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PhD in Accelerator Physics (XXXVII cycle)

**Development of a VHEE
accelerator in Sapienza for the
treatment of deep seated
tumors: planning and
radioprotection challenges of a
FLASH compact machine.**

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Introduction

Cancer treatment remains one of the foremost challenges in modern medicine, with a constant need for therapies that offer greater efficacy, reduced invasiveness, and improved patient quality of life. Among the leading treatment options, radiotherapy has evolved significantly, progressing from traditional X-rays to the use of charged particles such as protons and electrons. Despite these advancements, limitations remain that can affect therapeutic effectiveness and the patient experience due to side effects that often reduce their quality of life. The use of Very High Energy Electrons (VHEE) has been already explored in the past and shown promise in targeting deep-seated tumors. However, technical barriers, especially those related to accelerating VHEE beams in a compact design suitable for a clinical setting, have historically prevented VHEE therapy from being considered a real clinical alternative option to conventional Radio Therapy (RT) and Particle Therapy (PT). Today, breakthroughs in accelerator technology, particularly the development of C-band and X-band LINACs capable of achieving higher accelerating gradients, alongside the discovery of the FLASH effect (a method of delivering radiation at ultra-high dose rates that has the potential of significantly reducing the damage to healthy tissues), have re-fueled the interest in VHEE therapy. In this promising context, the SAFEST project (SApienza Flash Electron Source for radio-Therapy) at Sapienza University of Rome represents a pioneering initiative. SAFEST is dedicated to advancing VHEE therapy by developing a compact, hospital-compatible linear accelerator (LINAC) capable of producing VHEE beams at FLASH intensities. This accelerator is intended to serve both as a research tool and as a potential clinical asset, suitable for VHEE therapy trials with a focus on deep-seated tumors.

The objective of my Ph.D. research has been to develop, based on the design and delivery characteristics of the SAFEST LINAC, a Treatment Planning System (TPS) tailored to VHEE therapy, with specific capabilities for FLASH-mode treatment optimization. Chapter 1 provides an overview of the fundamentals of radiotherapy and examines the technological advancements that have improved treatment precision, discussing the state-of-the-art of conventional External Beam Radiotherapy (EBRT). Following a discussion on the physical principles underlying EBRT, the chapter explores the biological mechanisms that drive therapeutic success and introduces advanced techniques, including Intensity-Modulated Radiation Therapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). Chapter 2 delves into VHEE radiotherapy, analyzing its potential for treating deep-seated tumors and its synergy with the FLASH effect — a yet to be understood observed reduction of healthy tissue toxicity when treatments are delivered at ultra high dose rates (> 40 Gy/s). This chapter discusses the phenomenology of the FLASH effect, the parameters that define it, and the technical challenges involved in delivering VHEE beams in FLASH mode. Chapter 3 is dedicated to the SAFEST project itself. This chapter thoroughly details the accelerator's design parameters, the

structure of the radiofrequency cavities, and the beam dynamics solutions required to produce safe, high-quality VHEE beams for clinical applications. It also discusses the compact design strategies that make SAFEST suitable for a hospital setting, facilitating VHEE's clinical potential. Chapter 4 covers the development of a VHEE TPS for clinical applications. Here, the FRED software is presented as a dose-evaluation tool, alongside optimization algorithms such as simulated annealing methods designed to minimize radiation exposure to healthy tissues. This chapter also discusses TPS applications for various tumor types, with a particular focus on intracranial lesions and pancreatic tumors. As the task of planning a VHEE treatment is completely novel in the context of EBRT applications, I had to start from scratch, and borrow from similar RT techniques (e.g. IMRT) the knowledge about how to define the geometry of the VHEE irradiations. While RT and PT have decades of experience that are routinely applied to the tasks of treatment planning, the unique features of VHEE are just starting their exploring phase. One of the toughest challenges of my work has been starting to explore the uncharted land of VHEE planning. Chapter 5 addresses the radioprotection challenges inherent in implementing a VHEE LINAC for clinical use. It covers the production of secondary particles and the dispersed radiation fields surrounding the LINAC environment, proposing shielding solutions to ensure clinical safety in compliance with regulatory standards.

Chapter 1

Radiation Therapy: Physical bases and state-of-art

Cancer remains one of the most significant global health challenges, affecting millions of people each year. According to the World Health Organization [1], cancer is a leading cause of death worldwide, with nearly 10 million deaths in 2020 alone. The weight of cancer is immense, not only due to its high incidence and mortality rates but also because of the profound impact it has on patients, families, and healthcare systems. As the global population ages and lifestyle factors contribute to increasing cancer rates, the need for effective, accessible, and advanced treatment options is more crucial than ever. Radiation therapy is a cornerstone of modern oncological treatment, using the power of ionizing radiation to kill cancer cells while striving to preserve the integrity of surrounding healthy tissues. This therapeutic modality, which has evolved significantly since its inception over a century ago, now integrates advanced physical principles and cutting-edge technological innovations to enhance its efficacy and precision. The intersection of physics and medicine within radiation therapy not only underscores the complexity of its mechanisms but also highlights the continuous progress driven by scientific research and clinical advancements. This chapter delves into the fundamental physical bases of radiation therapy, elucidating the principles that govern the interaction of radiation with biological matter. It explores the types of radiation employed, including photons, electrons, and heavier charged particles, and their respective roles in clinical practice. The mechanisms of radiation energy deposition, dose distribution, and the resultant biological effects form the core of this discussion, providing a comprehensive understanding of how radiation achieves its therapeutic objectives. In addition to the foundational concepts, this chapter provides an examination of the current state of the art in radiation therapy.

1.1 External Beam Radiotherapy basics

External Beam Radiation Therapy (EBRT) is one of the most common and widely used methods of radiation therapy for treating cancer. It involves directing high-energy radiation beams at a tumor from outside the body. The goal of EBRT is to deliver a precise dose of radiation to the cancerous area while minimizing exposure to the surrounding healthy tissues. Before treatment begins, detailed planning is essential. This involves using imaging techniques such as CT scans, MRI, or PET scans to visualize the tumor's exact size, shape, and location. These images help

create a 3D model of the tumor and surrounding tissues, allowing to plan the precise delivery of radiation. During the simulation process, the patient is positioned in a way that can be consistently reproduced during each treatment session, often using custom molds or immobilization devices to ensure accuracy. The target area is marked on the skin or using temporary tattoos to guide the treatment. The patient lies on a treatment table, and the accelerator rotates around them, delivering radiation from multiple angles. This helps concentrate the radiation dose on the tumor while sparing healthy tissues. EBRT is usually given over several weeks, with patients receiving treatments once a day, five days a week. The total number of sessions depends on the type and stage of cancer, as well as the treatment goals. There are several advanced types of EBRT that enhance the precision and effectiveness of radiation delivery. 3D Conformal Radiation Therapy (3D-CRT) uses 3D imaging to target the tumor precisely, allowing for better dose distribution and reduced impact on healthy tissues. Intensity-Modulated Radiation Therapy (IMRT) takes this a step further by modulating the intensity of the radiation beams, which allows for even more precise dose delivery to the tumor while further minimizing exposure to healthy tissues. Volumetric Modulated Arc Therapy (VMAT) is similar to IMRT but delivers radiation in a continuous arc around the patient, making the treatment faster and potentially more effective. Stereotactic Body Radiotherapy (SBRT) delivers very high doses of radiation to small, well-defined tumors in fewer sessions and is often used for tumors in the lungs, liver, and other organs. Image- Guided Radiation Therapy (IGRT) uses imaging during treatment to ensure precise delivery of radiation, accounting for any movement of the tumor or patient. EBRT can be used to treat various types of cancer in different anatomical regions, including the prostate, breast, lung, pancreas, and head and neck. It can also be used after surgery to eliminate remaining cancer cells and reduce the risk of recurrence, or before surgery to shrink tumors, making them easier to remove. Its versatility also lies in the fact that it can be performed with different types of particles: photons, ions (protons, carbon ions, helium), and electrons. The various types of interactions between particles and matter will be explained in the following.

1.2 Biological parameters

Dose deposition

The absorbed dose D in tissue is defined as the mean energy deposited by ionizing radiation absorbed by a mass element dm :

$$D = \frac{d\bar{\epsilon}}{dm} \quad (1.1)$$

where $d\bar{\epsilon}$ is the mean amount of energy absorbed by the elementary piece of matter. The dose unit is the Gray ¹(labeled Gy).

The biological effect of dose on tissue results from the energy transfer to cellular components, primarily the DNA. The extent and type of damage depend on the particle's energy and its type, but the overarching outcome is the disruption of the cell's normal functions. In fact, radiation can cause direct or indirect DNA damage:

- Direct damage occurs when the radiation damages the DNA molecule, breaking the double-helix structure. This often results in double-strand breaks, which are difficult for the cell to repair.

¹One Gray is equal to an absorbed energy of one Joule in one kilogram of matter.

Such damage can hinder DNA replication, prevent the production of essential proteins, and ultimately lead to cell death (apoptosis);

- Indirect damage arises from the creation of free radicals, particularly when radiation interacts with water molecules in the cellular environment. These free radicals can cause single-strand breaks in the DNA, which are generally less severe and more likely to be repaired by the cell's natural mechanisms. However, when large amounts of free radicals are generated, especially in short time spans, they can overwhelm the repair systems and contribute to cell death.

The severity of biological effects depends not only on the total absorbed dose but also on the type of radiation and its energy (see Fig. 1.1). For example, heavy charged particles like protons and

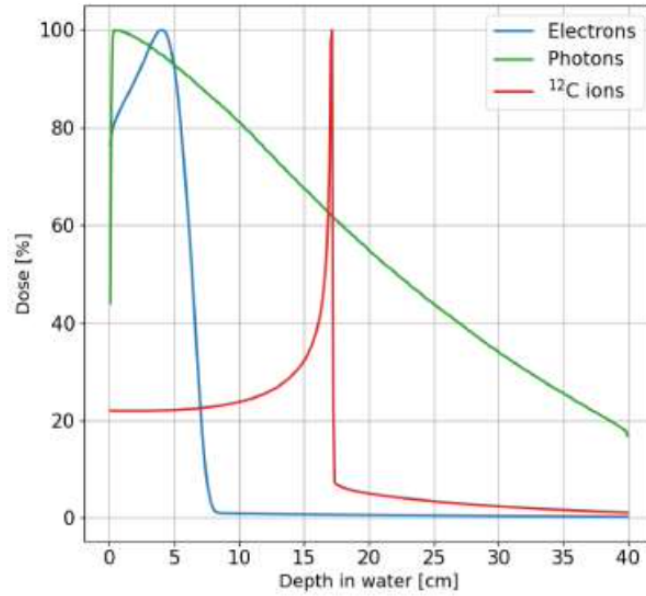


Figure 1.1: Dose profiles along the beam axis for 15 MeV electrons (blue line), 5 MeV photons (green line) and 300 MeV/u ^{12}C ions (red line) in a water phantom of $20 \times 20 \times 40 \text{ cm}^3$ obtained using FRED Monte Carlo software [28].

carbon ions are more likely to cause direct damage, which is harder to repair, whereas photons or electrons tend to produce a higher proportion of indirect damage. This effect is related to the particles Linear Energy Transfer (LET) and the ionisation density that will be introduced and detailed in the following. In clinical radiotherapy, this biological effect is crucial for targeting cancer cells while minimizing damage to surrounding healthy tissues. Understanding the balance between direct and indirect damage allows clinicians to design more effective treatment plans that exploit the unique properties of different radiation types to maximize tumor control while reducing side effects. In addition, also the *Dose equivalent* can be defined: it is the measure of the energy absorbed by the tissue normalized by the biological effect dependent on the specific nature of the radiation. In the SI, it is expressed in Sieverts (Sv) and it is calculated by multiplying the absorbed dose in Gy by the radiation weighting factor W_R which is dependent on the type and energy of the radiation. The dose equivalent serves as a widely used method for quantifying radiation exposure in medical contexts, evaluating the impact of common sources encountered in the clinical context including exposure to radioactive isotopes, diagnostic imaging and scattered secondary radiation within treatment rooms.

Linear Energy Transfer

Linear Energy Transfer (LET) is a measure of how much energy a ionizing particle transfers to the crossed material (typically tissue) per unit distance. It describes the density of energy deposition along the particle's path and is usually expressed in units of $keV/\mu m$. LET is defined as the local absorbed energy per unit path length:

$$LET = \frac{dE_{\Delta}}{dx} \quad (1.2)$$

where E_{Δ} is the total energy lost by the charged particle due to collisions in traversing a distance dx , minus the kinetic energies of electrons eventually released with energies in excess of Δ [34]. Particles with high LET (such as alpha particles, protons, or heavy ions) are characterised by a very high density of energy deposition, causing more severe biological damage, especially to DNA with a high probability of inducing cellular apoptosis through double strand breaks. On the other hand, low LET radiation (like X-rays, gamma rays, and electrons) distributes energy more sparsely, causing damage primarily through the generation of free radicals, which leads to a larger contribution from the indirect damage.

Relative Biological Effectiveness

To compare the biological damage caused by different types of ionizing radiation for the same absorbed dose, the Relative Biological Effectiveness (RBE) is introduced. RBE is defined as the ratio of the dose of a reference radiation (typically X-rays or γ -rays) to the dose of the radiation in question, i. e. ions, to produce an identical biological effect (isoeffect):

$$RBE_{iso} = \frac{D_X}{D_{ref}} \quad (1.3)$$

where D_{ref} is the dose needed to kill a given amount of cells for X-rays and D_X is the one needed to kill the same amount of cells for the particle under interest. The RBE is a complex quantity, depending on physical parameters (i.e., particle type, dose, LET, dose-rate) as well as on biological ones (i.e., tissue type, cell cycle phase, oxygenation level, end point). RBE can also vary with changes in dose fractionation, i.e., the way the total dose that is prescribed for a given treatment is delivered to the patient in smaller fractions, during several treatment sessions.

Oxygen Enhancement Ratio

The Oxygen Enhancement Ratio (OER) is a critical concept in radiobiology and radiotherapy, describing the impact of oxygenation on the biological effectiveness of ionizing radiation. It quantifies the increased sensitivity of cells to radiation in the presence of oxygen compared to hypoxic (oxygen-deficient) conditions. The OER is defined as the ratio of the radiation dose required to achieve a specific biological effect (e.g., cell death) under hypoxic conditions to the dose required under normoxic (oxygenated) conditions. Mathematically, it is expressed as:

$$OER = \frac{D_{hypoxic}}{D_{aerobic}} \quad (1.4)$$

Typically, OER values range from 2 to 3 for low-LET radiation (such as X-rays and gamma

rays), meaning that cells are two to three times more resistant to radiation damage when deprived of oxygen. This is because oxygen enhances the fixation of radiation-induced DNA damage (particularly double-strand breaks) by reacting with free radicals formed during radiation exposure, making the damage irreparable. In contrast, in the absence of oxygen, cells are more capable of repairing radiation-induced damage, thereby reducing the overall biological impact. For high-LET radiation (such as protons and carbon ions), the OER is significantly lower, often approaching 1, indicating that the effectiveness of high-LET radiation is less dependent on the oxygenation level of the tissue. This property makes particle therapy especially advantageous for treating hypoxic tumors, which are typically more resistant to conventional radiotherapy using low-LET radiation.

Radiobiological bases

Radiotherapy employs ionizing radiation to administer a dose adequate for effectively eradicating cancer cells. This dosage represents a delicate balance between achieving tumor control and minimizing severe complications in surrounding healthy tissues. The correlation between the radiation dose and the likelihood of a biological effect is commonly represented by a sigmoid curve, which illustrates the Tumor Control Probability (TCP) and the Normal Tissue Complication Probability (NTCP)[10]. As depicted in Fig. 1.2, both probabilities approach zero at lower doses and converge to one at higher doses; however, in some cases, the TCP may never reach unity with existing treatment modalities.

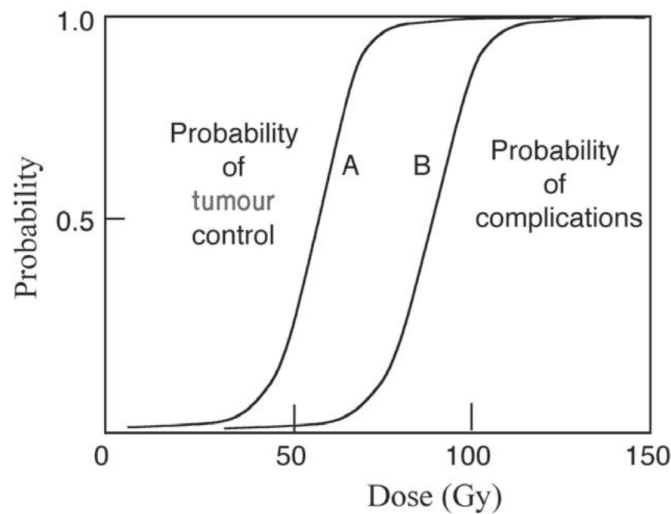


Figure 1.2: Representation of TCP in curve A and of NTCP in curve B [58].

The define therapeutic index serves as a quantitative measure of the relative safety of a radiation treatment, comparing TCP and NTCP values. The goal of optimizing radiotherapy protocols and exploring innovative techniques is to enhance this therapeutic index, facilitating improved tumor control while minimizing treatment-related toxicity. Several factors, including temporal and spatial fractionation of the radiation dose, as well as the integration of surgery, chemotherapy, and pharmacological interventions, can significantly impact this index, potentially making it more favorable.

1.3 Radiotherapy with photons

Radiotherapy with photons is the most common form of EBRT. Photons can penetrate deep into the body, depending on their energy, allowing them to target tumors located in various tissues and organs. In photon therapy, high-energy X-rays generated by bremsstrahlung radiation of electrons accelerated by a compact linear accelerator are used to deliver precise doses of radiation to the tumor. The history of photon radiotherapy dates back to the discovery of X-rays by Wilhelm Conrad Roentgen in 1895. This groundbreaking discovery opened the door to the medical use of radiation, and within a few years, the first therapeutic applications of X-rays were being explored. Early pioneers like Emil Grubbe and Marie Curie played a fundamental role in developing the initial techniques and understanding the potential of radiation for treating cancer. By the 1920s, radiation therapy had become a recognized medical discipline, with improvements in equipment and techniques continually enhancing its effectiveness. The introduction of the linear accelerator in the 1950s revolutionized photon therapy by providing a reliable and precise source of high-energy X-rays exploiting the bremsstrahlung interaction in high Z materials. This innovation allowed for deeper penetration and better targeting of tumors, significantly improving treatment outcomes. In the following decades, technological advancements such as computerized treatment planning, CT imaging, and the development of conformal radiation techniques like IMRT and VMAT further refined photon therapy. These innovations allowed for more accurate dose distribution (that will be introduced and detailed in the following), reduced side effects, and the ability to treat more complex tumors. This section aims to give a brief overview of the principles behind photon-based radiotherapy and highlight its lasting importance in modern cancer treatment.

1.3.1 Interactions of Photons with matter

In radiation therapy, understanding how photons interact with matter is essential for effectively targeting and destroying cancer cells. This chapter provides a brief overview of the key interactions between photons and matter, including:

- **Photoelectric effect:** when a photon interacts with an electron that is bound to an atom, it can transfer all its energy to the electron, ejecting it from the atom. This process is more likely to occur when the photon energy is 'low' (below 100 keV), in materials with high atomic numbers and is significant in diagnostic imaging and certain therapeutic contexts.
- **Rayleigh Scattering:** it is the elastic scattering of light by particles much smaller than the wavelength of the radiation. It occurs when the scattering particles are significantly smaller than the wavelength of the incoming radiation, typically less than 1/10th of the wavelength. The energy (and thus the wavelength) of the incoming photon is not changed, while the direction of the light does.
- **Compton Scattering:** in this interaction, a photon collides with a loosely bound outer electron, transferring part of its energy to the electron and scattering in a different direction. Compton scattering is the dominant interaction at the energy levels commonly used in radiation therapy, affecting dose distribution within tissues.

- **Pair Production:** when a high-energy photon (above 1.022 MeV) passes near the nucleus of an atom, it can be transformed into an electron-positron pair. This interaction becomes significant at very high photon energies and is relevant for advanced radiotherapy techniques.

These interactions (Fig. 1.3) collectively determine how energy is deposited in tissues, influencing both the effectiveness and side effects of photon-based radiotherapy. Understanding these mechanisms allows for precise treatment planning and optimization.

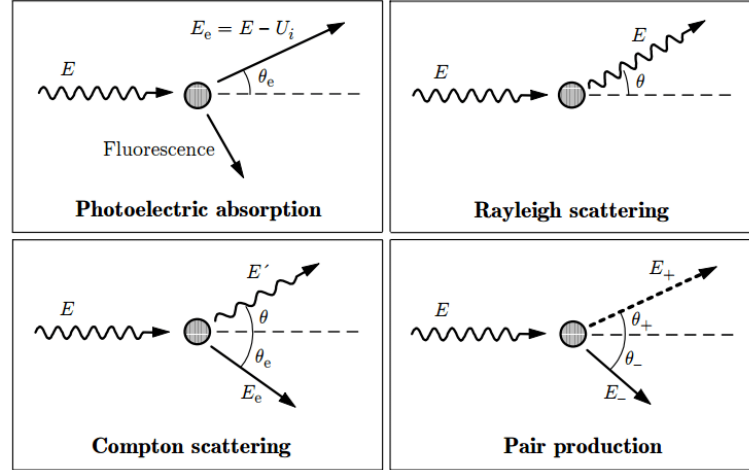


Figure 1.3: Basic interactions of photons in matter: Photoelectric effect, Rayleigh, Compton scattering and Pair Production.

Imagine a mono-energetic gamma ray beam being detected after passing through an absorber with variable thickness (Fig. 1.4). Each interaction process mentioned removes the gamma-ray photon from the beam, either through absorption or by scattering it away from the detector's direction. This results in a simple exponential attenuation of the gamma rays (Fig. 1.4).

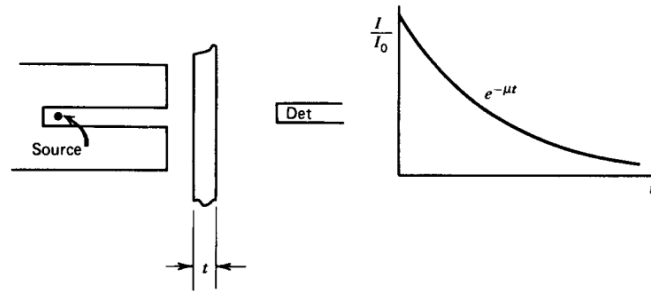


Figure 1.4: The exponential transmission curve for gamma rays measured under "good geometry" conditions [39].

The linear attenuation coefficient is defined as the sum of the probabilities of each process per unit path length, representing the likelihood that a gamma-ray photon will be removed from the beam:

$$\mu = \sigma(\text{Photoelectric}) + \sigma(\text{Rayleigh}) + \sigma(\text{Compton}) + \sigma(\text{Pair Production}) \quad (1.5)$$

The number of transmitted photons I is then given by:

$$I = I_0 e^{-\mu t} \quad (1.6)$$

where I_0 is the initial photons number. The mean free path λ is defined as the average distance traveled in the absorber before an interaction takes place and it is equal to the reciprocal of μ :

$$\lambda = \frac{\int_0^\infty x e^{-\mu x} dx}{\int_0^\infty e^{-\mu x} dx} = \frac{1}{\mu} \quad (1.7)$$

The relative significance of the three primary processes—photoelectric effect, Compton scattering, and pair production—across various absorber materials and gamma-ray energies is depicted in Fig. 1.5. The line on the left indicates the energy at which photoelectric absorption and Compton scattering are equally probable, based on the absorber's atomic number. The line on the right shows the energy at which Compton scattering and pair production have equal probabilities. This creates three distinct regions in the plot, each dominated by photoelectric absorption, Compton scattering, or pair production. The following sections provide a detailed description of the aforementioned four processes.

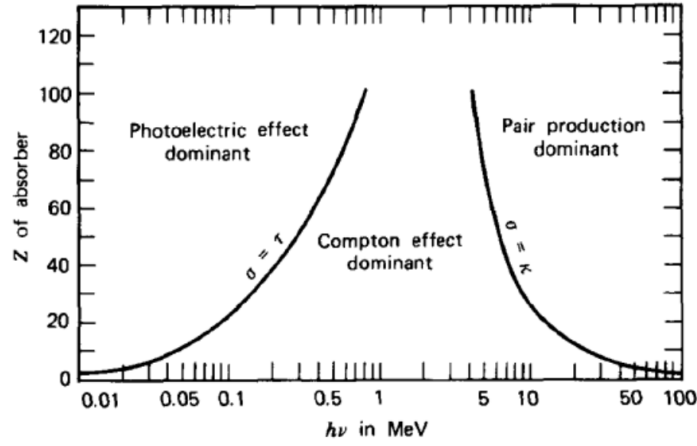


Figure 1.5: The relative importance of the three major types of gamma-ray interaction. The lines show the values of Z and $h\nu$ for which the interaction cross section of two neighboring effects are equal. [23]

Photoelectric effect

The photoelectric effect is the emission of electrons from a material caused by electromagnetic radiation. When an electron within some material absorbs the energy of a photon and acquires more energy than its binding energy, it is likely to be ejected [46]:



In 1905, Einstein proposed a theory of the photoelectric effect using a concept that light consists of tiny packets of energy known as photons or light quanta. Each packet carries energy $h\nu$ that is proportional to the frequency ν of the corresponding electromagnetic wave. The proportionality constant h has become known as the Planck constant. In the range of kinetic energies of the electrons that are removed from their varying atomic bindings by the absorption of a photon of energy $h\nu$, the highest kinetic energy E_{max} :

$$E_{max} = h\nu - W \quad (1.9)$$

where W is the minimum energy required to remove an electron from the surface of the material. The probability of the photoelectric effect interaction is measured by its cross σ , that is a function of the atomic number of the target atom Z and photon energy. In a crude approximation, for photon energies above the highest atomic binding energy, the cross section is given by:

$$\sigma \propto \frac{Z^4}{(h\nu)^3} \quad (1.10)$$

The photoelectric effect rapidly decreases in significance in the gamma-ray region of the spectrum, with increasing photon energy. It is also more likely from elements with high atomic number. Consequently, high- Z materials make good gamma-ray shields at low energies (below 100 keV), which is the principal reason why lead ($Z = 82$) is preferred and most widely used.

Compton scattering

Compton scattering is an inelastic process in which the photon loses energy and changes direction after colliding with an electron (see Fig. 1.3). The process can be described as:

$$\gamma + e^- \rightarrow \gamma' + e^- \quad (1.11)$$

During the collision with the initial photon with energy $h\nu$, a scattered photon is emitted at an angle θ with reduced energy $h\nu'$, and the electron recoils at angle ϕ with total energy E' . As a result of losing energy, the scattered photon has a longer wavelength (lower energy) than the incident photon. The change in wavelength $\Delta\lambda$ is given by the Compton equation:

$$\Delta\lambda = \lambda' - \lambda = \frac{h}{m_e c} (1 - \cos\theta) = \lambda_c (1 - \cos\theta) \quad (1.12)$$

The quantity $h/(m_e c)$, obtained for $\theta = 90^\circ$, is known as the *Compton wavelength*, and for the electrons is equal to 0.0243 Å. In addition, eq.1.12 shows that the change in photon wavelength is independent of the incident photon wavelength and is determined only by the photon scattering angle. The amount of energy transferred to the electron and the corresponding change in the photon's wavelength depend on the scattering angle θ . The larger the angle, the greater the energy transfer and the greater the wavelength shift. The energy of the scattered photon can be calculated using the Compton formula:

$$E' = \frac{E}{1 + \frac{E}{m_e c^2} (1 - \cos\theta)} \quad (1.13)$$

Fig. 1.6 presents the scattered photon energy E' as a function of the incident photon energy E for a variety of scattering angles.

The cross section for the energy-transfer during Compton scattering can be precisely computed with Quantum Electrodynamics; the differential expression $d\sigma/d\Omega$ is formally referred to as the *Klein-Nishina* formula:

$$\frac{d\sigma}{d\Omega} = \frac{r_e^2}{2} \frac{1}{[1 + \gamma(1 - \cos\theta)]^2} \left(1 + \cos^2\theta + \frac{\gamma^2(1 - \cos\theta)^2}{1 + \gamma(1 - \cos\theta)} \right) \quad (1.14)$$

where r_e is the classical electron radius and $\gamma = \frac{h\nu}{m_e c^2}$. The total cross section is calculated by

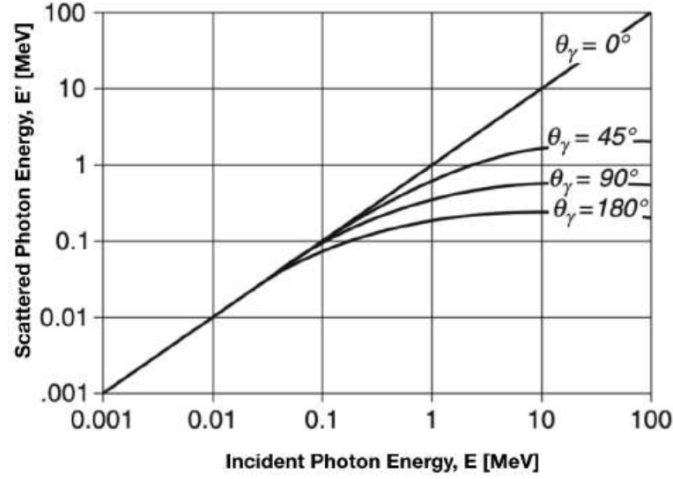


Figure 1.6: Compton (incoherent) scatter: scattered photon energy as a function of incident photon energy for different scattering angles [46]

integrating the differential cross section over the full solid angle (4π steradians): it is directly proportional to the number of electrons Z and inversely proportional to the photon energy:

$$\sigma \propto \frac{Z}{h\nu} \quad (1.15)$$

From the Klein-Nishina formula, it is also possible to derive several significant quantities: for example, the fraction of the total energy carried by the scattered photon, and the probability distribution of the energy transmitted to the recoil electron. The latter distribution presents a sharp drop at the maximum recoil energy which is known as the Compton edge, and is given by:

$$E_{max} = h\nu \left(\frac{2\gamma}{1 + 2\gamma} \right) \quad (1.16)$$

Pair Production

Pair production is a quantum phenomenon where a high-energy photon, typically a gamma ray, interacts with the electric field of a nucleus (or, less commonly, an electron) and transforms into an electron-positron pair. This process only occurs if the photon's energy exceeds a certain threshold, which corresponds to the combined rest mass energy of the electron and positron ($2m_e c^2 = 1.022 \text{ MeV}$). During the process, the photon does not simply vanish into matter. Instead, it interacts with the electric field of a nearby atomic nucleus (or an electron). The presence of the nucleus is crucial because it conserves momentum during the process, as photons cannot interact directly in empty space to produce particles without violating the conservation of momentum. After pair production, the positron will eventually lose energy through interactions with surrounding matter and, upon slowing down, annihilate with an electron. This annihilation produces two photons, each with an energy of 0.511 MeV , which are emitted in opposite directions to conserve momentum. The cross section of pair production, which quantifies the probability of the process occurring, depends on both the photon energy and the atomic number of the material's nucleus. The higher the photon energy and the atomic number, the more likely pair production becomes. The exact calculation of the pair production cross section is complex and involves quantum electrodynamics

but at energies much higher than the threshold, the cross section can be approximated with the following formula:

$$\sigma \propto Z^2 \ln\left(\frac{2E_\gamma}{m_e c^2}\right) \quad (1.17)$$

1.3.2 State-of-the-art: IMRT and VMAT techniques

In the evolving landscape of radiation therapy, precision and efficiency are paramount in the quest to maximize tumor control while minimizing damage to surrounding healthy tissue. Two of the most advanced and widely adopted techniques that have revolutionized this field are Intensity-Modulated Radiation Therapy and Volumetric Modulated Arc Therapy. Both techniques represent significant advancements over conventional radiotherapy methods, offering superior dose distribution, greater control over radiation delivery, and enhanced patient outcomes.

