Quo vadis oncological Hyperthermia Update 2016
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Quo vadis oncological Hyperthermia
Update 2016

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Visiting professor (bio-electrodynamics) at Pazmany P. Catholic University, Hungary
Visiting Professor (fractal physiology) at Chiba University, Japan
Challenge of targeting in oncology

- Primary tumor: Destroy the tumor effectively
- Invasion: Block the invasion & dissemination
- Dissemination: Metastasis
- Malignancy looks local, but it isn’t.

Challenge of impact of cytotoxic chemotherapy on 5-year survival in 2004 (American adults)

<table>
<thead>
<tr>
<th>Malignancy</th>
<th>ICD-9</th>
<th>Number of cancers in people aged &gt; 20 years*</th>
<th>Absolute number of 5-year survivors due to chemotherapy†</th>
<th>Percentage 5-year survivors due to chemotherapy‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck</td>
<td>140–149, 160, 161</td>
<td>5139</td>
<td>97</td>
<td>1.9</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>150</td>
<td>1521</td>
<td>82</td>
<td>4.9</td>
</tr>
<tr>
<td>Stomach</td>
<td>151</td>
<td>3601</td>
<td>20</td>
<td>0.7</td>
</tr>
<tr>
<td>Colon</td>
<td>153</td>
<td>13,936</td>
<td>146</td>
<td>1.0</td>
</tr>
<tr>
<td>Rectum</td>
<td>154</td>
<td>5533</td>
<td>189</td>
<td>3.4</td>
</tr>
<tr>
<td>Pancreas</td>
<td>157</td>
<td>3567</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Lung</td>
<td>162</td>
<td>20,741</td>
<td>410</td>
<td>2.0</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>171</td>
<td>858</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Melanoma</td>
<td>172</td>
<td>8646</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Breast</td>
<td>174</td>
<td>31,133</td>
<td>446</td>
<td>1.4</td>
</tr>
<tr>
<td>Uterus</td>
<td>179–182</td>
<td>4611</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cervix</td>
<td>180</td>
<td>1825</td>
<td>219</td>
<td>12</td>
</tr>
<tr>
<td>Ovary</td>
<td>183</td>
<td>3602</td>
<td>269</td>
<td>8.9</td>
</tr>
<tr>
<td>Prostate</td>
<td>185</td>
<td>23,242</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Testis</td>
<td>186</td>
<td>989</td>
<td>373</td>
<td>37.7</td>
</tr>
<tr>
<td>Bladder</td>
<td>188</td>
<td>6667</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Kidney</td>
<td>189</td>
<td>3722</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Brain</td>
<td>191</td>
<td>1824</td>
<td>68</td>
<td>3.7</td>
</tr>
<tr>
<td>Unknown primary site</td>
<td>195–199</td>
<td>6200</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Non-Hodgkin's lymphoma</td>
<td>200 + 202</td>
<td>6217</td>
<td>653</td>
<td>10.5</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>201</td>
<td>846</td>
<td>341</td>
<td>40.3</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>203</td>
<td>1721</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>154,971</strong></td>
<td><strong>3306</strong></td>
<td></td>
<td><strong>2.1%</strong></td>
</tr>
</tbody>
</table>

*Numbers from Ref. [22].
†Absolute numbers (see text).
‡% for individual malignancy.

Challenges with medical paradigm

Cancer is loss of complexity!

New paradigm is mandatory in oncology!

Challenge of personalization

The necessary object of the treatment is not the tumor itself, but the PATIENT with tumor!

When a study is well personalized, then no perfect cohorts could be collected.

How to make cohorts? Poison everybody up to his/her tolerance limit.
Search for new medical possibilities

Present answers on challenges

- In radiotherapy:
  - tomo-therapy,
  - proton-therapy

- In chemotherapy:
  - nano-applications,
  - personalized therapies,
  - targeted therapies
  - cancer-stem-cell therapies,
  - immune therapies
  - check-point inhibitors

- In hyperthermia:
  - interventional (invasive) hyperthermia (RF-ablation, laser induced hyperthermia, electroporation)
  - nanoparticle-heating,
  - immune-modulation by heat
  - find new complementary applications

Radio and chemo treatment modalities are developing quicker than hyperthermia

The change of paradigm is missing. How to think differently?

