Pharmacoeconomic study of oncothermia (modulated electro-hyperthermia) in the treatment of lung cancer
Sergey V. Roussakow*
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Pre-requisites of the study

- Lung cancer is a fatal disease with one of the least 5-year survivals among all cancers (14-17% in USA and 12-14% in EU).
- In Russia (2012), share of lung cancer is 18.7% in men and 3.6% in women, and it is the first reason of cancer mortality in Russia (17.3% of all cancer deaths).
- Current treatments show low efficacy and can’t change the trend of high mortality.
- Thus, study of possibilities to improve the prognosis in lung cancer is of outstanding significance in oncology.
Oncothermia solution

- Oncothermia (local, deep, radiofrequency, modulated electro-hyperthermia) is one of the promising methods of lung cancer treatment.
- This is a new technology based on the local effect of high-frequency electromagnetic field (13.56 MHz), modulated by fractal noise in a range 0.5 kHz, performed by capacitive coupling and functionally asymmetric electrodes.
- The relevance of the present study is determined by the possibility to improve the quality of treatment of lung cancer while reducing health care costs.

Methods

- Retrospective pharmacoeconomical observational study
- Systematic review of oncothermia trials on lung cancer treatment
- Cost-Utility Analysis
- Budget Impact Analysis
Structure of Study

- **Context**
  - The relevance of the problem, information on intervention and methods of comparison

- **Clinical estimation**
  - Systematic review of clinical evidences
  - New intervention is more effective (superiority)
  - New intervention is not less effective (noninferiority)

- **Translation**
  - Adaptation of the clinical results for economic analysis

- **Economic evaluation**
  - Cost-Utility Analysis or Cost-Effectiveness Analysis
  - Cost Minimization Analysis

- **Other analyses**
  - Budget Impact Analysis
  - Cost-Benefit Analysis

Systematic review

- In accordance with PRISMA and CHSRI recommendations.

- Databases:
  - US NIH (http://clinicaltrials.gov)
  - EudraCT (https://www.clinicaltrialregister.eu)
  - UMIN (http://act.nihr.ac.jp)/
  - Cochrane Library (http://www.cochranelibrary.com/)
  - BMC (http://www.biomedcentral.com/)
  - Wiley Online Library (http://onlinelibrary.wiley.com/)

- Other sources:
  - Oncothermia Journal (http://www.oncothermia-journal.com/journal/)
  - Conference Papers at ICHS, DGH, ESHO, STM, JSHO
Systematic Review: Endpoints

- Primary Endpoints:
  - Overall Survival
- Secondary Endpoint:
  - Health-related Quality of Life (for QALY calculation)

Search Flowchart

- Primary search result: 11 studies
- Excluded (duplicate): 1 study
- Excluded (no survival data): 5 studies
- Excluded (only 1-year survival): 1 study
- Included into Systematic Review: 4 studies
### Systematic Review: Accepted Studies

<table>
<thead>
<tr>
<th>Name of Study</th>
<th>Country</th>
<th>Type</th>
<th>NOP</th>
<th>LOE</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting</td>
<td>Canada</td>
<td>48</td>
<td>2c</td>
<td></td>
<td>Parmar G. A retrospective assessment of loco-regional hyperthermia and fever-range whole body hyperthermia in an integrative oncology setting. XXXII Annual Conference of the International Clinical Hyperthermia Society (ICHS), 10-12 Jul 2015, Nidda, Germany.</td>
</tr>
<tr>
<td>TOTAL:</td>
<td></td>
<td></td>
<td>458</td>
<td>2a</td>
<td></td>
</tr>
</tbody>
</table>

