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

Effetto Flash:
La ricerca multidisciplinare tecnologica, dosimetrica e radiobiologica necessaria alla sua ottimale implementazione clinica

Fabio Di Martino

U.O. Fisica Sanitaria (AOUP)

- Cosa sappiamo sull'effetto Flash
- Perché sappiamo così poco
- Cosa sarebbe fondamentale sapere per la sua ottimale e completa implementazione clinica
- Come si possono ottenere le risposte cercate e cosa può fare in questo senso il CPFR

Quello (poco) che sappiamo, che l’effetto è innescato da dose-rate > 40-100 Gy/s, T < 100-200 ms, D > 5-10 ??? è la causa delle difficoltà avute fino ad ora per conoscere meglio l’effetto perché è alla base di problemi:

Tecnologici

Dosimetrici

Radiobiologici

Clinici

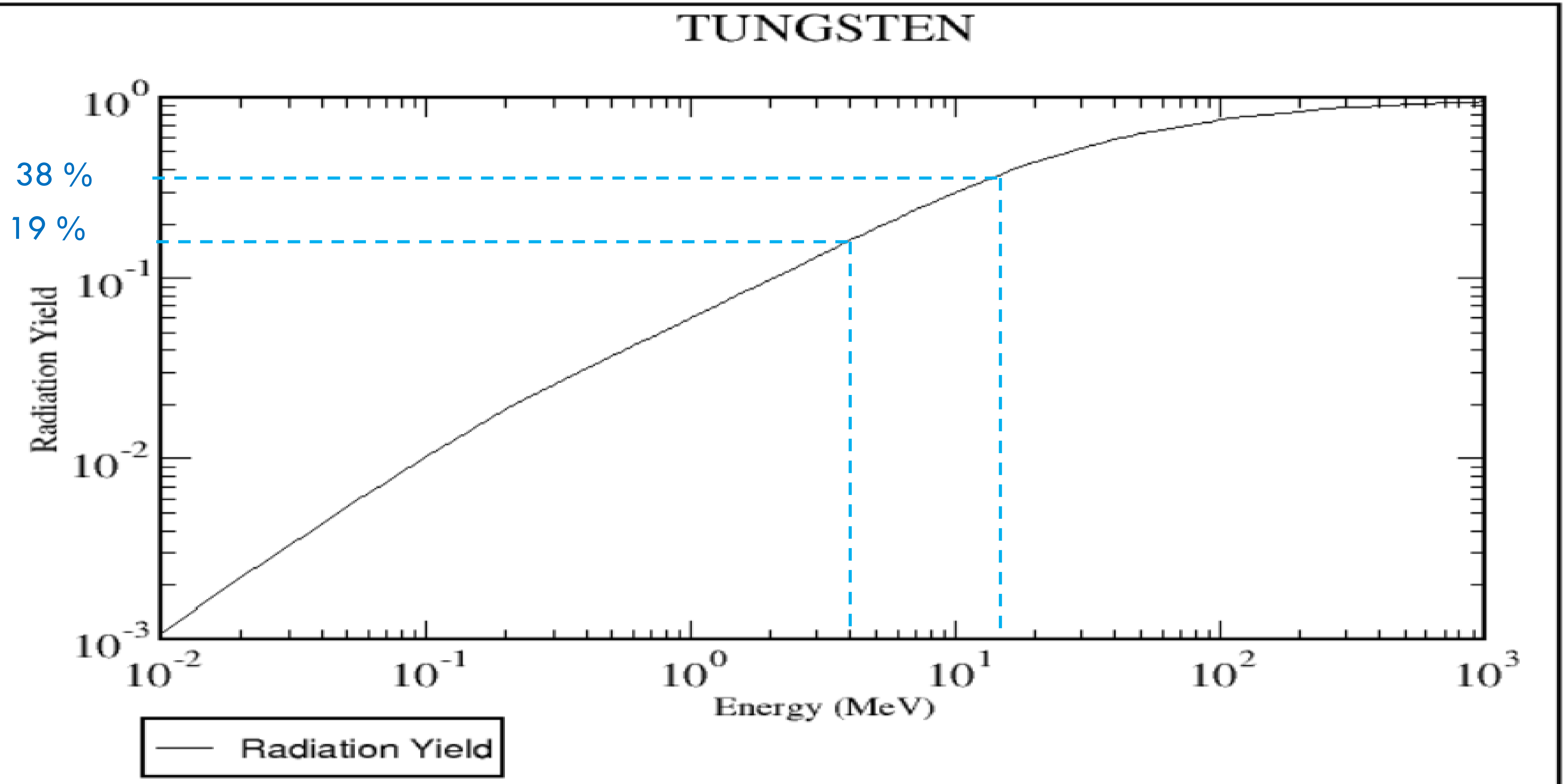
Problemi tecnologici

Difficoltà a produrre altissimi valori di dose-per-pulse in modo uniforme, stabile e riproducibile su volumi sufficientemente ampi

Difficoltà a monitorare l'erogazione del fascio

Difficoltà a sviluppare i sistemi di sicurezza necessari all'impiego clinico

Electrons vs X-ray



[NIST Website](https://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html)
https://physics.nist.gov/PhysRefData/Star/Text/ESTAR.html

Electron vs X-ray

POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Habib Zaidi, Geneva University Hospital, Geneva, Switzerland: habib.zaidi@hcuge.ch; Jing Cai, The Hong Kong Polytechnic University, Hong Kong: jing.cai@polyu.edu.hk; and/or Gerald White, Colorado Associates in Medical Physics: gerald.white@mindspring.com. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

FLASH radiotherapy: Newsflash or flash in the pan?

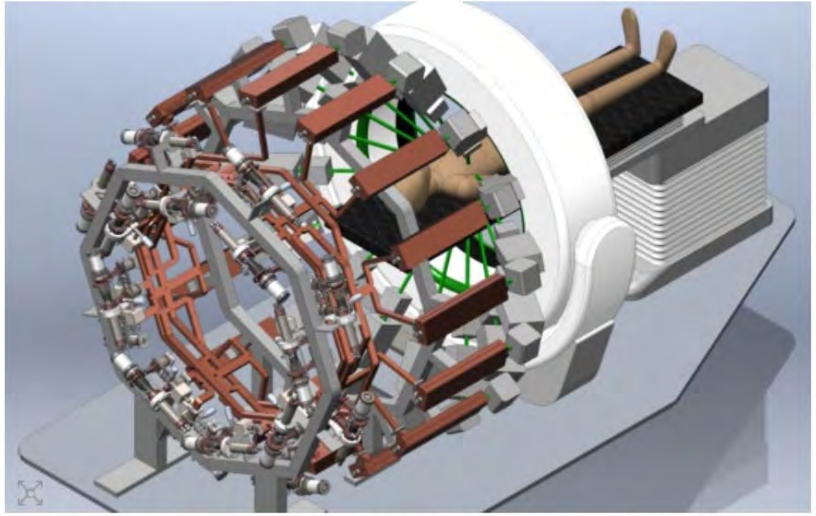
Peter G. Maxim, Ph.D.
Department of Radiation Oncology, Indiana University School of Medicine, Indianapolis IN 46202, USA
(Tel: 317-944-1185; E-mail: pmaxim@iu.edu)

Paul Keall, Ph.D.
ACRF Image X Institute, University of Sydney, Camperdown, NSW 2006, Australia
(Tel: 61-2-8627-1159; E-mail: paul.keall@sydney.edu.au)

Jing Cai, Ph.D., Moderator

PHASER linac will translate FLASH radiotherapy to the clinic

04 Jul 2019 Tami Freeman



Conceptual rendering of the PHASER system. (Courtesy: *Radiother. Oncol.* 10.1016/j.radonc.2019.05.005)

1. *Does FLASH delivery technology exist for humans? No.* And it will not exist for the foreseeable future. Ignoring VMAT, let's assume that a state-of-the-art treatment would require five to seven intensity-modulated beams. As massive amounts of radiation are being delivered in a short time, real-time adaptive radiotherapy would be necessary to ensure the delivered dose is close to the planned dose. To achieve the benefits of FLASH and delivering the entire dose quickly, the following technologies — that currently do not exist — need to be developed:

a. A configuration of five to seven FLASH beams to be delivered simultaneously.
b. Fast FLASH intensity modulation. Currently limited by leaf speed, intensity modulation on a subsecond scale requires new technology to be built.
c. Real-time FLASH adaptation. Given the higher requirements on motion management for stereotactic radiation therapy,[18] it is even more important for the FLASH beam to be adapted in real-time to ensure the beam and the target are aligned.

Electrons vs Protons

A lot of research is ongoing on protons, but:

Electrons are easier to accelerate !

