevated ion concentration on the tumor, accumulates the elecrtic field and generates local hyperthermia



Lab-EHY 100 device electrode system for *in vitro* mEHT treatment



Panc1 pancreas adenocarcinoma cell cluture on light microscope (Ob.: 40×)

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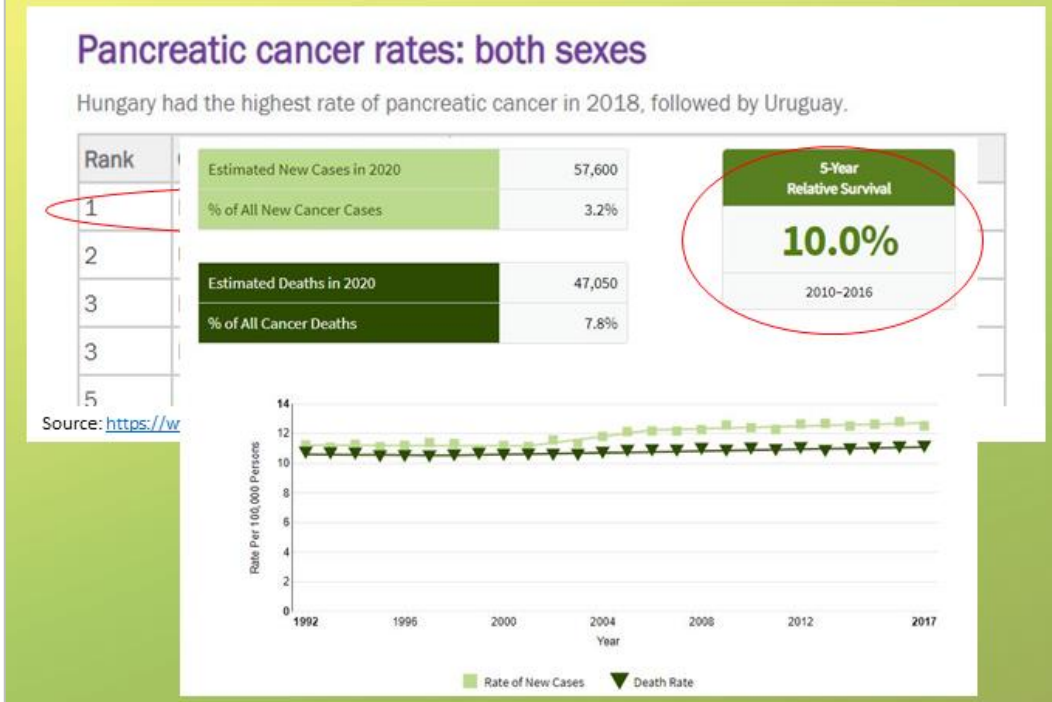

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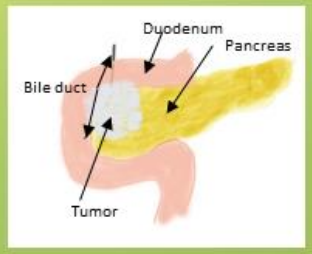

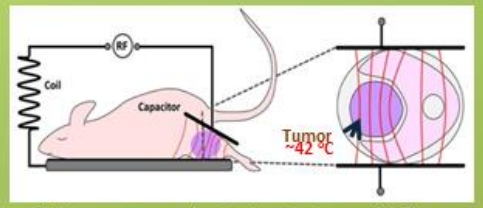

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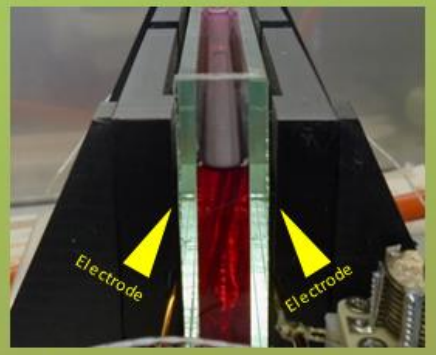

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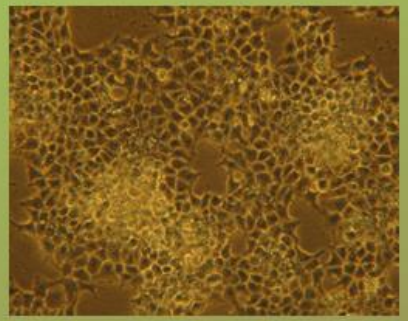

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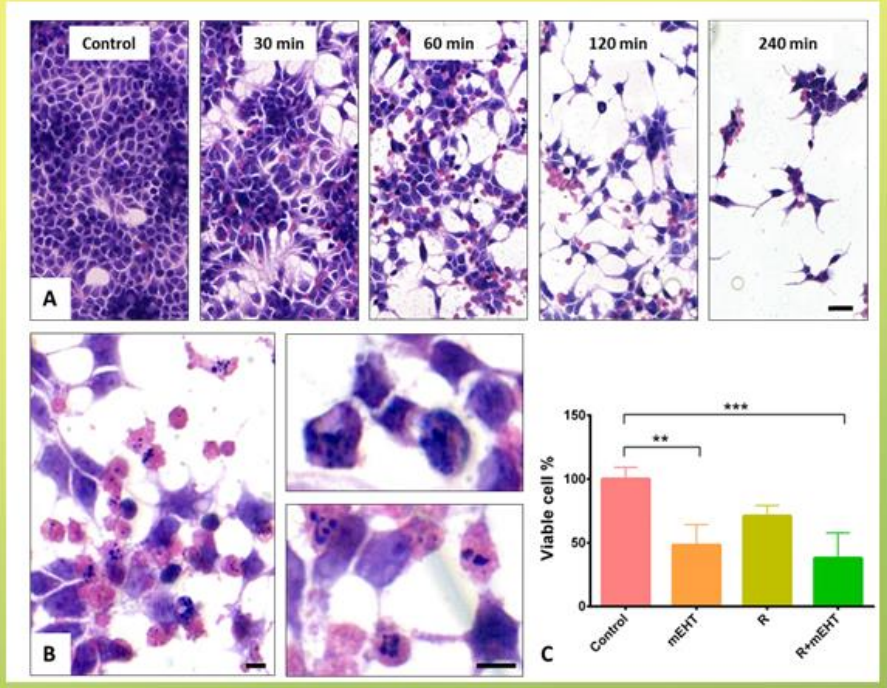
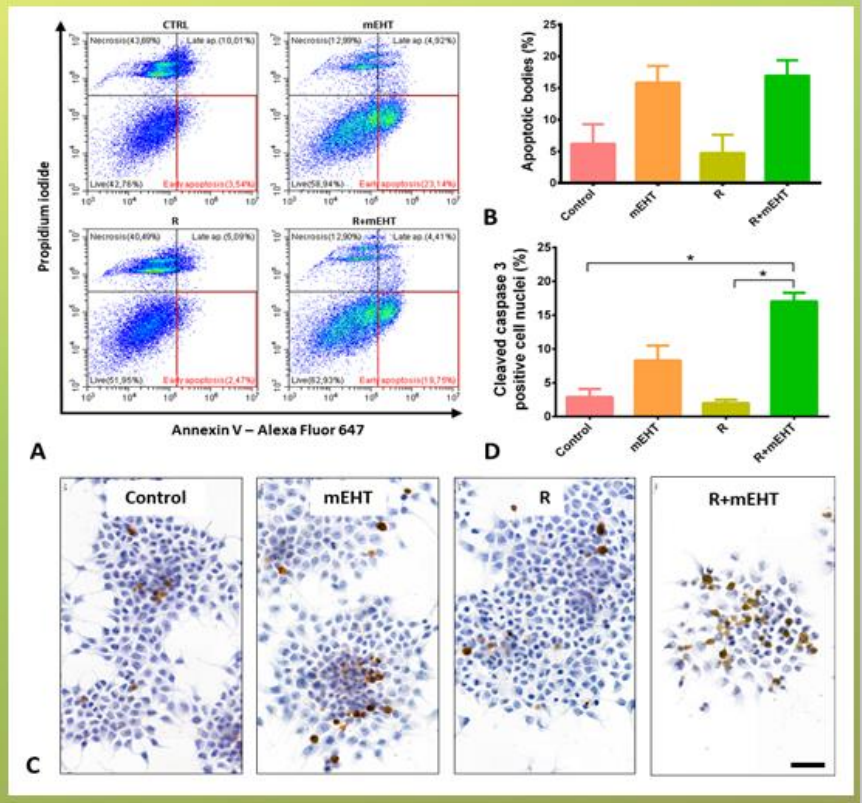


Hematoxylin and eosin staining of Panc1 cell cultures demonstrating **cell loss** and the major changes in cell morphology 24 h after different mEHT treatment durations (A). Scale bar: 40 µm. Higher magnifications reveal nuclear shrinkage, chromatin condensation (upper right), and apoptotic bodies (lower right) after 60 min treatment (B). Scale bars: 10 µm.



Cleaved/activated caspase-3 immunoreactions (C) (scale bar = 50µm) and graphical representation of its results (D).

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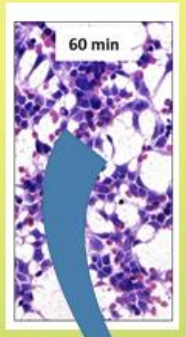
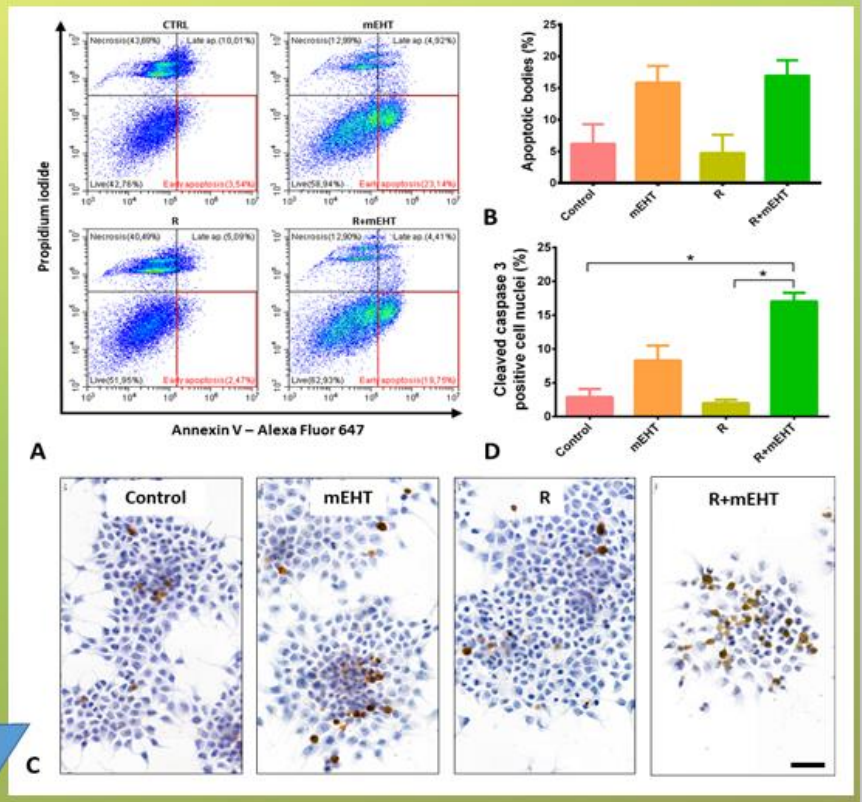


Apoptosis dominated programmed cell death induced by **60 min mEHT** in Panc1 cultures. Flow cytometry results of **Annexin V and propidium iodide** double stained tumor cells 24 hours after treatments (A). Graphical representation of early apoptotic bodies in proportions of the whole population.



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Cleaved/activated caspase-3 immunoreactions (C) (scale bar = 50µm) and graphical representation of its results (D).

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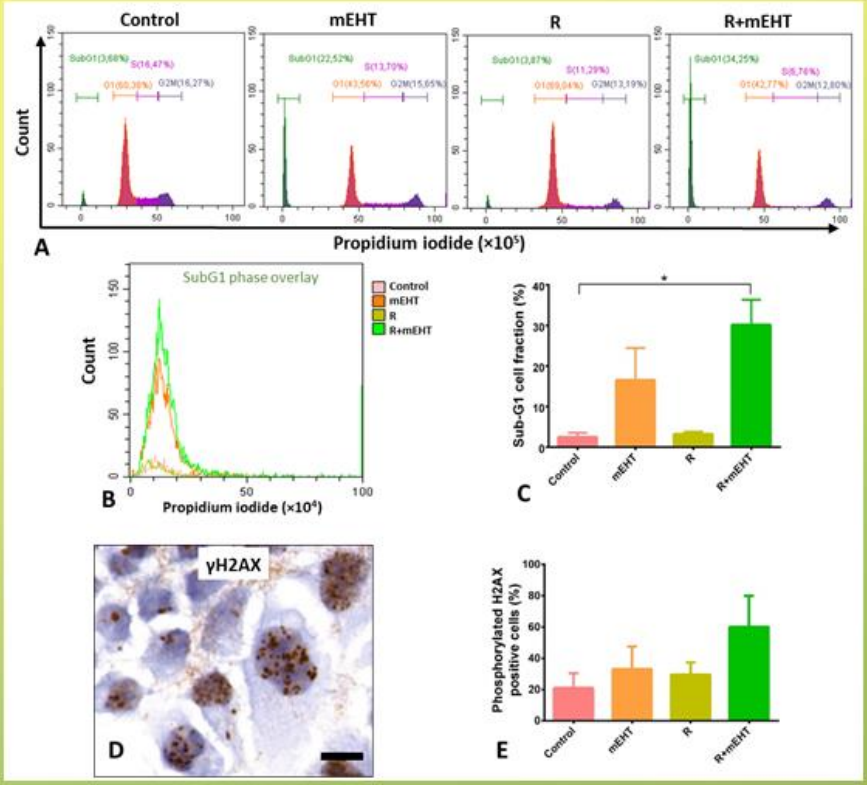

Treatment related elevated **subG1-fractions** and moderate increase in **nuclear phosphorylated H2AX protein** levels in Panc1 cultures 24 h post-treatment.

The paper is published and it's accesible from: https://www.mdpi.com/1422-0067/21/14/5100/htm

Open Access Article

Modulated Electro-Hyperthermia Resolves Radioresistance of Panc1 Pancreas Adenocarcinoma and Promotes DNA Damage and Apoptosis In Vitro

by Gertrud Forika [1], Andrea Balogh [2], Tamas Vancsik [2], Attila Zalatnai [1], Gabor Petovari [1], Zoltan Benyo [2] and Tibor Krenacs [1,*]

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Abstract

The poor outcome of pancreas ductal adenocarcinomas (PDAC) is frequently linked to therapy resistance. Modulated electro-hyperthermia (mEHT) generated by 13.56 MHz capacitive radiofrequency can induce direct tumor damage and promote chemo- and radiotherapy. Here, we tested the effect of mEHT either alone or in combination with radiotherapy using an in vivo model of Panc1, a KRAS and TP53 mutant, radioresistant PDAC cell line. A single mEHT shot of 60 min induced ~50% loss of viable cells and morphological signs of apoptosis including chromatin condensation, nuclear shrinkage and apoptotic bodies. Most mEHT treatment related effects exceeded those of radiotherapy, and these were further amplified after combining the two modalities. Treatment related apoptosis was confirmed by a significantly elevated number of annexin V single-positive and cleaved/activated caspase-3 positive tumor cells, as well as sub-G1-phase tumor cell fractions. mEHT and mEHT+radioterapy caused the moderate accumulation of γH2AX positive nuclear foci, indicating DNA double-strand breaks and upregulation of the cyclin dependent kinase inhibitor $p21^{waf1}$ besides the downregulation of Akt signaling. A clonogenic assay revealed that both mono- and combined treatments affected the tumor progenitor/stem cell populations too. In conclusion, mEHT treatment can contribute to tumor growth inhibition and apoptosis induction and resolve radioresistance of Panc1 PDAC cells. View Full-Text

Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

Lea Danics[1], Csaba András Schvarcz[1], Pedro Viana[1], Tamás Kaucsár[1], Tamás Vancsik[2], Tibor Krenács[2], Zoltán Benyó[1], Péter Hamar[1]

[1]Institute of Translational Medicine, Semmelweis University,
Budapest, Hungary
[2]1st Department of Pathology and Experimental Cancer Research, Semmelweis University,
Budapest, Hungary

Citation: Danics L. et al. (2020): Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death, Oncothermia Journal 29: 110 – 115,
www.oncotherm.com/sites/oncotherm/files/2021-02/Danics_Heatshockresponse

Abstract

Breast cancer is one of the most frequent cancer types among women worldwide. Triple-negative breast cancer (TNBC) is a highly aggressive type with very poor survival due to the lack of targeted therapy. Here we tested the efficiency of mEHT treatment alone and in combination with heat shock response (HSR) inhibitors in the 4T1 mouse TNBC isograft model. Tumors were treated with ergonomic pole electrode and LabEHY 200 device at 0.7 ± 0.3 W for 30 min every 48 h. Tumor growth was followed by IVIS, caliper, and ultrasound. Tumor destruction histology and molecular changes using immunohistochemistry and RT-qPCR were also revealed. In vivo, mEHT treatment transitionally elevated Hsp70 expression in surviving cells indicating heat shock-related cell stress, while IVIS fluorescence showed a significant reduction of viable tumor cell numbers. Treated tumor centers displayed significant microscopic tumor damage with prominent signs of apoptosis, and major upregulation of cleaved/activated caspase-3-positive tumor cells. Serial sampling demonstrated substantial elevation of heat shock (Hsp70) response 12h after the treatment which was exhausted by 24h after treatment. Heat shock inhibitors Quercetin or KRIBB11 could synergistically amplify mEHT-induced tumor apoptosis in vitro. In conclusion, modulated electro-hyperthermia exerted a protective heat shock response as a clear sign of tumor cell stress. Exhaustion of the HSR manifested in caspase-dependent apoptotic tumor cell death and tissue damage of triple-negative breast cancer after mEHT monotherapy. Combined therapy with HSR inhibitors synergistically increased the effect of mEHT, which finding has great translational potential.

