Beyond state-of-the-art instrumentation for the end stations

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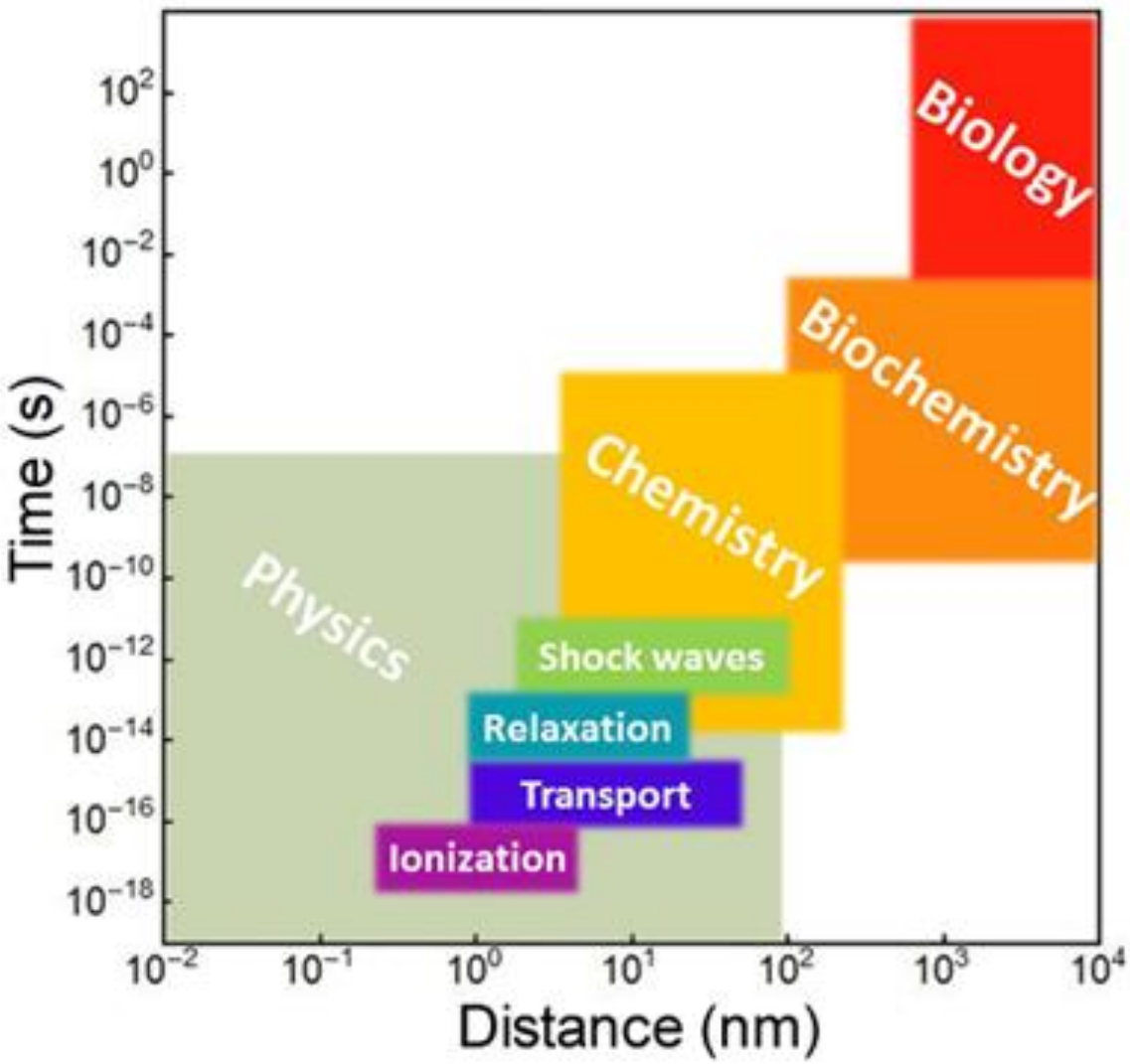
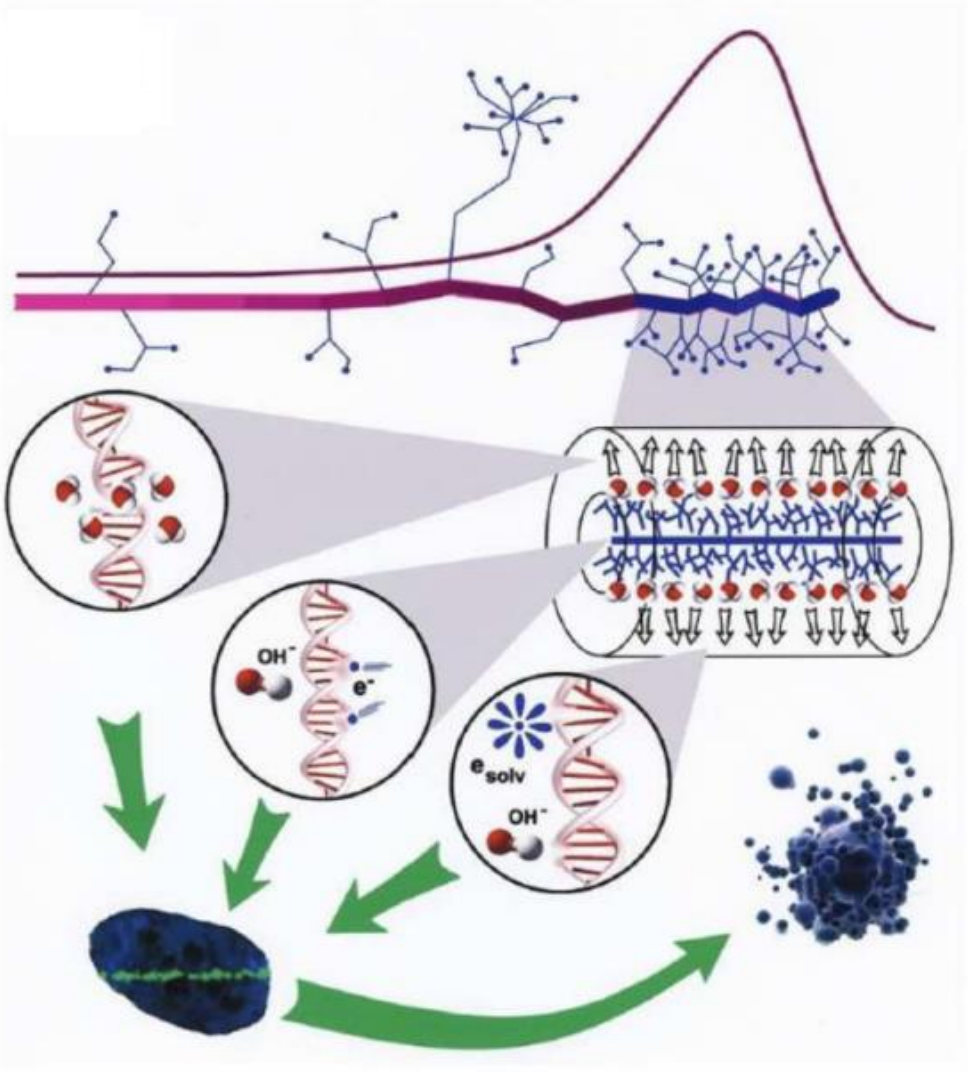
Biological / clinical requirements of end-station designs