IMRT

IMRT is an advanced technique that delivers highly precise radiation to a patient through multiple small beamlets, each with its own distinct radiation intensity, or fluence [16]. IMRT is nowadays considered as the gold standard for tumor treatments; its major strength lies in its ability to treat complex tumor shapes, such as concave or ring-shaped volumes, with great precision. This is achieved through a process called *inverse planning*, in which the desired dose distribution is defined first, and then an algorithm calculates the optimal beamlet fluence to meet that goal. This approach is the natural evolution of older *forward planning* techniques, which relied on trial-and-error adjustments to match the dose prescription. In inverse planning, high-resolution imaging, particularly Computed Tomography (CT), plays a crucial role. The CT scan provides a detailed 3D map of the patient's tissue densities and energy attenuation coefficients, which is broken down into small volume elements, or voxels. Each voxel is assigned specific dose constraints depending on whether it belongs to the tumor or nearby critical structures. The planning process then involves configuring various beam parameters, such as the number of radiation fields and their angles relative to the gantry (the rotating arm of the treatment machine). A Treatment Planning System (TPS) calculates the optimal combination of fluences for each beamlet and determines the movement of the multi-leaf collimator (MLC), a device that shapes the radiation beams according to the planned direction and beamlet intensity. The MLC adjusts dynamically to modulate the radiation, ensuring that the dose precisely conforms to the target while sparing healthy tissue. This iterative process continues until all constraints are met, optimizing the treatment plan to align with clinical objectives. IMRT delivery can vary based on the capabilities of the linear accelerator. The fluence may be modulated through static beam segments, or dynamically, with real-time adjustments to the MLC during treatment. In some cases, the gantry also rotates while modulating the radiation dose, offering an additional level of control. All these machine characteristics are hence used in the treatment optimisation step.

VMAT

Volumetric Modulated Arc Therapy (VMAT) is an advanced evolution of IMRT, capable of delivering highly precise radiation doses to a tumor by continuously rotating the linear accelerator around the patient. Unlike traditional techniques, which deliver radiation from a few fixed angles, VMAT provides full 360° rotation while adjusting both the shape and intensity of the radiation beam

in real-time. This dynamic delivery enables efficient and accurate dose distributions over a shorter treatment time compared to other methods like IMRT. In VMAT, the radiation dose is modulated through simultaneous adjustments to several parameters: the speed of the gantry, the shape of the beam (using MLC), and the dose rate. The continuous arc motion allows for more complex dose distributions with fewer interruptions, enhancing the precision of the treatment. One of the key advantages of VMAT is its efficiency. The technique typically reduces treatment times because radiation is delivered in a single or few arcs, as opposed to multiple static fields. This results in a faster procedure while still maintaining high levels of precision and customization in the dose distribution. VMAT is particularly beneficial for treating tumors in challenging locations, where complex dose shaping and delivery are required.

1.4 Radiotherapy with charged particles

Radiotherapy with charged particles represents a cutting-edge approach in cancer treatment, offering distinct advantages over conventional photon-based therapies. Unlike X-rays or gamma rays, charged particles such as protons, carbon ions, and electrons have unique physical properties that allow for more precise energy deposition within the tumor, while reducing exposure to surrounding healthy tissues. This precision is particularly evident with protons and carbon ions due to the *Bragg Peak* phenomenon, where the particles release most of their energy at a specific depth, making them highly effective for treating tumors near critical structures. In addition to protons and carbon ions, the use of electrons in radiotherapy spans both low energy and very high energy electron (VHEE) treatments. Intraoperative electron radiation therapy (IOeRT) [1] [29], a low-energy electron technique, delivers a concentrated dose directly to the tumor bed during surgery, targeting residual cancer cells while sparing nearby organs. On the other end of the spectrum, VHEE offer promising potential for deeper-seated tumors, combining the flexibility of electron beams with increased penetration depth. In this chapter, the principles, technologies, and clinical applications of charged particle therapy across the energy spectrum and their growing role in modern radiotherapy will be explored.

1.4.1 Interactions of charged particle with matter

Energy loss

A heavy charged particle moving through matter primarily loses energy through ionization and excitation of atoms. As it passes, the charged particle exerts electromagnetic forces on atomic electrons, transferring energy to them. This energy may be enough to eject an electron from its atom, resulting in ionization (producing δ rays or knock-on electrons), or it may leave the atom in an excited (but non-ionized) state. A heavy charged particle transfers only a small fraction of its energy during each electronic collision. Because the particle's deflection in these collisions is minimal, it travels in a nearly straight line, losing energy continuously in small increments as it interacts with atomic electrons. Electrons and positrons also lose energy continuously as they move through matter, but they can transfer a significant portion of their energy in a single collision with an atomic electron, as they share the same mass. This leads to larger deflections during collisions. Due to their low mass, electrons are often scattered at large angles by atomic nuclei, and unlike heavy

charged particles, they do not follow straight paths through matter. Additionally, electrons can be sharply deflected by nuclei, leading to the emission of photons in a process known as *Bremsstrahlung*. Because of these distinct behaviors, the explanation of physical processes must differentiate between the interactions of heavy and light charged particles.

Radiotherapy of deep-seated tumors requires ion beam ranges in tissue of up to 30 cm corresponding to specific energies up to 220MeV/u for protons and helium ions, 430MeV/u for carbon ions, and $\sim 500\text{MeV/u}$ for oxygen ions with particle velocities $\beta = v/c \simeq 0.7$. At these velocities the energy loss rate dE/dx , also called *Stopping Power*, is dominated by inelastic collisions with the target electrons and can be well described by the *Bethe-Bloch* formula [81]:

$$-\frac{dE}{dx} = 2\pi N_A r_e^2 m_e c^2 \cdot \frac{Z^2}{\beta^2} \cdot \frac{Z_{tg} \rho_{tg}}{A_{tg}} \cdot \left[\ln\left(\frac{2m_e c^2 \beta^2 \gamma^2 W_{max}}{I^2}\right) - 2\beta^2 - 2\frac{C}{Z_{tg}} - \delta(\gamma) \right] \quad (1.18)$$

where:

- $N_A = 6.022 \cdot 10^{23}$ is the Avogadro number;
- Z_{tg} is the target atomic number;
- A_{tg} is the target mass number;
- ρ_{tg} is the target density;
- $m_e = 0.510998 \text{ MeV}$ is the electron mass;
- $c = 2.998 \text{ m/s}$ is the speed of light in the vacuum;
- $r_e = 2.817 \cdot 10^{-13} \text{ cm}$ is the classical electron radius;
- Z is the unitary charge of the projectile;
- β is the projectile velocity relative to c ;
- γ is the Lorentz factor of the projectile;
- $W_{max} = \frac{4m_e M E_k}{(m_e + M)^2}$ is the maximum energy transferable in a collision in which M is the incident particle mass and E_k its own initial kinetic energy;
- I is the ionization potential of the target and it has to be calculated using the quantum mechanical approach or empirically measured in experiments;
- C is the shell correction that must be included to consider electrons atomic binding;
- δ is the density correction, in fact, as the particle energy increases, its electric field flattens and extends, so that the distant-collision contribution increases as $\ln(\beta\gamma)$. However, real media become polarized, limiting the field extension and effectively truncating this part of the logarithmic rise.

Due to the $1/\beta^2$ dependence the energy loss increases with decreasing particle energy and increases also proportionally to the square of the charge Z of the impinging particle, see Fig.1.7. The minimum

weakly depends on the kind of incident particles, and particles that have the corresponding kinetic energy are called MIP (Minimum Ionizing Particles). For particles travelling in the same material, the stopping power varies due to their charge Z and the mass M , leading to different Bethe-Bloch curves. Bethe-Bloch formula expresses average energy losses, since it refers to processes of a stochastic

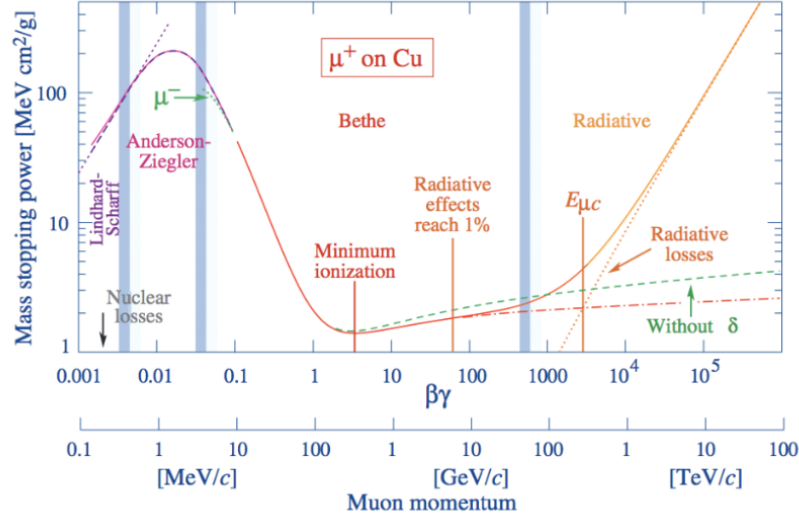


Figure 1.7: Total energy loss dE/dx for a muon in Copper target as a function of $\beta\gamma = p/Mc$. At low energy, the energy loss according to the Bethe-Bloch formula decreases approximately as $1/\beta^2$ with increasing energy. It reaches a minimum for approximately $\beta\gamma = 1$. For highly relativistic cases $\beta\gamma > 1$, the energy loss increases again, logarithmically due to the transversal component of the electric field. The dotted part on the right indicates the behavior of $-dE/dx$ for heavy charged particles, with or without density correction.

nature. In other words, if n identical particles having all the same initial energy pass through the same portion of material in general they undergo different energy losses. Bethe's formula provides the average value of these energy losses while the fluctuations around the average value are described by the Landau distribution.

Electron interactions in a medium differ from those of heavy charged particles because electrons interact with both the orbital electrons and the nuclei of the absorbing material: similar to heavy charged particles, beta particles —such as electrons and positrons— can excite and ionize atoms; however, these particles also radiate energy via *Bremsstrahlung*. All the charged particles, that have enough kinetic energy and experience an acceleration emit radiation in the same way. However, at the range of kinetic energies of interest for particle therapy applications, only electrons (the lighter ones) experience a significant contribution from this kind of energy loss. The total stopping power for beta particles is hence the sum of two components: the *collisional stopping power* and the *radiative stopping power*.

$$\left(\frac{dE}{dx}\right)_{\text{tot}}^{\pm} = \left(\frac{dE}{dx}\right)_{\text{col}}^{\pm} + \left(\frac{dE}{dx}\right)_{\text{rad}}^{\pm} \quad (1.19)$$

The *collisional stopping power* for beta particles differs from that of heavy charged particles due to two key factors: first, a beta particle can lose a large fraction of its energy in a single collision with an atomic electron, which has an equal mass; second, an electron is identical to the atomic electron it collides with, while a positron is its antiparticle. In quantum mechanics, this particle

identity implies that it is impossible to distinguish experimentally between the incident and the struck electron after a collision. Energy loss is defined so that the electron with lower post-collision energy is considered the struck particle. The *collisional stopping power* formula for electrons and positrons can be written as:

$$\left(-\frac{dE}{dx}\right)_{coll}^{\pm} = \frac{4\pi^2 Z^2 e^4 n}{mc^2 \beta^2} \left[\ln \frac{mc^2 \tau \sqrt{\tau+2}}{\sqrt{2}I} + F^{\pm}(\beta) \right] \quad (1.20)$$

where $\tau = T/mc^2$ with T the kinetic energy for the incident electron/positron and

$$\begin{cases} F^{-}(\beta) = \frac{1-\beta^2}{2} \left[1 + \frac{\tau^2}{8} - (2\tau+1)\ln 2 \right] \\ F^{+}(\beta) = \ln 2 - \frac{\beta^2}{24} \left[23 + \frac{14}{\tau+2} + \frac{10}{(\tau+2)^2} + \frac{4}{(\tau+2)^3} \right] \end{cases} \quad (1.21)$$

The other symbols in these equations, including I, were defined when introducing the Bethe-Bloch formula.

For heavy charged particles, the acceleration during atomic collisions is typically small, leading to a negligible contribution from *Bremsstrahlung*. In contrast, beta particles, having much smaller mass, can be strongly accelerated by the same electromagnetic forces. The *Bremsstrahlung* emission occurs when a beta particle is deflected in the electric field of a nucleus, or to a lesser degree, in the field of an atomic electron or by an external magnetic field. At high energies, this radiation is emitted predominantly in the direction of the particle's travel. The proximity of the beta particle to the nucleus and its energy determine the degree of screening and, consequently, the amount of energy lost. The maximum energy of a *Bremsstrahlung* photon is equal to the kinetic energy of the incoming particle, and the photon energy spectrum is roughly flat up to this maximum. The efficiency of *Bremsstrahlung* production varies with atomic number Z, scaling approximately as Z^2 . Thus, for a given beta particle energy, *Bremsstrahlung* losses are significantly higher in high-Z materials like lead compared to low-Z materials such as water. The ratio of radiative to collisional stopping power for an electron with total energy E (in MeV) in an element of atomic number Z can be approximated by the following formula:

$$\frac{(-dE/dx)_{rad}^{-}}{(-dE/dx)_{col}^{-}} = \frac{ZE}{800} \quad (1.22)$$

Range and range straggling

The *range* of a charged particle refers to the distance it travels in a material before coming to rest, which can be calculated by integrating the reciprocal of the stopping power over the particle's kinetic energy:

$$R(T) = \int_T^0 \left(-\frac{dE}{dx}\right)^{-1} dE \quad (1.23)$$

This provides an estimate of the path length based on the Continuous-Slowing-Down Approximation (CSDA), assuming that the energy loss occurs at a constant rate without accounting for fluctuations from atomic collisions. For particles like protons and carbon ions, the CSDA range offers a good approximation of the depth at which the Bragg peak occurs, as these particles generally travel in near-straight trajectories with limited dispersion. However, due to the statistical nature of energy loss processes, not all particles of the same type and initial energy follow identical paths. Some

particles will undergo more or fewer collisions, leading to variations in the energy loss and resulting in a statistical distribution of ranges around a mean value. This phenomenon, known as *range straggling*, occurs because the energy loss is not continuous but fluctuates, resulting in different final ranges for otherwise identical particles. In a first approximation, this distribution can be described as Gaussian, with the mean range corresponding to the midpoint of the range distribution curve (see Fig.1.8). For heavy charged particles, such as protons or alpha particles, the effects of multiple

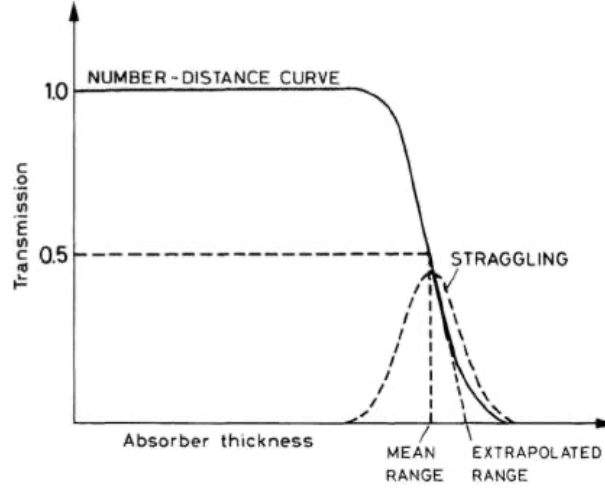


Figure 1.8: Typical range number-distance curve. The distribution of ranges is approximately Gaussian in form.[41]

Coulomb scattering are typically minimal, so their actual path lengths closely match the calculated straight-line range. However, electrons exhibit more pronounced fluctuations in energy loss due to both collisions and *Bremsstrahlung* radiation, and they are highly susceptible to scattering by atomic nuclei. This causes electrons to follow more tortuous paths, making the CSDA range less accurate for predicting their actual penetration depth. In such cases, the range calculated using the CSDA can differ by 20-400%, depending on the material and energy involved, and should be considered only a rough estimate for electrons. Overall, range straggling must be accounted for when considering the range of charged particles, as it influences both the accuracy of dose delivery in medical applications and the precision of experimental measurements.

Multiple Coulomb Scattering

Multiple Coulomb Scattering (MCS) describes the cumulative effect of many small-angle deflections experienced by a charged particle as it traverses a material. These deflections arise from repeated Coulomb interactions between the charged particle and atomic nuclei, each causing only a slight angular deviation, but together leading to significant path deviation. The RMS angle of deflection due to MCS is given by the Rossi formula:

$$\theta_{RMS} = \frac{13.6 \text{ MeV}}{\beta c p} z \sqrt{\frac{x}{X_0}} \left[1 + 0.038 \ln \left(\frac{x}{X_0} \right) \right] \quad (1.24)$$

where p is the particle momentum, x is the thickness of the material and X_0 is the radiation length of the material, which describes the mean distance over which a high-energy particle loses all but

$1/e$ of its energy due to *Bremsstrahlung*. This formula assumes that scattering occurs at small angles, which is valid for most materials and particle energies. The scattering angle increases with the thickness of the material and decreases with higher particle momentum. The effect of MCS is most pronounced for lighter particles, such as electrons, which are more easily deflected. This scattering causes particles to follow a zigzag path, deviating from a straight line. For heavy charged particles, such as protons or alpha particles, the deflections are generally small due to their higher mass and total kinetic energy, making their trajectories more linear. In addition to scattering angles, the lateral displacement of the particle due to MCS can also be quantified. The mean lateral displacement from the original trajectory after passing through a material of thickness x can be approximated as:

$$y_0 \sim \theta_{RMS} \cdot x \quad (1.25)$$

For clinical applications, especially in radiation therapy, understanding and accounting for MCS is crucial when delivering particle beams to precisely target a tumor. Multiple scattering affects the sharpness of the dose deposition, broadening the beam as it travels deeper into the tissue. While for heavy particles the impact is minimal, for lighter particles like electrons, the trajectory spread must be carefully considered during treatment planning.

1.4.2 Particle Therapy

As mentioned briefly before, Particle Therapy (PT) is a specialized form of radiation therapy that uses charged particles, such as protons or heavier ions (e.g., carbon ions), to treat cancer. Unlike conventional radiotherapy, which employs X-rays or gamma rays, particle therapy takes advantage of the unique physical properties of charged particles to deliver highly localized doses. As these particles traverse tissue, they lose energy gradually along their path, culminating in a sharp dose deposition, the Bragg peak. This peak occurs just before the particle comes to rest, as shown in Fig. 1.9, allowing clinicians to target the tumor with millimeter precision while sparing surrounding healthy tissues. The key benefit of particle therapy lies in its ability to modulate the energy of the

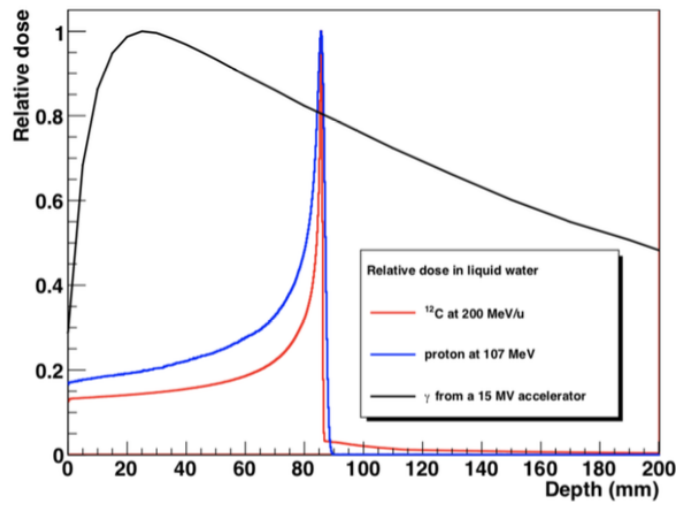


Figure 1.9: Evaluation of the relative dose with respect to the penetration depth in water for different particles, at different energies.

beam so that the Bragg peak is delivered directly within the tumor, resulting in minimal entrance

dose and virtually no exit dose. This precise targeting reduces the radiation exposure to adjacent organs and critical structures, making particle therapy especially advantageous for treating tumors near sensitive tissues such as the brain, spinal cord, or the eyes. Two main therapy approaches are currently available for therapeutic applications:

1. **Proton therapy**, which uses protons, is the most widely available form. Protons, being lighter, can be accelerated more easily and do not undergo fragmentation processes and are particularly effective for treating pediatric cancers and tumors that are resistant to conventional radiation.
2. **Heavy ion therapy**, such as carbon ion therapy, uses heavier particles that have a higher LET than protons. These ions deposit more energy per unit distance traveled, making them more effective for treating radioresistant tumors and hypoxic tumor regions that do not respond well to low-LET radiation like X-rays or protons. At the same time it should be noted that it requires more complex accelerating facilities and heavy projectiles undergo a fragmentation process that can lead to undesired dose tails behind the Bragg Peak that have to be carefully evaluated at the treatment planning stage.

In addition to its precision, PT offers a radiobiological advantage. Charged particles, especially heavier ions, are heavily ionising particles and are more effective in inducing the cell apoptosis, increasing the likelihood of irreparable damage and enhancing the therapeutic effect. This makes particle therapy an increasingly important tool for treating radioresistant tumors and lesions that are surrounded by healthy organs that are radiosensitive. The depth of penetration of heavy charged particles can be precisely controlled by adjusting their energy, allowing the Bragg peak precisely target different tumor depths. The achievable high level of dose conformity reduces the risk of side effects and long-term complications, which is particularly important for pediatric patients or for cancers located in critical anatomical regions. While particle therapy offers significant advantages, it is also associated with higher costs and the need for more complex infrastructure, such as large particle accelerators.

1.4.3 Radiotherapy with electrons

Electron beam therapy is usually applied to treatment of superficial or subcutaneous disease, exploiting the electrons interaction with matter distinct features that differentiate it from photon or proton beams. In fact, low energy electron beams have a sharp dose build-up followed by a rapid dose fall-off, which occurs over a few centimeters of tissue, as shown Fig. 1.10.

This rapid dose fall-off limits the dose delivered to deeper tissues, making it a key advantage when treating superficial lesions and avoiding damage to organs placed behind the target volume. The energy of the beam determines the maximum penetration depth and the shape of the depth-dose curve. Higher-energy electron beams (up to an energy of 20 MeV maximum) penetrate deeper but still maintain their characteristic fall-off. For instance, a 6 MeV electron beam might penetrate to a depth of around 3 cm, while a 15 MeV beam can reach up to 6 cm, with the most dose being delivered at the surface. Low energy electron beams have already found significant application in radiotherapy through techniques like Intra-Operative Electron Radiation Therapy, which effectively utilizes electrons to target tumors during surgery.

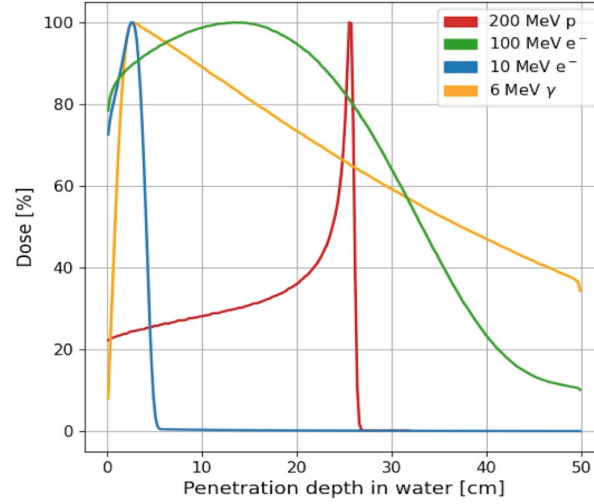


Figure 1.10: Absorbed dose depth distributions, normalised to their peak value, obtained from a MC simulation using the FRED software, of mono-energetic electron, proton and photon beams interacting with water. The simulated energies are in the range of interest for RT applications.

IOeRT technique

Intra-Operative Electron Radiation Therapy is the most commonly used technique in clinical applications involving electron beams. It delivers a precise, high dose of ionizing radiation (typically 15-25 Gy) to the tumor or tumor bed during surgery, aiming to eradicate any microscopic residual tumor cells that may remain after the surgical removal, thereby reducing the risk of local recurrence [7]. In cases where tumor removal is not feasible, IOeRT can also be used to treat the target volume to reduce the tumor size and allow for the consequent surgery whenever it is possible. The surgical setting provides direct access to tissues that have to be treated, enabling clear visualization of the target area and allowing surgeons to physically separate normal tissues from the target volume. This setup maximizes the radiation dose delivered to the target while sparing surrounding healthy tissues. IOeRT's ability to deliver highly conformal doses enables the use of large single-fraction treatments, with the protection of healthy tissues and Organs at Risk (OARs) ensured, whenever needed, through mechanical displacement and/or intraoperative shielding.

In the following chapter, I will introduce and review in detail the possible clinical applications of electrons of very high energies (above 50 MeV). While such projectiles were explored in the past, they were never considered a real interesting alternative to the use of photons and protons in radiotherapy for several reasons. In the following chapter I will discuss the known limitations of a VHEE based approach and the reasons behind the recent renewed interest in this type of therapy.

Chapter 2

Very High Energy Electron radiotherapy

The currently available electron beam energies in radiation therapy (4-30 MeV) are limiting their clinical potential, as these beams primarily deposit their energy in superficial tissue layers, making them unsuitable for treating deep seated tumours. Additionally, as the electrons approach their range limit, they exhibit considerable spatial spreading, which compromises the precision and conformality of their dose distributions. The potential for treating deeper tumors with the use of higher energy electrons (30-50 MeV) has been already investigated in the past [38], exploring basic electromagnetic scanning of these beams, demonstrating its utility in specific cases. However, the elementary beams used in this scanning approach were so widely dispersed that their diameter at the patient's surface spanned several centimeters, allowing only rudimentary intensity modulations, such as the use of beam wedges. The limitations in dose delivery with electron beams in the 30-50 MeV range suggest that they are not versatile enough for broad applications in external beam radiotherapy, particularly in techniques like IMRT. Therefore, to achieve adequate penetration for treating tumors at any depth in the body, it becomes necessary to consider very high energy electrons (50-250 MeV). Very High Energy Electron (VHEE) radiotherapy offers significant potential for treating deep-seated tumors with improved ballistic properties compared to both conventional low-energy electrons and photon beams, making them an attractive option for a wider range of clinical applications.

2.1 VHEE proposal

Despite earlier preliminary attempts, the use of VHEE in the 50 to 250 MeV range for radiotherapy was rigorously proposed and studied in the early 2000s. Initial studies [20] [57] [59], employing Monte Carlo simulations, demonstrated that electrons in the 150 to 250 MeV range were capable of reaching deep-seated tumors within patients (see Fig. 2.1).

The penetration capability of VHEE beams has been demonstrated to be sufficient, with effectiveness depending largely on the beam configuration, whether it is a single field, parallel opposed, or orthogonal. In addition, the depth of maximum dose is strongly influenced by the geometrical size of the beam: Fig. 2.2 helps visualizing the reduction of the dose lateral spread by means of an increased field energy.

As electron beams penetrate deeper into tissue, their dose distribution tends to widen, particularly at lower energies, but this broadening becomes comparable with the one actually experienced in conventional radiotherapy when beam energy exceeds 100 MeV. Historically, such high energies were

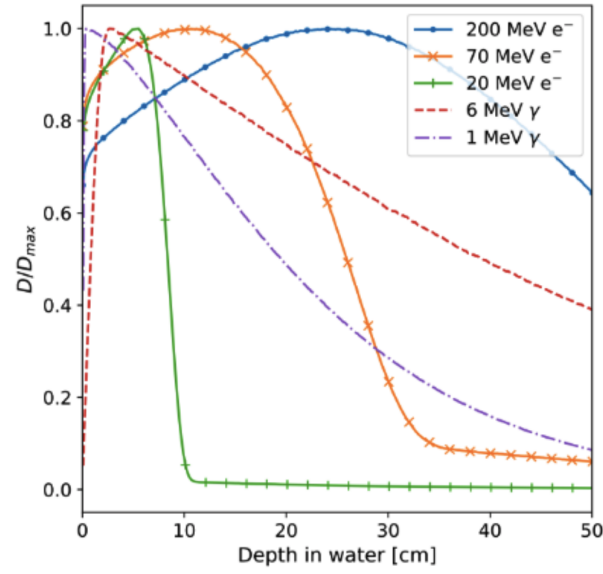


Figure 2.1: Absorbed dose depth distributions, normalised to their peak value, obtained from a MC simulation of mono-energetic electron and photon beams interacting with water. The simulated energies are in the range of interest for RT applications [62].

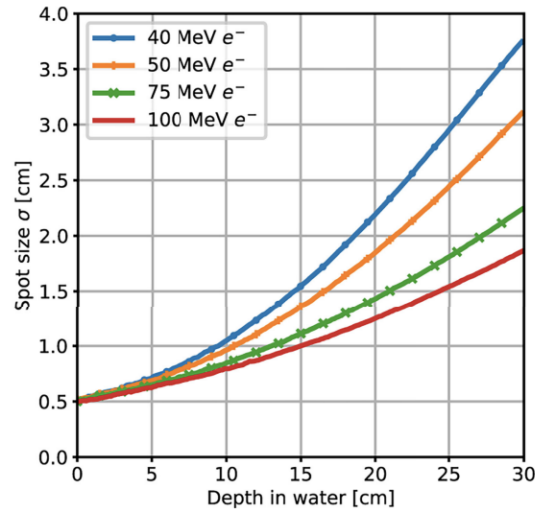


Figure 2.2: MC simulation results for the lateral spread of VHEE beams of different energies as a function of their depth in water [62].

not considered practical for clinical use due to concerns about cost, complexity, and the large size of the required equipment. However, recent technological advances have addressed many of these challenges, enabling the development of compact accelerators, with field up to 50 MV/m and very high intensities (see section 2.3).

One of the principal advantages of VHEE radiotherapy is its low dependence on tissue heterogeneities. Unlike low-energy electrons, which are significantly scattered by variations in tissue density, VHEE beams exhibit reduced sensitivity to such heterogeneities. Studies using Monte Carlo simulations [20] [57] have demonstrated that dose uniformity is well-preserved at interfaces between tissues of varying densities, such as lung, bone, and air cavities. Experimental validation of this phenomenon has been carried out at facilities like CERN's CLEAR test stand, where 156 MeV VHEE beams were shown to maintain dose uniformity with less than 5-8% variation when crossing interfaces of differing tissue densities [40]. The fact that VHEE beams provide a more uniform dose distribution, even in the presence of tissue heterogeneities (see Fig. 2.3), improves the lateral dose falloff, enhancing the ability to spare surrounding healthy tissues.

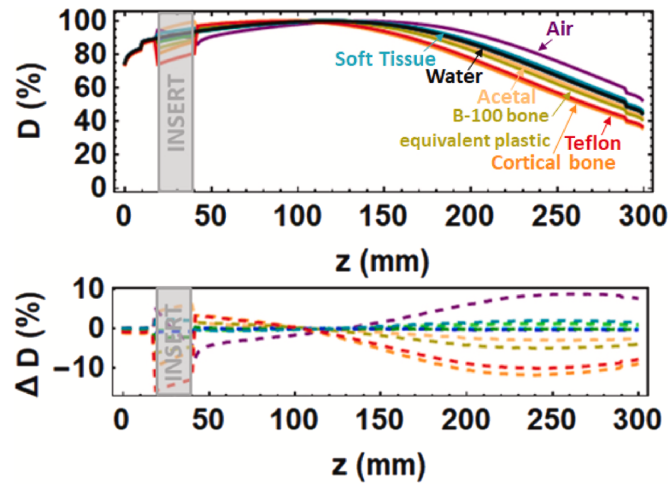


Figure 2.3: Simulated integrated dose-depth profiles for VHEE beams (150 MeV, beam width $\sigma = 5$ mm) with various 2 cm thick media inserts embedded at 2 cm. Dose differences ΔD from a dose profile in water are shown with dashed lines.[40].

