International Guideline Proposal for Hyperthermia based Oncological Treatments -- an Initiative from Hungary

Marcell A. Szasz[1], Gyongyver Szentmartoni[1], Peter Arkosy[2], Tibor Csoszi[3], Zsofia Dankovics [4], Gabor Rubovszky [5], Andras Csejtei [4], Gabor Pajkos[6], Bela Piko[7], Erika Borbenyi[1], Magdolna Dank[1]

[1] Cancer Center, Semmelweis University, Budapest, Hungary
[2] Department of Oncology, Oncotherapy and Rehabilitation, Kenézy Gyula University Hospital, Debrecen, Hungary
[3] Oncoradiology Center, Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary
[4] Department of Oncoradiology, Markusovszky Teaching Hospital, Szombathely, Hungary
[5] Department of Chemotherapy B and Clinical Pharmacology, National Institute of Oncology, Budapest Hungary
[6] Department of Oncology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary
[7] Memorial Oncology Center, Pándy Kálmán County Hospital, Gyula, Hungary

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Background

Hyperthermia is composed of a wide variety of treatment methods which ranges from physiotherapy to oncology and can have various physical and technical background. Even the definition needs careful consideration and is subject to discussion. Dosing may vary between the equipments of individual vendors. There was substantial development in this field, thus, the previously proposed guidelines and protocols do not fully apply to all approaches and devices.

Aims

Our objective in this presentation is to summarize our knowledge about the utilization of hyperthermic therapy from the practical perspective and propose a guideline which seems timely and necessary. In line with this, definition, dosing will be discussed, and the objective is to provide a recommendation for the implementation of the hyperthermia and also take into consideration data analysis and comparability.

Methods

We would like to collect the experience of the centers which utilize hyperthermia in any oncological treatment fashion, gather a collective wisdom on best practices, filter and organize the procedures into an adaptable recommendation, and establish standards and quality control.

Results

The literature for hyperthermia guidelines will be reviewed, clinical evidences will be referenced, discussion and credentials on recommendations will be collected and a guideline will be developed, drafted into a manuscript with all national and international contributors.

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Szász A. Marcell[1], Szentmártoni Gyöngyvér[1], Árkosy Péter[2], Csőszi Tibor[3], Dankovics Zsófia[4], Rubovszky Gábor[5], Csejtei András[4], Pajkos Gábor[6], Pikó Béla[7], Borbényi Erika[1], Dank Magdolna[1]

(1) Cancer Center, Semmelweis University, Budapest, Hungary

(2) Department of Oncology, Oncotherapy and Rehabilitation, Kenézy Gyula University Hospital, Debrecen, Hungary

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(6) Department of Oncology, Bács-Kiskun County Teaching Hospital, Kecskemét, Hungary

