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FLASH RADIATION THERAPY: ACCELERATOR ASPECTS

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Abstract

One of the new paradigms in radiation therapy (RT) is the FLASH dose delivery irradiation technique. The FLASH methodology consists in delivering millisecond pulses of radiation (total beam-on time < 100-500 ms) delivered at a high mean dose-rate (> 40-100 Gy/s) and pulse amplitude (≥ 106 Gy/s), over 2000 times faster than in conventional RT. New accelerator ideas are under development or are being tested to deliver this type of beam. In this paper we will report the accelerator technology used for the pre-clinical studies and the necessary developments to deliver this novel dose RT technique.

INTRODUCTION

Radiation therapy (RT) is one of the most effective cancer treatment and control, and is used in the treatment of 50 to 60% of cancers. Over 95% of the cancer treatment using RT techniques are realised with linear accelerators delivering MV photons or electron of less than 25 MeV. These machines are combined with multi-leaf collimators to adapt the beam to the tumour shape and imaging devices for positioning the patient. One of the main limitations of RT is that the dose delivered to the tumour is constrained by the dose that can be tolerated by the surrounding normal tissues. Recently, a strategy to overcome this limitation, based on the optimisation of the dose delivery method by using non-conventional temporal microstructures of the beam was proposed [1]. The so-called FLASH-RT has emerged. In the following, a short review of the main pre-clinical radiobiology studies is presented with a special focus on the accelerators used to deliver a FLASH irradiation. Subsequently the up-to-date machine designs for clinical applications are discussed.

THE FLASH EFFECT

The "FLASH effect" was proposed by Favaudon et al. at Institut Curie (France) [1] as the result of very high dose-rate irradiation (pulse amplitude ≥ 10^6 Gy/s, or mean dose rate > 40 Gy/s), short beam-on duration (≤ 500 ms) and large doses per fraction (≥ 10 Gy) on in-vivo samples [2]. The lung fibrogenesis in C57BL/6J mice receiving 15–17 Gy in bilateral thorax irradiation with 4.5 MeV pulsed electron beams was investigated. Animals were exposed to single doses in short pulses so that the total irradiation time was less than 500 ms. Mice were also exposed to "conventional" (CONV) dose-rate irradiations (≤ 0.03 Gy/s). No complications were developed on the healthy tissues after a FLASH irradiation (up to 23 Gy), while the CONV treatment generates lung fibrosis in the totality of the irradiated animals. In contrast, FLASH was as efficient as CONV when irradiating tumours (Fig. 1).

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These results were also reproduced and thoroughly extended by several teams in the last five years. In particular, the group headed by Dr. Vozenin in Lausanne (Switzerland) reported excellent results on mice, cats, pigs (summarised in a review article [3]), and a promising outcome in the treatment of a first human patient has also been reported [4]. Very recently, the biological mechanisms that underlie the FLASH effect in lung have also been identified [5].

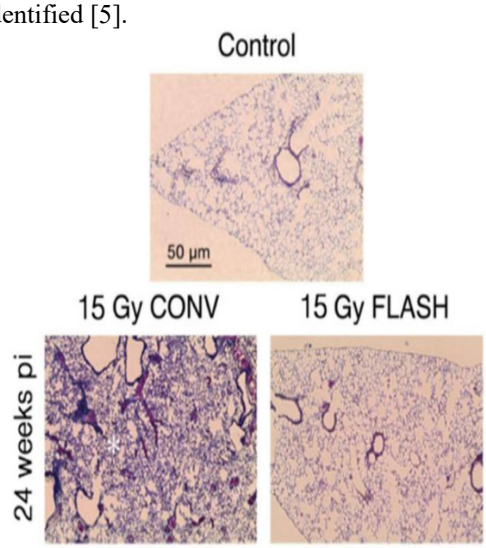

Figure 1: FLASH irradiation spares lung at doses known to induce fibrosis in mice following conventional dose-rate irradiation (CONV) (modified from [1]).

ACCELERATORS USED IN THE PRE-CLINICAL FLASH STUDIES

In the next section, an overview of the machines used to study the FLASH effect is presented.

