Flash therapy

[.. mostly FRIDA]

A. Sarti

Retreat della sezione INFN di Roma


WARNING
Disturbing Content!
Viewer Discretion is Advised
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Why are even talking about that today..

https://linkinghub.elsevier.com/retrieve/pii/S0167814019329597

FIRST IN HUMAN | VOLUME 139, P18-22, OCTOBER 01, 2019

Treatment of a first patient with FLASH-radiotherapy

Jean Bourhis • Wendy Jeanneret Sozzi • Patrik Gonçalves Jorge • ... Jean-François Germond • Raphaël Moeckli [1] • Marie-Catherine Vozenin [1] • Show all authors • Show footnotes

Published: July 11, 2019 • DOI: https://doi.org/10.1016/j.radonc.2019.06.019 • Check for updates

1a : Day 0

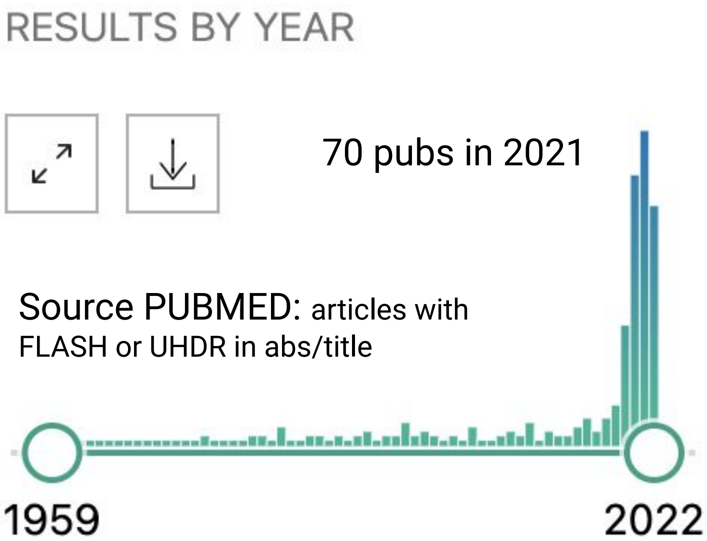
1b : 3 weeks

1c : 5 months

.. “Our patient had a long history of localized RT (110 different irradiations in about 10 years) and doses needed to control the lesions were typically 20–21 Gy in 6–10 fractions. Despite these relatively low total doses, the acute toxicity of these treatments was found to be relatively severe in the context of the particular skin frailty of this patient, **with commonly 3–4 months for complete healing**.”

The tumor started to shrink around 10 days after irradiation with a **complete tumor response at 36 days** which was durable for the subsequent 5 months

Why is it interesting?



Source PUBMED: articles with FLASH or UHDR in abs/title

.. because it works… and we do not (yet) understand why!

& INFN is the perfect place for giving a helping hand… as we need measurements… and for measurements we need:

- Accelerators capable of delivering FLASH beams
- Detectors capable of monitoring FLASH rates

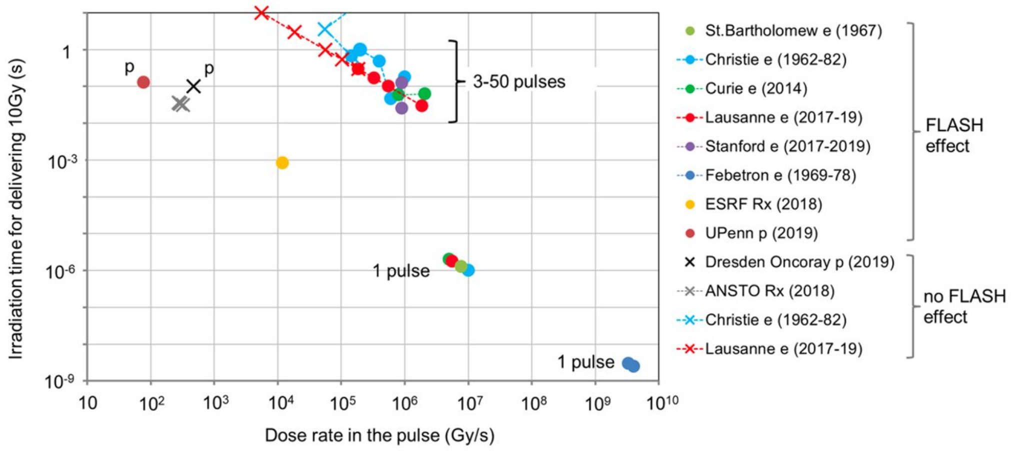
And afterwards we need modeling and simulations to understand how much we can gain from it….

“~~Physics~~ FLASH is like sex: sure, it may give some practical results, but that's not why we do it.” — (based on.. Richard P. Feynman quote)

Not an easy task [that's why it's fun!]

Even discussing 'what is FLASH' proves to be difficult…

- High dose rate [100 Gy/s?].. And here a lot of discussion can start if you are talking about 'average' or 'instantaneous' dose rates… but to cut short along story → **2-3 OoM wrt current clinical practice**
- Dose above a given threshold [4-6 Gy].. At the Organs at Risk (OARs)!



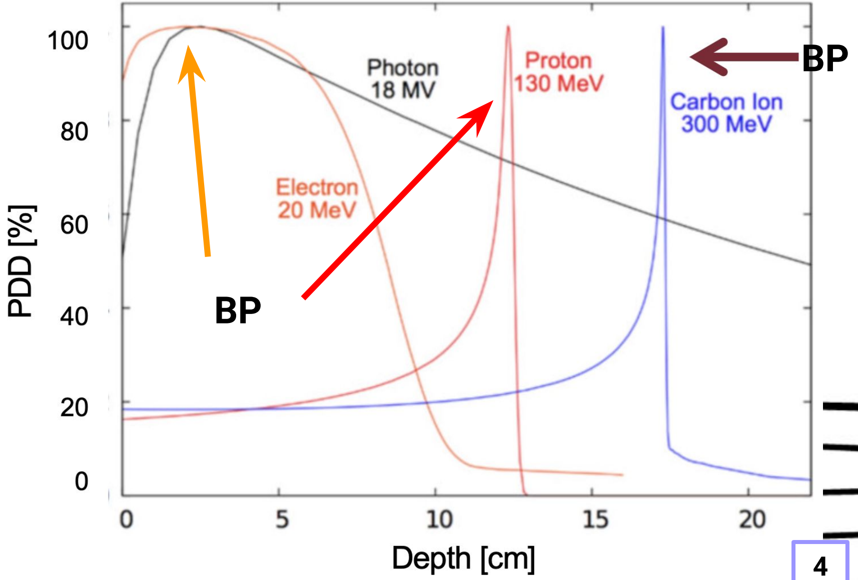
What are the options so far for 'clinical-like' FLASH beams:

- e-: beams with FLASH intensity are already available.. But at 'low energy'
- p: FLASH intensities are doable.. Problem is
- γ : only at specific synchrotron facilities and 40 Gy/s top… producing flash RT beams is proving to be really difficult!