Grant support: NVKP_16-1-2016-0042

38th Conference of the International Clinical Hyperthermia Society

The 5th of November 2020

Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

Lea Danics[1], Csaba András Schvarcz[1], Pedro Viana[1], Tamás Kaucsár[1], Tamás Vancsik[2], Tibor Krenács[2], Zoltán Benyó[1], Péter Hamar[1]

[1] Institute of Translational Medicine, Semmelweis University, Budapest, Hungary

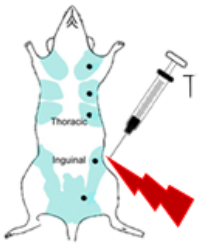
[2] 1st Department of Pathology and Experimental Cancer Research

Grant support: NVKP-6-1-2016-0042

Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

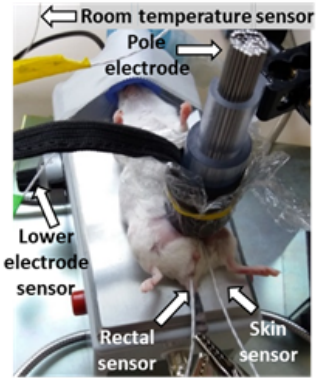
PROTOCOL

♀ Balb/C mice



10^6 4T1 TNBC cells

2 × mEHT Labet HY-200 40°C 30min

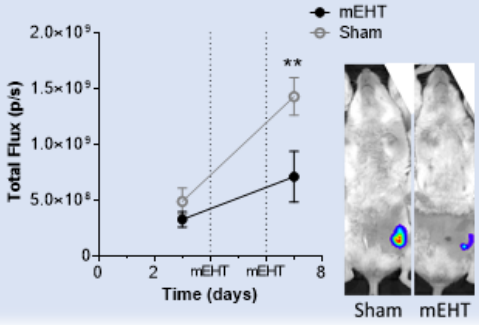


SAMPLING

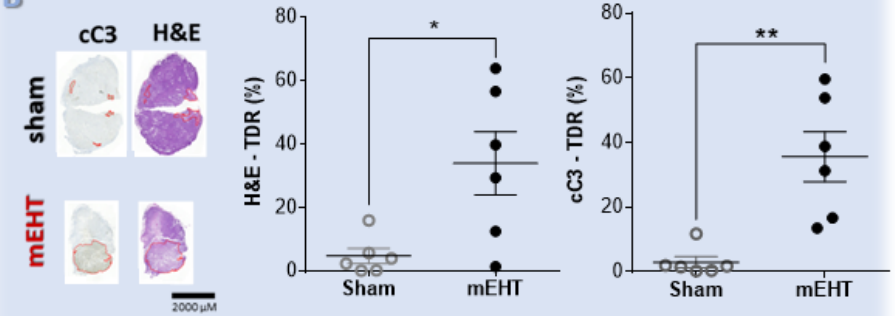
24h post-treatment

38th ICHS Conference - 5 November 2020

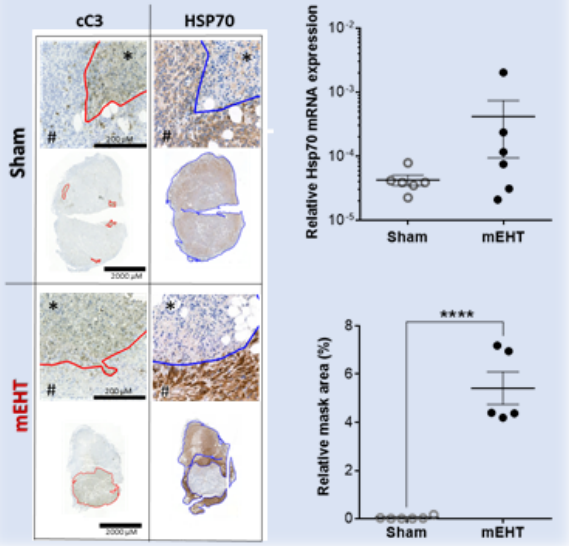
A In Vivo Imaging of viable tumor cells



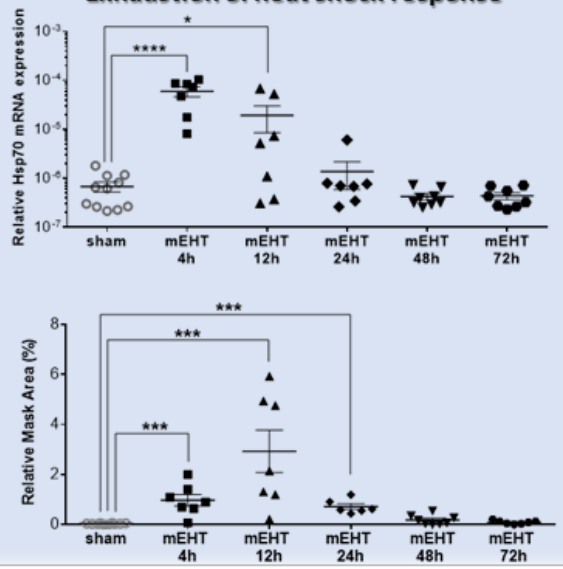
B Tumor Destruction Ratio



C Heat shock response (HSR)



D Exhaustion of heat shock response



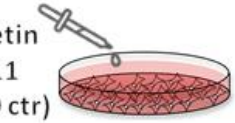
Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

PROTOCOL

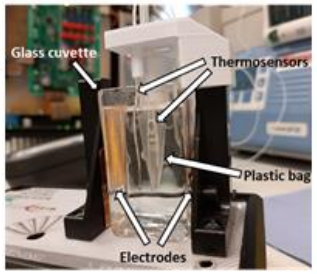
1 CULTURING
4T1 TNBC cells

2 INCUBATION
with HSR inhibitors

Quercetin
KRIBB11
(DMSO ctr)



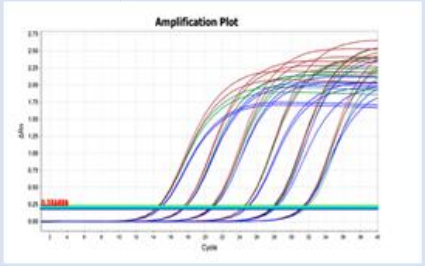
3 TREATMENT
LabEHY-200
42°C 30min

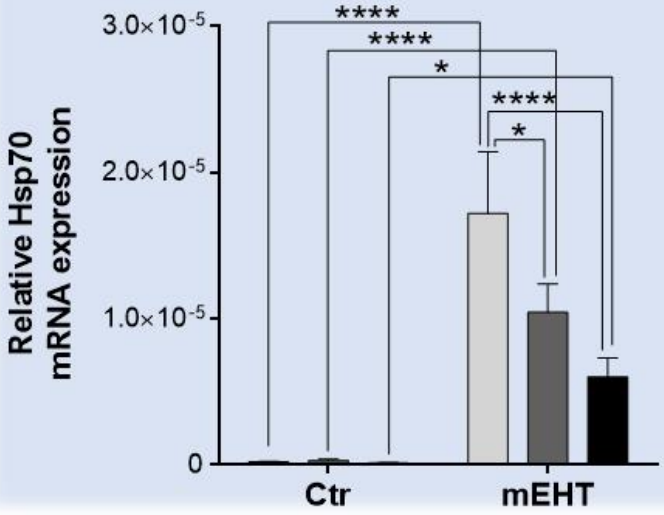


4 SAMPLING & ANALYSIS

A Hsp70 RT-qPCR

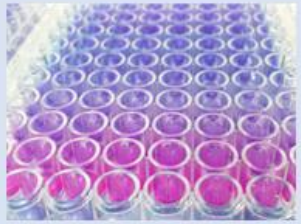
2h post-treatment

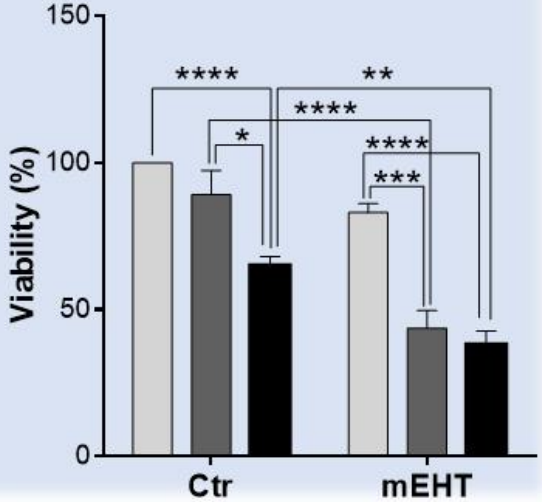




B Resazurin viability assay

24h post-treatment





DMSO (0.1%) Que (50uM) KRIBB11 (5uM)

38th ICHS Conference – 5 November 2020

Modulated electro-hyperthermia in combination with heat shock response inhibitors significantly increase tumor cell death

CONCLUSIONS

- Repeted mEHT resulted in significant tumor destruction in vivo
- mEHT induced roboust Hsp70 elevation
- Hsp70 response was exhausted at 48 hours after treatments
- **Inhibition of heat shock response potentiates the therapeutic effect of mEHT**

Thank You for Your kind attention!

38th Conference of the International Clinical Hyperthermia Society - The 5th of November 2020

Grant support: NVKP-6-1-2016-0042

Modulated electro-hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model

Csaba Schvarcz[1], Lea Danics[1], Pedro Leroy[1], Zoltán Benyó[1], Tamás Kaucsár[1], Péter Hamar[1]

[1]Institute of Clinical Experimental Research, Semmelweis University, Budapest, Hungary

Citation: Schvarcz C. et al. (2020): Modulated electro-hyperthermia inhibits tumor progression in a triple negative mouse breast cancer model, Oncothermia Journal 29: 116 – 122, www.oncotherm.com/sites/oncotherm/files/2021-02/Schvarcz_Triplenegativemouse

Abstract

Introduction: Effective therapy of triple-negative breast cancer (TNBC) has not yet been achieved. Modulated electro-hyperthermia (mEHT) is a novel therapeutic option, based on the selective heating and energy transfer to the tumor tissue by electromagnetic field.

Aims: Our aim was to investigate the effects of repeated mEHT treatment in a triple-negative mammary carcinoma bearing mouse model.

Method: 4T07 cells were inoculated orthotopically in female BALB/c mice. Tumor growth was monitored by caliper and ultrasound (Phillips Sonos 5500). Treatments started 7 days after inoculation and were repeated 3 or 5 times, on every other day. Tumor samples were taken 24 hours after last treatment for histology and molecular biology processes. Tumor destruction rate was assigned on H&E and cleaved caspase-3 stained sections, while HSP70, Ki67, CD3 and MPO expression were analyzed on immunohistochemical sections digitally (CaseViewer Software – 3DHistech). Circulating immune cells (CD4+, CD8+ lymphocytes, granulocytes, MDSCs) were analyzed with flow cytometry.

Results: mEHT caused 6.1 fold higher HSP70 elevation in the tumor tissue, compared to the sham group ($p<0.001$). Tumor size significantly decreased (tumor weight sham: 288.3±58.1 mg vs mEHT: 85.3±21.3 mg, $p<0.05$) with the elevation of tissue destruction and reduction of Ki67 positive nuclei number (sham: 2823.4±211.9 pcs/mm2 vs mEHT: 1736.7±315.3 pcs/mm2, $p<0.05$) in treated tumors. mEHT optimized the systemic immune-response with the elevation of lymphocytes and reduction of granulocytosis and the number of MDSCs.

Conclusion: Our findings suggest, that repeated mEHT could reduce tumor growth with heat-shock-mediated tissue destruction and impaired cell proliferation and could optimize systemic immune-response. Thus, mEHT could be a possible alternative adjuvant therapeutic strategy for TNBC cancer patients.

NVKP_16-1-2016-0042

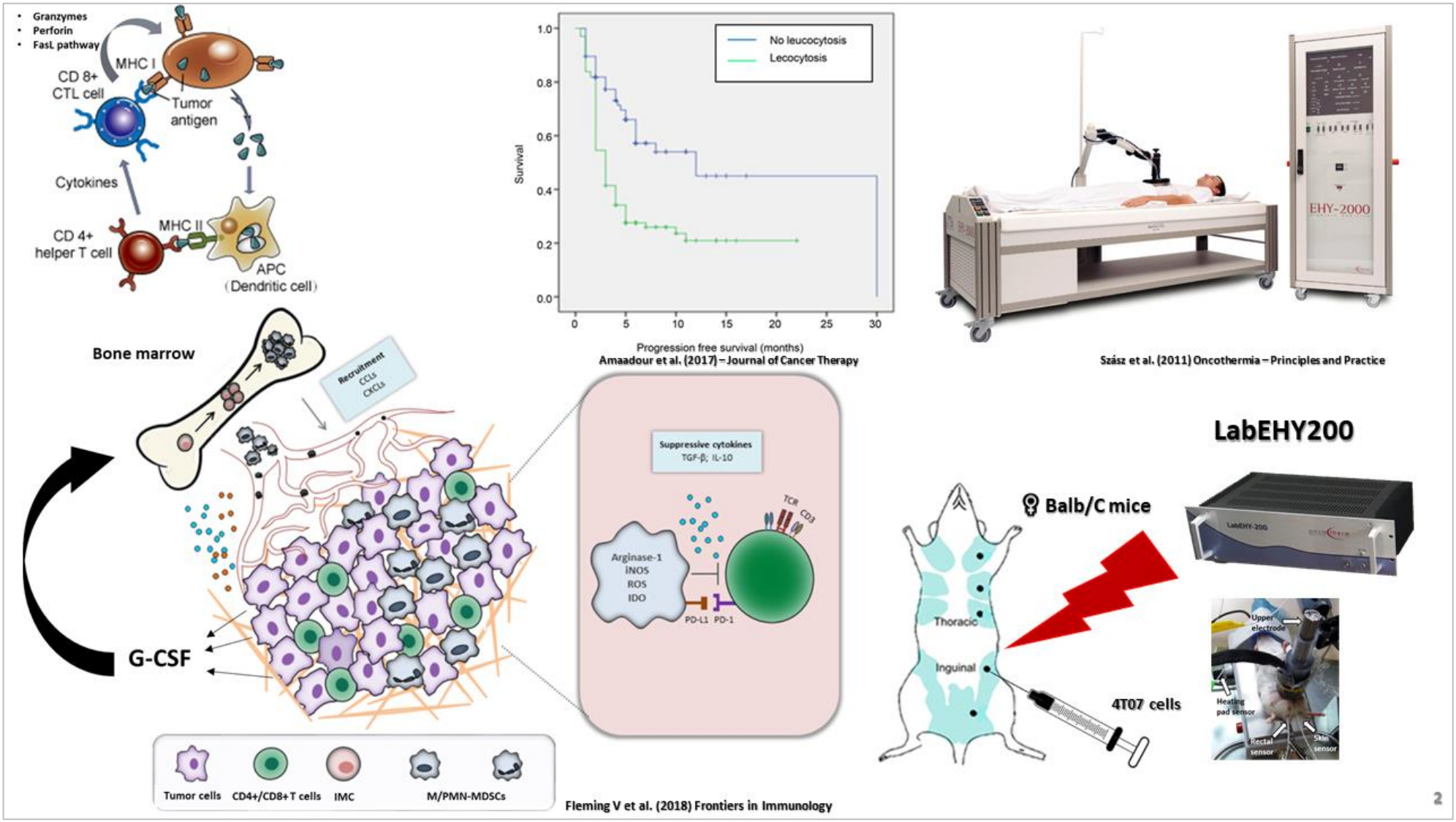
Modulated electro hyperthermia inhibits tumor progression and reverses adverse systemic immune response in TNBC mouse model

Schvarcz Csaba, Danics Lea, Benyó Zoltán, Kaucsár Tamás,Pedro Leroy, Zolcsák Zita, Hamar Péter

Translational Medicine Institute, Semmelweis Egyetem

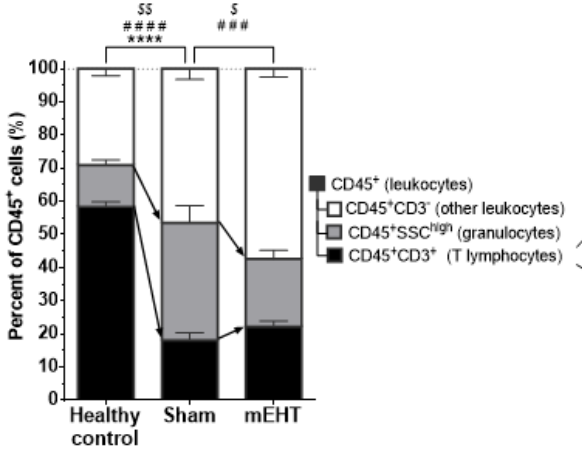
38th Conference of the International Clinical Hyperthermia Society
5. November 2020.

