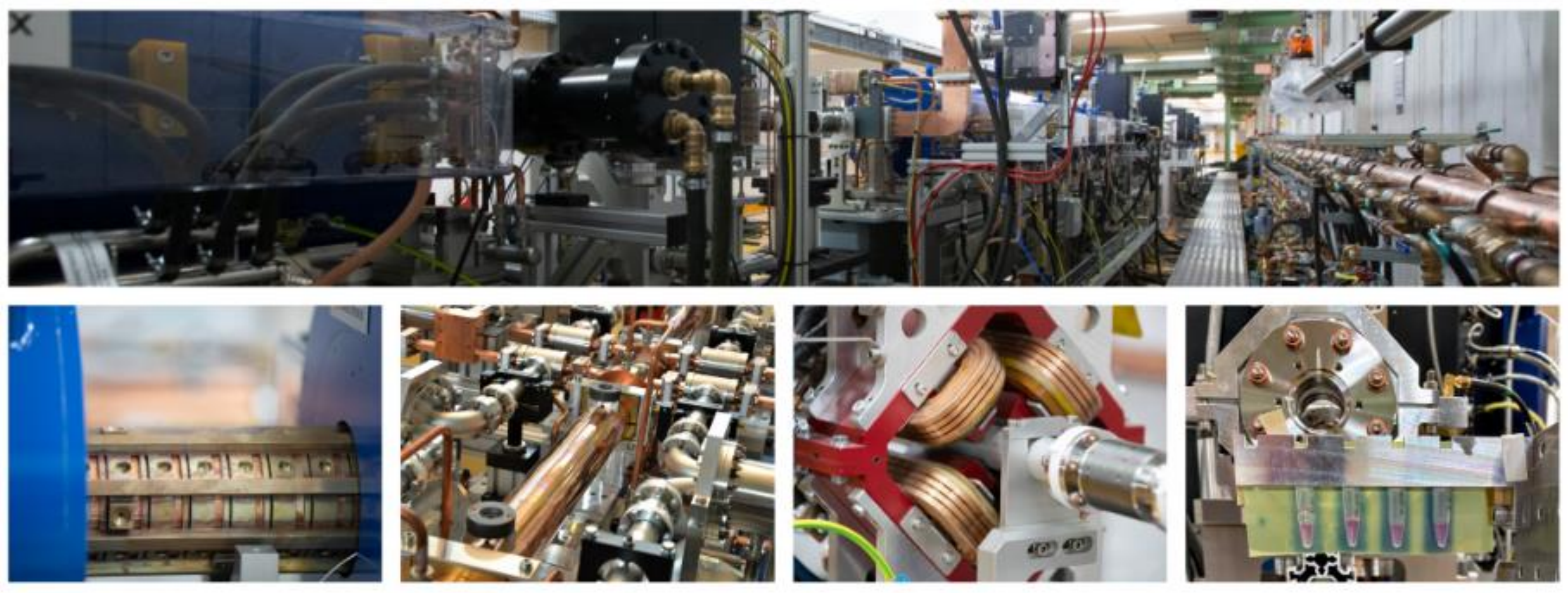
Very High Energy Electron Radiotherapy Conference (VHEE23)



Very High Energy Electrons: Clinical Perspective and Constraints for a Medical Device VHEE Flash

Giuseppe Felici, SIT S.p.A.

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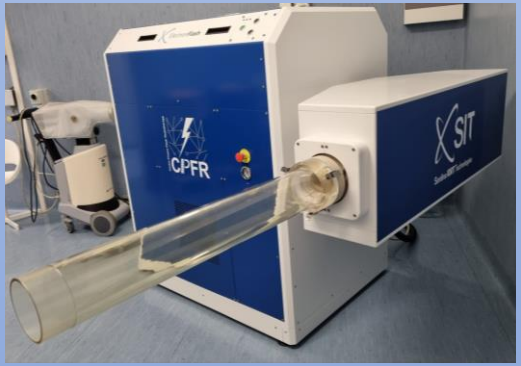
Scientific Awareness
- What are the questions?
- Identifying the challenges

Technological Development
- The most useful tools for the research;
- The right devices for clinical translation

Let's find the best solutions without overshooting !





VHEE
LINAC

XSIT
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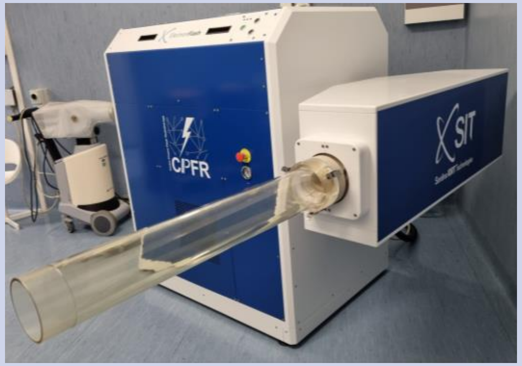
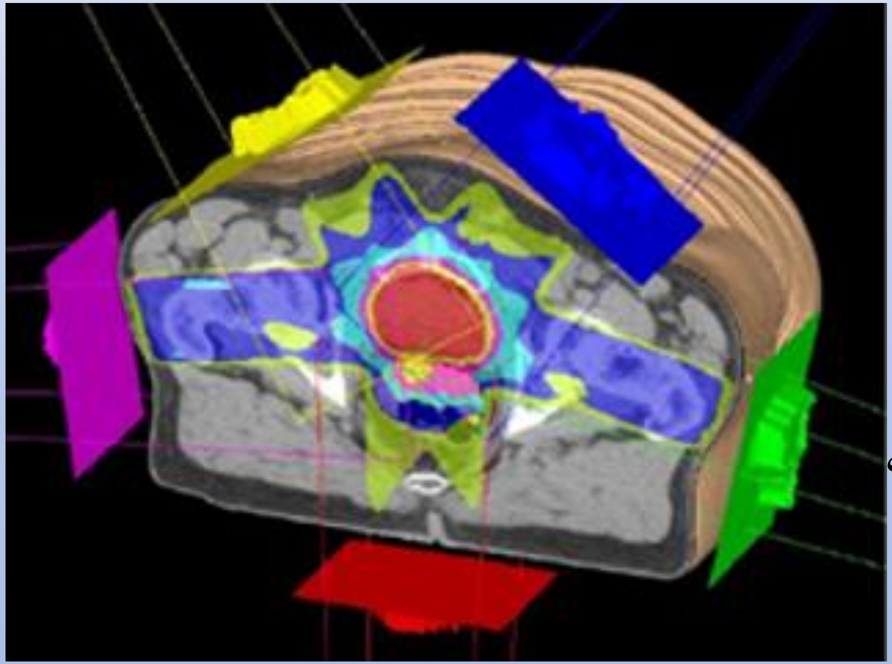
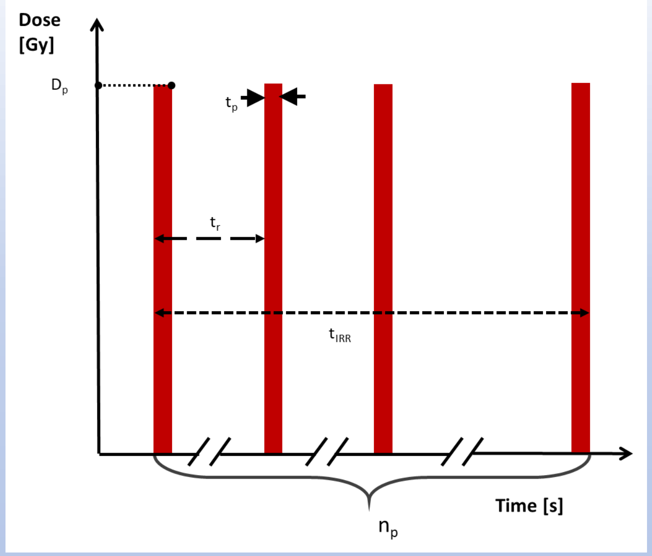
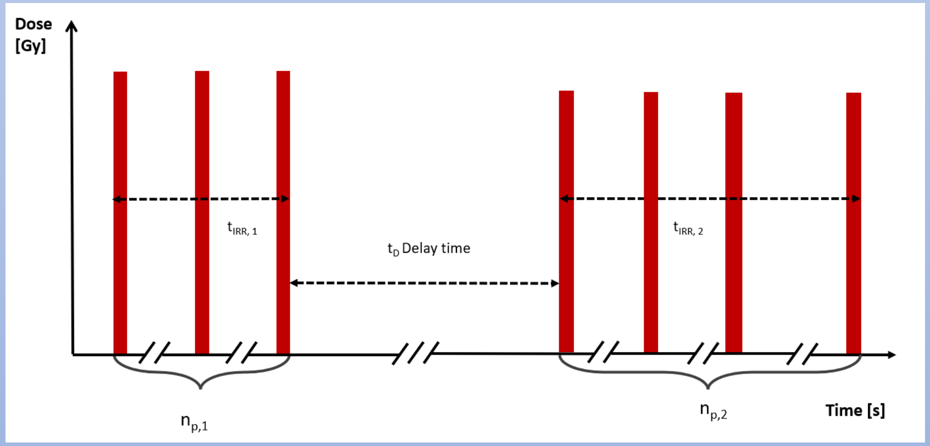
The pursuit of the VHEE Flash Medical Device represents the culmination of an extensive and intricate research and development trajectory.