Additionally, VHEE radiotherapy presents a more cost-effective option compared to proton therapy, primarily because the technology for generating VHEE beams is simpler and more accessible. Proton therapy, in contrast, requires large and expensive infrastructure such as synchrotrons or cyclotrons to accelerate protons to the necessary energies for deep-seated tumor treatments. Historically, despite the higher cost, proton therapy has been favored for its precision in targeting deep tumors, owing to the Bragg peak effect, which allows for maximum dose delivery to the tumor while minimizing damage to surrounding healthy tissues. However, proton therapy requires the addition of large margins to ensure the entire PTV receives the appropriate dose, to avoid the risk of underdosing. This issue is not present with VHEE therapy, but until recently, its clinical use was limited because accelerating electrons to 200 MeV with equipment compact enough for hospital settings was not feasible. As it will be explained in detailed in 2.2, today VHEE holds great promise for FLASH radiotherapy, a cutting-edge technique that leverages ultra-high dose rates to induce the FLASH effect. This approach has been shown to significantly reduce normal tissue toxicity while

maintaining tumor control. VHEE's capability to deliver high doses per fraction in FLASH mode makes it a strong contender for transforming modern radiotherapy, offering both precision and the potential for reduced side effects.

Delivery Techniques for VHEE Beams

Recent technological advancements, such as laser-plasma wakefield accelerators [44] and state-of-the-art C-band and X-band RF structures [3], capable of generating accelerating fields up to 50 MV/m with high intensity, have paved the way for the development of more compact and cost-effective VHEE facilities compared to traditional proton acceleration systems. As a result of these innovations (which will be discussed in detail in Chapter 3), VHEE beams can now be delivered using advanced techniques such as electromagnetic pencil beam scanning (PBS), double scattering (DS), or focused beam, all of which offer high precision in dose distribution.

- *Double scattering* is a technique traditionally used in proton therapy and has been adapted for electron therapy, including VHEE beams. In this method, the beam is passed through two scattering foils that spread the electrons uniformly across the treatment area. The first scattering foil generates an initial spread, while the second refines the dose uniformity across the field. This method is useful for producing broad, homogeneous dose distributions over larger treatment areas, however it has a limited capability to conform the dose to irregular or small volumes, leading to potential higher doses to surrounding healthy tissues.
- *Pencil Beam Scanning technique* is a highly precise method where a narrow, focused beam of VHEE is magnetically scanned across the treatment area in a raster-like fashion. This method allows for modulation of the beam intensity at each point, enabling excellent dose conformity. This is particularly useful for treating irregularly shaped tumors or minimizing the dose to surrounding healthy tissue. It offers superior dose modulation and precision and can minimize the dose to healthy tissues while focusing the radiation on the tumor. The main limitation rely on the fact that a complex control systems for beam steering and precise dose calculations is needed, as it can be sensitive to tissue heterogeneities and motion.
- In *focused beam* delivery, VHEE beams are magnetically focused using quadrupole or solenoid magnets to reduce beam spread and improve dose concentration. This method aims to maintain a high-intensity, narrow beam profile throughout its travel in the patient's body. Magnetic focusing reduces the lateral spread of the electrons, allowing for better dose delivery to deep-seated tumors with a smaller penumbra compared to other methods. This kind of delivery technique requires highly advanced magnetic systems and precise beam control and it is also more sensitive to setup errors and patient motion.

Each of these delivery methods offers unique benefits and challenges. Future research and advancements in accelerator and beam control technologies will likely continue to refine these methods for broader clinical applications.

2.2 The FLASH Effect: Phenomenology and Parameters

Nowadays radiotherapy is one of the most widely implemented strategies for tumor treatment and more than 50% of cancer patients are treated with RT, usually paired with chemotherapy and or surgery. Traditional radiotherapy (CONV-RT), which began with the use of X-rays and later extended to include other forms of ionizing radiation such as protons and electrons, has always been constrained by the balance between effective tumor control and minimizing damage to healthy tissues. Over the decades, innovative techniques, such as those mentioned in the previous chapters, from Particle Therapy to IMRT and VMAT, were developed to improve precision and reduce collateral damage. However, while these advances improved spatial targeting, the biological response to radiation, particularly in terms of normal tissue sparing, remained a challenge. The concept of ultra-high dose-rate (UHDR) delivered radiotherapy, or what is now referred to as the *FLASH effect*, emerged from early experimental work in the mid-20th century, but it was not until recent decades that the phenomenon began to gain serious scientific interest. In the 1960s and 1970s, preliminary studies [12] [32] showed that delivering radiation at ultra-high dose rates (several orders of magnitude higher than conventional treatments) could result in unexpected biological outcomes. However, the technology to consistently and safely deliver such high dose rates was lacking, and the phenomenon was not fully understood: in fact, the crucial differential effect—where healthy tissue benefits while tumor cells remain vulnerable—was not initially recognized. Early experiments, particularly those conducted in vitro, showed a protective effect on both healthy tissue and tumors alike. Without in vivo testing on patients, the advantage of FLASH therapy was unclear, as the lack of selectivity suggested no therapeutic benefit if both healthy and cancerous tissues were equally shielded. Fast forward to the 21st century, advancements in accelerator technology have allowed for a deeper investigation of the FLASH effect. The development of modern linacs capable of delivering UHDR led researchers like Favaudon et al. (2014) [25] to demonstrate that this approach could significantly reduce harm to healthy tissues while maintaining effective tumor control. Their pivotal study reignited interest in the FLASH effect by showing that mice exposed to UHDR experienced far less damage to normal tissues, such as the lungs, compared to those treated with conventional rates. Since then, numerous studies have been conducted to further explore the mechanisms, potential applications, and technological requirements of FLASH radiotherapy. The phenomenon has since captured the attention of the global radiotherapy community, offering a new paradigm where radiation toxicity can be minimized without compromising treatment efficacy. The FLASH effect is now viewed as one of the most exciting developments in the field of radiation oncology, with the potential to reshape the future of cancer treatment [74].

2.2.1 FLASH parameters

In contrast to CONV-RT, where the dose delivery takes times in the order of several minutes at dose rates typically around 0.01 to 0.1 Gy/s, FLASH radiotherapy is characterized by dose rates exceeding tens Gy/s [70] [14] [15], delivering the same therapeutic dose in less than 100 ms. The factors that contribute to induces the FLASH effect must be carefully controlled to consistently reproduce these favorable outcomes. Here, the conditions that differentiate FLASH radiotherapy and how they contribute to its unique behavior are defined.

Dose-rate per pulse

One of the parameters distinguishing FLASH radiotherapy from conventional treatments is the *dose rate per pulse* $\dot{D}_p$, also referred to as the *instantaneous dose rate*. This parameter is defined as the ratio of the dose delivered in a pulse (D_p) to the pulse duration (t_p), depicted in Fig. 2.4. Thus, the dose rate per pulse can be mathematically expressed as:

$$\dot{D}_p = \frac{D_p}{t_p} \quad (2.1)$$

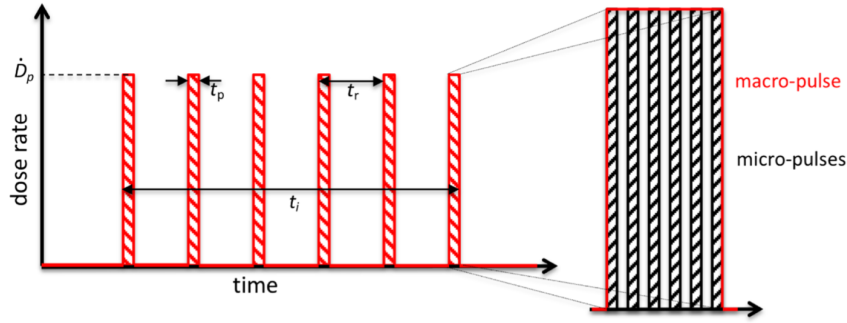


Figure 2.4: Schematics of pulsed beam temporal structure. [22]

However, determining the exact value of D_p is not a simple task, as it depends on various factors like the particle fluence, the beam energy and its spatial distribution in three dimensions. For practical purposes, the dose per pulse can be estimated by dividing the total absorbed dose D_{tot}^{abs} during the full treatment session (lasting t_i) by the number of pulses (N_p) delivered:

$$D_p \simeq \frac{D_{tot}^{abs}}{N_p} \quad (2.2)$$

In typical clinical linear accelerators, the pulse duration ranges between 1 and $5\mu s$ [9], and D_p can vary between 10^{-4} and 10^{-2} Gy [22]. As a result, the dose rate within a single pulse, $\dot{D}_p$, can reach values between 10^2 and 10^4 Gy/s. As previously mentioned, increasing the instantaneous dose rate plays a pivotal role in triggering the dose-rate-dependent biological effects that define the FLASH effect. Several studies [14] [67] [79] have highlighted that the tissue-sparing benefits of FLASH irradiation appear to be contingent upon delivering a minimum threshold dose within each pulse. The precise value of this threshold, its variability across different tissues and its potential interdependence with other parameters (such as total dose, pulse duration, and dose rate) remain areas of research. Recent findings suggest that to induce the full FLASH effect, the dose per pulse must exceed 1 Gy, a value that is substantially higher than those typically used in CONV-RT, where pulse doses are generally two orders of magnitude lower. To achieve this, maintaining pulse widths similar to those found in conventional treatments while raising the dose rate within a single pulse to at least 10^6 Gy/s is necessary. In fact, some systematic studies have pushed this required value even further, with recommendations suggesting $\dot{D}_p$ levels exceeding 10^7 Gy/s to ensure the desired biological outcomes[22]. Delivering such high doses in extremely short time frames has brought to light a series of technological limitations that have become the focus of research in accelerator physics, spanning from beam delivery to beam monitoring. The main showstoppers and the proposed

solutions will be described in detail in the dedicated section 2.3.

Mean dose-rate

The *mean dose rate* $\dot{D}_m$ refers to the total dose delivered during a multi-pulse treatment session divided by the irradiation time t_i . This quantity is influenced by several factors, including the Pulse Repetition Frequency (PRF), the pulse duration and the dose per pulse D_p . The PRF, which determines how often pulses are delivered, varies between different machines and typically ranges from 10 to 400 Hz [6] [22] in modern clinical linacs used for treatments such as IMRT or VMAT. This interval allows optimal beam modulation between pulses while also imposing a minimum time requirement for irradiation. For a fixed number of pulses N_p with a constant PRF, the mean dose-rate for the delivered dose D can be calculated as follows:

$$\dot{D}_m = \frac{D}{t_i} = \frac{D}{N_p t_r} = \frac{D_p}{t_r} \quad (2.3)$$

with t_r taken as the time interval between consecutive pulses (the inverse of the PRF). It can also be referred to the dose rate per fraction when considering the dose delivered in a single treatment fraction. In CONV-RT, mean dose rates are typically in the range of 1.8 to 6 Gy/min, which translates to around 0.01 to 0.1 Gy/s. However, achieving UHDR in FLASH therapy requires significantly higher values for $\dot{D}_m$, which can reach 10^2 to 10^3 Gy/s.

FLASH regime

The *Flash regime* refers to a specific set of conditions under which the FLASH effect can be triggered during a treatment. The critical parameters for this regime revolve around dose rate, pulse characteristics, and the overall treatment delivery dynamics, which must differ significantly from those of conventional radiotherapy.

- One of the most essential parameters is the *Dose rate per pulse* $\dot{D}_p$, previously defined. To achieve the FLASH effect, studies indicate that the instantaneous dose rate must exceed 10^6 Gy/s, with some sources pushing this threshold beyond 10^7 Gy/s [22].
- The PRF also plays a crucial role in determining the total dose delivery. In modern linacs, used for clinical radiotherapy, this value usually falls between 10 and 400 Hz [6] [22]. However, in FLASH therapy, the PRF must be carefully adjusted to balance the instantaneous dose rate and the overall treatment time.
- The *Mean dose rate* $\dot{D}_m$ in Flash radiotherapy aims for values reaching $10^2 - 10^3$ Gy/s [73], well above the conventional range of 0.03 to 0.1 Gy/s [14], leading to drastically shorter irradiation times, often below a second for a single fraction. Achieving such high mean dose rates involves delivering the dose in a single or very few pulses within a fraction of a second, as the effect seems to depend on administering the dose over very short periods.
- *Irradiation time* is another critical element. For FLASH therapy, it is essential to deliver the required dose in milliseconds or less. This contrasts with conventional treatments that spread the dose delivery over minutes or even hours. Short irradiation times, coupled with high instantaneous and mean dose rates, are central to replicating the FLASH effect.

- *Fractionation*, the practice of dividing the total radiation dose into multiple smaller doses administered over time, is a fundamental principle in conventional radiotherapy. It aims to maximize tumor control while allowing healthy tissues time to repair. In the context of FLASH radiotherapy, the debate around fractionation is still ongoing, with studies providing mixed results regarding its impact on the FLASH effect. When the radiation dose is split into multiple fractions, as is standard in conventional treatments, the advantages of the Flash effect appear to diminish or even vanish in some cases [45]. One reason for this reduction of the sparing effect on the OARs could be related to the difficulty in maintaining the average dose rate at FLASH levels in multi fraction setups (in which the dose is reduced, as split in multiple fractions). Researchers are currently investigating whether adjustments to the inter-fraction timing, dose-per-fraction, or even the number of pulses within each fraction might preserve the FLASH effect. Some studies also suggest that the response to fractionated FLASH irradiation might vary across different tissue types and tumor models, indicating that the biological mechanisms underpinning the FLASH effect could be tissue- or context-specific.
- Additionally, *pulse width* and *beam fluence* are vital technical parameters. Pulse widths for linacs used in FLASH therapy typically range from 1 to 5 μs , when speaking of electron radiotherapy. The beam fluence, or the number of particles per unit area, directly influences the dose rate per pulse and is critical for ensuring that sufficient radiation is delivered.

For FLASH therapy, a common strategy is to increase D_p (dose per pulse) while maintaining a PRF similar to conventional therapy, resulting in much higher $\dot{D}_m$ values and significantly reducing the overall irradiation time. For instance, with a PRF of 1000 Hz, the instantaneous dose rate $\dot{D}_p$ may reach 10^3 Gy/s, only slightly above conventional values, to satisfy the FLASH prescriptions but when PRF is reduced to 50 Hz, D_p needs to be increased to 10^7 Gy/s to achieve the FLASH conditions.

2.2.2 Experimental evidences

To date, several studies have consistently demonstrated that FLASH irradiation provides significant normal tissue sparing. The groundbreaking work by Favaudon et al. [25] first established the potential of this effect by showing that single-fraction FLASH electron beams could spare normal lung tissue in mice, while maintaining comparable tumor control to conventional radiotherapy. They investigated lung fibrogenesis in C57BL/6J mice exposed either to short pulses (≤ 500 ms) of radiation delivered at ultrahigh dose rate (≥ 40 Gy/s, FLASH) or to conventional dose-rate irradiation (≤ 0.03 Gy/s, CONV) in single doses. The team measured the rate of formation of pulmonary fibrosis regions at 36 weeks post-irradiation. Subsequently, they observed that, when electrons were delivered in a single short pulse at $\dot{D}_m$ values of 40-60 Gy/s, with a total irradiation time of less than 500 ms, they induced fewer pulmonary lesions compared to exposure at the conventional dose-rate. In fact, a higher dose of 30 Gy delivered via UHDR was required to produce levels of pulmonary fibrosis similar to those seen in the previous case. FLASH irradiation also spared normal smooth muscle and epithelial cells from acute radiation-induced apoptosis. In contrast, FLASH was as efficient as CONV in the repression of tumor growth. Since then, multiple experiments have validated these findings across various models and tissues, including brain, skin, and intestinal tissues, suggesting a broad applicability of the effect. Montay-Gruel et al. [52] [50] further advanced this research,

demonstrating that FLASH-RT mitigates cognitive decline and avoids neurotoxicity in rodent models, even at high doses that would typically cause severe side effects. More recent studies have explored different modalities, such as proton and photon FLASH irradiation, showing similar protective effects on normal tissues while maintaining effective tumor control. For example, Vozenin et al. [72] demonstrated FLASH effects using proton beams in a preclinical setting, with results indicating a similar normal tissue sparing effect observed in electron-based studies. In 2019, the first human trial of FLASH radiotherapy was conducted on a 75-year-old patient suffering from multi-resistant T-cell cutaneous lymphoma, treated using the Oriatron eRT6 linac [15]. The patient's 35 mm lesion was exposed to a dose-rate exceeding 10^6 Gy/s, delivered in 10 discrete 1 μ s pulses. The treatment delivered a cumulative dose of 15 Gy, with a $\dot{D}_m$ of 167 Gy/s, and each pulse depositing 1.5 Gy. Within 10 days post-irradiation, the lesion started to regress, and 36 days after the procedure, a complete tumor response was observed. This positive outcome was sustained over the following five months. In terms of side effects, the patient did not experience the same acute skin reactions (such as edema and epithelitis) previously encountered with CONV-RT, and no significant late toxicities were reported up to two years after treatment. These findings align with prior preclinical studies, where significant normal tissue sparing was observed in higher single-dose experiments (28 to 34 Gy) across smaller tissue volumes. The ability of the FLASH effect to spare healthy tissue has since been corroborated by numerous institutions using a variety of beam modalities (electrons, protons, and photons) and across a wide range of species and organs. FLASH-RT has shown protective effects in several biological endpoints, including lethal dose determination, skin and gut reactions, and early and late neurotoxicity [33]. Nonetheless, some studies have reported no significant sparing of normal tissues when subjected to UHDR irradiation. These conflicting results may arise from variations in critical parameters such as beam energy, dose-rate homogeneity, and differences in investigated biological endpoints. A factor that contributes to the difficulty in obtaining a clear set of parameters and conditions that imply a sizeable FLASH effect is the heterogeneity across key variables already discussed, including total dose, instantaneous dose-rate, pulse rate, and fractionation schemes in the different experiments carried out worldwide. The need for further research and standardized protocols remains clear, as evidenced by the diversity of outcomes. Fig. 2.5, which summarizes the characteristics of preclinical UHDR irradiation beams, illustrates the wide range of irradiation times and pulse doses yet to be fully explored. Such research will be crucial in determining how best to replicate the protective effects of FLASH-RT consistently across different clinical settings.

2.2.3 Modeling of the FLASH effect

Parametrizing the FLASH effect according to dose delivery and plan characteristics is a critical aspect of understanding and quantifying how ultra-high dose-rate irradiation selectively spares normal tissues while maintaining tumor control. Grasping the influence of the FLASH effect on various dose-delivery parameters—such as total dose, beam delivery timing, and fractionation schemes—is crucial for its effective application in clinical settings. It's also important to quantitatively assess how different biological systems and endpoints respond to FLASH irradiation. Recent treatment planning studies have attempted to model the FLASH effect using simple binary "yes/no" threshold models, which yield abrupt, step-like responses. In some cases, these models have revealed a hormetic effect, where a slight increase in dose beyond a certain threshold paradoxically leads to a reduced protective effect on normal tissues. A quantification of the magnitudes of the FLASH normal

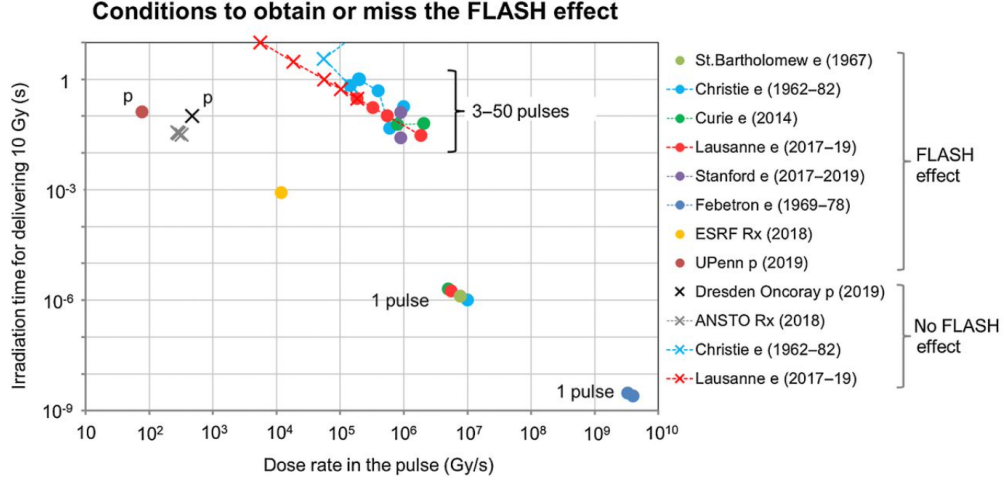


Figure 2.5: Summary of the temporal dosimetry characteristics of the published experimental data describing the FLASH effect in vivo or in vitro (colored dots), those that have not been able to observe the FLASH effect (black, gray crosses) and the dose-rate de-escalation studies showing the range in which the FLASH effect is lost (colored crosses). The horizontal axis denotes the dose-rate per pulse for electrons (e), protons (p) and synchrotron radiation (Rx). The vertical axis corresponds to the total irradiation time needed for delivering 10 Gy[51].

tissue sparing has been done by Böhlen et al. [17]. To achieve this, existing in vivo experimental data on the FLASH sparing effect for normal tissues have been reanalyzed and represented as isoeffect dose ratios on a standardized scale based on dose. These data were then modeled using a phenomenological function, which is derived from the typical response patterns observed for Normal Tissue Complication Probability (NTCP). Similar to the concept of RBE for different radiation types, the FLASH-modifying factor (FMF) for ultra-high dose rate irradiations is defined as the ratio between the doses required at conventional dose rates (D_{CONV}) and UHDR (D_{UHDR}) to produce the same biological effect for a specific system and endpoint:

$$FMF = \frac{D_{CONV}}{D_{UHDR}} \quad (2.4)$$

The FMF is the reciprocal of the dose-modifying factor commonly mentioned in various studies on the FLASH effect. An FMF value less than 1 indicates sparing of normal tissues under UHDR compared to conventional irradiation, meaning that tissue protection increases as the FMF decreases. Using this concept with a slightly modified naming convention, similar to that applied in proton and ion beam therapy, a dose D delivered at UHDR can be transformed into an equivalent FMF-weighted dose, D_{FMF} , that would produce the same biological effect if delivered at conventional dose rates:

$$D_{FMF} = FMF \cdot D \quad (2.5)$$

To offer a practical phenomenological parametrization of the dose dependence for experimental FMF values, a continuous two-parameter function was proposed to describe the data through goodness-of-fit metrics:

$$FMF = \begin{cases} 1 & \text{if } D \leq D_T \\ (1 - FMF^{min}) \frac{D_T}{D} + FMF^{min} & \text{if } D > D_T \end{cases} \quad (2.6)$$

Where D is the dose, D_T is the minimum threshold dose needed for the FLASH effect to occur, and FMF_{min} represents the minimum value of the FMF achievable as the dose increases. A smaller FMF_{min} value reflects a stronger FLASH effect, meaning more sparing of normal tissue compared to conventional radiotherapy. The FMF of the pooled mammalian data follow a consistent general trend as a function of single-fraction dose that can be parametrized by the sudden effect transition function reported in Eq. 2.6. The results analyzed by Bohlen are shown in Figure 2.6 together with the best fit of all the data points (the 95% prediction interval, light grey band, and 95% confidence interval, dark grey band, are shown as well on the figure to give an idea of the uncertainties affecting the model).

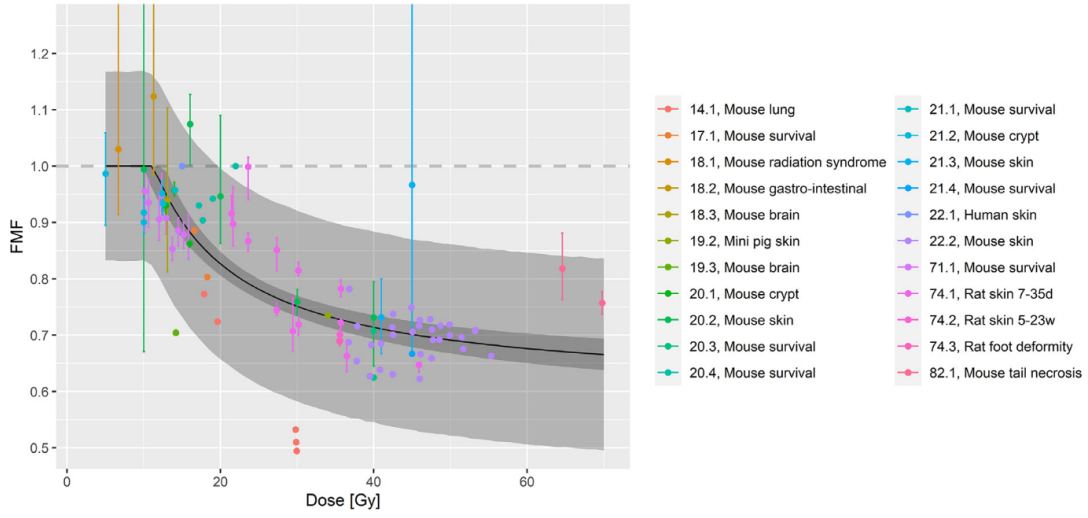


Figure 2.6: Pooled mammalian data by identification, plotted as FMF versus single-fraction ultra-high dose rate dose. A regression to the data using the sudden effect transition function is shown (solid line) with the 95% prediction interval (light gray band) and 95% confidence interval (dark gray band).[17]

2.3 Technological Challenges in Particle Acceleration for FLASH Radiotherapy

The implementation of FLASH-RT poses significant technological challenges, particularly in the field of particle acceleration. Achieving high instantaneous dose rates pose substantial technical hurdles, particularly in terms of beam control and real-time verification. Traditional accelerators used in conventional radiotherapy are not inherently designed to produce the short, high dose pulses required for FLASH. Delivering radiation at these dose rates necessitates significant modifications to increase the instantaneous beam current and PRF without sacrificing beam quality or uniformity. Additionally, maintaining beam stability during ultra-high dose rate delivery represents a challenge, especially due to space charge effects, where the dense concentration of charged particles within each pulse can lead to instabilities, beam spread, and difficulties in accurate beam focusing. These instabilities can compromise the precision needed for targeted radiotherapy. The challenges become even more complex when different types of particles — such as protons, photons and electrons — are used in FLASH-RT.

Gamma Rays: Dose Intensity and Modulation

Achieving the UHDR necessary for FLASH with gamma rays presents a significant challenge due to the difficulty in modulating photon beams to deliver the required dose intensities in short time frames. Gamma-ray sources, primarily utilized in conventional radiotherapy, typically achieve dose rates in the range of 0.01-0.1 Gy/s, far below the UHDR threshold for FLASH, that should exceed 40 Gy/s. One of the primary limitations is the inability of conventional photon-based systems to deliver high doses rapidly due to the relatively low flux of photons emitted per unit time. Current linacs designed for photon therapy implement the Bremsstrahlung interaction to produce the gammas and are not optimized for the extreme dose rates required for FLASH. Additionally, modulating the beam intensity within such short durations while maintaining accurate targeting is a major technical hurdle. Thus, realizing FLASH with gamma rays would require a re-engineering of photon delivery systems or the development of new technologies capable of generating much higher photon fluxes.

Protons: Balancing Conformality and Energy Requirements

For protons, the challenges of FLASH radiotherapy stem from the need to balance dose conformality and UHDR irradiation. Proton therapy is traditionally lauded for its high conformal dose distribution due to the Bragg peak effect, where the majority of the dose is deposited at a specific depth, minimizing exposure to surrounding healthy tissues. However, achieving UHDR with protons is complicated by the need for high beam energies to penetrate deep into tissues while maintaining the precise targeting required for tumor conformality. This creates two key challenges: first, the required beam intensity for UHDR proton therapy far exceeds what is possible with current clinical proton accelerators. Traditional proton accelerators deliver protons in pulses, but achieving the necessary pulse structures for FLASH would demand a significant increase in both the energy and number of protons per pulse. Secondly, to maintain the benefits of proton conformality while reaching UHDR, the energy modulation of the beam must be highly precise. Accelerator technologies would need to be upgraded to manage these high-energy, high-dose rates, requiring significant advancements in beam control and delivery.

VHEE Electrons: Lack of Existing Technology for UHDR

Electrons have historically posed significant technological challenges for FLASH radiotherapy, primarily due to the lack of infrastructure capable of delivering ultra-high dose rate very high energy electron beams in clinical settings. While low-energy electron beams are already being used for FLASH, and most of the existing radiobiological research—both in vitro and in vivo—has been conducted using them, the challenge lies in achieving high-energy FLASH. Delivering ultra-high dose rates with high-energy electrons is relatively straightforward; the real obstacle is developing a clinical-grade machine that can generate these beams. Although efforts are underway to create such equipment, it does not yet exist, and current high-energy FLASH experiments must be conducted at research facilities like CLEAR. While the potential benefits of electron-based FLASH therapy are clear, translating these theoretical advantages into practical clinical solutions remains challenging. One of the key issues lies in developing accelerators that can deliver medium-to-high energy electrons across multiple treatment fields at FLASH intensities in a clinically compliant environment. Such accelerators must not only provide the necessary beam power and dose rates but also fit within

the constraints of a hospital setting. This means balancing high performance with a compact and efficient design, which is essential for widespread clinical adoption, aware of the fact that size and complexity of traditional high-energy accelerators make them unsuitable for routine clinical use. In this context, various technologies are being explored, with particular attention given to linear accelerators operating in the X-band (11.424 GHz) and C-band (5.712 GHz) frequency ranges. X-band linacs, with their higher operating frequencies, offer the potential for compact designs and are being investigated for their ability to deliver the required dose rates. Similarly, C-band linacs provide a promising alternative, combining high electron energy with a more manageable system footprint. However, both technologies face significant engineering hurdles, particularly in optimizing beam stability, pulse duration, and ensuring precise beam delivery across the treatment field. Achieving consistent ultra-high dose rates without compromising the quality and uniformity of the electron beam remains a critical challenge.

In light of these challenges, Chapter 3 delves deeper into the characteristics of these accelerators, with a particular emphasis on the solution proposed by the SAFEST project, which aims to design and build a C-band linac prototype capable of delivering FLASH beams.

Beam monitoring challenges

One of the most significant challenges in FLASH-RT is also real-time beam monitoring, which is crucial for advancing our understanding of the FLASH effect, validating the various theoretical models proposed, and ensuring compliance with future regulatory standards concerning treatment accuracy, safety, and efficacy. Traditional radiotherapy detectors are typically designed for lower dose rates and are not equipped to handle the intense, ultra-fast pulses associated with FLASH-RT. The high dose per pulse characteristics of UHDR beams can overwhelm conventional detectors, leading to sizeable saturation effects, inaccuracies in dose measurement and beam characterization. This lack of precision can introduce substantial uncertainties into the treatment process and hinder the full utilization of newly developed FLASH-capable facilities. Currently, the monitoring of FLASH beams is still in its developmental phase. However, significant technical challenges remain, such as ensuring high temporal resolution, managing detector saturation, and maintaining accuracy across a wide range of dose rates. As a result, the absence of a standardized monitoring system for FLASH beams not only limits the reproducibility of experimental results but also poses a barrier to the broader clinical adoption of FLASH-RT. Overcoming these challenges will be key to unlocking the full potential of FLASH therapy and ensuring its safe and effective use in clinical settings.

Chapter 3

The SAFEST project

The interest of the scientific community in FLASH radiotherapy is underscored by the numerous dedicated workshops, conferences, and the growing number of scientific papers published in recent years on this subject. As I have discussed in Chapter 2, one of the challenges faced in the study of the FLASH effect is the lack of facilities capable of delivering beams of the energies and intensities of interest for UHDR experiments. The longstanding collaboration between Sapienza and INFN researchers in accelerator technology, as well as other FLASH-related fields, represented a unique occasion for the development of advanced electron sources for electron FLASH radiation. A joint interdisciplinary team from Sapienza and INFN was established in 2021 with the goal of designing a compact VHEE LINAC based on advanced accelerator technologies capable of providing dose rates compatible with FLASH requirements. Such project (named SAFEST as in : SApienza Flash Electron Source for radio-Therapy) will be described in detail in the following. The facility that is being developed and implemented within SAFEST will support a wide range of research activities, from beam diagnostics to radiobiological experiments, and will be accessible to both internal and external users.

