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FLASH Therapy: An innovation in radiation therapy

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Summary. — Radiation Therapy (RT) is nowadays the most common methodology to treat cancer cells. The most important requirement is to destroy the tumor and to minimize the damage of the healthy tissues as well as any side effect. In this scenario, an innovative technique has been proposed and already tested: the FLASH Therapy, which uses short pulses of electrons at very high dose rates. It foresees millisecond pulses of radiation (beam on time < 100–$500\,\text{ms}$) delivered at a high dose-rate (> 40–$300\,\text{Gy/s}$). These bursts of radiation are less harmful to healthy tissues but just as efficient as conventional treatment to inhibit tumor growth. We will discuss the genesis of this methodology, its implementation based on an electron linear accelerator and its evolution.

1. – Introduction

Radiation Therapy (RT) is an essential contributor for cancer cure. It can be divided into radiotherapy (conventional RT) and particle therapy. Radiotherapy delivers photons (X or γ rays) or electrons. Particle therapy uses protons (proton-therapy), ions and neutrons (hadrontherapy). Photons and electrons release most of their energy a few cm above the entrance of the beam in the patient body continuing to deposit dose outside the tumor target (fig. 1). Much of the ionizing radiation is delivered in healthy tissues with harmful effect. To solve this problem, multiple beam angles with static or dynamic techniques are used. Protons or ions deliver most of their energy at the end of their path in a short region called Bragg peak.

Nowadays there are more than 13000 S-band medical LINAC worldwide [1] with nominal energy between 5 and 30 MeV. Their compactness, efficiency and reliability have been key to their success for clinical applications. For proton and ion therapy 250–400 MeV cyclotron- and synchrotron-based systems are used. The main problem of these accelerators is that they are complex and need to be recovered in very big facilities; for this reason they are very expensive. Their realization is therefore limited and nowadays there are just 95 facilities in operation in the world (fig. 2) [2]. Scientists thought about FLASH Therapy as an alternative to conventional RT and expensive particle therapy.

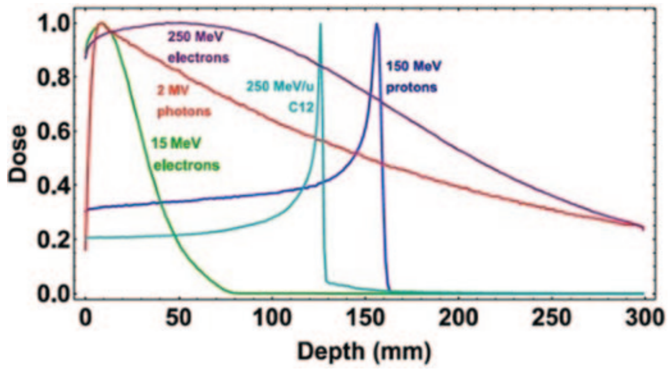

Fig. 1. – Dose profile in radiation therapy.

2. – FLASH Therapy

FLASH Therapy is an innovative technique in radiation therapy based on an old idea. In 1966 [3] Hornsey and Alper described the toxicity reduction in normal tissue using mouse models. In 1971 Hendry and his team confirmed this theory and showed that high dose rate electron beams induced hypoxia and reduced the damage in healthy tissues [4]. In 2014 a report of Favaudon and Vozenin (Curie Institute) revealed the differential response to high dose rates between normal and tumor tissue irradiated with FLASH-RT [5]. Finally in 2019 the first cancer treatment in a patient was done at Losanna University [6].

FLASH Therapy is a new way to deliver the dose. It uses high dose microsecond pulses of radiation (fig. 3), beam on time <100–500 ms, and high dose for each pulse. The FLASH-RT produces the FLASH effect that is the improvement of the healthy tissue tolerance to the delivered dose. FLASH irradiation time is over 1000 times shorter than conventional treatments, for a given dose delivered to the patient. This makes it possible to deliver a higher curative dose, opening new perspectives for the treatment of the tumor radiation resistance.