Prototypes Low-Energy Electron LINACs

Kinetron, the "reference" accelerator used by Dr. Fauvaudon at Institut Curie is a S-band linear electron accelerator designed by a French company (CGR-MeV) in 1987 to investigate free radical reactions in macromolecules at the submicrosecond time-scale and the electron transfer kinetics [6] (Fig. 2). It is a compact electron linac with nominal energy of 4.5 MeV, and a set of parameter easily adjustable as the pulse repetition frequency (0.1 – 200 Hz), the pulse length (0.05 – 2 µs) and with a mean dose rate up to 7000 Gy/s. The Kinetron is powered by a magnetron and is fitted with a thermionic triode electron gun. Precise adjustment of the grid potential of the triode allows the total control of the emitted current and pulse width in the FLASH operating mode. A more complete description of the machine parameters can be found in [6, 7].

Oriatron eRT6, the general design of the machine by PMB-Alcen was derived by the Kinetron. The 6 MeV

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experimental linac was recently installed at the Lausanne University Hospital (Switzerland) also for preclinical studies. The specificity of the eRT6 accelerator design is the possibility to work at high-dose rates using a much higher beam current (maximum peak current ~ 300 mA and mean value of 30 µA) than conventional electron clinical machines (peak current ~ 1mA and mean value of 0.1 µA). More details can be found in [8].

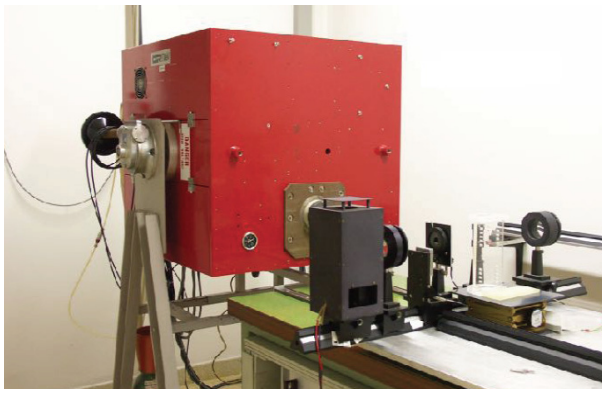

Figure 2: Kinetron accelerator.

Modified Clinical Electron LINACs

The following linacs [9, 10] have been successfully employed to deliver electron beams with dose rate exceeding 200 Gy/s. The bremsstrahlung target was removed and the irradiation position of the samples was chosen to be an intermediate position inside the treatment head allowing a good compromise between dose rate, field size and flatness. However, the field sizes obtained are only suitable for small-animal experiments.

Schüler et al. [9] succeeded in delivering FLASH dose-rates (~ 200 Gy/s) using a modified Varian Clinac 21EX at 9 and 20 MeV. A 13-fold increase in dose rate was observed for the 9 MeV beam at 400 nA and a 40-fold for the 20 MeV beam at 110 nA.

Lempart et al. [10] also proposed some methods to achieve an increased dose rate (up to 300 Gy/s) on an 8 MeV Elekta Precise linac in particular by removing the scattering foils from the beam path.

Photons Sources: Synchrotron Light Sources

To date, FLASH effect using photons beams has been demonstrated using ultrahigh dose rate x-ray beams generated at a synchrotron light source (the European Synchrotron Research Facilities - ESRF, France) [11]. A quasi-continuous 100 keV x-rays beam was delivered with an in-slice dose rate of 12,000 Gy/s (200 mA peak current, mean dose rate 37 Gy/s). Despite a major interest as a research tool, synchrotron beams are now limited as they can only cover small field sizes, and in addition kV x-rays are usually not well suited for the treatment of deep-seated tumours.

Protons Sources: Cyclotrons

Several research groups are investigating the feasibility of FLASH-RT with proton beams. In particular, the capabilities of proton accelerators to achieve high instantaneous pulsed dose rate and high mean dose rate as required for the FLASH effect [12, 13, 14] are investigated. A group from Institut Curie (France) published an example of irradiation setup that can be found in Fig. 3 [12]. Very recently, Diffenderfer el al. [15] has demonstrated a significant FLASH effect while irradiating mice intestine (loss of proliferating cells in intestinal crypts) with a 230 MeV scattered proton beam at high dose-rate (around 90 Gy/s) with an isochronous cyclotron. This promising result is however mitigated by the maximum field size that can be used to ensure such a dose rate, limited to a few cm diameter targets.

