Use of Radiofrequency Hyperthermia to improve cancer therapy

Presentation of the Philippine Launching Event of Oncothermia 2024.06.01.

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https://youtu.be/NiBrjACZnQc,
https://www.youtube.com/playlist?list=PLEaAiXVgvMsEazu16PMNSqcJjZKF1yB3Y

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

CHARITÉ
UNIVERSITÄTSMEDIZIN BERLIN

Use of radiofrequency hyperthermia to improve cancer therapy

Department of Radiation Oncology | Charité – Campus Virchow Klinikum

Pirus Ghadjar | June 2024 | Manila

Charité at a glance

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

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

Last updated 12/31/2023

Rankings

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

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Agenda/Contents

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

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

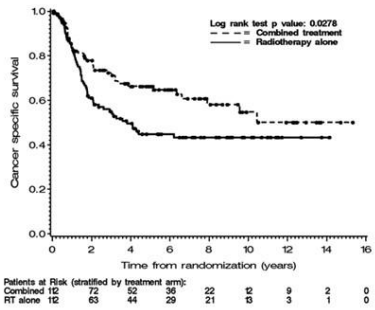
1

Completed randomized trials to improve radiation therapy

Addition of chemotherapy to radiation therapy

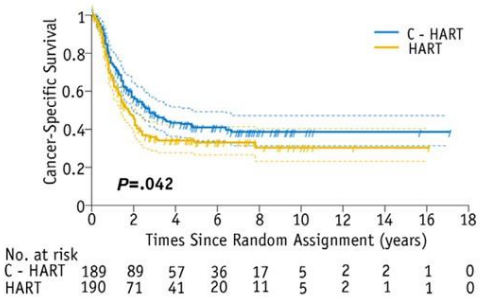
Two clinical trials in advanced head and neck cancer

SAKK 10/94 Trial



Ghadjar 2011

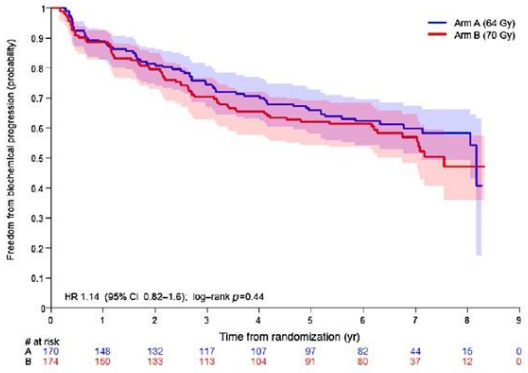
ARO 95/06 Trial



Budach & Ghadjar 2015

Dose intensified postprostatectomy salvage radiation therapy for prostate cancer

The SAKK 09/10 trial

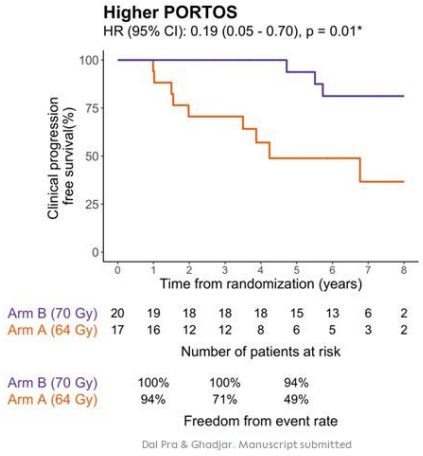


Ghadjar 2021

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

Personalized therapy

Translational analysis of the SAKK 09/10 trial



Dal Pra & Ghadjar. Manuscript submitted

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

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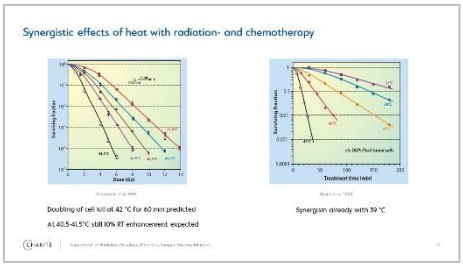
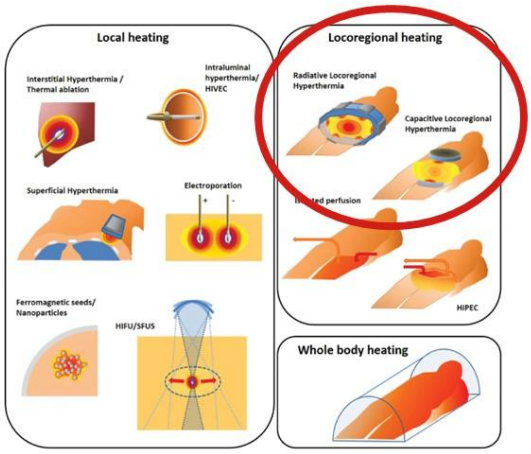
Potential of hyperthermia

