Feasibility Study of a Prostate Cancer FLASH Therapy Treatment With Electrons of High Energy

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Feasibility study of a prostate cancer FLASH therapy treatment with electrons of high energy

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ABSTRACT

Prostate cancer is among the most common cancers in men and one of the leading causes of death worldwide. Different therapies are adopted for its treatment and generally radiotherapy with photons (RT) is the preferred solution in almost all cases. Up to now, in addition to photons, only protons have been implemented as alternative radiotherapy. The use of Very High Energy Electron (VHEE) beams (100−200 MeV) has been suggested in literature but the needed accelerators are more demanding, as far as space and cost are concerned, with respect to standard photon devices, with only limited advantages when compared to protons or other heavy ions.
In this contribution we investigate how recent developments in electron beam therapy could reshape the landscape of prostate treatments. The VHEE Treatment Planning System obtained combining an accurate Monte Carlo (MC) simulation with a simple modelling of the FLASH effect (healthy tissues sparing at very high dose rates) is compared with conventional RT. The results demonstrate that FLASH therapy with VHEE beams of 70-130 MeV could represent a valid alternative to standard RT allowing a better sparing of the healthy tissues surrounding the tumour, in the framework of an affordable technological development.

1 Introduction

Prostate cancer has become the third most common cancer in men (nearly 10% of all men cancers) and is the fifth leading cause of death worldwide[1,2].
When prostate cancer is detected, different curative treatment options are available, such as surgical removal of the prostate, brachytherapy (positioning of sealed radioactive sources in the tumour proximity), external photon beam radiotherapy (EBRT) or proton therapy, androgen deprivation therapy, chemotherapy, immunotherapy, as well as combinations of these techniques. EBRT is an established technique to treat deep-seated tumours (like prostate cancer) that uses high energy photons to stop cancer cells from dividing and growing, slowing or stopping the tumour growth. There are different technical implementations of such RT treatments and the radiation oncologist, with the help of the medical physicist, recommend the most appropriate one on a case by case basis. In particular, the Intensity Modulated Radiation Therapy (IMRT) is a wide-spread technique used to cure earlier stages of prostate cancer, being associated with minimal rectal and bladder toxicity and hence high favourable risk-to-benefit ratios[3]. IMRT is a particular form of three-dimensional radiotherapy and uses advanced computerised inverse planning programs to calculate a highly conformal dose distribution in the target volume modulating the intensity of the radiation beams coming from different directions. Each beam is subdivided into multiple small beams, called segments, created with multileaf collimators without wedges, each with an independent intensity level, for irradiating tumours with irregularly shaped volumes. In this way it is possible to improve the tumour coverage with a better sparing of the surrounding healthy tissues.
The treatment planning proceeds in the following steps: the definition of the target volume, Planned Treatment Volume (PTV),

that accurately defines the area to be treated, and of the Organs at Risk (OAR), that identify the organs that have to be preserved from irradiation. Generally, for this purpose Computed Tomography (CT) images of the patient are acquired and used. Once the number and orientation of the beams is defined by the planner, the outcome (absorbed dose distribution) is optimised in terms of the tumour absorbed dose prescribed by the physician and the OARs dose constraints[4].

The beams arrangement, namely the number and direction of irradiation fields, is chosen to minimise the prescribed dose to the normal tissues placed along the beam path. The beams number is kept below nine to avoid long planning and treatment times that are not beneficial for the patient, and to reduce the amount of scattered radiation[5]. The beam intensities are varied to find a configuration that provides the best match with the desired plan and the resulting fluency distributions are converted into collimator leaf positions.

In order to minimise the damage to the OARs, IMRT requires multiple treatment sessions on different days allowing the normal tissues healing from the harmful effects of ionizing radiation that happens faster than for cancer tissues. The total number of fractions (treatments) depends on the type of cancer, size, location of the tumour, doses to normal structures, stage of tumour, and the patient's health. Usually, patients are treated once or twice a day for five days a week, for several weeks. In the conventional fractionation scheme for patients with intermediate-risk or high-risk localized prostate cancer, prostate cancer treatment with photons is based on 38 up to 40 fractions of 180-200 cGy each. However, nowadays the hypo-fractionation, i.e. reduction of the number of total fractions and increase of dose value for fraction ($>$ 225 cGy for fraction), is being considered while taking particular care in avoiding sub-lethal doses that could lead to a tumour radioresistence and/or recurrence.

One of the IMRT intrinsic limitations is related to how photons interact with the patient body: the absorbed dose peaks few mm after entering the patient body while, afterwards, it exponentially decreases irradiating the healthy tissues placed along the beam direction before or after the PTV. The type and severity of side effects that can be induced by such unwanted irradiation depend on the amount of absorbed dose and healthy tissues exposed. Most side effects are temporary and tolerable, whereas others may develop over months, or even years later. Examples are frequent urination, difficult or painful urination, blood in the urine, abdominal cramping, diarrhoea, rectal bleeding, rectal leaking, fatigue, sexual dysfunction, skin reactions, secondary cancers in the irradiated region.

Radiation-induced toxicities are a significant limiting factor to the RT efficacy: attempts to reduce the OAR absorbed dose while preserving the needed PTV irradiation will result in an fundamental improvement of this kind of therapy.

The specific interactions of charged particles with matter (resulting in the so-called Bragg Peak distribution) can help in sparing the OARs, while keeping the same PTV coverage[6,7]. This characteristic has been already exploited since twenty years in Particle Therapy (PT) which uses protons and carbon ion beams. However, an advanced and effective technology with dedicated facilities (acceleration lines, treatment rooms, gantry, etc.) is needed to treat with proton and carbon beams, resulting in a high cost per treatment. Furthermore, PT treatments suffer from the range uncertainties that are affecting the treatment plans: as protons and carbon ions are heavy charged particles, their ballistic precision results in a very high localisation of the absorbed dose deposition. Safety margins have to be introduced to account for uncertainties in the patient positioning, organs movement, changes in the patient morphology with respect to the imaging used to plan the treatment. Electrons, being much lighter, result in treatment plans that are much more robust against these types of range uncertainties, providing a safe irradiation minimising the need of dedicated safety factors.

VHEE beams have thus been explored as well as other charged particles, as they have enough energy to reach deep seated tumours. However, the photons and positrons produced along the path to the target make the obtained irradiation intrinsically less selective with respect to the one achievable using protons or carbon ions.

Comparing VHEE treatments with standard photon RT ones, the conformity of the former absorbed dose distribution is comparable with latter only at the expense of using a large number of electron fields (order of tens, at least) and a beam energy larger than 100 MeV. Both requests contributed, so far, to make the VHEE solution more expensive and technologically challenging for a clinical center with respect to IMRT or other photon-based RT solutions.

This landscape could change in the near future. Several pre-clinical studies recently claimed that the toxicity in healthy tissues related to tumour treatments can be significantly reduced (from 80% down to 60%), while keeping the same efficacy in cancer killing, if the dose rate is radically increased ($\sim$10 Gy/s, or even more) with respect to conventional treatments ($\sim$0.01 Gy/s). Such effect is known as the FLASH effect[8,9]. Recently the first patient affected by a highly resistant skin lymphoma was treated using the FLASH irradiation approach and low energy electron beam (40 MeV) with a promising result[10].

Hereinafter, the delivery of ultra high dose rate beams capable of inducing the FLASH effect reducing the damage undergone by healthy tissues will be referred to as FLASH radiotherapy (FLASH RT).

An intense research activity is ongoing trying to explore the translation of FLASH RT to the treatment of deep seated tumour using photons, protons and also VHEE. Nevertheless, the implementation of such high intensity beams still has to match significant technical issues.

While the electron beams (in particular the low energy ones, as used in Intra-Operative Radiation Therapy) have been already produced at FLASH intensities, the implementation of high current intensities in RT with photons is currently limited by technical aspects. As far as X-ray beams are concerned, the X-ray tube anode should meet the requirements of resisting to an enormous instantaneous power, necessary for FLASH RT applications[9], without melting or being destroyed. If instead few MeV external RT photons, produced from linear electron accelerators that already proved to be capable of reaching FLASH intensities, are considered the achievable intensity is limited by the photons production mechanism, occurring via the Bremsstrahlung effect, that greatly reduce the final beam intensity. Providing photon beams of the required intensity in a clinical centre environment with this technique is therefore a challenge that has yet to be addressed. Concerning protons, the technical challenge is currently the development of an ultra fast pencil beam scanning technique capable of fully covering the PTV volume at the high dose-rates needed by FLASH RT applications[11].

Even if the electron beams production with FLASH intensities seems more at hand with respect to the photon and proton cases, in the recent past the use of electrons to treat deep-seated tumours at standard RT intensities was not adopted. The absorbed dose distribution of electrons with energy lower or equal to 100 MeV, while using few irradiation fields, was not suitable to provide the proper PTV coverage with the prescribed absorbed dose, while sparing the adjacent OARs.