3.1 Linear Accelerator

A Linear Accelerator (LINAC) is a device that uses electric fields to accelerate charged particles—such as electrons, protons, or ions—along a straight path increasing their kinetic energy [78] [65]. The operation of a LINAC, though relatively straightforward, is highly effective: particles are accelerated by a series of electromagnetic fields oscillating at different radio frequencies (RF). As we will explore in detail in the next section, these fields are applied across a series of electrodes or drift tubes, and as the charged particles pass through the gaps between them, they gain energy. The linear configuration of a LINAC allows for efficient particle acceleration. Over the years, its technology has evolved significantly and found diverse applications in fields such as medical radiation therapy, industrial processing, and high-energy physics research. In medicine, LINACs are widely used for cancer treatment, delivering high-energy X-rays or electron beams. One of the key advantages of LINACs is their ability to accelerate particles to high energies over relatively short distances, making them more efficient and compact than other types of accelerators. They can be customized for a wide range of uses, from small, tabletop devices in medical clinics to large, research-grade machines. Their linear design simplifies the acceleration process, eliminating the need for the complex magnetic

systems required to bend particles in circular accelerators. However, LINACs also come with certain limitations. Achieving extremely high particle energies requires longer structures, which makes compact high-energy LINACs challenging to build and maintain. Additionally, as particles approach the speed of light, the precise timing of the electromagnetic fields becomes more difficult, introducing technical challenges. LINACs also consume more energy than circular accelerators because they lack a mechanism to reuse electric fields after the particles have passed through them. Despite these challenges, this kind of technology remain fundamental to modern science and technology. Their versatility, precision, and ability to deliver high-energy particle beams in straight trajectories make them indispensable in both clinical and research environments. Recent innovations, particularly the development of X-band and C-band accelerators, have made LINAC technology even more compact, efficient, and powerful. As these advancements continue, LINAC designs are expected to further broaden their applications, pushing the boundaries of what can be achieved in medical treatments and scientific exploration.

3.1.1 Acceleration process

The Lorentz force is the foundation of particle acceleration in any accelerator system, including LINACs. It describes the force experienced by a charged particle moving through electric and magnetic fields. The general form of the Lorentz force is expressed as:

$$\vec{F}_L = q\vec{E} + q(\vec{v} \times \vec{B}) \quad (3.1)$$

where q is the particle charge, moving with velocity $\vec{v}$ and the vectors $\vec{E}$ and $\vec{B}$ are the electric and magnetic field. In LINACs, the primary contribution to particle acceleration comes from the electric field $\vec{E}$, which imparts energy to the charged particles, propelling them forward. The particles are injected into the accelerator at low speeds, and the electric fields within the accelerator cavities increase their energy step by step. Magnetic fields $\vec{B}$ are not primarily responsible for accelerating particles in LINACs but are instead used for beam focusing and steering, as will be discussed in the section on beam dynamics 3.1.3.

The first practical implementation of a LINAC was developed by Rolf Wideröe in the 1920s. His design is regarded as the precursor to modern RF accelerators and introduced the concept of using RF fields to accelerate particles. In fact, Wideröe's device used alternating RF electric fields between a series of drift tubes, synchronizing the fields with the motion of the particles to ensure they gained energy during each pass through the gaps. The proposed scheme is illustrated in Fig. 3.1.

The basics of its operation are as follows: a voltage generator producing Alternating Current (AC) alternates the voltage applied to a series of electrodes in such a way that particles experience no force while moving through the drift tubes (Drift Tube Linac, or DTL), and are only accelerated when they cross the gaps between the tubes. This process works efficiently if the length of each drift tube (or the distance between the centers of the accelerating gaps, L_n) increases as the particle's velocity increases during acceleration. This ensures that the time the particles take to travel between gaps remains constant, corresponding to half of the RF period. When this condition is satisfied, the particles encounter a synchronous accelerating voltage and gain energy according to the relation $\Delta E = q\Delta V$ at each gap crossing. As illustrated in Fig. 3.2, a RF acceleration process does not allow to accelerate a continuous particle beam but the beam needs to be *bunched* with a distance between

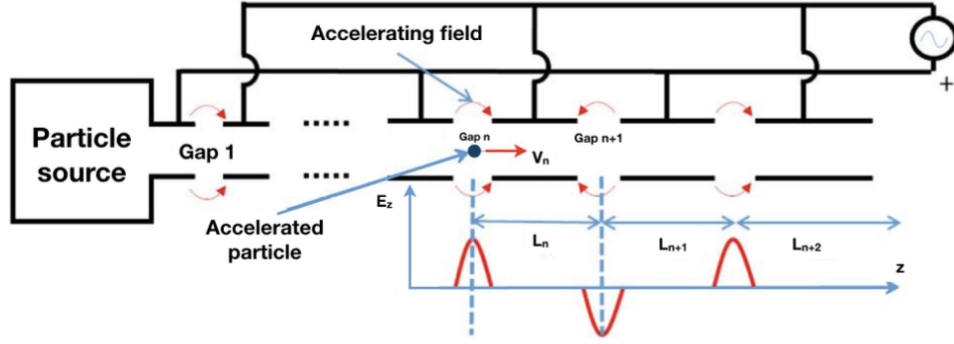


Figure 3.1: Conceptual scheme of a Wideröe linac.

bunches exactly equal to the RF period. Assuming that the particles motion is along the z-axis, the

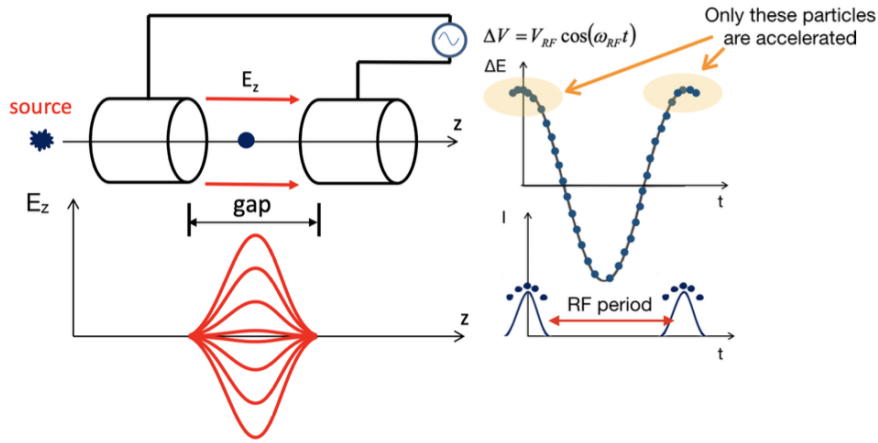


Figure 3.2: Scheme of RF acceleration processes between two electrodes.

behavior of the accelerating electric field and voltage are given by the following relations:

$$E_z(z, t) = E_{RF}(z) \cos(\omega_{RF} t) \quad (3.2)$$

for the electric field, and:

$$\Delta V = V_{RF} \cos(\omega_{RF} t) \quad (3.3)$$

for the potential, with $\omega_{RF} = 2\pi f_{RF}$ and $V_{RF} = \int_{gap} E_{RF}(z) dz$. The energy gain per electrode (supposing a symmetric accelerating field with respect to $z=0$) is given by:

$$\Delta E = q \int_{gap} [E_z(z, t)] dz \quad (3.4)$$

where $E_z(z, t)$ is the electric field seen by the particles. With some calculation we get:

$$\Delta E = q V_{RF} T \cos(\phi_{inj}) = q \hat{V}_{acc} \cos(\phi_{inj}) = q V_{acc} \quad (3.5)$$

where ϕ_{inj} is the injection phase of a generic particle and T is called the *transit time*, which is always

less than 1. Since the RF voltage is oscillating in time while the beam is traversing the gap, we defined the effective peak accelerating voltage ($\hat{V}_{acc}$) as the RF voltage (V_{RF}) multiplied by T. If we consider a Wideröe structure, the energy gain, at each gap, is equal to $\Delta E_n = qV_{acc}$ while the particle velocity increases. In order to be synchronous with the accelerating field at the center of each gap, the time of flight (t_n) between gaps is given by:

$$t_n = \frac{L_n}{\bar{v}_n} = \frac{T_{RF}}{2} \quad (3.6)$$

and thus:

$$L_n = \frac{1}{2}\bar{v}_n T_{RF} = \frac{1}{2}\bar{\beta}_n c T_{RF} = \frac{1}{2}\bar{\beta}_n \lambda_{RF} \quad (3.7)$$

where T_{RF} is the generator RF period, $\bar{v}_n$ is the average particle velocity between the gap n and n+1 and λ_{RF} is the RF wavelength. For this reason, the distance between the centers of two consecutive gaps has to be increased as reported in Eq.3.7. The energy gain per unit length is then given by:

$$\frac{\Delta E}{\Delta L} = \frac{qV_{acc}}{L_n} = \frac{2qV_{acc}}{\lambda_{RF}\bar{\beta}_n} \quad (3.8)$$

However 3.8 implies that the Wideröe acceleration technique cannot be applied to relativistic particles, since the condition $L_n \ll \lambda_{RF}$ (necessary to model the tube as an equipotential region) requires $\bar{\beta}_n \ll 1$. Moreover, when particles velocity increases the drift tube gets longer, reducing the acceleration efficiency (energy gain per unit length $\Delta E/\Delta L$).

These limitations pushed to develop more efficient accelerating structures than simple drift tubes. In order to avoid electromagnetic radiation processes and to allow the use of high frequency sources, the accelerating system had to be enclosed in a metallic volume: a RF cavity.

3.1.2 Accelerator structure: RF cavities

RF cavities are critical elements in particle accelerators, responsible for transferring energy to charged particles using electromagnetic fields oscillating at radio frequencies. These cavities work by confining electromagnetic waves in resonant chambers, where, as previously shown, oscillating electric fields can accelerate particles as they pass through. The geometry and dimensions of the cavities are carefully designed to resonate at specific frequencies, ensuring efficient acceleration. The two main types of RF cavities are **Standing Wave (SW)** and **Travelling Wave (TW)**, each offering distinct ways of accelerating particles.

Standing Wave cavities

A SW cavity is a resonant structure where the electromagnetic fields oscillate back and forth within a confined space, forming stationary waves. This reflection creates a wave pattern where certain points (nodes) have zero electric field strength, and others (antinodes) have maximum field strength. Particles are accelerated through the antinodes, gaining energy each time they pass through the region with a strong electric field, as depicted in Fig.3.3.

The wave equation describing the electric field in a standing wave cavity is:

$$E(z, t) = E_0 \cos(kz) \cos(\omega t) \quad (3.9)$$

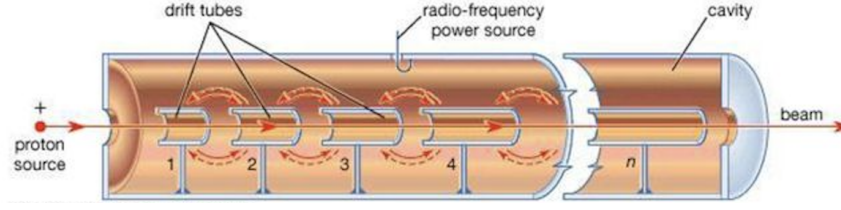


Figure 3.3: Schematic representation of a LINAC utilizing SW cavities. Particles gain energy as they pass through the antinodes, while the length of the drift tubes and the RF field are synchronized with the particle velocity to ensure continuous acceleration.

where:

- $E(z, t)$ is the electric field at position z along the cavity and time t ;
- E_0 is the maximum field amplitude;
- $k = \frac{2\pi}{\lambda}$ is the wave number;
- ω is the angular frequency of the oscillating field;

One main advantage of SW cavities is their high efficiency in transferring RF power to the particle beam, as the RF energy is confined and reflected within the cavity. They are also generally more compact, allowing them to achieve high electric field gradients in a relatively short space. However, their design and tuning are more complex, and they require precise synchronization of the particle motion with the oscillating electric field. The N-cell structure behaves like a system of N coupled oscillators with N coupled multi-cell resonant modes. The mode in which the two cells oscillate are detailed below.

For a SW cavity the first figure of merit is the *Shunt impedance* R defined by:

$$R = \frac{\hat{V}_{acc}^2}{P_{diss}} [\Omega] \quad (3.10)$$

where $\hat{V}_{acc}$ is the accelerating voltage for a given dissipated power into the cavity (P_{diss}). This parameter qualifies the efficiency of the cavity: the higher its value, the larger is the achievable accelerating voltage for a given dissipated power. It is also convenient to introduce the shunt impedance per unit length, defined as:

$$r = \frac{R}{L} = \frac{\hat{V}_{acc}^2/L^2}{P_{diss}/L} = \frac{\hat{E}_{acc}^2}{p_{diss}} \quad (3.11)$$

where L is the cavity length, $\hat{E}_{acc}$ the average accelerating field and p_{diss} the dissipated power per unit length.

In addition, the *Quality factor* of the accelerating mode can be defined by the ratio of the cavity stored energy (W) and the dissipated power (P_{diss}) on the cavity walls:

$$Q = \omega_{RF} \frac{W}{P_{diss}} \quad (3.12)$$

It can be easily demonstrated that the ratio R/Q is a pure geometric factor and it does not depend

upon the cavity wall conductivity or operating frequency. This is the reason why it is always taken as a geometric design qualification parameter. The R/Q of a single cell is of the order of 100.

Travelling Wave cavities

In contrast to SW cavities, TW cavities allow the RF wave to propagate continuously through the cavity in the same direction as the particle beam. Particles "ride" this travelling electromagnetic wave, continuously gaining energy as they move along the cavity. The wave travels at the same speed as the particles, ensuring that the particles remain in phase with the accelerating field (see Fig. 3.4). The electric field in a travelling wave cavity can be described by the wave equation:

$$E(z, t) = E_0 \cos(kz - \omega t) \quad (3.13)$$

where $E(z, t)$, E_0 , k and ω are the same quantity previously defined for SW structures. In this case, the electric field is a travelling wave moving in the $+z$ -direction. The key parameter in TW cavities

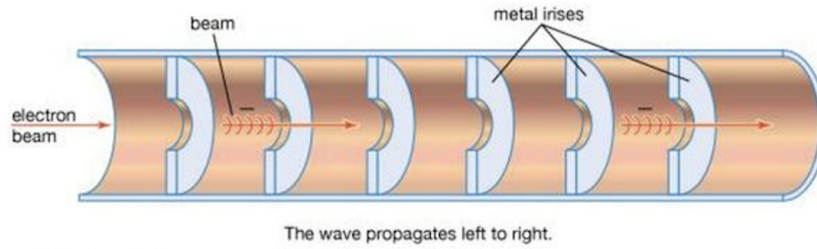


Figure 3.4: Schematic representation of a LINAC utilizing TW cavities. In this design, charged particles are accelerated by riding a continuously propagating RF wave that travels along the cavity in the same direction as the particle beam. The RF field moves at the same phase velocity as the particles, allowing for sustained acceleration over long distances.

is the *phase velocity* of the RF wave, which must match the velocity of the particles for continuous acceleration. This can be expressed as:

$$v_{ph} = \frac{\omega}{k} \quad (3.14)$$

To maintain synchronization, the cavity is designed so that the phase velocity equals the velocity of the particle beam. TW cavities are often used in high-energy electron accelerators, such as those found in linear colliders and free-electron lasers. These systems can achieve continuous acceleration over long distances, but they are less efficient than standing wave cavities because the RF energy propagates through the cavity and is absorbed at the end, rather than being reused.

Beyond the general distinction between SW and TW RF cavities, the operating mode of these cavities—particularly standing wave cavities—determines how the electromagnetic fields oscillate inside the structure. These modes define the spatial configuration of the electric and magnetic fields and significantly impact the efficiency and effectiveness of particle acceleration. Common operating modes include 0 -mode, π -mode, and $\pi/2$ -mode, each offering distinct characteristics for different applications:

- In 0 -mode, all sections of the cavity oscillate in phase with one another. This means that the electric field has the same direction and amplitude in each cell at any given moment, see Fig.3.5.

Thus in a structure operating in this mode, the particles experience uniform acceleration in every cavity section simultaneously. To maintain the synchronism between the beam and the accelerating field at each gap, the distance between the accelerating gaps L_n has to be varied according to the formula:

$$L_n = \overline{\beta_n} \lambda_{RF} \quad (3.15)$$

However, 0 -mode is rarely used in modern particle accelerators because it does not allow for optimal synchronization between the RF fields and the particle beam. While simple in terms of field distribution, this mode is inefficient for accelerating particles to high energies because it limits the energy gain per unit length of the accelerator.

- The π -mode is one of the most commonly used configurations in SW cavities, especially for high-energy applications. In this mode, adjacent cells within the cavity oscillate with opposite phases: when the electric field in one cell is positive, the field in the neighboring cell is negative (see Fig.3.5). This creates a configuration where the particle is accelerated through alternating cells, gaining energy from the changing electric field direction. The periodic reversal of the field ensures that particles remain in phase with the accelerating fields as their velocity increases. The π -mode is particularly effective for high-energy particle acceleration because it maximizes the energy transfer to the particles while maintaining a compact accelerator design. This mode also allows for efficient synchronization between the RF field and particle motion, making it a preferred choice in many LINACs.
- In $\pi/2$ -mode, the phase difference between adjacent cells is $\pi/2$ radians. This mode offers a compromise between the 0 -mode and π -mode, with the electric field in each cell oscillating in a way that ensures more stable beam dynamics, as shown in Fig.3.5. The $\pi/2$ -mode is typically used in disk-loaded structures in travelling wave cavities, where each cell interacts with the particle beam in a controlled manner. One of the advantages in this case is that it provides smoother field distribution across the cavity, which can result in better beam stability and reduced energy spread among particles. This mode is often used in sections of accelerators where precise control over the beam is necessary, such as during the transition from low to high energies.

In a multi-cell system the different resonant modes are distributed in a curve called dispersion curve. As an example, the case of a 9-cell structure is reported in Fig.3.6. Each mode has a bandwidth proportional to the quality factor and, over a certain number of coupled cavities, the overlap of the tails of adjacent modes can introduce problems for field equalization and structure operability. This limits the maximum number of multi-cell structures to around 10-15. Since the criticality of a working mode depend on the frequency separation between the working mode and the adjacent modes, the $\pi/2$ -mode, from this point of view, is the most stable one. Unfortunately, for this mode it is possible to demonstrate that the accelerating field is zero every two cells. In spite of this mechanical complication with respect to a π -mode system, this allows to increase the number of cells to more than 20 without problems.

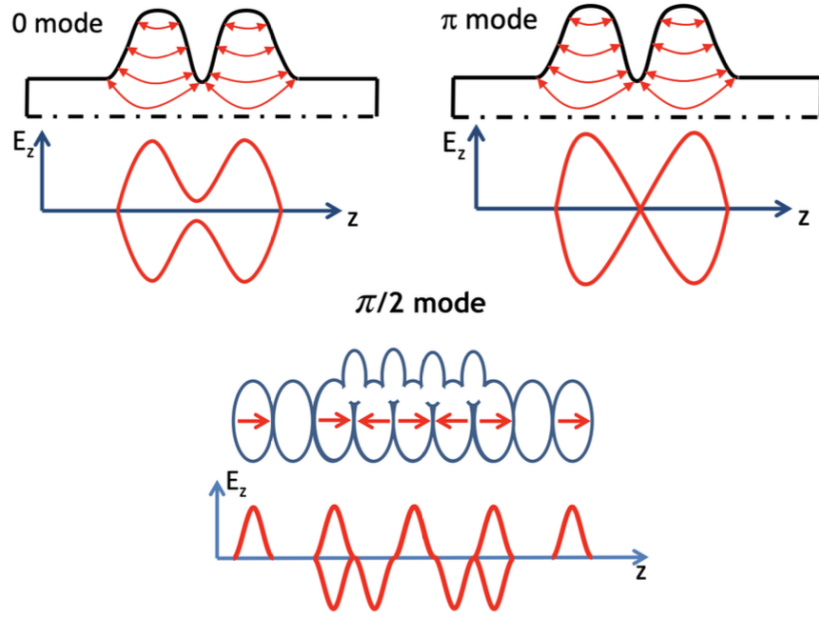


Figure 3.5: Resonant modes in a system of two coupled cavities for 0 – mode and π – mode mode and of 9 coupled cavities.

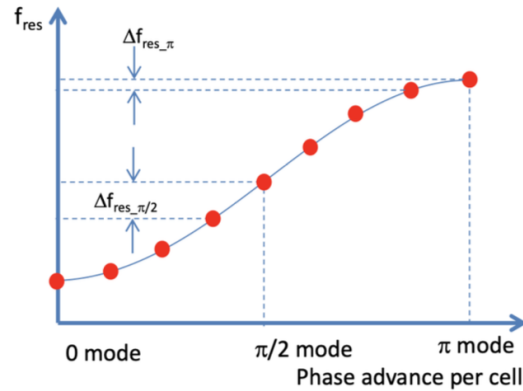


Figure 3.6: Resonant modes distributed in the “dispersion curve” for a 9-cell multi-cell structure.

3.1.3 Beam dynamics concepts

The study of beam dynamics is a key part of designing particle accelerators, as it can be used to describe how particle beams behave as they travel through the accelerator. In a LINAC, beam dynamics are typically divided into two categories: *longitudinal* and *transverse dynamics*. The careful design of both dynamics help ensure that the beam is properly accelerated and remains focused, maintaining high quality throughout the process.

Longitudinal beam dynamics

Longitudinal beam dynamics focuses on the motion of particles along the direction of travel, primarily concerned with their energy and phase as they move through the accelerator. In a SW LINAC, particles pass through a series of accelerating gaps or RF cavities, where electric fields

oscillate and provide the energy needed for acceleration. The key to stable acceleration is *phase stability*. This principle works by maintaining a specific phase relationship between the particles and the oscillating RF field. The ideal particle, known as the *synchronous particle*, crosses each gap at a phase angle called the *synchronous phase* ϕ_s and its energy gain per gap is described by:

$$\Delta E = q\hat{V}_{acc}\cos(\phi_s) \quad (3.16)$$

Here, ΔE is the energy gain, q is the particle's charge, and $\hat{V}_{acc}$ is the peak accelerating voltage. Looking at the plot of Fig.3.7 is it easy to understand that particles that arrive slightly later than the synchronous particle (with $t_1 > t_s$ and $\phi_1 > \phi_s$) will experience a stronger electric field and gain more energy, and thus will have a higher velocity than the synchronous one, allowing them to catch up. Similarly, particles that arrive earlier (with $t_1 < t_s$ and $\phi_1 < \phi_s$) will receive less energy, causing them to slow down. In conclusion, the synchronous phase on the positive slope of the RF voltage provides a longitudinal focusing of the beam allowing to have a stable beam acceleration. On the contrary, the synchronous phase on the negative slope of the RF voltage is an unstable position. Since it relies on particle velocity variations, longitudinal focusing does not work for fully relativistic beams.

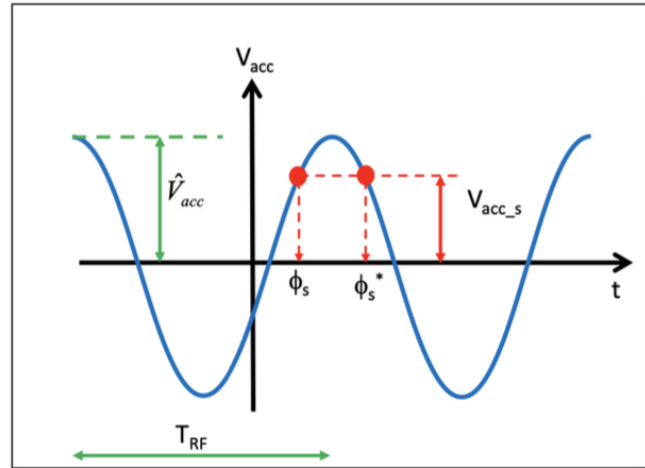


Figure 3.7: Sketch of accelerating voltage in each gap.

Transverse beam dynamics

While *longitudinal dynamics* deals with how particles are accelerated, *transverse beam dynamics* addresses how they behave in the directions perpendicular to their motion. As particles pass through the RF cavities, they are also affected by electric and magnetic fields that can push them off-axis, potentially causing the beam to spread out. As an example, the transverse forces as a function of the longitudinal coordinate are reported in Fig.3.8 for an accelerating gap of $L = 3$ cm, working at $f_{RF} = 350$ MHz, for two different injection phases. From the plot, it is evident that the transverse forces are equal to zero in the center of the gap, while they have an opposite sign at the entrance and at the exit of the gap itself. Inside the accelerating gaps, these transverse forces are usually zero at the center, but they increase near the entrance and exit, where they can lead to defocusing. This effect is particularly strong at low energies, and it diminishes as the particles reach higher velocities

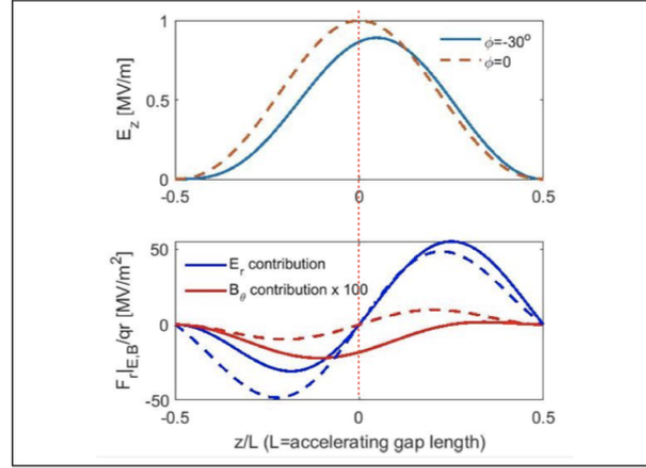


Figure 3.8: Transverse forces as a function of the longitudinal coordinate in traversing the accelerating gap

because it scales as $1/\gamma^2$ (where γ is the relativistic factor). The transverse momentum gained from these forces is given by:

$$\Delta p_r = -\frac{\pi q E_{acc} L \sin \phi}{c \gamma^2 \beta^2 \lambda_{RF}} \quad (3.17)$$

Here, E_{acc} is the average accelerating field, and L is the length of the accelerating gap. As particles reach higher energies, the effect of these transverse forces diminishes, especially for relativistic particles like electrons. Another factor that affects transverse dynamics is the *space charge effect*—the repulsion between particles in the beam due to their electric charges. This effect is particularly noticeable at low energies and in beams with high currents. The force from space charge can be described as:

$$F_{SC} = q \frac{I}{2\pi\epsilon_0 R_b^2 \beta c \gamma^2} r_q \hat{r} \quad (3.18)$$

Where I is the beam current, R_b is the beam radius, and r_q is the radial position. As particles gain speed, the space charge effect becomes less significant, but it can still be a challenge in the early stages of acceleration. To counteract both the defocusing effects of the RF fields and the space charge forces, quadrupole magnets are used to focus the beam. Quadrupoles are designed to focus in one plane while defocusing in the other, and by alternating these magnets in a specific arrangement (called a FODO lattice)[61], the beam can be focused in both transverse directions. These magnets are placed between the accelerating structures to keep the beam tightly focused as it accelerates.

3.1.4 LINACs for FLASH therapy

Several facilities around the world are now equipped to explore the use of VHEE beams in FLASH therapy. For the purposes of this discussion, VHEE are defined as electrons within the energy range of 70 to 250 MeV and an accelerator designed for FLASH therapy must be capable of producing electron beams with UHDR, delivering tens of Gy to the target in fractions of a second. This requires the accelerator to generate extremely high beam currents in a short time ($\sim 200\text{mA}$ in $\sim 3\mu\text{s}$), ensuring the entire tumor receives the therapeutic dose within milliseconds, while preserving the FLASH effect on healthy tissues. The most important ones that have been key to advancing research in dosimetry and ultra-high dose-rate applications are:

1. **CLEAR (CERN Linear Electron Accelerator for Research) - CERN, Switzerland:** Originally developed as a probe beamline for the CLIC Test Facility, CLEAR was converted in 2017 into a research facility capable of producing bunched electron beams using a photoinjector coated with cesium telluride. The accelerator is capable of producing electron beams with energies up to 220 MeV after three S-band acceleration structures;
2. **NLCTA (Next Linear Collider Test Accelerator) - SLAC, USA:** this accelerator produces high-brightness electron beams through an S-band RF photoinjector. It reaches energies of 120 MeV after passing through two high-gradient X-band RF structures;
3. **SPARC (Sources for Plasma Accelerators and Radiation Compton with Lasers and Beams) - INFN-LNF, Italy:** it consists of a photoinjector with a copper photocathode, followed by three S-band traveling wave accelerating sections. This setup allows SPARC to produce electron beams with energies up to 170 MeV;
4. **CLARA (Compact Linear Accelerator for Research and Applications) - Daresbury, UK:** it is another facility that can produce ultrabright electron beams. Though its primary focus is on accelerator physics and free-electron laser research, it is also being explored for its potential in delivering VHEE beams for FLASH therapy.

While these existing VHEE FLASH facilities mark significant advancements in the field, several additional projects are currently under construction or in the planning stages, aimed at further optimizing and expanding the accessibility of high-energy electron beams for FLASH therapy. For example, the PHASER system is an ambitious project designed specifically for clinical use, while laser-plasma accelerators [31] are being explored for their potential to generate compact and cost-effective VHEE beams. In the following paragraph I am going to discuss in detail a new approach for the compact acceleration of electrons at FLASH intensities using a C-band linac solution that is currently being pursued as a joint project by Sapienza and INFN. I will present innovative design and goals for advancing VHEE-based FLASH treatments.

3.2 The SAFEST project

As just demonstrated, there are currently very few facilities worldwide that can deliver VHEE beams with the specific FLASH parameters necessary for advanced research. This creates a significant need for more facilities that can support the growing scientific community in conducting biological studies on small animals, as well as performing preclinical tests to investigate the therapeutic effects of high-dose electron beams delivered at high energies (between 70 and 250 MeV). The creation of a dedicated facility in Italy would allow a comprehensive study of the VHEE FLASH effect, ranging from understanding the basic biological mechanisms to preclinical applications. Additionally, such a facility could become a hub for developing cutting-edge technologies related to electron sources, dosimetry devices—essential for accurately monitoring doses during irradiation—and advanced electron beam delivery systems. In particular, precise control of the dose rate is critical for radiobiological studies, where it is crucial to correlate FLASH dose parameters with normal cell survival rates after irradiation.

At present, researchers at Sapienza University, in collaboration with the National Institute for

Nuclear Physics (INFN), are involved in several activities related to FLASH radiotherapy. These include the development of compact electron accelerators [24], innovative beam monitoring [71], dosimetry systems [60], and radiobiological research. Furthermore, software development is ongoing to optimize the FLASH effect for patients[62]. The long-standing collaboration between Sapienza and INFN researchers in accelerator technology and related fields, such as beam monitoring and Monte Carlo simulations of particle interactions with biological tissues, provides a solid foundation for advancing electron sources dedicated to FLASH radiation. In 2021, a joint interdisciplinary team from Sapienza and INFN was formed to design a compact VHEE-LINAC based on advanced accelerator technologies. This facility is intended to serve as both a research platform and a tool suitable for hospital environments. It will be available to a broad interdisciplinary research team at Sapienza and open to external national and international researchers.