(7) Memorial Oncology Center, Pándy Kálmán County Hospital, Gyula, Hungary

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- Physics student at Eötvös Loránt University (TTK)
- M.D./Ph.D. Ast. Professor - 2nd Department of Pathology, Semmelweis University, Budapest, Hungary
- Senior scientist - "Lendület" Cancer Biomarker Research Group, Hungarian Academy of Sciences, Budapest, Hungary
- Consultant Pathologist - Clinical Pathology/Cytology, Karolinska University Hospital, Stockholm, Sweden
- Chief of Pathology - Centre of Excellence in Biological and Medical Mass Spectrometry, Biomedical Centre, Lund University, Lund, Sweden
- Consultant – LoDoCo Ltd.
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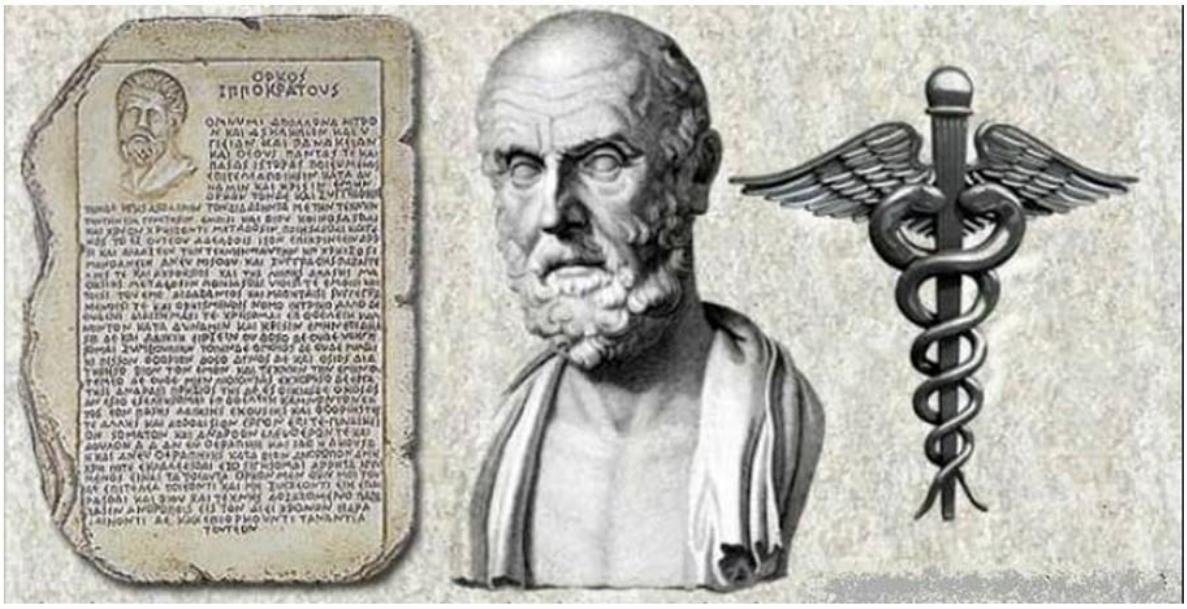
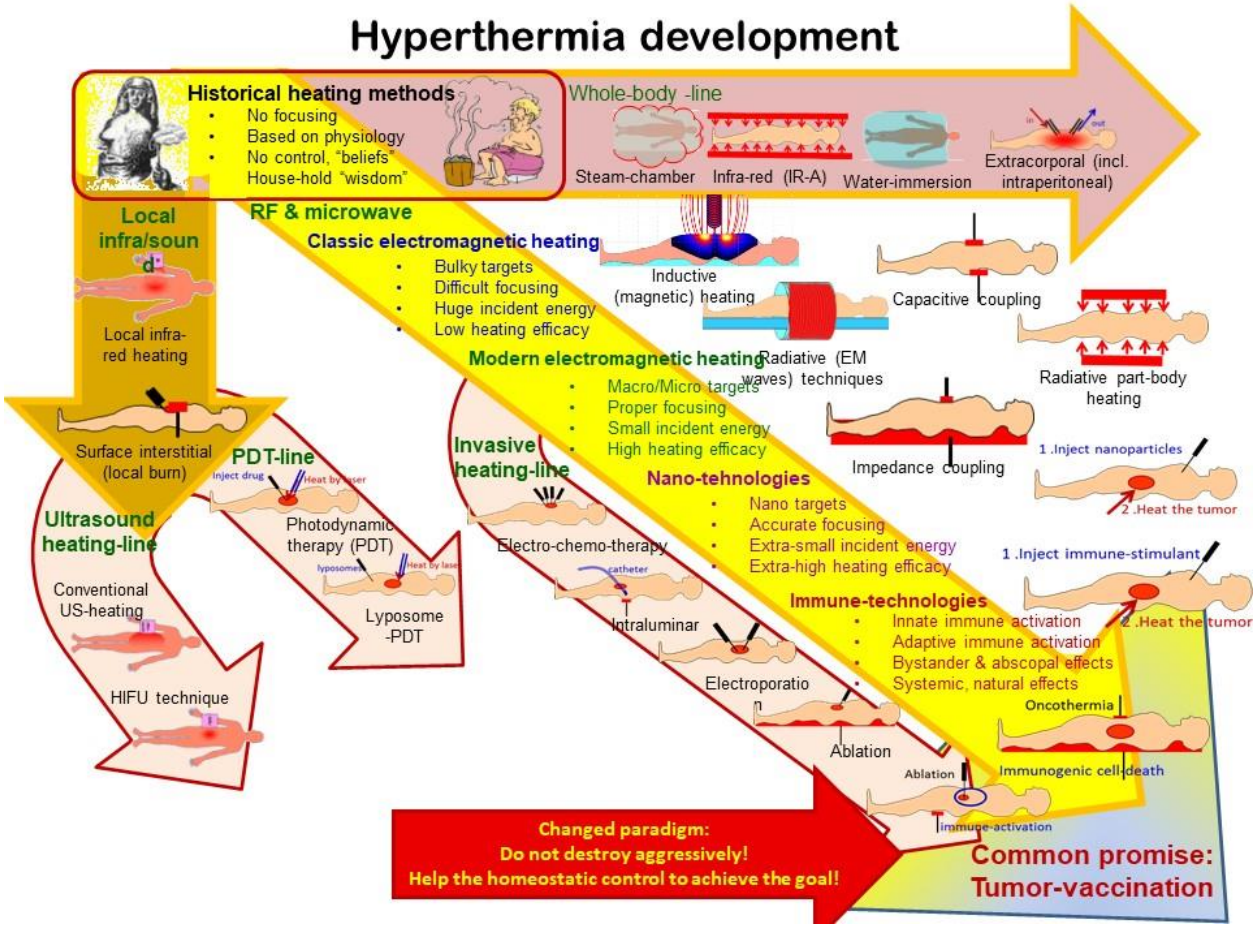
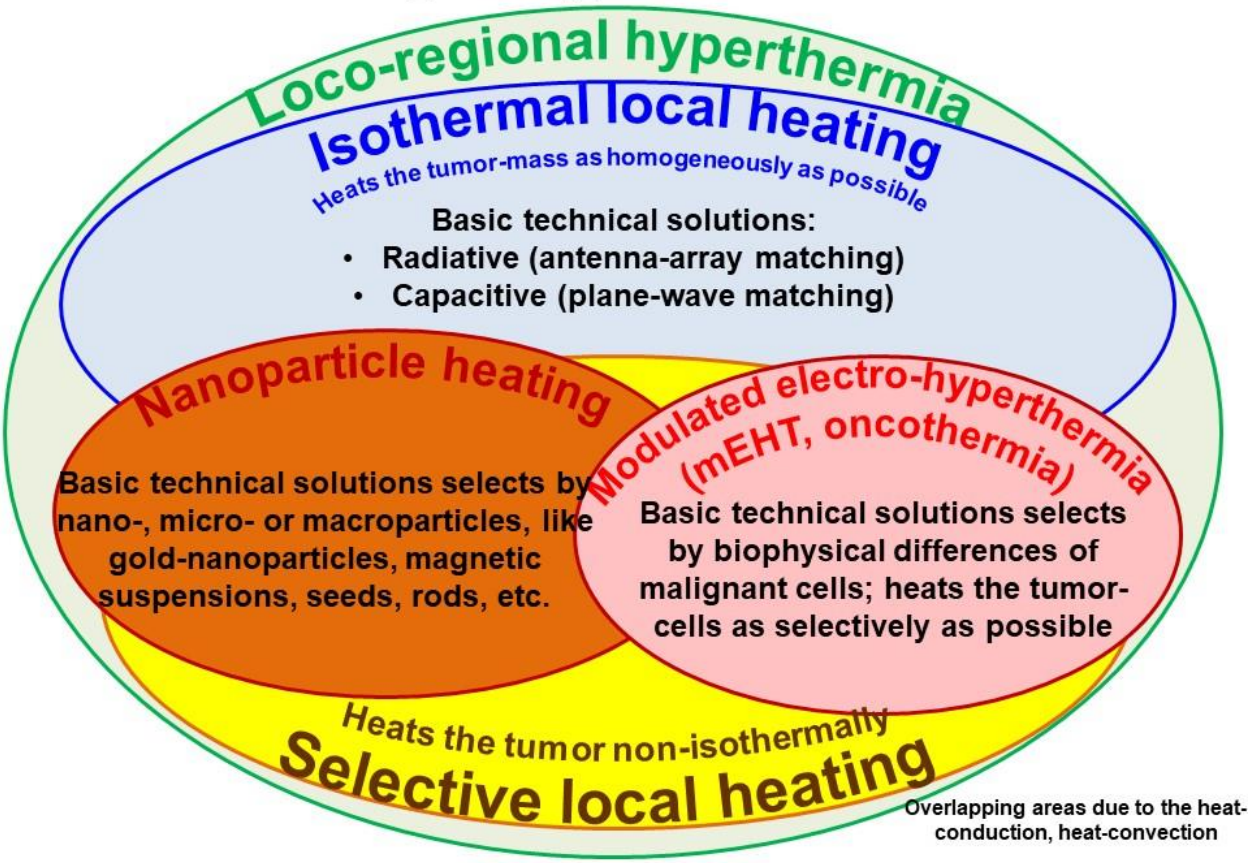
- Head of Science - Cancer Center, Semmelweis University, Budapest, Hungary
- Research Fellow - Division of Oncology and Pathology, Department of Clinical Sciences Lund, Lund University, Lund, Sweden
- Secretary General, Hungarian Society of Senology
- Member of Board of Curators, International Academy of Pathology, Hungarian Division