Radiobiology, basic investigation	First clinical application IOeRT and dermatologic cases	Deep seated tumours – VHEE (Very High Energy Electrons)
ElectronFlash	LIAC Flash	VHEE FLASH
	 	VHEE LINAC





Flash approach adds a new 'dimension' to RT paradigm: Beam time structure



Obviously, adding a new 'dimension' is not removing the others!

ElectronFlash

- Adjustable mean dose rate between 0.005 – 1300 Gy/s with reference field Ø10 cm;
- Instantaneous dose rate higher than 10^6 Gy/s with reference field Ø10 cm;
- Mean dose rate up to 10.000 Gy/s with small applicator (IDR up to 10^7 Gy/s);
- Allows to modify different temporal beam structure's parameters:
  - ➢ Dose per pulse;
  - ➢ Pulse duration (0.2 – 4 μs);
  - ➢ Pulse repetition frequency (PRF: 1 -500 Hz);
- Beam monitoring:
  - ➢ Delivered dose (for each pulse and integral);
  - ➢ Beam energy;
- Optimized Human Machine interface;
- Compliant with IEC 60601-2-1.

International patent deposited in 2019, obtained in 2021

GOBIERNO DE ESPAÑA

MINISTERIO DE CIENCIA E INNOVACIÓN

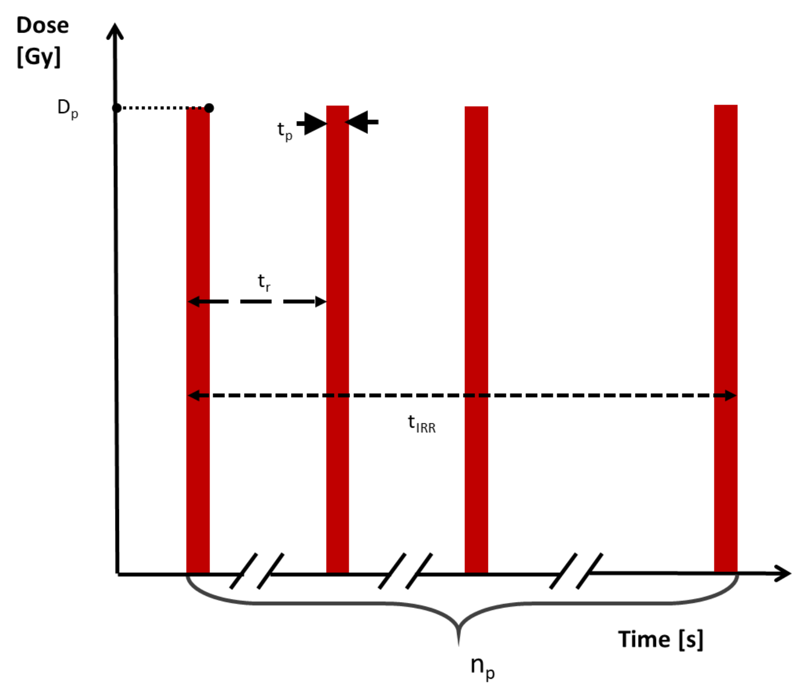
Ciemat

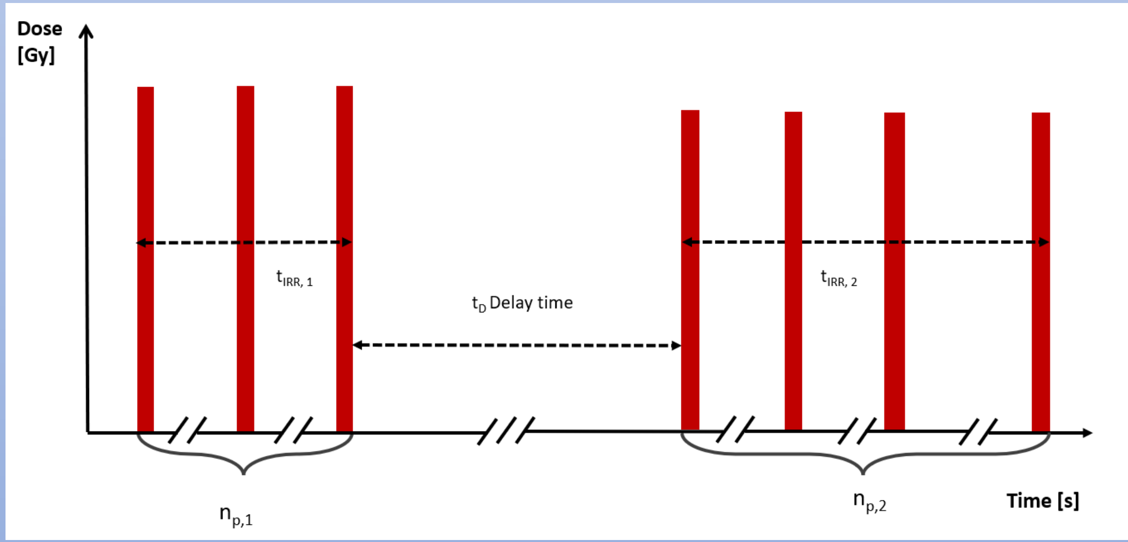
Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas

ElectronFlash

ElectronFlash, initially designed as per the specs provided by Institut Curie, has become the benchmark to test and validate new dosimeters and new dosimetric approaches (Flash diamond, ultra-thin IC chambers, ALLS chamber, UHDR scintillators, etc.). It offers the best performance not only in terms of maximum dose rate but particularly it can vary independently all the Temporal beam structure parameters.

It offers the best platform to study Flash effect.





A lot of work has been done, and maybe the best is yet to come…

Moving to clinic …

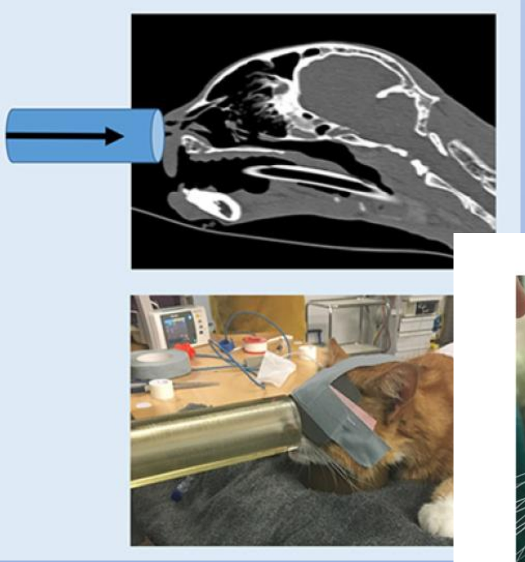
$$'Flash' effect \neq 'Flash\ Radiotherapy'$$

We don’t want to make Cowboy RT.
Under which conditions ‘Flash Radiotherapy’ is meaningful?
It’s mandatory identifying adequate technological solutions which guarantee ‘the basic safety and essential performance’ of the Medical electron accelerators.

CLINICAL CANCER RESEARCH | TRANSLATIONAL CANCER MECHANISMS AND THERAPY

Dose- and Volume-Limiting Late Toxicity of FLASH Radiotherapy in Cats with Squamous Cell Carcinoma of the Nasal Planum and in Mini Pigs

Carla Rohrer Bley[1], Friederike Wolf[1], Patrik Gonçalves Jorge[2,3,4], Veljko Grilj[2,3,4], Ioannis Petridis[2,3], Benoit Petit[2,3], Till T. Böhlen[4], Raphael Moeckli[4], Charles Limoli[5], Jean Bourhis[2], Valeria Meier[1], and Marie-Catherine Vozenin[2,3]



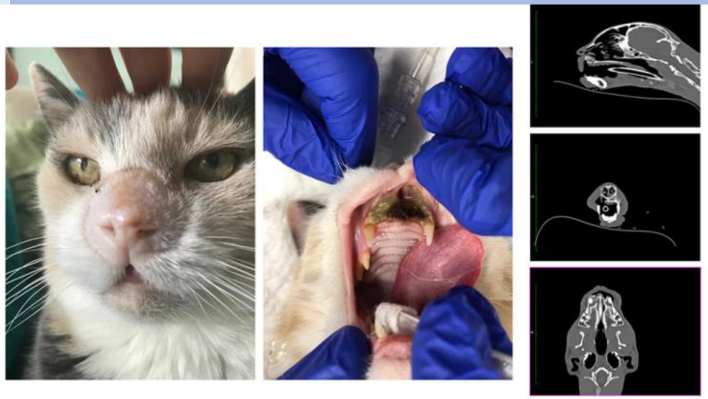


Figure 3.
Pictures show the clinical situation of the cat (CatNr 6) 14 months post-FLASH treatment. The cat presented with no external sign of complication (left) but showed maxillary and mucosal necrosis (middle). Right, Extension of the necrosis on lateral, frontal, and sagittal CT-scan sections.