- **Measure physical processes**
  - Dose
  - Range
- **Image biological / biochemical processes**
  - Imaging markers
  - Novel imaging techniques
  - Temporal resolution
  - Spatial resolution
- **Identify translational endpoints**
  - Bench-to-bedside
  - Bedside-to-bench
- **End-station design should be nimble**
- …….



Solov'yov AV, Verkhovtsev AV, Mason NJ, **Amos RA**, *et al*. Condensed matter systems exposed to radiation: Multiscale theory, simulations, and experiment. arXiv:22311.13402v1 [physics.chem-ph] (Submitted to Chemical Reviews)



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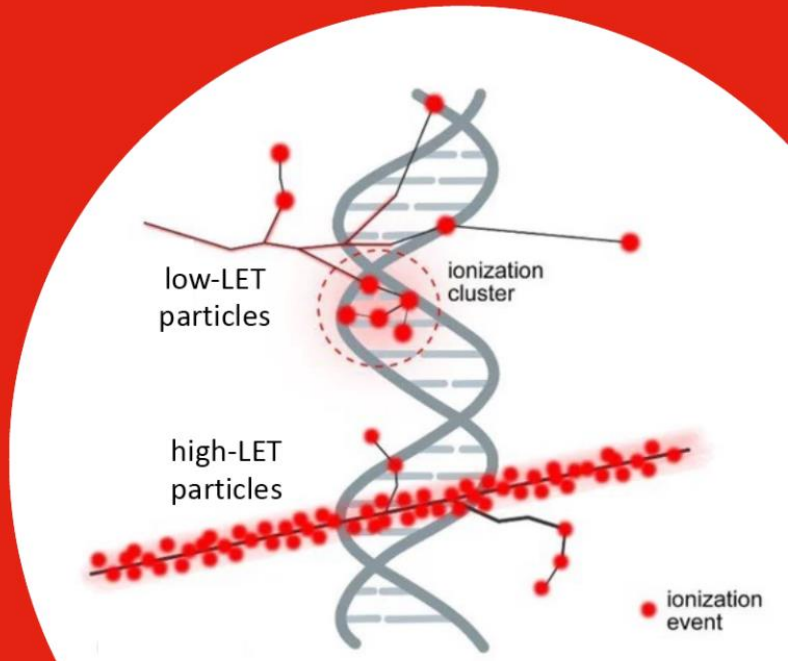
Advancing Radiobiology Technology

