FLASH Radiotherapy

Promises, Mysteries and Challenges of the radiotherapy of the future (?)

Emanuele Scifoni

INFN
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Trento Institute for Fundamental Physics and Applications

Outline

- The Promises: **What is FLASH? Historical background**
- The Mystery: **Radiobiological mechanism** *Does it really work? And how?*
- The Challenges:
  - **Dosimetry** *If it work, can we control it?*
  - **Dose Delivery** *If It work and we can control it can we give it to patients?*
  - **(and Planning ?)**

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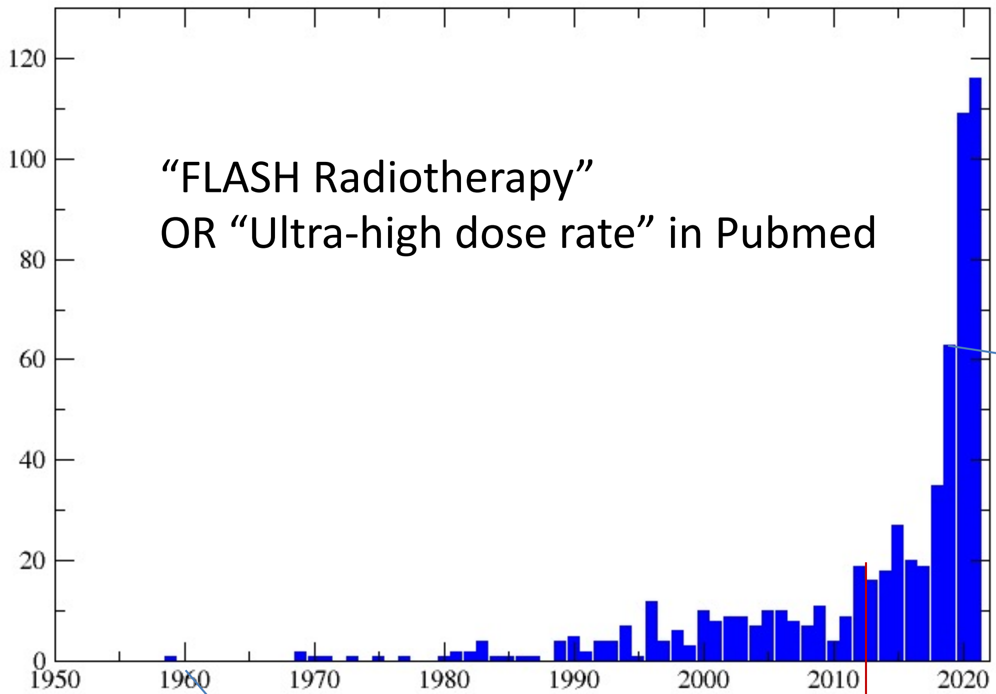
- What is FLASH?

FLASH: an exploding topic




Clinical Oncology 31 (2019) 407–415

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

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/erview

ological Benefits of Ultra-high Dose Rate FLASH Radiotherapy:
eeping Beauty Awoken

-C. Vozenin *†, J.H. Hendry ‡, C.L. Limoli §

- Dewey an Boag'59

Science Translational Medicine AAAS

Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice
Vincent Favaudon *et al.*
Sci Transl Med **6**, 245ra93 (2014);
DOI: 10.1126/scitranslmed.3008973

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The last 2 year boom

The Hottest Topic in Radiation Oncology!

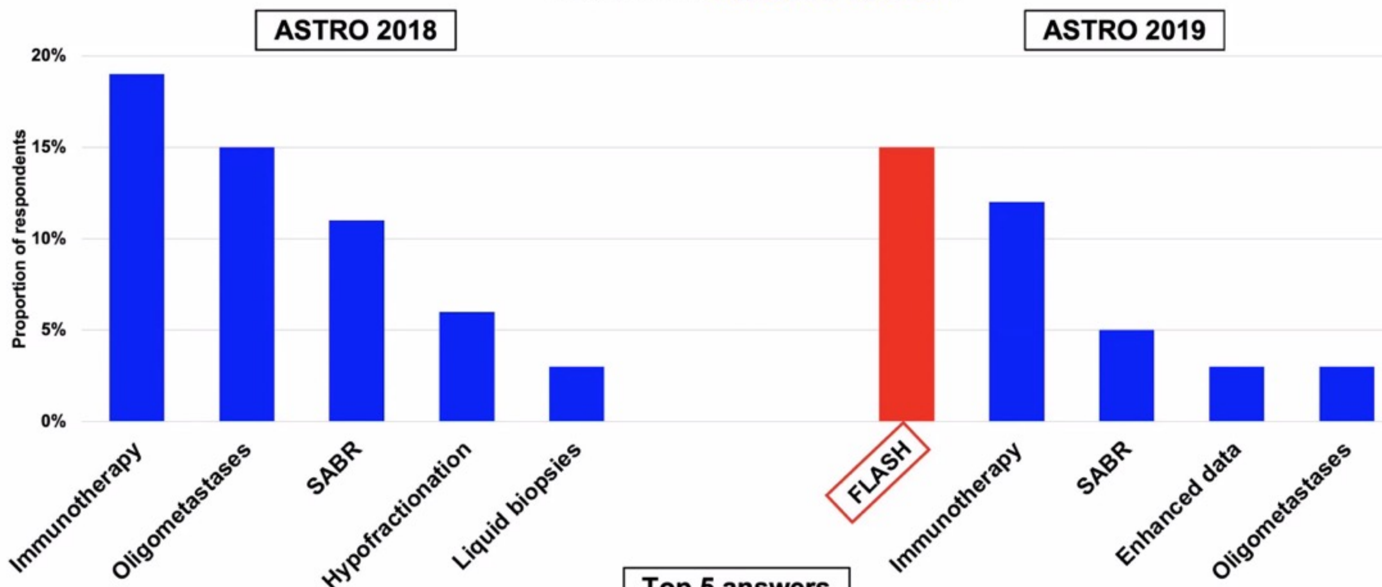
ARTICLE IN PRESS

International Journal of Radiation Oncology • biology • physics
www.redjournal.org

EDITORIAL

Responses to the 2018 and 2019 "One Big Discovery" Question: ASTRO Membership's Opinions on the Most Important Research Question Facing Radiation Oncology...Where Are We Headed?

ASTRO Meeting Survey:
What is the One Big Discovery that needs to be translated into the clinic RIGHT NOW?



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FRPT 2021 – FLASH Radiotherapy and Particle Therapy Conference

Topic A: Radiation Modalities

- A1 – Which conditions (radiation type, dose rate, dose per pulse, total irradiation time) are optimal for FLASH RT?
- A2 – Quality assurance and real time measurement of FLASH doses: ionisation chambers, film, solid state detectors, scintillators
- A3 – How FLASH RT is delivered: electrons, photons, protons, heavy ions: equipment involved, how beam is delivered, experimental end stations etc?
- A4 – FLASH radiation protection; simulation and measurement for research and clinical treatment
- A5 – Spatially fractionated radiotherapy, mini beams, micro beams etc.
- A6 – New horizons in FLASH, spatially fractionated radiotherapy and particle therapy: Laser driven ions, VHEE etc.
- A7 – Abstracts from INSPIRE and UHD Pulse projects; can be from those involved in the projects or through collaborative projects (for example trans national access projects through INSPIRE)

Topic B: Mechanisms

- B1 – Physics: modelling the FLASH effect, Geant 4 DNA, other code
- B2 – Physico-Chemistry: FLASH chemistry, oxygen contribution, ROS
- B3 – Biology: molecular level, DNA damage, oxidative stress, inflammation; cellular level; tissue level
- B4 – In vitro and in vivo studies,
- B5 – Flash and drug / immune radiation combinations

Topic C: Flash in the Clinic

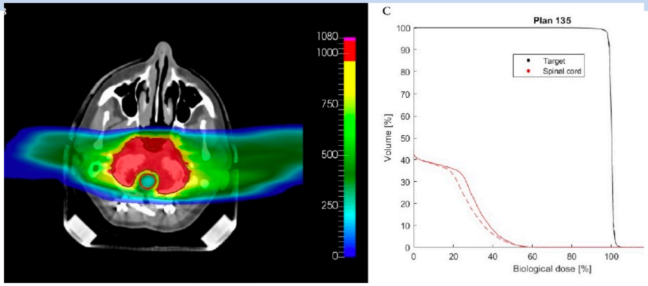
- C1 – QA and dosimetry
- C2 – TPS development for FLASH
- C3 – Treatment regimen, fractionation, volume, combination
- C4 – Clinical trial design and methodology, regulations
- C5 – Patient selection (how many patients might benefit from FLASH?), FLASH clinical workflow, health economics
- C6 – Clinical trial: FLASH-IORT and superficial tumours; FLASH – proton; synchrotron trial; innovative trials

700 Participants!

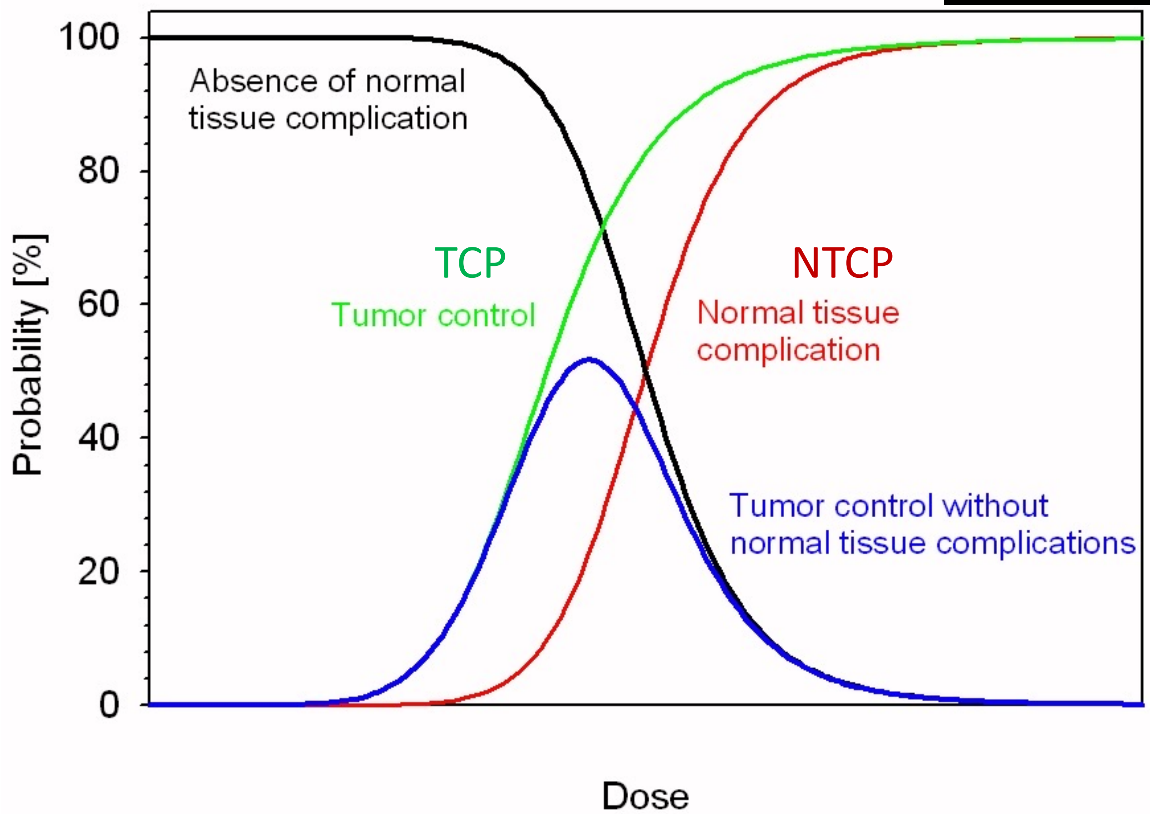
Opening Sessions and Invited Talks	Sponsored Sessions	Networking Events
FLASH Modalities	FLASH Mechanisms	FLASH Clinic
INSPIRE	FLASH Teaching Lecture	UHD Pulse

Main Scope of Radiotherapy

Balance between **desired** effects (tumour control) and **harmful** effects (normal tissue damage) induced by radiation dose



Battestini et al. subm. Front Oncol. 2021



The Therapeutic Window

TCPWC= TCP(1-NTCP)

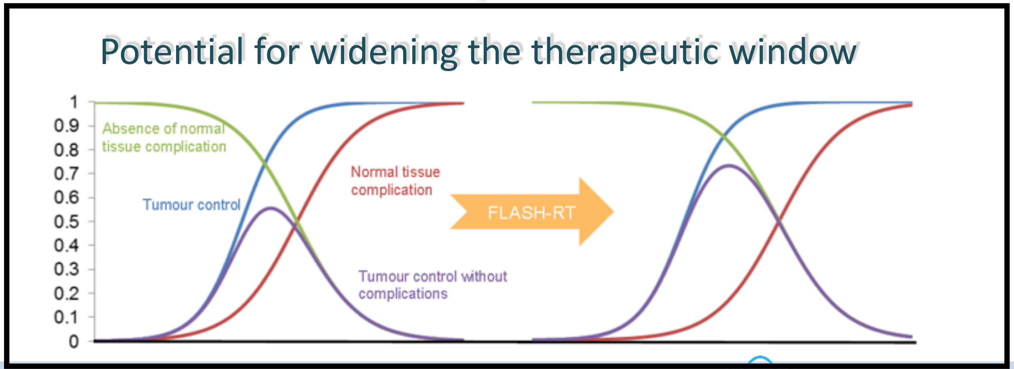
FLASH RT: what's that

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

(>40 Gy/s overall dose rate, for a total irradiation time <100 ms , but much higher rates (up to 10^9 Gy/s) during each pulse)

aiming to get **unchanged tumor control** and **protection in the normal tissue.**

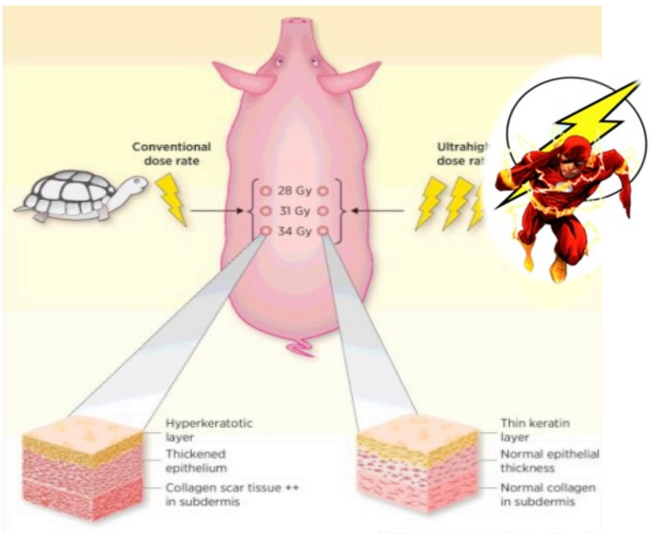
TCPWC=TCP(1-NTCP)



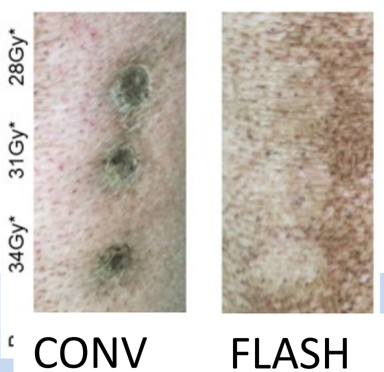
The FLASH Effect

Irradiation with **ultra-high dose rate**

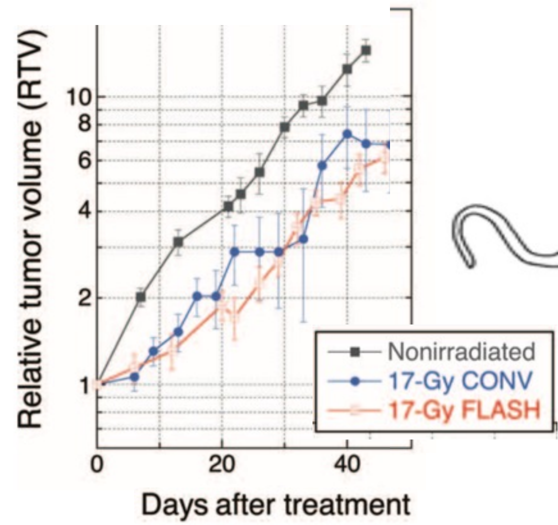
- Decreasing of the normal tissue response



Vozenin et al. 2019, Clin. Canc. Res.



- Preservation of the tumor responses



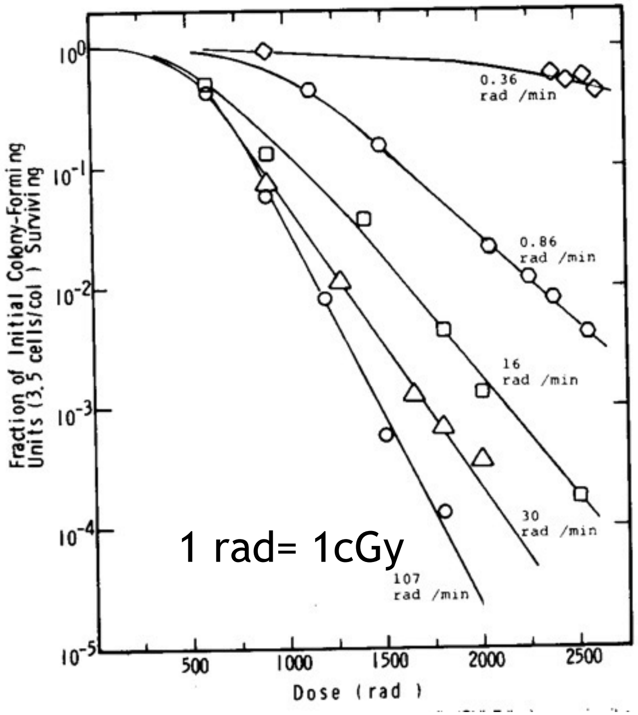
V. Favaudon et al. 2014, Sci. Transl. Med.

Radiobiology

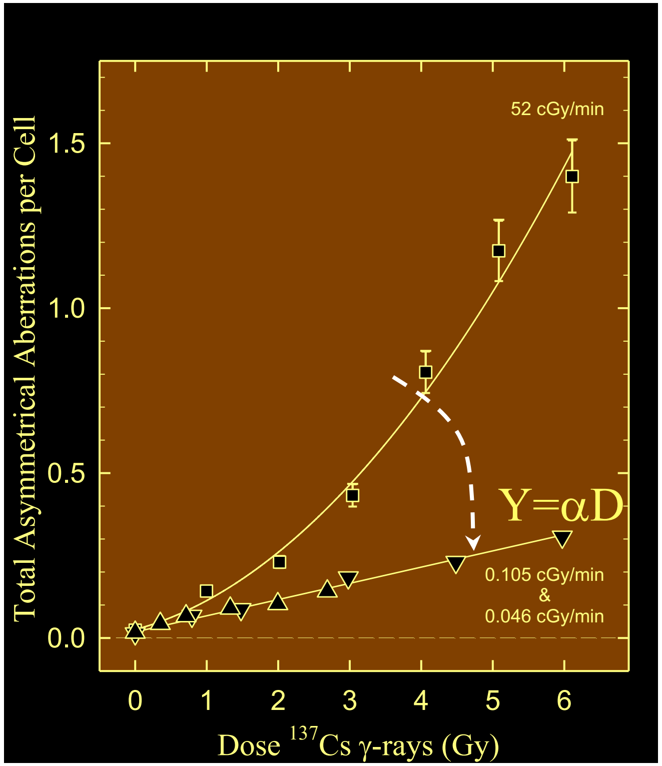
Does it really work? And how?

Dose Rate effect
in conventional Radiobiology

Clonogenic Survival



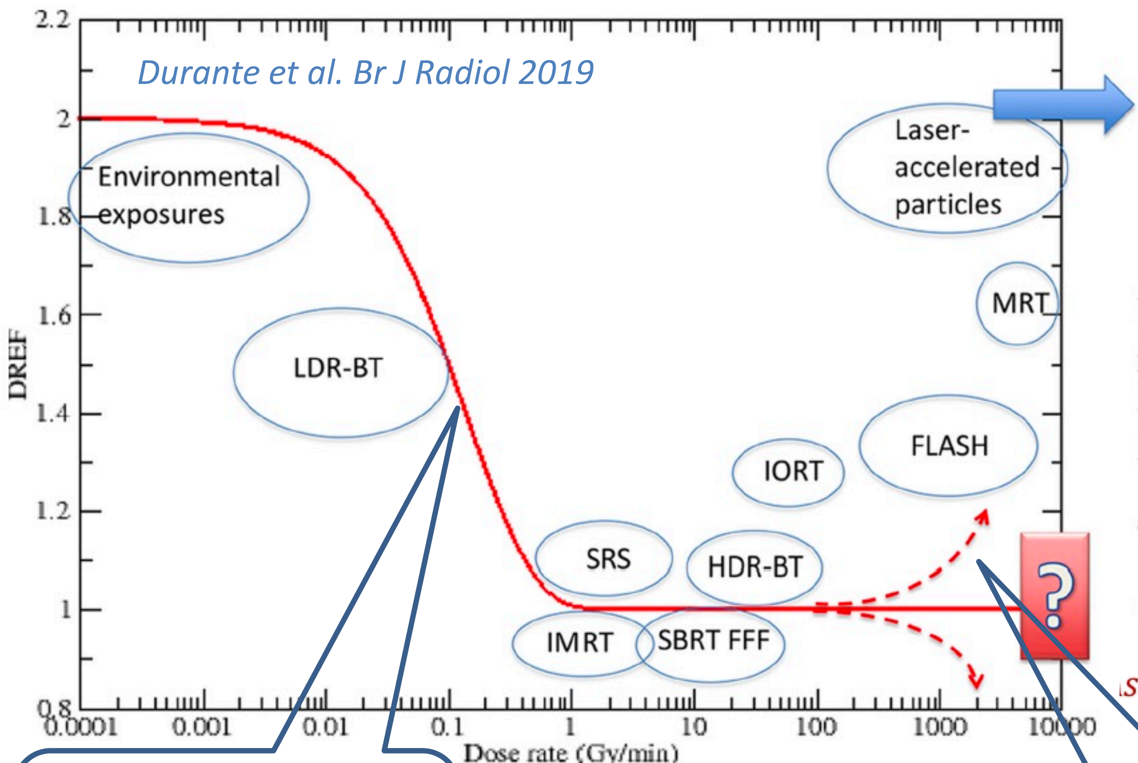
Chromosome Aberrations



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

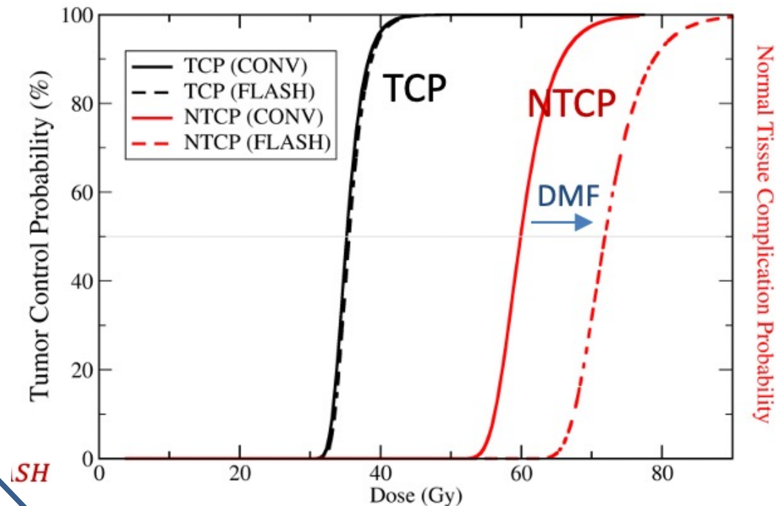
Mechanistic Explanation easy: **Potentially Letal Damage** allowed to be repaired

Ultrahigh Dose Rate Response and FLASH



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

Dose-Rate Effectiveness Factor



This we understand (sublethal damage repair etc..)

This we presently **DON'T** understand

FLASH Basic questions:

- **WHY** this happens?
- How is it possible to justify an "inverse" protective effect with increasing dose rate?
- How is it possible to justify having it selectively for NT while maintaining unchanged tumor control?