+ something unexpected!
[and actually FLASH unrelated]

e⁻ are 'back in the business'! [thanks to but independently of.. FLASH!]

- Nice prospects for compact acceleration to reach deep tumours
- Naturally provide SOBP @ fixed energy → good for FLASH!
- Can be easily accelerated @ FLASH rates [already done for low energies]
- Current best candidates for FLASH clinical translation [see slide 2!]

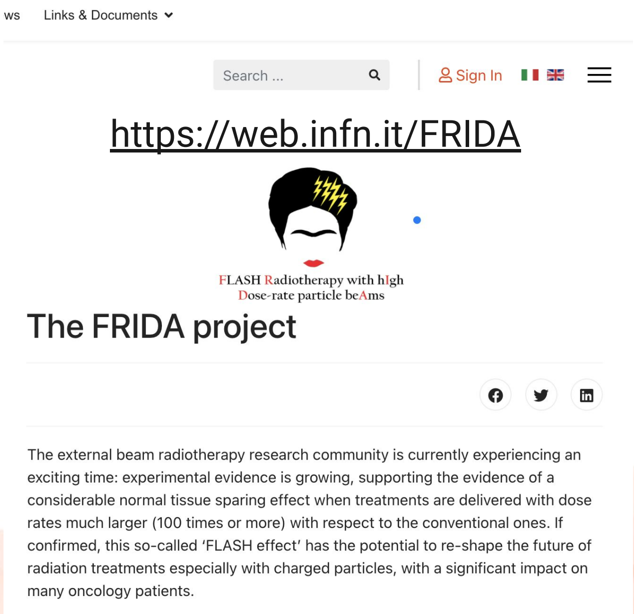


That's why.. there's FRIDA

INFN CSN5 call , ~ 1M€, 7 INFN units, 30 FTE, 100 people
PI (A. Sarti) + WP2 coord (A. Mostacci) + WP4 coord (A. Schiavi) … All from Roma1, all with A.

FRIDA goals

- Explore the time scales at which the FLASH effect occurs, refine the experimental characterization and modelling of the effect.
- Develop compact, high intensity sources and delivery solutions for EBRT with e- and p
- Explore novel detection strategies both for dosimetry and beam monitoring applications
- Assess the FLASH effect potential using dedicated MC simulations and an ad hoc modelling of the NT sparing to provide optimised treatments that can be compared with state of the art RT and PT results



@RM1: De Gregorio, De Simoni, Ficcadenti, Franciosini, Giuliano, Marafini, Migliorati, Palumbo, Patera, Taini, Trigilio: 6.1 FTE

1st of all: Facilities now...

Upgrade of UNITO Linac and TIFPA p-Lab
FLASH IORT @ PI

Electrons

- **SIT: the company will give access to the FLASH machines (low energy) that are in development**
- **UNIPI: SIT IORT flash accelerator**
- **TO: a low energy linac**
- PI: CNR-INO lab
- **BTF @ LNF?**

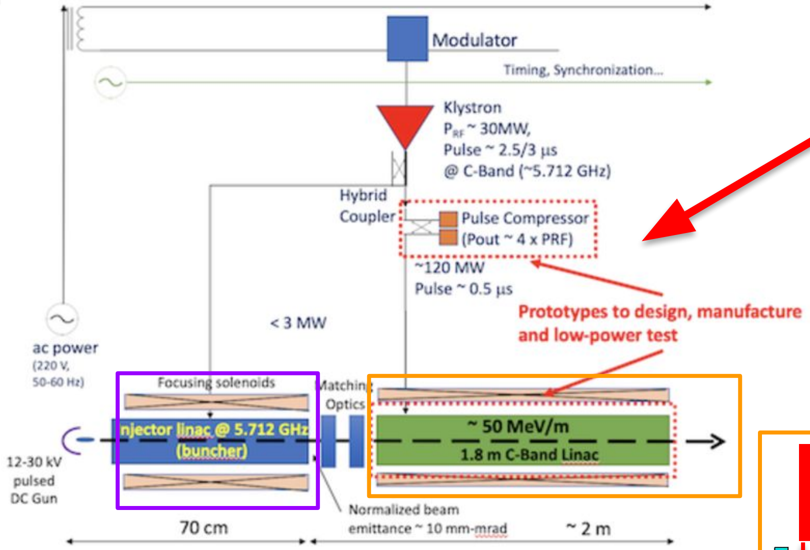
Protons

- **CNAO: is making available the research room for FLASH testing and experimentation**
- **TIFPA: an upgrade of the IBA accelerator will be implemented along what already done in Dresden**
- ELIMED /Queens (UK) beamlines

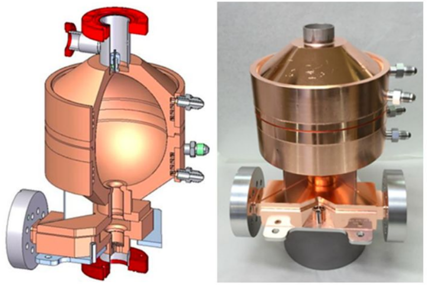
Everyone is eager to see some FLASH beam: FRIDA can represent quite of an opportunity

