Institute of radiation physics, Switzerland

Introduction to FLASH-RT

C. Bailat, PhD
Radiometry group leader
FLASH-RT in short: Irradiation at ultra high dose-rate increases the differential response between normal and tumour tissue.
Institute of Radiation Physics (IRA)

IRA: ~60 Collaborators

IRA provides expertise in:
- Medical physics
- Radiation protection
- Radiochemistry
- Radiopharmacy
- Radiometrology
CHUV is one of five university hospitals.

Connected to the biology and medicine department of UNIL

Over 11,000 employees

Over half a million annual hospitalization days

My name is Claude and I am a radiometrologist...

IRA: ~60 Collaborators

IRA provides expertise in:
- Medical physics
- Radiation protection
- Radiochemistry
- Radiopharmacy
- Radiometrology

Who can’t predict the weather
Metrology is the science of measurement

Measurement requires common knowledge

Need to share a common perception of what is meant by expressions such as meter, kilogram, liter, watt, etc.

Confidence is vital in enabling metrology to link human activities together across geographic and professional boundaries.
Metrology is the science of measurement

The International System of Units (SI)

The recommended practical system of units of measurement is the International System of Units (Système International d’Unités), with the international abbreviation SI.

The SI is defined by the SI Brochure, which is published by the BIPM.

In a landmark decision, Member States voted on 16 November 2018 to revise the SI, changing the world’s definition of the kilogram, the ampere, the kelvin and the mole.

This decision, made at the 26th meeting of the General Conference on Weights and Measures (CGPM), means that from 20 May 2019 all SI units are defined in terms of constants that describe the natural world. This will assure the future stability of the SI and open the opportunity for the use of new technologies, including quantum technologies, to implement the definitions.

The seven defining constants of the SI are:

- the caesium hyperfine frequency \( \Delta\nu_{\text{Cs}} \)
- the speed of light in vacuum \( c \)
- the Planck constant \( h \)
- the elementary charge \( e \)
- the Boltzmann constant \( k \)
- the Avogadro constant \( N_A \); and
- the luminous efficacy of a defined visible radiation \( K_L \).

The SI was previously defined in terms of seven base units and derived units defined as products of powers of the base units. The seven base units were chosen for historical reasons, and were, by convention, regarded as dimensionally independent: the metre, the kilogram, the second, the ampere, the kelvin, the mole, and the candela. This role for the base units continues in the present SI even though the SI itself is now defined in terms of the defining constants above.
Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement,
Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement
Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement, the meter.

2. The realization of units of measurement by scientific methods, the realization of a meter through the use of laser beams.

→ Primary measurements (another subject by itself!)
Metrology covers three main tasks:

1. The definition of internationally accepted units of measurement,

2. The realization of units of measurement by scientific methods,

3. The establishment of traceability chains in documenting the accuracy of a measurement,
And then comes the BIPM …. The umbrella organization!

BIPM: bureau international des poids et mesures
Units of measure for radioactivity

- The number of falling apples can be compared to the Becquerel (number of disintegrations per second).
- The number of apples that hit the sleeper can be compared to the Gray (absorbed dose).
- The effect on the body, based on the size or weight of the apples, can be compared to the Sievert (effective dose).
History of FLASH radiotherapy (FLASH-RT)?

1970s

1st observation

Now and beyond

Clinical transfer

TIMELINE
FLASH-RT timeline: from effect to RT

1970s
- 1st observation

Since 2014
- Preclinical studies

2018
- Transfer to pig model

2019
- Phase I trial
- First in human

2021?
- Phase III trial (ongoing)
- Clinical transfer
FLASH timeline

1970s
1st observation

Since 2014
Preclinical studies

2018
Transfer to pig model

2019
Phase I trial
First in human

2021?
Phase III trial (ongoing)
Clinical transfer
- 4-6 MeV electron beam
- Pulsed e-beam of high intensity with some flexible parameters
eRT6: **pulsed** 6 MeV e-beam of **high intensity** with some flexible parameters

\[ \dot{D}_m = D_p \cdot f \]
\[ D_p = \frac{D_p}{w} \]