1. Think about the patient in his/her personal complexity
2. Be less toxic, do the treatment rather smartly and less aggressively
3. Use the personal immune activity of the patient
4. Think about the survival and quality of life instead of the response rates

Change of paradigm in oncology

Immuo-oncology! Hyperthermia is a good partner for change of paradigm!
Historic approach in oncologic hyperthermia

Local therapies
- Carl DW. Busch (1826-1881)
- Arnaud d’Arsenal (1851-1946)

Whole-body therapies
- Internal inducing
  - J. Wagner-Jauregg (1857-1945)
  - William Coley (1862-1936)

External inducing
- M. von Ardenne (1907-1957)
- M. Hecker (1926-2007)

1910
- Selectotherm (von Ardenne) 1910

1910
- Selectotherm (von Ardenne) 1910

1960
- Ultratherm

1952
- Pyrostat-501

1992
- Aquatherm

1997
- WBH2000, Oncotherm

Oncothermia Journal, Volume 18, December 2016
Pioneering of the combined hyperthermia

Modern approach in oncologic hyperthermia

Typical nowadays whole-body hyperthermia devices

- Reflective [Heckel Medizintechnik, Germany]
- Filtered [vonArdenne, Germany]
- Extracorporeal (perfusion) [RanD, Italy]
- RF-capacitive [Oncotherm, Germany]

Typical nowadays local hyperthermia devices

- Magnetic (inductive) [Magforce, Germany]
- Radiative (antenna array) [BSD Medical, (Pyrexar) USA]
- Electric (radiative capacitive) [Celsius42, TCS, Germany]
- Electric (radiative capacitive) [Thermotron RF-8, Japan]
Hyperthermia methods

Presently less than 2% of cancer patients are treated with hyperthermia worldwide

WHY??

Challenges of the market

The conventional hyperthermia methods had lost their “attractive behavior”, and they are abandoned in many University places.

No governmental University makes hyperthermia with Thermotron in Japan.

BSD closed its reference clinic at Duke University, USA.
Challenges of the market

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Controversies in clinical results. WHY is it so?

Temperature spreads!
It increases the blood-flow trying to compensate the heating.
We need blood-flow for complementary therapies
- radio [blood-oxygen]
- chemo [drug delivery])

Supply extra nutrients for tumor!
Dissemination is highly possible!

The blood-flow is not controlled, it intensifies at the most proliferating boundary of the tumor!
Challenges of temperature

Blood-compensates, tries keeping the temperature constant

Hot- and cold-spots produce different temperatures at the same incident power.

Challenges with clinical results (local hyperthermia)

Breast study (superficial) (England/Netherlands)

Challenges with clinical results

Superficial tumors study (USA) (RT+HT)

Local control
HT = hyperthermia
RT = radiotherapy

P = 0.02

Overall survival

Toxicity study

Temperature over 40°C suppresses the immune-cell activity

NK cell activity
Lymphocyte-activated killer cell activity

The effects of different incubation times and temperatures on NK cell cytotoxicity (n=2-27)

Hietanen T et al. Restoring Natural Killer Cell Cytotoxicity After Hyperthermia Alone or Combined with Radiotherapy, ANTICANCER RESEARCH 36: 555-564 (2016)

NK cells activation in the course of HT

Ostapenko VV et al. Immune-related Effects of Local Hyperthermia in Patients with Primary Liver Cancer, Hepato-Gastroenterology 2005; 52:1502-1506
Challenges in patient’s complains