### CEBM Levels of Evidence (2016)

<table>
<thead>
<tr>
<th>Level</th>
<th>Interventional Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Systematic reviews (with homogeneity) of RCTs</td>
</tr>
<tr>
<td>1b</td>
<td>Individual RCT (with narrow Confidence Interval)</td>
</tr>
<tr>
<td>2a</td>
<td>Systematic reviews (with homogeneity) of Cohort Studies</td>
</tr>
<tr>
<td>2h</td>
<td>Individual Cohort Study (including low quality RCT)</td>
</tr>
<tr>
<td>2c</td>
<td>“Outcomes” Research</td>
</tr>
<tr>
<td>3a</td>
<td>SR (with homogeneity) of Case-Control Studies</td>
</tr>
<tr>
<td>3b</td>
<td>Individual Case-Control Study</td>
</tr>
<tr>
<td>4</td>
<td>Case-series (and poor quality cohort and case-control studies)</td>
</tr>
<tr>
<td>5</td>
<td>Expert opinion without explicit critical appraisal, or based on physiology, bench research or “first principles”</td>
</tr>
</tbody>
</table>
Analysis of Evidences

Study 1 (Dani et al., 2011):
Description

- Retrospective, 2-center, cohort, single arm study
- Non-small cell lung cancer (N=258):
  - Peterly Hospital (Budapest) (PFY, n=61)
  - HTT-Med Clinic (Budapest) (HTT, n=197)
- Recruitment period: Oct 1997 - Dec 2003
- Average age 57.2±0.65 yrs, median 57 yrs (16-84), normal distribution
- Gender structure: 67.8% males
- Inoperable (St. IIIb-IV): 29% at Dx, 75% at 1st EHY (61% St. IV)
- Oncothermia included in the complex treatment
- Average time to start of oncothermia 11.9±1.07 m, median 6.2 m
  (0.2-142) or 49.8%±1.8% of OS, median 50.7% (0.68-99)
- Oncothermia applied in the III quartile of survival time
Study 1 (Dani et al., 2011):
Survival

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (Dx)</td>
<td>69.0%</td>
<td>42.7%</td>
<td>23.3%</td>
<td>16.9%</td>
<td>8.2%</td>
<td>20.5</td>
</tr>
<tr>
<td>OS (1st EHY)</td>
<td>37.4%</td>
<td>22.1%</td>
<td>10.2%</td>
<td>2.1%</td>
<td>1.4%</td>
<td>8.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Since Dx</th>
<th>Absolute</th>
<th>Discounted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY/patient</td>
<td>1.6</td>
<td>1.55</td>
</tr>
<tr>
<td>QALY**/patient</td>
<td>1.04</td>
<td>1.01</td>
</tr>
</tbody>
</table>

* 3% annual discount rate
** Average HRQoL throughout ST = 0.65

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Study 1 (Dani et al., 2011):
Quality Control

- Full sample (no exclusions or extractions) – confirmed by check of primary trial documentation
- No inclusion criteria (not limited by Age, Stage of disease or performance status)
- Censoring rate 19% (48/258):
  - Lost during follow-up 11% (28/258)
  - Right-censored (alive to the end of the trial) 8% (20/258)
- Exact death determination by Hungarian Civil Register
Study 2 (Dani et al., 2003):
Description

- Retrospective, monocenter, cohort, double-arm study
- Non-small cell lung cancer (N=186) (Szent Barbala Hospital, Tatabánya):
  - Study arm (SA), standard treatment + oncotherapy (n=147)
  - Control arm (CA), standard treatment only (n=39)
- Average age: SA=57 yrs, CA=57.3 yrs
- Gender structure: SA=67.8% males, CA=79.2% males
- Metastatic cancer at Dx: SA=59%, CA=45%
- Metastatic cancer at 1st EHY: 88%
- Oncotherapy included in the complex treatment

Study 2 (Dani et al., 2003):
Survival

[Graphs showing survival rates for Stage IIIA (n=31/14) and Stage IIIB-IV (n=87/18)]
Study 2 (Dani et al., 2003): Survival