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



Available locoregional heating technology to treat advanced solid tumors



Kok et al. 2020

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

Hyperthermia is an effective Radiosensitizer

38 clinical trials including almost 3500 patients

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

+ 15% increased complete response rate

Cancer Treatment Reviews 41 (2015) 742–753

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Anti-Tumour Treatment

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

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

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

Datta et al. 2015

Hyperthermia + RT improves survival in RCTs

Head and neck

● *Hyperthermia Original Contribution*

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

RICCARDO VALDAGNI, M.D.*† AND MAURIZIO

Glioblastoma

● *Clinical Investigation*

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

Sneed et al. 1998

Rectal cancer

Thermoradiotherapy of patients with locally advanced carcinoma of the rectum

Berdov et al. 1990

Cervical cancer

CLINICAL INVESTIGATION — Cervix

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

Franckena et al. 2008

Hyperthermia enhances effectiveness of Chemotherapy

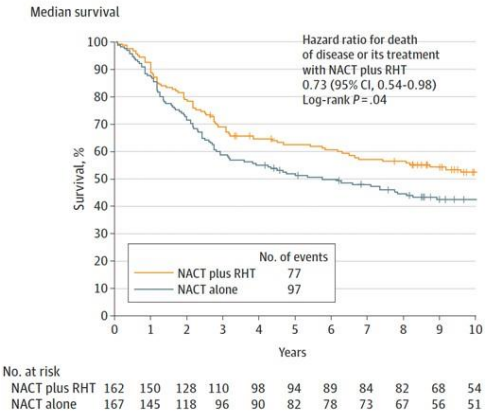
JAMA Oncology | Original Investigation

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

The EORTC 62961-ESHO 95 Randomized Clinical Trial

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

Issels et al. 2018



No. at risk

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

European Society of Hyperthermic Oncology (ESHO)

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

Hans Crezee – President

Pirus Ghadjar – Vice President

Lars Lindner – Vice President

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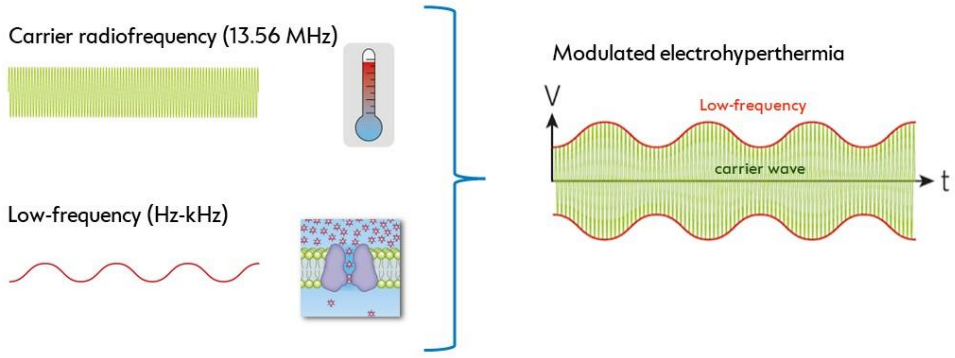
Recent preclinical results of modulated electrohyperthermia

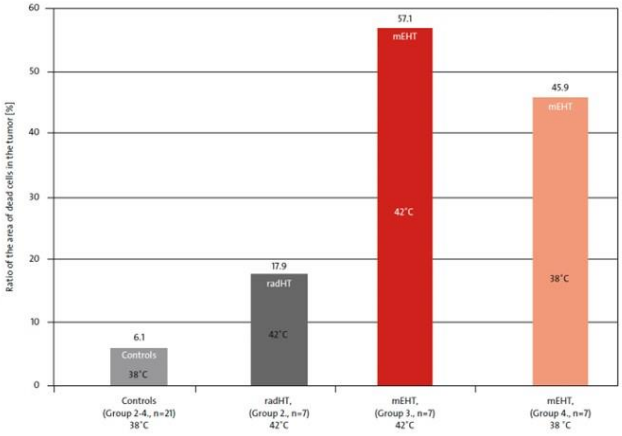
Modulated electrohyperthermia (mEHT)



Wust et al. 2022

Modulated electrohyperthermia (mEHT)

Evidence of "cellular anticancer effects"



