From Pre-clinical to Clinical Use

FLASH Radiation Therapy

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Penn Medicine

RADIATION ONCOLOGY
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Questions that Still need Answers for FLASH

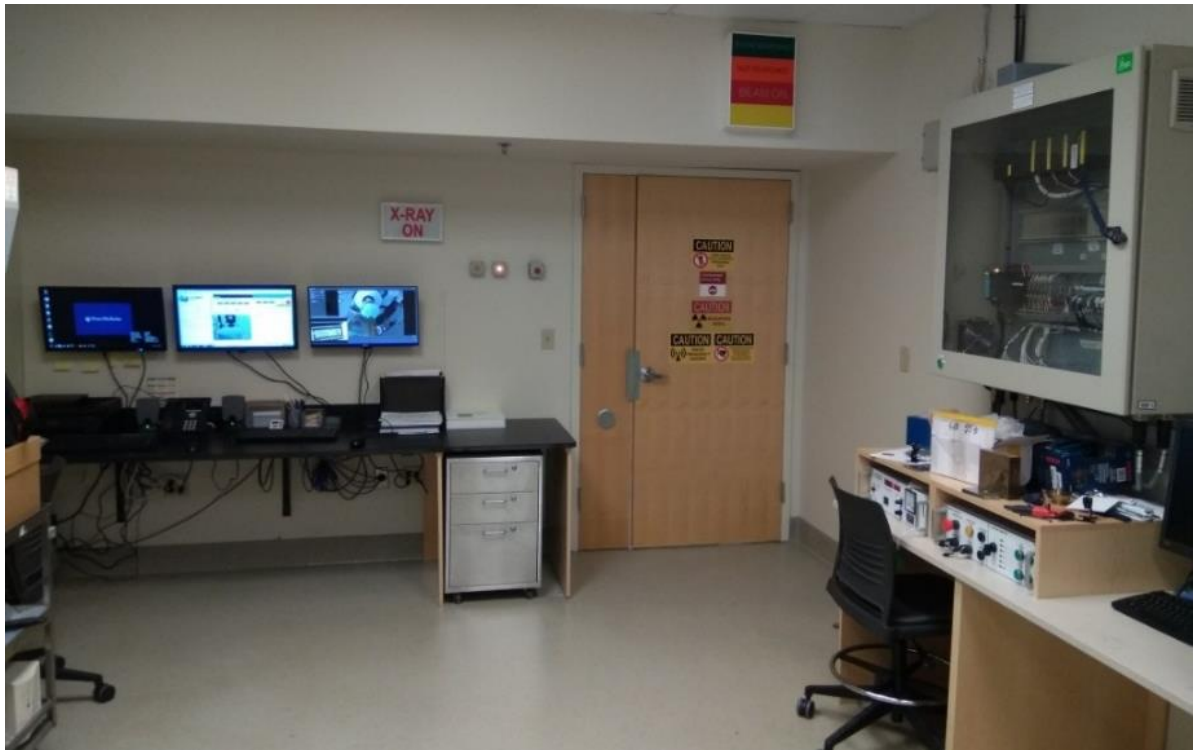
- What are the biologic mechanisms of FLASH? - we have theories and early indications, but there is still a lot to learn
- Is scattering or scanning is the appropriate delivery mechanism?
- Dose and fractionation need to be completely rethought?
  - Single fraction FLASH vs fractionated FLASH
  - FLASH 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

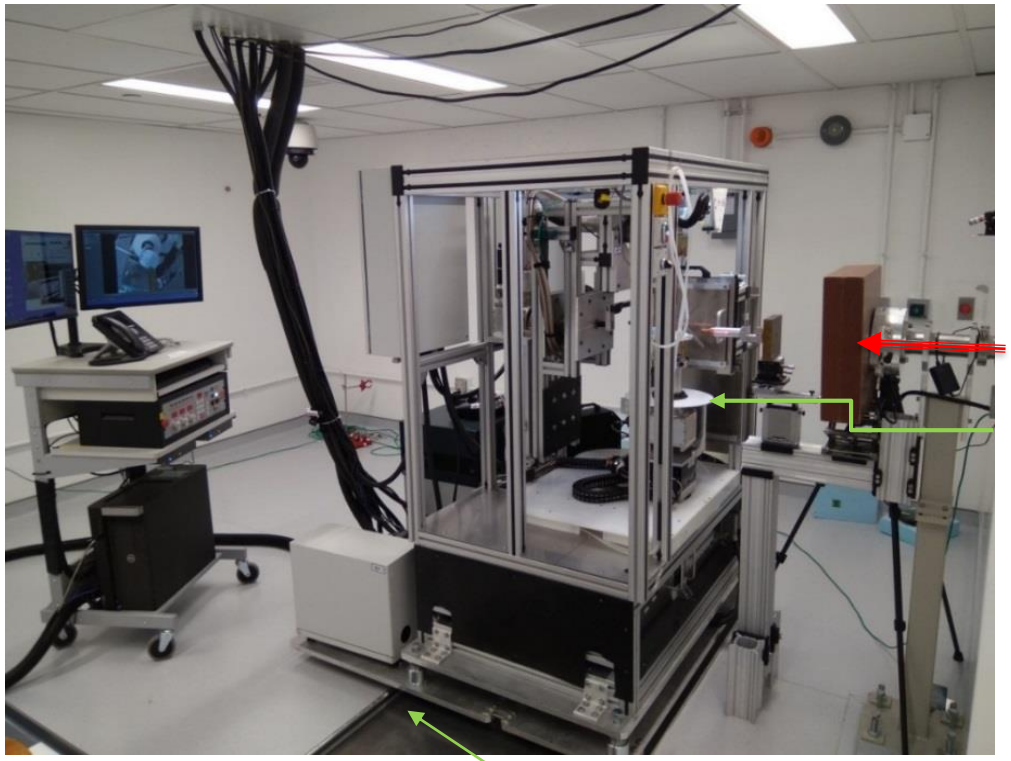
- We need to be cautious about jumping into clinical trials too quickly
- There is a lot of work to do in the preclinical setting
- Gene Therapy is a good reminder– we can hurt people if we do this wrong and too quickly and put the field back years
- Small and large animal studies are critical to defining 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

