FLASH Radiation Oncology: Hype or Hope


Schuiten: L'Experience Cruciale

Prof. Dr. Dirk Verellen
AReRO group – Antwerp University

Universiteit Antwerpen

iridium netwerk
Topzorg in radiotherapie

What's the fuzz all about?

- Introduction of high energy photons
- Introduction of CT and dose calculation
- Introduction of IMRT
- Introduction of IGRT, SBRT, ART, ...
- Introduction of protontherapy
- Introduction of MRI-linac
- Introduction of PET-linac

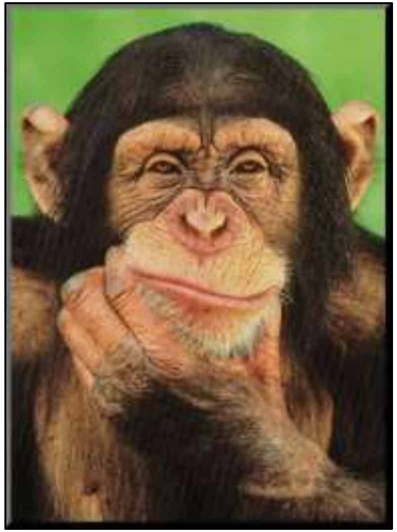
- ...

- Incremental steps ... evolution ...

Definition of FLASH

- Oxford Dictionary:

"to shine in a bright but brief way"



- Radiobiology: "Flash"
- Physics: "Ultra-High Dose Rate"

What's the fuzz all about?

www.ScienceTranslationalMedicine.org 16 July 2014 Vol 6 Issue 245 245ra93

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]

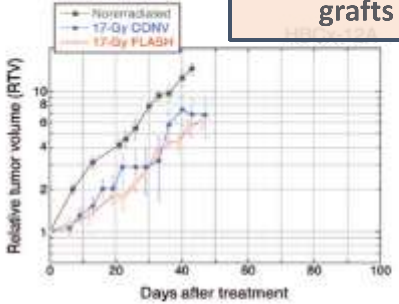
[1]Institut Curie, Centre de Recherche, 91405 Orsay, France. [2]INSERM U612, 91405 Orsay, France. [3]Pathology Laboratory, Ecole Nationale Vétérinaire d'Alfort, Université Paris-Est, 94704 Maisons Alfort, France. [4]Université Paris-XI, 91405 Orsay, France. [5]INSERM U1030, Institut Gustave-Roussy, 94805 Villejuif, France. [6]Institut Curie, Centre de Recherche, 75248 Paris 05, France. [7]INSERM U900, 75248 Paris 05, France. [8]Mines ParisTech, 77305 Fontainebleau, France. [9]CNRS, UMR144, 75248 Paris 05, France. [10]Radio-Oncologie/Radiothérapie, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland. [11]INSERM U967, Commissariat à l'Energie Atomique (CEA), Division des Sciences du Vivant (DSV), Institut de Radiobiologie Cellulaire et Moléculaire (IRCM), 92265 Fontenay aux Roses, France.
*Corresponding author. E-mail: vincent.favaudon@curie.fr

RT → Toxicity evaluation

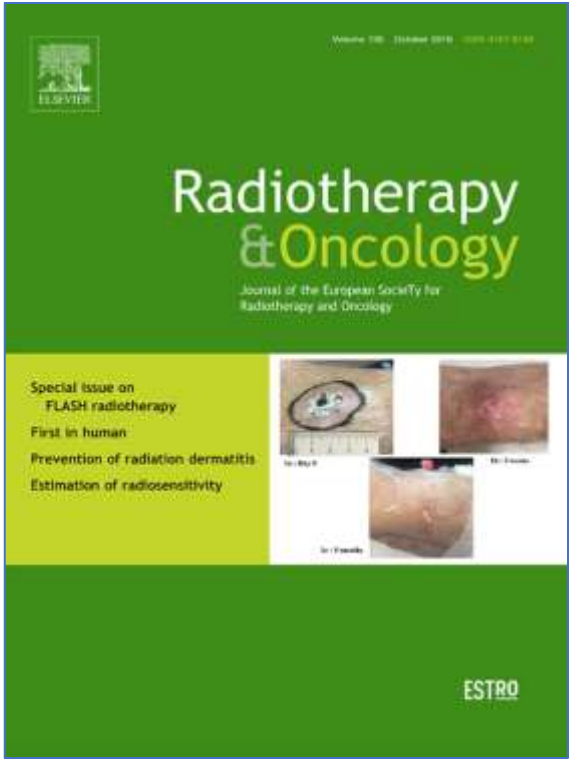
Control Not irradiated	17 Gy Conventional RT	17 Gy FLASH

HEALTHY	FIBROTIC	HEALTHY

Iso-effect on tumour grafts



What's the fuzz all about?



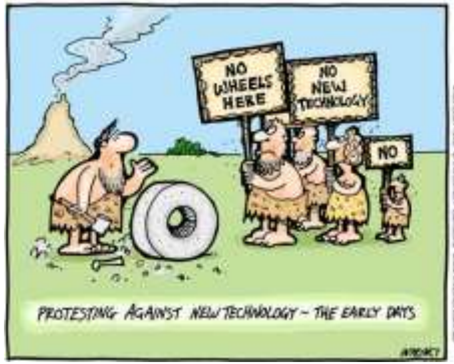
- "Remarkable healthy-tissue sparing properties without impacting the overall treatment efficacy ...
- ... in a number of pre-clinical studies"

→

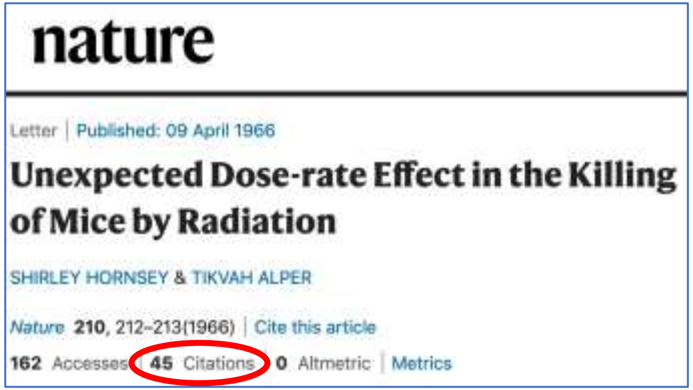
- *Differential effects between normal and tumour tissue*
- *Increase dose without further harming surrounding healthy tissue*

Is it new?

- Normal tissue sparing by “FLASH” (*the term was coined by Favaudon et al.*) had already been described in … **1966**!



  - Hornsey S, Alper T. Unexpected dose-rate effect in the killing of mice by radiation. Nature, 1966; 210: 212-213.



nature

Letter | Published: 09 April 1966

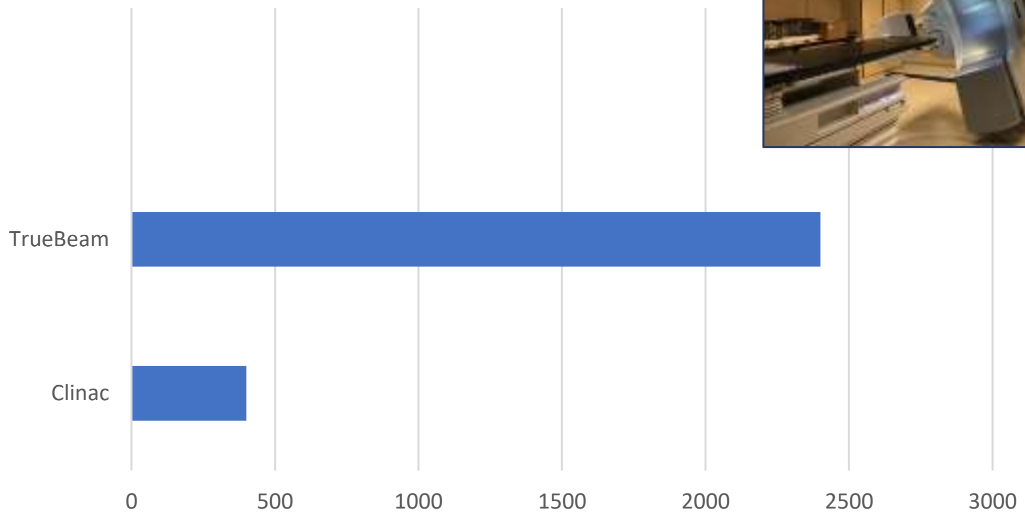
Unexpected Dose-rate Effect in the Killing of Mice by Radiation