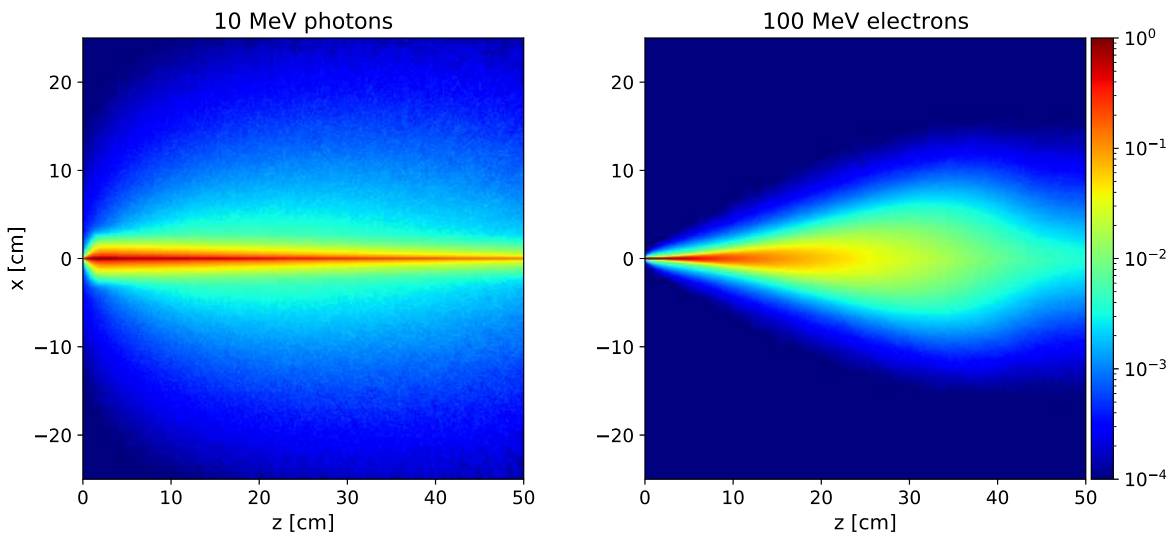

Figure 1. Absorbed dose distributions inside water generated from monochromatic beams of 10 MeV photons (Left) and 100 MeV electrons (Right).

The different interactions in matter of electrons and photons are the root cause of these different behaviours as it can be seen in Figure 1 that shows the energy deposition profile of photons with energy commonly used in RT ($\simeq$ 10 MeV) and electrons with an energy of 100 MeV that allows to reach deep seated tumours. The increased transverse beam size as a function of the penetration depth increases the difficulty in sparing the OARs, using configurations with few fields, when using electrons with respect to photons.

The specific details of such distributions (range, broadening) depend on the beam initial energy, but the main features are similar in the energy range of interest for therapeutic applications. While photons do not exhibit any 'peak' in the dose deposition but only an exponential decrease of the absorbed energy in water (Figure 1, left), electrons show a broad peak at a depth that is function of the initial energy (Figure 1, right). The mildly peaked longitudinal behaviour of the electron distribution seems to be better suited to be adapted on a target volume with respect to the photon ones (see Figure 2, left). As shown in Figure 2 (right) the electron lateral distribution widens as the beam penetrates into the patient, in particular for lower energy beams. This effect has to be accounted for when planning the single pencil beam (PB) direction used to ensure the PTV coverage: the broadening of an electron beam with starting Gaussian circular shape ($\sigma = 0.5$ cm) was therefore studied with respect to different penetration depth in water. This broadening, typical of light charged particles, strongly reduces the efficacy of collimators in adapting the shape of the absorbed dose distribution to the PTV in the transverse plane.

When the number of irradiation fields is increased and the electron energies are pushed well beyond 100 MeV, an electron treatment comparable or better than the standard RT one can be obtained [6,7]. However, such energies were not, so far, considered

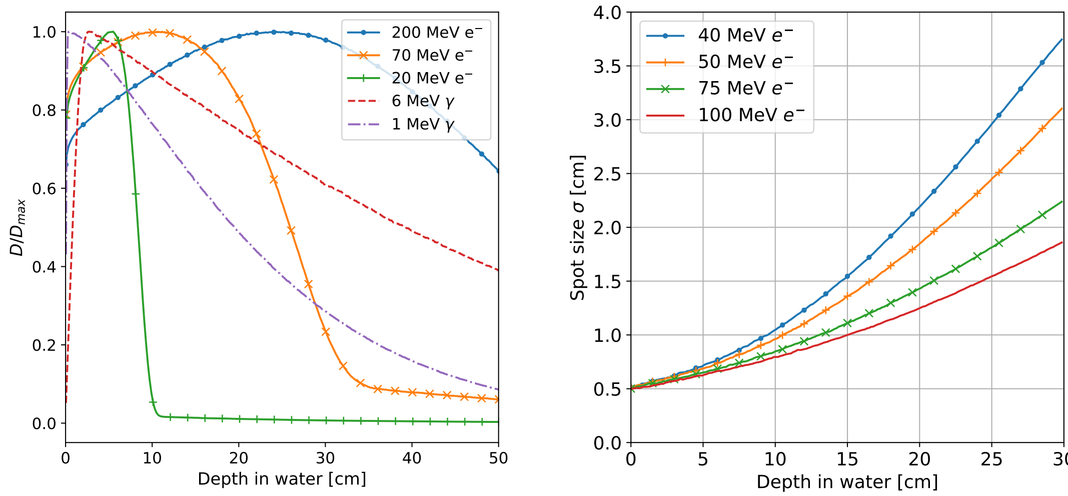

Figure 2. (Left) Absorbed dose depth distributions, normalised to their peak value, obtained from a MC simulation of mono-energetic electron and photon beams interacting with water. The simulated energies are in the range of interest for RT applications. (Right) MC simulation results for the lateral spread of VHEE beams of different energies as a function of their depth in water.

suitable to be used in clinical practice due to cost, complexity and space encumbrance. Some of these issues can nowadays be addressed thanks to the recent technological advances in the electrons acceleration field allowing to design electron beams with the required energy in small spaces (gradients up to 50 MeV/m, matching the requirements for implementation in clinical centres) and with very high intensities[12–14].

In this context, in this manuscript we explore the feasibility of a change of paradigm in the treatment of deep sited cancers focusing on the use of VHEE beams with energy limited in the 50-100 MeV energy range, taking into account the FLASH effect. Recently, a simulation has been carried out to study the feasibility of high energy (40 MeV) electrons FLASH irradiation of paediatric brain tumour with promising results[15]. In our manuscript, instead, we have investigated the treatment of prostate cancer.

We used a real prostate IMRT treatment to benchmark the FLASH VHEE performances. We performed a full MC simulation in which the interactions of the electrons with the patient tissues are accurately accounted for, assigning tissue morphology and density as from the reference clinical CT used for the IMRT treatment planning. The FLASH effect is modelled on the basis of the available experimental evidence introducing a Dose Modifying Factor (DMF) to account for the reduced damage due to the FLASH effect in human healthy tissues[16,17].

Some assumptions were made in this proof of concept study as, for example, the electron beams characteristics that depend on the accelerating system that does not exists yet. To be conservative in this first attempt focused on evaluating the impact of a VHEE FLASH RT, we assumed that: i) the VHEE AND IMRT irradiation fields are the same; ii) the VHEE beams have transverse size ($O \sim$ mm) and divergence ($O \sim$ mrad) that are typical of current linear accelerators achieving the needed energy and intensity; iii) the electron "pencil beam" paints each irradiation field like in active PB scanning techniques currently adopted in PT. This technical solution is much easier to implement for electron beams with respect to the proton case due to the very reduced magnetic rigidity of the VHEE beam. Finally, we compared the results of our FLASH VHEE model with the real case of a prostate cancer treatment with the reference IMRT case, showing the potential of the FLASH electron RT.

2 Results

To evaluate the feasibility of VHEE treatments implementing the FLASH effect, a comparison with a clinical case of a prostate tumour treated using IMRT with seven fields has been performed. The tumour (PTV) coverage and the dose absorbed by the OARs have been compared, carrying out a quantitative analysis using the Dose Volume Histograms (DVH), with the results obtained in a real IMRT case, from a patient treated at the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome.

The clinical target volume consists of a k-prostate without seminal vesicles. Patient had intermediate-risk prostate cancer and hence was treated with conventionally fractionated EBRT of 78 Gy in 39 fractions. A 6 MV-ONCOR Linear Accelerator, produced by Siemens, was used for the treatment.

