Clinical translation of FLASH radiation therapy: What has been done and the challenges still ahead.
Outline

1. Veterinary experience

2. Ongoing / Upcoming clinical trials

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy
1. Veterinary experience: Cats & Dogs – Electrons

- Experimental / Modified medical LINAC, Electron 4.5 - 6, 10 MeV
- Single-fraction
- Single-beam
- A few pulses (µs, > 1 Gy) per fraction
- Dose rate : 130 – 500 Gy/s

<table>
<thead>
<tr>
<th>Dose escalation</th>
<th>Treatment time (ms)</th>
<th>Field size (mm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cats 25 – 41 Gy</td>
<td>80 - 300</td>
<td>20 x 30</td>
</tr>
<tr>
<td>Dogs 15 – 35 Gy</td>
<td>30 - 75</td>
<td>80 x 40</td>
</tr>
</tbody>
</table>

Feasibility / Safety studies, Dose-escalation Superficial tumors:
- Feline Nasal Planum Squamous Cell Carcinoma
- Canine Sarcoma, Mastocytoma, Plasmacytoma, Melanoma, Squamous Carcinoma

Konradsson et al. Front Oncol 2021
1. Veterinary experience: Cats & Dogs – Electrons

**Feasibility / Safety studies, Dose-escalation Superficial tumors:**
- Feline Nasal Planum Squamous Cell Carcinoma
- Canine Sarcoma, Mastocytoma, Plasmacytoma, Melanoma, Squamous Carcinoma

**Complete response:** 5/6 cats, 5/10 dogs
**Partial response / Stable disease:** 3/10 dogs
**Recurrence / Progressive disease:** 1/10 cats, 2/10 dogs
**Side effects:** mild (depilation, grade 1), except 1 dog (35 Gy), medium (moist desquamation, grade 3); no severe early or late reactions.

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Konradsson et al. Front Oncol 2021
Fidel et al. Vet Radiol Ultrasound, 2001
1. Veterinary experience: Dogs – Protons

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Breed</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Dose rate (Gy/s)</th>
<th>Dose (Gy)</th>
<th>FLASH or standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Black Lab</td>
<td>11.0</td>
<td>F</td>
<td>33.1</td>
<td>76.2</td>
<td>8.1</td>
<td>F</td>
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<tr>
<td>2</td>
<td>St Bernard</td>
<td>4.5</td>
<td>M</td>
<td>61.4</td>
<td>61.0</td>
<td>4.0</td>
<td>F</td>
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<tr>
<td>3</td>
<td>Mastiff</td>
<td>6.0</td>
<td>M</td>
<td>57.0</td>
<td>10.0</td>
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<tr>
<td>4</td>
<td>Mastiff</td>
<td>6.5</td>
<td>M</td>
<td>59.6</td>
<td>0.5</td>
<td>8.0</td>
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<tr>
<td>5</td>
<td>Rottweiler</td>
<td>8.0</td>
<td>M</td>
<td>55.2</td>
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<tr>
<td>6</td>
<td>Mixed Breed</td>
<td>8.0</td>
<td>M</td>
<td>25.2</td>
<td>0.5</td>
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<tr>
<td>7</td>
<td>Doberman/Great Dane Mix</td>
<td>5.5</td>
<td>F</td>
<td>45.9</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
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<tr>
<td>8</td>
<td>Mixed Breed</td>
<td>7.0</td>
<td>F</td>
<td>29.8</td>
<td>0.5</td>
<td>8.0</td>
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<td>9</td>
<td>Golden Retriever</td>
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<td>10</td>
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<td>Great Pyrenees</td>
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<td>M</td>
<td>45.4</td>
<td>0.5</td>
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<td>F</td>
</tr>
<tr>
<td>13a</td>
<td>Mixed Breed</td>
<td>8.0</td>
<td>M</td>
<td>36.0</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
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<tr>
<td>14a</td>
<td>Doberman</td>
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<td>M</td>
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<td>8.0</td>
<td>F</td>
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<tr>
<td>15</td>
<td>Labrador Mix</td>
<td>10.0</td>
<td>M</td>
<td>42.5</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
</tr>
<tr>
<td>16</td>
<td>Great Dane</td>
<td>5.0</td>
<td>M</td>
<td>71.0</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
</tr>
<tr>
<td>17</td>
<td>Rottweiler</td>
<td>6.0</td>
<td>M</td>
<td>34.4</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
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<tr>
<td>18</td>
<td>Rottweiler/Husky</td>
<td>10.0</td>
<td>M</td>
<td>46.3</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
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<tr>
<td>19</td>
<td>Greyhound</td>
<td>1.5</td>
<td>M</td>
<td>28.0</td>
<td>0.5</td>
<td>8.0</td>
<td>F</td>
</tr>
</tbody>
</table>

- Medical Cyclotron, Proton 230 MeV
- Single-fraction
- Single beam (Double scattering), before BP
- Quasi-continuous beam
- Dose rate: 60 – 130 Gy/s (FLASH) + 0.5 Gy/s (CONV)

- Side effects, within 5 days (preoperatively): 1 tumor lysis.
- Absence of increase of inflammation marker (TGF-β1), comparable with preclinical mouse models.