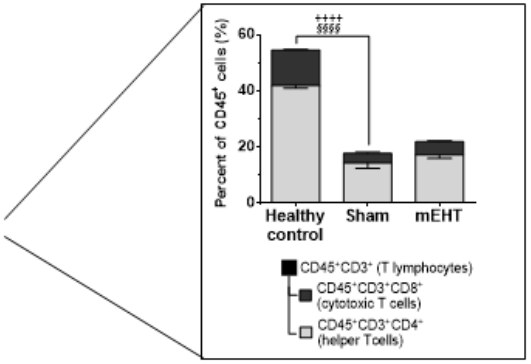
NVKP-6-1-2016-0042 project
Dr. Korányi András Alapítvány

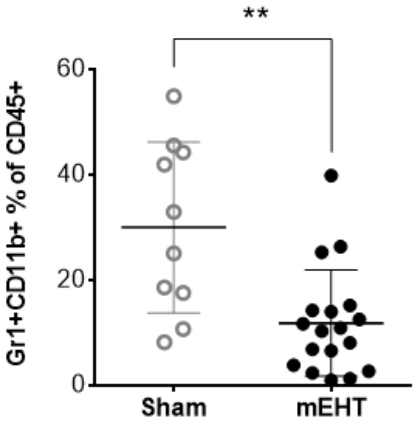

Granzymes
Perforin
FasL pathway
MHC I
CD 8+
CTL cell
Tumor
antigen
Cytokines
MHC II
CD 4+
helper T cell
APC
(Dendritic cell)
No leucocytosis
Lecocytosis
Survival
Progression free survival (months)
Amaadour et al. (2017) – Journal of Cancer Therapy
Bone marrow
Recruitment
CCLs
CXCLs
G-CSF
Suppressive cytokines
TGF-β; IL-10
Arginase-1
iNOS
ROS
IDO
TCR
CD3
PD-L1
PD-1
Tumor cells
CD4+/CD8+T cells
IMC
M/PMN-MDSCs
Fleming V et al. (2018) Frontiers in Immunology
Szász et al. (2011) Oncothermia – Principles and Practice
EHY-2000
LabEHY200
Balb/C mice
Thoracic
Inguinal
4T07 cells
Upper electrode
Heating pad sensor
Rectal sensor
Skin sensor
2

Immune-response

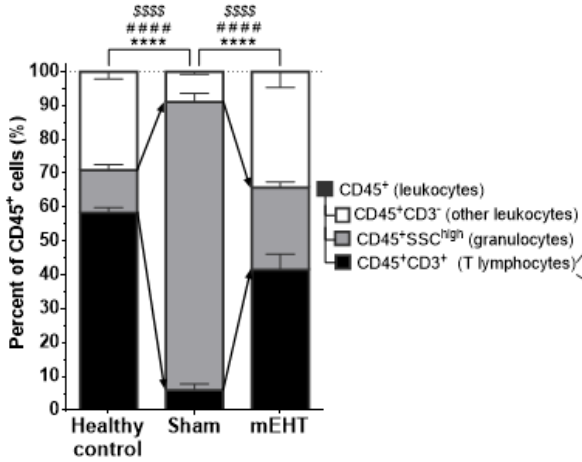
3x mEHT

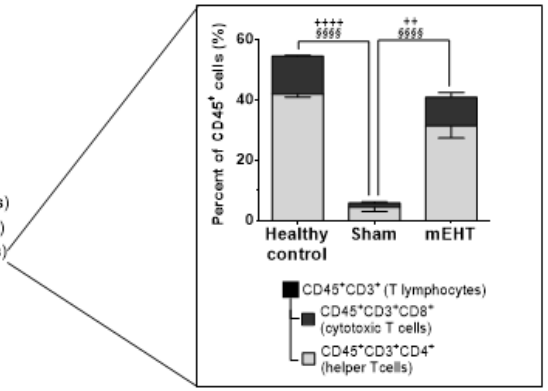


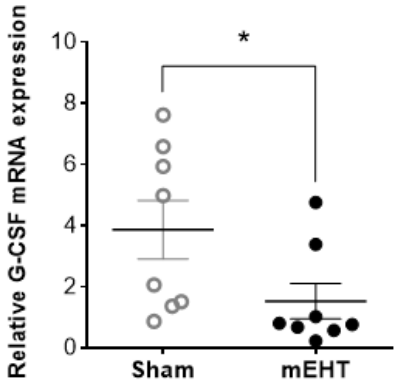


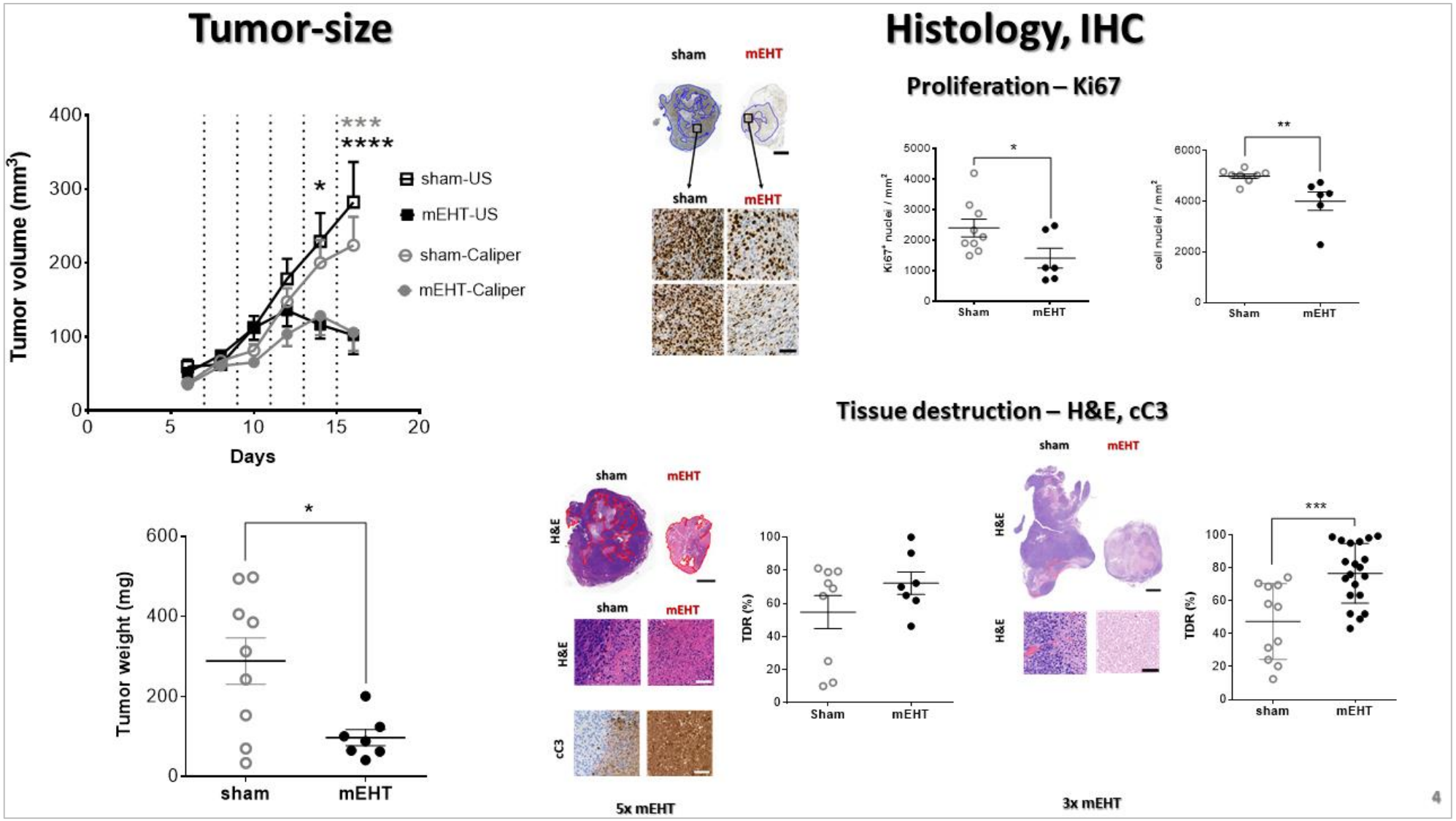


5x mEHT








Tumor-size
Tumor volume (mm³)
Days
sham-US
mEHT-US
sham-Caliper
mEHT-Caliper
***
****
*
sham
mEHT
Histology, IHC
Proliferation – Ki67
Ki67⁺ nuclei / mm²
cell nuclei / mm²
Sham
mEHT
Tissue destruction – H&E, cC3
H&E
cC3
TDR (%)
Tumor weight (mg)
5x mEHT
3x mEHT

Conclusions

- mEHT has positive effects on the systemic anti-tumoral response: reverses adverse leukemoid reaction, decreases the ratio of MDSCs with decreasing GCSF levels and increases lymphocyte ratio
- effectively inhibits growth of tumors
- inhibits the proliferation of tumors
- causes tumor tissue damage in a cC3-meidated way

5

A biophysical framework to analyze (pre-)clinical data on non-thermal effects

Peter Wust[1], Pirus Ghadjar[1]

[1]Department of Radiation Oncology, Charité Universitätsmedizin,
Berlin, Germany

Citation: Wust P., Ghadjar P. (2020): A biophysical framework to analyze (pre-)clinical data on non-thermal effects, Oncothermia Journal 29: 123 – 124,
www.oncotherm.com/sites/oncotherm/files/2021-02/Wust_Biophysical

Abstract

Introduction: The existence of non-thermal effects of electromagnetic fields (EMF) is controversially discussed since decades. Earlier investigations did not identify evidences of for any risks of radiofrequency (RF) EMF at safety levels and denied the existence of non-thermal effects.

Objectives: Careful review of available preclinical and clinical data upon non-thermal effects, which are classified and analyzed by a novel membrane model

Material and Methods: Recently, preclinical studies ascertained additional cytotoxic effects, if RF-hyperthermia (HT) is applied at 13.56 or 27 MHz in comparison to water bath (WB)-HT at the same temperature. These effects can be further enhanced by amplitude modulation (AM) in the Hz to kHz-range. Preclinical data are confirmed by clinical studies and observations, in particular if EMF applications with AM are considered.

Results: A subtle analysis of preclinical and clinical data of WB-HT and conventional HT reveals numerous hints that non-thermal effects exist. A critical evaluation of all available empirical data provides sufficient evidence for non-thermal effects EMF, which have the potential to improve oncologic treatments.
In the next step, plausible biophysical and electrophysiological models are evaluated to decipher these non-thermal effects. Nanoheating of protein clusters in lipid rafts has been postulated but needs excessive levels of local power not consistent with physical assessments. Basis for novel theories are models of ion channels, which function like rectifiers and low pass filter. It can be deduced that AM-RF induces ion fluxes and membrane vibrations at specific resonance frequencies. This model can explain non-thermal cytotoxic effects via ion disequilibrium (especially regarding Ca2+) and/or resonances with hole formation in the membrane, if AM-RF radiates for some time perpendicular to the membrane comprising a given density of ion channels.

Conclusions: Non-thermal effects induced by AM-RF are very probable. We recommend further evaluations. Higher effectiveness of AM-RF in tumors can occur because of their specific tumor environment, cancer-specific ion channels (channelomes) and membrane elasticities differing from normal tissues with increasing malignancy. Suitable oncological applications can lead to significant improvements.

Remark of the managing editor: to see the corresponding presentation please visit our YouTube channel.

Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia

Ming Kuo[1, †], Jih-Jong Lee[2, †], Yu-Shan Wang[3,4], Hsin-Chien Chiang[4], Cheng-Chung Huang[4], Pei-Jong Hsieh[4], Winston Han[4], Chiao-Hsu Ke[1], Albert TC Liao[1], Chen-Si Lin[1]

[1]Department of Veterinary Medicine, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan
[2]Graduate Institute of Veterinary Clinical Science, School of Veterinary Medicine, National Taiwan University, Taipei, Taiwan
[3]Institute of Molecular Medicine and Bioengineering, National Chiao Tung University, Hsinchu, Taiwan
[4]JohnPro Biotech Inc., Taipei, Taiwan

Citation: Kuo M. et al. (2020): Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia, Oncothermia Journal 29: 125 – 134,
www.oncotherm.com/sites/oncotherm/files/2021-02/Kuo_Potentialenhancement

Abstract

Background: Modulated electro-hyperthermia (mEHT) is a form of hyperthermia used in cancer treatment. mEHT has demonstrated the ability to activate host immunity by inducing the release of heat shock proteins, triggering apoptosis, and destroying the integrity of cell membranes to enhance cellular uptake of chemo-drugs in tumor cells. Both curcumin and resveratrol are phytochemicals that function as effective antioxidants, immune activators, and potential inhibitors of tumor development. However, poor bioavailability is a major obstacle for use in clinical cancer treatment.

Methods: This purpose of this study was to investigate whether mEHT can increase anti-cancer efficacy of nanosized curcumin and resveratrol in in vitro and in vivo models. The in vitro study included cell proliferation assay, cell cycle, and apoptosis analysis. Serum concentration was analyzed for the absorption of curcumin and resveratrol in SD rat model. The in vivo CT26/BALB/c animal tumor model was used for validating the safety, tumor growth curve, and immune cell infiltration within tumor tissues after combined mEHT/curcumin/resveratrol treatment.

Results: The results indicate co-treatment of mEHT with nano-curcumin and resveratrol significantly induced cell cycle arrest and apoptosis of CT26 cells. The serum concentrations of curcumin and resveratrol were significantly elevated when mEHT was applied. The combination also inhibited the growth of CT26 colon cancer by inducing apoptosis and HSP70 expression of tumor cells while recruiting CD3+ T-cells and F4/80+ macrophages.

Conclusions: The results of this study have suggested that this natural, non-toxic compound can be an effective anti-tumor strategy for clinical cancer therapy. mEHT can enable cellular uptake of potential anti-tumor materials and create a favorable tumor microenvironment for an immunological chain reaction that improves the success of combined treatments of curcumin and resveratrol.

