FLASH Radiotherapy: A Look at Ultra-high Dose Rate Research and Treatment Plans

Anthony Magliari, MS CMD
2019 AAMD National Meeting
I am employed by Varian Medical Systems on the Medical Affairs team. My job currently includes testing new products and providing feedback. I’ve spent a portion of my time over the last two years as a member of Varian’s “FLASH core team”. I used development builds of Eclipse and Non Clinical modes of the ProBeam delivery system for examples.

Previous AAMD talks:
- 2016 Role of the Dosimetrist in the Knowledge Based Planning Era
- 2017 IMRT and VMAT: current and future best practices

DISCLAIMER:
The views expressed in this presentation are mine, and mine alone. They do not represent those of Varian Medical Systems.
Disclaimer 2: FLASH Intellectual Property

- Varian intends to leverage all intellectual property protections and are committed to protecting our innovations throughout the world.

- To date, we have filed over fifteen patent applications worldwide related to FLASH therapy and enabling technologies. Varian already has two issued patents in technologies to support particle therapy delivery in less than one second.

**US granted patents/pending applications**
U.S. No. 9,855,445 ; U.S. No. 10,092,774 ; U.S. No. 10,183,179; 15/850,472; 15/842,693; 16/041,636; 15/656,973; 15/657,052; 15/657,094; 15/657,010; 15/657,072; 15/656,937; 15/657,036; 62/700,783; 16/146,972

**Foreign counterpart applications**
Disclaimer 3: FLASH Intellectual Property

- **U.S. No. 9,855,445**  Radiation therapy systems and methods for delivering doses to a target volume

  A radiation therapy system includes an accelerator and beam transport system that generates a beam of particles. The accelerator and beam transport system guides the beam on a path and into a nozzle that can aim the beam toward an object. The nozzle includes a beam energy adjuster that can adjust the beam by, for example, placing different thicknesses of material in the path of the beam to affect the energies of the particles in the beam to deliver a dose to the object with a Spread Out Bragg Peak.

- Claim 17,24 wherein the dose delivered along the segment is at least four grays and is delivered in less than one second.

- **U.S. No. 10,092,774**  Dose aspects of radiation therapy planning and treatment

  Radiation treatment planning includes accessing values of parameters such as a number of beams to be directed into sub-volumes in a target, beam directions, and beam energies. Information that specifies limits for the radiation treatment plan are accessed. The limits include a limit on irradiation time for each sub-volume outside the target. Other limits can include a limit on irradiation time for each sub-volume in the target, a limit on dose rate for each sub-volume in the target, and a limit on dose rate for each sub-volume outside the target. The values of the parameters are adjusted until the irradiation time for each sub-volume outside the target satisfies the maximum limit on irradiation time.

- **U.S. No. 10,183,179**  Triggered treatment systems and methods

  In various embodiments, a radiation therapy method can include loading a planning image of a target in a human. In addition, the position of the target can be monitored. A computation can be made of an occurrence of substantial alignment between the position of the target and the target of the planning image. Furthermore, after the computing, a beam of radiation is triggered to deliver a dosage to the target in a short period of time (e.g., less than a second).
FLASH Radiotherapy

Part 1: A Look at Ultra-high Dose Rate Research

Part 2: Treatment Planning Challenges and Examples
THE PROMISE OF
FLASH Therapy
Ultra-high dose external beam therapy delivered in less than 1 second, in 1 to 3 treatments.
Ultra high dose rates

- **FLASH**: 720,000 cGy
- **ProBeam**: 10,000 cGy
- **TrueBeam**: 2,400 cGy
- **Clinac**: 400 cGy

FLASH Range: 40 Gy/sec – 120 Gy/sec
FLASH spares normal tissue

Improving Normal Tissue Complication Probability (NTCP)

While maintaining Tumor Control Probability (TCP)

Thereby widening the therapeutic window

FLASH therapy promise:

- Improving Normal Tissue Complication Probability (NTCP)
- While maintaining Tumor Control Probability (TCP)
- Thereby widening the therapeutic window

Increasing the effective ionizing radiation dose by 10% could increase tumour control rates by 5-30%
Less normal tissue toxicity:

