Promise of FLASH - Protons

Lei Dong, Ph.D.

Professor and Director of Medical Physics Division
Department of Radiation Oncology
Hospital of the University of Pennsylvania

AAPM – 2019
TU-L-SAN1-2
San Antonio, TX

PENN RADIATION ONCOLOGY
Penn Medicine

Learning Objectives

- **Learn how to produce ultra-high dose rate (FLASH) using protons**
- **Discuss current limited research on proton FLASH**
- ***Discuss potential challenges using FLASH proton beams**

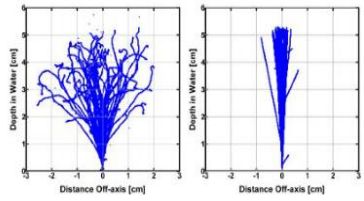
Disclosures

- **Research grants: NIH; Varian**
- **Speaker Bureau Honorarium: Varian**
- **Consortium: Varian FlashForward™**
- **Opinions expressed are solely my own; I may be wrong!**

Protons are preferred for treating deep-seated tumors

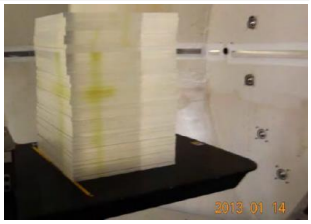
10 MeV electrons
50 histories

80 MeV protons
50 histories



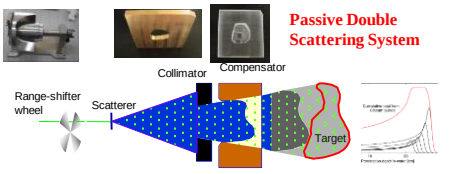
Evidence of High Dose Rate Using Clinical Proton Beams

- **High dose rate in proton PBS mode**
  - During proton beam dose calibration, ion collection efficiency is low when impropriate chamber and bias are used: Pion=1.03!
  - Estimated dose rate 10Gy/s in uncontrolled clinical mode

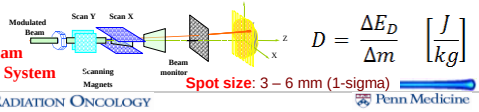


Radiation Survey at Scripps Proton Therapy Center, Varian ProBeam™, 2013

How can we have such a high dose rate in PBS?



Passive Double Scattering System



Pencil Beam Scanning System

$$D = \frac{\Delta E_D}{\Delta m} \quad \left[\frac{J}{kg}\right]$$

Spot size: 3 – 6 mm (1-sigma)

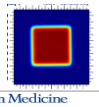
How many protons per second do you need at nozzle?

- **The dose and flux relationship for a thin-buildup geometry**

$$D = 1.602 \times 10^{-10} \left(\frac{S(E)}{\rho}\right)_w \phi$$

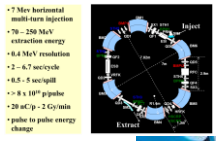
- **For typical pencil beam ~ 1cm, the general estimate for a single spot at high energy (200 MeV):**
  - 22 nA at nozzle to give 100 Gy/s
  - 10 Gy requires at least 1.5x10^10 (15Gps) protons (~ dose for the size of a pencil beam)

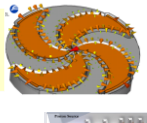
- **Field size could be a strong limitation using current systems**
  - DS/US/PBS to spread beam laterally
  - 5cm x 5cm at 100 Gy/s requires ~600 nA at the nozzle!



Beam Delivery Options and Timing

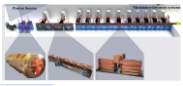
Synchrotron (pulsed beam) Cyclotron (microwave frequency)





Mevion Synchrocyclotron

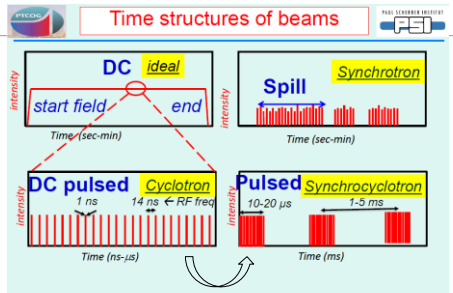
IBA ProteusOne S2C2 model Synchrocyclotron



Proton Linac

S250	MEVION	SC Syn	250 MeV	20 T 1.8 m	- ?	500 Hz period	~ 9 T
S2C2	IBA	SC Syn	230 MeV	<50 T 2.5 m	- ?	1 kHz period	~ 6.56 T

Time structures of beams



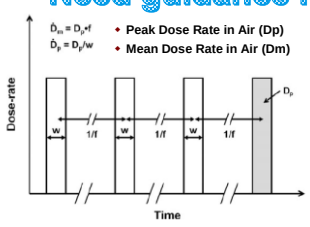
Marco Schippers - PSI

Defining Dose Rates – This is complicated!

