FLASH Radiotherapy

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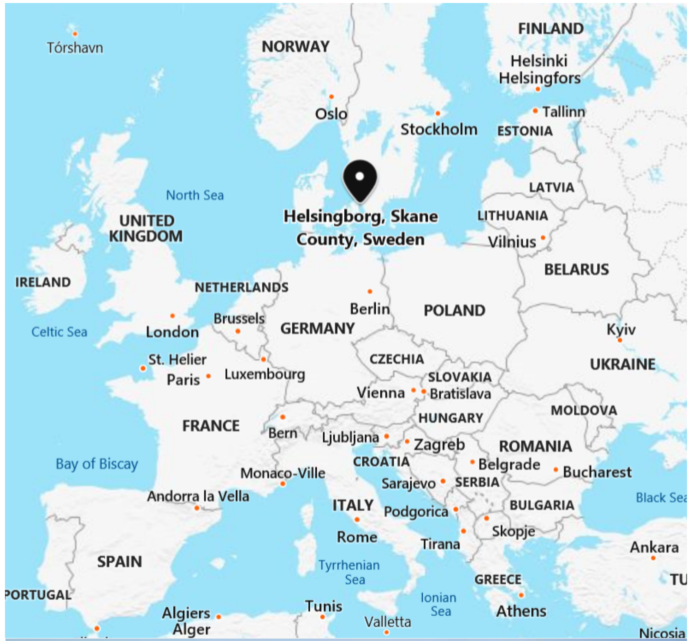
September 25, 2020

Disclosure

Member of the Local Organizing Committee

- Medical Physicist from Helsingborg, Sweden
- M.Sc. and Ph.D. in Medical Radiation Physics at Lund University, Sweden.
- 2014-2017, Post-doc on FLASH Radiation in Lausanne, Switzerland
- From 2017, Medical physicist at the Radiotherapy department at Skåne University Hospital, Started/headed a research group focused on FLASH Radiotherapy.
- From October 2019, Group leader – FLASH Radiation at Oxford Institute for Radiation Oncology



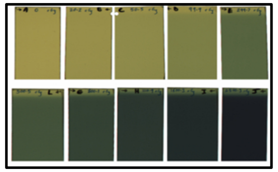
What is FLASH?

- Radiation delivered at ultra-high dose rates (FLASH)
  - Potential Benefits for Radiotherapy:
    - Enables full treatments (or fractions) in a few hundreds/tenths of a second.
    - No motion during treatment.
      - Could minimize treatment (PTV) margins related to motion.
        - Less normal tissue exposed to the treatment dose.
  - Pre-clinical studies show:
    - Less normal tissue toxicity, i.e. the "FLASH effect"
      - Dose modifying factor: **1.2-1.5**
    - Similar tumour control.
      - Dose modifying factor: **1**
  - Challenges to meet before clinical implementation:
    - How does it work?
    - How do we use it in a clinical setting?
    - How do we get similar dosimetric accuracy as we are used to?

Wilson *et al.*
Front. Oncol. 2019

Dosimetry
5 Types of dosimeters used for Flash RT

- Passive dosimeters validated as dose rate independent dosimeters up to >10^7 Gy/s:
  - Radiochromic films (Gafchromic EBT3 & XD)
    - Jaccard & Petersson *et al. Med. Phys.* 2017

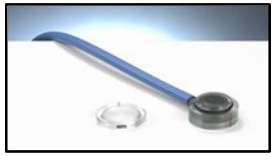


  - Thermoluminescent dosimeter (TLD-100)
    - Karsch *et al. Med. Phys.* 2012

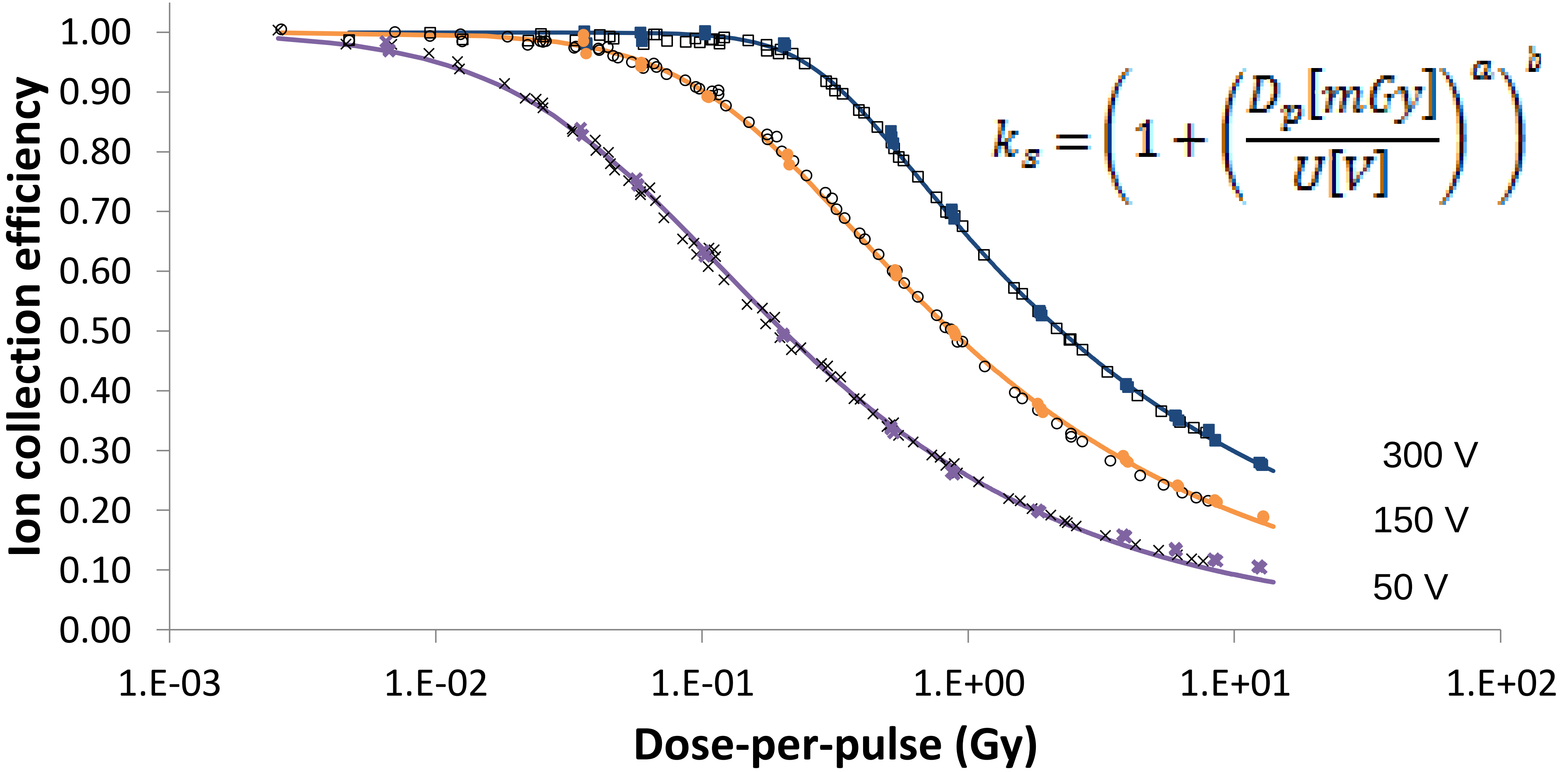
  - Alanine pellets
    - Montay-Gruel & Petersson *et al. Radiother. Oncol. 2017*

  - Methyl viologen
    - Favaudon *et al. Sci. Transl. Med.* 2014

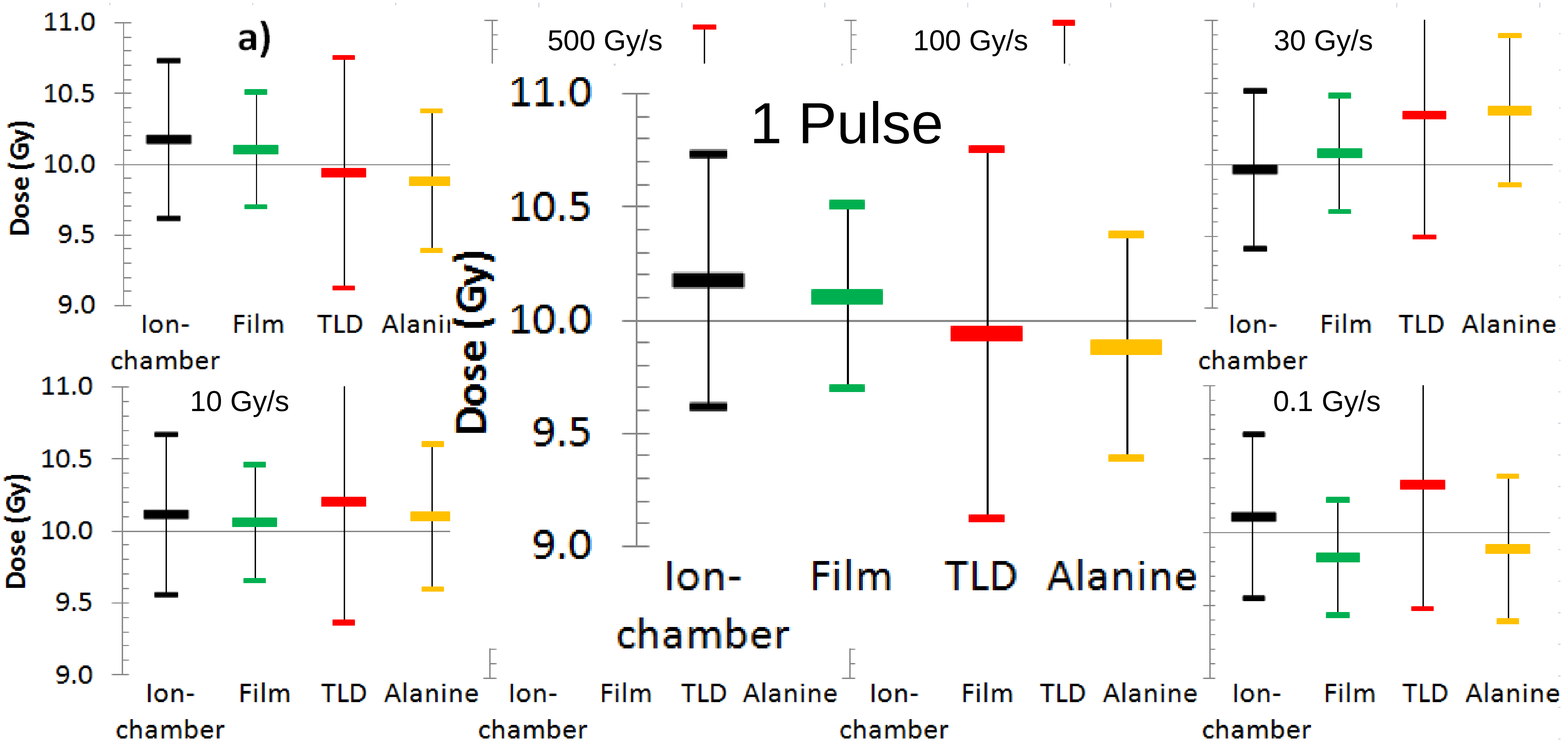
- Active dosimeters show large dose-per-pulse dependence
  - Advanced Markus ionization chamber (PTW)
    - Petersson & Jaccard *et al. Med. Phys.* 2017



