Innovative electron linear accelerators for FLASH radiotherapy.

Luigi Palumbo

Università di Roma La Sapienza & INFN

on behalf of

Alesini D., Battistoni G., Bosco F., Carillo M., Cuttone G., De Arcangelis D., Faillace L., Felici G., Ficcadenti L., Franciosini G., Gallo A., Giuliano L., Migliorati M., Mostacci A., Patera V., Spataro B., Torrisi G.

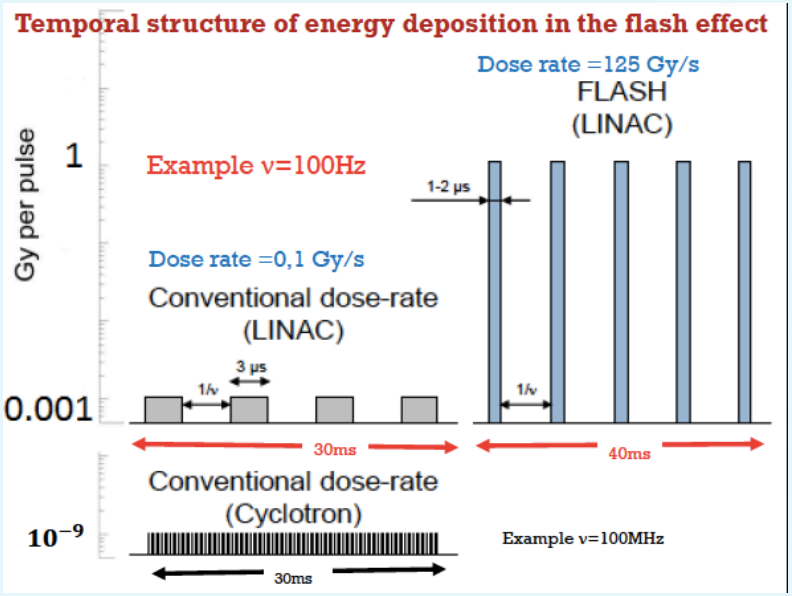
SIF - 15 September 2021

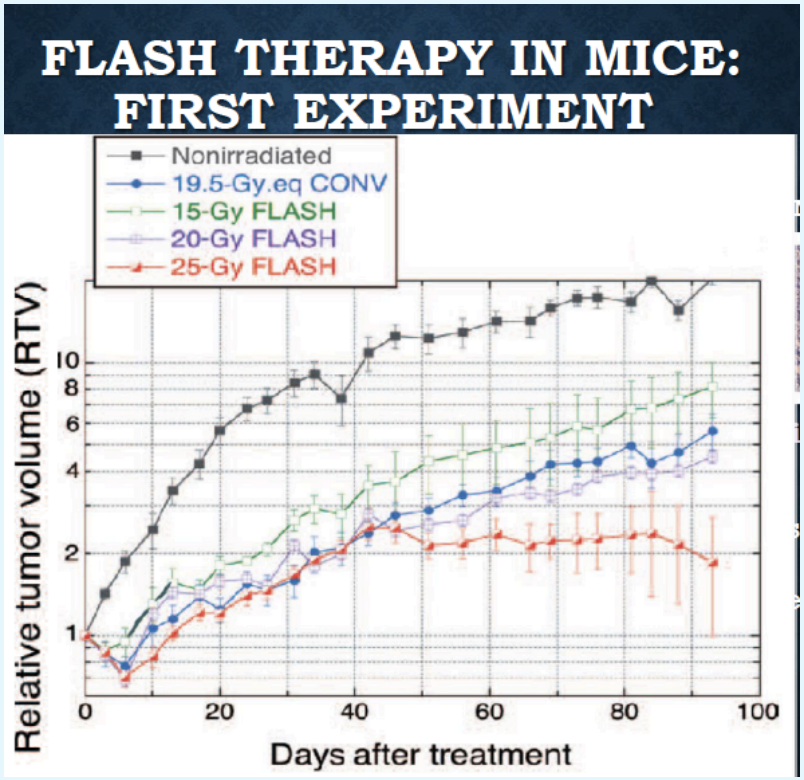
Flash therapy is a revolution in the cancer cure: it spares healthy tissue from the damage of the ionizing radiation maintaining the tumor control as efficient as in conventional radiotherapy. To allow the implementation of the revolutionary FLASH therapy concept into actual clinical use it is necessary to have linear accelerators able to deliver very high dose rate (> 10^6 Gy/s) in very short time of irradiation (< 100 ms).

Recently, our group was involved in the design of the first electron linear accelerator dedicated to the Flash irradiation (S-band, energy of 7 MeV, peak current of 100 mA). The accelerator was built by Sordina Iort Technology S.p.A, and it is in operation at the Marie Curie Institute in Orsay (France). A first prototype of a novel C band (5.712 GHz) electron linear accelerator for FLASH therapy able to reach 10–12 MeV is being developed.

In order to treat deep tumors, the energy should achieve the range of 70–100 MeV. We investigate the main issues in the design of a compact C band electron linac-VHEE, aiming to reach a high accelerating gradient and high peak current required for medical Flash radio therapy treatments.

The FLASH Radiotherapy is a revolutionary new technique in the cancer cure: it spares healthy tissue from the damage of the ionizing radiation maintaining the tumor control as efficient as in theconventional radiotherapy.





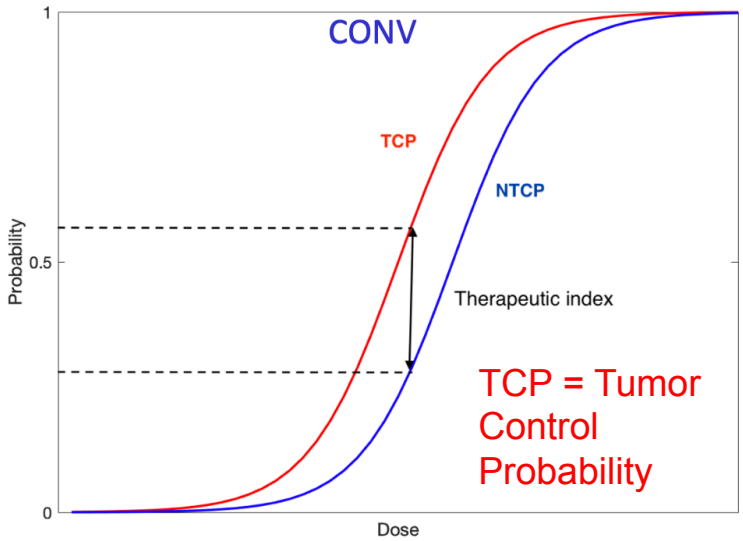
V. Favaudon et al., Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice, Sci Transl Med. 6, 245ra293, 2014.

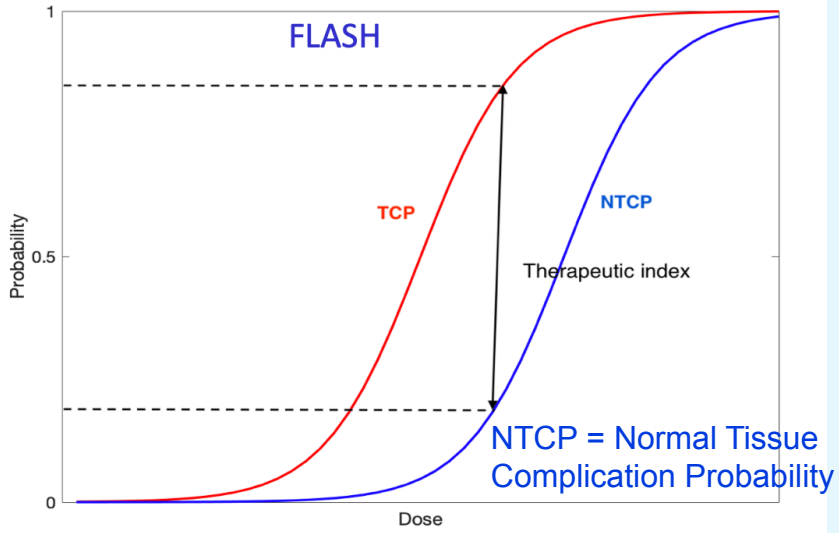
FLASH effect

It has been reported evidence for the sparing effect on healthy tissue if the dose is delivered at very high rate and very short time.

The effect has been reported (many times) on organs and on animals.

Many radiobiological models suggested the oxygen concentration plays a crucial role. A huge radiobiology research activity is going on.





Flash parameters

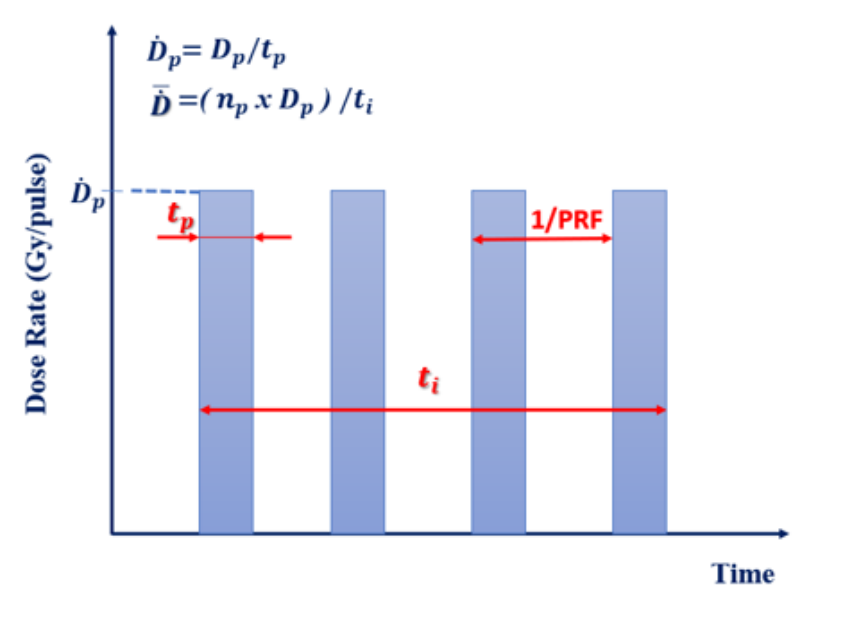


Table 1: Main FLASH parameters for the irradiations.