24 October 2023
Institute of Physics, London, UK



Radiation Biology and Biophysics

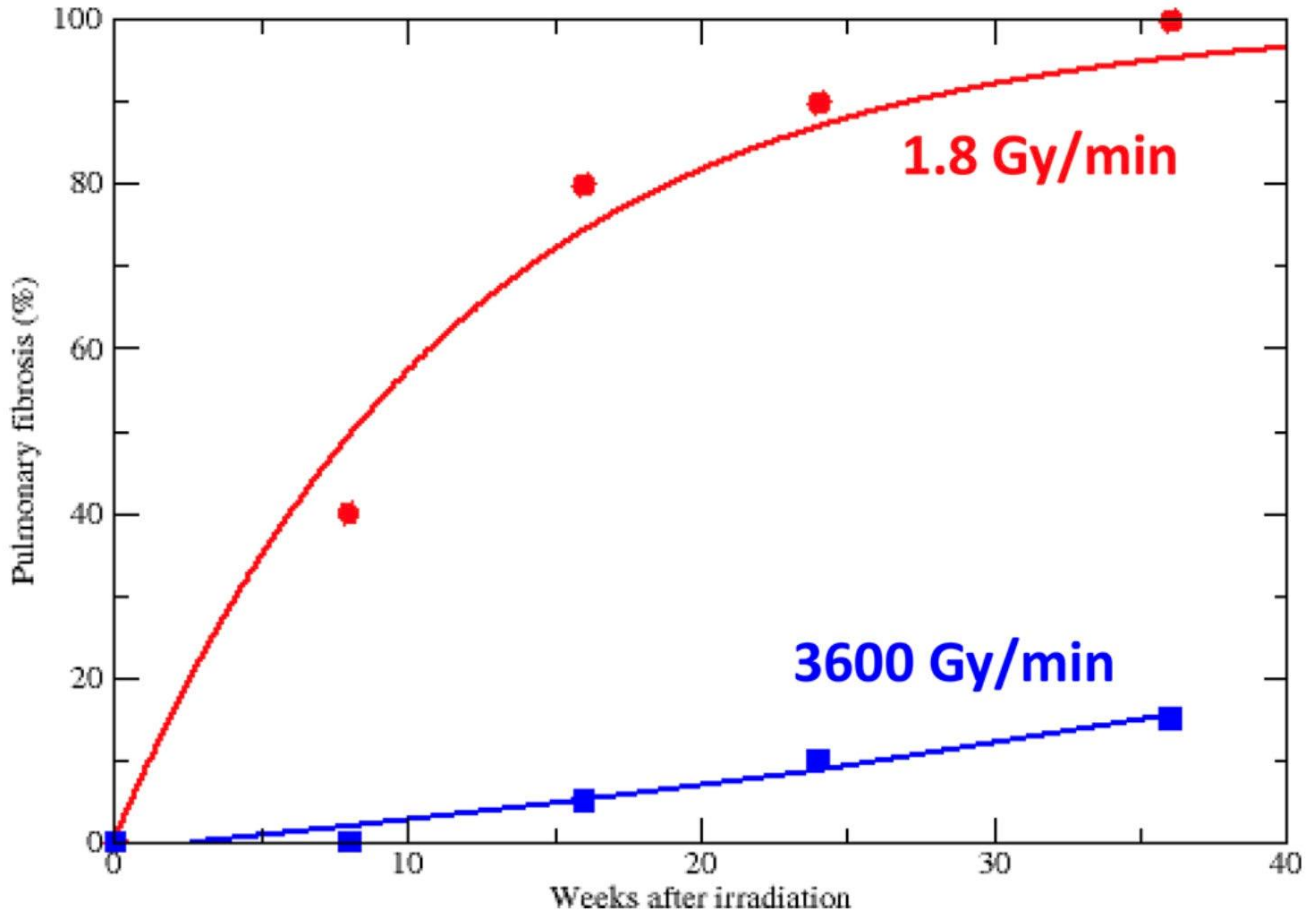
Novel Accelerator Systems

Novel Instrumentation & Computing

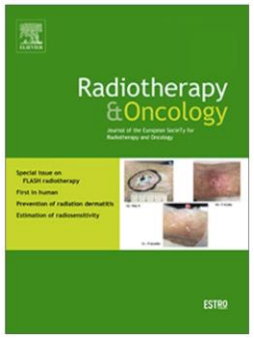
Biomedical and Clinical Impact

FLASH-RT: Ultra-high dose rate (UHDR) radiotherapy

Dose rate >40 Gy s^{-1}



Data from:
Favaudon V, *et al.* Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. *Sci Transl Med* 2014; 6: 245ra93.



