The place and role of clinical hyperthermia in oncological thermotherapy: let’s define what we are talking about
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Sergey V. Roussakov
Galenic Research Institute

34th Annual Conference of the International Clinical Hyperthermia Society
Pesaro, Italy
22nd September 2016

<table>
<thead>
<tr>
<th>T, °C</th>
<th>Type of Thermal Therapy</th>
<th>Type of Tumor Damage</th>
<th>Effect to Cells and Tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>Thermal Ablation (TA)</td>
<td>Acute Damage (&lt;15')</td>
<td>Carbonization</td>
</tr>
<tr>
<td>85</td>
<td>High-Intensity Thermal Therapy (HITT)</td>
<td>Sub-Acute Damage (15-90')</td>
<td>Direct Cell Damage (Protein Denaturation)</td>
</tr>
<tr>
<td>65</td>
<td>Oncological Hyperthermia (OHT)</td>
<td>Delayed Damage (days)</td>
<td>Indirect Cell Damage</td>
</tr>
<tr>
<td>50</td>
<td>Febrile Therapy (Mild HT)</td>
<td>No Damage or Tumor Growth Stimulation</td>
<td>Therapeutic Hyperthermia</td>
</tr>
<tr>
<td>37</td>
<td>Subfebrile Range</td>
<td>No</td>
<td>Improvement of Tissue Trophism</td>
</tr>
<tr>
<td></td>
<td>Normothermia</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

- Oncological Hyperthermia (OHT)
- Critical OHT
- Extreme OHT
- Moderate OHT
- Febrile Therapy (Mild HT)
THE PROBLEM OF HYPERThERMIA:
IT DIES
Radiotherapy with or without hyperthermia in the treatment of superficial localized breast cancer: results from five randomized controlled trials

International Collaborative Hyperthermia Group (Verhulst et al., 1996)

- The overall CR rate for RT alone was 41% and for combined treatment arm was 59%, giving an odds ratio of 2.3.
- Not all trials demonstrated an advantage for the combined treatment.
- The implication of these encouraging results is that hyperthermia appears to have an important role in the clinical management of this disease, and there should be no doubt that further studies of the use of hyperthermia are warranted.

Hyperthermia at cervical cancer: the results of three randomized trials.

Hyperthermia and radiotherapy (RT) show promise in the treatment of cervical cancer.
Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)

To our knowledge, this is the first randomised phase 3 trial to show that regional hyperthermia increases the benefit of chemotherapy. Adding regional hyperthermia to chemotherapy is a new effective treatment strategy for patients with high-risk STS, including STS with an abdominal or retroperitoneal location.
Additive effect of cisplatin plus hyperthermia

Hypothermic potentiation of cis-diaminedichloroplatinum (II) cytotoxicity in Chinese hamster ovary cells resistant to the drug

Wallner KE, DeGregorio MW, Li SC

Cancer Res. 1986

The cytotoxic effect of cis-diaminedichloroplatinum (II) on cultured Chinese hamster ovary cells at elevated temperatures: Arrhenius plot analysis

Ibranski M, Kohn I, Mazurko H, Genauer I F

Int J Cancer 1995

Enhancement of cisplatin sensitivity and platinum uptake by 40 degrees C hyperthermia in resistant cells

Ohtsuka T, Saito H, Tanaka N, Matsumoto H, Sugimoto C, Saito T, Hayashi S, Kano E

Cancer Lett. 1997

Cisplatin sensitization by concurrent mild hyperthermia in parental and mutant cell lines deficient in homologous recombination and non-homologous end joining repair

Raghoor G P, Li IF, Yang DP, LefBlanc JM

Oncol Rep 2000

European Adjuvant Trial (HEAT)

Randomized phase III clinical trial

Number: 2008-004802-14

Adjuvant Pancreatic Cancer

Staging

Surgical Resection

N+ R1 or L (N, MW)