Parameter	Description	Value
PRF	Pulse repetition frequency	> 100 Hz
t_p	Pulse width	0.1-4.0 μs
t_i	Total irradiation time	< 100 ms
$\bar{\dot{D}}$	Time-averaged dose rate	> 100 Gy/s
$\dot{D}_p$	Dose-rate in a single pulse	$> 10^6$ Gy/s
D_p	Dose in a single pulse	> 1 Gy

Is the evidence robust?

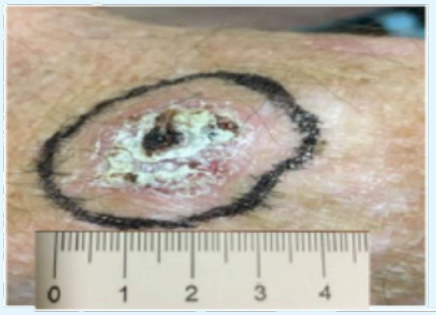
The evidence seems robust, even if the exact features are yet to be explored. The first patients has been already treated!!!

Treatment of a first patient with FLASH-radiotherapy

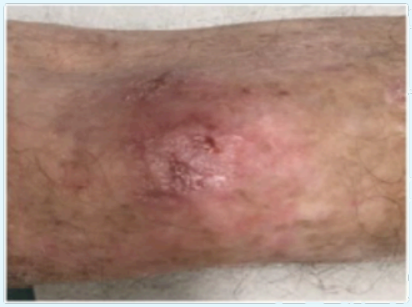
Jean Bourhis [a,b,*], Wendy Jeanneret Sozzi [a], Patrik Gonçalves Jorge [a,b,c], Olivier Gaide [d], Claude Bailat [c], Fréderic Duclos [a], David Patin [a], Mahmut Ozsahin [a], François Bochud [c], Jean-François Germond [c], Raphaël Moeckli [c,1], Marie-Catherine Vozenin [a,b,1]

[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

- Paziente 75-enne con linfoma cutaneo multi-resistente
- 15 Gy in 90 ms con un fascio di elettroni di 5.6 MeV
- Nei tessuti sani si è osservato solo un leggero aumento della vascolarizzazione
- Risposta completa (regressione macroscopica completa) sul tumore a 5 mesi

Electron low energy IORT beam has been used!!!

Atun R, et al. Lancet Oncol 2015;16:1153-86.

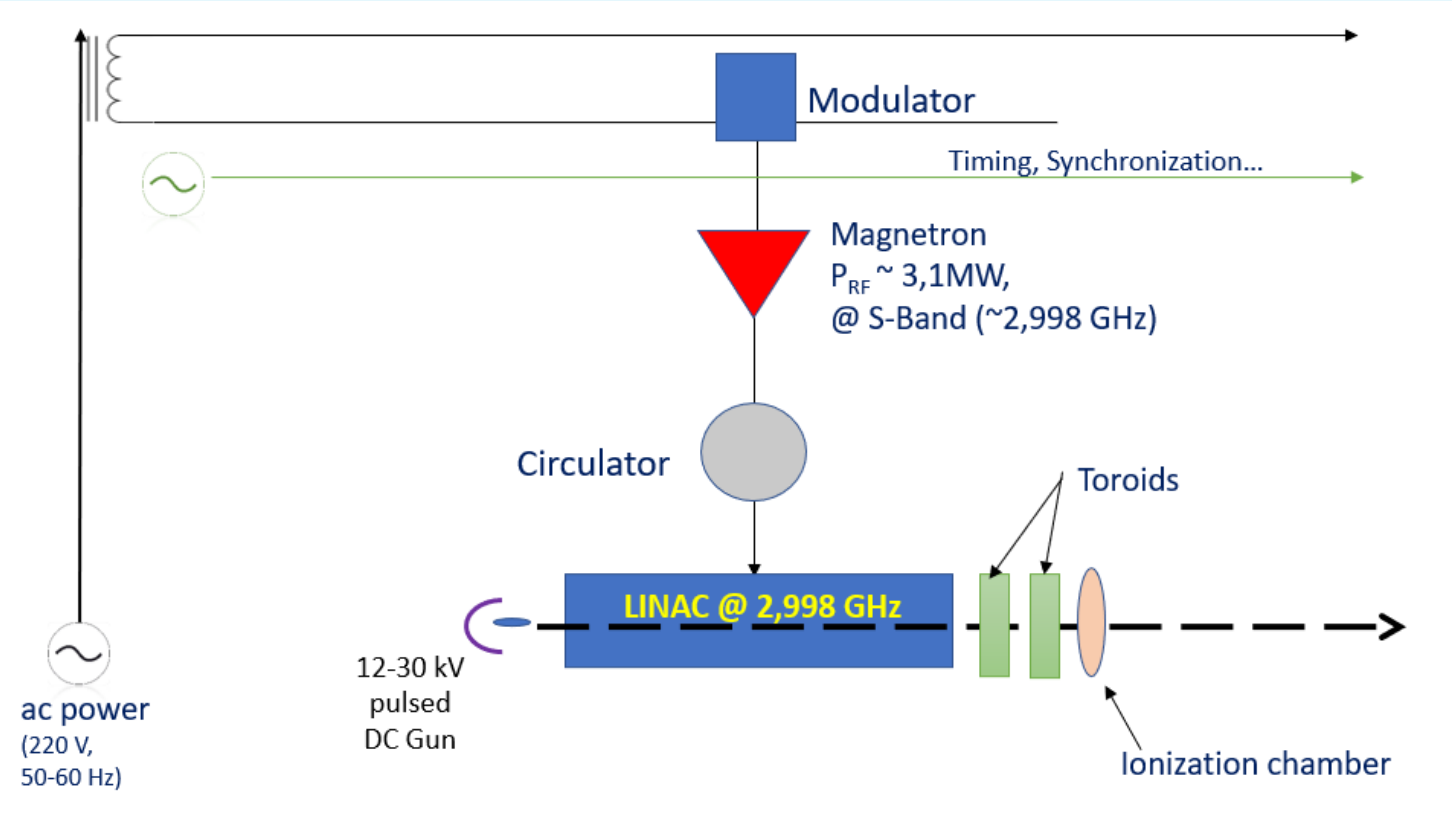
Sapienza & INFN on Flash-RT

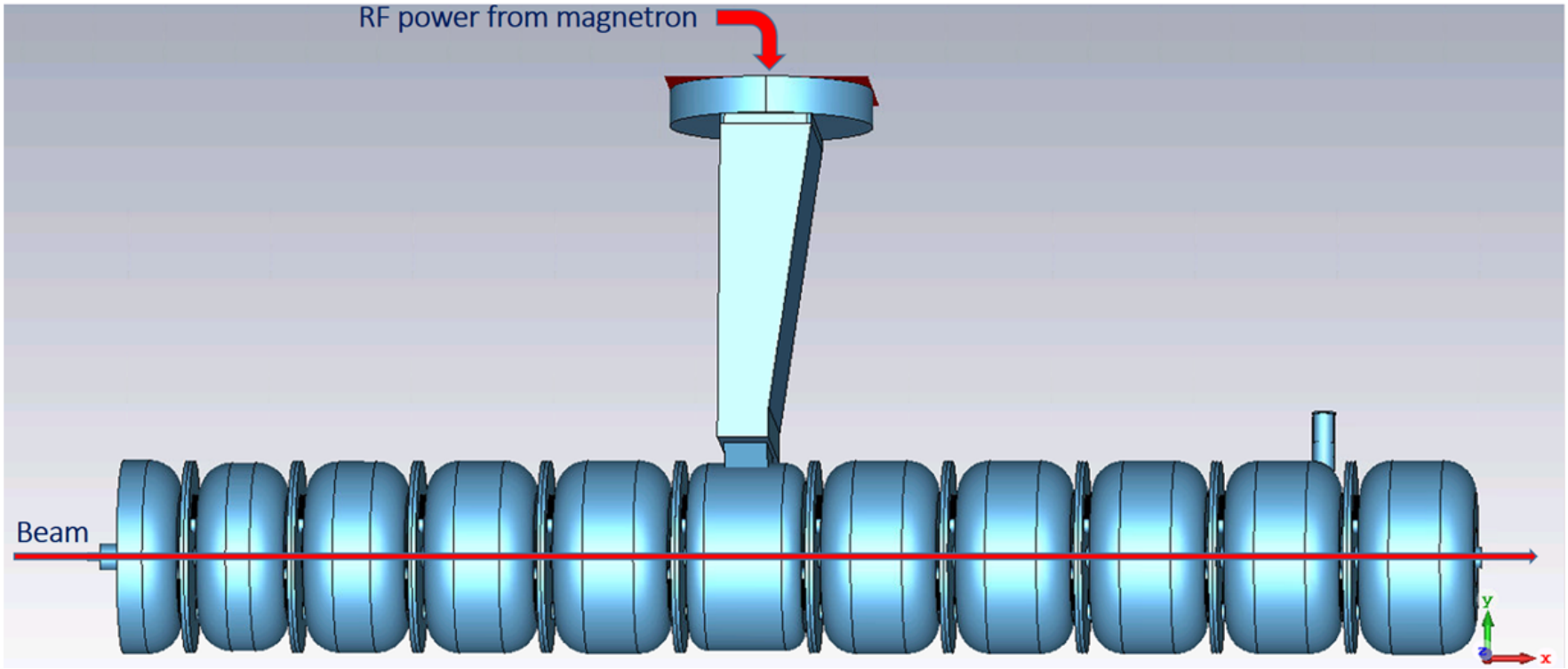
Sapienza & INFN group has invested on the e-FLASH technology, and has already commercial patnership on it. The group is centered at the SBAI Departement and has a twofold interest on FLASH RT:

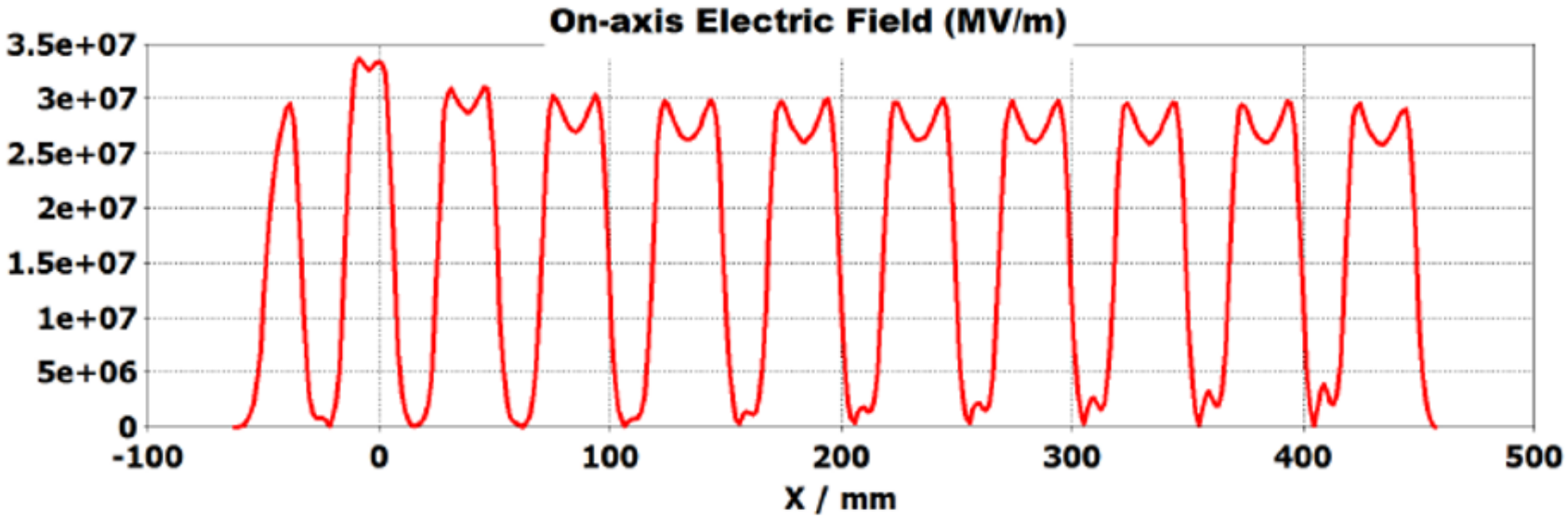
A huge effort has been put on realization of the first FLASH IORT machine with SIT company. The next future target of this team is the development of compact VHEE demonstrator

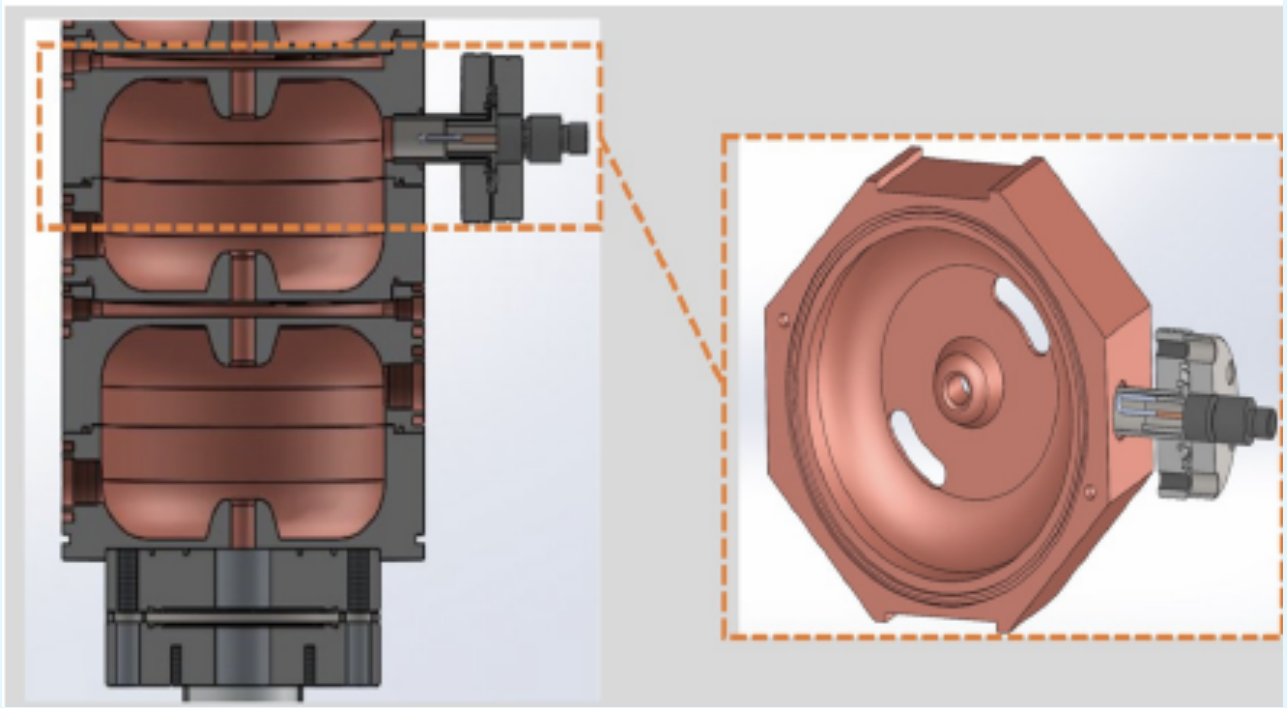
The second pillar of this effort has been the developmentof a new TPS software based on MC dose evaluation, able to treat electron, photon and protons and to run on GPU

1. Development of 5-7 MeV e-Linac for Flash-RT




RF power from magnetron
Beam
y
x


On-axis Electric Field (MV/m)
3.5e+07
3e+07
2.5e+07
2e+07
1.5e+07
1e+07
5e+06
0
-100
0
100
200
300
400
500
X / mm



Biperiodic structure ~ 3 GHz
Accelerting mode $\pi/2$
Magneting coupling

PHYSICAL REVIEW ACCELERATORS AND BEAMS **24,** 050102 (2021)

Compact *S*-band linear accelerator system for ultrafast, ultrahigh dose-rate radiotherapy

L. Faillace,[1,6,*] S. Barone,[2] G. Battistoni,[3] M. Di Francesco,[2] G. Felici,[2] L. Ficcadenti,[4] G. Franciosini,[4,5] F. Galante,[2] L. Giuliano,[1,4] L. Grasso,[2] A. Mostacci,[1,4] S. Muraro,[3] M. Pacitti,[2] L. Palumbo,[1,4] V. Patera,[1,4] and M. Migliorati[1,4]

LINAC-FLASH 7 MeV – constructed by SIT Company – First machine M. CURIE Paris

Table 2: Main characteristics of the EF4000

Characteristics EF4000	Value
Output energy	5 - 7 MeV
Pulse repetition frequency	1 - 250 Hz
Pulse width	0.5 - 4 μs
Maximum peak beam current	120 mA
Dose rate per pulse	$> 10^6$ Gy/s
Mean Dose rate	1000 Gy/s
Max Dose per pulse	30 Gy in a surface of ⌀ 10 mm

Anversa Hospital / PISA

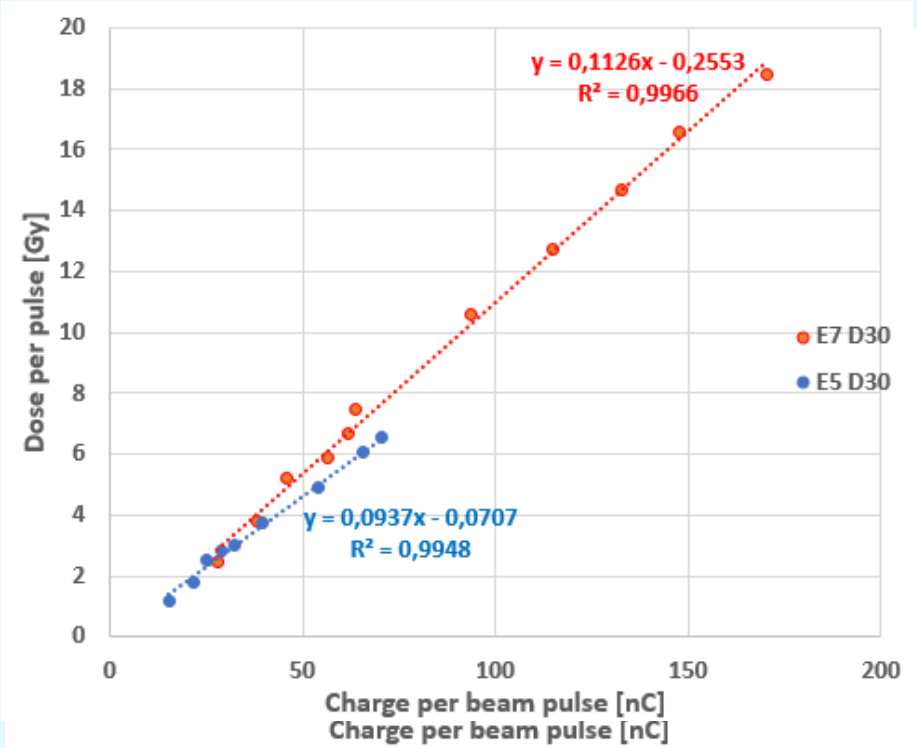
COMMISSIONING OF LINAC AT M.CURIE INSTITUTE (Paris)

