Mild Hyperthermia in Cancer Therapy

Gerard C. van Rhoon
g.c.vanrhoon@erasmusmc.nl
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1. Employment or Leadership Position
   - Erasmus MC Cancer Institute, Rotterdam

2. Advisory Role or Expert Testimony
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   - President of the European Society for Hyperthermic Oncology

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Definitions for heating tissue

**Hyperthermia (mild):**
Mild Temperatures 40-44°C
Duration: 60-90 min
Multiple (4-6) fraction

**Thermal Ablation:**
High Temperatures >65 °C
Short duration: 5-15 min
Single fraction

Direct Cell Kill
Hyperthermia Works!!

Biology: hyperthermia is one of the strongest sensitizers for radiotherapy and chemotherapy
Hyperthermia Amplifies Radiation and Drugs

**Body temperature**

- 43 °C: Cellular cytotoxicity enhanced at low pH and in S-phase
- 42 °C: Radiation: DNA damage repair blocked
- 41 °C: Sensitization radiation and drug
- 40 °C: Increased blood perfusion
- 39 °C
- 38 °C
- 37 °C
- 36 °C

- Heat alone: Direct cell kill
- RT: more cell kill
- RT & CT more effective
- Better oxygenation
  Higher drug concentration
  → RT & CT more effective
Sequential application of Hyperthermia to Radiotherapy: Objective enhance local controle

Impact of sequence & time interval of radiotherapy and hyperthermia on sensitization effect
Hyperthermia Works!!

Biology: hyperthermia is one of the strongest sensitizers for radiotherapy and chemotherapy

Has been shown beneficial for patients with
• advanced tumors
• recurrent tumors in previously irradiated areas
• 24 positive randomized trails RT or CT ± HT
• 10 inconclusive randomized trails on RT or CT ± HT (many of those criticized for low quality of heating)
**Inoperable melanoma**

J. Overgaard et al.  
*Lancet* 1995; 540-3

- Radiation plus hyperthermia: 46%
- Radiation alone: 28% (p=0.0058)

Time since treatment (months)

**Local advanced cervical cancer**

Van der Zee et al. *Lancet* 2000; 355:1119

Cervix 3-yrs overall survival

- 27% → 51%

**Localised high-risk soft-tissue sarcoma**

Issels et al., *Lancet Oncology* 2010, 561-70

- EIA + RHT
  - Hazard ratio = 0.70
  - CI = [0.54 - 0.92]
  - P = 0.011

- EIA
  - No. at Risk:
    - EIA: 169
    - EIA+RHT: 172
Hyperthermia Works!!

Biology: hyperthermia is one of the strongest sensitizers for radiotherapy and chemotherapy

Has been shown beneficial for patients with

- advanced tumors
- recurrent tumors in previously irradiated areas
- 24 positive randomized trails RT or CT ± HT
- 10 inconclusive randomized trails on RT or CT ± HT (many of those criticized for low quality of heating)

- In most trials: hyperthermia does not enhance late toxicity
- Clinical experience that it can be applied to frail elderly people (who are excluded for surgery or intolerant for chemotherapy)
Most common techniques to induce hyperthermia use electromagnetic energy:

- Ultrasound
- Infrared
- Laser
- Magnetic nano-particles
Hyperthermie systemen Erasmus MC

Superficial Hyperthermia:
tumors up to 4 cm depth.

Loco regional hyperthermia:
Tumor locations in Head and Neck region

Regional deep hyperthermia:
Tumor locations at depths > 4 cm, i.e. Pelvis, thorax.

Focus ~ 4 cm

Focus ~ 10-14 cm

Plane Wave penetration

Power Deposition

Depth in Tissue (cm)
Energy steering to obtain optimal heating

Focused energy deposition at depth: circumferential EM field, constructive interference.

Main challenges
- Measure temperature at depth
- Target energy to the tumor
- Prevent acute thermal toxicity
- Solutions have been implemented during last decennium.
Thermal dose effect relationships indicate the need to maximize tumor temperature.

Of 444 patients, 40% showed a positive correlation between T50 and applied energy.

Franckena et al., 2009 European J Cancer

Fatehi et al., 2007, Int. J. of Hyperthermia
Hyperthermia Treatment Planning (HTP): an essential part for optimal treatment delivery

**Workflow**

1. Image Data (CT/MR)
2. Segmentation
3. Treatment Setup Model
4. EM Simulation & Optimization
5. Thermal Simulation & Optimization

SAR

T
VEDO is an online HTP-GUI to guide energy steering during actual treatment delivery
VEDO is an online HTP-GUI to guide energy steering during actual treatment delivery.
Clinical experience from hyperthermia

- The human body has an efficient physiological defense mechanism to limit temperature increase under thermal stress (despite a high RF-power input it is hard to increase the average temperature)

Variable thermal regulation response within a patient after a deep hyperthermia treatment for 90 minutes at 40-42 °C
Clinical experience from hyperthermia

- The human body has an efficient physiological defense mechanism to limit temperature increase under thermal stress (despite a high RF-power input it is hard to increase the average temperature)
- High temperatures at the skin are sensed as burning pain
- High temperatures at depth are sensed as pressure pain, urging, period pain, etc.
- Responding to pain complaints can adequately confine thermal toxicity
- Areas with reduced sensitivity have a high risk for burns (skars have also a reduced perfusion making them extra vulnerable to thermal damage)
Loco-regional deep heating
Typical values

RF-power and temperature data analysis of 444 patients with primary cervical cancer
Fatehi et al., 2007, Int. J. of Hyperthermia

Whole body SAR for therapeutic temperatures: 9-10 (± 2) W/kg
Max. Forward power applied: 768-934 (± 185) W

More power is needed for heavier patients though average temperature is lower.

