Medicina di precisione alla frontiera tra fisica, biologia e tecnologie avanzate al Centro Pisano per la Radioterapia Flash

Prospettive cliniche della FLASH-RT: l'impatto di un nuovo paradigma di terapie oncologiche

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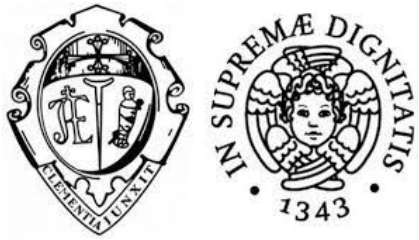
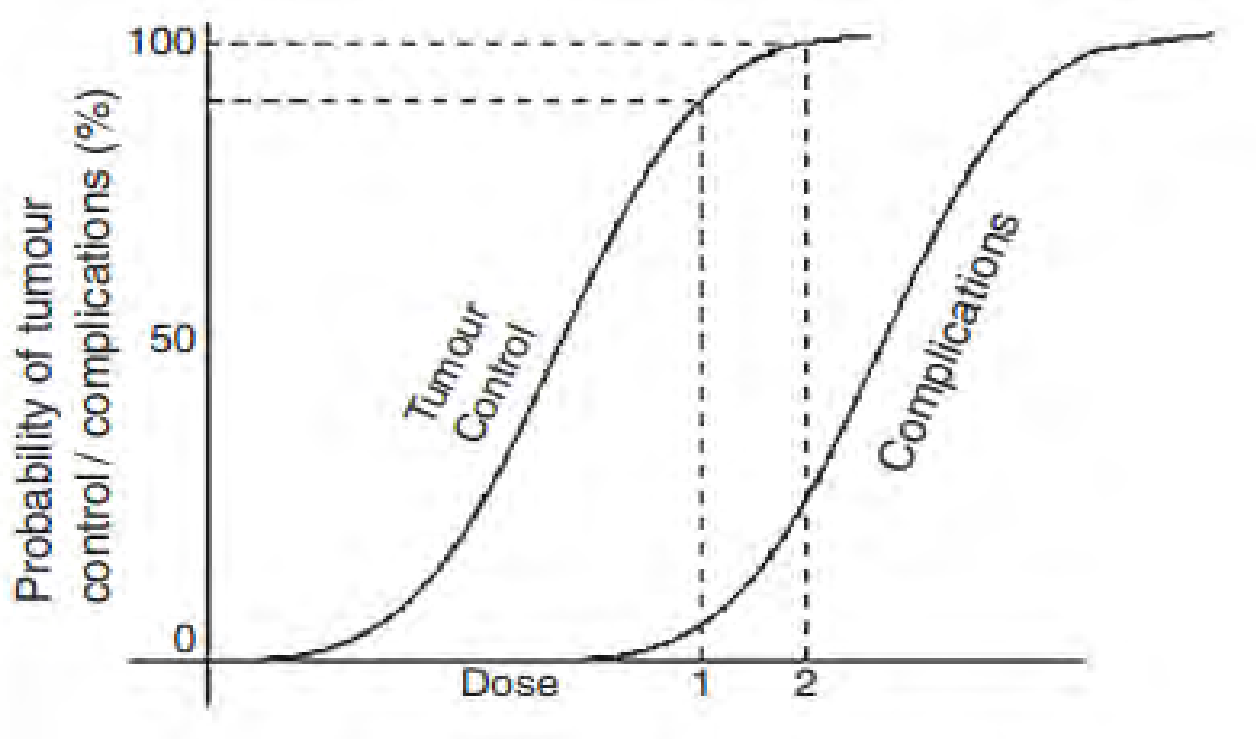
U.O. Radioterapia (AOUP)



Radiation-Therapy

- Locoregional treatment
- No sistemic adverse effects
- Cornerstone of treatment for tumor (curative and palliative setting)
- About two-thirds of all cancer patients will receive radiation therapy as part of their treatment.

Radiation-Therapy



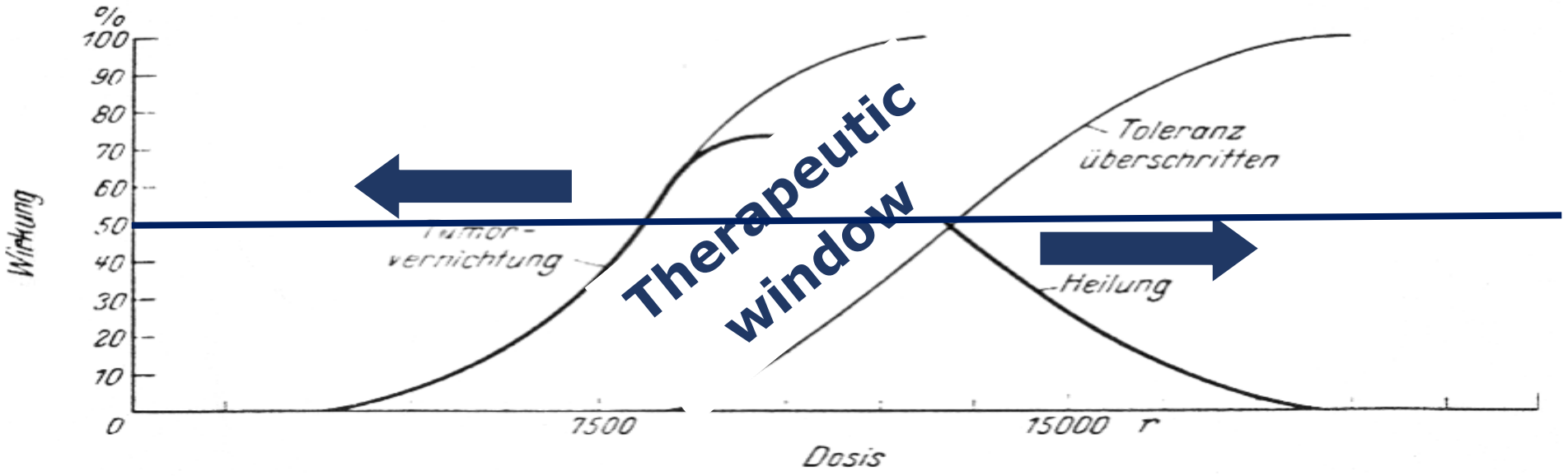
The goal of radiotherapy is to deliver as much dose to the tumour whilst sparing normal tissue. Every dose of radiation delivered to a patient, with the aim of cure of a tumour, is limited by the possibility of serious damage to normal tissues. The balance between the probability of tumour control (TCP) and the risk of normal tissue complications (NTCP) is a measure of the therapeutic ratio of the treatment

Our eternal challenge!

Erfahrungen über die Verträglichkeitsgrenze für Röntgenstrahlen und deren Nutzanwendung zur Verhütung von Schäden*).