Advanced Markus saturation



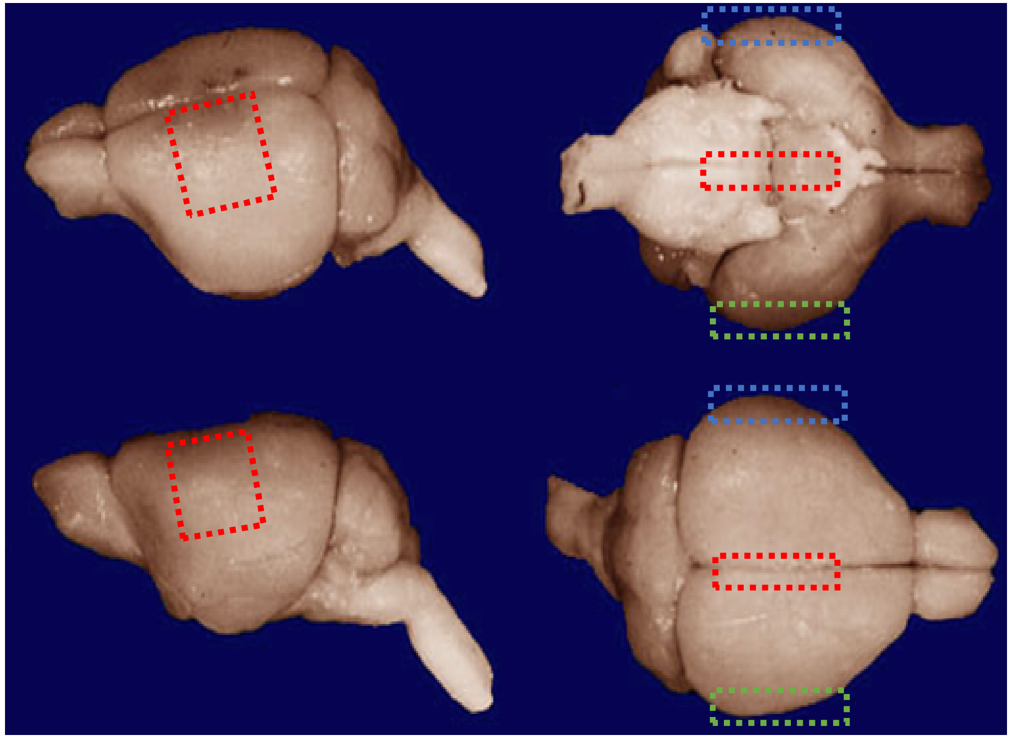
Petersson *et al.*
Med. Phys. 2017



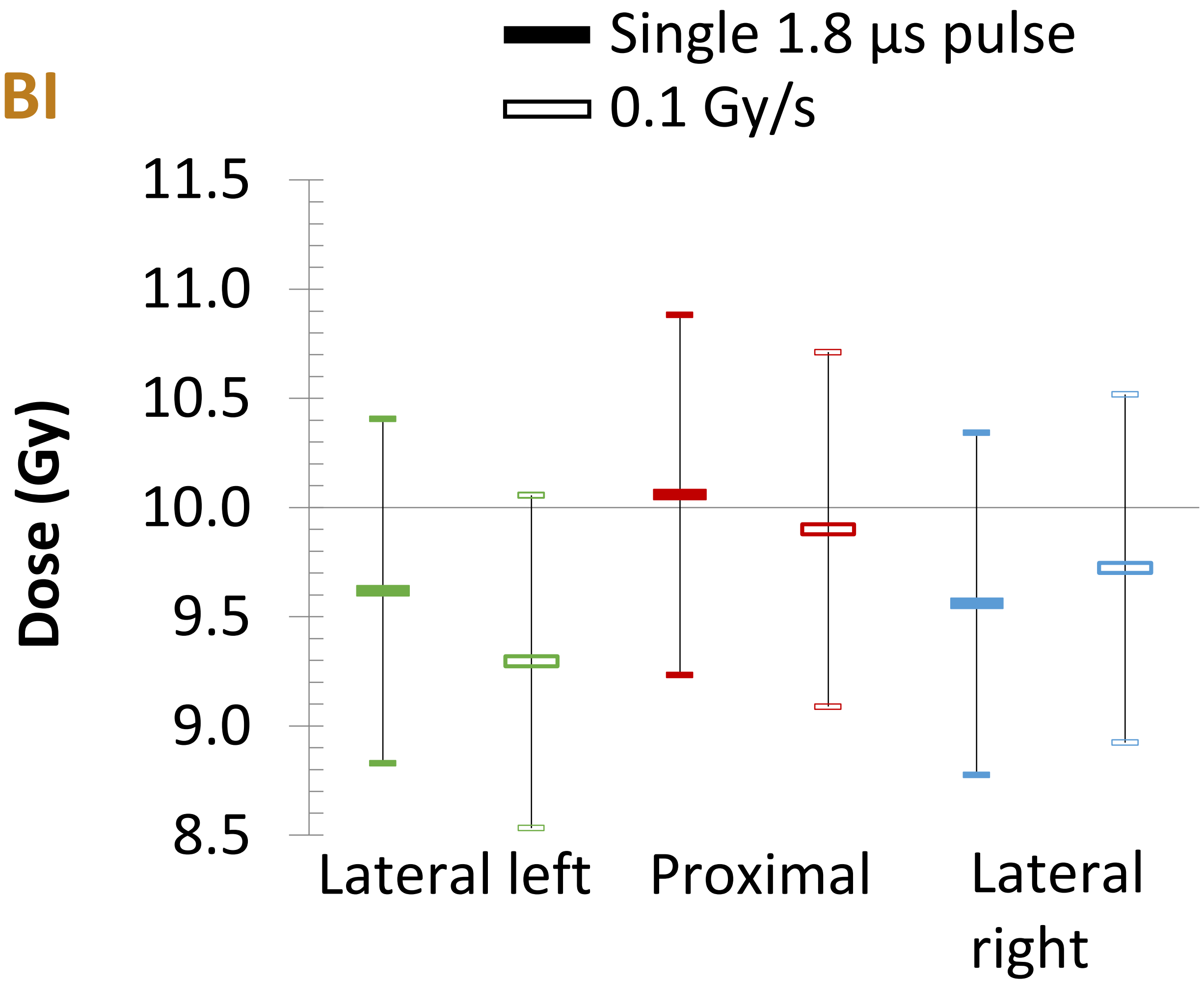
Absorbed dose measurements at surface of solid water phantom for delivery of 10 Gy WBI at different dose rates

In situ measurements for 10 Gy WBI

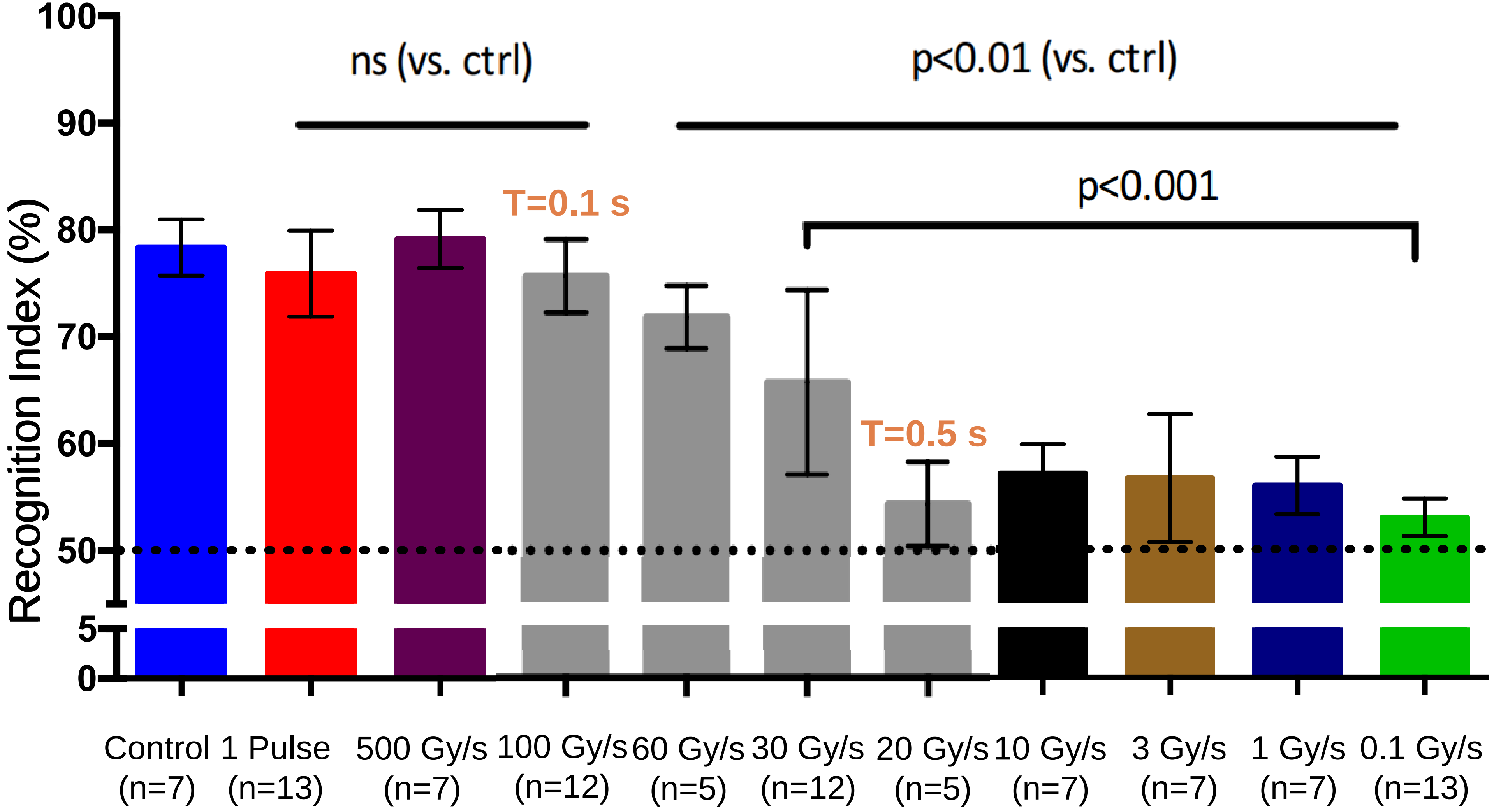
Delivery parameters specified (Prescribed dose) according to dose measurement at the surface of a (solid) water phantom



Validation of dose delivery
TLD implanted in the brain of a sacrificed mouse, between the two hemispheres



Normal tissue toxicity – 10 Gy **W**hole **B**rain **I**rradiation in mice
Novel **O**bject **R**ecognition test: 2 Months post RT



Montay-Gruel & Petersson *et al.*
Radiother. Oncol. 2017

Irradiation of a mini-pig

26 mm Ø fields

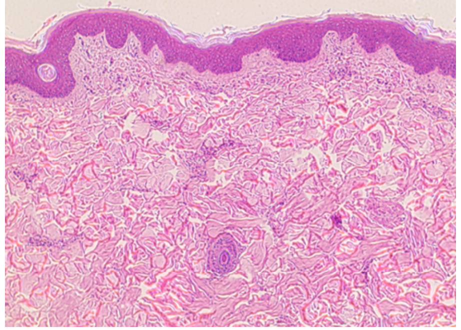
28, 31, 34 Gy with 5 Gy/min and 300 Gy/s

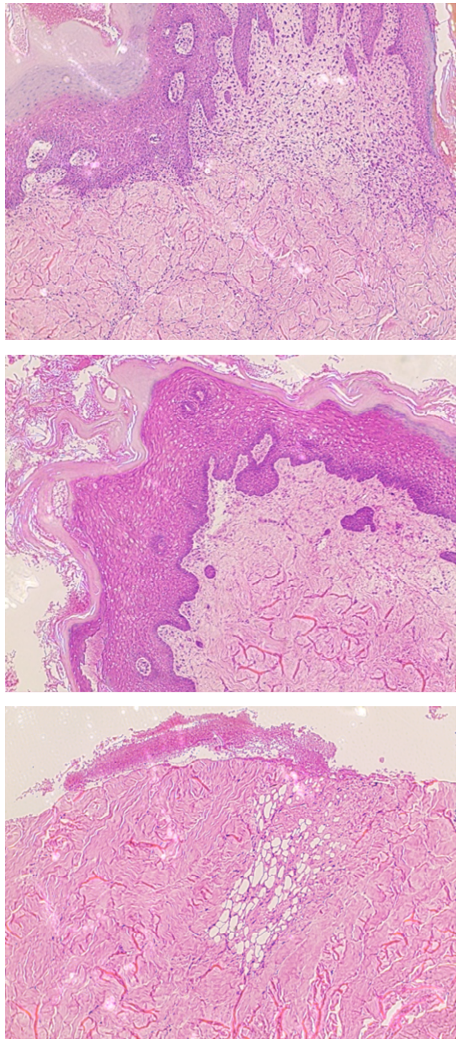
Delivered doses verifed *in vivo* with film and Alanine dosimetry