SHIRLEY HORNSEY & TIKVAH ALPER

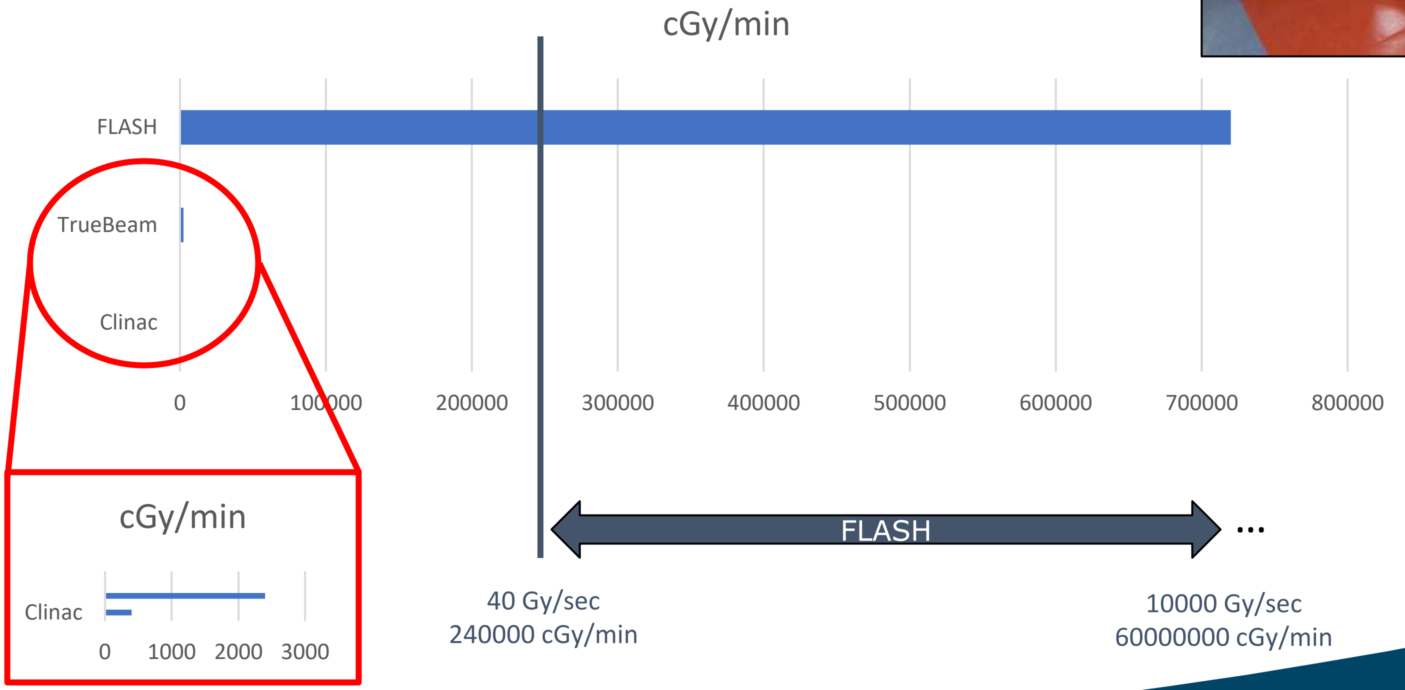
Nature **210**, 212–213(1966) | Cite this article

162 Accesses | **45** Citations | **0** Altmetric | Metrics

It's all about dose rate

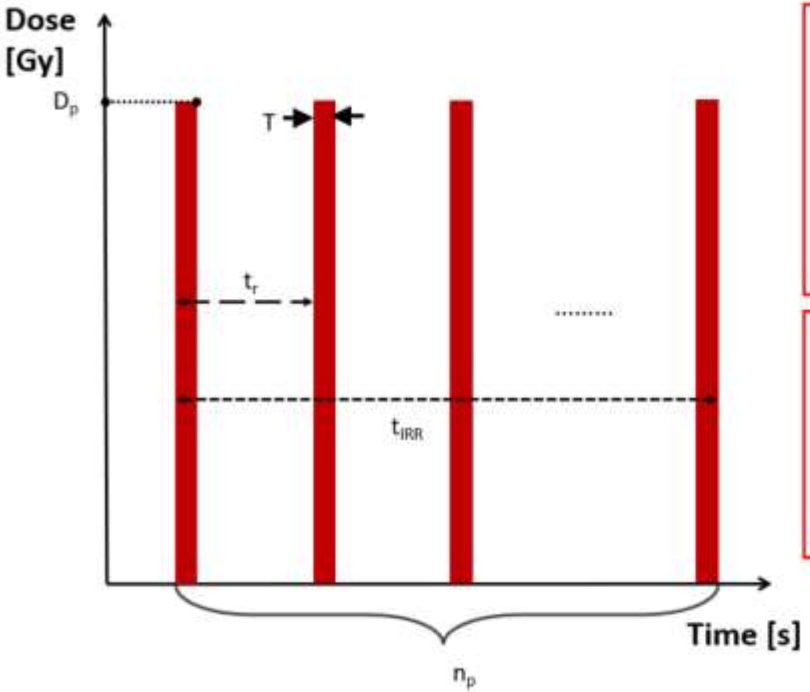


It’s all about dose rate … not dose



... but it's more complicated ...

Temporal beam structure and dose rates



T Pulse width [s]

D_p Dose per singe pulse [Gy]

PRF Pulse Repetition Frequency [Hz]

n_p number of pulses

t_r time between two pulses = $1/PRF$ [s]

t_{IRR} total irradiation time = $\frac{n_p - 1}{PRF} + T$ [s]

DR Average dose rate [Gy/s]

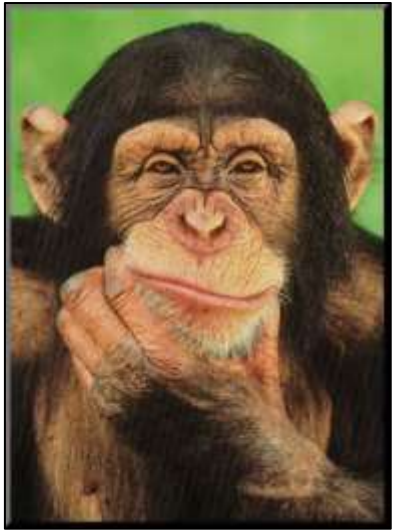
$$DR = \frac{\text{Tot Dose}}{t_{IRR}} = \frac{n_p \cdot D_p}{t_{IRR}} \approx D_p \cdot PRF$$

IDR Instantaneous dose rate [Gy/s]

$$IDR = \frac{D_p}{T}$$

Challenges: Delivery

- Photons, protons, electrons?
- 1 beam, multiple beams, spot scanning, …
  …, rotational, non-coplanar, **IOeRT** ?
- Trade off:
  - **dose rate** versus **plan conformality?**
- **Total dose, fractionation, dose per fraction?**
- Motion management, IGRT:
  - **"freeze the anatomy"**?
- **Reproducibility?????**
- Dose calculation and Treatment Planning System
- **Beam monitoring and control!!!!**



