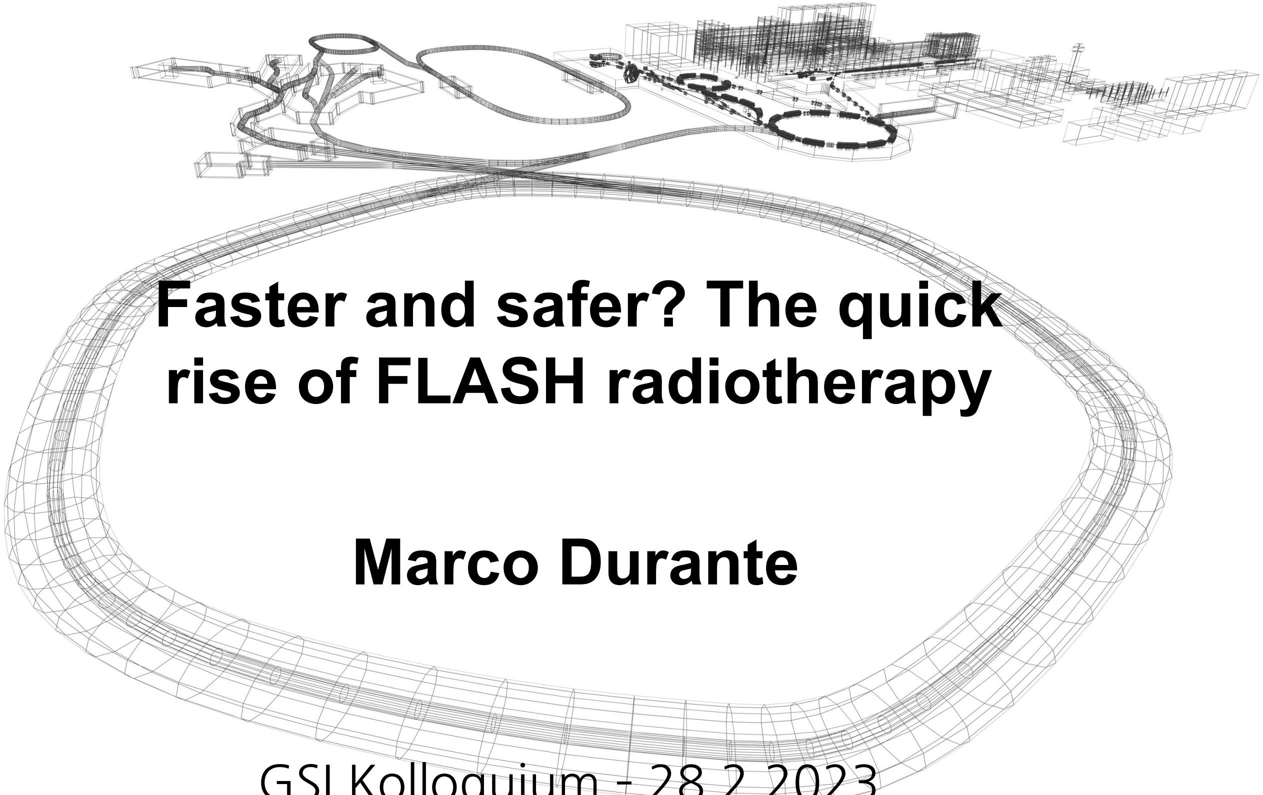


Faster and safer? The quick rise of FLASH radiotherapy

Marco Durante

GSI Kolloquium - 28.2.2023

FAIR Phase 0 Research Program

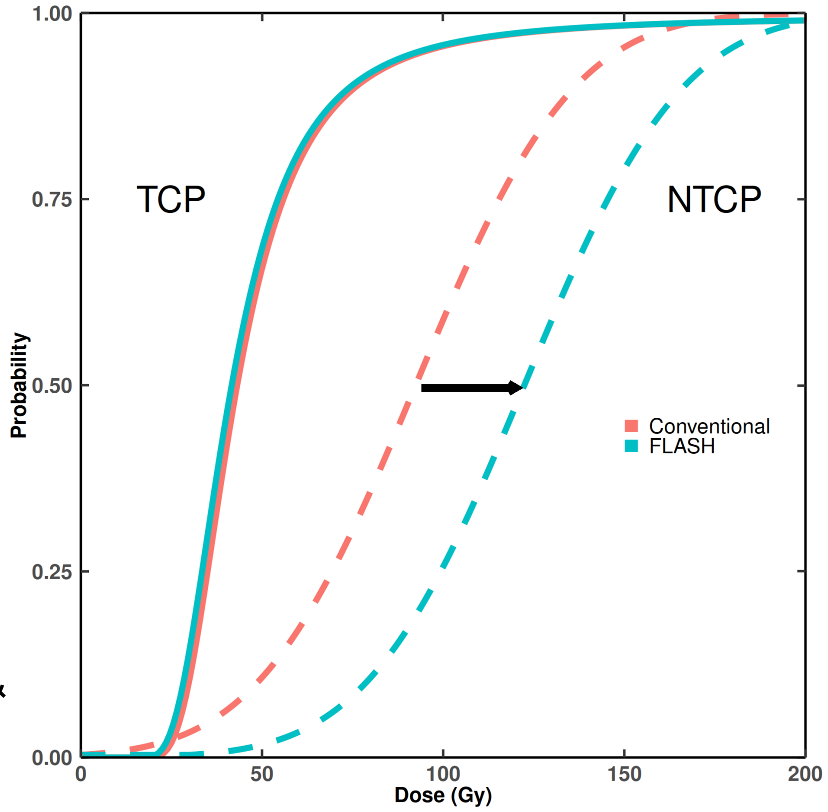
FLASH RT: what's that

FLASH Radiotherapy, is a novel approach of RT using ultra-high dose rate

(>40 Gy/s overall dose rate,whereas conventional radiotherapy is around 1 Gy/min)

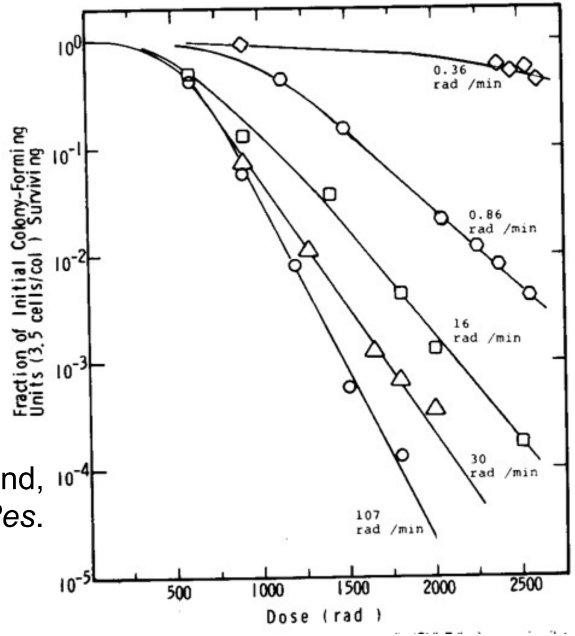
aiming to get **unchanged tumor control protection (TCP)** and **decreased normal tissue complication probability (NTCP).**

Vozenin, Bourhis & Durante, *Nat. Rev. Clin. Oncol*. 2022



Dose Rate effect in conventional Radiobiology

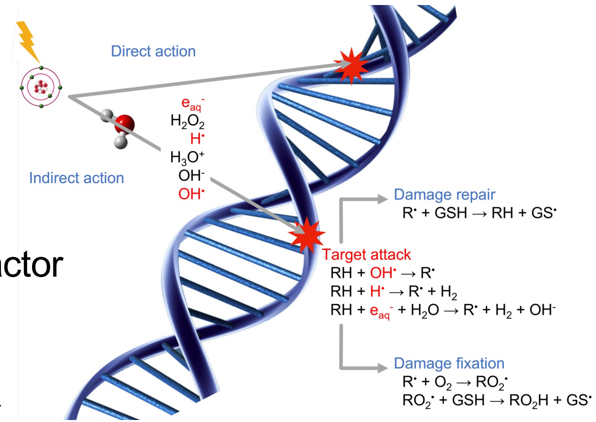
Clonogenic Survival



M.M. Elkind, *Radiat. Res.* 1977

Dose-Rate Effectiveness Factor

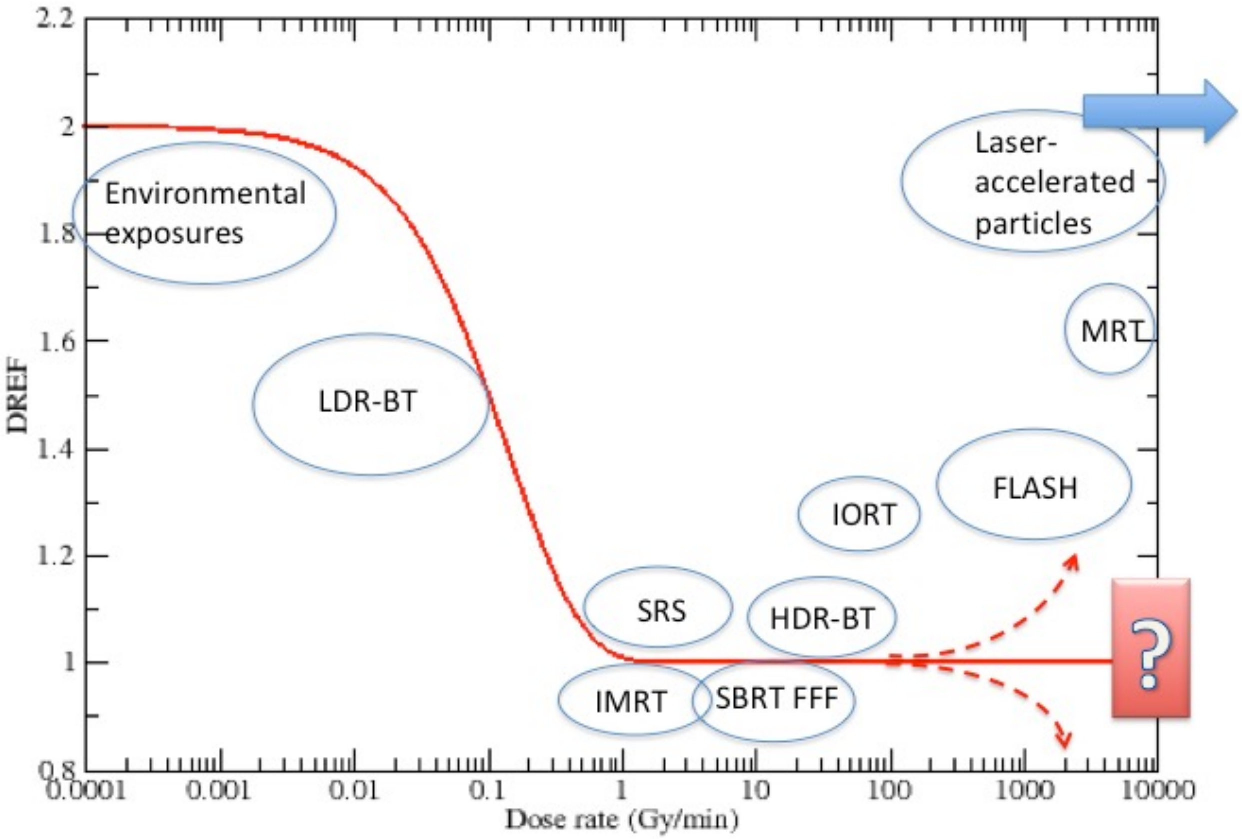
$$DREF = \frac{D(\dot{D})}{D(\dot{D}_{ref})}\bigg|_{same\ effect}$$