Hippocrates

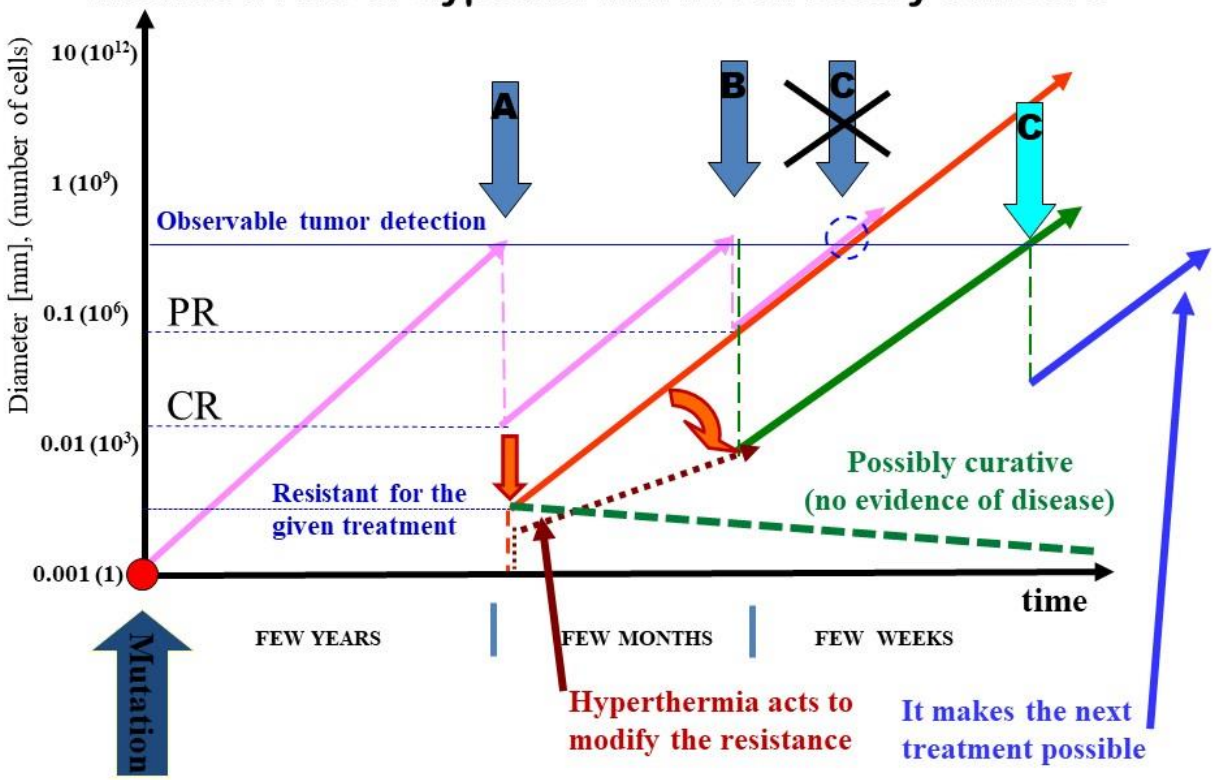




Local/regional hyperthermia methods



Intended role of hypethermia in refractory cancers

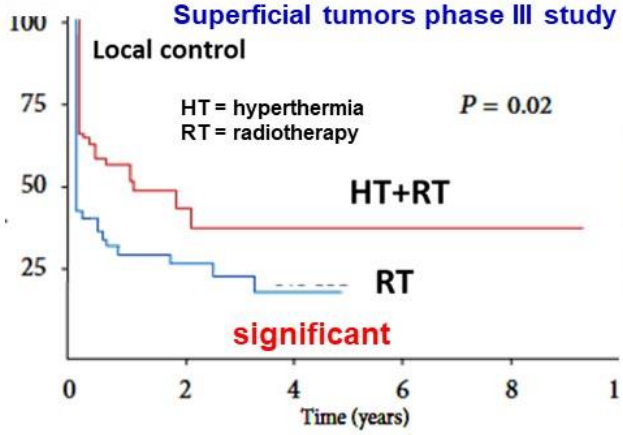


Hyperthermia has controversies between the

local response and control ⟺ **overall survival**

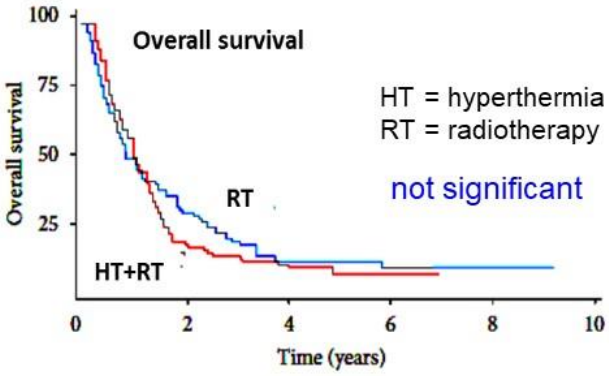
Local control and survival time are not in harmony