<table>
<thead>
<tr>
<th>Region (regions as in figure 2)</th>
<th>Complaint occurrence (%)</th>
<th>Average DTC (± SE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdomen mid</td>
<td>27.6</td>
<td>3.5 ± 0.1</td>
</tr>
<tr>
<td>Lower back mid</td>
<td>18.8</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>Tailbone/inguin</td>
<td>8.0</td>
<td>2.1 ± 0.2</td>
</tr>
<tr>
<td>Buttocks left</td>
<td>7.9</td>
<td>4.9 ± 0.2</td>
</tr>
<tr>
<td>Buttocks right</td>
<td>6.4</td>
<td>5.7 ± 0.2</td>
</tr>
<tr>
<td>Vagina/perineum</td>
<td>6.3</td>
<td>1.4 ± 0.2</td>
</tr>
<tr>
<td>Pubic bone</td>
<td>4.3</td>
<td>1.9 ± 0.2</td>
</tr>
<tr>
<td>Groin/Hip right</td>
<td>3.5</td>
<td>7.9 ± 0.3</td>
</tr>
<tr>
<td>Bladder</td>
<td>3.2</td>
<td>2.8 ± 0.2</td>
</tr>
<tr>
<td>Groin/Hip left</td>
<td>3.1</td>
<td>7.4 ± 0.3</td>
</tr>
<tr>
<td>Abdomen left</td>
<td>3.0</td>
<td>5.7 ± 0.7</td>
</tr>
<tr>
<td>Abdomen right</td>
<td>1.4</td>
<td>5.5 ± 0.5</td>
</tr>
<tr>
<td>Lower back left</td>
<td>1.1</td>
<td>6.9 ± 0.4</td>
</tr>
<tr>
<td>Thigh left</td>
<td>0.9</td>
<td>9.0 ± 0.16</td>
</tr>
<tr>
<td>Legs</td>
<td>0.7</td>
<td>NaN (outside HTP models)</td>
</tr>
<tr>
<td>Stomach/upper abdomen</td>
<td>0.7</td>
<td>9.7 ± 1.3</td>
</tr>
<tr>
<td>Foot</td>
<td>0.5</td>
<td>NaN (outside HTP models)</td>
</tr>
<tr>
<td>Thigh right</td>
<td>0.4</td>
<td>7.7 ± 3.0</td>
</tr>
<tr>
<td>Thigh top</td>
<td>0.3</td>
<td>10.8 ± 0.8</td>
</tr>
<tr>
<td>Systemic</td>
<td>0.3</td>
<td>NaN (no fixed region)</td>
</tr>
<tr>
<td>Lower back right</td>
<td>0.1</td>
<td>7.4 (no SE, single complaint)</td>
</tr>
</tbody>
</table>

Distribution of the occurrence of complaints in all regions, and corresponding DTC values. (DTC = distance of complaint)

Challenges with techniques

➤ Surface cooling

The uncontrolled loss of energy **blocks the normal dosing**, it **cannot be measured** by the incident energy (J/kg), (as it is usual in radiotherapy)

**Measurement of the temperature** could be the basic of the dose only.

Challenges with techniques

Temperature measurement and its problems

Conventional temperature measurements
- Infrared radiation (measures the surface only)
- Radiometry (near surface measurement and very inaccurate)
- MRI (inaccurate, very expensive)
- Invasive temperature measurements (point-sensor, complications)

Complications could be
- inflammation
- ulcerous wound
- infection
- internal bleeding
- risk of metastases

Challenges with techniques

Instead of commercial RF-technology, a specialized modern electronics developed for the special tasks is requested

Understanding that the applied devices are decisional, they make different bio-electromagnetic effects
Challenges with techniques

The shielding and the operational cost of the device itself is expensive.

<table>
<thead>
<tr>
<th>Frequency Interval</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>13.56 MHz ± 6.68 kHz</td>
<td></td>
</tr>
<tr>
<td>27.12 MHz ± 160.00 kHz</td>
<td></td>
</tr>
<tr>
<td>40.68 MHz ± 20.00 kHz</td>
<td></td>
</tr>
<tr>
<td>915 MHz ± 13 MHz</td>
<td></td>
</tr>
<tr>
<td>2450 MHz ± 50 MHz</td>
<td></td>
</tr>
<tr>
<td>5800 MHz ± 75 MHz</td>
<td></td>
</tr>
<tr>
<td>24125 MHz ± 125 MHz</td>
<td></td>
</tr>
</tbody>
</table>

Thermotron RF-8 (8 MHz)

BSD2000 and BSD3000

Shielding is necessary around the room

To treat or not to treat?
To heat or not to heat?
To choose or not to choose?

That is the question.
Change of paradigm in therapies

Feedback to keep the homeostasis

Classical oncotherapies

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

Constrained treatment

Body in homeostasis

Disease

New paradigm

Supports the homeostasis

Quality of life & Survival time

Cooperative treatment

Attacks the homeostasis

Hyperthermia methods

Part of immuno-oncology

Tumor-specific immune effects
New approach in oncologic hyperthermia

Systemic immune action
Carl DW. Bueche (1826–1881)
Unification thermal & electric cell-killing
Arsène d'Arquyval (1851–1940)
New start with
- precise targeting
- abscoanal effect
- immune-actions

Oncothermia
Germany, Oncotherm

Typical nowadays local hyperthermia devices

- Magnetic (inductive) [Magforce, Germany]
- Radiative (antenna array) [ BSD Medical, (Pyrexar) USA]
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After nanothermia treatment

Nano-range

Cooling down
(6 min → 30 min)

Kill the primary tumor

Mitochondria
Cyt c
Mitochondria
Bax

Apoptosis proceeds
(4 h → 48 h)

TUNEL

Untreated

Treated...

