HYPERTHERMIA

- Inducing a **controlled** temperature rise in solid tumors
- Goal temperature **41-43°C** for **1 hr**
- Always combined with RT and/or CT
- 1x/2x a week
HEAT

→ Increase of blood flow;
→ Increase in permeability of cells membrane;
→ Increase of intratumoral drug uptake
HT + RT RATIONALE

A. Oei et al., Radiation Oncology, 2015
HYPERTHERMIA - RANDOMIZED STUDIES

- Effect without HT
- Effect with HT

- CR

- Bladder: 70% (70%), 37% (37%)
- Cervix: 74% (53%), 6% (25%)
- Rectum: 25% (6%), 41% (39%)
- Breast: 59% (42%), 39% (42%)
- Breast (P.I): 79% (66%), 68% (68%)
- Various superficial: 79% (48%), 74% (48%)
- Various superficial(P.I): 79% (48%), 74% (48%)
- Head& Neck: 42% (28%), 24% (24%)
- Melanoma: 48% (28%), 28% (28%)

- "Medline" search
  Hyperthermia NOT fever AND cancer AND clinical trials

- 38 clinical trials
- 1987-2014

Datta et al. 2015, Cancer Treatment Reviews
HYPERTHERMIA - RANDOMIZED STUDIES

2-3 yrs LC

- Bladder: 33% Effect without HT, 42% Effect with HT
- Cervix: 51% Effect without HT, 70% Effect with HT
- Rectum: 8% Effect without HT, 16% Effect with HT
- Various superficial: 25% Effect without HT, 48% Effect with HT
- High risk ST Sarcoma: 55% Effect without HT, 66% Effect with HT

Effect without HT: Effect with HT

Datta et al. 2015, Cancer Treatment Reviews

- “Medline” search
  Hyperthermia NOT fever AND cancer AND clinical trials
- 38 clinical trials
- 1987-2014
HYPERTHERMIA - RANDOMIZED STUDIES

2-yrs OS

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Effect without HT</th>
<th>Effect with HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>22%</td>
<td>28%</td>
</tr>
<tr>
<td>Cervix</td>
<td>51%</td>
<td>65%</td>
</tr>
<tr>
<td>Rectum</td>
<td>10%</td>
<td>29%</td>
</tr>
<tr>
<td>High risk ST Sarcoma</td>
<td>72%</td>
<td>78%</td>
</tr>
</tbody>
</table>

Datta et al. 2015, Cancer Treatment Reviews

- “Medline” search
  Hyperthermia NOT fever AND cancer AND clinical trials
- 38 clinical trials
- 1987-2014
<table>
<thead>
<tr>
<th>TUMOR</th>
<th>SND TREATMENT</th>
<th>PRIMARY OBJECTIVE</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRIMARY</td>
<td>Stage I/II</td>
<td>S+Adjuvant RT/CT</td>
<td>CR</td>
</tr>
<tr>
<td>PRIMARY</td>
<td>Stage III/IV</td>
<td>(Neo-adjuvant CT+) S+Adjuvant RT/CT</td>
<td>Surgery/Conservative Surgery CR</td>
</tr>
<tr>
<td>LOCO-REGIONAL RECURRENT</td>
<td></td>
<td>S/RT/Re-RT/CT</td>
<td>LC</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>QoF</td>
</tr>
<tr>
<td>METASTATIC</td>
<td>Oligometastatic</td>
<td>Curative RT/CT</td>
<td>OS</td>
</tr>
<tr>
<td></td>
<td>Diffuse</td>
<td>RT/CT</td>
<td>Palliation</td>
</tr>
</tbody>
</table>

**Hyperthermia**

- Radiotherapy effect
- Chemotherapy effect
- Without increasing normal tissue acute or late toxicity
MULTICHANNEL PHASED ARRAY SYSTEM