Definitely cheaper, both technology and installation

Electrons can provide higher dose rates

The experimental evidence was obtained using electron beams

The collimation of the beam requires not negligible mechanical times

Technical Challenges for FLASH Proton Therapy

Simon Jolly[a,*], Hywel Owen[b,c], Marco Schippers[d], Carsten Welsch[b,e]

[a] University College London, United Kingdom
[b] Cockcroft Institute of Accelerator Science and Technology
[c] University of Manchester, United Kingdom
[d] Paul Scherrer Institute, Switzerland
[e] University of Liverpool, United Kingdom

↓

….. Nevertheless the dosimetric characterization of the electron beams may be the most challenging!!!


RADIO
ONCOLOGIE
Danger
High voltage
Danger
High voltage
Unil
UNIL | Université de Lausanne
CHUV

institut Curie

Ultra-High Dose Rate Linear Accelerator: KINETRON

(1987 - 🛠🛠)

frontiers in Physics

ORIGINAL RESEARCH
published: 11 September 2020
doi: 10.3389/fphy.2020.00374

Transforming an IORT Linac Into a FLASH Research Machine: Procedure and Dosimetric Characterization

Giuseppe Felici[1], Patrizio Barca[2], Salvatore Barone[1], Eleonora Bortoli[2], Rita Borgheresi[2], Silvia De Stefano[1], Massimo Di Francesco[1], Luigi Grasso[1], Stefania Linsalata[2], Daniela Marfisi[2], Matteo Pacitti[1] and Fabio Di Martino[2]**

[1] R&D Department, Sordina IORT Technologies, Aprilia, Italy, [2] U.O. Fisica Sanitaria, Azienda Universitaria Ospedaliera Pisana, Pisa, Italy

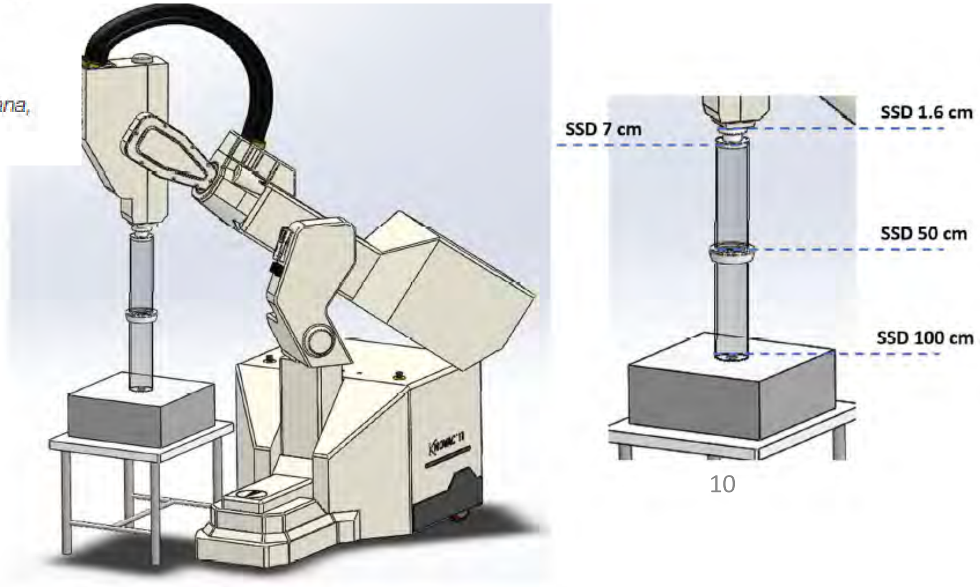
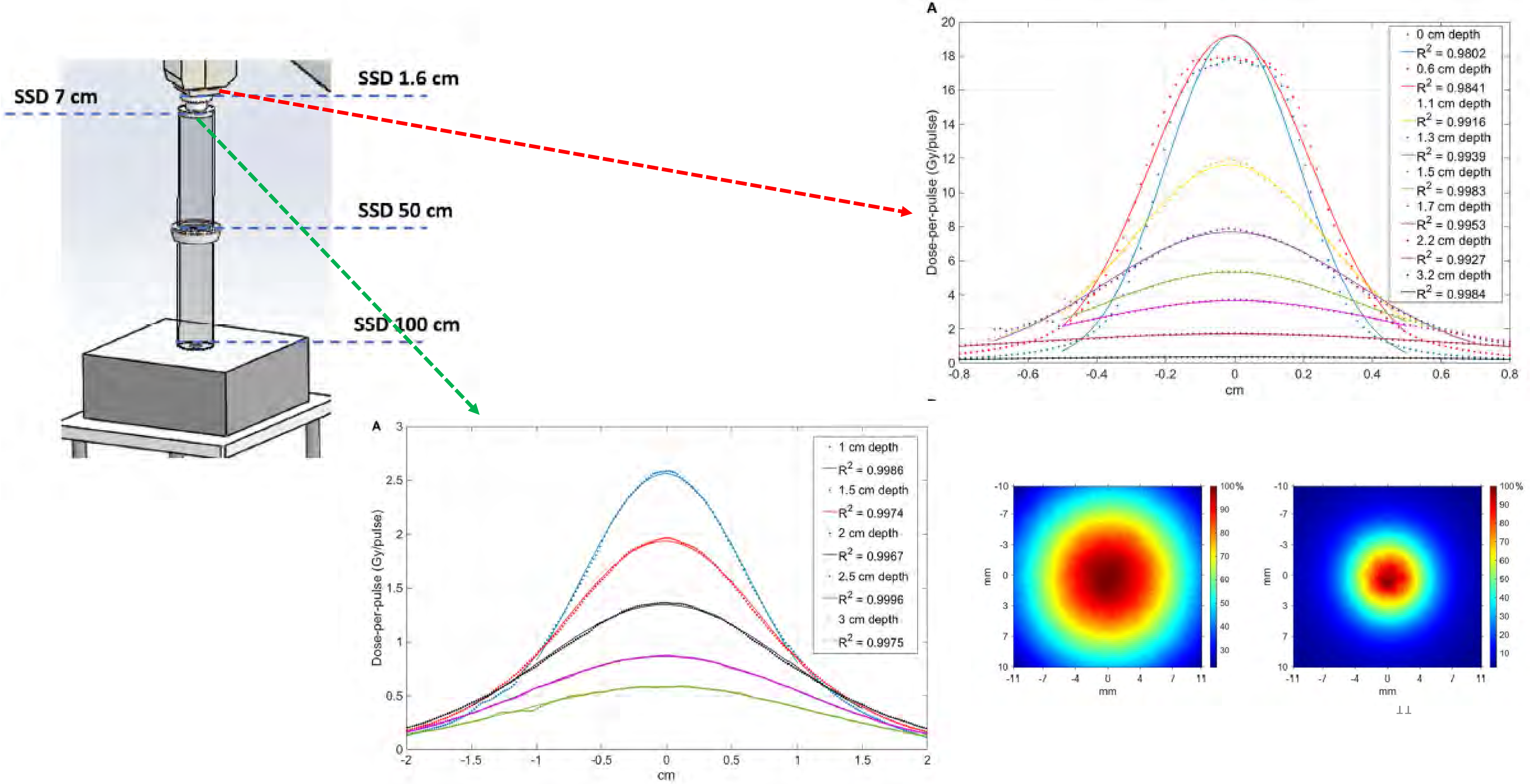
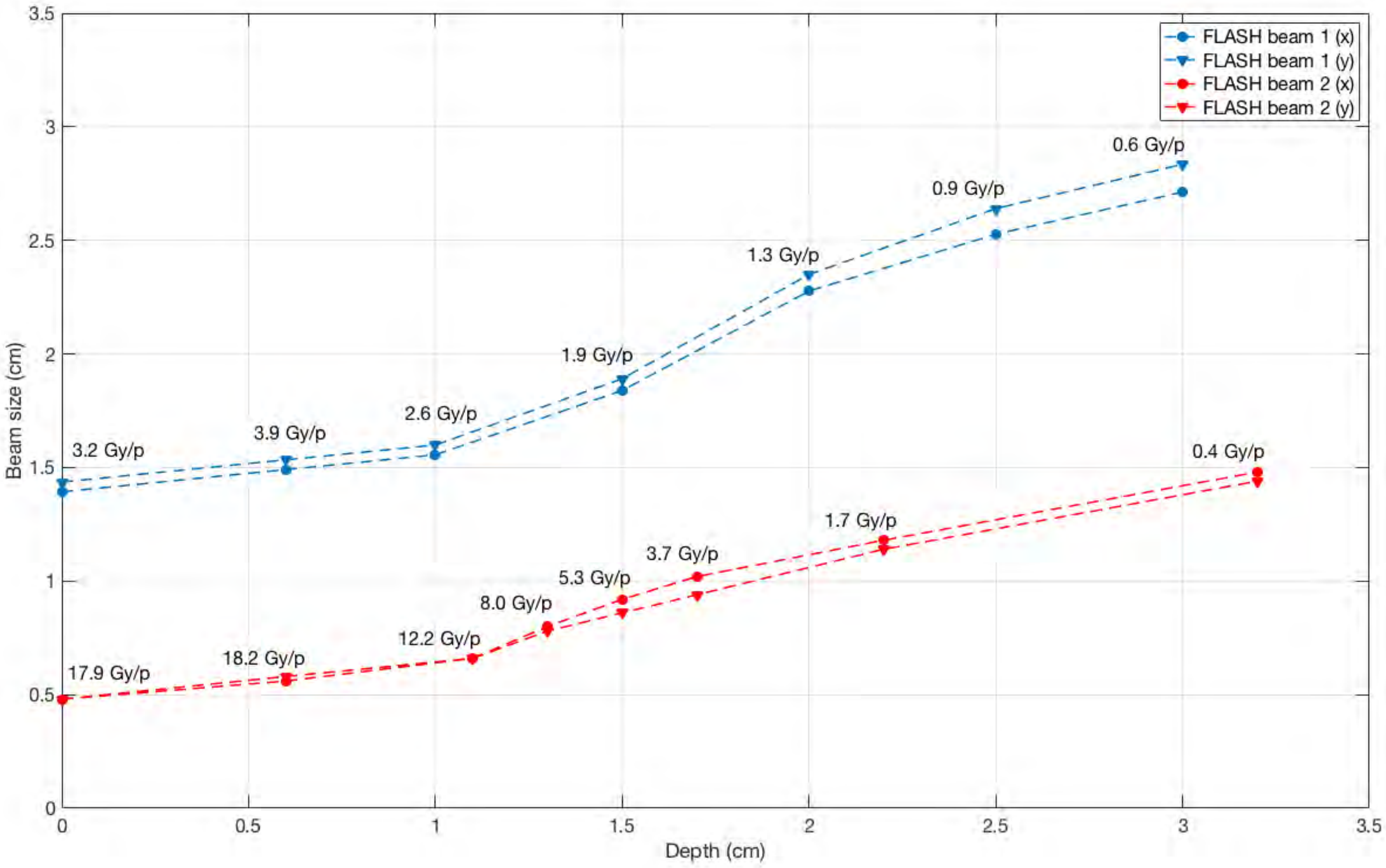


