ISBN: 978-3-95450-184-7 doi:10.18429/JACoW-IPAC2018-MOPML051

FIRST PERFORMANCE CALCULATIONS FOR VERY HIGH ENERGY ELECTRON RADIATION THERAPY EXPERIMENT AT PRAE*

A. Faus Golfe†, LAL, Univ. Paris-Sud and Paris-Saclay, CNRS/IN2P3, France
A. Mazal, A. Patriarca, V. Favaudon, P. Verrelle, P. Poortmans, C. Fouillade, S. Heinrich, Institute Curie, Centre de Protonthérapie d'Orsay, Orsay, France
R. Delorme, Y. Prezado, IMNC, Univ. Paris-Sud and Paris-Saclay, CNRS/IN2P3, France
A. Hrybok, Taras Shevchenko Univ. of Kyiv, Ukraine

Abstract

The PRAE project (Platform for Research and Applications with Electrons) aims at creating a multidisciplinary Research and Development (R&D) platform at the Orsay campus, joining various scientific communities involved in radiobiology, subatomic physics, instrumentation, particle accelerators, medical physics and clinical research around a high-performance electron accelerator with beam energies up to 70 MeV (planned 140 MeV), in order to perform a series of unique measurements for challenging R&D. In this paper we will report the first optics design and performance evaluations of a multidisciplinary operated Very High Energy Electrons (VHEE) innovative Radiation Therapy (RT) device, in particular by using Grid and FLASH methodologies, which are likely to represent a major breakthrough in RT. Functional specifications include dose rates from 2 Gy/min to 100 Gy/sec, beam sizes with diameters from 0.5 mm to ≥10 cm, homogeneous beam distributions (+/- 2-3%) and monitoring devices with an accuracy in the order of 1-2% for single or multiple beams and single or multiple fractions in biological and preclinical applications. High energies (>140 MeV) would also be needed for GRID therapy.

INTRODUCTION

The widest use RT modality is the conventional linear accelerator delivering 6-10 MV photons beams and in a small proportion, 3-25 MeV electrons. Higher photon energies (eg up to 25 MV) are or have been in use for deep clinical targets, but their application is being reduced in particular for the associated neutron production and for an increased interest of short low-energy linacs delivering full rotational techniques with sharp lateral penumbra. The main limitation of RT is the maximum dose that could be tolerated by the surrounding normal tissues. Conventional photon RT is characterized by almost exponential attenuation and absorption; hence the maximum energy is delivered 1-2.5 cm below the beam entrance, continuing to deposit energy at distances beyond the target volumes (Figure 1). To compensate for this, multiple beams angles with static or dynamic techniques are used. Another possibility to overcome the limitations of photons is to use RT with particles (proton or light ions), since this deposit more of their energy at the end of the energy range (Bragg peak). The use of protons has grown

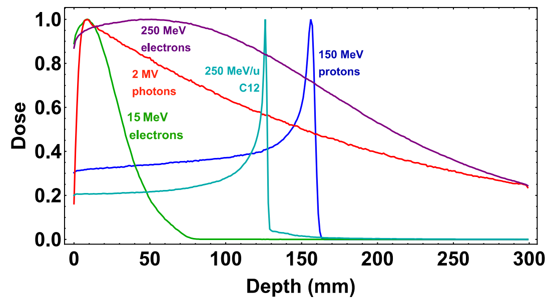

Figure 1: Dose profile for various particle beams in water (beam widths r=0.5 cm), [1].

over the last 20 years, exploiting the ballistic advantage of protons to limit the doses outside of the target volumes in a superior way compared to photons. The major drawbacks of proton RT are the higher technical complexity, the management of uncertainties, an inferior image guidance compared to the last generation of photon RT infrastructure and the high price of both the installation as the operation. A challenge thereby is to make particle RT accelerators as cheap as photon RT facilities. For this, we explore as possible alternative the use of VHEE electrons.