Skin
FLASH spares the skin from toxicity

Mini-pig: 36 weeks post-RT  (5 Gy/min vs 300 Gy/s)

- No erythema, no moist desquamation,
- No fibronecrosis, no hyperkeratosis
- No inflammatory infiltrates, no dermal remodelling

Vozenin MC et al. Clin Cancer Res 2018
Preservation of hair follicles and stem cells

Preservation of hair follicles

Preservation of CD34+ epidermal stem cells

Vozenin MC et al. Clin Cancer Res 2018
Less normal tissue toxicity:

Brain
Whole brain FLASH irradiation spares memory

Mice

>100 Gy/s

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>FLASH (50 Gy)</th>
<th>Conv (10 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic Toxicity</td>
<td>No toxicity</td>
<td>Max tolerated dose(MTD) reached</td>
</tr>
<tr>
<td>Cognitive Skills two months post irradiation</td>
<td>No change</td>
<td>Drop in cognitive skills</td>
</tr>
<tr>
<td>Cellular toxicity</td>
<td>Minor cell killing and astrocyte modification</td>
<td>High level of cell killing and astrocyte remodeling</td>
</tr>
<tr>
<td></td>
<td>Better survival of neural stem cells</td>
<td>Complete eradication of neural stem cells</td>
</tr>
</tbody>
</table>

Montay-Gruel P et al. Rad Oncol 2017
Less normal tissue toxicity:

Gastro-Intestinal
Crypt regeneration

Schüler et al. IJROBP 2016.

Ki 67 (a biomarker of cell proliferation) expression is increased in FLASH vs Conventional irradiation.
Is there any compromise of anti-cancer efficacy?
Dose escalation in cats with SCC of nasal planum

<table>
<thead>
<tr>
<th>Cat n°</th>
<th>Dose (Gy)</th>
<th>Response at 3 months</th>
<th>Response at 6 months</th>
<th>Response at 16 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>CR</td>
<td>Clinical recurrence</td>
<td>dead</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Euthanasia at 8 mo</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>5</td>
<td>34</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>CR</td>
<td>CR</td>
<td>CR</td>
</tr>
</tbody>
</table>

Vozenin MC et al. Clin Cancer Res 2018
Effect of FLASH and CONV on tumor xenografts

FLASH 17 Gy is as effective as CONV 17 Gy at reducing growth

FLASH 25 Gy showed complete tumor growth arrest 40 days post-IR without any skin damage

Favaudon et al Science Trans Med 2014
Summary: Flash spares normal tissue with tumor control

High dose rate electron RT – published pre-clinical results

<table>
<thead>
<tr>
<th>Normal Tissue:</th>
<th></th>
<th>Normal Tissue:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain(^1,2), Lung(^3), GI(^4), Skin(^3,5)</td>
<td>CONV (e-, γ and X-rays)</td>
<td>CONV (e-, γ and X-rays)</td>
</tr>
<tr>
<td>FLASH (e-)</td>
<td>10-30 Gy</td>
<td>10-20 Gy</td>
</tr>
<tr>
<td>Dose (Gy)</td>
<td>37-500</td>
<td>0.03-0.05</td>
</tr>
<tr>
<td>Dose Rate (Gy/sec)</td>
<td>1hr to 36 weeks</td>
<td></td>
</tr>
</tbody>
</table>

Flash increases normal tissue sparing compared to conventional dose rate

<table>
<thead>
<tr>
<th>Tumor:</th>
<th></th>
<th>Tumor:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast(^6), H&amp;N(^6), Lung(^6), GBM(^7), Squamous cell(^8)</td>
<td>CONV (e-, γ and X-rays)</td>
<td>CONV (e-, γ and X-rays)</td>
</tr>
<tr>
<td>FLASH (e-)</td>
<td>17-41 Gy</td>
<td>13-17 Gy</td>
</tr>
<tr>
<td>Dose (Gy)</td>
<td>40-100</td>
<td>0.03-0.05</td>
</tr>
<tr>
<td>Dose Rate (Gy/sec)</td>
<td>5-135 days</td>
<td></td>
</tr>
</tbody>
</table>

