From Pre-clinical to Clinical Use

FLASH Radiation Therapy

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Questions that Still need Answers for FLASH

- What are the biologic mechanisms of FLASH? - we have theories and early indications, but there is still a lot to learn
- Is scattering or scanning is the appropriate delivery mechanism?
- Dose and fractionation need to be completely rethought?
  - Single fraction FLASH vs fractionated FLASH
  - FLASH alone vs Conventional treatment plus FLASH boost
  - Single course FLASH vs Intermittent delivery
  - Impact of multiple fields in a FLASH treatment
- Should we be doing FLASH with grid therapy?
- What are the potential synergies with chemotherapy and immunotherapy?
- What are the differential effects of FLASH on various normal tissues?
- Does conformality matter anymore?
- Many, many, more
Careful Stepwise Development of FLASH is Critical

- We need to be cautious about jumping into clinical trials too quickly
- There is a lot of work to do in the preclinical setting
- Gene Therapy is a good reminder— we can hurt people if we do this wrong and too quickly and put the field back years
- Small and large animal studies are critical to defining the mechanisms of action
- Significant technical refinement will be needed to deliver optimal care
- Ultimately, appropriate sites of treatment will need to be defined for clinical trials
Facility supports:
- 23 Penn investigators for animal RT
- Core Facility for P01 “Immune Checkpoints and Radiation in Cancer”
- Current FLASH RT efforts
“FLASH” Radiation Project at Penn

Accurate dosimetry

Biological validation (cells & mice)

Identify & study mechanism

Test in canine models

Human Clinical Trials

Q: Does the FLASH mechanism involve interaction with immune system?
Q: Can we do FLASH PBS? Can we treat at Bragg Peak?

July 2018
Oct 2018
Jan 2019
Sept 2019
2021-22?
Double Scattered Proton FLASH Set Up
Mice were whole body-irradiated either with 1 Gy/s or 75 Gy/s irradiation at a **single dose of 7.5Gy**.
Preliminary data from murine studies: fibrosarcoma tumor

- FLASH does not alter tumor response

Irradiation of fibrosarcoma tumor with 30 Gy

Flash or Standard RT 30 Gy
Injection of $5 \times 10^5$ MH6419 cells / flank

Tumor volume $\sim 100 \text{ mm}^3$

IR 12/18 Gy

Days post injection

Tumor volume 400-500 mm$^3$

Stem Cell Damage/fibrosis

Tumor growth/survival

Focal Proton RT of PanCa and Small Intestine
Intestinal Fibrosis 8 Weeks Post-Proton Radiation

**p<0.001; non-parametric t-test on FR vs SR vs NR**
Whole Abdomen Proton Radiation - Crypt Cell Proliferation

Day 3.5 post IR

Whole intestine scan: scale bar, 1mm; 10x magnification: scale bar, 50μm; *p<0.05, **p<0.01, ***p<0.001

Cengel et al, IJROBP 2020
Canine Osteosarcoma Pilot Trial

- PennVet Client Dogs with extremity Osteosarcoma enrolled on approved study
- Flash vs Standard Proton RT 4-5 days preoperatively
  - Toxicity outcomes: pain, fracture, skin fibrosis/breakdown, histopathologic damage to mesenchymal or hematopoietic compartments, gene expression profiling
  - Efficacy outcomes: histopathologic evidence of response, immunohistochemical evidence of DNA damage, apoptosis, gene expression profiling
We have Treated 10 Canine Patients to Date
Some thoughts about Clinical Targets

- Consider normal tissues that currently have significant early toxicity from radiation
  - lung, liver, head and neck, GI
- Look at tumors we will get early answers on tumor control, or impact
  - lung, liver, Head and neck, pancreas, sarcoma
- Consider tumors where radiation is considered in the neoadjuvant setting prior to surgery
  - sarcoma, pancreas, esophagus

- At Penn- We are thinking our first trials will be in sarcoma and retreatment of some of the settings above
Key Learnings for FLASH Radiation Thus Far

- FLASH effect is real and has been demonstrated in electrons, photons and protons
- FLASH shows normal tissue protection
- FLASH shows at least similar tumor control
- Stem cells appear to be spared more with FLASH radiation
- Dosimetry and control of the beam are critical to see the FLASH effect – small perturbations in the beam can negate the effect
- FLASH effect is lost with reducing dose rate below 40 Gy/sec
- There is a window of impact with FLASH
- FLASH proton radiation has the potential to be a major disruptor in oncology
Why can FLASH be a Disruptor

- Has the potential to significantly compress radiation treatments - radiation becomes more like a surgical procedure
- It could improve the quality of life of our patients with reduced toxicity and time commitment
- Bringing together biology and technology in new ways
- As FLASH can cause different immune pathways to be activated and different gene expression – whole new opportunities for drug/radiation combinations
- Opens up the possibility of expanding to benign diseases in new ways
- Has the potential to significantly reduce the cost of radiation and at the same time financially be successful with Alternative Payment Models
Summary

- FLASH has the opportunity to change the cancer treatment paradigm and upend many of our current assumptions with radiation delivery.
- However, we need to systematically evaluate and define the potential through rigorous science.
- We need to define the mechanisms of action in small animals.
- We need to take FLASH into larger animals before human studies with protons.
- Clinical trials and cooperation will be critical in evaluating the potential with FLASH.