In conclusion, our study is the first to shed light on certain caveats in the path toward clinical translation of FLASH-radiotherapy and shows that implementation of single-high-dose and large field irradiations will present challenges for minimizing long-term toxicities even with FLASH dose rates. We believe that clinical trials with domestic animal patients (cats and dogs) are safe and quick way to investigate FLASH-radiotherapy benefit and avoid possible failure in human clinical trial. At the technological level, implementation of state-of-the art ballistics, imaging and treatment plan should be coupled with FLASH capabilities and systematic characterization of the beam parameters will be required to unravel the full potential of FLASH-radiotherapy, which remains a significant hurdle with existing technology.

First clinical translation: IOERT

LIACFLASH

- Energy: 6, 8, 10 and 12 MeV
- Conventional and Flash dose rate
- Flash performance as ElectronFlash
- Dimensions and weights fully compatible with standard Operating Room
- No additional shielding required in any Operating Room (beam stopper only)
- 8 degrees of freedom
- Dedicated Monte Carlo based TPS
- Automatic image guided docking

https://www.soiort.com/flash-clinical-technology/

LIACFLASH: designed to provide on board imaging, treatment planning & image guidance

- Reference system generated by optical tracker;
- 3D US imaging integrated;
- It can work both with US and CT-like images;
- image guided docking
- Treatment validation after docking
- Fully mobile system usable in multiple OR.

NEW!

- Fast MC based dose engine;
- From direct to inverse planning.

A. Sarti ‘A feasibility study of IORTFLASH using a GPU based Fast MC’

LIACFLASH: designed to comply with IEC Standards (present and future ones)

IEC

IEC 60601-2-1

Edition 3.0 2009-10

INTERNATIONAL STANDARD

NORME INTERNATIONALE

Medical electrical equipment –
Part 2-1: Particular requirements for the basic safety and essential performance of electron accelerators in the range 1 MeV to 50 MeV

- **Temporal beam structure (pulse duration, PRF):**
  - Irradiation parameters to be set (…). MU is not enough!
  - HMI
- **Monitoring challenge**

- **TPS:**
  - Beyond DVH: adding DRVH & IDRVH, # pulses, irradiation time…
  - Mandatory interface with Treatment Unit (IORT)

- **Radiation protection monitoring**

And now, VHEE Flash Medical Device!

SIT works in the Italian VHEE network, together with La Sapienza and UniPisa. The project has been funded in the framework of Italian PNRR, https://www.healitalia.com/home-page .
The project has officially started on 1st December 2022.

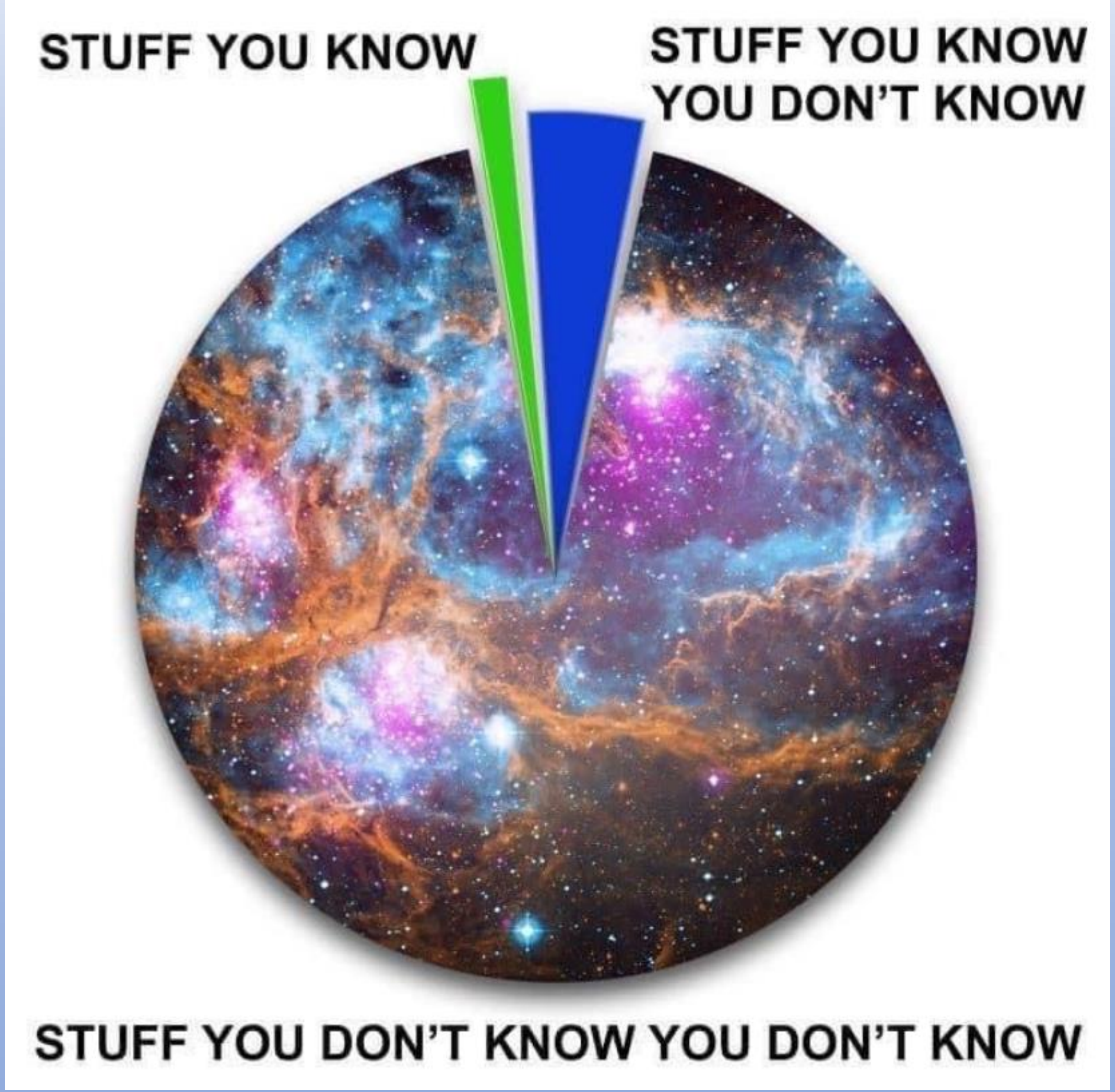
VHEE Flash Medical Device - Design Specs

VHEE Flash MD must

- **treat all (or the majority of) deep seated tumours**
- **be installed within a standard RT bunker, and operated according the standard RT workflow**
- **have a reasonable budget**

1. **A compact LINAC system up to XXX MeV**
2. **An effective and compact dose delivery system – hic sunt leones**
3. **Adequate Dose Monitoring system (standard compliant) - Its design depends on the dose delivery adopted**
4. **Adequate TPS**
   a) **Beyond DVH (DRVH, irr. Time, # pulses…)**
   b) **How to deal with Flash? Are DMF enough?**
5. **Installation and Radiation Protection**
6. **Standard Compliance – no IEC standard exists for VHEE today (IEC 60601-2-1 is up to 50 MeV only and does not deal with pencil beam, just in case)**

VHEE Flash Medical Device



Is this the situation ?

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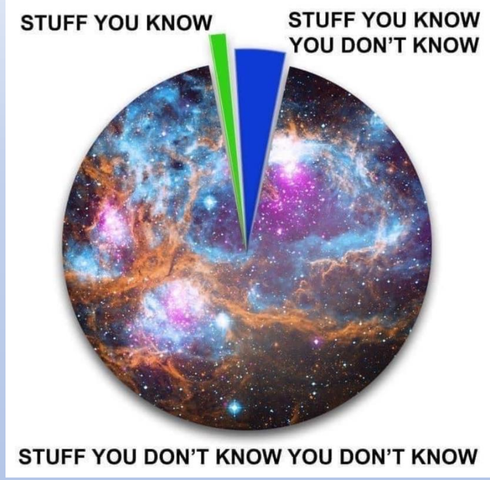
VHEE Flash Med. Dev.