FIGURE 1 | Four collimation configurations obtained acting on Novac7 collimation system architecture.


SSD 1.6 cm
SSD 7 cm
SSD 50 cm
SSD 100 cm
A
Dose-per-pulse (Gy/pulse)
cm
0 cm depth
R^2 = 0.9802
0.6 cm depth
R^2 = 0.9841
1.1 cm depth
R^2 = 0.9916
1.3 cm depth
R^2 = 0.9939
1.5 cm depth
R^2 = 0.9983
1.7 cm depth
R^2 = 0.9953
2.2 cm depth
R^2 = 0.9927
3.2 cm depth
R^2 = 0.9984
A
Dose-per-pulse (Gy/pulse)
cm
1 cm depth
R^2 = 0.9986
1.5 cm depth
R^2 = 0.9974
2 cm depth
R^2 = 0.9967
2.5 cm depth
R^2 = 0.9996
3 cm depth
R^2 = 0.9975
mm
100%


HIGH VOLTAGE
IONIZING RADIATION


FLASH beam 1 (x)
FLASH beam 1 (y)
FLASH beam 2 (x)
FLASH beam 2 (y)
Beam size (cm)
Depth (cm)
3.2 Gy/p
3.9 Gy/p
2.6 Gy/p
1.9 Gy/p
1.3 Gy/p
0.9 Gy/p
0.6 Gy/p
17.9 Gy/p
18.2 Gy/p
12.2 Gy/p
8.0 Gy/p
5.3 Gy/p
3.7 Gy/p
1.7 Gy/p
0.4 Gy/p
0
0.5
1
1.5
2
2.5
3
3.5

Caratteristiche ottimali che deve avere un Linac Flash per gli esperimenti

- Possibilità di variare i parametri del fascio in modo continuo e riproducibile su ampi volumi ed entro un ampio range

- Possibilità di irradiare in condizioni CONV e FLASH non variando il setup sperimentale

- Possibilità di variare I parametri di interesse in modo indipendente

- Possibilità di avere un sistema di monitoraggio della fluenza e dell'energia del fascio affidabile

Temporal structure of the beam

Table 1: Terminology used throughout the text.

Term	Symbol	Description
Pulse width	-	The duration of a single pulse.*
Mean dose-rate	$\bar{\dot{D}}$	Mean dose-rate for a multi-pulse delivery.
Intra-pulse dose-rate†	$\dot{D}_P$	Dose-rate in a single pulse.*
Dose per pulse	DPP	Dose in a single pulse.*
Pulse repetition frequency	PRF	Number of pulses delivered per unit time.*
Irradiation time	t_i	Total irradiation time from the beginning of the first delivered pulse to the end of the last delivered pulse.
Ultrahigh dose-rate	-	Radiation delivered with mean dose-rate of > ~40 Gy/s
FLASH-RT	-	Ultrahigh dose-rate RT that presents decreased damage to normal tissues compared to RT delivered with conventional dose–rate of ~0.04 Gy/s.

* Pulses are considered to be macro-pulses unless otherwise stated (see also Figure 1).

† In literature sometimes referred to as the instantaneous dose-rate.

TEMPORAL BEAM STRUCTURE

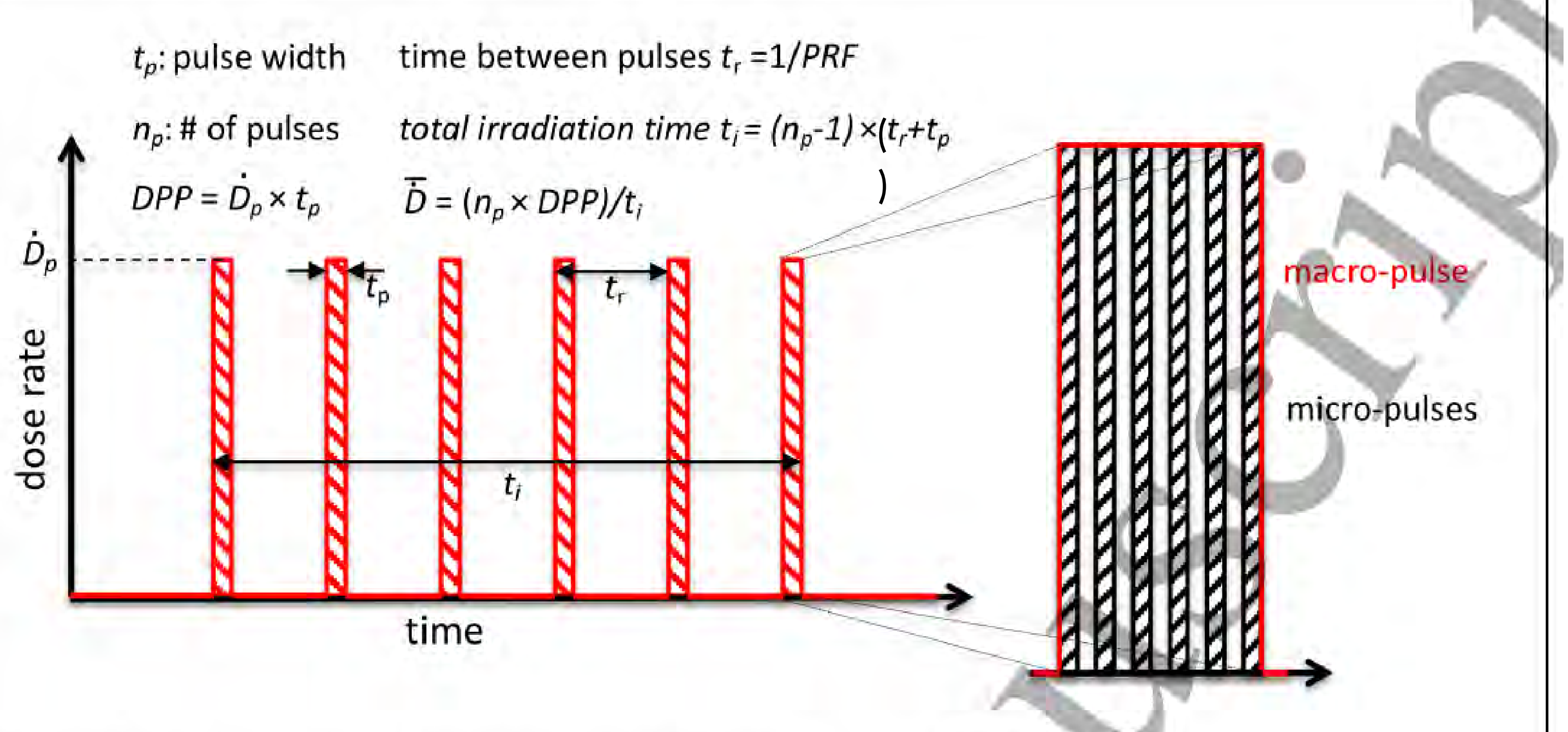


Figure 1: Schematics of beam temporal structure.