Small Animal Radiation Facility-SARRP with proton beam layout

Prep/Control room with remote anesthesia/SARRP/proton beam operations



Vault with Image-Guided Proton/Photon irradiators



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

July 2018

Oct 2018

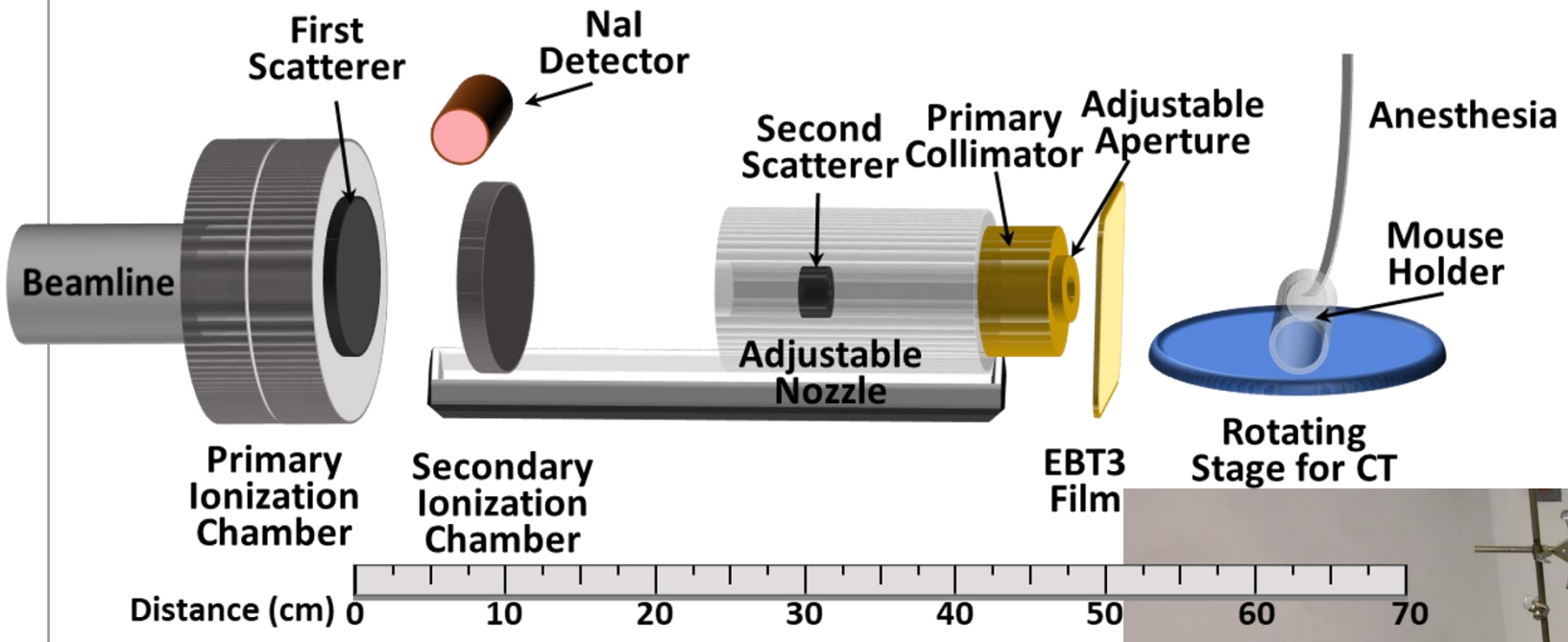
Jan 2019

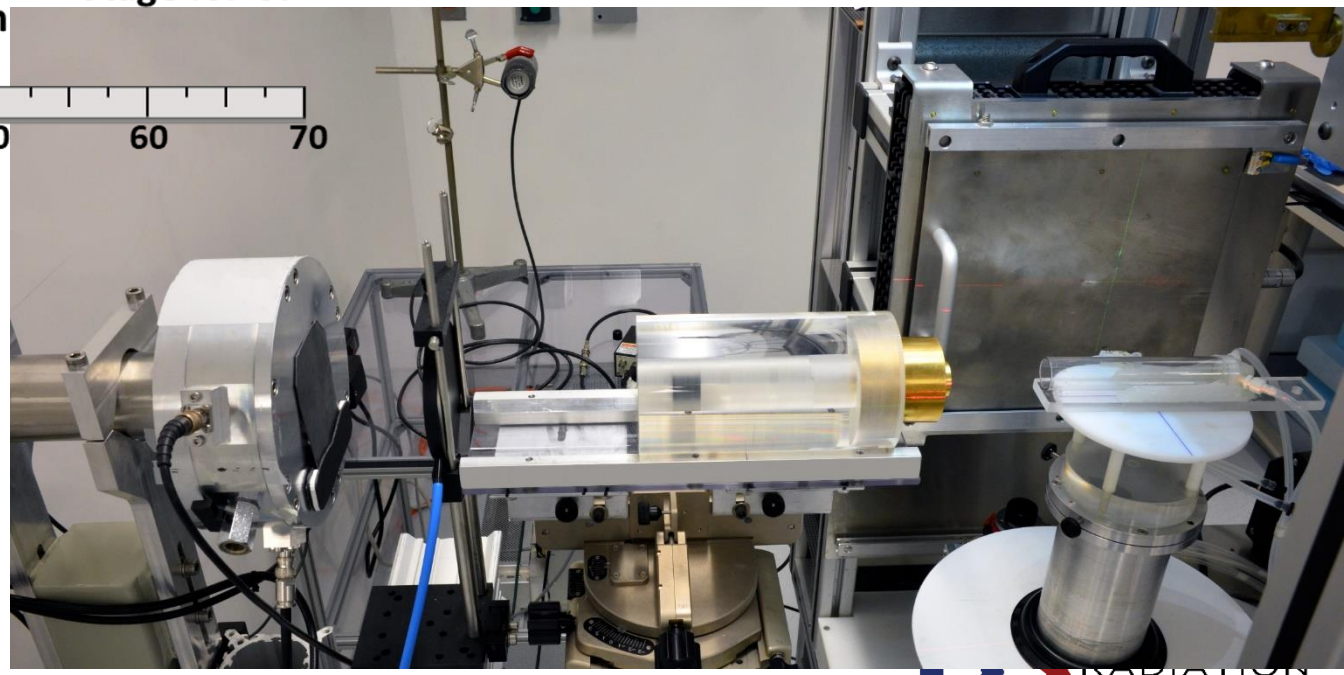
Sept 2019

2021-22?