Stuff we know	**Stuff we don't know**	**Stuff we don't know we don't know**
LINAC	Dose delivery system	?
TPS	Dose monitoring system	
Dose monitoring system	Standards	
Radiation Protection		

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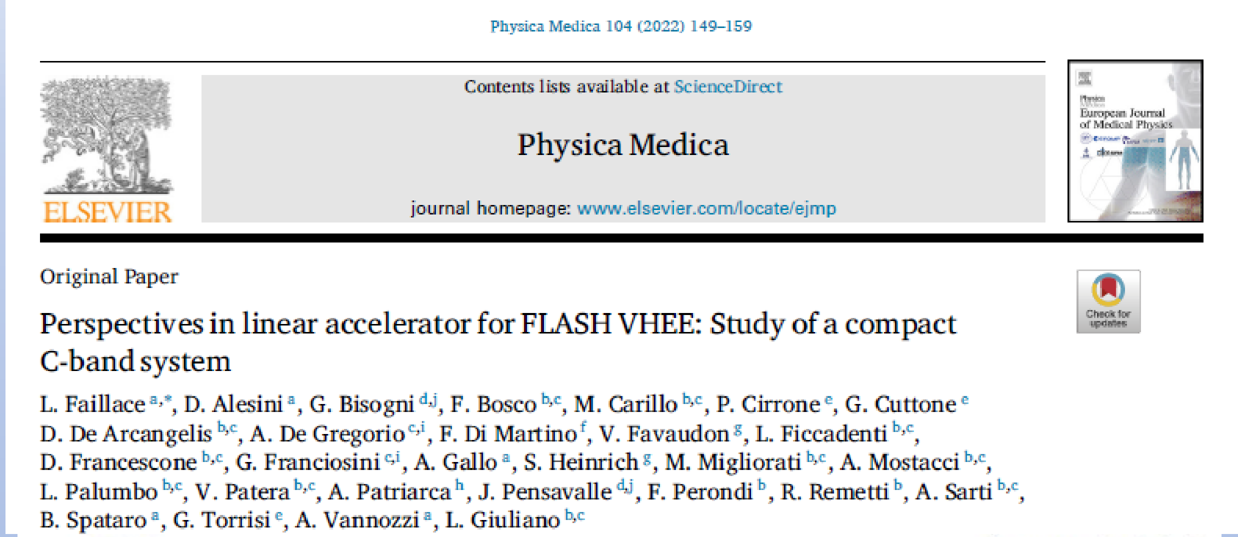
LINAC: Please refer to Luigi Palumbo talk (Wed 12/07, 11.50), Luigi Faillace talk (Wed 12/7, 12.50) and Lucia Giuliano (Thu 13/7, 14.55)

Reaching the required energy in the minimum volume with the adequate beam time structure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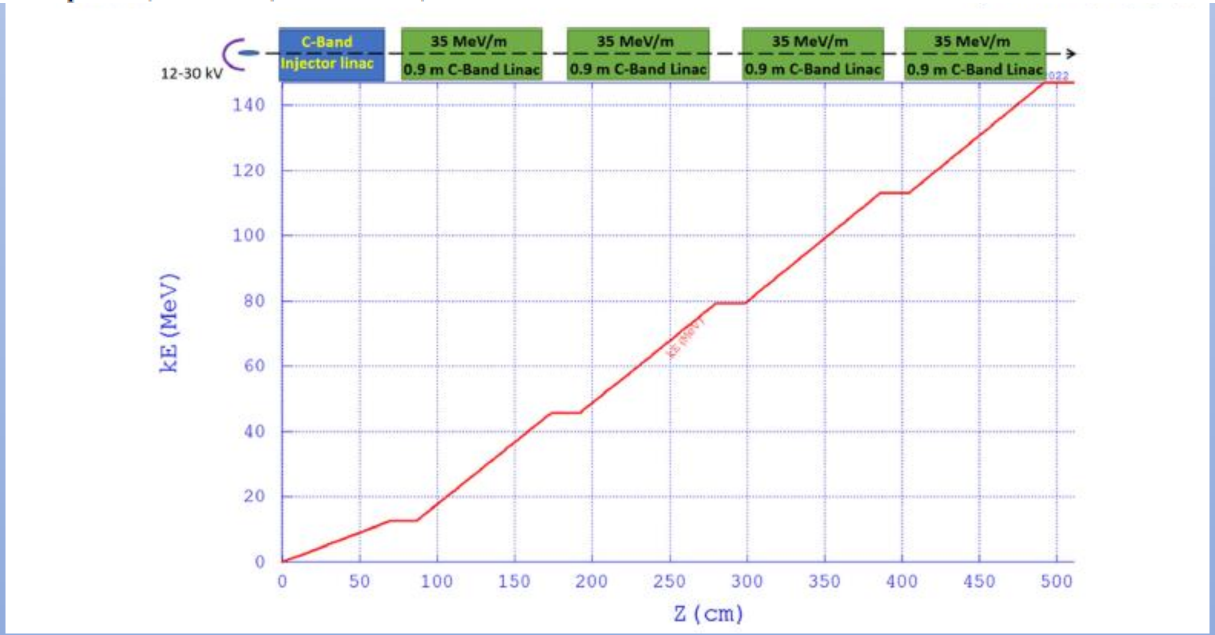
journal homepage: www.elsevier.com/locate/ejmp

Original Paper

Perspectives in linear accelerator for FLASH VHEE: Study of a compact C-band system

L. Faillace [a,*], D. Alesini [a], G. Bisogni [d,j], F. Bosco [b,c], M. Carillo [b,c], P. Cirrone [e], G. Cuttone [e]
D. De Arcangelis [b,c], A. De Gregorio [c,i], F. Di Martino [f], V. Favaudon [g], L. Ficcadenti [b,c],
D. Francescone [b,c], G. Franciosini [c,i], A. Gallo [a], S. Heinrich [g], M. Migliorati [b,c], A. Mostacci [b,c],
L. Palumbo [b,c], V. Patera [b,c], A. Patriarca [h], J. Pensavalle [d,j], F. Perondi [b], R. Remetti [b], A. Sarti [b,c],
B. Spataro [a], G. Torrisi [e], A. Vannozzi [a], L. Giuliano [b,c]



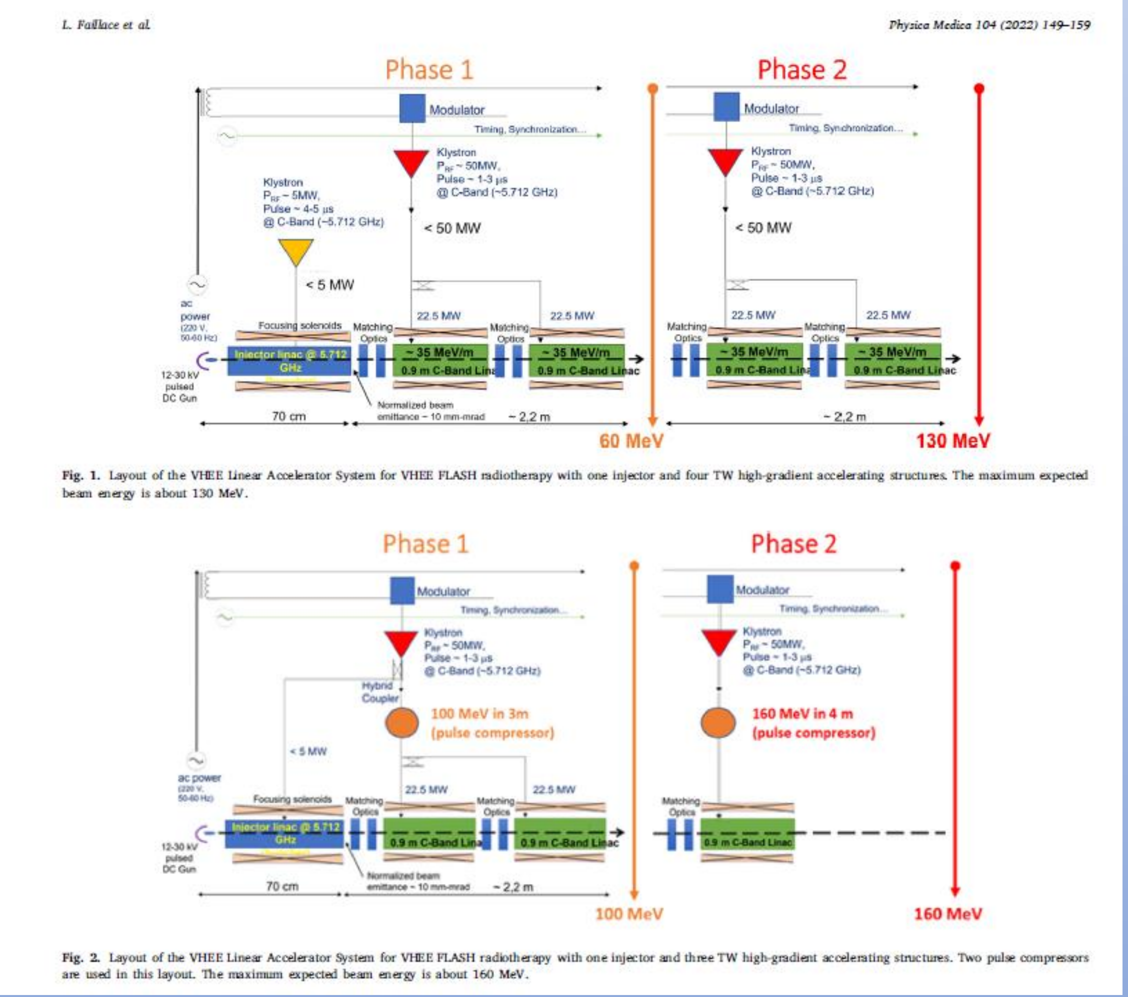


Fig. 1. Layout of the VHEE Linear Accelerator System for VHEE FLASH radiotherapy with one injector and four TW high-gradient accelerating structures. The maximum expected beam energy is about 130 MeV.

Fig. 2. Layout of the VHEE Linear Accelerator System for VHEE FLASH radiotherapy with one injector and three TW high-gradient accelerating structures. Two pulse compressors are used in this layout. The maximum expected beam energy is about 160 MeV.