It is observed a sparing effect at **decreasing** dose rate (at very low dose rate – "protracted" irradiation)

Mechanistic Explanation easy: **Sublethal Damage** allowed to be repaired

DREF range



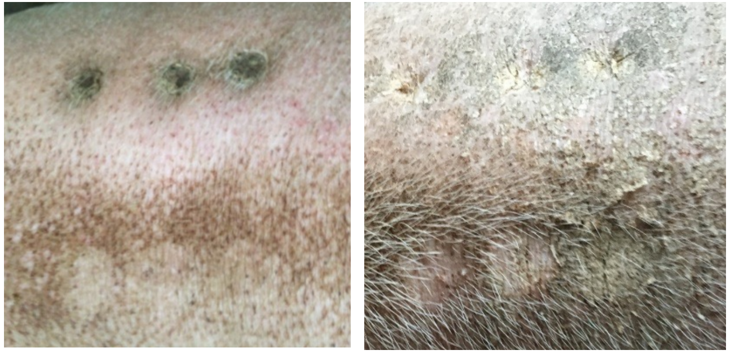
Durante *et al.*, *Br. J. Radiol*. 2017

Ultra-high dose rate (FLASH): normal tissue sparing

9 mo post-RT 3 years post-RT

CONV

FLASH



34Gy 31Gy 28Gy 34Gy 31Gy 28Gy

Vozenin *et al.*, *Clin. Cancer Res*. 2019

The FLASH Effect: preserving tumor control

4.8 Gy x 10 f

30 Gy in 20 ms

Vozenin *et al., Clin. Cancer Res. 2019*

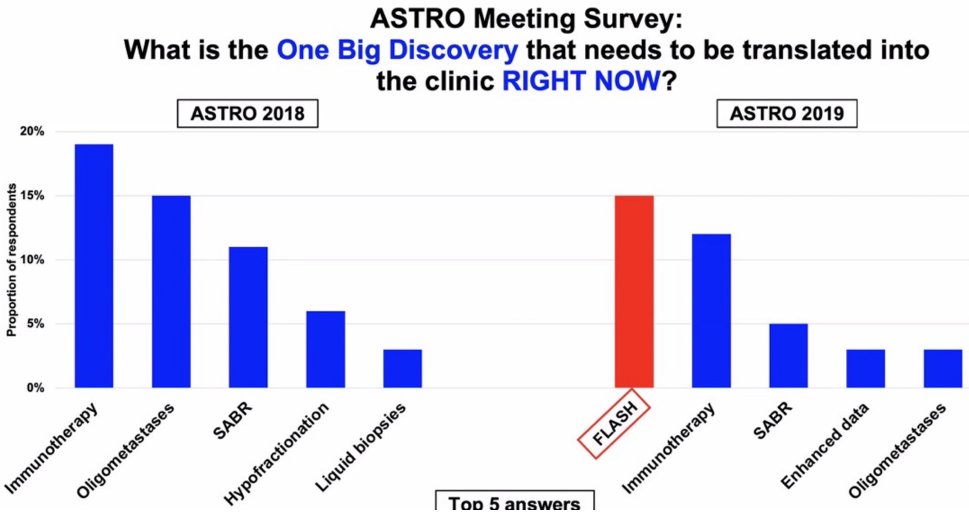
FLASH „boom“

ARTICLE IN

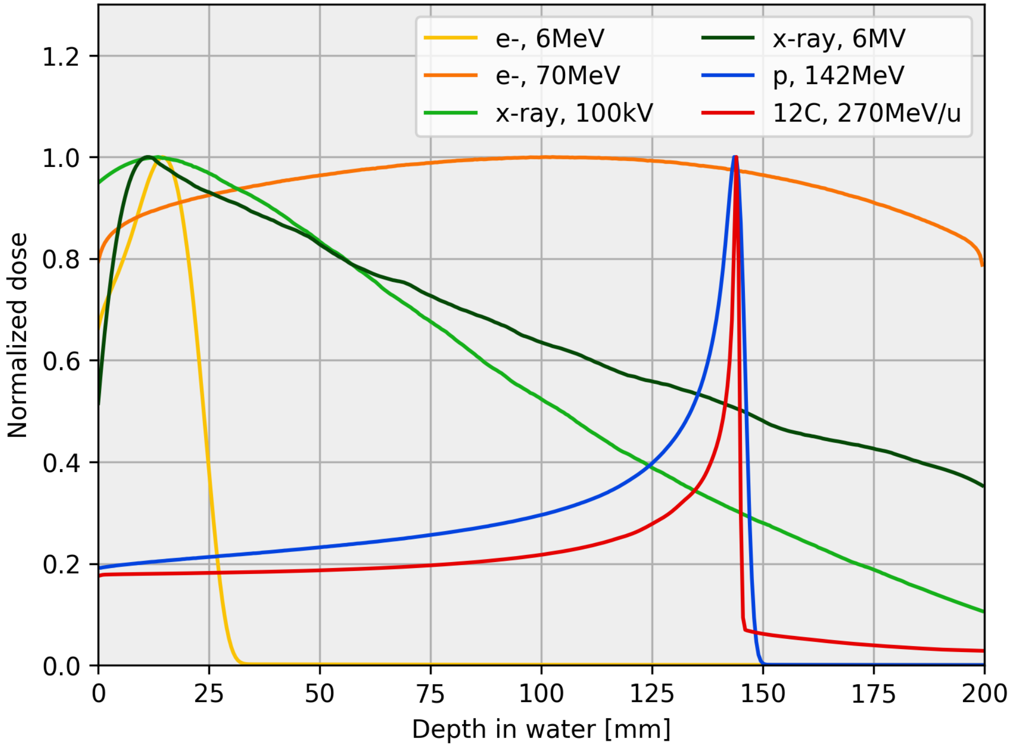
The Hottest Topic in Radiation Oncology!

EDITORIAL

Responses to the 2018 and 20
Discovery” Question: ASTRO M
Opinions on the Most Importa
Question Facing Radiation Onc
We Headed?