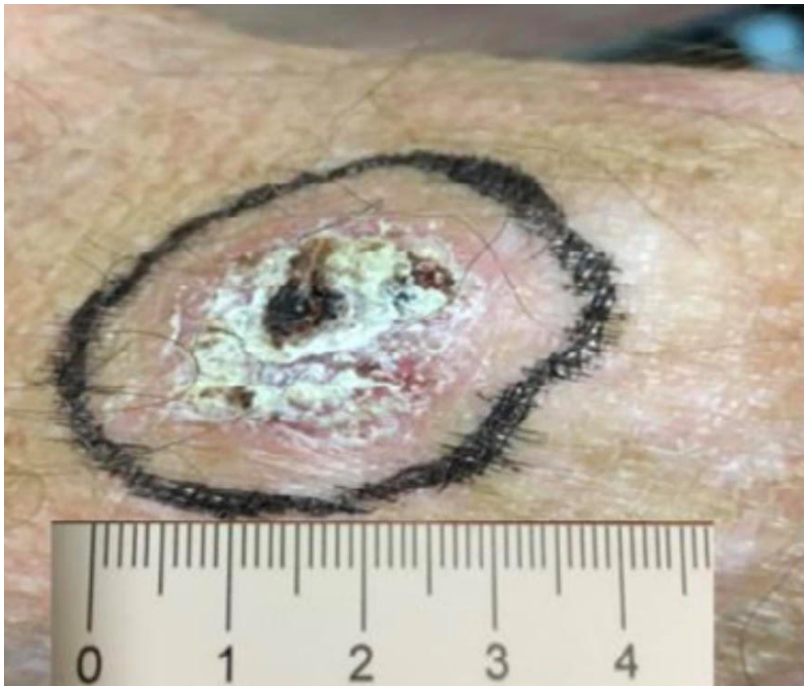
First in Human

Treatment of a first patient with FLASH-radiotherapy

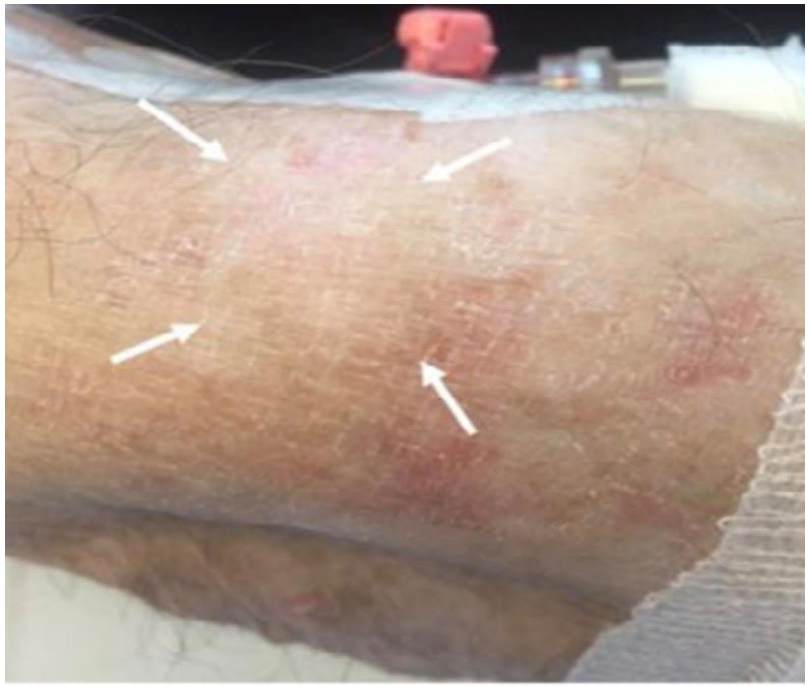
Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