Organ	dosimetric constraints
Target volume	78 Gy on at least 95%, $V_{95\%} > 95\%$, $V_{105\%} < 95\%$, never above 107%
Rectum	$V_{50} < 50\%$, $V_{60} < 35\%$, $V_{65} < 25\%$, $V_{70} < 20\%$, $V_{75} < 15\%$
Anus	$V_{30} < 50\%$
Bulbourethral Glands	$\overline{D} < 50$ Gy
Femurs	$\overline{D} < 52$ Gy, $V_{60} < 5\%$
Bladder	$\overline{D} < 65$ Gy, $V_{65} < 50\%$, $V_{70} < 35\%$, $V_{75} < 25\%$, $V_{80} < 15\%$

Table 1. Set of requirements that have to be satisfied by the planned treatment[18]. The checks are performed using the DVH information obtained using the Pinnacle software to evaluate the expected absorbed dose in the different patient tissues. $\overline{D}$ is the mean dose absorbed by a given organ or region. V_{XX} is the fraction of volume of a given OAR (or PTV) that absorb a given (XX Gy) amount of dose. The requirement V_{XX} <YY% should be read as: YY% of the referred organ or region must absorb less than XX Gy.

Figure 3 shows the patient treatment plan optimised by the medical physicists using the Pinnacle software (RTP System Version 16, https://pinnacle-software.com/) ensuring the proper PTV coverage and OARs sparing according to the dosimetric constraints. Three different views of the absorbed dose distribution, overlaid on the patient CT, are shown.

To evaluate if the optimised plan is adequate for the treatment, there are few key parameters that are considered. Organs have a particular architecture, adapted to their function, that has a strong impact on their tolerance to radiotherapy. Broadly, organs can be divided in two categories, parallel and serial organs. Parallel architecture is translated into the presence of functional, almost independent, sub-units: if one sub-unit is damaged by radiation, the organ will lose a fraction of its functional capacity, but the remaining sub-units will be sufficient to ensure a satisfactory global function, so that each organ will have a minimum volume to retain normal function. On the other hand, a serial organ shows functional sub-units, each of which is essential to maintain global functionality: the destruction of one sub-unit results in the complete breakdown of the global function, just as it happens for instance in the spinal cord, or in the small bowels. The treatment is considered adequate if some given dosimetric endpoints (associated to clinical side effects) are not exceeded. For parallel organs, dosimetric endpoints are expressed as the fraction of volume (V_{XX}) that absorbs a given amount of dose (XX Gy), whereas for serial organs the value of the maximum absorbed dose (and the associated volume) should be considered[18]. For the prostate treatment, all OARs in the pelvic region have a predominantly parallel architecture.

Table 1 shows the V_{XX} limits for all the OARs considered in the prostate treatment.

In order to verify the feasibility of a prostate treatment using VHEE FLASH RT, the patient CT information has been used as input for a MC simulation performed using the FLUKA[19,20] software.

The simulation has been used to compute the expected absorbed dose using VHEE of different energies (70 and 100 MeV) and implementing the normal tissues sparing in terms of a Dose Modifying Factor (DMF) as detailed in section 3.2. The dose

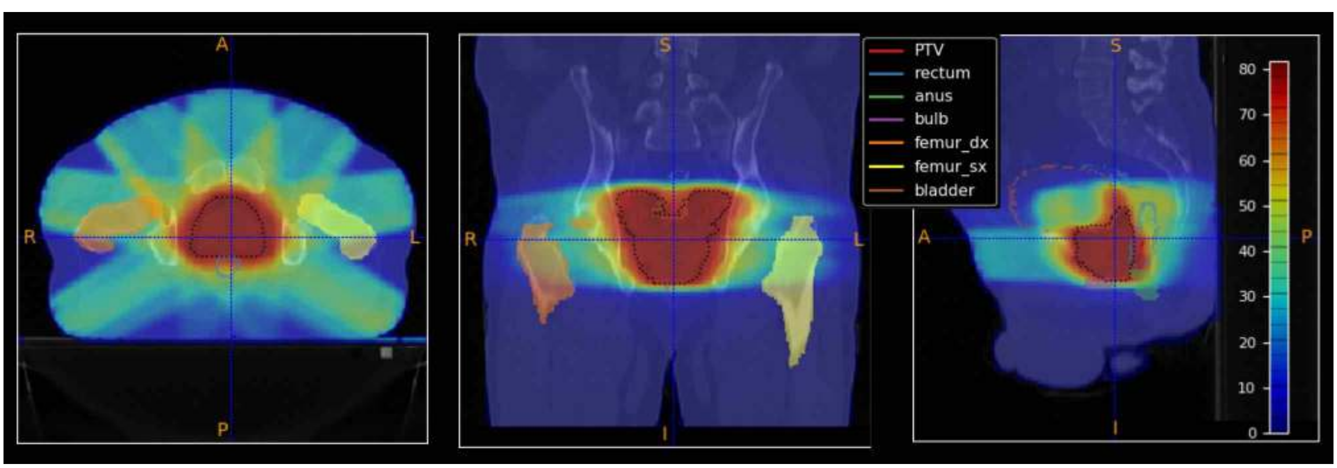

Figure 3. Patient CT overlapped with the dose map optimised using the Pinnacle TPS software for an IMRT treatment using 7 photon beams. The OARs are shown: the femurs in yellow and orange, the bladder surface in brown, the rectum surface in dark blue. The PTV is shown in red. The absorbed dose related to the full treatment (39 fractions of 2 Gy each) is shown.

maps and the relative DVH have been obtained for both energies and DMFs equal to 1, 0.8 and 0.6.

The treatment plan optimisation has been performed for the full set of energies and DMFs independently. The obtained absorbed dose maps have been used to compute the DVH and check the achievable PTV coverage. The results have been summarised in table 2.

The result of the treatment plan optimisation, obtained for an energy of 70 MeV and a DMF of 0.8 is shown in Figure 4. The same views and centering points have been chosen in order to ease the comparison with the results obtained with the conventional RT approach shown in Figure 3.

A more quantitative analysis that can be used to compare the results obtained with standard IMRT and electrons is provided by the study of the DVHs. Figure 5 shows the DVH relative to the dose maps shown respectively in Figures 3 and 4.

When comparing the results obtained with VHEE FLASH RT (figure 4, table 2) with the ones obtained with the conventional

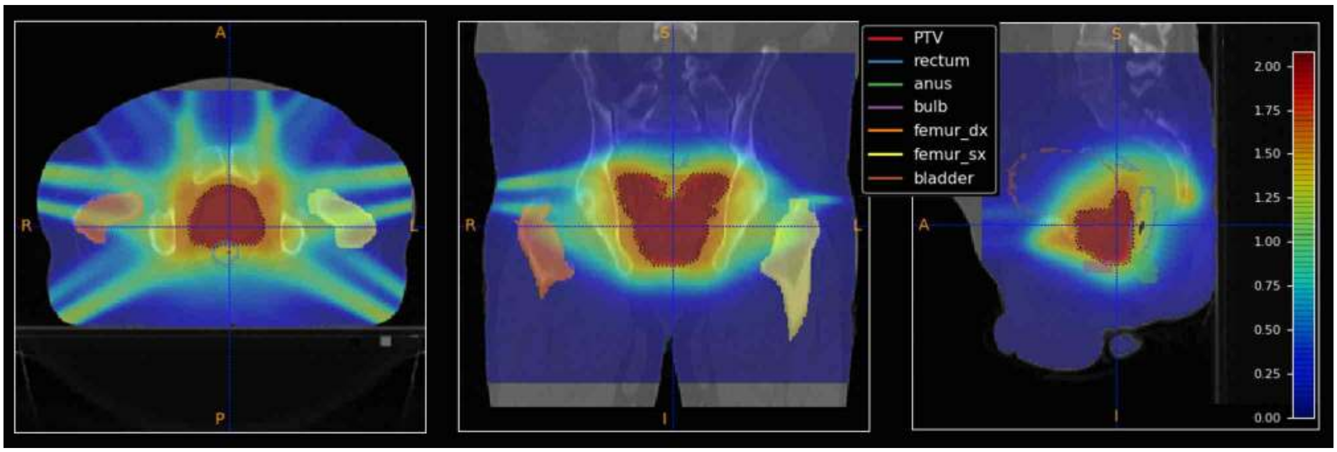

Figure 4. Patient CT overlapped with the dose map optimised using the output of a FLUKA simulation using VHEE of 70 MeV and a DMF of 0.8. The OARs are shown: the femurs in yellow and orange, the bladder surface in brown, the rectum surface in dark blue. The PTV is shown in red. The absorbed dose related to only one fraction (2 Gy) is shown.