$$\dot{D} = \text{Inst Dose Rate} = \frac{DPP}{t_p}$$

$$\bar{\dot{D}} = \text{Avg. Dose Rate} = \frac{\#N_{pulses} \cdot DPP}{\text{total irradiation time}}$$

Temporal beam structure

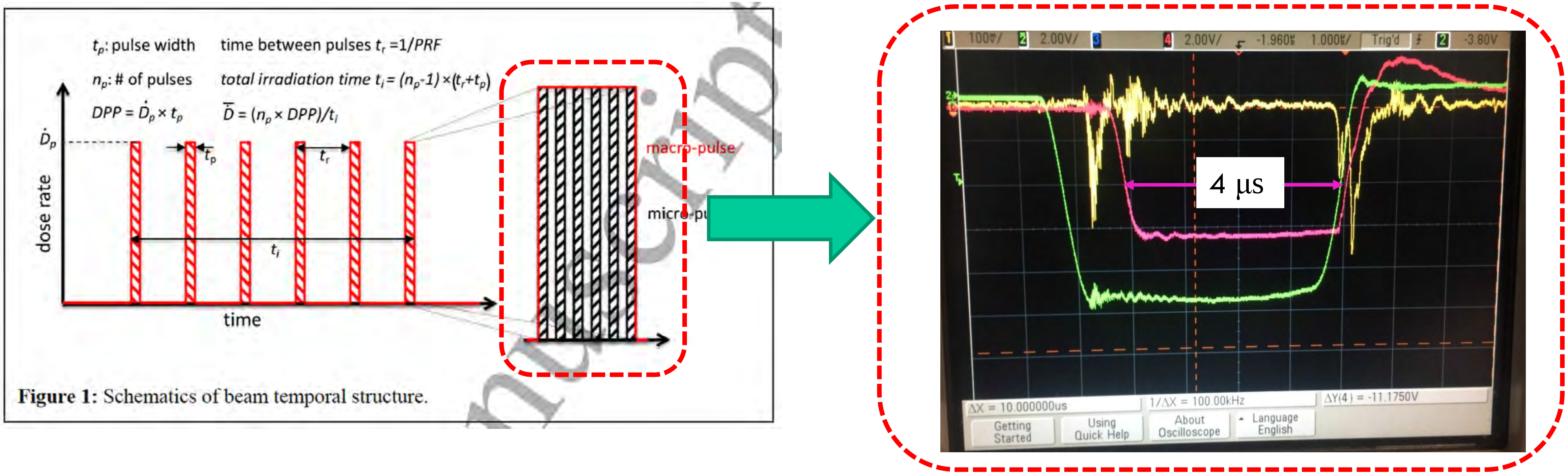


Figure 1: Schematics of beam temporal structure.

$$\begin{cases} t_p & 1-4\ \mu s \\ t_r = \frac{1}{PRF};\ PRF_{MAX} = 400\ Hz \rightarrow t_r \geq 2.5\ ms \end{cases}$$

The time scale of ionization chambers is given by (ion) charge collection time. It varies in the range ~ 4 µs (IBA PPC 05, 300 V) up to ~ 60 µs (PTW Roos, 200 V).

Charge collection time << t_r

Hence, for electron beams, there is no correlation between two consecutive pulses and DPP is the relevant parameter

The Joint Research Project UHDpulse –
“Metrology for advance
particle beams with ultr

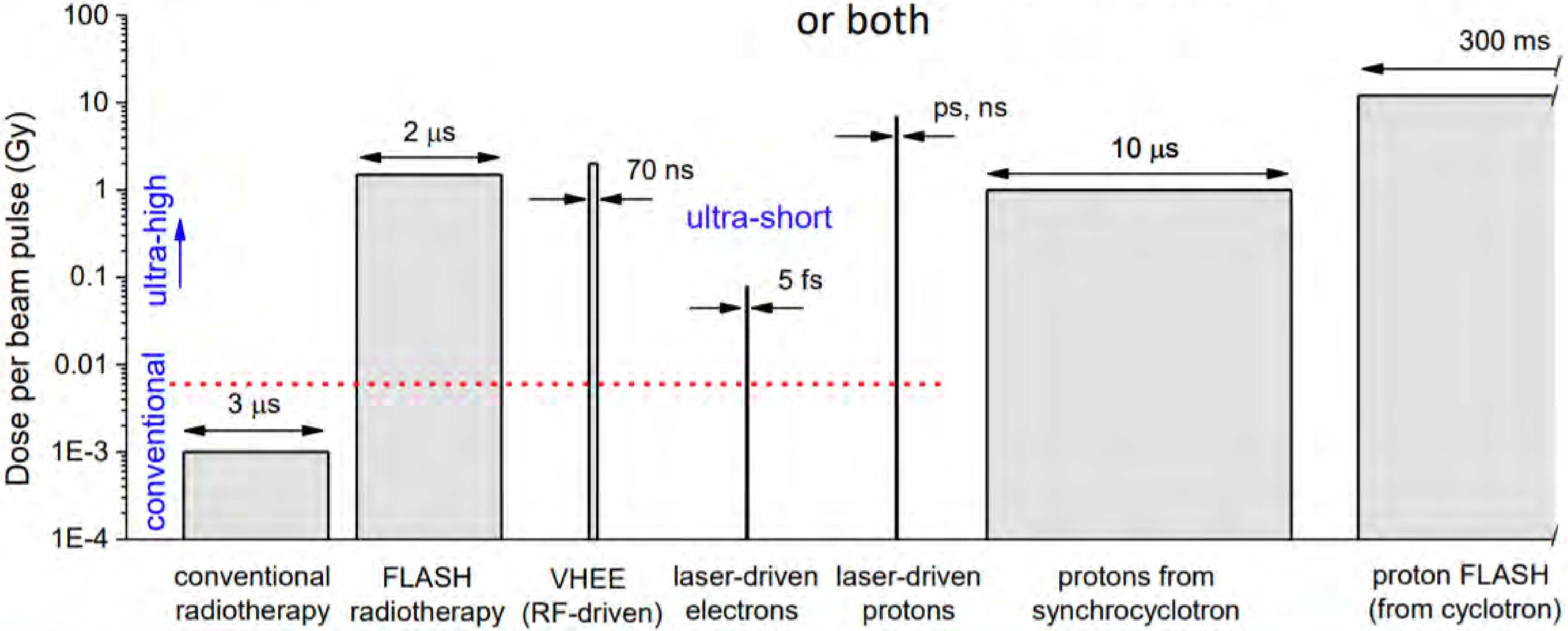
Andreas Schüller on behalf o
Department 6.2 “Dosimetry for Radiation T

NCRI CTRad Meeting: “Transforming Rad
14.2.20, Wellcome Collection, London

particle beams with ultra-high pulse dose rates

electrons, protons

ultra-high dose per pulse,
ultra-short pulse duration
or both



DO CURRENT MODELS PROPERLY DESCRIBES FLASH ELECTRONS DOSIMETRY ?
NO

ORIGINAL RESEARCH ARTICLE
Front. Phys. | doi: 10.3389/fphy.2020.570697

FLASH Radiotherapy with electrons: issues related to the production, monitoring and dosimetric characterization of the beam

Provisionally accepted We'll notify you at publication.

Fabio Di Martino[1*], Patrizio Barca[1], Salvatore Barone[2], Eleonora Bortoli[1], Rita Borgheresi[1], Silvia De Stefano[2], Massimo Di Francesco[2], Luigi Grasso[2], Stefania Linsalata[1], Daniela Marfisi[1], Matteo Pacitti[2] and Giuseppe Felici[2]

[1]U.O. Fisica Sanitaria, Pisana University Hospital, Italy
[2]Other, Italy

...

This shows that the shielding effect due to the electrical field produced by the movement of the charges during their collection, begins to be not negligible before the collection is completed. Therefore, such feature must be taken into account for obtaining an accurate model of ionization chambers in the FLASH region.

:al theory of recombination in ionization chambers [30] neglects the effect of the electric ated by the charges in motion after the ionization event. Such hypothesis is no longer true ng with a FLASH beam due to the extremely high ionization density. The simple analysis reported clarifies this point. Charge distribution inside a plane parallel chamber is shown 'l.