Challenges: Delivery

Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator

Emil Schüler, PhD,* Stefania Trovati, PhD,* Gregory Kin... Frederick Lartey, PhD,* Marjan Rafat, PhD,* Ma... A. Joe Praxel,* Billy W. Loo, Jr, MD, PhD... and Peter G. Maxim, PhD*,†

*Department of Radiation Oncology and †Sta... Cancer Institute, Stanford University School of Medicine, Stanford, California

Linacs

Very high-energy electron (VHEE) beams in radiation therapy; Treatment plan comparison between VHEE, VMAT, and PPBS

Emil Schüler
Department of Radiation Oncology, Stanford School of Medicine, Stanford University, Stanford, CA, USA

Kjell Eriksson and Elin Hynning
RaySearch Laboratories AB, Stockholm, Sweden

Steven L. Hancock, and Susan M. Hiniker
Department of Radiation Oncology, Stanford School of Med... CA, USA

Magdalena Bazalova-Carter
Department of Physics and Astronomy, University of Vic... BC, Canada

Tony Wong
Seattle Cancer Care Alliance Proton Therapy Center, Seattle, WA, USA

Quynh-Thu Le, Billy W. Loo Jr.,* and Peter G. Maxim
Department of Radiation Oncology, Stanford School of Medicine, Stanford University, Stanford, CA, USA

Towards VHEE

X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice

Pierre Montay-Gruel[a], Audrey Bouchet[b], Maud Jaccard[c], David Patin[c], Raphael Serduc[b,*], Warren Aim[b], Kristoffer Petersson[a,c], Benoit Petit[a], Claude Bailat[c], Jean Bourhis[a], Elke B... Marie-Catherine Vozenin[a,1]

X-rays

International Journal of Radiation Oncology biology • physics

www.redjournal.org

Biology Contribution

Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System

Annalisa Patriarca, PhD,* Charles Fouil... Michel Auger, MSc,* Frédéric M... ...édéric Pouzoulet, PhD,‡ Catherine Nauraye, PhD,* Sophi... ...ich, PhD,‡ Vincent Favaudon, PhD,† Samuel Meyroneinc, MSc,* Rémi Dendale, MD,* Alejandro Mazal, PhD,* Philip Poortmans, MD, PhD,* Pierre Verrelle, MD, PhD,*,§ and Ludovic De Marzi, PhD*

Protons

Challenges: Delivery

- Proton experiments: IBA

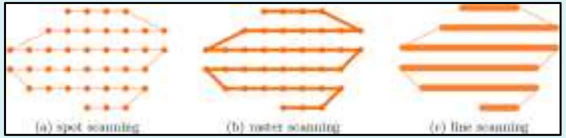
Institute Curie – France

UPENN - USA

UMCG – The Netherlands

- Proton experiments: Varian

Question:
How to define UHDR in spot scanning delivery?



Challenges: Delivery

Commercial electron machines

http://pmb-alcen.com

Mobetron®
Clinical Electron
EBRT System

http://intraop.com

http://soiort.com

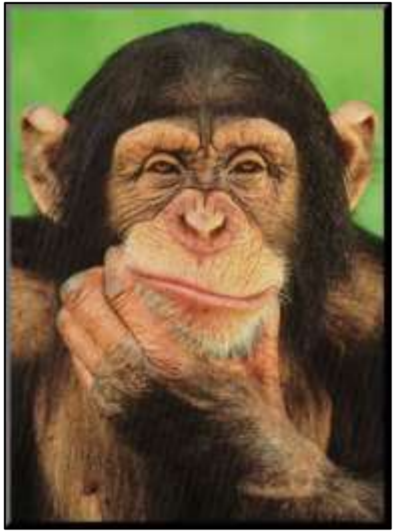
iridium network
Topzorg in radiotherapie

Challenges: Delivery

- Collaboration Iridium/UA – SIT on pre-clinical research
  - **ElectronFLASH**: prototype serial number 2
  - Real-time control of energy & output
  - 5, 7, 9, 10, 12 MeV Electrons
  - Average dose rate: **0.005 – 10,000 Gy/s**
  - Pulse heigth (Dose Per Pulse): up to 40 Gy/pulse
  - Pulse width: 0.5 – 4.0 µs
  - Pulse Rate Frequency: 1- 350 Hz

Challenges: Physics

- Dose measurement (ultra high dose per pulse)?
  - Ion chambers: the golden standard????
  - Radiographic film: the current standard????
  - Alanine
  - Scintilators
  - Ultra thin ionization chambers
  - microDiamond
  - 2D OSL
  - …
- Traceability!!!
- Real-time output and energy monitoring?
- Dose calculation?
- Motion management (freeze the anatomy …): IGRT!!!



Challenges: Physics

MEDICAL PHYSICS

The International Journal of Medical Physics Research and Practice

SPECIAL ISSUE PAPER | Open Access

A roadmap to clinical trials for FLASH

Paige A. Taylor, Jean M. Moran, David A. Jaffray, Jeffrey C. Buchsbaum

First published: 02 April 2022 | https://doi.org/10.1002/mp.15623

The more rigorously we test early phase trials, the more success we can expect later with larger, multi-institutional trials.

Dose traceability

- Primary Standard Dosimetry Laboratories
- Infrastructure for QA
- International standards, and Codes of Practice

Absolute dosimetry

- Accurate and precise
- Reproducible
- AAPM ESTRO EFOMP Task group 359
- Codes of Practice (guidelines AAPM, ESTRO, IAEA)

Beam monitoring

- Output and energy stability
- Treatment interruption and restart
- Patient positioning, IGRT (freeze the anatomy), modulation

QA for clinical trials

- Machine independent QA
- Machine validation for FLASH effect
- Pre-treatment and in vivo dosimetry

An example: absolute dosimetry

High dose-per-pulse electron beam dosimetry — A model to correct for the ion recombination in the Advanced Markus ionization chamber

Kristoffer Petersson,[a)] Maud Jaccard, Jean-François Germond, Thierry Buchillier, and François Bochud

frontiers

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

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]

Physics in Medicine & Biology — IPEM Institute of Physics and Engineering in Medicine

ACCEPTED MANUSCRIPT

Physics and biology of ultrahigh dose-rate (FLASH) radiotherapy: topical review

To cite this article before publication: Nolan Matthew Esplen et al 2020 Phys. Med. Biol. in press https://doi.org/10.1088/1361-6560...

RESEARCH ARTICLE — MEDICAL PHYSICS

Development of an ultra-thin parallel plate ionization chamber for dosimetry in FLASH radiotherapy

Faustino Gómez[1,2] | Diego M. Gonzalez-Castaño[2] | Nicolás Gómez Fernández[2] | Juan Pardo-Montero[3,4] | Andreas Schüller[5] | Alessia Gasparini[6,7] | Verdi Vanreusel[6,7,8] | Dirk Verellen[6,7] | Giuseppe Felici[9] | Rafael Kranzer[10,11] | Jose Paz-M...