Superficial tumors phase III study



Jones EL, et al.; J Clin Oncol. 23:3079-85, 2005

HT



Non-small-cell lung cancer

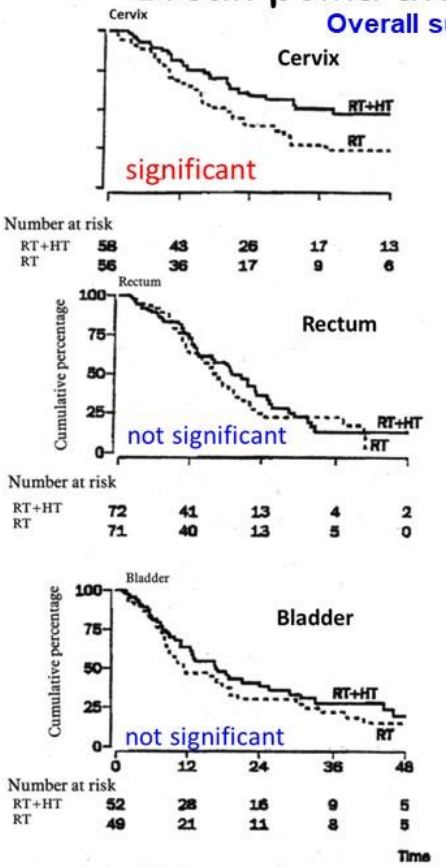
Initial site of disease progression after treatment

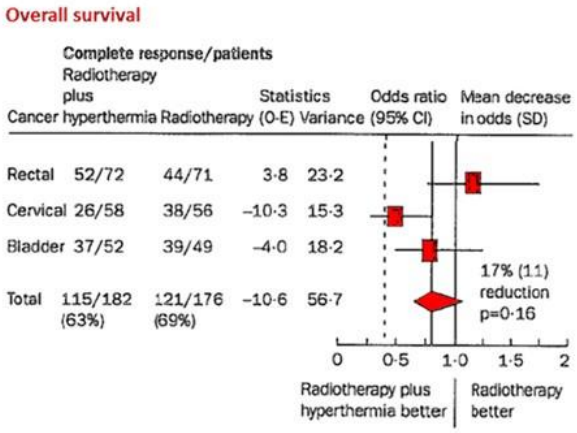
	RT (n = 40)	RT + HT (n = 40)	P-value
No recurrence	3	4	
Primary tumor and/or regional lymph nodes	15	7	
Distant metastasis	2	10	0.07
Both locoregional and distant[a]	3	4	
Unknown/missing	17	15	

[a]Patients in whom the interval between locoregional disease progression and distant metastasis was less than or equal to 1 month

Michihide Mitsumori, Zeng Zhi-Fan Praskovya Oliynychenko Jeong Ho Park, Ihl Bohng Choi Hideo Tatsuzaki · Yoshiaki Tanaka, Masahiro Hiraoka; (2007) Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: a multi-institutional prospective randomized trial of the International Atomic Energy Agency, Int J Clin Oncol (2007) 12:192–198

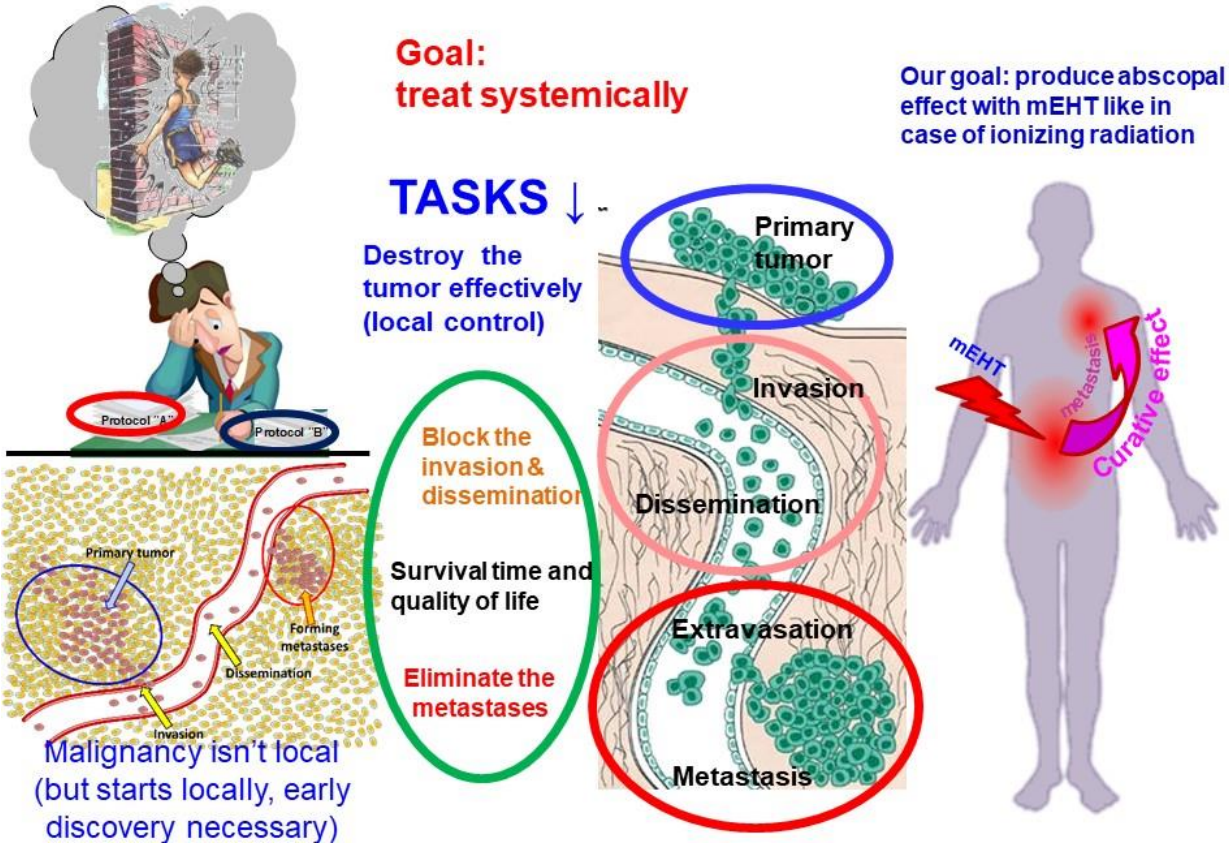
Break-point: the pelvic tumors – Lancet publication