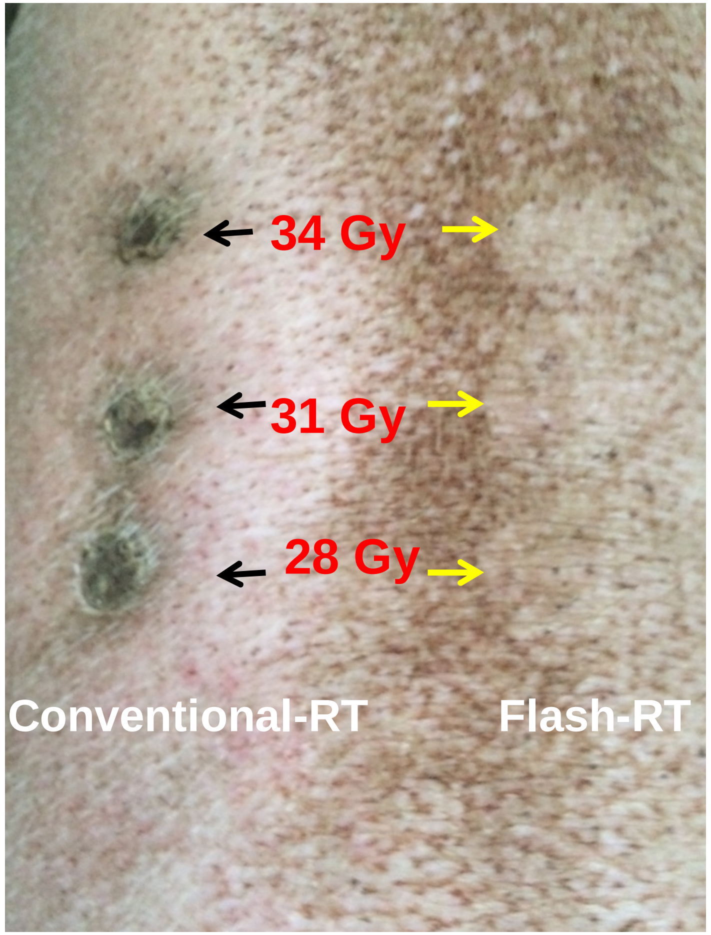
Vozenin, De Fornel, & Petersson *et al.*
Clin. Cancer Res. 2019

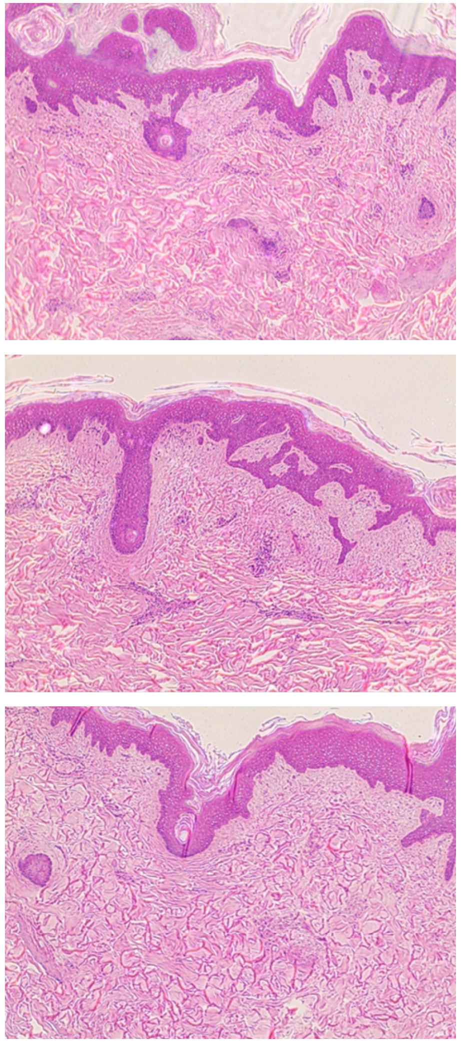
9 months post-RT

→ FLASH effect > 20%









Vozenin, De Fornel, & Petersson *et al.*
Clin. Cancer Res. 2019

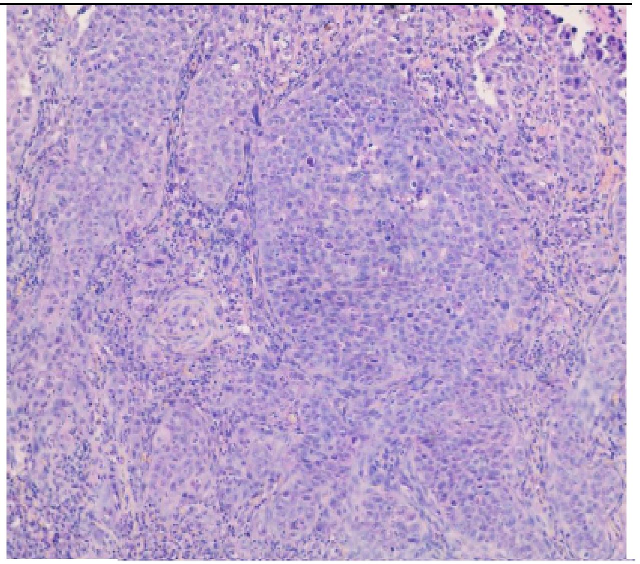
First clinical study with FLASH

Veterinarian study: A phase I dose-escalation trial, treatment of Squamous Cell Carcinoma

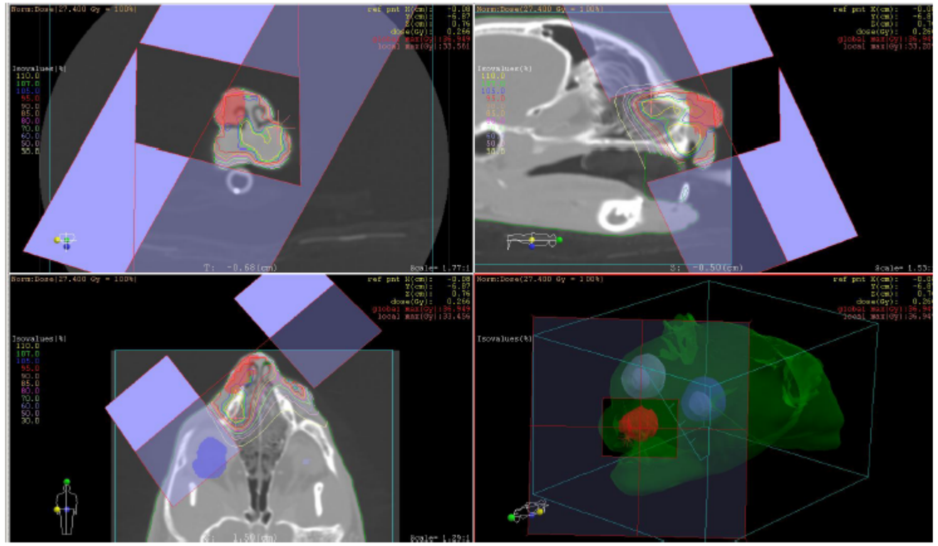
T3N0M0 Treatment example: 27 Gy in 0.09 s, 25x34 mm^2 field size

Vozenin, De Fornel, & Petersson *et al. Clin. Cancer Res. 2019*

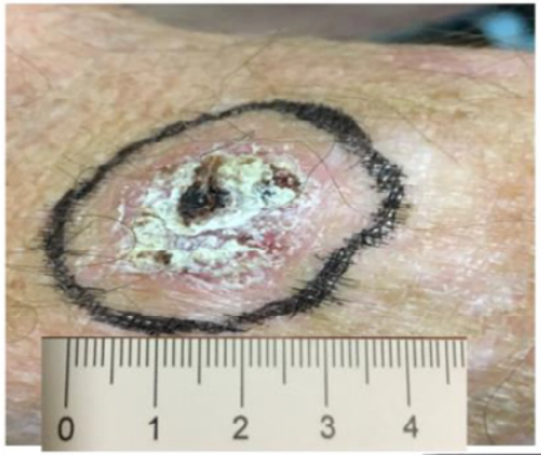
Pre-RT



14 months Post-RT



First patient treated with FLASH



1a : Day 0

1b : 3 weeks

1c : 5 months

75-year-old patient had a CD30+ T-cell cutaneous lymphoma.
Treated with 15 Gy in 0.09 s, i.e. at a dose rate of 167 Gy/s.
in Lausanne, Switzerland, 2018.

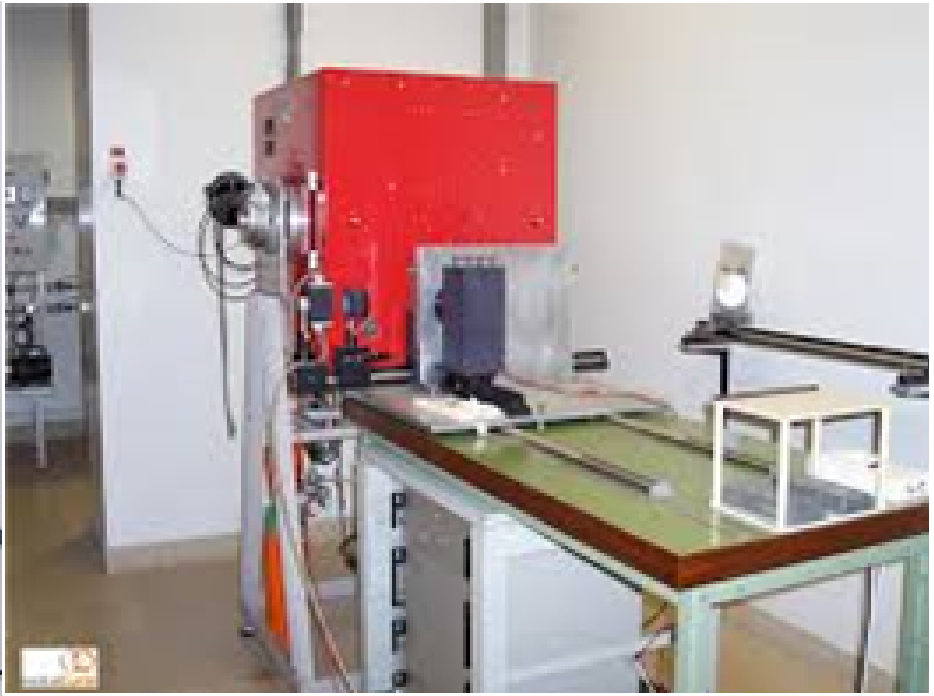
Bourhis *et al.*
Radiother. Oncol. 2019

Radiation sources used in published FLASH research

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

At CHUV, in Lausanne, Switzerland
Jaccard et al. Med. Phys. 2018

Prototype 4.5 MeV electron Linac



At Institute Curie, in Orsay, France
Favaudon *et al. BioChemistry 1990*
Favaudon *et al. Sci. Transl. Med. 1990*

Modified clinical linacs used in FLASH studies

Varian Clinac 21EX
Stanford, USA

Schüler *et al.*
Int J Radiat Biol 2016

Elekta Precise
Lund, Sweden

Lempart *et al.*
Radiother. Oncol. 2019

Veterinarian clinical studies
- In Lund

- First dog:
  - Grade 1 soft tissue sarcoma
    - Incomplete excision after surgery
    - 15 Gy in 0.03 s, i.e. 500 Gy/s
    - Field size of 8 x 4 cm², **10 mm bolus material**

7 days post-RT

30 days post-RT

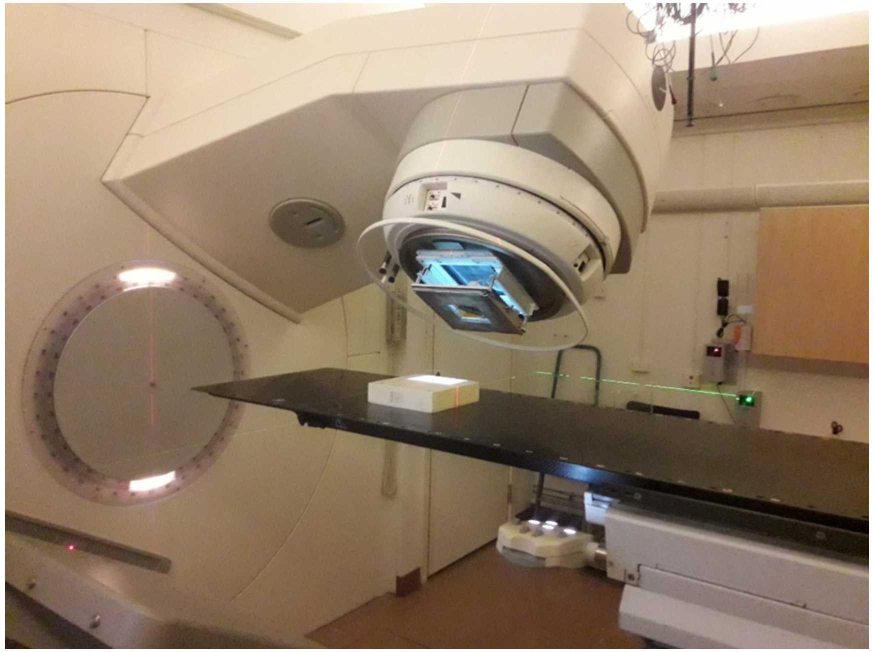
Elekta Precise in Lund

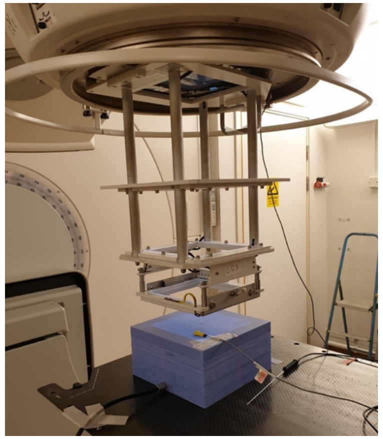
Veterinarian Clinical studies:

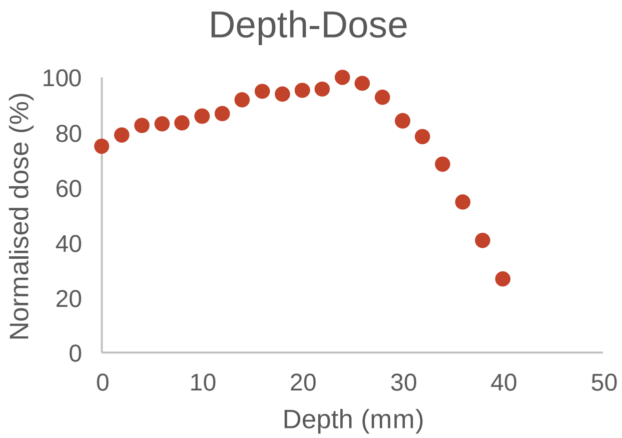
- Shorten applicator (SSD = 70 cm)
  - Cerrobend inserts
  - Dose rate at dose maximum:
    - ≈500 Gy/s
- Beam characteristics – 10 MeV e^-
  - Measured with Gafchromic EBT3

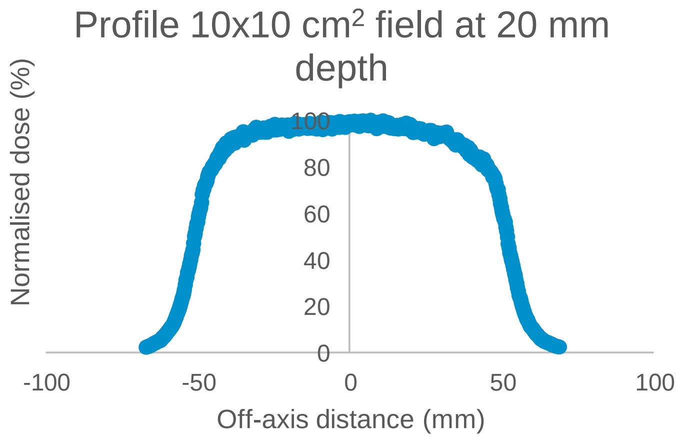
Human Clinical studies:

- In preparation
- Clinical applicator (SSD = 100 cm)
  - Dose rate ≈ 200 Gy/s





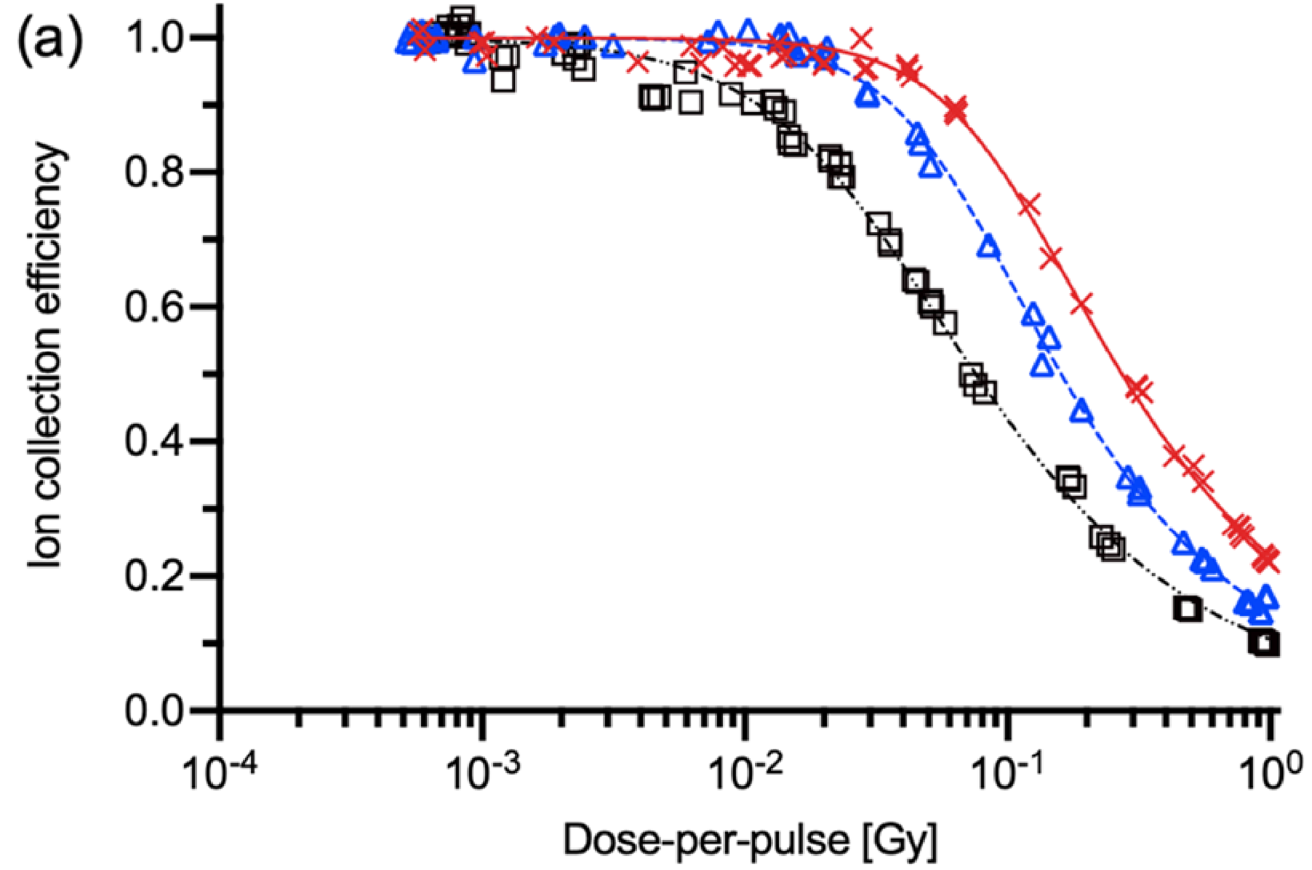


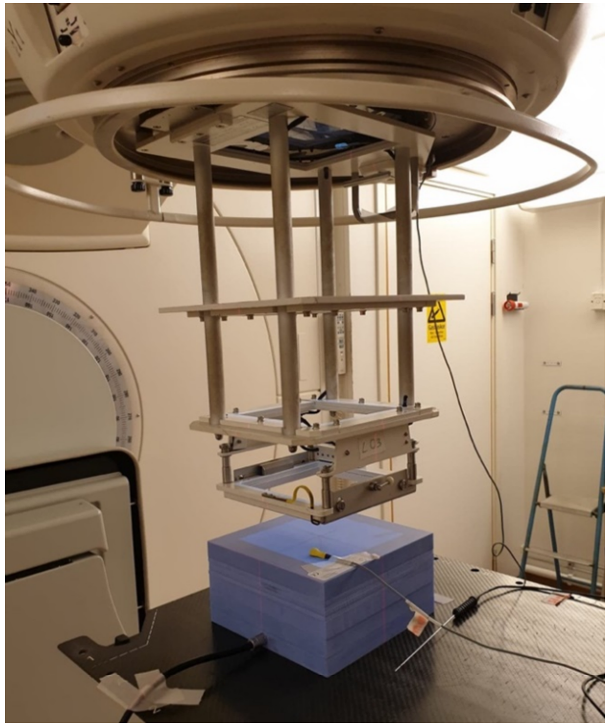


Increasing the polarizing/bias voltage or decreasing electrode distance

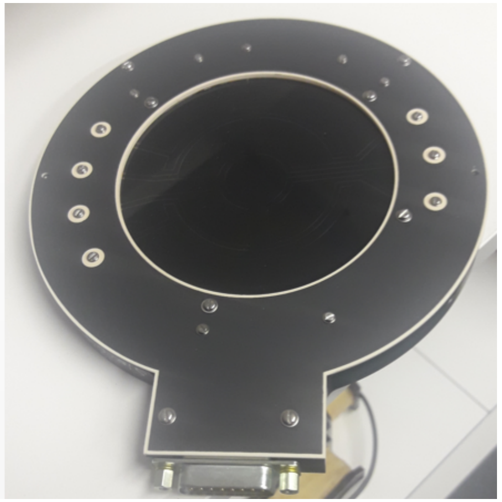
- Dose measurements at iso-center (SSD=100cm) → 200 Gy/s
  - Much higher dose-per-pulse at the transmission chamber position
- Fitting function:

$$k_s = \left(1 + \left(\frac{DPP[mGy] \cdot 10}{U[V]}\right)^a\right)^b$$





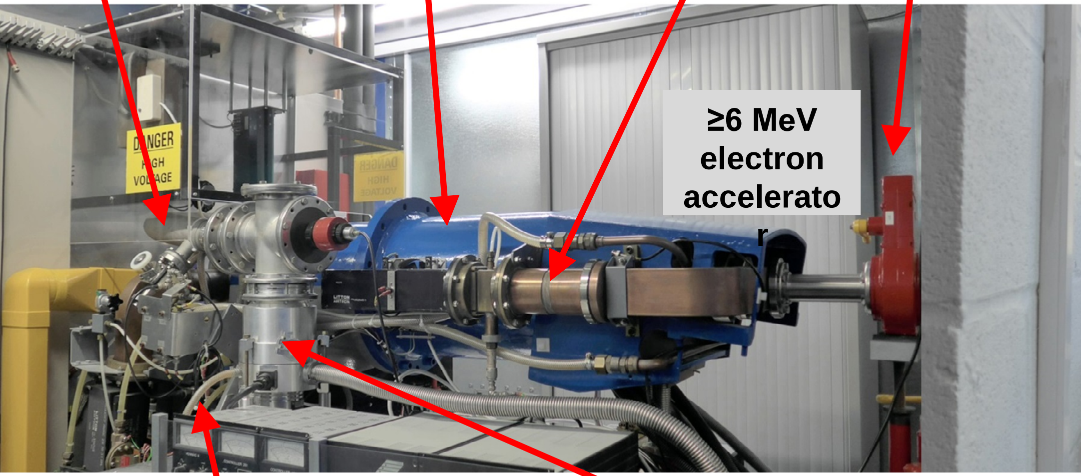
Konradsson *et al.*
Rad. Res. 2020



University of Oxford – 6 MeV electron linear accelerator

Based on an Elekta/Philips SL75-5

Electron gun Waveguide + focusRF dump Gate valve



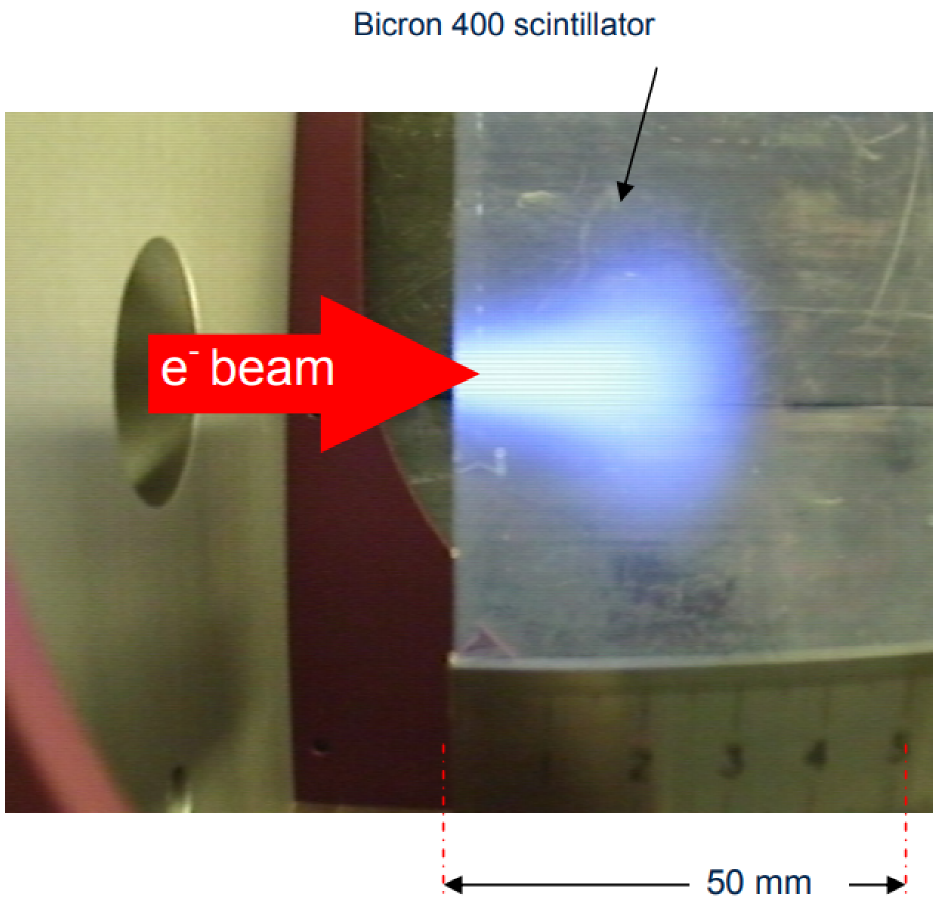
Magnetron and isolator Vacuum system

Beam Characteristics

- 6 MeV electron (e^-) beam → ≈ homogeneous dose 0-20 mm depth, depth >30 mm ≈ no dose
- Maximum beam size: 50 mm Ø
- Average dose rate:
  few Gy/min → 30 000 Gy/s
- Dose/pulse: mGy → >100 Gy