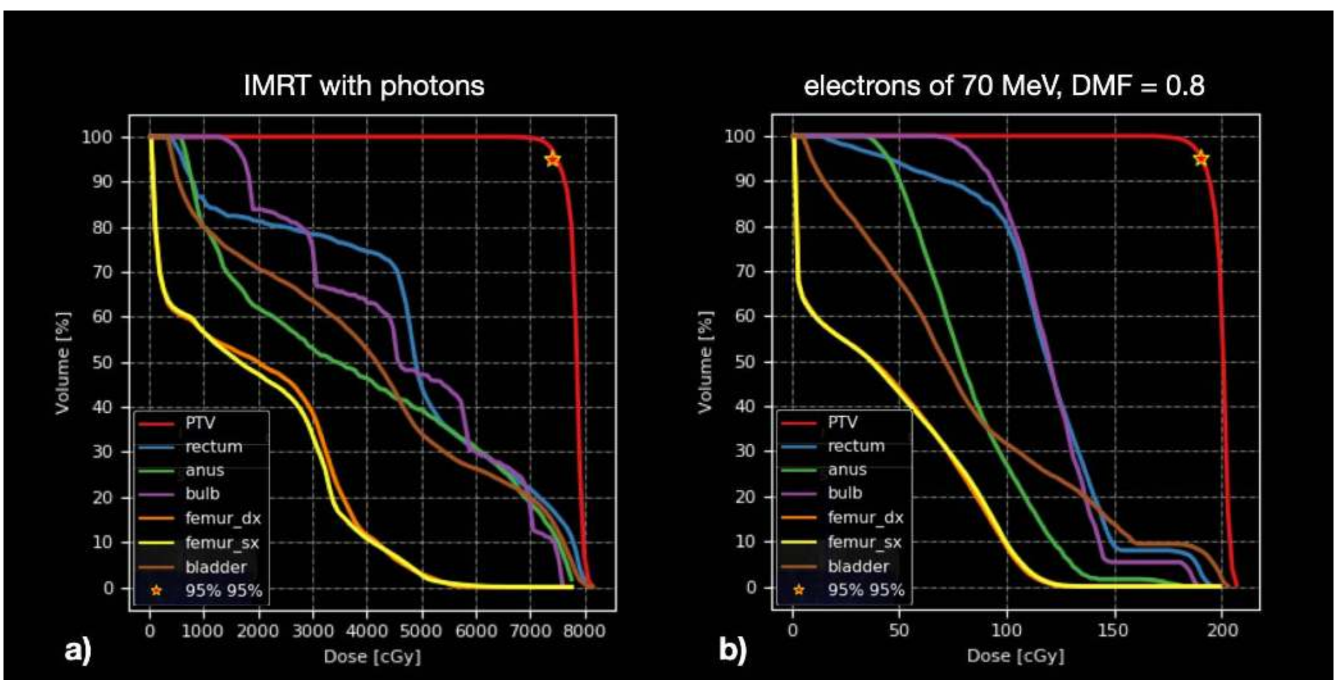

Figure 5. DVH histograms for the PTV and the OARs. Left: results obtained with photons (standard IMRT, 7 fields) for the 39 fractions foreseen in the patient treatment (78 Gy in total). Right: results obtained with electrons of 70 MeV and a DMF of 0.8 for a single fraction foreseen i the patient treatment (2 Gy).

E = 130 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	$V_{95\%}$ 95 % $V_{105\%}$ -	$V_{95\%}$ 99.6 % $V_{105\%}$ 0.15 %	$V_{95\%}$ 99.9 % $V_{105\%}$ 0.74 %
Rectum	V_{75} 1% V_{50} 27 %	V_{75} 4 % V_{50} 17 %	V_{75} 8 % V_{50} 8 %
Anus	V_{30} 36%	V_{30} 37%	V_{30} 39%
Bulbourethral Glands	$\overline{D}$ 47 Gy	$\overline{D}$ 50 Gy	$\overline{D}$ 47 Gy
Femurs	$\overline{D}$ 14 Gy	$\overline{D}$ 14 Gy	$\overline{D}$ 14 Gy
Bladder	$\overline{D}$ 35 Gy V_{70} 17% V_{65} 20%	$\overline{D}$ 36 Gy V_{70} 19% V_{65} 10%	$\overline{D}$ 33 Gy V_{70} 10% V_{65} 10%
E = 100 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	$V_{95\%}$ 97 % $V_{105\%}$ - %	$V_{95\%}$ 99.6 % $V_{105\%}$ 0.1 %	$V_{95\%}$ 99.9 % $V_{105\%}$ 0.9 %
Rectum	V_{75} 0.3% V_{50} 35 %	V_{75} 4 % V_{50} 21 %	V_{75} 8 % V_{50} 8 %
Anus	V_{30} 58%	V_{30} 55%	V_{30} 50%
Bulbourethral Glands	$\overline{D}$ 57 Gy	$\overline{D}$ 55 Gy	$\overline{D}$ 47 Gy
Femurs	$\overline{D}$ 18 Gy	$\overline{D}$ 17 Gy	$\overline{D}$ 15 Gy
Bladder	$\overline{D}$ 43 Gy V_{70} 20% V_{65} 23%	$\overline{D}$ 41 Gy V_{70} 9% V_{65} 9%	$\overline{D}$ 35 Gy V_{70} 9% V_{65} 9%
E = 70 MeV	DMF 1	DMF 0.8	DMF 0.6
Target volume	$V_{95\%}$ 92 % $V_{105\%}$ 0.3 %	$V_{95\%}$ 96.5 % $V_{105\%}$ 0.4 %	$V_{95\%}$ 99.9 % $V_{105\%}$ - %
Rectum	V_{75} 0.3 % V_{50} 71%	V_{75} 1 % V_{50} 36 %	V_{75} 8 % V_{50} 8 %
Anus	V_{30} 92%	V_{30} 53%	V_{30} 49%
Bulbourethral Glands	$\overline{D}$ 51 Gy	$\overline{D}$ 47 Gy	$\overline{D}$ 47 Gy
Femurs	$\overline{D}$ 18 Gy	$\overline{D}$ 16 Gy	$\overline{D}$ 14 Gy
Bladder	$\overline{D}$ 35 Gy V_{70} 13% V_{65} 18%	$\overline{D}$ 32 Gy V_{70} 9% V_{65} 9%	$\overline{D}$ 37 Gy V_{70} 9% V_{65} 9%

Table 2. Values of V_{XX} and $\overline{D}$ for the PTV and different organs obtained from a FLUKA MC simulation performed with electrons of different energies and different DMFs. Results for 130, 100, 70 MeV and DMFs 1, 0.8 and 0.6 respectively are reported. The values shown in red are the ones that do not satisfy the requirements shown in table 1.

RT approach (Figure 3), and by looking at the DVHs shown in Figure 5, it is possible to note that:

- electrons in the energy range considered in this manuscript (from 70 to 100 MeV) cannot be used to treat a prostate cancer using the IMRT irradiation scheme and only 7 fields at conventional dose rates. If the DMF is set to 1, implying that no FLASH effect is present, it is not possible to ensure the PTV full coverage. This conclusions is mainly driven by the difficulty in optimising the treatment and the PTV coverage while keeping the dose to the OARs to an acceptable level. A performance comparable with IMRT is only achievable increasing the number of fields, and the energy of the electrons.
- when a DMF of 0.8 is implemented, the organs sparing is guaranteed and the PTV coverage improves significantly. While at 70 MeV there is still a significant dose absorbed by the rectum and the anus, at higher energies both the OARs sparing and the PTV coverage is ensured. By increasing the number of fields or changing the entrance points it should be possible to further improve the OARs sparing even at 70 MeV.
- A DMF of 0.6 seems to open the game also to electrons of low energies resulting in a significantly better performance when compared to standard IMRT. In this case a 70 MeV electron beam could set the new standard for RT treatments. It is clear that if such a big FLASH effect is confirmed even for internal organs, the need of having beams of high energy decreases, simplifying the machine design process and its integration in the clinical centre treatment rooms environment.

Consistently with what already obtained elsewhere[7], without the FLASH effect the energy needed to deliver treatments that are of comparable efficacy with respect to IMRT or VMAT must be greater than 100 MeV. However, if the FLASH effect is taken into account, lower energies can be exploited opening a completely new landscape for the clinical implementation of VHEE treatments.

2.1 Prompt positron signal

Another result that was obtained studying the absorbed dose by the patient tissues in VHEE treatments concerns the production of positrons. High energy electron beams produce photons, and hence positrons, that mainly annihilate at rest, producing two back-to-back photons of 511 keV energy, that can be exploited as Positron Emission Tomography (PET) signal. The production point of these PET photons has been studied to check the correlation of their spatial emission distribution with the absorbed dose in the treated volume.

From an experimental point of view, the PET signal detection in FLASH RT poses a significant technical challenge, in particular in terms of data acquisition rate capability. However the presence and significance of the PET signal could drive the needed R&D efforts to exploit it for treatment control or monitoring applications. Figure 6 shows the correlation between the distribution of the absorbed dose in the PTV (in grey-scale) with, overlaid, the PET photons production. In the present work we report the existence of such correlation between the two distributions, leaving the quantitative modelling of such correlation to future papers.