Transition processes

Mileoperoxidase

72h

168h

Innate immune induction

(48 h → 168 h)
CD3+

CD8

168h

Adaptive immune reaction

(4 → 168 h → ...)

NKG2D

membrane

HSP90

NAGA/mouse

Tumor

168h

Killer metastatic tumor
(abscoanal effect)
Toward to tumor-vaccination

Damage-Associated Molecular Patterns (DAMP)
- CRT (calreticulin)
- HMGB1
- HSPs (HSP70, HSP90)
- Death receptors (DRs)

Apoptotic tumor cells (early stage)

Direct activation of innate immune system (NK, granulocytes)
Nonspecific antitumor response

DAMP molecules released to the extracellular matrix
Cytkine production (IL-12, TNF)
Action of the adaptive immune system

Apoptotic tumor cells (late stage)

Mature DC
- DC activation
- Antigen processing
- DC maturation

Tumor cells
- Specific cytotoxic lysis of tumor

APC (antigen presenting cell)
- Antigen presentation
- Specific T cell activation

CD4+ T cell (helper T-cells)
CD8+ T cell (killer T-cells)

CELL DEATH

Block the invasion and dissemination

<table>
<thead>
<tr>
<th>β-catenin</th>
<th>E-cadherin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthermia, 42 °C</td>
<td>Oncothermia 42 °C</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β-catenin</th>
<th>E-cadherin</th>
</tr>
</thead>
<tbody>
<tr>
<td>37°C</td>
<td></td>
</tr>
<tr>
<td>42°C</td>
<td></td>
</tr>
<tr>
<td>RF8</td>
<td></td>
</tr>
<tr>
<td>Oncothermia</td>
<td></td>
</tr>
<tr>
<td>58°C</td>
<td></td>
</tr>
</tbody>
</table>

In vitro A431 + human fibroblast co-culture, E-cadherine and β-catenin; 24h after the treatments


Cancer is not local!

Oncothermia is active in all fields!

- Selective attacks on cancer-cells
- Induces apoptotic cell-destruction
- Reestablishes the adherent connections
- Locally activates the immune system
- Forms damage associated molecular pattern (Tntr, mHSP70, mHSP90, HMGB1, Calreticulin, etc.)
- Creates abscopal effect

Change of Paradigm of Hyperthermia in basic effects

<table>
<thead>
<tr>
<th>Old Paradigm</th>
<th>New Paradigm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induces high blood-flow</strong>, supports the growth of tumor and risks metastases</td>
<td><strong>Should be selective</strong>, must not gain the contra-effective blood-flow, only mild</td>
</tr>
<tr>
<td>Aims necrosis killing the tumor. Minor apoptosis happens through internal signal path (mitochondria)</td>
<td>Should kill the malignant cells by apoptosis. Apoptosis happens through external (membrane) signal path</td>
</tr>
<tr>
<td><strong>Breaks</strong> the intercellular junctions</td>
<td>Should <strong>reestablish</strong> the intercellular junctions</td>
</tr>
<tr>
<td><strong>Intervenes</strong> in homeostatic control</td>
<td>Should <strong>support</strong> homeostatic control</td>
</tr>
<tr>
<td><strong>Blocks</strong> immune cells by excess heat-energy, with too high temperature</td>
<td>Should activate immune cells for <strong>immunogenic</strong> cell-death</td>
</tr>
<tr>
<td>Has high heat-toxicity risk by excess heat-energy</td>
<td>Should have <strong>low risk</strong> by controlling energy dose</td>
</tr>
<tr>
<td>Forces to pursue absolute degree of temperature of tumor as a whole</td>
<td>Should produce <strong>igniting effect</strong> of temperature on membrane of tumor cell</td>
</tr>
<tr>
<td><strong>Concentrates</strong> on local tumor control</td>
<td>Should be centered on the <strong>systemic</strong> tumor control (abscoopal effect)</td>
</tr>
</tbody>
</table>
### Change of Paradigm of Hyperthermia in clinical practice