IMPROVEMENT is necessary which is the direction of immuno-oncology

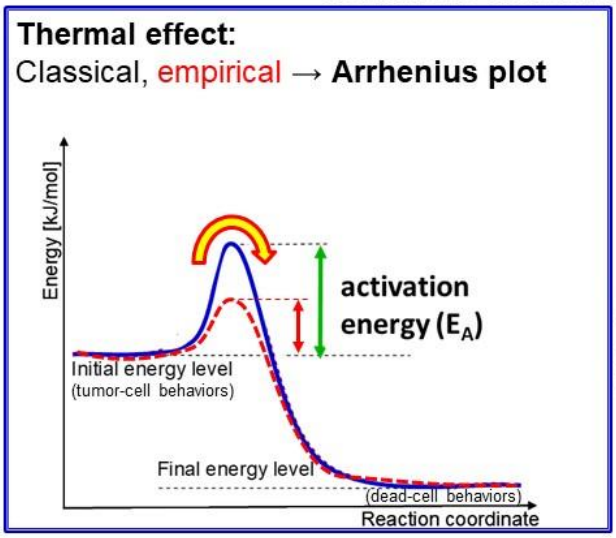
Challenge in oncology – malignancy is systemic

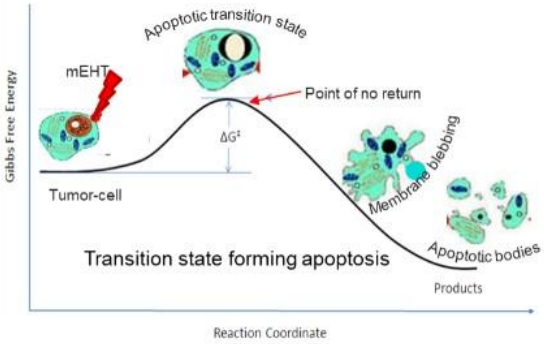


Unfortunately presently
we have no correct definition.
We have no convenient
dose-definition either.

When we have no correct definitions about our topic why we expect, that other disciplines accept us

Scientific definition of thermal effect





Dosing, safety and reproducibility

Conventional tumor-therapies

- ✓ **Concept** is to apply the largest tolerable dose [mg/m^2], [J/kg]
- ✓ **Efficacy** is measured by off-situ diagnostics
- ✓ **Safety** is measured by toxicity limit (dose-escalation studies) [mg/m2], [J/kg]

Hyperthermia dose in guidelines (Sapareto & Dewey 1984)

Cumulative Equivalent Minutes - CEM43^{o}CT$_x$ [min]

Refers to the necrotic cell killing over 43°C

Percentage of the area of the target

Measured in minutes!

It is based on immediate necrotic effect!

Sapareto and Dewey,CEM43, dose model (Sapareto SA, Dewey WC; (1984) THERMAL DOSE DETERMINATION IN CANCER THERAPYInt.J.Rad. Oncol. Biol. Phys. 10:787-800)

Challenge of dose of hyperthermia

$CEM43^oCT_x$ Calibrated in vitro

Sapareto and Dewey,CEM43, dose model (Sapareto SA, Dewey WC; (1984) THERMAL DOSE DETERMINATION IN CANCER THERAPY Int.J.Rad. Oncol. Biol. Phys. 10:787-800)

$$CEM43^oCT_x = \sum_{time} t_i R^{(43^oC - T_x)}$$

Fits to the clinical data

Francena M, et al: Hyperthermia dose-effect relationship in 420 patients with cervical cancer treated with combined radiotherapy and hyperthermia. Eur. J. Cancer, 45:1969-1978 (2009)

$$TRISE = \sum_{time} t_i \frac{(T_{50} - 37^oC)}{time\ of\ rise}$$

corresponding principle

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

Rough average (unprecise)

Actual absorption (correct approximation)

The correct dose

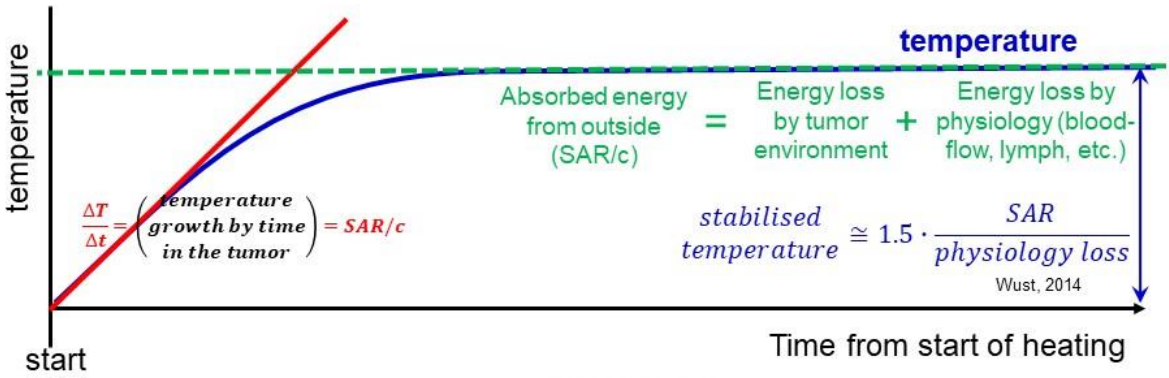
$$Absorbed\ energy = \sum_{time} t_i (SAR(t))$$

measured in Gy (J/kg)

(like in ionizing radiation)