Tumor control was the same or better with Flash compared to conventional dose rate

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Proton FLASH with the ProBeam® system
FlashForward™ Program

2014
First Investigations into Ultra-high Dose Rates using protons

2015
Electron Flash Toxicity and Tumor Control Studies

Stanford University Medical Center

2016
First Proton Flash Toxicity Study
Varian modified a non-clinical Clinac to study ultra-high dose rates using electrons

University of Maryland Dept of Radiation Oncology

2017
First Proton Flash Tumor Control Study
Varian filed First Patent for FLASH - Radiation therapy systems and methods for delivering doses to a target volume > 4 Gy/sec U.S. No. 9,855,445

Cincinnati Proton Therapy Center

2018
Varian filed an additional 14 patents in the U.S. and 9 counterpart filings internationally.

2019
Translational Science Group at Varian

COLLABORATORS

Maryland
Proton Treatment Center

Cincinnati
Proton Therapy Center
Varian pre-clinical proton experiments

- **392 Mice**
  - Age and sex matched

- **6 Cohorts**
  - Sacrificed 1h-36 weeks after RT

- **3 Groups**
  - Control
  - Conventional protons (1 Gy/sec)
  - Flash protons (40Gy/sec)
Flash resulted in a reduction in radiation induced dermatitis and fibrosis

Normal tissue toxicity studies

25% reduction in fibrosis* with FLASH vs. Conventional (17.5 Gy)

35% reduction in dermatitis* with FLASH vs. Conventional (17.5 Gy)

LUNG FIBROSIS
(Graded by independent pathologist, blinded on treatment groups)

DERMATITIS

*Average fibrosis scores

Source: Varian proprietary data
## Normal Tissue and Tumor control studies

Different sites for evaluation of normal tissue toxicity and tumor response.

<table>
<thead>
<tr>
<th>Lung</th>
<th>Brain</th>
<th>Head &amp; Neck</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Toxicity</strong></td>
<td><strong>Effect of FLASH and conventional radiation on lung cancer mouse models (wild type and genetically modified)</strong></td>
<td><strong>Induction of oral mucositis in mice</strong></td>
</tr>
<tr>
<td>Fibrosis induction in tumor microenvironment mimicking normal tissue</td>
<td>Neurocognitive evaluation of rats after FLASH and conventional radiation</td>
<td></td>
</tr>
<tr>
<td><strong>Tumor Control</strong></td>
<td><strong>Effect of FLASH and conventional radiation on mouse models of medulloblastoma and glioblastoma</strong></td>
<td><strong>Evaluation of FLASH vs conventional on 3D organoids of normal skin and HNSCCs</strong></td>
</tr>
<tr>
<td>Effect of FLASH and conventional radiation on lung cancer mouse models (wild type and genetically modified)</td>
<td></td>
<td>Tumor growth in mouse xenografts of HNSCC after FLASH and conventional</td>
</tr>
</tbody>
</table>

800 mice and 200 rats
Tumor control preliminary results:
Proton FLASH vs Proton Conventional vs No RT

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Control (Untreated) (n=12)</th>
<th>Flash (n=24)</th>
<th>Conventional (n=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approximate tumor volume (mm$^3$)</td>
<td>60 ± 10</td>
<td>10 ± 2</td>
<td>15 ± 3</td>
</tr>
</tbody>
</table>

Tumor control was the same or better with Flash compared to conventional dose rate

Lung Cancer

Source: Varian proprietary data
FLASH Treatment Planning Examples

Transmission and Bragg Peak

*Patents Pending and Issued
Always begin here: Percent Depth Doses

- X-rays (20 MeV)
- X-rays (4 MeV)
- Electrons (4 MeV)
- Protons (150 MeV)
Traditional Spread Out Bragg Peak PDDs
shallow and thin vs deep and fat
Through Body vs. Bragg Peak

Treatment Planning
Pros and Cons

**Transmission**
- All Flash pre-clinical studies have been performed in the transmission fields (electrons & now protons)
- Less dose-rate variation in target volume
- No range uncertainty
- Sharper lateral penumbra
- Use of exit beam for QA
- Less variation in RBE
  - Higher integral dose (similar to photons)