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>MST</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (EHY)</td>
<td>58.0%</td>
<td>28.0%</td>
<td>12.0%</td>
<td>5.0%</td>
<td>1.0%</td>
<td>15</td>
</tr>
<tr>
<td>OS (Control)</td>
<td>36.0%</td>
<td>4.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>13.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Since Dx</th>
<th>Study arm (EHY+)</th>
<th>Control arm (no EHY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absolute</td>
<td>Disc*</td>
</tr>
<tr>
<td>LY/pat</td>
<td>1.04</td>
<td>1.02</td>
</tr>
<tr>
<td>QALY**/pat</td>
<td>0.68</td>
<td>0.67</td>
</tr>
</tbody>
</table>

* 3% annual discount rate
** Average HRQoL throughout ST: SA=0.65, CA=0.55

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Study 3 (Parmar, 2015)

- Retrospective, monocenter, cohort, single arm study
- Integrated Health Clinic (Fort Langley, BC, Canada)
- Non-small cell lung cancer stage IV (N=30)
- Stage IV at Dx: 100%
- Oncothermia included in the complex treatment
- Oncothermia applied in the III quartile of survival time

<table>
<thead>
<tr>
<th>Year</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td>64.8%</td>
<td>33.5%</td>
<td>33.5%</td>
<td>26.8%</td>
<td>13.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Since Dx</th>
<th>Absolute</th>
<th>Discounted*</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY/patient</td>
<td>1.72</td>
<td>1.65</td>
</tr>
<tr>
<td>QALY**/patient</td>
<td>1.12</td>
<td>1.07</td>
</tr>
</tbody>
</table>

* 3% annual discount rate
** Average HRQoL throughout ST =0.65
Study 4 (Lee, 2011):

**Description**

- Prospective, monocenter, cohort, double-arm study
- Gangnam Severance Hospital, Yonsei University, Korea
- Small cell lung cancer (N=31):
  - Study arm (SA), chemotherapy + oncotherapy (n=23)
  - Control arm (CA), chemotherapy only (n=8)
- Recruitment period: ongoing study
- Oncotherapy in combination with chemotherapy in 1st-2nd line treatment of SCLC.

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**Study 4 (Lee, 2011): Survival**

<table>
<thead>
<tr>
<th>Year</th>
<th>Study arm</th>
<th>Control arm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>59.0%</td>
<td>25.0%</td>
</tr>
<tr>
<td></td>
<td>47.0%</td>
<td>25.0%</td>
</tr>
</tbody>
</table>

Since Dx:

- **LY/pat**
  - Study arm (EHY+): 1.06
  - Control arm (no EHY): 1.05
- **QALY**/pat
  - Study arm (EHY+): 0.69
  - Control arm (no EHY): 0.67

Average HRQOL throughout ST: SA=0.65, CA=0.55
### Comparison of Overall Survival

<table>
<thead>
<tr>
<th>Dataset</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncothermia (pooled average)</td>
<td>66.6%</td>
<td>40.6%</td>
<td>24.3%</td>
<td>17.9%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Standard treatment USA (SEER)</td>
<td>41.6%</td>
<td>26.8%</td>
<td>21.0%</td>
<td>17.9%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Standard treatment EU (Eurocare-5)</td>
<td>39.0%</td>
<td>22.7%</td>
<td>17.1%</td>
<td>14.5%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Standard treatment East. Europe (Eurocare-5)</td>
<td>32.4%</td>
<td>18.0%</td>
<td>13.7%</td>
<td>11.7%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Best radiochemotherapy</td>
<td>54.2%</td>
<td>35.6%</td>
<td>23.8%</td>
<td>15.6%</td>
<td>15.1%</td>
</tr>
</tbody>
</table>

#### Graphical Representation

![Comparison of Overall Survival Graph](image-url)

- **Oncothermia (pooled average)**
- **Standard treatment (USA)**
- **Standard treatment (EU)**
- **Standard treatment (East. Europe)**
- **Best combined radiochemotherapy**
- **Best sequential RT + Ctx**
Why long-term survival drops down?