Technical requirement: high efficacy of energy absorption

Challenge of the dose of oncological hyperthermia



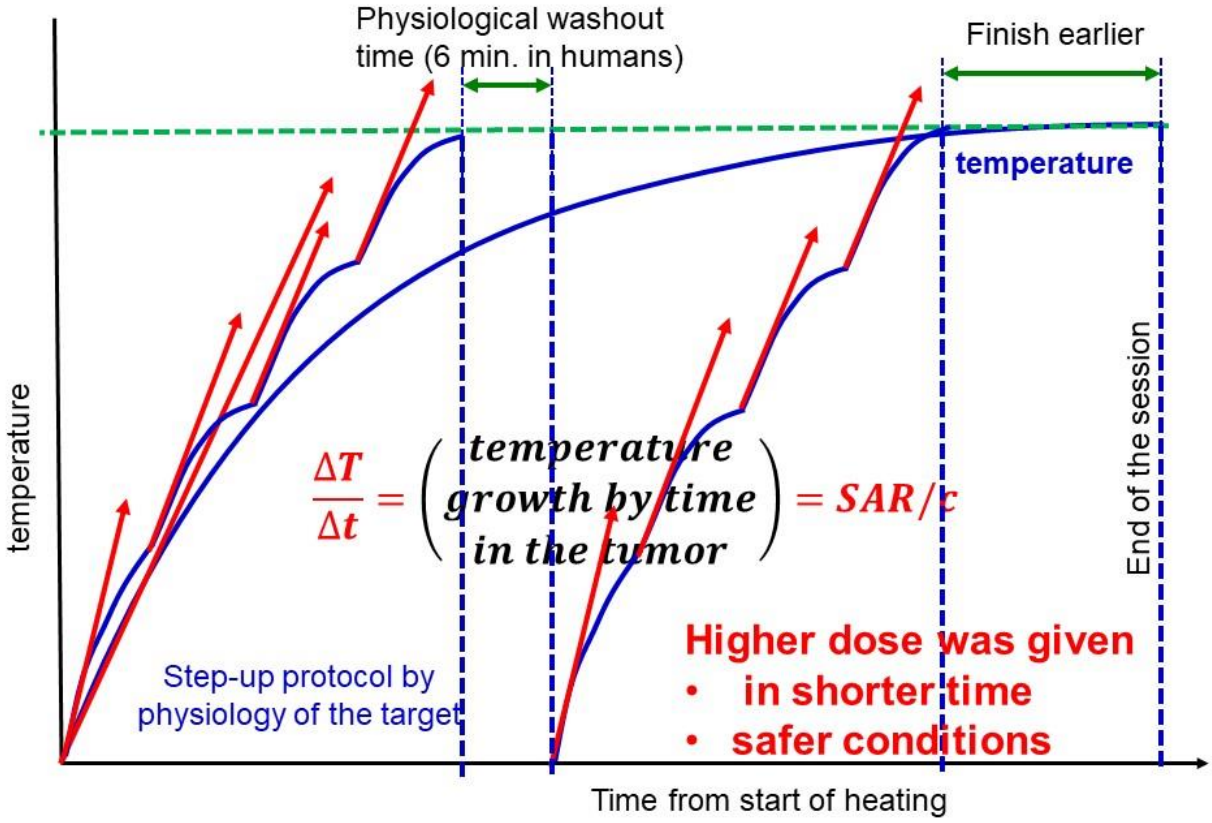
Our tasks:

1. Keep the time-dependent part (SAR) large
2. Keep the environmental and physiology part small
3. Measure the dose as absorbed energy:

measured in Gy (J/kg)
(like in ionizing radiation)

$$AE = \sum_{\substack{\{i\} \\ steady-state}} c\frac{\Delta T}{\Delta t}$$

Challenge of the dose of oncological hyperthermia



General challenge

How to raise the prestige of hyperthermia again to the top of oncotherapies, like it was at its start?

Challenge of definition of oncological hyperthermia

No clear definition of oncological hyperthermia is declared

Present convention on definition

Oncology encyclopaedia – hyperthermia is therapeutic heat

Medicine.net – overheating of the body

National Cancer Institute – body tissue is exposed to high temperatures (up to 45°C)

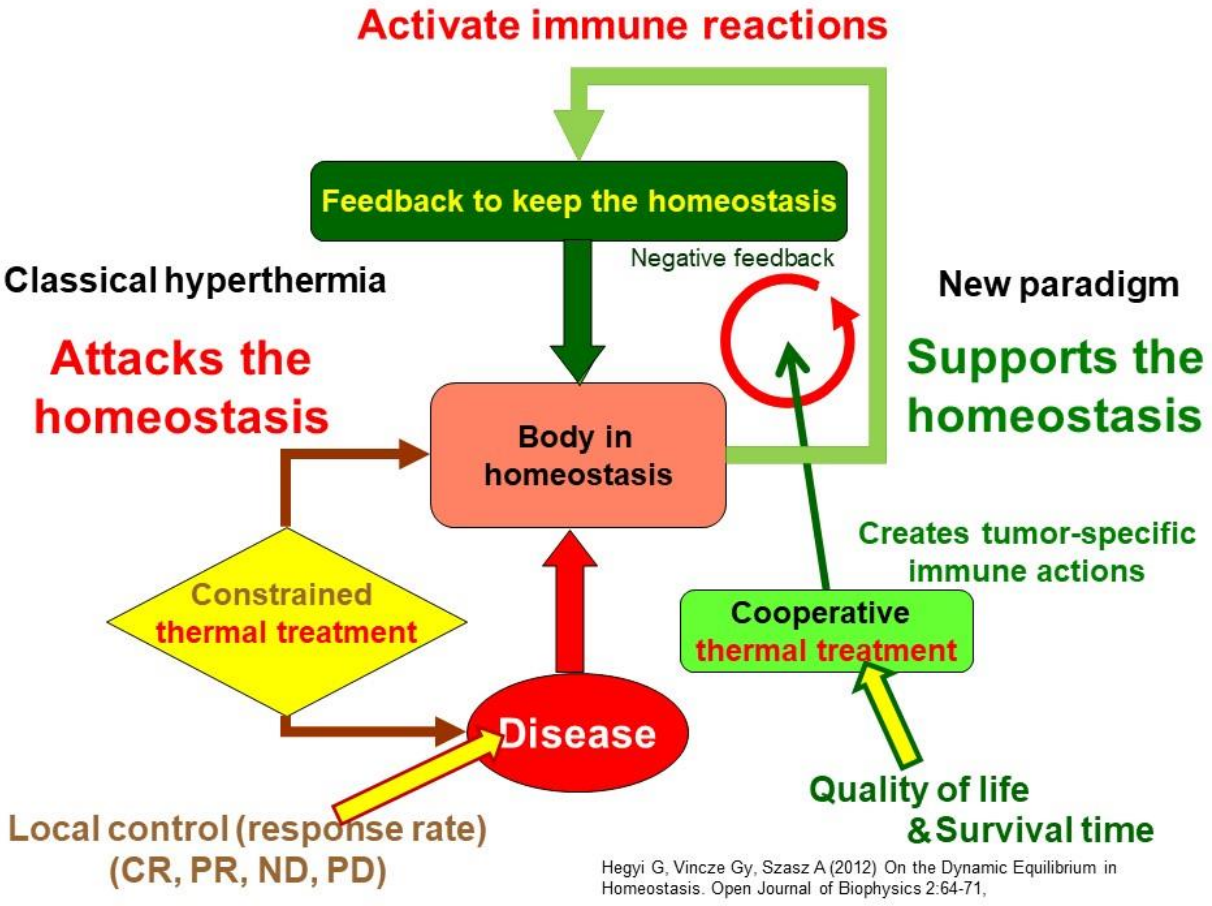
Wikipedia – body tissue is exposed to slightly higher temperatures to damage and kill cancer cells or to make cancer cells more sensitive to the effects of radiation and certain anti-cancer drugs