Andocs et al. 2009

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

Mode of action of mEHT

A decade of preclinical research

International Journal of Molecular Sciences

MDPI

Review

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

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

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

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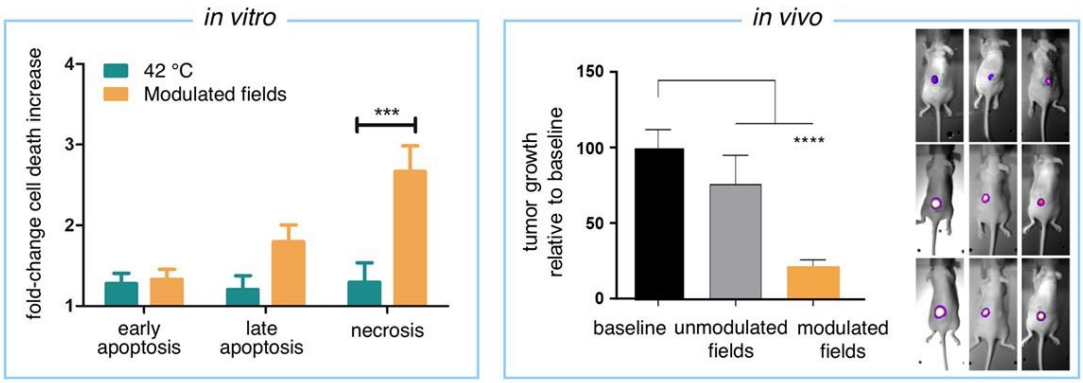
- Induction of ion fluxes and ion disequilibrium
- Induction of DNA double-strand breaks
- Induction of immunogenic cell death
- Increased chemotherapy drug uptake
- Radiosensitizing by reduction of hypoxia

Krenacs et al. 2020

Benefit due to the use of amplitude modulation

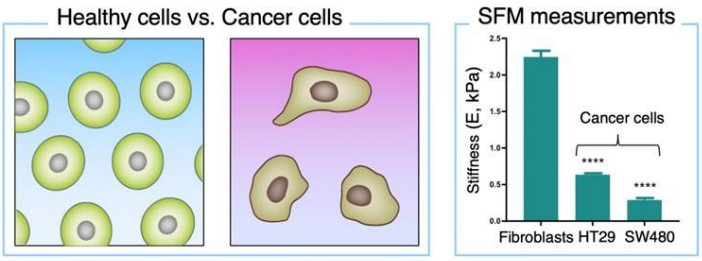
In vitro and *in vivo* evidence



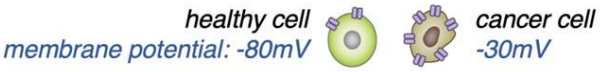
Wust et al. 2022

Potential for cancer cell specific therapy

Based on cell mechanics and ion channel expression



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



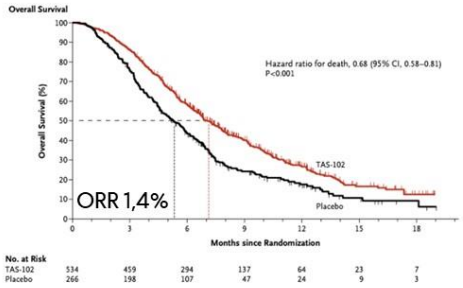
Wust et al. 2022

4 Running clinical trials at Charité

Live-RF Phase II trial

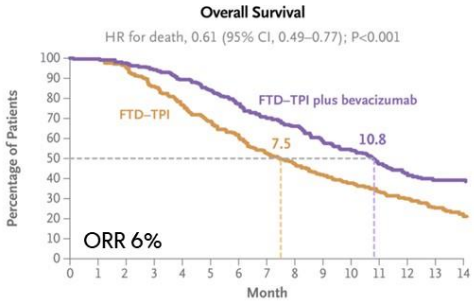
mEHT + chemotherapy in colorectal cancer patients with liver metastasis

Lonsurf (TAS-102)



Mayer et al. 2015

Lonsurf (TAS-102) + Bevacizumab



Prager et al. 2023

Live-RF Phase II trial

mEHT + chemotherapy in colorectal cancer patients with liver metastasis

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

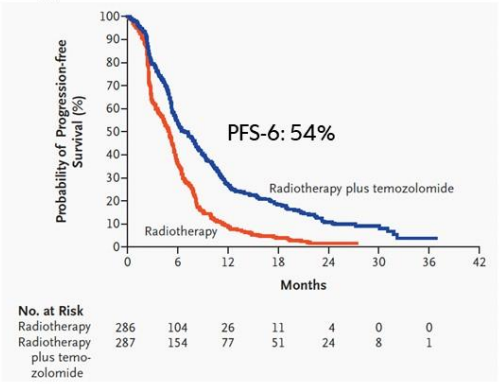
Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su	Mo	Tu	We	Th	Fr	Sa	Su
TAS-102																												
Bevacizumab																												
Recovery																												
mEHT		*		*					*		*				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

ClinicalTrials.gov ID NCT05991102

Brain-RF Phase II trial

mEHT + radiochemotherapy in newly diagnosed glioblastoma

"Stupp" Protocol



Brain-RF Phase II trial

mEHT + radiochemotherapy in newly diagnosed glioblastoma

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

Radiochemotherapy schedule:

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

Adjuvant Chemotherapy schedule:

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

ClinicalTrials.gov ID NCT06140875

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Future developments

Future developments

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


Let us improve the lives of patients with cancer