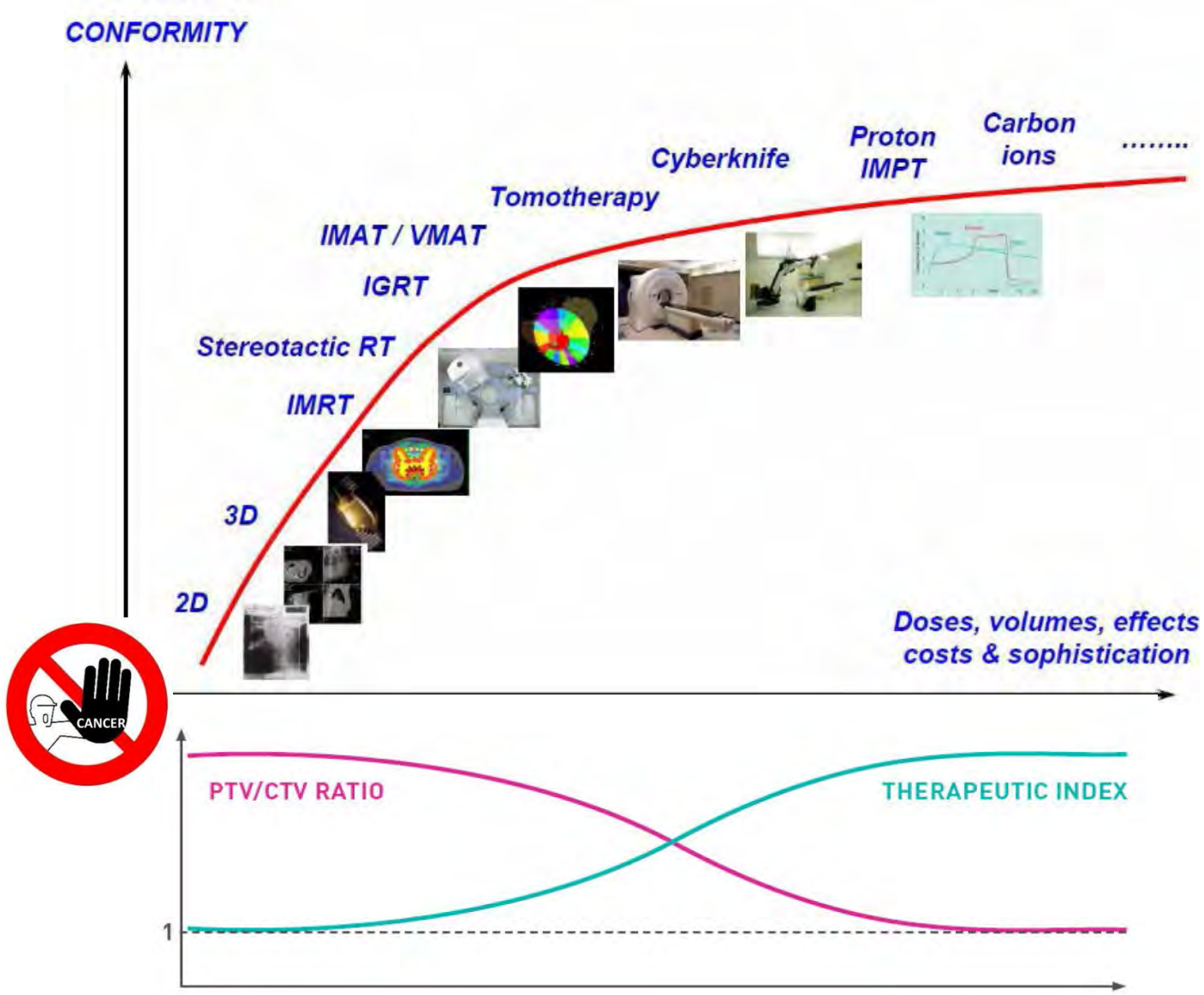
Von

H. Holthusen, Hamburg.



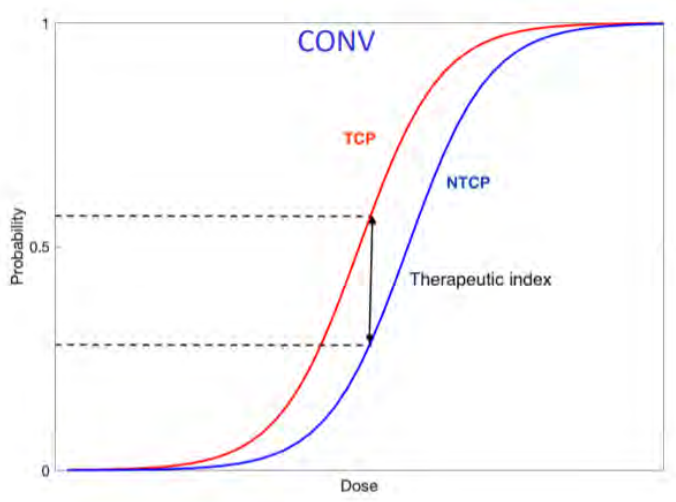
*) Vortrag vor der Deutschen Röntgengesellschaft am 24. April 1936

Technological advances in radiationtherapy



Current state of the art techniques of radiotherapy (IGRT, IMRT and stereotactic radiotherapy) are approaching a plateau

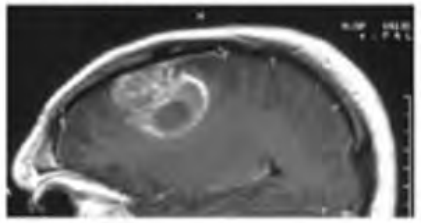
Once we accept our limits, we go beyond them ***(Albert Einstein)***



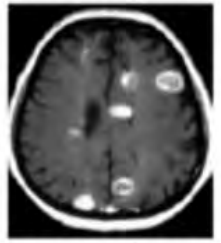
Limitation of ”Conventional” RT

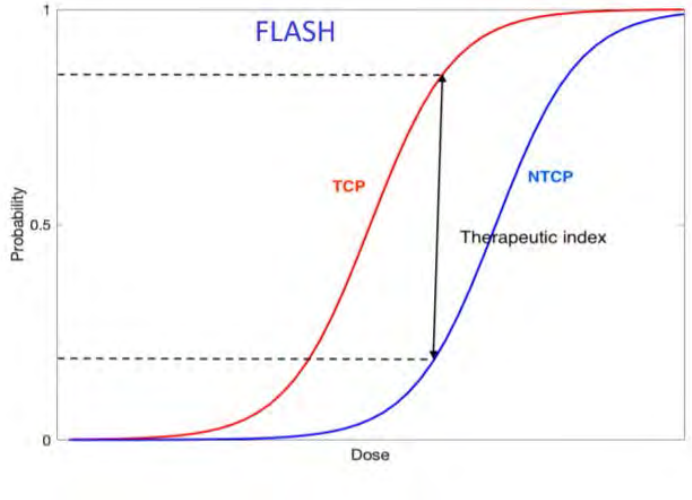
radiation-induced

Radioresistant, bulky and diffuse cancers *(glioblastomas)*



Non-localized tumors *(metastases)*





“Radiation-therapy technology able to deliver at **ultra-high dose rate (≥40 Gy/sec)** **a total dose in 100-200 msec** allow to **treat tumors without inducing drastic toxicities** on the surrounding normal tissues”

possibility of widening the therapeutic "window"

possibility of increasing the therapeutic doses

WHAT DO WE MEAN BY FLASH RADIOTHERAPY AND FLASH EFFECT?