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( w )</td>
<td>pulse width</td>
<td>0.5 – 2.2 ( \mu s )</td>
</tr>
<tr>
<td>( f )</td>
<td>pulse repetition frequency</td>
<td>10 – 200 Hz</td>
</tr>
<tr>
<td>( \dot{D}_p )</td>
<td>dose-rate in pulse</td>
<td>( 10^3 – 5 \cdot 10^6 ) Gy / s</td>
</tr>
<tr>
<td>( D_p )</td>
<td>dose per pulse</td>
<td>( 10^{-3} – 10 ) Gy</td>
</tr>
<tr>
<td>( \dot{D}_m )</td>
<td>mean dose-rate</td>
<td>( 10^{-2} – 1000 ) Gy / s</td>
</tr>
</tbody>
</table>
Flash parameters vs conventional

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flash</th>
<th>Conv</th>
</tr>
</thead>
<tbody>
<tr>
<td>$GT (V)$</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>$w (\mu s)$</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>$f (Hz)$</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>$\dot{D}_m (Gy/s)$</td>
<td>200</td>
<td>0.05</td>
</tr>
<tr>
<td>$\dot{D}_p (Gy/s)$</td>
<td>$4.5 \times 10^5$</td>
<td>$4.9 \times 10^3$</td>
</tr>
</tbody>
</table>

- **EFFECT**
  - Time to deliver 20Gy: ~200 ms (\(\mu s\))

- **NO EFFECT**
  - Time to deliver 20Gy: ~500 sec (8 min)
Flash parameters vs conventional

**Table I. Parameter definitions and corresponding dose-rates (at a SSD of 1 m and at the depth of dose maximum in water) of the Flash and Conv functioning modes of the eRT6.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Flash</th>
<th>Conv</th>
</tr>
</thead>
<tbody>
<tr>
<td>$GT$ (V)</td>
<td>300</td>
<td>100</td>
</tr>
<tr>
<td>$w$ (µs)</td>
<td>2.2</td>
<td>1.0</td>
</tr>
<tr>
<td>$f$ (Hz)</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>$\dot{D}_m$ (Gy/s)</td>
<td>200</td>
<td>0.05</td>
</tr>
<tr>
<td>$\dot{D}_p$ (Gy/s)</td>
<td>$4.5 \times 10^5$</td>
<td>$4.9 \times 10^3$</td>
</tr>
</tbody>
</table>

**WHAT DOES IT MEAN?**

Time to deliver 20Gy
Tumor growth: 10 Mio cells engrafted in mice

No clear difference
Mice survival: Glioblastoma; 15 Gy WBI

No difference in survival
Novel Object Recognition on 10Gy WBI mice

Clear difference!
Survival is the same using Flash-RT or conventional RT, BUT cognitive abilities are preserved.
Treatment of Cats patient using Flash-RT

- Good tolerance of Flash-RT
  (single dose ~30 Gy)
  - Only mild acute reactions
  - Irreversible alopecia
  - Percentage Survival fraction of 84%
    at 1 year

FLASH effects found in mini-pig
Conventional irradiation induces necrosis at same dose.

Differential response between normal and tumour tissue increased at ultra-high dose-rates:

- Healthy tissue protection compared to conv. RT
- Equivalent tumor control than in conv. RT

Short treatment time also offers motion management and an increased patient comfort.

First patient treated in 2018 (CD30+ T-cell cutaneous lymphoma).

*J. Bourhis et al (2019)*
How do you compare 2 experiments in time and space

1970s
1st observation

Since 2014
Preclinical studies

2018
Transfer to pig model

2019
Phase I trial
First in human

2021?
Phase III trial (ongoing)
Clinical transfer

How do you repeat an experiment

How do you guarantee prescribed dose
How do you compare 2 experiments in time and space

How do you repeat an experiment

How do you guarantee prescribed dose

1970s

1st observation

Since 2014

Preclinical studies

2018

Transfer to pig model

2019

Phase I trial

2021?