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TPS: Please refer to Giacomo Traini talk (Thu 13/7, 12.30)

Identifying the best beam delivery strategy and its technologic implementation

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 Frascati Toppi[1,9], Giacomo Traini[2], Antonio Trigilio[2,5] and Vincenzo Patera[1,2]*

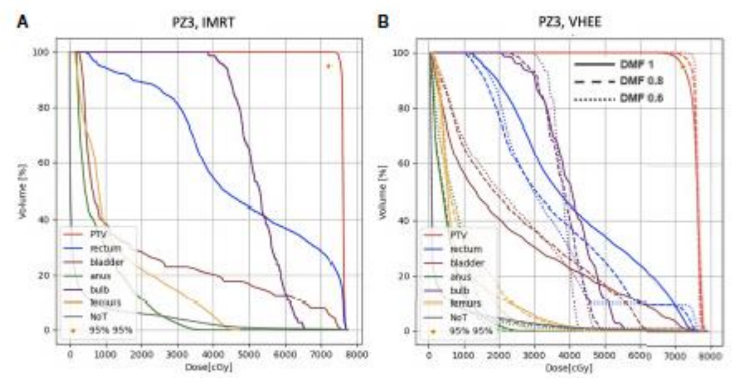

FIGURE 8 | DVH histograms for the PTV and the OARs of PZ3. The biological dose relative to the normal tissue (NoT) is shown as well. **(A)** Results obtained with photons (standard IMRT, 5 fields) for the 38 fractions foreseen in the patient treatment (76 Gy in total). **(B)** Results obtained with electrons of different energies (see **Table 1**) and using different DMF values: the solid line shows results obtained without any FLASH effect, while dashed and dotted lines show the impact of a DMF equal to 0.8 and 0.6 respectively.

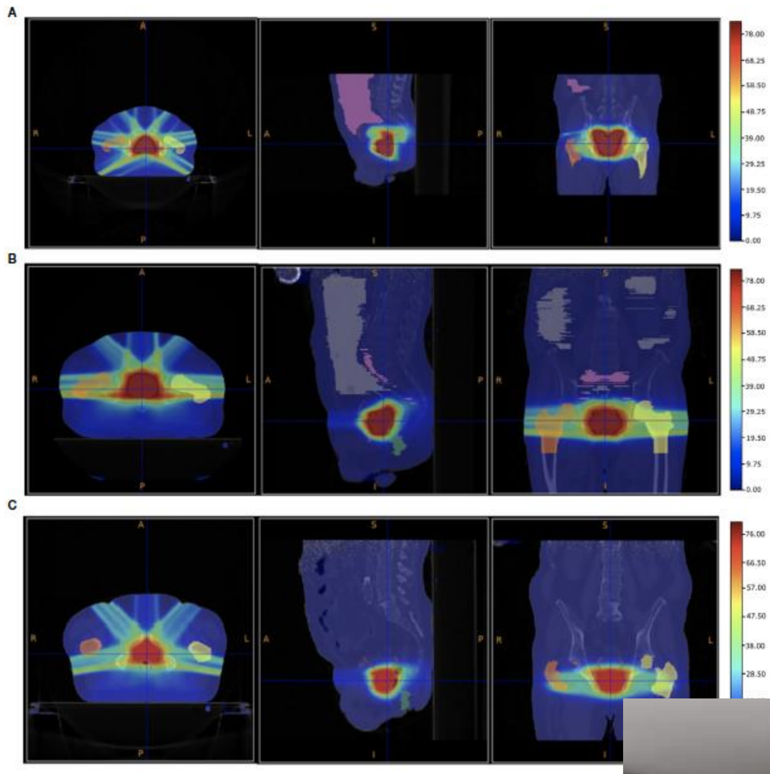

FIGURE 5 | Patient PZ1 **(A)**, PZ2 **(B)** and PZ3 **(C)** CTs overlapped with the biological dose maps optimised using the output o with energies listed in **Table 1** and a DMF of 1 (no FLASH effect). The OARs are shown: the femurs in yellow and orange, the b surface in dark blue. The PTV is shown in red.

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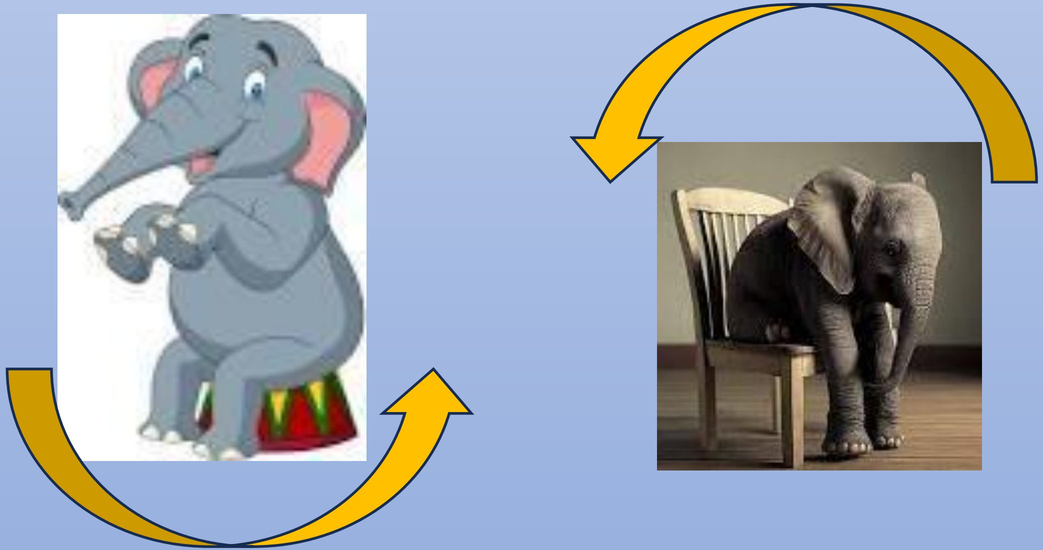
Dose delivery system

Identifying the best dose delivery strategy and its technologic implementation…

The solution could be putting the elephant (or the patient) on a <u>chair</u> in <u>full upright position</u>!

(Some more research needed here)



…It's the elephant in the room !

(Credits Vincenzo Patera)

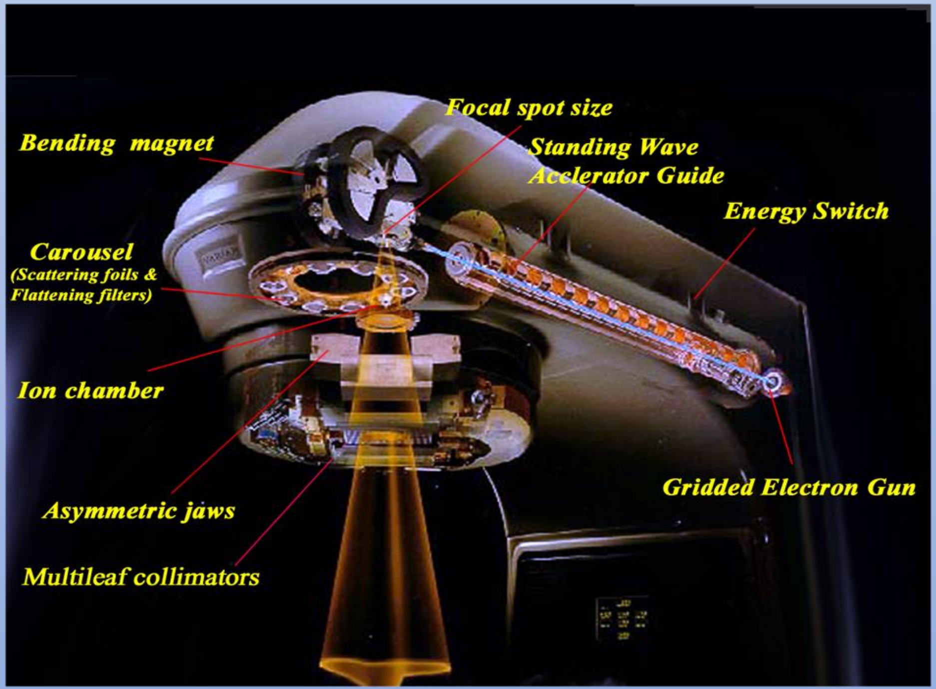
Radiation protection

NCRP 151 approach in terms of Time Averaged Dose Rate (TADR) must be adopted.
Otherwise, RP can become a real SHOW STOPPER!
It’s important the whole Scientific Community put this challenge on the appropriate tables (ESTRO has started)

Where does stray radiation come from?

The stray radiation produced by a medical linac, according to NCRP 151, can be identified as

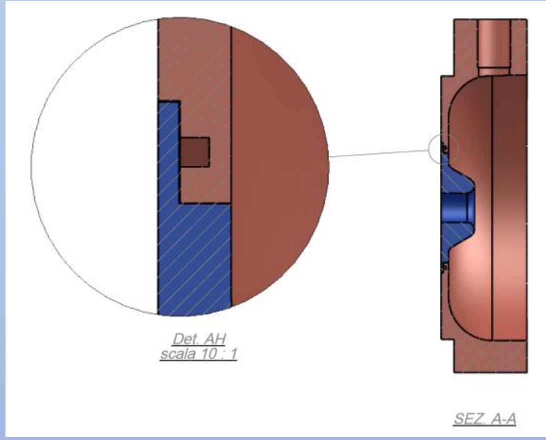
1. direct beam;
2. leakage radiation (**LR**);
3. scattered radiation from the patient (**PSR**);
4. scattered radiation from the walls (**WSR**);
5. secondary radiations (including photo neutrons and neutron capture gamma rays) produced in the accelerator head or in scattering throughout the room.