"Radiation-therapy technology able to deliver at **ultra-high dose rate (≥40 Gy/sec)** **a total dose in 100-200 msec** allow to **treat tumors without inducing drastic toxicities** on the surrounding normal tissues"

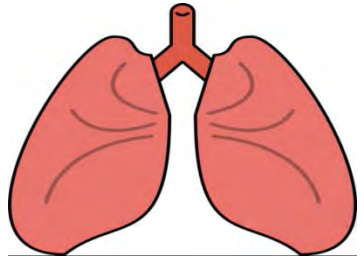
The **FLASH Effect** is a biological phenomenon that consists in a remarkable sparing of normal tissues while the killing effect on tumors is maintained

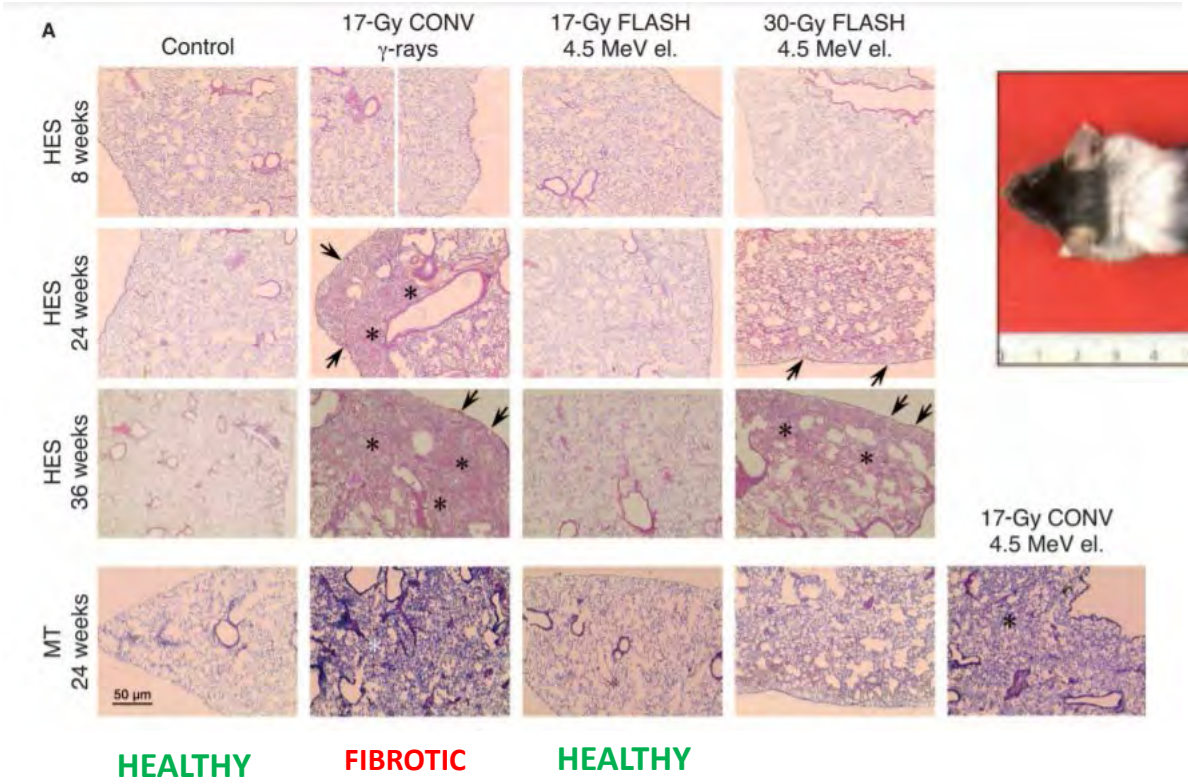
RESEARCH ARTICLE

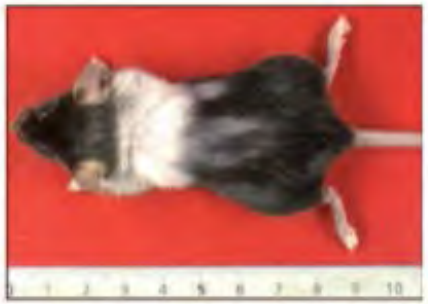
RADIATION TOXICITY

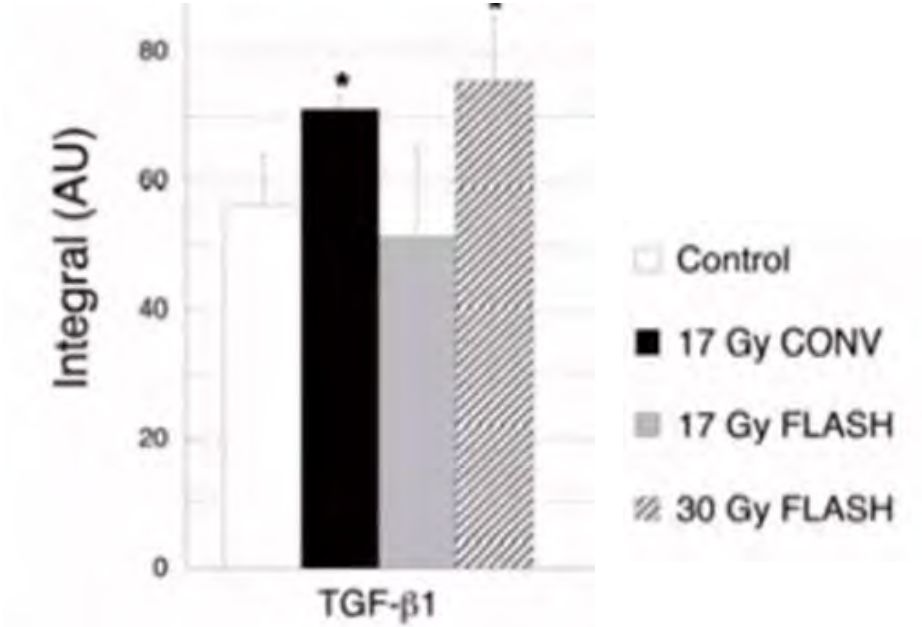
Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice

Vincent Favaudon,[1,2]* Laura Caplier,[3†] Virginie Monceau,[4,5‡] Frédéric Pouzoulet,[1,2§] Mano Sayarath,[1,2¶] Charles Fouillade,[1,2] Marie-France Poupon,[1,2‖] Isabel Brito,[6,7] Philippe Hupé,[6,7,8,9] Jean Bourhis,[4,5,10] Janet Hall,[1,2] Jean-Jacques Fontaine,[3] Marie-Catherine Vozenin[4,5,10,11]



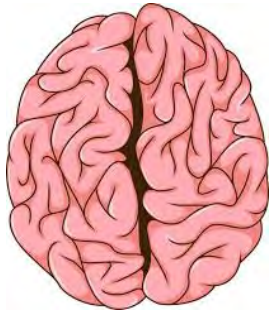






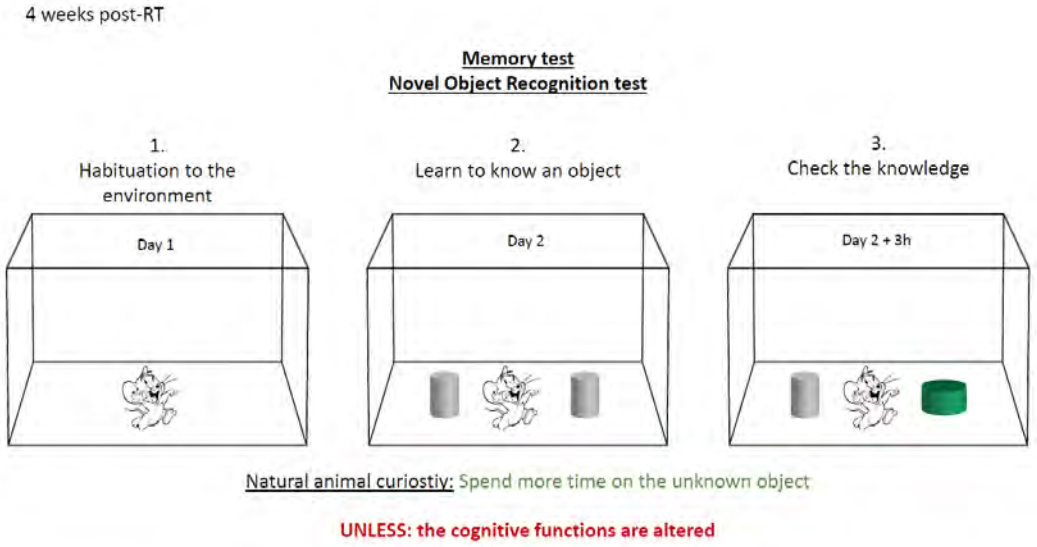
Favaudon et al Sci Transl Med. 2014

Whole brain irradiation - 10 Gy in single dose 6 MeV

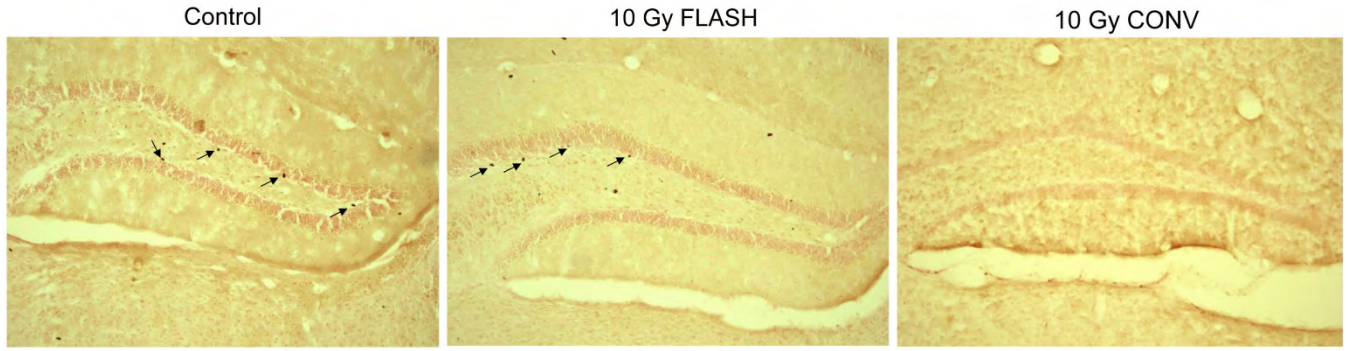


Flash-RT neuroprotective effect is lost below 30 Gy/s but fully preserved above 100 Gy/s

FLASH preserves mouse memory and neurogenesis in the hippocampus provided the beam-on time does not exceed 100 ms



Flash WBI preserves memory and neurogenesis in the hippocampus

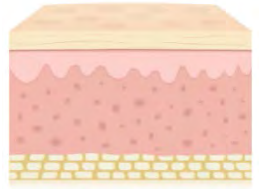


BrdUrd incorporation for visualisation of replicating progenitors (stem) cells (2 months pi)