SCIENTIFIC REPORTS

OPEN **The challenge of ionisation chamber dosimetry in ultra-short pulsed high dose-rate Very High Energy Electron beams**

A new model for volume recombination in plane-parallel chambers in pulsed fields of high dose-per-pulse

M Gotz[1,2], L Karsch[1,2] and J Pawelke[1,2,3]

[1] OncoRay-National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Fetscherstr. 74, PF 41, 01307 Dresden, Germany
[2] Institute of Radiation Physics, Helmholtz-Zentrum Dresden-Rossendorf, Bautzner Landstraße 400, 01328 Dresden, Germany

RESEARCH ARTICLE — MEDICAL PHYSICS

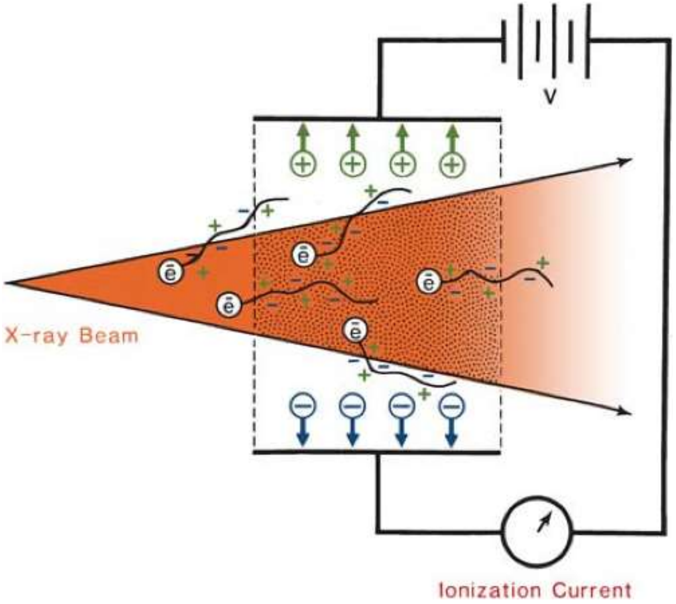
Design, realization, and characterization of a novel diamond detector prototype for FLASH radiotherapy dosimetry

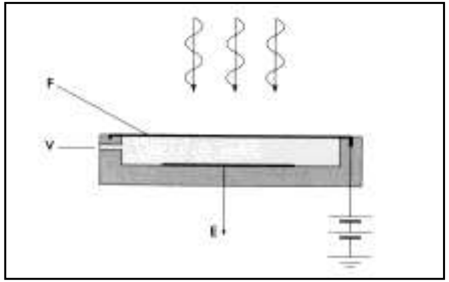
Marco Marinelli[1] | Giuseppe Felici[2] | Federica Galante[2] | Alessia Gasparini[3,4] | Lucia Giuliano[5] | Sophie Heinrich[5] | Matteo Pacitti[2] | Giuseppe Prestopino[1] | Verdi Vanreusel[3,4] | Dirk Verellen[3,4] | Claudio Verona[1] | Gianluca Verona Rinati[1]

iridium network — Topzorg in radiotherapie

An example: absolute dosimetry

- The basics ... k_s - k_{pol}





An example: absolute dosimetry

- Dose Rate (DR): 1.0 – 24.0 Gy/min
- Pulse Rate Frequency (PRF): 200 – 400 Hz
- Dose/pulse (DR[Gy/sec]/PRF):
  - **~ 0.000[illegible] - 0.002 Gy/p**
  - Varian TB 6FFF: 0.00065 Gy/p
  - Varian TB 10FFF: **0.00111 Gy/p**

FLASH: ~ 40Gy/pulse ???

- Dose Rate (DR): 2.0 – 20 Gy/min
- Pulse Rate Frequency (PRF): 5 – 40 Hz
- Dose/pulse:
  - **~ 0.004 - 0.050 Gy/p**

An example: absolute dosimetry

Absorbed Dose to water according to IAEA TRS 398 formalism

Absorbed dose to water at the reference depth z_{ref} in water for a reference beam of quality Q_0

$$D_{w,Q} = M_Q \cdot N_{D_w,Q_0} \cdot k_{Q,Q_0}$$

$$M_Q = M' \cdot \prod_i k_i = M' \cdot k_{T,P} \cdot k_H \cdot k_{pol} \cdot k_s$$ *M' measured signal*

k_{Q,Q_0} *Factor to correct for the difference between the response of an ionization chamber in the reference beam quality Qo used for calibrating the chamber and in the actual user beam quality, Q*

k_s *Factor to correct the response of an ionization chamber for the lack of complete charge collection (due to ion recombination).*

chamber type	interelectrodic spacing (cm)	polarization (V)
PTW Roos	0,2	200
PTW Adv. Markus	0,1	400
IBA PPC 05	0,06	300

327 Scalchi et al.: Reference dosimetry for IORT using NOVAC and LIAC 327

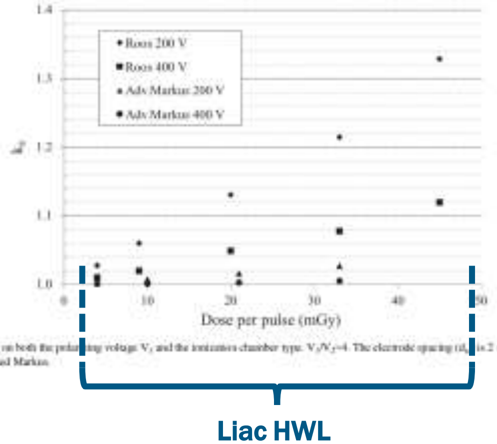
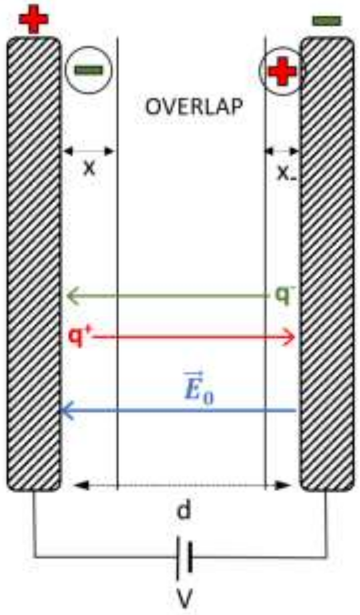


Fig. 4. Dependence of k_s on both the polarizing voltage V_1 and the ionization chamber type. $V_1/V_2=4$. The electrode spacing (d) is 2 mm for the Roos chamber and 1 mm for the Advanced Markus.

Only 0.05 Gy/p!!!
What about 40 Gy/p???

An example: absolute dosimetry

- Recombination effect … and … self shielding



d: interelectrodic distance

V: applied voltage

E_0: electric field (E_0 = V/d)

Research paper

A new calculation method for the free electron fraction of an ionization chamber in the ultra-high-dose-per-pulse regimen

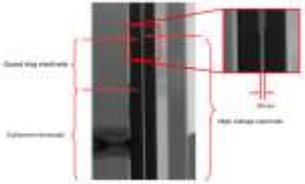
Fabio Di Martino[1,2,4], Damiano Del Sarto[2], Salvatore Barone[5], Maria Giuseppina Bisogni[2,3,4], Simone Capaccioli[2,3], Federica Galante[5], Alessia Gasperini[6,7], Giulia Mariani[5], Matteo Pacitti[5], Fabiola Paiar[2,4,8], Jake Harold Pensavalle[3,4], Francesco Romano[9], Stefano Ursino[2,4,8], Verdi Vanreusel[6,7], Dirk Verellen[6,7] and Giuseppe Felici[5]

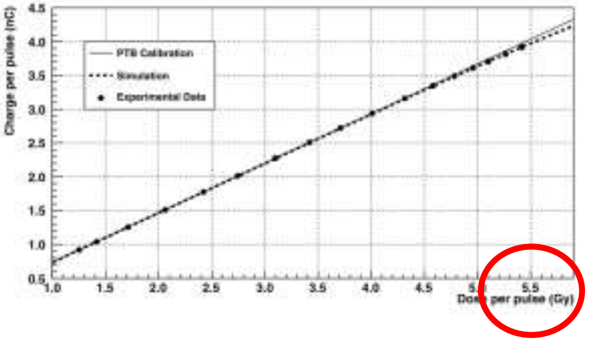
Di Martino *et al Phys Medica 2022 (subm)*

An example: absolute dosimetry

- Recombination effect … and … self shielding:

Ultra-Thin IC





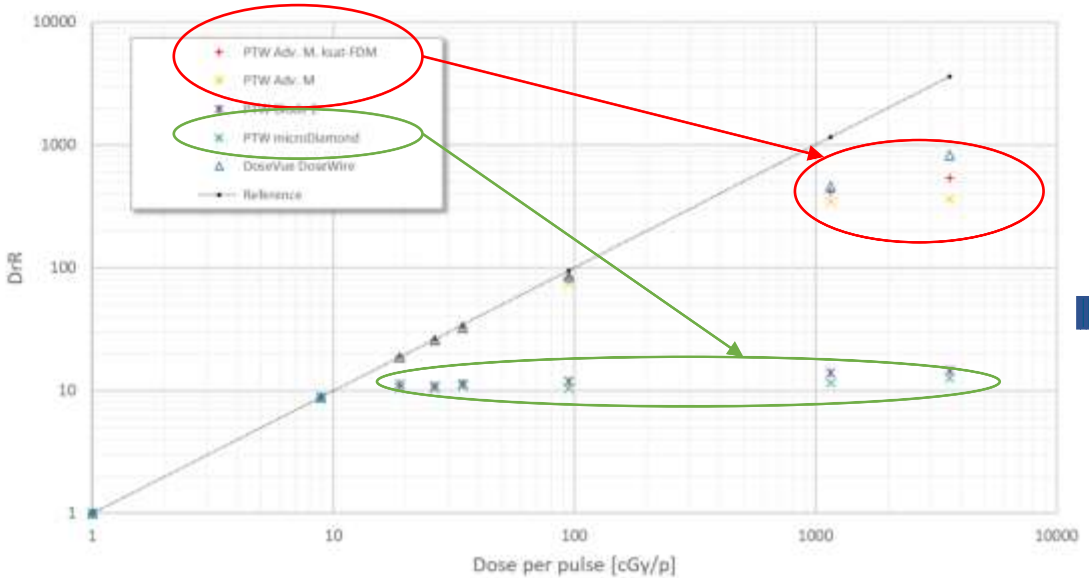
Gomez Rodriguez F *et al* Med Phys 2022

ALLS, nobel gas IC

Di Martino F *et al* Physica Medica 2022 (subm)

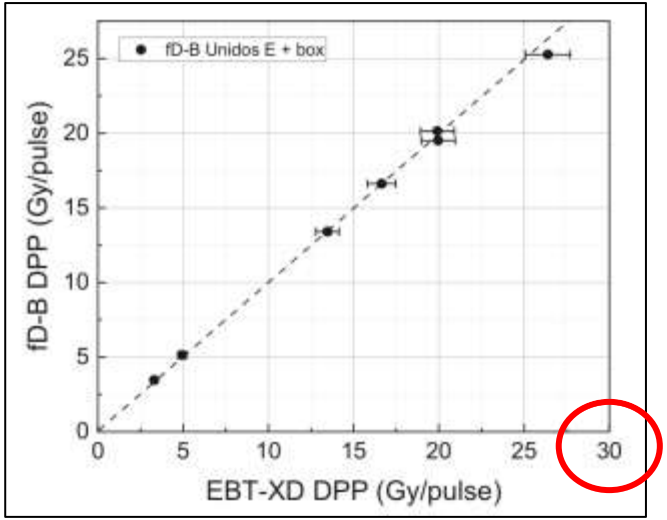
An example: absolute dosimetry

- From microDiamond towards FLASH Diamond



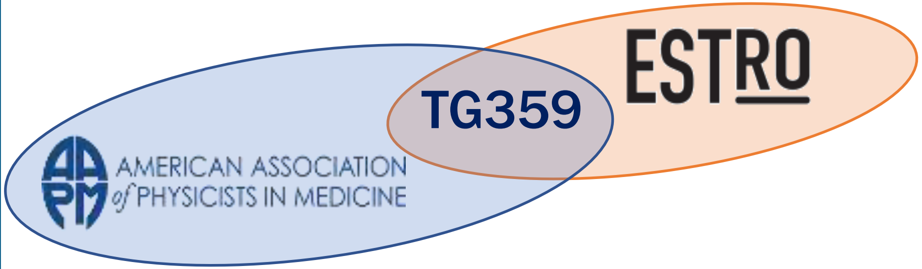
DrR: Dosimeter reading Ratio

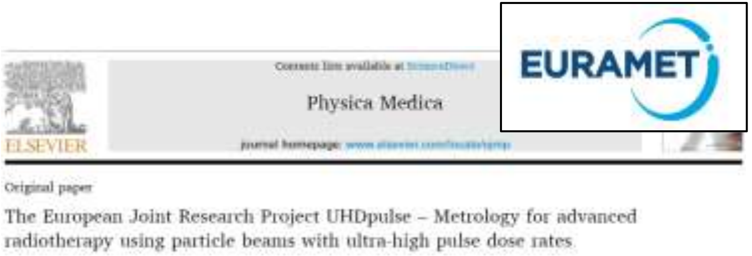
Di Martino *et al Appl Sci 2020*



Marinelli *et al Med Phys 2022*

International collaborations




ELSEVIER

Physica Medica

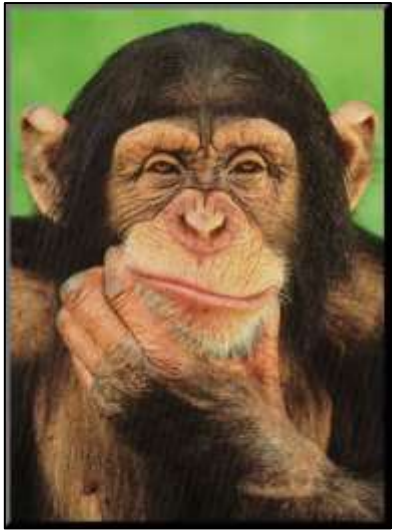
EURAMET

Original paper

The European Joint Research Project UHDpulse – Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates

Challenges: Radiobiology

- Understanding the underlying mechanism
  - **Hypoxia**: radiochemical depletion of oxygen making normal tissue hypoxic?
    - Doubling oxygen concentration seems to reverse FLASH effect (Neurocognitive experiment, Montey-Gruel *et al.*)
  - Modulation of inflamatory cytokines?
  - Differential **immunological responses** between tumour and normal tissues?
  - Are the above **downstream effects or independent** mechanisms?
  - What about **late effects**?
  - Controled studies – independent verification?



Some hypotheses … so far

Hypotheses	In support	Against	NT vs. Tumor
O_2 depletion	Loss of FLASH effect with increased O_2 tension Models of O_2 depletion	Models of O_2 depletion.	Differential O2 tension between tumor and NT
ROS production (quantity or nature)	Measurements of H_2O_2 production	ROS production depends on the physical absorbed dose (?)	Differential scavenging capacities of NT vs tumor
Other radiation induced –tress / metabolic pathway (NOS, Fe…)	Models	-	Differential stress response
DNA damage, cell cycle	Less DSB observed after FLASH	Direct DNA damage depends on physical absorbed dose (?)	Inefficacious DDR in tumor cells
Lipid peroxidation	Pilot experiments (unpublished data)	-	Differential lipidic membrane composition, structure, plasticity
Stem Cell pool	Numerous data in favor of a stem cell hypothesis	Cannot be a primary hypothesis Tumor stem cells	Nature of NT stem cells vs TSCs
Differential cell death	Numerous data in favor of a cell death hypothesis (apoptosis, senescence…)	Cannot be a primary hypothesis	Differential cell death pathways between NT and tumors
Vascular system	Data on the brain and tumor vasc	Cannot be a primary hypothesis	Nature and morphology of the NT vs. tumor vasculature
Immune system	Differential inflammatory response Time of exposure to immune cells	FLASH effect observed in immunocompromised animals	Differential immune response in NT and tumor tissues

