FLASH RADIATION THERAPY – CURRENT STATUS AND THE WAY TO THE CLINIC

LATEST RESULTS AND ADVANCES TOWARDS CLINICAL FLASH-RT

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Latest results and advances towards clinical FLASH-RT

Latest preclinical results on the brain

Glioblastoma and cognition

Juvenile model to foresee medulloblastoma treatment

Clinical transfer

Which beam parameters?

Which technology with electrons?

What are the challenges?
FLASH-RT is efficacious against GBM and protects the brain functions

Montay-Guel et al (in revision)
Please do not circulate
Towards hypo-fractionation?

Montay-Gruel et al (in revision)

Please do not circulate.
What about complete tumor control?

Montay-Gruel et al (in revision)
Please do not circulate
Advantages of protecting the normal tissue

Medulloblastoma patients

→ Long term survival achieved >80% pediatric cases
→ Surgery followed by cranio-spinal RT + chemo

→ Significant impairments
cognition,
mood disorders,
endocrine dysfunction,
cerebrovascular complications

WBRT 8 Gy FLASH / CONV-RT
3 week old pups
Cognitive investigation
Conservation of complex cognitive functions in young animals

A

Training Sessions (days 1-3)

Update Session (day 4)

Test Session (day 5)

Original
Updated
Novel
Initial

B

Update Session

2 months post-RT

4 months post-RT

Discrimination Index (%)  

- Control
- CONV
- FLASH

Discrimination Index (%)  

- Control
- CONV
- FLASH
Cellular preservation

Absence of neurogenesis impairment

Absence of neuroinflammation

Preservation of the endocrine system
Integrity of the adult cerebrovascular system after FLASH-RT

Preservation of tight junctions

A

Control
Lectin
Claudin-5
Occludin
Merged

CONV

FLASH

B

Blood Vessel Volume 1 Month

Colocalized eNOS 1 Month

A

Lectin / Image Vou (μm³)

Colocalized / Lectin (μm³)

Control
CONV RT
FLASH RT

Control
CONV
FLASH

24 Hours
1 Week

Hippocampus

SVZ

Occludin
Claudin-5

24 Hours
1 Week
Are electron beams suitable to transfer FLASH-RT to the clinics?
What are the challenges?
What do we know about the optimal parameters to obtain the FLASH effect?
What do we know about the optimal parameters to obtain the FLASH effect?

**FIGURE 1** | (Ideal) Pulsed FLASH-RT delivery. A schematic view of a pulsed beam delivery, specifying some parameters which seem to be important for inducing the FLASH effect.
Which technologies are currently available for a clinical transfer?

What are the challenges?

<table>
<thead>
<tr>
<th>Radiation source</th>
<th>Modality of radiation</th>
<th>Advantages (+)</th>
<th>Disadvantages (-)</th>
<th>Currently available for FLASH-RT clinical studies, with which main limitations?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very High Energy Electron linear accelerator (69, 69) or Laser plasma accelerators (70, 71)</td>
<td>100–250 MeV Electrons</td>
<td>Good depth penetration. Electromagnetic steering and focusing. Not sensitive to tissue heterogeneity.</td>
<td>Low pulse rate (1–10 Hz) for Laser plasma accelerators. Limited beam size.</td>
<td>No</td>
</tr>
<tr>
<td>Cyclotrons, synchrotrons or Synchrocyclotron (11, 76)</td>
<td>100–250 MeV Protons</td>
<td>Good depth penetration. Electromagnetic steering possible. Limited dose-bath. Electromagnetic steering.</td>
<td>Large expensive sources. Sensitive to tissue heterogeneity. Higher LET in Bragg peak. Beam scanning or scattering required to cover target volumes.</td>
<td>Yes, FLASH effect might be lost with beam scanning and/or higher LET.</td>
</tr>
<tr>
<td>Synchrotron (24, 32)</td>
<td>50–600 keV X-rays</td>
<td>Microbeam Radiation Therapy possible.</td>
<td></td>
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<tr>
<td>Electron linear accelerator with high density target (20)</td>
<td>6–10 MV X-rays</td>
<td>Good depth penetration. Narrow penumbra. Minor beam size limitation.</td>
<td>Multiple beam angles required.</td>
<td>No</td>
</tr>
</tbody>
</table>
External beam RT with 5-6 MeV LINAC is suitable for superficial skin tumor treatments

First in Human

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis a,b,*, Wendy Jeanneret Sozzi a, Patrik Gonçalves Jorge a,b,*, Olivier Gaide d,
Claude Bailat c, Frédéric Duclos a, David Patin a, Mahnut Ozhahin a, François Bochud a,
Jean-François Germond c, Raphaël Moeckli c, Marie-Catherine Vozenin a,b,1

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Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of the PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 4 epithelitis NCI-CTCAE v. 5.0); (c) at 5 months.
Intra Operative RT will overstep the depth penetration challenge associated with electron beams

- Relatively high single doses
- Access to deeper tumors
- Extremely fast beam-on time: advantage for surgery
- Protection of the surrounding normal tissues

Multiple clinical applications
Conclusions

More and more preclinical data showing in different models

- Protection of the normal tissues: from cellular effect to organ function
- Efficacious anti tumor effect with single doses or hypo fractionated regimen

Current studies are aiming at defining the optimal parameters to reach the FLASH effect

- Mean dose rate
- Instantaneous (intra-pulse dose rate)
- Pulse repetition (frequency)
- Dose per pulse
- Total dose
- Total delivery time

Clinical transfer is almost ready, with challenges yet to overcome (electrons)

- Penetration in the tissue (possibility of IORT or superficial tumors with EBRT)
- No available VHEE technology available yet
Animal Facilities of Epalinges and Irvine