Keywords: Modulated electro-hyperthermia (mEHT), curcumin, resveratrol, nanosized, apoptosis, tumor microenvironment

38th Conference of the International Clinical Hyperthermia Society

November 5, 2020

Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro- hyperthermia (mEHT)

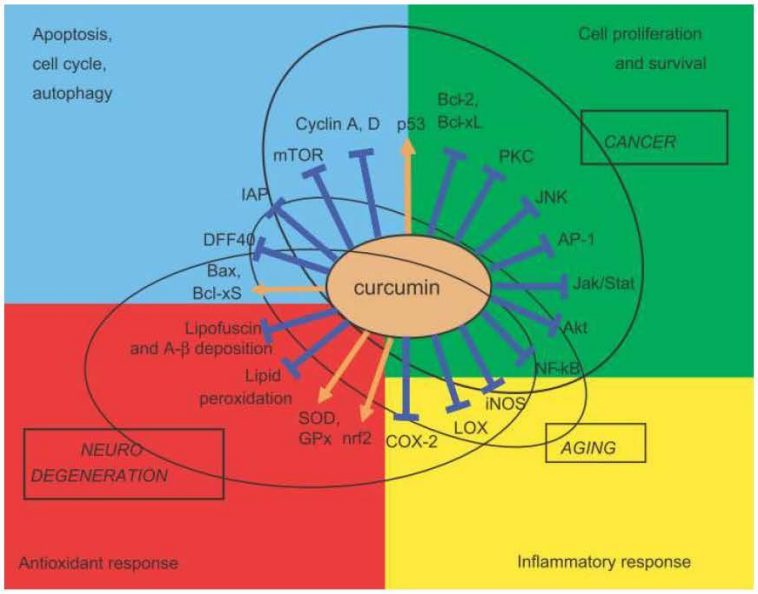
Samuel Yu-Shan Wang, PhD

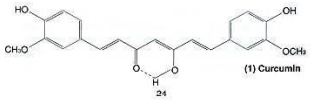
Molecular Medicine and Biochemical Engineering,
National Chiao Tung University, Hsinchu, Taiwan

Introduction

- mEHT was widely used to promote the synergistic effects in a variety of cancer therapies
- Both curcumin and resveratrol are phytochemicals that function as effective antioxidants, immune activators, and potential inhibitors of tumor development.
- Poor bioavailability is a major obstacle for the using of curcumin and resveratrol in clinical cancer treatment.
- We have developed a unique platform for nanosized curcumin and resveratrol.
- This purpose of this study was to investigate whether mEHT can increase anti-cancer efficacy of nanosized curcumin and resveratrol.

Curcumin

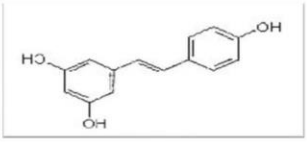


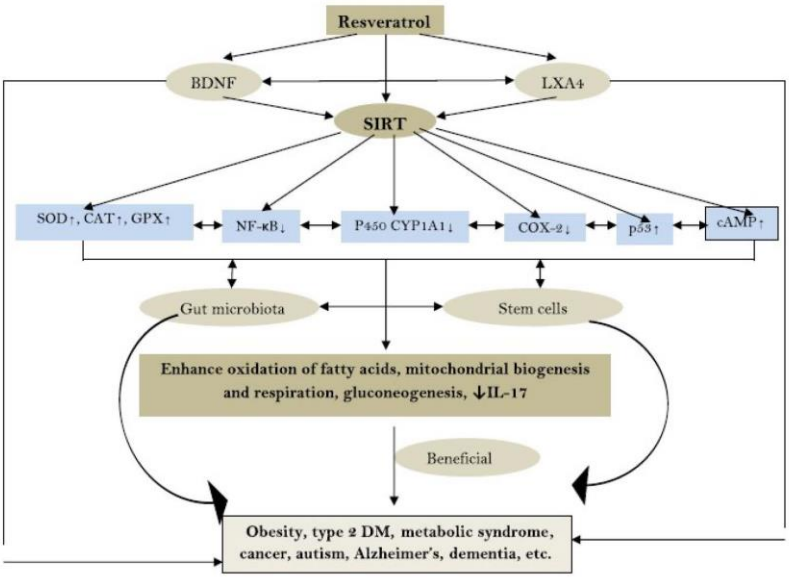


Evid Based Complement Alternat Med. 2007

3

Resveratrol



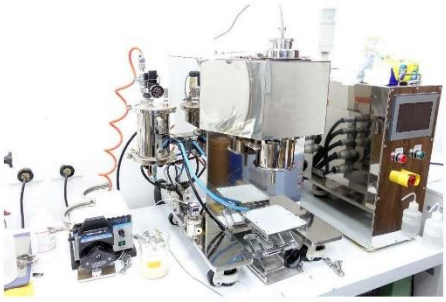


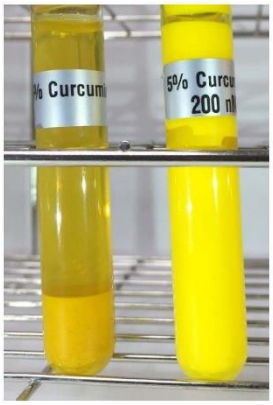
Nutrition 32 (2016) 174–178

4

A unique platform for nanosized curcumin and resveratrol

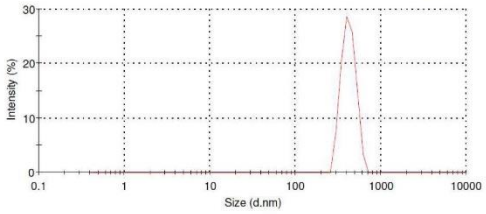
Nano bead mills





Before and after nanosizing

Particle sizes after nanosizing



5

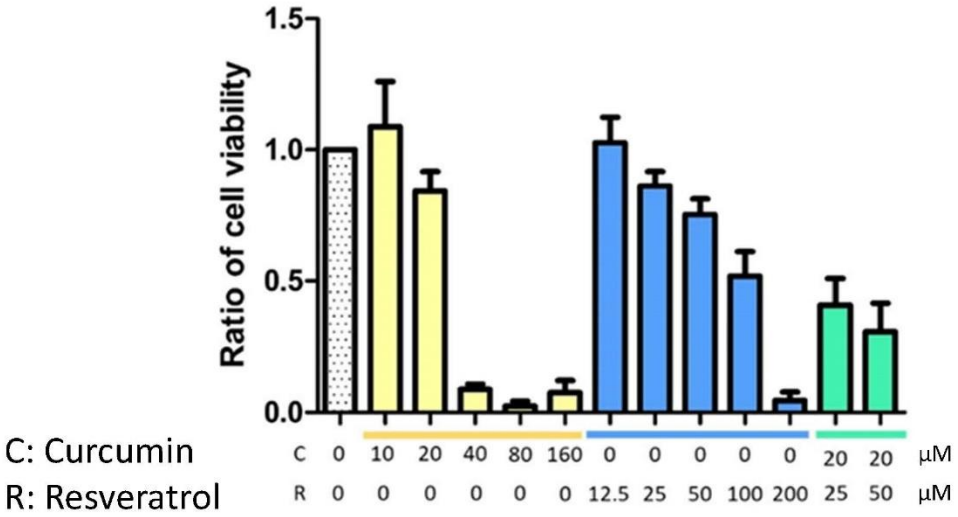
Nano formulation of curcumin plus resveratrol enhanced the absorption in serum of rat model

Table 1. Pharmacokinetic parameters derived from rat plasma. *

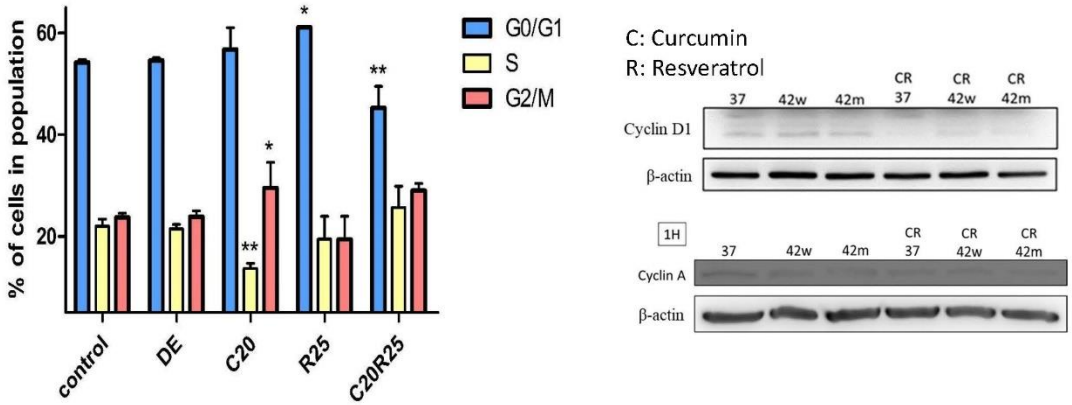
* AUC: area under the blood concentration vs time curve; C_{max}: maximum concentration; and T_{max} : time to reach C_{max}.

Sample	$AUC_{(0\text{-last})}$ (ng*hr/mL)	C_{max} (ng/mL plasma)	T_{max} (hr)
Curcumin suspension	46.3 ± 30.7	18.9 ± 20.1	2.5 ± 1.8
Curcumin nanoparticles	215 ± 46.4	37.7 ± 21.8	2.17 ± 1.44
Resveratrol suspension	1608 ± 284	522 ±152	2.67 ± 0.58
Resveratrol nanoparticles	1632 ± 286	782 ± 105	0.83 ± 1.01

Nano formulation of curcumin plus resveratrol inhibited the cell viability in CT26

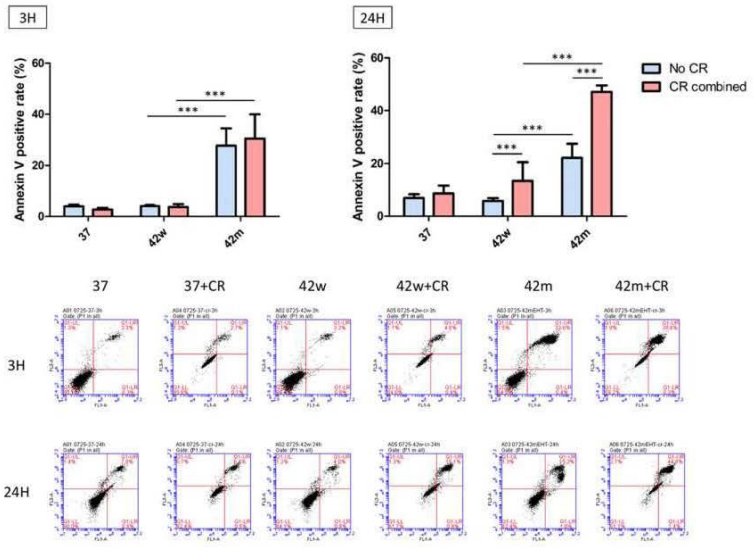


Nano formulation of curcumin plus resveratrol induced cell cycle arrest in CT26



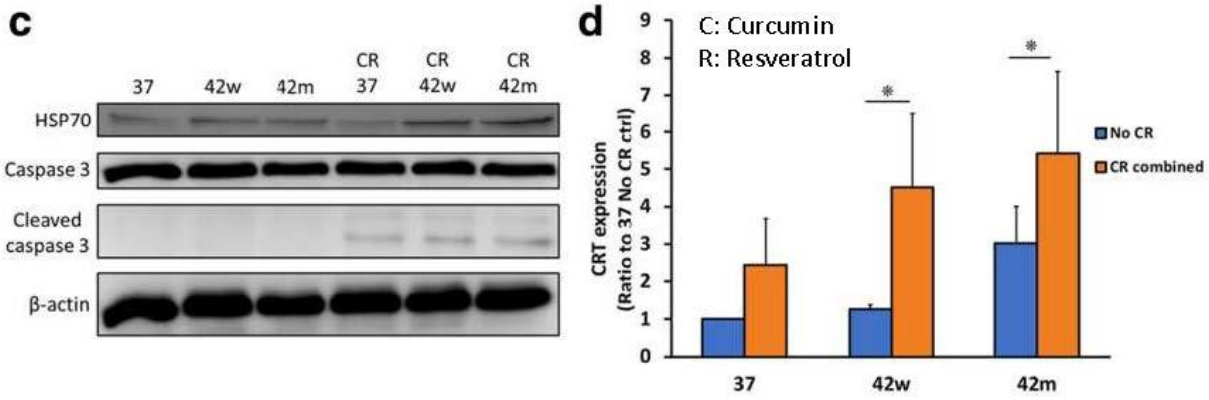
Both Cyclin D1 and Cyclin A decreased after CR treatment on CT26 to reveal decreased cell viability was partially due to their damaging cell cycle progression.

Nano formulation of curcumin plus resveratrol with mEHT increased significant apoptosis in CT26



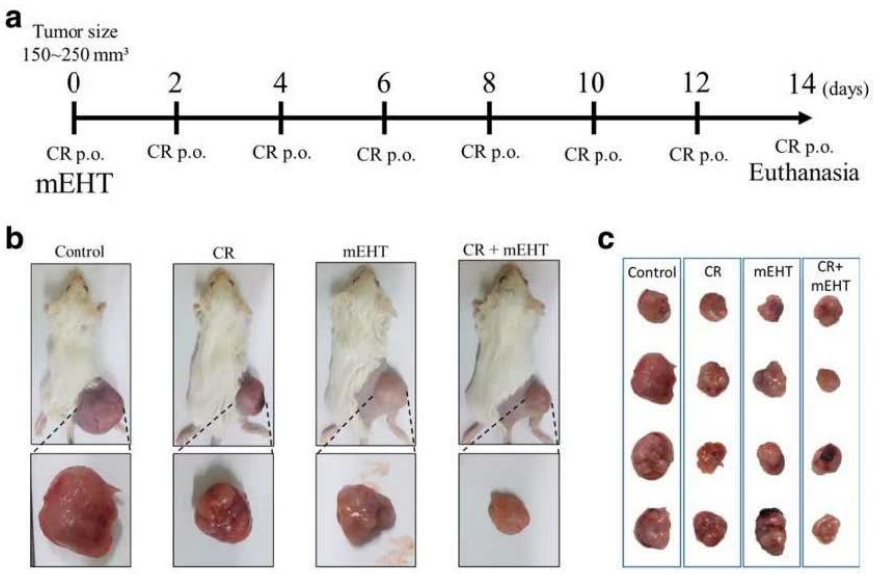
C: Curcumin
R: Resveratrol

Nano formulation of curcumin plus resveratrol with mEHT increased significant apoptosis in CT26



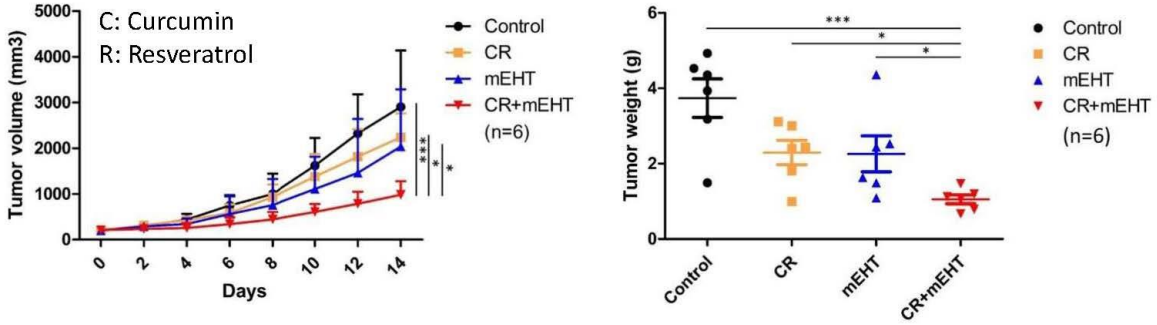
These results showed mEHT combined with curcumin and resveratrol induce cell apoptosis and immunogenic cell death to trigger further immune response.