3 Methods

The treatment plan optimisation, when using VHEE, and the calculation of the expected absorbed dose in the patient tissues have been performed by means of a dedicated MC simulation based on the patient Computed Tomography (CT). The results have been used as input for the calculation of the DVH. In the following we present in detail how the MC simulation was performed, how the FLASH effect was implemented and how the plan was optimised.

3.1 Absorbed Dose Evaluation

In this study we used a MC software (FLUKA[19,20]) to evaluate the VHEE dose release. FLUKA is widely used in medical applications and it is known to describe the electromagnetic interactions of photons and electrons with matter with very high precision.

To compute the absorbed dose per incoming particle FLUKA needs, as input, the CT information, the points from which the incoming radiation is originated, with respect to the CT position that identifies the patient, and the particle beam features (energy, beam spread) at the production point. The CT information has been provided by the Department of Radiotherapy, Policlinico Umberto I, "Sapienza" University of Rome.

When planning a treatment the details about the radiation production depend on the characteristics of the accelerator and beam delivery technologies. Currently there are a lot of independent attempts aiming at developing high intensity machines capable of delivering the needed electrons energy in the shortest possible distance. While 'S-band' accelerators achieve at most 10 MeV/m gradients, the advent of 'C-band' accelerating structures[12–14] will allow to reach the 50 MeV/m needed for the VHEE implementation in a clinical centre. However such machines are not yet available in clinical centres, and hence there is no available experimental input or measurement that can be used for the beam model simulation implementation. In the following some sound assumptions have been made, based on the current attempts of building C-band accelerators capable of providing the necessary intensity and energy while meeting the spatial occupancy constraints[21].

We have assumed that the accelerator will be capable of covering the energy range between 70 and 130 MeV, providing highly collimated beams with an angular aperture of few milliradians. We also assumed that the target volume will be actively scanned with thin electron PBs, all of the same energy, and that the accelerator will be capable of providing the required intensities. This assumption has been made to verify the VHEE FLASH RT feasibility using the simplest accelerator system and fastest (mono-energetic) delivery technique. Of course the possibility to let each PB energy to vary, as currently done in the active scanning system of PT, leaves very large margins of improvement in the treatment optimisation.

As a starting point for the study of the DVH, the actual IMRT treatment was mimicked as much as possible using for the VHEE the very same 7 different fields with the same entry points. Each field was built using pencil beams with a starting radius of 5 mm (RMS) and the initial direction of each PB belonging to a given field was computed to ensure that the convolution of

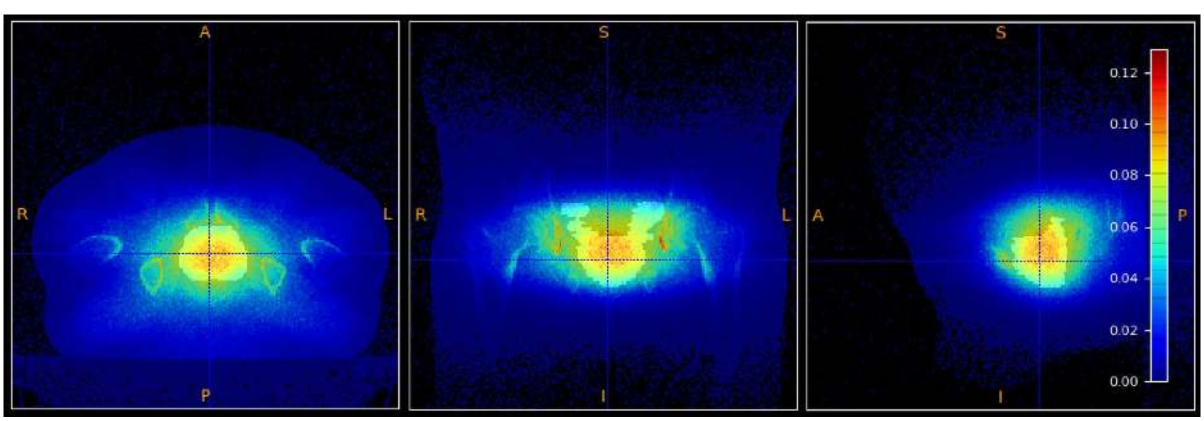

Figure 6. Absorbed dose in the PTV (shown in grey-scale) overlaid to the spatial emission distribution of prompt positrons.

all the PBs was properly covering the PTV. Figure 7 shows a slice of the CT with the prostate highlighted using black contour lines. The optimised absorbed dose distribution when using VHEE is superimposed to the CT together with a sketch illustrating the maximum aperture for each of the seven fields, in the same plane of the CT slice. Several PBs have been used to span and cover the aperture of each field in each slice: only the most external ones are shown in different colours.

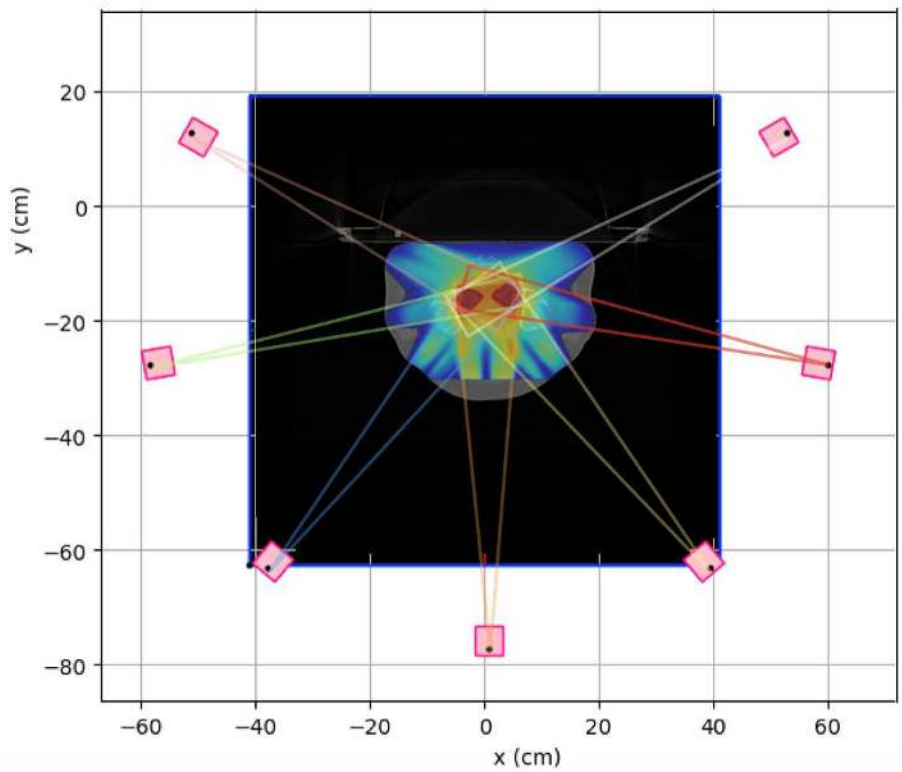

Figure 7. Pictorial view of the prostate target volume (highlighted using a black contour line) with superimposed the seven VHEE different fields. The lines in different colours are showing the maximum aperture for each field. Several PBs have been used to span and cover each field, in each slice: only the most external ones are shown.

To define the initial direction of each PB within its field we considered the PB broadening reported in Figure 2 (right). To guarantee a significant overlap of nearby PBs and to ensure a flat coverage of the PTV, the angular distance between two nearby PBs has been set to obtain a spacing of 0.5 cm in the transverse plane at the tumour iso-centre level.

Once the radiation type, its energy and origin point/directions are defined, the MC simulation is used to compute the absorbed dose inside the patient tissues and a simple model is used to account for the FLASH effect. The absorbed dose distributions are used as input to the algorithms that optimise the treatment plan. The optimisation is done with respect to the fluence of each PB, with the aim to match the PTV and OARs dose constraints derived from the medical prescriptions.

3.2 Dose Modifying Factor

Pre-clinical studies have shown how the FLASH effect allows to reduce the radiation-induced toxicity while maintaining an equivalent tumour control efficacy, enhancing the therapeutic value of VHEE beams. To quantify the reduced radiation-induced toxicity in normal tissues in the FLASH approach, when comparing to conventional RT, the DMF is introduced. The DMF expresses in a quantitative way the organs response change with respect to a reference condition. Report 30 (ICRU)[22] defines the DMF as the ratio of the dose under reference conditions (D_R) to that under the modified conditions (D_T) needed to produce the same level of effect: $DMF_{ICRU} = D_R/D_T$. In our case, the R and T conditions are respectively the conventional and FLASH RT irradiation modes.

Modifying factors are commonly derived from the comparison of dose-effect curves and the application of the Linear-Quadratic model on experimental data. However, *in vitro* studies did not elicit any significant difference between conventional and FLASH therapy, in both tumour and non-tumour cell lines[23].