5-25 MeV electrons are classically used in the clinic but, due to their physical energy deposition profile, their use is restricted to treat superficial tumors. Increasing the energy above 70 MeV (VHEE) will overcome these limitations and, in addition, present the following advantages: i) the penetration becomes deeper and the transverse penumbra sharper thus allowing a more precise treatment of deeper tumors ii) the small diameter VHEE beams can be scanned avoiding mechanical solutions such as the multileaf collimator iii) a rather smaller sensitivity to tissue heterogeneity can be achieved with VHEE beams under certain conditions [1] iv) VHEE accelerators may be constructed at significantly lower cost than current proton facilities.

Currently, there is a growing interest in the biomedical community for VHEE beams ranging from 70 to 300 MeV [2-3] and, before an eventual integration of VHEE therapy in the clinic, some mechanistic and preclinical studies are required. The PRAE accelerator will thus enable radiation biologists and radiation oncologists to investigate the molecular and cellular impacts of VHEE beams on normal tissues (e.g. brain, lung, gut) as well as tumors and compare these effects to conventional radiation therapies (e.g. 5-25 MeV electrons, photons). VHEE therapy would be of particular interest for treating deep, large or small tumours with several distinct beam entrances within the same radiotherapy session, doing better than current photon-based

*Work supported by ANR-10-LABX-0038, ANR-11-IDEX-0003-01 and IDEATE (LIA) France-Ukraine [20]
† fausgolf@lal.in2p3.fr

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treatments in terms of doses delivered to surrounding healthy tissues [3]. This would allow to treat patients with VHEE beam directly or with innovative ways of dose delivery like Grid therapy mini-beams [4] or ultra-high dose rates FLASH beam [5], easier to produce with electron than with photon beams.

In the following sections we will present the first optics design and performance evaluation for a VHEE experiment at 70 MeV in the PRAE accelerator to deliver Grid therapy mini-beams and sub-millisecond ultra-high dose rates FLASH beams.

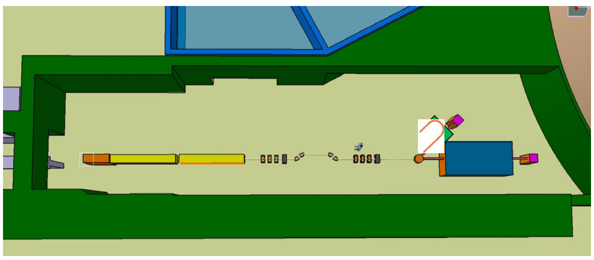

Figure 2: Schematic view of the PRAE accelerator (140 MeV) with the two experimental beam lines.

THE PRAE ACCELERATOR

The PRAE accelerator consists of a photo-injector, an acceleration section and two beam lines with the corresponding experimental setups: the subatomic physics and radiobiology research axes share the direct line and the instrumentation platform is located in the deviated line, as shown in Figure 2.

Table 1: PRAE Accelerator Performances

Parameters	
Energy	70 – 140 [MeV]
Charge (variable)	0.00005 – 2 [nC]
Normalized emittance	3-10 [mm mrad]
RF frequency	3.0 [GHz]
Repetition rate	50 [Hz]
Bunch length, rms	< 10 [psec]
Energy spread, rms	< 0.2 %
Bunches per pulse	1

A beam energy compressor section (ECS) follows the accelerating structure before separating in the direct (ProRad/Radiobiology) and the deviated line (Instrumentation). Two quadrupole triplets provide flexible beam optics to cope the different beam characteristics and operation modes depending on the application. The performances of the PRAE accelerator are summarized in Table 1. Detailed description of the accelerator and beam dynamics simulations is found in [6-7] respectively.

GRID OR MINI-BEAM THERAPY

One possible strategy to further improve the healthy tissue tolerance by using the concept of Spatially Fractionated Radiation (SFR) dose is the Grid or Mini-Beam Therapy (MBRT). In contrast to conventional RT the lateral dose-profile resulting of such grid-irradiation consist in a pattern of high doses in "peaks " and low doses in "valleys".