**Bragg Peak**
- Standard of care with proton therapy
- Use Physical advantage of proton
- More tissue sparing
- Higher RBE
- Higher dose-rates
  - More beam angles (single energy)
  - Range shifting close to the patient required
  - Higher range/motion uncertainty
  - No pre-clinical studies yet with Bragg Peak and Flash
Simplest Example: FLASH Transmission on Breast
Dosimetric example of site potentially treatable with single FLASH beam
Simple Lung Example: Three Coplanar Transmission Fields

2014 AAPM / ROR SBRT Lung Plan Challenge case

<table>
<thead>
<tr>
<th>Field</th>
<th>Irradiation Time [seconds]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0691</td>
</tr>
<tr>
<td>2</td>
<td>0.0675</td>
</tr>
<tr>
<td>3</td>
<td>0.1306</td>
</tr>
</tbody>
</table>

Perez, Magliari PTCOG e-poster 2019
More Lung Examples: Bragg Peak & Transmission(same beams)

2014 AAPM / ROR SBRT Lung Plan Challenge case
Target “chunking”
To place the Bragg Peak at the most distal edge of the target
Beams (NonCoplanar)

Each field is positioned perpendicular to each corresponding chunk of target
Optimize and Calculate

Spots
Bragg Peak

Example Lung Flash Plan

- Favaudon 2014: 20 Gy at 40 Gy/sec
- Goal: Deliver flash dose rates while limiting healthy tissue irradiation time to 0.5 sec\(^1\)
- Minimize scanning over healthy tissue twice\(^2\)
  - Single energy fields targeting distal edge
  - Reduce overlap of fields in healthy tissue
- 20 Gy in single fraction

\(^1\)DOSE ASPECTS OF RADIATION THERAPY PLANNING AND TREATMENT (PATENT ISSUED)
\(^2\)GEOMETRIC ASPECTS OF RADIATION THERAPY PLANNING AND TREATMENT (PATENT PENDING)
Transmission

Example Lung Flash Plan

• Same patient
• Same gantry angles (could be optimized)
• Minimize time healthy tissue is irradiated while using the proton plateau region

<table>
<thead>
<tr>
<th>Field</th>
<th>Irradiation Time (seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0591</td>
</tr>
<tr>
<td>2</td>
<td>0.0890</td>
</tr>
<tr>
<td>3</td>
<td>0.0784</td>
</tr>
<tr>
<td>4</td>
<td>0.0941</td>
</tr>
<tr>
<td>5</td>
<td>0.0366</td>
</tr>
<tr>
<td>6</td>
<td>0.0454</td>
</tr>
</tbody>
</table>

All fields are ~40 Gy/sec

ProBeam Flash Mode Prototype & Eclipse Simulation

1TRIGGERED TREATMENT SYSTEMS AND METHODS (PATENT ISSUED)
FLASH Example GBM
13 Bragg Peak NonCoplanar Fields at 12 Gy

<table>
<thead>
<tr>
<th>Field</th>
<th>Irradiation Time [seconds]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0225</td>
</tr>
<tr>
<td>2</td>
<td>0.0399</td>
</tr>
<tr>
<td>3</td>
<td>0.0178</td>
</tr>
<tr>
<td>4</td>
<td>0.0436</td>
</tr>
<tr>
<td>5</td>
<td>0.0101</td>
</tr>
<tr>
<td>6</td>
<td>0.0302</td>
</tr>
<tr>
<td>7</td>
<td>0.0194</td>
</tr>
<tr>
<td>8</td>
<td>0.0437</td>
</tr>
<tr>
<td>9</td>
<td>0.0617</td>
</tr>
<tr>
<td>10</td>
<td>0.0396</td>
</tr>
<tr>
<td>11</td>
<td>0.0337</td>
</tr>
<tr>
<td>12</td>
<td>0.0074</td>
</tr>
</tbody>
</table>
FLASH Example GBM

13 Bragg Peak NonCoplanar Fields at 12 Gy
FLASH Example GBM
10 Coplanar Transmission Fields, 12 Gy
Thank you