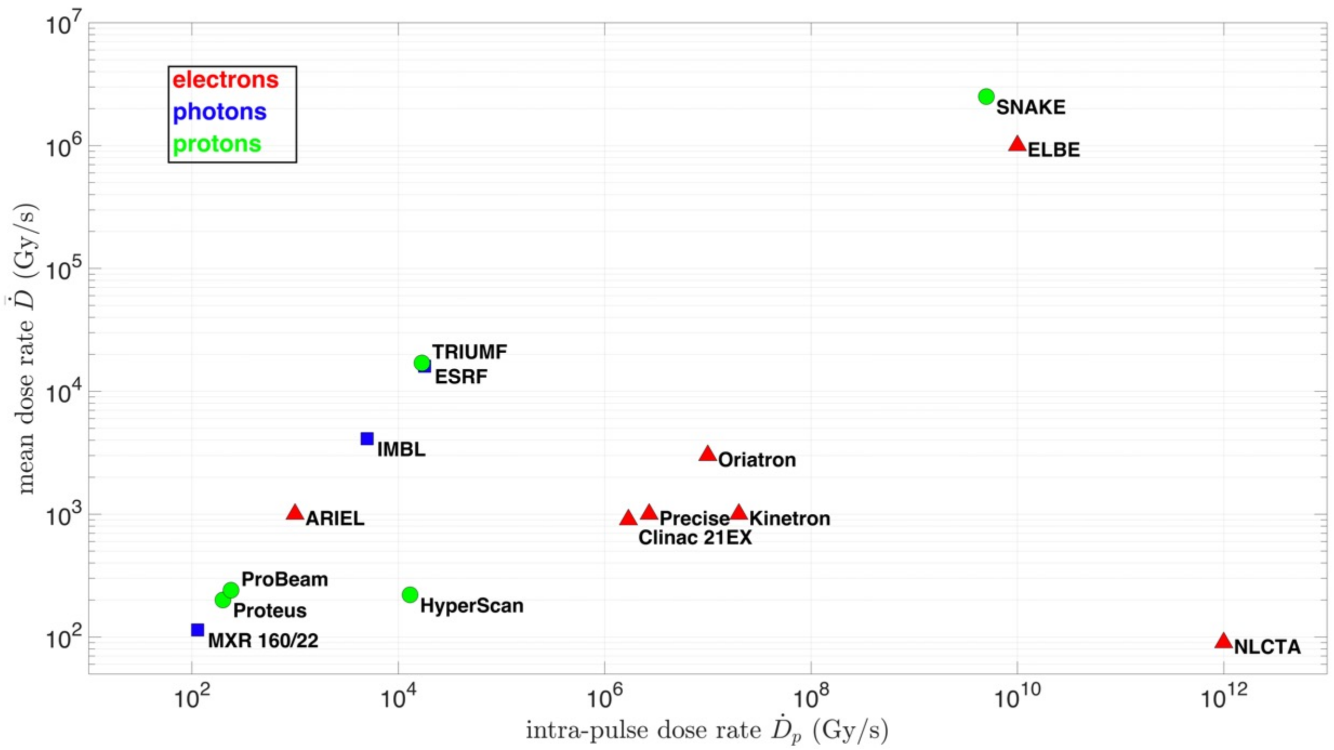


FLASH radiation modalities



Vozenin, Bourhis & Durante, *Nat. Rev. Clin. Oncol*. 2022

Employed facilites

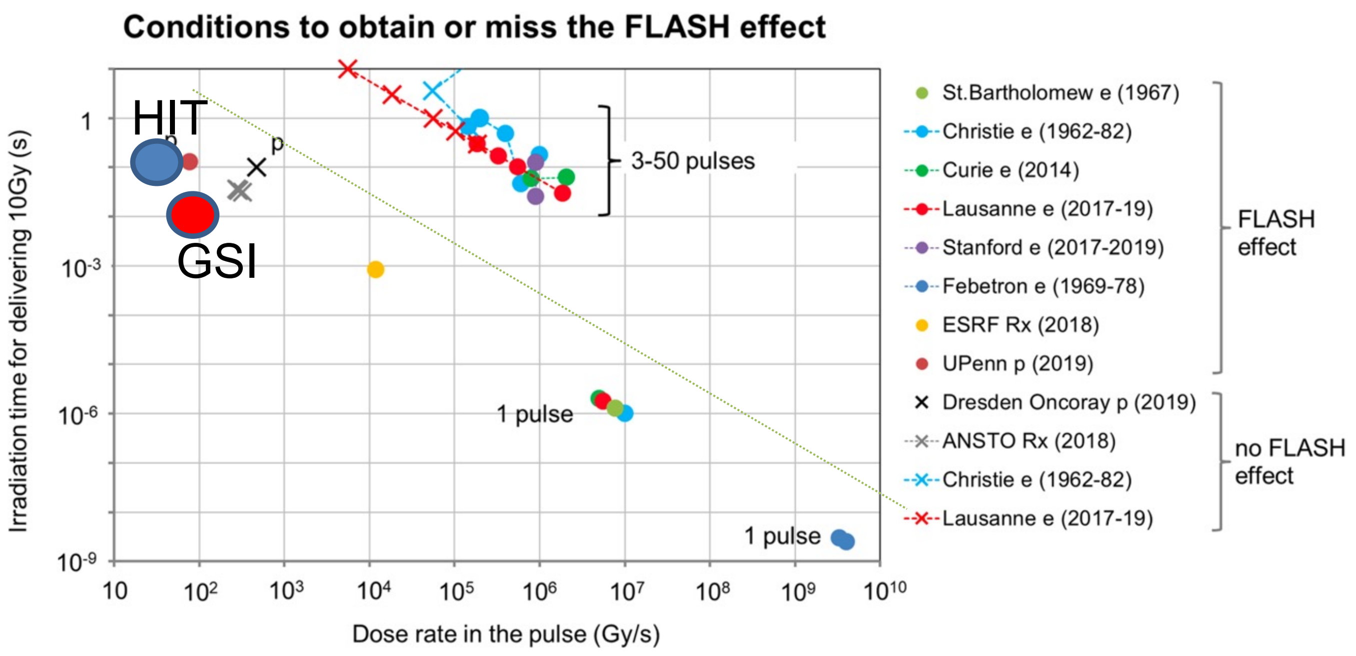


No heavy ions until 2020

Esplen *et al. Phys.Med. Biol.* 2020

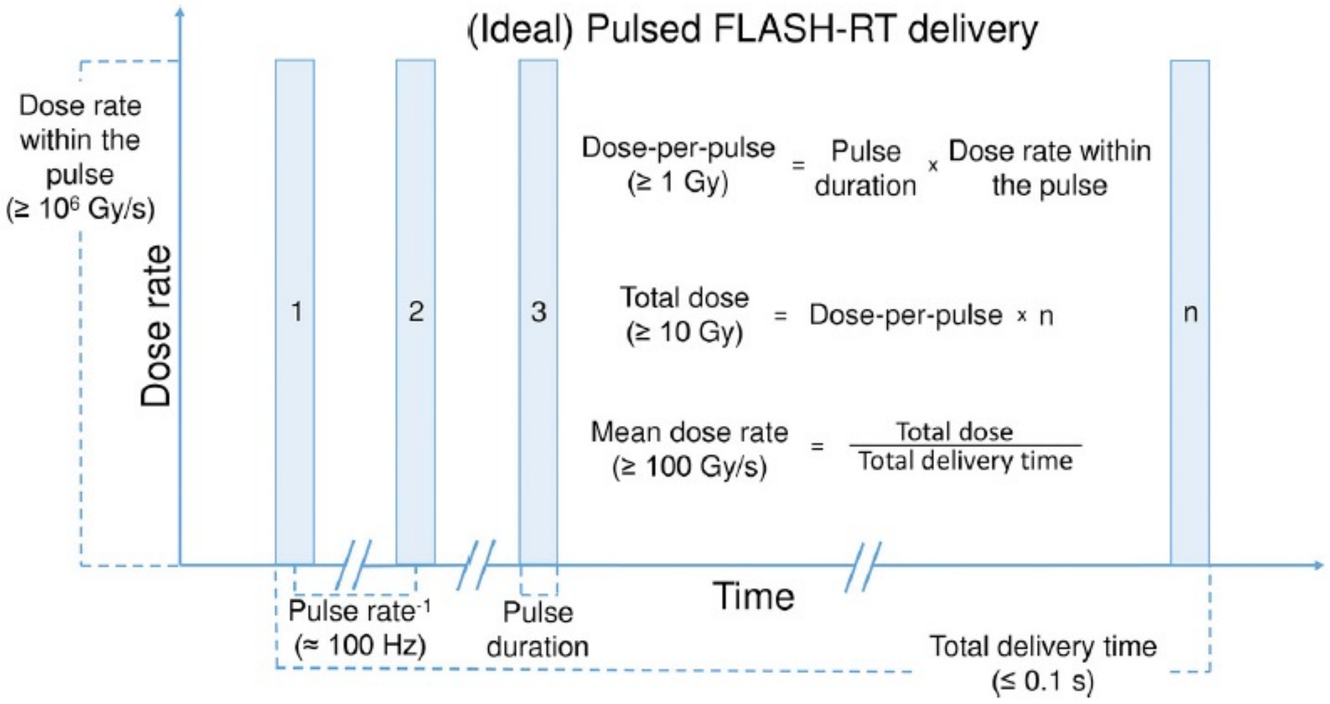
Parameters for FLASH/noFLASH

Figure 1



Montay-Gruel et al. Clin Cancer Res 2020

Ideal time-structure



Wilson et al. Front Oncol. 2020

Clinical translation

Fig. 4 | Treatment of cutaneous lymphoma with FLASH radiotherapy. a, FLASH and conventional radiotherapy were directly compared in a 75-year-old patient who presented with two cutaneous lymphoma lesions. The same single dose (15 Gy) was delivered on the same day either in 90 ms as FLASH radiotherapy, or in 2.87 min as conventional radiotherapy. **b**, The maximal grade of skin reaction was detected around week 3, with a grade 1 reaction in both treated lesions. **c**, The skin recovered a normal appearance around day 85 after either FLASH or conventional radiotherapy. These data suggest that, in this dose range, the incidence of acute skin reactions is comparable with the two radiotherapy modalities.

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

Clinical trial at CHUV with electrons for superficial lesions

FLASH and Conventional radiotherapy directly compared in a 75-years old patient with two cutaneous skin lymphoma lesions treated with **5.4 MeV electrons** in a single fraction of 15 Gy in 90 ms (FLASH) or 2.87 minutes (conventional)

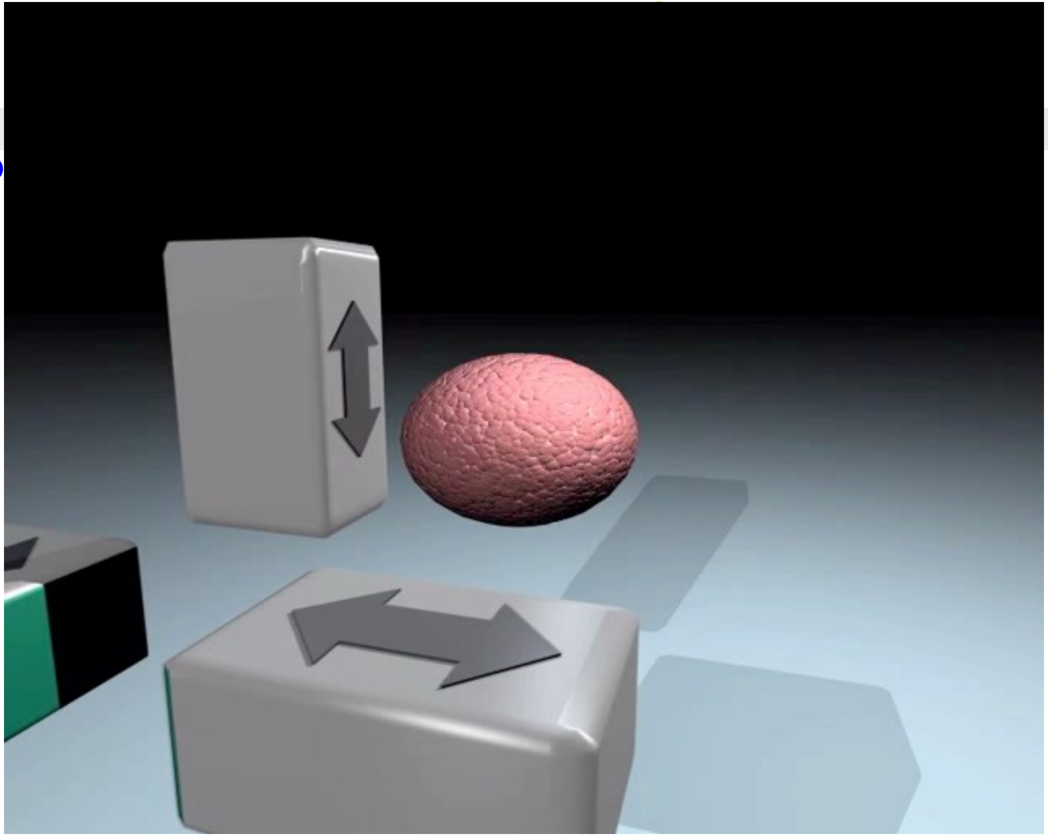
- Maximal grade of skin reaction: around week 3, with a grade 1 reaction in both treated lesions.
- The skin recovered a normal appearance around day 85 after either FLASH or conventional radiotherapy.
- These data suggest that, in this dose range, the incidence of acute skin reactions is comparable with the two radiotherapy modalities

Multi-energy raster scanning lasts too long for FLASH

- Synchrotron Cycle > 1 sec , normally ~ 5-10 sec
- each energy step requires a new cycle