CT26 tumors were inhibited by nano formulation of curcumin plus resveratrol combined with mEHT treatment



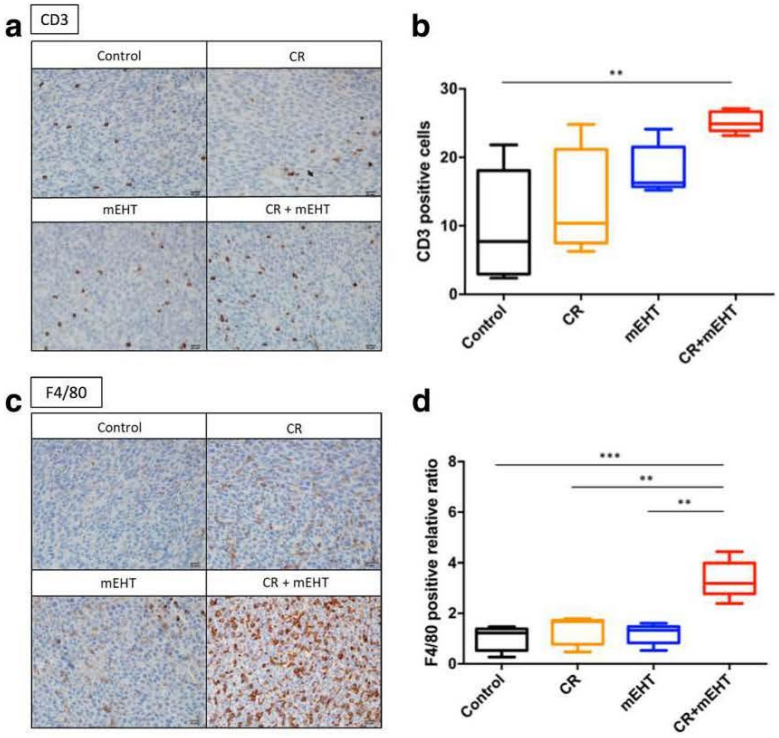
C: Curcumin
R: Resveratrol

CT26 tumors were inhibited by nano formulation of curcumin plus resveratrol combined with mEHT treatment



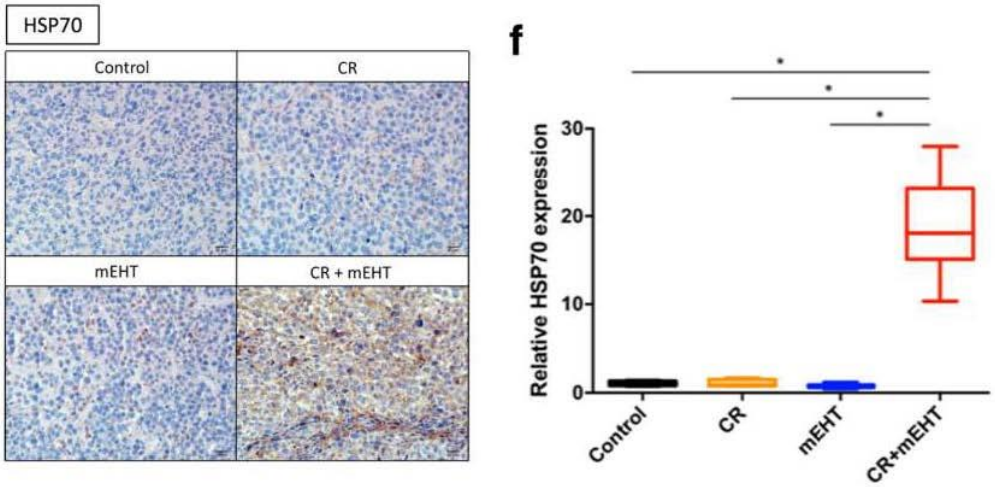
These results were in concordance with our *in vitro* findings and indicated that curcumin and resveratrol oral administration combined mEHT treatment could significantly suppress tumor growth.

Increased infiltration of macrophages and T-lymphocytes were observed in tumors treated by CR and mEHT combination



This indicates that in addition to reduced tumor cell viability, combined treatment of CR and mEHT could also trigger host immunity by recruiting T-cells and macrophages.

Increased of Hsp70 expression was observed in tumors treated by CR and mEHT combination



This results support our hypothesis that potential immune activation was induced by CR treatment and mEHT for CT26 tumor eradication.

Conclusions

- This study indicates that nano-formulated curcumin plus resveratrol compound shows enhanced bioavailability when combined with mEHT, synergistically increasing HSP-release and immune response, leading to enhanced anti-tumor efficacy in CT26 tumors.
- Further clinical studies are needed to confirm the safety and effectiveness of nano-formulated curcumin and resveratrol when combined with mEHT.

Kuo *et al. BMC Cancer* (2020) 20:603
https://doi.org/10.1186/s12885-020-07072-0

BMC Cancer

RESEARCH ARTICLE Open Access

Potential enhancement of host immunity and anti-tumor efficacy of nanoscale curcumin and resveratrol in colorectal cancers by modulated electro-hyperthermia

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

Tamas Vancsik[1, 2], Domokos Mathe[3], Anett Benedek[2], Ildiko Horvath[2], Nikolett Hegedus[3], Ralf Bergmann[3], Csaba Schvarcz[2], Erno Papanek[2], Tibor Krenacs[1], Zoltan Benyo[2], Andrea Balogh[2]

[1]1st Department of Pathology and Experimental Cancer Research, Semmelweis University, Budapest, Hungary
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[3]Deptartment of Biophysics and Radiation Biology Semmelweis University, Budapest, Hungary

Citation: Vancsik T. et al. (2020): Modulated electro-hyperthermia and combined primary, immortalized NK-cell therapy in human A2058 xenograft model, Oncothermia Journal 29: 135 – 144, www.oncotherm.com/sites/oncotherm/files/2021-02/Vancsik_ImmortalizedNKcell

Abstract

Introduction: Earlier we showed that modulated electro-hyperthermia (mEHT) promoted the expression and release of the potential immunogenic damage associated molecular pattern proteins and it reduced MHC-I and melan-A levels in B16F10 melanoma cells. The number of cytotoxic T cells were moderately reduced, the amount of NK cells was unchanged. NK cells could effectively recognize and kill cells which lack MHC-I. Here we tested the effect mEHT on tumor growth and tumor microenvironment with respect to infiltration and cytotoxicity of NK cells in A2058 human melanoma xenograft model *in vivo*.

Material and methods: A2058 melanoma cells were inoculated into both flanks of BALB/C NOD/SCID immunocompromised mice. After two weeks, 30-min 42°C mEHT was applied on the right-side tumors. One day after mEHT treatment, primary human NK-cells or the NK92MI NK-cell line labeled with fluorescent dye were injected subcutaneously above the lumbar region of the spine. NK-cell distribution was measured by *in vivo* fluorescent imaging. Tumor size was monitored using ultrasonic caliper. Tumor damage, growth arrest, heat stress and apoptosis related markers were assessed with immunohistochemistry. NK-attracting CXCL mRNA expression was determined after *in vitro* mEHT treatement of A2058 cells.

Results: mEHT induced significant tumor growth inhibition. Heatshock and apoptotic tumor cell death was proven by the significant elevation of relative dead tumor area, γH2AX, p53 and cleaved caspase-3 and hsp70 positive areas, accompanied by MMP-2 expression.*In vivo,* both the primary NK- and NK92MI-cells accumulated into the mEHT-treated side and further enhanced the damaging effect. Significant elevation of CXCL-11 mRNA level,was induced by in vitro treatment while the CXCL-9, and -10 dropped.

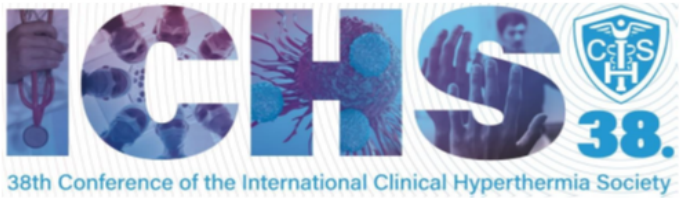
Conclusion: Our result show that mEHT can induce p53-mdiated caspase-dependent apoptosis in an A2058 melanoma xenograft model. Furthermore, mEHT treatment may provide a favorable micro-environment for the attraction and invasion of NK-cells, possibly by inducing CXCL-11 expression and promoting MMP-2 production of solid xenografts.

This study was funded by NKFIH-NVKP_16-1-2016-0042.

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

Tamas Vancsik[1, 2], Anett Benedek[2], Domokos Mathe[3], Ildiko Horvath[3], Nikolett Hegedus[3], Ralf Bergmann[3], Csaba Schvarz[2], Erno Papanek[2], Tibor Krenacs[1], Zoltan Benyo[2], Andrea Balogh[2]

[1]1st Department of Pathology and Experimental Cancer Research
[2]Institute of Clinical Experimental Research
[3]Deptartment of Biophysics and Radiation Biology Semmelweis University



Introduction I.

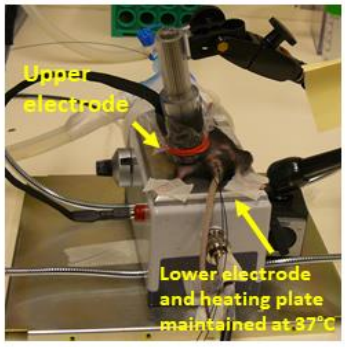
Melanoma

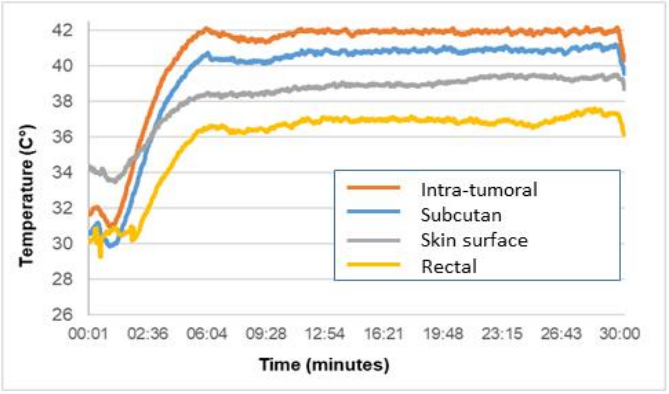
- SEER: poor (16.2%) five-year survival rate of melanoma patients with regional/distant spreading.
- Effectively suppressed adaptive anti-tumor immune response by the tumor cells.
- Potential targets:
  - PD-L1 and CTLA-4 checkpoint proteins produced by tumor cells, may induce programmed cell death of the effector CD8+ cytotoxic T-cells.
- mEHT as a complementary:
  - tumor-damaging effects by irreversible heat and cell stress
  - tolerable for patients, with almost no side-effects.
  - Upregulation and release of damage-associated molecular pattern (DAMP) proteins, which are accompanied by progressive immune-mediated secondary tumor-damage (immunogenic cell death)*

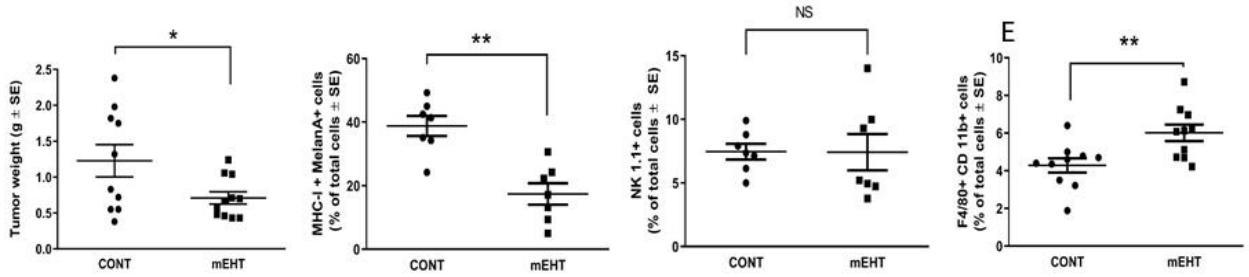
*Vancsik, T.; Kovago, C.; Kiss, E.; Papp, E.; Forika, G.; Benyo, Z.; Meggyeshazi, N.; Krenacs, T. **Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts.** J. Cancer 2018, 9, 41–53.

Introduction II.

Mouse B16F10 melanoma allografts in inimmunocompetent C57Bl/6 mouse model







Besztercei B[1], Vancsik T[2], Benedek A[1], Major E[1], Thomas MJ[1], Schvarcz CA[1], Krenács T[2], Benyó Z[1], Balogh A[3]. **Stress-Induced, p53-Mediated Tumor Growth Inhibition of Melanoma by Modulated Electrohyperthermia in Mouse Models without Major Immunogenic Effects.** Int J Mol Sci. 2019 Aug 17;20(16). pii: E4019. doi: 10.3390/ijms20164019.

Aims of study

Human A2058 melanoma xenografts in immonodeprived NOD SCID mouse model

Hypothesis

mEHT can reduce MHC-I on tumor cell surface and induce tumor cell stress, thus can activate the natural killer cells to eradicate the malignant cells.

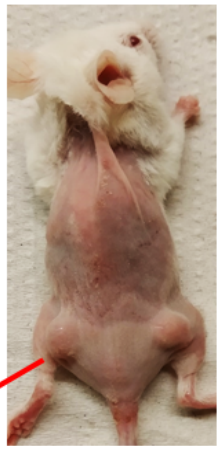
Model

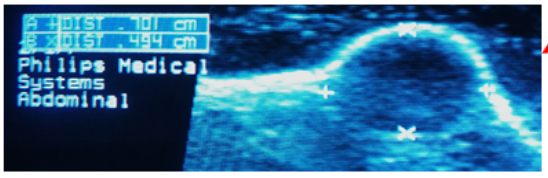
- A2058 human melanoma cell line; functional p53
- NOD/SCID mice: deficient in T, B, NK cells and complement system
- 30 min of 42°C mEHT
- subcutan injected fl. labelled human NK cells

Analysis

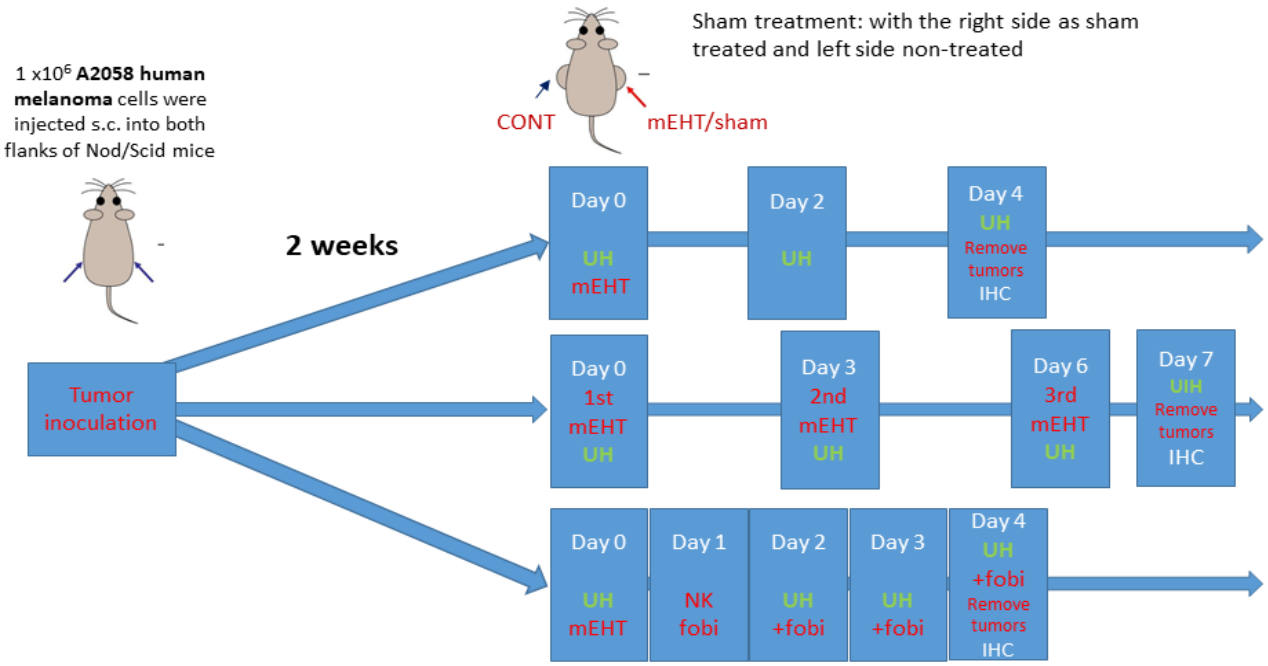
- tumor growth monitoring with UH measurement
- in vivo imaging of NK distribution with FOBI detection system
- IHC: cytochrome-c, caspase-3, AIF, HSP70, p53, p21, H2AX, F4/80