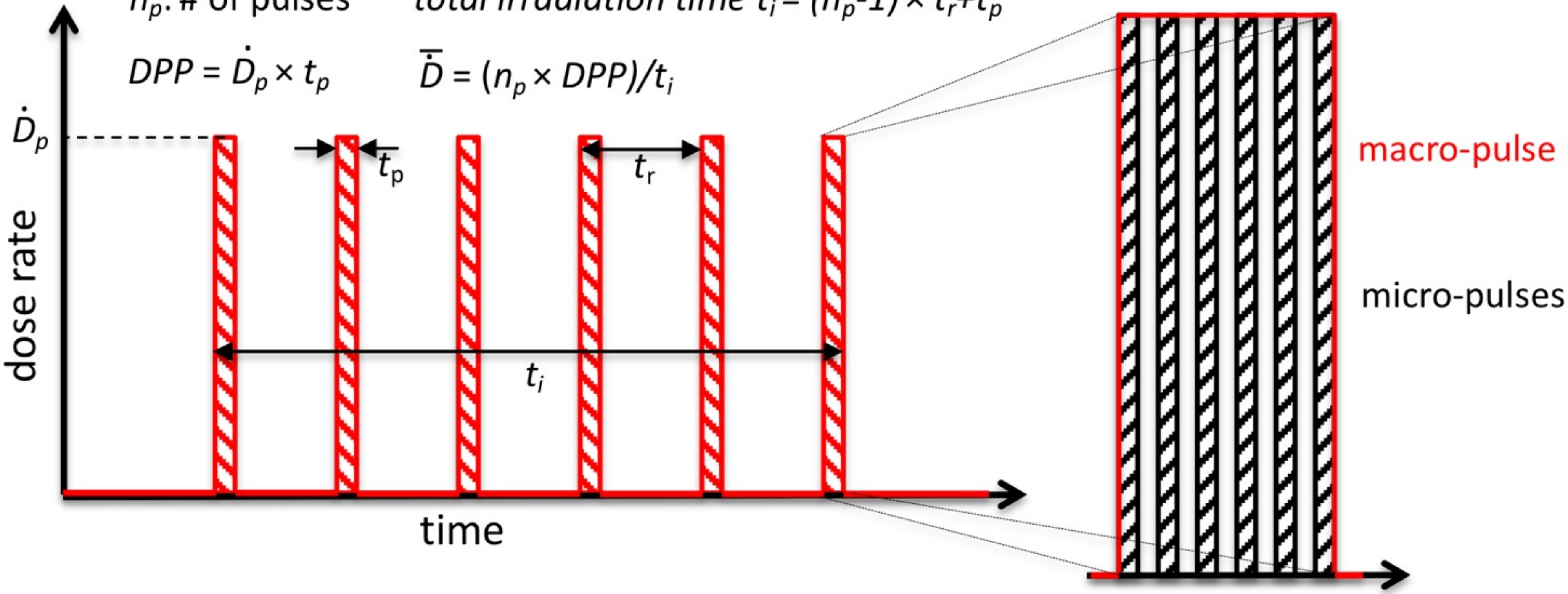
- **WHEN** (for which irradiation parameters) this happens?

Dose Delivery time structure

t_p: pulse width — time between pulses $t_r = 1/PRF$

n_p: # of pulses — *total irradiation time* $t_i = (n_p - 1) \times t_r + t_p$

$DPP = \dot{D}_p \times t_p$ — $\bar{\dot{D}} = (n_p \times DPP)/t_i$

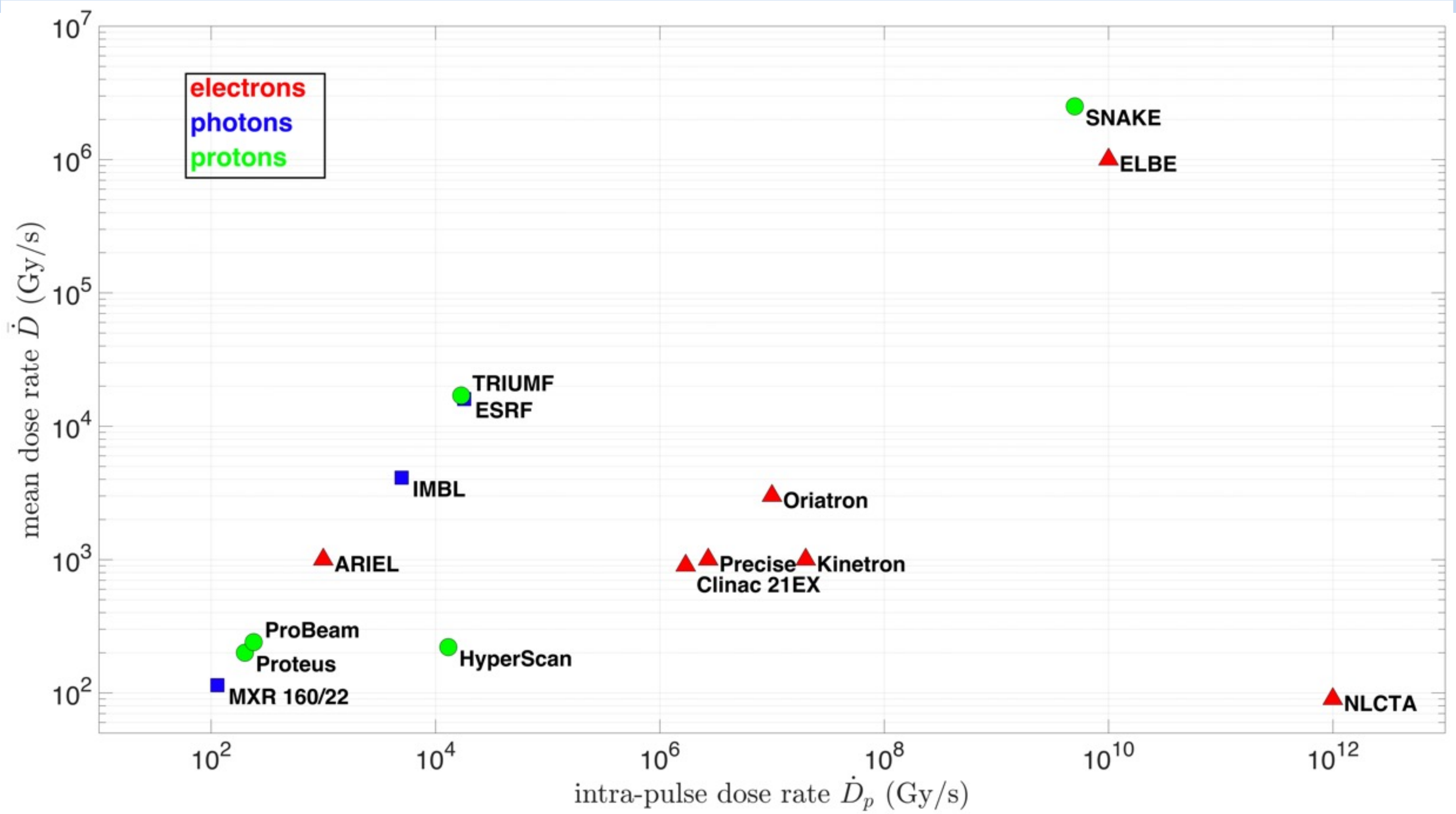


Pulse frequency

$$\dot{n} = \frac{n_p}{t_i}$$

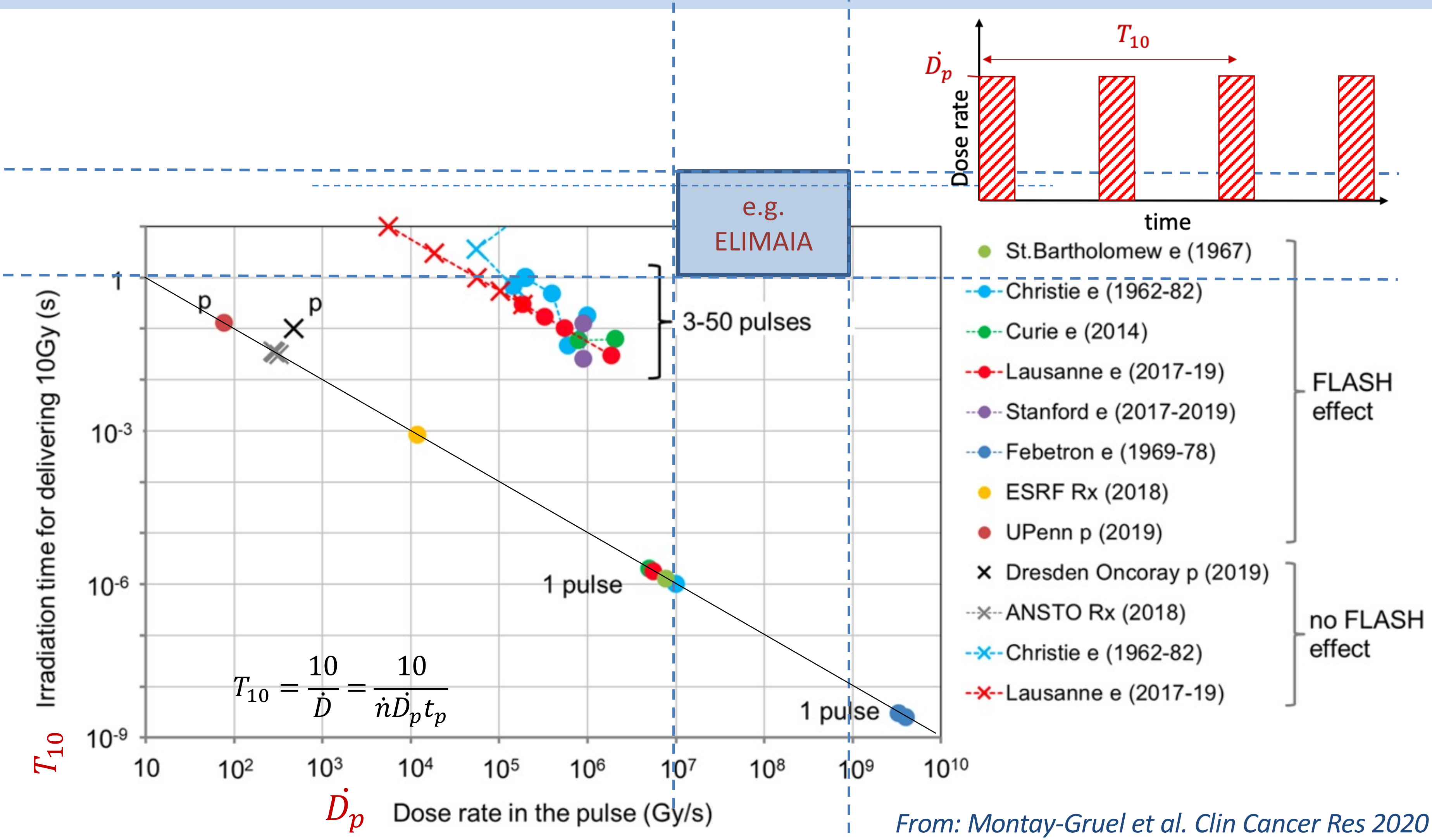
Esplen et al. PMB 2020

Employed facilites



Esplen et al. PMB 2020

Parameters for observing FLASH/noFLASH



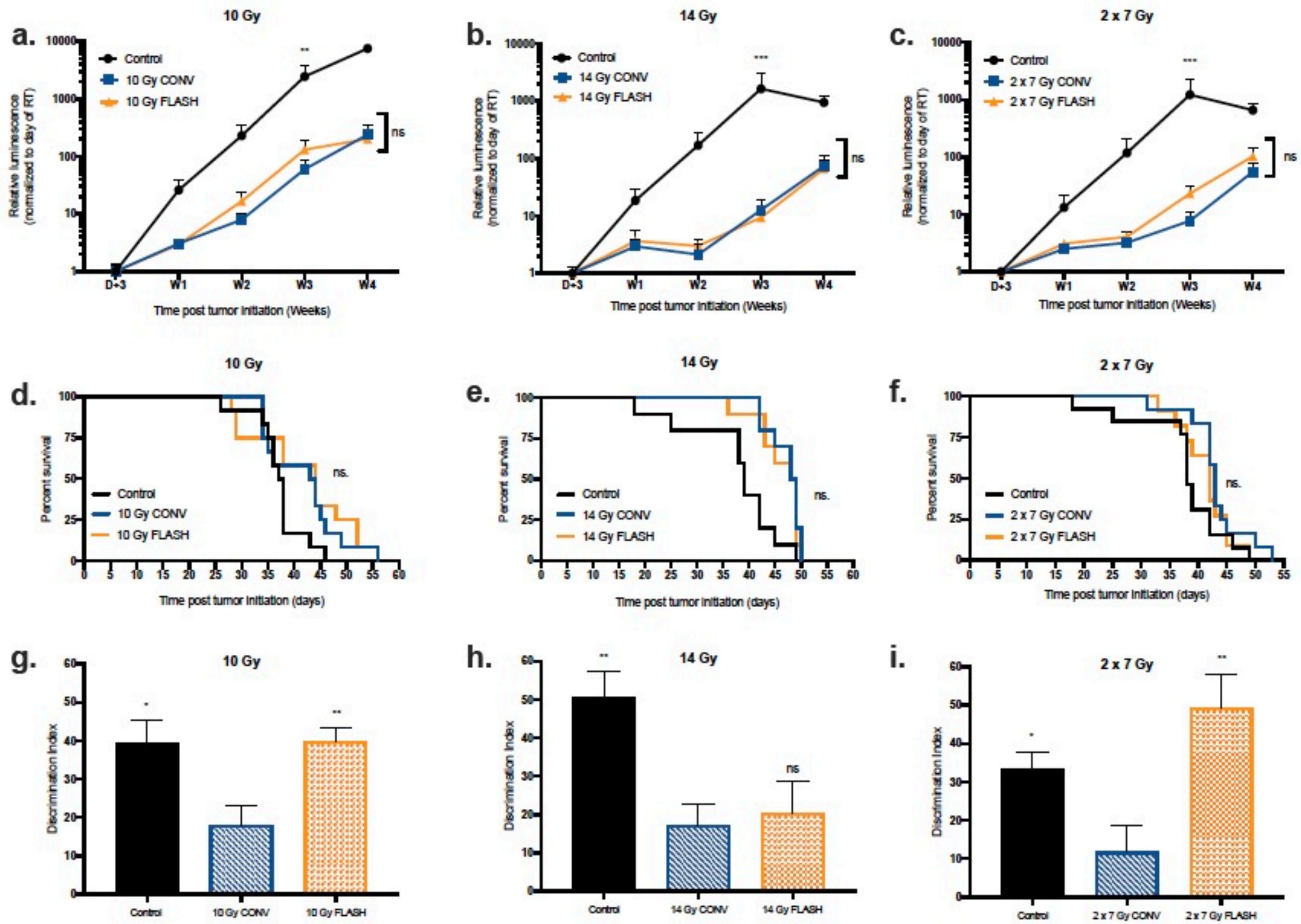
From: Montay-Gruel et al. Clin Cancer Res 2020

Impact of Fractionation

Tumor growth delay

Survival

Cognition (Novel Object Recognition)



Montay-Gruel et al. Clin Cancer Res 2020

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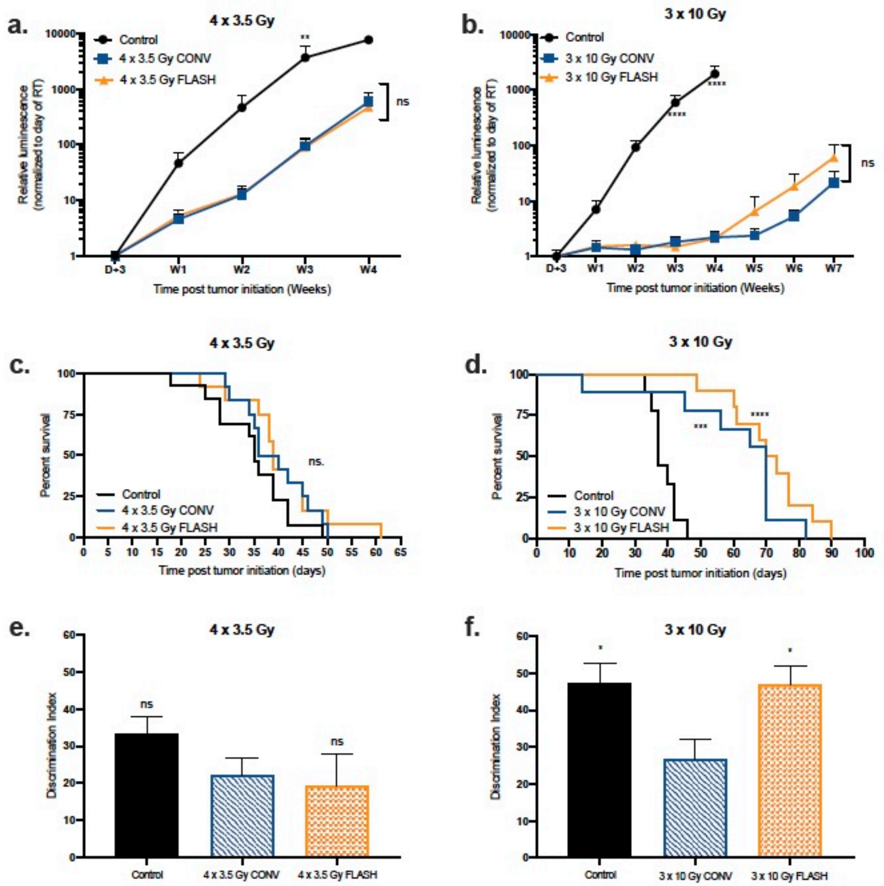
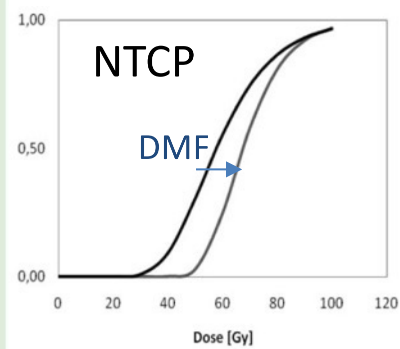


Dose modifying factor: NT

Let's be quantitative

Wilson `Front Oncol 2020

In vivo studies			Irradiation delivery technique			
Model	Assay	FLASH dose modification factor (Bold if >1)	Total dose (Gy)	Dose rate (Gy/s)	Pulse rate (Hz)	Modality of radiation
Zebrafish embryo (16)	Fish length	**1.2–1.5**	10–12	10^6-10^7	Single pulse	Electron
Zebrafish embryo (29)	Fish length, survival, and rate of oedema	1	0–43	100	0.106×10^9	Proton
Whole body irradiation of mice (34)	LD50	**1.1**	8–40	17–83	400	Electron
Thoracic irradiation of mice (10)	TGFβ signaling induction	**1.8**	17	40–60	100–150	Electron
Thoracic irradiation of mice (18)	Number of proliferating cells, DNA damage, expression of inflammatory genes	**>1 Significant Differences**	17	40–60	100–150	Electron
Abdominal irradiation of mice (33)	Survival	<1 Significant Difference	16	35	Likely 300	Electron
Abdominal irradiation of mice (12)	LD50	**1.2**	22	70–210	100–300	Electron
Abdominal irradiation of mice (17)	Survival, stool formation, regeneration in crypts, apoptosis, and DNA damage in crypt cells	**>1 Significant Differences**	12–16	216	108	Electron
Whole brain irradiation of mice (25)	Novel object recognition and object location tests	**>1 Significant Differences**	30	200, 300	108, 180	Electron
Whole brain irradiation of mice (13)	Variety of neurocognitive tests	**>1 Significant Differences**	10	$5.6 \cdot 10^6$	Single pulse	Electron
Whole brain irradiation of mice (14)	Novel object recognition test	**>1 Significant Differences**	10	$30–5.6 \cdot 10^6$	100 or single pulse	Electron
Whole brain irradiation of mice (8)	Novel object recognition test	**≥1.4**	10	$5.6–7.8 \cdot 10^6$	single pulse	Electron
Whole brain irradiation of mice (24)	Novel object recognition test	**>1 Significant Difference**	10	37	1,300	X-ray
Total body and partial body rradiation of mice (32)	TD50	1	3.6–28	37–41	1,388	X-ray
Thoracic irradiation of mice (11)	lung fibrosis, skin dermatitis, and survival	**>1 Significant Difference**	15, 17.5, 20	40	?	Proton
rradiation of mouse tail skin (49)	Necrosis ND50	**1.4**	30 and 50	17–170	50	Electron
rradiation of mouse skin (27)	Early skin reaction score	**1.1–1.6**	50–75	2.5 mean, 3×10^4 in the pulse	23–80	Electron
rradiation of rat skin (26)	Early skin reaction score	**1.4–1.8**	25–35	67	400	Electron
rradiation of mini-pig skin (15)	Skin toxicity	**≥1.4**	22–34	300	100	Electron



$$DMF_{NT} = \frac{TD_{50}^{FLASH}}{TD_{50}^{CONV}}$$

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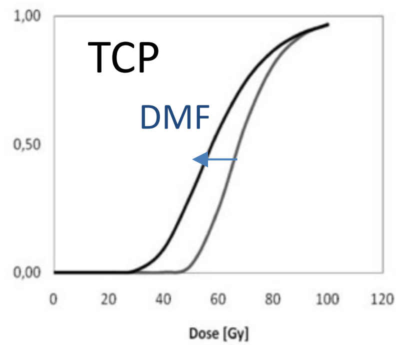
Dose modifying factor: Tumor

Let's be quantitative

Wilson `Front Oncol 2020

In vivo studies			Irradiation delivery technique			
Model	**Assay**	**FLASH dose modification factor (Bold if >1)**	**Total dose (Gy)**	**Dose rate (Gy/s)**	**Pulse rate (Hz)**	**Modality of radiation**
Thoracic irradiation of orthotopic engrafted non-small cell lung cancer Lewis lung carcinoma) in mice (36)	Tumor size and T-cell Infiltration	**>1 Differences in tumor size (significant) and T-cell infiltration**	18	40	?	Proton
Thoracic irradiation of orthotopic engrafted mouse lung carcinoma TC-1 Luc+ in mice (10)	Survival and tumor Growth Delay	1	15-28	60	100–150	Electron
Abdominal irradiation of mice (17)	Number of tumors, tumor weights	1	12–16	216	108	Electron
Whole brain irradiation of nude mice with orthotopic engrafted H454 murine glioblastoma (8)	Tumor Growth Delay	1	10–25	2.8–5.6·10^6	Single pulse	Electron
Local irradiation of subcutaneous engrafted Human breast cancer HBCx-12A and head and neck carcinoma HEp-2 in nude mice (10)	Tumor Growth Delay	1	15–25	60	100–150	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (8)	Tumor Growth Delay	1	0–35	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted U87 human glioblastoma in nude mice (19)	Tumor Growth Delay	1	10–30	125–5.6·10^6	100 or single pulse	Electron
Local irradiation of subcutaneous engrafted Human hypopharyngeal squamous cell carcinoma ATCC HTB-43 in nude mice (35)	Tumor Growth Delay in irradiated Mice and RBE	1	20	0.008 mean, ≈10^9 in pulse	<<1	Proton
Treatment of locally advanced squamous cell carcinoma (SCC) in cat patients (15)	Tumor response and survival	1 Similar response as in published studies with CONV-RT	25–41	130–390	100	Electron
Treatment of CD30+ T-cell cutaneous lymphoma T3 N0 M0 B0 in human patient (9)	Tumor response	1 Similar response as previous treatments with CONV-RT	15	167	100	Electron



$$DMF_T = \frac{TD_{50}^{CONV}}{TD_{50}^{FLASH}}$$

The first clinical result

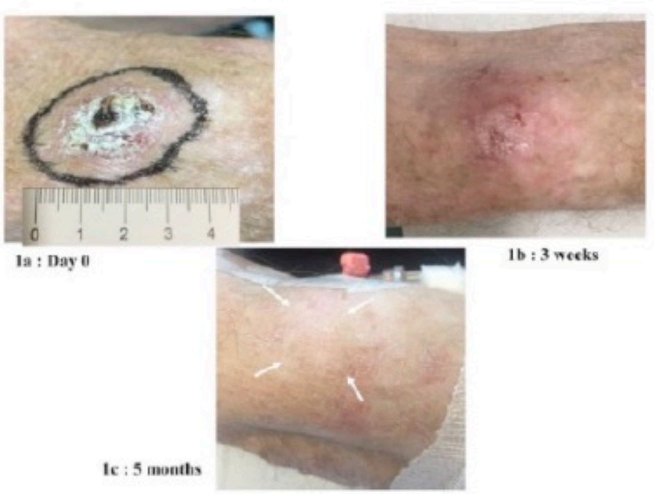
Contents lists available at ScienceDirect
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

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]

[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University of Lausanne; and [d] Department of Dermatology, Lausanne University Hospital and University of Lausanne, Switzerland



- multiresistant CD30+ T-cell cutaneous lymphoma disseminated throughout the whole skin surface.
- Localized skin RT previously used over 110 times for various ulcerative and/or painful cutaneous lesions progressing despite systemic treatments.
- Treatment given to a 3.5-cm diameter skin tumor with a 5.6-MeV linac specifically designed for FLASH-RT.
- Prescribed dose to the PTV = 15 Gy, in 90 ms.
- Results: At 3 weeks, i.e. at the peak of the reactions, a grade 1 epithelitis (CTCAE v 5.0) along with a transient grade 1 oedema (CTCAE v5.0) in soft tissues surrounding the tumor were observed.
- Clinical examination was consistent with the optical coherence tomography showing no decrease of the thickness of the epidermis and no disruption at the basal membrane with limited increase of the vascularization.
- In parallel, the tumor response was rapid, complete, and durable with a short follow-up of 5 months

The first Clinical trial

ClinicalTrials.gov

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Home > Search Results > Study Record Detail ☐ Save this study

Breneman et al.
(with protons)

Feasibility Study of FLASH Radiotherapy for the Treatment of Symptomatic Bone Metastases (FAST-01)

⚠ 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.

Sponsor:
Varian Medical

Information provided by (Responsible Party):
Varian Medical

Inclusion/Exclusion Criteria

- Key inclusion criteria
  - Up to 3 painful bone metastasis(-es) in the extremities
  - Pre-defined treatment field sizes
- Key exclusion criteria
  - Prior radiotherapy to the treatment site(s)
  - Tumor lysis of >50% of the circumferential bone cortex
  - Patients with fractures or metal implants in the treatment field

Cincinnati Children's | University of CINCINNATI

Study Details | Tabular View | No Results Posted | Disclaimer | How to Read a Study Record

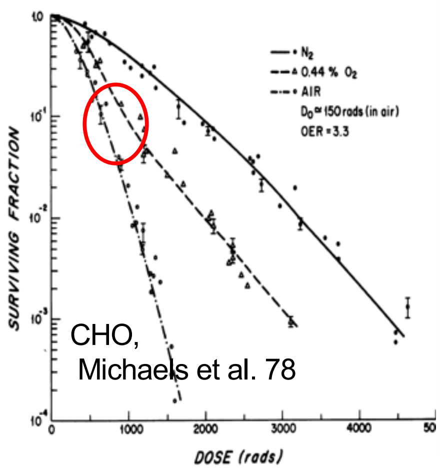
Study Description Go to ▾

Brief Summary:
This purpose of this study is to assess the feasibility of FLASH radiotherapy for the palliative treatment of painful bone metastases. FLASH radiotherapy is radiation treatment delivered at ultra-high dose rates compared to conventional radiation treatment.