- However for FLASH
  8 Gy with 40 Gy/s
  should by appied in **t < 200 ms**

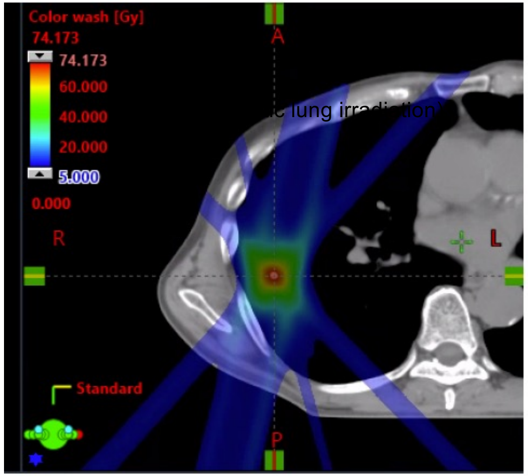
⇨ the normal multi-layer raster scanning
for 3D conformal irradiation
does not work
(neither for proton cyclotron, IBA, VARIAN …)
⇨big issue for FLASH in particle therapy

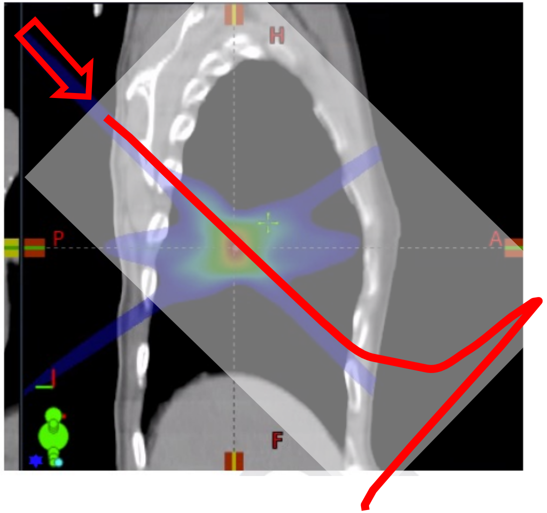


Durante *et al.*, *Nat. Rev. Phys*. 2021

Transmission beam technique

- Using 244 MeV proton transmission beam (VARIAN proton machine)
- Penetration of the whole patient with the beam





Issues:

- Not conformal as IMPT (scanning)
- SOBP advantage lost
- Higher integral Dose
- Many fields and long irradiation time for the treatment

However:

Clinical study started Treatment of symptomatic Bone Metastases
Cincinnati Proton Centre

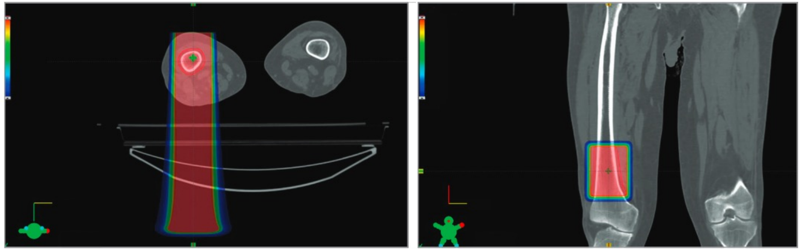
van Marlen *et al., Int J Radiat Oncol Biol Phys* 2020

JAMA Oncology | Original Investigation

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases
The FAST-01 Nonrandomized Trial

Anthony E. Mascia, PhD; Emily C. Daugherty, MD; Yongbin Zhang, MS; Eunsin Lee, PhD; Zhiyan Xiao, PhD; Mathieu Sertorio, PhD; Jennifer Woo, BSc; Lori R. Backus, BA; Julie M. McDonald, CCRP; Claire McCann, PhD; Kenneth Russell, MD; Lisa Levine, PhD; Ricky A. Sharma, MD, PhD; Dee Khuntia, MD; Jeffrey D. Bradley, MD; Charles B. Simone II, MD; John P. Perentesis, MD; John C. Breneman, MD

8 Gy x 1 f



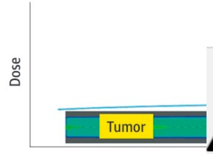


Table 2. Adverse Events (Possibly, Probably, or Definitely) Attributed to FLASH Treatment (N = 10)

Adverse events[a]	Patient, No. (%)
Acute (≤3 mo posttreatment)	
Edema, limb (grade 1)	1 (10)
Erythema (grade 1)	1 (10)
Extremity pain (grade 2)	1 (10)
Fatigue (grade 1)	1 (10)
Pruritus (grade 1)	2 (20)
Skin hyperpigmentation (grade 1)	4 (40)

FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases in the Thorax (FAST-02)

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

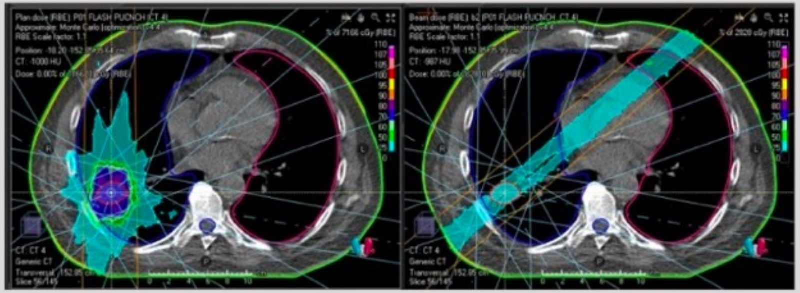
ClinicalTrials.gov Identifier: NCT05524064

Recruitment Status : Not yet recruiting
First Posted : September 1, 2022
Last Update Posted : September 1, 2022

See Contacts and Locations

Go for **Conformal** FLASH

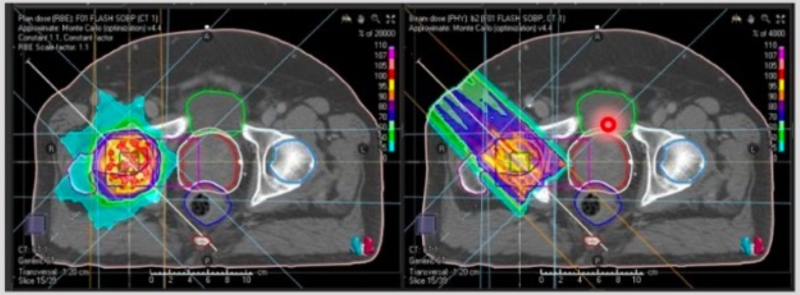
Transmission style irradiation with many beams at highest energy



- \+ Simple planning (?)
- \- Irradiation of tissue down stream of target
- \- Potentially get Bragg peaks in body
- \- Many beams (>5?)
- \- Takes time to change beam angle

Flash with the Plateau

SOBP style irradiation with few beams



- -/+ Complex (but standard) planning
- \- Need static device to shape the SOBP
- \- Patient & Beam specific device
- \+ No irradiation of tissue down stream of target
- \+ Enables RBE & LET & robust optimization
- \+ Few beams
- \- Takes time to change beam angle

Flash with the Bragg Peak

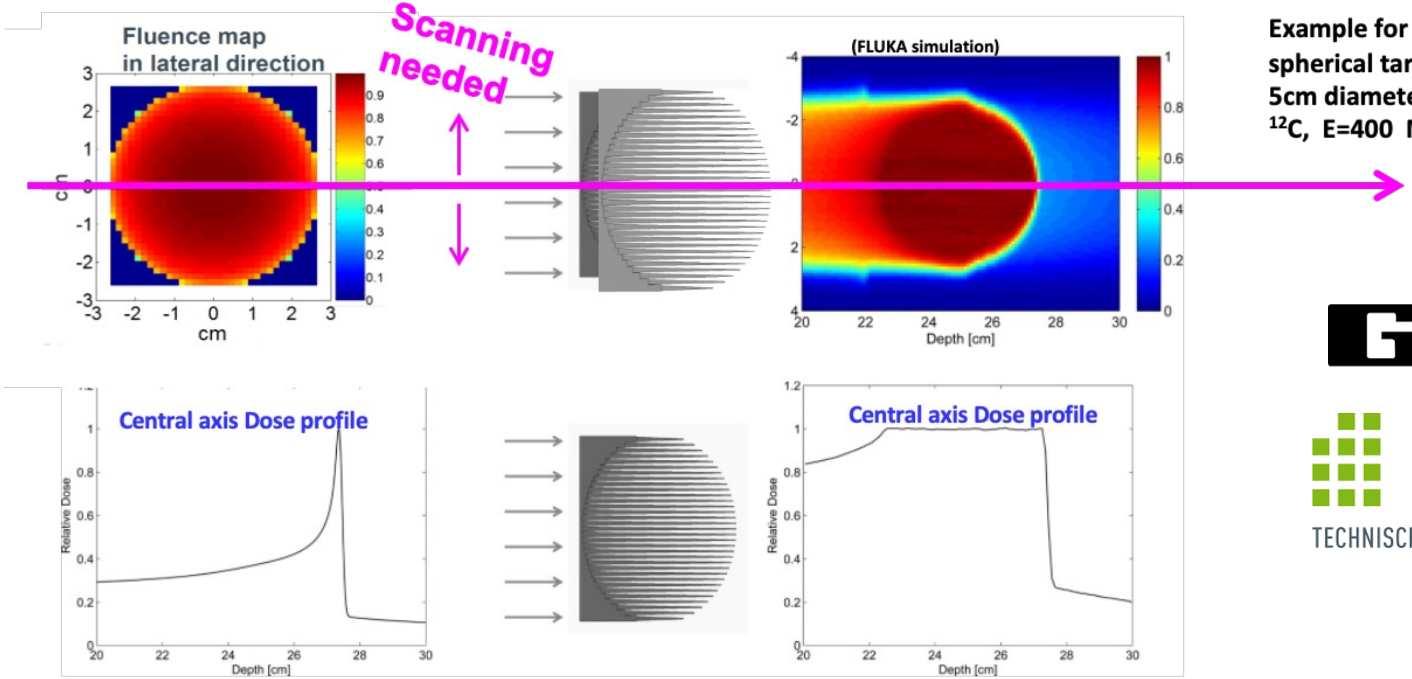
Developing FLASH treatment planning for the IBA Proteus system using the RayStation TPS

PTCOG 59 - September 13, 2020

Erik Traneus (RaySearch Laboratories AB), Rudi Labarbe, Laurent Collignon – (Ion Beam Applications S. A)