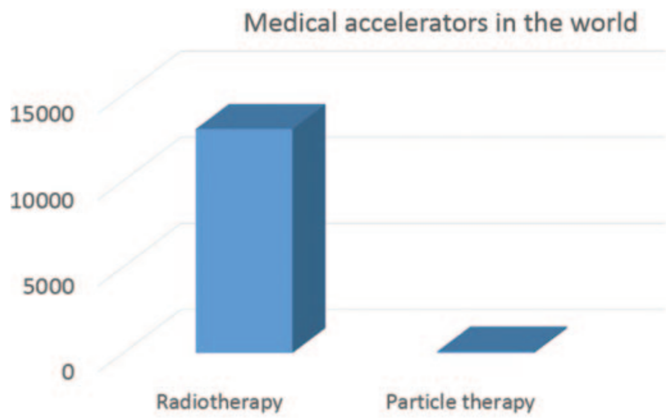

Fig. 2. – Medical accelerators in the world.

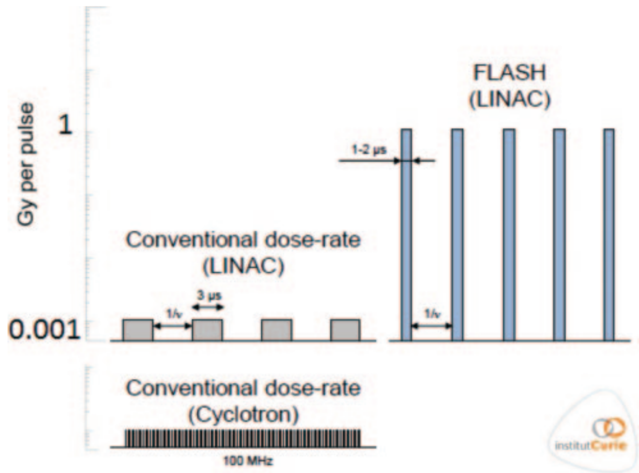

Fig. 3. – Temporal structure of energy deposition in FLASH Therapy (courtesy of V. Favaudon).

2˙1. *Experiments with FLASH-RT*. – The first experiment with FLASH radiotherapy was done in mice [5]. Mice were irradiated in conventional RT and FLASH-RT modality. For the conventional irradiation, researchers used a Cs-137 irradiator with nominal energy equal to 0.66 MeV (table I). For the FLASH irradiation, an electron LINAC with nominal energy equal to 5.6 MeV was used. The spread out dose was the same (17 Gy) but the dose rate was very different: 0.03 Gy/s for conventional RT and 60 Gy/s for FLASH-RT. The outcome of this study revealed that FLASH irradiation avoided side effects in healthy tissues but remained as efficient as conventional irradiation in the repression of tumor growth.

As shown in fig. 4, the relative tumor volume 90 days after treatment was comparable using conventional radiotherapy and FLASH Therapy at the same dose (20 Gy). The real revolution is that FLASH irradiation avoid radiation-induced fibrosis in healthy tissues. Irradiating healthy tissues without causing significant damages allows to increase the dose used and becomes more efficient in the tumor cure.

Table I. – *Parameters for the first experiment with FLASH-RT.*

	γ-rays	Electrons
Facility	Cs-137 irradiator	LINAC
Nominal energy (MeV)	0.66	4.5
Pulse *vs.* continuous	continuous	pulsed
Pulse repetition frequency (Hz)	–	150
Dose	17	17
Mean dose rate (Gy/s)	0.03	60
Temporal width of pulse μs	–	1