3.2.1 Facility Parameters and Layout

The core of the facility is a LINAC delivering a high intensity electron beam capable of operating at FLASH dose rates (with an average dose rate > 40 Gy/s). The proposed layout design of the accelerating structure, pictured in Fig. 3.9, is composed of three modules, each dedicated to a research line to investigate different electron energies (9, 60 and 130 MeV):

- In Module 1, located on the left, the first accelerating SW injector is designed to accelerate a current from a pulsed DC gun to approximately 200 mA at an energy range of 9-12 MeV. This LINAC design is based on the experience obtained from the development of the SW ElectronFLASH system[24], which originated from designs created by the Sapienza team. The standing wave scheme was selected primarily due to the extensive expertise the project team has gained with such structures. However, a traveling wave accelerating structure could also be considered for the injector;
- Module 2 involves beam matching using quadrupoles (matching optics) before injecting the beam into a compact linear TW accelerating structure. This structure, with a high accelerating gradient (up to around 40 MeV/m), raises the electron beam energy to approximately 60 MeV;
- In Module 3, the energy is further increased to about 130 MeV through two additional 90 cm long accelerating structures, each followed by quadrupoles to ensure matching conditions. Solenoids surrounding the accelerating structures provide the necessary beam focusing.

The system operates using traditional RF feeding methods to deliver the necessary power for electron acceleration. At the heart of this system is a klystron, which is a specialized vacuum tube that amplifies RF signals. The first klystron, with a capacity of 5 MW, is strategically placed upstream of a circulator. The role of the circulator is crucial—it directs RF power in one direction and prevents any reflected waves from bouncing back to the klystron, thereby protecting it from potential damage. This klystron is responsible for powering the injector, which initiates the generation and acceleration of the electron beam.

In addition, a second, more powerful klystron rated at 50 MW is utilized to energize the first module of acceleration, which is divided between two LINACs that are each 0.9 meters long. The RF power from this klystron is split and guided to these LINACs through a network of waveguides made of hollow metal tubes effectively directing electromagnetic waves to ensure efficient power

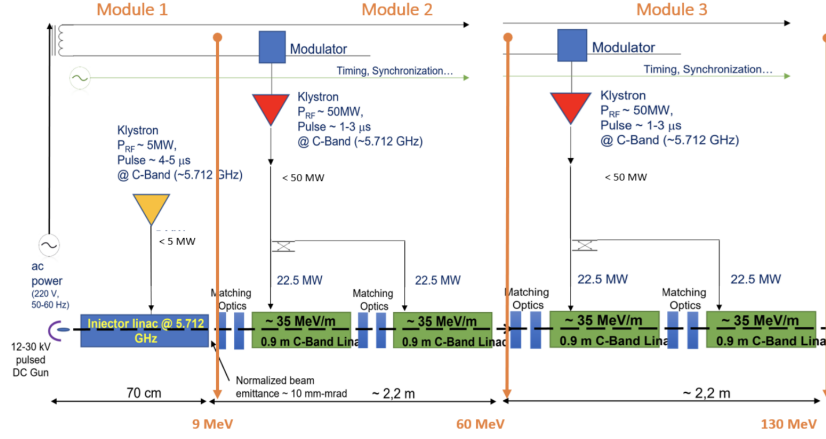


Figure 3.9: Modular layout of the projected SAFEST VHEE-FLASH linac.

transmission. Another 50 MW klystron supports the other two LINACs, emphasizing the importance of robust power distribution in the system. The decision to use TW structures instead of SW ones for high-gradient acceleration stems from the desire to simplify the design by eliminating the need for circulators in high-power environments.

Moreover, the team's previous experience in designing traveling wave structures has played a pivotal role in shaping the current design. In a TW accelerator, the speed of the electron bunch approaches that of light, allowing for a unique phase relationship between the bunch and the accelerating field. This ensures that the electron bunch remains on the crest of the accelerating wave throughout the process, which leads to efficient acceleration even over long distances, maximizing the overall performance of the system. The parameter list that have been considered for the VHEE LINAC design are shown in Table 3.1. The entire LINAC system, including its three main modules, fits

VHEE LINAC parameters		
Beam Energy	E_{beam}	>130 MeV
RF frequency	f_{RF}	5.712 GHz
Pulse repetition frequency	PRF	100 Hz
Pulse duration	t_p	<3 μs
Charge per pulse	Q_p	600 nC
Pulse current	I_p	200 mA
Dose-rate per pulse	$\dot{D}_p$	$>10^7$ Gy/s
Dose per pulse	D_p	$>>1$ Gy
Total treatment time	t_{tot}	<100 ms
Average Dose-rate	$\dot{D}$	>100 Gy/s

Table 3.1: Parameter list of the VHEE LINAC.

comfortably within a room measuring $7 \times 12 m^2$. The accelerator itself is less than 6 meters long, leaving ample space for additional equipment, like dipoles and quadrupoles, to guide the beam toward the experimental area. Three dipoles are needed in any setup to create two parallel experimental lines, while the quadrupoles maintain the beam's transverse profile as it moves. In some cases, scattering materials can be used in the experimental area to widen the beam instead of using the final set of quadrupoles. Each accelerator module includes focusing solenoids to help control the beam size as it travels through the system. The klystrons and modulators are housed in a separate room

that also contains essential cooling systems for the LINAC. This layout ensures that all areas—the LINAC, experimental setups, service rooms, and control room—can be accessed independently, making it easier to manage and maintain the system.

3.2.2 Beam delivery

As previously discussed, the beam delivery system plays a crucial role in modern RT, and this holds true for the SAFEST project as well. The research activities associated with this system are vital for defining the final characteristics of the entire clinical device. This component significantly influences how patients are irradiated and must be closely aligned with the specific clinical details of the anticipated treatment. In particular, designing multi-field treatments targeted at different lesions requires optimizing the number of fields, field directions, and beam features to cater to the pathology and morphology of each individual patient. The dose delivery system must provide the flexibility and performance necessary to meet the requirements of the Treatment Planning System (TPS) for that specific patient. Details on the TPS developed specifically for optimizing these treatments, along with its results, will be presented in Chapter 4. In this landscape within the SAFEST project among the very many possibilities to irradiate the patient, we will concentrate on two quite opposite solutions: flat beam and active scanning.

Flat Beam delivery

As discussed in Section 2.1, this delivery system utilizes a flat beam for each treatment field. In the SAFEST project, the approach to implement this technique is designed to ensure that the entire tumor region is irradiated with a wide beam of specified energy. The energy is calibrated so that the peak dose distribution coincides with the tumor isocenter. From the perspective of the accelerator, producing a flat beam capable of delivering several Gy over a transverse area larger than 100 cm^2 presents challenges due to the large charge that must be accelerated. However, this method is considered optimal for achieving the high dose rates required for the FLASH regime. Furthermore, the intensity of the beam can be adjusted more easily between treatment fields, simplifying operational procedures. The SAFEST LINAC will generate collimated narrow electron beams at the end of the acceleration stage. To achieve the required transverse size for the patient, the system can employ standard magnetic quadrupoles, although a scattering filter presents another viable option. This scattering filter, constructed from low-Z materials, will expand the beam through multiple scattering effects, minimizing the production of *Bremsstrahlung* photons. For example, with a beam exiting the LINAC at a 3 mm FWHM, Fig. 3.10 illustrates the transverse beam size after traveling 50 cm in air and passing through carbon and aluminum scattering filters. Materials such as Silicon Carbide may also be utilized in a system of MLC, which are effective in shaping the scattered beam in the transverse plane to conform the dose to the tumor volume.

Active scanning delivery

The SAFEST LINAC naturally produces collimated narrow electron beams, making the implementation of an active scanning system an intuitive choice. As detailed in 2.1, this method requires precise adjustments in the charge delivered between two distinct pulses to effectively maximize dose conformality. In the active scanning approach, the pencil beam generated by the LINAC is directed

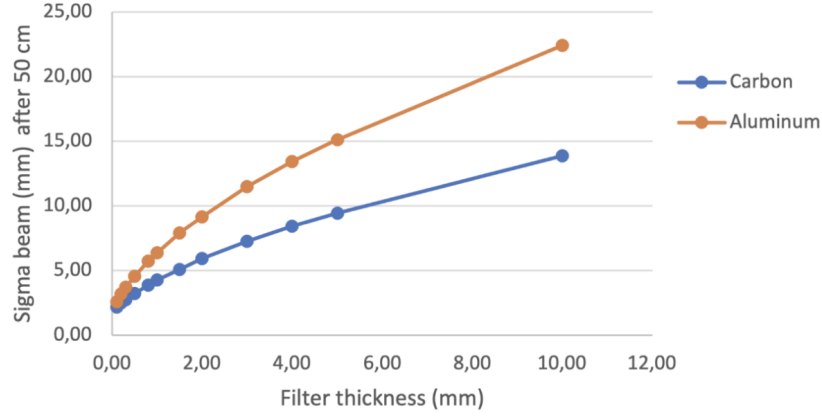


Figure 3.10: Transverse beam size after a path of 50 cm in air after the crossing of a C and Al scattering filters.

towards the target volume using a two-dimensional dipole electromagnet. This electromagnet alters the beam direction with each pulse by changing the current supplied. Notably, the magnetic field required to deflect a 100 MeV electron beam is significantly lower than that needed for a proton beam, owing to the reduced magnetic rigidity of the VHEE beam. For instance, as illustrated in Fig. 3.11, considering a field of view of $20 \times 20 \text{ cm}^2$ and a distance of 0.5 m between the scanning magnet and the patient, implementing a maximum magnetic field $\vec{B} = 0.3 \text{ T}$ would result in a curvature radius $R = 1.7 \text{ m}$ using a 20 cm long dipole. In this way it would be possible to rapidly sweeping the beam across the tumor region, with a highly effective treatment delivery.

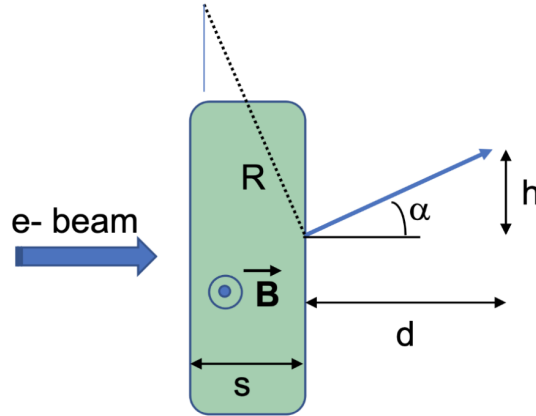


Figure 3.11: Sketch of a scanning bending magnet.

3.2.3 Accelerating structures design

Injector

The first section of the VHEE accelerator, known as Module 1, is an **injector** designed to generate an electron beam with an energy of 9-12 MeV and a peak current of 200 mA. This injector uses a SW structure with magnetic coupling between its accelerating and coupling cavities. The cavities operate in the $\pi/2 - \text{mode}$, while magnetic coupling is achieved through off-axis holes connecting the cells. This design helps maintain efficient acceleration with a null electric field in

the coupling cavities. Figure 3.12 shows a half of a given accelerating cell with off axis holes for the magnetic coupling. Electrons are initially produced in the gun section, where a commercial

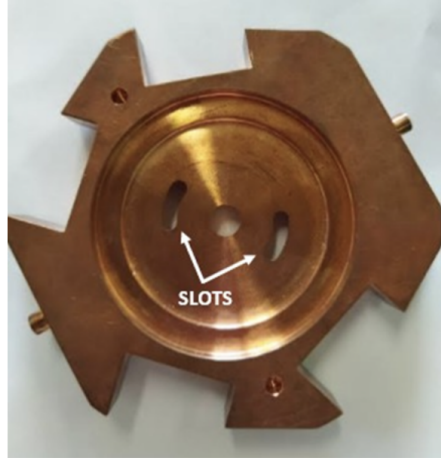


Figure 3.12: Off axis slots for the magnetic coupling of the SW structure.

Electron Gun triode is used. In this setup, electrons are emitted from a thermionic cathode and regulated by a grid placed between the cathode and the anode. The anode has a hole that allows the electron beam to pass through, ensuring precise control over the emission process. The output beam specifications have been studied using SUPERFISH – POISSON software [13], taking into account the internal electron gun field map. The electron gun geometry is shown in Fig.3.13 together with the field map necessary to simulate the motion of particles produced by the cathode.

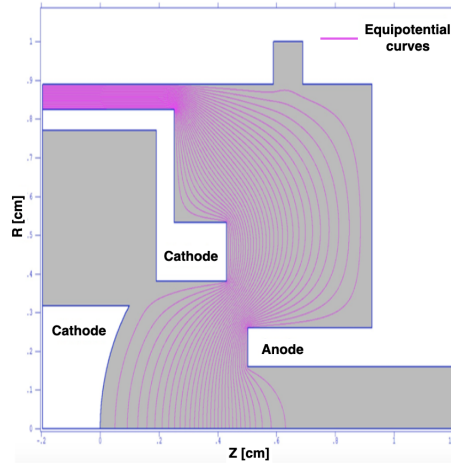


Figure 3.13: Electron gun geometry with equipotential lines.

High gradient accelerating structures

The C-band high gradient TW accelerating structures (Modules 2 and 3) operate with a phase advance per cell $\phi_0 = 2\pi/3$ which guarantees the best efficiency for this type of accelerating cavities. A single RF structure increases the beam energy up to about 35 MeV in a space of about 90 cm, thus respecting the available space constraints. The electromagnetic characterization and the design of the single cell constituting the TW structure were performed with the help of CST Studio Suite [53]. Following preliminary results of beam dynamics, the cell has been simulated with values of

the iris radius a in the range of 3 ± 7 mm, ensuring that for each a the frequency of the monopolar accelerating mode supported by the cell is exactly at 5.712 GHz. The approach used within SAFEST in the LINAC design makes it modular. If higher energies are required in the future—such as for treating deeper tumors—it will be straightforward to extend the system by adding additional accelerating cavities with similar design characteristics.

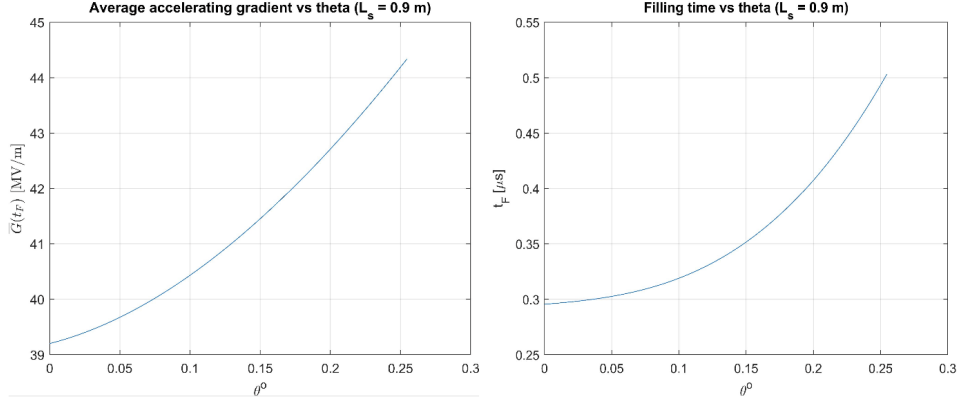


Figure 3.14: Left: average accelerating gradient as function of the tapering angle; Right: filling time as function of the tapering angle.

3.2.4 Beam dynamics studies

Each TW LINAC section in the VHEE regime is composed of 50 cells. The electromagnetic field maps of each TW structure have been generated with the SUPERFISH code and imported into the TSTEP code [82] for beam dynamics simulations. The accelerating loaded gradient is supposed to be 35 MV/m and all LINACs are phased with the electron beam in on-crest operation. A sketch of the LINACs layout and the beam energy gain are shown in Fig.3.15. The maximum energy is around

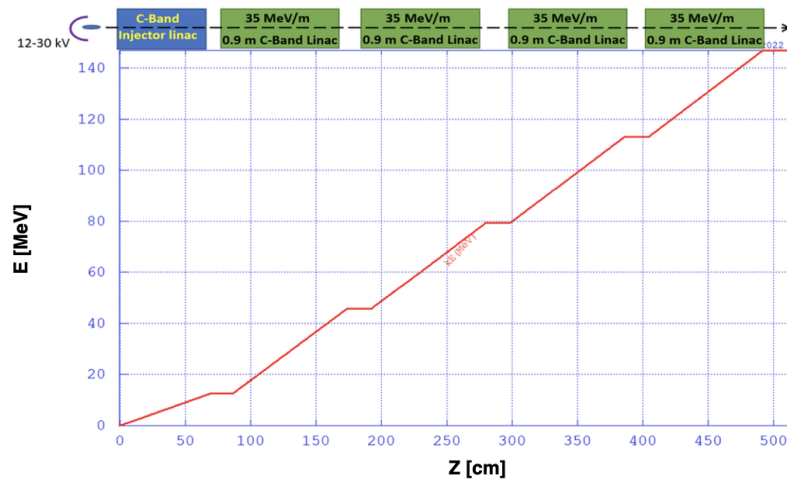


Figure 3.15: Beam energy gain. 12 MeV from the injector into four 90 cm long TW linacs with an accelerating loaded gradient of 35 MV/m. The beam current at the exit is 200 mA.

145 MeV in this condition, well above the design value of 130 MeV. This modular layout confirmed the possibility of optimal transport of the beam up to desired maximum current of 200 mA at exit.

In addition, understanding *beam emittance* is crucial for evaluating the performance of the accelerator. Emittance quantifies the spread of the particle positions and momenta in the transverse plane, providing insight into the beam's quality and focusing capabilities. Lower emittance indicates a tighter beam, which is essential for applications requiring high precision. In Fig. 3.16, the RMS beam envelope, i.e. the spatial distribution and size of the particle beam, is shown. The high-gradient LINACs induce beam RF focusing able to confine the beam without the use of solenoids, which are, nevertheless, foreseen in the facility design. The final LINAC exit is located at about 500 cm. The beam transverse RMS size is about 0.8 mm. The beam phase-space plots at the LINAC exit

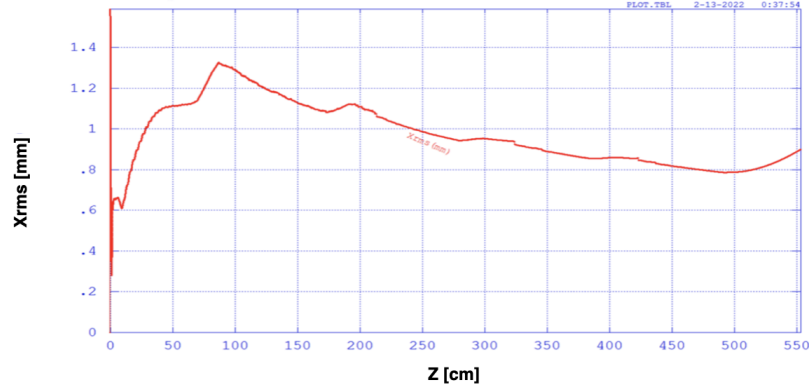


Figure 3.16: RMS Electron beam envelope from the cathode up to the last linac exit at 500 cm.

are given in Fig.3.17. The bunch length is around 20 ps FWHM. The energy spread FWHM value is $<0.2\%$. The beam spot shows a FWHM value of 1.8 mm with the total transverse distribution concentrated in about a 4 mm diameter. The normalized transverse beam emittance is in the order of 10 mm-mrad.

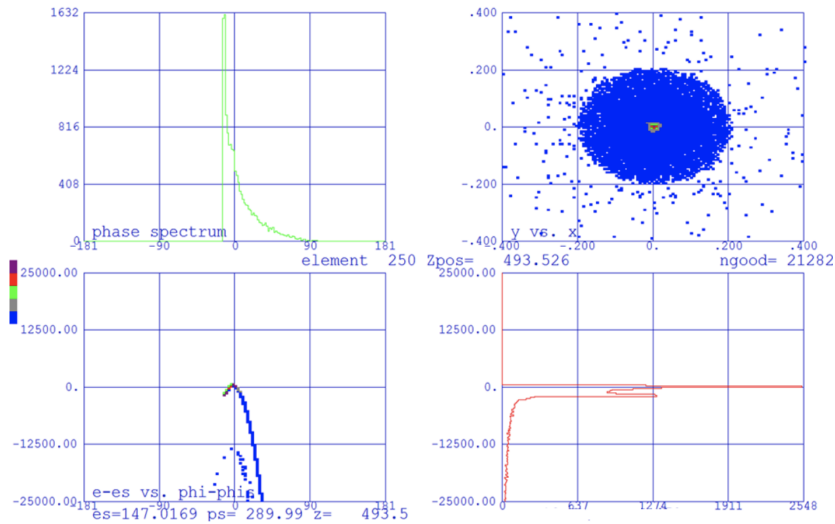


Figure 3.17: Phase-space plots at the exit of the fourth high-gradient linac.

3.2.5 Beam Monitoring and Control Solutions

The proposed VHEE FLASH accelerator will also incorporate advanced beam monitoring and control systems, which are essential for optimizing performance and ensuring safety. Real-time monitoring at UHDR presents a unique challenge in the context of FLASH-RT, as it is crucial for achieving key objectives: advancing our understanding of the FLASH effect to refine therapeutic beam parameters, providing a robust testing ground for the various hypotheses regarding its mechanism, and ensuring compliance with future safety and efficacy standards for FLASH-RT treatments. Conventional radiotherapy detectors, such as ionization chambers, are designed for standard dose rates and may not function reliably under the extreme conditions of UHDR beams. This gap in monitoring technology creates significant obstacles in accurately characterizing dose delivery at UHDR, raising concerns about the precision and safety of treatment outcomes. The main problems of adapting existing monitoring systems to UHDR settings rely on saturation, recombination effects, insufficient temporal resolution and calibration limits. For this reason, several solutions have been explored or are under development. The main additional requirements for a beam monitoring detector with respect to the ones used for reference dosimetry are: high spatial resolution for beam flatness and symmetry measurements, high temporal resolution, high level of beam transparency (as monitors must perturb the beam transport as little as possible), large response dynamic range (as demanded by modern treatment regimes with complex fields), and radiation hardness, since the detectors are a permanent fixture integral to the delivery system and always exposed to radiation[60]. One approach is to improve ionization chambers by incorporating faster electronics and applying real-time corrections for ion recombination, allowing them to handle the high ionization densities typical of UHDR beams [69]. Diamond detectors and plastic scintillators offer another solution, as they can respond more quickly to high dose rates without the saturation issues found in traditional systems [47] [18]. Calorimeters, which directly measure the energy deposited in a material, also provide an alternative, as they are unaffected by ion recombination or saturation, making them ideal for absolute dose measurements in UHDR regimes. Additionally, optical fiber dosimetry and Cherenkov-based detectors offer high temporal resolution and continuous real-time feedback, making them suitable for monitoring rapid dose delivery. Here's a brief overview of the beam monitoring components proposed within the SAFEST project:

- **Beam Position Monitors:** these monitors use advanced strip-line technology made from stainless steel electrodes. They are designed to accurately determine the beam's position and charge, providing essential feedback to the control system. This helps ensure that the beam is precisely where it needs to be for effective operation;
- **Transverse Spot Size Measurement:** High-resolution measurement of the beam's spot size is achieved through Optical Transition Radiation (OTR) screens. To address thermal load issues that can affect standard materials, a thin Kapton film coated with aluminum can be used. A CCD camera captures and analyzes the resulting images to determine the beam's position and size, making it easier to fine-tune the accelerator's output;
- **Beam Current Measurement:** measuring the beam current is a fundamental aspect of ensuring the accelerator functions correctly. For beams with energies above 10 MeV, non-destructive transformers are employed to gauge the current without interfering with the beam. For lower

energy beams, Faraday cups are utilized to provide direct measurements, albeit destructively;

- Control System: the accelerator's control architecture is built on the EPICS framework, a robust system that promotes compatibility with research facilities around the world. It manages feedback from various devices, including radio frequency signals, vacuum systems, and diagnostic tools, facilitating seamless operation of the entire accelerator.

Chapter 4

Treatment Planning System for FLASH VHEE

VHEE, as already discussed in previous chapters, offer significant advantages for treating deep-seated tumors, particularly when delivered in UHDR due to their potential to reduce damage to healthy tissues. Despite the clear potential of VHEE and FLASH, one major hurdle stands in the way: there is currently no dedicated Treatment Planning System (TPS) that can optimize VHEE-FLASH therapy. A TPS is an essential tool in radiation oncology, allowing clinicians to plan and calculate the expected distribution of absorbed doses with precision, ensuring a balance between efficacy and safety. Without a specialized TPS for VHEE, it's challenging to bring this innovative therapy into clinical practice, especially when the unique biological effects of FLASH needs to be carefully controlled and different conditions (yet to be understood and defined) have to be matched to trigger it. As VHEEs and FLASH-RT are not yet clinically available, none of the commercial TPS could be tested on realistic clinical cases, and the adaptation of current calculation codes to VHEEs is not yet widespread. Few research tools (open source or commercial software) exist for testing FLASH or VHEE modalities in complex geometries, as well as for the possible introduction of the FLASH effect into mathematical models of dose optimisation functions. The objective of my work, presented in this chapter, was to bridge that gap by developing a TPS specifically for VHEE, capable of optimizing treatment plans in FLASH mode. Starting from the design of the VHEE accelerator machine (discussed in detail in the previous chapter 3), this work focuses on creating a system that uses FRED, a Monte Carlo-based software developed in-house as first step in the full optimisation chain. FRED exploits the power of GPUs to achieve computational speed-ups by a factor of a thousand compared to traditional Monte Carlo simulations—an essential step for enabling real-time treatment planning, and I have used it to compute the absorbed dose maps needed as input for the optimisation process.

In this chapter, I will outline the key features of the Monte Carlo software, as well as the optimization algorithms that serve as the core of the in-house TPS. Additionally, the results of treatment studies conducted on various patients and tumor types will be presented, illustrating how VHEE could potentially become a compelling alternative to the radiotherapy techniques currently used, with or without accounting for the FLASH potential sparing.

4.1 Treatment Planning Systems

A TPS is an essential software in modern radiation therapy that plays a central role in the design, calculation, and optimization of radiation treatments for cancer patients. Its purpose is to define the overall radiation fluence, its geometry and energy configuration to ensure that the prescribed radiation dose is delivered to the tumor while minimizing exposure to surrounding healthy tissues, particularly critical organs that are sensitive to radiation. The key steps that are defining the TPS workflow are:

1. **Acquire the input data:** the treatment planning process starts from the detailed imaging of the patient, typically consisting of a Computed Tomography (CT) scan, although Magnetic Resonance Imaging (MRI) and Photon Emission Tomography (PET) scans can also be used to define the volumes under treatment and the target volume. These images provide a 3D model of the patient's anatomy, allowing clinicians to accurately visualize the tumor (known as the Planning Target Volume, or PTV) and the surrounding organs-at-risk (OARs). The TPS uses this anatomical data as a foundation to calculate how radiation will interact with the tissues;
2. **Tumor and Organ Delineation:** specialists then use the TPS to define the boundaries of the tumor and nearby organs that must be protected. This process, known as *contouring*, is critical because the precision of these boundaries directly affects the spatial distribution of the absorbed dose that will have to be optimised. Contouring ensures that the tumor receives the maximum dose while minimizing exposure to healthy tissues;
3. **Treatment planning configuration:** once the planning CT images are obtained and the organs are delineated, the oncologist prescribes the doses and sets the dosimetric constraints. Then medical physicists translate the oncologist's clinical objectives into a technically feasible plan making key decisions, such as the number of fields, the beam energy and the beam entry points (gantry angles). This process is based on the specialists clinical experience and judgment and it is typically aided by algorithms within the TPS, which simulate numerous combinations of parameters and propose configurations that best meet the dosimetric constraints;
4. **Dose Calculation:** one of the TPS's most important tasks is to calculate the absorbed dose maps within the patient. The calculation involves complex physical and mathematical models that simulate how radiation—whether it's photons, protons, or electrons—interacts with different types of tissue of different densities;
5. **Optimization Process:** the TPS then optimizes the treatment plan by adjusting the plan parameters—such as the number of radiation beams, their angles, energy and intensity—so that the prescribed dose is delivered to the tumor while sparing nearby organs. This is done using computational minimization techniques. The optimization process is usually guided by a cost function which essentially measures how well a proposed treatment plan meets clinical goals, balancing the need to maximize coverage of the tumor while minimizing the dose to nearby critical structures, that must be under the levels that sensitive tissues can safely absorb. Through iterative adjustments, the TPS seeks to minimize the value of this cost function, producing a treatment plan that optimally delivers the required dose to the PTV while respecting the safety limits for OARs;

6. **Plan Evaluation and Implementation:** once the treatment plan is optimized, the system generates tools like Dose-Volume Histograms (DVHs) to help clinicians assess whether the plan meets the necessary clinical requirements. A DVH is a graphical tool used in radiation therapy to assess the distribution of radiation dose within a patient's body, providing a clear way to evaluate the effectiveness and safety of a treatment plan. The DVH displays the relationship between the radiation dose absorbed by the volume of a specific tissue, organ, or target. Another fundamental tool for evaluating a treatment plan is the analysis of isodose curves. Isodose maps are graphical representations that show curves connecting points in space where the dose is constant, in this way it is possible to display the contours of regions where the dose reaches a predefined value. They can be visualized on various planes (sagittal, coronal, axial) to provide a comprehensive view of the dose distribution. Isodose maps are crucial tools used by radiation therapists to assess the effectiveness of the treatment plan, ensuring tumor coverage while minimizing the exposure of surrounding healthy tissues and organs at risk. After approval, the TPS exports the plan to the radiotherapy machine (such as a linear accelerator or a proton therapy system), which is then programmed to deliver the treatment exactly as designed.
7. **Quality Assurance:** after planning the treatment, the final phase involves performing a quality assurance of the plan: a water phantom is used to verify that the optimized plan matches the plan delivered by the machine. Once this step is complete, the patient is ready to be irradiated.

4.2 Dose calculation: the FRED software

Different 3D dose computation techniques can be used in case of clinical applications. The two main types of approaches to evaluate the dose released inside the patient are the one that implements analytical algorithms and the one that proceeds by carrying on a Monte Carlo simulation. Both of them have advantages and limitations and studies are in progress to improve the efficacy of both software tools.

Analytical algorithm

Most commercial TPS tools are based on analytical algorithms[66] [30]. These tools convert the patient morphology obtained from diagnostic examinations into a water-equivalent path length geometry. This means that each grid voxel is re-scaled by a factor equal to the ratio between the density of the tissue and the density of the water. If we consider a scanning technique, the dose distribution of each spot is modeled by a single pencil beam and described with a 2D distribution function on the transverse plane. The dose distribution of a single pencil beam is described both longitudinally and laterally using analytical functions, that are obtained for each available energy through fits of both MC simulations and experimental data. The primary advantage of analytical algorithms is their speed, as their calculation times are much shorter compared to full Monte Carlo simulations, making them practical for clinical settings where fast simulations are needed. However, this speed comes with a trade-off in accuracy. Analytical models can struggle in cases where there are significant, and sudden, variations in tissue density. In these scenarios, the limited

precision achievable in dose calculation can lead to significant deviations in the treatment planning optimisation, potentially resulting in underdosing the tumor or overdosing nearby critical organs. This limited accuracy can be a concern when treating areas with complex tissue compositions, where precise dose delivery is crucial for both treatment efficacy and patient safety.

Monte Carlo

In order to exceed the limitations of the analytical algorithm related to the accuracy of dose distribution computation, Monte Carlo simulations can be used. It has been demonstrated that the use of MC in PT implied a significant reduction in treatment planning margins [56], due to its accurate physical treatment of the interaction of the beam with the patient tissues. However, the major drawback of MC-based TPSs is their heavy computational demands, which is why full Monte Carlo simulations are usually reserved for particularly challenging cases, final plan validation or research purposes. The high processing power required makes it impractical for routine clinical use. Recently, the development of Graphics Processing Units (GPUs) has transformed this landscape. GPUs have made it possible to create fast Monte Carlo tools, which drastically reduce the computation time compared to traditional CPU-based Monte Carlo methods [36][35]. This dramatic improvement in speed is due to both hardware acceleration and optimized algorithms, making it feasible to use Monte Carlo simulations in regular clinical settings. In the next section, the fast MC algorithm FRED will be introduced in detail. Its electromagnetic model has been employed as the dose engine for calculating dose distributions in the TPS developed in-house as part of this doctoral research.