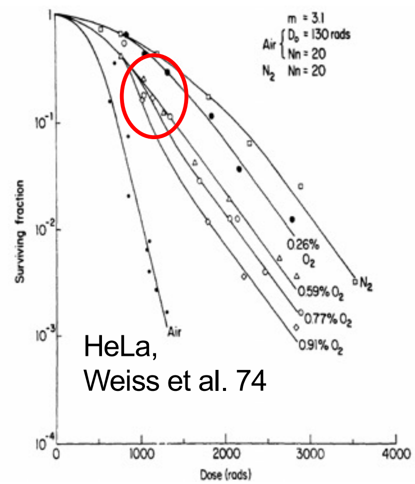
FLASH - depends on oxygen concentration

Known from the early FLASH experiments in the 60ies
confirmed in cell cultures, tail clamp exp., hyperbaric breathing …

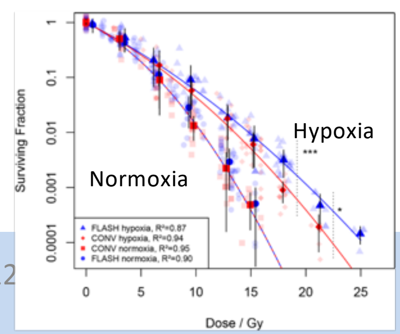
In vitro



CHO,
Michaels et al. 78

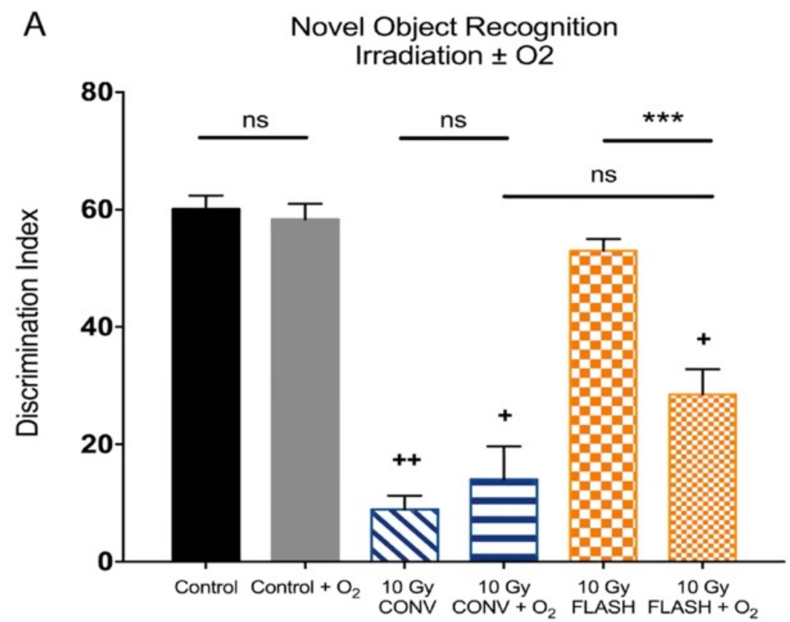


HeLa,
Weiss et al. 74



Adrian et al.,
Br. J. Radiol. (2019)

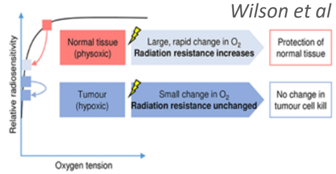
In vivo



Pierre Montay-Gruel, et al. PNAS (2019)

Main FLASH mechanistic hypothesis

Transient Hypoxia (O_2 Depletion)



Wilson et al 2020

- G. Pratx, D. S. Kapp, A computational model of radiolytic oxygen depletion during FLASH irradiation and its effect on the oxygen enhancement ratio, PMB (2019)
- K. Petersson, et al. A quantitative analysis of the role of oxygen tension in FLASH radiotherapy, IJROBP (2020)
- G. Adrian, et al., The FLASH effect depends on oxygen concentration, Brit. J. Radiol. (2020)
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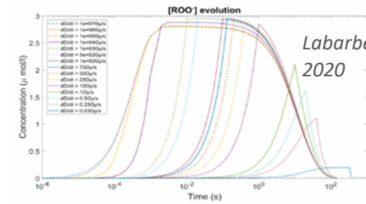
- Zakaria, A. et al.. (2021). Transient hypoxia in water irradiated by swift carbon ions at ultra-high dose rates: implication for FLASH carbon-ion therapy. Canadian Journal of Chemistry,
- Zhu, H, et al. "Modeling of cellular response after FLASH irradiation: a quantitative analysis based on the radiolytic oxygen depletion hypothesis." arXiv subm.(2021).

Organic radical-radical recombination



Labarbe et al 2020

- R. Labarbe, et al. "A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect." Radiother. Oncol. (2020
- D. R. Spitz, et. al., An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses, Radiother. Oncol. (2019)
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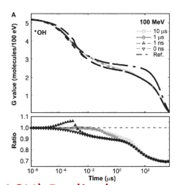
- D. Boscolo et al.. (2020). Impact of target oxygenation on the chemical track evolution of ion and electron radiation. International Journal of Molecular Sciences, 21(2), 424.
- D. Boscolo, et al. May oxygen depletion explain the FLASH effect? A chemical track structure analysis. Radiother Oncol, 162:68-75.
- Y. Lai et al "Modeling the effect of oxygen on the chemical stage of water radiolysis using GPU-based microscopic Monte Carlo simulations, with an application in FLASH radiotherapy" Phys Med Biol 2020

2019-2021 (!)

Intertrack Effects



Ramos et al 2020

- A.M. Zakaria, et al. "Ultra-High Dose-Rate, Pulsed (FLASH) Radiotherapy with Carbon Ions: Generation of Early, Transient, Highly Oxygenated Conditions in the Tumor Environment." *Rad. Res.* (2020).
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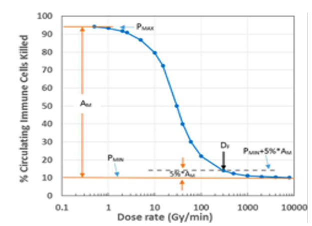
Immune system driven



Zhou et al 2020

- the differential responses to ionizing radiation between normal and tumor tissues. Radiation Medicine and Protection, 1(1), 35-40.
- Jin J. Y., et al. FLASH Dose Rate Effect on Circulating Immune Cells: A Potential Mechanism for FLASH-RT?. International Journal of Radiation Oncology, Biology, Physics, 2020, 108.3: S7.
- Jin, Jian-Yue, et al. "Ultra-high dose rate effect on circulating immune cells: A potential mechanism for FLASH effect?." Radiotherapy and Oncology 149 (2020): 55-62

Spatiotemporal Scales of Radiation Damage

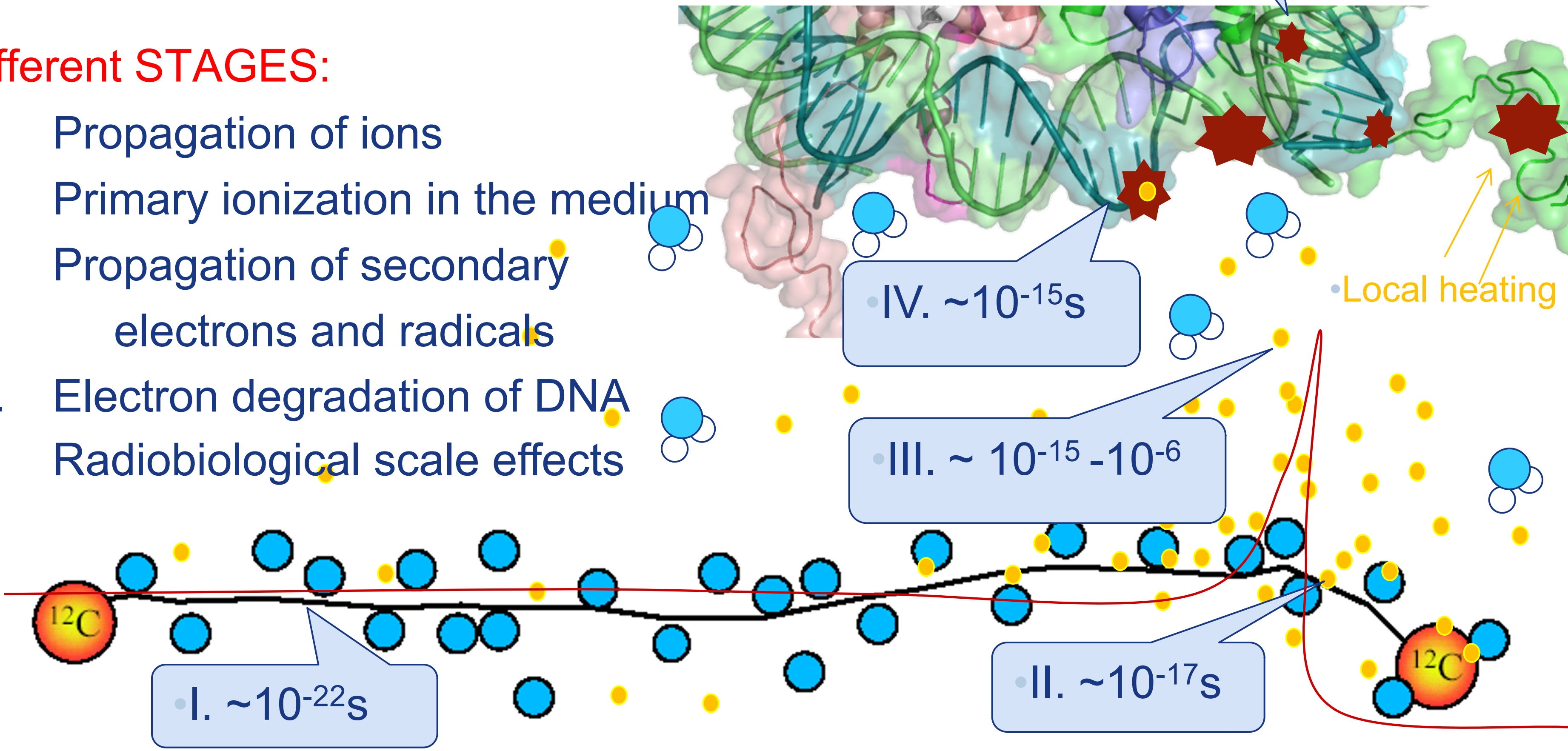
even for ions, 2/3 of resulting biodamage carried by electrons: LOW LET/HIGH LET regimes

Multiscale phenomena

Surdutovich ,Scifoni, Solov'yov et al. PRE (2009), Eur.Phys News (2009), Mut.Res.Rev. (2010)

Different STAGES:

- I. Propagation of ions
- II. Primary ionization in the medium
- III. Propagation of secondary
- electrons and radicals
- IV. Electron degradation of DNA
- V. Radiobiological scale effects



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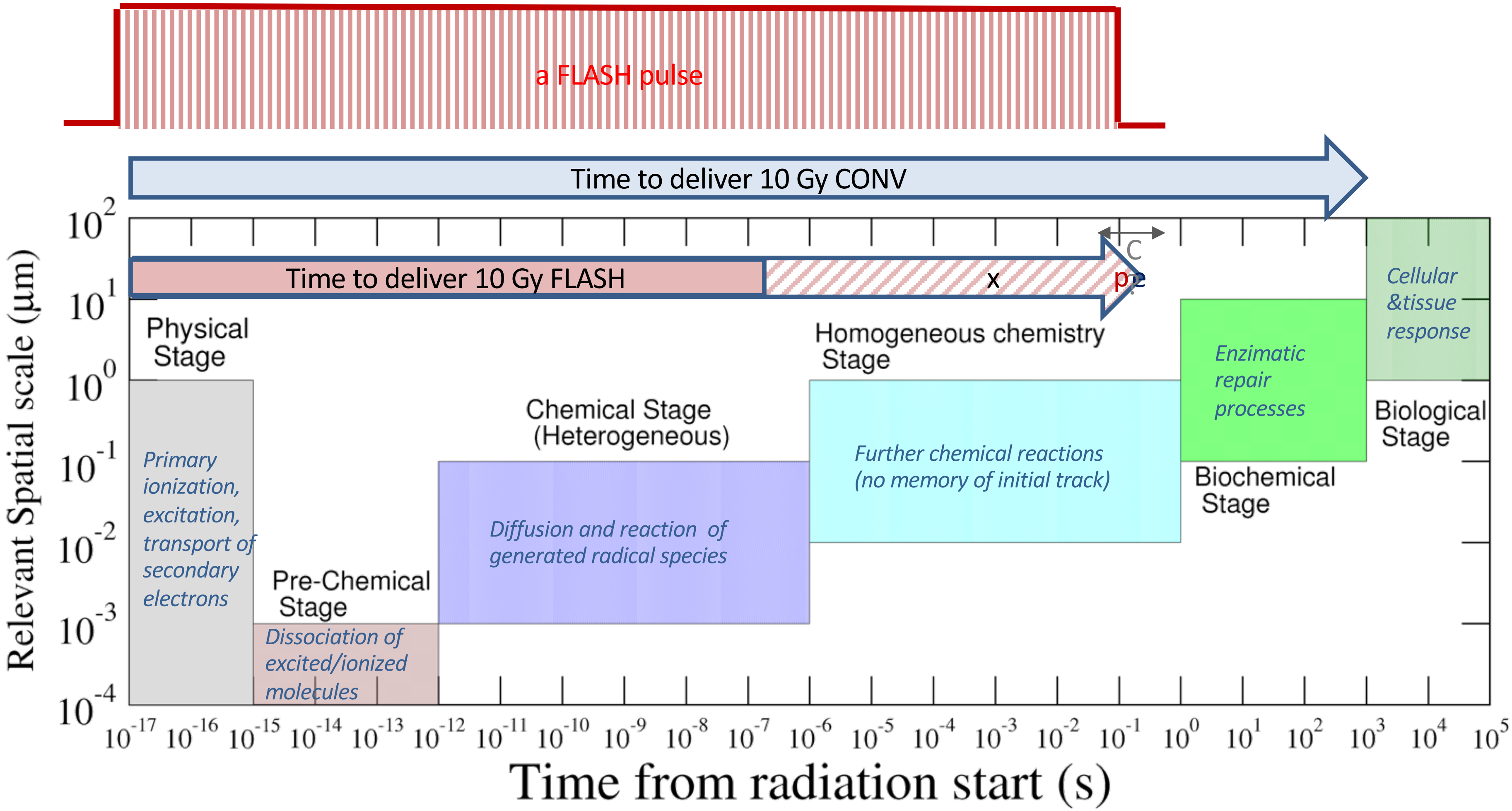
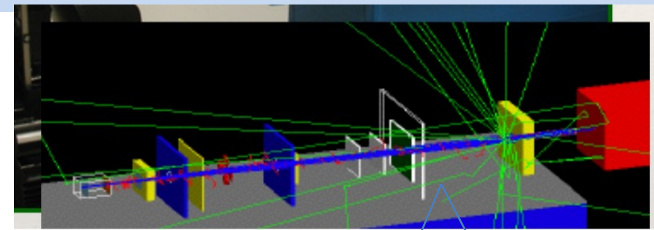
Spatio-temporal Scales of Radiation Damage



Weber, Scifoni, Durante 2021

Monte Carlo Methods for Radiation Research

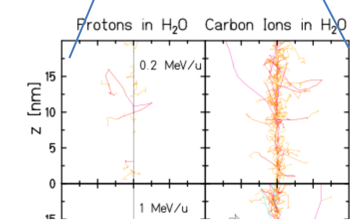


- **MC radiation transport codes**
  =Condensed history codes.

(GEANT4(*), FLUKA, PHITS, SHIELD-HIT, EGS4, MCNPX, ..)

\+ possibility to describe entire irradiation geometry

\- Imposition of thresholds (i.e. G4: e->~900eV)



- **MC Track Structure codes**
  =Event by Event. Stochastic (physics+chemistry)

(PARTRAC, TRAX, GEANT4DNA, TOPASnBIO, RITRACKS…)

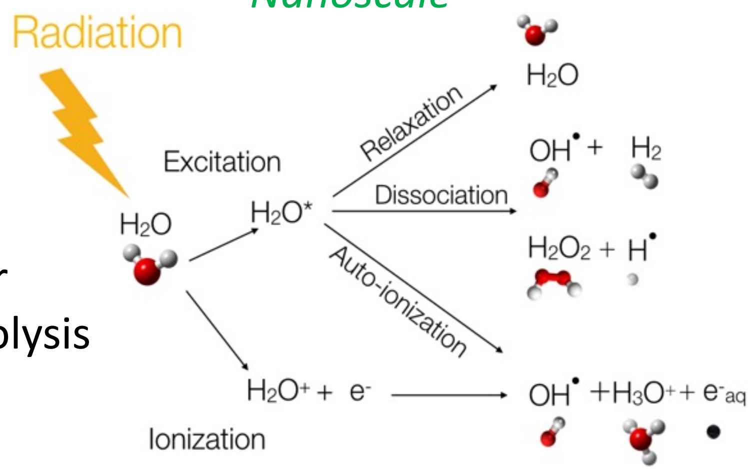
\+ no, or negligible (~1eV) energy/space threshold

\- Limited portion of track describable (normally “track segment”)

(*) with its wrappers TOPAS, GATE, MCHIT

(2-fold) Oxygen and radiation interplay

Nanoscale



Water Radiolysis

- irradiation generates free radicals which react with the dissolved **molecular oxygen** in the target:

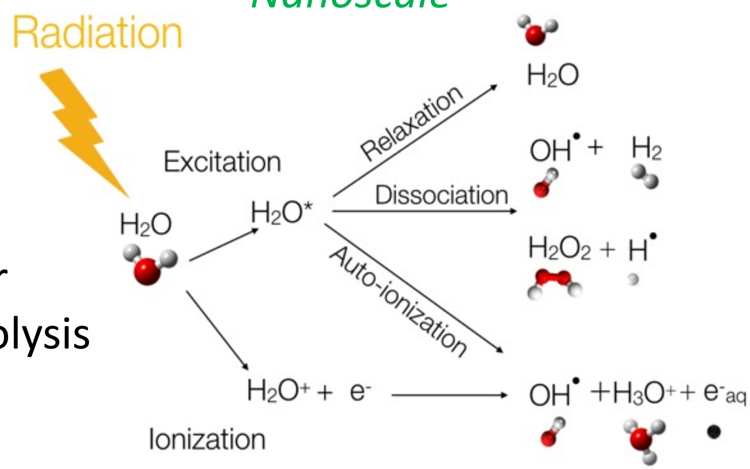
$$e_{aq}^{-} + O_2 \rightarrow O_2^{\bullet -}$$
$$H^{\bullet} + O_2 \rightarrow HO_2^{\bullet}$$

- high doses of radiation gradually remove the O_2 to produce toxic superoxide or perhydroxyl
- shown already in historical experiments (*Weiss et al. 1974*)

(2-fold) Oxygen and radiation interplay

Nanoscale

Water Radiolysis



- irradiation generates free radicals which react with the dissolved **molecular oxygen** in the target:

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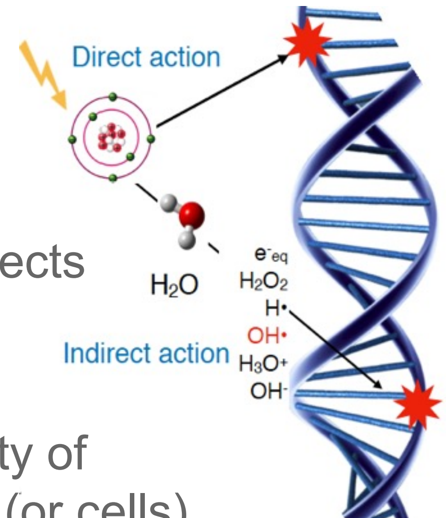
- high doses of radiation gradually remove the O_2 to produce toxic superoxide or perhydroxyl
- shown already in historical experiments (*Weiss et al. 1974*)

Macroscale

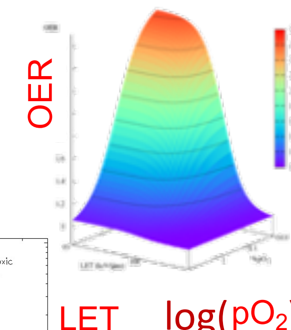
Radiobiological oxygen enhancement

- oxygen is a strong **sensitizer** towards indirect radiation effects

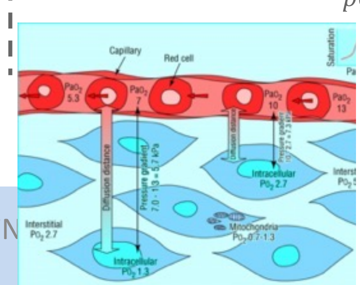


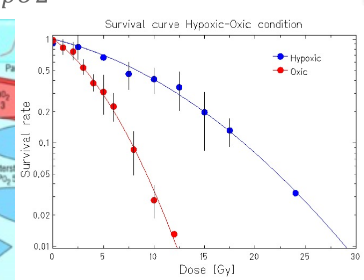
- increase in sensitivity of oxygenated tissues (or cells) compared to hypoxic ones is described by **OER**

$$OER(pO_2) = \frac{D_{anoxia}}{D_{pO2}}\Big|_{same\ effect}$$

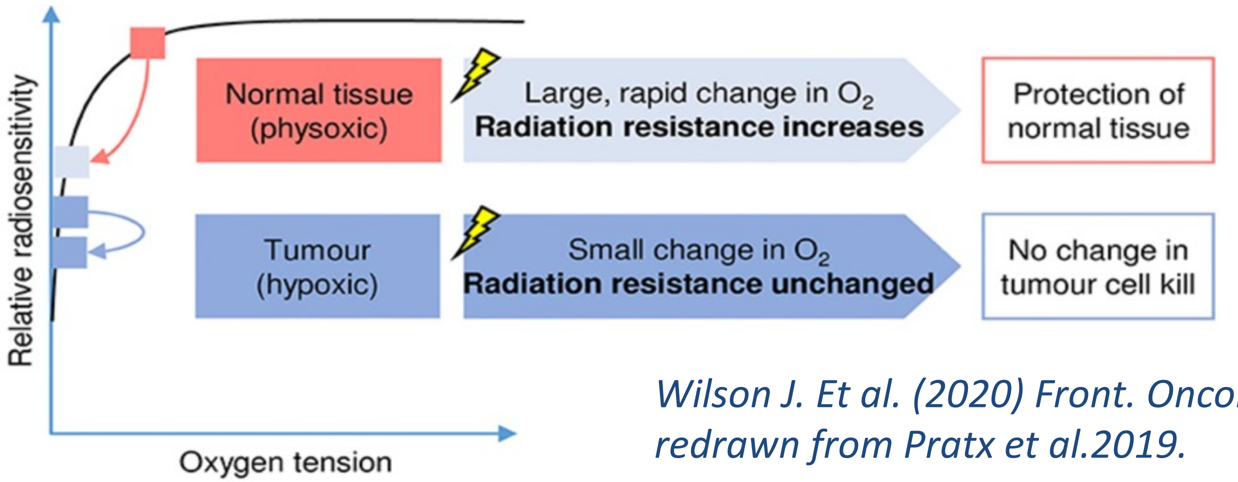


Scifoni et al. 2013

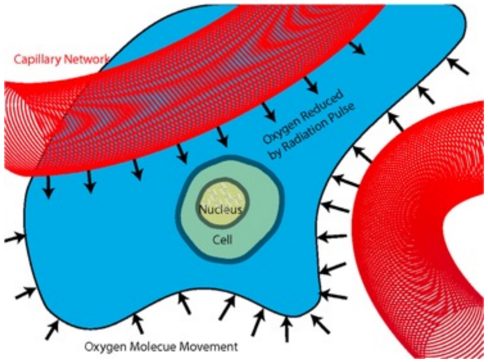




The Oxygen Depletion Hypothesis (ROD)

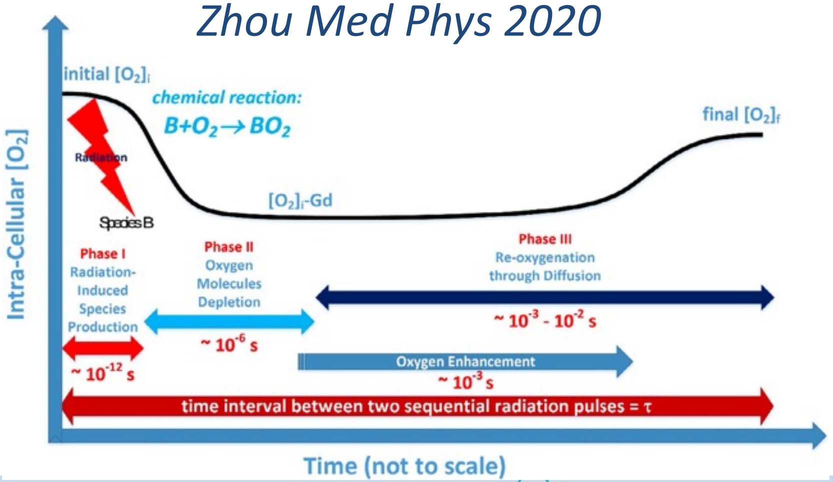


Wilson J. Et al. (2020) Front. Oncol redrawn from Pratx et al.2019.