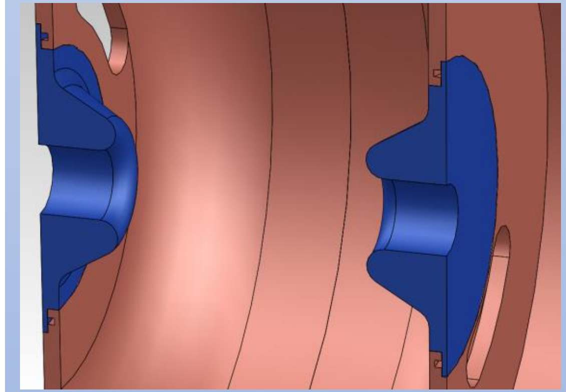


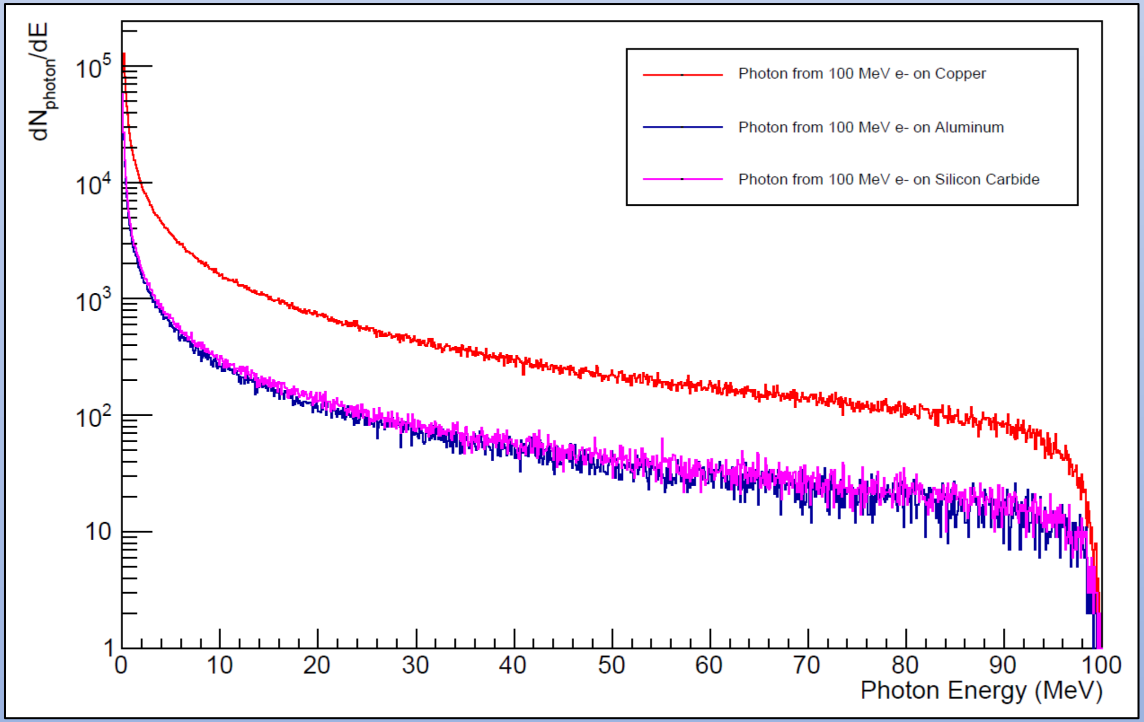
What is doable? Before shielding, minimize Leakage(LR)

$$SR = PSR + LR + WSR$$

In order to minimize SR, the wisest (and only) option is minimizing the leakage.
Leakage is produced by the scattering of the e-beam within the accelerating tank, that's why a solution could be to reduce its Z number!







patent deposited together with La Sapienza

This is however not enough to manage entirely RP challenge

Low Z linac

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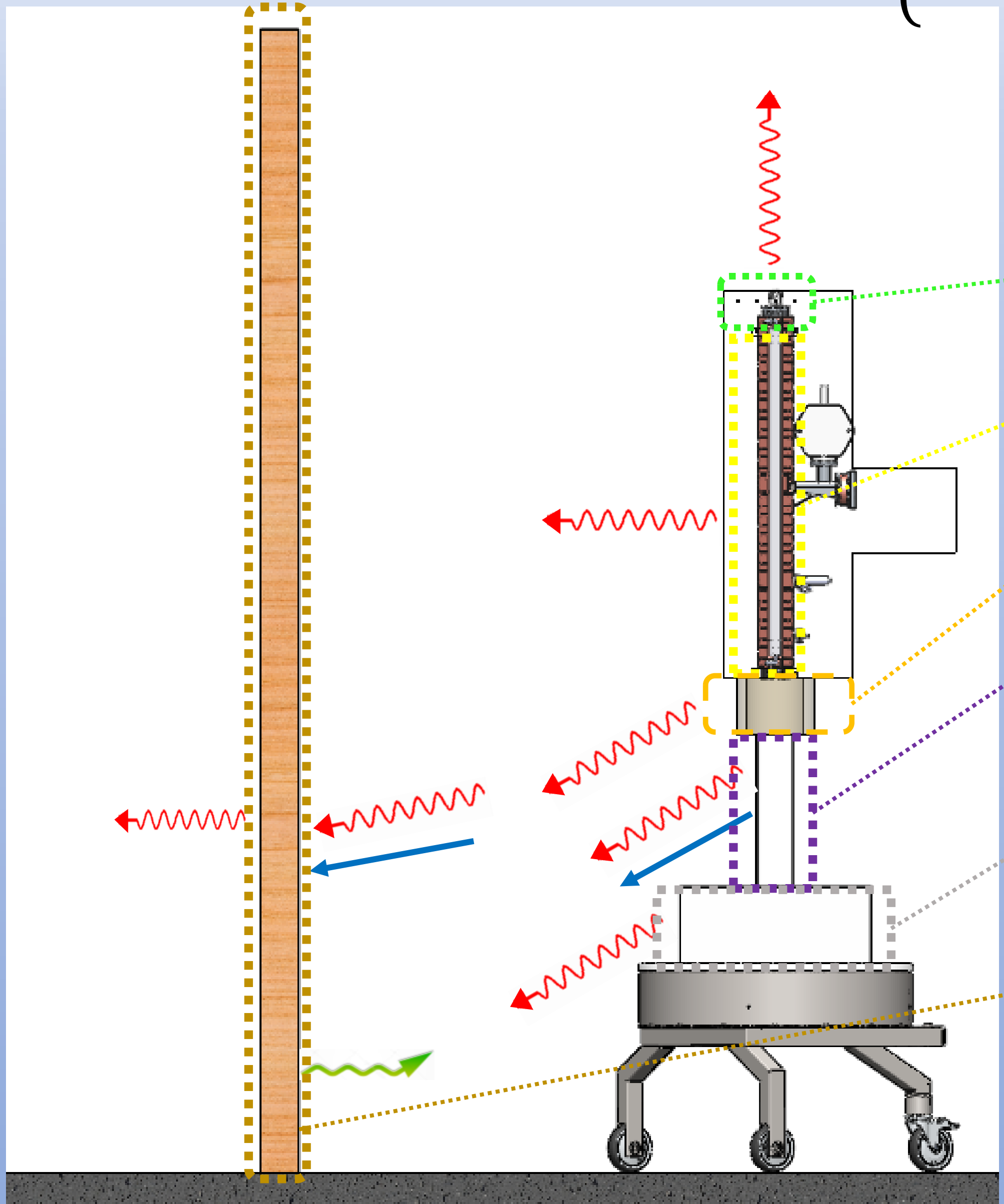
Let’s use IORT as easy reference (hydrogen atom)…

$$\begin{cases} SR = PSR + LR + WSR \\ LR = L_X^{B} + L_X^{AG} + L_X^{PBLD} + L_X^{AP} + L_{e-}^{AP} \end{cases}$$



LEAKAGE RADIATION

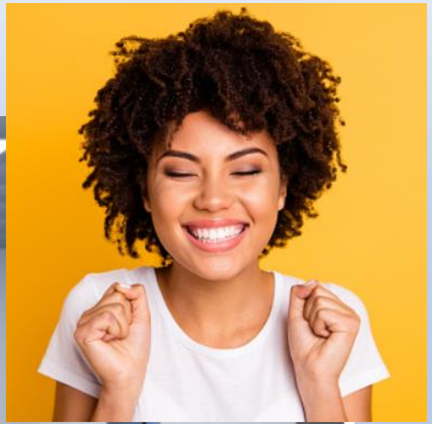
1. L^{B}_{X} Backward radiation (180°)
2. L^{AG}_{X} Accelerating waveguide (0° – 360°)
3. L^{BLD}_{X} Primary BLD (0° - 90°)
4. L^{AP}_{X} , L^{AP}_{e} Applicator (0° - 90°)