Courtesy of Rudi Labarbe

Beam application with 3D Range Modulators: Single-energy Irradiation



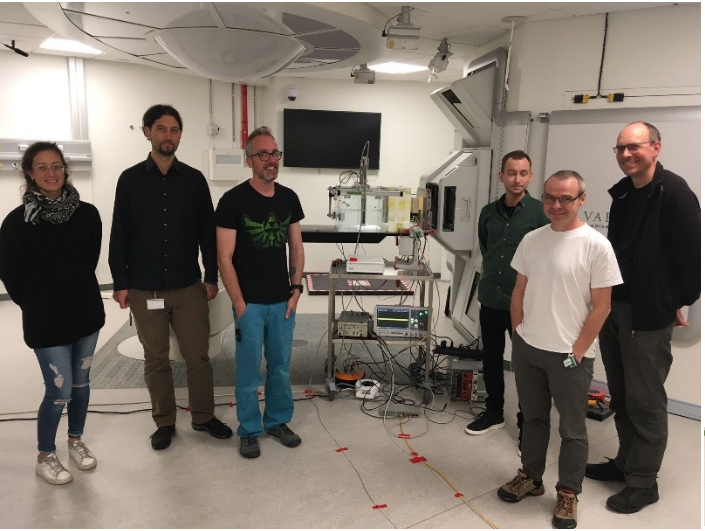
Example for a spherical target volume, 5cm diameter, ^{12}C, E=400 MeV/u

Simeonov *et al.*, *Phys. Med. Biol*. 2017

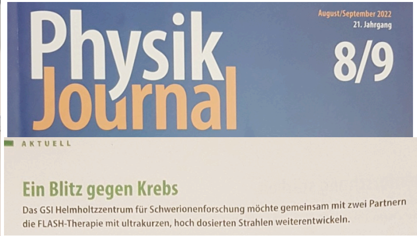
Simeonov *et al.*, *Z. Med. Phys*. 2020

GSI-Varian co-operation on range modulators for pFLASH

- A contract for about ½ millions € has been signed with Varian Medical Systems to install the GSI range modulator in Varian facilities interested in pursuing proton therapy FLASH
- The system has been installed for research purposes by our GSI scientists (U. Weber & C. Schuy) in the proton therapy centers in Delft and Aarhus.



Aarhus, DCPT, Denmark


Physik Journal

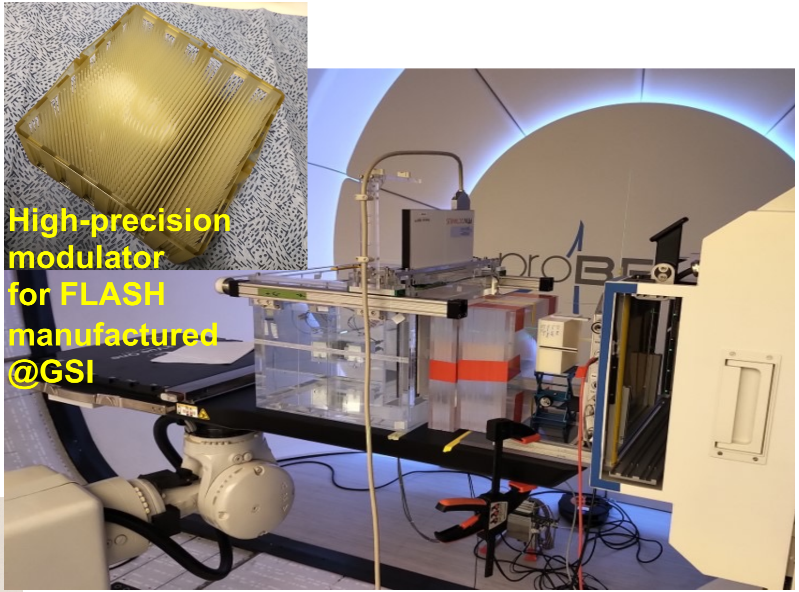
August/September 2022
21. Jahrgang

8/9

AKTUELL

Ein Blitz gegen Krebs

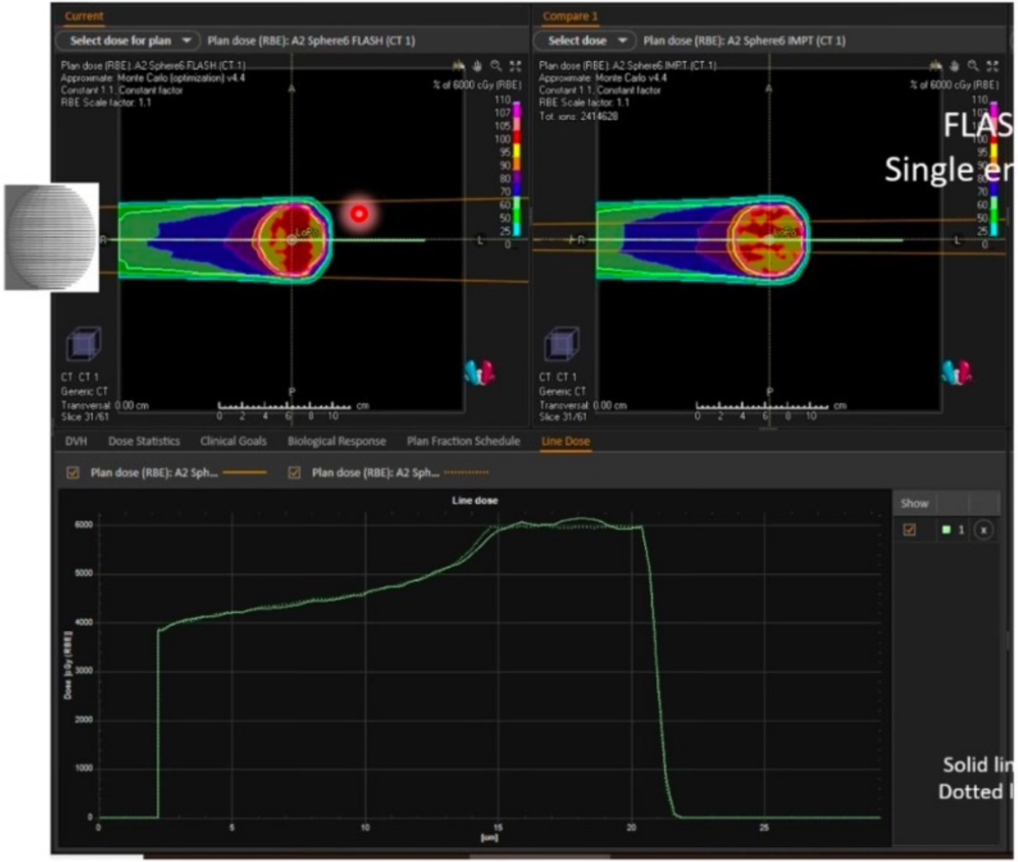
Das GSI Helmholtzzentrum für Schwerionenforschung möchte gemeinsam mit zwei Partnern die FLASH-Therapie mit ultrakurzen, hoch dosierten Strahlen weiterentwickeln.



FLASH setup @Holland PTC

Delft, HPTC, The Netherlands

Conformal FLASH: Treatment planning

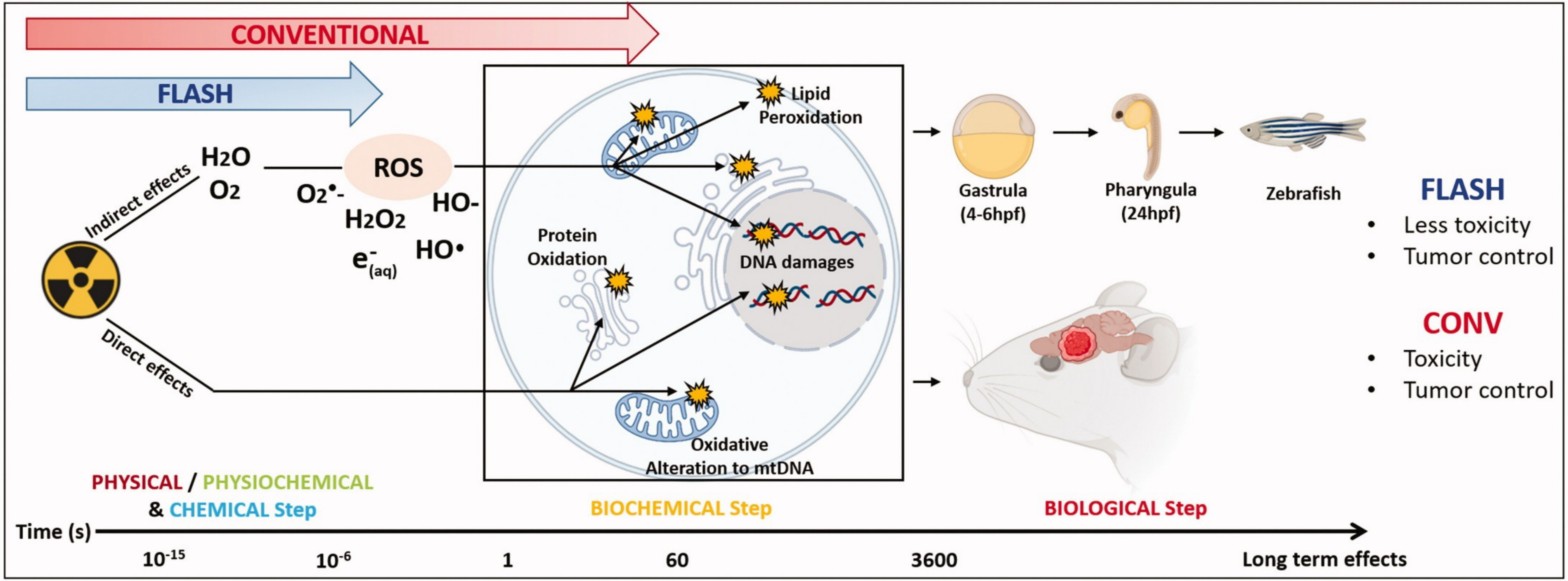


Developing FLASH treatment planning for the IBA Proteus system using the RayStation TPS