4.2.1 Fast paRticle thERapy Dose evaluator: FRED

Nowadays, one of the TPS most important research and development active line is the one devoted to the computing time reduction while keeping the highest possible accuracy, opening the way for many clinical applications where the time factor is crucial. To date, most of the implementations are designed for photon and proton therapy applications, as detailed in [63] [36] [68] [49] [37] [76], which are capable to evaluate a treatment plan in a few minutes. An intermediate approach has been followed by the developers of FROG (Fast Recalculation on GPU [48]), which exploits an analytical algorithm running on GPU for fast plan recalculation in particle therapy with p , ^{12}O and ^{16}O ions. In this context, the Applied Radiation Physics Group (ARPG) at "Sapienza" University of Rome, has developed the FRED (Fast paRticle thERapy Dose evaluator) Monte Carlo tool. FRED is a software that exploits the GPU hardware devoted to the recalculation of proton and carbon ions treatment plans, and recently it has been expanded in order to also track light ions, electrons, positrons, and photons. By rapidly recalculating a complete treatment plan within minutes, instead of hours, this tool paves the way for many clinical applications where the time factor is important. In developing the algorithms, the goal is to balance accuracy, calculation time, and GPU execution guidelines. To do so, the most effective physical models from the literature have been chosen, avoiding the simulation of all the process that are not giving a significant contribution to the absorbed dose calculation. For many processes, FRED relies on a library of pre-computed look-up tables instead of performing an explicit calculation. This approach performs extremely well on GPU cards where hardware interpolation can be exploited using the so-called texture units. The treatment plan, simulated by the MC tool, consists of the whole set of beam directions, particle

energy, spot shape, and fluences. A plan is hierarchically decomposed into fractions, each fraction having one or more fields, i.e. treatment directions, with each field consisting of a series of PBs, in the case of PBs scanning delivery technique. As already discussed, the PB encapsulates all the accelerator parameters that can be controlled in a given treatment facility. It corresponds to a single source of particles, controlling direction, angular divergence, and the energy or momentum spectrum of the particles to be traced. During the calculation, each PB generates a user-prescribed number of primary particles, which are traced one by one in parallel by the tracing kernel. The simulation domain is called *Phantom*, and it could represent both a uniform volume of material (e.g. liquid water or PMMA, for testing purposes) or a patient's 3D CT image. The *Phantom* is divided by a Cartesian uniform grid in voxels, each storing information on the local density and atomic composition. The translation of CT values from Hounsfield units (HU) to material properties is performed using a built-in or user-supplied conversion table [64]. The simulation setup is performed by parsing a text file of input parameters, or it can be prepared by a series of python scripts that parse a DICOM file tree containing patient CT scans together with morphological decomposition, radiation therapy plans, and TPS-calculated dose maps. Once the complete geometry has been imported, the primary particles are generated using the plan prescription. Particles are produced inside the accelerator beam-line in a vacuum and tracked one-by-one until they go out of the geometry simulation, or when their energy goes below a pre-defined threshold that has been optimised balancing tracking speed and accuracy.

As far as proton beams are concerned, FRED is already used as a quality assurance tool in the clinical center of Maastricht and Krakow and as a research tool at several clinical and research centers in Europe (e.g. Krakow, Trento, Maastricht, Lyon and PSI). The implemented models and FRED performance were extensively tested versus several measurements in each treatment center that adopted the software and also bench-marked against the most solid full-MC codes FLUKA and GEANT4. The agreement with the two MCs is very good for all models in the energy range of PT (50-250 MeV)[63].

Since few years, FRED software has been updated including a model of carbon ions interactions with matter[19]. The dose engine for carbon ions relies on physics models analogous to the ones used in the FRED protons model, explained in detail in [63], except for the Multiple Coulomb Scattering and the nuclear interactions. In particular the nuclear model, developed completely from scratch, has been parameterized using data already published and this is, as for now, a unique characteristic of FRED.

Recently, the electromagnetic FRED model has been implemented as well. For its relevance and extensive use of this thesis, I am detailing its content in the next paragraph.

4.2.2 Electromagnetic FRED model

The electromagnetic FRED code structure is the same already implemented for hadron tracking: the front-end interface is written in C++, allowing to set up the simulation environment (CT importing, beam energy, and direction setup), while the tracking kernel is coded using CUDA toolkit [55]. FRED architecture foresees a first initialisation stage operated on CPU, where the simulation environment is defined (grid size and dimension, material definition, treatment plan details) and the main physical quantities and properties needed for particle transport are pre-computed and stored in the GPU texture units. The particle tracking is fully operated by GPU, adopting a history-based

approach in which each particle history is followed by a single GPU thread. Tracks are generated step-by-step using a class II MC algorithm [11], i.e. the physical processes acting on the particle are divided into condensed-history or continuous models, and point-like or discrete interaction models [27]. The full FRED operation flow is summarised in Fig. 4.1. To balance accuracy and computation

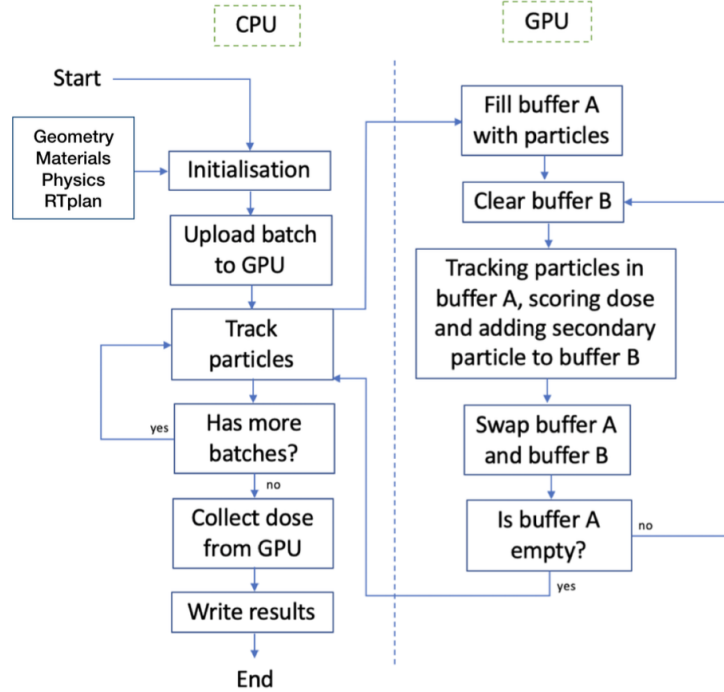


Figure 4.1: Sketch of the FRED architecture, in which the operation on charge of CPU and GPU are distinguished [27].

time, FRED relies on a set of look-up tables (LUT) in which most of the information and parameters needed for particle transport and process simulation are stored at the initialization stage. Such an approach is very efficient on GPU, which are equipped with *texture* units, a dedicated hardware for fast linear interpolation. To test the accuracy of the electromagnetic FRED model, photon and electron beams of 1-100 MeV were simulated in homogeneous and heterogeneous phantoms, and the resulting dose maps were compared to those obtained using state-of-art MCs, as FLUKA [26], [8] and GEANT4 [2], [4], performed in the same conditions, i.e. same geometry, beam and same energy threshold. For the FLUKA simulations the 2020.0.10 version was used, while for GEANT4 the emstandard-opt4 physics constructor, which has most accurate standard and low-energy models, was chosen to obtain a higher accuracy when tracking electrons, positrons and photons. In all the MC simulations the transport and production threshold T_{th} was set to 50 keV for electrons/positrons and to 10 keV for photons. The first results were obtained simulating electron pencil-beams with 10 and 100 MeV energies, that after being generated in vacuum were impinging on a 500 μm thick water target. The electrons energy loss and the deflection angle at the target exit were in excellent agreement with what obtained with FLUKA and GEANT4, as can be observed in Fig. 4.2. In particular, the FRED mean energy loss is compatible with the FLUKA and GEANT4 ones within 2.4% and 1.0% respectively. The same agreement, always within 5.0% and 2.5%, was also met for the mean exit angle. The tests were conducted also on both a homogeneous phantom and a

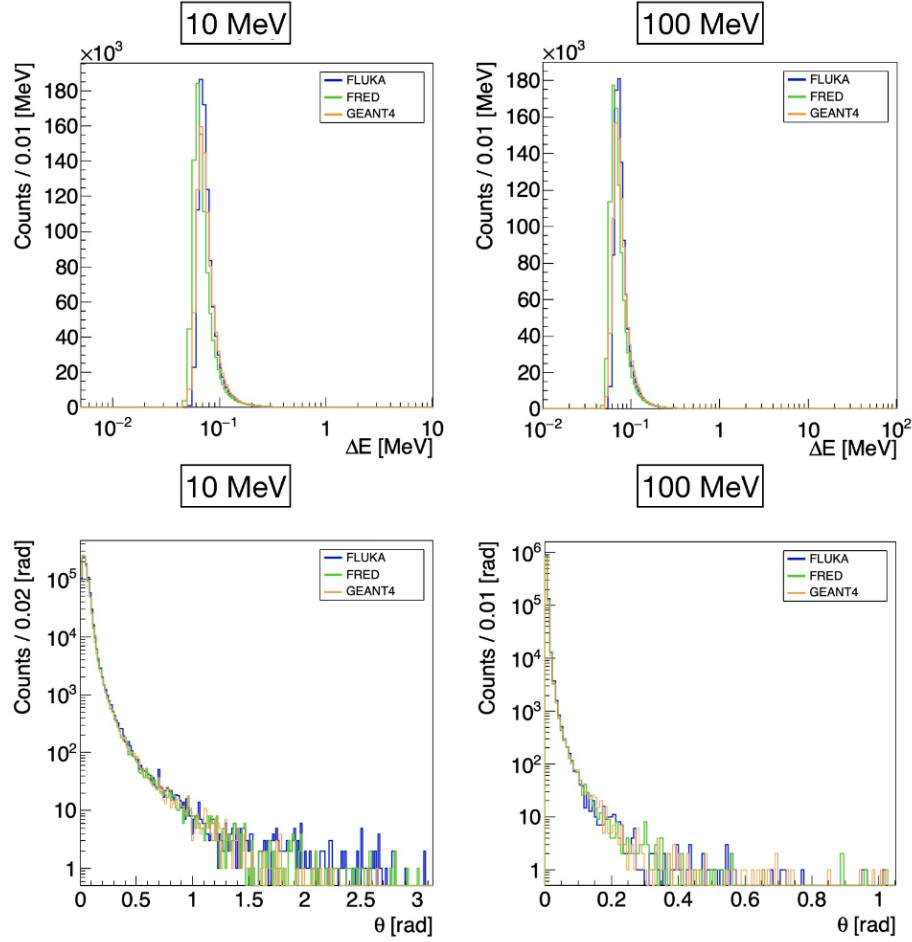


Figure 4.2: Comparison between FLUKA (blue), GEANT4 (orange) and FRED (green) energy loss (up) and deflection angle (down) of electron pencil-beams crossing a water target $500\mu\text{m}$ thick [27].

non-homogeneous phantom. Fig. 4.3 shows the depth dose distributions and lateral dose profiles at the peak value for 1, 10, and 100 MeV electron pencil-beams ($\text{FWHM} = 0\text{ cm}$) impinging on a homogeneous water phantom obtained using FRED, FLUKA and GEANT4. The target dimensions were chosen depending on the particle energy: for 1 MeV electrons, a size of $1\text{ cm} \times 1\text{ cm} \times 1\text{ cm}$ was implemented with a voxel size of 0.005 cm in all the directions. For 10 and 100 MeV simulations, a water phantom of $20\text{ cm} \times 20\text{ cm} \times 15\text{ cm}$ and $20\text{ cm} \times 20\text{ cm} \times 50\text{ cm}$ with a voxel dimension of 0.05 in x and y plane and 0.1 along z were used, respectively. In all simulations the particles enter the phantom along the z-axis after being generated in vacuum. The profiles, that represent the absorbed dose in Gy/primary, were obtained from a simulation performed using 10^7 primary electrons to minimize the statistical fluctuations. The lateral dose profiles were selected at the peak value of the FRED integrated depth dose distributions, i.e. at 0.16 cm, 2.60 cm and 14.0 cm for 1, 10 and 100 MeV. Figure 4.3 also shows the relative dose differences. As it can be seen the agreement between the simulations is always within 2.5%. To test the FRED performance in heterogeneous materials, HeadNeck CT scans were used. Fig.4.4 shows the FRED and FLUKA 2D dose maps and their projection on the x, y, and z planes, obtained simulating a 110 MeV electron field (composed of 386 pencil beams with a Gaussian transverse profile of $\text{FWHM} = 0.5\text{ cm}$) impinging on the HeadNeck CT. Such irradiation corresponds to one of the three fields of a real patient treatment, treated with

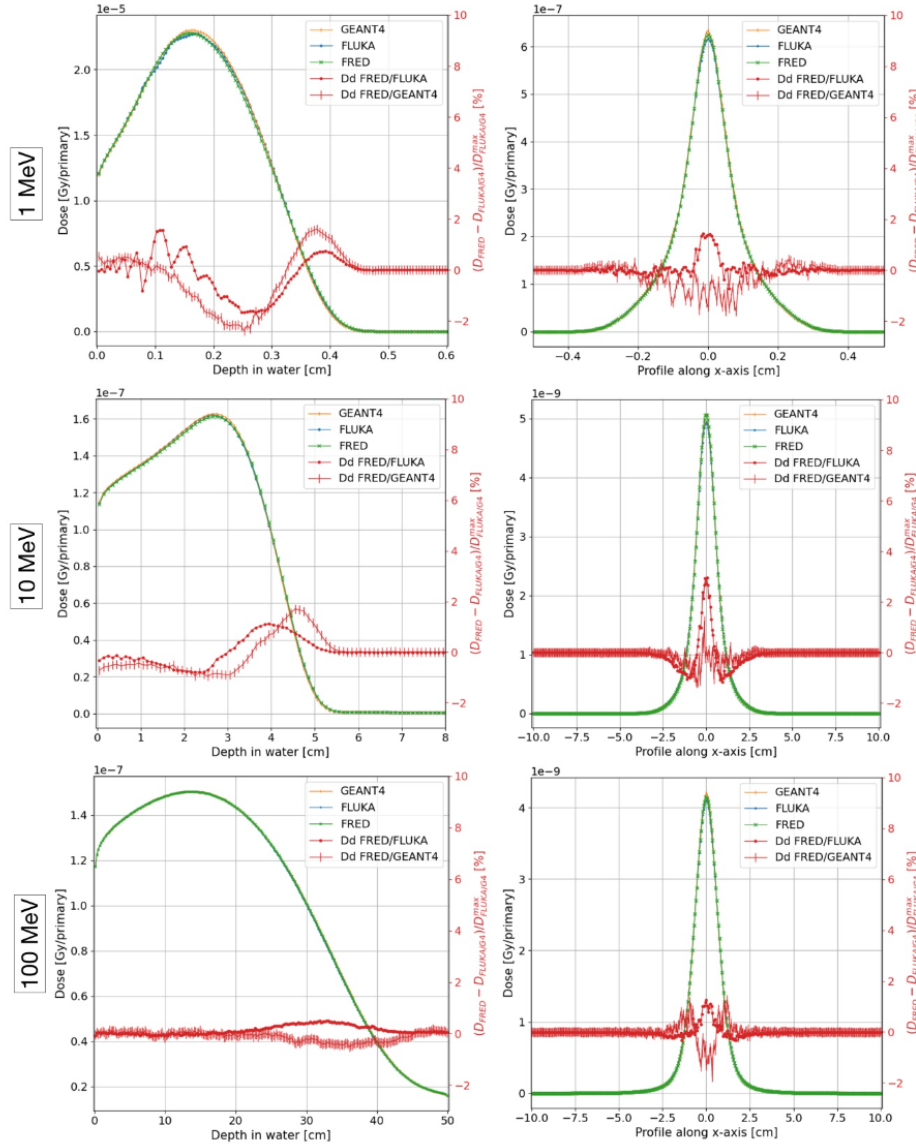


Figure 4.3: Longitudinal (left) and lateral (right) dose profiles for 1,10 and 100 MeV electron pencil beams impinging on water phantom, simulated with FRED (green line), FLUKA (blue line) and GEANT4 (orange line). All the lateral profiles are evaluated at the depth for which the dose is maximum. The red curves report the dose difference (Dd) between FRED and FLUKA (dot marker line) and between FRED and GEANT4 (vertical marker line). [27].

protons with energies ranging from 87 to 130 MeV at the Azienda Provinciale per i Servizi Sanitari (APSS in Trento). The CT has a voxel size of $0.6\text{mm} \times 0.6\text{mm} \times 1\text{mm}$ respectively along the $x \times y \times z$ directions. To reduce the statistical MC fluctuations, the simulation was performed using 10^6 primaries for each pencil beam. To assess the FRED accuracy the global and local gamma-index analysis (with 2mm/3% acceptance criteria) was performed. The obtained results were a global and local gamma-index pass rate between FRED and FLUKA dose distributions of 99.40% and 99.28%, evaluated with a threshold of 5%, with a gamma average value equal to 0.35 and 0.40 respectively. The γ distribution is reported in Fig.4.5.

Thanks to the electromagnetic model of FRED, our TPS is capable of calculating dose with an accuracy better than 3%, achieving the precision required for clinical implementation in VHEE therapy.

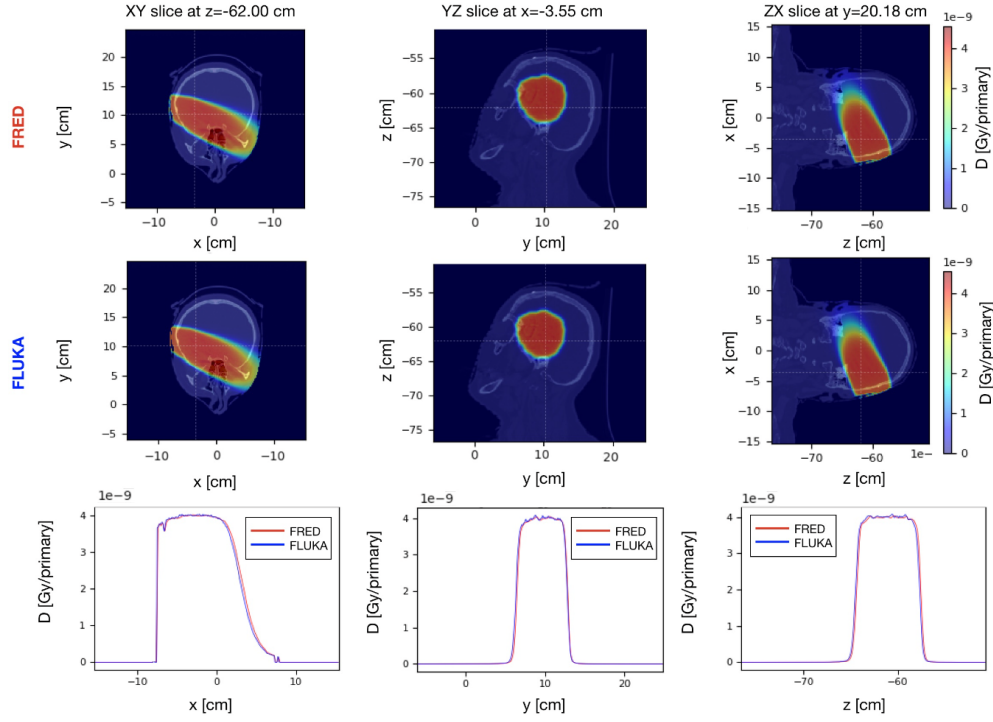


Figure 4.4: A comparison of the dose distributions inside the patient obtained with FRED (top row figures and histogram distribution shown using a red line) and FLUKA (center row figures and histogram distribution shown using a blue line) simulations is reported. The two first rows show the 2D dose distributions on the XY slice at $z=-62.00$ cm (left), YZ slice at $x=-3.55$ cm (center) and on the ZX slice at $y=20.18$ cm (right). The projection of the 2D figures is shown on the bottom. The statistical uncertainties were not included in the plot since they cannot be seen [27].

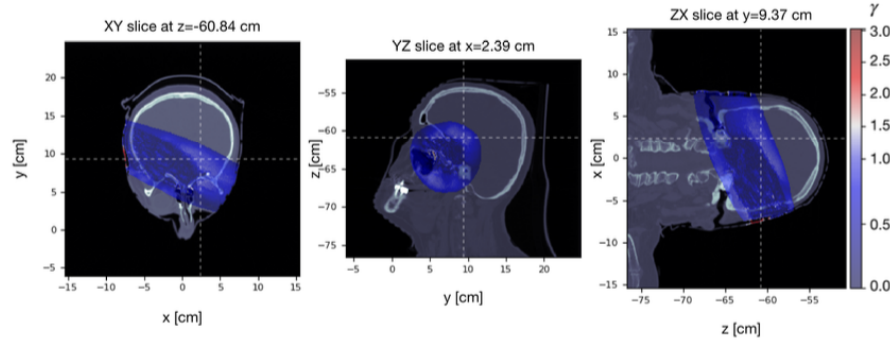


Figure 4.5: Global γ -index distribution of the maps shown in Fig.4.4. The 2mm/3% global gamma-index pass rate between FRED and FLUKA dose distributions is 99.4%, evaluated with a threshold of 5%, with a gamma average value equal to 0.35 [27].

4.3 Optimization tools

In the context of TPS, optimization tools play a crucial role in determining the most effective configuration of beam parameters to achieve the desired therapeutic outcome. These tools are designed to compute the optimal dose distribution by adjusting factors such as beam angles, energies, and intensities, while adhering to clinical constraints on PTV and OARs. At the core of these optimization tools is the minimization of a *cost function*, a mathematical expression that quantifies the trade-off between competing objectives, such as maximizing tumor coverage and minimizing

damage to healthy tissues. The cost function defined and implemented in the TPS for VHEE, developed as part of this thesis project, is reported hereafter:

$$\chi^2 = \sum_{i \in PTV} \frac{(d_i - D_{PTV})^2}{D_{PTV}^2} + \sum_{i \in OARj} \eta_i \frac{(d_i - D_{OARj})^2}{D_{OARj}^2} \cdot \theta(d_i - D_{OARj}) \quad (4.1)$$

where the first term $(d_i - D_{PTV})$ represents the dose conformity to the target. For each voxel i in the PTV the difference between the actual dose d_i and the prescribed dose D_{PTV} is squared. This drives the dose delivered to the target to be as close as possible to the prescribed dose. The second term, instead, penalizes excessive dose to organs at risk: for each organ j it sums the doses delivered to voxels within that organ, if the dose d_i exceeds the maximum acceptable dose D_{OARj} the difference is squared and weighted by η_i which represents the importance of sparing that particular organ. In addition, the heaviside function $\theta(d_i - D_{OARj})$ ensures that only doses exceeding the maximum allowable dose for a given OAR enter the cost function. In general, the TPS uses various algorithms to iteratively adjust treatment parameters. Currently, the most widely used optimization methods in clinic are gradient-based algorithms as well as heuristic approaches like simulated annealing and genetic algorithms.

I equipped the TPS I have developed as part of my thesis with two distinct minimization methods, allowing the user to select the most appropriate approach based on the specific parameters to be optimized. The design of these optimization tools was carefully tailored for treatment planning with a machine capable of delivering both flat beams and active scanning techniques, as outlined in Chapter 3. To do that, one of the methods is a gradient-based optimization algorithm, inspired by the Lomax approach [42], originally designed and used primarily for proton therapy, which efficiently optimizes the intensity of individual pencil beams. This method is particularly suited for scenarios where fine modulation of beam intensities is required to achieve highly conformal dose distributions but can be easily implemented only in the context of 1 dimensional optimisations (e.g. in which only the PB fluences are varied). The second method utilizes simulated annealing, offering the flexibility to optimize both the intensity (either uniformly or with varying modulation) and the energy of each individual beam. This dual capability allows for greater control over the treatment plan, particularly in cases where energy modulation is critical. In the subsequent sections, I will provide a detailed overview of these optimization techniques, highlighting their key characteristics, specific applications, and strengths in treatment planning for VHEE therapy.

4.3.1 Gradient-based algorithm

Gradient-based optimization methods are widely used in treatment planning systems due to their efficiency and ability to handle large-scale problems like the ones typical for radiotherapy applications. These methods leverage gradient information to iteratively adjust treatment parameters and minimize the defined cost function, achieving optimal dose distributions. At the core of gradient-based optimization lies the calculation of the gradient of the cost function $\chi^2(\mathbf{x})$ where $\mathbf{x}$ represents the vector of treatment parameters (such as beam intensities, angles, or energies). The gradient $\nabla \chi^2(\mathbf{x})$ provides information about the direction of the steepest increase in the cost function. By following the negative gradient direction, these methods iteratively adjust $\mathbf{x}$ to minimize $\chi^2(\mathbf{x})$. For the optimization of individual pencil beam intensities, with the beam energy fixed, the TPS

I developed utilizes a specific gradient-based approach known as the LOMAX method, designed specifically for IMRT-like treatments [42], employing a *conjugate gradient* algorithm to efficiently minimize the cost function. Rewriting the cost function to explicitly express the pencil beam intensity vector, we have:

$$\chi^2(\vec{I}) = \sum_{i \in PTV} (d_i(\vec{I}) - D_{PTV})^2 + \sum_{i \in OAR^j} \eta_i (d_i(\vec{I}) - D_{OAR^j})^2 \theta(d_i - D_{OAR^j}) \quad (4.2)$$

where $\vec{I}$ is the vector of the PBs intensities and the other quantities were described previously. To optimize the beamlet intensities, the gradient of the cost function $\nabla \chi^2(\vec{I})$ with respect to the intensity vector $\vec{I}$ is calculated. The gradient gives the direction of the steepest ascent (or descent, if negated) of the cost function, as follow:

$$\nabla \chi^2(\vec{I}) = 2 \sum_{i \in PTV} (d_i(\vec{I}) - D_{PTV}) \cdot \frac{\partial d_i}{\partial I_n} + 2 \sum_{i \in OAR^j} \eta_i (d_i(\vec{I}) - D_{OAR^j}) \theta(d_i - D_{OAR^j}) \cdot \frac{\partial d_i}{\partial I_n} \quad (4.3)$$

where $\frac{\partial d_i}{\partial I_n}$ represents the sensitivity of the dose at voxel i with respect to the n -th pencil beam intensity. Instead of using standard gradient descent, the conjugate gradient method improves the efficiency of optimization by considering the previous step direction, helping to avoid zig-zagging behavior and accelerating convergence. The conjugate gradient method updates the PB intensities $\vec{I}$ as follows:

$$\vec{I}_{n+1} = \vec{I}_n + \alpha_n \vec{p}_n \quad (4.4)$$

where α_n is the step size (learning rate) determined through a line search and $\vec{p}_n$ is the conjugate direction, calculated as:

$$\vec{p}_n = -\nabla \chi^2(\vec{I}_n) + \beta_n \vec{p}_{n-1} \quad (4.5)$$

The conjugate direction $\vec{p}_n$ is a linear combination of the current gradient and the previous direction. The parameter β_n determines how much of the previous direction is carried forward and is given by:

$$\beta_n = \frac{\nabla \chi^2(\vec{I}_n)^T \cdot \nabla \chi^2(\vec{I}_n)}{\nabla \chi^2(\vec{I}_{n-1})^T \cdot \nabla \chi^2(\vec{I}_{n-1})} \quad (4.6)$$

The algorithm continues to iterate, updating $\vec{I}$ until one of the following conditions is met: a maximum number of iterations is reached or the change in the cost function between iterations is below a predefined threshold.

The conjugate gradient method implemented in this optimization process assumes that the Hessian matrix—representing the second-order partial derivatives of the cost function with respect to the PB intensities—is symmetric and positive definite. This symmetry ensures that the search directions in the optimization process are conjugate with respect to the Hessian, meaning each new search direction is orthogonal to the previous ones in the transformed space. When the Hessian is non-symmetric, this key assumption breaks down. Additionally, the LOMAX method assumes that the cost function is approximately quadratic near the minimum. However, if the cost function is highly non-linear (for example, in optimization problems involving energy modulation techniques), the conjugate gradient method may not provide a good approximation. This is the reason why if one wants to select the energy of the field together with the intensity of each PB, it may be necessary to combine this

method with other non-linear optimization technique. To achieve this, in the TPS I developed, minimization methods such as Simulated Annealing are used whenever the beam energy needs to be optimized in addition to the treatment beam intensities.

4.3.2 Annealing minimization methods

Simulated Annealing

Simulated annealing (SA) is a probabilistic optimization technique inspired by the physical process of annealing in metallurgy, where materials are heated and then slowly cooled to reduce defects and achieve a stable crystalline structure. In the context of minimization, SA is used to find a global minimum of a cost function, particularly in complex, high-dimensional spaces where traditional gradient-based methods may get trapped in local minima. The problems solved by SA are formulated by an objective function of many variables, subject to several mathematical constraints, which perfectly aligns with the mathematical framework underlying treatment plan optimization, as explained in the previous section. Being $\chi^2(\vec{x})$ the cost function previously defined, where $\vec{x}$ in this case represents the set of parameters (such as PBs intensities and beam energies) to be optimized, the algorithm looks for the minimum of the function:

$$\min_{\vec{x}} \chi^2(\vec{x}) \quad (4.7)$$

To do so, it starts with an initial solution x_0 and an initial temperature T_0 . The temperature T is a control parameter that gradually decreases over the course of the optimization. At high temperatures, the algorithm explores the solution space more freely, while at low temperatures, it focuses on exploiting the current solution. At each iteration, the algorithm generates a new candidate solution x_{new} by perturbing the current solution $x_{current}$:

$$x_{new} = x_{current} + \Delta x \quad (4.8)$$

where Δx is a small random change in the solution. The acceptance of x_{new} depends on how it affects the objective function $\chi^2(\vec{x})$. If:

$$\chi^2(x_{new}) < \chi^2(x_{current}) \quad (4.9)$$

then, the new solution is accepted. If not, the new solution is accepted with a probability given by the Metropolis criterion:

$$P = e^{-RT} \quad (4.10)$$

where T is the current temperature and R is a factor that depends on the difference in the cost function and two fixed adimensional parameters (a and w_{cost}) that makes the user able to tune the algorithm based on the required speed and accuracy. In the algorithm I developed, the term R has been chosen in the following form:

$$R = \frac{\Delta \chi^2}{\chi^2} \cdot \frac{a}{w_{cost} \cdot T} \quad (4.11)$$

This probabilistic acceptance allows the algorithm to escape local minima early in the process by accepting worse solutions with a higher probability when the temperature is high. As the temperature

decreases, the acceptance of worse solutions becomes less likely, guiding the search toward the global minimum. In fact, there is a cooling schedule controlling how the temperature decreases over time. The one implemented in the VHEE TPS is here reported:

$$T = 1 - \log\left(\frac{k}{MAX_k}\right) \quad (4.12)$$

where k is the current iteration and MAX_k is the maximum iteration value set. In this way, the temperature T is reduced slowly to allow sufficient exploration of the solution space. The dependence of SA progression on the initial temperature for linear annealing schedule is shown in 4.6. The

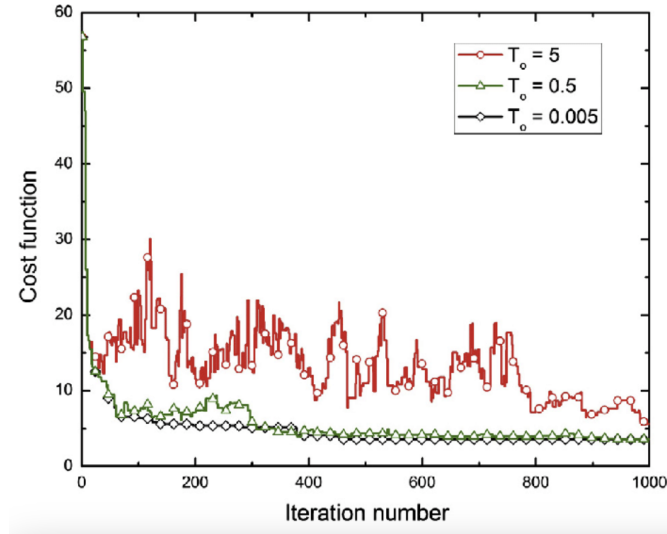


Figure 4.6: Dependence of Simulated Annealing progression on the initial temperature for linear annealing schedule [83].

algorithm stops when a termination criterion is met, such as when the temperature falls below a predefined threshold T_{min} or after a maximum number of iterations. By this point, the solution should be near the global minimum.