75 yr old patient with multi-resistant CD30+ T-Cell cutaneous lymphoma

FLASH-RT - 15 Gy in 90 ms



Day 0

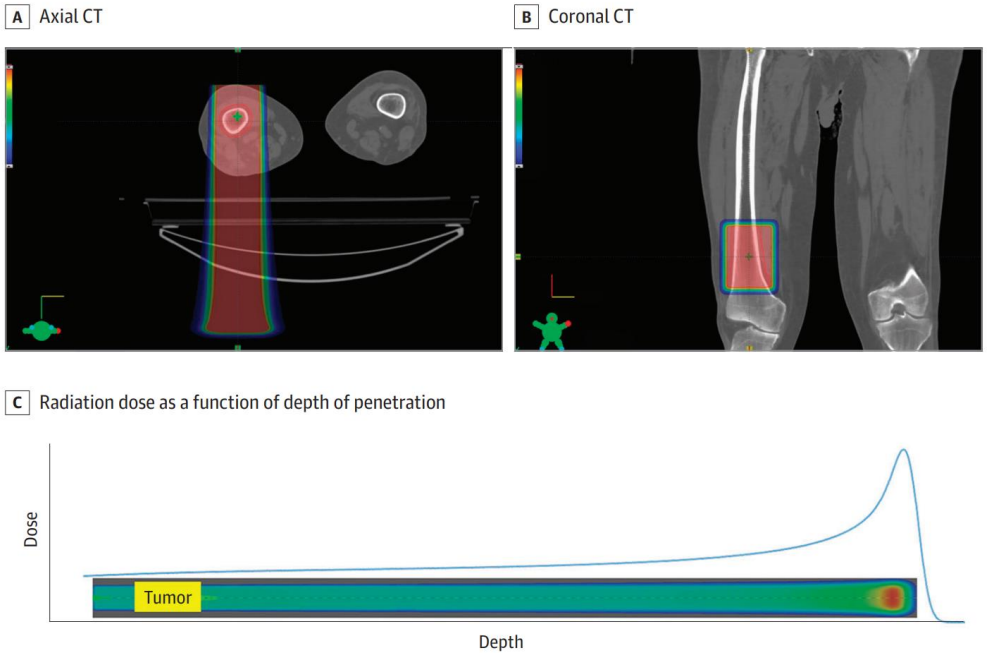


5 Months

JAMA Oncology | Original Investigation

Proton FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases

The FAST-01 Nonrandomized Trial



Key Points

Question Is proton FLASH radiotherapy, delivered at 1000 times the dose rate of conventional-dose-rate photon radiotherapy for its potential normal tissue-sparing effects, feasible for the palliation of painful bone metastases in the extremities?

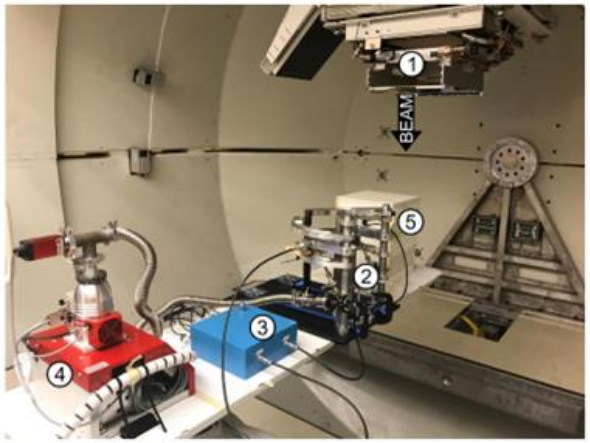
Findings This nonrandomized trial of 10 patients with bone metastases in the extremities found that proton FLASH was clinically feasible, and its safety was supported by the minimal severity of related adverse events. In this small sample size, the efficacy of FLASH treatment for pain relief appeared to be similar to that of conventional-dose-rate photon radiotherapy.

Meaning The results of this study confirm the workflow feasibility of delivering ultra-high-dose-rate proton FLASH radiation treatment in a routine clinical setting and support the further exploration of proton FLASH radiotherapy.

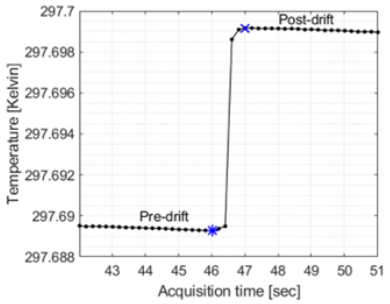
nature portfolio
scientific reports
https://doi.org/10.1038/s41598-023-28192-0

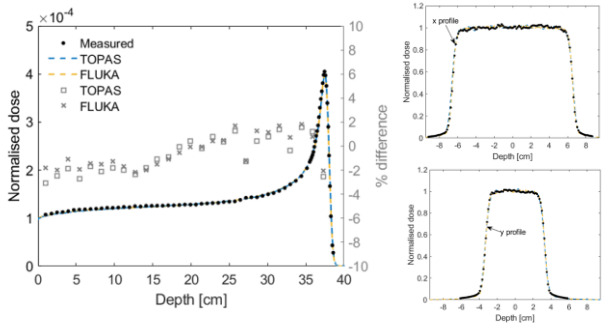
Absolute dosimetry for FLASH proton pencil beam scanning radiotherapy

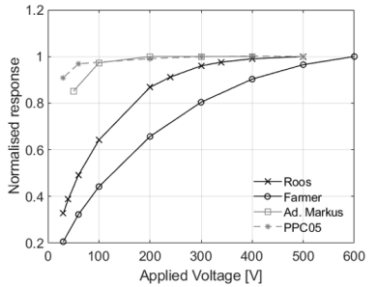
Ana Lourenço[1,2]✉, Anna Subiel[1], Nigel Lee[1], Sam Flynn[1,3], John Cotterill[1], David Shipley[1], Francesco Romano[4], Joe Speth[5,6], Eunsin Lee[5,6], Yongbin Zhang[5,6], Zhiyan Xiao[5,6], Anthony Mascia[5,6], Richard A. Amos[2], Hugo Palmans[1,7] & Russell Thomas[1,8]