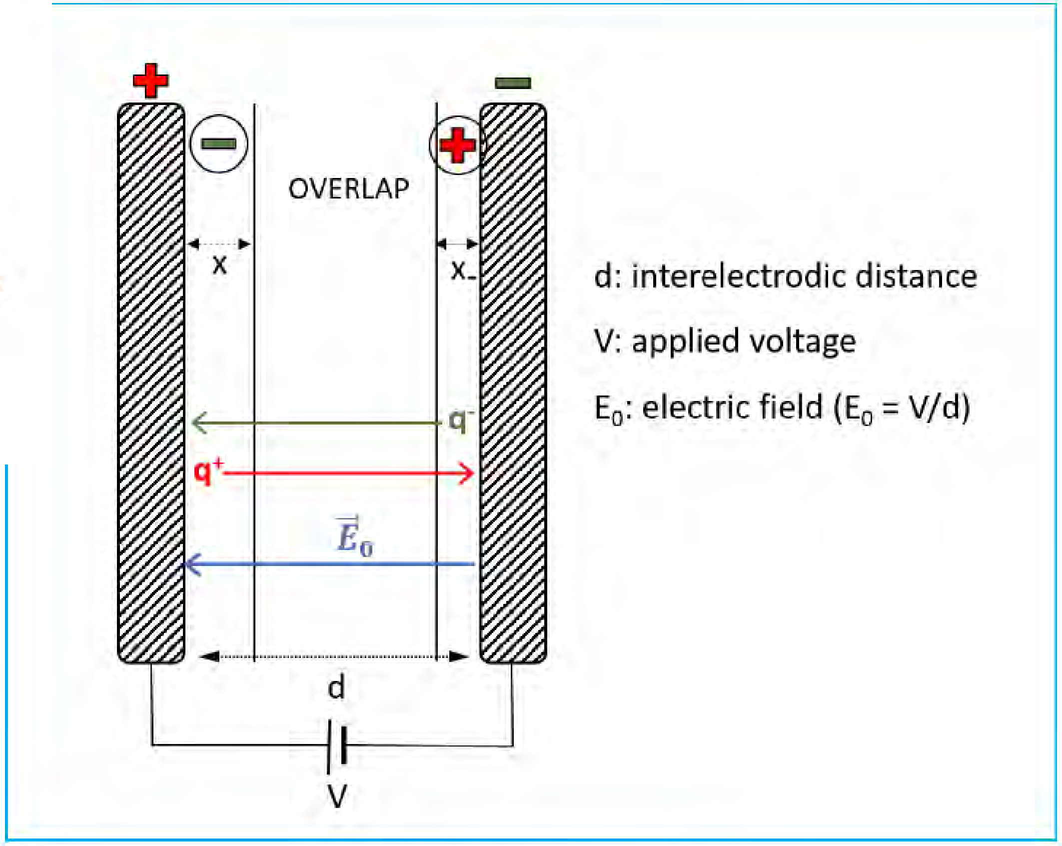


Figure 11: ionization chamber modelling.

Ionization chamber and dose-per-pulse

	Conventional $D_p \leq 0.5\,cGy/p$	**IOeRT** $D_p \leq 20\,cGy/p$	**UHD** $1Gy/p \leq D_p \leq 40\,Gy/p\,??$
What is E inside IC?	$E = E_0 = V_0/d$	$E = E_0 = V_0/d$	$E \neq E_0 = V_0/d$
Is p relevant for saturation evaluation?	No	Yes	A new theory must be developed and a new type of chamber designed
Does E change within pulse time and within IC volume?	$\frac{\delta E}{\delta x} = 0; \frac{\delta E}{\delta t} = 0$	$\frac{\delta E}{\delta x} = 0; \frac{\delta E}{\delta t} = 0$	$\frac{\delta E}{\delta x} \neq 0; \frac{\delta E}{\delta t} \neq 0$
Methods to evaluate k_{sat}	Two-voltage method	Laitano et al. Di Martino et al.	???

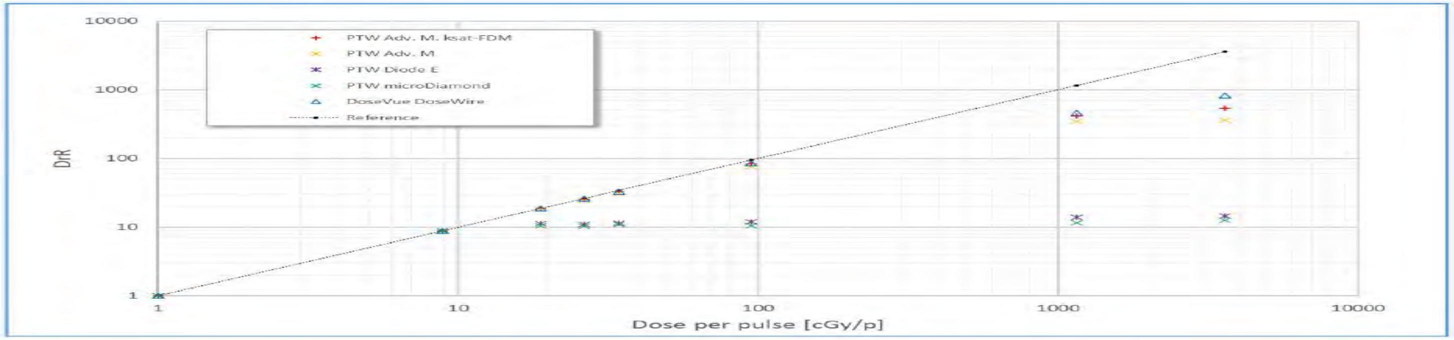
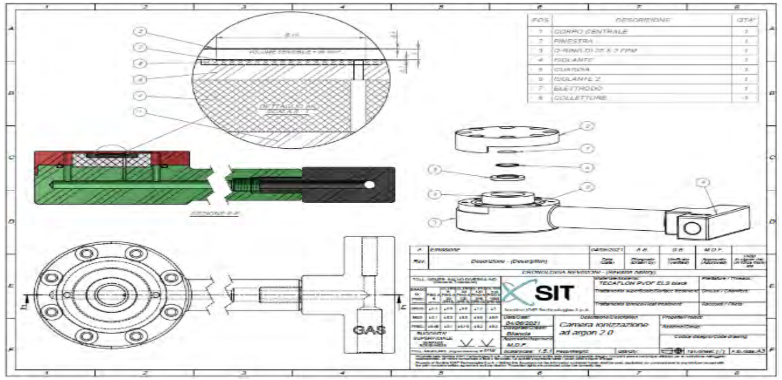


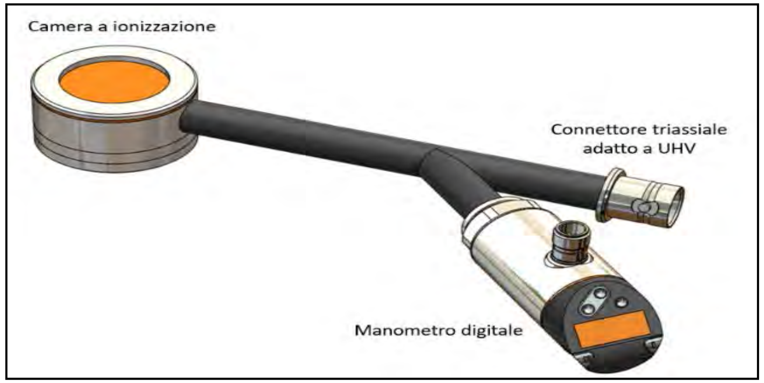
Figure 9: DrR vs. dose per pulse.