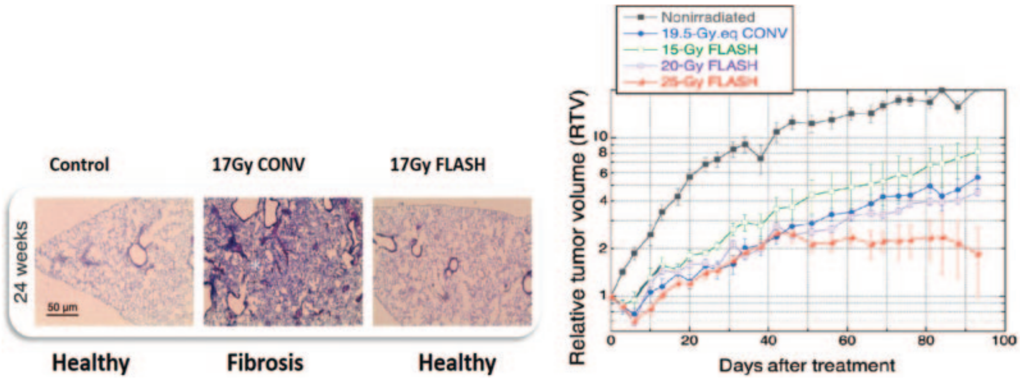

Fig. 4. – Outcome of the first study with FLASH-RT.

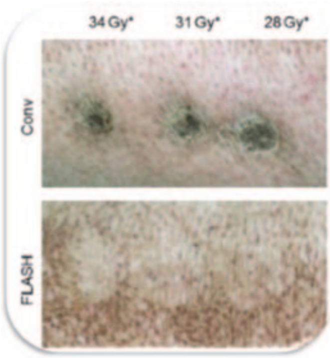

Fig. 5. – FLASH effect confirmed in large mammals.

The FLASH effect has been confirmed also in large mammals. The skin of a female pig was irradiated with FLASH-RT and conventional RT.

For this experiment, a LINAC has been used in conventional and FLASH modality with nominal energy equal to 4.5 and 6 MeV. The dose delivered in the spots was

TABLE II. – *Parameters for treatment with FLASH-RT in large mammals.*

	CONV	FLASH
Facility	LINAC	LINAC
Nominal energy (MeV)	4.5	6
Pulse *vs.* continuous	pulsed	pulsed
Pulse repetition frequency (Hz)	10	200
Dose	28-31-34	28-31-34
Mean dose rate (Gy/s)	0.08	300
Temporal width of pulse μs	few μs	1

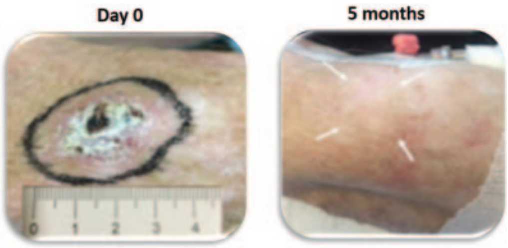

Fig. 6. – First treatment with FLASH-RT in the patient.

28, 31 and 34 Gy, respectively. The dose rate in conventional treatment was 0.08 Gy/s and for the FLASH one was 300 Gy/s [7]. Thirty-six weeks post radiotherapy, macroscopic visualization showed normal skin in FLASH-irradiated spots and necrosis lesions in conventional irradiated spots (see fig. 5 and table II).

The first patient treatment was done in Losanna Hospital. The patient was a 75 years old man with a radiotherapy multiresistant cutaneous lymphoma on the skin surface. The patient showed complete tumor regression after 5 months of FLASH Therapy treatment (see fig. 6 and table III) [6].

3. – Medical linear accelerator for FLASH Therapy

The experiments described above have been done using a high dose per pulse linear accelerator (LINAC) [8]. In medical LINAC particles are generated from an electron gun by thermionic effects (fig. 7). The extraction of electrons from the surface of a cathode is controlled by a voltage applied to the anode. The tension applied on the anode controls the injection current which is linked to the mean dose rate in the pulse of radiation.