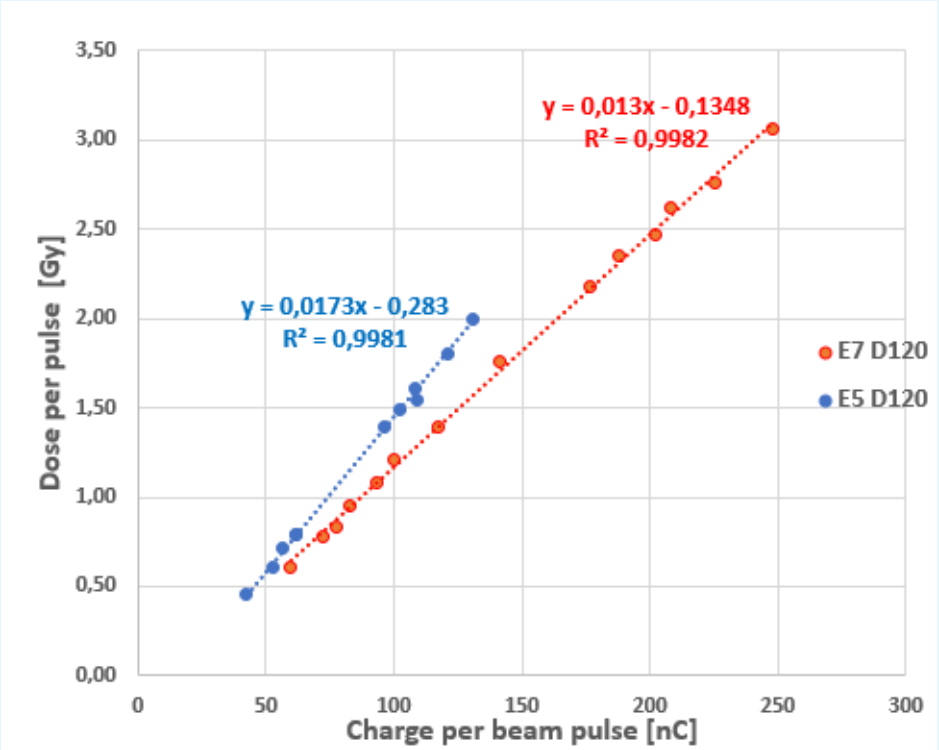
Dose measurements at 5 and 7 MeV

Diameter applicator mm	7 MeV dose per pulse at 4 μs		5 MeV dose per pulse at 4 μs	
	Conventional [Gy]	FLASH [Gy]	Conventional [Gy]	FLASH [Gy]
120	0.04	3	0.004	2
100	0.06	5	0.007	3
50	0.15	13	0.014	9
40	0.19	16	0.018	10
35	0.23	19	0.021	12
30	0.24	19	0.022	12
10	0.21	30	0.024	15

BEAM PARAMETERS AND DOSE RATES MEASUREMENTS OF THE ELECTRON FLASH LINAC AT CURIE INSTITUTE (Report in prep.)
L.Giuliano, G.Franciosini, L. Faillace, M.Migliorati, L.Palumbo G. Felici, F.Galante A. Patriarca M. Dutreix, V.Favaudon and S. Heinrich