- Currently oncothermia is applied as a 3rd, 4th line treatment after fail of the previous treatment, or if other treatment is impossible.
- As such oncothermia sample consists of the patients with poor prognosis:
  - Low performance status (ECOG 2-4) not eligible for CTx and RT;
  - CTx and RT resistant patients;
  - Patients with relapse or progression.
- Oncothermia is used in 3rd quartile of SS, where chances for success significantly lower.
- Effect of basis:
  - Treatment results in USA are 10-20% better than in EU
  - Treatment results in Hungary are 10-20% worse than in EU
  - The main trials were performed in Hungary from 1997 to 2002 (before entrance to EU in 2004), when the treatment quality was even lower.

Incremental Utility of Oncothermia

<table>
<thead>
<tr>
<th>Best radiochemotherapy</th>
<th>Standard treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sequencial</td>
</tr>
<tr>
<td>LYG/pat</td>
<td>0.36</td>
</tr>
<tr>
<td>Discounted LYG/pat</td>
<td>0.34</td>
</tr>
<tr>
<td>Added QALY/pat</td>
<td>0.23</td>
</tr>
<tr>
<td>Disc. Added QALY/pat</td>
<td>0.18</td>
</tr>
</tbody>
</table>

- Oncothermia provides increment of utility versus all comparators.
- The lesser increment is versus best combined chemoradiotherapy (0.04 QALY/pat)
- The maximal increment is versus Eastern European standard treatment (0.42 QALY/pat)
Incremental Utility of Oncothermia

Cost-Utility Analysis
Cost-Utility Analysis of Oncothermia versus Radiotherapy in Treatment of Lung Cancer
Oncothermia vs Radiotherapy: Comparison of cohorts

<table>
<thead>
<tr>
<th></th>
<th>Oncothermia</th>
<th>Radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Trial</td>
<td>Dani, 2011</td>
<td>van den Hout, 2006</td>
</tr>
<tr>
<td>Country</td>
<td>Hungary</td>
<td>Netherlands</td>
</tr>
<tr>
<td>Number of patients</td>
<td>258</td>
<td>297</td>
</tr>
<tr>
<td>Average age</td>
<td>57.4</td>
<td>69</td>
</tr>
<tr>
<td>Males</td>
<td>68%</td>
<td>80%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>80%</td>
<td>47%</td>
</tr>
<tr>
<td>Treatment line</td>
<td>3rd-4th</td>
<td>1st</td>
</tr>
<tr>
<td>Time to treatment</td>
<td>11.9 months</td>
<td>1 month</td>
</tr>
</tbody>
</table>
| Pre-treatment            | 2.69 courses/pat     | 0.2 courses/pat     

Oncothermia vs Radiotherapy: Comparison of Survival

- **Year**: 1, 2, 3, 4, 5
- **Oncothermia**: 37.4%, 22.1%, 10.2%, 2.1%, 1.4%
- **Radiotherapy**: 16.0%, 6.5%, 2.5%, 2.0%, 0.0%
- **Increment**: 21.4%, 15.6%, 7.7%, 0.1%, 1.4%
Oncothermia vs Radiotherapy: Economic Assessment

- Life discounting 3%/year.
- Monetary discounting not used.
- Radiotherapy HRQoL=0.57.
- Though oncothermia always improves life quality versus radiotherapy, the equal HRQoL=0.57 was used for both trials.
- Radiotherapy costs = 3,869 $/pat.
- Oncothermia costs = 1,727 $/pat:
  - Cost of 1 session EUR 140 (exchange rate 2005 = 1.4 $/EUR).
  - Direct non-medical costs calculated proportionally to radiotherapy costs.