Randomization

Start 4-8 weeks postop

Follow up

Primary endpoint DFS

DFS: 10 months

+35%
Manufacturing Hyperthermia “Positive” Results: the inner kitchen on the example of HLAI trial

Valle et al., 2010
Stage III-IV no Surgery

- GEM + CEM INCR Cis
- MST 11.7
- +45%
- PFS 8.0
- +60%

HEAT Trial, 2011
Stage I-II + Surgery

- GEM + CEM INCR Cis+HT
- MST 19.0
- +35%
- DFS 14.0

The world after hyperthermia
Thank you for attention

Huilgol trial

Figure 2.1: Cancer of the Head and Neck: Relative Survival Rate (%) by Primary Site, Ages 20+, 12 SEER Areas, 1988-2001
Huilgol trial

“The 5-year relative survival rates were 74.5% for the lip, 42.7% for the anterior tongue, 25.5% for the posterior tongue, 45.1% for the mouth, 29.7% for the oropharynx, 38.7% for the nasopharynx, 29.1% for the hypopharynx, and 41.2% for the larynx.” (Mumbai: 1987-1991).


“The overall 5-year survival rate was in the range of 20-43% for oral cancer, 8-25% for pharyngeal cancers and 25-62% for laryngeal cancer.” (Mumbai, 1987-1989; 25% of stage IV).


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Estimation of general toxicity

<table>
<thead>
<tr>
<th>Control group</th>
<th>Hyperthermia group</th>
</tr>
</thead>
<tbody>
<tr>
<td>General toxicity</td>
<td>+18%</td>
</tr>
<tr>
<td>Complications of thermometry</td>
<td>+4%</td>
</tr>
<tr>
<td>Burns</td>
<td>+18%</td>
</tr>
<tr>
<td>Pain</td>
<td>+45%</td>
</tr>
<tr>
<td>Tissue necrosis</td>
<td>+7%</td>
</tr>
<tr>
<td>Bolus pressure</td>
<td>+31%</td>
</tr>
<tr>
<td>Other HT complications</td>
<td>+23%</td>
</tr>
</tbody>
</table>

TOTAL INCREASE: x 3 times +142%
Estimation of severe toxicity

Control group | Hyperthermia group
---|---
General toxicity | +0.6% |  
Complications of thermometry | +1.2% |  
Burns | +0.3% |  
Pain |  +4.3% |  
Tissue necrosis | +2.5% |  
Bolus pressure | +4.9% |  
Other complications of HT | +8.6% |  
TOTAL INCREASE |  +24% | x 20 times

Prof. Pang trial

<table>
<thead>
<tr>
<th>Objective response rate %</th>
<th>0%</th>
<th>10%</th>
<th>20%</th>
<th>30%</th>
<th>40%</th>
<th>50%</th>
<th>60%</th>
<th>70%</th>
<th>80%</th>
<th>90%</th>
<th>100%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current trial</td>
<td>78%</td>
<td>64%</td>
<td>22%</td>
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<tr>
<td>Prior art (averaged)</td>
<td>75%</td>
<td>48%</td>
<td>55%</td>
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<tr>
<td>Yin J (2007)*</td>
<td>65%</td>
<td>46%</td>
<td>42%</td>
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<td></td>
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<tr>
<td>Wang H (2015)*</td>
<td>71%</td>
<td>44%</td>
<td>42%</td>
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</tr>
<tr>
<td>Li Z (2010)</td>
<td>73%</td>
<td>46%</td>
<td>42%</td>
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</tr>
<tr>
<td>Yu X (2007)</td>
<td>77%</td>
<td>46%</td>
<td>42%</td>
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</tbody>
</table>

[Study group | Control group | Relative increase]
Neo adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study (Issels et al., 2010)

Where is hyperthermia?

International Congress of Hyperthermic Oncology

Thermal Therapy: Hot Science, Cool Medicine and All That Jazz
New Orleans, April 11-15, 2016