Dose vs. pulse charge

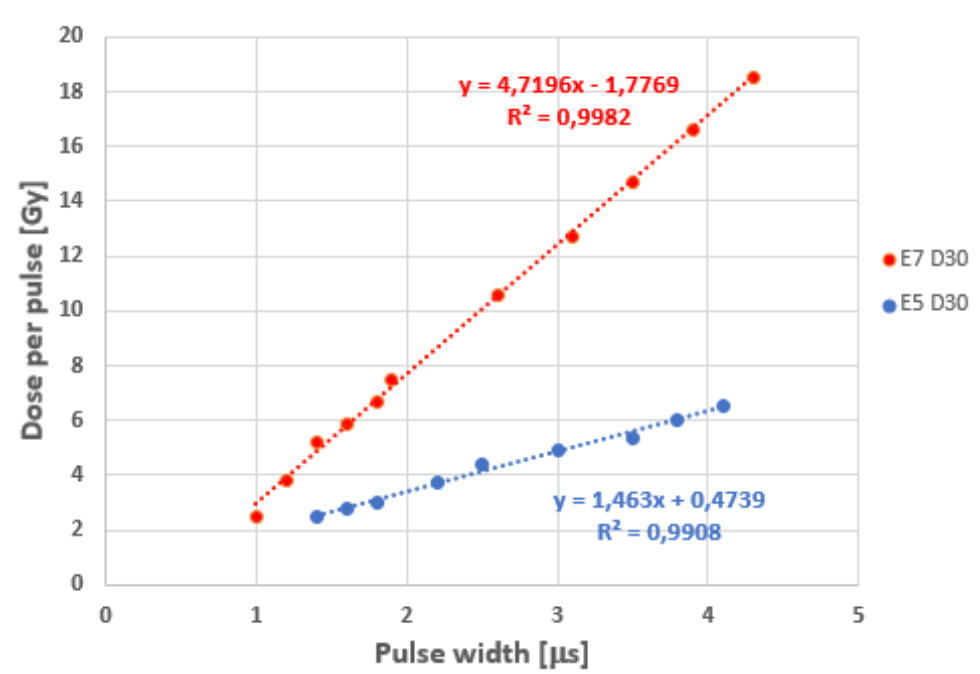


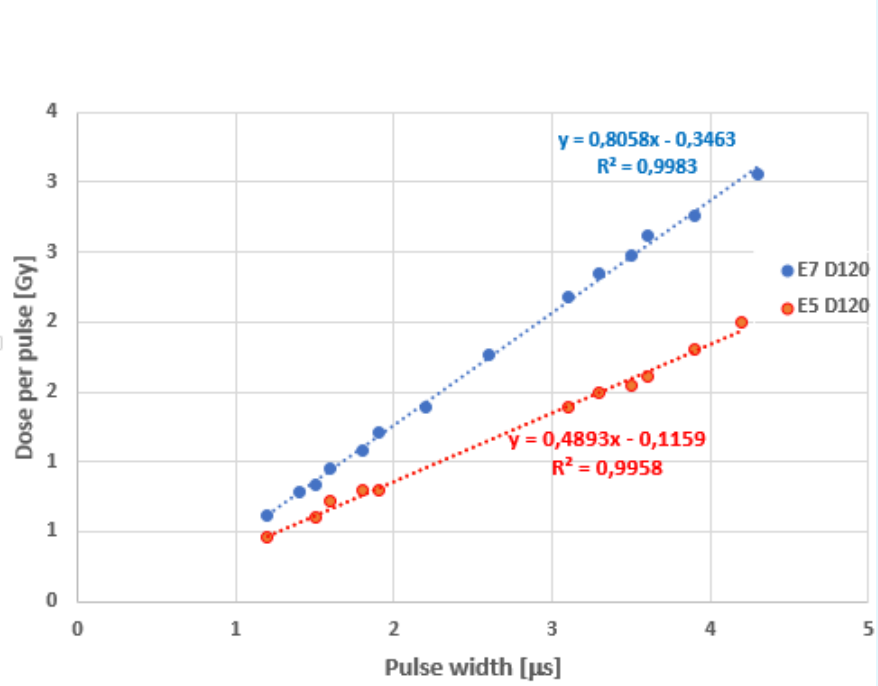


Applicator diameter 30 mm

Applicator diameter 120 mm

Dose vs. pulse width μs

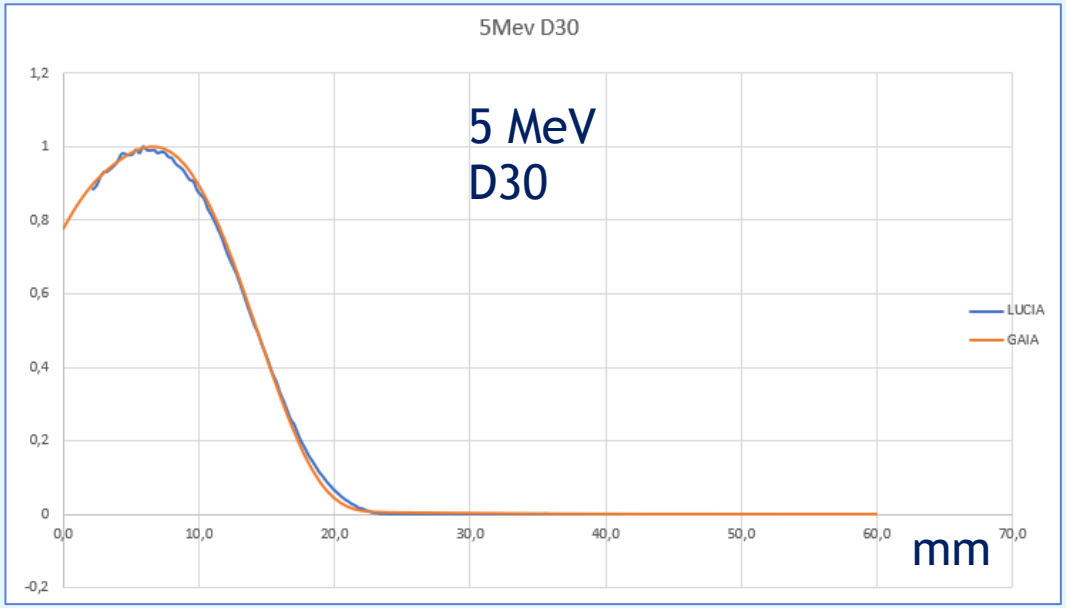


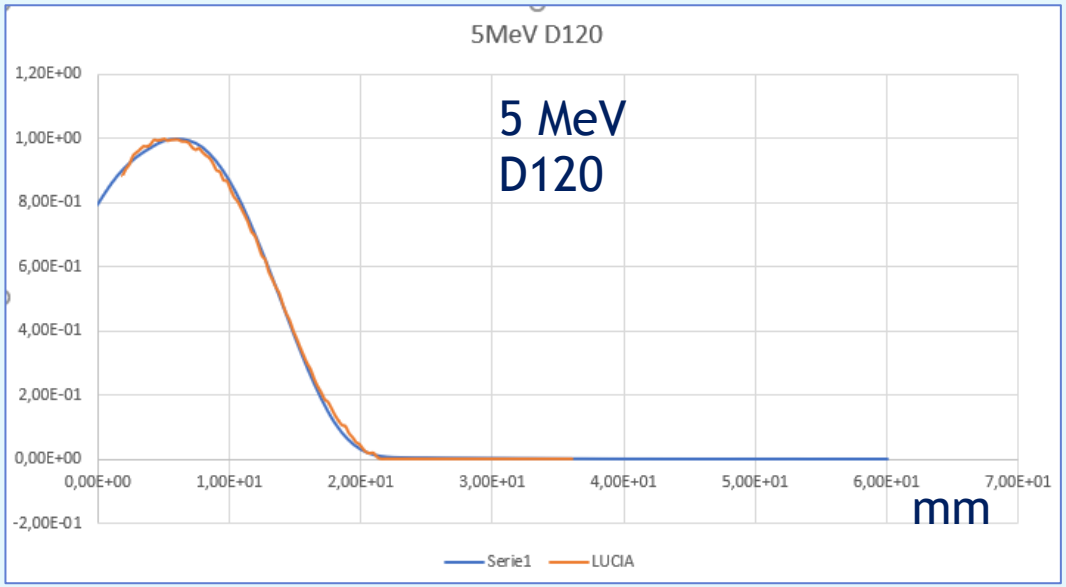


Applicator diameter 30 mm

Applicator diameter 120 mm

Dosimetric analysis - 5 MeV - PDD

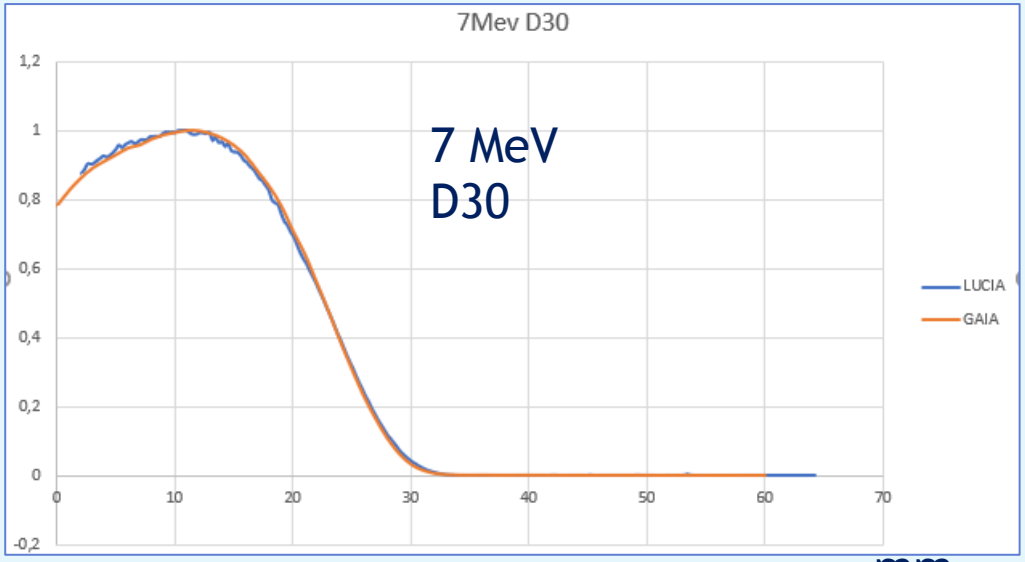




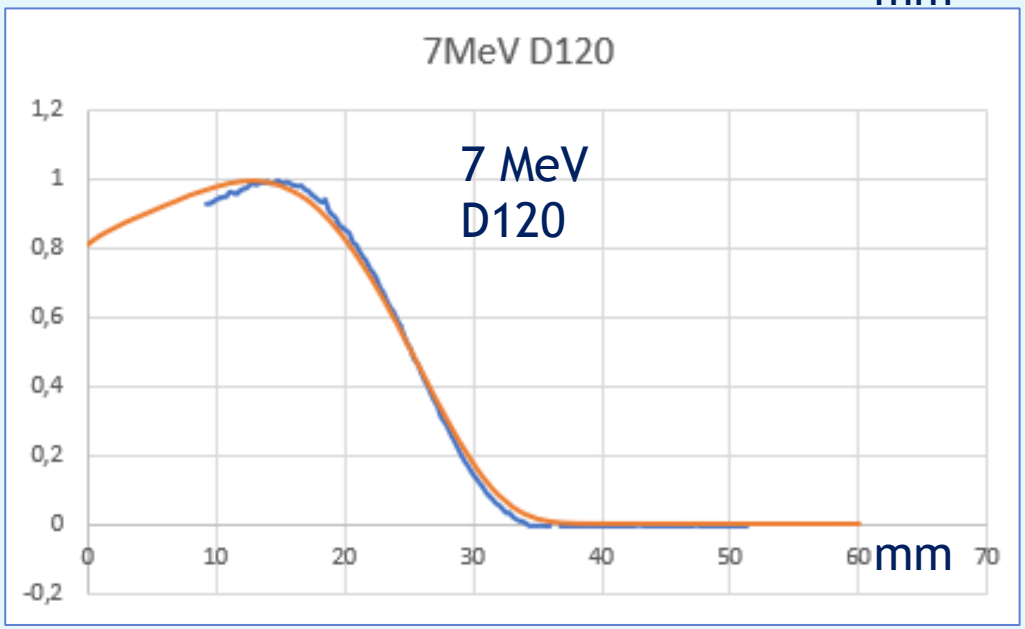
The Percent Depth Dose (PDD) and beam transverse profile were investigated using Gafchromics films at different depth in a poly-methyl methacrylate (PMMA) phantom
(L. Giuliano - blue curves)

The dosimetric quantities to be compared to experimental measurements are evaluated by means of the FLUKA Monte Carlo software.
(G. Franciosini- red curves)

Dosimetric analysis - 7 MeV - PDD

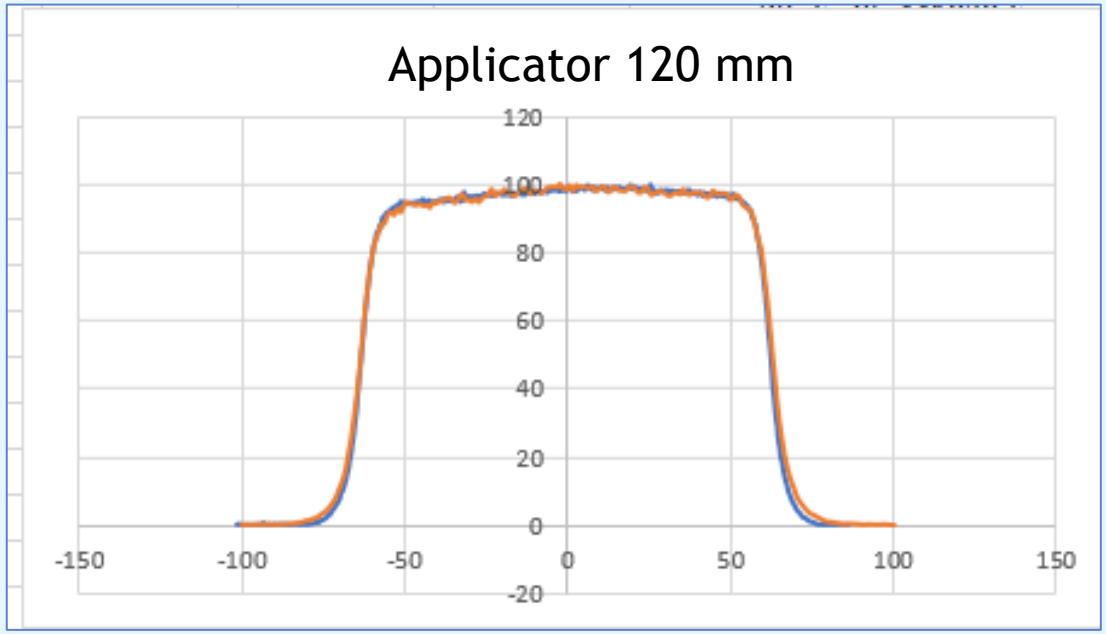


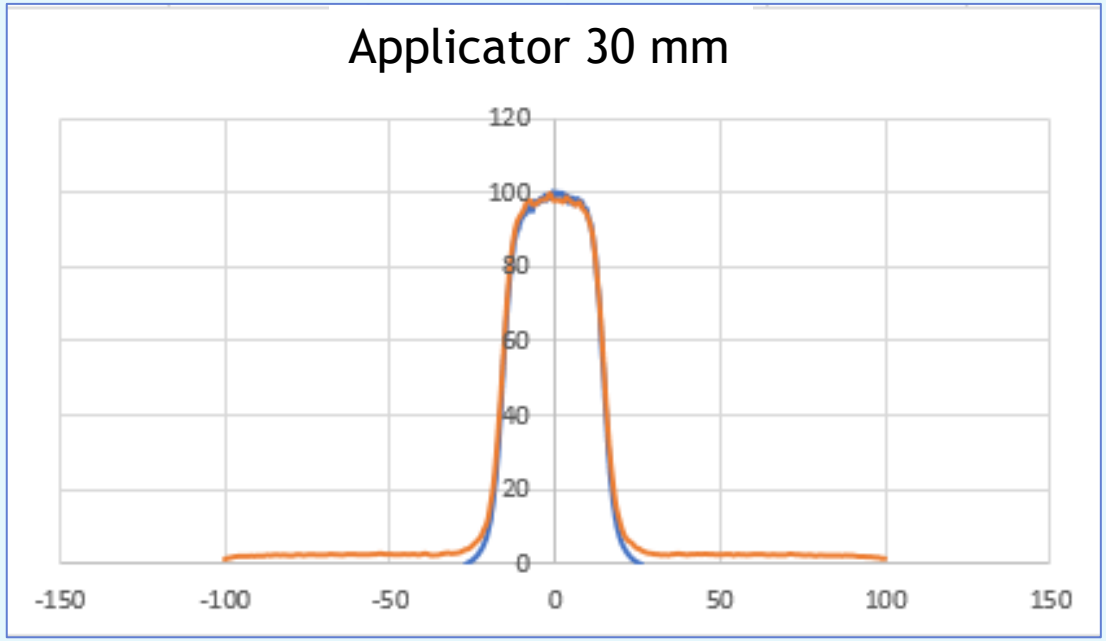
The Percent Depth Dose (PDD) and beam transverse profile were investigated using Gafchromics films at different depth in a poly-methyl methacrylate (PMMA) phantom
(blue curves)