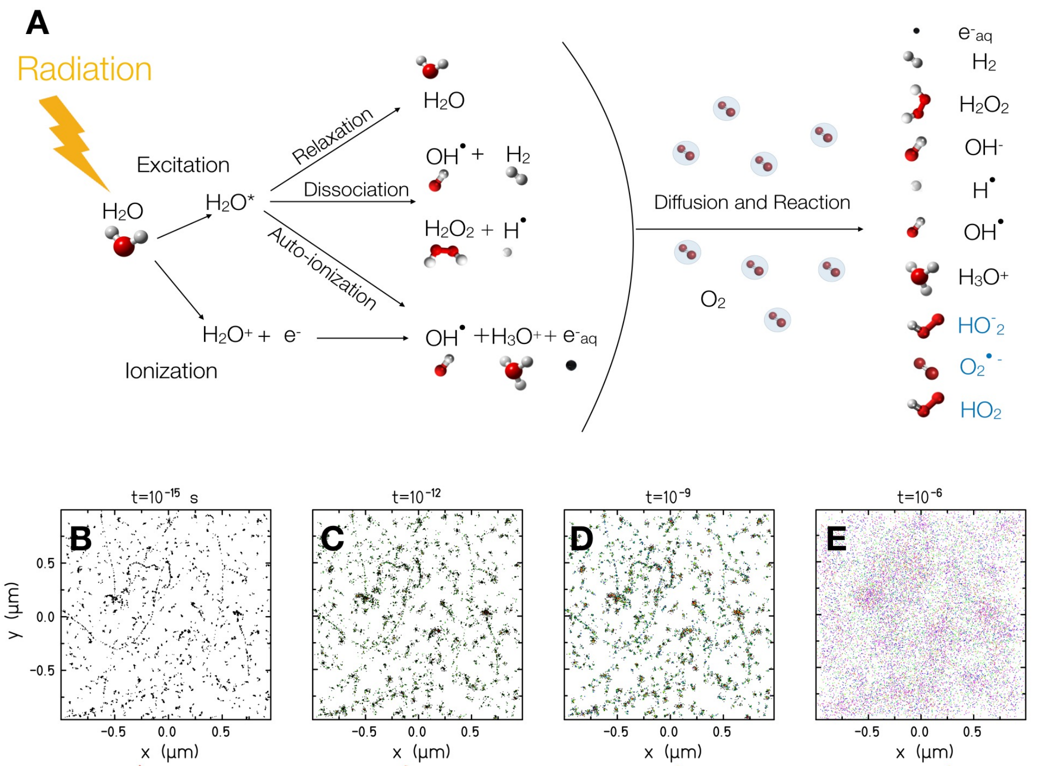
- Ultrahigh dose rate:
  Oxygen consuption too quick for redifussion to restore initial levels
- Transient hypoxia generated -> induced radioresistance
- Already suggested in *Hall&Brenner 1991*

Zhou Med Phys 2020



Methods: the TRAX-CHEM code

A Pisan story..



Boscolo et al. CPL 2018
Boscolo et al. IJMS 2020,
Boscolo et al Radiother Oncol 2021

ELSEVIER
Chemical Physics Letters
journal homepage: www.elsevier.com/locate/cplett

Research paper

TRAX-CHEM: A pre-chemical and chemical stage extension of the particle track structure code TRAX in water targets

D. Boscolo[a], M. Krämer[a,*], M. Durante[b], M.C. Fuss[a], E. Scifoni[a,b]

International Journal of *Molecular Sciences*
MDPI

Article

Impact of Target Oxygenation on the Chemical Track Evolution of Ion and Electron Radiation

Daria Boscolo[1,*], Michael Krämer[1], Martina C. Fuss[1] and Marco Durante[1,2,3] and Emanuele Scifoni[3]

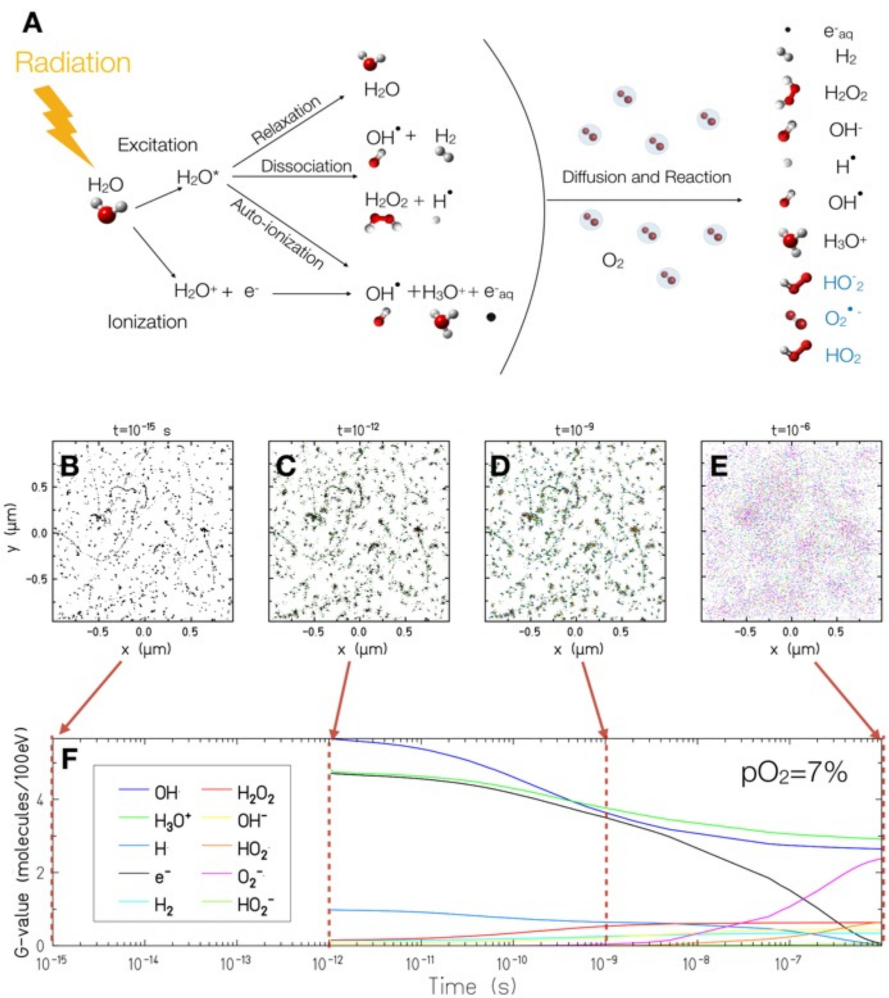
ELSEVIER
Radiotherapy and Oncology
journal homepage: www.thegreenjournal.com

Original Article

May oxygen depletion explain the FLASH effect? A chemical track structure analysis

Daria Boscolo[a], Emanuele Scifoni[b], Marco Durante[a,c,*], Michael Krämer[a], Martina C. Fuss

A radiation chemical approach



Boscolo et al. RO 2021

TRAX-CHEM code + analytical model

Monte Carlo Track structure code for physical and chemical interactions

- Ion / electron scattering processes
- Radical production
- Step-by-step diffusion and reactions in water
- Dissolved oxygen
  - **diffusion** as random jump acc. Einstein-Smoluchowski, $\lambda = \sqrt{6D\Delta t}$
  - **reactions** via reaction radius $a_{AB} = \frac{k_{AB}}{4\pi(D_A + D_B)}$

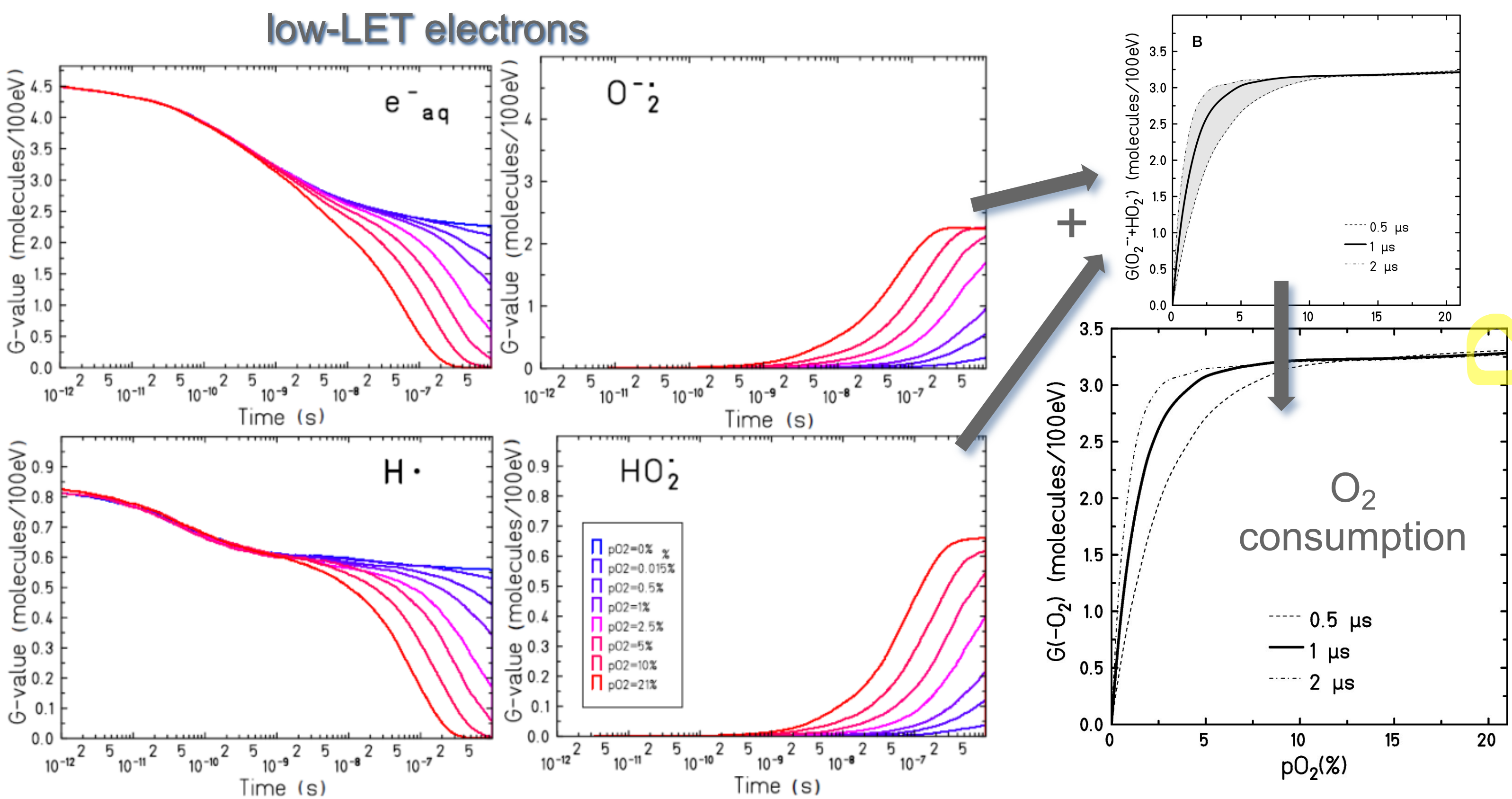
Output: Time-dependent radical yields (G-values) and species localization, O_2 consumption yield

+

- Assumption of short irradiation pulse without rediffusion of O_2 (~ms), represents upper limit
- Instantaneous $[O_2]$ and OER used to compute

$$D_{OER,DYN} = \int \mathrm{OER}\left([O_2](D)\right)\, dD$$

TRAX-CHEM predicted oxygen depletion



3.28 mol./
100eV =
0.33 µM/Gy

Boscolo et al. IJMS 2020

Boscolo et al. Radiother Oncol 2021

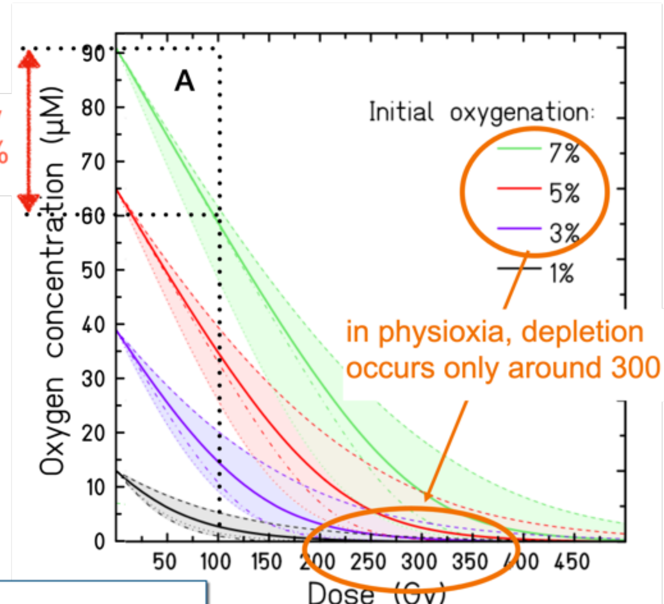
Is ROD realistic?

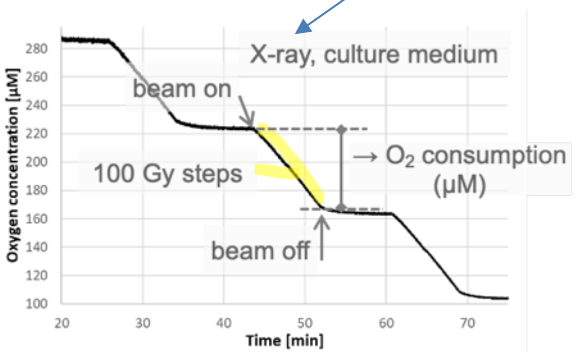
Year	Lead Author		O2 depletion per 100Gy
1949	Day M.J.	Exp	3,3 %
1969	Evans N.T.S.	Exp	2,6 %
1974	Weiss H.	Exp	3,3 %
1975	Ling C.	Model.	2,6 %
1986	Michaels H.B.	Exp	3.3%
2019	Pratx	Model.	5.5%
2020	Petersson	Model.	5% - 10%
2020	Zhou S.	Model.	2.6%
2020	Hu A.	Model.	3.7%
2020	Labarbe R.	Model.	2.2%
2020	Vozenin	Exp	2.1% - 2,7%
2020	Boscolo	Model.	2.4%
2020	Boscolo	Exp	2,3% - 2,7%

Adapted from M. C. Vozenin RRS 2020

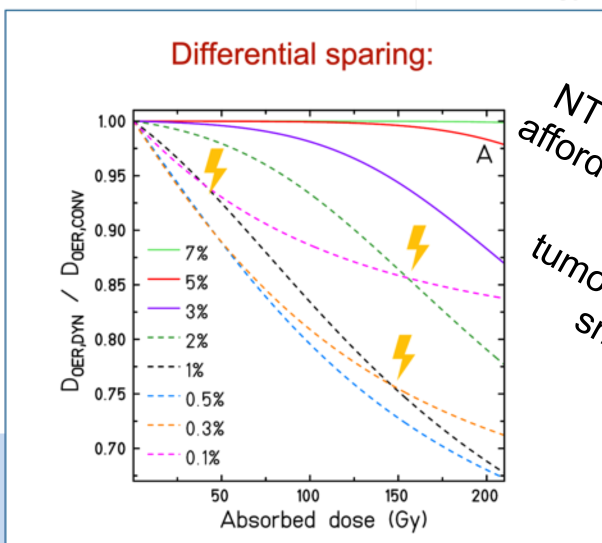
Boscolo et al Radiother Oncol 2021

In 100Gy
pO_2~2.4%



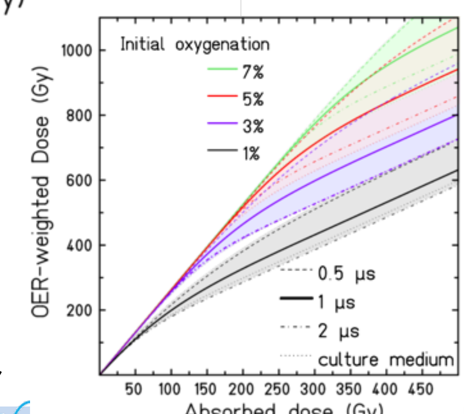


Consistent with Measurements with p @ TIFPA



NT oxygenations
afford **less sparing!**

tumor oxygenations:
small effect



Analyis on the exp data

Boscolo et al Radiother Oncol 2021

OER impact for the published in vivo results

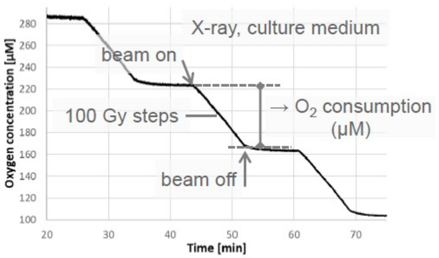
	FLASH			
Experiment	Dose (Gy)[a]	$pO_{2,ini}$ (%)[b]	$pO_{2,fin}$ (%)	$D_{OER,DYN}$ (% of conv.)
Mouse whole brain (*14*)	10	3.4	3.13	100
Minipig skin (13)	31	5.3	4.39	100
Cat, healthy skin/ mucosa (13)	33	5.9	4.91	100
Cat squameous cell carcinoma (13)	33	1.9	1.27	98.5
Mouse lung (*12*)	17	5.6	5.09	100
Lung tumor (*12*)	17	2.1	1.74	99.3
Human patient, healthy skin (*15*)	15	5.3	4.86	100
Human skin lymphoma (*15*)	15	1.5	1.24	99.1

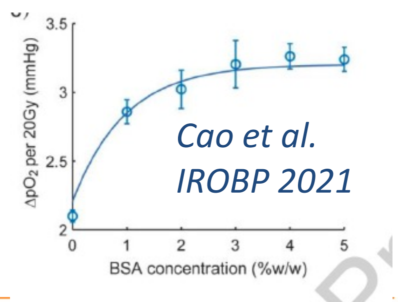
O depletion Measurements

Different Oxygen sensors tested:
OXYLITE, OXYPHORE, PRESENS, TROXSP5

Impact of Medium

Within a +50% effect





Cao et al. IROBP 2021

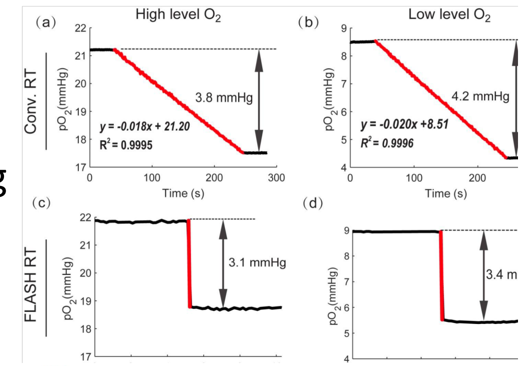
radiation type	oxygen consumption [µM/Gy]			
	water	PBS buffer	Ham's F12	Matrigel
X-ray	0.30±0.03	0.31±0.05	0.49±0.1	0.34±0.03
clinical linac	0.37±0.02	0.35±0.02	0.44±0.1	- - -

M.Fuss , RRS 2020, in prep.

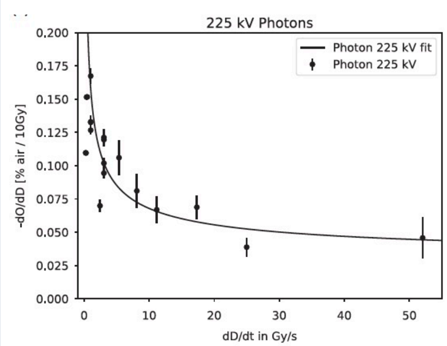
Impact of Dose Rate

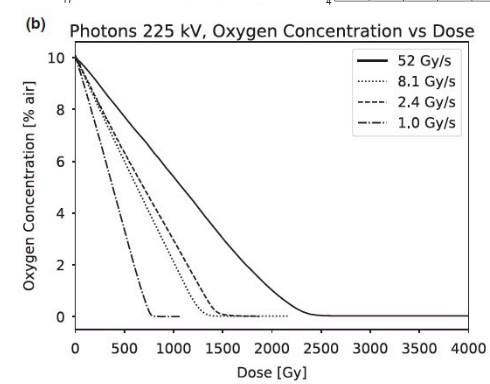
FLASH appears depleting **LESS** then CONV…

($e_{aq}+e_{aq}$?)_



Cao et al. IJROBP 2021





Jansen et al. Med Phys 2021

See J.Jansen Talk

Trento Institute for Fundamental Physics and Applications

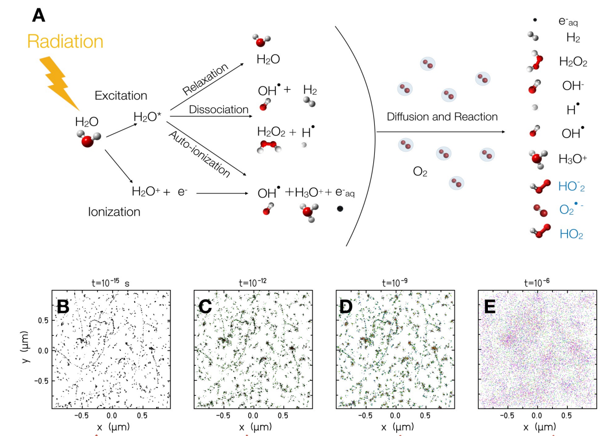
Some facts/hypothesis

- Lower production of H_2O_2/contribution of O_2
  - (Montay-Gruel et al, PNAS, 2019; Adrian et al, BJR, 2019)
- Lower level of persistent DNA damage and senescent cells
  - (Fouillade et al, CCR, 2019)
- Metabolism including redox
  - (Spitz et al, RO, 2019)
- Inflammation/Immune system (increasing popularity)
  - (Favaudon et al, STM 2014; Montay-Gruel et al, PNAS, 2019)
- Signaling pathways/Stem cells protection
  - (Montay-Gruel et al, RO, 2017)

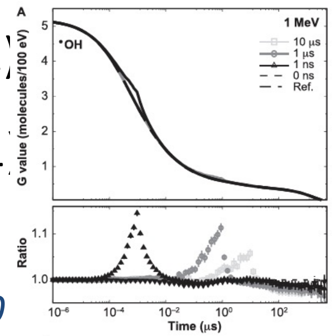
Tools -Codes for exploring FLASH Chemistry

Heterogeneous stage (and slightly beyond…)

- TRAX-CHEM (Boscolo et al. 2020)
- TOPASnBIO (Ramos et al. 2020)
- gMicroMC (Lai et al. 2021)
- Geant4-DNA (Tran et al. 2021)
- IONLYS-IRT (Alanazi et al. 2021
- NASIC (Zhou et al.2021)



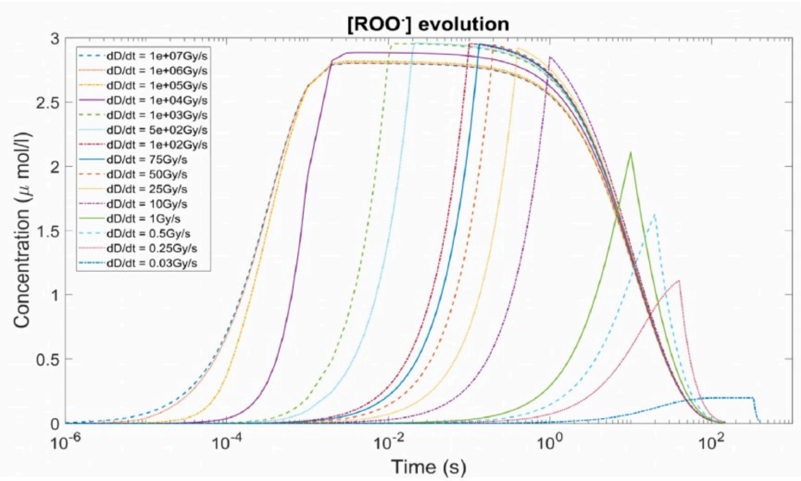
Boscolo et al. 2021 u.r.