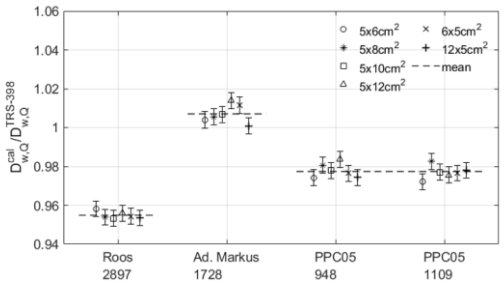


1. gantry
2. NPL primary-standard proton calorimeter (PSPC)
3. instrumentation for the NPL PSPC
4. vacuum pump
5. ion chamber setup



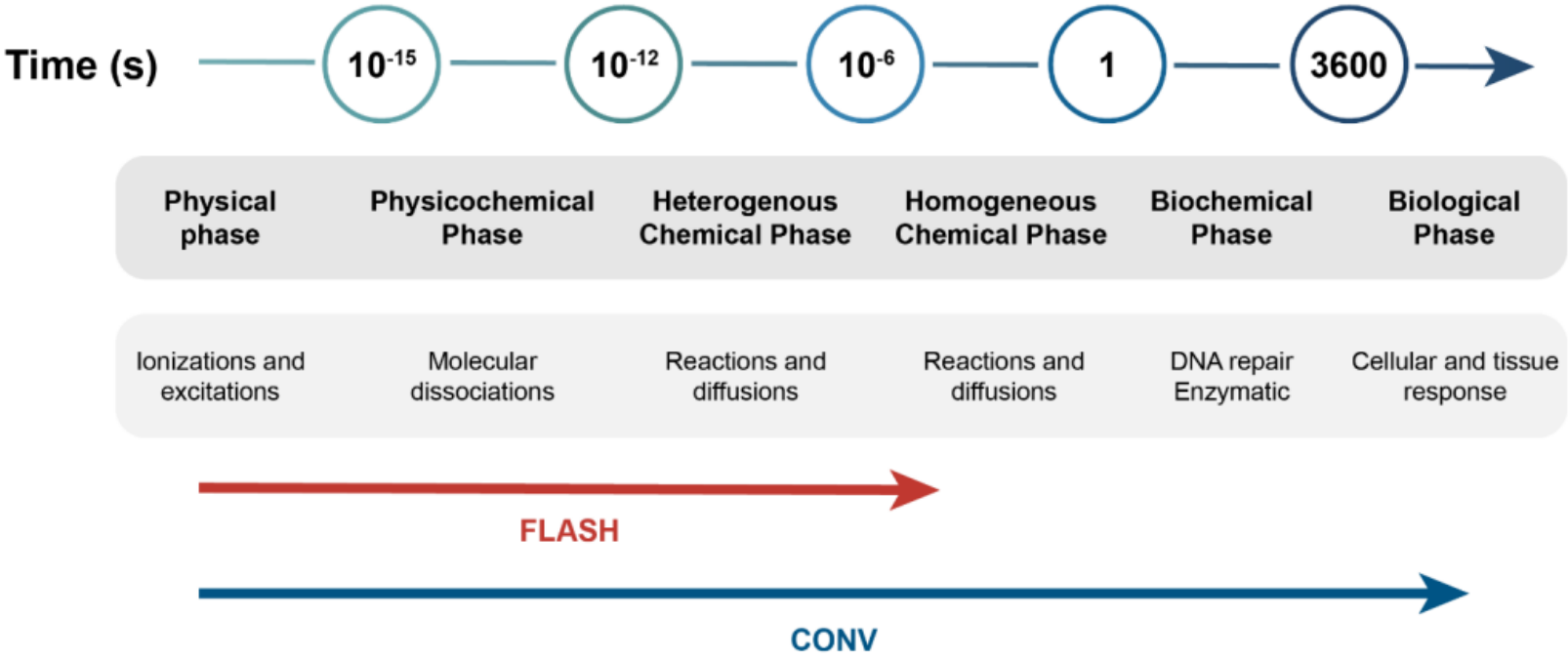






Calorimetry measurements were performed, and necessary correction factors established for absolute dosimetry of FLASH proton pencil beam scanning. This enabled the safe and accurate implementation in the clinic of this new treatment modality. The NPL PSPC accurately measures the dose delivered with an uncertainty two times smaller than the dose derived from ionisation chambers. The response of the calorimeter is dose-rate independent, as opposed to the response of ionisation chambers which need to be very well characterised at FLASH dose-rates since large ion recombination effects occur. The overall uncertainty on the dose measured with the NPL PSPC is 0.9% (1σ) which is in line with recommendations[33,34] for reference dosimetry for effective radiotherapy treatments.