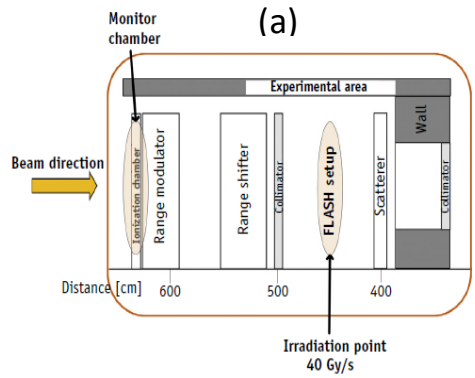

Figure 3: (a) Beamline used for the proof of concept of FLASH proton irradiation at Institut Curie and (b) setup for small animal experiments.

ACCELERATORS FOR CLINICAL FLASH IRRADIATIONS

In the attempt to bring FLASH-RT towards clinical operations, the accelerator "magic bullet" is still to be defined. Among the challenges to be solved, from the accelerator point of view one should answer the question: how to produce beam intensities capable of delivering tens of Gy in less than 500 ms, and preferably not more than 100 ms? There is an evident need to increase by hundreds-fold the beam output of the machine, which ideally has to fit existing clinical vaults, should be easy to operate and

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maintain, cost-affordable, and which can be coupled with imaging devices for the patient positioning (all the more so since the irradiation will be very short and hypofractionated). To date, the only proposed solution is a MV photon source – the PHASER (Pluridirectional High-energy Agile Scanning Electronic Radiotherapy) [16] (Fig. 4). The favorable depth-dose characteristics and reduced entrance doses of MV photons remain interesting for future 3D volume optimization. But according to the authors the use of Very High Energy Electrons (VHEE) is also a possible alternative as VHEE may be advantageous in terms of depth-dose profile, reduced lateral scattering (low penumbrae) and enabling pencil beam scanning, favoring better dose conformity and integral dose intermediate between photons and protons.

PHASER

To answer the question: how to produce hundreds-fold beam output (with respect to conventional accelerators)? Maxim et al. [16] proposed the use of a new accelerator science to invent an innovative RF power distribution: DRAGON Distributed RF-coupling Architecture with Genetically Optimized cell desigN. The idea is to distribute the RF power independently to each cell without coupling between the cells: in this way the system achieves higher efficiency (80% vs 20% for standard clinical linacs), higher shunt impedance (2.5-4-fold: 200 MΩ/m at X-band) and a higher repetition rate.

In order to fit the existing treatment vaults, the authors propose the use of compact RF phased-Array Power Distribution of waveguides (RAPiD) : 16 (at least) power input combine the power of modular small klystrons (klystrinos) in order to feed the 16 output port, that are coupled with 16 stationary beamlines capable to deliver intensity modulated beams without any mechanical device/motions by using a dedicated electron beam scanning system (Scanning Pencil-beam High-speed INtensity-modulated X-ray source (SPHINX). Thanks to a stationary bremsstrahlung target and a fixed collimator it is possible to perform intensity modulated treatment without collimators. To perform positioning for the treatment a solution is also provided.

To conclude, the various solutions proposed by the SLAC/Stanford team show that R&D on accelerator and RF power designs can make RT more affordable, allows a better exploitation of the potential of FLASH irradiations, a reduction in costs, and space requirements can be ensured by multiplexing the RF sources (the peak power from each source can be reduced). High clinical efficiency can be obtained by combining multiple linacs with CT scanners for motion management.

The authors also proposed a system to deliver VHEE FLASH RT. Technically they suggest the production of a spatially patterned electron source by projecting an optical image into a photocathode. The electron "image" is then accelerated intact through a high-gradient DRAGON linac, steered and augmented to the treatment volume, producing an intensity-modulated treatment field.