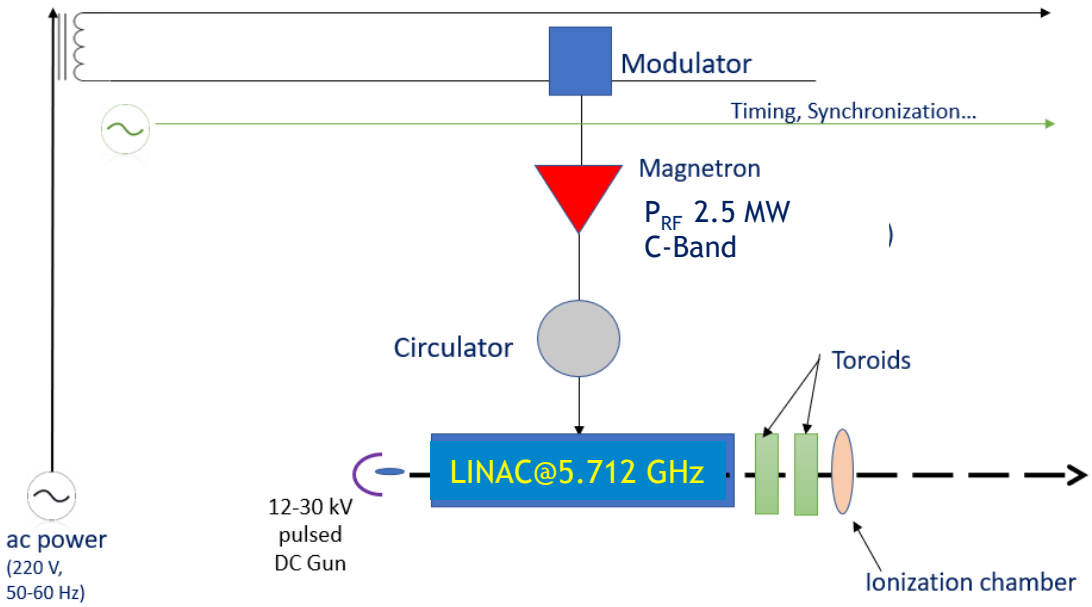
The dosimetric quantities to be compared to experimental measurements are evaluated by means of the FLUKA Monte Carlo software. (red curves)

TRAVERSE DOSE PROFILE AT 100% PDD





2. Development of a C-Band Linac 12 MeV, for Flash-RT (SIT Company)



Parameter	Value
Frequency	5.712 GHz
Magnetron Power	2.5 MW
Number of accelerating cells	32
Linac length	~82 cm
Output Energy	12 MeV
Output Beam Current	50 mA

3D MODEL AND ON AXIS ELECTRIC FIELD

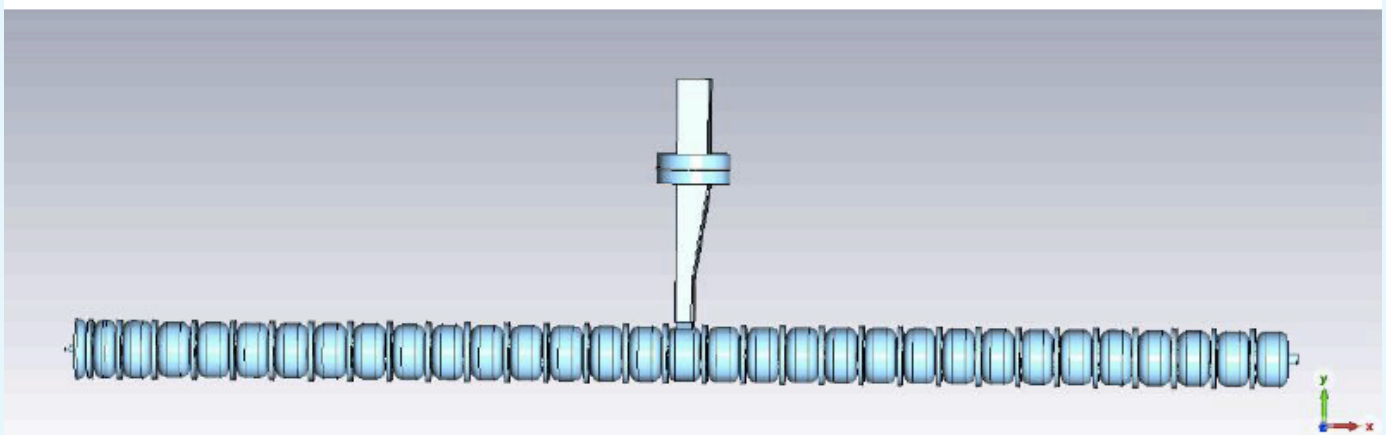
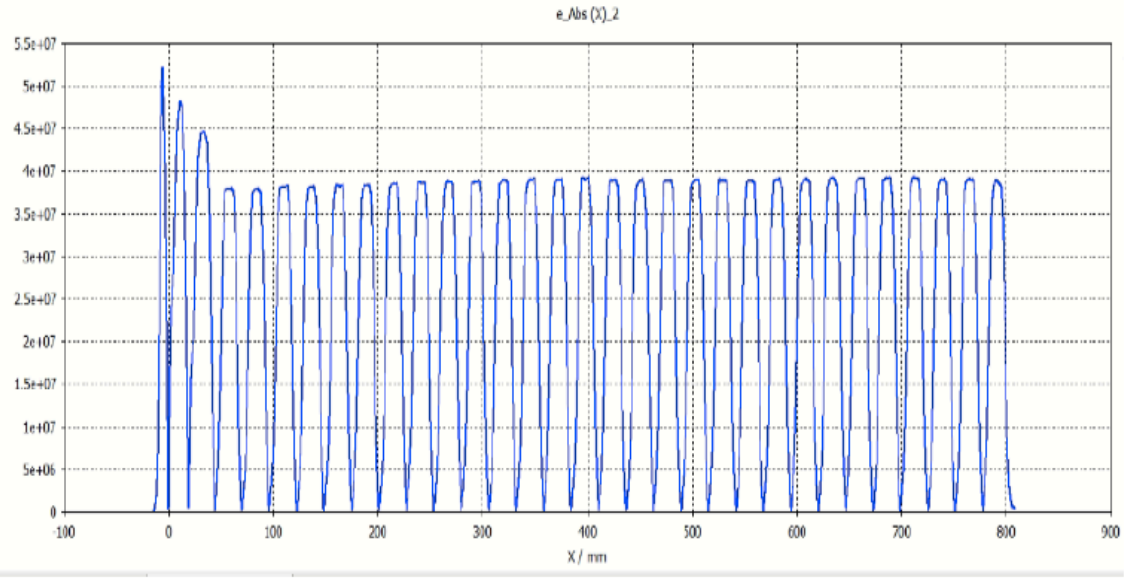


Fig. 1: Modello 3D da CST del linac in banda C composto da 32 celle acceleranti



3. simulazione con la guida d'onda e la RF window per la sintonizzazione del linac completo;

ENERGY vs CURRENT

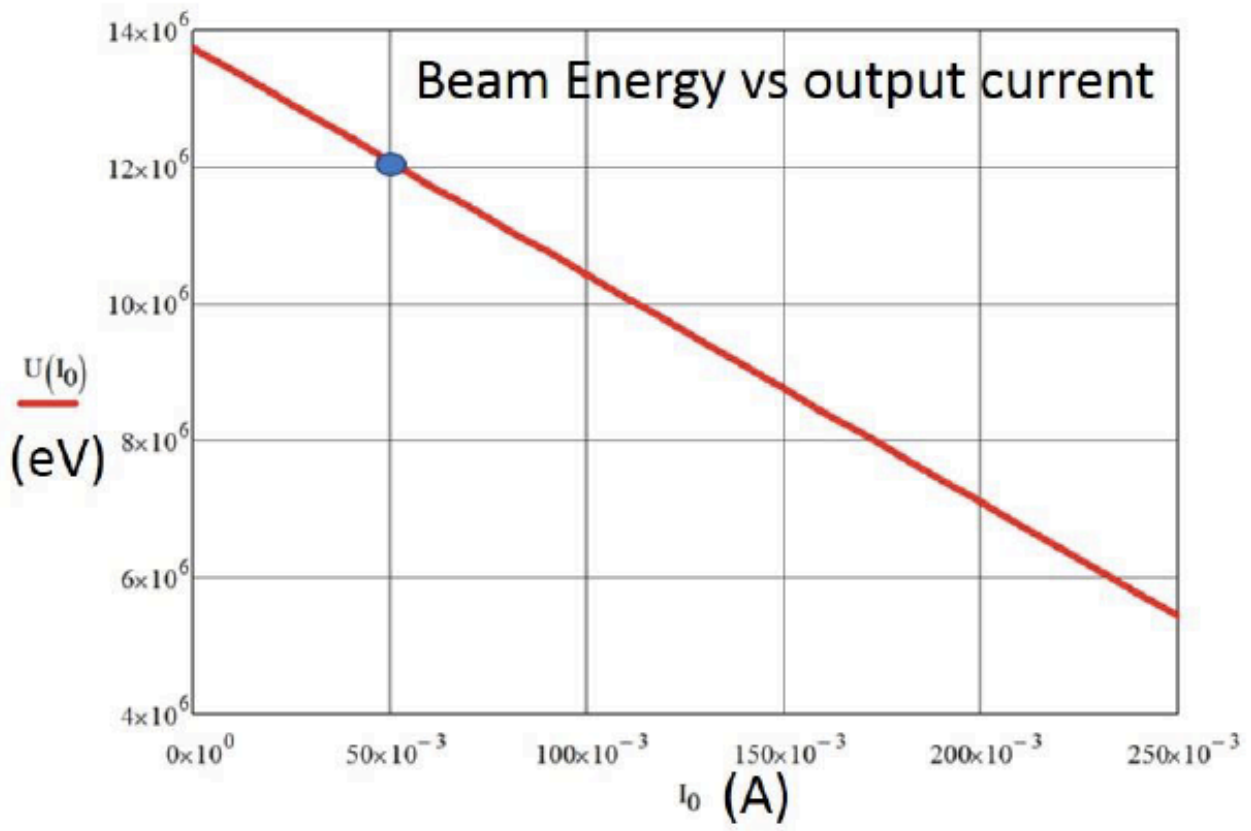
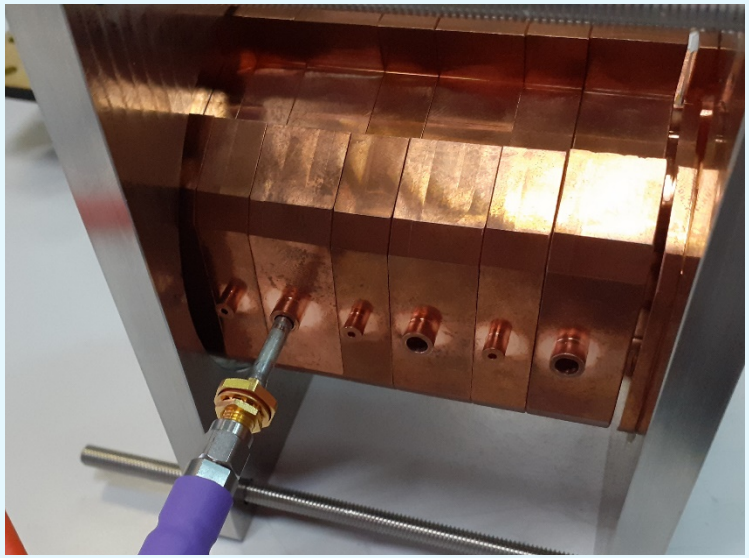


