The Current Status and Future Outlook of FLASH RT Delivery Systems

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Disclosures

• Employment – Indiana University School of Medicine

• Founder – TibaRay, Inc.
What is FLASH?

Ultra-rapid radiation treatment (dose rate > ~40 Gy/sec)

How does it compare to conventional dose rate RT?

Varian TrueBeam dose rate (calibration conditions) = 24 Gy/min = 0.4 Gy/s
(at 10 MV FFF mode for an open field)

Varian TrueBeam dose rate (real world) = 10 Gy/min = 0.1667 Gy/s
(10 MV FFF intensity modulated plan)
Why FLASH - Therapeutic index

Holthusen’s hypothesis

Tumor destruction

Tumor-vernichtung

Tolerance exceeded

Cure

Heilung

Bild 6.

Holthusen Strahlenther Onkol 1936
Ultra-rapid “FLASH” RT: New biology

Normal organ sparing

Lung

Brain

Hippocampal neurogenesis (BrdU) & memory (novel object recognition) 2 mo after 10 Gy WBI

Montay-Gruel
Radiother Oncol 2017

Favaudon Science Translat Med 2014
FLASH – Current technologies (preclinical)

MeV electrons at Lausanne U, Stanford, IU and Lund U

Synchrotron kV x-rays at ESRF (Grenoble)

>100 MeV protons at Curie, U Penn, Groningen

Schüler IJROBP 2017
Jaccard Med Phys 2018
Montay-Gruel Radiother Oncol 2018
Patriarca IJROBP 2018
Kim Phys Med Biol 2019
Lempart Radiother Oncol 2018
MeV electron FLASH -RT at CHUV

Prototype 6 MeV electron Linac
PMB-Alcen, Peynier, France

- Oriatron 6e
- Dose rates: few Gy/min - >1000 Gy/s
- Wide range of parameters
- Gun current, pulse-repetition frequency, pulse width, and SSD
- Dosimetry characterized
MeV electron FLASH -RT at Lund University

- Elekta linac:
- Clinical electron energies
- >1000Gy/s at short SSD
- Pulse by pulse control
- Diode signal amplified and counted by MCU
- Triggered thyratron
- Dosimetry characterized
Proton FLASH RT at U Penn / Groningen

• IBA Proton RT

• March 2019 IBA announced first proton FLASH-RT at University Medical Center Groningen

• May 2020 – Mevion/Wash U announced 226Gy/s FLASH at Bragg peak using 230MeV proton beam
Proton FLASH RT at U Maryland

• Varian FLASH Forward Consortium / U Maryland
• Modified clinical ProBeam
• FLASH (40Gy/s) vs conv proton RT (1Gy/s)
• 30% reduction in lung fibrosis with FLASH in mice
• Reduced incidence of skin dermatitis and improved overall survival in FLASH- vs conventionally-treated mice

Ghirdani Annual conference AACR 2019
Proton FLASH RT at Institut Curie

- 138 MeV and 198 MeV:
  - > 40 Gy/s
- 3D printed Lucite ridge filter
- 2 cm spread-out Bragg peak
- Offline animal immobilization
- Camera alignment system
- Aperture for irradiation

Patriarca IJROBP 2018
FLASH experiments at Stanford and IU
FLASH total abdomen irradiation

~16 MeV FLASH e⁻

Levy/Rankin, Wang/Loo/Maxim Unpublished 2019
FLASH total abdomen irradiation

16 Gy (lethal dose)

14 Gy (sublethal dose)

Normal female C57BL/6 mice

Levy/Natarajan/Wang bioRxiv 2019
FLASH total abdomen irradiation

Syngeneic orthotopic (peritoneal) ID8 ovarian cancer in C57BL/6

Levy/Natarajan/Wang *bioRxiv* 2019
FLASH proton total abdomen irradiation

Proton beam 230 MeV treating in plateau region

15 Gy @ 78 Gy/s FLASH vs. 0.9 Gy/s “standard”

MH641905 flank tumors

Diffenderfer IJROBP 2020
FLASH – Summary of biological findings

Compared to conventional dose rate irradiation, FLASH achieves:

• Reduced normal tissue injury
  – Multiple organ systems: lung, brain, intestinal tract, skin
  – Multiple mouse strains, multiple species

• Equal or better tumor killing \textit{in vivo}
  – Multiple tumor models
PHASER: Next generation radiation therapy

Pluridirectional High-energy Agile Scanning
Electronic Radiotherapy (PHASER)

- **400X faster**: Freezes motion, ultimate precision
- **FLASH RT**: New biological advantages
- Compact & economical: Global access to RT
Multi-center FLASH collaboration

NCI program project grant proposal

- 4 projects on brain tumor and normal brain responses to FLASH, and mechanisms – led by Stanford, UCI, Lausanne U, and U Iowa
- 3 cores including FLASH irradiation infrastructure and neurocognition – led by Stanford/IU and UCI

FLASH electron linac facility at Lausanne U/CHUV
Immediate next step: preclinical system

FLASH Experimental X-ray Conformal Therapy (FLASH-EXaCT)

International collaboration:
UC Irvine, Stanford Rad Onc/SLAC, Lausanne U/CHUV, Indiana U, U Iowa
Take home points

• Ultra-rapid FLASH has shown the potential for increased therapeutic index for cancer therapy in multiple preclinical models

• Radically new technologies are being developed to deliver FLASH for general cancer radiotherapy indications

• There is much more to be studied biologically, technologically, and clinically