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

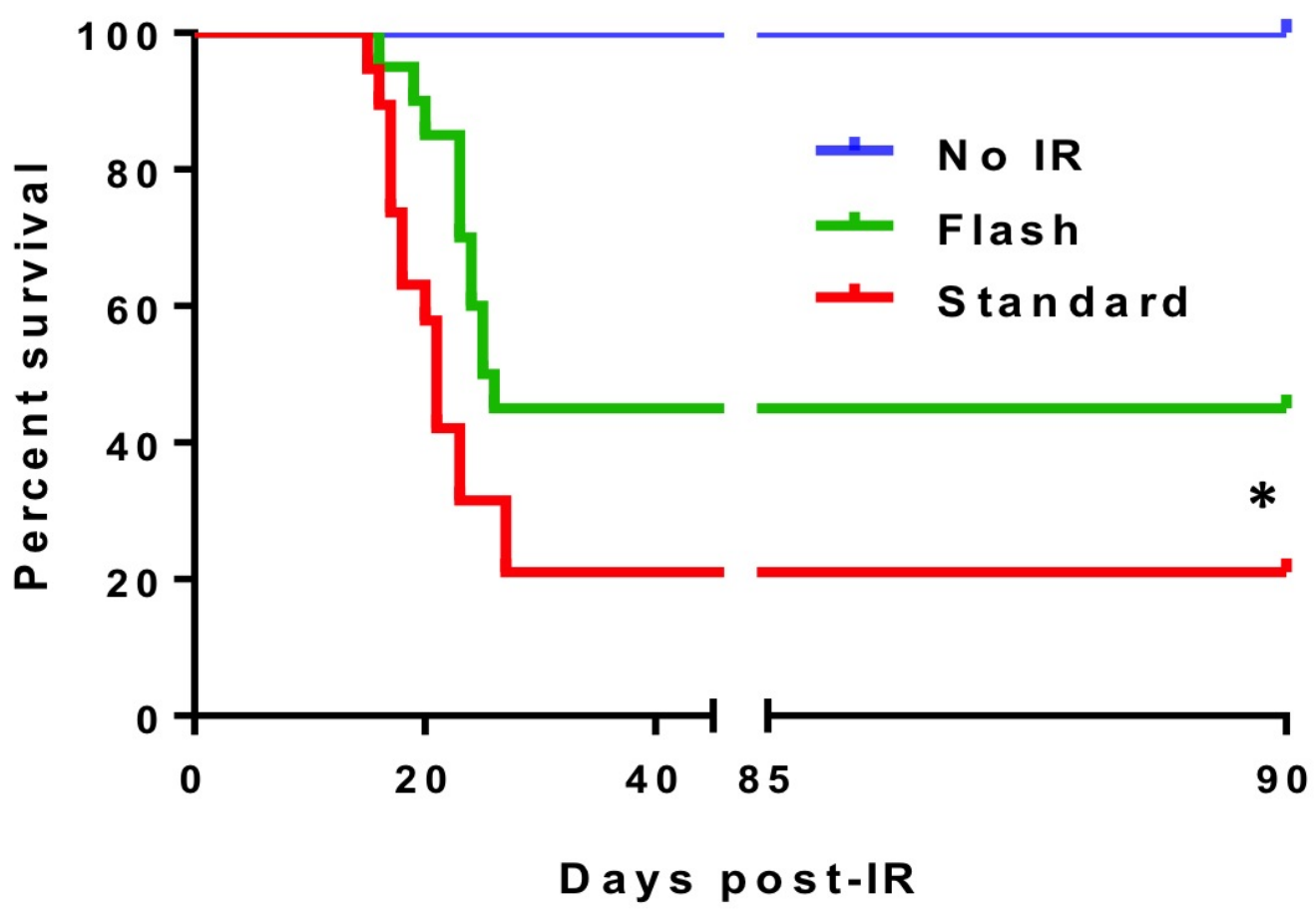
Double Scattered Proton FLASH Set Up





Increased survival of C57/Bl6 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**.

