Dosimetry for advanced radiotherapy approaches using particle beams with ultra-high pulse dose rates (UHPDR) in the EMPIR UHDpulse project

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Outline

- Interest in UHPDR RT
- Challenges of dosimetry of UHPDR beams
- The EMPIR UHDpulse project
- First results
  - ionization chamber dosimetry in UHPDR VHEE beams
- Conclusions
Why are we interested in UHPDR RT?

- subcutaneous lymphoma
- delivery: 10 pulses (1 us) in 90 ms with 1.5 Gy/pulse

**FLASH effect!**

![Graph showing TCP, NTCP, and FLASH NTCP curves](image)

Favaudon, et al. Sci Transl Med 2014; 6

Review of FLASH studies (Wilson et al. Frontiers in Oncology 2020)

Summary of irradiation parameters and outcomes for in vivo studies investigating the FLASH effect

**Normal tissues**

<table>
<thead>
<tr>
<th>Model</th>
<th>Assay</th>
<th>FLASH dose modification factor (Bold if &gt; 1)</th>
<th>Total dose (Gy)</th>
<th>Irradiation delivery technique</th>
<th>Dose rate (Gy/s)</th>
<th>Pulse rate (Hz)</th>
<th>Modality of radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zebrafish embryo (1)</td>
<td>Fish length</td>
<td>1.3-1.5</td>
<td>10-12</td>
<td>Single pulse</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zebrafish embryo (3)</td>
<td>Fish length, survival, and rate of ocularia</td>
<td>1</td>
<td>0-43</td>
<td>100</td>
<td>0.106 x 10^4</td>
<td>Proton</td>
<td></td>
</tr>
<tr>
<td>Whole body irradiation of mice (8)</td>
<td>LD50</td>
<td>1.1</td>
<td>8-40</td>
<td>17-43</td>
<td>400</td>
<td>Electron</td>
<td></td>
</tr>
<tr>
<td>Thoracic irradiation of mice (6)</td>
<td>TGFbeta signaling induction</td>
<td>1.8</td>
<td>17</td>
<td>40-60</td>
<td>100-150</td>
<td>Electron</td>
<td></td>
</tr>
<tr>
<td>Thoracic irradiation of mice (9)</td>
<td>Number of proliferating cells, DNA damage, expression of inflammatory genes</td>
<td>&gt; 1</td>
<td>Significant Differences</td>
<td>40-60</td>
<td>100-150</td>
<td>Electron</td>
<td></td>
</tr>
</tbody>
</table>

**Tumour tissues**

<table>
<thead>
<tr>
<th>Model</th>
<th>Assay</th>
<th>FLASH dose modification factor (Bold if &gt; 1)</th>
<th>Total dose (Gy)</th>
<th>Irradiation delivery technique</th>
<th>Dose rate (Gy/s)</th>
<th>Pulse rate (Hz)</th>
<th>Modality of radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoric irradiation of orthotopic engrafted non-small cell lung cancer (Lewis lung carcinoma) in mice (10)</td>
<td>Tumor size and T-cell infiltration</td>
<td>18</td>
<td>40</td>
<td>?</td>
<td>Proton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thoric irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Lue in mice (11)</td>
<td>Survival and tumor Growth Delay</td>
<td>15-28</td>
<td>60</td>
<td>100-150</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal irradiation of mice (12)</td>
<td>Number of tumors, tumor weights</td>
<td>12-16</td>
<td>26</td>
<td>108</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain irradiation of nude mice with orthotopic engrafted H445 murine glioblastoma (13)</td>
<td>Tumor Growth Delay</td>
<td>10-25</td>
<td>2.8-5.8 x 10^5</td>
<td>Single pulse</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal irradiation of mice (16)</td>
<td>Local irradiation of subcutaneous engrafted Human breast cancer HEBV-1:2A, and head and neck carcinoma HEP-2 in nude mice (17)</td>
<td>15-25</td>
<td>60</td>
<td>100-150</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain irradiation of nude mice with orthotopic engrafted U87 human glioblastoma in nude mice (18)</td>
<td>Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)</td>
<td>10-30</td>
<td>125-5.10^6</td>
<td>100 or single pulse</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole brain irradiation of nude mice with orthotopic engrafted Human hypopharyngeal squamous cell carcinoma ATCC HT1080 in nude mice (20)</td>
<td>Local irradiation of subcutaneous engrafted human hypopharyngeal squamous cell carcinoma ATCC HT1080 in nude mice (21)</td>
<td>20</td>
<td>0.008 mean, 4 x 10^5 in pulse</td>
<td>&lt;1</td>
<td>Proton</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of locally advanced squamous cell carcinoma (SOC) in cat patients (22)</td>
<td>Tumor response and survival</td>
<td>25-41</td>
<td>120-300</td>
<td>100</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of C3H/HeJ T-cell cutaneous lymphoma T3 N1 D0 ID in human patient (23)</td>
<td>Tumor response</td>
<td>15</td>
<td>167</td>
<td>100</td>
<td>Electron</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Challenges of dosimetry of UHPDPR beams

Loss of collection efficiency in IC

CONV.  FLASH
Mean dose rate ➔ 0.05 Gy/s  vs  40-1000 Gy/s
Dose per pulse ➔ 0.3 mGy  vs  1-10 Gy
Dose in a pulse ➔ $10^2$ Gy/s  vs  $10^6$ Gy/s
Delivery time ➔ few min  vs  <1s