Early results

• Pre-clinical

Institut Curie: Kinetron
Mean Dose Rate: 0.01 – 7500 Gy/s

Early results

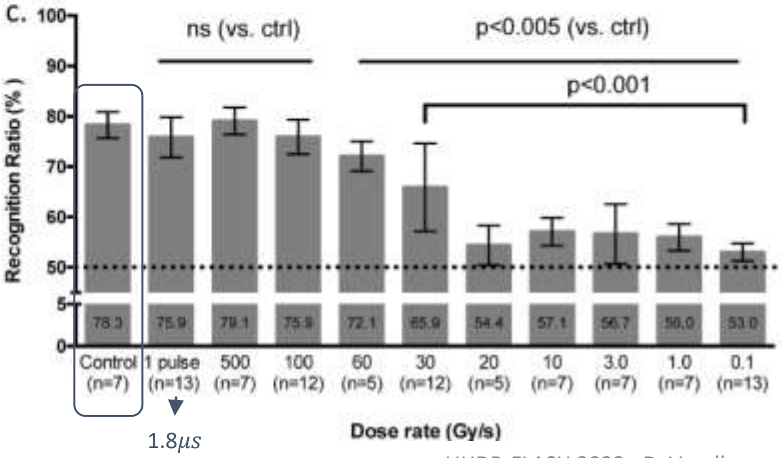
Radiotherapy and Oncology (2017) http://dx.doi.org/10.1016/j.radonc.2017.05.003

Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100 Gy/s

Pierre Montay-Gruel [a,b,1], Kristoffer Petersson [c,1], Maud Jaccard [c], Gaël Boivin [a], Jean-François Germond [c], Benoit Petit [a], Raphaël Doenlen [d], Vincent Favaudon [b], François Bochud [c], Claude Bailat [c], Jean Bourhis [a,1], Marie-Catherine Vozenin [a,*,1]

[a] Department of Radiation Oncology/DO/CHUV, Lausanne University Hospital, Switzerland; [b] Institut Curie, INSERM U1021/CNRS UMR3347, Université Paris-Saclay, Orsay, France; [c] Institute of Radiation Physics (IRA), Lausanne University Hospital; and [d] Faculty of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Switzerland