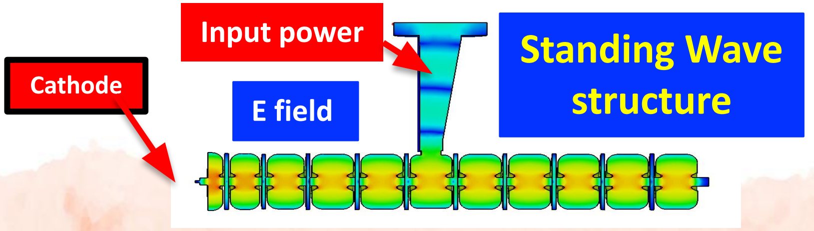
.. and then

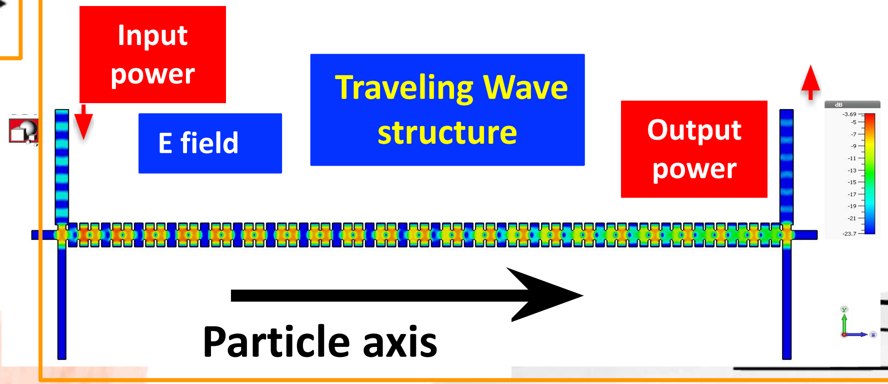
Compact C band option



Doubling beam energy enhancing peak RF power at the expense of pulse width



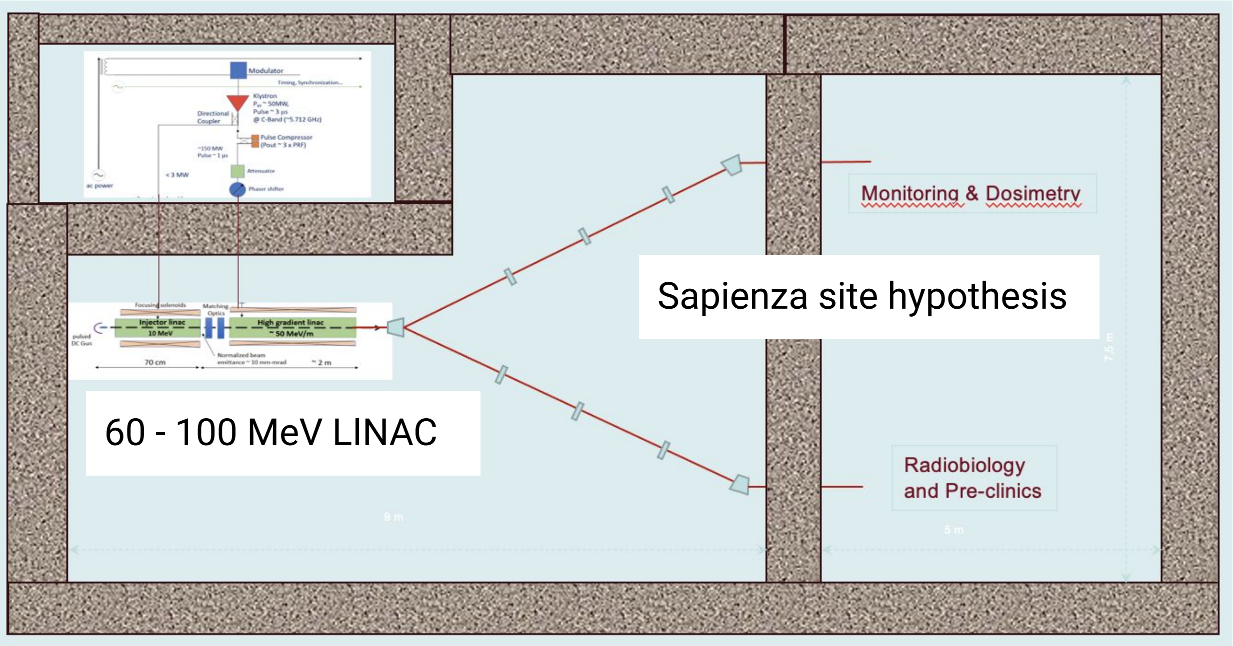




Courtesy of A. Mostacci

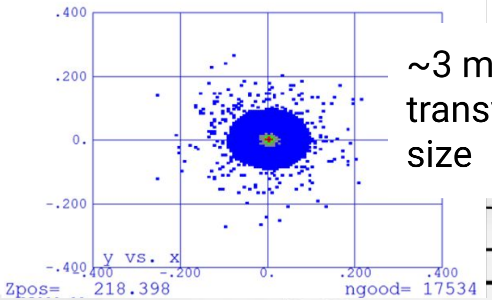
The sapienza - INFN joint effort

The ‘FLASH’ wave brings the opportunity to build a research facility in Sapienza to test the accelerator prototype and study the FLASH effect & VHEE potential



VHEE LINAC

	Description	Proposed Value for New Linac
E	Beam Energy	60 - 130 MeV
f	RF frequency	5.712 GHz
PRF	Pulse repetition frequency	> 100 Hz
t_p	Pulse width	1 - 3 μs
Q_p	Pulse Charge	200 - 600 nC
I_p	Pulse Current	200 mA
$\dot{D}_p$	In-Pulse Dose-Rate	>> 10^7 Gy/s



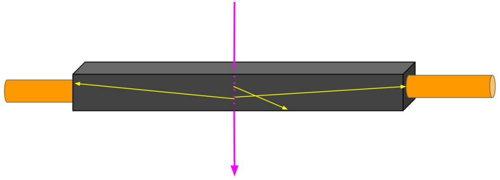
~3 mm transverse size

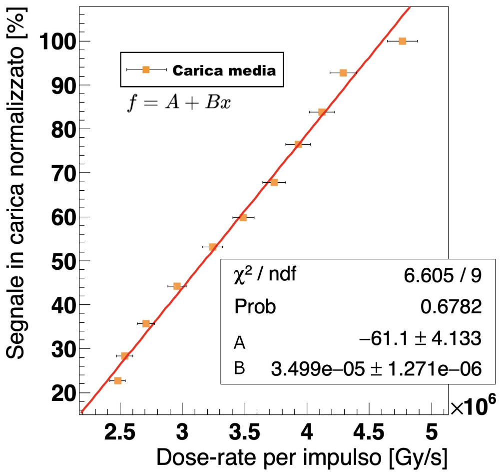
Courtesy of V. Patera & L. Palumbo

Knowing the dose (dose-rate)

- Current technologies cannot be ‘easily’ adapted to cope with 3 OoM increase in dose rates while retaining same accuracy/precision: saturations and non-linearities are kicking in.
- Many attempts within FRIDA to provide solutions / upgrade of current technologies… @ RM1 we are pursuing a new approach: **use induced air-fluorescence** to monitor the beam & measure the dose/instantaneous dose rates