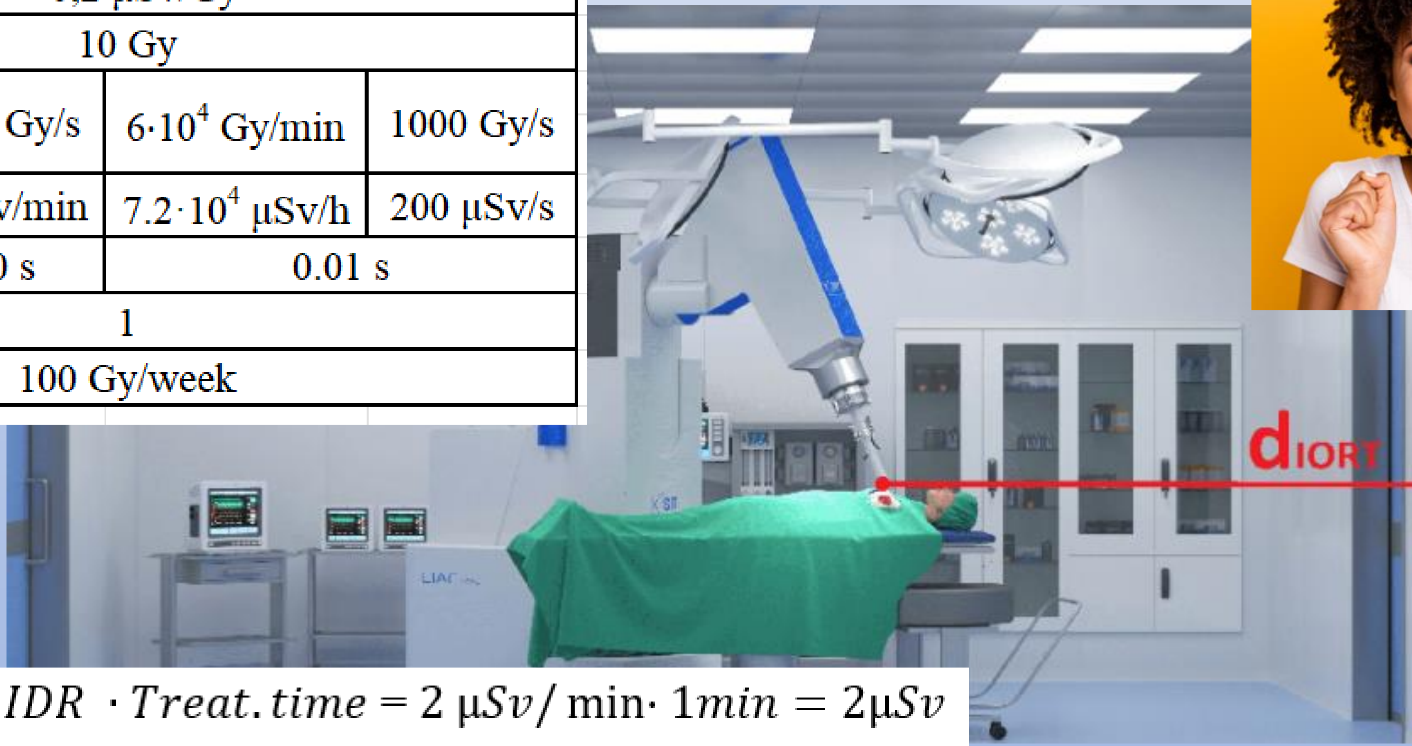
PATIENT SCATTERED RADIATION

WALL SCATTERED RADIATION

IOeRT RP according to TADR ICRP & NRCP

	CONVENTIONAL		FLASH	
Stray Rad @ 3 m	<0,2 µSv/Gy			
Total Dose	10 Gy			
Average Dose Rate $\dot{D}_0$	10 Gy/min	0.17 Gy/s	$6\cdot10^4$ Gy/min	1000 Gy/s
Stray Rad IDR	120 µSv/h	2 µSv/min	$7.2\cdot10^4$ µSv/h	200 µSv/s
Treatment Time	1 min	60 s	0.01 s	
# MAX Patient/Hour	1			
MAX weekly W	100 Gy/week			





CONVENTIONAL $R_h = H_{pt} = IDR \cdot Treat.time = 2\ \mu Sv/\min \cdot 1min = 2\mu Sv$

FLASH $R_h = H_{pt} = IDR \cdot Treat.time = 200\ \mu Sv/s \cdot 0.01s = 2\mu Sv$

CONVENTIONAL $R_w = \frac{IDR \cdot W \cdot U}{\dot{D}_0} = \frac{120\,\frac{\mu Sv}{h} \cdot 100\,\frac{Gy}{week}}{600\ Gy/h} = 20\,\frac{\mu Sv}{week}$

FLASH $R_w = \frac{IDR \cdot W \cdot U}{\dot{D}_0} = \frac{7.2\cdot10^5\,\frac{\mu Sv}{h} \cdot 100\,\frac{Gy}{week}}{3.6\cdot10^6\ Gy/h} = 20\,\frac{\mu Sv}{week}$

IOeRT RP according to IDR

	CONVENTIONAL		FLASH	
Stray Rad @ 3 m	<0,2 µSv/Gy			
Total Dose	10 Gy			
Average Dose Rate $\dot{D}_0$	10 Gy/min	0.17 Gy/s	$6 \cdot 10^4$ Gy/min	1000 Gy/s
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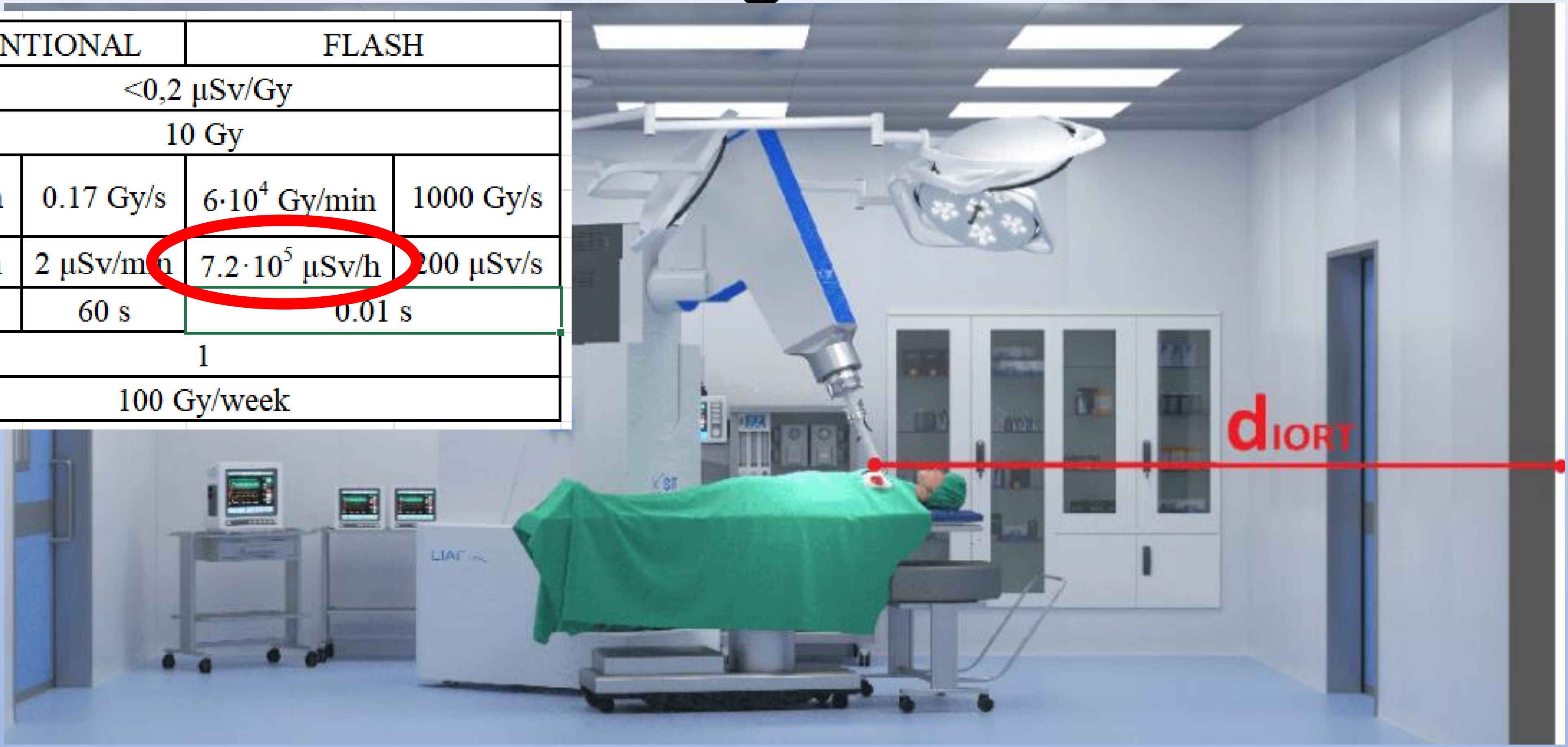
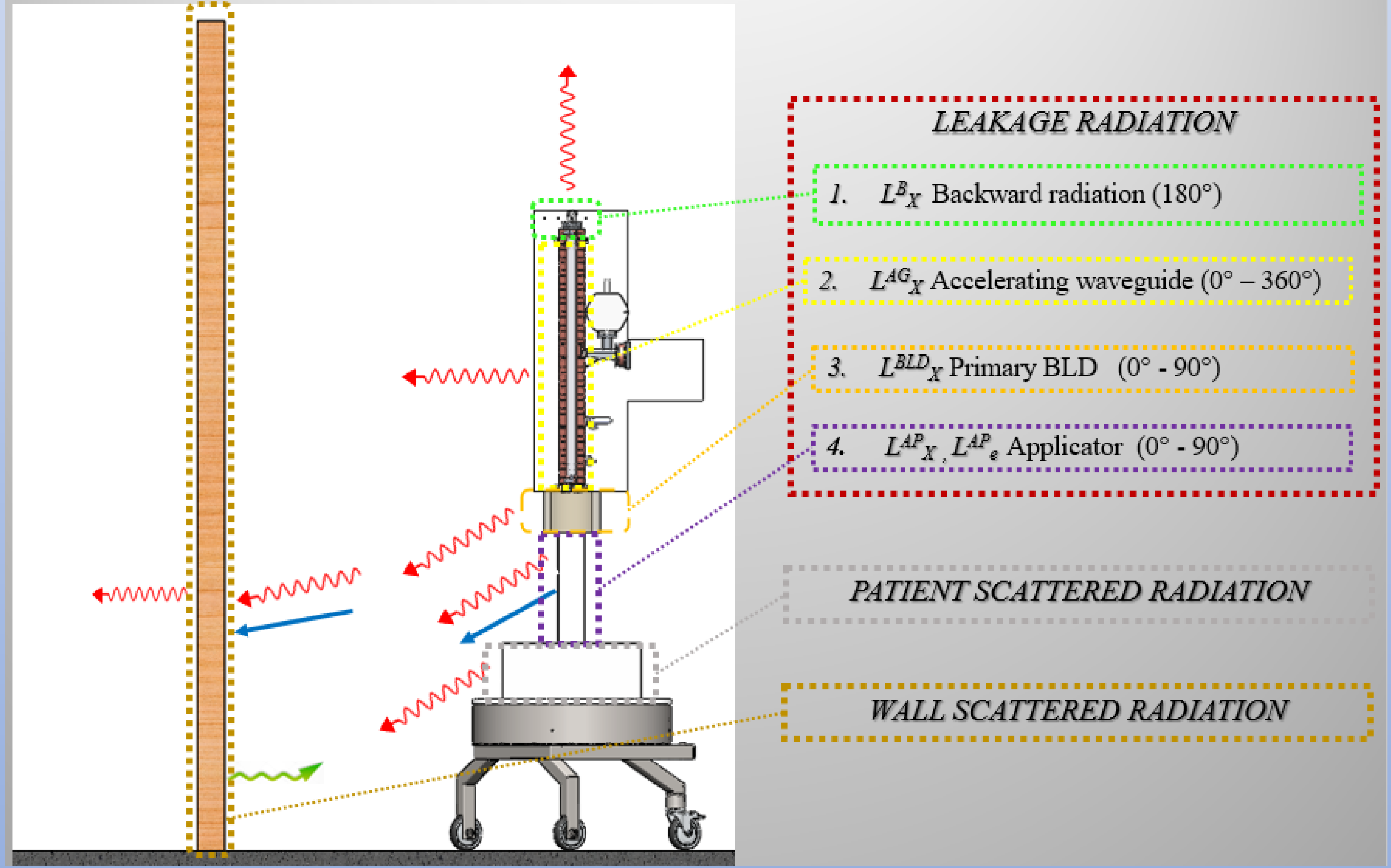