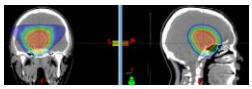
Need guidance from biology!

$\dot{D}_m = D_p \cdot f$
$\dot{D}_p = D_p / w$

- Peak Dose Rate in Air (Dp)
- Mean Dose Rate in Air (Dm)



- Instantaneous Voxel Dose Rate
- Mean Voxel Dose Rate
- Dose-weighted Mean Voxel Dose Rate

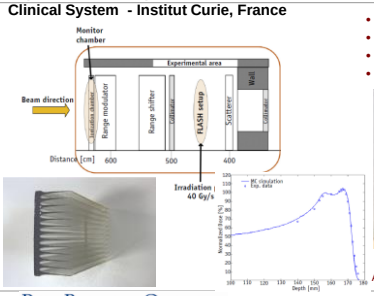


Jaccard et al. Med Phys 45(2) 2018

What are some proton facilities doing on FLASH?

PENN RADIATION ONCOLOGY
Penn Medicine

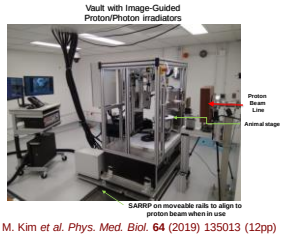
Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System - Institut Curie, France



- 1.2 cm x 1.2cm Collimation
- Ridge Filter – Use SOBP
- 40 Gy/s
- Image guidance

Annalisa Patriarca et al. IJROBP 2018

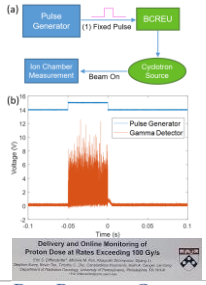
Small Animal Radiation Facility-SARRP with proton beams - UPENN

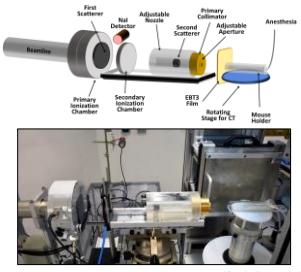


Facility supports:
- 23 Penn investigators for animal RT
- Core Facility for P01 "Immune Checkpoints and Radiation in Cancer" (Vonderheide)
- Current FLASH RT efforts

M. Kim *et al. Phys. Med. Biol.* **64** (2019) 135013 (12pp)

Penn Group Proton Irradiation Setup

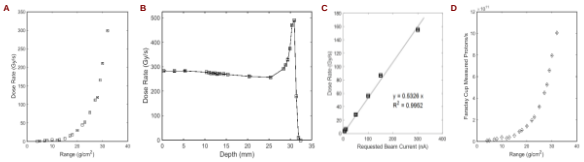




Diffenderfer *et al., in revision*

Parameters and dose rate verification of FLASH proton RT setup

Characterization of maximum possible dose rate vs proton range (A), depth in water (B), requested beam current (C) as measured by an ionization chamber and Faraday cup (D).



Diffenderfer *et al., in revision*

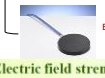
Dealing with High Dose Rate

SOBP – DS/US

Thimble ionization chamber

PBS

High-bias Thimble ionization Chamber
Parallel Plate Chambers (preferred)



BraggPeak™ chamber

Electric field strength vs. chamber geometry

2. Cylindrical chamber geometry can be characterized in terms of the radius of the outer electrode a; the radius of the inner electrode b; the field strength $E(r)$ at radius r; and the applied potential P

$$E(r) = \frac{P}{r \ln(a/b)}$$

Electric field strength vs. chamber geometry

1. Neglecting edge effects, plane-parallel chambers have uniform field strength throughout the chamber volume. For an applied potential P, and a distance between the plates d:

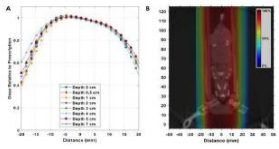
$$E(x) = P/d$$

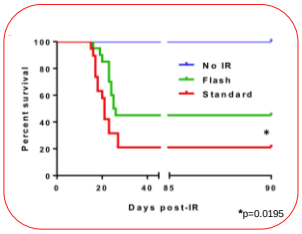
FA Attix – Introduction to Radiation Dosimetry

K. Petersson et al. Med Phys. 2017

Increased survival of C57BL/6 mice treated with FLASH vs conventional WBRT

Mice were whole body-irradiated either with 1 Gy/s or 75 Gy/s irradiation at a **single dose of 7.5Gy**.