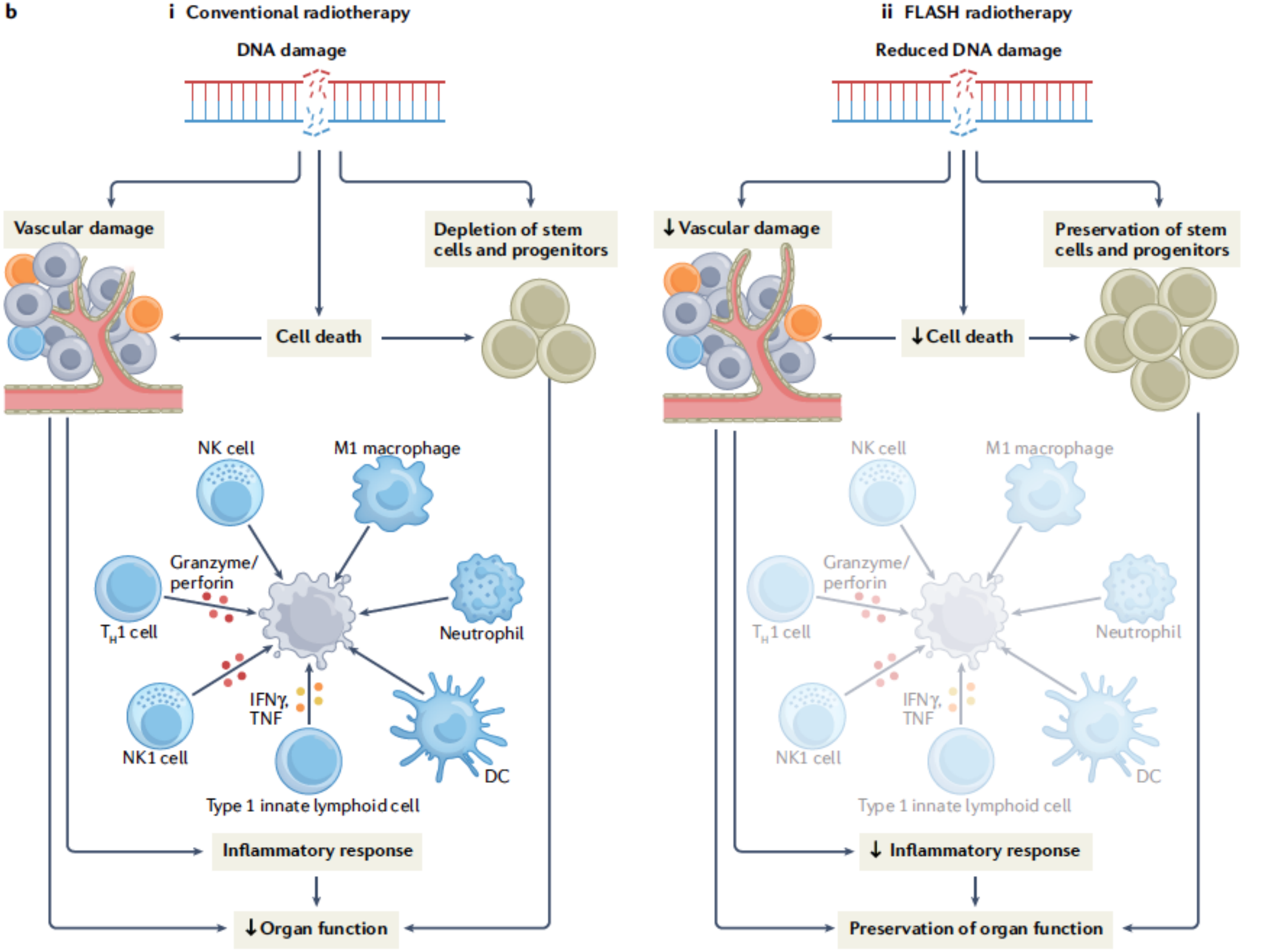
Hedgehog modelling implemented in a research version of the RayStation TPS

RaySearch Laboratories | iba

Understanding the FLASH mechanism



Kacem *et al., Int. J. Radiat. Biol.* 2022

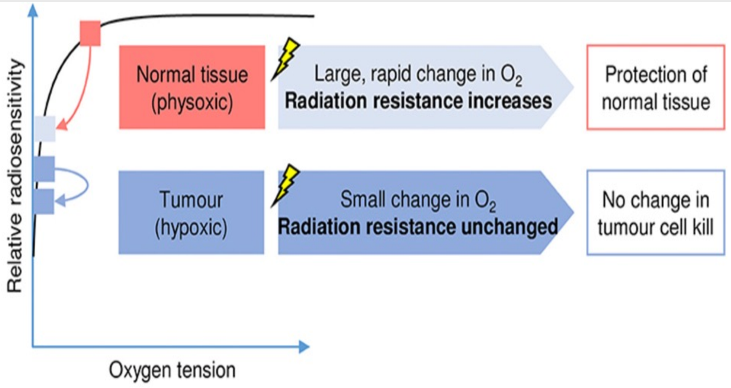


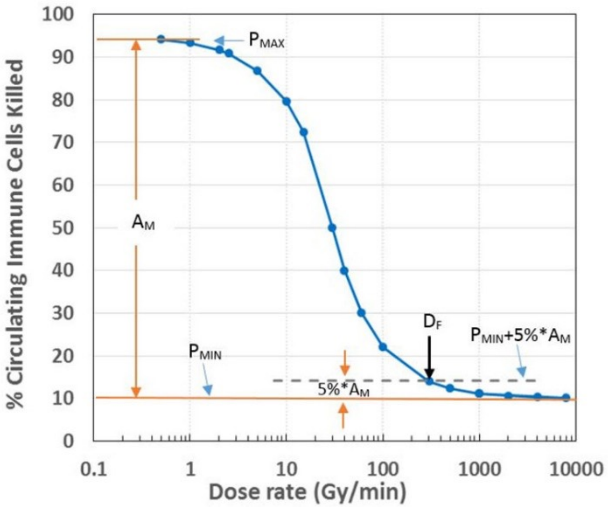
Vozenin, Bourhis & Durante, *Nat. Rev. Clin. Oncol*. 2022

FLASH mechanisms

- Oxygen depletion
- Free radical production/recombination
- Intertrack effects
- Sparing of the immune system

All these mechanisms are LET-dependent





Why are we interested in HI-FLASH?

- Widening the therapeutic window in C-ion therapy (12 centers in operation worldwide, many more in planning stage)
- Exploiting the reduced toxicity to use heavier ions such as ^{20}Ne or ^{40}Ar (LBNL pilot trial)
- Understanding the FLASH mechanisms: most of the current hypothesis would predict a *decreased* sparing effect at high-LET

First test of C-ion FLASH at HIT in 2020

FLASH with C-ions @HIT

Beam: 278 MeV/u ; ^{12}C ; Ø ≈ 5 mm (FWHM)

Challenging conditions:

Extraction time: < 120-200 ms ; typ. 150 ms

Beam intensity HIT:

≈ **7 ×10⁸** ± 20% ions per spill available
⇨ **0.5 × 10⁸ ions per second**

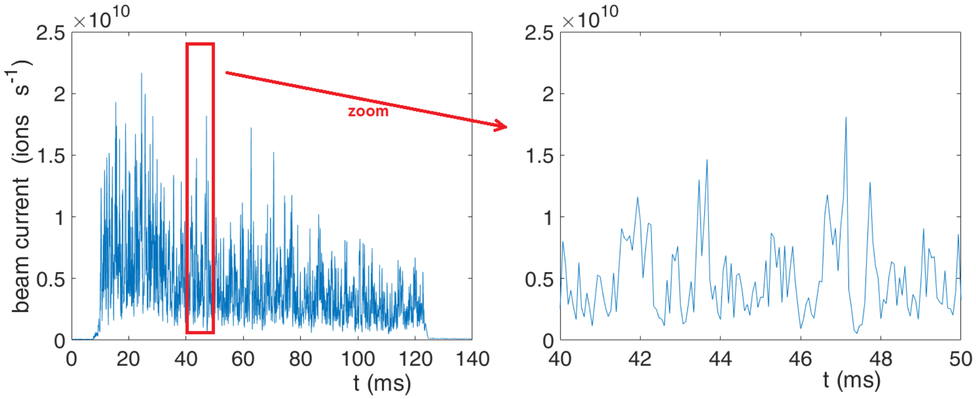
Beam spot size: FHWM = 5 mm

Dose-rate: typ. **40-60 Gy/s**

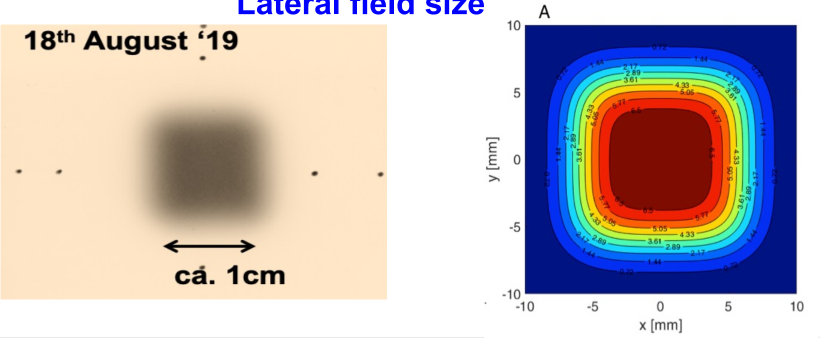
Field size: ~ 10 x 10 mm² (80% iso-dose)

Weber *et al.*, *Med. Phys*. 2022

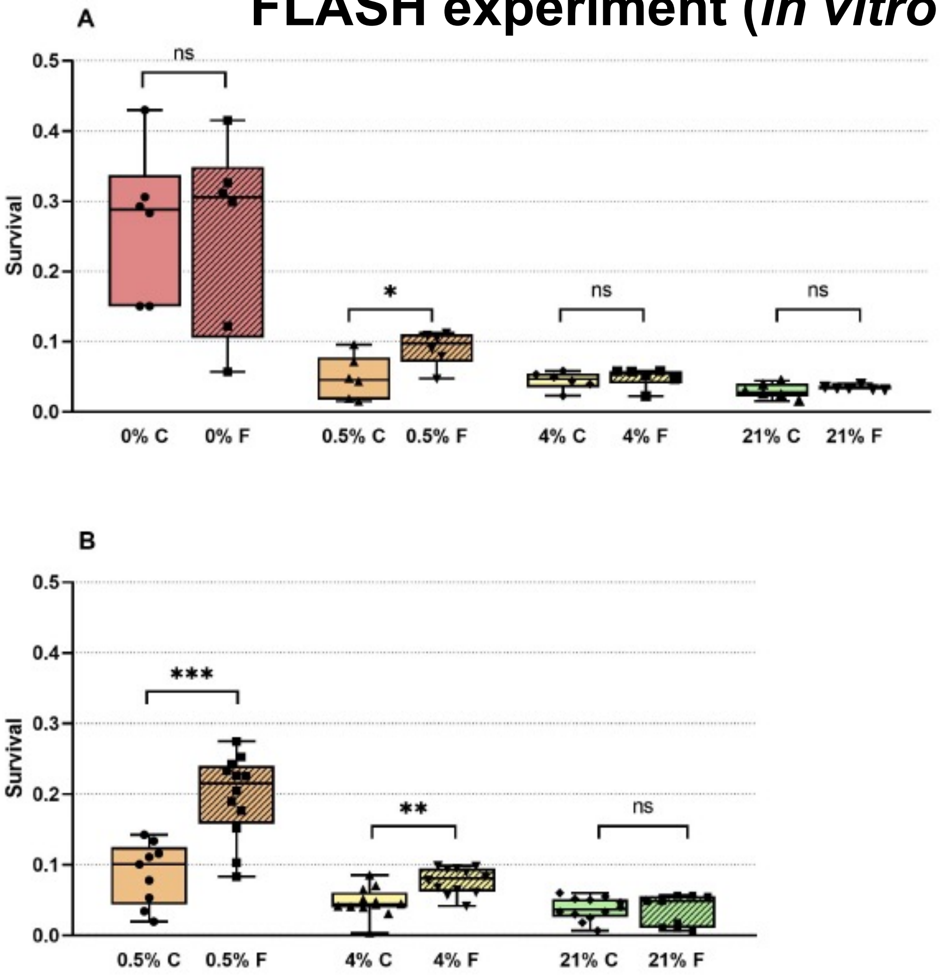
Flash beam extraction (5 ×10⁸ ions within ≈120 ms)