In order to lower IDR below 10 µSv/h …
…around 5 TVL would be needed, more than 75 cm of concrete each wall, and more than 120 on the floor (plus the beam stopper) …

IOeRT RP & IDR… R&D last hope ? NO

$$\begin{cases} SR = PSR + LR + WSR \\ LR = L_X^B + L_X^{AG} + L_X^{PBLD} + L_X^{AP} + L_{e-}^{AP} \end{cases}$$



Stray Radiation produced by IOeRT linac has been thoroughly studied. The minimum amount possible is the PSR, which, for a 12 MeV beam, IS NOT LESS THAN 0.1 µSv/Gy.
Therefore, there is no technological solution available: only a correct regulatory approach can allow the Flash translation to the clinical practice!

IMPORTANT: only a correct regulatory approach can allow the Flash translation to the clinical practice!

Standards

No IEC Standard today …

IEC 60601-2-1

Edition 3.0 2009-10

INTERNATIONAL STANDARD

NORME INTERNATIONALE

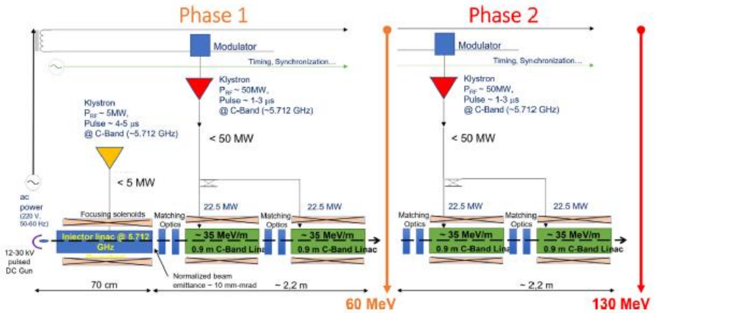
No pencil beam mode included

Medical electrical equipment –
Part 2-1: Particular requirements for the basic safety and essential performance of electron accelerators in the range 1 MeV to 50 MeV

Conclusion and take-home message

R&D process is moving fast , several challenges, no one unsolvable.
Let’s put the elephant in the room on a moving chair

L. Faillace et al. Physica Medica 104 (2022) 149–159



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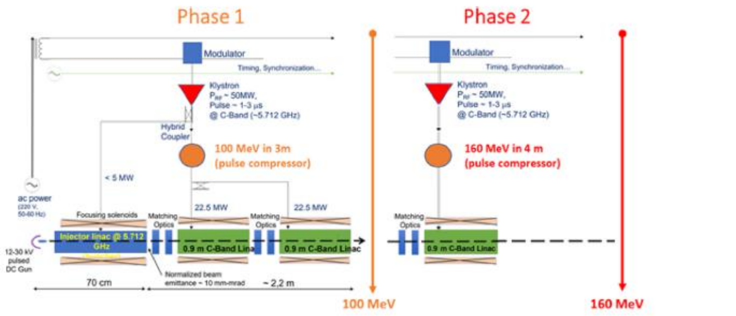

Fig. 2. Layout of the VHEE Linear Accelerator System for VHEE FLASH radiotherapy with one injector and three TW high-gradient accelerating structures. Two pulse compressors are used in this layout. The maximum expected beam energy is about 160 MeV.

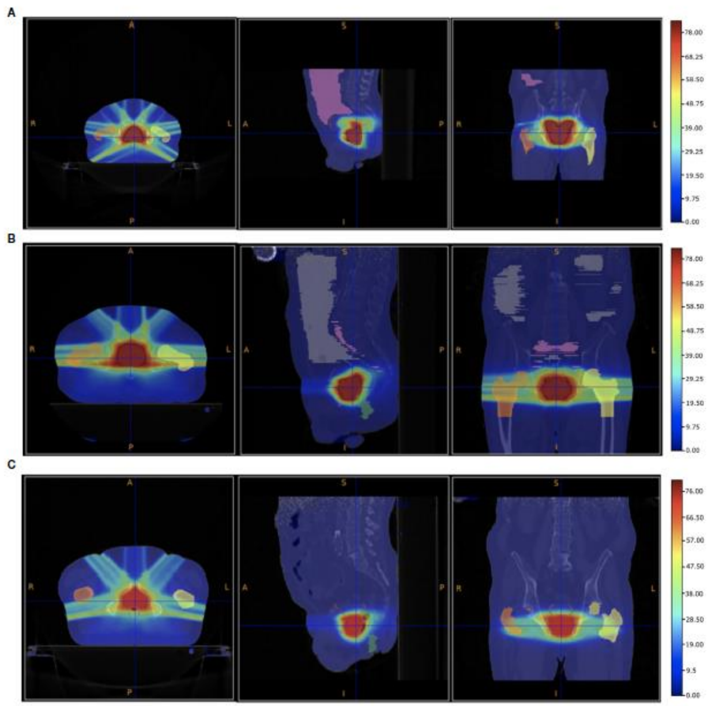

FIGURE 5 | Patient PZ1 **(A)**, PZ2 **(B)** and PZ3 **(C)** CTs overlapped with the biological dose maps optimised using the output of a FLUKA simulation using VHEE with energies listed in **Table 1** and a DMF of 1 (no FLASH effect). The OARs are shown: the femurs in yellow and orange, the bladder surface in brown, the rectum surface in dark blue. The PTV is shown in red.

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