Oncothermia vs Radiotherapy: Cost-Utility Analysis

<table>
<thead>
<tr>
<th></th>
<th>QALY/pat</th>
<th>$/pat</th>
<th>CER ($/QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncothermia</td>
<td>0.408</td>
<td>1,727</td>
<td>4,230</td>
</tr>
<tr>
<td>Radiotherapy</td>
<td>0.151</td>
<td>3,869</td>
<td>25,619</td>
</tr>
<tr>
<td>Increment (OT – RT)</td>
<td>0.257</td>
<td>-2,142</td>
<td>-8,328</td>
</tr>
</tbody>
</table>

ICER = - 8,328 $/QALY

This means that radiotherapy generates $8,238 extra costs per each QALY compared to oncothermia use.
Sensitivity Analysis

- Radiotherapy costs:
  - Average: 8.081 $/pat
  - Median: 8.609 $/pat
  - Minimum: 3.874 $/pat
  - Maximum: 14.491 $/pat

- Oncothermia costs:
  - Minimum: 1.283 $/pat
  - Average: 1.727 $/pat
  - Maximum: 3.095 $/pat (300 EUR/session)

- ICER = $3,008 — $51,342 $/QALY

- Radiotherapy instead of oncothermia generates $3,000 — $50,000 of extra costs per QALY.

Cost-Utility Analysis

Cost-Utility Analysis of Oncothermia versus Chemotherapy in Treatment of Lung Cancer
**Oncothermia vs Chemotherapy**

- **Oncothermia of 3rd-4th line versus 1st line Chemotherapy**
- **Platinum-based Chemotherapy adds 0.49-0.63 LY/pat (average 0.585).**
- **Chemotherapy costs 5,932-202,176 $/QALY (average 42,841 $/QALY)**
- **ICER = -10,825 -- -250,000 $/QALY**
- **Chemotherapy instead of oncothermia generates >$10,000 of extra costs per QALY.**

**Budget Impact Analysis**
Budget Impact Analysis: Model 2
Pre-requisites

- Utility of conventional chemoradiotherapy cancer treatments averages 0.4 QALY/pat (0.3-0.85 QALY/pat)
- Oncothermia in complex treatment provides the same of higher utility (0.4-1.0 QALY/pat)
- Thus, oncothermia provides enough enhancement of any method from bimodal intervention to substitute the other one.
- Therefore, oncothermia can substitute chemotherapy OR radiotherapy in bimodal intervention.

Budget Impact Analysis: Model 2
Pre-requisites

- Radiotherapy alone is modestly effective in lung cancer treatment but its effect is strongly potentiated by platinum-based chemotherapy.
- At the same time, concurrent chemotherapy increases toxicity of radiotherapy, namely radiation induced lung injury (radiation pneumonitis) and radiation esophagitis.
- With total dose >40 Gy and concurrent chemotherapy, the both radiation-induced lung and esophagus injury are almost inevitable (100%).
- The substitution of chemotherapy by oncothermia can reduce the toxicity and increase survival.
Budget Impact Analysis: Model 2
Pre-requisites

The results of the trial (2012) performed in radiation oncology center of Research Institute named after academician Meshalkin in Novosibirsk (Russia):

- 38 patients with non-small cell lung cancer (all stages) were treated in 2010 by 3D-conformal radiotherapy (total dose 64.25 Gy (equivalent dose 70-76 Gy), single dose 2.75 Gy 5 x week) in combination with oncothermia (10 sessions, 3 x week, 150W x 90 min).
- Beneficial response 95%, including objective response (CR + PR) in 53% and stable disease in 42%; 5% of progression.

1-year survival – 97.4%!

Results

- Oncothermia in the 3rd-4th line complex treatment of lung cancer provided better 1-3 year survival compared to any 1st line conventional treatment except of surgery, including the best chemoradiation treatment.
- Oncothermia provided virtually the same utility as the best concurred chemoradiation treatment (+0.04 QALY/pat) and the better utility than standard treatment in USA and Europe (+0.42 QALY/pat versus Eastern Europe).
- Oncothermia showed the better cost-utility compared to radiation therapy with ICER = -3,000 — -50,000 $/QALY.
- Oncothermia showed the better cost-utility compared to chemotherapy with ICER = -10,000 — -250,000 $/QALY.
- Thus, oncothermia is pharmaco-economically preferable treatment versus either radiotherapy or chemotherapy in complex treatment of lung cancer.
Thank you for attention