Medical Dictionary – much higher than normal body temperature induced therapeutically or iatrogenically

The Am.Canc.Soc. – body is exposed to higher than normal temperatures, changes take place inside the cells

Oncothermia definition

Oncological hyperthermia is a method to kill **malignant cells** by **heat-inducing absorbed** energy and/or **sensitize** certain complementary therapies



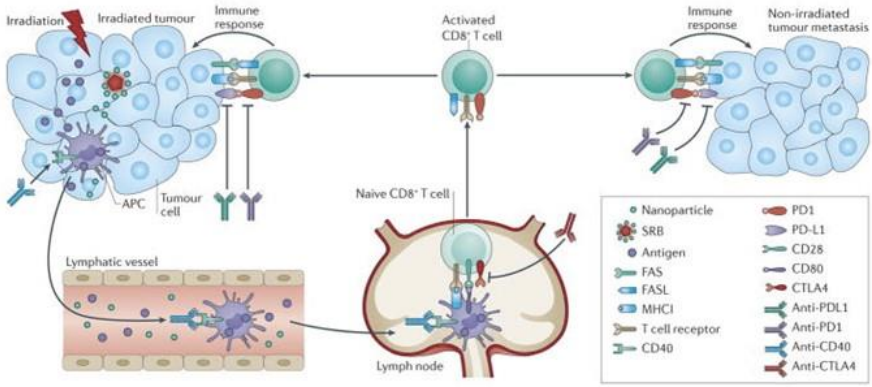
Hegyi G, Vincze Gy, Szasz A (2012) On the Dynamic Equilibrium in Homeostasis. Open Journal of Biophysics 2:64-71,

Local absorbance, systemic effects

- DAMP (damage associated molecular pattern)
  - Heat-shock proteins

- ICD (immunogenic cell death)
  - Apoptosis
  - Dendritic cells, T cell response

- Abscopal effect (mediated by the immune system)



Ngwa, Nature Rev Cancer 2018

Clinics in practice

- INDICATION
  - NOT only locally advanced but palliative as well by curative intent
  - Treatment decision in hand of certified and accredited physician and tumor board
  - According to local law and ethics

- PERSONEL
  - physician on duty
  - Nurses
  - Planning (by the decision of the tumor board)
  - others upon need

Practical measures - endpoints

- DEMAND
  - localization dependent applicator,
  - starting and ending energy,
  - intervals

Survival time and quality of life in the same time

- Disease-free survival
- Progression-free survival
- Time to progression

- Overall survival and quality of life

Treatment indications

- **Any solid tumor, primer, metastatic or recurrent**
- **Patient is treatable with any TNM and stage**
- **Combined treatment:**
  - Applied to **increase treatment efficacy**
  - and for the **resensitisation of tumours**
  - to standard treatment protocols.
- **Complementary applications:**
  - Curative goal:
    - Increase the efficacy of the applied concomitant treatment
    - Resentisize the tumor even in refractory state.
  - Palliative goal:
    - Pain reduction
    - Increase the quality of life
- **Monotherapy:**

Only when other conventional therapy is non-applicable, (organ failure, labor-results, refractory state, no result expected by conventional therapies, psycho-resistance, other reasons not considering conventional therapies).

Basic treatment conditions

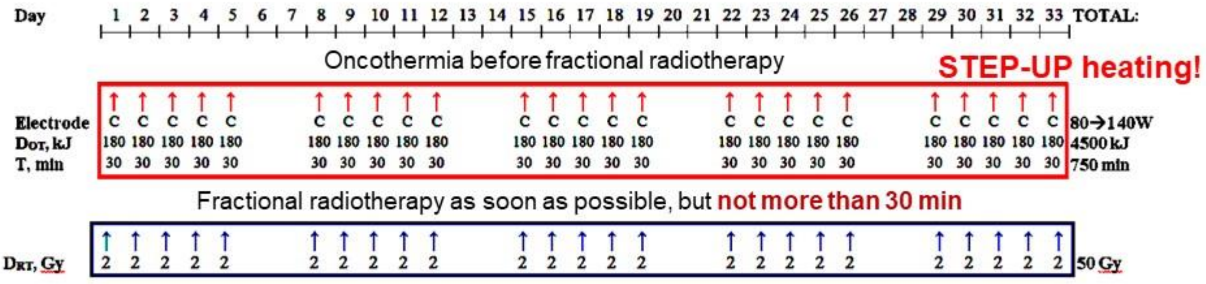
- **First conventional therapy must be applied if possible**
- **Personal adjustment**
- **No daily hyperthermia treatment, except potentiation**
- **Oncothermia is complementary therapy with well-known others**
- **Step-up heating is necessary for combined therapies. (The rate of growth is decided by the tolerance of patients.)**
- **Step-down heating is necessary for monotherapy. (The rate of decrease decided by the tolerance of the patient.)**
- **Modulation adaptation is necessary for sensitive (brain) treatments.**
- **Relaxed conditions have to be formed around the patient**
- **Not too long, not too short effective treatment time (45-90 mins)**
- **Give information to the patient and relatives about the dose (energy) only at the end of the treatment. No temperature or other parameters are open for them during the session.**