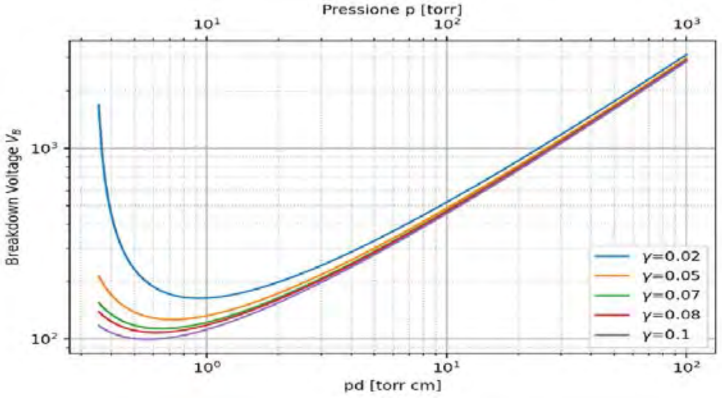
Theory and development of a flash gas chamber

$$\dot{q_V} = \frac{D_p \cdot \overline{S}_W^{GAS} \cdot k_Q \cdot \rho \cdot \left(\frac{\rho}{\rho_0}\right)}{T \cdot \frac{W}{e}} - \frac{\mu_0 \cdot \left(\frac{\rho_0}{\rho}\right)}{2\epsilon_0 \epsilon_r} \cdot q_V^2 - \frac{\mu_0 \cdot \left(\frac{\rho_0}{\rho}\right) \cdot V}{d^2} \cdot q_V$$

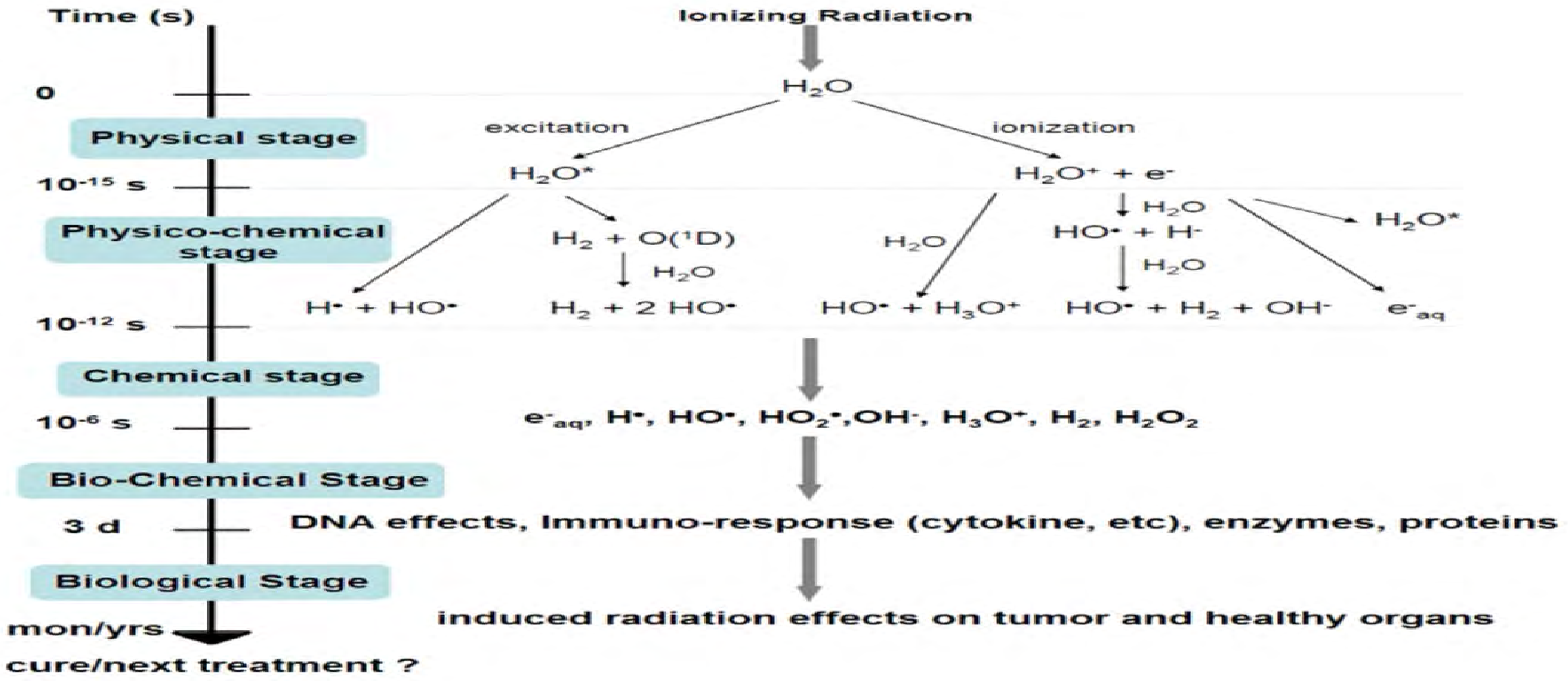
Prototype







Radiobiolgy: the times of the various phases



Radiobiolgy: the Hypotesis

- **Lower production of H2O2/contribution of O2**

  (Montay-Gruel et al, PNAS, 2019; Adrian et al, BJR, 2019)

- **Lower level of persistent DNA damages and senescent cells**

  (Fouillade et al, CCR, 2019)

- **Metabolism including redox**

  (Spitz et al, RO, 2019)

- **Inflammation/Immune system** **(the most popular in recent RVs)**

  (Favaudon et al, STM 2014; Montay-Gruel et al, PNAS, 2019)

- **Signaling pathways / Stem cells protection**

  (Montay-Gruel et al, RO, 2017)

Cosa non sappiamo e sarebbe fondamentale sapere?

I **meccanismi radiobiologici** alla base dell'effetto

La **dipendenza quantitativa dell'effetto da parametri del fascio** determinanti nell'innescarlo quali la dose, il dose-rate, il dose-per-pulse, l'instantaneous dose-per-pulse, la durata del trattamento…

La **dipendenza quantitativa dell'effetto dal tipo di tessuto irradiato** e dalla geometria di irraggiamento

Cosa fare per arrivare alla Flash Radiotherapy

Esperimenti radiobiologici quantitativi e studi teorici computazionali

Realizzazione di Linac clinici

Realizzazione di studi pre-clinici, protocolli dosimetrici e planning

E inoltre per poter trattare target profondi (VHEE)

Radiobiologia campi adiacenti se si vuole erogare il fascio in modalità pencil beam

Studi quantitativi dell'effetto volume

Dipendenza dalla dose per capire se e come frazionare e se e come utilizzare campi multipli per conformare la dose

CPFR: the dedicated Linac (Electronflash)

The ElectronFlash linear accelerator works in electron mode only.

The device has two different nominal electron energies:

- 5 MeV and 7 MeV
- 7 MeV and 9 MeV
- 10 MeV and 12 MeV

Adjustable radiation field between Ø12 cm and Ø 1cm, both circular and squircle

Dose rate range adjustable between 0.1 – 1500 Gy/s with reference field Ø10 cm

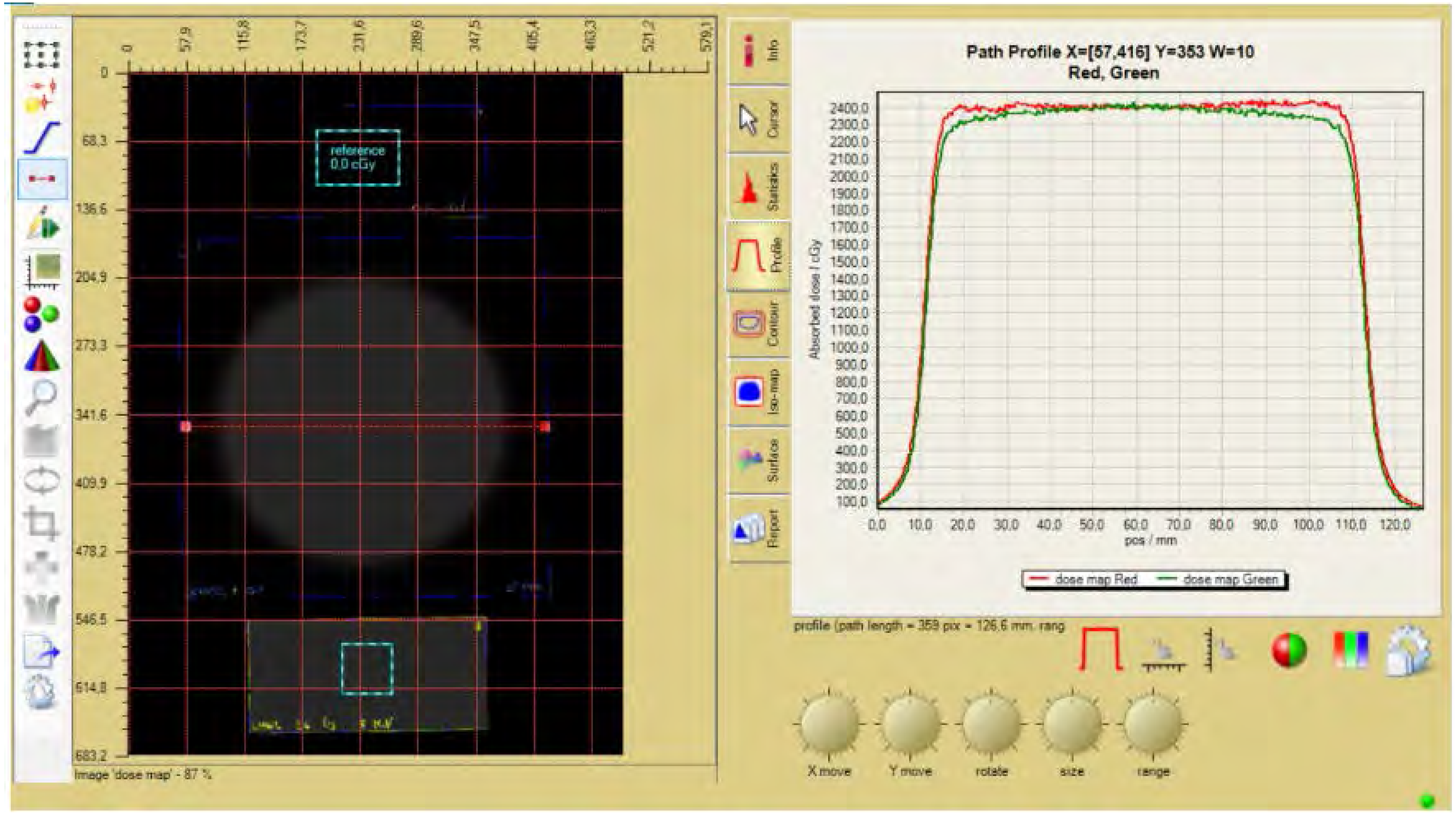
Dose per pulse up to 20 Gy/pulse and Dose rate up to 5000 Gy/s with Ø 4 cm