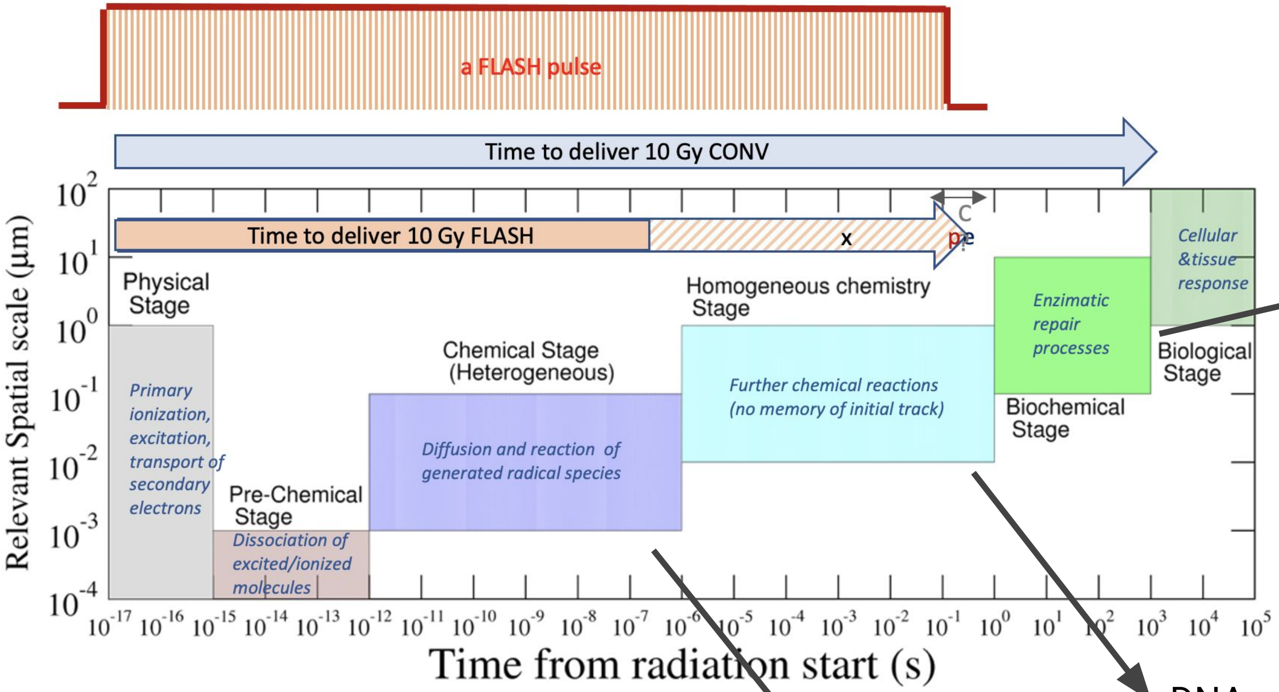
PTFE box, **PVC** inside (light absorbing material to avoid saturation) + 2 PMTs





Courtesy of M. Marafini, G. Traini, A. Trigilio

Understanding FLASH



Weber, Scifoni, Durante Med Phys 2021.

NTCP modelling

DNA repair kinetics

Radiation chemistry

The FLASH potential..

While getting the tools ready to play.. (and some of them are really in an advanced state..)
Before rushing.. **We need thinking**.. It's crucial that we clearly define what are the first things that we need to implement and explore from

FLASH != magic

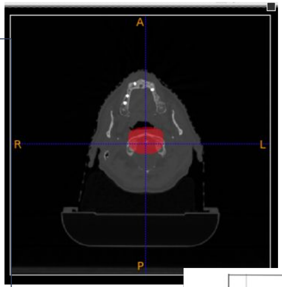
Cannot be 'blindly' applied to all districts/pathologies!

Interaction with clinics is crucial: we can profit from the knowhow of a network built inside 'Scuola di Specializzazione in Fisica Medica' (A. Migliorati, V. Patera, A. Sarti), RM hospitals (Policlinico, San Camillo & CampusBiomedico), national and international treatment centres…

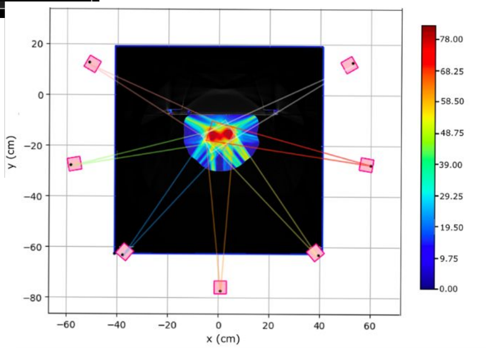
The FLASH potential..

While getting the tools ready to play.. (and some of them are really in an advanced state..) Before rushing.. **We need thinking**.. It's crucial that we clearly define what are the first things that we need to implement and explore from the **a)** district **b)** radiation/beam delivery

Choice of the pathology and acquisition of the CT scans and constraints



Fix the geometry treatment and the beam energies



- **Choice of the district not easy: should be compliant with severe hypofractionation, there must be something to be gained wrt standard RT**
- **While p and γ have 50 (100) years of experience, e- for deep seated is rather new: planning is an entirely new game…**

The FLASH potential..

While getting the tools ready to play.. (and some of them are really in an advanced state..)
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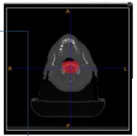

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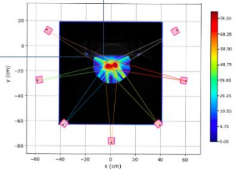
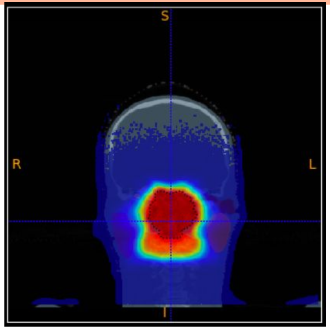


D_{ij} evaluation with Monte Carlo simulations



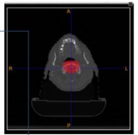
Optimisation of beam fluences

- **Evaluating the dose distributions is a computational nightmare. Fast MC can help, but nevertheless you need to 'optimise' the fluence in a multiparametric space.. Machine learning can help! (see talk from C. M. Terracciano)**

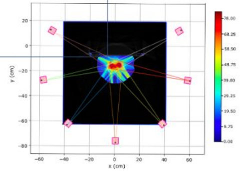
The FLASH potential..

While getting the tools ready to play.. (and some of them are really in an advanced state..) Before rushing.. **We need thinking**.. It's crucial that we clearly define what are the first things that we need to implement and explore from the **a)** district **b)** radiation/beam delivery **c)** constraints **d)** FLASH modeling points of view.