Such techniques allow delivering large cumulative doses of radiation for treating the tumour, while reducing healthy tissue complications [8-9]. Remarkably high normal tissue dose tolerances (up to 100 Gy in one fraction) have been observed in in vivo biological experiments in the rat brain using SFR approaches that employ micrometric keV photon beams, as mini-beams (beam width of 400-700 μm) [10], which also produced significant tumour growth delay [11]. It is also evident that the advantages of VHEE beams for grid-therapy would benefit from the low lateral scattering and long penetration depth to allow the reduction of grid-size, up to sub-millimetric beams, and with direct magnetic collimation to construct the grid pattern. A theoretical proof of concept for this innovative approach in the treatment of brain-cancer has been recently explored [4] and some pre-clinical evaluation of other mini-beam approaches, such as proton MBRT [12] are being made at the Proton Therapy Centre at Orsay. To capitalise these initial encouraging results a first proof-of-concept with electrons will be made in PRAE.

First beam optics design calculated with the MADX program [13] is shown in Figure 3 to get transverse beam sizes ($\sigma_{x,y}$) of less than 700 μm with low beam divergence ($\sigma_{x',y'}$). The last dipole, indicating the starting of the instrumentation R&D platform, is not active in this case and for the sake of simplicity the ECS has not been taking into account.

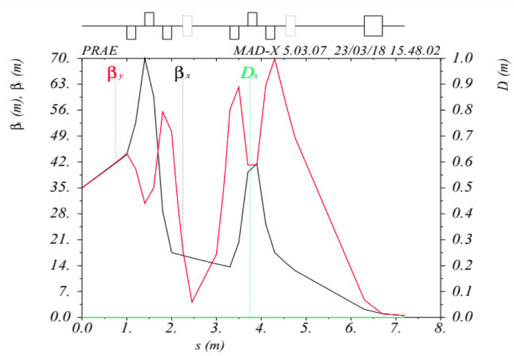

Figure 3: Beam optics design for mini-beam experiment at PRAE direct line without the ECS chicane and using two quadrupole triplets calculated with MADX.

Tracking simulations of a Gaussian bunch through the under vacuum accelerator beam line (Figure 3), an air gap of 10 cm and liquid water phantom of 3 cm depth has been performed with a Geant4 (Penelope module) based program BDSIM [14] for 70, 140 and 300 MeV. Results are illustrated in Figure 4 and summarized in Table 2. A benchmarking of the BDSIM results with MADX for the vacuum part and with the results with GATE (Geant4-based) in air and water has been made [15]. From these first results we could conclude that the mini-beam experiment is feasible but more promising using a higher-energy beam (>140 MeV). An extra focusing in air could be used to further

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improve the Grid-pattern in depth. Some preliminary simulations of this extra focusing in air with BDSIM are on going.

Table 2: Transverse beam sizes and divergences sequentially at the accelerator vacuum window, after 10 cm air gap and 3 cm depth in water, for 70, 140 and 300 MeV.

Parameters	Energies [MeV]		
	70	140	300
$\sigma_{x,y}$ vacuum [µm]	166 159	170 159	170 159
$\sigma_{x',y'}$ vacuum[µrad]	321 318	318 323	318 323
$\sigma_{x,y}$ air [µm]	198 183	186 182	173 162
$\sigma_{x',y'}$ air [µrad]	3141 3045	1673 1868	830 801
$\sigma_{x,y}$ water [µm]	615 646	533 561	334 350
$\sigma_{x',y'}$ water [µrad]	63511 61522	37372 36542	19934 20162

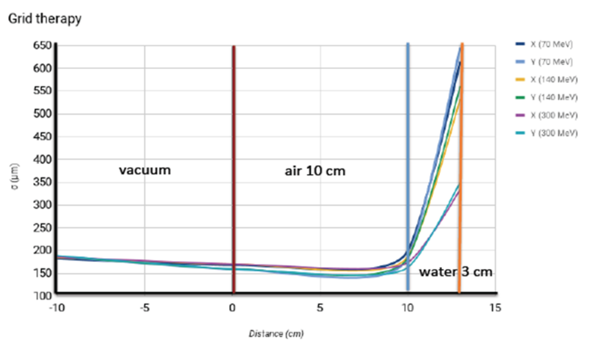

Figure 4: Beam widening for 70, 140, 300 MeV from end of vacuum window (0 in the horizontal scale), 10 cm air gap and 3 cm depth in water, calculated with BDSIM.