Phase III trial (ongoing)

Clinical transfer

Dosimetry/traceability
The narrative is set after the facts..... We had to work in the dark for some years....

First some pre-clinical irradiation examples
Dosimetry for Cats – Phase 3 randomized trial

Dosimeters positioning

34 Gy single fraction
RT FLASH

14 months post-RT
Vozenin et al. 2018

Patient positioning
Beam characterization

Example: carbon collimator (26 mm diameter)

Dose profile (at prescription depth)

Depth dose

Jorge et al (2019)
Mice total body irradiations (TBI)
Dosimetric preparation performed using TLD and water (~mice) inside the box.

<table>
<thead>
<tr>
<th>Prescribed dose [Gy]</th>
<th>Delivery time [ms]</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>20</td>
<td>0.96</td>
</tr>
</tbody>
</table>
Mice total body irradiations (TBI)
Dosimetric validation performed using TLD and MOUSE inside the box.

<table>
<thead>
<tr>
<th>Prescribed dose [Gy]</th>
<th>Depth [cm]</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.5</td>
</tr>
</tbody>
</table>

X1: TLD head (between skin and skull)
X2: TLD front leg exit (between skin and muscle)
X3: TLD back leg entrance (between skin and muscle)
X4: TLD thorax (between skin and ribs)
X5: TLD under the gut (in the abdominal cavity)
X6: TLD back (between skin and spinal cord)

<table>
<thead>
<tr>
<th></th>
<th>Flash</th>
<th>Conv</th>
</tr>
</thead>
<tbody>
<tr>
<td>X1 at 3 mm</td>
<td>6.58</td>
<td>6.48</td>
</tr>
<tr>
<td>X2 at 16 mm</td>
<td>7.25</td>
<td>7.10</td>
</tr>
<tr>
<td>X3 at 1 mm</td>
<td>6.32</td>
<td>6.96</td>
</tr>
<tr>
<td>X4 at 7 mm</td>
<td>7.87</td>
<td>7.36</td>
</tr>
<tr>
<td>X5 at 10 mm</td>
<td>8.37</td>
<td>7.53</td>
</tr>
<tr>
<td>X6 at 3 mm</td>
<td>6.7</td>
<td>Not done</td>
</tr>
</tbody>
</table>
TLD in mouse brain

- Prescribed dose: 10 Gy
  → 10 Gy in the central part
- Slightly less on the sides
- Similar values in both modes
Mini-pig

Dosimetric preparation performed with a alanine pellets at the surface of a solid water phantom.

<table>
<thead>
<tr>
<th>Prescribed dose [Gy]</th>
<th>Delivery time [ms]</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>90</td>
<td>1.079</td>
</tr>
</tbody>
</table>
Zebrafish embryos

Dosimetric preparation performed with a wrapped TLD inside the 2ml Eppendorf tube.

<table>
<thead>
<tr>
<th>Prescribed dose [Gy]</th>
<th>Delivery time [ms]</th>
<th>$R$</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.002</td>
<td>1.039</td>
</tr>
</tbody>
</table>
The dosimetry relies on adequate detectors and traceability.
Adequate $\rightarrow \sim 5\%$ uncertainty
Traceability $\rightarrow$ if one wants to compare across users and/or sites

How is the traceability chain from primary to absorbed dose to water for a specific organ in external beam radiotherapy?
~6 steps of the traceability chain

traceability chain for external beam radiotherapy
1) Primary standard

Water calorimeter for example

<table>
<thead>
<tr>
<th></th>
<th>Cont.</th>
<th>High energy XR</th>
<th>High energy electrons</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 %</td>
<td>1.0 %</td>
<td>1.6 %</td>
<td></td>
</tr>
</tbody>
</table>
1) Primary standard
2) Secondary standard

<table>
<thead>
<tr>
<th>Cont.</th>
<th>High energy XR</th>
<th>High energy electrons</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 %</td>
<td>1.0 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>2</td>
<td>1.1 %</td>
<td>1.4 %</td>
<td>1.4 %</td>
</tr>
</tbody>
</table>