Oncothermia synergy with radio-therapies

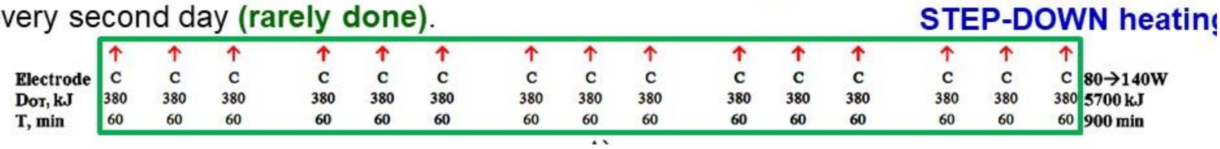
Oncothermia has to be carefully fitted to the blood-perfusion and neo-vascularization of the actually treated tumor. It could be applied before or after the radio treatment.

Oncothermia is applied as potentiation before radiotherapy when the blood-flow is not satisfactory. Low dose (also fraction) of **oncothermia is given before** every radiotherapy fractions.

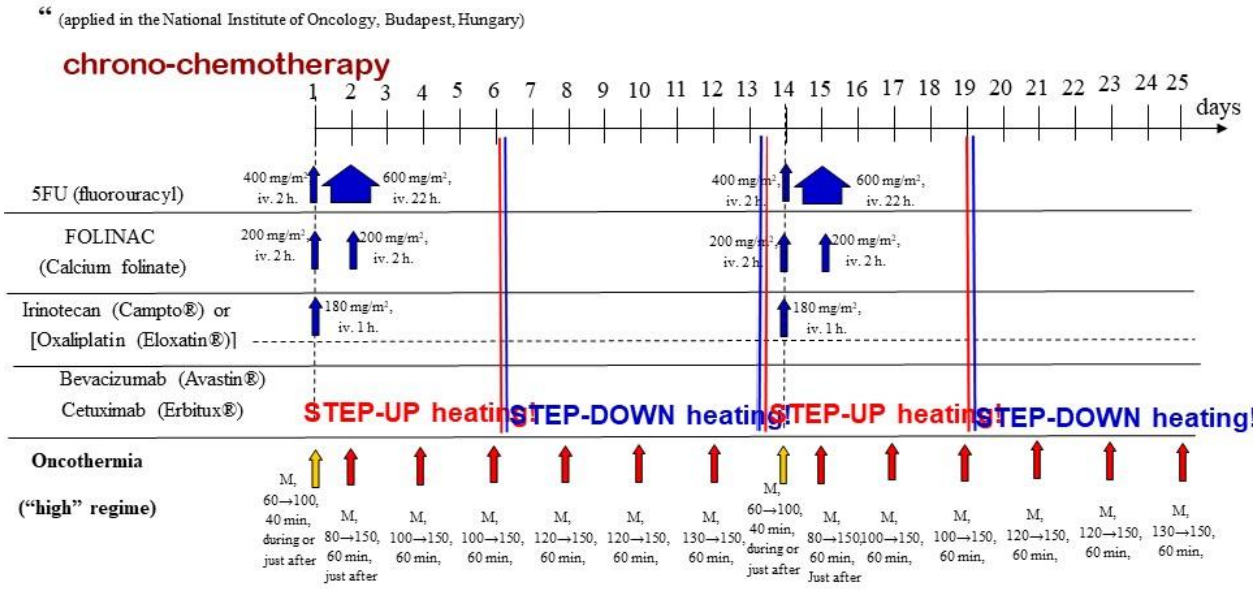
Example (fractional radiotherapy):



After the fractional potentiation oncothermia **can be applied** in its complete protocol every second day **(rarely done)**.



Chrono-chemotherapy (e.g. DeGramont protocol)



Contraindications

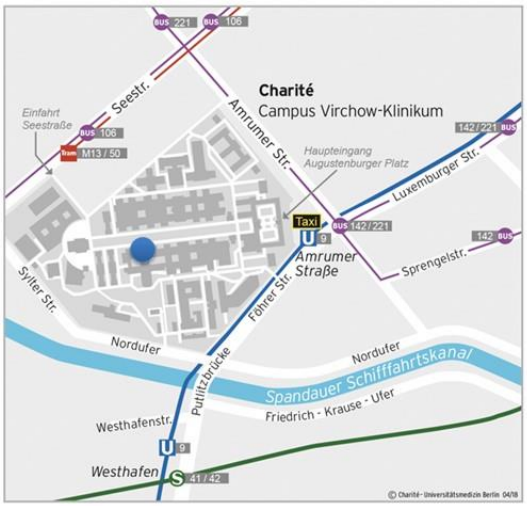
- **Pacemakers / field sensitive devices**
  (depends on the actual ESM standard and the position of the treatment)
- **Patients who are unable to communicate the complains**
- **Conditions, e.g. epilepsy, sensitive to electromagnetic fields**
- **Patient has immune-suppression due to organ-transplant**
- **When the patient is not able to form the position for the treatment**
- **DON'T treat pregnant women.**

Precautions BE CAREFUL!

- The applicator should not be applied over open wounds.
- Tumors close to large metallic implants should be treated with caution.
- Treatment is prohibited through any implantation by plastic surgery (like breast implant)
- Patients with acute systemic or localised **infections or inflammatory** processes.
- **Elderly** patients have a higher pain under the heavy applicator.
- Areas in which there is a large amount of **fat** must be closely monitored for surface burns and subcutaneous fibrosis.
- Thick **hair** in the treated area (hair, pubic hair, etc.).
- **Fluid** may affect the energy distribution (e.g. urine or ascites).
- The applicator has to be fixed **correctly**
- When the applicator is over a volume having **low blood-flow**.

OPEN DISCUSSION AND CONTRIBUTION

szaszam@gmail.com



THANK YOU