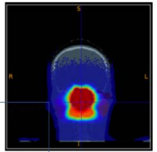
Choice of the pathology and acquisition of the CT scans and constraints



Fix the geometry treatment and the beam energies

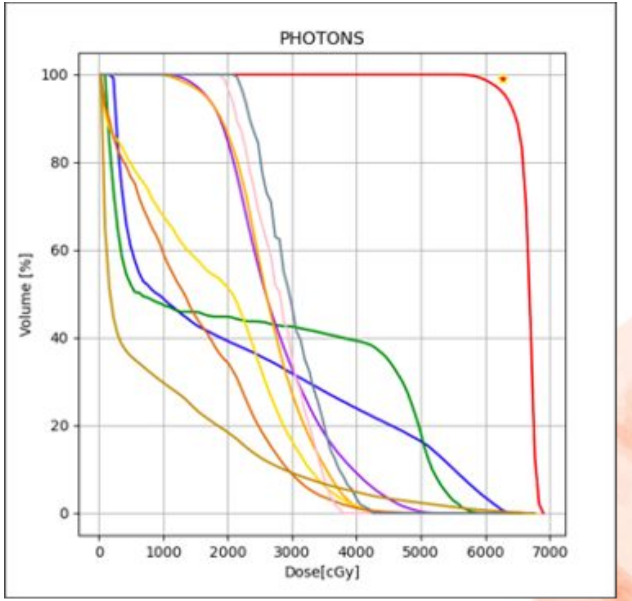


D_{ij} evaluation with Monte Carlo simulations



Optimisation of beam fluences

The end of the game [DVHs]



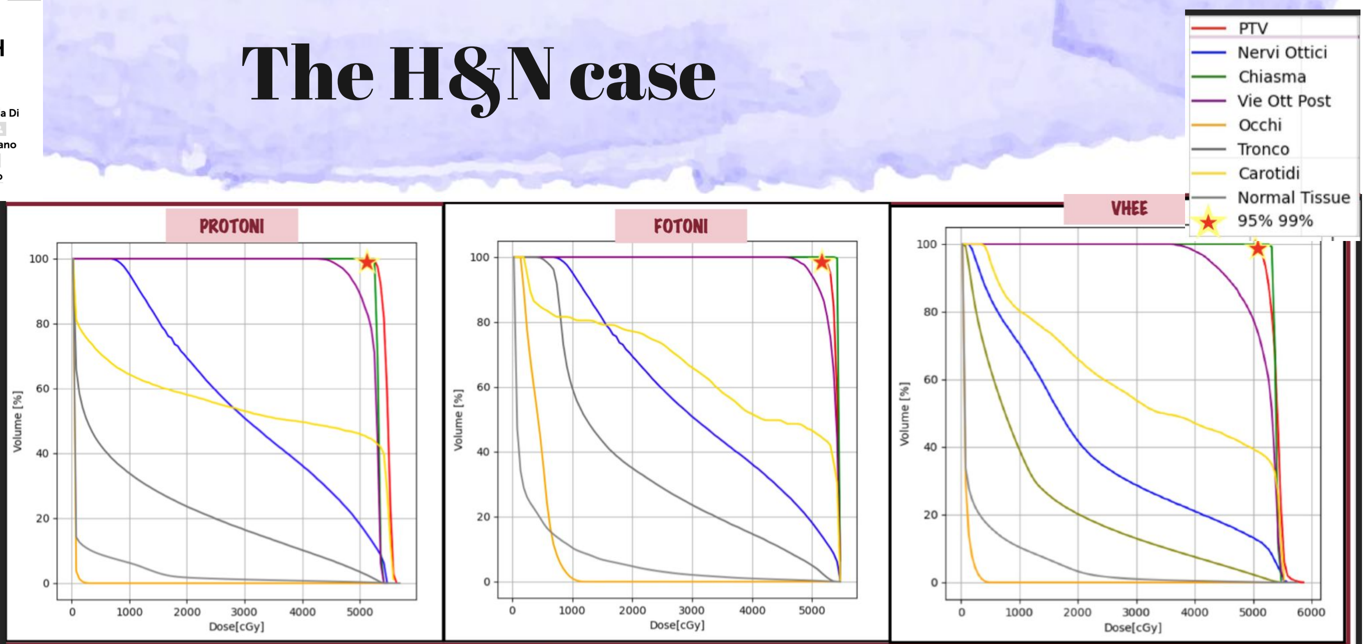
Front. Oncol., 23 December 2021 | https://doi.org/10.3389/fonc.2021.777852

Deep Seated Tumour Treatments With Electrons of High Energy Delivered at FLASH Rates: The Example of Prostate Cancer

Alessio Sarti[1,2], Patrizia De Maria[3], Giuseppe Battistoni[4], Micol De Simoni[2,5], Cinzia Di Felice[6], Yunsheng Dong[4], Marta Fischetti[1,2], Gaia Franciosini[2,5], Michela Marafini[2,7], Francesco Marampon[8], Ilaria Mattei[4], Riccardo Mirabelli[2,5], Silvia Muraro[4], Massimiliano Pacilio[6], Luigi Palumbo[1,2], Loredana Rocca[1], Damiana Rubeca[1], Angelo Schiavi[1,2*], Adalberto Sciubba[1,9], Vincenzo Tombolini[8], Marco Toppi[1,9], Giacomo Traini[2], Antonio Trigilio[2,5] and Vincenzo Patera[1,2]

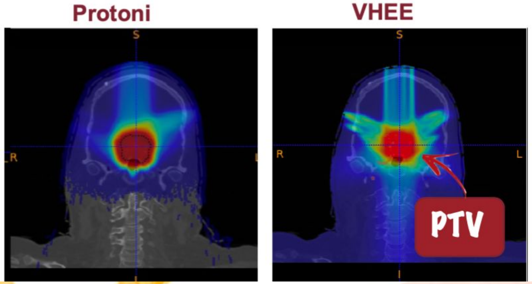
The H&N case

After a first 'proof of concept' exercise on prostate cancer, time came for a more interesting study: the head & neck district… **FIRST example of low energy/small n. of fields example for VHEE**