Local reference conditions
1) Primary standard
2) Secondary standard
3) Local conditions

For example:
Depth → use of percentage dose depth curves (PDD);
Energy → beam quality correction factor ($N_Q$)
1) Primary standard
2) Secondary standard
3) Local conditions

<table>
<thead>
<tr>
<th></th>
<th>Cont.</th>
<th>High energy XR</th>
<th>High energy electrons</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 %</td>
<td>1.0 %</td>
<td></td>
<td>1.6 %</td>
</tr>
<tr>
<td>2</td>
<td>1.1 %</td>
<td>1.4 %</td>
<td></td>
<td>1.4 %</td>
</tr>
<tr>
<td>3</td>
<td>1.7 %</td>
<td>1.4 %</td>
<td></td>
<td>1.7 %</td>
</tr>
</tbody>
</table>
## Uncertainty budget

<table>
<thead>
<tr>
<th>Cont.</th>
<th>High energy XR</th>
<th>High energy electrons</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 %</td>
<td>1.0 %</td>
<td>1.6 %</td>
</tr>
<tr>
<td>2</td>
<td>1.1 %</td>
<td>1.4 %</td>
<td>1.4 %</td>
</tr>
<tr>
<td>3</td>
<td>1.7 %</td>
<td>1.4 %</td>
<td>1.7 %</td>
</tr>
<tr>
<td>4</td>
<td>2.9 %</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>3.0 %</td>
<td>2.1 %</td>
<td>11.5 %</td>
</tr>
<tr>
<td>6</td>
<td>2.0 %</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Total</td>
<td>5.0 %</td>
<td>3.1 %</td>
<td>12 %</td>
</tr>
</tbody>
</table>
Uncertainty budget

<table>
<thead>
<tr>
<th>Cont.</th>
<th>High energy XR</th>
<th>High energy electrons</th>
<th>Brachytherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.9 %</td>
<td>1.0 %</td>
<td>n.a.</td>
</tr>
<tr>
<td>2</td>
<td>1.1 %</td>
<td>1.4 %</td>
<td>1.4 %</td>
</tr>
<tr>
<td>3</td>
<td>1.7 %</td>
<td>1.4 %</td>
<td>1.7 %</td>
</tr>
<tr>
<td>4</td>
<td>2.9 %</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>5</td>
<td>3.0 %</td>
<td>2.1 %</td>
<td>11.5 %</td>
</tr>
<tr>
<td>6</td>
<td>2.0 %</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>Total</td>
<td>5.0 %</td>
<td>3.1 %</td>
<td>12 %</td>
</tr>
</tbody>
</table>
Our Goals for a safe use of FLASH-RT:
Ensure a **reliable and accurate** dose delivery

- Reliable
- Accurate
- Reproducible vs time

**REPEATABILITY**

**TRACEABILITY**

**STABILITY**
REPEATABILITY

RELATIVE DOSIMETRY
- Time resolution
- Response to beam parameters
- Energy response

TRACEABILITY

RELATIVE STABILITY
- short (minutes)
- medium (hours)
- long (days)

ABSOLUTE DOSIMETRY:
Calibration traceable to international standards (primary meas., NMI).

STABILITY

MEASUREMENT

Solid water  |  EBT3 film
Primary collimator
Irradiation bench

BEAM

[Diagram showing targets and measurements]
Ensure a **reliable** and **accurate** dose delivery

- Reliable
- Accurate
- Reproducible vs time

→ Agreement across various locations
Ensure a **reliable** and **accurate** dose delivery

- Reliable
- Accurate
- Reproducible vs time
EMPIR project UHDpulse
“Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates”

• Reliable
• Accurate
• Reproducible vs time
• Beam is not **standard** (dose rate, field size, …) 
  → no primary standard, no commissioning protocol, etc etc etc!!!