Dose per pulse up to 40 Gy/pulse and Dose rate up to 10000 Gy/s with Ø 1 cm

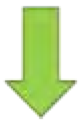
Real-time control of both beam energy and output

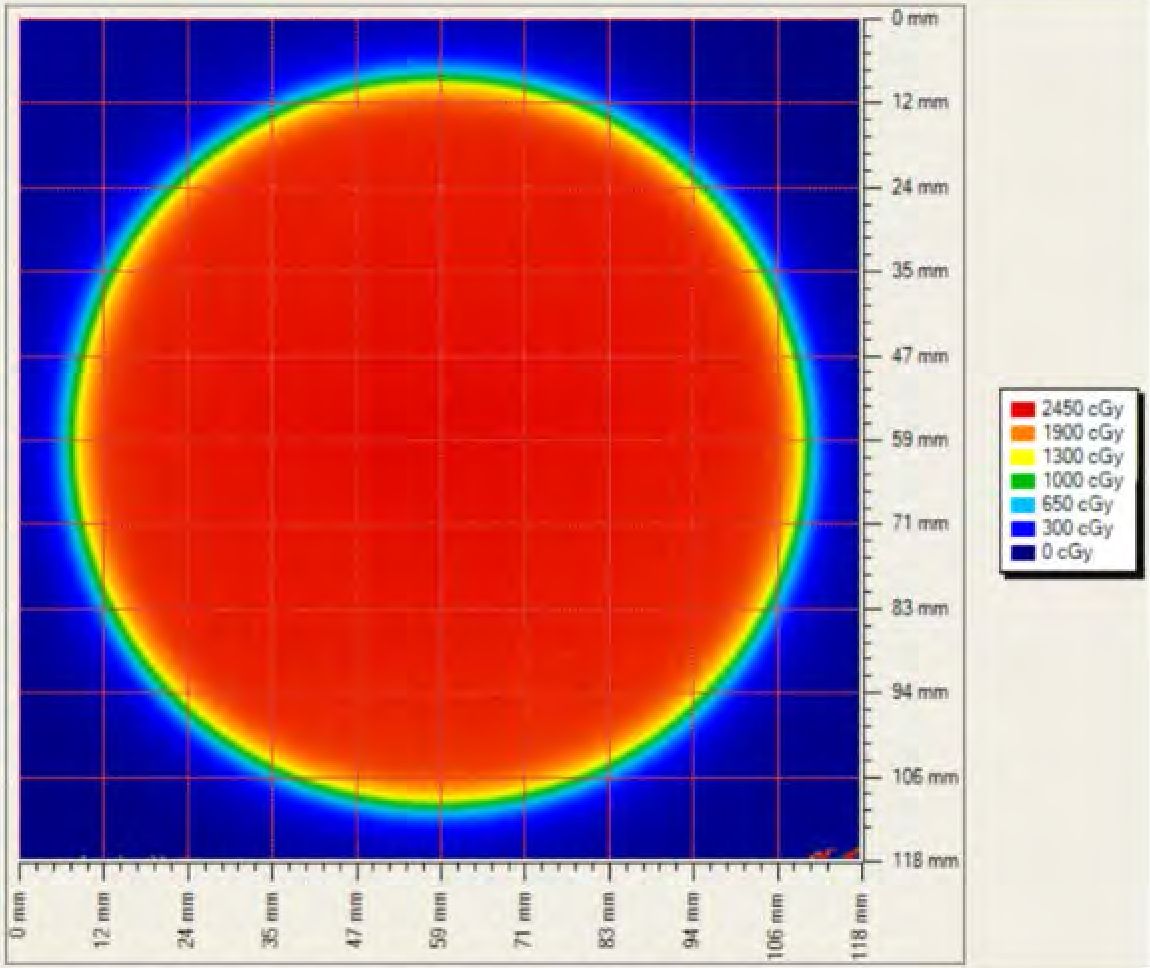
Compliant with EN 60601-2-1


ElectronFlash
Centro Pisano Flash Radiotherapy
CPFR

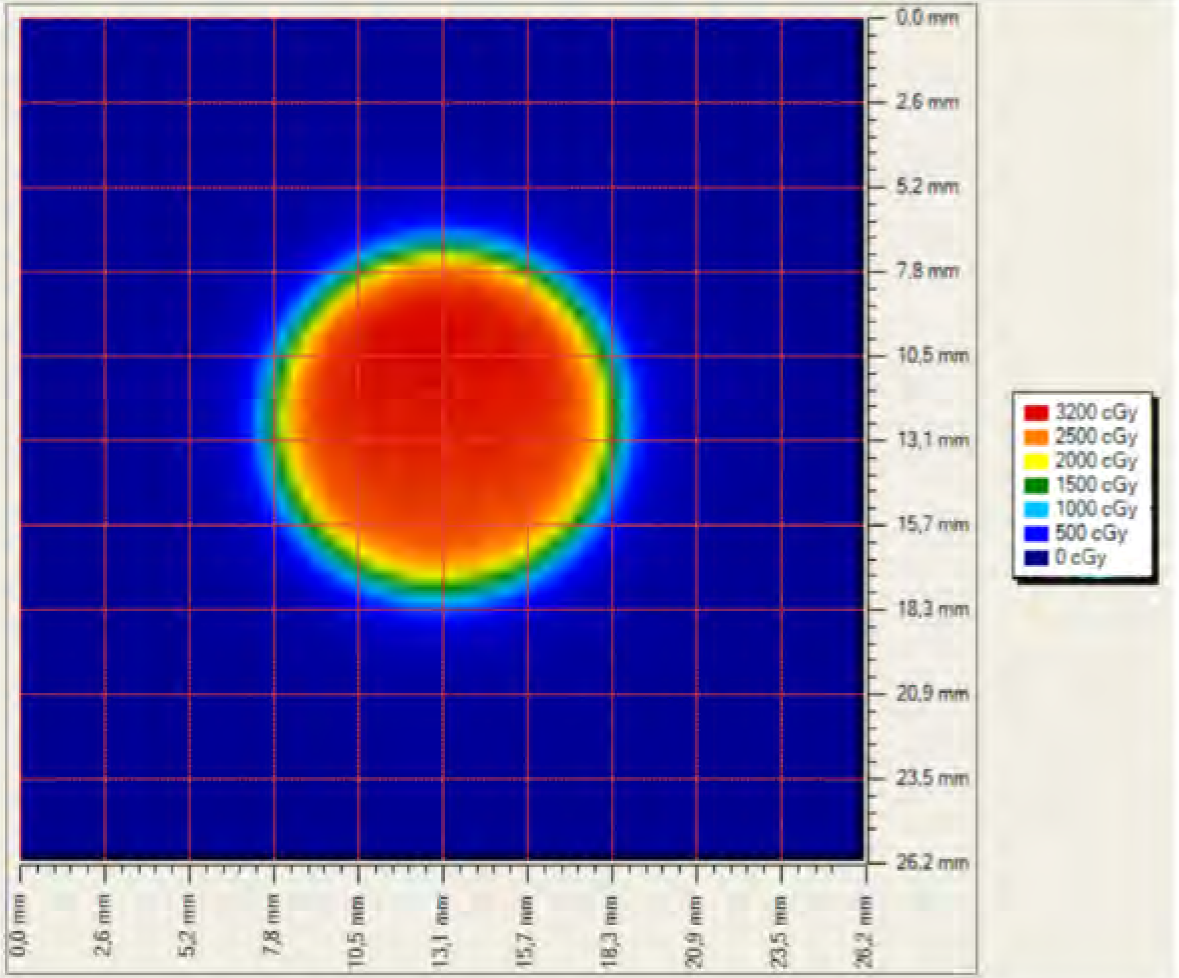


reference
0.0 cGy
Image 'dose map' - 87 %
Info
Cursor
Statistics
Profile
Contour
Iso-map
Surface
Report
Path Profile X=[57,416] Y=353 W=10
Red, Green
Absorbed dose / cGy
pos / mm
dose map Red
dose map Green
profile (path length = 359 pix = 126,6 mm, rang
X move
Y move
rotate
size
range