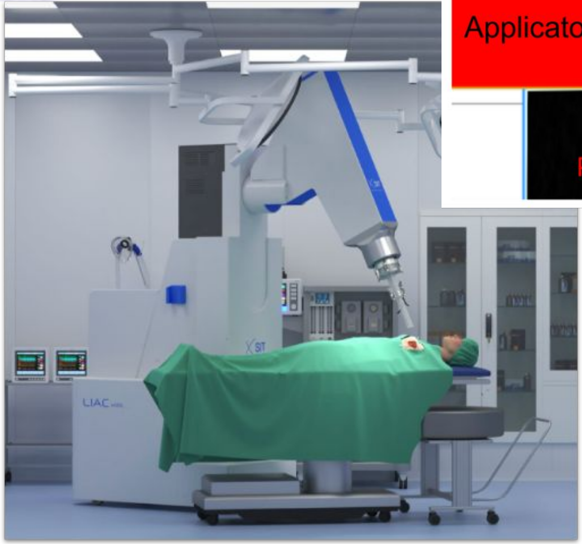


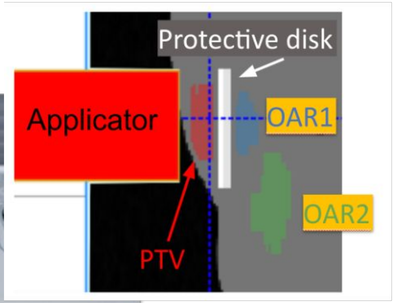
CONFRONTO TRA I VINCOLI DOSE-VOLUME

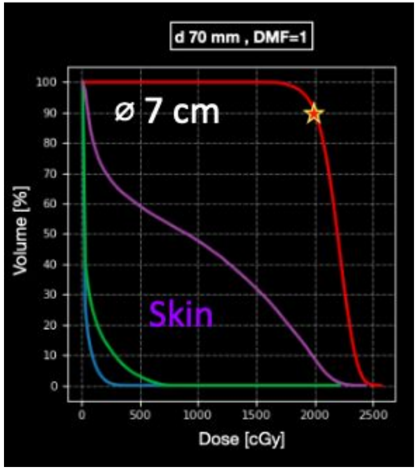
Organo		Protoni	Fotoni	VHEE
PTV	$V_{95\%}$	100%	100%	99.44%
	$V_{100\%}$	90.62%	81.60%	67.41%
	$V_{105\%}$	0.01%	0.01%	1.16%
Nervi Ottici	D_{max}	53.52 GyRBE	54.36 GyRBE	55.61 GyRBE
Chiasma	D_{max}	53.60 GyRBE	54.19 GyRBE	54.59 GyRBE
Vie Ottiche Posteriori	D_{max}	53.81 GyRBE	54.30 GyRBE	55.13 GyRBE
Occhi	D_{max}	2.82 GyRBE	12.62 GyRBE	4.76 GyRBE
Tronco Encefalico	D_{max}	54.26 GyRBE	53.61 GyRBE	54.73 GyRBE
Arterie Carotidi	$V_{105\%}$	0.03%	9.17%	0.19%

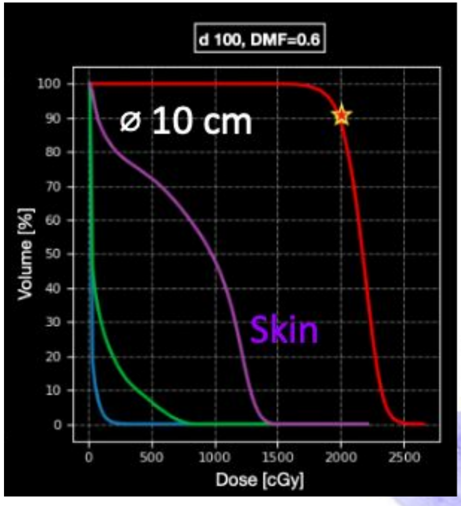


Going FLASH: the IOeRT case









Most likely first example of clinical translation of FLASH.. No TPS so far: being developed right now exploiting GPU fast MC + ecographic input / CT adaptation using breach images

(since now you're probably asleep..)

To satisfy the high expectations of splatter slides, I've just added at the end the 'future' of IOeRT: the treatment of prostate cancer.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3287028/

Conclusions

Exciting time ahead of us

We have the **tools and the knowledge to contribute to the field**: this is an excellent opportunity to contribute to a technology that has the potential to **re-shape the radiotherapy landscape**.. Starting from IOeRT!

Accelerators and detectors R&D

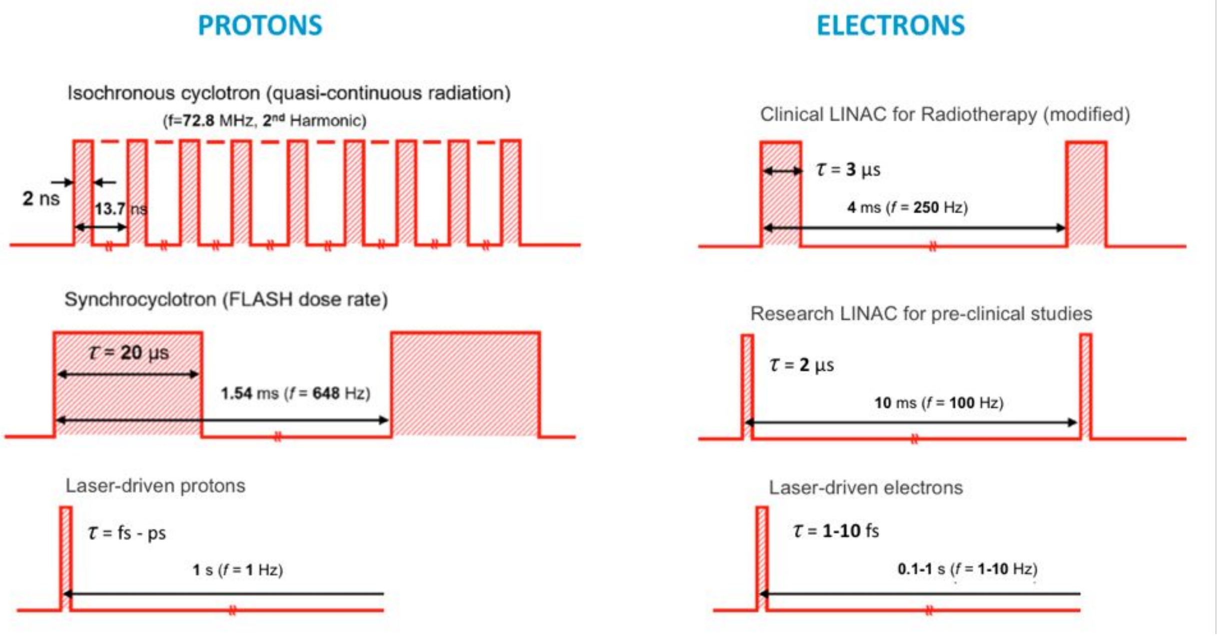
We need to provide access to **facilities and reliable dose measurements** that are the prerequisite for doing the experiments needed to decide the fate of the FLASH effect: the sooner the better!
[and **VHEE have a reason on their own**]

MC simulations and computing

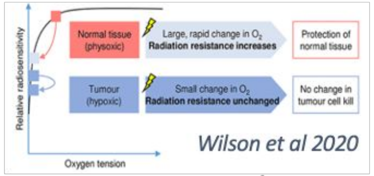
Solving the problem of evaluating the FLASH impact potential helps focusing the efforts in the correct direction: the key is the synergy with **fast MC simulation techniques** and solution of **optimisation problems in many dimensions**

Spare slides

A crucial role is played by the dose delivery time structure..