This solution is motivated by the much lower beam current needed when treating directly with VHEE (no bremsstrahlung target), and by the potential advantages of using VHEE in RT, like a flatter depth-dose profile than photons or a less sensitivity to heterogeneities [17]. In addition, thanks to recent high-gradient linac technology developments, (CLIC >100 MV/m, W-band >200MV/m) VHEE (100–250 MeV) could be a cost-effective option in RT. In this regard, several groups have realized dosimetry studies at multiple facilities with VHEE at high dose rates [18, 19, 20, 21].

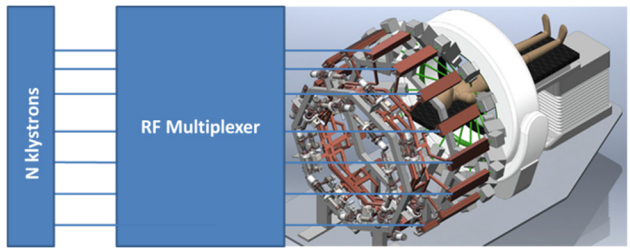

Figure 4: PHASER design (modified from [14]).

CONCLUSION

FLASH-RT pre-clinical studies, with different particle sources and types, has demonstrated an increased therapeutic index enabling higher doses well tolerated by normal tissues, and represents a promising irradiation technique aiming at reducing RT potential side effects. Multidisciplinary teams are working together to provide further studies that enable to understand the impact of the total dose per fraction, temporal patterning and fractionation scheme, total exposure rate, protocols for the beam calibration and absolute dosimetry [22], radiation quality impact on the tissue response, as well as the fundamental biological mechanisms. The accelerator community could play an important role in the development of alternative solutions to provide FLASH irradiators, in order to develop future clinical trials, and help to find some strategies to irradiate large volumes in less than a few hundreds of ms with important doses.

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REFERENCES

[1] V. Favaudon *et al.*, "Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumour tissue in mice", *Sci.Transl Med* 2014;6:245-293. DOI: 10.1126/scitranslmed.3008973

[2] A. Mazal *et al.*, "FLASH and minibeams in radiation therapy: the effect of microstructures on time and space and their potential application to protontherapy.", *Br J Radiol* 2020; 93: 20190807. DOI: 10.1259/bjr.20190807

ISBN: 978-3-95450-213-4 ISSN: 2673-5490 doi:10.18429/JACoW-IPAC2020-THVIR12

[3] M. C. Vozenin *et al*., "Biological Benefits of Ultra-high Dose Rate FLASH Radiotherapy: Sleeping Beauty Awoken", *Clin Oncol (R Coll Radiol)* 2019;31(7):407-415. DOI: 10.1016/j.clon.2019.04.001

[4] J. Bourhis, W. J. Sozzi, P. G. Jorge *et al.,* "Treatment of a first patient with FLASH-radiotherapy", *Radiother Oncol*. 2019;139:18-22. DOI: 10.1016/j.radonc.2019.06.019

[5] C. Fouillade, S. Curras-Alonso, L. Giuranno *et al*., "FLASH irradiation spares lung progenitor cells and limits the incidence of radio-induced senescence", *Clin Cancer Res.* 2020;26:1497-1506. DOI: 10.1158/1078-0432.CCR-19-1440

[6] V. Favaudon *et al*., "Time-resolved dosimetry of pulsed electron beams in very high dose-rate, FLASH irradiation for radiotherapy preclinical studies", *Nucl. Instrum. Methods*, Volume 944, 2019, 162537, ISSN 0168-9002, https://doi.org/10.1016/j.nima.2019.162537.

[7] P. Lansonneur *et al*., "Simulation and experimental validation of a prototype electron beam linear accelerator for preclinical studies." *Phys Med.* 2019;60:50-57. DOI: 10.1016/j.ejmp.2019.03.016

[8] M. Jaccard, M.T. Durán, K. Petersson, *et al.*, "High dose-per-pulse electron beam dosimetry: Commissioning of the Oriatron eRT6 prototype linear accelerator for preclinical use", *Med Phys*. 2018; 45(2):863-874. DOI: 10.1002/mp.12713