- 70 MHz
- Loco-regional HT
- Focal area ~ 12 cm
- Target temperature: 41-43 °C
CLINICAL INDICATIONS

Cervix and uterus
Rectum
Bladder
Prostate
Esophagus
Soft tissue sarcoma
Deep seated melanoma
Pancreas
FROM RESEARCH TO MARKET

AMC-4

AMC-8
(2003 – 2013)
SUCCESFUL PHASE III TRIAL
*(Van der Zee, 2000)*

<table>
<thead>
<tr>
<th>Tumor Site</th>
<th>Complete Response</th>
<th>2-Yr Local Control</th>
<th>3-Yr Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>51% RT 73% RT+HT</td>
<td>39% RT</td>
<td>24% RT</td>
</tr>
<tr>
<td>Cervix</td>
<td>57% RT 83% RT+HT</td>
<td>56% RT+HT</td>
<td>31% RT+HT</td>
</tr>
<tr>
<td>Rectum</td>
<td>15% RT 20% RT+HT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

12 YEARS FOLLOW UP

OVERALL SURVIVAL

FRANCKENA ET AL IJROBP 2008
PRODUCT DEVELOPMENT

2012

2017
PHILOSOPHY
DESCRIPTION & COMPARISON

MECHANICS

THERMOMETRY

COOLING SYSTEM

RF
BED MOVEMENT

Manual positioning of the bed
- easy and comfortable patient preparation
- fast emergency removal
Automatic record of gantry and antennas position
MECHANICS

- AP: 33 - 73 cm
- LAT: 46 - 60 cm

ADAPTATION TO DIFFERENT SIZE
Crs = (Peso totale x fattore di sicurezza) – peso totale
Crs = (Peso totale x fattore di sicurezza) – peso totale
MECHANICS
INTEGRATED POSITIONING LASERS
DESCRIPTION & COMPARISON

- MECHANICS
- THERMOMETRY
- COOLING SYSTEM
- RF CONTROL
ANTENNAS

- 70 MHz
- Waveguide applicator
SIMULATED SAR DISTRIBUTION

Focal area ~ 12.5 cm

P = intensity
ϕ = position

20.5 cm
FOCUS STEERING

$\Delta \phi = 10^\circ \rightarrow \Delta s = 1\text{cm}$
FOCUS STEERING
FOCUS STEERING
FOCUS STEERING

Magnitude E-field (V/m) [Measurements4D_Z20-205950.txt]

- X position [mm]
- Y position [mm]
- Left, 30 Watt, 30°
- Top, 30 Watt, 0°
- Bottom, 30 Watt, -30°
- Right, 30 Watt, 0°

Color scale:
- 0
- 132

ALBA 4D
DEEP YIELD THERAPEUTIC SYSTEM
FOCUS STEERING
MAJOR REQUIREMENTS
PHASED ARRAY SYSTEM FOR DEEP HT

PHASED ARRAY INTRINSIC ISSUES → SUB-OPTIMAL TARGET HEATING

PC → GENERATOR → AMP → APPL. #1 → APPL. #N

CRITICAL POINT

DESIRED $\Phi$

$\Phi$ DRIFT

SHIFT OF THE FOCUS POSITION

Time
MAJOR REQUIREMENTS

PHASED ARRAY SYSTEM FOR DEEP HT

FEEDBACK SYSTEM

OPTIMAL TARGET HEATING

PC → GEN./VVM → AMP → APPL. #1 → APPL. #N

DRIFT CORRECTION

Phase /Power Control Loop

Time
$a_i =$ forward power of i-esimo ch
$b_i =$ reflected power of i-esimo ch

$\mathbf{b} = \mathbf{S} \cdot \mathbf{a}$

$\mathbf{S} = \begin{pmatrix}
S_{11} & \cdots & S_{1N} \\
\vdots & \ddots & \vdots \\
S_{N1} & \cdots & S_{NN}
\end{pmatrix}$