Timelines for FLASH vs CONV dose rate radiation delivery

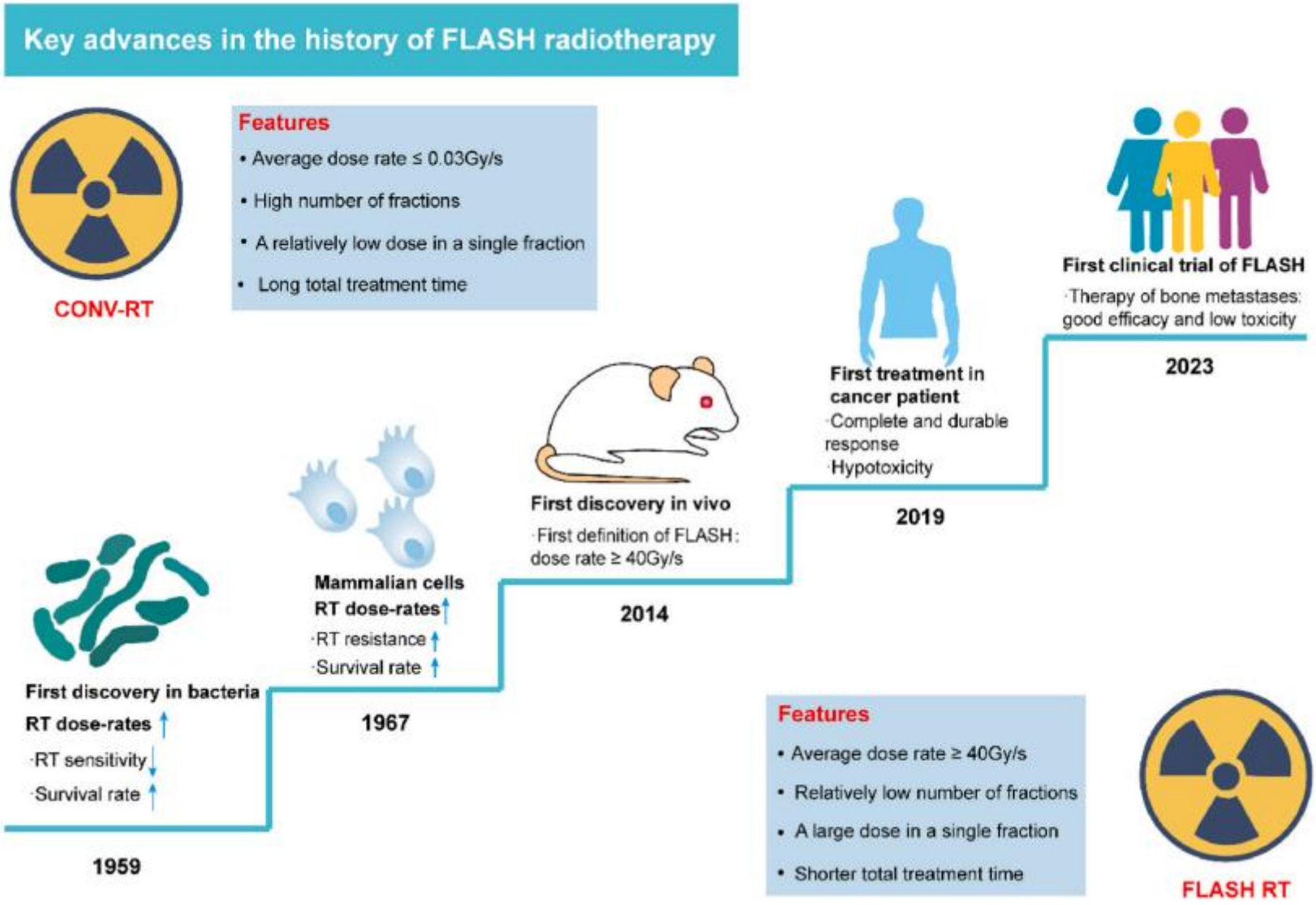


- CONV interferes with the chemical and biological phases.
- FLASH does not interact with the biochemical phases.