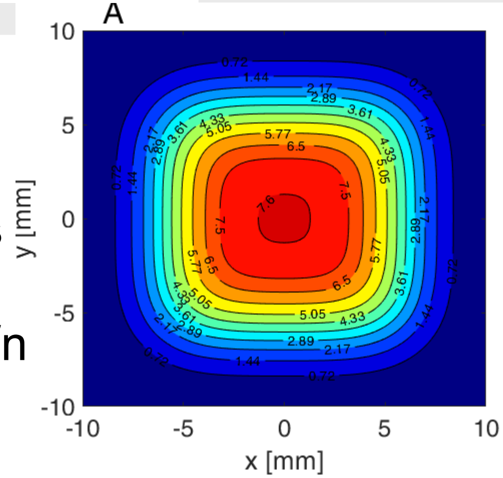
Lateral field size

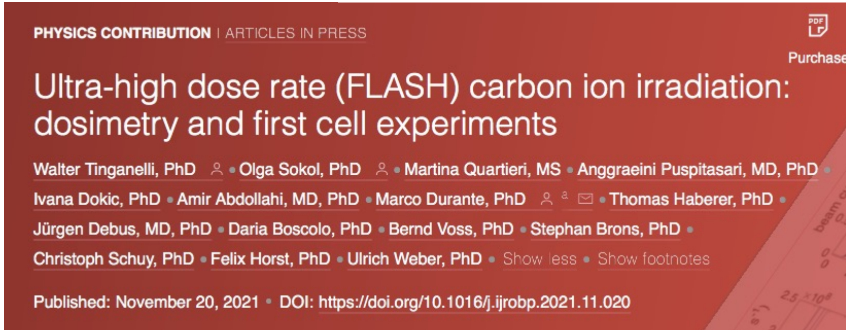


FLASH experiment (*in vitro @HIT*)



CHO-K1 cells
7.5 Gy
^{12}C 280 MeV/n




PHYSICS CONTRIBUTION | ARTICLES IN PRESS

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Ultra-high dose rate (FLASH) carbon ion irradiation: dosimetry and first cell experiments

Walter Tinganelli, PhD • Olga Sokol, PhD • Martina Quartieri, MS • Anggraeini Puspitasari, MD, PhD • Ivana Dokic, PhD • Amir Abdollahi, MD, PhD • Marco Durante, PhD • Thomas Haberer, PhD • Jürgen Debus, MD, PhD • Daria Boscolo, PhD • Bernd Voss, PhD • Stephan Brons, PhD • Christoph Schuy, PhD • Felix Horst, PhD • Ulrich Weber, PhD • Show less • Show footnotes

Published: November 20, 2021 • DOI: https://doi.org/10.1016/j.ijrobp.2021.11.020

ANTICANCER RESEARCH *43*: 581-589 (2023)
doi:10.21873/anticanres.16194

Ultra-high Dose-rate Carbon-ion Scanning Beam With a Compact Medical Synchrotron Contributing to Further Development of FLASH Irradiation

MASASHI YAGI[1,2], SHINICHI SHIMIZU[1], KAZUMASA MINAMI[3], NORIAKI HAMATANI[2], TOSHIRO TSUBOUCHI[2], MASAAKI TAKASHINA[2], MASUMI UMEZAWA[4], TAKUYA NOMURA[4], WATARU MUKOYOSHI[4], TEIJI NISHIO[5], MASAHIKO KOIZUMI[3], KAZUHIKO OGAWA[6] and TATSUAKI KANAI[2]

208 MeV/n
6.5 Gy in a 100 ms pulse
12x12 mm^2

Phys. Med. Biol. **68** (2023) 025015 https://doi.org/10.1088/1361-6560/aca387

Physics in Medicine & Biology

IPEM
Institute of Physics and Engineering in Medicine

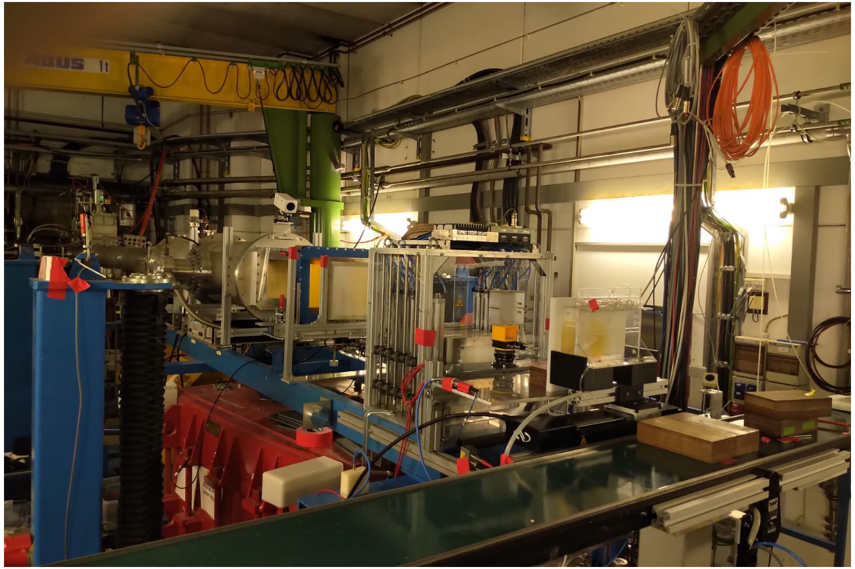
PAPER

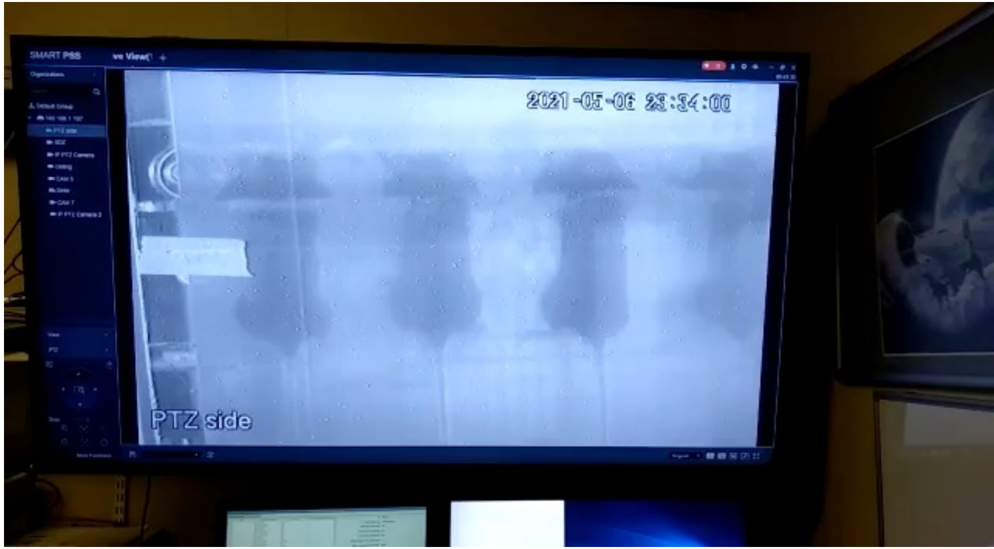
Cellular irradiations with laser-driven carbon ions at ultra-high dose rates

Pankaj Chaudhary[1,2,*], Giuliana Milluzzo[2,3], Aodhan McIlvenny[2], Hamad Ahmed[2,4], Aaron McMurray[2], Carla Maiorino[1,3,6,8], Kathryn Polin[2], Lorenzo Romagnani[2,5], Domenico Doria[2,6], Stephen J McMahon[1], Stanley W Botchway[7], Pattathil P Rajeev[4], Kevin M Prise[1,*] and Marco Borghesi[2,*]

9.5 MeV/n
1 Gy in 400 ps pulse
4x4 mm^2

FLASH @ GSI (2021 beamtime)