Particles travel into the RF cavity and receive an increase in energy and velocity. The RF cavity is powered by an RF generator (magnetron). Besides, a circulator is used to avoid reflections from the RF cavity to the magnetron in order not to destroy it. Nowadays only a few accelerators have been realized for FLASH Therapy having a nominal energy between 4.5 and 6 MeV. They are able to deliver high dose rate up to 1000 Gy/s to a surface of irradiation of $10 \times 10\,\text{cm}^2$. These LINAC are nowadays used for preclinical study or clinical studies for superficial tumors. There are also LINAC modified for FLASH Therapy, one is in Stanford and the other one is in Lund. Their energy is 20 MeV and the delivered dose rate is between 0.1 and 250 Gy/s. They are also used for preclinical study. In addition to electron beam LINAC, FLASH Therapy

Table III. – *Parameters for first patient treatment with FLASH-RT.*

	FLASH
Facility	LINAC
Nominal energy (MeV)	5.6
Pulse *vs.* continuous	pulsed
Pulse repetition frequency (Hz)	100
Dose	15
Mean dose rate (Gy/s)	166
Temporal width of pulse μs	1

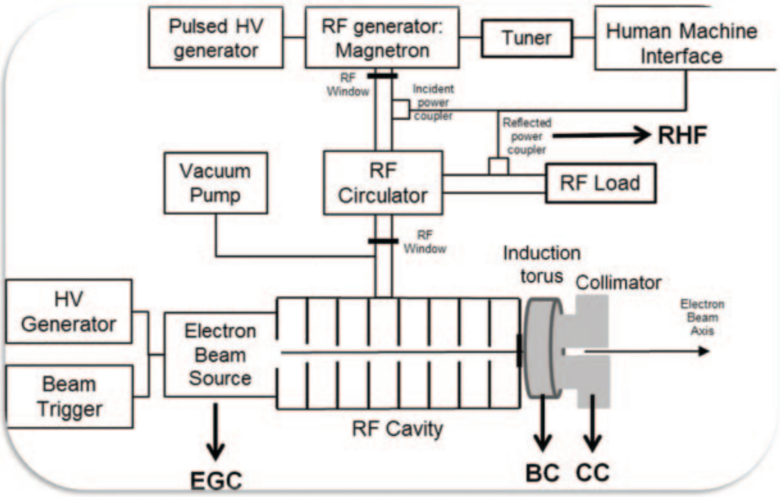

Fig. 7. – High dose per pulse linear accelerator.

with protons is also very promising and some companies and institutes are working in this direction. There are modified proton accelerators with dose rate from 40 Gy/s to 200 Gy/s. They irradiate $20 \times 20\,\text{cm}^2$ of surface and are in development for pre-clinical studies.

Sapienza University is supported by S.I.T. Sordina IORT Technologies S.p.A. for the development of a new electron beam LINAC for FLASH Therapy. The accelerator will be developed to perform other preclinical studies because there are a lot of questions to solve in FLASH-RT. First of all, researchers want to understand the FLASH-RT limits in terms of minimum and maximum dose in time that they can deliver to obtain the FLASH effect. Secondly, they want to clarify biological mechanisms underlying the FLASH effect. The most important issue will be to define a protocol for clinical practice to allow the clinical use of FLASH-RT.

3˙1. *Target performance for pre-clinical studies.* – Electrons will have variable energy between 5 and 7 MeV. The surface irradiated will be variable from $4{\times}4\,\text{cm}^2$ to $10{\times}10\,\text{cm}^2$. High homogeneity for *in vitro* screening will be the most important requirement to satisfy. The target dose per pulse will be 5 Gy and the mean dose rate will be above 1000 Gy/s. The dose rate in one pulse will be between 10^6 and 10^7 Gy/s.

4. – Conclusions

We have described FLASH Therapy, it releases high Gy level dose in microsecond pulses (beam on time $<$100–500 ms). These bursts of radiation are less harmful to healthy tissues but just as efficient as conventional dose rate radiation to inhibit tumor growth. Several studies on animals and clinical treatment on one patient have demonstrated the big potentiality of the FLASH Therapy. A few LINAC accelerators have been used for preclinical studies about FLASH Therapy. A novel accelerator is currently in development (S.I.T.-Sapienza University cooperation) to be used in pre-clinical studies, tunable and with advanced performances.

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