Intrinsic factors that potentially influence FLASH vs CONV mechanisms

Factor	Normal Tissue	Tumor	Normal and Tumor
	Oxygen depletion hypothesis		
Oxygen [23,24]	Rapid oxygen depletion	Small change in oxygen	-
ROS [4,25]	Reduction of ROS	No change of ROS	-
Oxygen to hydroperoxide conversion [25]	High removal of hydroperoxides	Slow removal of hydroperoxides	-
Capillary oxygen Tension [24]	Higher	Lower	-
	DNA damage hypothesis		
Yields of DNA damage [26]	Smaller amounts of DSBs	Higher amount of DSBs	-
Pattern of DNA Damage [27]	Higher amount of clustered DNA damage will lead to activation of different factors (DNA repair, immune system)	Lower amount of clustered DNA damage will lead to activation of different factors (DNA repair, immune system)	-
DNA damage repair pathways [28,29]	Unknown pathway, decreasing ROS and DNA damage	PARP-TGF-β pathway	-
Factors induced by DNA damage [30,31]	-	-	Initiation of cGAS-STING pathway is different between tumor and healthy tissue
	Immune hypothesis		
TGF-β and other immune factors [18,26]	Reduction of TGF-β	Induction of TGF-β	-
Immune cells and microenvironment [32]	-	Increase of T-lymphocytes into the tumor microenvironment	-
Immunogenic cell death [33]	-	-	Effects of FLASH on immunogenic cell death remain unclear

DSBs: double-stranded breaks; PARP: poly (ADP-ribose) polymerase; ROS: reactive oxygen species, TGF-β: transforming growth factor-beta.



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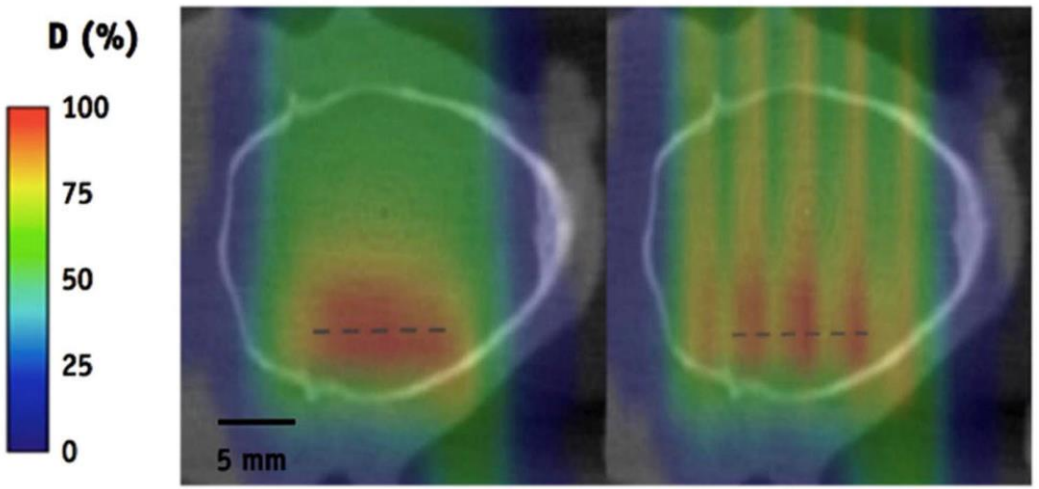
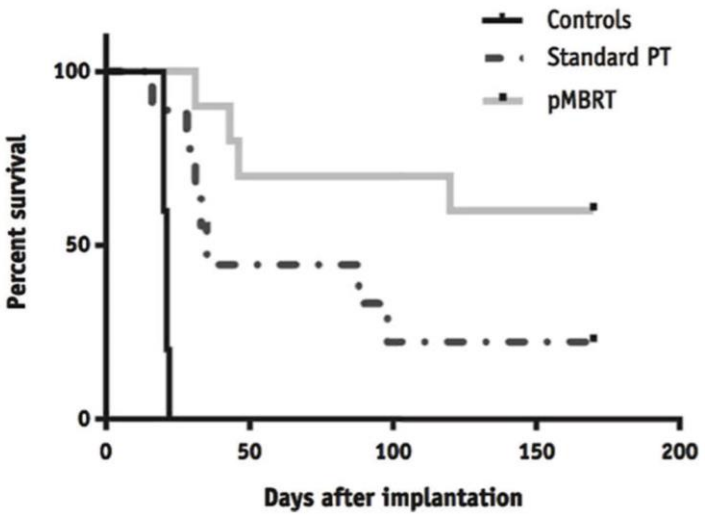
Tumor Control in RG2 Glioma-Bearing Rats: A Comparison Between Proton Minibeam Therapy and Standard Proton Therapy





Results: Tumor control was achieved in the 2 irradiated series, with superior survival in the pMBRT group compared with the standard proton therapy group. Long-term (>170 days) survival rates of 22% and 67% were obtained in the standard proton therapy and pMBRT groups, respectively. No tumor was observed in the histopathological analysis. Although animals with long-term survival in the standard radiation therapy exhibit substantial brain damage, including marked radionecrosis, less severe toxicity was observed in the pMBRT group.

Prezado Y. *et al. Int J Radiat Oncol Biol Phys* 2019 Jun 1;104(2):266-271

Thank you for your attention!

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