• Need to adapt our methodology established using conventional LINACs.
Five different dosimeters:

- Films
- Ionization chamber
- Thermoluminescent dosimeter (TLD)
- Methyl viologen
- Alanine
Five different dosimeters:

- Films
- Ionization chamber
- Thermoluminescent dosimeter (TLD)
- Methyl viologen
- Alanine
Our strategy:

- 5 different detecting principles
- Start with reference conditions (conventional LINAC) and extrapolate to Flash
- Films
- Ionization chamber
- Thermoluminescent dosimeter (TLD)
- Methyl viologen
- Alanine
Redundancy of dosimetric measurements ➔ traceability

Agreement within 3 % for FLASH and within 2 % for CONV
Dose-rate independent

- Radiochromic films
- TLD
- Alanine

Dose-rate dependent

- Ionization chambers
  - Advanced Markus

High dose-per-pulse $\rightarrow$ Saturation


Our Goals for a safe use of FLASH-RT:
Ensure a reliable and accurate dose delivery

- Reliable
- Accurate
- Reproducible vs time
Dosimetric procedure for UHDR-RT

Procedure developed for three setups:

a) PMMA box (mice)
b) Water Tank (zebrafish)
c) Collimator (mini-pig)

Differences between setups:

• Depth
• SSD
• Collimators
• Surrounding matter
• Field size

Uncertainty 15% → 3%
• Our framework suffers from a major drawback:
  • We are monitoring the beam before and after irradiation, but not during!!!

• We insure an adequate beam output repeatability, but still, s… happens!

• On conventional LINACS: semi-transparent ionization chamber
  • 📊 for FLASH…. Saturation → non linearity

… and now what??
• Beam monitored by measuring the charge/current

• Two AC Current Transformers (ACCT):
  • CONV - 10 mA full scale
  • UHDR - 300 mA full scale
General strategy we adopted *(recipe for non-disaster)*

- Listen to users (especially if there are not physicists....)
- Take your validated tools
- Move stepwise away from reference conditions and document
- Use redundant techniques
- Use various detecting principles
- Move one parameter at a time and document
Traceability refers to an unbroken chain of comparisons relating an instrument's measurements to a known standard.

How do we build a chain of traceability?
METROLOGY means traceability

Traceability refers to an unbroken chain of comparisons relating an instrument's measurements to a known standard.

How do we build a chain of traceability?
Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
  - Calibrations → instruments

Highest level of accuracy

Lowest level of accuracy
Building a chain of traceability

- International prototype
- Primary national standard
- Secondary standards
- Working standards - Calibrations → instruments

Highest level of accuracy

Lowest level of accuracy

Preclinical FLASH-RT
Building a chain of traceability

International prototype

Primary national standard

Secondary standards

Working standards
  - Calibrations → instruments

Highest level of accuracy

Needs to set this value pragmatically
(level of the investigated effect, tools, time, ...)

Lowest level of accuracy

U = ?

Preclinical FLASH-RT
Building a chain of traceability

Highest level of accuracy

International prototype
Primary national standard
Secondary standards
Working standards - Calibrations \(\rightarrow\) instruments

Lowest level of accuracy

U about 5%

Preclinical FLASH-RT
Building a chain of traceability

- International prototype
- Primary national standard
- Secondary standards
- Working standards
  - Calibrations → instruments

Highest level of accuracy

SIR

U ~ 2-3 %

UHDpulse

Calibration lab, NMI, ...

Lowest level of accuracy

U ~ 5-10 %

Preclinical FLASH-RT
Now what….

Radiometrologists are still improving dosimetry (UHDpulse project)

Radiobiologists are still designing experiments to test FLASH effects in various locations

Radiochemists and physicists are designing experiments to understand the FLASH effect

Beam physicists are designing new irradiation facilities

Physicists are designing detectors

And companies are writing patents to make money…..
Whole Brain Irradiation (WBI)
Conventional dose rate RT vs. FLASH-RT

Flash is really a flash

Conventional dose rate RT

Dose delivered in minutes

FLASH-RT

Dose delivered in about 0.1 seconds