Quantum Simulated Annealing

The algorithm I developed also includes the use of an alternative method called Quantum Simulated Annealing (QSA), which is more suitable for very large, complex, and non-convex optimization problems, where traditional methods are too slow or inefficient. It is a variant of SA that leverages principles from quantum mechanics to further improve exploration of the solution space. In particular, QSA is related to *quantum tunneling*, a quantum phenomenon where a particle can "tunnel" through energy barriers instead of having to climb over them, as would be required in classical systems. It can happen that in classical SA the system can become stuck in local minima because it relies on thermal fluctuations to jump out of them, see 4.7. Instead of relying on thermal energy to explore the solution space, quantum tunneling, on the other hand, allows the system to escape from local minima more efficiently, even when the "barriers" (i.e., sharp changes in the cost function) are high. In this case, the probability of accepting a new solution, even if the cost function

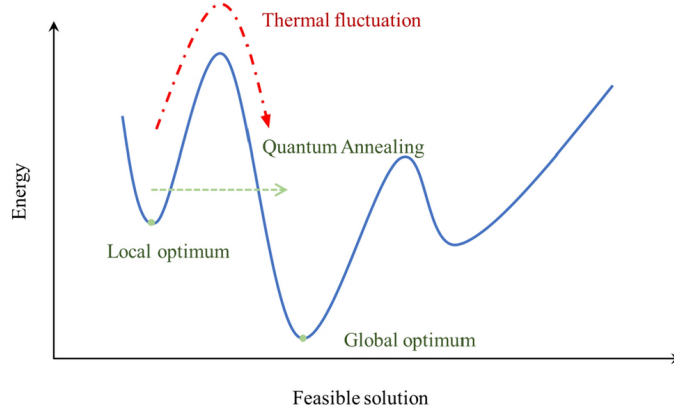


Figure 4.7: Comparison between simulated annealing and quantum annealing [77].

is higher (see 4.10), is ruled by the factor R that becomes:

$$R = \sqrt{\frac{\Delta\chi^2}{\chi^2} \cdot \frac{1}{w_{cost}} \cdot \frac{a}{T}} \quad (4.13)$$

where all the parameters are above defined. This mechanism can be used to speedup the convergence towards the real global minimum of the cost function, avoiding being trapped in local minima.

4.4 VHEE TPS applications

The primary objective of my Ph.D. thesis is to explore the potential of VHEE-based radiotherapy, using the TPS I have developed, through a feasibility study conducted *in silico* using as input the cases of patients to which treatment plans were already clinically delivered. To do this, I started from the VHEE treatment plan design, assuming the use of the active scanning technique for the beam delivery that I have already discussed in a previous paragraph 2.1. The number of VHEE beams, the (initial) energies for each field, the number of pencil beams, along with their sizes and spatial distribution, were defined using the criteria that will be detailed in section 4.4.1. Once the configuration was set, the absorbed dose maps were obtained by MC computation for each PB in the treatment plan, using FRED. At that point, the fluence of each PB and/or the energy of each field was optimized to ensure the required PTV coverage while sparing the OARs, according to what presented in section 4.3. In this thesis, to explore the feasibility of VHEE for treating deep-seated tumors with a limited number of irradiation fields, two different anatomical regions were considered: intracranial lesions and three different patients affected by pancreatic tumors. In the first case, a meningioma was chosen to investigate how VHEE could be used to manage challenging irradiation geometries, where the PTV is closely surrounded by several OARs, making their sparing difficult. Furthermore, the reason for selecting these regions to assess the FLASH potential is that they provide an excellent opportunity to test the ability of conventional and FLASH irradiation to offer additional sparing for the OARs, which are currently limiting the dose prescribed to the PTV. Moreover, the study of the three patients with pancreatic cancer is particularly interesting because the management of pancreatic cancer is challenging due to the aggressive biological behavior of the disease and the toxicity induced into the main organ at risk, the duodenum, where the maximum absorbed dose should not exceed a threshold value to avoid severe consequences, including death.

The results of VHEE irradiation were compared with state-of-the-art conventional photon or PT treatments (used to actually treat the patients) by evaluating the optimized dose maps, isodose maps, and DVHs (tools that will be thoroughly explained in the following). Additionally, the potential of the FLASH effect for treating these pathologies was explored by analyzing optimizations performed through the modeling of the effect (according to what has been described in section 2.2.3).

4.4.1 Treatment plan design

VHEE irradiation was simulated assuming the compact C-band beam acceleration and delivery technology detailed in chapter 3, which will be capable of delivering, with an active scanning-like approach, beams of the required energy with variable angular aperture (~ 1 mrad) and a negligible energy spread. The patient's planning CT, the entry points and the dosimetric constraints for each organ, together with the prescribed dose for the PTV, are provided by the hospital where the patients were treated, while the PB configuration and the energy of each field had to be carefully chosen in order to achieve the best VHEE plan structure.

Pencil Beam configuration

The size and aperture of the electron PBs used to irradiate the PTV were defined following an approach similar to active scanning implemented in proton beam delivery. A plane perpendicular to the line joining the electron beam emission point with the PTV centre was used to project the PTV and define the area that has to be covered by the single pencil beam in each field. The PBs have a Gaussian distribution, with a Full Width Half Maximum (FWHM) set to a reasonable value to ensure proper overlap (and guarantee PTV coverage) for electrons of energies in the range between 70 and 130 MeV, whose target is a deep-seated tumor and therefore experience significant broadening due to multiple scattering interactions. Additionally, to reduce the number of spots per single beam, and thus the computational time required for both treatment planning and delivery (with FLASH delivery regime in mind where the lesser the PBs are, the faster we go and the higher is the dose rate), the spot spacing between two adjacent PBs varies according to the irradiation geometry and target volume. Near the PTV edge, where we are targeting the best possible dose conformity to avoid unnecessary dose to the surrounding OARs, the PB spatial distribution is denser, with narrower PBs; conversely, at the center of the PTV, where the most important goal is dose homogeneity across the whole PTV, it is possible to decrease the PBs spatial density and implement PBs with a larger FWHM. A geometrical region is hence defined for each field within which the PBs are more densely distributed, based on the size and anatomical location of the tumor. An example is shown in Fig.4.8, where the projections of the PTV and the distribution of the PBs for each of the 5 fields planned for the VHEE simulation on a patient with pancreatic cancer are presented (details and results will be discussed in section 4.4.3). In red, the outer margin is shown (in this case, set at 0.9 cm): within this region, PBs were simulated with a FWHM of 0.7 cm and positioned with a spacing of 0.7 cm from each other; in the central part of the PTV, on the other hand, PBs have a FWHM of 1.2 cm and a spot spacing of 1 cm. Once the size and spacing of each pencil beam are defined, the selection of the beam energies planned for the treatment is made using a single pencil beam, delivered at the center of the PTV, ensuring that the absorbed dose peak placed at the center of the tumor is maximized while simultaneously minimizing the dose absorbed by the surrounding healthy tissue.

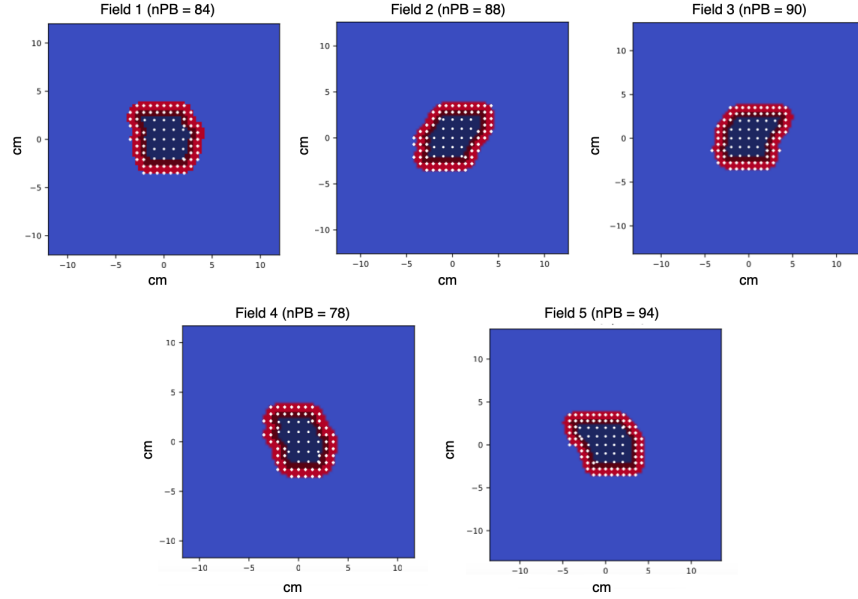


Figure 4.8: Projections of the PTV and the distribution of the PBs for a 5 fields plan on a pancreatic patient. The outer margin (in red) is set at 0.9 cm. The FWHM of the PBs inside this margin is 0.7 cm, with a spacing of 0.7 cm; in the central part of the PTV (dark blue), PBs have a FWHM of 1.2 cm and a spot spacing of 1 cm.

Field Energy selection

The selection of the beam energies for the treatment, in the range of VHEE (70-150 MeV) is made looking at the dose distributions obtained simulating a single PB delivered at the center of the PTV, ensuring that the absorbed dose peak at the center of the tumor is maximized while simultaneously minimizing the dose absorbed by the surrounding healthy tissue. To do this, for each beam, the plot shown in Fig.4.9 is analyzed. In this figure, the dose release profiles of the single PB are shown at the top, with different colors representing different energies. At the bottom of the plot, the geometric profile of the PTV (in red) and the patient's body (in black) are displayed. The energy associated with the curve that shows a maximum value at the center of the PTV and minimal values at its edges is selected. The method just described provides a qualitative analysis of the VHEE beam energy values that best approximate the goal of an effective treatment plan, namely, a plan capable of delivering the maximum dose to the tumor while preserving the surrounding healthy organs. The values selected in this way are used for the simulation of dose maps, which are then input into the TPS minimization methods. If the goal is to optimize only the intensity of individual PBs, these values represent the final energies of the optimized plan. Alternatively, when using the option offered by simulated (or quantum simulated) annealing to also optimize the beam energies, these values serve as a starting point for optimization, from where the algorithm explores the surrounding phase space. In this second case, it is necessary to provide the TPS with dose maps across the entire range of energies to be explored, so that the optimization can select the energy value that minimizes the cost function.

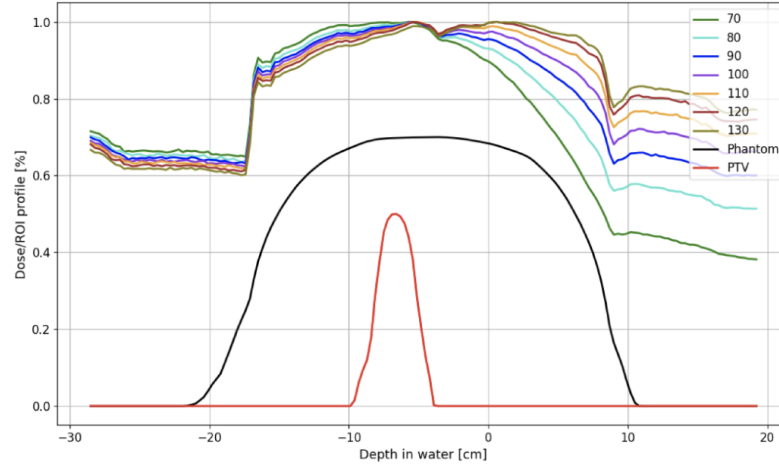


Figure 4.9: Dose distribution of a single PB simulated to be delivered at the center of the PTV. At the top the dose release profiles with different colors representing different energies. At the bottom the geometric profile of the PTV (in red) and the patient's body (in black). This profiles refer to a pancreatic case study.

FLASH EFFECT parametrization

To explore the potential impact of the FLASH effect in VHEE treatments, I have made some assumptions, based on the currently available experimental data and took into account the beam delivery technology that might be used. A dose rate that exceeds 40 Gy/s has been assumed in the following, for all the fields and the OARs of interest, ensuring that a sizeable contribution from the FLASH irradiation can be obtained. The biological dose in FLASH delivery mode was evaluated for all the OARs voxels using the model detailed in 2.2.3. The specific values of D_{th} (dose threshold) and FMF_{min} (minimum FLASH modifying factor) that can be used in the aforementioned model to account for the specifics of VHEE treatment, are strongly dependent on the outcome of the ongoing experimental campaign [74]. The FLASH effect sparing characterization in terms of the absorbed dose, dose rate, and fractionation schemes is being constantly improved but does not cover yet clinical conditions. To explore different scenarios I therefore performed a first attempt of biological dose optimization together with a parameters scan, varying D_{th} and FMF_{min} in a reasonable range of values that have been identified using the preliminary data already available. In this way I had the chance to investigate how the reduced damage to the OARs can be used to enable an escalation to the PTV dose prescription and improve the tumor control.

4.4.2 Study of intracranial lesions

The first study performed on intracranial lesions is based on the input data from two patients (labeled as M1 and C1) who underwent PT at the Azienda Provinciale per i Servizi Sanitari (APSS) centre in Trento for a meningioma (M1) and a chordoma (C1). Both patients were treated with protons using a conventional dose rate ($\sim$ Gy/min), and the prescriptions currently in use at the Trento therapy centre. The target volume was identified, and the constraints on PTV coverage, OAR sparing, and details on the irradiation approach were defined. More information about the two PT plans, containing the prescriptions expressed in terms of the biological dose and hence in Gy (RBE) or absorbed dose multiplied by the relative biological effectiveness (RBE), is reported as follows:

- Patient M1: Three fields were used, with a prescription to the PTV of 54Gy(RBE) in 27 fractions. The dosimetric constraints are listed in 4.1.
- Patient C1: Four fields were used. The treatment was delivered with a simultaneously integrated boost (SIB) technique for a total dose of 60 Gy(RBE) to the boost PTV and 54 Gy(RBE) to the PTV in 30 fractions. A sequential boost of 6 Gy (RBE) in three fractions was then delivered to the boost PTV increasing its final dose to 66 Gy(RBE). The dosimetric constraints are listed in 4.2.

Patient M1		
Organ	Dosimetric constraint	Volume [cc]
PTV	$V_{95\%} > 95\%, D_{max} \leq 105\%$	20.71
Optic nerves	$D_1 \leq 54 \text{ Gy(RBE)}$	0.95
Chiasm	$D_1 \leq 54 \text{ Gy(RBE)}$	0.03
Posterior optical path	$D_1 \leq 54 \text{ Gy(RBE)}$	0.45
Eyeballs	$D_1 \leq 40 \text{ Gy(RBE)}$	8.14
Brainstem	$D_1 \leq 54 \text{ Gy(RBE)}$	28.19
Carotid arteries	$D_{max} \leq 105\%$	1.15

Table 4.1: Planning prescriptions for patient M1. D_{max} and D_{mean} are the maximum and average dose absorbed in the volume of interest, respectively. V_{XX} is the fractional volume of a given OAR (or PTV) receiving a dose of (XX Gy). $V_{95\%} > 95\%$ requirement means that 95% of the volume should receive more than 95% of the prescribed dose. $D_1 \leq YY \text{ Gy}$ requirement means that the minimum dose in the hottest 1% of the volume should not exceed YY Gy. Total volume (in cc) of the PTV and OARs is listed in the last column.

Patient C1		
Organ	Dosimetric constraint	Volume [cc]
PTV	$V_{95\%} > 95\%, D_{max} \leq 107\%$	99.15
PTV boost	$V_{95\%} > 95\%, D_{max} \leq 107\%$	71.94
Brainstem	$D_1 \leq 55 \text{ Gy(RBE)}$	27.09
Spinal cord	$D_1 \leq 54 \text{ Gy(RBE)}$	8.25
Parotid glands	$D_{mean} \leq 26 \text{ Gy(RBE)}$	26.26
Middle ears	$D_{mean} \leq 30 \text{ Gy(RBE)}$	3.80
Cochlea	$D_{mean} \leq 35 \text{ Gy(RBE)}$	0.35

Table 4.2: Planning prescriptions for patient C1. D_{max} , D_{mean} , V_{XX} , and D_1 definitions and uses are same as those explained in the caption of Table 4.1

The clinical proton plans delivered to the patients were sent to the Medical Physics Unit of Policlinico Umberto I in Rome to carry out the IMRT treatment planning, together with the

dose prescriptions, the details about the OARs constraints, and the CT imaging data. The same information was also used to plan VHEE treatments. The IMRT plans were optimised assuming a static field delivered on a 6 MV-Elekta Versa HD linear accelerator [54] and using the Pinnacle [80] software suite (RTP system version 16, <https://pinnacle-software.com/>), according to the prescribed dose and constraints provided by the Trento APSS particle therapy centre. Both IMRT plans comprised seven fields and matched the requirements set in 4.2 and 4.1. Two beam configurations were defined for each patient: three or seven fields for M1 and four or seven fields for C1, using the beam directions chosen for IMRT and PT plans. When designing the VHEE plan configuration, the FWHM of each PB was set to 1 cm and the energies needed to irradiate the target were chosen, as explained in 4.4.1, resulting in:

- **M1 - three fields:** [110, 110, 100] MeV;
- **M1 - seven fields:** [90, 100, 100, 110, 100, 100, 90] MeV;
- **C1 - four fields:** [120, 90, 90, 120] MeV;
- **C1 - seven fields:** [120, 80, 60, 60, 60, 60, 90] MeV;

As an example, a schematic view of the irradiation geometry overlaid on the absorbed dose map for the 3-fields plan for patient M1 is shown in Figure 4.10. No treatment optimization was performed in this case, i.e., the figure shows the absorbed dose for pencil beams containing 10^6 electrons each. For all configurations, after obtaining the absorbed dose maps performing MC simulations for each

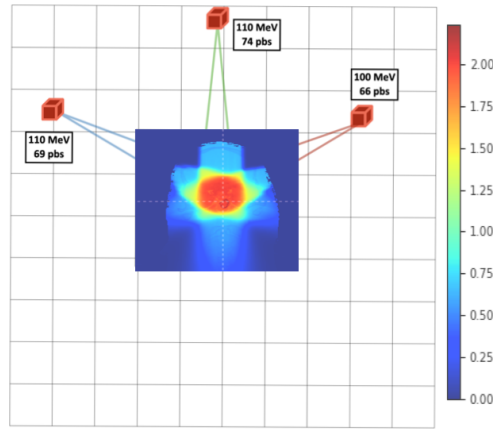


Figure 4.10: Absorbed dose distribution of M1, in Gy per single fraction, used as an input for the optimisation process. The figure shows the configuration of the plan using three fields, reporting the number of PBs of and the energy of each beam. All pencil beams have 10^6 electrons.

PB in the treatment plan, the fluence of each PB is chosen to ensure the required PTV coverage and OAR sparing. The optimization algorithm used for these patients is the gradient-based, and the absorbed dose maps for the three techniques (IMRT, PT, and VHEE) were used to compute the DVHs and quantitatively compare the treatment plans. The DVH comparisons are shown in Fig. 4.11 (IMRT vs. VHEE) and Fig. 4.12 (PT vs. VHEE) for M1 and in Fig. 4.13 (IMRT vs. VHEE) and Fig. 4.14 (PT vs. VHEE) for C1.

The optimised isodose curves for all the patients and radiation types are shown in Appendix A. As an example, Fig. 4.15 shows the isodose curves for the 3-fields VHEE plan for patient M1, and Fig. 4.16 shows those for the 4-fields VHEE plan for patient C1.

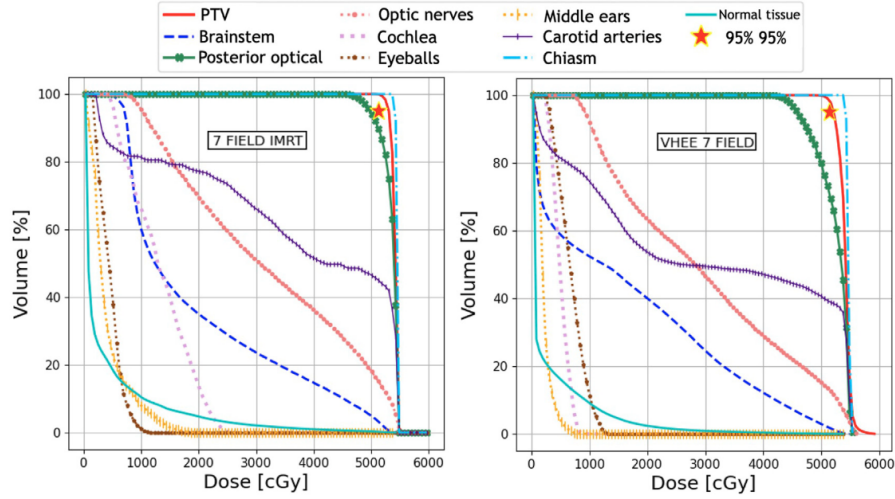


Figure 4.11: Plan comparison between IMRT and VHEE for patient M1. DVHs for the PTV and OARs from the IMRT plan are reported on the left, whereas the VHEE results obtained assuming an irradiation with seven fields are shown on the right. The absorbed dose relative to the unspecified normal tissue is also shown.

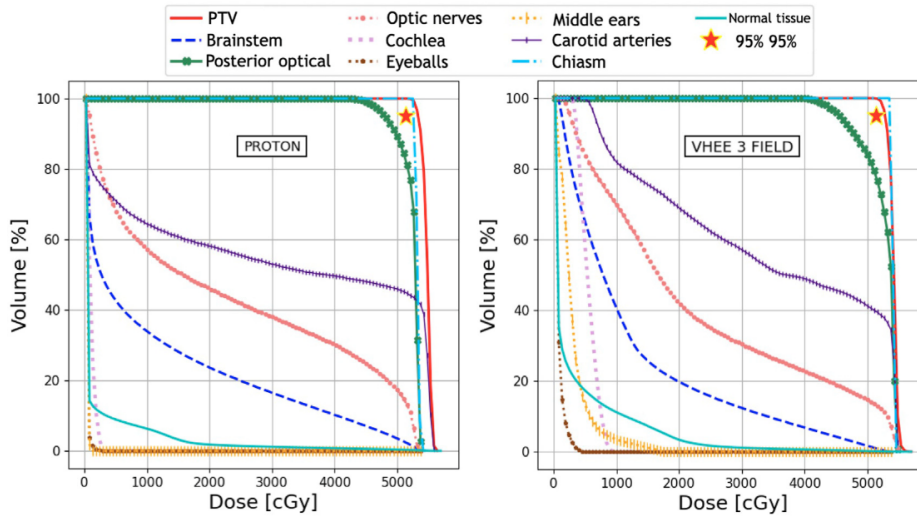


Figure 4.12: Plan comparison between PT and VHEE for patient M1. DVHs for the PTV and OARs from the PT plan are reported on the left, whereas the VHEE results obtained assuming an irradiation with three fields are shown on the right. The absorbed dose relative to the unspecified normal tissue is also shown.

Figure 4.11 illustrates that both IMRT and VHEE plans are of comparable quality: IMRT offers superior PTV coverage, whereas VHEE is more effective in sparing the cochlea. Additionally, Figure 4.12 shows that the three-field VHEE configuration provides better PTV coverage than the seven-field configuration, achieving a performance level similar to that of the PT plan. Table 4.3 provides quantitative analysis to support these findings, presenting key values for assessing plan quality across all M1 treatment plans. For patient C1, a more complex case, the sparing of OARs constrains PTV coverage in all plans. In this scenario, the priority was to minimize the absorbed dose to the brainstem and spinal cord, even if this compromised the desired PTV coverage. For this patient, the DVH analysis shown in Fig. 4.13 and 4.14 for the 4-fields and 7-fields VHEE configurations suggests that increasing the number of fields can enhance target coverage, with the

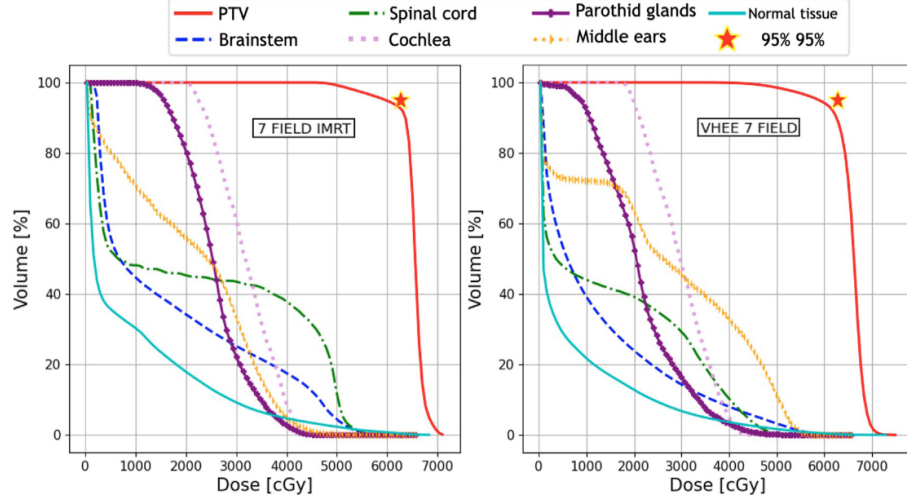


Figure 4.13: Plan comparison between IMRT and VHEE for patient C1. DVHs for the PTV and OARs from the IMRT plan are reported on the left, whereas the VHEE results obtained assuming an irradiation with seven fields are shown on the right. The absorbed dose relative to the unspecified normal tissue (NoT in the legend) is also shown.

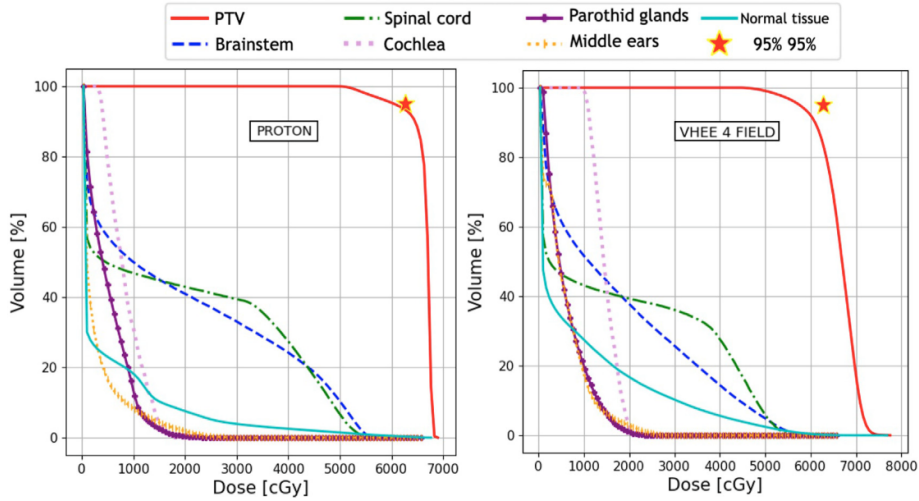


Figure 4.14: Plan comparison between PT and VHEE for patient C1. DVHs for the PTV and OARs from the PT plan are reported on the left, whereas the VHEE results obtained assuming an irradiation with four fields are shown on the right. The absorbed dose relative to the unspecified normal tissue (NoT in the legend) is also shown.

PTV boost coverage (in terms of V95%) improving from 85.5% to 90.6%. Table 4.4 presents the V_{XX} , D_{mean} , and D_1 values used to evaluate the C1 plan. While VHEE plans provide lower PTV coverage, they improve spinal cord sparing. The comparison between four - fields and seven - fields irradiations highlights how different field configurations can optimize OAR sparing. For instance, there is a notable difference in the mean dose received by the ear canals, cochlea, and parotid glands in these two setups. In summary, the PT, IMRT, and VHEE plans developed for both M1 and C1 meet the clinical requirements and fulfill the prescribed constraints. For patient M1, an optimization was also performed under FLASH regime. In this case, since PTV coverage is already satisfactory without leveraging the FLASH effect, applying it would lead to further reduction in the dose absorbed by OARs, thus enhancing OAR sparing. As shown in Fig. 4.17, the transparent bands

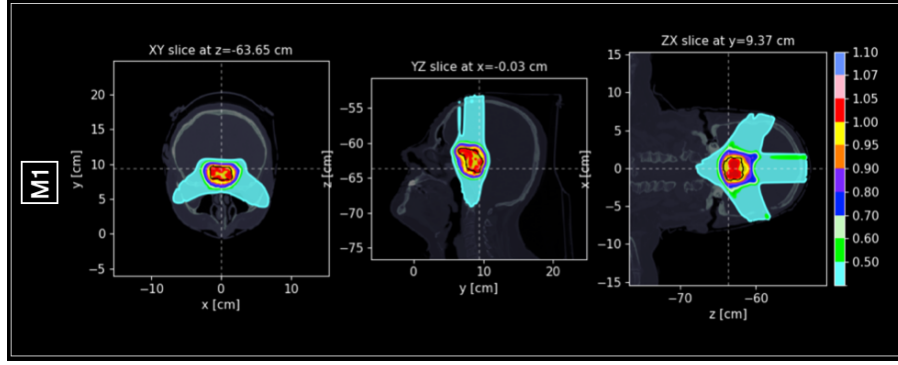


Figure 4.15: Optimized isodose distributions for patient M1 normalized to the value used as an input for the optimization process, i.e. 54 GyRBE. The distributions are overlapped to the CTs. The PTV contour is also shown in black.

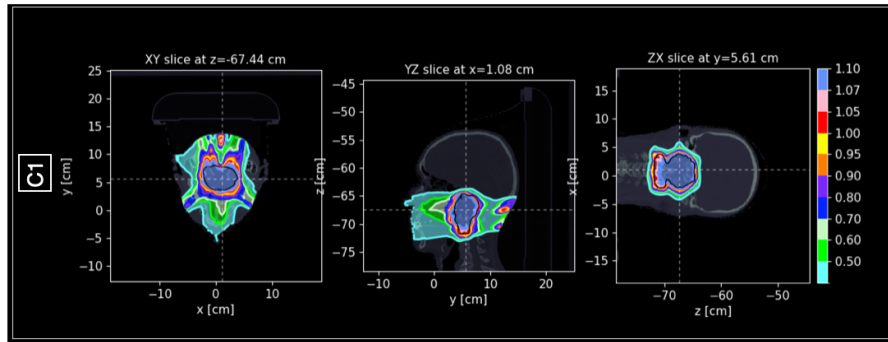


Figure 4.16: Optimized isodose distributions for patient C1 normalized to the value used as an input for the optimization process, i.e. 54 GyRBE. The distributions are overlapped to the CTs. The PTV contour is also shown in black.

illustrate the potential dose reduction achievable if the plan is delivered under UHDR conditions. These bands span from $FMF_{min} = 0.8$ (representing significant sparing) at the left edge to 1 (no FLASH effect) at the right edge, and are based on a D_{th} value of 40 Gy, considering the entire treatment plan without factoring in fractionation specifics.