A2058 melanoma xenografts in NOD SCID mouse

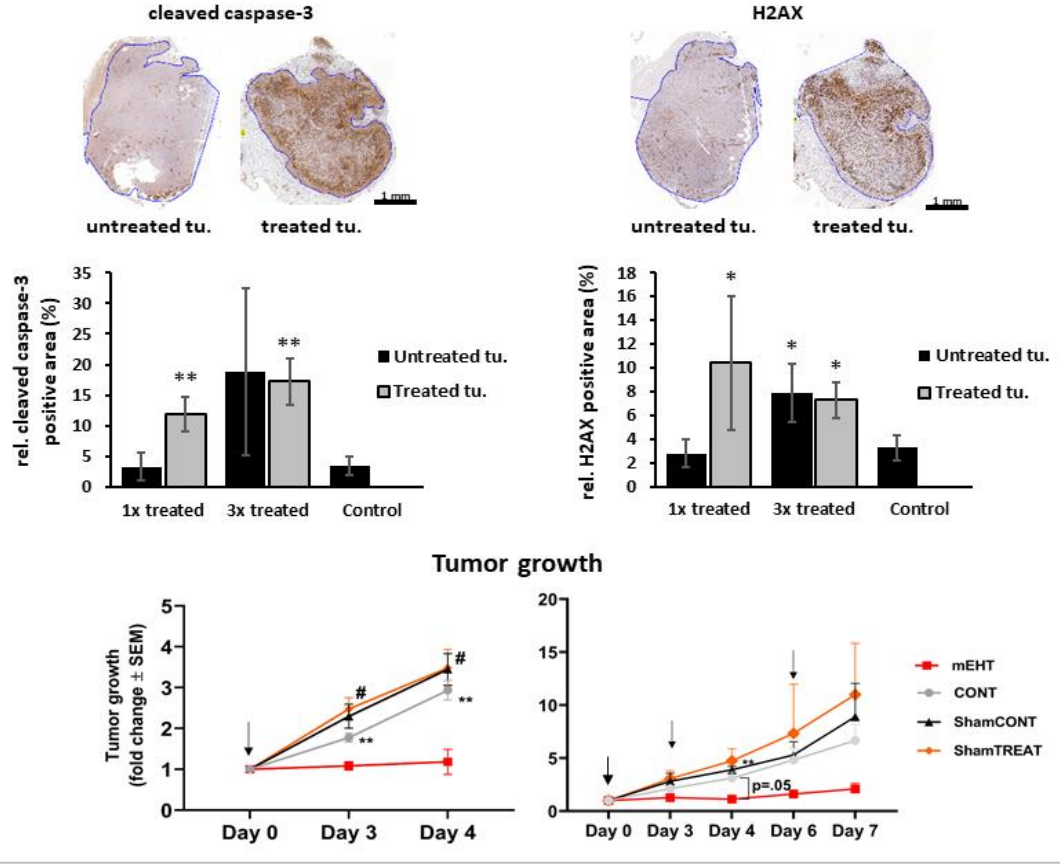




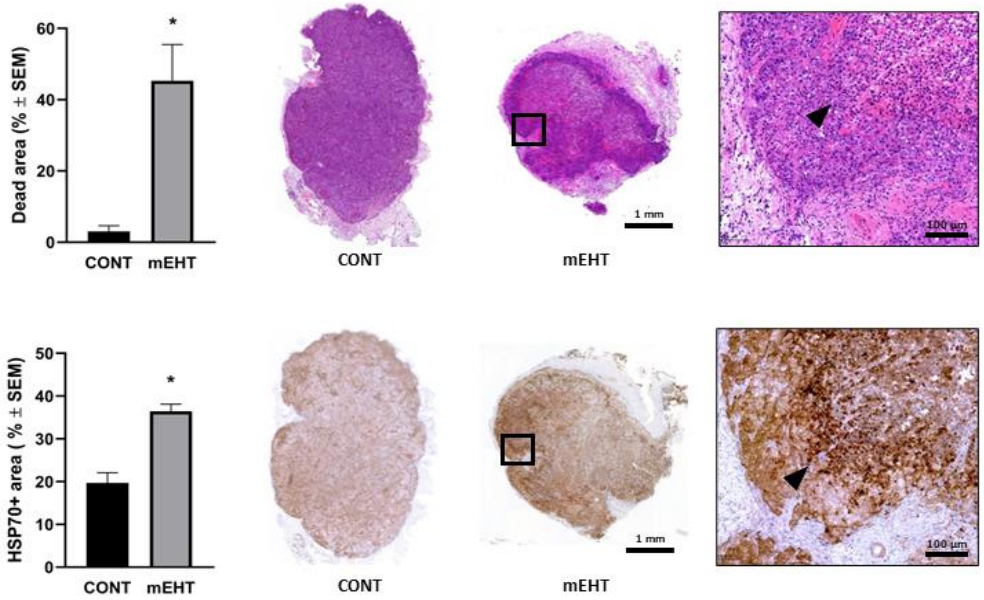
Experimental protocols: treatment is done one or multiple times



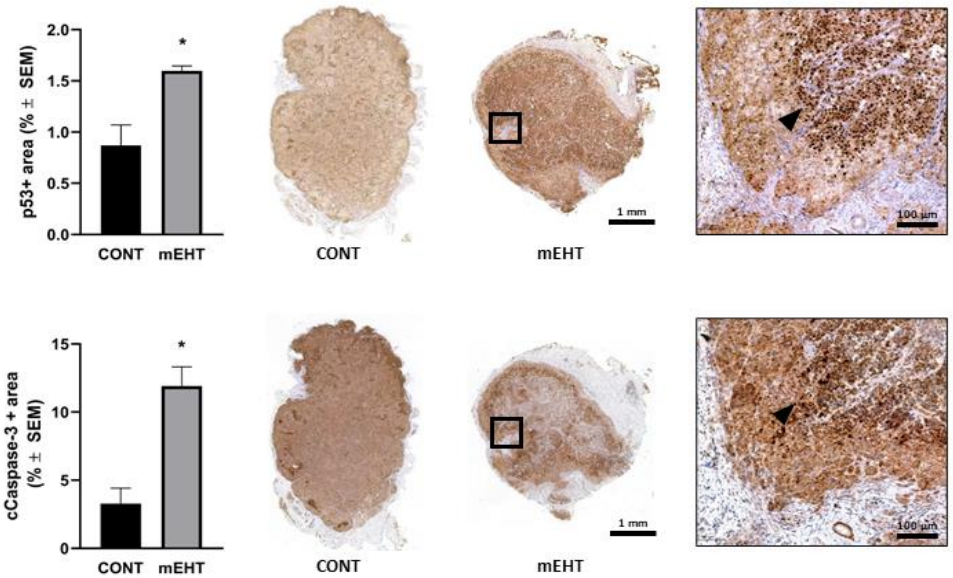
IHC markers analysed so far in the 1 x and 3 x treated tumors



Tumor damage and heat stress

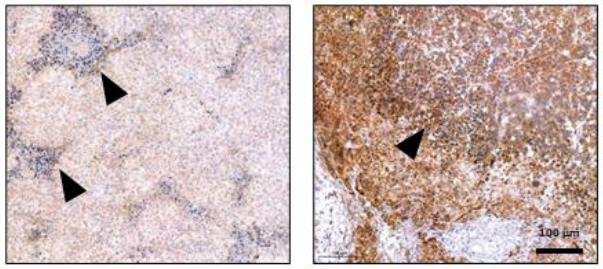


p53 dependant apoptosis

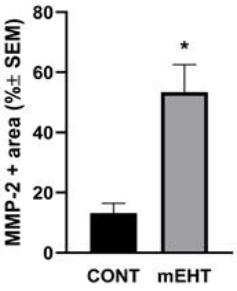


Changes in the tumor microenvironment

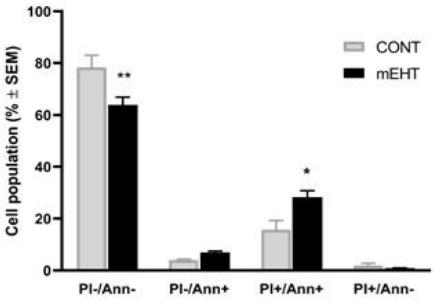
matrix metalloprotease-2 expression *in vivo*

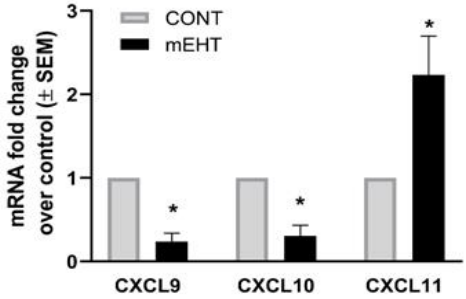


CONT mEHT



tumor cell apoptisos and NK-attractive cytokine mRNA expression *in vitro*





NK-cell therapy

Source of human NK cells:

- Isolation and expansion of primary human NK cells (CD56, granzyme expression)
- Commercially available NK92mi cell line

Functional analysis:

- ***in vitro*** kill of A2058 melanoma cells

Subcutan injection to lumbar region

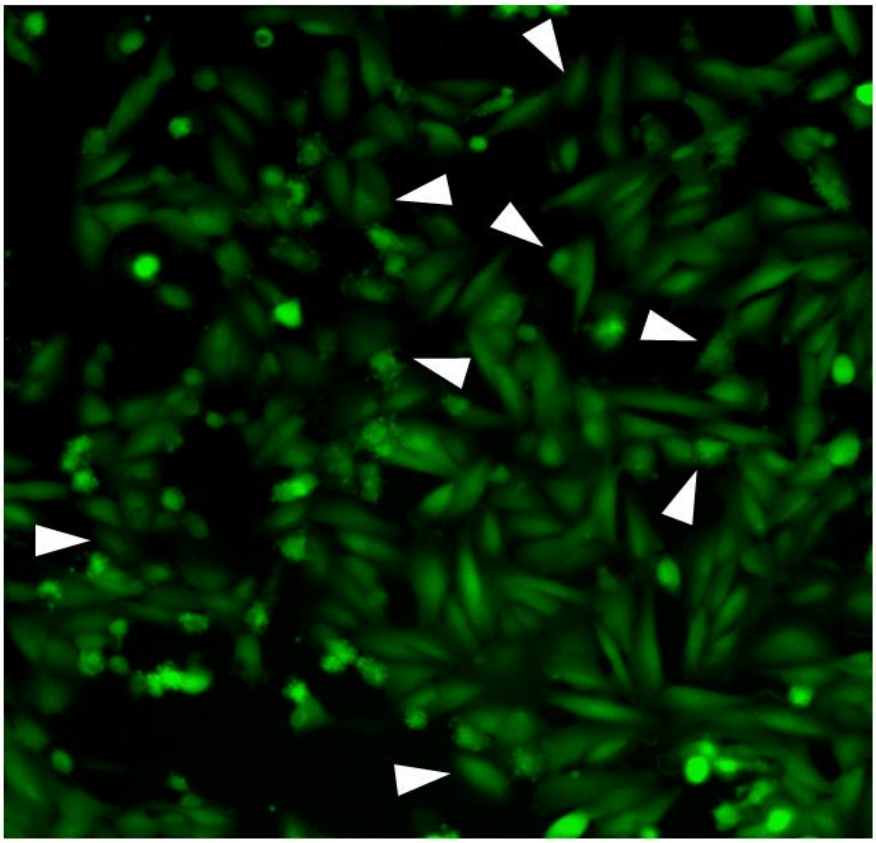
*FOBI *in vivo* detection system

Detect their localization:

- NK cells were labelled with far red fluorescent dye and using ***in vivo*** imaging*

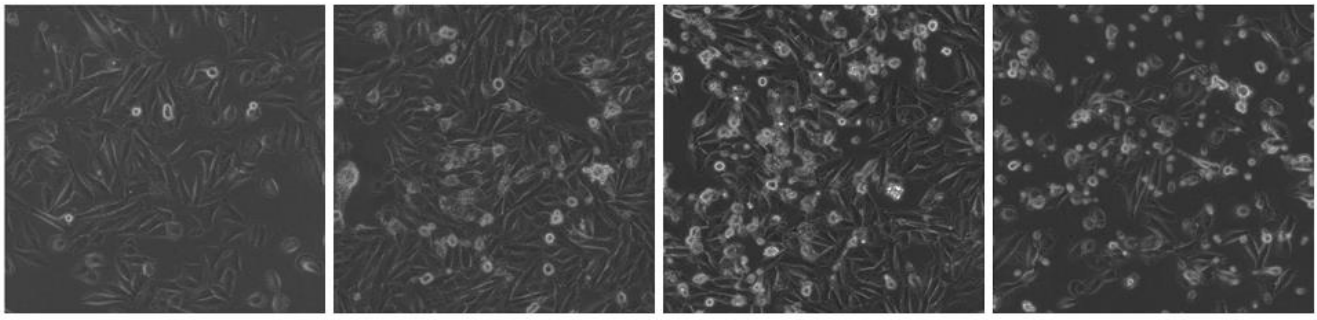
In vitro citotoxicity of primary NK cells: life cell imaging

Calcein loaded
A2058 cell culture
In a 12 well plate
$15*10^4$ NK-cells/well
35 minutes
1 picture/20 sec



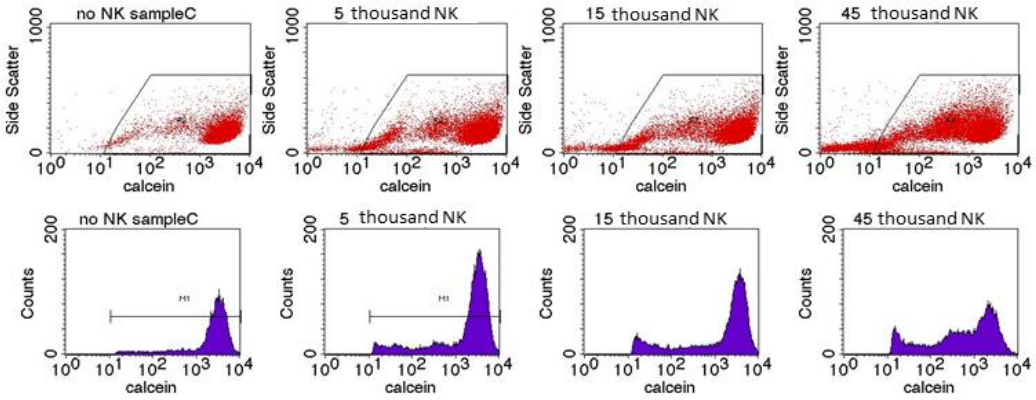
In vitro citotoxicity: microscopy

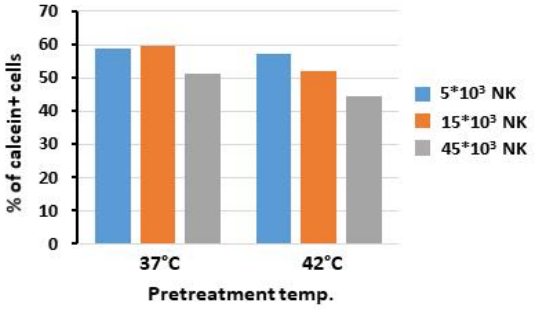
0 NK | $5*10^4$ NK-cells/well | $15*10^4$ NK-cells/well | $45*10^4$ NK-cells/well



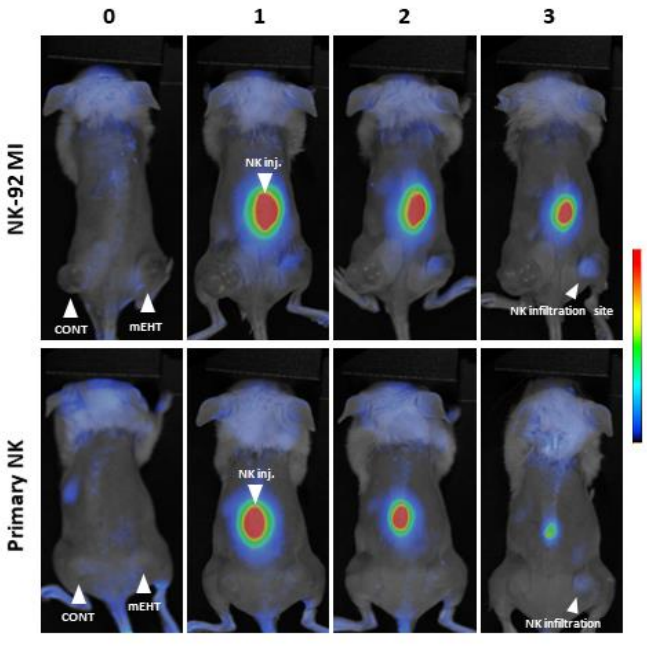
~2 hrs co-culturing

Primary NK *in vitro* citotoxicity: calcein release assay

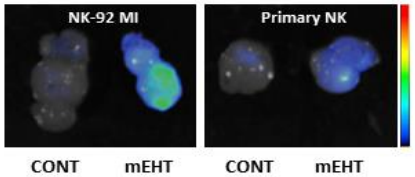




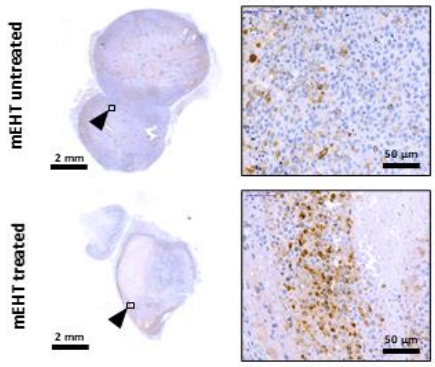
Days relative to mEHT treatment and NK cell injection