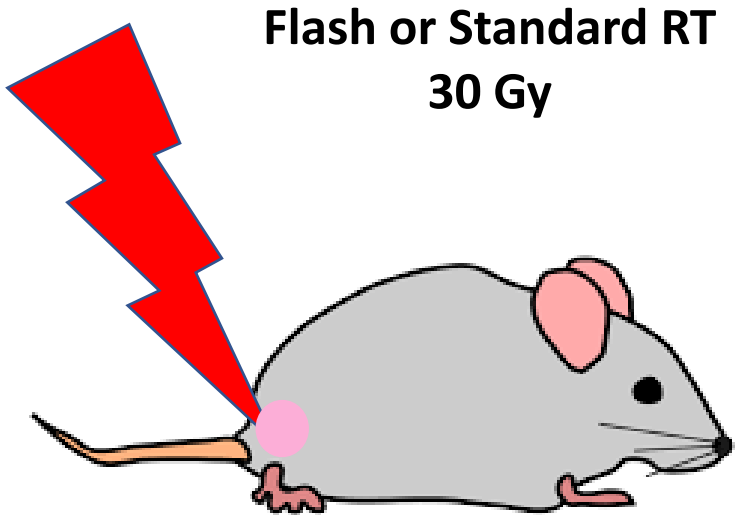


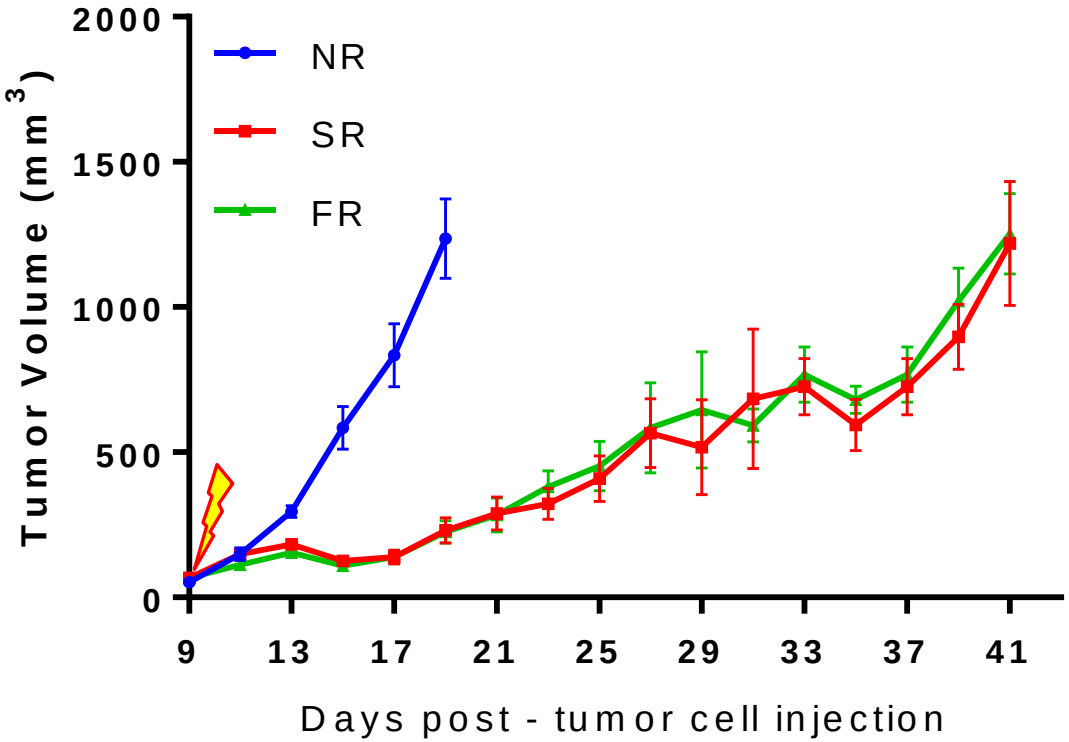
*p=0.0195

Preliminary data from murine studies: fibrosarcoma tumor

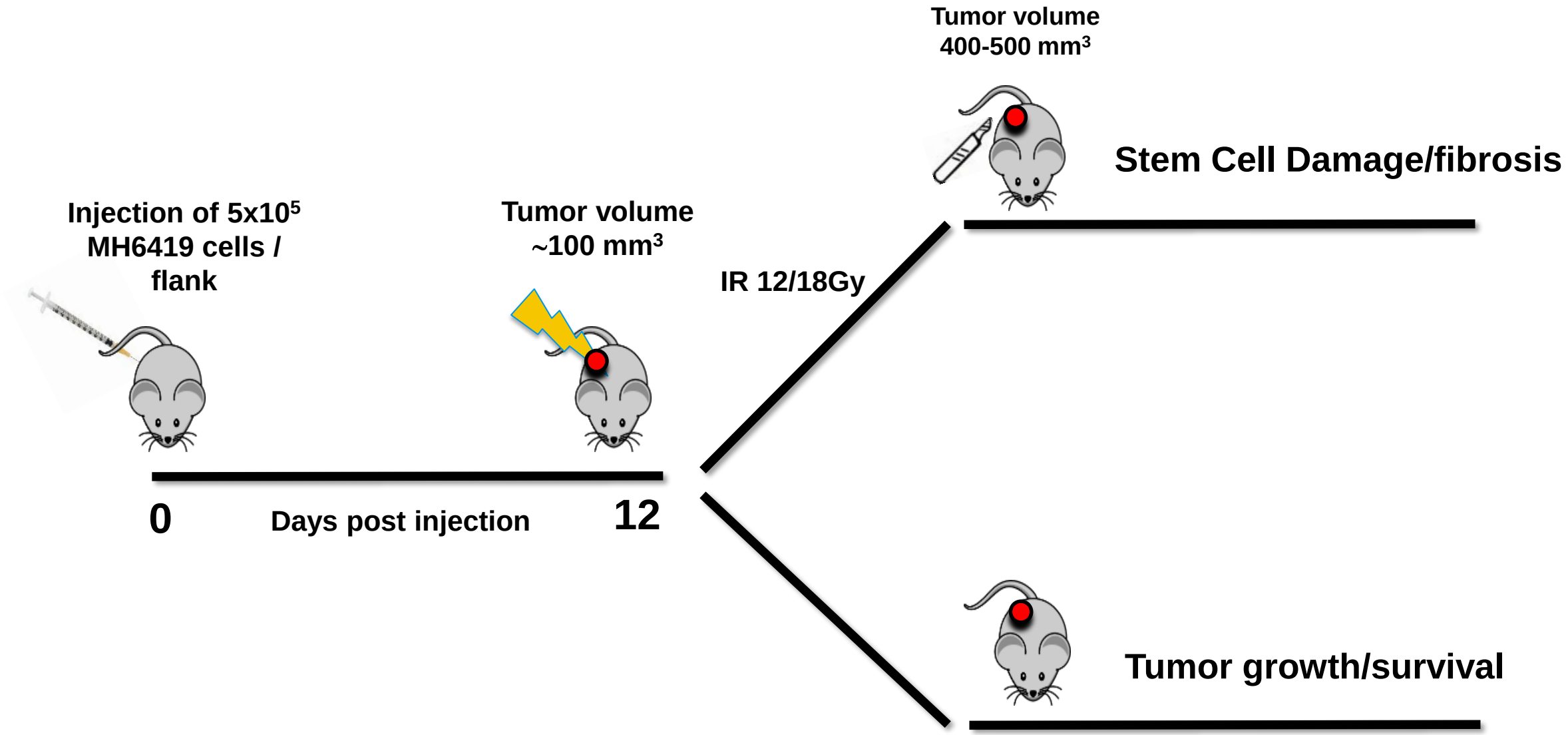
- **FLASH does not alter tumor response**