NEW DOSIMETRY TOOLS & METHODS NEEDED

USE THE RIGHT TOOL FOR THE RIGHT JOB

Petersson et al., Med Phys 44 (2017) 1157
EMPIR UHDpulse project

EMPIR Call: 2018 / Health (JRP)
Coordinator: Andreas Schüller (PTB)
Duration: 2019-2022
Start: 1. Sept. 2019
Funding: 2.1 M €

Topic: tools for traceable dose measurements for:
- FLASH radiotherapy
- VHEE radiotherapy
- laser driven medical accelerators

5 National Metrology Institutes
leading in the field of dosimetry
3 academic hospitals
pioneers in FLASH-RT
3 universities
experts in detector development
pioneer in laser-driven beams
3 national research institutes
pioneer in detector development
dosimetry expert
1 European research institute
laser-driven beam research
5 companies
expert in detector development

NMI’s
WP6 (coordin.)
WP1
WP2
WP5 (impact)

Irradiation facility provider

Radiation detector developer

WP3
WP4

5 companies
expert in detector development

http://uhdpulse-empir.eu/
Beams with ultra-high pulse dose rates

Courtesy of A. Schueller
WP1: Primary standards
- Definition of reference conditions
- Reference radiation fields
- Adapting primary standards (water calorimeter, Fricke dosimeter)
- Prototype graphite calorimeters for laser-driven beams

WP2: Secondary standards, relative dosimetry
- Transfer from primary standards
- Characterizing established detector systems
- Formalism for reference dosimetry for future Code of Practice

WP3: Detectors for primary beam
- Novel and custom-built active dosimetric systems
- Beam monitoring systems

WP4: Detectors and methods outside primary beam
- Active detection techniques for pulsed mixed radiation fields of stray radiation
- Methods with passive detectors
First experimental results: UHPDR VHEEs

OBJECTIVE: To study ion collection efficiency as a function of dose-per-pulse at instantaneous dose rates $5.0 \times 10^6 – 3.1 \times 10^8$ Gy/s for VHEE beams (energies suitable for deep-seated tumours)

- BEAM PARAMETERS: 200 MeV, x and y $\sigma$ of 5 mm, $\Delta E$ between 0.25 and 6.5%
- side-by-side measurements: PTW Roos chamber and NPL’s graphite calorimeter
- quantification of the recombination factor $k_{s,abs}$ for the Roos chamber for a range of collecting voltages: 75 V – 600 V

![Test-stand at the CLEAR facility, with the calorimeter, ion chamber and monitor chamber placed along the beam line with the beam travelling from right to left.](image)

<table>
<thead>
<tr>
<th>Nominal Beam Charge (nC/pulse)</th>
<th>$D_{w,cal}$ (Gy/pulse)</th>
<th>$k_{s,abs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>75 V</td>
<td>200 V</td>
</tr>
<tr>
<td>0.05</td>
<td>1.3</td>
<td>0.98</td>
</tr>
<tr>
<td>0.2</td>
<td>3.41</td>
<td>1.87</td>
</tr>
<tr>
<td>0.25</td>
<td>2.46</td>
<td>1.33</td>
</tr>
<tr>
<td>1</td>
<td>6.00</td>
<td>3.07</td>
</tr>
<tr>
<td>2.2</td>
<td>8.80</td>
<td>4.12</td>
</tr>
<tr>
<td>3</td>
<td>11.96</td>
<td>5.67</td>
</tr>
<tr>
<td>4.5</td>
<td>14.99</td>
<td>6.87</td>
</tr>
<tr>
<td>6</td>
<td>18.94</td>
<td>8.54</td>
</tr>
<tr>
<td>7.5</td>
<td>19.54</td>
<td>8.77</td>
</tr>
<tr>
<td>9</td>
<td>21.38</td>
<td>9.30</td>
</tr>
<tr>
<td>10.5</td>
<td>22.99</td>
<td>9.95</td>
</tr>
</tbody>
</table>

$k_{s,abs} = \frac{D_{w,cal}}{M k_{pol} k_{TP} k_{Q_0} N_{D,w,Q_0} k_{abs}}$
Results cont.

- \( k_s \) up to 10 (V = 200V) \( \rightarrow \) collection eff. 10%
- \( k_s \) up to 4 (V = 600V) \( \rightarrow \) collection eff. 25%
- \( k_{s,abs} \) compared with \( k_{s,TVA} \) (two-voltage method)

- Available recombination models include Boag’s free-electron fraction models (Boag 1996)
- By optimising the free-electron fraction parameter in these equations, we were able to determine a best fit of our data.
- All analytical models of Boag and Di Martino show similar predictions of the recombination factor and estimations of the free electron fraction
- Analytical (Boag 1996, Di Martino 2005) and logistic (Petterson 2017) models tested
- The logistic model from Petersson shows the best fit to data over the whole dose-per-pulse range, however this model has no physical meaning and simply relies on two fitting constants \( \alpha \) and \( \beta \)
Conclusions

- Tools and methods established for dosimetry of conventional RT sources are not suitable for UHPDR beams
- Challenges of dosimetry for ultra-high pulse dose rate to be addressed within EMPIR UHDpulse project
- Metrological and validated tools will be provided to support accurate preclinical studies and to enable future clinical applications for UHPDR beams
Thank you for your attention

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