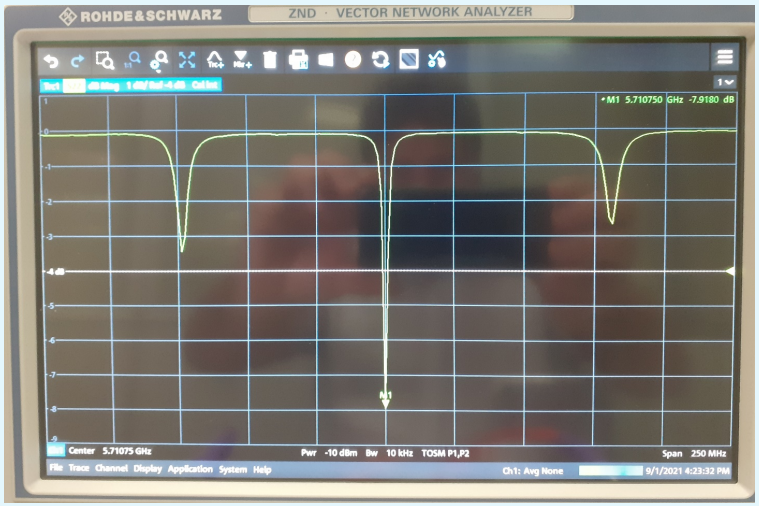
Fig. 6: Curva di carico del linac. Energia del fascio in funzione della corrente.

ACCELERATOR CELLS PROTOTYPING

Courtesy SIT company



FIRST TESTS



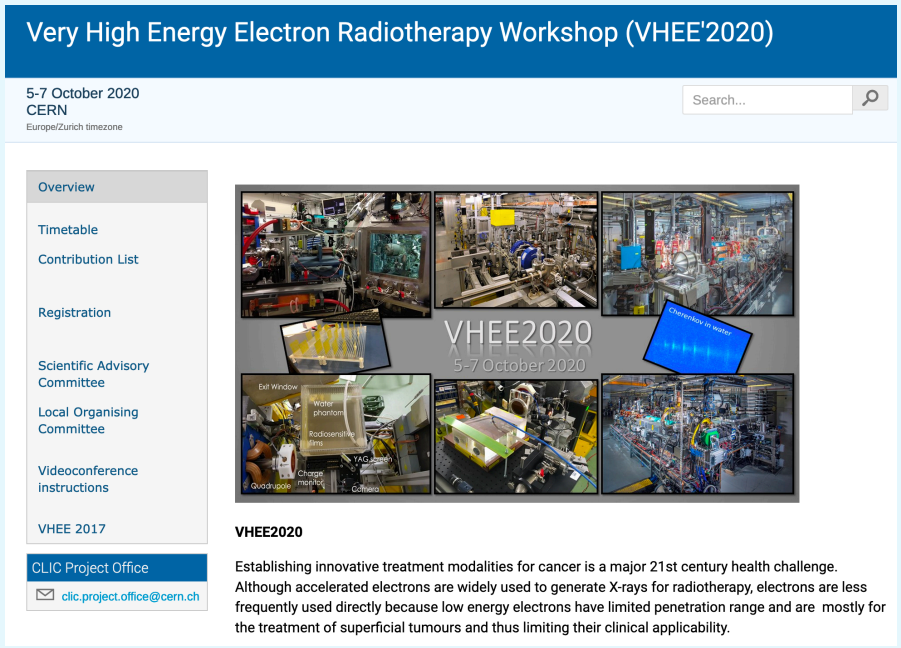
FINAL FULL PROTOTIPE EXPECTED TO BE COMPLETED BY THE END OF 2021

3. Development of a C-Band Linac 50-130 MeV, (VHEE) Flash-RT for deep tumors

To treat deep tumors the electron energy must be increased. Never introduced such VHEE in clinical RT till now!

The electron beams with E>50 MeV are suitable to this scope.

Standard LINACs (excluding laser plasma) can easily provide the needed beam: transverse spot size of ~ mm and angular divergence below tenth of degree.



The discovery of FLASH effect and the technology innovation in accelerator physics are fostering interest and activities on VHEE-Flash-RT

SAPIENZA & INFN EFFORT for VHEE-FLASH-RT

PRELIMINARY STUDY OF A COMPACT LINAC VHEE-FLASH 60-100 MeV

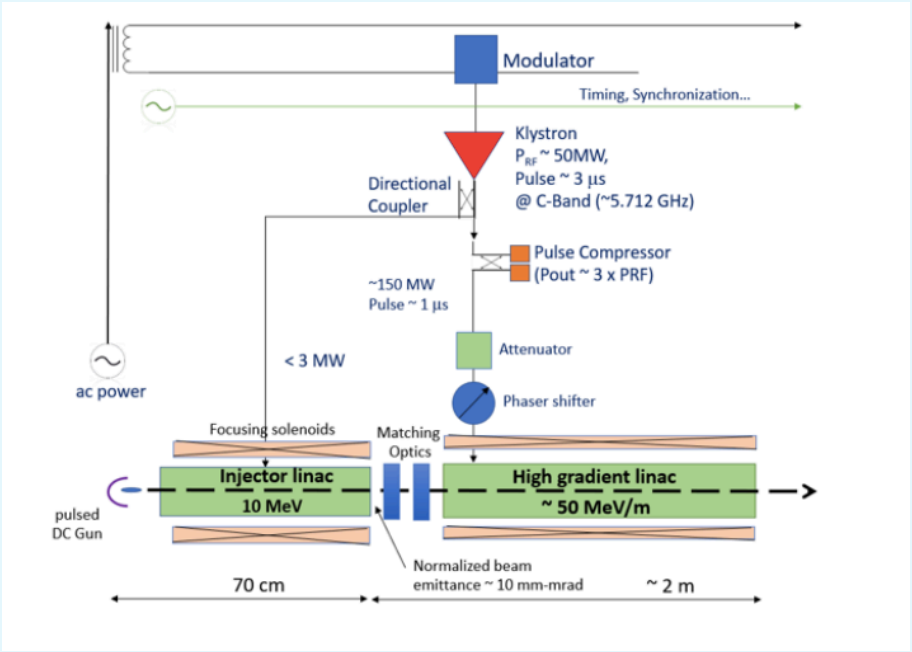


Table 5: Dose parameters for VHEE FLASH LINAC

Parameter	Value
Beam energy	100 – 60 MeV
Pulse width	1.0 – 3.0 μs
Pulse charges	200 – 600 nC
D_p	4 – 12 Gy in ⌀10 cm
$\dot{D}$	> 100 Gy/s
$\dot{D}_p$	> 10^6 Gy/s

PRELIMINARY STUDIES OF A COMPACT VHEE LINEAR ACCELERATOR SYSTEM FOR FLASH RADIOTHERAPY

L. Giuliano *[1,2], D. Alesini[3], M. Behtouei[3], F. Bosco[1,2], M. Carillo[1,2], G. Cuttone[4]
D. De Arcangelis[1,2], V. Favaudon[5], L. Ficcadenti[1,2], S. Heinrich[5], M. Migliorati[1,2], A. Mostacci[1,2]
L. Palumbo[1,2], A. Patriarca [5], B. Spataro [3], G.Torrisi[4], L. Faillace[1,3]

[1]Sapienza University, Rome, Italy
[2] INFN/Roma1, Rome, Italy
[3]INFN/LNF, Frascati, Italy
[4] INFN/LNS, Catania,Italy
[5] Curie Institute, Orsay, France

IPAC Conference, 2021

FRIDA: Gr. V INFN call

FLASH Radiotherapy with hIgh Dose-rate particle beAms

A community of 80 researchers distributed in 7 INFN sections & Labs: CT, LNS, Milano, Pisa, Roma1, TIFPA, Torino.

a solid international network of research centres and companies (SIT, STLab) are the resources to accomplish the research program.