Canine Osteosarcoma

Velalopoulou et al. Cancer Res 2021

Keith Cengel, ESTRO 2021

Dose | Treatment time (ms) | Field size
--- |---------------------|-----------
Dogs | 8 – 12 Gy           | ~ 100     | ~ cm²    
1. Veterinary experience

2. Ongoing / Upcoming clinical trials

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy
2. Ongoing / Upcoming clinical trials: Cutaneous Lymphoma

- Experimental LINAC, Electron 6 MeV
- Single-fraction
- Dose: 15 Gy
- Single beam
- 10 pulses (1µs) per fraction
- Field size: 3.5-cm diameter
- Treatment time: 0.09s
- Dose rate: 167 Gy/s

- Complete response
- Side effects: redness, oedema, no severe early or late reactions.

First human patient treated with FLASH RT
*Bourhis et al. Radiother&Oncol 2019*

Ongoing:
- Dose escalation trial (skin melanoma metastasis) 22 – 34 Gy
- Randomized trial FLASH vs CONV

Jean Bourhis, ESTRO 2021
2. Ongoing / Upcoming clinical trials: Bone metastasis - Protons

FAST-01 (FeAsibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases)
*Cincinnati Children’s/UCHealth Proton Therapy Center, 2020*
*PI: John Breneman, MD*

**Palliative treatment of Bone metastasis**

- Medical Cyclotron, Proton
- **Single-fraction**
- Dose: 8 Gy
- **Single beam, before BP**
- Quasi-continuous beam
- treatment field sizes: 7.5 cm x 7.5 cm; 7.5 cm x 10 cm; 7.5 cm x 12 cm; 7.5 cm x 14 cm; 7.5 cm x 16 cm; 7.5 cm x 18 cm; 7.5 cm x 20 cm

**Endpoints:**
- Equivalent Pain response
- Any possible adverse side effects
- Workflow feasibility
2. Ongoing / Upcoming clinical trials: Intraoperative electron RT

- **Mobetron – IntraOp**
- **FLASH LIAC – SIT**
- **FlashKnife – PMB**

- Electron 6 – 10 – 12 MeV
- Single-fraction
- Dose: 10 – 35 Gy
- Single beam
- A few pulses per fraction
- Field size: 3 – 12 cm diameter
- Dose rate: Hundreds of Gy/s
2. Ongoing / Upcoming clinical trials: Intraoperative electron RT

<table>
<thead>
<tr>
<th>eIORT Indication</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial breast irradiation</td>
<td>Volume/Dose increase</td>
</tr>
<tr>
<td>Breast Boost</td>
<td>Lowered Side effects</td>
</tr>
<tr>
<td>Extremities Soft Tissue Sarcoma</td>
<td>Lowered Side effects</td>
</tr>
<tr>
<td>Skin cancer - Non-melanoma</td>
<td>Lowered Side effects, Hypofractionation</td>
</tr>
<tr>
<td>Recurrent Rectal Cancer</td>
<td>Both</td>
</tr>
<tr>
<td>Unresected pancreatic Cancer</td>
<td>Both</td>
</tr>
<tr>
<td>Retroperitoneal Soft Tissue Sarcoma</td>
<td>Both</td>
</tr>
<tr>
<td>High-grade Brain Tumor</td>
<td>Both</td>
</tr>
<tr>
<td>Skin cancer - Melanoma</td>
<td>Both (EBRT)</td>
</tr>
</tbody>
</table>

Philip Poortmans, ESTRO 2021
1. Veterinary experience

2. Ongoing / Upcoming clinical trials

3. Some remaining challenges for clinical use of FLASH (VHEE) therapy
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**FEASIBILITY**

1. Large volumes
2. Higher fluence (particle/cm²)
3. Scanning technique
4. Re-irradiation of parts of the volume
5. Within < ~ 300 ms
6.
7.
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

**FEASIBILITY**

1. Large volumes
2. Reference dose
3. Direct reading
4. Accuracy / spatial resolution
5. Traceability
6. VHEE?

Task Group No. 359 – Chair Dimitris Mihailidis
FLASH (ultra-high dose rate) radiation dosimetry
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

**FEASIBILITY**

1. Large volumes
2. Reference dose
3. Beam monitoring
4. 
5. 
6. 
7.

![Graph showing dose per pulse and total IR duration](image)

- **Dose-per-pulse < Total dose / 5**
- Total IR duration
- Amplitude
- Time (µs)

**Time (µs)**

1

$10^4$

//

**Gy**
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

**EFFICACY**
FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
3. Beam monitoring
4. Multiple beams to achieve conformational dose distribution
5. Re-irradiation of parts of the volume
6. Within < ~ 300 ms ???
7. 2 crossing beams

3 intensity-modulated beams

Volumetric Arc-therapy
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

**EFFICACY**

FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
3. Beam monitoring
4. Multiple beams to achieve conformational dose distribution
5. Daily fractionation
6. Patient/Tumor positioning
7. In-vivo dosimetry

Where $D$ is the total dose
$d$ is the fractional dose
$T$ is the overall time of the treatment
- $\alpha/\beta$ ratio of 10 is typically used for tumors.
- $\alpha/\beta$ ratio of 3 is typically used for normal tissues.

$$BED = D \left[ 1 + \frac{d}{\alpha/\beta} \right] - K (T - T_K)$$
3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

ACCURACY

FLASH have to compete with modern RT techniques

1. Large volumes
2. Reference dose
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3. Some remaining challenges for clinical use of FLASH (VHEE) therapy

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5. Daily fractionation
6. Patient / Tumor positioning
7. In-vivo dosimetry
8. ...

Sophie Heinrich | Strathclyde Virtual Workshop: Ultra-high Dose Rate RT | 20 September 2021
CONCLUSION

GREAT HOPES...
BUT A LOT TO THINK ABOUT!

Thank you for your attention

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