Three weight groups
Acute hyperthermia toxicity to subcutaneous tissue

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms</td>
<td>267</td>
</tr>
<tr>
<td>1</td>
<td>Symptoms lasting less than 3 days</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Symptoms lasting 3-14 days</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>Symptoms lasting 3-14 days, or causing a delay or interruption of treatment</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Symptoms requiring surgery</td>
<td>1</td>
</tr>
</tbody>
</table>

Patients with toxicity had:

- thicker (0.7 cm) dorsal subcutaneous fat
- were larger in anterior-posterior (0.9 cm) and lateral (1.5 cm) directions.

After adjustment for these factors, only the average intraluminal TRISE increase correlated with toxicity probability (TRISE 1.7 ºC higher, p = 0.010)

Five patients developed grade 3 neurotoxicity
Location complaints matches with predicted location hot-spot

Pain!
Location complaints matches with predicted location hot-spot

\[ \text{Pain!} \]

Closest HS in model

\[ \text{~90\% of complaints have a predicted hotspot in the same region as the actual complaint} \]
No clear relation between max SAR values (10ml) during treatment and complaints

- No complaints
- Complaints
- Toxicity
Exposure of the brain during deep microwave hyperthermia in the Head and Neck region has been accessed for 16 patients


*f.adibzadeh@erasmusmc.nl
Hyperthermia Unit, Departement of Radiation Oncology,
Erasmus MC- Cancer Center, Rotterdam, The Netherlands
HT treatment planning
overview

CT scan
- segmentation

Patient model

Applicator model

EM simulation & optimization

T simulation & optimization

~200 slices

Purposes: decision making, optimization, analyses
HT treatment planning overview

- CT scan
  - segmentation
- Patient model
- Applicator model
- EM simulation & optimization
  - T simulation & optimization

Purposes: decision making, optimization
Induced psSAR in the brain: Influence of brain tissue segmentation

- Segmentation details:

*Brain exposure decreases in detailed model compared to homogeneous model by 21.5%*
Induced psSAR in the brain (10 g)

Basic restriction was exceeded up to 26 times.
HT-related acute health effect

- Common Toxicity Criteria (CTC) is a standardized classification of adverse effects used in cancer therapy evaluation, developed by National Cancer Institute.

**CTC Grades definition:**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mild adverse event; asymptomatic or mild symptoms; Clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>2</td>
<td>Moderate adverse event; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>3</td>
<td>Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>5</td>
<td>Death related to adverse event</td>
</tr>
</tbody>
</table>

*Activities of Daily Living (ADL)*

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*
Observed acute toxicity for the 16 selected patients

Table 3. Observed acute toxicity for the selected HT patients. Note that the number of incidents were counted, i.e. not just one incident per patient, so every treatment session always led to one score.

<table>
<thead>
<tr>
<th></th>
<th>CTC-grade</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr of patients</td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Nr of HT</td>
<td>74</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTC-grade</td>
<td>0</td>
<td>74</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>CTC-grade</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-grade</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>CTC-grade</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-grade</td>
<td>4</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CTC-grade</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Prs motory</td>
<td>74</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Prs sensory</td>
<td>71</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Headache</td>
<td>73</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Pain in Eye</td>
<td>73</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Dizziness</td>
<td>73</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Nausea*</td>
<td>71</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CNS-related</td>
<td>Vomiting*</td>
<td>72</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcut burns</td>
<td>Subcut skin</td>
<td>70</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcut burns</td>
<td>Subcut fat</td>
<td>72</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcut burns</td>
<td>Subcut muscle</td>
<td>72</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subcut burns</td>
<td>Subcut bone</td>
<td>69</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* Nausea and vomiting may stem from reactions in the CNS but also from many other causes. In this study they are considered as CNS-related acute effects.
Evaluation of acute adverse effects from prolonged exposure to deep RF head and neck hyperthermia reveals that although the brain was exposed up to 14 times the common basic restriction on psSAR10g, there is no indication of any induced serious neurological adverse effect. This study provides initial data that enables to determine the basic restrictions based on the functional change that is to be prevented and the level of safety to ensure prevention.
Temperature simulations in hyperthermia treatment planning of the head and neck region: Rigorous optimization of tissue properties

Verhaart R, Strahlenther Onkol 2014

Perfusion ($\omega$) and thermal conductivity ($k$) were simultaneously optimized for muscle, fat, and tumor by minimizing the cumulative error between measured and simulated temperature points at steady state Temperature (Tss) in a group of 17 patients.
Summary

Hyperthermia is valuable adjuvant to radiotherapy and chemotherapy in the treatment of cancer.

Toxicity associated with hyperthermia is mainly acute and consists of thermal burns, mostly of grade 1-2.

The high energy exposure levels of EMF for hyperthermia can be informative for potential assessment of threshold levels for EMF effects in critical tissues, such as brain, as this is one of the few occasions where human tissue is exposed above the ICNIRP guidelines. First analysis of such human data have not shown adverse, acute effects at levels 14 times of the common basic restriction guideline of ICNIRP.
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www.erasusmc.nl/radiotherapie

Members of the Rotterdam Hyperthermia group

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