Irradiation of fibrosarcoma tumor with 30 Gy

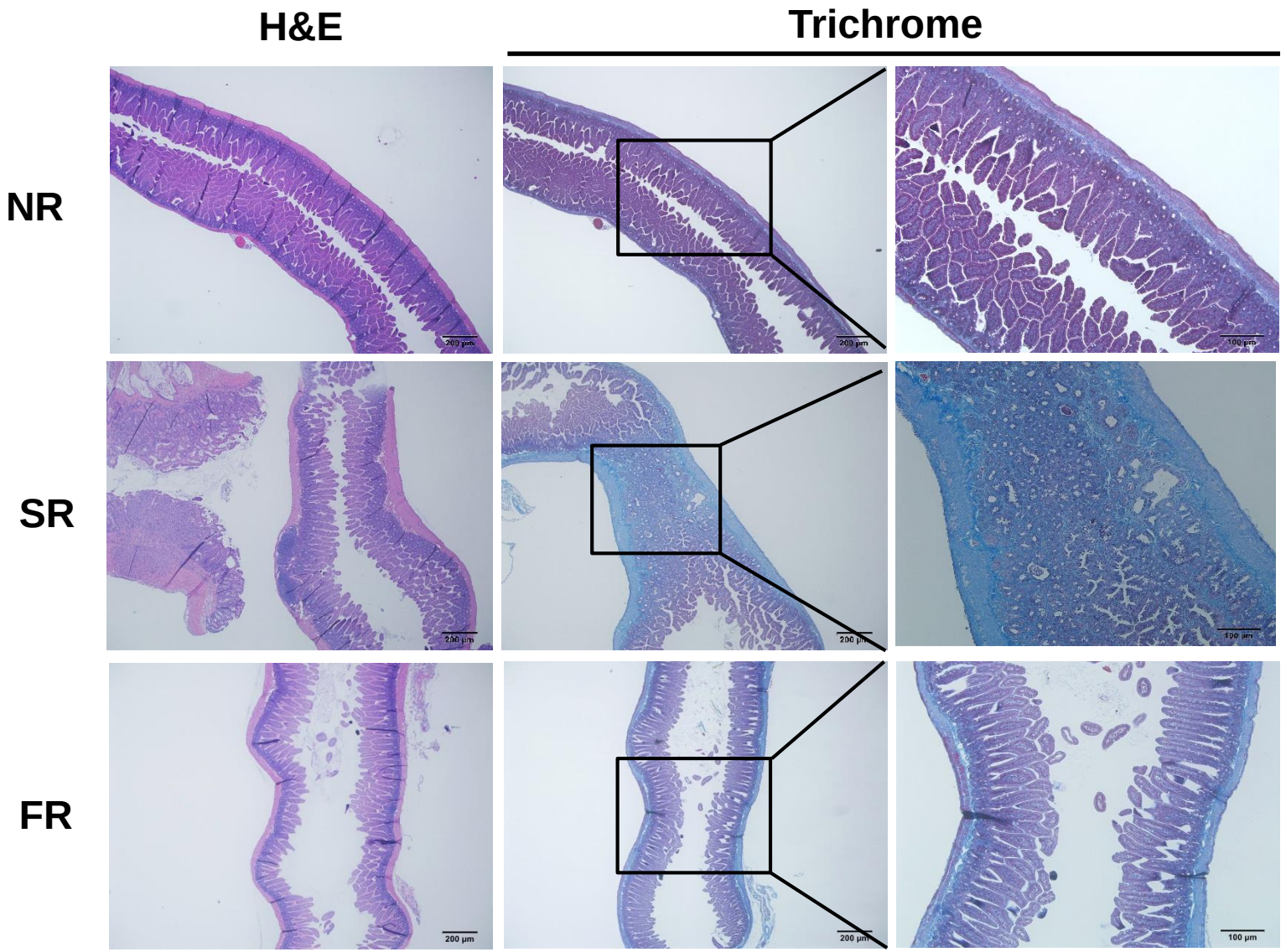


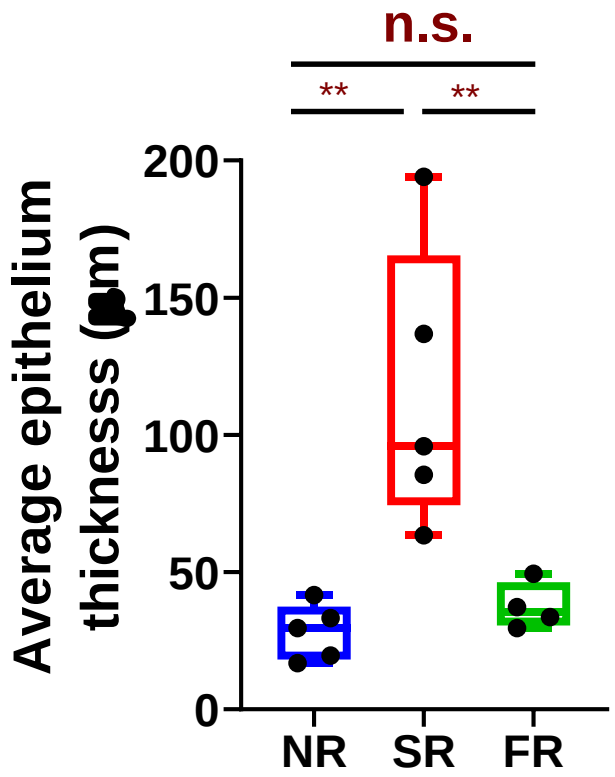