10 Gy in less than 100 ms – **6 MeV electrons**



- Preservation of memory and learning skills
- Preservation of neural stem cells

Early results

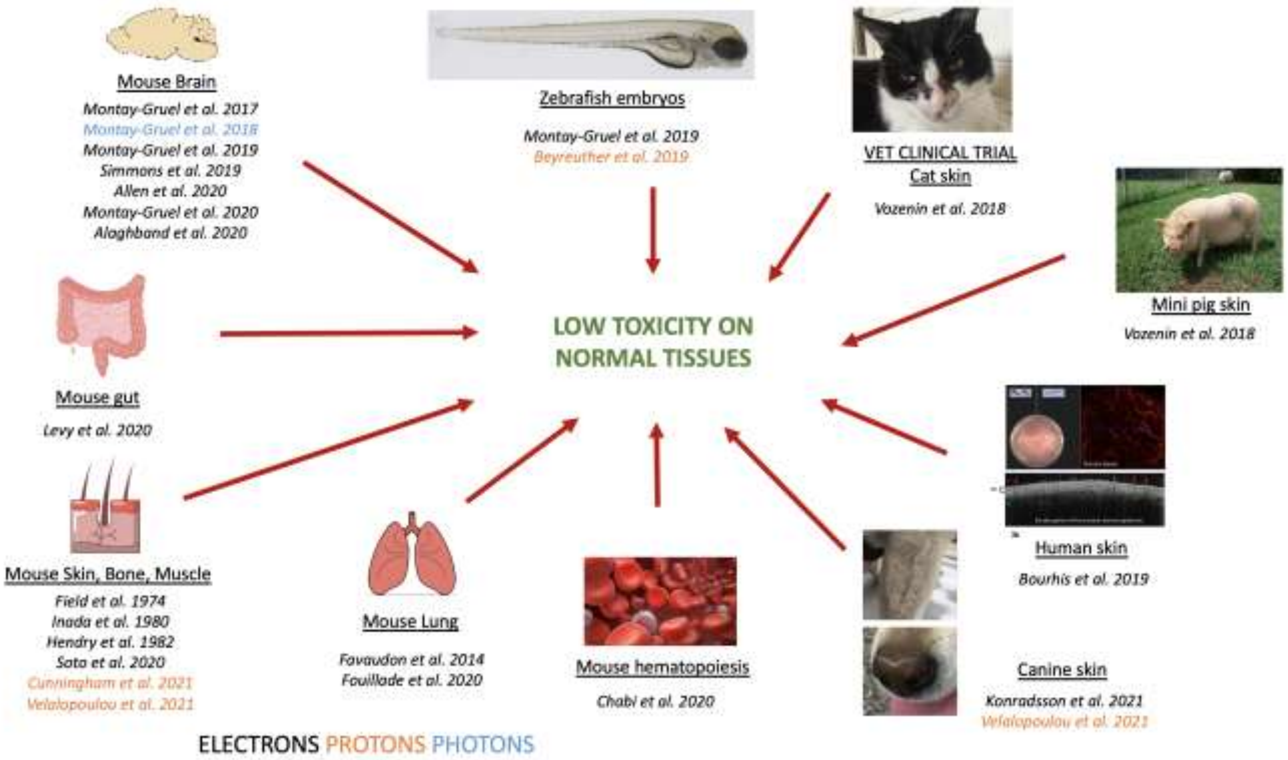
Long-term Follow up-3y post-RT

CONV

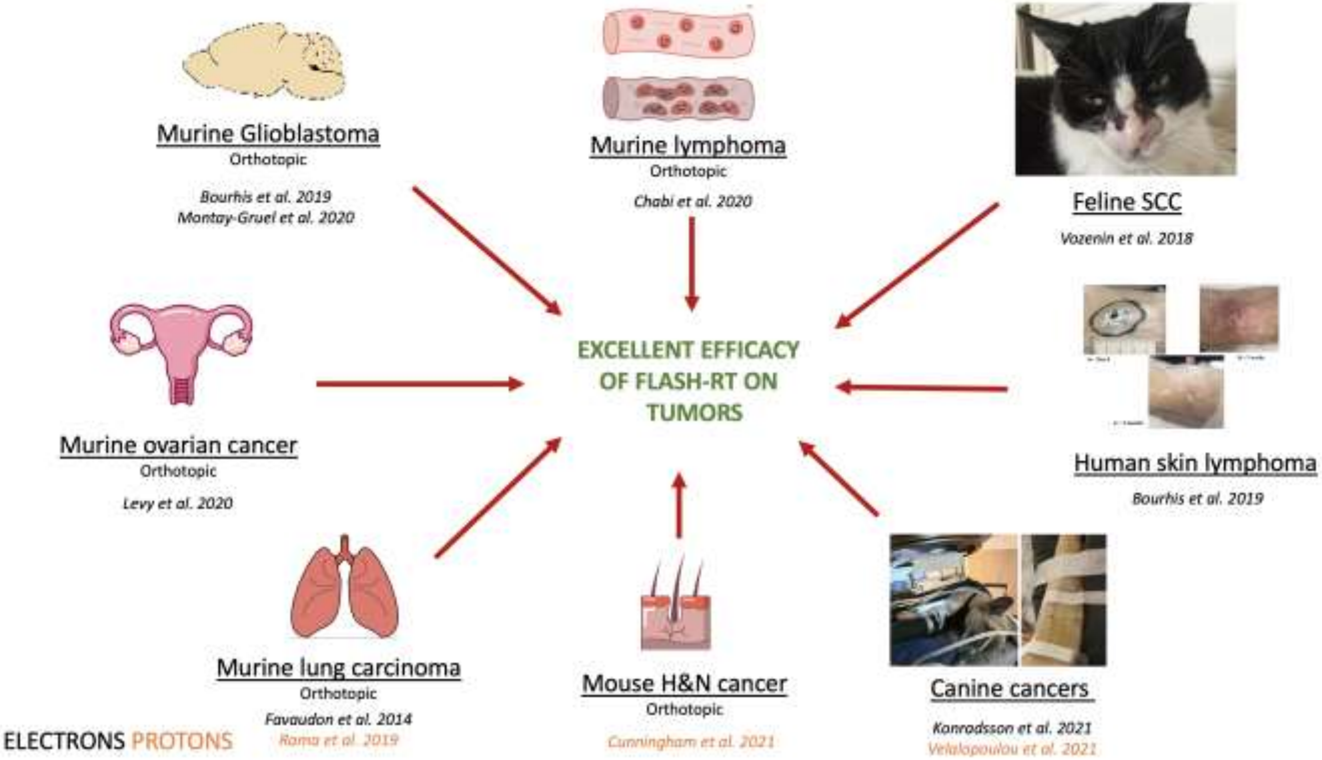
FLASH

Slide courtesy MCat Vozenin

FLASH: ... toxicity



FLASH: ... tumour control



Early results

- First in man

Radiotherapy and Oncology 139 (2019) 18–22

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

First in Human

Treatment of a first patient with FLASH-radiotherapy

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

[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

- 1 subject:
  - 95% confidence interval on an n=1 study span … **2.5-100%**

Early results

- First in man

Fig. 1. Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

- 3.5 cm diameter skin tumour
  - Multiresistant CD30+ T-cell cutaneous lymphoma
- D_p(PTV): 15Gy in 90ms
- 5.6 MeV electrons
- Single field – single fraction
- Only grade 1 acute toxicity
- Complete tumour respons

- 1 subject:
  - 95% confidence interval on an n=1 study span ... **2.5-100%**

Newsflash or flash in a pan?

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)

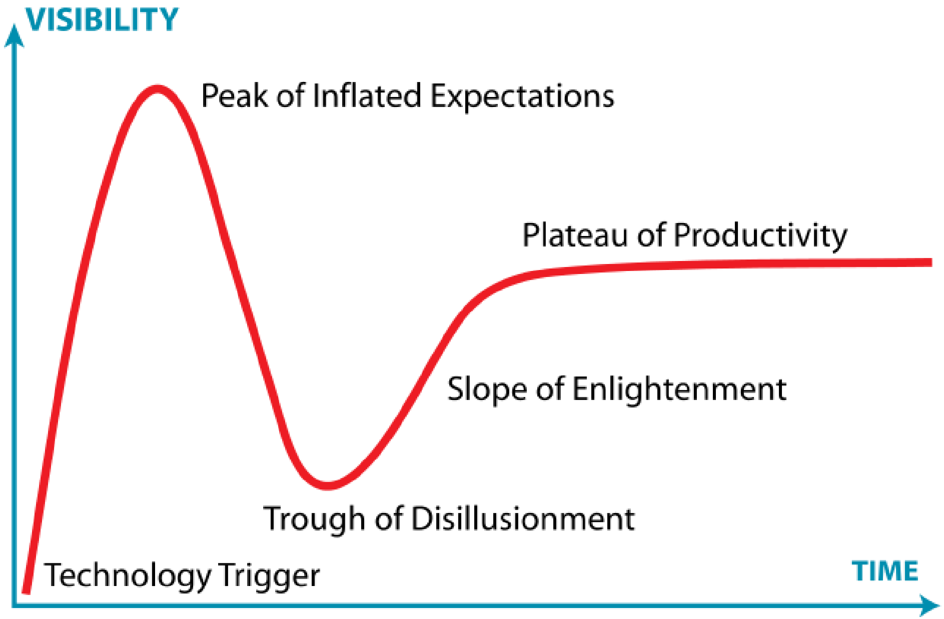
Jing Cai, Ph.D., Moderator mailto:

(Received 17 June 2019; accepted for publication 22 June 2019; published 29 August 2019)

[https://doi.org/10.1002/mp.13685]

4287 Med. Phys. 46 (10), October 2019 0094-2405/2019/46(10)/4287/4 4287

Hype or Hope?


VISIBILITY
Peak of Inflated Expectations
Plateau of Productivity
Slope of Enlightenment
Trough of Disillusionment
Technology Trigger
TIME

UHDR and FLASH at Iridium Netwerk / UA

Medical physics

- Detector development and implementation
- Dosimetric Framework
- In vitro and in vivo dosimetry
- Multimodality and image guidance

Radiobiology

- In vitro and in vivo models of breast cancer
- 3D culturs and organoids
- In vitro and in vivo models of skin cancer

Radiation Oncology

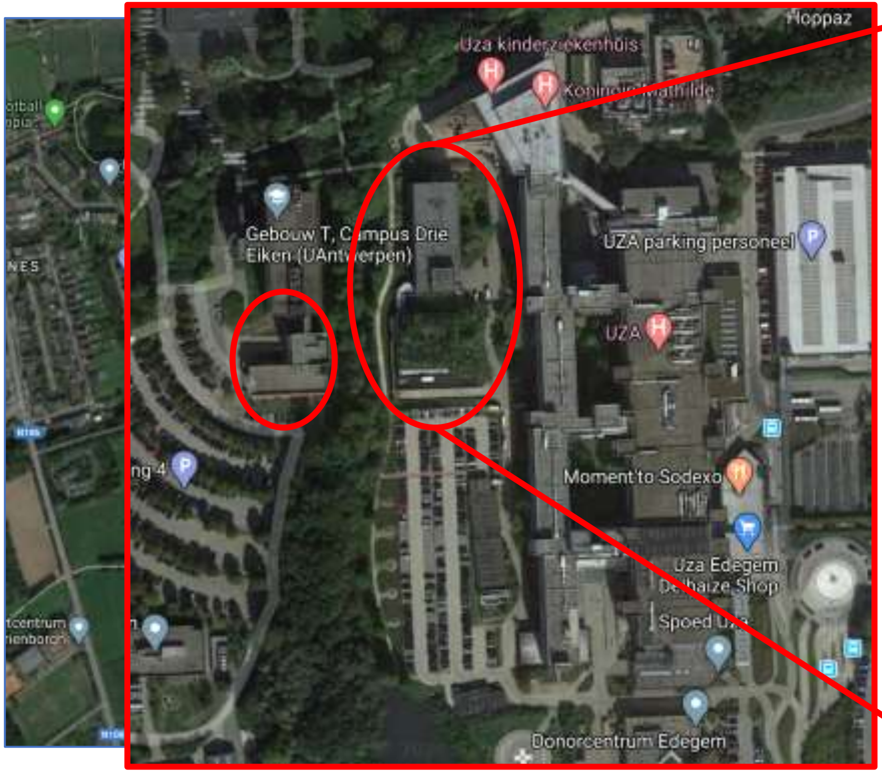
- Clinical translation of FLASH-RT (IOeRT)