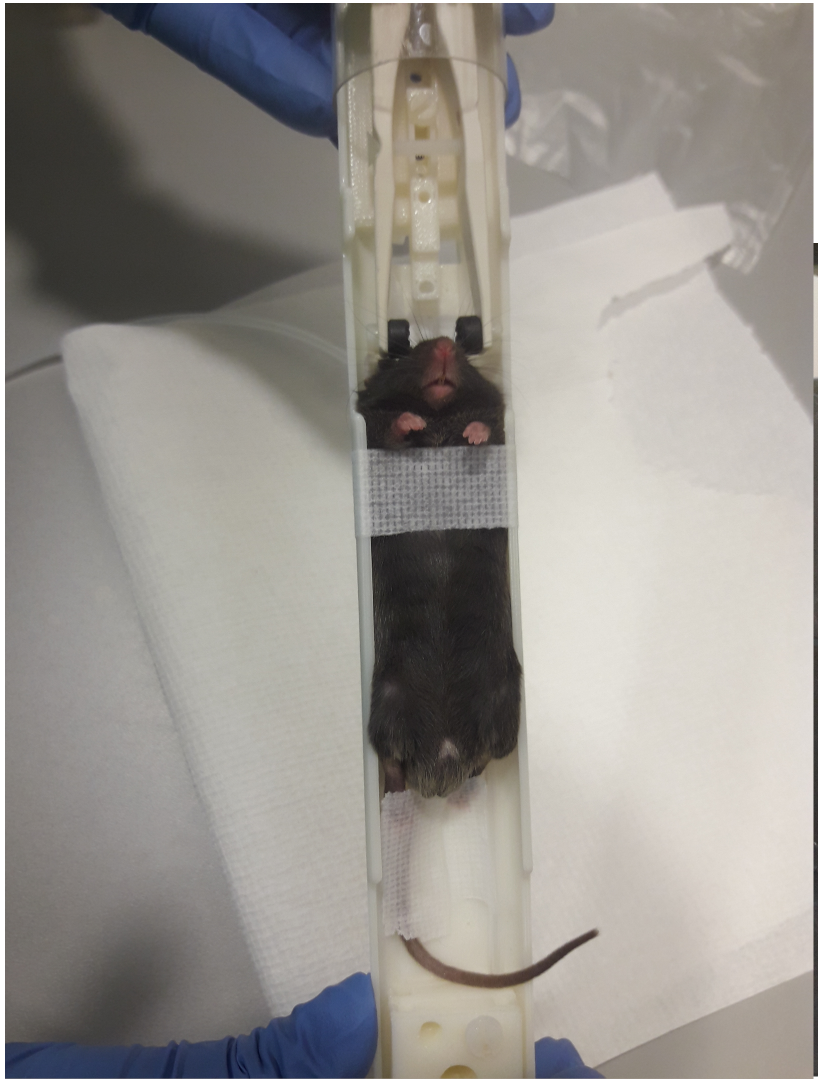
Highly suitable for pre-clinical FLASH radiation studies!

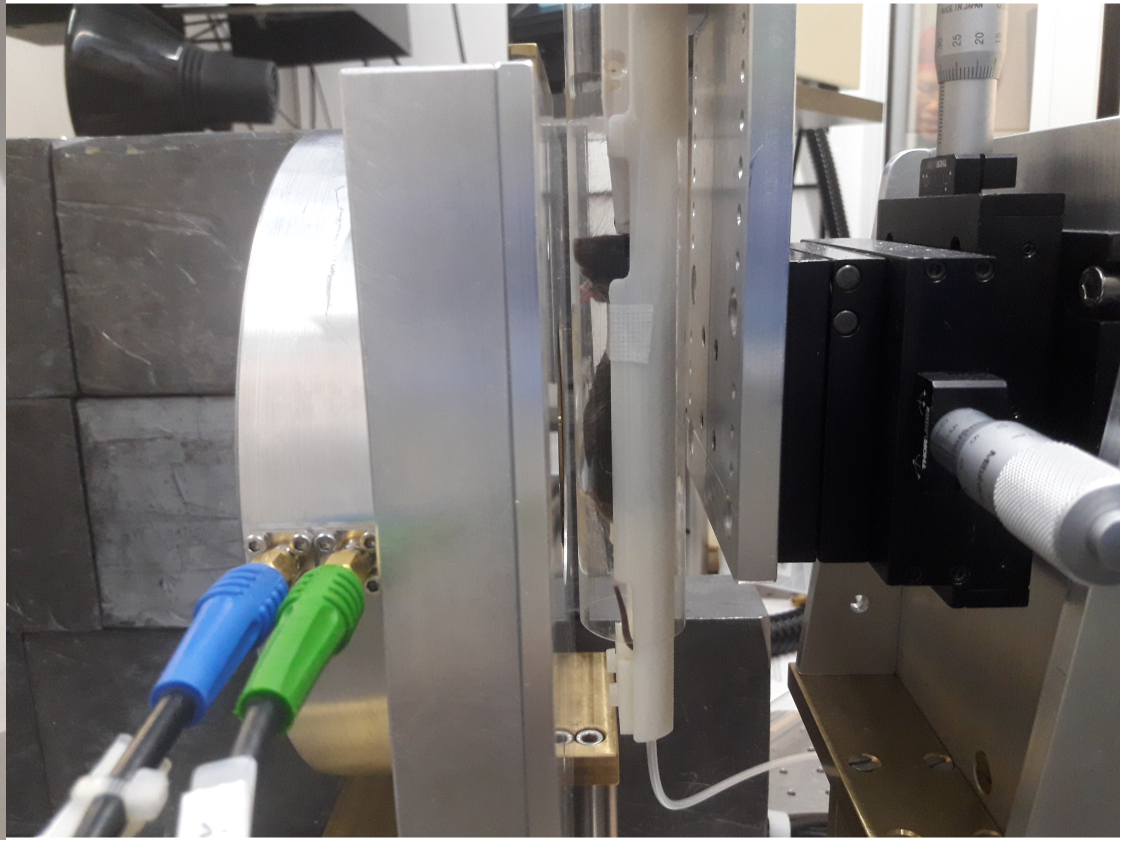
Not suitable for clinical studies!



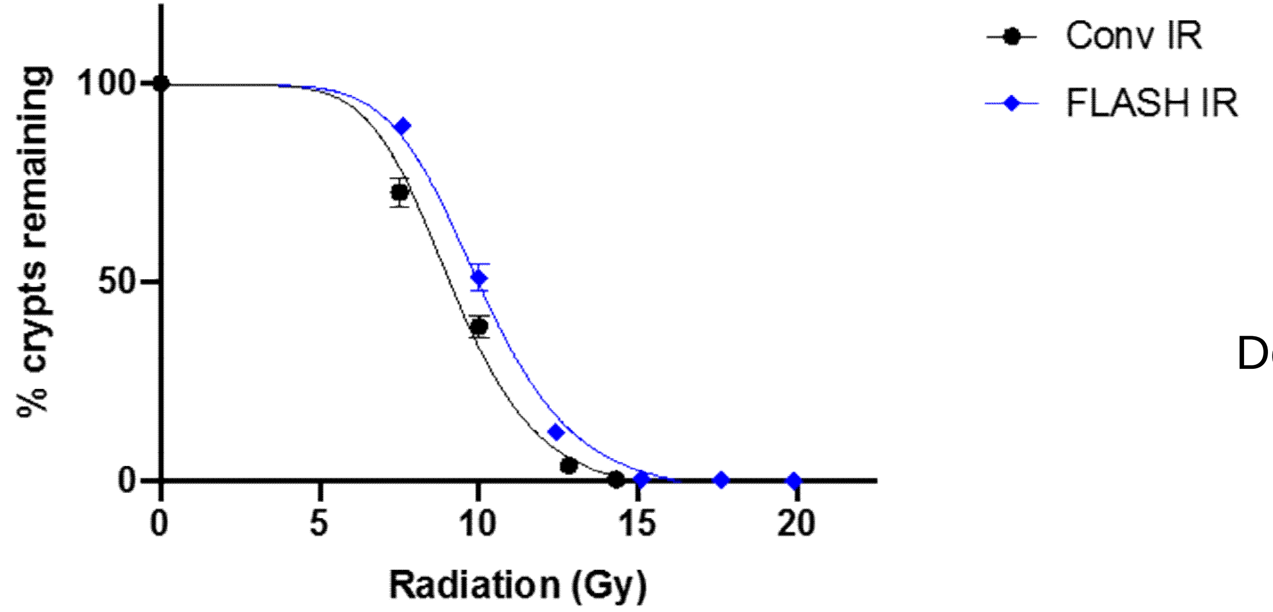
Electron beam luminescence in solid scintillator