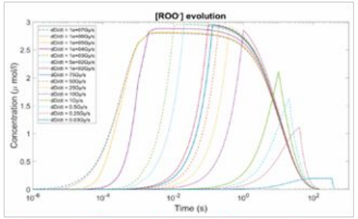


F. Romano et al., Medical Physics (Supplemental issue "FLASH radiotherapy: Current Status and Future Developments", edited by K. Parodi, J. Farr and D. J. Carlson.), under review



Wilson et al 2020

2019-2021 (!)



Labarbe et al 2020

Transient Hypoxia (O_2 Depletion)

- 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)
- R. Abolfath, et al, "Oxygen depletion in FLASH ultra-high-dose-rate radiotherapy: A molecular dynamics simulation." *Med. Phys.* (2020).
- S. Zhou, et al. "Minimum dose rate estimation for pulsed FLASH radiotherapy: A dimensional analysis." *Med. Phys.* (2020).
- A. Hu, et al. "Oxygen depletion hypothesis remains controversial: a mathematical model of oxygen depletion during FLASH radiation."" subm.*arXiv (2021)*
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Organic radical-radical recombination

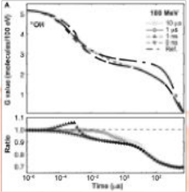
- **R. Labarbe, et al. "A physicochemical model of reaction kinetics supports peroxyl radical recombination as the main determinant of the FLASH effect." Radiother. Oncol. (2020**
- D. R. Spitz, et. al., An integrated physico-chemical approach for explaining the differential impact of FLASH versus conventional dose rate irradiation on cancer and normal tissue responses, Radiother. Oncol. (2019)
- C. Koch, Re: Differential impact of FLASH versus conventional dose rate irradiation, Radiother. Oncol. (2020
- **D. R. Spitz, et al, Response to Ling et al. regarding, Radiother. Oncol. (2020).**
- **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**

Intertrack Effects

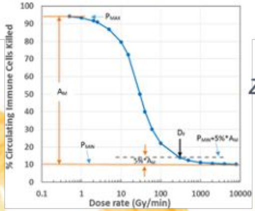
- A.M. Zakaria, et al. "Ultra-High Dose-Rate, Pulsed (FLASH) Radiotherapy with Carbon Ions: Generation of Early, Transient, Highly Oxygenated Conditions in the Tumor Environment." *Rad. Res.* (2020).
- J. Ramos-Méndez, et al. "LET-Dependent Intertrack Yields in Proton Irradiation at Ultra-High Dose Rates Relevant for FLASH Therapy." *Rad. Res.* (2020).
- Alanazi, A., et al.. (2021). A computer modeling study of water radiolysis at high dose rates. Relevance to FLASH radiotherapy. Radiation research, 195(2), 149-162.

Immune system driven

- Zhou, G. (2020). Mechanisms underlying FLASH radiotherapy, a novel way to enlarge 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.



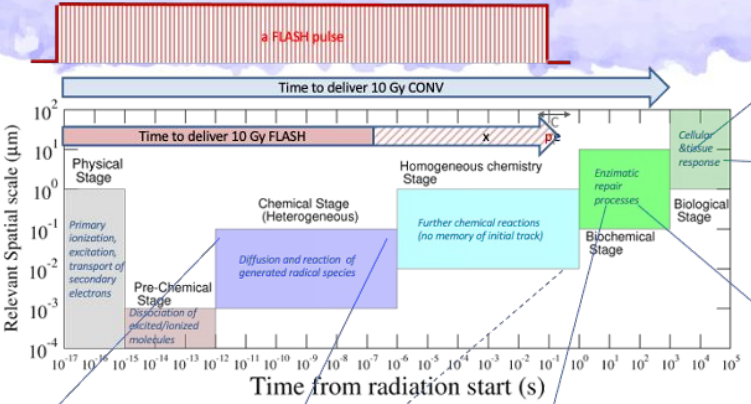
Ramos et al 2020



Zhou et al 2020

- **Multiscale modelling of the FLASH effect**

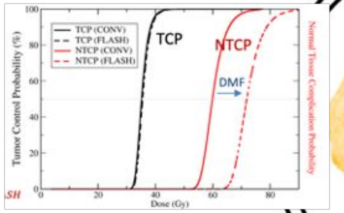
- **Dedicated in vitro/ex vivo experiments**