Different results, instead, were obtained performing *in vivo* studies. There are already a significant number of papers that are documenting the evaluation of the healthy tissues 'sparing', in FLASH conditions, by looking at the reduced onset of after-treatment toxicities in different organs[16,17]. In these pre-clinical studies an experimental Dose Modifying Factor (DMF_{exp}), defined as the inverse of DMF_{ICRU}, was used to quantify the reduced damage that is induced in the healthy tissues when the dose is delivered in very short pulses (FLASH RT).

Abdominal, skin, lung and brain irradiation has been considered to demonstrate the preliminary evidence of significantly reduced radiation-induced toxicity after FLASH vs conventional irradiation. All DMF_{exp} values measured so far and the relative detailed references are summarised here[16,17]. In our study we have used the $DMF_{ICRU} = \frac{1}{DMF_{exp}}$ values from the aforementioned references.

We decided to divide the organs in groups based on their radiosensitivity and define accordingly the DMF_{ICRU} values of the organs that have not yet been studied. Considering both the abdominal and skin irradiation, we decided to assume $DMF_{ICRU} = 0.8$ as a reasonable value to describe the expected effect for all the abdominal and pelvic organs and $DMF_{ICRU} = 0.6$ for the skin. Concerning the PTV, we assumed that the FLASH irradiation maintains the same treatment efficacy as demonstrated in *in vivo* studies.

The absorbed dose in FLASH RT treatments has been computed using the different DMF_{ICRU} values for the PTV and the OARs by means of the following relation: $D_{biological} = DMF_{ICRU} \times D_{absorbed}$. The treatment plans have been optimised using, for all the OARs and normal tissues crossed by the beam, three sets of DMF values: 1, 0.8 and 0.6. The first one has been used in order to compare with standard VHEE results in conventional delivery mode, while the other two have been used to explore two possible ranges of OARs sparing: a conservative approach in which the DMF is set to 0.8 accordingly to the preliminary experimental findings and the best case scenario in which a DMF of 0.6 could be reached.

3.3 Treatment optimisation

Once the absorbed dose maps have been obtained for each PB in the treatment plan, the fluence of each PB is optimised to ensure the required PTV coverage while sparing the OARs. The implemented algorithm defines a cost function to be minimised that consists of two terms: the first one is used to constrain the absorbed dose inside the PTV to the goal value for each fraction (2 Gy, in our case) while the other term is related to the OARs and it is activated whenever a threshold in the OAR voxels is surpassed. In the latter case, the optimiser uses the threshold as goal inside the OAR, only for the over-threshold voxels. To take into account the huge volume difference (and hence number of voxels) between the PTV and the OARs or the normal tissues crossed by the beam, a voxel weighing in the cost function is implemented. Furthermore, to account for the different priorities when minimising the cost function, each PTV voxel has a weight equal to one while the OARs and normal tissue voxels enter the cost function multiplied by a weight equal to 10%. Such weighing strategy is the same as the one currently implemented in standard software tools used for TPS planning (e.g. Pinnacle). The output of the optimisation process is the absorbed dose map used to compute the DVHs and compare with the standard IMRT treatments optimised using the Pinnacle RTP software.

4 Discussion

The results obtained on a real case of prostate cancer demonstrate the potential for a paradigm change when treating deep seated tumours with external RT beams. The implementation of VHEE FLASH RT could allow the proper PTV coverage, while achieving a better OARs sparing, with the additional benefit of reducing the impact of range uncertainties (large in PT) in the treatment planning.

We have not addressed the technical challenges posed by the acceleration and the delivery of a FLASH VHEE RT beam in the standard hospital treatment room environment, but we have provided references to the recent technical development in the field of electron acceleration that makes VHEE FLASH integration in the clinical routine realistic in a near future.

In this manuscript we report indications that the VHEE FLASH RT could be capable of providing better results with respect to a real case of standard IMRT prostate treatment.

To put the comparison on solid grounds the irradiation geometry (7 fields) was not changed and it was assumed that the PTV could be covered using the same active scanning methods already implemented in PT treatments. The active scanning technical implementation would be much easier in the VHEE case due to the electrons lower magnetic rigidity when compared to protons or heavier ions. We also considered, conservatively, a treatment where all the pencil beams had the same energy. These assumptions lead unavoidably to a sub-optimal VHEE performance, but nevertheless it was possible to optimise a treatment plan in which the dose coverage of the PTV was ensured, matching the conventional RT prescriptions, while achieving a better sparing of the OARs in comparison to the delivered IMRT plan.

Some simplifications were also used in the modeling of the FLASH effect. In particular, a constant overall reduction factor between 0.6 and 1 has been applied to all the healthy tissues and OARs to mimic the FLASH sparing effect. However, this crude approximation indicates that even in case of a modest (20%) gain in the healthy tissues sparing, impressive results can be obtained.

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Figures

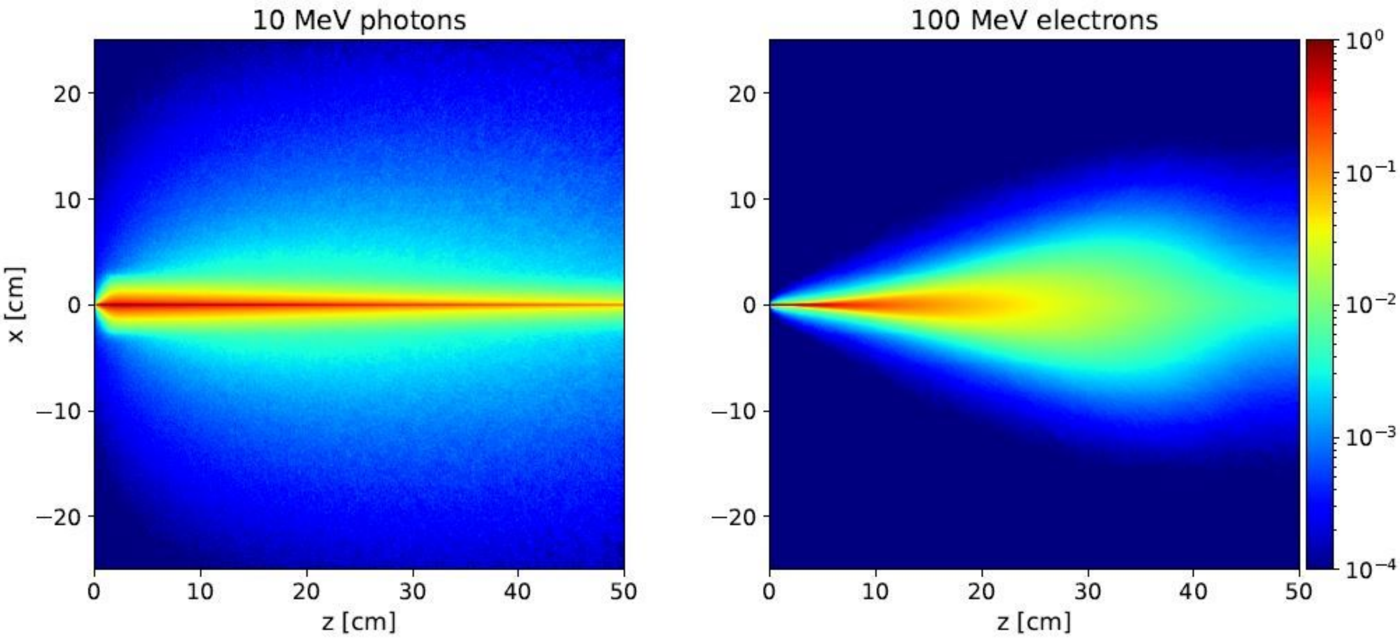

Figure 1

Absorbed dose distributions inside water generated from monochromatic beams of 10 MeV photons (Left) and 100 MeV electrons (Right).