Focal Proton RT of PanCa and Small Intestine



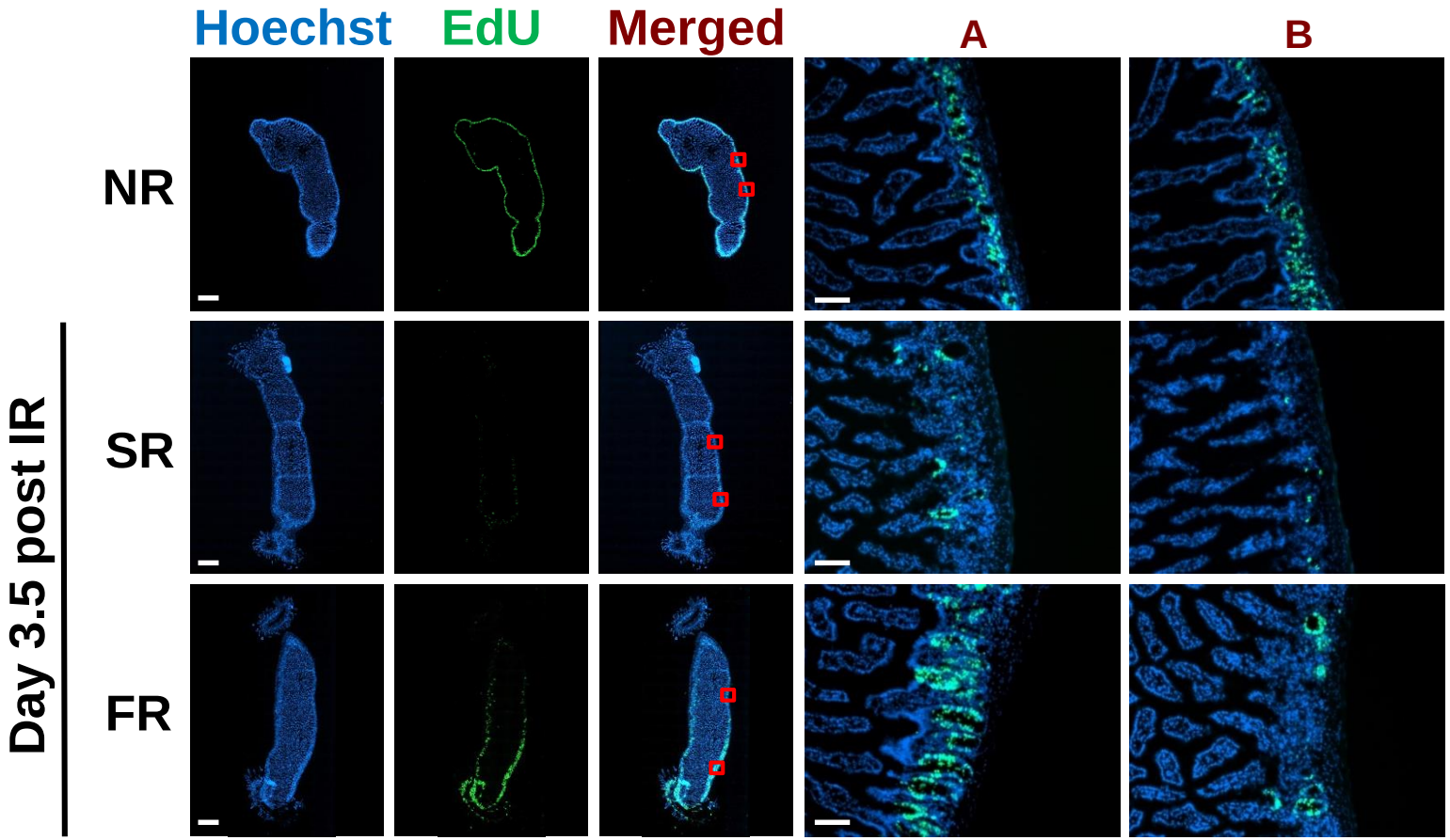
Intestinal Fibrosis 8 Weeks Post-Proton Radiation