Montay-Gruel et al. Radiother Oncol 124: 365-9, 2017

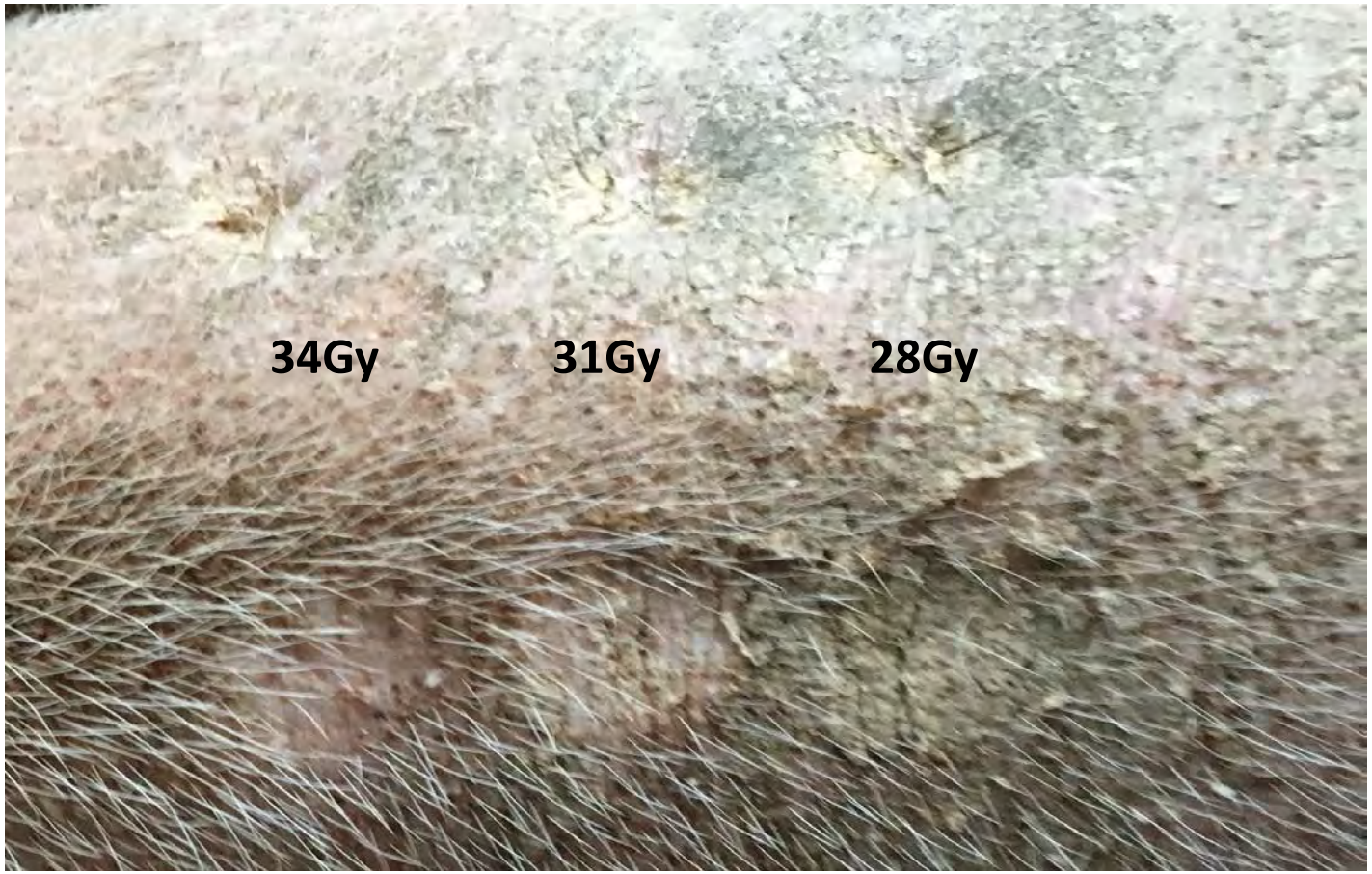
The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients

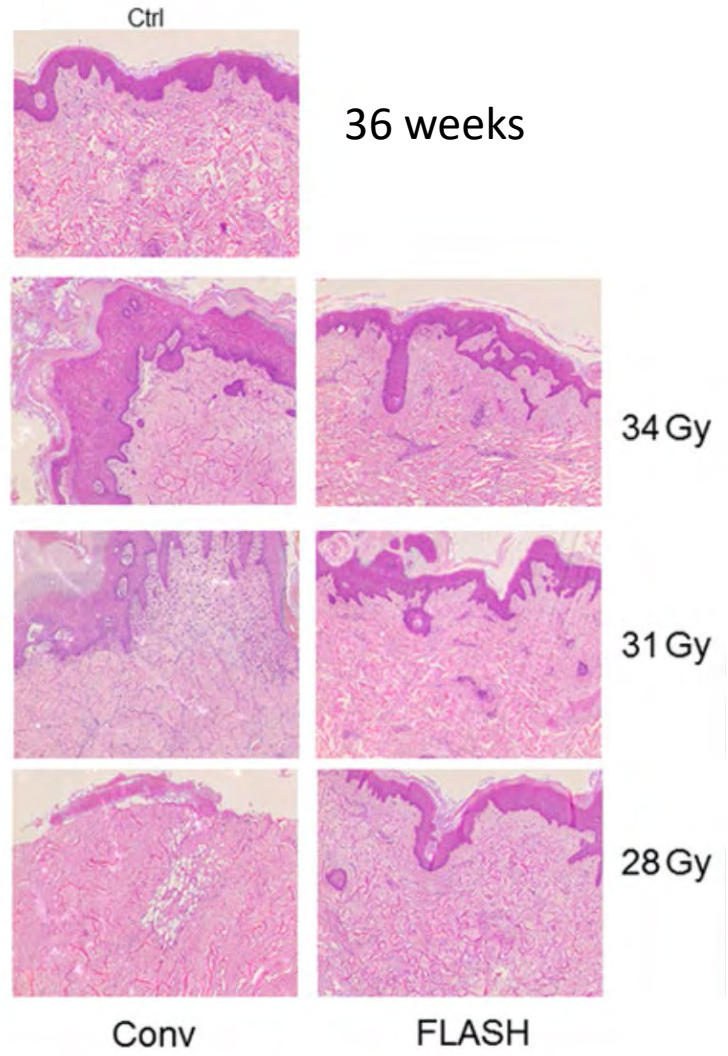
Marie-Catherine Vozenin[1&], Pauline De Fornel [2&], Kristoffer Petersson[1,3 &], Vincent Favaudon[4], Maud Jaccard[1,3], Jean-François Germond[3], Benoit Petit[1], Marco Burki[5], Gisèle Ferrand[6], David Patin[3], Hanan Bouchaab[1], Mahmut Ozsahin[1], François Bochud[3], Claude Bailat[3], Patrick Devauchelle[2*] and Jean Bourhis[1, 6*]