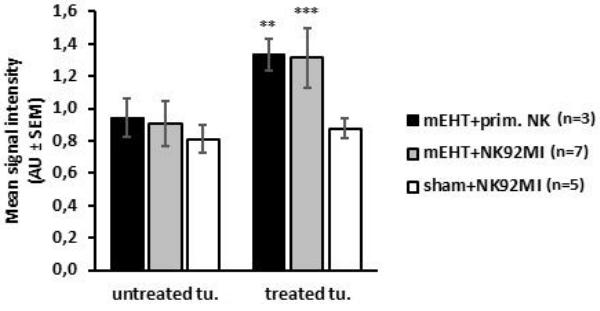
Tumors isolated after termination



CD57 IHC

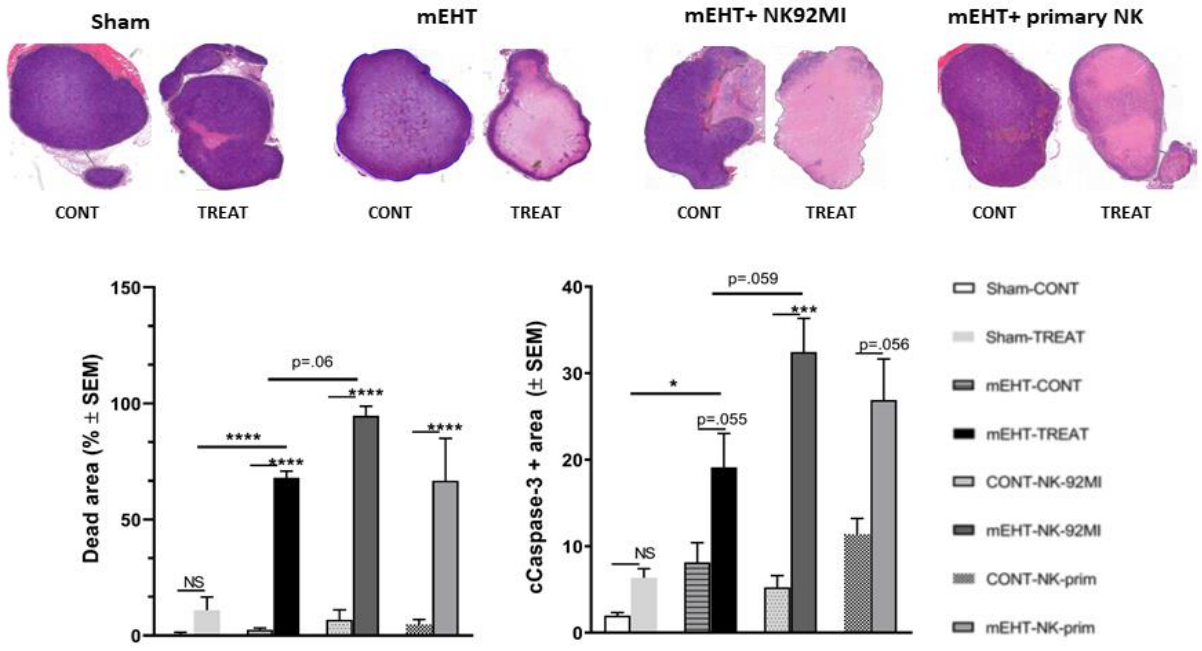


Post mEHT/sham day 3



0.01>p*>0.001
0.001>p***

Apoptotic area in context of NK-cell therapy



p>0.05: n=3; further elements are under evaluation

Discussion

In a A2058 Xenograft model:

mEHT-related effects:

- p53 activation→tumor growth inhibition
- DNA DSB and caspase-dependent apoptosis
- favorable micorenvironment attracting NK cell traficking

In vitro NK cell tumor cytotoxicity, and its accumulation on the mEHT treated tumor sites suggests the involvement of NK cells in A2058 melanoma cell killing

Further testing for the NK-attractive and -inductive factors is needed

Where to go from here?

Andras Szasz[1]

[1]Biotechnics Department, St. Istvan University,
Godollo, Hungary

Citation: Szasz A. (2020): Where to go from here?, Oncothermia Journal 29: 145 – 157,
www.oncotherm.com/sites/oncotherm/files/2021-02/Szasz_Wheretogo

Abstract

Introduction: Hyperthermic oncology has great achievements but also raises questions about the basic mechanisms and clinical applications of the method. Despite its long history, the debates about its possibilities are intensely vivid, the pros and cons strongly and rigidly polarize professionals and develop a barrier to wide application and approval by medical and governmental associations.

Method: It is a relevant requirement to clarify at least the most challenging questions about the basics from my long time experience in the field using my own results and considering the also widely available international literature together with professional expert's opinions.

Results: I list just a few sensitive challenges for questions that come up as standard in current oncology practice in relation to hyperthermia:

- What are the basic mechanisms behind successes and failures?
- Should local or systemic treatment be preferred?
- What is the optimal temperature?
- What is the dose that defines the treatments?
- What about monotherapy?
- Why is it mainly applied to locally advanced and non-metastatic cases?
- How is it related to emerging physical therapies?
- How is hyperthermia involved in the newer concepts of immunotherapy?
- Why is hyperthermia not widely accepted by the oncology community?

Discussion: The challenge is obvious. We have more and more proven details on the challenge that heat alone is not effective enough to solve the problems of cancer and its development, due to the various complex physiological feedback mechanisms in humans. Probably the heating provides hot environment to the tumor, which promotes molecular and physiological processes. This way hyperthermia in cooperation with applied complementary treatments influences the malignancy, eliminates the cancer cells and tries to restore healthy functions. The application of bioelectromagnetic effects could guide changing activities from general tumor destruction to complex regulated and controlled reactions to achieve curative goals.

Conclusion: My presentation would like to make decisive proposals on these hot topics and connected challenges and show what the necessary steps are to move forward.

ICHS 2020
Web-conference

Where to go from here?

Prof.Dr. Andras Szasz

Professor, Head of Department of Biotechnics,
St. Istvan University, Hungary

Skeptic development - What to blame?

- **(1964)** "All of these methods [hyperthermia] **impress the patient** very much; they **do not impress their cancer** at all." **[1]**.
- **(1979)** ... microwave hyperthermia device is a **"gun shooting in the dark room" [2]**.
- **(1993)** "The mistakes made by the hyperthermia community may serve as **lessons, not to be repeated** by investigators in other novel fields of cancer treatment" **[3]**.
- **(2001)** "The biological effects are impressive, but physically the heat delivery is problematic",... "The biology is with us, the **physics are against us**". **[4].**
- **(2004)** "The biology and the physics are with us, but the **physiology is against us**" **[5]**.
- **(2019)** "Physics is our friend, but **we have not noticed** it" **[6], [7], [8].**

[1] Bauer KH, (1964) Das krebsproblem, Springer, Berlin
[2] Susskind C., (1979) "The "story" of nonionizing radiation research," Bulletin of the New York Academy of Medicine, 55:1152–1163,
[3] Storm FK (1993) What happened to hyperthermia and what is its current status in cancer treatment? J Surg Oncol 53:141-143
[4] Nielsen OS, Horsman M, Overgaard J (2001) A future of hyperthermia in cancer treatment? (Editorial Comment), European Journal of Cancer, 37:1587-1589
[5] The Kadota Fund International Forum 2004-Clinical group.pdf
[6] Wust P, Ghadjar P, Nodobny J, beck M, Kaul D, Winter L, Zschaeck S, (2019) Physical analysis of temperature-dependent effects of amplitude-modulated electromagnetic hyperthermia, International Journal of Hyperthermia, 36:1245-1253,
[7] Wust P. (2019) Physical rationale about amplitude modulated radiofrequency hyperthermia, ESHO-2019 Warsaw, Poland, 22-24. 05. 2019
[8] Wust P. (2019) Advantages of amplitude modulation in the radiofrequency hyperthermia, IX. DGHT-Kongress, Berlin, 20-21. 09. 2019

The challenges: questions seeking answers

- ❑ The principial challenge
- ❑ The heating challenge
- ❑ The dosing challenge
- ❑ Technical challenge
- ❑ The immuno-oncology challenge
- ❑ Challenge of emerging therapies

Pitfall of oncology: lost of the complexity

Inductively
study the details and build up the systemic picture

Philosophy of Western medicine - Hippocrates (400 BC)

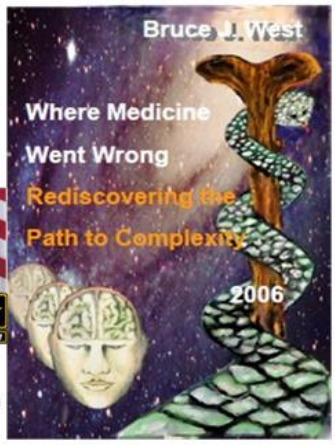
"Nil Nocere"
- Help the nature -

Oncology: hyperthermia

"organ (tissue) failure"
⟹ "reductional"

Reductionism dominates the present medical practice.

Bruce West
Chief scientist
Army Research Office (U.S.)



Deductively
study the system and deduct the details from it

Philosophy of Eastern medicine Lao Zi (500 BC)

"Be harmonic"
- Nature is harmonic -

Oncology: herbal medicine

"energetical failure?"
⟹ "holistic"

Both approaches are necessary!

Oncology ⟹

TASKS ⟹ Destroy the tumor effectively | Block the invasion & dissemination | Eliminate the metastases

Measure ⟹ Local control | Survival time and quality of life

Hyperthermia ⟹ destroy the cancer cells, (inductive way)
block their systemic effects, (deductive way)

Complex thinking is necessary in hyperthermia!

The challenges: questions seeking answers

- ❑ The principial challenge
- ❑ The heating challenge
- ❑ The dosing challenge
- ❑ Technical challenge
- ❑ The immuno-oncology challenge
- ❑ Challenge of emerging therapies

Pitfall of oncology: lost of the complexity

Inductively
study the details and build up the systemic picture

Philosophy of Western medicine - Hippocrates (400 BC)

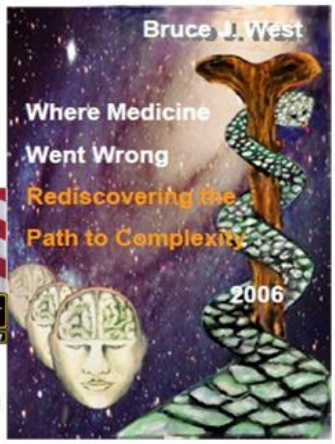
"Nil Nocere"
- Help the nature -

Oncology: hyperthermia

"organ (tissue) failure"
⟹ "reductional"

Reductionism dominates the present medical practice.

Bruce West
Chief scientist
Army Research Office (U.S.)



Deductively
study the system and deduct the details from it

Philosophy of Eastern medicine Lao Zi (500 BC)

"Be harmonic"
- Nature is harmonic -

Oncology: herbal medicine

"energetical failure?"
⟹ "holistic"

Both approaches are necessary!

Oncology ⟹

TASKS ⟹ Destroy the tumor effectively | Block the invasion & dissemination | Eliminate the metastases

Measure ⟹ Local control | Survival time and quality of life

Hyperthermia ⟹ destroy the cancer cells, (inductive way)
block their systemic effects, (deductive way)

Complex thinking is necessary in hyperthermia!

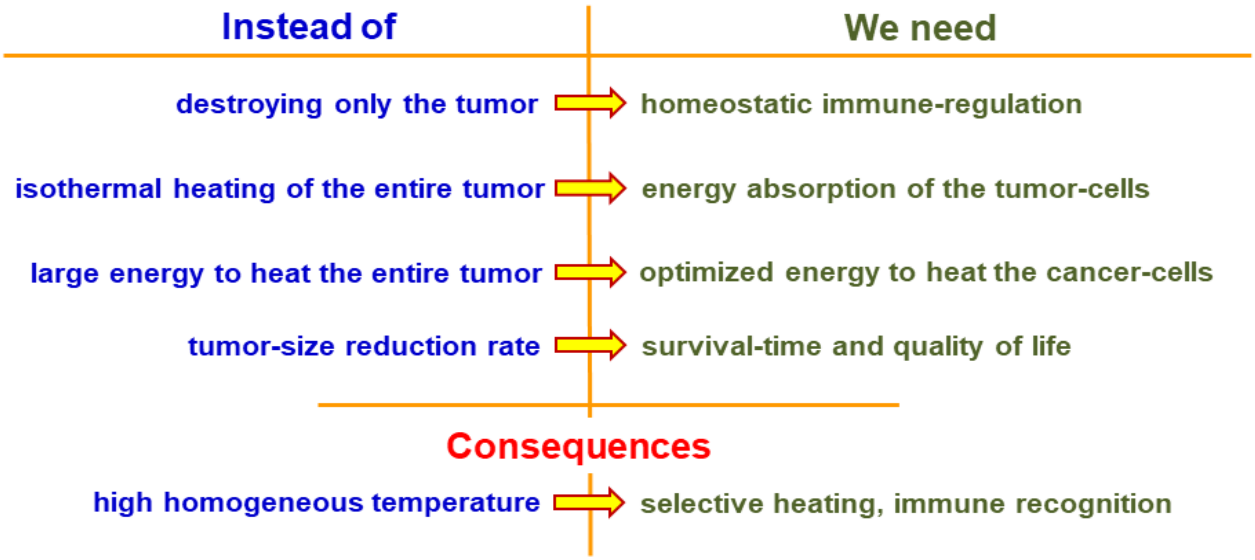
Change the treatment paradigm

Tumor-oriented hyperthermia

FROM

TO

Patient-oriented hyperthermia



The challenges: questions seeking answers

- ☑ The principial challenge
- ☑ The heating challenge
- ❑ The dosing challenge
- ❑ Technical challenge
- ❑ The immuno-oncology challenge
- ❑ Challenge of emerging therapies

Dose-definition has to based on clinical results

Present dose unit $CEM43°CT_x$ (measured in minutes)

$$CEM43^0C = \sum_{\{i\}}^{steady-state} t_i R^{(43-T_i)}$$

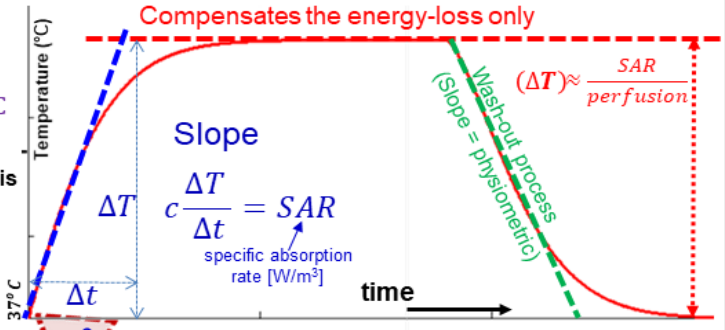
R=0.25, $T \leq 43°C$

R=0.5, $T > 43°C$

Arrhenius plot and its break fits to same damage necrosis for asynchronous Chinese hamster ovary cells, in vitro.