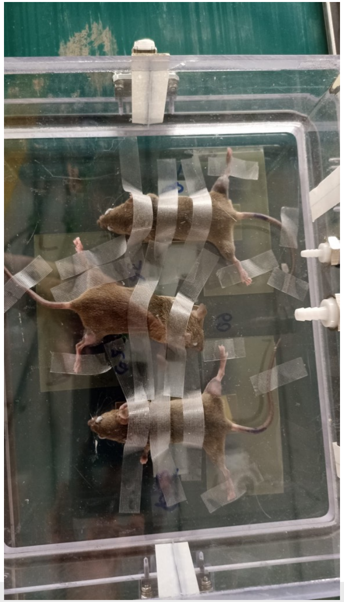
Weber *et al.*, *Med. Phys.* 2022

- HIT ≈ 5×10^8 ions per spill
  ⇨ 8 Gy | 50 Gy/s for 10 × 10 mm^2

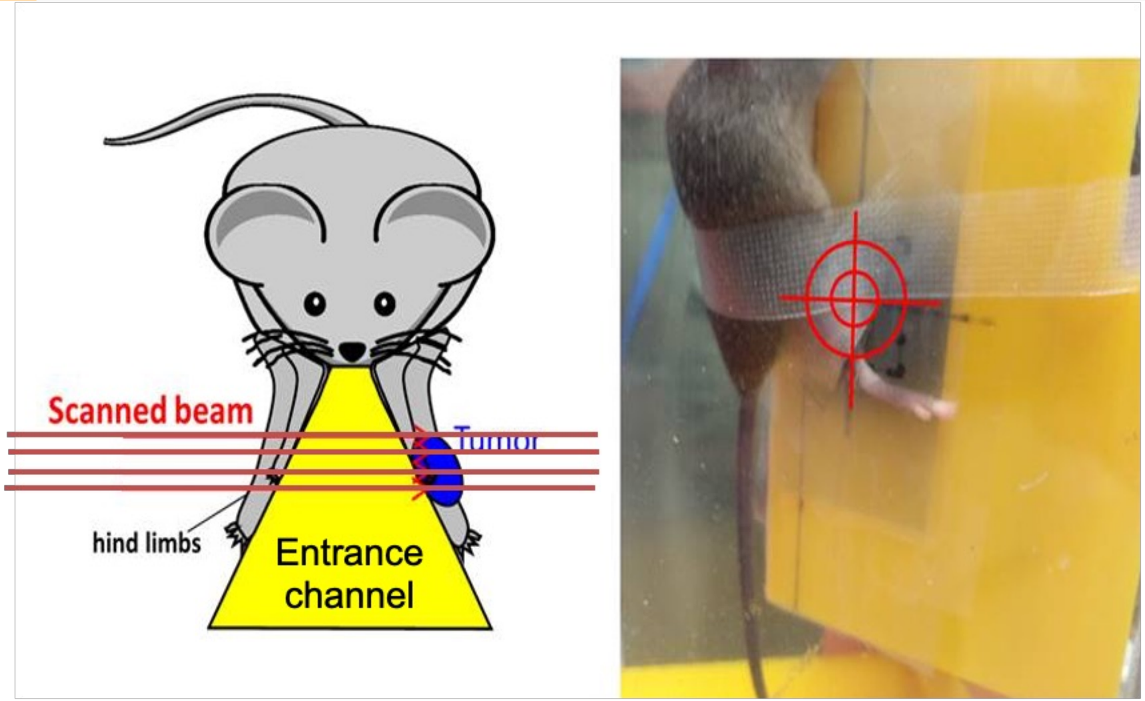
- GSI > 5×10^9 ions per spill (reliable)
  ⇨ 18 Gy | 100 Gy/s > 20 × 20 mm^2

Field wide enough for in vivo FLASH experiments (at GSI only)

Test shoot before delivey on mice (video), recorded on Gafchromic film



FLASH in vivo Carbon ion experiment



- GSI SIS18 FAIR-phase-0: **12C-ions: 240 MeV/n**
- LET on target= **14.5-15.5 keV/µm (plateau)**
- FLASH: Total dose **18 Gy;**
- +/-0.3 Gy accuracy;
- Single synchrotron spill of **150 ms** +/- 20 ms
- Containing **5 x10^9 12C-ions**;
- Average dose-rate calculated as target dose per total irradiation time reached 100 Gy/s.

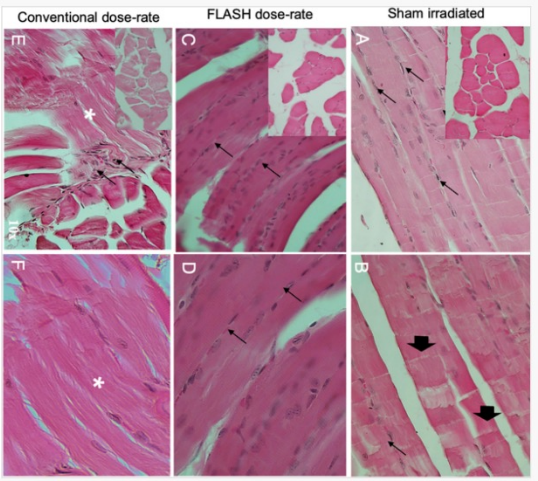
FAIR Phase 0 Research Program

D= 18 Gy.
Entrance channel

Tinganelli *et al.*, *Radiother. Oncol.* 2022

In collaboration with:

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION



Morphology and structural changes outcome in healthy muscles stained with hematoxylin-eosin.

A, B Muscle tissue in sham irradiated control;
C,D Muscle tissue of animals FLASH irradiated;
E, F Muscle tissue of animals Conventional irradiated.

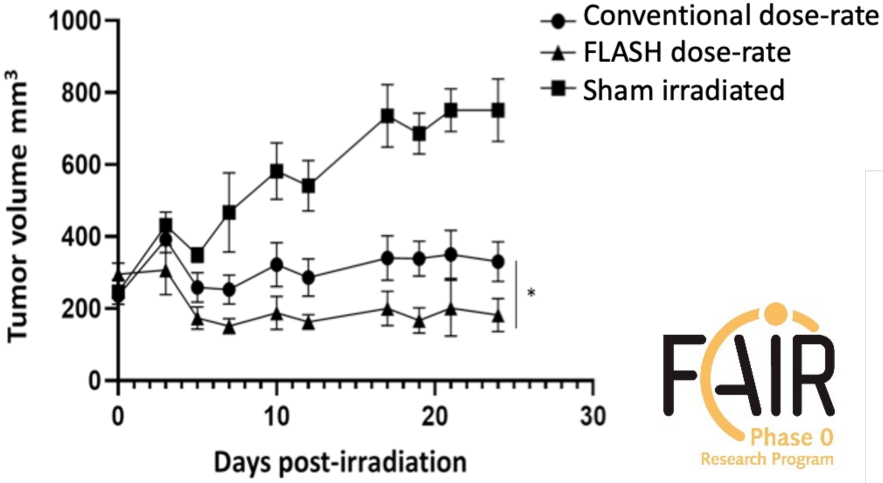
C, D: regular striation, and nuclei with typical peripheral localization (arrows), in the longitudinal section;

E, F Disorganized myofibers structures (asterisk) and nuclei localization (arrows).

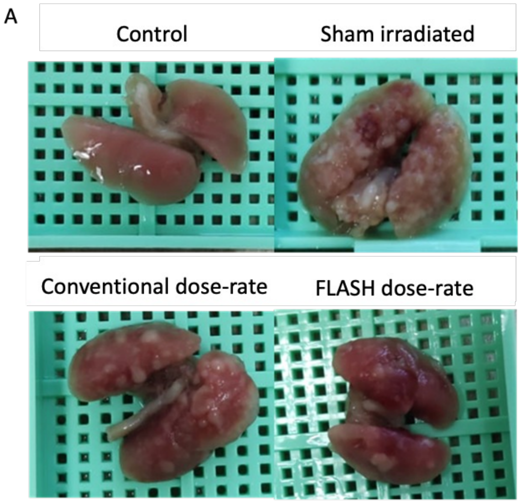
Magnification: A, C, E 200 , B, D, F 400.

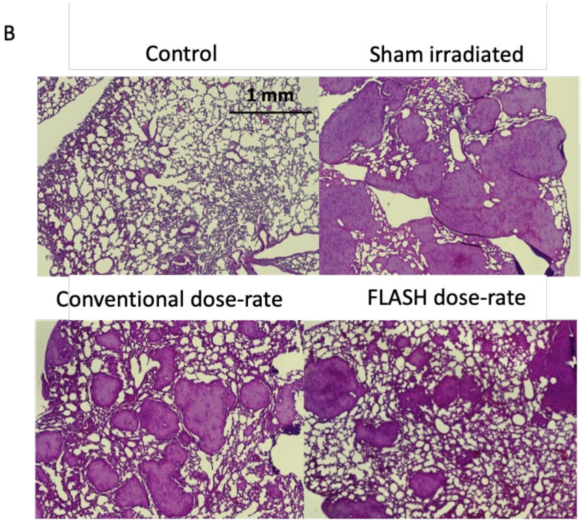
FLASH with carbon ions: Tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

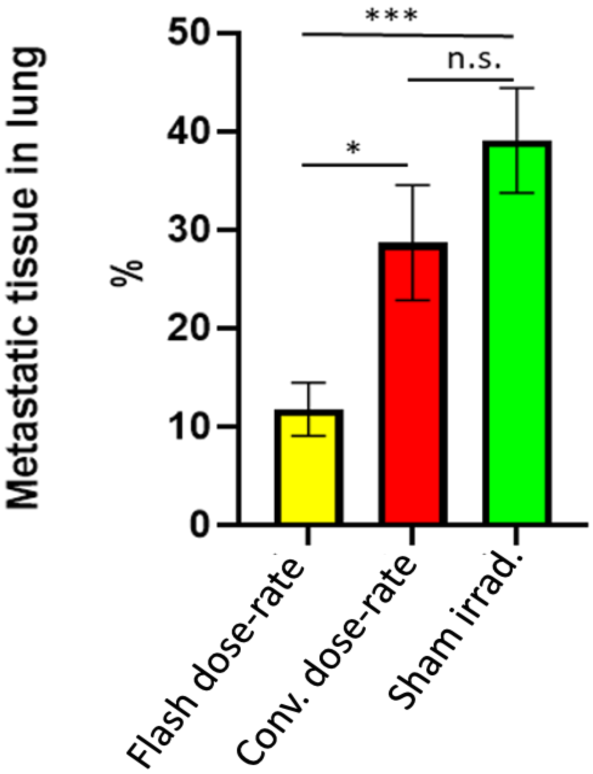
Walter Tinganelli [a], Uli Weber [a], Anggraeini Puspitasari [a], Palma Simoniello [b], Amir Abdollahi [c], Julius Oppermann [a], Christoph Schuy [a], Felix Horst [a], Alexander Helm [a], Claudia Fournier [a], Marco Durante [a, d]



LUNG METASTASIS







Original Article

FLASH with carbon ions: Tumor control, normal tissue sparing, and distal metastasis in a mouse osteosarcoma model

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CONCLUSIONS

- FLASH is very promising for the future of radiation oncology
- Whilst charged particles are the most mature technique for clinical translational, more pre-clinical research is needed
- Following experiments with electrons, photons, and protons, we confirmed for the first time the FLASH effect with high-energy ^{12}C-ions *in vitro* and *in vivo*.
- In addition to the reduction of normal tissue toxicity, we measured reduced tumor growth and distal metastasis. The suppression of lung metastases, may be a unique feature of particle beams.
- Beamtime in 2024-2025 at GSI will clarify the role of C-ions in FLASH radiotherapy and the potential for clinical translation

Thank you very much!

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