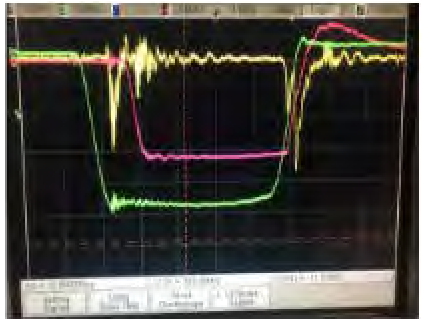


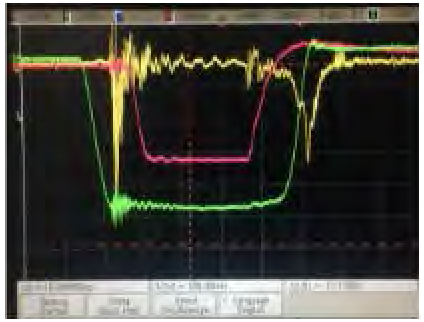


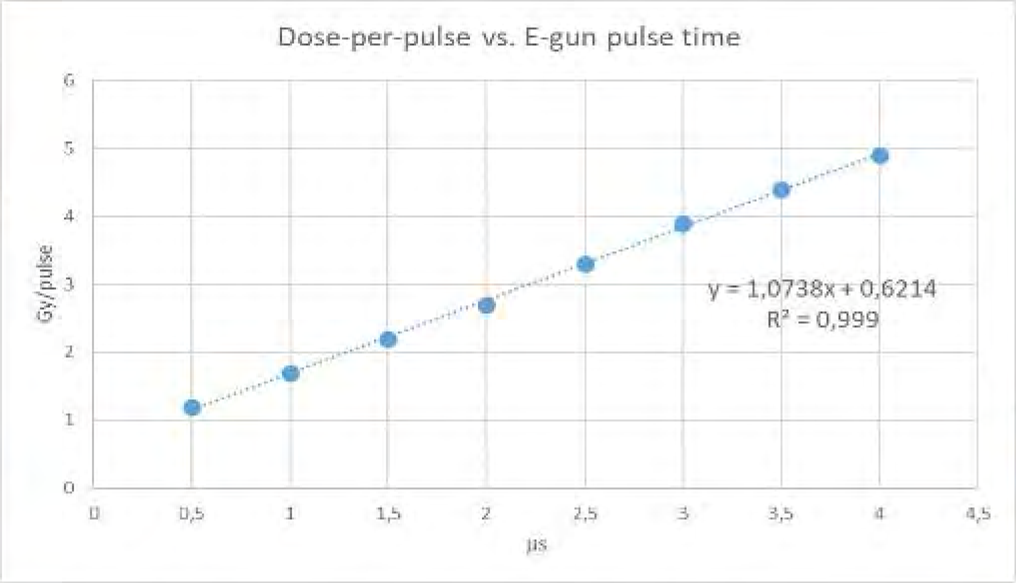
Flatness	better than 2%
Symmetry	better than 2%
Average Dose Rate	up to 1200 Gy/s
Dose Rate in Pulse	up to $1.2 \cdot 10^6$ Gy/s

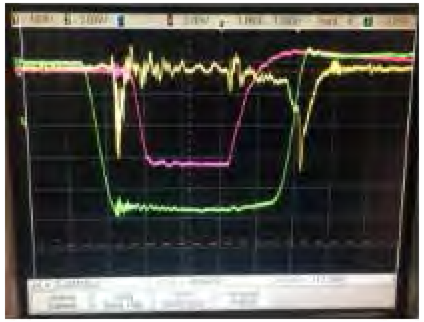


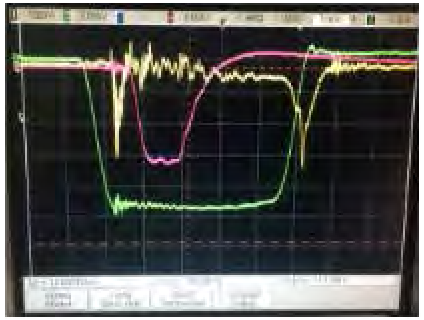
Flatness	better than 7%
Symmetry	better than 2%
Average Dose Rate	up to 10000 Gy/s
Dose per Pulse	up to 40 Gy/p
Dose Rate in Pulse	up to $1 \cdot 10^7$ Gy/s






Dose-per-pulse vs. E-gun pulse time
Gy/pulse
0
1
2
3
4
5
6
0
0,5
1
1,5
2
2,5
3
3,5
4
4,5
µs
y = 1,0738x + 0,6214
R² = 0,999





Pulse MU
Total MU
CVD
Avg Temperature
pulse MU 1
pulse MU 2
pulse mu
pulse count
total MU 1
total MU 2
total mu
pulse count
Pulse: 145 / 7000
Energy: 7MeV
Elapsed: 28.8 s
Pulse MU [1]: 6.682
Pulse MU [2]: 6.769
Total MU [1]: 967.104 / 0.000
Total MU [2]: 978.920 / 0.000

CPFR: the research

Radiobiology

- In vitro experiments (organoids…)
- In vivo experiments (serial and parallel organ at risk…)
- Theoretical models (Monte Carlo code EGS4-DNA…)

Dosimetry

- Study of the saturation effects of "old dosimeters" (theory of ionization chamber recombination…)
- Development of new dosimeters (scintillators, cerenkov…)

Technology

- Development and optimization of the production and the monitoring Of the beam
- Development and optimization of the beam collimation system

Pre-Clinical Trials

- Selection of organs and patients, interactions with other therapeutic approaches…???

FLASH effect: from experimental evidences to clinical practice

Experimental evidence (state of the art)

Understanding of the **radiobiological mechanisms** underlying the effect

Develop a clinical **Flash LINAC**

Preclinical studies

Foundamental for its optimization

DOSIMETRY

Necessary for its realization

knowledge of the quantitative relationship both between the effect and the **parameters of the beam** (dose-rate, dose-per-pulse, LET…) and with the **characteristics of the irradiated tissue** (type, volume…)

Develop clinical **dosimetric protocols**

Develop clinical **Treatment Planning System**

Radiotherapy FLASH in the clinical practice (final goal!)

ELECTRONFLASH

AOUP

Radiobiology laboratory

Quantitative radiobiological experiments in vivo/vitro → understand the radiobiological mechanisms and its quantitative dependencies

Dosimetric studies → implement clinical dosimetric protocols

Preclinical studies → obtain the necessary authorizations for human treatment

↓

Clinical trials (dermatological cancers)

Prof F Paiar (UNIPI)
Radiaton Oncologist
Clinical implications / Radiobiology

Dr F Di Martino (AOUP)
Medical Physicist
Dosimetry/LinacManagement/Planning/
Radiobiology

Dr M Costa (CNR)
Biologist
Preparation and analysis of biological models

Prof F Cella Zanacchi (UNIPI)
Biophysicist
Analysis of irradiated biological material

Prof G Bisogni (UNIPI/INFN)
Medical Physicist
Dosimetry/Planning

Dr V Tozzini (CNR)
Modeling and computer simulations
of radiation effects

Collocazione CPFR nel panorama internazionale

- Quarto centro europeo ad occuparsi di Flash-RT

- Terzo centro europeo dotato di LINAC dedicato Electronflash

  Marie Curie Institute (Parigi)-2020

  Iridium Network (Anversa)-2021?

  CPRF (Pisa)-Marzo 2022

- Primo ed unico centro europeo dotato di LINAC dedicato Electronflash con cannone elettronico a TRIODO

SCUOLA SUPERIORE
DI FISICA IN MEDICINA
PIERO CALDIROLA

Direttore: Annalisa Trianni

Corso residenziale

FLASH RADIOTHERAPY: RADIOBIOLOGIA, PROSPETTIVE CLINICHE, ASPETTI TECNOLOGI E DOSIMETRICI

PISA • 29-30 settembre 2022

Responsabile scientifico: Fabio Di Martino

The Hope!

Thank you - & to be continued!

...NFLASH 4000

...trons

...*10 cm^2 @ SSD 100 cm

...dose rate 0.1 – 1000 Gy/s; max 4000 Gy/1

...f energy & output