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

Marcell A. Szasz¹, Gyongyver Szentmartoni¹, Peter Arkosy², Tibor Csoszi³, Zsofia Dankovics⁴, Gabor Rubovszky⁵, Andras Csejtei⁴, Gabor Pajkos⁶, Bela Piko⁷, Erika Borbenyi¹, Magdolina Dank¹

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, Bacs-Kiskun County Teaching Hospital, Kecskemét, Hungary
⁷ Memorial Oncology Center, Pándy Kálmán County Hospital, Gyula, Hungary

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(1) Cancer Center, Semmelweis University, Budapest, Hungary
(2) Department of Oncology, Oncotherapy and Rehabilitation, Kenézy Gyula University Hospital, Debrecen, Hungary
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(4) Department of Oncoradiology, Markusovszky Teaching Hospital, Szombathely, Hungary
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(7) Memorial Oncology Center, Pándy Kálmán County Hospital, Gyula, Hungary

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. Marcell¹, Szentmártoni Gyöngyvér¹, Árkosy Péter², Csőszi Tibor³, Dankovics Zsófia⁴, Rubovszky Gábor⁵, Csejtei András⁴, Pajkos Gábor⁶, Pikó Béla⁷, Borbényi Erika¹, Dank Magdolna¹

(1) Cancer Center, Semmelweis University, Budapest, Hungary
(2) Department of Oncology, Oncotherapy and Rehabilitation, Kenézy Gyula University Hospital, Debrecen, Hungary
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(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.
- Consultant, patent pending – CiC Therapeutics Ltd.
- Developer – Treat4Life AB, Malmö, Sweden
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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 Genitourinary Pathology
- Member of Board of Curators, International Academy of Pathology, Hungarian Division
Hippocrates

Hyperthermia development

**Historical heating methods**
- No focusing
- Based on physiology
- Ne control, "beliefs"
- Household "wisdom"

**Whole-body line**
- Steam-chamber
- Infrared (IR)
- Water-immersion
- Extracorporeal (incl. intraperitoneal)

**RF & microwave**
- Classic electromagnetic heating
  - Bulky targets
  - Difficult focusing
  - High incident energy
  - Low heating efficacy

**Modern electromagnetic heating**
- Macro/Micro targets
- Proper focusing
- Small incident energy
- High heating efficacy

**Invasive heating line**
- Photodynamic therapy (PDT)
- Electro-chemo therapy
- Lyposome PDT
- HIFU technique
- Conventional US heating
- PDT-line
- Ultrasound heating line

**Nano-technologies**
- Nano targets
- Accurate focusing
- Extra small incident energy
- Extra high heating efficacy

**Immune-technologies**
- In situ immune activation
- Adaptive immune stimulation
- Bystander & adhesive effects
- Systemic, natural effects

**Common promise: Tumor-vaccination**

**Charged paradigm:**
- Do not destroy aggressively!
- Help the homeostatic control to achieve the goal!
Local/regional hyperthermia methods

**Loco-regional hyperthermia**
- Heats the tumor-mass as homogeneously as possible

**Isothermal local heating**
- Heats the tumor non-isothermally
- Basic technical solutions:
  - Radiative (antenna-array matching)
  - Capacitive (plane-wave matching)

**Nanoparticle heating**
- Basic technical solutions selects by nano-, micro- or macroparticles, like gold-nanoparticles, magnetic suspensions, seeds, rods, etc.

**Modulated electro-hyperthermia (meHT, oncothermia)**
- Basic technical solutions selects by biophysical differences of malignant cells; heats the tumor-cells as selectively as possible

**Intended role of hyperthermia in refractory cancers**

- Observable tumor detection
- PR
- CR
- Resistant for the given treatment
- Possibly curative (no evidence of disease)

Hyperthermia acts to modify the resistance

It makes the next treatment possible

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*Oncothermia Journal, Volume 24, October 2018*
Hyperthermia has controversies between the local response and control overall survival

Local control and survival time are not in harmony

Non-small-cell lung cancer

Initial site of disease progression after treatment

<table>
<thead>
<tr>
<th></th>
<th>RT</th>
<th>RT + HT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 40)</td>
<td>(n = 40)</td>
<td></td>
</tr>
<tr>
<td>No recurrence</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Primary tumor and/or regional lymph nodes</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Distant metastasis</td>
<td>2</td>
<td>10</td>
<td>0.07</td>
</tr>
<tr>
<td>Both locoregional and distant*</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Unknown/missing</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
</tbody>
</table>

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

Break-point: the pelvic tumors – Lancet publication

Overall survival

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Radiotherapy plus</th>
<th>Odds ratio</th>
<th>Mean decrease in odds (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectal</td>
<td>52/72</td>
<td>3.6</td>
<td>23.2</td>
</tr>
<tr>
<td>Cervical</td>
<td>26/58</td>
<td>-10.3</td>
<td>15.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>37/52</td>
<td>-4.0</td>
<td>18.2</td>
</tr>
<tr>
<td>Total</td>
<td>115/182</td>
<td>-10.6</td>
<td>56.7</td>
</tr>
</tbody>
</table>

*Radiotherapy plus hyperthermia better*

IMPROVEMENT is necessary which is the direction of immuno-oncology

Challenge in oncology – malignancy is systemic

Goal: treat systemically

TASKS ↓

- Destroy the tumor effectively (local control)
- Block the invasion & dissemination
- Survival time and quality of life
- Eliminate the metastases
- Malignancy isn’t local (but starts locally, early discovery necessary)

Our goal: produce abscopal effect with mEHT like in case of ionizing radiation
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.
Dosing, safety and reproducibility

Conventional tumor-therapies
- **Concept** is to apply the largest tolerable dose [mg/m²], [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 - CEM₄₃⁰⁰Cₜₓ [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!

Challenge of dose of hyperthermia

**CEM₄₃⁰⁰Cₜₓ Calibrated in vitro**

\[
CEM₄₃⁰⁰Cₜₓ = \sum_{\text{time}} t_i R^{(43°C-T_x)}
\]

Fits to the clinical data


**TRISE** = \[
\sum_{\text{time}} t_i \frac{(T_{50} - 37°C)}{\text{time of rise}}
\]

The correct dose

\[
Absorbed\ energy = \sum_{\text{time}} t_i (SAR(t))
\]

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:

\[ AE = \sum_{(l)} c \frac{\Delta T}{\Delta t} \]

(measured in Gy (J/kg)

Challenge of the dose of oncological hyperthermia

Physiological washout time (6 min. in humans)

Finish earlier

Higher dose was given
- in shorter time
- safer conditions

Step-up protocol by physiology of the target
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

Activate immune reactions

Classical hyperthermia

Attacks the homeostasis

Constrained thermal treatment

Local control (response rate) (CR, PR, ND, PD)

Feedback to keep the homeostasis

Negative feedback

New paradigm

Supports the homeostasis

Creates tumor-specific immune actions

Cooperative thermal treatment

Quality of life & Survival time

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)

![Diagram of immune response](image)

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
    - Resensitize 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):**

![Diagram showing oncothermia before fractional radiotherapy]

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