- CT: Amato, Bartolotta, Borgese, D'Oca, Italiano, Marrale, Romano, Tomarchio (3.8 FTE)
- LNS: Bravatà, Calvaruso, Cammarata, Catalano, Cirrone, Cuttone, Forte, Guarrera, Mauro, Ficarra, Milluzzo, Minafra, Petringa, Russo, Sorbello, Torrisi (FTE: 4.7)
- Milano: Bortolussi - Bacci - Dong - Drebot - Giove - Mattei - Muraro - Massa - Mattei - Mettiver - Russo - Sarnu - Serafini (2 FTE)
- Pisa: Belcari, Bisogni, Costa, Del Sarto, Di Martino, Gizzi, Kraan, Labate, Marasciulli, Morrocchi, Paiar, Rosso, Sportelli, Strettoi, Ursino, Vannini, Zanacchi (2.8 FTE)
- Roma1: Faillace, Ficcadenti, Franciosini, Giuliano, Marafini, Migliorati, Mostacci, Palumbo, Patera, Sarti, Schiavi, Toppi, Traini, Trigilio (2.5 FTE)
- TIFPA: Attili, Bellinzona, Bisio, Boscolo, Cordoni, Croci, Fuss, Manghi, La Tessa, Scifoni, Schwarz, Tommasino (4.0 FTE)
- Torino : Abujami, Aprà, Cirio, Martì Villarreal, Monti, Picollo, Vignati (4.3 FTE)

VHEE & the FRIDA project

Goal of FRIDA is a CSN5 interdisciplinary call proposal addressing all the crucial areas related with FLASH therapy. 4 work-packages

- ✓ **mechanism modelling & radio-biology experiments;**
- ✓ **beam delivery techniques ;**
- ✓ **Detectors for beam monitoring;**
- ✓ **treatment planning development**

- ✓ **Explore the time scales at which the FLASH effect occurs**
- ✓ **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**
- ✓ **Explore clinical potential of FLASH EBRT**

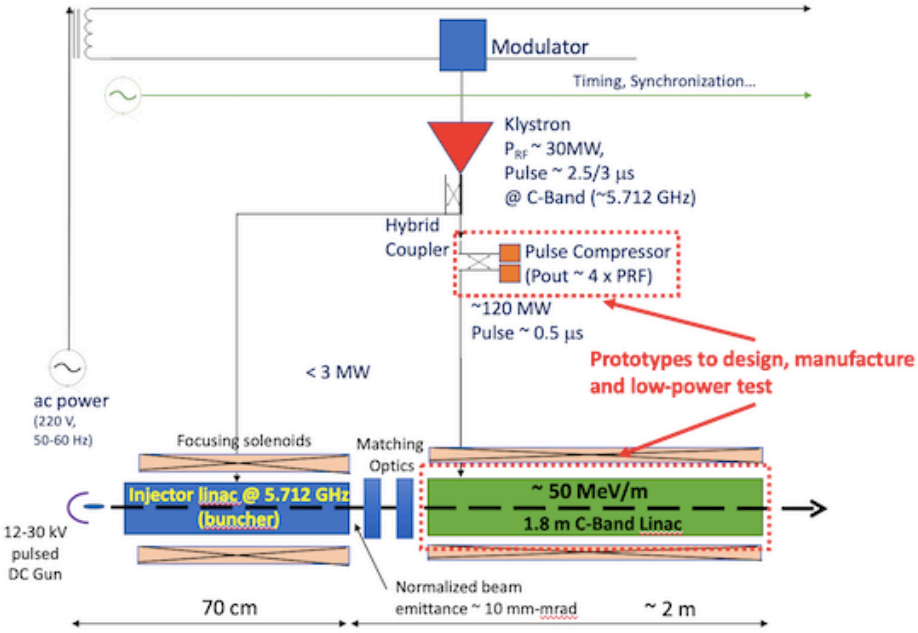
Budget ~1 ME, Project Approved

ROMA1, LNS, LNF, Milano, TIFPA ….

WP2 - FLASH beam delivery

WP2.1 VHE electrons C-band electron flash linac

The delivery of high-energy electron beams (up to 100 MeV) is achieved by an operation RF frequency in C-Band (5.712 GHz) able to provide a satisfactory compromise of system compactness and high-energy electron delivery. The high energy can be achieved in a compact foot-print since nominall accelerating gradients of linacs operated in C-band have shown values up 50 MeV/m. Therefore, the investigation of such options offers the possibility of delivering 100 MeV electron beams within only 3 m length.



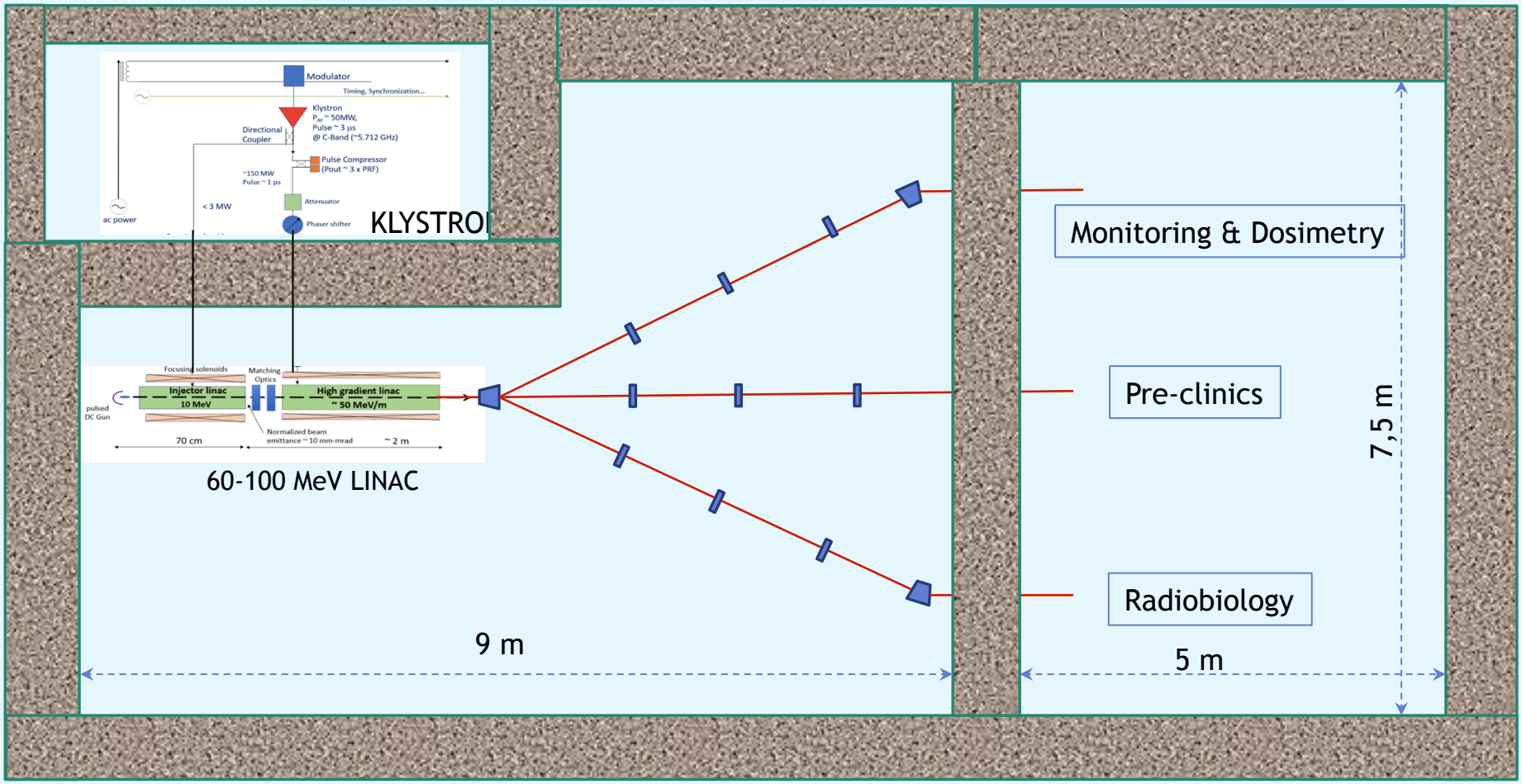
JOINT WORKING GROUP FOR FLASH-VHEE-RT FEASIBILITY STUDY

SAPIENZA
Cardinale Vincenzo
Cenci Giovanni
Giuliano Lucia (& INFN)
Marampon Francesco
Migliorati Mauro (& INFN)
Mostacci Andrea (& INFN)
Patera Vincenzo (& INFN)
Palumbo Luigi (& INFN)
Sarti Alessio (& INFN)
Tombolini Vincenzo

INFN
Alesini David
Bisogni Maria Giuseppina
Cuttone Giacomo (Resp. INFN for Life Science)
Faillace Luigi
Gallo Alessandro
Pablo Cirrone
Torrisi Giuseppe

By the end of 2021

VHEE-LINAC- FLASH RT Research Laboratory (Concept)



CONCLUSIONS

- FLASH-RT WITH ELECTRON IS A REVOLUTIONARY PROMISING NEW TECHNIQUE
- THERE IS AN EXPONENTIALLY GROWING RESEARCH ON RADIOBIOLOGY
- MORE CLINIC RESEARCH CENTERS ARE BEING INVOLVED
- THERE IS STRONG INDUSTRIAL INTEREST DUE TO A POTENTIAL HUGE MARKET
- KNOW-HOW IS AVAILBLE IN ITALY (UNIVERSITY AND RESEARCH INSTITUTES)
- A FIRST S-BAND 5-7 MeV FLASH LINAC HAS BEEN DEVELOPED FOR SIT COMPANY
- SECOND PROTOTYPE C-BAND 12 MeV IS IN CONSTRUCTION
- FLASH-RT OPENS NEW OPPORTUNITIES TO THE CURE OF DEEP TUMORS
- A LARGE COMMUNITY OF RESEARCHERS IS PROPOSING RESEARCH PROJECTS (PRIN, INFN-call)
- MonteCarlo STUDIES CONFIRM THE ADVANTAGES OF FLASH-VHEE vs CONVENTIONAL TRATMENTS.
- A JOINT GROUP SAPIENZA-INFN IS BEING DEVELOPING A FEASIBILITY STUDY OF A VHEE FLASH-LINAC AT THE ENERGY 50-130 MeV