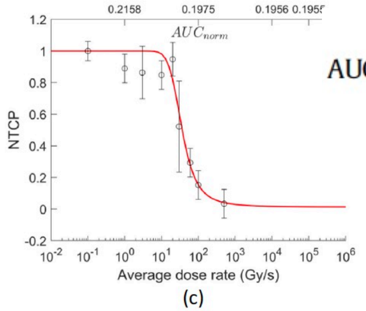


Ramos et al. RR 2020

$$e^-_{aq} + O_2 \longrightarrow O_2^{\bullet -}$$
$$H^\bullet + O_2 \longrightarrow HO_2^\bullet$$

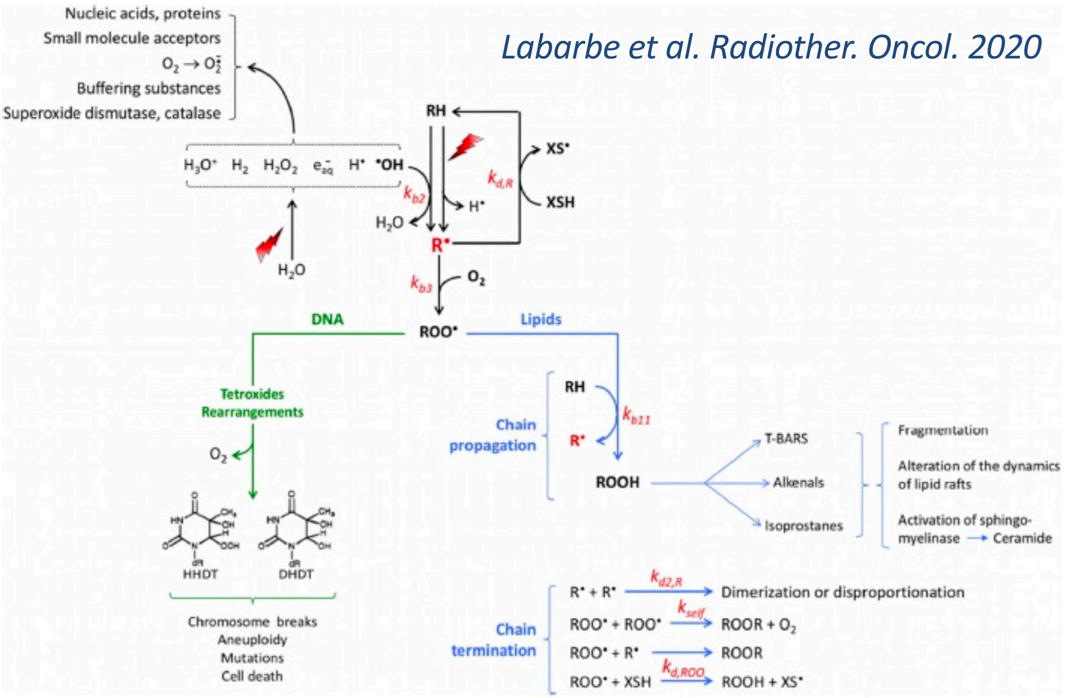
Radical recombination hypothesis





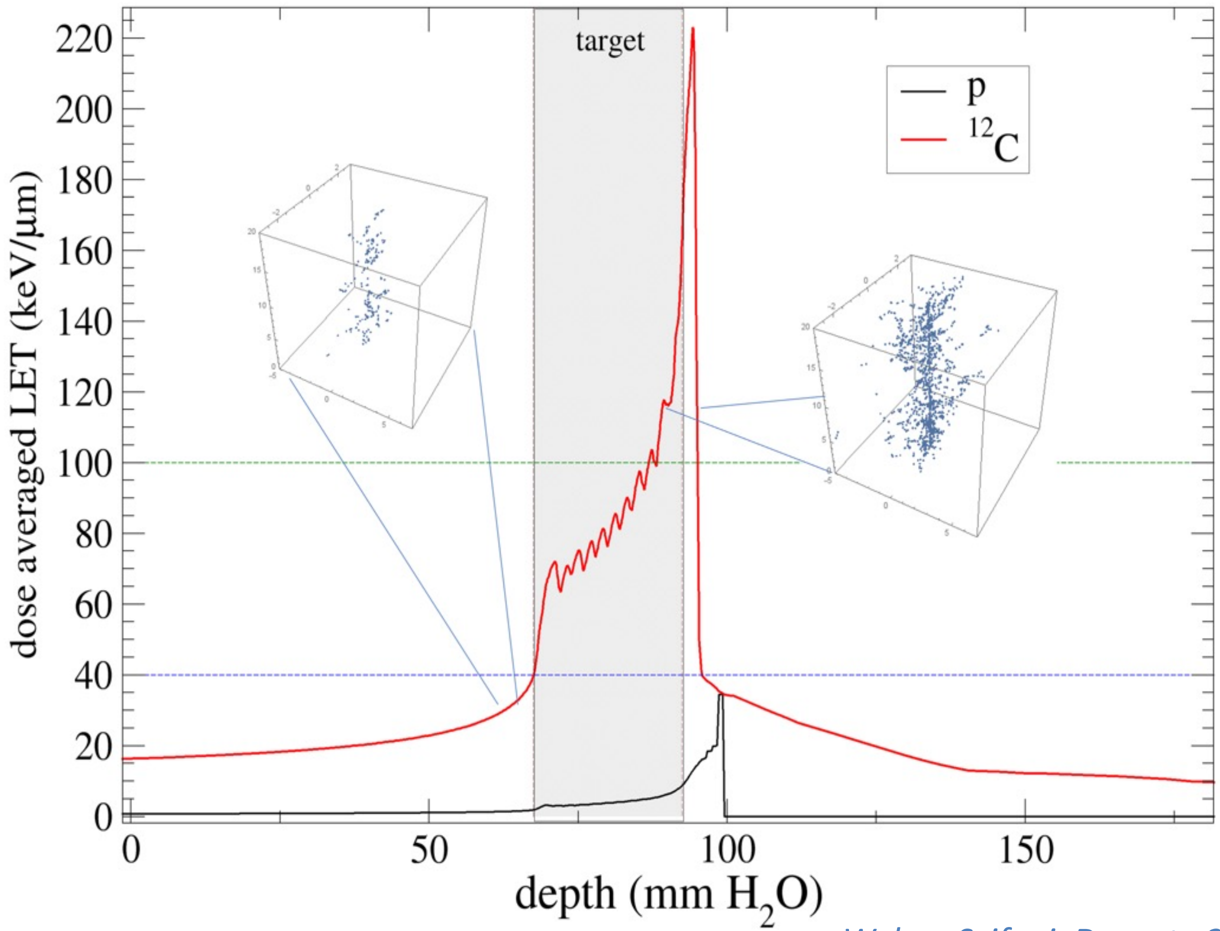
$$AUC_{ROO} = \int_0^{T_{sim}} [ROO\cdot](t) \cdot dt$$

Labarbe et al. Radiother. Oncol. 2020



$$NTCP_{model}\left(D,\frac{dD}{dt}\right) = 1/\left(1+exp\left(-\gamma\cdot\left(AUC_{norm}\left(D,\frac{dD}{dt}\right)-AUC_{50}\right)\right)\right)$$

Impact of LET?

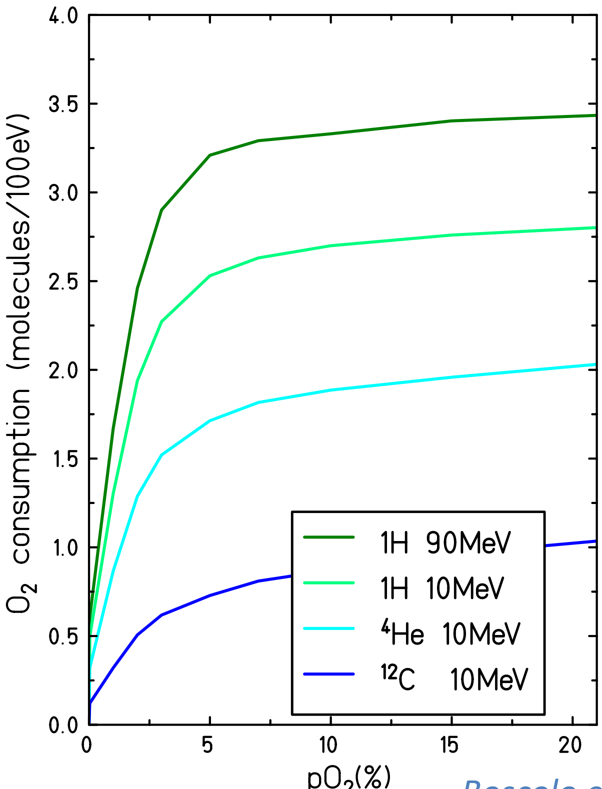


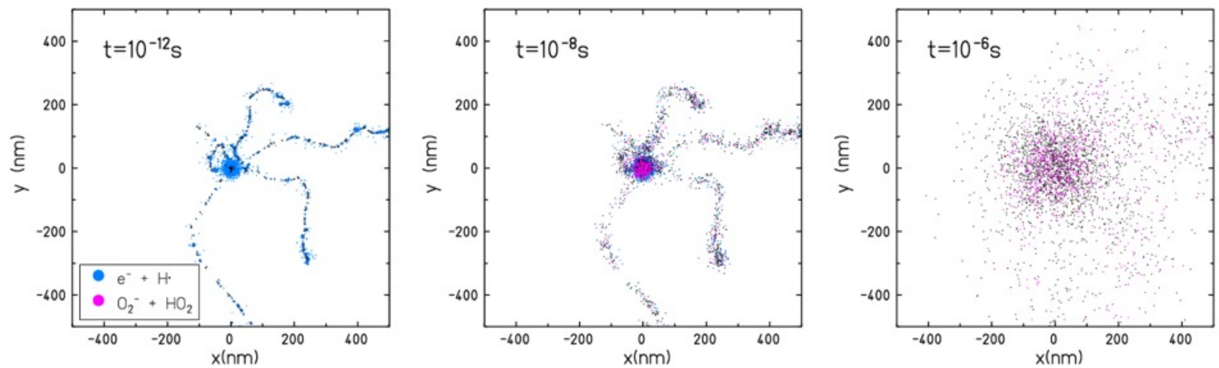
Weber, Scifoni, Durante 2021

O depletion at different LET

Low LET
→ primary radicals sparsely dispersed
→ prominent reaction with O2

High LET
→ track recombination of radicals
(track density effect)
→ less reactions with O2

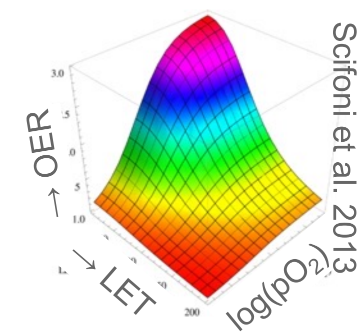




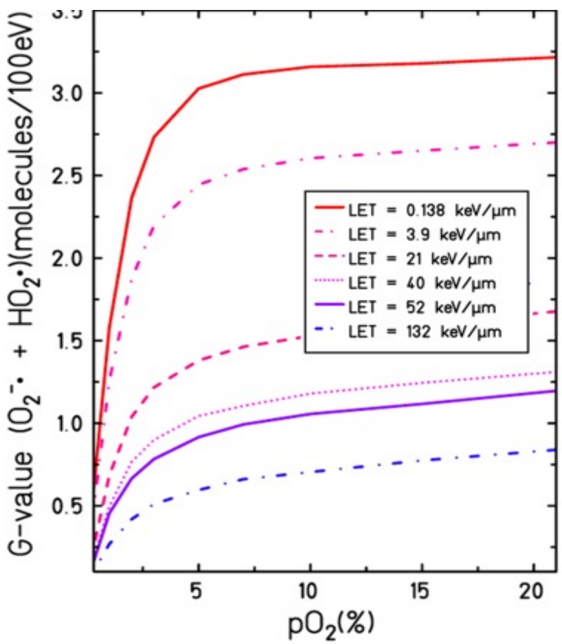
^{12}C 10MeV/u (160 keV/μm)

Boscolo et al. Int J. Mol. Sci 2020

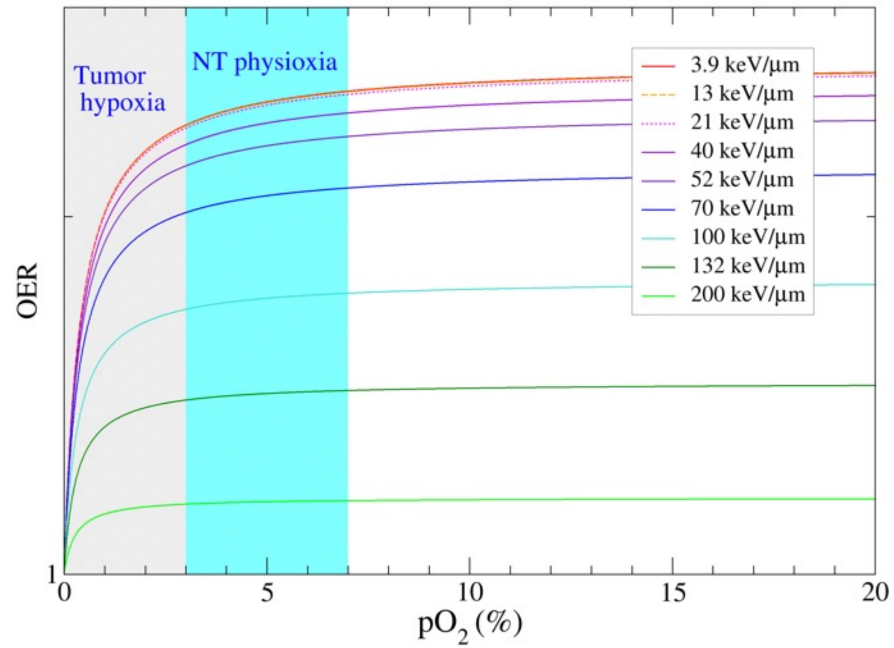
Sensitivity on hypoxia even
Smaller at high LET



LET impact on Radical yeld and depletion



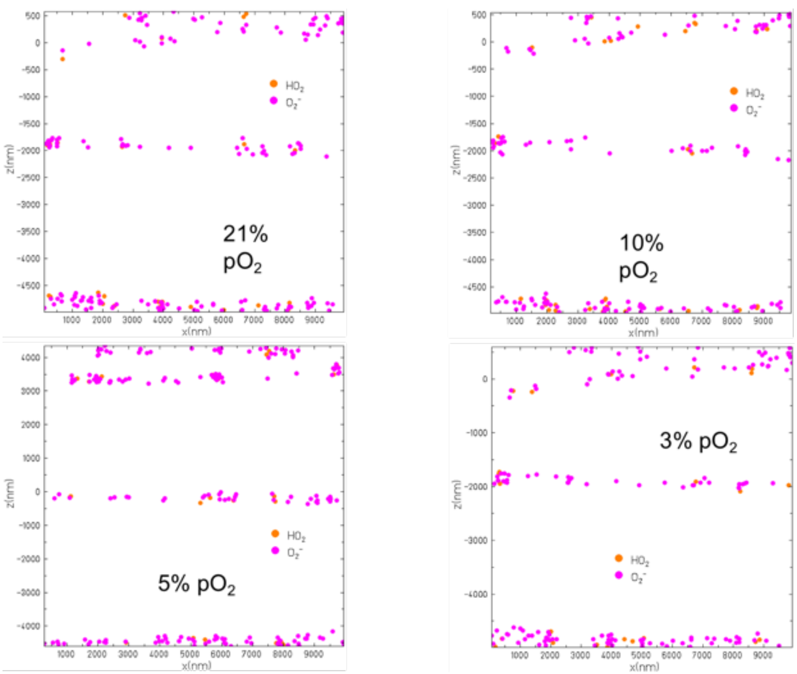
Boscolo et al. 2020



Weber, Scifoni, Durante 2021

Track structure effects at different LET

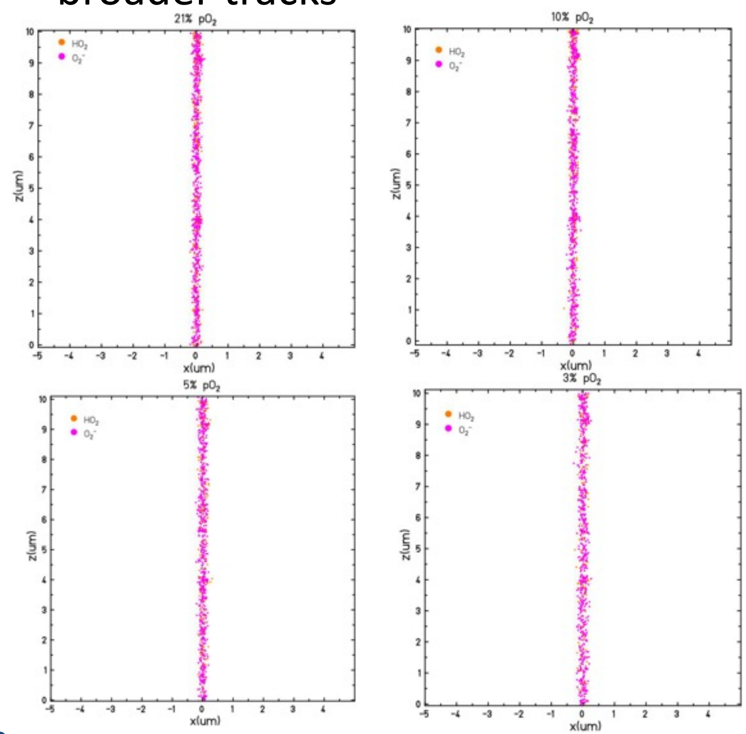
No Intertrack effect possible in the timescale of the given dose ranges,
i.e. for **1MeV electrons** (300Gy/s in 1μs) in "cellular dimensions"



Prel. calcs courtesy of M.Fuss and D. Boscolo

See also *Watanabe 2001 Radiat Phys Chem*

For **protons 10 MeV**, (4.5 keV/μm) even more difficult intertrack, considering 1 traversal/25 cells. Denser but not broader tracks

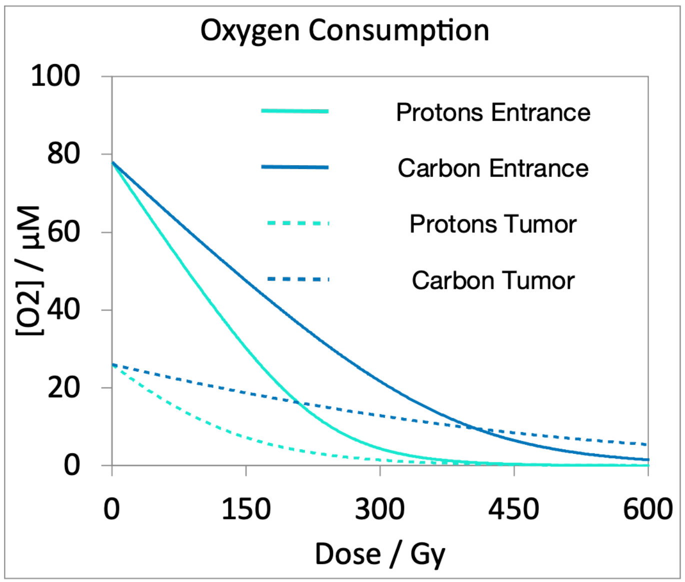


For **Carbon 10 MeV, 1/1000 traversal**

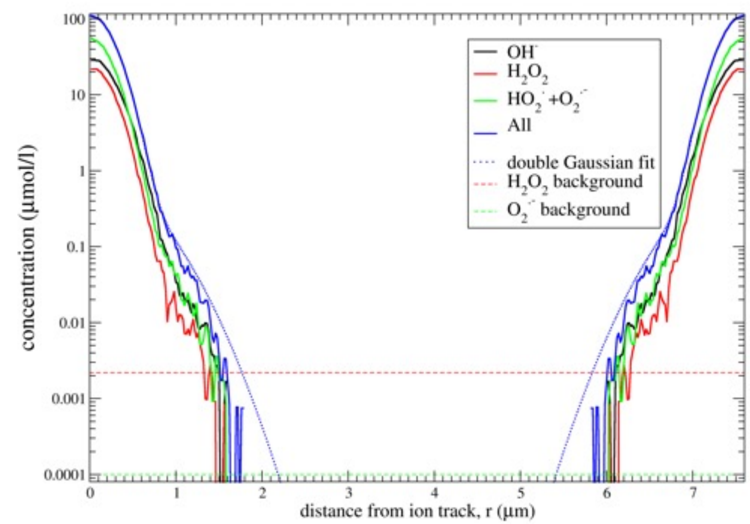
Track structure effects at different LET

For several mechanisms is expectable a strongly reduced FLASH effect

Less Oxygen depletion



Less intertrack probability



Scifoni et al. PTCOG 2021

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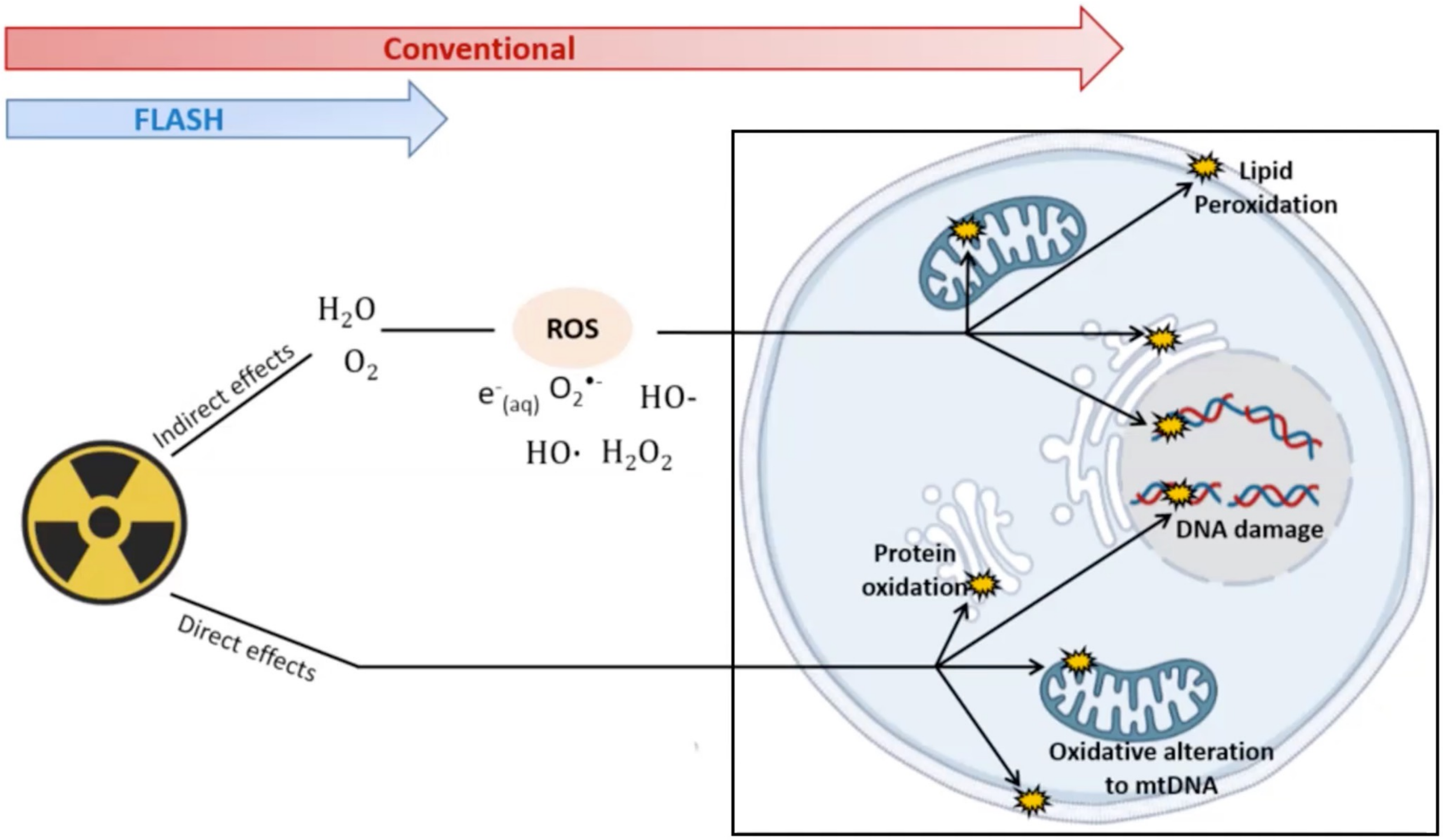
Further Mechanistic routes



Kacem et al., IJRB, 2021, in press

TD-DNA damage modeling in FLASH conditions

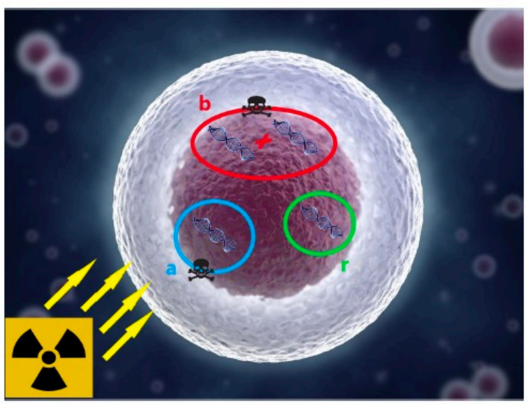
- Time dependent implementation of GSM^2 a Microdosimetry based model to generalize the DNA damage repair kinetics (DDRK)) including the dependence on the dose-rate time structure, and chemical yields *(Cordoni et al FRPT 2021)*

RADIATION RESEARCH 197, 000–000 (2022)
0033-7587/22 $15.00

DOI: 10.1667/RADE-21-00098.1

Cell Survival Computation via the Generalized Stochastic Microdosimetric Model (GSM2); Part I: The Theoretical Framework

Francesco G. Cordoni,[a,b] Marta Missiaggia,[b,c,1] Emanuele Scifoni[b] and Chiara La Tessa[b,c,2]