CONV

FLASH





RESEARCH ARTICLE

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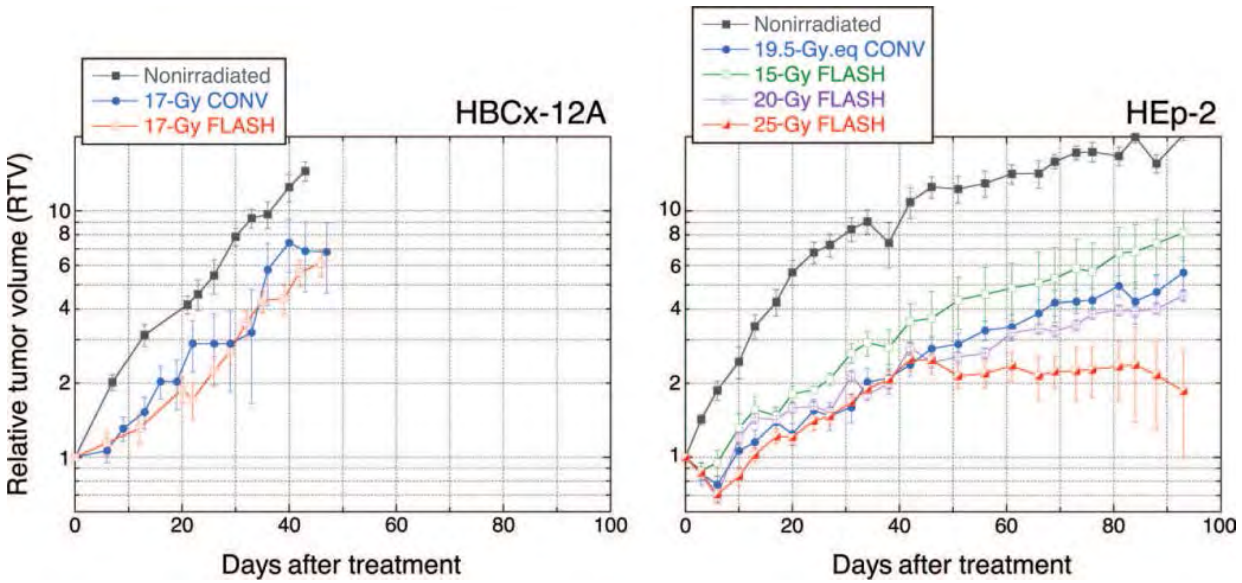
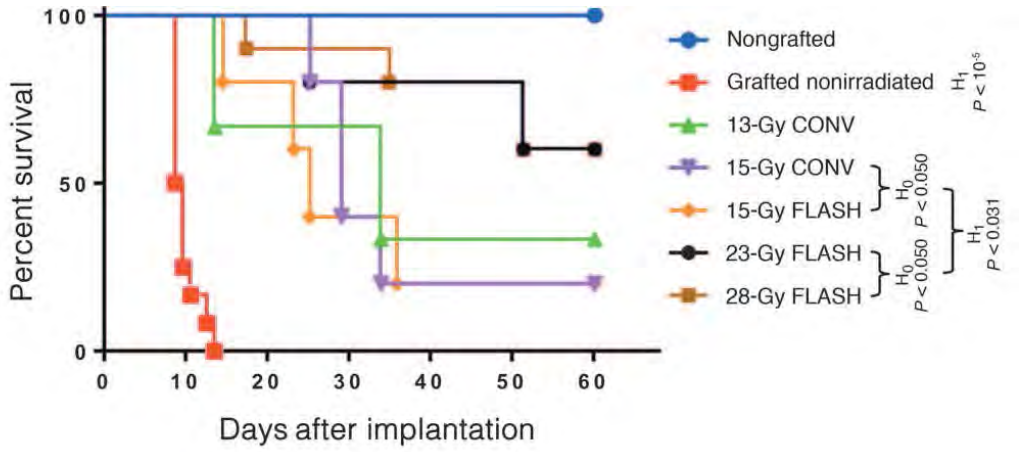
FLASH is as efficient as CONV in controlling Xenografted human tumors



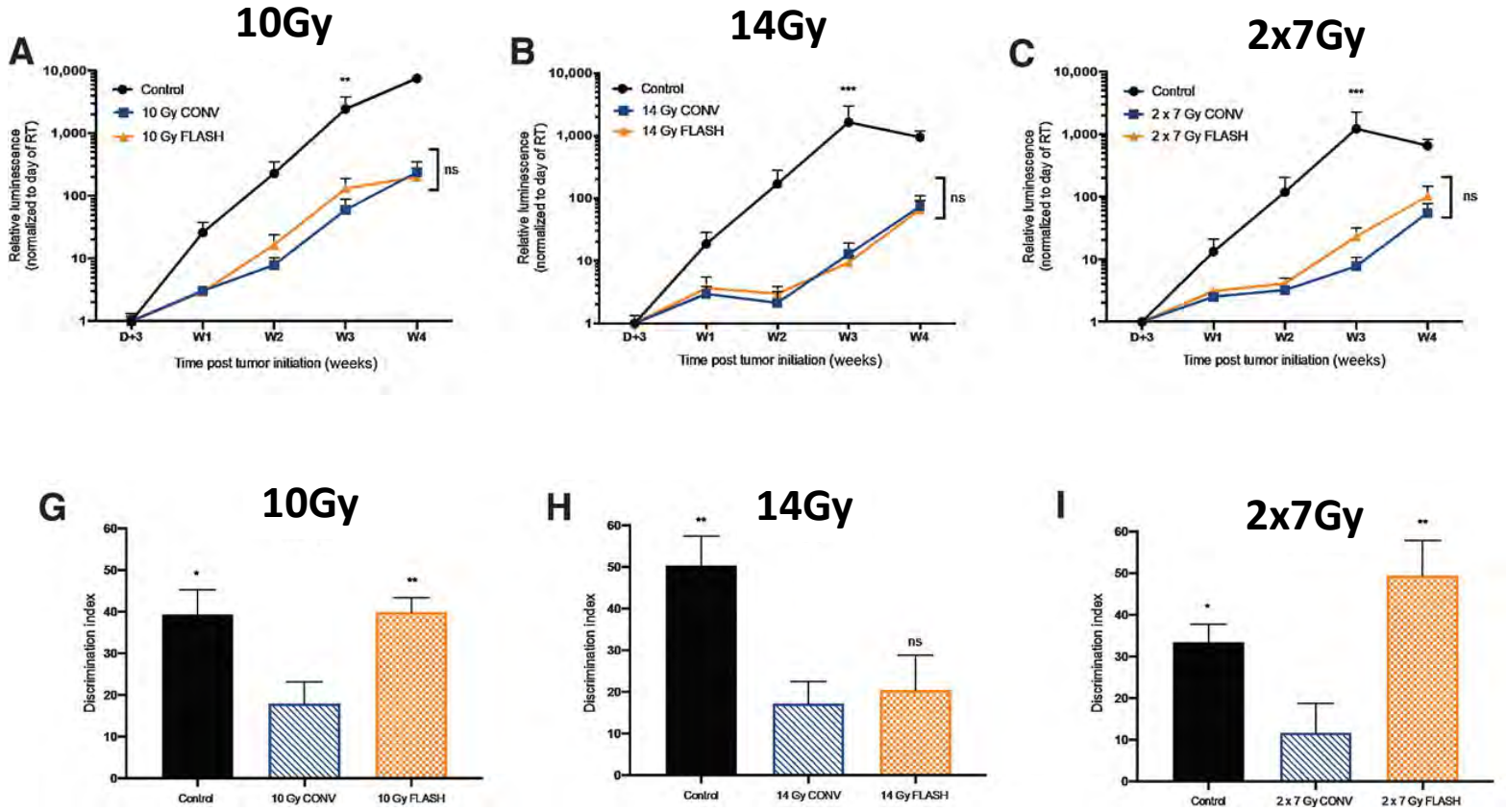
FLASH is as efficient as CONV in controlling syngeneic, orthotopic lung tumors