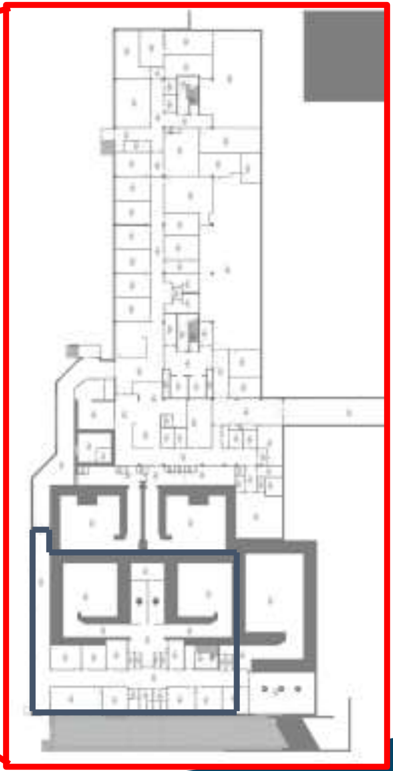
SIT

ElectronFLASH (the ELF)

iridium network
Topzorg in radiotherapie

UHDR and FLASH at Iridium Netwerk / UA





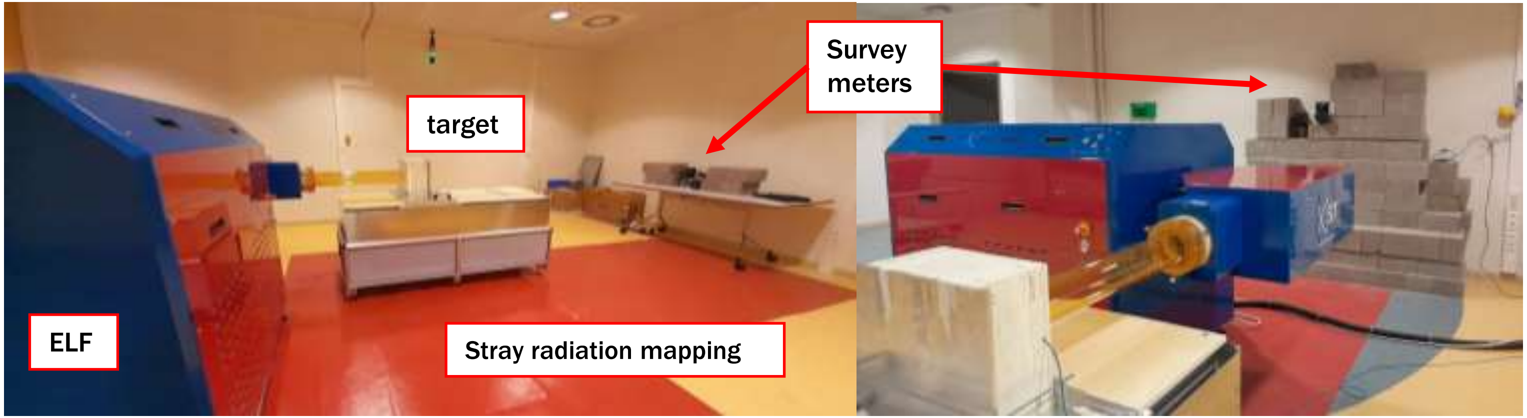
Safety and Radioprotection

- Ozone production

<0.01 ppm at usual doses	0.05 ppm with 16 kGy	0.1 ppm with 28 kGy	→ ventilation

institut Curie

- Radioprotection



iridium network
Topzorg in radiotherapie

Safety and Radioprotection

- Ozone production

<0.01 ppm at usual doses | 0.05 ppm with 16 kGy | 0.1 ppm with 28 kGy → ventilation

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- Radioprotection
  - Optimal design of treatment rooms

SAPIENZA UNIVERSITÀ DI ROMA

  - Personal dosimetry (non saturating, fast responding active dosimeters)

SCK•CEN STUDIECENTRUM VOOR KERNENERGIE CENTRE D'ETUDE DE L'ENERGIE NUCLEAIRE

Based on PODIUM project
H-EU CONCERT project: Personal on-line Dosimetry Using Computational Methods

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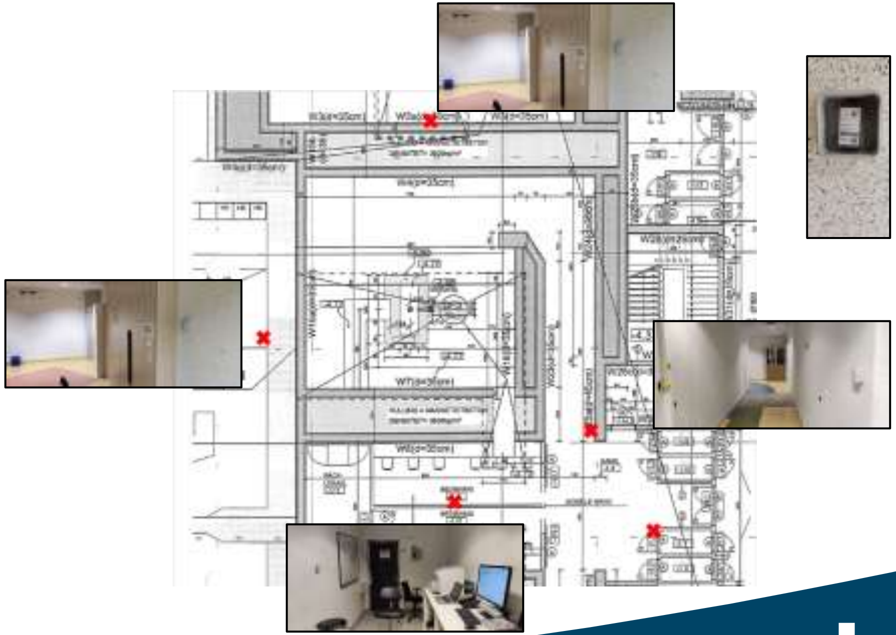
Safety and Radioprotection

- Some food for thought and how to support clinical implementation
  - On the concept of **IDR < 10 µSv/h**?
  - Referring to NCRP:

    - It is reasonable to design a barrier to meet a weekly value equal to 1/50 of the annual shielding design goal (ie **20 µSv/w**)
    - Further scaling the shielding design goal to **shorter intervals is NOT appropriate** and may be **incompatible with the ALARA** principle
    - Specifically, the use of measured Instantaneous Dose-equivalent Rate (IDR) with the linac operating at maximum output, **does NOT properly represent the true operating conditions** and radiation environment of the facility
    - NCRP 151 recommends: Time Averaged Dose-equivalent Rate (TADR): **Rw and Rh**

Safety and Radioprotection

- Some food for thought and how to support clinical implementation
- Long term, permanent radiation monitoring required
  - Cf IOeRT in non-shielded OR



Safety and Radioprotection

- Some food for thought and how to support clinical implementation
  - On **Treatment Dose** and **Dose Rate**:
    - Total treatment dose is not so different from conventional treatment doses and treatment fractionations.
      - From conventional fractionation to hypofractionation and ultra-hypofractionation
    - One might argue that it is another step in the evolution towards higher dose rates
      - From conventional dose rate to FFF high dose rates towards UHDR.
  - How about Workload (W)?
    - **Patient W** (Gy/w) will be comparable (or even lower compared) to current W
    - **Physics W** (Gy/w), however, might be much higher.
      - Consider performing commissioning/acceptance measurements after hours or at different (shielded) location
      - Optimizing machine QA by balancing low and UH dose rate

Acknowledgements

University of Antwerp
CORE | Center for Oncological Research

Faculty of Medicine and Health Sciences
Iridium Netwerk
AReRO group (CORE)

Radiobiology
Pierre Montay – Gruel
Adrien Arrigo
Louize Brants

Radiation Oncology
Philip Poortmans
Paul Meijnders
Ines Joye
Melanie Machiels
Daan Nevens
Piet Dirix
Daan Stas

Medical Physics
Alessia Gasparini
Dirk Verellen
Verdi Vanreusel
Michaël Claessens

Universiteit Antwerpen
netwerk iridium Topzorg in radiotherapie
GZA Ziekenhuizen GasthuisZusters Antwerpen Sint-Augustinus - Sint-Vincentius - Sint-Jozef
UZA

SCK•CEN Studiecentrum voor Kernenergie Centre d'Etude de l'Energie Nucléaire
Research in dosimetric applications group
Filip Vanhavere
Launa de Freitas Nascimento

NuTeC Nucleair Technologisch Centrum
AGFA HealthCare
Università di Roma Tor Vergata
SAPIENZA Università di Roma
USC Universidade de Santiago de Compostela
SIT Sordina IORT Technologies
institut Curie
CHUV