$S_{ii}:$ the lower the better
Impedance Mismatching

The more the load ≠ 50 Ohm, the more reflected power \( b_i \) is high. The reflected power \( b_i \) is high, leading to instabilities in the line. This is not reliable for measurements from bi-directional couplers.

\[ a_i = \text{forward power of i-esimo ch} \]

\[ b_i = \text{reflected power of i-esimo ch} \]
WATER BOLUS

“C “ shaped top water bolus

- OPTIMAL ADAPTATION
- INDEPENDENTLY THERMO-REGULATED
- AUTOMATIC RECORD OF WATER VOLUME

Rectangular bottom bolus
WATER BOLUS

DIFFERENT TOP BOLUS
ACCORDING TO PATIENT SIZE
WATER BOLUS
DESCRIPTION & COMPARISON

- MECHANICS
- RF CONTROL
- COOLING SYSTEM
- THERMOMETRY
Invasive thermometry is the ONLY ESHO approved measuring system.
Invasive thermometry is the ONLY ESHO approved measuring system.

REAL TIME DOSIMETRY

- Rectum
- Spinal cord
- Oesophagus
- Water bolus
- Applicator

64 SENSORS

POSITIONED IN NATURAL CAVITIES
MULTI-TIPS TEMPERATURE PROBES
SPECIAL SUPPORT DEVICES
PATIENT COMFORT

- IPAD
- 4 FANS WITH ADJUSTABLE INTENSITY
Q.A

RADIOTHERAPY

HYPERTHERMIA
• Requisiti Essenziali
• Gestione del rischio
• Descrizione del prodotto
• Ciclo di sviluppo, disegno ed implementazione
• Valutazione clinica (pubblicazioni)
• Documenti di progettazione (disegni meccanici, schemi elettrici, data sheet componenti critici)
• Prove di compatibilità elettromagnetica
• Schede materiali a contatto con il paziente e prove biocompatibilità
• Progetto di etichettatura
• Depliant e Manuali
• Dichiarazione di conformità
PATIENT SPECIFIC IMAGING (CT SCAN)
IN TREATMENT POSITION

60 cm

WATERBOLUS

CT SCAN / X RAY
WITH THERMOMETRIC PROBES INSERTED
TARGET DELINEATION (BLADDER)

transversal  sagittal  coronal
PATIENT POSITIONING

TISSUE SEGMENTATION

Transversal

Sagittal

Coronal

muscle
fat
bone
air
target
SEGMENTATION BASED ON CT HOUNSFIELD UNITS
SAR SIMULATION (W/Kg)

Transversal

Sagittal

Coronal

≥ 100 W kg⁻¹

0 W kg⁻¹
Penne’s Bioheat equation

$$\rho_c c T = \nabla (k \nabla T) + c_b w_b (T - T_b) + Q$$

TEMPERATURE SIMULATION (°C)

Transversal

45°C

≤ 37°C

Sagittal

Coronal
Graphical user interface provides visualization and assistance during treatment.
Graphical user interface provides visualization and assistance during treatment.

SAR/temperature visualization
MODELING BIOHEAT TRANSFER

Different methods available

1. Continuum  ➔  Pennes bio heat equation
2. Discrete vessels  ➔  e.g. DIVA (Discrete vasculature)

Kok et al, 2013
15 prostate cancer patients treated with RT without HT. The effect of adding HT to RT was evaluated using the AMC-4 regional HT device and assuming a 1-h time interval between RT and HT.

**Conclusion:**
adding HT is equivalent to a radiotherapy dose escalation of about 10 Gy,

76 Gy RT ALONE  →  86 Gy RT+ HT
All data are recorded in a standardized way according to the guidelines.

READY FOR MULTICENTRIC STUDY
Thank you for your attention
HT INHIBITS DNA REPAIR

A. Oei et al., Radiation Oncology, 2015
HT INHIBITS DNA REPAIR

A. Oei et al., Radiation Oncology, 2015