*p=0.0195

Diffenderfer *et al., in revision*

PENN RadOnc FLASH Project: Participating Faculty and Staff

Biology
- Theresa Busch
- Keith Cengel
- Ann Kennedy
- Cam Koch
- Costas Koumenis
- Andy Minn
- John Verginadis

Clinical
- Alex Lin
- Amit Maity
- Jim Metz
- Sam Swisher-McClure

Physics
- Steve Avery
- Eric Diffenderfer
- Lei Dong
- Michelle Kim
- Khayrullo Shoniyozov
- Kevin Teo

Penn Vet School
- Lili Duda
- James Perry

Other Known Proton FLASH Experiments

Session LBPO.ET02 - Late-Breaking Research: Experimental and Molecular Therapeuti...

Add To My Itinerary

LB-280 / 26 - FLASH: A novel paradigm changing tumor irradiation platform that enhances therapeutic ratio by reducing normal tissue toxicity and activating immune pathways

- **C57BL/6 mice exposed to a single-dose of 15, 17.5 and 20 Gy**
- **Conventional (1Gy/sec protons) vs FLASH (40 Gy/sec) protons through whole thorax irradiation**
- **Up to a 30% reduction in lung fibrosis, as well as reduced incidence of skin dermatitis and improved overall survival**

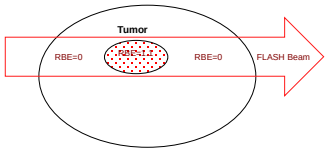
Swati Girdhani , Eric Abel , Alexander Katsis , Andrew Rodriquez , Shilpa Senapati , Angel KuVillanueva , Isabel L. Jackson , John Eley , Zeljko Vujaskovic , Renate Parry . Varian Medical Systems, Inc., Palo Alto, CA; University of Maryland, Baltimore, MD

Other FLASH-capable centers

- …
- Cincinnati Children Hospital
- University Medical Centre Groningen (UMCG), The Netherlands
- Rutherford Cancer Centre, Reading, United Kingdom (S2C2)
- …

FLASH – Proton Outcome in Human Studies

Treatment Planning with FLASH – Ideal Situation

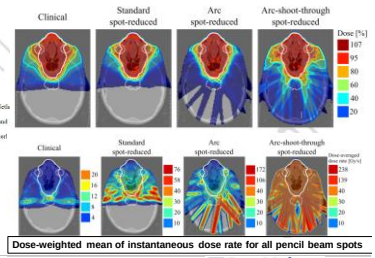


Towards FLASH Proton Therapy: the Impact of Treatment Planning and Machine Characteristics on achievable Dose Rates

Steven van de Water, PhD [1]
Sairos Safai, PhD [1]
Jacobus M. Schippers, PhD [1,2]
Damien C. Weber, MD [3,4,5]
Antony J. Lomax, PhD [1,3]

[1] Paul Scherrer Institute, Center for Proton Therapy, Villigen PSI, Switzerland
[2] Rijksuniversiteit Groningen, Department of Radiation Therapy, Groningen, the Netherlands
[3] University Hospital of Bern, Department of Radiation Oncology, Bern, Switzerland
[4] University Hospital of Zürich, Department of Radiation Oncology, Zürich, Switzerland
[5] ETH Zürich, Department of Physics, Zürich, Switzerland

Correspondence
Steven van de Water
Paul Scherrer Institute - Center for Proton Therapy
Forschungsstrasse 111
5232 Villigen PSI, Switzerland



Dose-weighted mean of instantaneous dose rate for all pencil beam spots

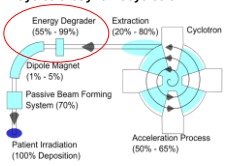
Room Shielding Considerations for Shooting-Through Technique

(no degrader ☺ proton beam may not stop inside a patient ☹

More efficient beam usage
Cheaper proton centers

Just like photons!

Cyclotron/Synchrocyclotron



Summary and Potential Challenges & Practice Changes

- **FLASH-protons also demonstrated significant normal tissue sparing in animal studies**
- **Biological effects and rationales of FLASH are unclear**
  - Different dose rate definitions and timing of dose delivery/ "fractionation" scheme
- **Field size limitation due to current accelerator design**
- **"Shoot-through" technique seems improving dose rate at the expense of dose conformality**
  - **No range uncertainty!!!**
- **Strategy changes for motion management**
  - **Synchronization of FLASH beam with patient's anatomy (no intra-fractional motion!)**
- **Dose rate becomes an important QA issue**
- **Treatment planning needs to incorporate machine delivery information**

Thank you!

Penn Physics Members
Michelle Kim, Ph.D.
Eric Diffenderfer, Ph.D.
Khayrullo Shoniyozov, Ph.D.
Steve Avery, Ph.D.
Kevin Teo, Ph.D.
Jennifer Zou, Ph.D.
David Carlson, Ph.D.