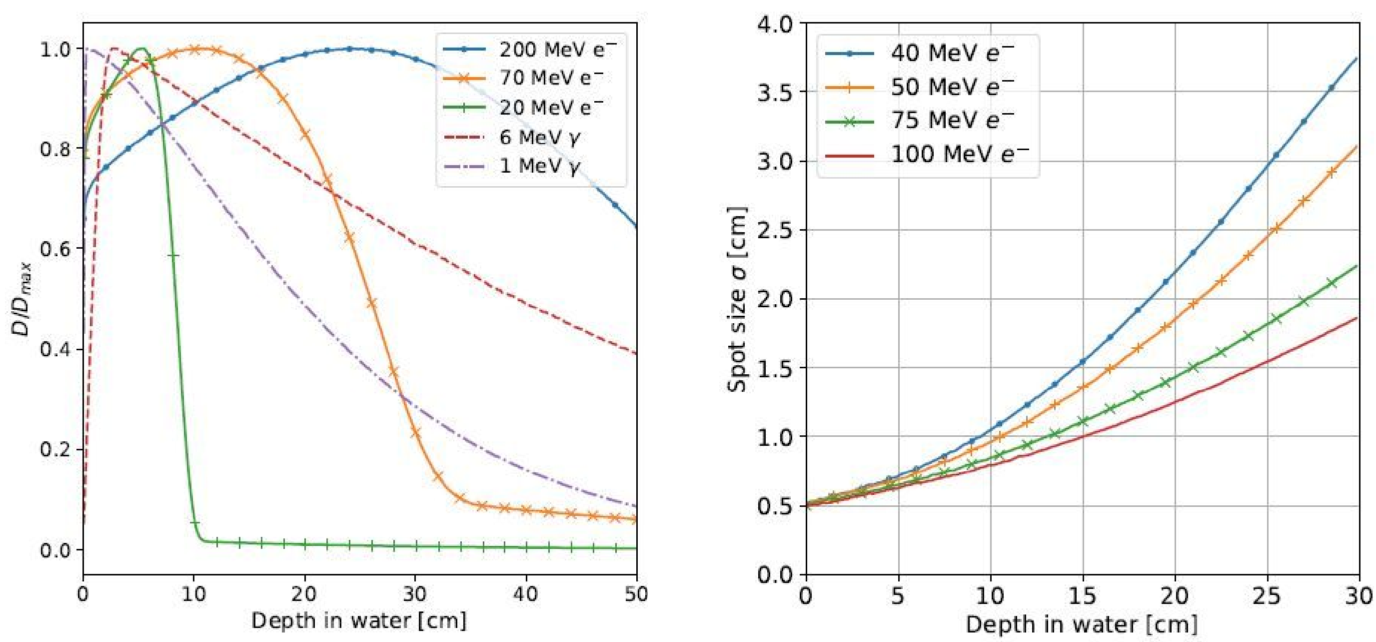

Figure 2

(Left) Absorbed dose depth distributions, normalised to their peak value, obtained from a MC simulation of mono-energetic electron and photon beams interacting with water. The simulated energies are in the range of interest for RT applications. (Right) MC simulation results for the lateral spread of VHEE beams of different energies as a function of their depth in water.

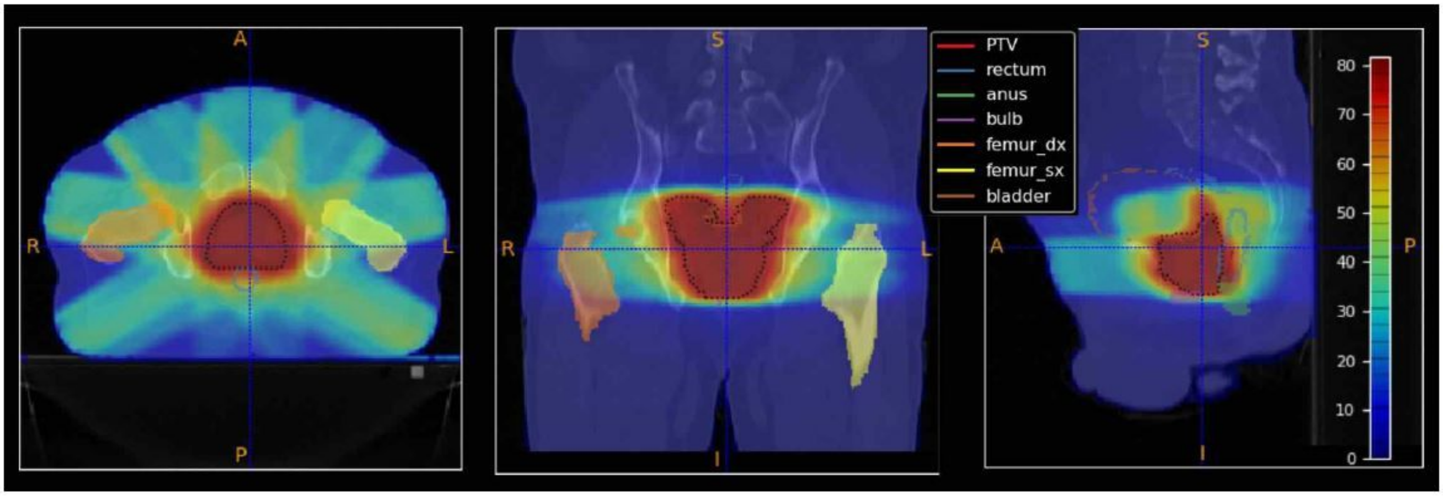

Figure 3

Patient CT overlapped with the dose map optimised using the Pinnacle TPS software for an IMRT treatment using 7 photon beams. 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. The absorbed dose related to the full treatment (39 fractions of 2 Gy each) is shown.

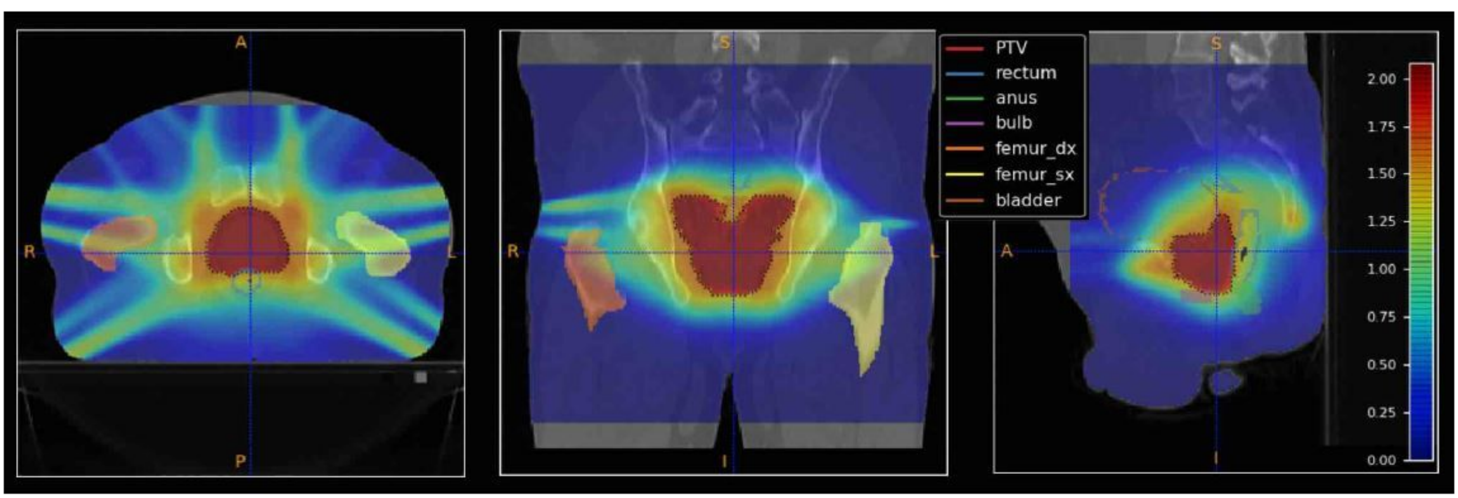

Figure 4

Patient CT overlapped with the dose map optimised using the output of a FLUKA simulation using VHEE of 70 MeV and a DMF of 0.8. 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. The absorbed dose related to only one fraction (2 Gy) is shown.