FLASH THERAPY

FLASH therapy experiments have been successfully tested with low energy electrons beams (4-6 MeV) only in small animals because of the low penetration of low-energy electrons. In 2014 the Institute Curie (IC) team demonstrated for the first time that FLASH irradiation spares normal lung tissue in mice from radio-induced fibrosis whilst leaving the anti-tumour efficiency unchanged [5]. The FLASH methodology consists of millisecond pulses of radiation (beam-on time ≤ 100-500 ms) delivered at a high dose-rate (≥ 40-100 Gy/s), hence over 2000 times faster than in conventional RT. Recently it has been shown that FLASH spares normal brain in mice from the loss of both memory and neural stem cells as endpoints [16]. Furthermore, on going studies using FLASH to cure non-operable squamous-cell carcinoma of the nasal planum in cats (shallow tumours fully irradiated by low energy electron beams). At the present time, melting of linear accelerator tungsten targets following high dose rate electron irradiation is a major technical problem preventing use of photon beam for FLASH irradiation of deep tumours [17]. The IC team is currently investigating the biological effect of FLASH treatment using protons beam (proto-FLASH) and the results of the first experiments are under analysis [18]. VHEE radiotherapy could be the most suitable to treat deep tumour targets in FLASH conditions with distinct beam entrances.

A preliminary study of the beam optics and performances in PRAE direct beam line has been made for two different scenarios for FLASH tests in small animals:

- Sparing brain from radiation-induced loss of stem cells: round transverse beam sizes of around 10 mm with a dose of 10 Gy with beam on time 100 ms (5 bunches at 50 Hz), i.e. 10Gy/s [16].
- Sparing lung from radiation-induced fibrosis: transverse beam sizes of around 26 mm in horizontal and 18 in vertical with a dose of 15 Gy with beam on time 500 ms (25 bunches at 50 Hz), i.e. 30 Gy/s.

Beam optics with MADX and BDSIM simulations for these two cases has been calculated with the same methodology that for the mini-beams and the results for the BDSIM simulations are shown in Figure 5.

Concerning the beam intensity required to cope with the necessary dose rates (10 and 30 Gy/s), taking into account the corresponding transverse beam area for these two scenarios (1x1 and 1.8x2.6 cm^2) and the mass stopping power value in liquid water for electrons at 70 MeV [19], 0.05 and 0.36 nC/s respectively are needed.

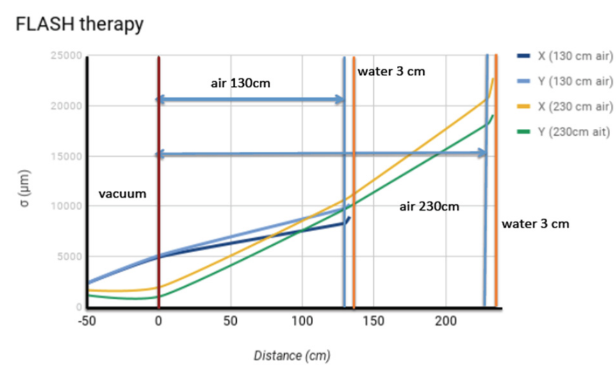

Figure 5: Beam widening for 70 MeV from end of vacuum window (0 in the horizontal scale), 130/230 cm air gap and 3 cm depth of water, calculated with BDSIM.

OUTLOOK AND PERSPECTIVES

A preliminary beam optics design and performance simulations for having a radiobiology experiment with Grid mini-beams and FLASH ultrahigh dose rate delivery treatment modalities at PRAE have been made. The results are encouraging and a deeper technical feasibility study is ongoing in order to demonstrate experimentally these innovative treatment modalities.

ACKNOWLEDGEMENTS

We would like to thank L. Nevay and N. Fuster Martinez for their help with the BDSIM simulations.

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