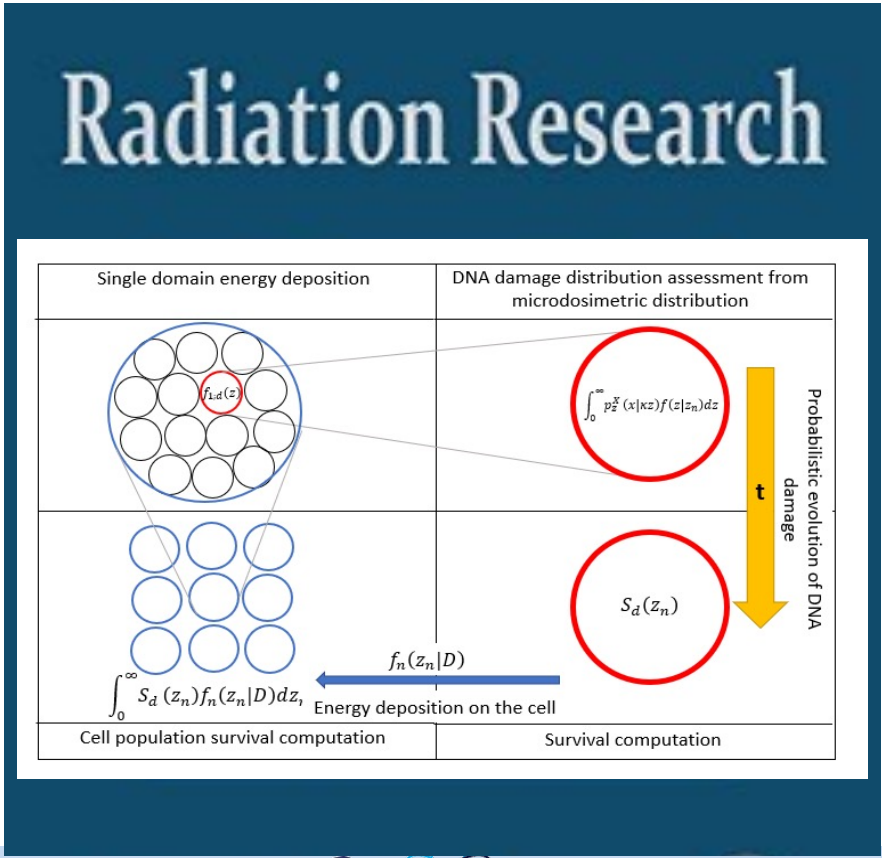
X and Y are random variables

X : number sub-lethal lesions

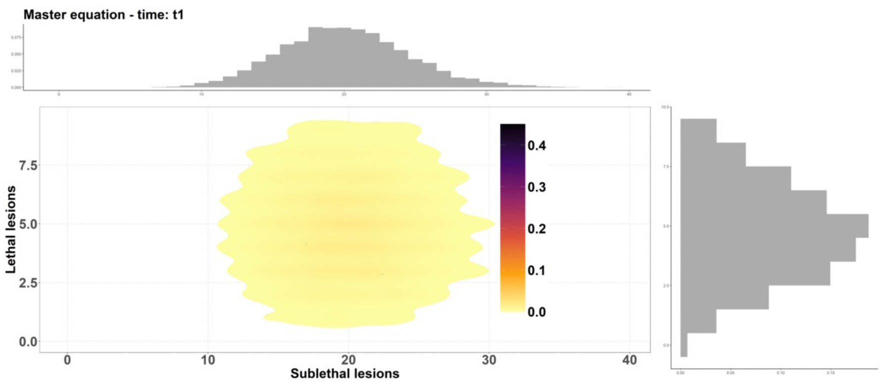
Y : number lethal lesions

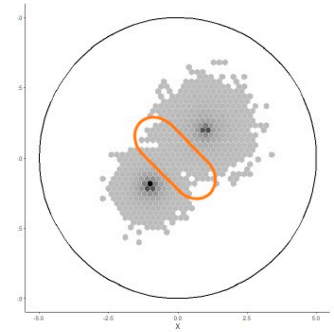
$$\begin{cases} X \xrightarrow{r\,:\,\text{repair}} \emptyset \\ X \xrightarrow{a\,:\,\text{death}} Y \\ X + X \xrightarrow{b\,:\,\text{double death}} Y \\ X \xrightarrow{\dot{d}\,:\,\text{dose rate}} X + Z_X \\ Y \xrightarrow{\dot{d}\,:\,\text{dose rate}} Y + Z_Y \end{cases}$$

Z_X and Z_Y are random variables that depend on microdosimetric distribution



TD-DNA damage modeling in FLASH conditions





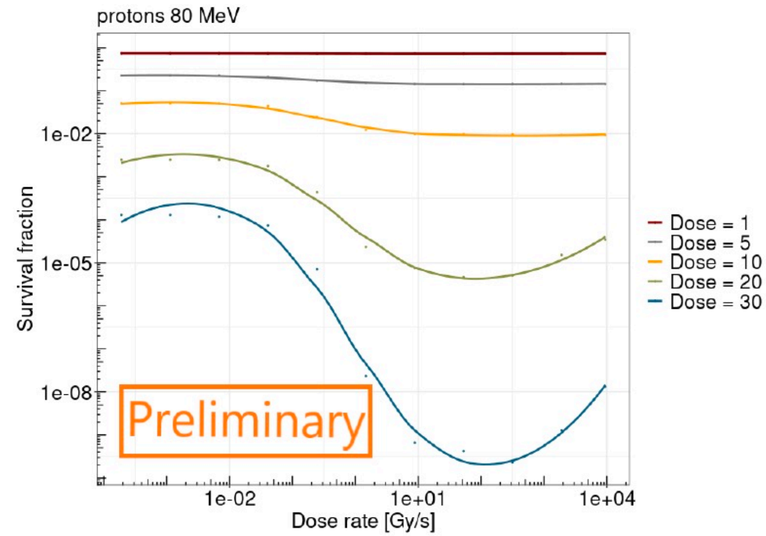
In the track overlap region the presence of free radicals reduces the yield of DNA damages induced by radiation

F.Cordoni PRPT 2021

$$\begin{cases} Y(t) = Z_Y([\xi(t)])\mathcal{P}^d\left(\int_0^t \dot{d}\, ds\right), \\ X(t) = Z_X([\xi(t)])\mathcal{P}^d\left(\int_0^t \dot{d}\, ds\right), \\ Z_X([\xi(t)]) \sim \int_0^\infty e^{-\kappa([\xi(t)])z}\frac{(\kappa([\xi(t)])z)^x}{x!} f_{1;d}(z)dz\,. \end{cases}$$

$$\begin{cases} Y(t) = Y_0 + \mathcal{P}^a\left(\int_0^t aX(s)ds\right) + \mathcal{P}^b\left(\int_0^t bX(s)(X(s)-1)ds\right) + \\ \quad + Z_Y(\xi(t))\mathcal{P}^d\left(\int_0^t \dot{d}\, ds\right) \\ X(t) = X_0 - \mathcal{P}^a\left(\int_0^t aX(s)ds\right) - \mathcal{P}^r\left(\int_0^t rX(s)ds\right) + \\ \quad -2\mathcal{P}^b\left(\int_0^t bX(s)(X(s)-1)ds\right) + Z_X(\xi(t))\mathcal{P}^d\left(\int_0^t \dot{d}\, ds\right), \\ \hline \frac{d}{dt}\left[e^-_{aq}\right](t) = f_{e^-_{aq}}(\xi(t)) + G_e\rho\dot{z}\,, \\ \frac{d}{dt}[O_2](t) = f_{O_2}(\xi(t))\,, \\ \frac{d}{dt}C_{H_2O_2}(t) = f_{H_2O_2}(\xi(t)) + G_{H_2O_2}\rho\dot{z}\,, \\ \frac{d}{dt}C_{OH\bullet}(t) = f_{OH\bullet}(\xi(t)) + G_{OH\bullet}\rho\dot{z}\,, \\ \frac{d}{dt}[H^\bullet](t) = f_{e^-_{aq}}(\xi(t)) + G_{H\bullet}\rho\dot{z}\,, \\ \frac{d}{dt}[H_2](t) = f_{e^-_{aq}}(\xi(t)) + G_{H_2}\rho\dot{z}\,, \\ \frac{d}{dt}C_{O_2^\bullet-}(t) = f_{O_2^\bullet-}(\xi(t))\,, \\ \frac{d}{dt}[R^\bullet](t) = f_{R\bullet}(\xi(t)) + G_{R\bullet}\rho\dot{z}\,, \\ \frac{d}{dt}[ROO^\bullet](t) = f_{ROO\bullet}(\xi(t))\,, \\ \xi = \left(\left[e^-_{aq}\right], [O_2], C_{H_2O_2}, C_{OH\bullet}, [H^\bullet], [H_2], C_{O_2^\bullet-}, [R^\bullet], [ROO^\bullet]\right). \end{cases}$$

Reaction table from Labarbe 2020



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Summary 1- Radiobiology

- FLASH radiotherapy proposes the use of ultrafast dose rate (>40 Gy/s) to achieve differential sparing of NT as well as maintaining effectiveness on the Tumor
- Increasing preclinical evidence of both **NT sparing** and unchanged **tumor control** has been collected
- The parameters for getting the effect include **intrapulse dose rate**, **overall dose rate**, **absolute dose**, with a minimum and maximum value for the latter
- Radiobiological mechanism is far to be understood: It is clear that oxygenation should play a role, but chemical-physical stage arguments alone are unable to now to explain the effect
- Implementation of FLASH conditions on literature examples doesn't support the hypothesis of a possible differential effect of Local Oxygen Depletion between target and normal tissue, at the doses used, rather pointing eventually to a possible inverse effect. The accounting of more complex mechanisms like Fenton pathway and ROO., redox Chemistry appears essential
- High LET radiation should imply even larger doses, thus is expected to be less efficient.

- OK, we don't understand why it works but it really seems to work:
  Thus, anyway, can this go to the clinic?

Dosimetry

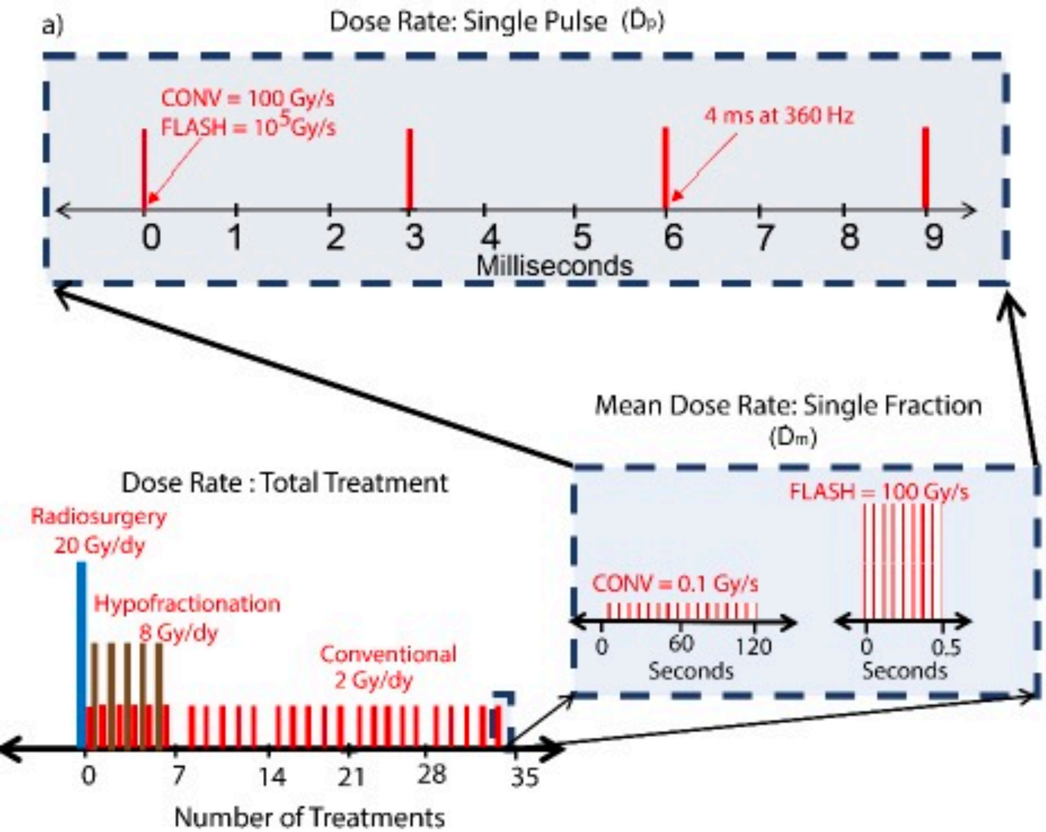
If it work, can we control it?

(...and btw, can we trust experiments?)

The dosimetric challenge

- Using ultra fast dose rate, implies a 2 fold need to control and measure the dose at unconventional levels:
  - In order to assure the correctness of experiment results (accuracy $<5\%$)
  - In order to potentially translate to the clinic $<1\%$

Multilevel Dose time structure



b)

Beam Characteristics	CONV	FLASH
Dose Per Pulse D_p	~0.4 mGy	~1 Gy
Dose Rate: Single Pulse $\dot{D}_p$	~100 Gy/s	~10^5 Gy/s
Mean Dose Rate: Single Fraction $\dot{D}_m$	~0.1 Gy/s	~ 100 Gy/s
Total Treatment Time T	~days/minutes	< 500 ms

Fig. 3) a) Dose rate schemes in radiation therapy indicating different interpretations of dose-rate. b) Typical temporal beam characteristics for conventional (CONV) and FLASH-RT using electrons.

Ashraf Front Oncol 2020

Charge based dosimeters

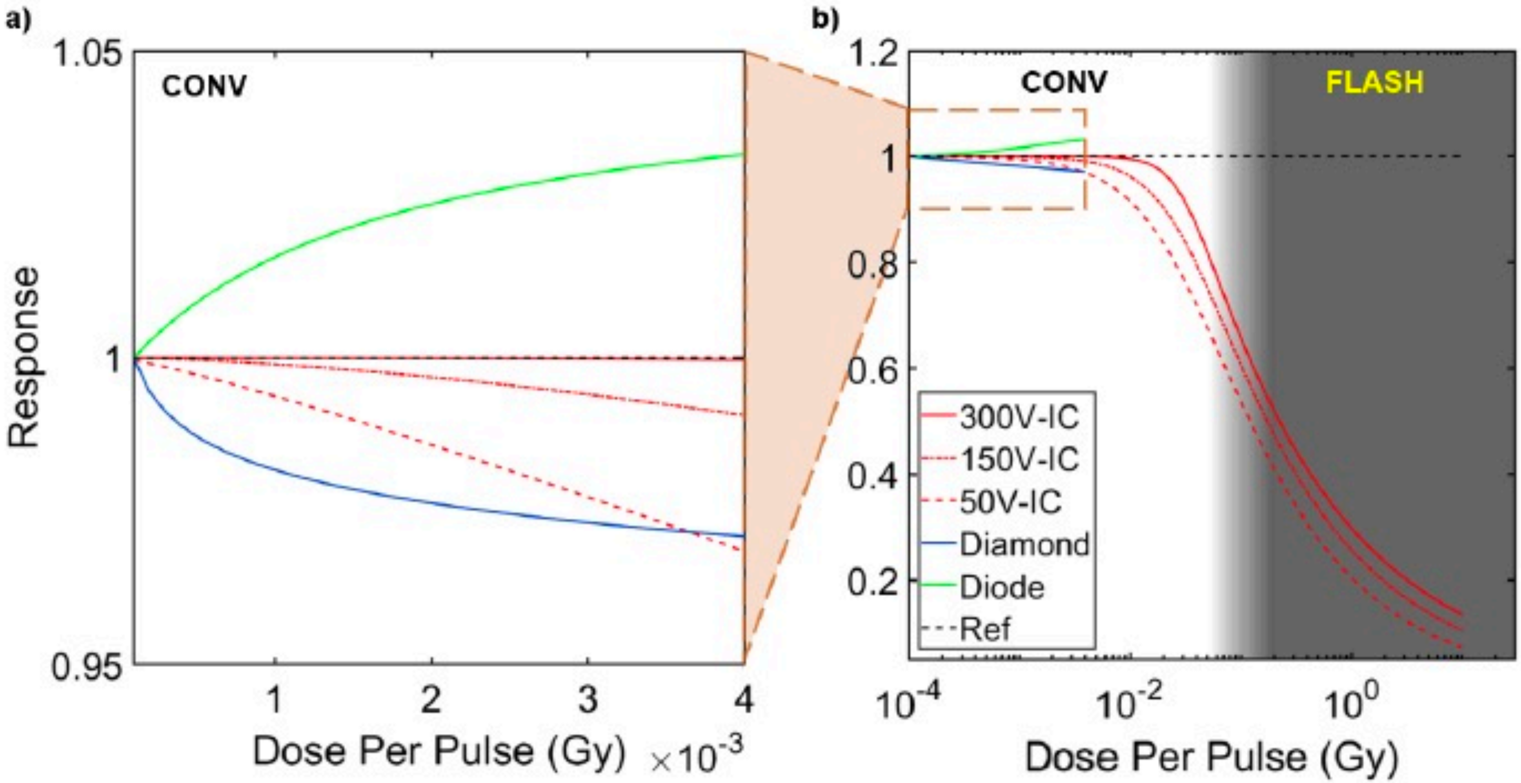
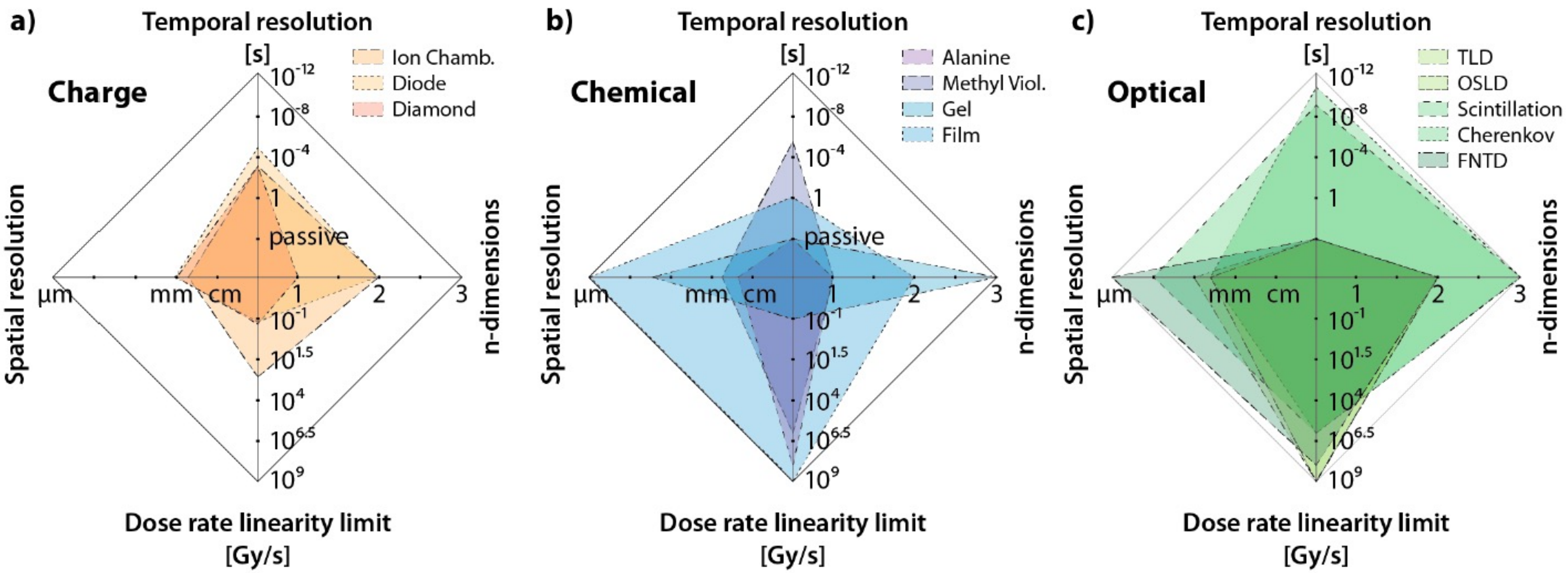


Fig 5) Model for charged based detector response based on Advanced Markus Chamber IC, PTW microDiamond, and Isorad Gold (n-type) diode detectors. Dose per pulse dependency of detector response are shown for a) conventional beams and b) FLASH beams. Advanced Markus Chamber IC response (charge collection efficiency) was calculated for three different bias voltages and the only charge-based detector to be tested in FLASH dose rates[41]. Model for diamond detector response (charge collection efficiency) and diode detector response (sensitivity) were only tested at conventional dose rates[42,43].

Ashraf Front Oncol 2020

Different types of dosimeters



Ashraf Front Oncol 2020

Dose Delivery (and Planning?)

If It work and we can control it can we give it to patients?

Many slldes courtesy from Marco Schwarz

FLASH dose delivery?

- Main task of radiotherapy
  - > dose delivery and dose shaping,

  Exploiting the available degrees of freedom

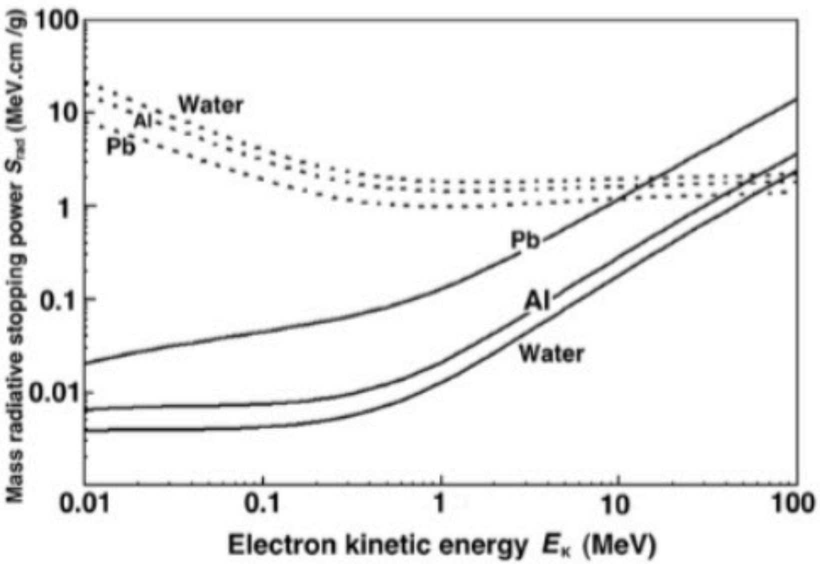
- Are 40 Gy/s achievable with current machines?
- If yes, are there still any degrees of freedom available for treatment planning?

- Different solutions for different **Radiation types**

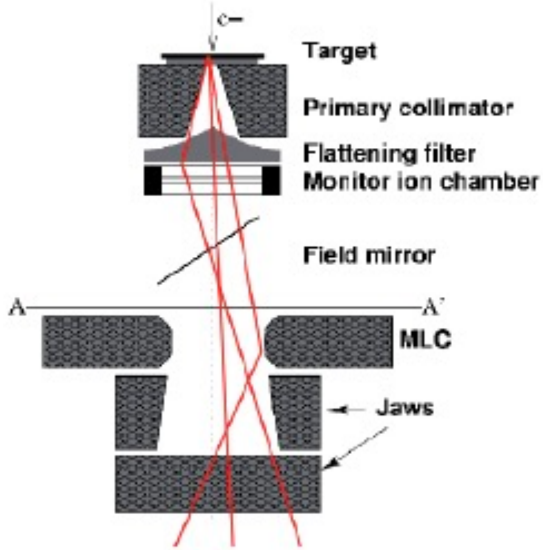
X-rays

Max dose rate with current FFF linacs:

Roughly 20Gy/min
(*roughly* two orders of magnitude lower)



Mass radiative stopping power = solid line
Mass collision stopping power = dotted line



Flash with photons:
Not even attempted with current equipment (which is used to treat the vast majority of RT patients)

Electrons (6-20 MeV)

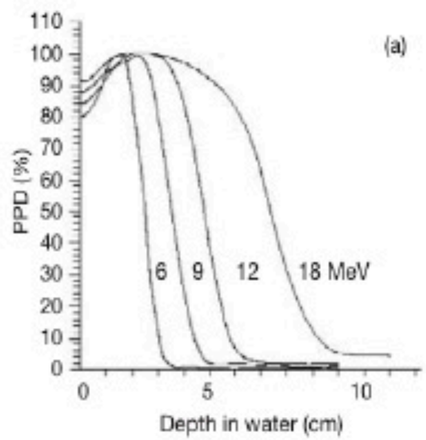
Good news

Bourhis
R&O 2020

5.6 MeV electrons
15Gy in 90ms (!)

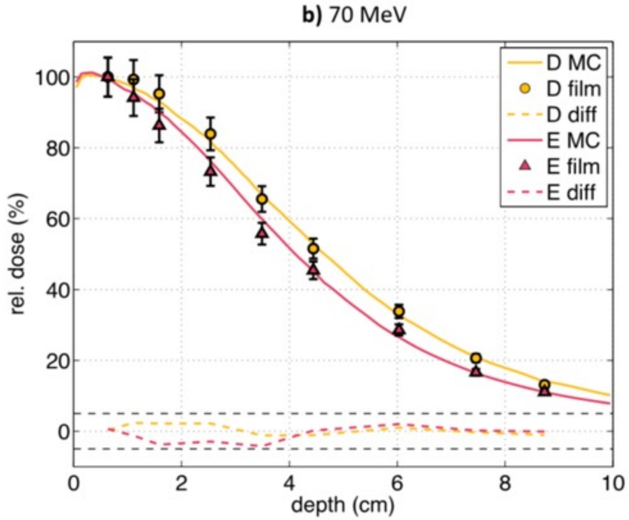
Less good news

Low energy electrons can be used only for superficial lesions & distal OAR

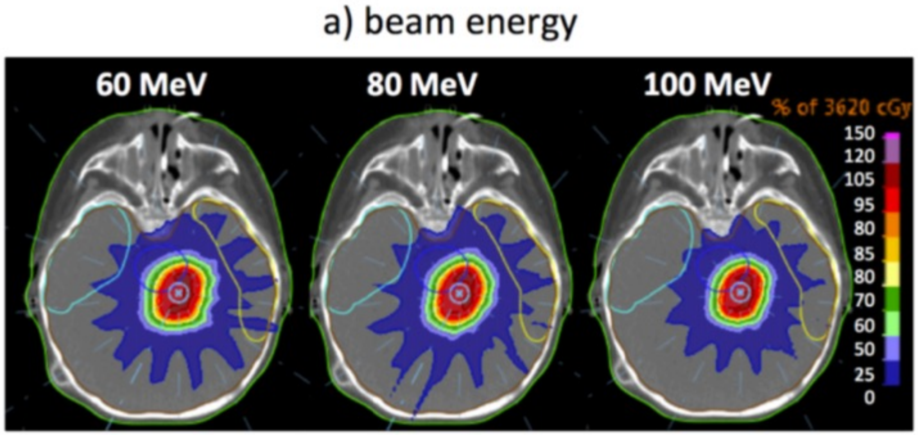


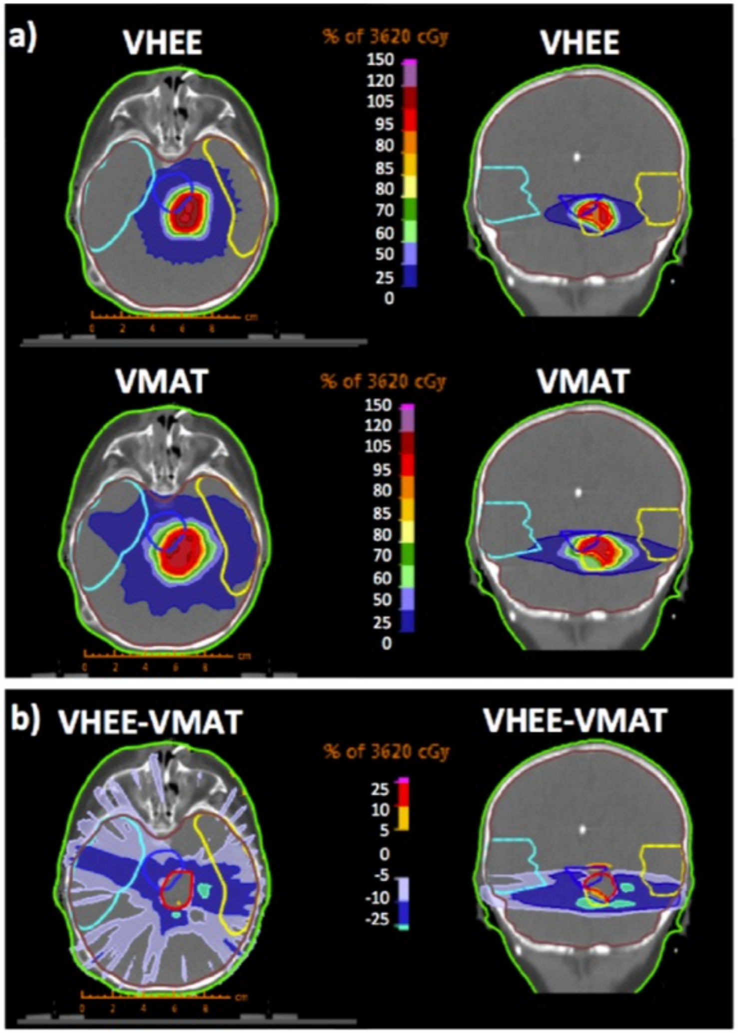
Treatment planning was
as simple as it gets due to flash
requirements

(Very) High Energy Electrons ?