<table>
<thead>
<tr>
<th><strong>Old Paradigm</strong></th>
<th><strong>New Paradigm</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Measures the <em>temperature</em> for control</td>
<td>The temperature measurement is <em>not necessary</em></td>
</tr>
<tr>
<td>Uses the CEM43°CTx as dose</td>
<td>Uses <em>energy-intake</em> for dose</td>
</tr>
<tr>
<td><em>Complicated</em> to use, difficult to tune</td>
<td><em>Simple</em> to use, automatically focuses on the actual malignancy</td>
</tr>
<tr>
<td>Concentrates on the <em>local</em> tumor only</td>
<td></td>
</tr>
<tr>
<td>Has thermal damages and thermal <em>toxicity</em></td>
<td>Has <em>no thermal toxicity</em></td>
</tr>
<tr>
<td>Does not control the distant <em>metastases</em></td>
<td>Controls the metastases by <em>abscopal</em> effect (tumor-specific immune reaction)</td>
</tr>
<tr>
<td>Has no effective <em>focusing</em> on malignant cells</td>
<td>Effectively <em>selects</em> the malignant cells in the heterogeneous tumor</td>
</tr>
<tr>
<td>No consideration on the physiologic <em>feedbacks</em> of the patient</td>
<td>Takes the <em>physiological</em> feedback into account</td>
</tr>
<tr>
<td>Relatively high <em>price/benefit</em> ratio</td>
<td>Relatively <em>cheap</em> with high benefit</td>
</tr>
</tbody>
</table>

### The new paradigm needs new thinking

*The old tool was better!*  

*Thank you for following my talk*
Take home message

In contrary that the hyperthermia was the very first treatment in oncology it is not widely accepted. It is in childhood yet!

We need new paradigm!

Never treat the tumor alone!

Treat the PATIENT who has tumor!

Take complexity into consideration, use the update advantages of immuno-oncology!

<table>
<thead>
<tr>
<th>Conventional hyperthermia</th>
<th>Oncothermia high nano-range</th>
</tr>
</thead>
<tbody>
<tr>
<td>high overall power</td>
<td>targeted power</td>
</tr>
<tr>
<td>complete (mass) heating strategy</td>
<td>selective (nano) heating strategy</td>
</tr>
<tr>
<td>CEM43°C, local control, kill the cells by constrain heat</td>
<td>survival time &amp; QoL</td>
</tr>
<tr>
<td>“teach” the system how to kill</td>
<td></td>
</tr>
</tbody>
</table>


Challenge in prospective studies
Challenge in prospective studies

Overall survival of mammary carcinoma (n=7,738)

Gant et al ASCO 2000

In study

Not in study

p<0.00001

Months

Challenge of targeting in oncology

Primary tumor

Which option do we have in refractory cases when the standard protocols fail?

Invasion

Dissemination

Metastasis

How to destroy it?

Protocol "A"

Protocol "B"
Challenge of targeting in oncology

How to block the invasion and dissemination of malignant cells?

Do we have adherent action?

Malignancy looks local, but it isn’t.

Challenge of targeting in oncology

What to do with metastases?

Are we blind?
Challenges with clinical results (whole-body hyperthermia)

Metastatic colorectal cancer
(Phase I/II prospective double arm study)

The heat-up time was defined as the time interval for heating the blood from 37.5 to 42.1°C, and it could vary considerably (60–150 min). The plateau phase started by reaching a temperature of 41.8°C in the aorta. It was kept stable for 60 min by properly adjusting the total power of the radiators, typically by reducing it to one-third of the initial power.

Progression-free survival for the two treatment groups in comparison. *Note that the graph does not represent a comparison of similar patient groups: all patients treated with SCMT plus chemotherapy previously had not responded to three courses of conventional chemotherapy. All patients treated with chemotherapy alone had a partial response after three courses.

Overall survival for the two treatment groups in comparison. *Note the graph does not represent a comparison of similar patient groups: all patients treated with SCMT plus chemotherapy previously had not responded to three courses of conventional chemotherapy. All patients treated with chemotherapy alone had a partial response after three courses.