Whole abdominal irradiation of mice

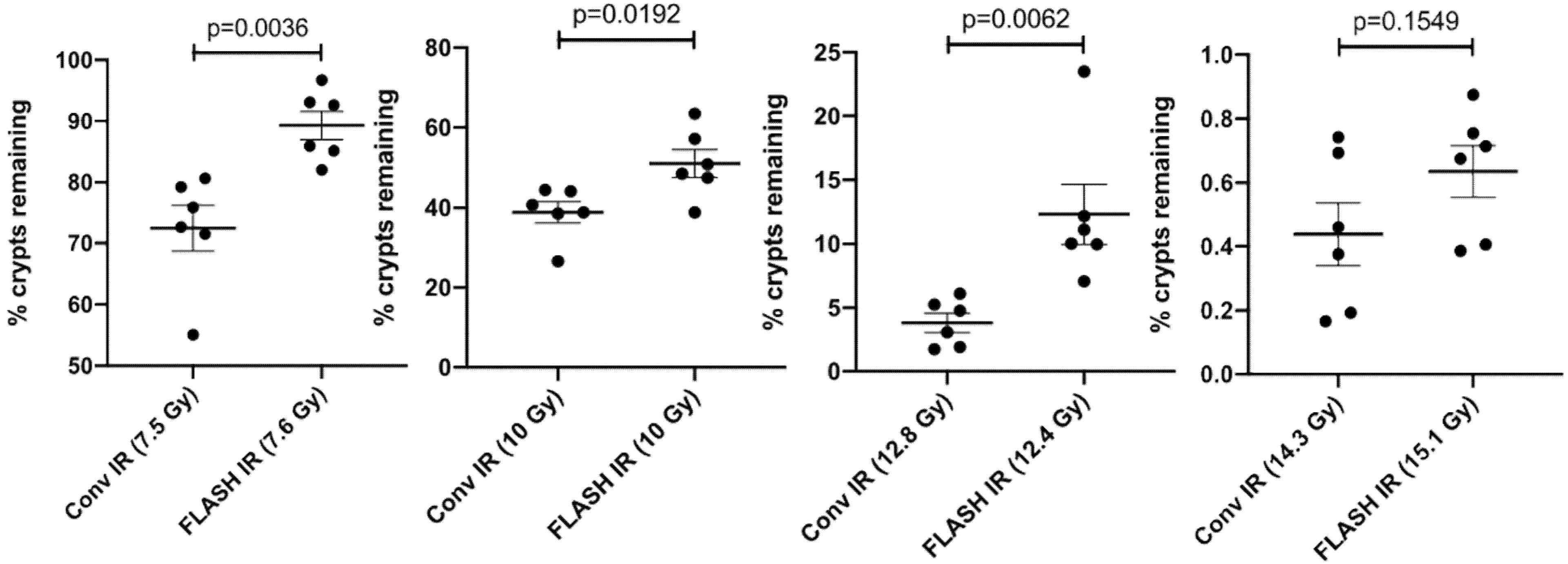




Ruan *et al.*
Unpublished data

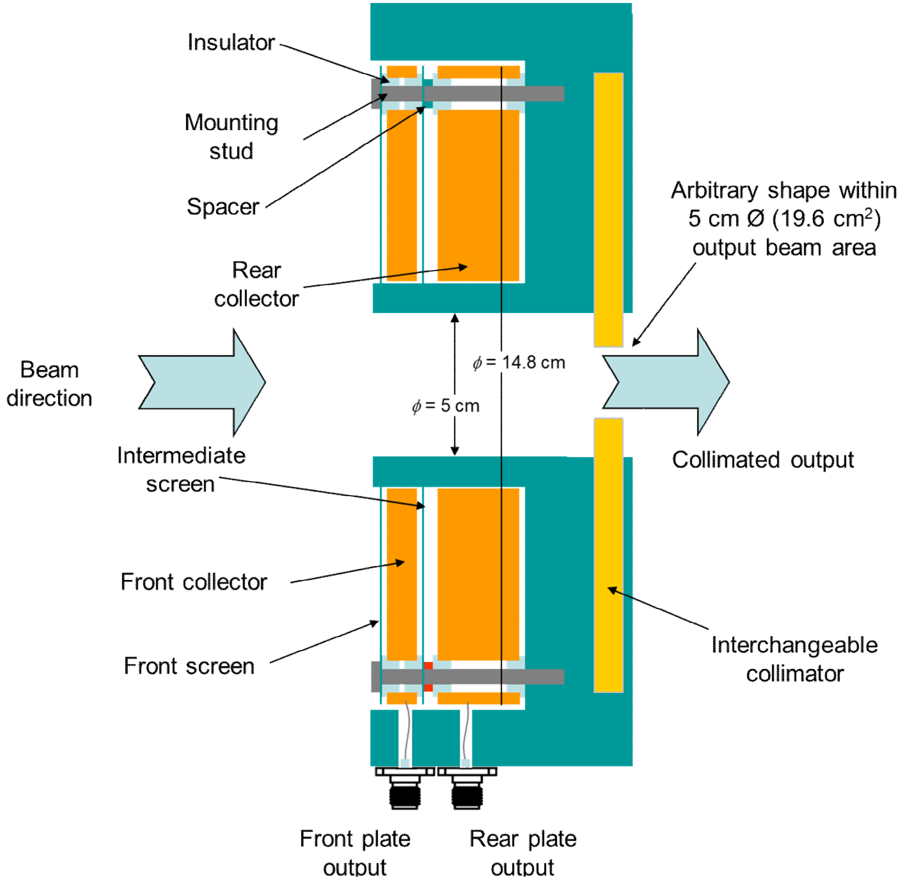


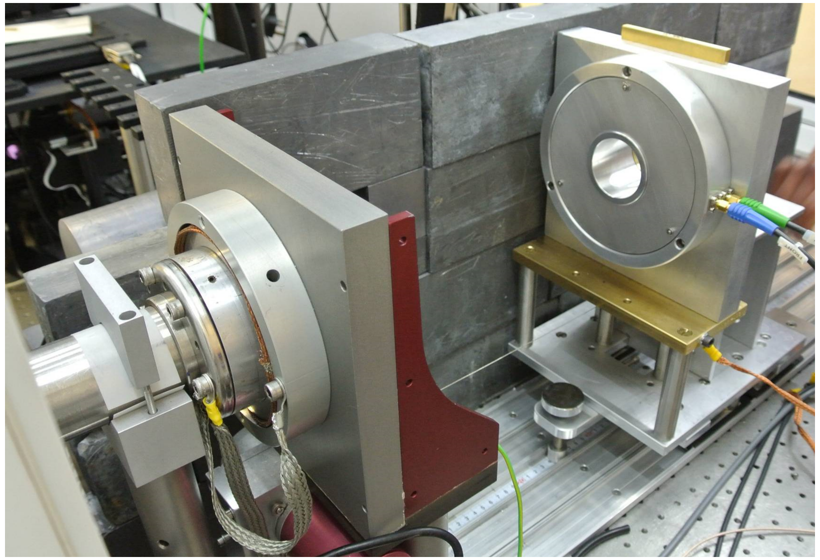
Dose modifying factor: **1.1**

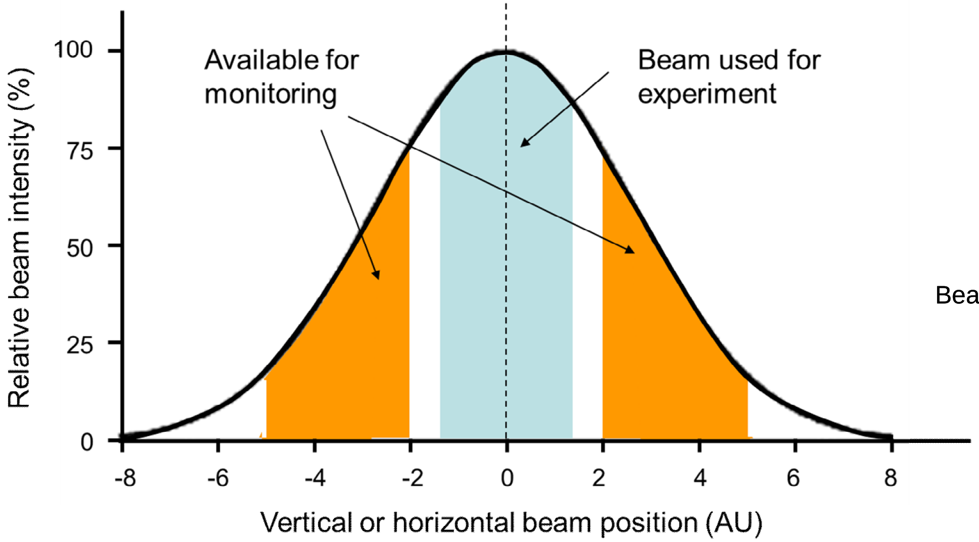


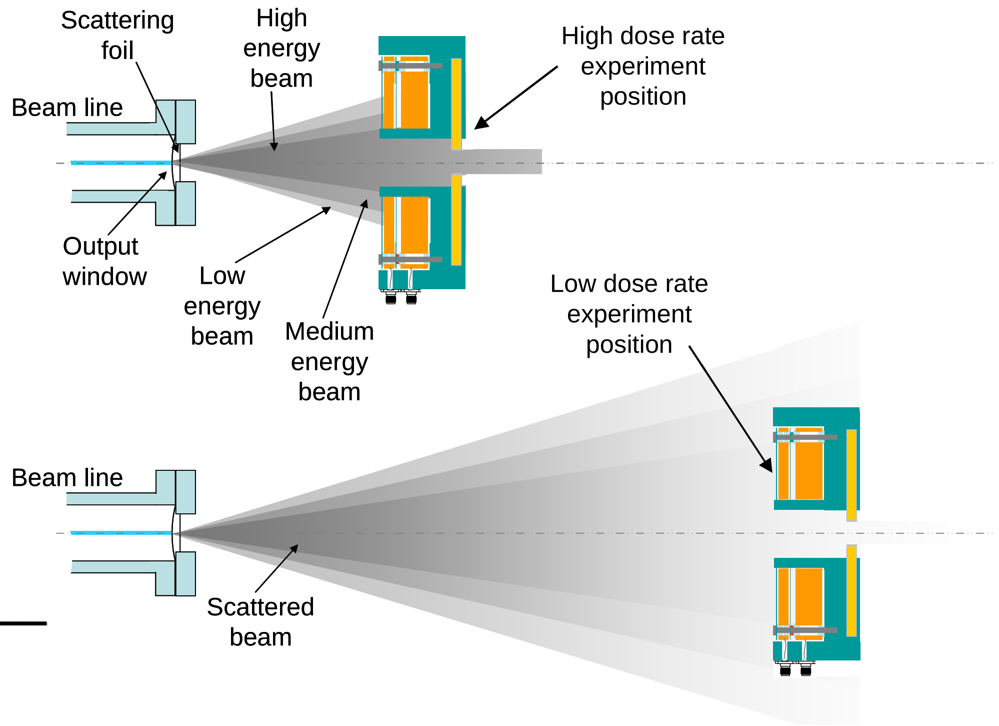
Beam energy monitor in Oxford

Courtesy of Prof B. Vojnovic



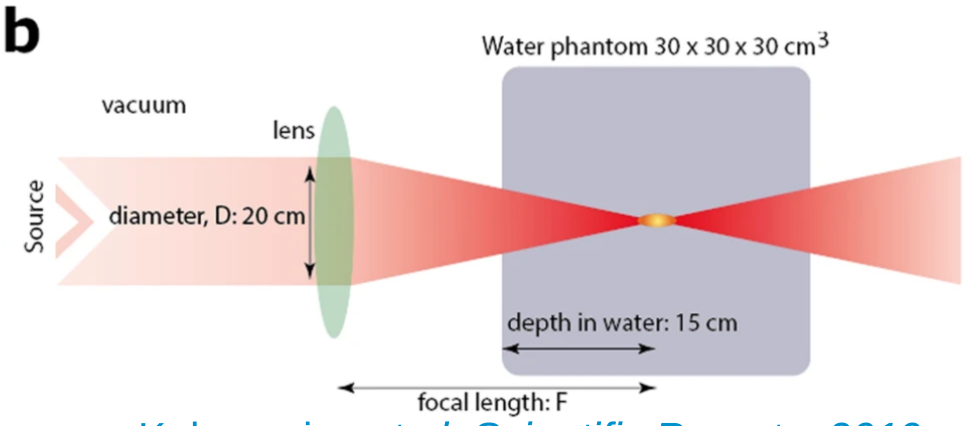




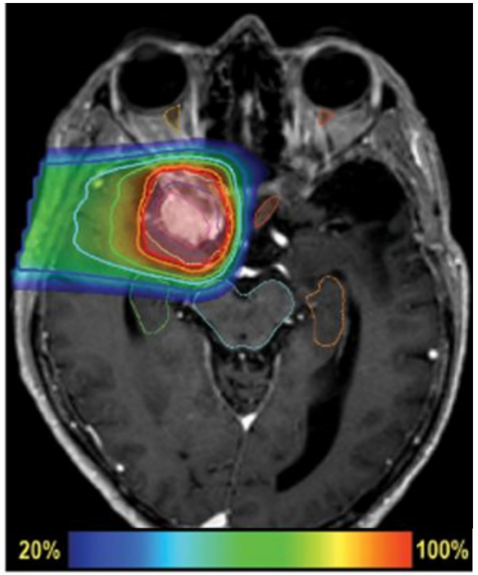


Technical solutions for treating deep-seated tumours with FLASH

- Very-high (100-250 MeV) energy electron beams?
  - Sharp penumbra
  - Can be focused to the target
  - Electrons become “heavy” (relativistic mass) at high beam energies.
  - Activation issues
- Protons?
  - Maybe, dose rates in spots of several hundreds Gy/s
  - Problems/challenges:
    - Scanning/scattering needed to cover the target volume
      - Dose rate decreases!
    - Several beam energies needed to cover the target volume in depth
      - Dose rate decreases!
    - Several beams needed for dose conformity
      - Dose rate decreases!
      - Takes time to change beam angle.