VHEE
Multiple high energy electron beams can generate dose distributions seemingly competitive with VMAT





Protons and heavier ions?

Let's start simple:

$$\dot{D} = \frac{i_p}{A}\frac{S}{\rho} \quad \frac{\text{Gy}}{\text{s}}$$

i_p= beam current in nA
A= transversal area in cm^2
S/ρ= Mass Stopping Power in $MeV*cm^2/g$

With values representative for current practice, e.g. i_p=2nA, A=25 cm^2 and S/ρ=5 $MeV*cm^2/g$

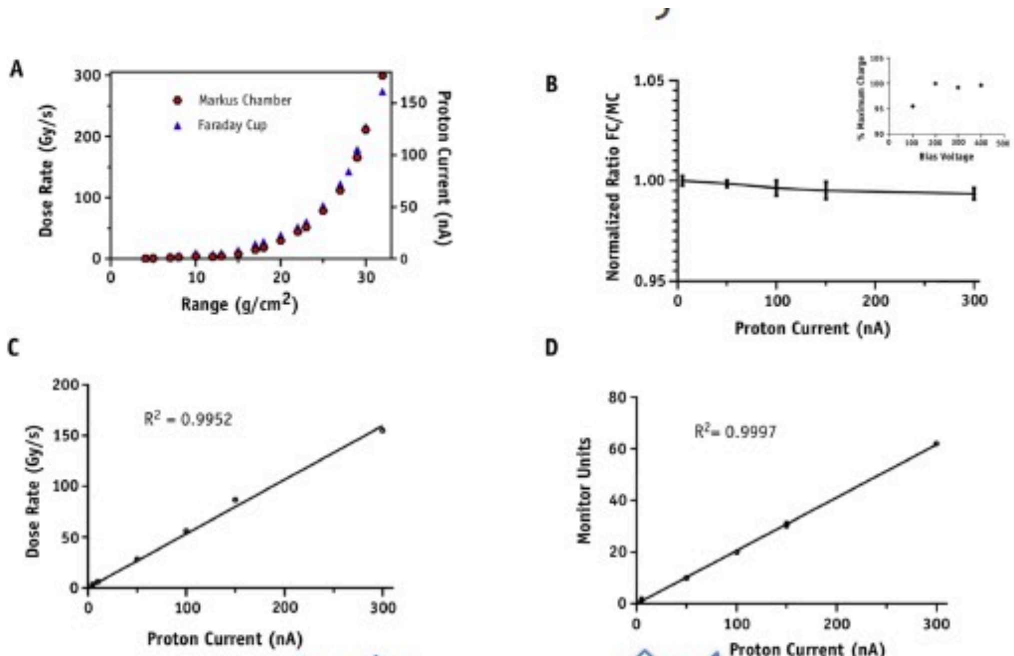
Doserate=0.4 Gy/s

So the question becomes:
Can we boost i_p to 200 nA with current equipment?

Courtesy of Marco Schwarz

First order answer: Yes we can!

Diffenderfer 2020



2019

Flash Irradiation Delivered in a Clinical Treatment Room

Varian: First Patient Treated in FAST-01 FLASH Therapy Trial

By News Release

2020

BUT….

Not all Proton systems are “flashable”..

Accelerator Type	Isochronous Cyclotron		Synchrocyclotron	
Vendor	IBA	Varian	IBA	Mevion
System	C230	PROBEAM	S2C2	S250
Maximum Energy (MeV)	230	250	250	250
Minimum Energy (MeV)	70	70	70	70
Peak Current(μA)	0.3	0.8	~ 18	~ 7
Max Ave. Current (nA)	300	800	~ 130	~ 32
Accel. Frequency (MHz)	106.1	72.8	87.6–63.2	133–90
Repetition rate	CW	CW	1 kHz	500–750 Hz
Treatment Pulse Length	>400 μs	>400 μs	7 μs	6 μs
Bunch Length	~ 2 ns	~ 2 ns	~ 2 ns	~ 2 ns
Max Part. per Bunch/Pulse	100,000	70,000	8×10^8	4×10^8
Electric/Central Field	1.7 T	2.4 T	5.75 T	9 T
References	[18,19]	[20,21]	[22]	[23–25]

Jolly 2020

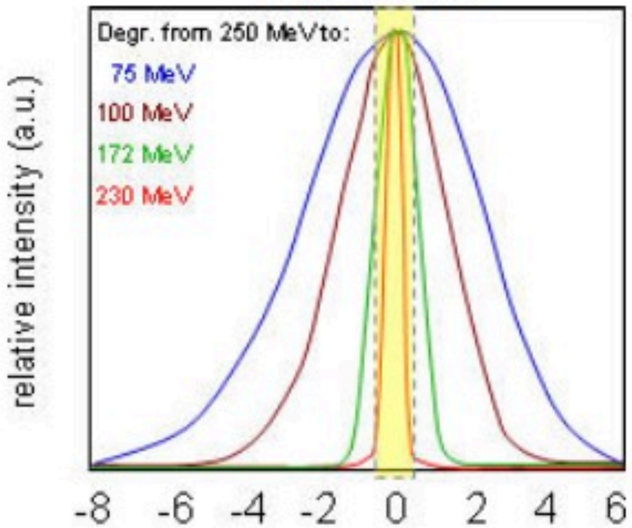
Many/most current PT systems

Relatively new PT systems

not all **energies** can be delivered at flash rate

Due to the degrader+energy selection system, there is a **lower bound of the energy** where flash dose rates can be achieved

Schippers 2012

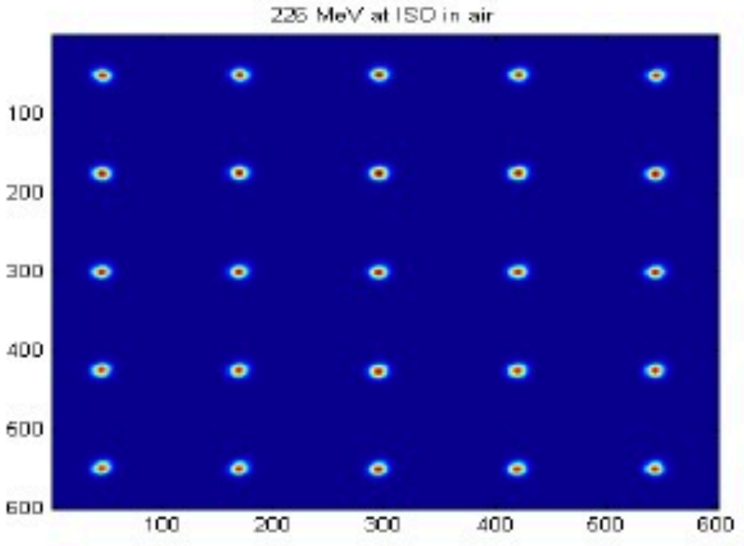


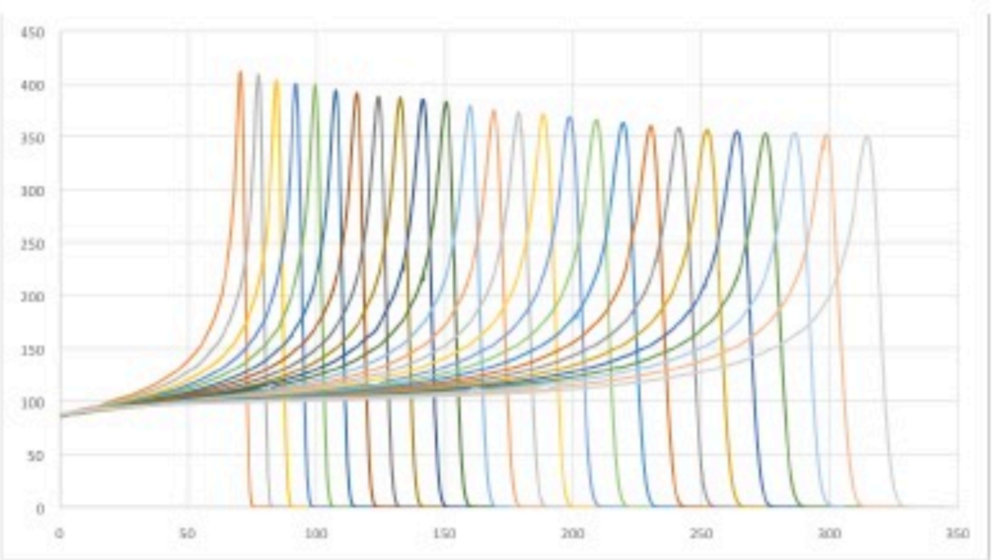
Not only beam attenuation, also beam scatter

Only the beam portion with a small enough emittance will be transported in the beam line

Largest beam loss happens here (at 70 MeV 99%+ of the beam is lost)

Pencil Beam Scanning Dead Times..





dead time between spots in the same energy layer: ≅ms

dead time between neighbouring energy layers @PSI≅80 ms
Everyone else: 0.5-2s

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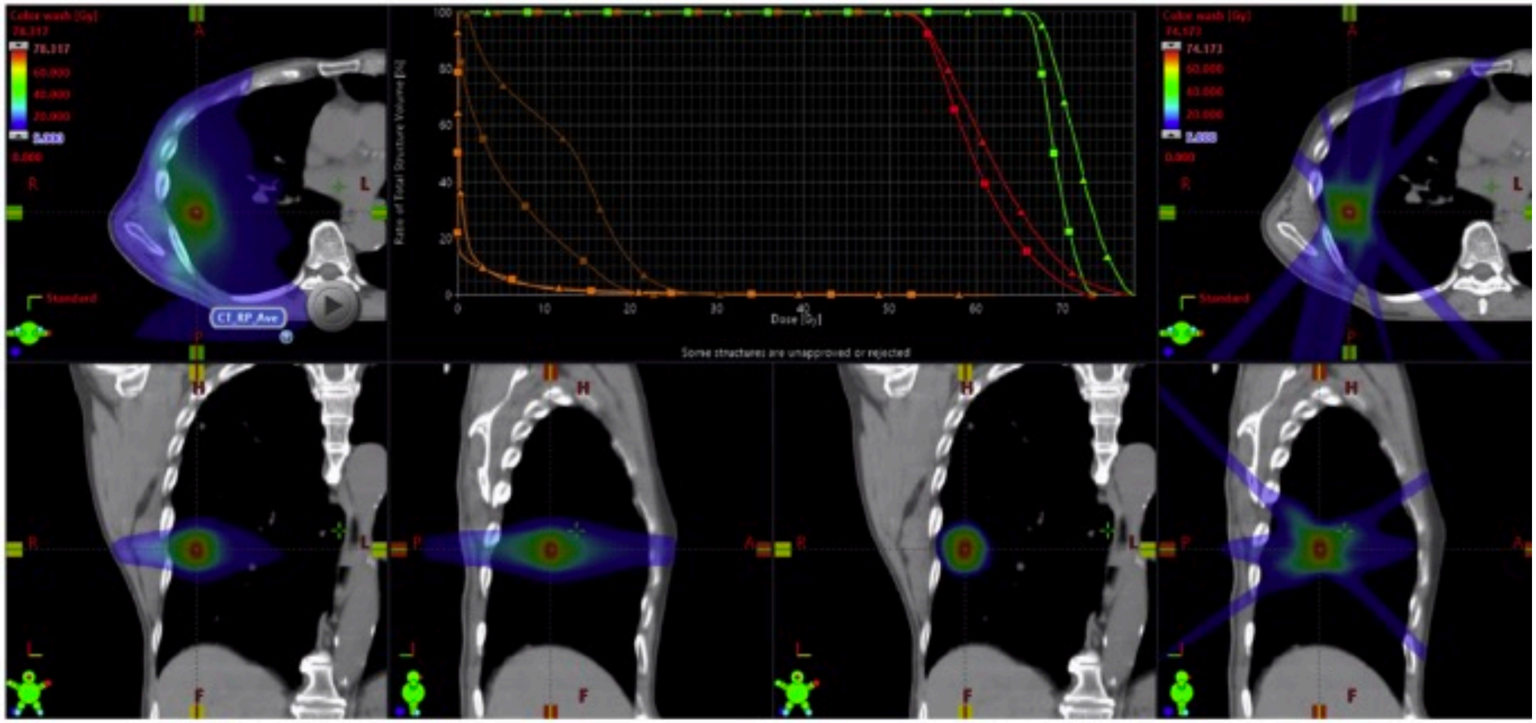
So, Game over, or…

..2 Options:

1st Option: Shoot-through

Forget about energy modulation and use protons as “expensive” photons in the Plateau

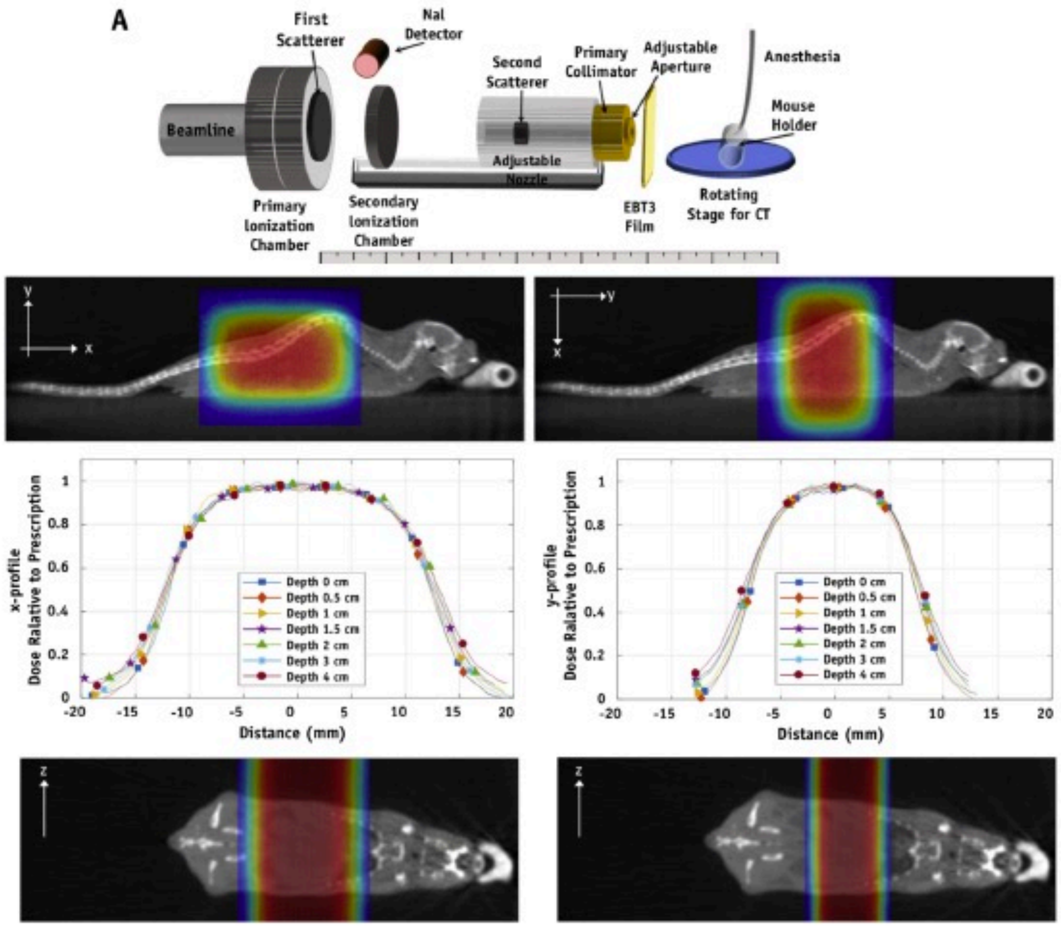


VMAT vs 10 non coplanar trasmission beams in lung sbrt

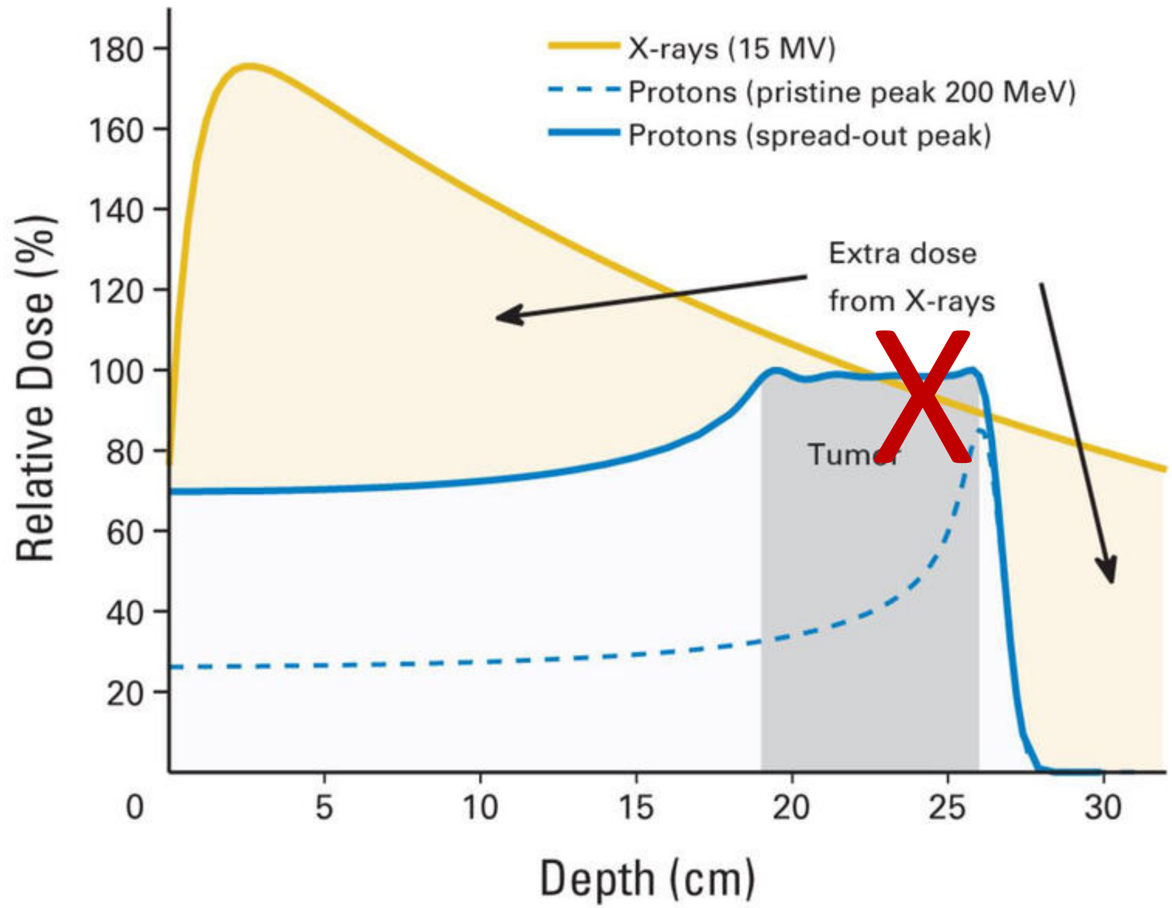
1st Option: Shoot-through

ALL Preclinical studies, (and Clinical) Used this Option

Diffenderfer 2020



So Forget about the nice Bragg Peak that everybody know and make protons so powerful?



But it seems it work…

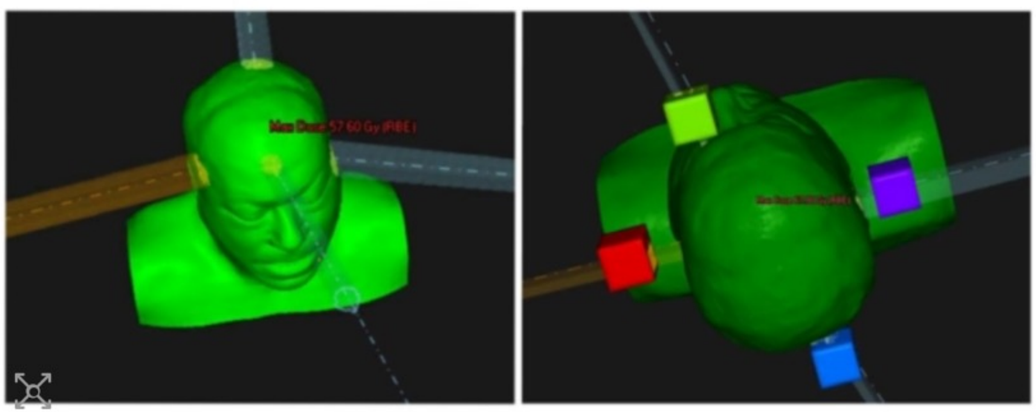
physicsworld | Magazine | Latest | People | Impact

particle therapy

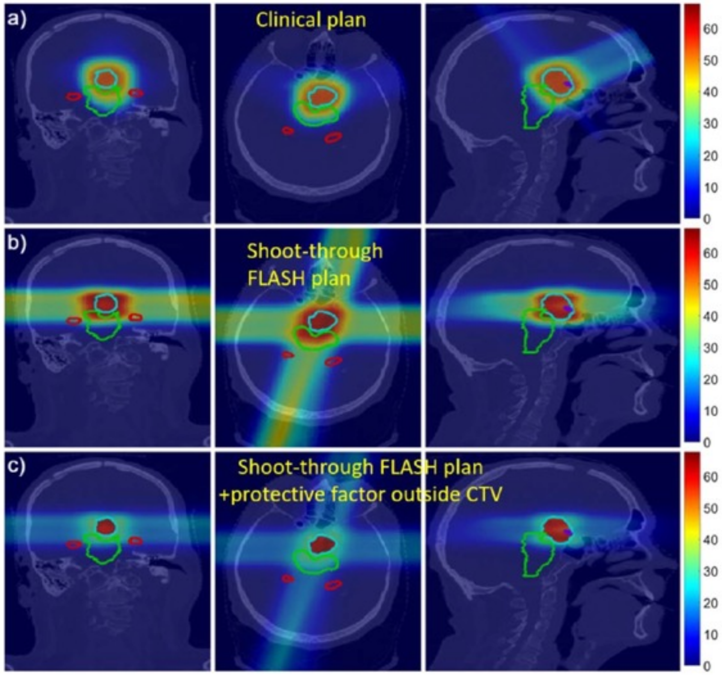
PARTICLE THERAPY | RESEARCH UPDATE

Shoot right through: FLASH protons could eliminate Bragg peak constraints

30 Apr 2021 Tami Freeman



Left: a conventional clinical proton beam arrangement with four beams terminating in the target. Right: a shoot-through FLASH plan with four proton beams aimed at fictitious target boxes outside the patient's head. (Courtesy: *Phys. Med. Biol.* 10.1088/1361-6560/abe55a)



For the shoot-through plan, it's assumed a hypothetical FLASH protective factor (DREF) for normal tissues of 2…. (!)