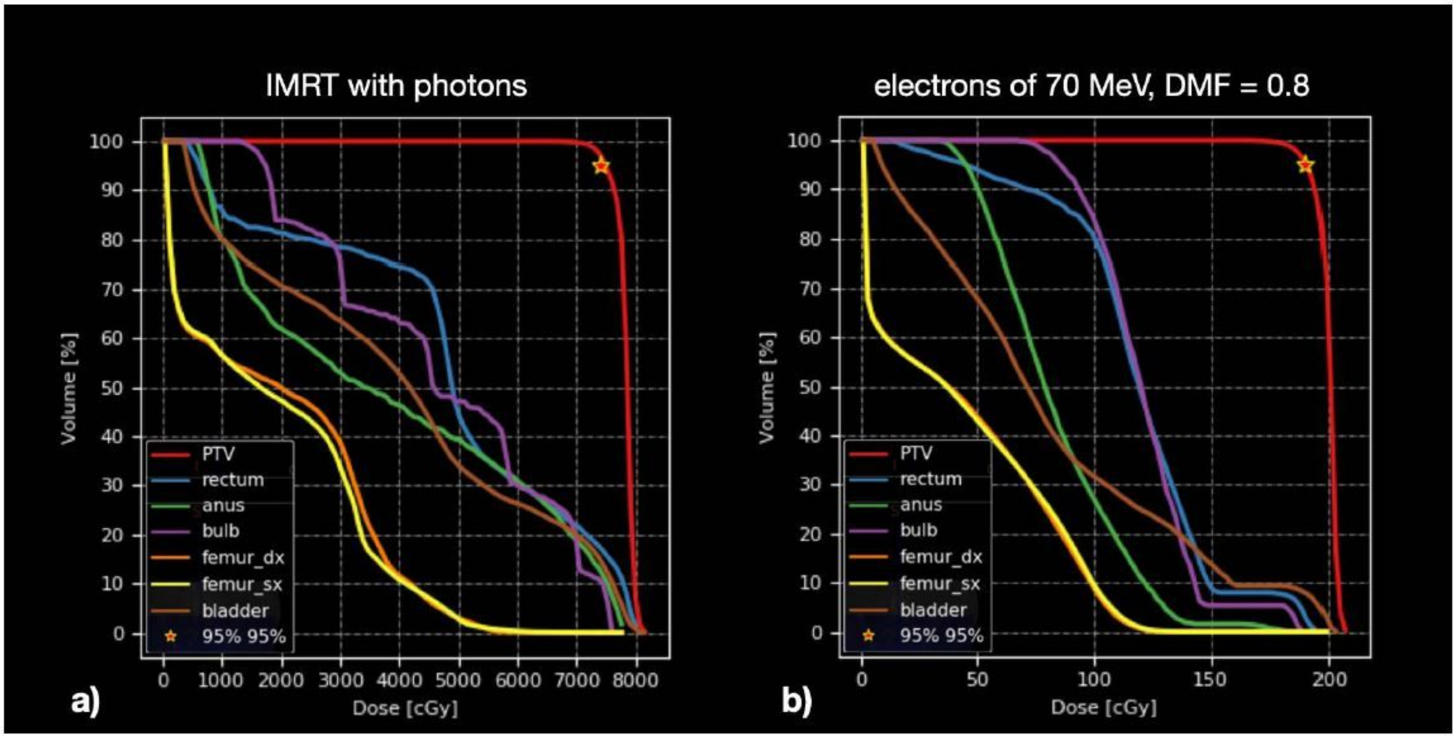

Figure 5

DVH histograms for the PTV and the OARs. Left: results obtained with photons (standard IMRT, 7 fields) for the 39 fractions foreseen in the patient treatment (78 Gy in total). Right: results obtained with electrons of 70 MeV and a DMF of 0.8 for a single fraction foreseen i the patient treatment (2 Gy).

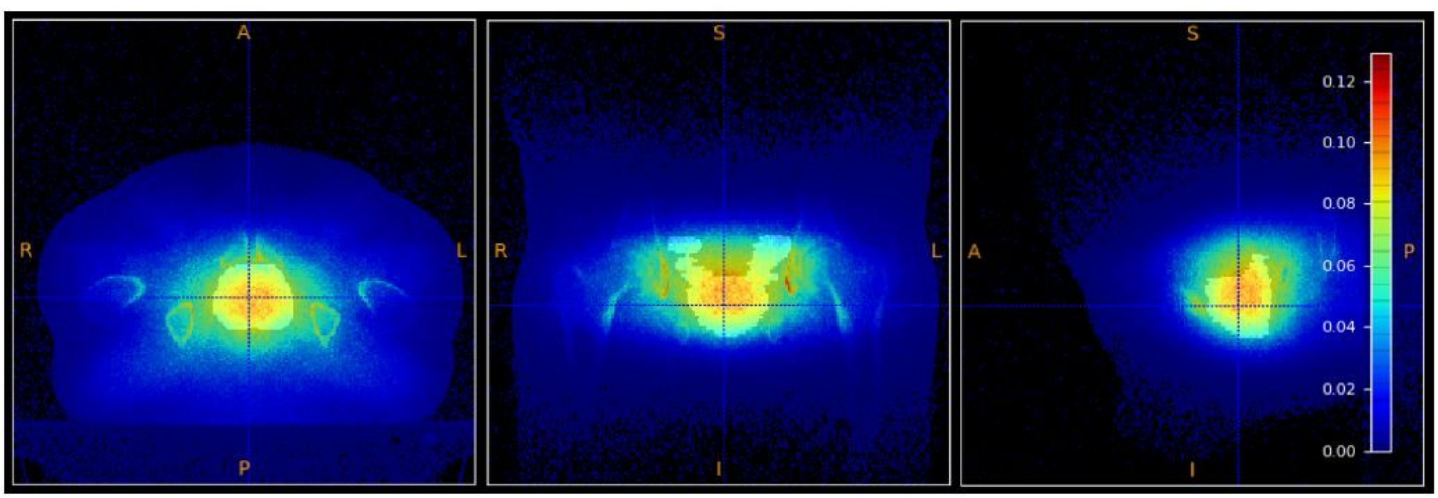

Figure 6

Absorbed dose in the PTV (shown in grey-scale) overlaid to the spatial emission distribution of prompt positrons. all the PBs was properly covering the PTV. Figure 7 shows a slice of the CT with the prostate highlighted using black contour lines. The optimised absorbed dose distribution when using VHEE is superimposed to the CT together with a sketch illustrating the maximum aperture for each of the seven fields, in the same plane of the CT slice. Several PBs have been used to span and cover the aperture of each field in each slice: only the most external ones are shown in different colours.

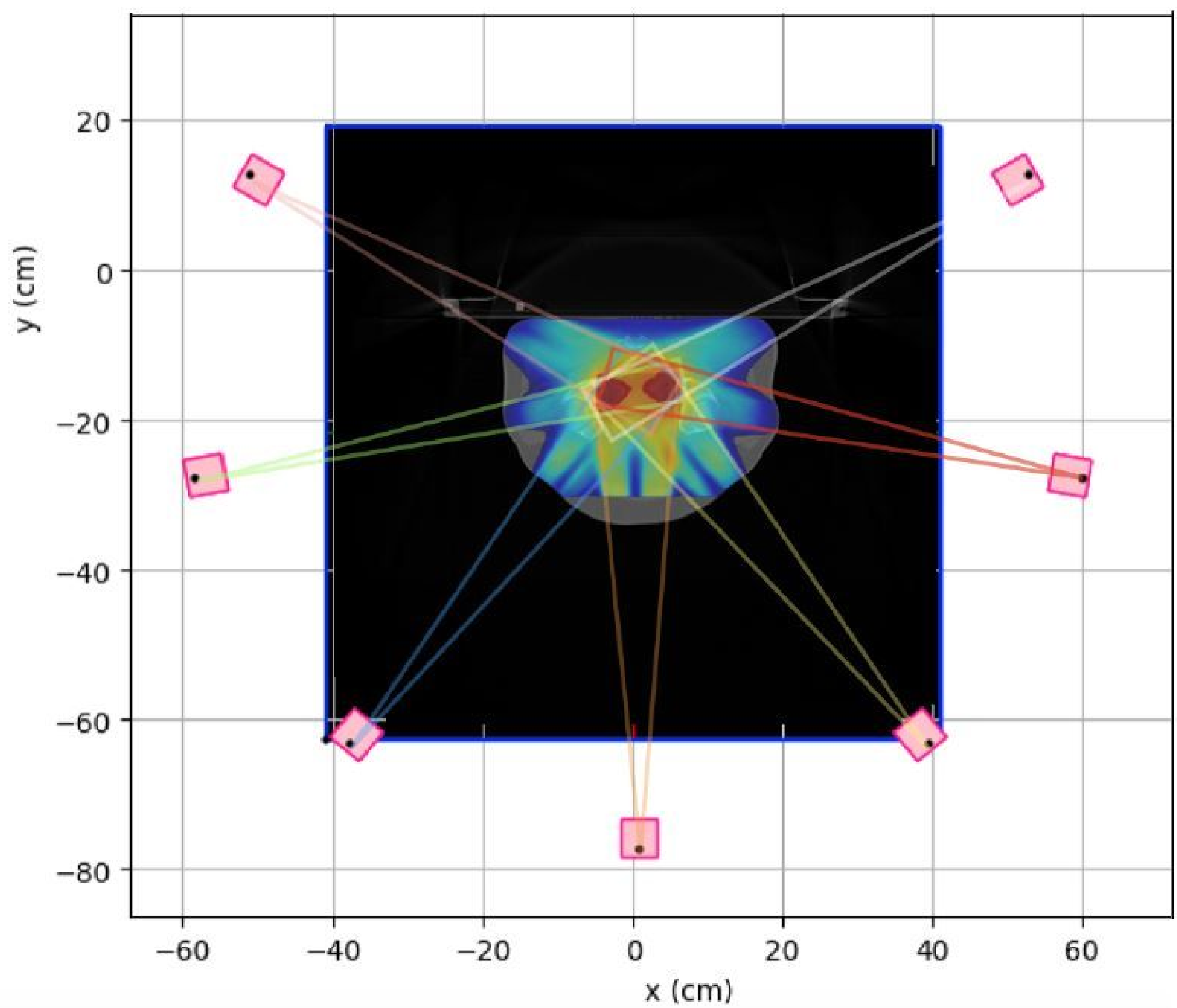

Figure 7

Pictorial view of the prostate target volume (highlighted using a black contour line) with superimposed the seven VHEE different fields. The lines in different colours are showing the maximum aperture for each field. Several PBs have been used to span and cover each field, in each slice: only the most external ones are shown.