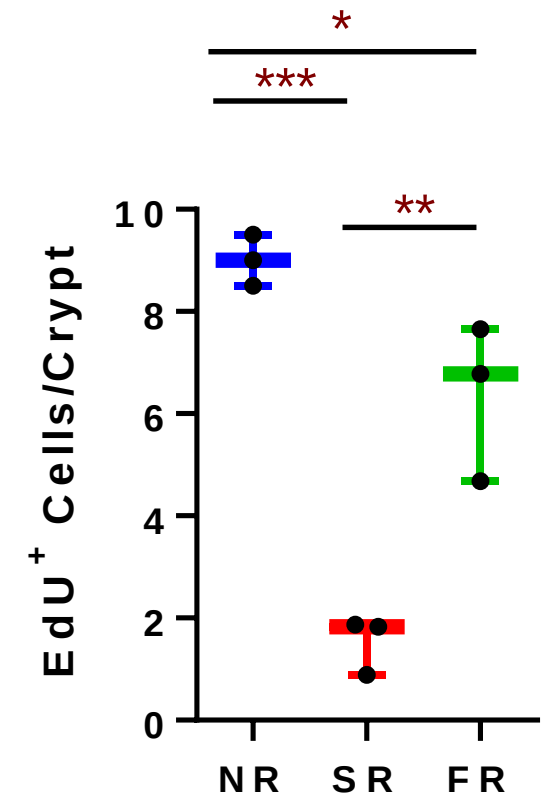




**p<0.001; non-parametric t-test on FR vs SR vs NR

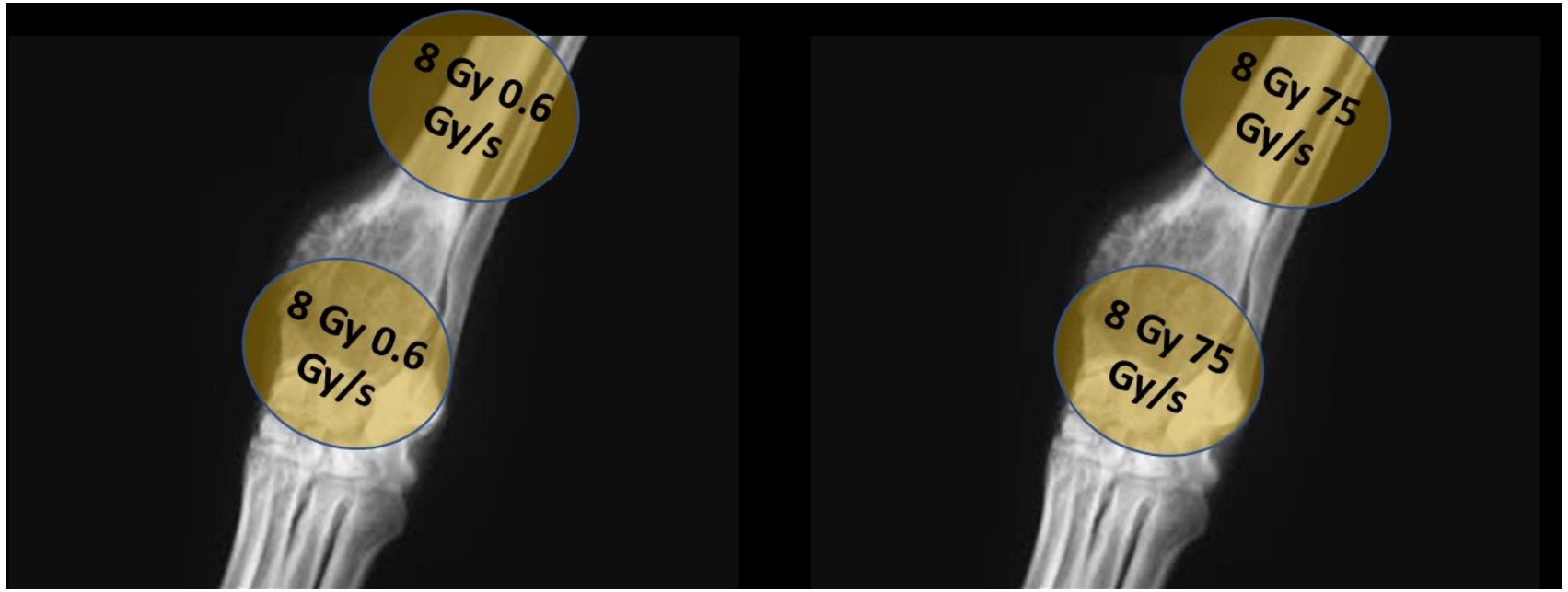
Whole Abdomen Proton Radiation - Crypt Cell Proliferation





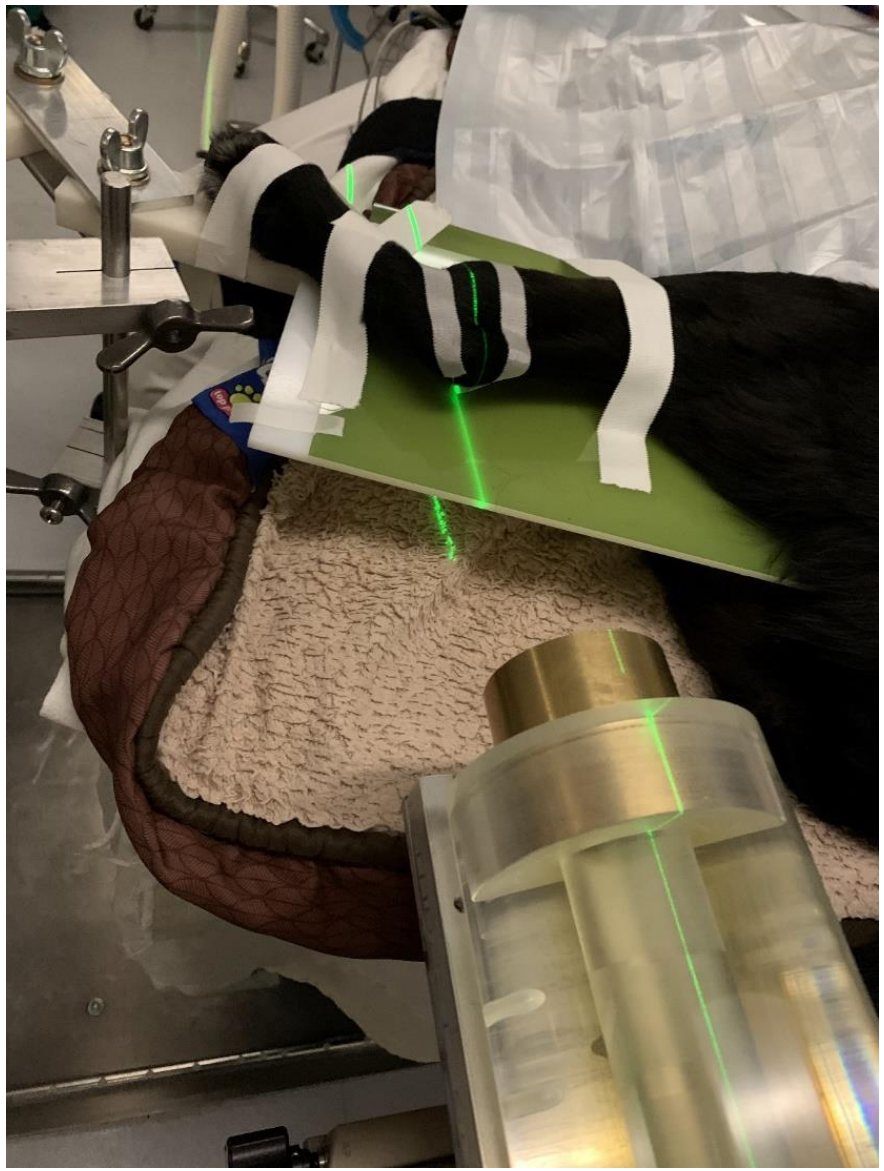
Whole intestine scan: scale bar, 1mm; 10x magnification: scale bar, 50μm; *p<0.05, **p<0.01, ***p<0.001