Extreme whole-body hyperthermia effect (41-42°C)


Extreme (40-42°C) whole-body hyperthermia worsened the effect of conventional treatment
CONCLUSION: The combination of LH + WBH with radiation therapy was not associated with an increase in local tumor control in comparison to use of LH with radiation therapy. The combination of LH + WBH also appeared to alter the biology of the metastatic process and was associated with more complications than LH. **We identified no rationale for further study** of LH + WBH in combination with radiation for treatment of solid tumors.

**Challenges of the market**

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Challenge in prospective studies

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- Gant et al ASCO 2000
- In study
- Not in study
- p<0.00001

Controversies in chemotherapy

Comparison of disease-specific survival in patients with lymph node disease who either received (23 patients) or did not receive (53 patients) chemotherapy.
Challenge of financing of chemotherapy

Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval
1965 - 2015

<table>
<thead>
<tr>
<th>Year of FDA Approval</th>
<th>Monthly Price of Treatment (2014 Dollars, log scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1970</td>
<td>$1000</td>
</tr>
<tr>
<td>1980</td>
<td>$10,000</td>
</tr>
<tr>
<td>1990</td>
<td>$100,000</td>
</tr>
<tr>
<td>2000</td>
<td>$1,000,000</td>
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<tr>
<td>2010</td>
<td>$10,000,000</td>
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X1,000

Example: cost of chemotherapy for colorectal cancer

- 1990: 97 x 6 months: 582 €
- 1996: 143 x 6 months: 1716 €
- 2003: 729 x 6 months: 8448 €
- 2004: 1224 x 6 months: 16888 €
- 2010: 5000 x 6 months: 60000 €

Cost of Cancer Care by Phase of Care, Colorectal, All Ages, Male and Female, in 2010 Dollars

U.S. Colorectal Cancer Incidence

U.S. Colorectal Cancer Mortality

https://www.mskcc.org/profile/peter-bach

https://costprojections.cancer.gov/graph.php

http://www.cancer.gov/research/surveillance/analyses/colorectal

Oncothermia Journal, Volume 18, December 2016   37
Historic approach in oncologic hyperthermia

Local therapies

- Carl D.W. Busch (1826-1881)
- Arnaud d’Arenval (1851-1946)

Whole-body therapies

Internal inducing
- J. Wagner-Jauregg (1857-1949)
- William Coley, (1862-1936)

External inducing
- N. von Ardenne (1907-1997)
- N. Heckel (1926-2007)

The oldest medical therapy: thermo-therapy

- Local heating → intensifies the metabolism, without extra supply → burning out
- Normal blood-flow (supplies the tumor)
- Healthy surrounding

Synergy with chemotherapy

- ATP decreases; deprivation of energy
- Lactic acid formation; acidosis

Synergy with radiotherapy

- Radiation alone
- Rad. + heat
- Heat + md.
The heating in laboratory experiments is perfect

When he would be mouse we could completely cure him...

**Challenge of financing of chemotherapy**

*Monthly and Median Costs of Cancer Drugs at the Time of FDA Approval 1965 - 2015*

https://www.mskcc.org/profile/peter-bach
### Observational and randomized clinical studies

<table>
<thead>
<tr>
<th>Treatment Evaluated</th>
<th>Outcome</th>
<th>OR and 95% CI</th>
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<tbody>
<tr>
<td>Nifedipine vs. control in patients with CAD*</td>
<td>Mortality</td>
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<td>50–60 mg</td>
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<tr>
<td>CAGB vs. PTCA in diabetic patients*</td>
<td>Mortality</td>
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<td>CAGB vs. PTCA in patients at high risk*</td>
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<td>CAGB vs. medical treatment in Duke study patients</td>
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<td>Beta-blockers vs. control</td>
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</tbody>
</table>

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**Results of Observational Studies and Randomized, Controlled Trials of Cardiac Treatments**

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**Results of Observational Studies and Randomized, Controlled Trials of Noncardiac Treatments**

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**Odds Ratio for Infection after Laparoscopic as Compared with Open Appendectomy**

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Comparison of primary outcomes between observational studies and randomized controlled trials. This figure is based on data from 13 review articles 1,3,8-14,16,17,20-31 and 10 meta-analyses of observational studies by the authors. OR, odds ratio; RR, relative risk; CI, confidence interval.

*Outcome reporting relative risk rather than odds ratio.