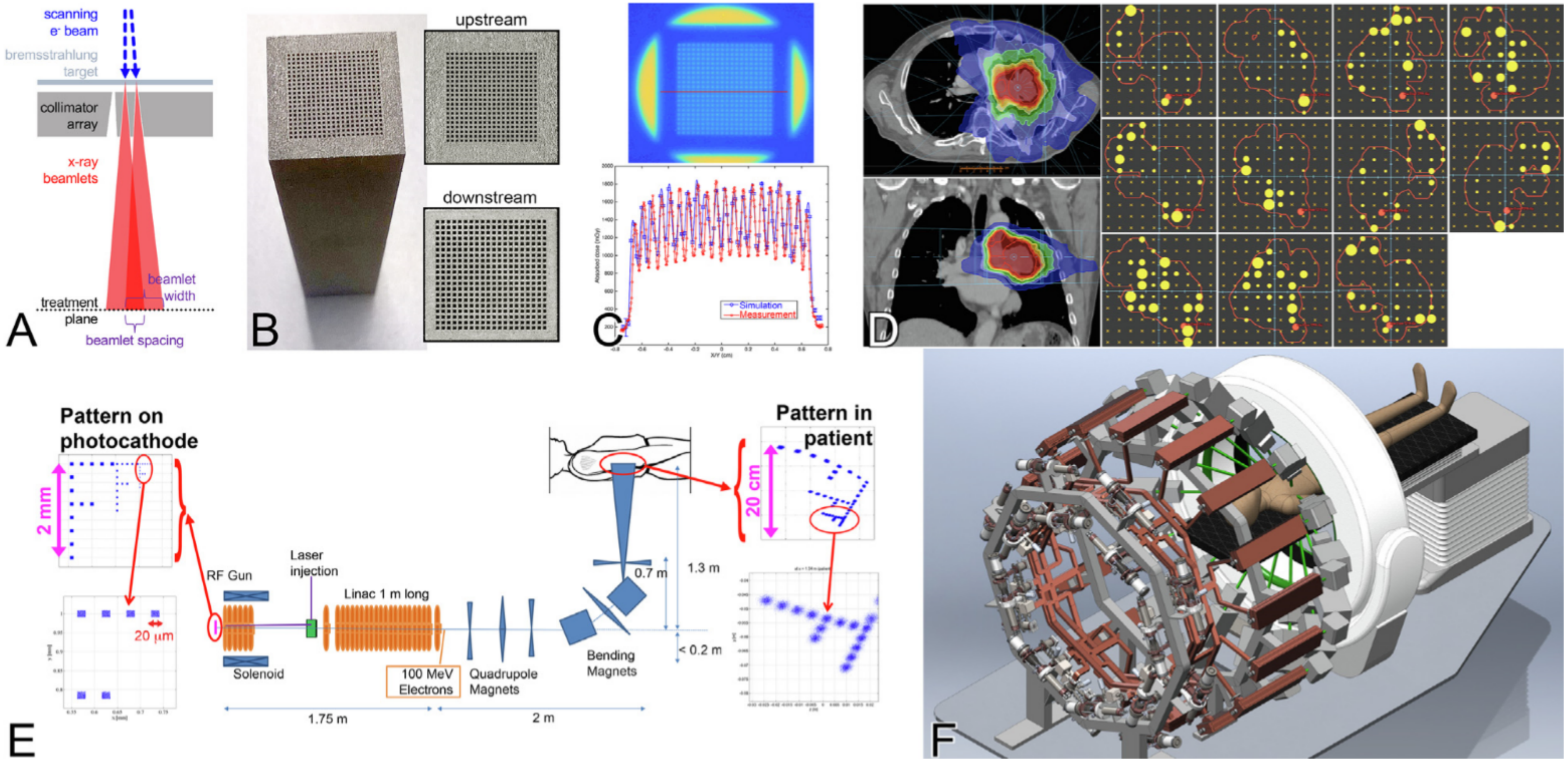
Kokurewicz *et al. Scientific Reports 2019*



Proton radiation beam

PHASER – a FLASH MV X-ray platform

Image-Guidance strategy to minimize margins for intra-fractional motion



Maxim *et al.*
Radiother. Oncol. 2019

Possible explanations of the "FLASH effect"

(Ultra-) high dose rate → less radiation effect/toxicity

Oxygen consumption too quick for diffusion to maintain adequate level of oxygenation
→ Dose-response curves show signs of hypoxia

Hall & Brenner, *Int. J. Radiat. Oncol., Biol., Phys.* 1991

Oxygen and mouse tail Radionecrosis

→ FLASH sparing mimics hypoxia

Hendry et al.
Rad. Res. 1982

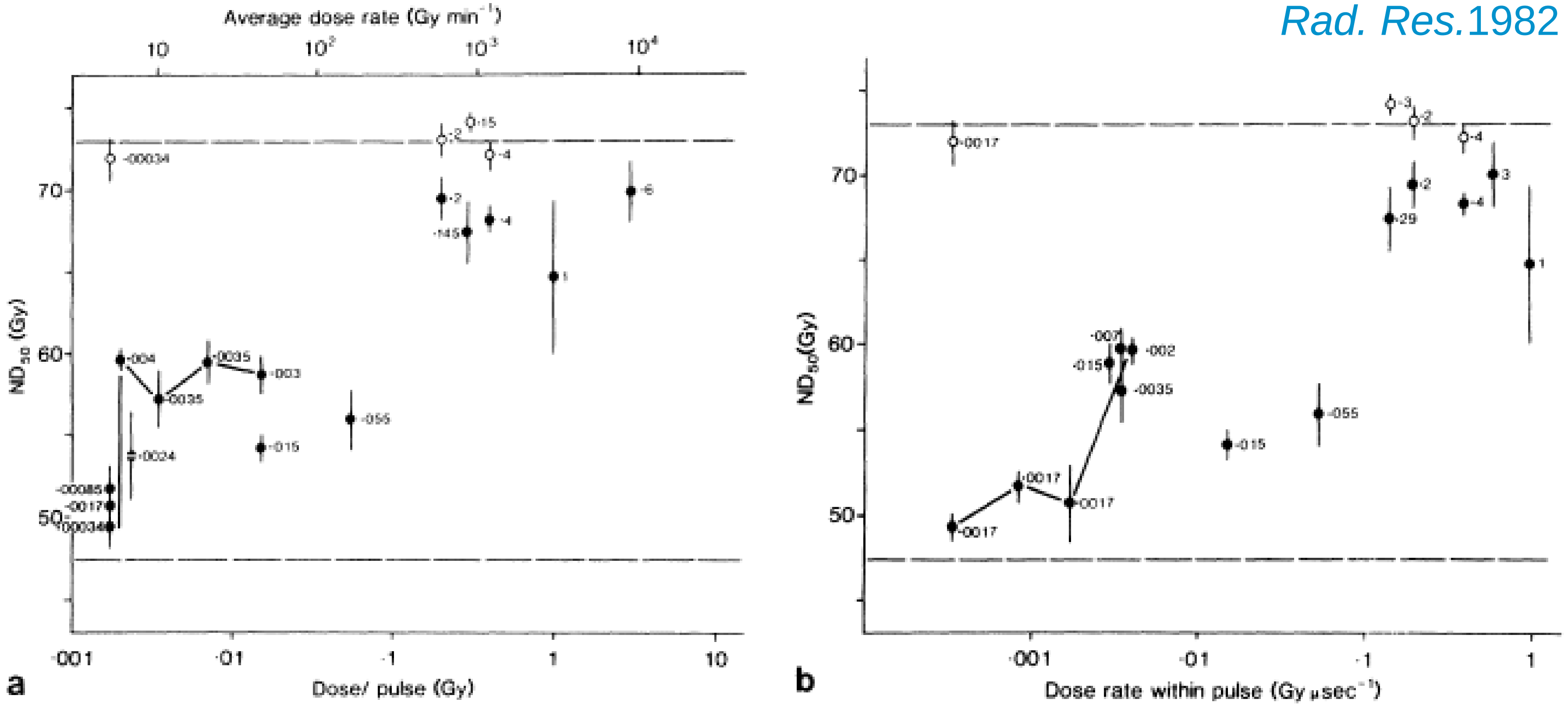
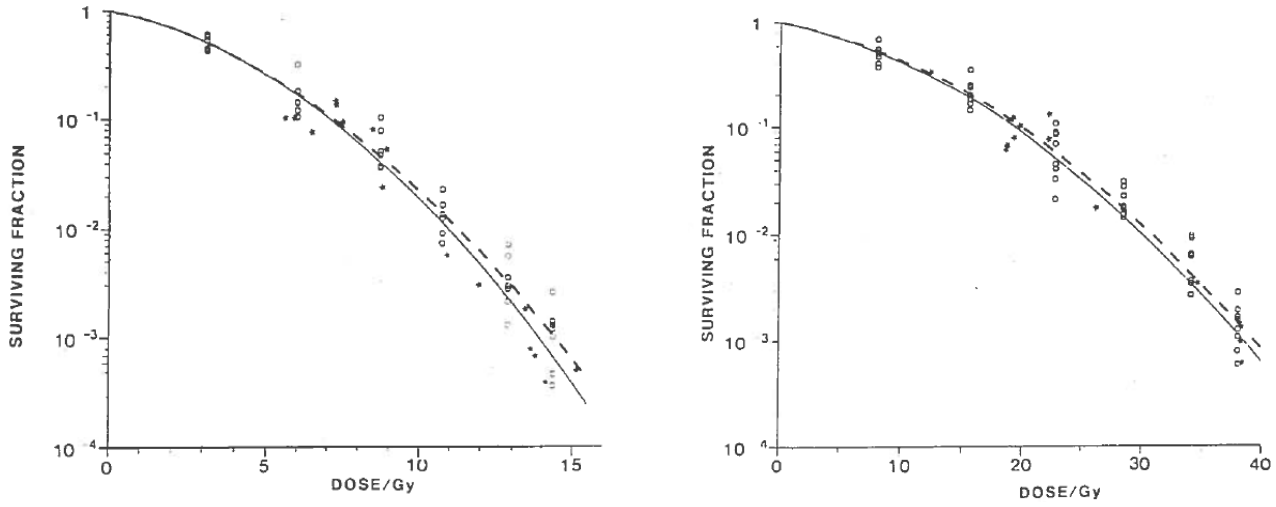


FIG. 1. ND_{50} versus dose per pulse (a) or intrapulse dose rate (b) of 10-MeV electrons. Standard errors are shown. Numbers against symbols refer to the intrapulse dose rate in Gy per μsec (a) or to dose per pulse in Gy (b). Solid circles—tails in air at 19–23°C. Split solid symbol in (a) represents a split 5-μsec pulse of 1 μsec + 3-μsec interval + 1 μsec. Open circles and upper dashed line—tails irradiated 5 min after tail clamping and gassing with nitrogen. Lower dashed line—ND_{50} expected at low (conventional) dose rates (see text).

In-vitro studies
Previously published results



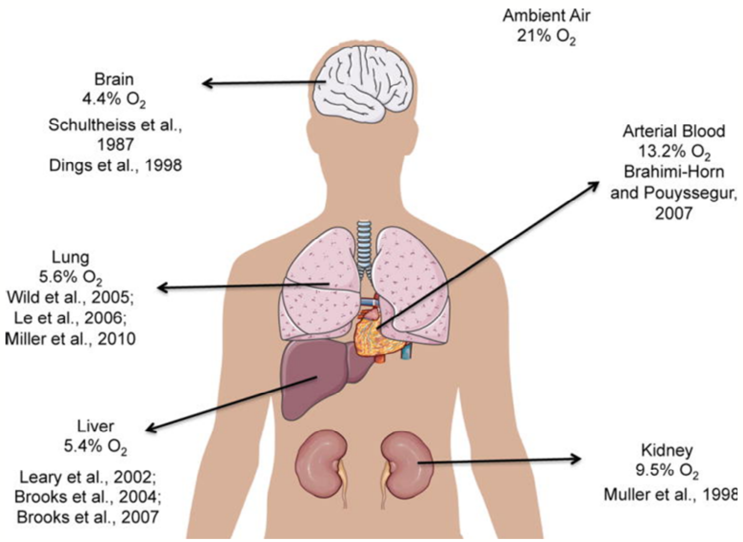
380 Gy/s vs. 5.8 Gy/min 20% O_2 Left, 0% O_2 Right

Fibroblast cells from chinese hamsters

No difference in response!