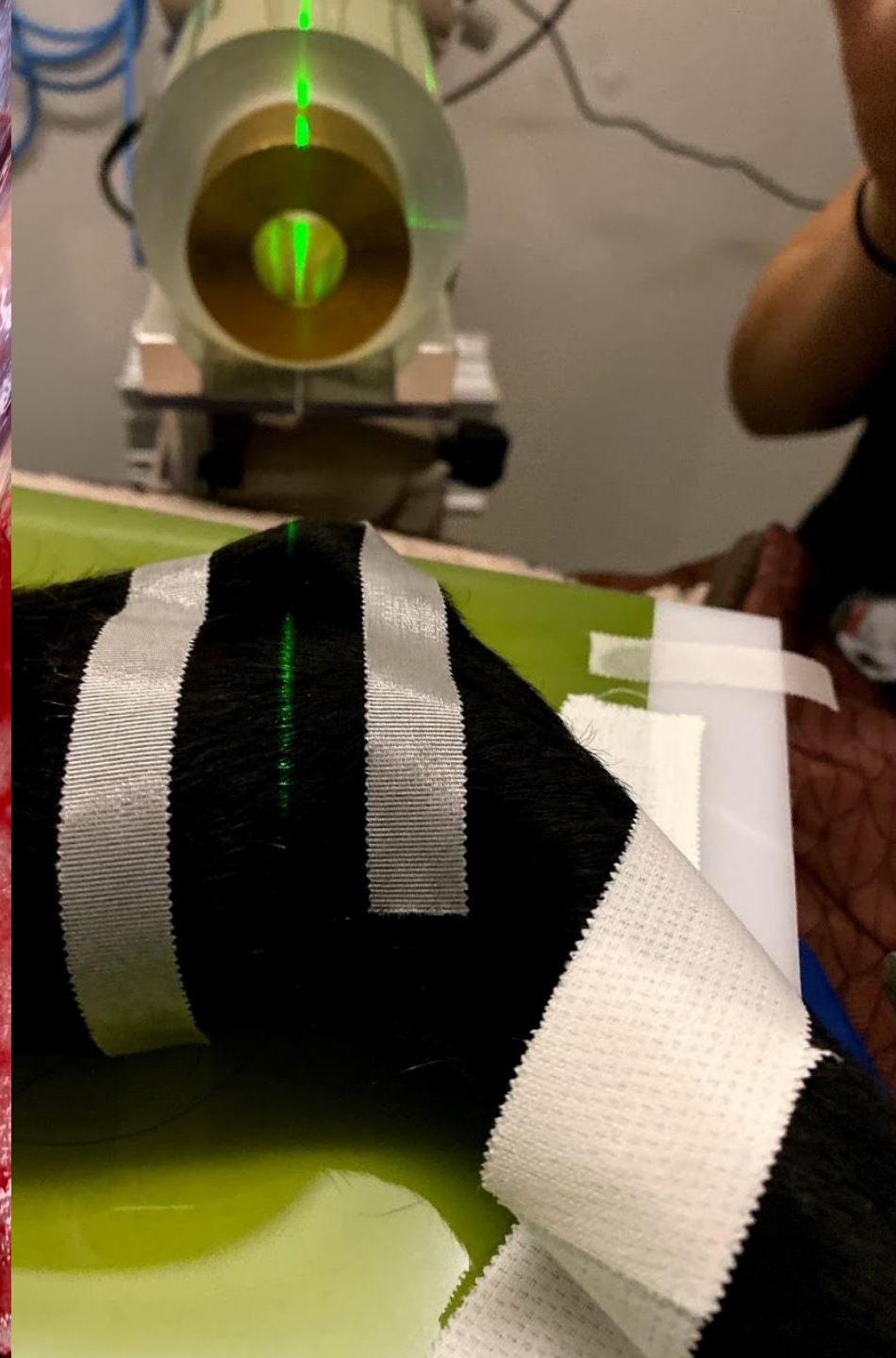
Canine Osteosarcoma Pilot Trial



- 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

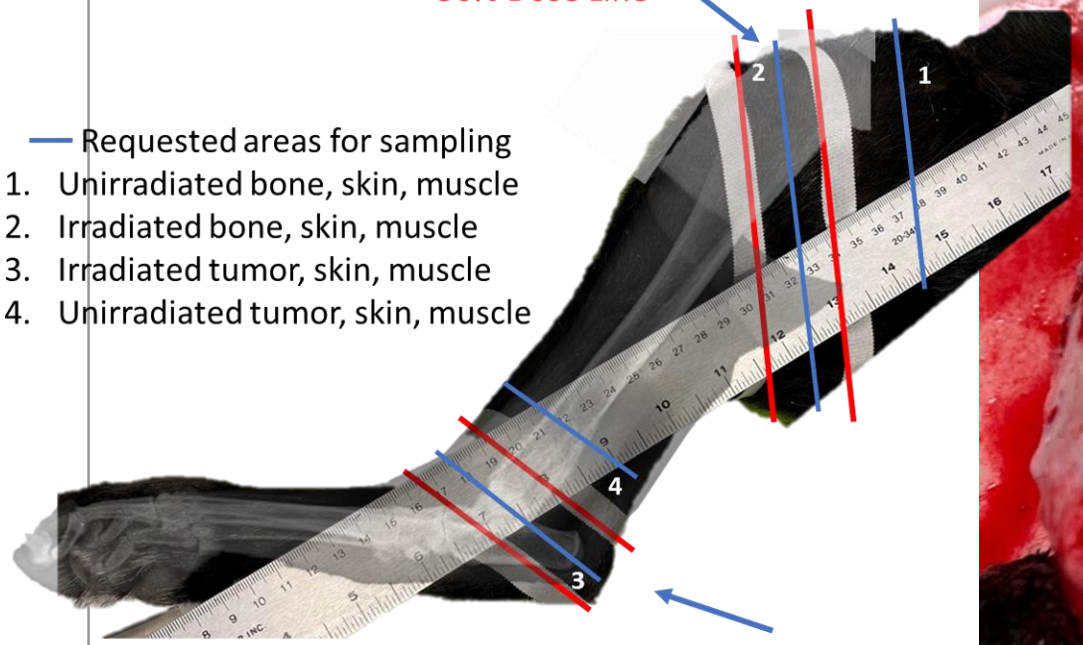
We have Treated 10 Canine Patients to Date





Irradiated normal
— 50% Dose Line

— Requested areas for sampling
1. Unirradiated bone, skin, muscle
2. Irradiated bone, skin, muscle
3. Irradiated tumor, skin, muscle
4. Unirradiated tumor, skin, muscle



Irradiated tumor
—50% Dose Line

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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