Favaudon et al Sci Transl Med. 2014

FLASH and CONV-RT have the same antitumor effect !

murine orthotopic glioblastoma model



Pierre Montay-Gruel et al. Clin Cancer Res 2021;27:775-784

Locally advanced T2/T3N0M0 squamous cell ca of nasal planum in cats

The advantage of FLASH radiotherapy confirmed in mini-pig and cat-cancer patients

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25 – 41 Gy

Before RT

@ 7 months

@ 14 months

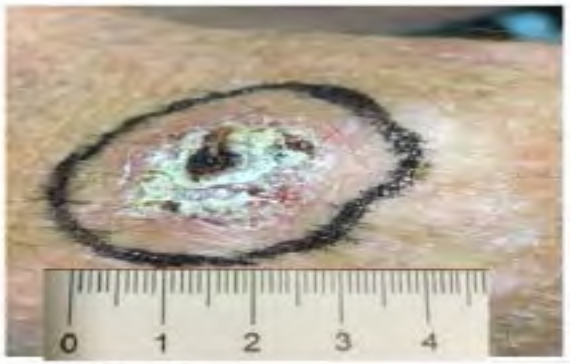
June 2018 · Clinical Cancer Research
DOI: 10.1158/1078-0432.CCR-17-3375

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]

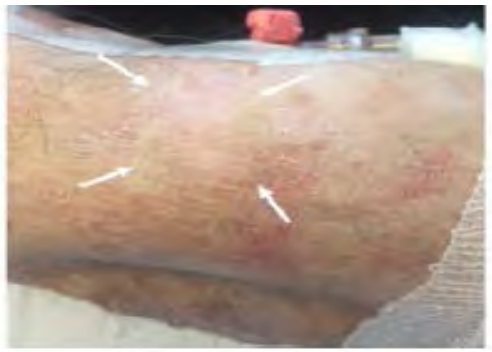
[a] Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [b] Radiation Oncology Laboratory, Department of Radiation Oncology, Lausanne University Hospital and University of Lausanne; [c] Institute of Radiation Physics, Lausanne University Hospital and University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

June 2019



1a : Day 0

1b : 3 weeks



1c : 5 months

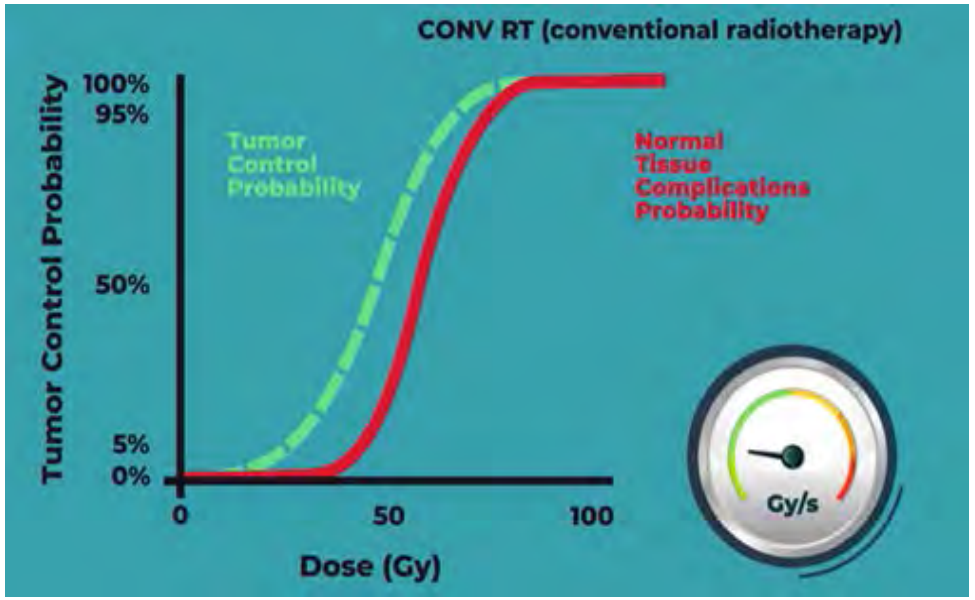
- 75-years old patient with a multi-resistant cutaneous lymphoma
- 15 Gy in 90 ms with 5.6 MeV electrons, to a :
- Healthy tissues: only limited increase of the vascularization.
- Tumour: fast & complete response, ongoing at 5 months

Bourhis et al Radiother Oncol. 2019

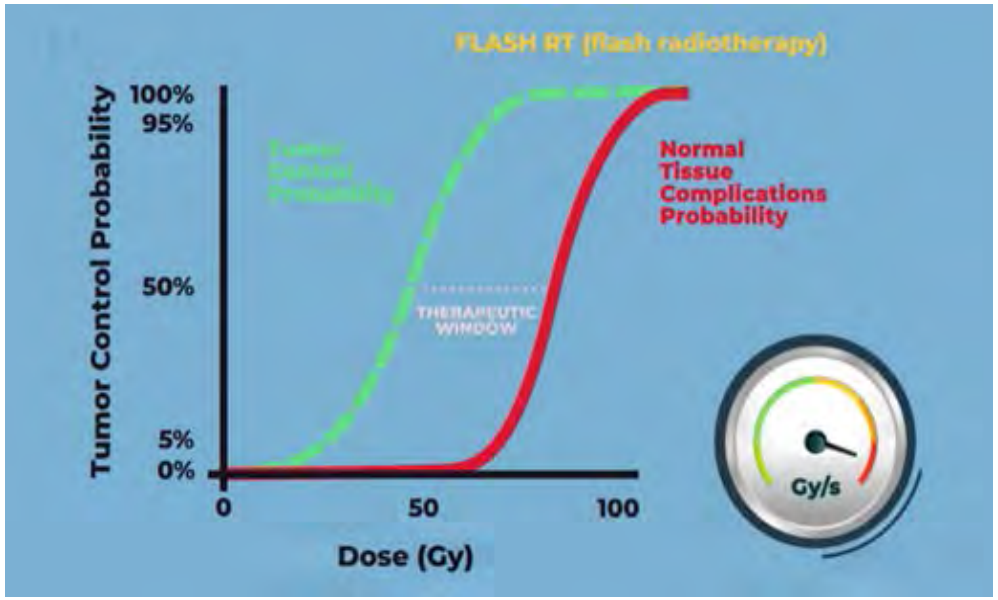
Experimental evidence

- The flash effect exists
- **It has been observed for different kind of normal tissues** (lungs, skin, brain ...) **and tumor (**breast,H&N,glioma,lung,GI) **and has been confirmed in several animal species** (mice, cats, zebrafish ...)
- Using mainly electron beams : electrons of energy 4-7 MeV
- Irradiation parameters: dose-rate > 40Gy/s, total irradiation time < 200ms