"I had the idea that if we could do FLASH protons, we could get rid of the 'tyranny' of the Bragg peak," - F. Verhaegen

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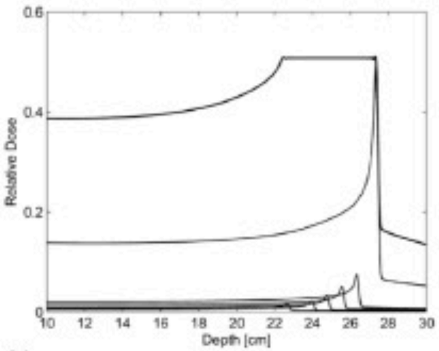
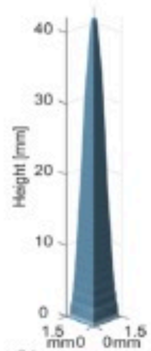
Option 2: Range Modulators

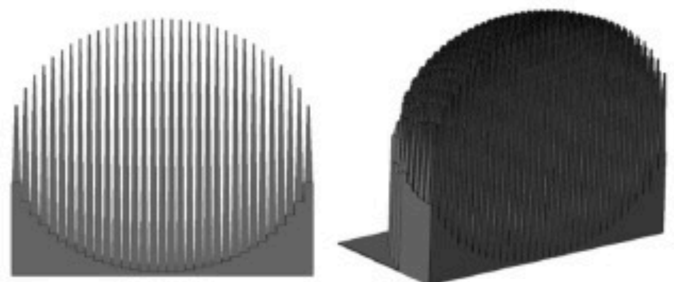
Or Hedgehog: treat with **one energy** and use hardware to create an SOBP



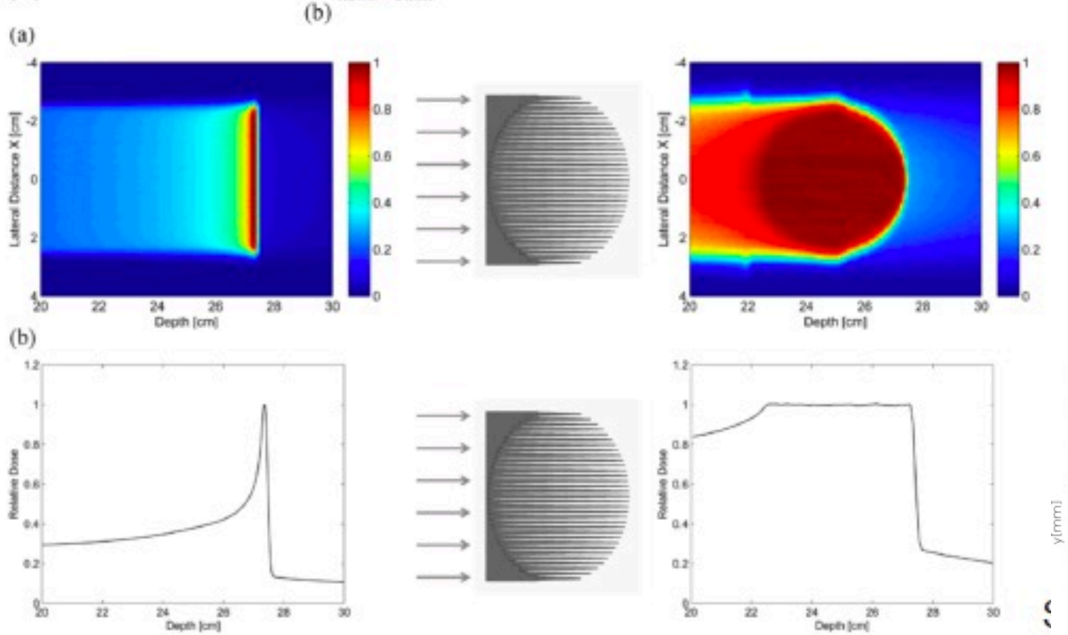
(a)



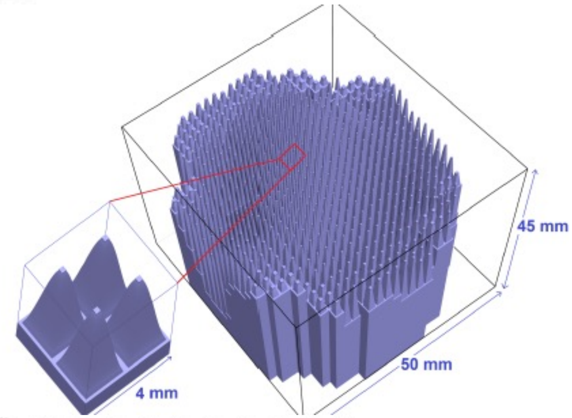
(b)

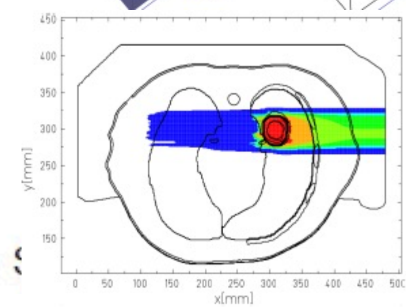


(a) (b)



Simenov et al. 2017





Weber, Scifoni, Durante 2021

Transmission beams vs “hedgehog”: pros and cons

Pro:

Transmission beam: We use the highest energy thus mazimizing the flash potential

Hedgehog: We take advantage of energy modulation and create conformal dose distributions

Con:

Transmission beam: protons delivered like this are just very expensive photons. Some beam directions may be forbidden because the Bragg peak is in the patient.

Hedgehog: we need (non trivial) field specific hardware. Some dose conformation possible, but how good is the lateral penumbra?
Both techniques: we are likely creating inferior dose distributions to full IMPT, i.e. there’s no flash for free. At least part of the flash benefit will be needed to compensate for that.

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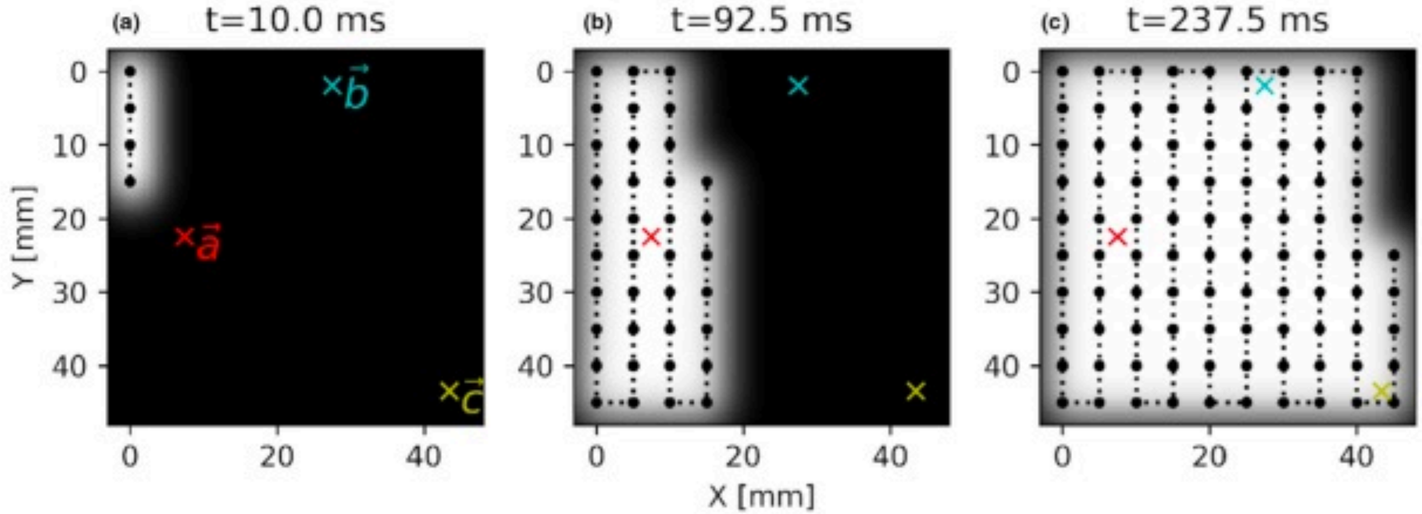
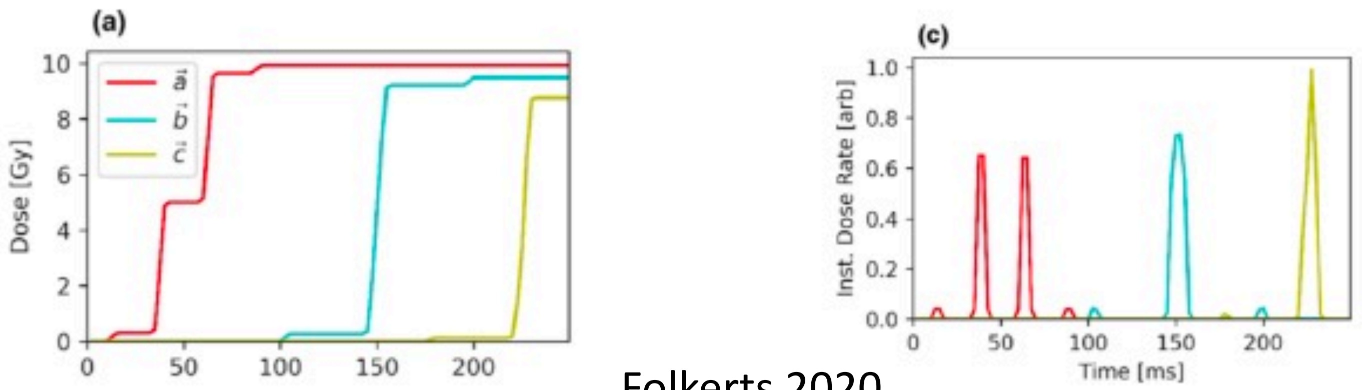
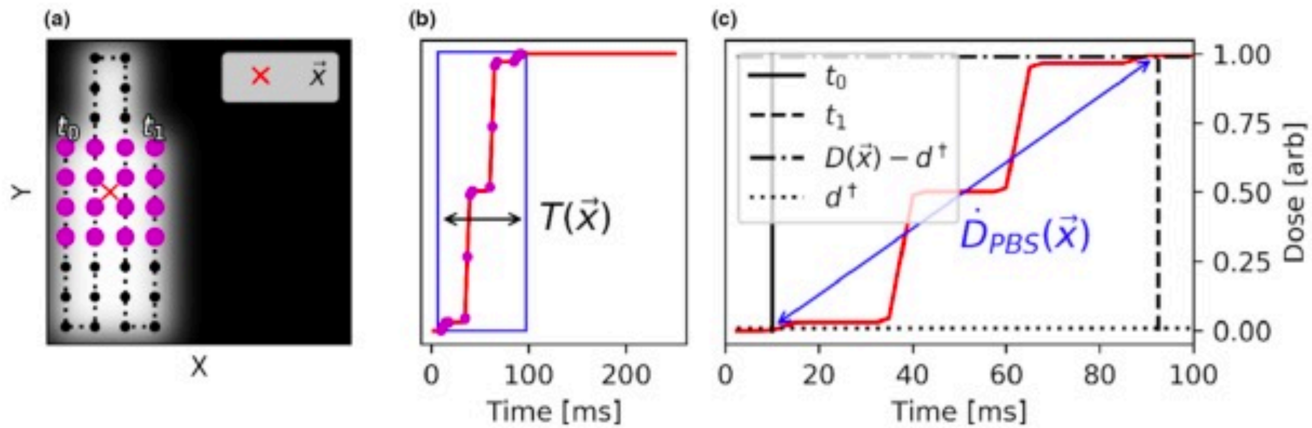
Adapting the definition of Dose rate

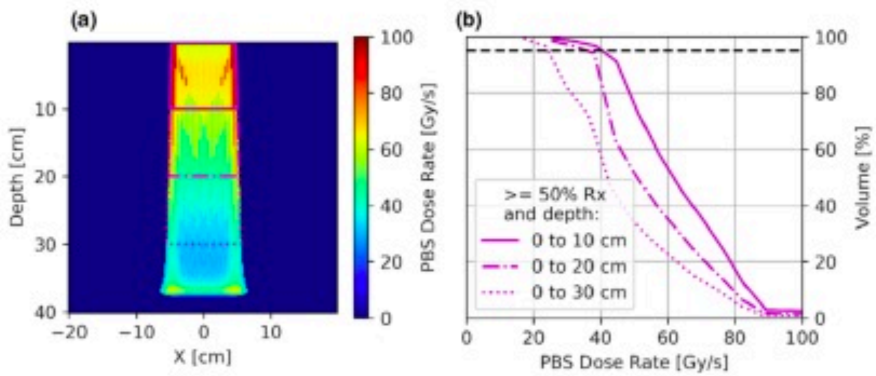




Folkerts 2020

$$\dot{D}_{\mathrm{PBS}}\left(\vec{x}\right)=\frac{D\left(\vec{x}\right)-2d^{\dagger}}{T\left(\vec{x}\right)}.$$

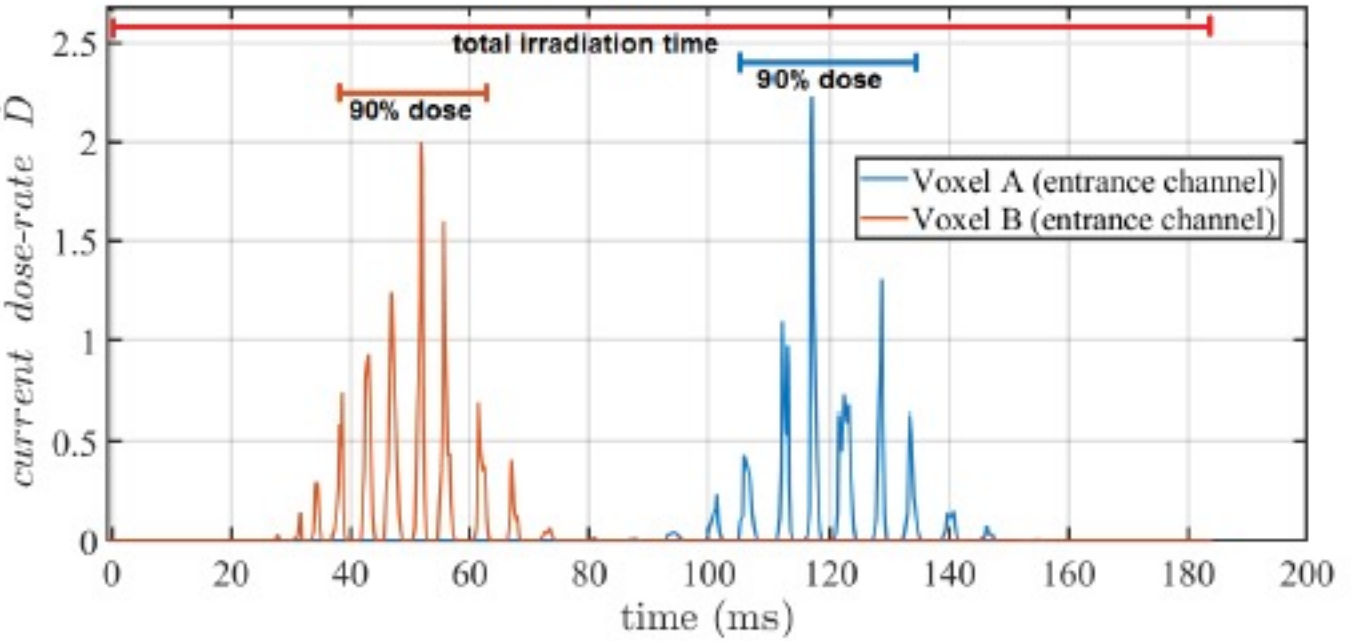




In analogy to DVH (and LVH)
a
DRVH is needed

Folkerts 2020

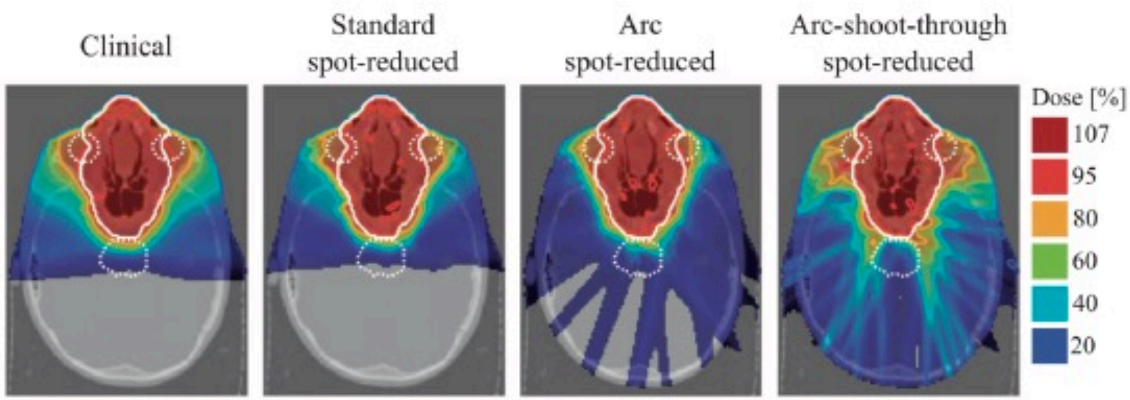
Dose rate per voxel



Weber, Scifoni, Durante 2021

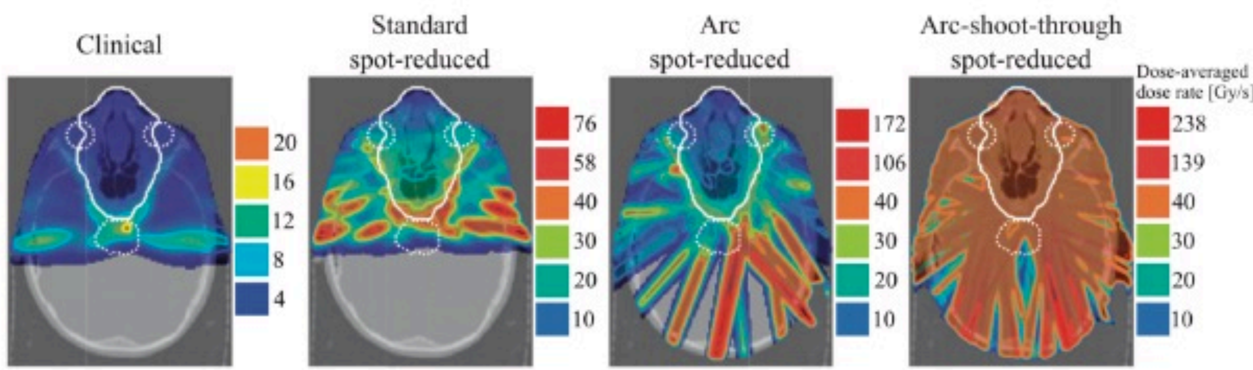
Dose Averaged Dose Rate

Dose rate - “generous hypothesis”

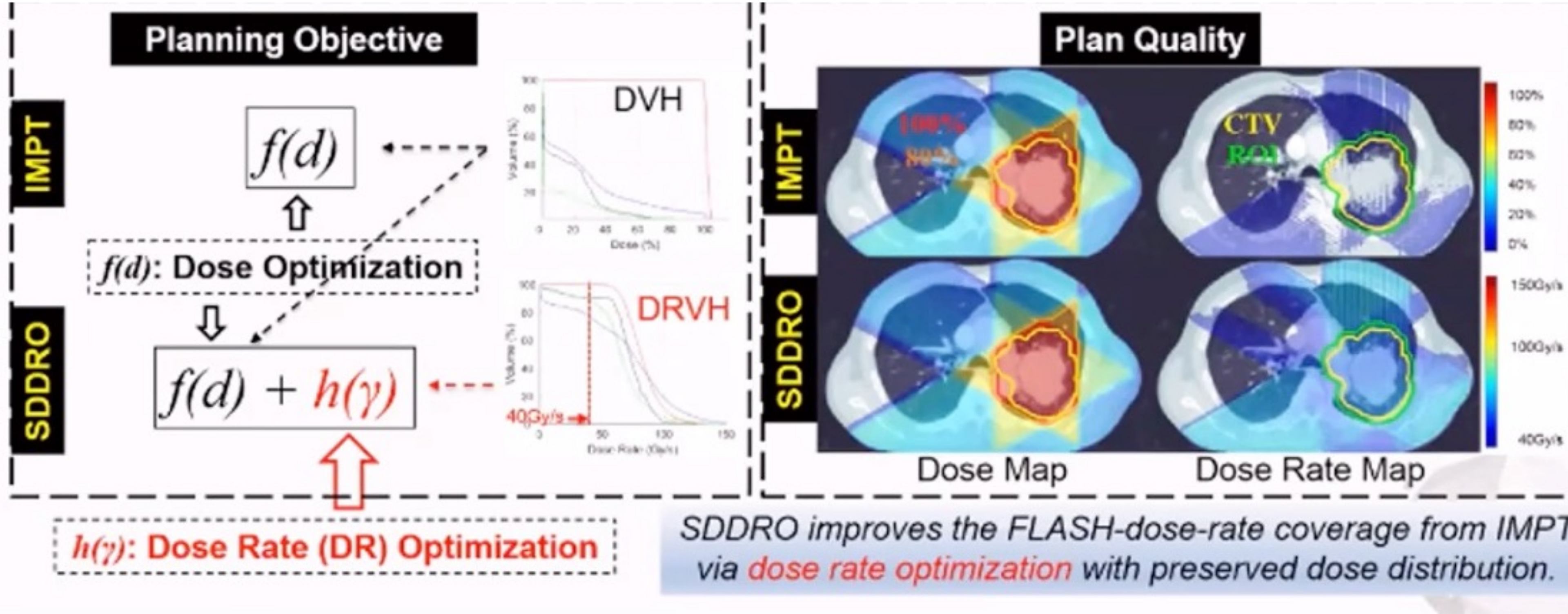


$$DADR_i = \sum_{j=1}^{n} \frac{(d_{ij}w_j)(d_{ij}BI_j)}{\sum_{j=1}^{n} d_{ij}w_j},$$

Van de Water 2019



Dose Rate optimization



Hao Gao FRPT 2021

Summary II – Dose delivery

- All this assume Dosimetry perfectly working (see previous section)

- All things considered, the residual degrees of freedom available for planning seem limited with current equipment.

- To better identify the room for Flash in the clinic, it is needed:

- Voxelwise time structure of the dose deposition available for plan evaluation.
This requires tighter coupling between planning and delivery than we have now.

- Open questions:
  - How multiple flash "segments" within a single fraction combine with each other.
  - Can we use multiple fields?
  - What is the volume effect for Flash?

- A minimum dose threshold at 5-10Gy may be very problematic for flash in the clinic.
  - How accurate are current threshold values? Is it a binary threshold?

- Time structure + realistic biological models are needed for Flash to be an optimisation parameter

In conclusion:

- FLASH is a **Biological** effect, with **Clinical** applications
- But is fundamentally depending on **Physics**, on different scales, sides and flavours

- New avenues for Physics research, in different fields, are opened through it

FRIDA - FLASH Radiotherapy with hIgh Dose-rate particle beAms project

INFN-CSNV Call 2022-2024

WP0
Coordination
A. Sarti

WP1
The FLASH mechanism
E. Scifoni (modeling)
G. Forte (bio experiments)

WP2
Beam delivery
A. Mostacci (e-)
G. A. P. Cirrone (p)

WP3
Beam/dose monitoring
A. Vignati (Beam monitoring)
G. Bisogni (Dose monitoring)

WP4
Treatment planning
A. Schiavi (Dose sim/optim.)
M. Schwarz (Treatment planning)

INFN
units
CT –F. Romano
LNS – G. Cirrone
MI – D. Giove
PI – G. Bisogni
RM1 – A. Sarti
TIFPA – E. Scifoni
TO – A. Vignati

Partners:
AZIENDA OSPEDALIERO UNIVERSITARIA PISANA
GSI
eli beamlines
HZDR HELMHOLTZ ZENTRUM DRESDEN ROSSENDORF
QUEEN'S UNIVERSITY BELFAST
UNIVERSITY OF SURREY
Consiglio Nazionale delle Ricerche

Is FLASH the next SRS/SBRT?

Or Hyperthermia 2.0?

J. Breneman @FRPT

What Do We (Clinicians) Need To Advance FLASH?

- Better understanding of biologic mechanisms responsible for FLASH effect
- Better understanding of dose parameters for FLASH effects(s)
  - Minimum dose and dose rate for fractionated treatment
  - Are these parameters different for different tissue types and tumors?
- Photon/proton units capable of delivering conformal FLASH
- In vivo comparisons of optimized FLASH vs fractionated or hypo-fractionated conventional dose rate photons

Cincinnati Children's | University of CINCINNATI

What is most important to the FLASH effect

- Physics Tony Lomax
- Chemistry Douglas Spitz
- Biology Charlie Limoli
- Clinic Phillip Poortmans

But only one can survive!

You choose

Physics (T. Lomax) won!

...simply telling that:

Reason 1 – It all depends on physics

The FLASH chain of events starts with physics

Reason 2 – Understanding the effect

Physicists are working hard to develop mechanistic models of the FLASH effect

Reason 3 – Treatment planning.

Only physics can provide tools to predict the 3D distribution of dose, dose-rate and the FLASH effect within the patient

Reason 4 - Dosimetry.

Only physics can ensure that the correct dose and dose-rate will be delivered

Reason 5 - Delivery.

Only developments in physics can *deliver* the radiation at the high dose rates required to trigger the FLASH effect

Main References

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