Challenge: Arrhenius plot may vary by cells, tissues, species and chosen endpoints

$(R^{43°C}_{mouse} = 0.25, 0.5; R^{43.5°C}_{human} = 0.13, 0.72)$



Rough average

corresponding principle

Francena M, et al: Hyperthermia dose-effect relationship in 420 patients .... Eur. J. Cancer, 45:1969-1978 (2009)

Fits to the clinical data

$$T_{RISE} = \frac{1}{\#sessions} \sum_{\#sessions} \int_0^{duration} \frac{(T_{50} - 37^oC)}{duration} dt$$

T_{50} = at least 50% of the target has such temperature

The correct clinical dose has to be a precise not only average measure

measured in J/kg [W*s/kg=J/kg=Gy]

$$SAR(t) = c\left(\frac{dT}{dt}\right)$$

$$Absorbed\ energy = \sum_{sessions} \int_0^{duration} \frac{1}{c}(SAR(t))dt$$

Technical requirement:
high efficacy of energy absorption

When the energy-absorption is not concentrated on the cancer, it is necessary to measure the temperature, knowing the approximate energy absorption

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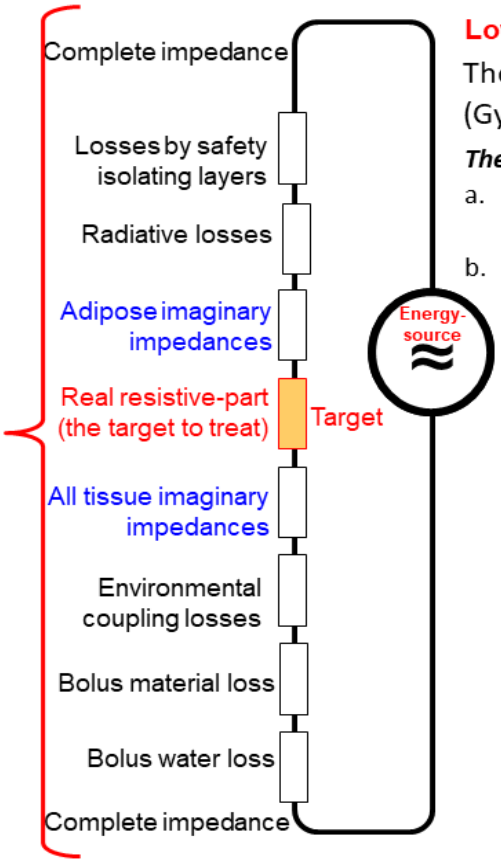
Technical demands and consequences



Low energy-loss allows to use the energy as dose.

The thermal dose characterizes the absorbed energy (Gy=J/kg), like in the practice of ionizing radiation

Thermometry is mandatory in the heating techniques where

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

Planning is a necessary tool estimating:

1. How much energy is absorbed?
2. Where is the energy focused?
3. How to avoid the unwanted hot-spots?

Planning has to be:

1. Adaptive for individual patients
2. Interactive during the implementation
3. Connected to the regulating software for in-situ adaptation of the treatment

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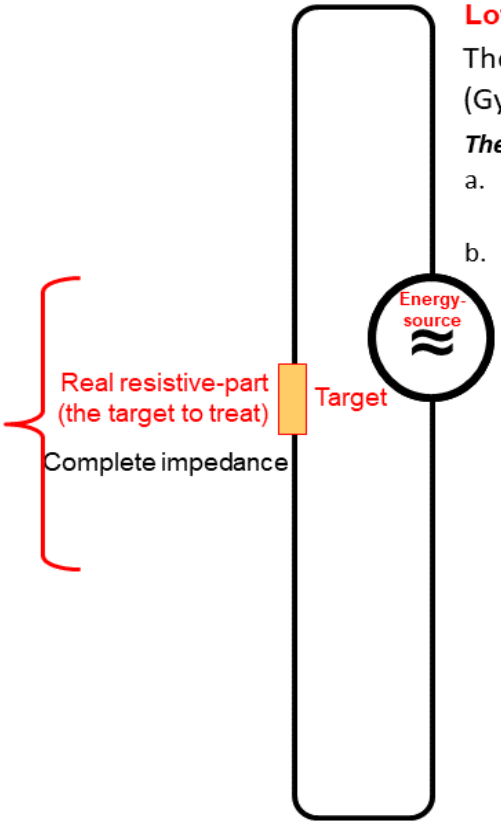

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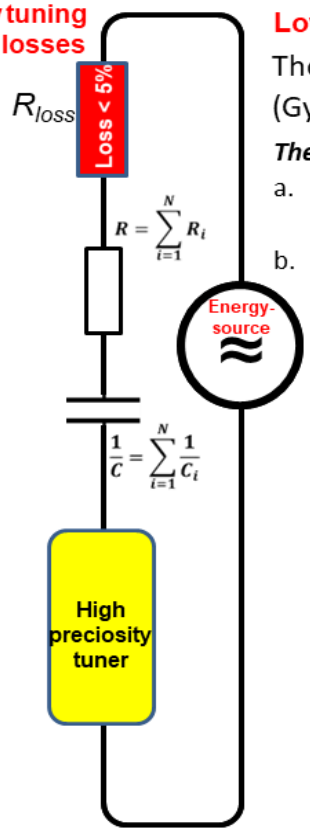
Technical demands and consequences

High preciosity tuning minimizing the losses



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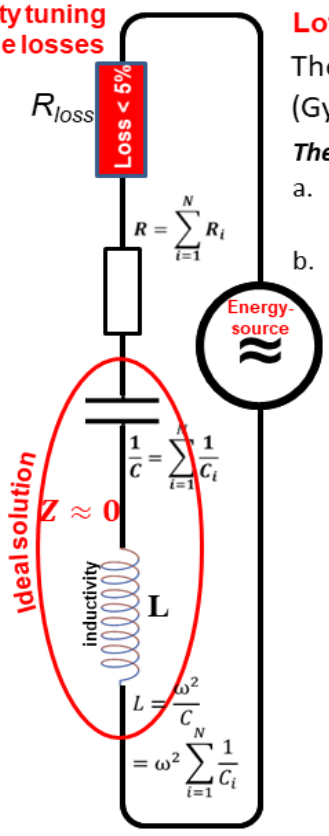

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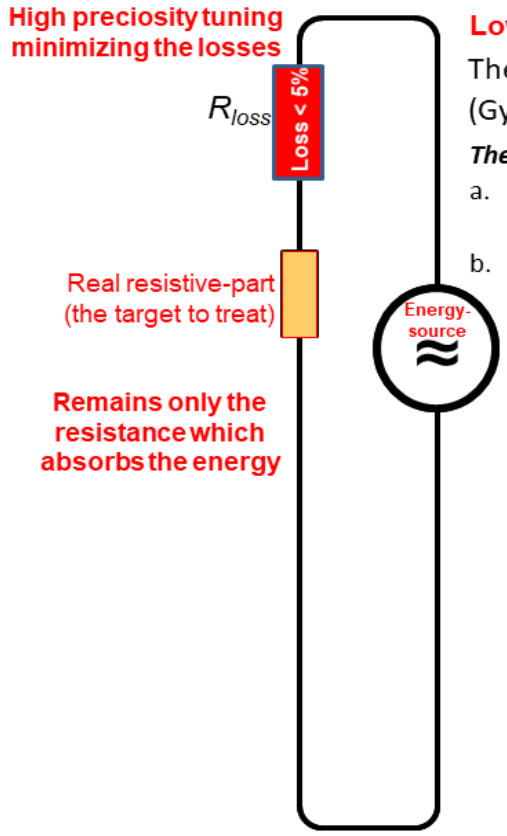

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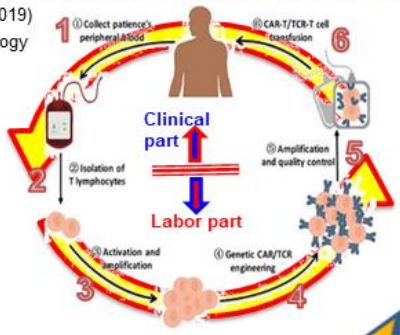
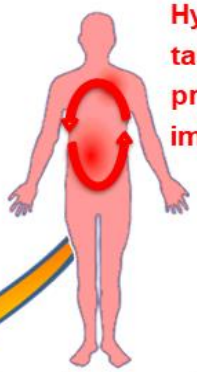
Immunogenic action is requested in hyperthermia too!

Chimeric antigen receptor preparation **CAR-T**

Zhao L-J, Cao YJ (2019)
Frontiers in Immunology



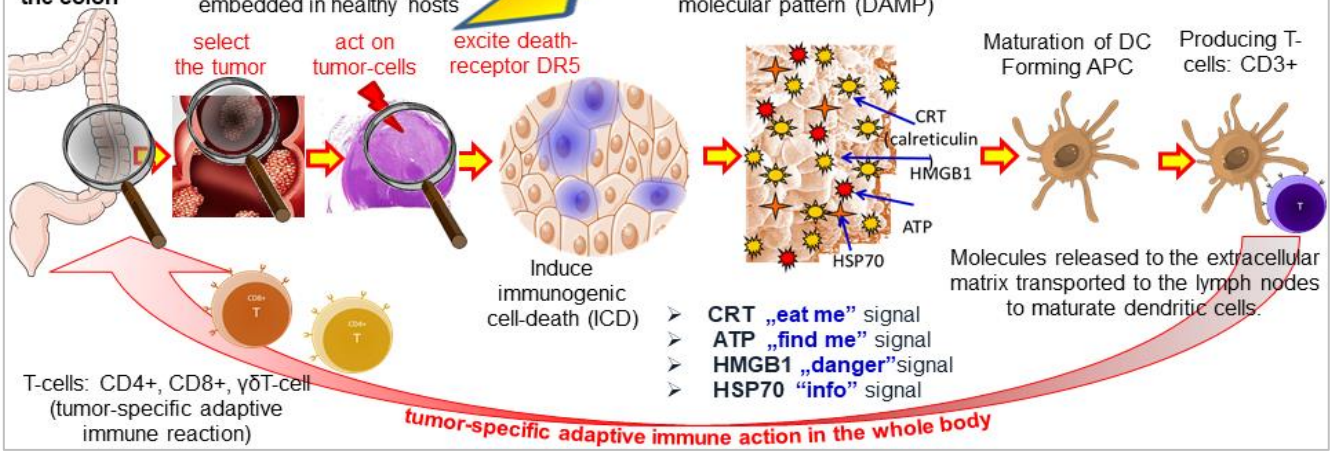
Hyperthermia can solve this task without external laboratory preparation. It makes in-situ immune surveillance!



Example:
Tumor in the colon

highly heterogeneous cell-population embedded in healthy hosts

Produces damage associated molecular pattern (DAMP)



Induce immunogenic cell-death (ICD)

- **CRT „eat me”** signal
- **ATP „find me”** signal
- **HMGB1 „danger”**signal
- **HSP70 “info”** signal

Molecules released to the extracellular matrix transported to the lymph nodes to maturate dendritic cells.

T-cells: CD4+, CD8+, γδT-cell (tumor-specific adaptive immune reaction)

tumor-specific adaptive immune action in the whole body

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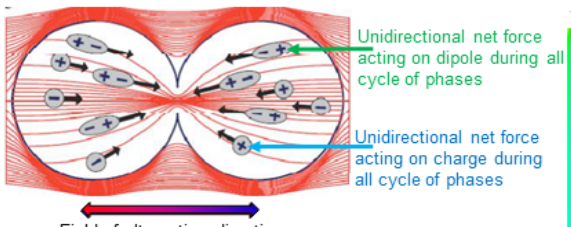
Cytokinesis block by tumor-treating-fields (TTF)

Principle of the tumor-treating-fields (TTF) (acts in cytokinesis)

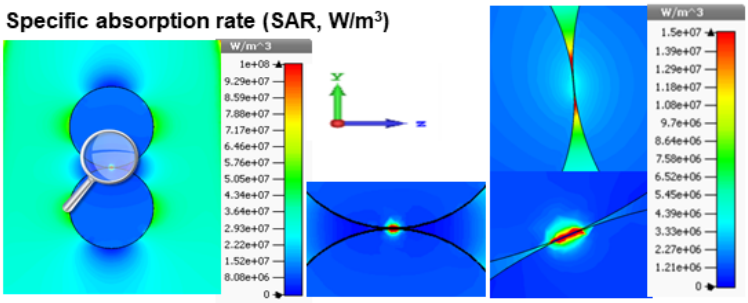


Kirson ED. et. al.: Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors, PNAS, June 12, 2007, Vol. 104. No. 24, 10152-10157

Selective hyperthermia also acts in cytokinesis, but in every directions

Effective in every directions

Specific absorption rate (SAR, W/m³)

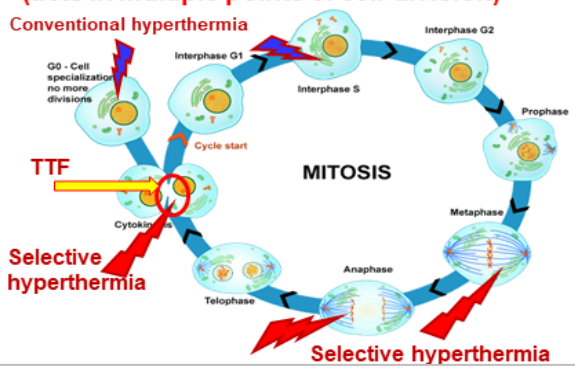


Papp E, et al. (2017) Energy absorption by the membrane rafts in the modulated electro-hyperthermia (mEHT), Open Journal of Biophysics, 7, 216-229

Multiple electrode-pairs for different directions, wear at least 18h/day

Carry it during the whole day even when asleep

Hyperthermia actions (acts in multiple points of cell-division)



Additionally: complex approach of hyperthermia

- ✓ applicable in most locations
- ✓ activates the immune-system
- ✓ makes abscopal effect
- ✓ sensitizes the radiotherapy
- ✓ has synergy with most chemotherapies
- ✓ less annoying for the patient

Answers are given according to my present knowledge

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Thank you for your kind attention

biotech@szie.hu

Challenge by dose - definition based on expriments

Hyperthermia dose definition

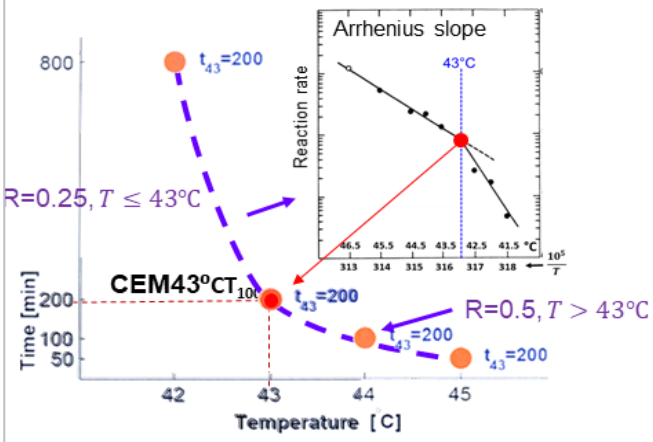
Cumulative Equivalent Minutes ← CEM | 43°C | T_x | [min]

Necrotic cell killing over 43°C

Percentage of the action on the target

Measured in minutes!

Asynchronous Chinese hamster ovary cells, in vitro,
Necrosis is measured in four points with the same damage



Sapareto SA, Dewey WC; (1984) Int.J.Rad. Oncol. Biol. Phys. 10:787-800)

$$CEM43^0C = \sum_{\{i\}}^{steady-state} t_i R^{(T_C - T_i)}$$

T_c=43°C

Complete dose unit forced to use:

$$CEM43°CT_x$$

(measured in minutes)

This dose considers immediate necrotic effect in vitro

Challenges: Arrhenius plot slopes may vary by

- Cells
- Tissues
- Endpoint
- Species

Arrhenius slope characteristics for mouse vs. human cells

		R value	
Species	Breakpoint	<Breakpoint	>Breakpoint
Mouse	43.0°C	0.25	0.5
Man	43.5°C	0.13	0.72

Yarmolenko PS. Thresholds of thermal damage and thermal dose models, https://www.icnirp.org/cms/upload/presentations/Thermo/ICNIRPWHOThermo_2015_Yarmolenko.pdf

Best fit R differs very much in other cells by temperatures over 43°C:
Cells with HSP: **R=0.311** (T=44°C)
Skin burns: **R=0.394** (T=44°C)
Microvascular disruption: **R=1.48** (T=44.5°C)
Muscle damage: **R=1.20** (T=50°C)
Skin burns: **R=1.20** (T=51°C)
PC3 cells: **R=1.08** (T=60°C)
HepG2 cells: **R=0.94** (T=70°C)

Pearce JA. (2013) Int.J.Hyperthermia 29:262-280

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KFI grant: 2019-1.1.1-PIACI-KFI-2019-00011

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- New automatic controlled step motor tuning system for rapid impedance matching to achieve faster tuning times
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