Zackrisson *et al. Acta Oncol. 1991*

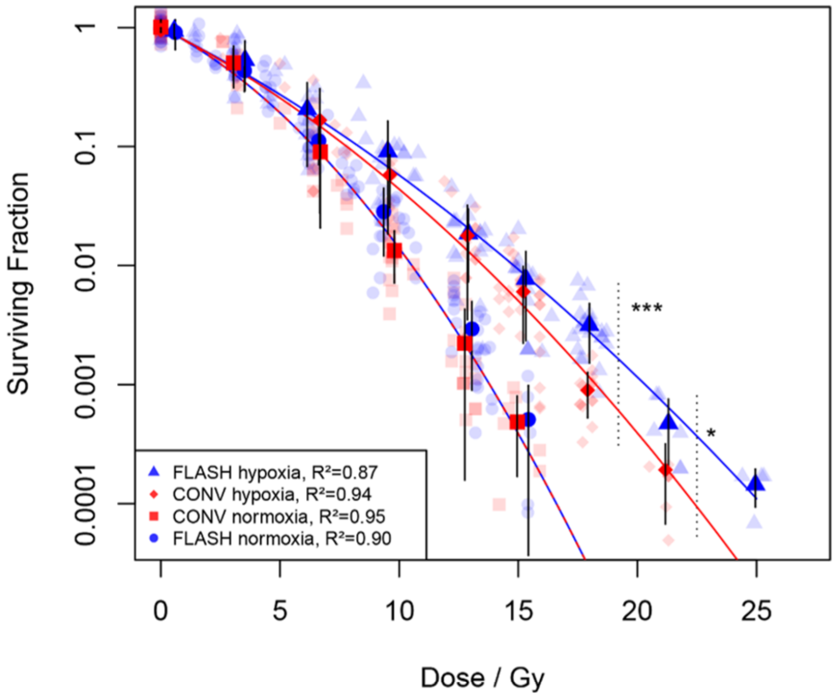
Natural environment for cells



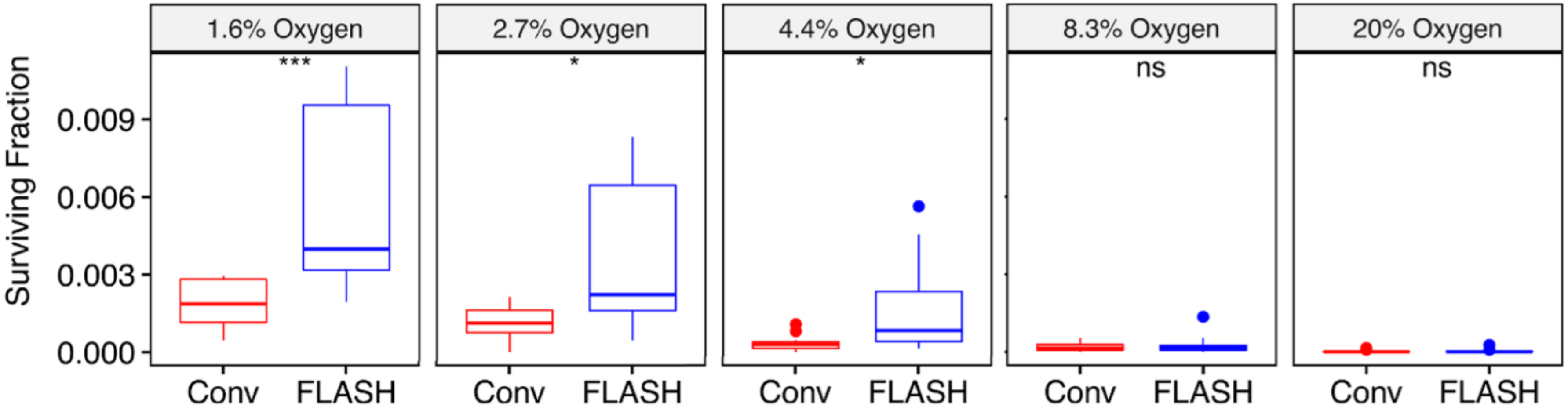
Jagannathan et al 2016

Courtesy of Krista Rantanen

In vitro study supporting the oxygen depletion hypothesis



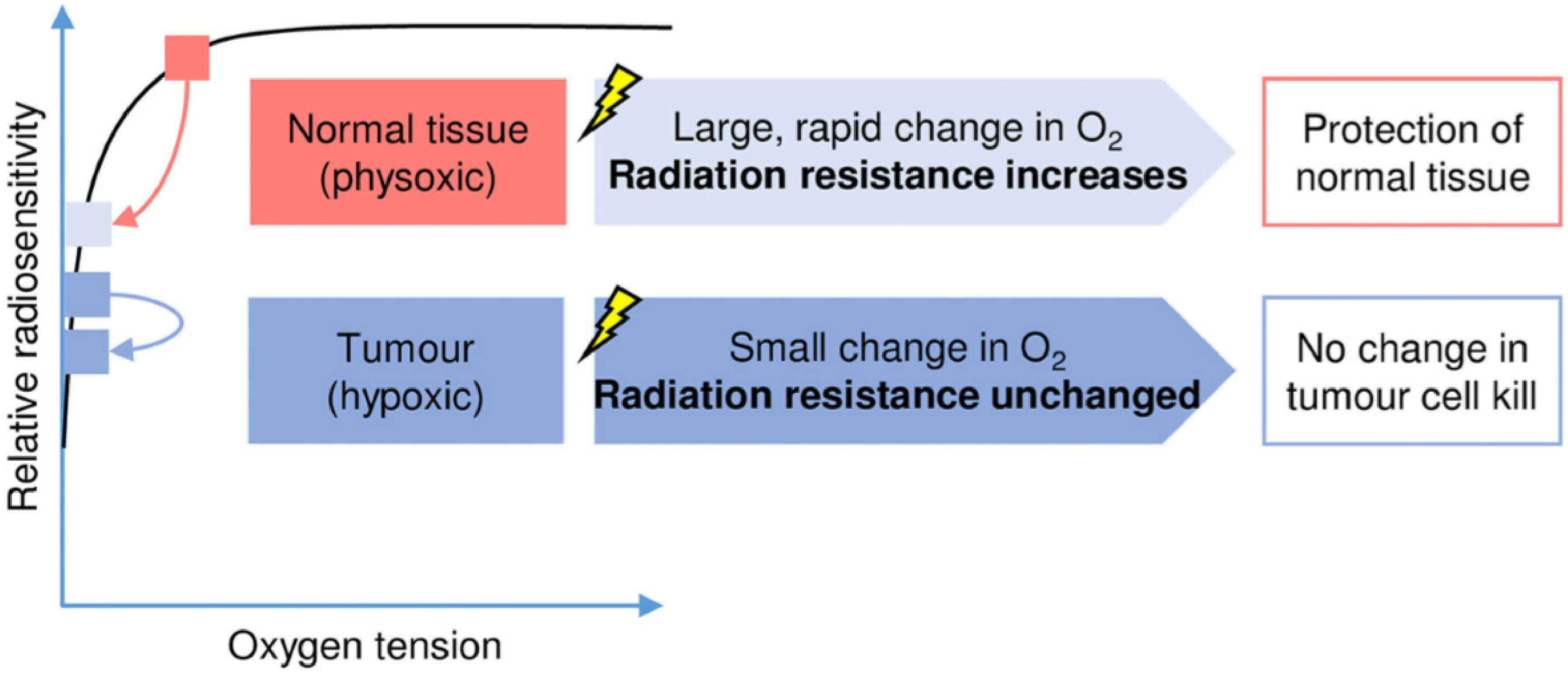
600Gy/s (FLASH) or 14 Gy/min (CONV)
for a 10 MeV electron beam



Adrian *et al.*
BJR. 2020

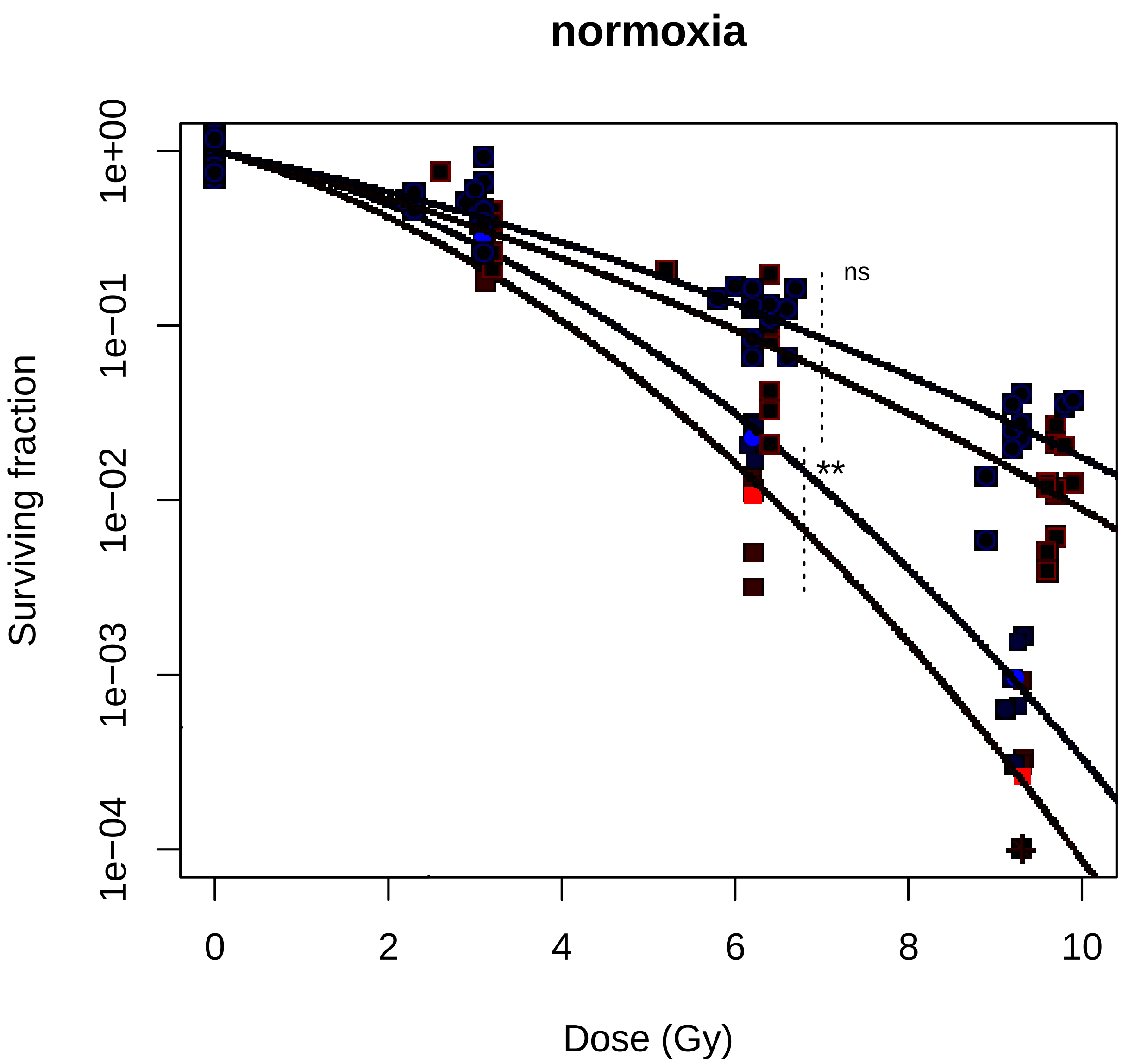
→ The FLASH effect depends on oxygen concentration

Possible explanations of the “FLASH effect”



Wilson *et al.*
Front. Oncol. 2020

Non-oxygen related FLASH effects (at lower doses)



600Gy/s (FLASH) or 14 Gy/min (CONV) for a 10 MeV electron beam

2 Different cell lines

Adrian et al.
Unpublished data

Other proposed explanations of the “FLASH effect”

- Radical-Radical interactions.
- Depletion of other chemicals, e.g. Nitric oxide.
- Difference in cell metabolisms normal/tumour tissue.
- Difference in ROS (reactive oxygen species) production.
- Difference in Immune response.
- Difference in DNA damage response.
- Difference in inflammatory response.

- We don’t yet know the mechanisms behind FLASH
- We don’t yet know the optimal delivery technique for FLASH

In Summary

- FLASH has huge Potential Benefits for Radiotherapy:
  - Enables full treatments (or fractions) in a few hundreds/tenths of a second.
    - “Freeze” motion during treatment.
    - Could minimize treatment (PTV) margins related to motion.
      - » Less normal tissue exposed to the treatment dose.
- Pre-clinical studies show:
  - Less normal tissue toxicity, i.e. the “FLASH effect”
    - Dose modifying factor: **1.2-1.5**
  - Similar tumour control.
    - Dose modifying factor: **1**
- Challenges to meet before clinical implementation:
  - How does it work?
    - Mechanisms other than oxygen depletion?
      - » See talk by Gabriel Adrian
  - How do we use it in a clinical setting?
    - Dosimetric challenges
      - » See talk at ASTRO 2020
    - New Image-Guidance strategies
    - Doses, dose rates needed?

  →We need to do more pre-clinical studies!

  →We need new irradiation delivery solutions!

My research is focused on solving these challenges!

Thanks!

Lund Team

Lausanne Team

Oxford Team