Weber, Scifoni, Durante subm. Med Phys

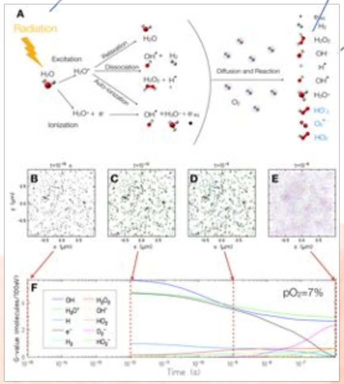
Task 1..3

NTCP modeling



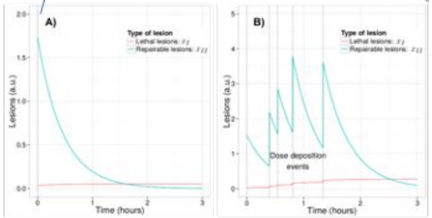
Task1.1

Radiation Chemistry From hetero to homo



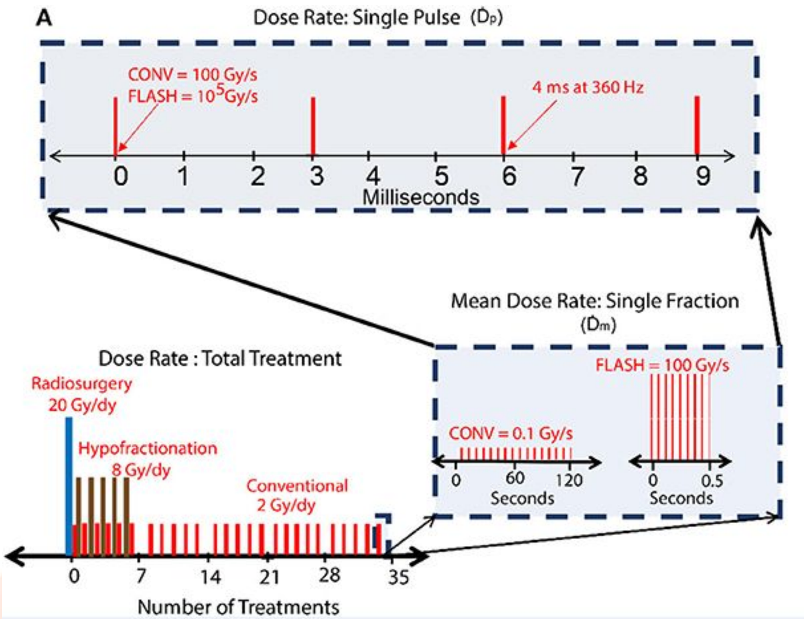
Boscolo et al. Radiother. Oncol. 2021

Task 1.2 DNA damage repair kinetics

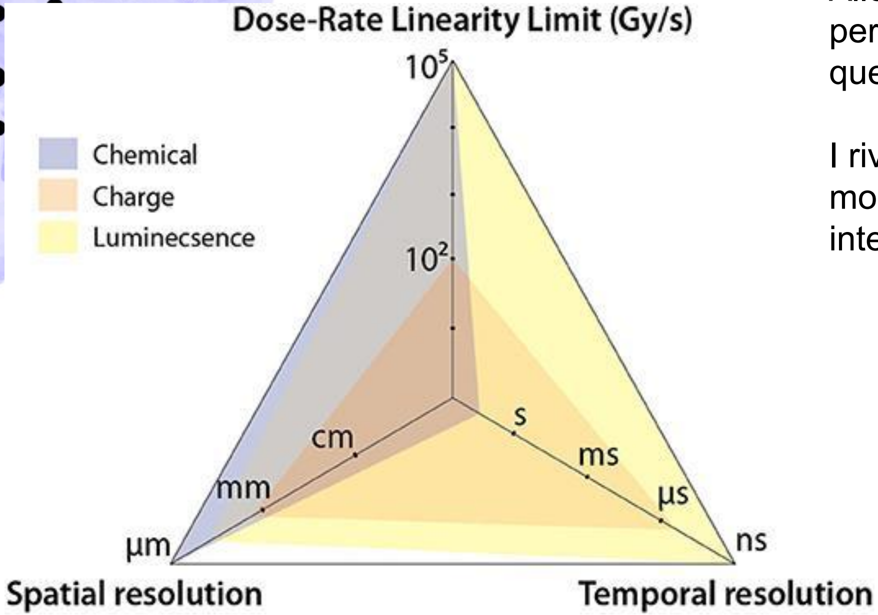


A) Time evolution of lethal (x_I) and potentially lethal/repairable lesions (x_{II}) for a single instantaneous irradiation according to the first order equations of the DDRK used in the MKM. B) Generalization of the temporal evolution for an arbitrary time structured irradiation. The dotted vertical lines represent the energy deposition events in the cell nucleus due to the passage of ionizing particles.

Manganaro wt al Med Phys 2017
Cordoni et al. Rad Res 2021



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



Alle intensità FLASH, il rateo di dose istantaneo e la dose per impulso sono ordini di grandezza più elevati rispetto a quelli della radioterapia convenzionale.

I rivelatori attualmente utilizzati non permettono di monitorare adeguatamente un fascio erogato alle intensità FLASH.

Requisiti necessari per un monitor in modalità FLASH:

- **linearità** con elevati ratei di dose;
- **risoluzione spaziale** (mm);
- monitoraggio **online** del fascio;
- indipendenza dall'**energia** del fascio.

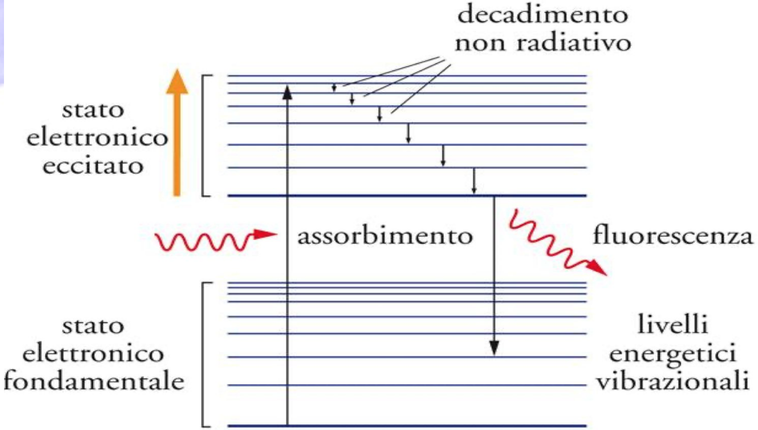
Rivelatori a **carica**: creazione e raccolta di cariche. **Scarsa risoluzione temporale**, **dipendenza dall'energia** e **saturazione** ad alte dosi.

Rivelatori **chimici**: materiali producono ioni e molecole se irradiati. **Scarsa risoluzione temporale.**

Rivelatori **luminescenti**: generazione di fotoni ottici a seguito della radiazione.

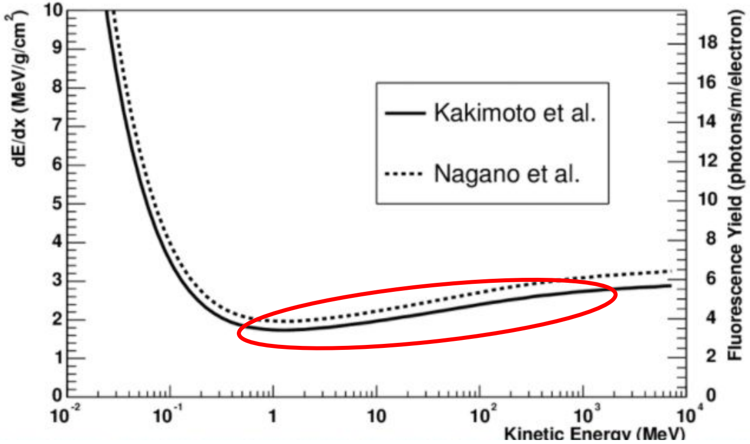
- **TLD** e **OSLD**: impurità nel reticolo cristallino creano dei centri di luminescenza.
- **Scintillatori**: più rapidi di TLD e OSLD.
- **Radiazione Cherenkov**: emissione NON isotropica di fotoni.

La **fluorescenza** presenta delle caratteristiche che rendono un **monitor di fascio** potenzialmente utile per soddisfare le richieste precedentemente elencate.



Radiazione incidente:

- elettroni della materia eccitati dall'energia della radiazione;
- gli elettroni passano ad uno stato instabile a più alta energia;
- l'elettrone decade ad un livello energetico fondamentale ed emette un fotone di fluorescenza.



Resa di fluorescenza:

- **numero di fotoni** emessi per **elettrone** e per **unità di lunghezza** del cammino.
- la resa (ph./m) di un elettrone è proporzionale a **dE/dx** ed è **quasi indipendente** dall'**energia cinetica** degli elettroni.

Il numero di fotoni di fluorescenza emessi a causa del passaggio di un elettrone è quasi piatto: **4 - 5** fotoni di fluorescenza nell'intervallo di energia **10 - 1000** MeV.

4 - 5 fotoni di fluorescenza per metro permettono di misurare i **$10^{10\text{-}12}$** elettroni erogati in modalità FLASH senza avere problemi di **saturazione**.