Clinical Perspectives



Limitation of ''Conventional'' RT
radiation-induced toxicities



FLASH radiation therapy

Flash-RT would allow:

- To treat radio-resistant tumors increasing total dose without the associated surrounding tissue toxicity of CONV-RT
- To treat diffuse/Non localized tumors where CONV-RT can not deliver tumoricidal doses
- To treat tumors where radiotherapy already offers good local control but without the side effects typical of CONV-RT
- Re-irradiation overcoming the dose limits of the first course of treatment

Theoretical

Radiobiological mechanisms of flash effect

Quantitative

:

• Factors affecting Flash Effect

- ✓ **Dose**
- ✓ **Dose per pulse**
- ✓ **Instantaneous dose per pulse**
- ✓ **Average dose rate**
- ✓ **Total irradiation time**

- ✓ **Volume effect**
- ✓ **Adjacent fields**

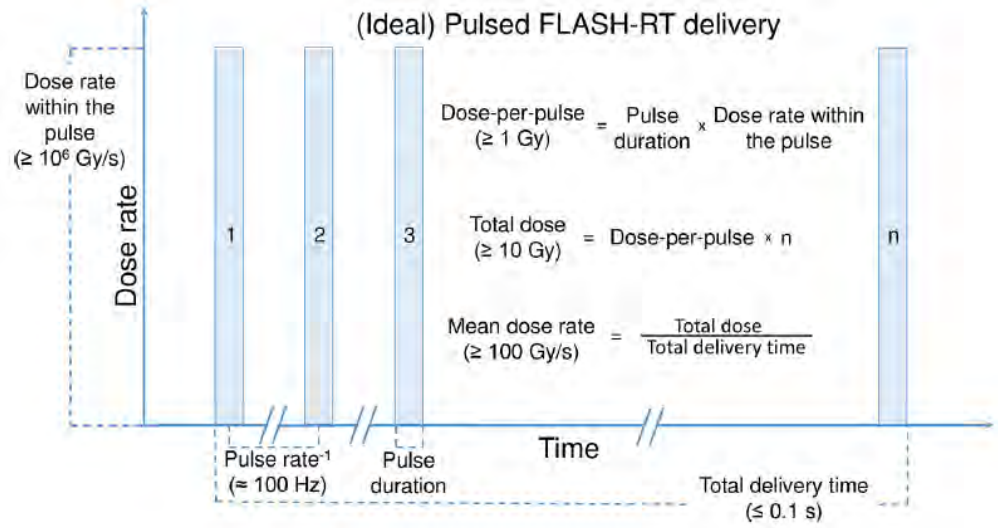
- ✓ **Fractionaction**

Technological

Dosimetry and beam monitoring for UHDP beams

Development of Flash linac with **V**ery **H**igh **E**nergy **E**lectrons (VHEE 100-250 MeV)

Open questions



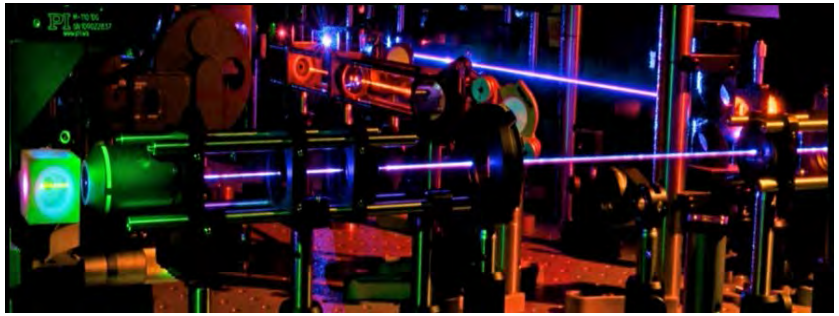
What do we need to understand theoretical and quantitative issues?

- ✓A dedicated Flash Device
- ✓Dosimetry for UHDP
- ✓A Multidisciplinary team

CPFR Facilities

Flash RadioBio Lab

Imaging Core-facilities for in vitro and in vivo exps



Pisa University Green Data Center

- ✓**FAIR Data: storage & managment**
- ✓ **Numerical Codes: shared -repository**
- ✓**High Performance Computing**

Triode-Gun- based EF LINAC

Quantitative experiments evaluating one beam parameter at a time keeping unchanged all the others

Switch from CONV to Flash keeping the experimental setup unchanged	Evaluation of beam parameters on FE changing one parameter at a time
• Decrease of **experimental uncertanties**	• **Variation of the pulse size keeping fixed the dose-per-pulse to study the dependence from the IDPP** (instantaneous dose-per-pulse) • **Variation of the irradiated volume keeping fixed the dose-per-pulse to study volume effect**

CPFR Research Program Main Goals

SKIN

- ✓2D biological array for radiobiological experiments
- ✓ Skin tumours: Flash-RT tumour response/ initial clinical application of low energy EF
- ✓ Healthy skin: fundamental organ at risk for the VHEE

BRAIN AND RETINA

- ✓Promising results from preclinical data (neurocognitive sparing flash effect)
- ✓Poor prognosis of primary tumors and metastases
- ✓Specific expertise in “in vivo” quantitative-functional analysis and “ex vivo” models

SPINAL CORD

- ✓Cornerstone of primary organs at risk in clinical practice
- ✓ Yet to be investigated (most available data focused on brain, lung and bowel)

CPFR Research Program Main Goals

CLINICAL GOALS

- *for Flash low-energy electron beams*

- **Pre-clinical in vivo studies**
- **Development of a clinical dosimetric protocol**
- **Development of a patient positioning and centering system**
- **Development of a specific TPS (Treatment Planning System)**

SKIN TUMORS
UVEAL MELANOMA
CLINICAL TRIALS

CONCLUSIONS

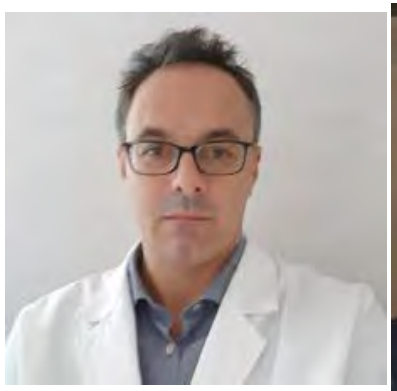
Flash-Radiotherapy is emerging as a treatment technique with the great potential to increase the therapeutic index of radiation.

There are still many open questions yet to be answered for its wide clinical use but today with the dedicated devices available, the skills and experience we can fill these gaps of knowledge.

To go **faster** in the development and **optimization of clinical devices** is essential to **join efforts** by creating a research network aimed to:

- ✓share experimental data and results
- ✓achieve common protocol (experimental, dosimetric, clinical).

Acknowledgments

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