[9] E. Schüler, S. Trovati, G. King, *et al.*, "Experimental Platform for Ultra-high Dose Rate FLASH Irradiation of Small Animals Using a Clinical Linear Accelerator", *Int J Radiat Oncol Biol Phys*. 2017;97(1):195-203. DOI: 10.1016/j.ijrobp.2016.09.018

[10] M. Lempart, B. Blad, G. Adrian, et al., "Modifying a clinical linear accelerator for delivery of ultra-high dose rate irradiation.", *Radiother Oncol.* 2019;139:40-45. DOI: 10.1016/j.radonc.2019.01.031

[11] P. Montay-Gruel, A. Bouchet, M. Jaccard et al., "X-rays can trigger the FLASH effect: Ultra-high dose-rate synchrotron light source prevents normal brain injury after whole brain irradiation in mice" *Radiother Oncol.* 2018;129(3):582-588. DOI: 10.1016/j.radonc.2018.08.016

[12] A. Patriarca, C. Fouillade, M. Auger et al., "Experimental set-up for FLASH proton irradiation of small animals using a clinical system", *Int J Radiat Oncol Biol Phys* 102 (3) (2018) 619–626. DOI: 10.1016/j.ijrobp.2018.06.403

[13] S. Van de Water, S. Safai, J. M. Schippers, D. C. Weber and A. J. Lomax, "Towards FLASH proton therapy: the impact of treatment planning and machine characteristics on achievable dose rates", *Acta Oncologica* 58 (2019) 1463–1469. DOI: 10.1080/0284186X.2019.1627416

[14] P. Van Marlen, M. Dahele, M. Folkerts *et al*., "Bringing FLASH to the clinic: Treatment planning considerations for ultrahigh dose-rate proton beams", *Int J Radiat Oncol Biol Phys*. 2019;106:621-629. https://doi.org/10.1016/j.ijrobp.2019.11.011

[15] E. S. Diffenderfer, I. I. Verginadis, M. N. Kim *et al*., "Design, Implementation, and in Vivo Validation of a Novel Proton FLASH Radiation Therapy System", *Int J Radiat Oncol Biol Phys*. 2020; 106(2):440-448. DOI: 10.1016/j.ijrobp.2019.10.049

[16] P. G. Maxim, S. G. Tantawi and B. W. Jr Loo, "PHASER: A platform for clinical translation of FLASH cancer radiotherapy", *Radiother Oncol*. 2019; 139:28-33. DOI: 10.1016/j.radonc.2019.05.005

[17] C. DesRosiers, V. Moskvin, A.F. Bielajew, L, Papiez, "150-250 meV electron beams in radiation therapy", *Phys Med Biol*. 2000; 45(7):1781-1805. DOI: 10.1088/0031-9155/45/7/306

[18] A. Lagzda, R. M. Jones, D. Angal-Kalinin, J. K. Jones, and K. Kirkby, "Relative Insensitivity to Inhomogeneities on Very High Energy Electron Dose Distributions", in Proc. *8th Int. Particle Accelerator Conf. (IPAC'17)*, Copenhagen, Denmark, May 2017, pp. 4791–4794. DOI: 10.18429/JACoW-IPAC2017-THPVA139

[19] M. Bazalova-Carter, M. Liu, B. Palma *et al*., "Comparison of film measurements and Monte Carlo simulations of dose delivered with very high-energy electron beams in a polystyrene phantom", *Med Phys.* 2015;42(4):1606-1613. DOI: 10.1118/1.4914371

[20] A. Subiel, V. Moskvin, G. H. Welsh *et al*., "Dosimetry of very high energy electrons (VHEE) for radiotherapy applications: using radiochromic film measurements and Monte Carlo simulations", *Phys Med Biol.* 2014;59(19):5811-5829. DOI:10.1088/0031-9155/59/19/5811

[21] L. Karsch, E. Beyreuther, T. Burris-Mog *et al*., "Dose rate dependence for different dosimeters and detectors: TLD, OSL, EBT films, and diamond detectors", *Med Phys.* 2012; 39(5):2447-2455. DOI: 10.1118/1.3700400

[22] Metrology for advanced radiotherapy using particle beams with ultra-high pulse dose rates. http://uhdpulse-empir.eu