Looking at these results, it is evident that VHEE (with a maximum energy of 110 MeV) were found to be suitable for treating deep-seated tumors in disease sites with challenging irradiation geometries, such as intracranial ones. This approach allowed a limited number of fields to achieve performance comparable to IMRT or PT. This result, obtained under the assumption of a conventional dose rate, is promising in itself, as it suggests that compact electron accelerators could provide appropriate treatment quality at a lower cost, thus representing a valid alternative to photons or proton treatments. The beam scanning method used for VHEE treatments can be used to achieve the desired absorbed dose conformity to the PTV while keeping each field mono-energetic. This condition plays a crucial role when discussing the suitability of VHEE for FLASH therapy irradiations: since there is no need to change the energy within a field, each field can be delivered in a very short time, making it easier to achieve an UHDR regime. The technological challenge of delivering more than one field in the short time required to ensure FLASH sparing of the OARs still needs to be addressed. However, one notable similarity between VHEE and proton plans is that the number of fields to be delivered is, in some cases, identical (e.g., the case of M1). The potential impact of FLASH in terms

M1	Parameter	PT	IMRT	VHEE 3-fields	VHEE 7-fields
PTV	$V_{95\%}$	100%	99.30%	98.97%	97.00%
PTV	$V_{105\%}$	0.01%	0.009%	0.05%	1.27%
Optic nerves	D_1	52.98 Gy	53.76 Gy	54 Gy	54 Gy
Chiasm	D_1	53.52 Gy	54 Gy	53.68 Gy	53.71 Gy
Posterior o. p.	D_1	53.58 Gy	53.82 Gy	53.94 Gy	53.67 Gy
Eyeballs	D_1	1.25 Gy	10.52 Gy	3.30 Gy	11.82 Gy
Brainstem	D_1	52.59 Gy	51.99 Gy	50.40 Gy	51.02 Gy
Carotid arteries	$V_{105\%}$	0.03%	9.11%	2.54%	1.16%

Table 4.3: Values of V_{XX} and D_1 for the PTV and different OARs relevant to the planning of patient M1. Different columns show the values obtained from the proton, IMRT, VHEE with three fields, and VHEE with 7-fields. The result obtained for the carotid arteries is given in terms of V_{105} . All the obtained values satisfy the requirements shown in Table 4.1.

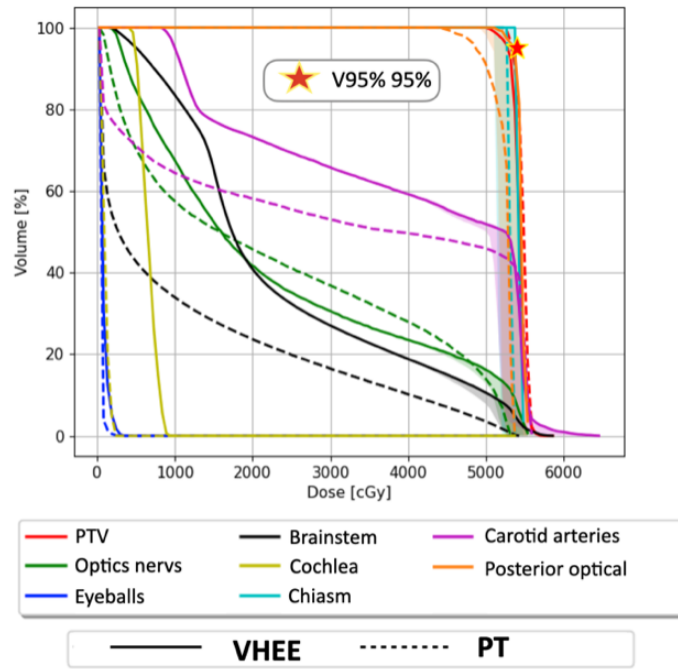


Figure 4.17: DVHs for the delivered PT plan (dashed line) and the simulated VHEE one (solid line) for patients M1. The transparent bands indicate the potential improvement achievable if the plan is delivered in UHDR conditions. The bands cover the range of parameters from $FMF_{min} = 0.8$ (a sizeable sparing), shown using a dotted line, to 1 (no FLASH effect), in solid line, and have been obtained for a D_{th} value of 40 Gy.

of OAR sparing has also been explored, with reasonable assumptions suggesting that a maximum sparing effect between 20% and 35% could be achieved.

C1	Parameter	PT	IMRT	VHEE 4-fields	VHEE 7-fields
PTV boost	$V_{95\%}$	93.57 %	92.96%	85.52%	90.61%
PTV boost	$V_{107\%}$	0%	3.05%	28.32%	6.12%
Brainstem	D_1	54.64 Gy	53.79 Gy	55.04 Gy	55.15 Gy
Spinal cord	D_1	53.39 Gy	54.04 Gy	53.54 Gy	47.77 Gy
Parotid glands	D_{mean}	4.74 Gy	25.29 Gy	5.73 Gy	20.82 Gy
Middle ears	D_{mean}	2.63 Gy	20.63 Gy	5.40 Gy	25.94 Gy
Cochlea	D_{mean}	7.98 Gy	31.54 Gy	14.32 Gy	29.39 Gy

Table 4.4: Values of V_{XX} , D_{mean} , and D_1 for the PTV and different OARs relevant for the planning of patient C1. Different columns show the values obtained from the proton, IMRT, VHEE with four fields, and VHEE with 7-fields plans. All the obtained values satisfy the requirements shown in Table 4.2.

4.4.3 Study of pancreatic tumor

Three patients (labeled as PT1, PT2 and PT3) with primary pancreatic neoplasms were retrospectively analyzed to evaluate the potential application of VHEE either delivered in conventional or FLASH conditions. All the patients, unfit for surgery, underwent VMAT treatments at the Fondazione Policlinico Universitario Campus Bio-Medico in Rome. The clinical treatments delivered to the patients were recomputed to generate an IMRT treatment plan, used as input for the geometry setup, following the approach documented in 4.4.1. As a result, the characteristics (position, and angle) of 7 static fields for PT1, and 5 for PT2 and PT3 were obtained and used to provide a reasonable starting point for the VHEE studies. The FWHM of each PB at the beam exit window, used for the simulation, was in the range between 0.7-1.2 cm, while the margin in which I reduced the spot spacing of the beams was chosen to be 2 cm. The irradiation geometry for all plans is shown in Fig. 4.18. As in the case of intracranial lesion, no treatment optimization was performed, i.e., the figure show the absorbed dose for pencil beams containing 10^6 electrons each, which are, once properly normalised, the inputs for the optimisation step. The prescribed PTV dose was 30 Gy for PT1 and PT3 and 32.5 Gy for PT2, delivered in 5 fractions. For PT2 and PT3, dose inhomogeneity was accepted, allowing for hot spots within the Clinical Target Volume (CTV, that accounts for both the primary tumor and nearby tumor cells that may require treatment to prevent recurrence) to receive up to 125% of the prescribed dose. The planning goals and the dosimetric constraints for the most relevant OARs, used for all the patients, are reported in Table 4.5. The initial energy choice was carried out as explained in section 4.4.1; in this case, the optimizations were performed using also the annealing algorithm, which is capable of optimizing both the intensity of individual PBs and the beam energy. The energy values shown in the figure 4.18 are the optimized ones. However, it should be stressed that when targeting the PTV in the three selected patients, the obtained dose distributions around the PTV showed only a mild dependence on the beam energy, and it was possible to achieve therapeutic plans of comparable quality using nearly all the energies in the explored range. Once the setup for all patients was finalized, the absorbed dose maps were obtained for each patient using FRED and used as input in the optimization stage together with the

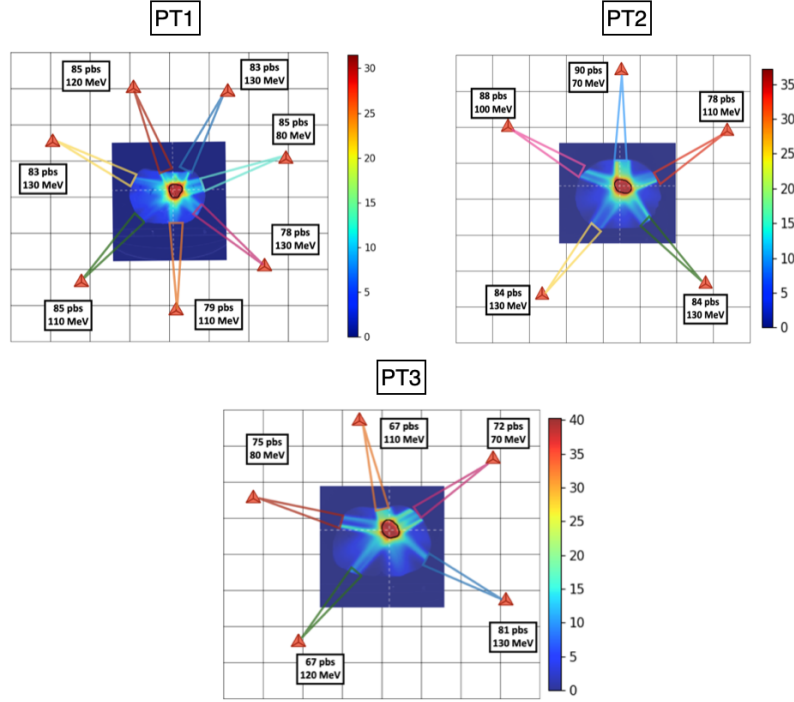


Figure 4.18: Absorbed dose distribution of PT1, PT2 and PT3, in Gy, used as an input for the optimisation process. The figure shows the configuration of the plan using 7 fields for PT1 and 5 fields for PT2 and PT3, reporting the number of PBs of and the energy of each beam. All pencil beams have 10^6 electrons.

requirements on the PTV coverage and OARs sparing goals listed in Tab. 4.5. The DVH comparison for the delivered VMAT and the simulated VHEE plans are shown in Fig.4.19 while the isodose maps obtained for the VHEE plans are shown in Fig. 4.20. The typical isodose distribution for IMRT-like treatments can be observed, as expected when delivering the VHEE plans respectively using 7 (for PT1) and 5 fields (for PT2 and PT3). The key parameters that can be evaluated for a quantitative comparison are the PTV coverage and the dose absorbed by the duodenum, placed in close proximity to the tumor. The results, summarized in Table 4.6 are of comparable quality, meet the constraints and are consistent with the clinical prescriptions.

In particular, in the case of PT1, the use of VHEE would result in a significant improvement in PTV coverage while keeping the dose delivered to the duodenum, and all the other surrounding OARs, within the optimal constraints. For PT2, although VMAT provides a slightly better tumor coverage, VHEE irradiation could provide an improved duodenal sparing, with a reduction of approximately 1.5 Gy in the maximum absorbed dose. Reducing the duodenum D_{max} would allow a higher PTV prescription, improving the treatment efficacy. For PT3, the two plans are comparable in all aspects and differ only by fractions of Gys. I have also explored the potential of FLASH irradiation in more detail in the case of PT1, performing a scan of the FMF_{min} and D_{th} parameters. The range of values chosen for the scan are based on currently available experimental data [17]. The results are reported in Fig.4.21 that shows the 95% absorbed dose values at 100% of the PTV volume corresponding to each set of values calculated while ensuring duodenal sparing according with the clinical prescription. Aim of my study was to test how much the dose to the PTV can be increased, while profiting from the additional sparing provided from the FLASH effect, while keeping the D_{max} RBE weighted dose of the duodenum within the constraints. The result demonstrates that as

ROI	Constraints	Volumes [cc]		
		PT1	PT2	PT3
PTV	$V_{95\%}^{PT1} > 95\%$ $V_{105\%}^{PT1} < 5\%$ $V_{100\%}^{PT2,PT3} > 95\%$ $D_{max}^{PT2} \leq 40.95 \text{ Gy}$ $D_{max}^{PT3} \leq 37.8 \text{ Gy}$	94.9	81.6	117.9
Duodenum	$V_{35Gy} < 0.1 \text{ cc}$ $V_{25Gy} < 10 \text{ cc}$	93.5	94.4	101.6
Bowel	$V_{30Gy} < 1 \text{ cc}$	1035.1	563	1511.4
Stomach	$V_{12Gy} < 50 \text{ cc}$ $V_{33Gy} < 0.1 \text{ cc}$	173.2	168.6	287.1
Spinal cord	$V_{25.3Gy} < 0.035 \text{ cc}$	60.3	111	109.2
Liver	$D_{mean} \leq 13 \text{ Gy}$ $V_{15Gy} < 700 \text{ cc}$	892.5	1202.8	1504
Kidneys	$V_{10Gy}^p < 45\%$	256.6	250.3	940.7

Table 4.5: Planning constraints adopted for PT1, PT2 and PT3 are summarised for each organ. D_{max} and D_{mean} are the maximum and average dose absorbed in the volume of interest, respectively. V_{XX} is the constraint on the volume (either total, expressed in cc or fractional V_{XX}^p , expressed in %) of a given OAR (or PTV) receiving a minimum dose of XX Gy. PTV and OARs total volumes (in cc) are listed for each patient.

the threshold dose and FMF_{min} values decrease, the absorbed dose by 100% of the PTV volume increases while keeping duodenal injury below the required threshold. It should then be possible to escalate the prescribed dose to the target volume, exploiting the FLASH effect. The exact gain will be computed once a more robust experimental quantification of the FLASH induced duodenal sparing will be available. In addition to the dose escalation study, the potential sparing for all the OARs was evaluated by selecting a pair of intermediate parameter values, specifically $FMF_{min} = 0.6$ and $D_{th} = 5\text{Gy}/\text{fraction}$, for all patients. Under these conditions, the biological dose was calculated and optimized. The comparison is shown in Fig. 4.19, where the transparent bands show the FLASH treatment plans. The DVHs show the better PTV coverage that can be achieved, while simultaneously reducing the maximum dose absorbed by critical OARs. This trend is evident for PT1 and PT3: at the cost of slightly increasing the absorbed dose below the FLASH threshold to improve the PTV coverage, a reduced damage to the duodenum and other OARs is obtained. Although less evident, a similar phenomenon occurs for PT2. In terms of clinical constraints, the results show that the maximum absorbed dose by the duodenum is, in all cases, decreased by approximately 2 Gy with an increase of the PTV coverage.

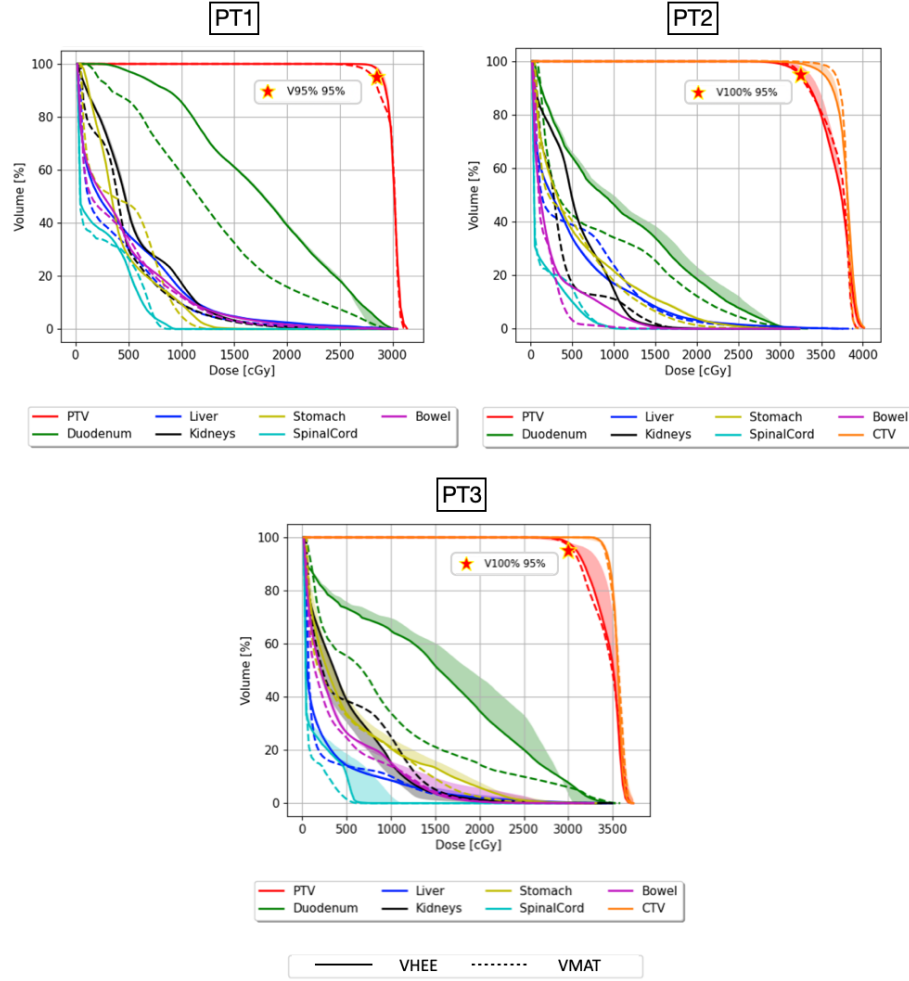


Figure 4.19: DVHs for the delivered VMAT plan (dashed line) and the simulated VHEE one (solid line) for patients PT1, PT2 and PT3. The transparent bands indicate the potential improvement achievable if the plan is delivered in UHDR conditions. The bands cover the range of parameters from $FMF_{min} = 0.6$ (a sizeable sparing), shown using a dotted line, to 1 (no FLASH effect), in dashed line, and have been obtained for a D_{th} value of 5 Gy.

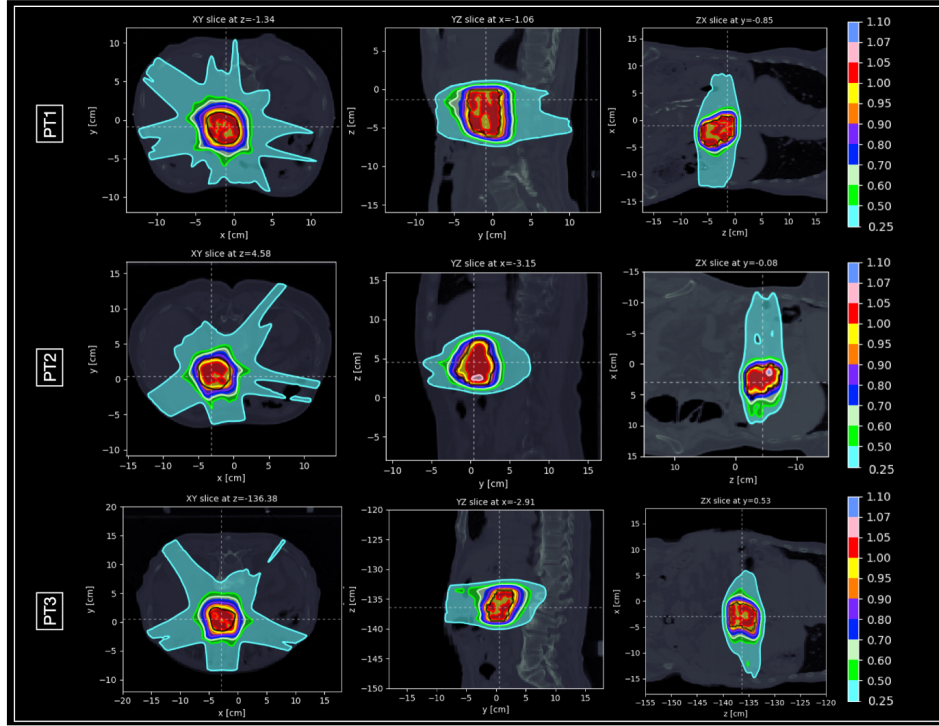


Figure 4.20: Optimized isodose distributions for patients PT1, PT2 and PT3, normalized to the value used as an input for the optimization process, i.e. 30 Gy, 37.5 Gy and 35.5 Gy respectively. The distributions are overlapped to the CTs. The PTV contour is also shown in black for each patient.

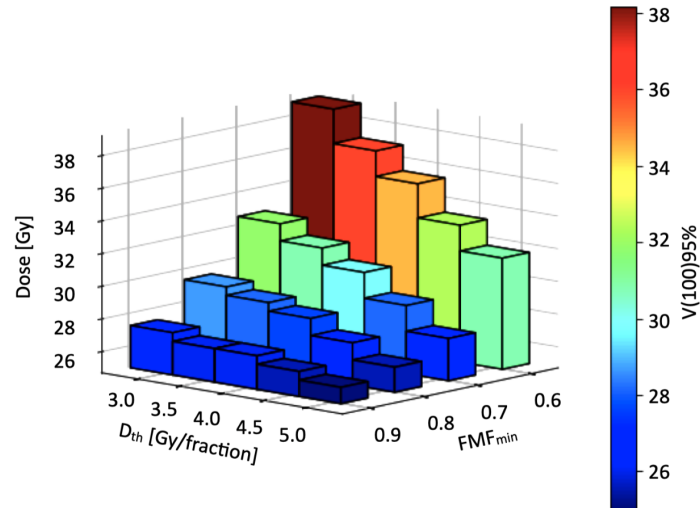


Figure 4.21: 3D visualization depicting the correlation among FMF_{min} values, shown along the x-axis, D_{th} shown along the y-axis, and the resultant increase of the 95% of the dose absorbed by the 100% of the PTV volume on the z-axis. This study was carried out by optimizing the biological dose according to [17] for PT1 and ensuring that the sparing of the duodenum was within the clinical prescriptions.

ROI	Constraints	VMAT	VHEE	FLASH
PT1				
PTV	$V_{95\%} > 95\%$ $V_{105\%} < 5\%$	97.00% 0.0063%	98.60% 0.24%	99.36% 0.42%
Duodenum	$V_{35Gy} < 0.1cc_{(man)}$ $V_{25Gy} < 10cc_{(opt)}$ D_{max}	0.00 cc 4.53 cc 30.25 Gy	0.00 cc 15.77 cc 30.43 Gy	0.00 cc 16.62 cc 28.36 Gy
Bowel	$V_{30Gy} < 1cc$ D_{max}	0.11 cc 30.79 Gy	0.10 cc 30.35 Gy	0.00 cc 28.79 Gy
Stomach	$V_{12Gy} < 50cc$ $V_{33Gy} < 0.1cc$ D_{max}	0.76 cc 0.00 cc 12.87 Gy	4.47 cc 0.00 cc 17.54 Gy	5.07 cc 0.00 cc 17.87 Gy
Spinal cord	$V_{25.3Gy} < 0.035cc$ D_{max}	0.00 cc 8.59 Gy	0.00 cc 9.14 Gy	0.00 cc 9.14 Gy
Liver	$D_{mean} < 13Gy$ $V_{15Gy} < 700cc$	3.6 Gy 25.5 cc	4.46 Gy 43.20 cc	4.55 Gy 45.96 cc
Kidneys	$V_{10Gy} < 45\%$	9%	17.08%	17.47%
PT2				
PTV	$V_{100\%} > 95\%$ $D_{max} < 40.95Gy$	98.6% 40.75 Gy	95.36 % 40.26 Gy	99.67 % 39.85 Gy
Duodenum	$V_{35Gy} < 0.1cc_{(man)}$ $V_{25Gy} < 10cc_{(opt)}$ D_{max}	0.00 cc 3.25 cc 32.98 Gy	0.00 cc 7.54 cc 31.54 Gy	0.00 cc 11.89 cc 31.10 Gy
Bowel	$V_{30Gy} < 1cc$ D_{max}	0.00 cc 17.90 Gy	0.00 cc 19.87 Gy	0.00 cc 20.78 Gy
Stomach	$V_{12Gy} < 50cc$ $V_{33Gy} < 0.1cc$ D_{max}	19.13 cc 0.00 cc 28.13 Gy	28.19 cc 0.00 cc 31.97 Gy	28.91 cc 0.00 cc 30.14 Gy
Spinal cord	$V_{25.3Gy} < 0.035cc$ D_{max}	0.00 cc 9.84 Gy	0.00 cc 10.64 Gy	0.00 cc 11.16 Gy
Liver	$D_{mean} < 13Gy$ $V_{15Gy} < 700cc$	5.42 Gy 107.46 cc	4.78 Gy 96.82 cc	4.88 Gy 102.36 cc
Kidneys	$V_{10Gy} < 45\%$	44.80 %	15.17%	14.94%
PT3				
PTV	$V_{100\%} > 95\%$ $D_{max} < 37.8Gy$	99% 37.59 Gy	98.32% 37.21 Gy	98.32% 37.21Gy
Duodenum	$V_{35Gy} < 0.1cc_{(man)}$ $V_{25Gy} < 10cc_{(opt)}$ D_{max}	0.007 cc 8.42 cc 35.88 Gy	0.02 cc 20.28 cc 35.11 Gy	0.02 cc 20.12 cc 31.06 Gy
Bowel	$V_{30Gy} < 1cc$ D_{max}	0.00 cc 28.26 Gy	0.15 cc 32.90 Gy	0.00 cc 29.91 Gy
Stomach	$V_{12Gy} < 50cc$ $V_{33Gy} < 0.1cc$ D_{max}	42.98 cc 0.00 cc 31.04 Gy	48.35 cc 0.03 cc 33.28 Gy	47.03 cc 0.00 cc 29.97 Gy
Spinal cord	$V_{25.3Gy} < 0.035cc$ D_{max}	0.00 cc 5.98 Gy	0.00 cc 7.74 Gy	0.00 cc 7.82 Gy
Liver	$D_{mean} < 13Gy$ $V_{15Gy} < 700cc$	2.34 Gy 46.71 cc	2.45 Gy 65.10 cc	2.43 Gy 66.48 cc
Kidneys	$V_{10Gy} < 45\%$	24.65 %	14.87 %	14.43%

Table 4.6: Planning constraints adopted for PT1, PT2 and PT3 are summarised for each organ. D_{max} and D_{mean} are the maximum and average dose absorbed in the volume of interest, respectively. V_{XX} is the constraint on the volume (either total, expressed in cc or expressed in %) of a given OAR (or PTV) receiving a minimum dose of XX Gy. The different columns are showing the values obtained from VMAT and VHEE plans respectively. The last column shows the results obtained taking into account the FLASH effect modeled using $FMF_{min} = 0.6$ and $D_{TH} = 5$ Gy. The optimised plans satisfy all the mandatory requirements.

Chapter 5

Radioprotection challenges

The VHEE plans that I have presented in the previous chapter have been optimised assuming the existence of a VHEE LINAC capable of delivering FLASH beams at energies up to 130 MeV, with the characteristics thoroughly described in Chapter 3. Such machine does not exist yet, but is being developed and built as a joint project of Sapienza University and INFN. Before building the accelerator in its final layout a prototype is being assembled to validate and test the different components, their integration and the feasibility of the proposed approach. This demonstrator will include the final injector, an initial SW section and a portion of the TW section, with the final goal of accelerating electrons up to 24 MeV. The prototype will be installed in the laboratories of the Department of Basic and Applied Sciences for Engineering (SBAI) at Sapienza University of Rome, and it is expected to be available for testing and research purposes starting from late 2025. Among the many aspects to be addressed for the installation and operation of a VHEE machine, one critical issue is radiation protection. The final design of the machine either operating in FLASH and conventional modes has to be compatible with a hospital environment. In order to ensure safe access and operation for users, workers, and university personnel in nearby offices, I conducted a comprehensive radiation protection study. This analysis provides a detailed estimate of the radiation doses dispersed in the surrounding environment and evaluates shielding solutions to ensure compliance with current regulations on radiation exposure for both workers and non-workers. This chapter will describe the key characteristics of the demonstrator, explore the fundamental interactions relevant to this type of radiation protection challenge, and outline the methodology used to calculate the dispersed radiation flow based on beam dynamics simulations. Finally, the results of the study and the recommended shielding solutions for mitigating the resulting radiation will be presented.

5.1 Secondary Particle Production

The radiation fields of interest in VHEE accelerators are primarily composed of photons and neutrons. Prompt photon fields are generated by *Bremsstrahlung*, which is the predominant electromagnetic process when high energy electron beams interact with matter or electromagnetic fields. The intensity of *Bremsstrahlung* increases with beam energy, as described in 1.4.1, and for electron energies above 50 MeV, the X-ray component is expected to exceed 10% of the total. From a radiation protection perspective, the *Bremsstrahlung* component produced in the accelerating structure or

within tissues is significant and has to be taken into account when calculating energy deposition in different phantom materials. Although secondary neutrons are also produced, their contribution is considerably smaller—several orders of magnitude lower than that of photons. This is demonstrated in Fig. 5.1, which presents the equivalent dose rates for secondary particles, expressed as a function of beam energy. The figure also indicates that muon production is possible at very high electron energies. Muons can be generated by *Bremsstrahlung* photons with energies exceeding 211 MeV, though this energy threshold is likely higher than the maximum energy that VHEE would reach in radiotherapy applications.

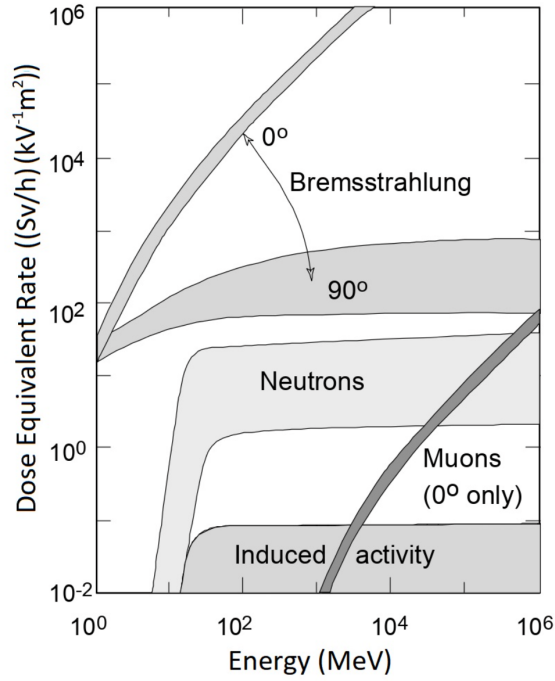


Figure 5.1: Electron secondary particles equivalent dose rates per unit beam power. The band widths indicate the expected variation that can be obtained depending on the target details. [75]

Bremsstrahlung photons

As discussed in Section 1.4.1, VHEE beams lose a significant portion of their energy through the emission of *Bremsstrahlung* radiation. The power of the emitted photons P can be quantified using the Larmor formula:

$$P = \frac{q^2 a^2}{6\pi\epsilon_0 c^3} \quad (5.1)$$

where q is the charge of the particle, and a is its acceleration, which is inversely proportional to the particle's mass. This relationship explains why the *Bremsstrahlung* radiation produced by an electron is six orders of magnitude greater than that produced by a proton (when subjected to the same accelerating force). According to Duane-Hunt's law [21], the maximum energy a photon can have, produced via *Bremsstrahlung*, is equal to the kinetic energy of the incident electron, i.e., $E_k = h\nu$ where $h\nu$ is the photon energy. The direction in which this photon emission is most likely

to occur can be described by the following equation [58]:

$$\theta_{max} = \arccos \left[\frac{1}{3\beta} (\sqrt{1 + 15\beta^2} - 1) \right] \quad (5.2)$$

The *Bremsstrahlung* production in a thick target has two primary components: a forward-peaked component, as described in 5.2, and a wide-angle component. The forward-peaked component contains the most energetic and penetrating photons. Its spectrum is proportional to the energy of the incident electron beam and is influenced by the target's atomic number Z , as higher- Z materials produce and attenuate more *Bremsstrahlung* radiation. The wide-angle component, on the other hand, is made up of lower-energy photons. For electron beam energies above 50 MeV, this component has a spectrum that is largely independent of the incident beam's energy and instead scales with the beam power. Nearly 99.9% of the photons in this wide-angle distribution have energies below 10 MeV. These photons are produced by small-angle *Bremsstrahlung* from secondary electrons, which have been scattered at large angles due to multiple scattering events within the target material.

Neutrons

Neutrons are primarily produced through the nuclear interactions of high-energy photons, as photons have a larger nuclear cross section compared to electrons. Although neutrons constitute only a small fraction of the particles generated in an electromagnetic cascade, they remain significant due to their unique characteristics. As neutral particles, neutrons do not interact via Coulomb forces, making them one of the most penetrating components of the secondary radiation generated during particle cascades. Additionally, neutrons have a higher biological damage potential compared to other particles, such as photons or electrons. This is reflected in their radiation weighting factor ω_r , which, unlike the constant value of 1 for photons and electrons, reaches a peak value of 20 around 1 MeV. Neutron production by *Bremsstrahlung* photons occurs through three main processes:

- Giant-resonance production (10–30 MeV): in this region, the absorption of a photon excites the nucleus, which subsequently de-excites by emitting a neutron. This process dominates neutron production in VHEE beams, with an isotropic neutron yield for light nuclei at approximately 20 MeV and for heavy nuclei around 15 MeV;
- Quasi-deuteron production and decay (50–300 MeV): beyond 30 MeV, neutrons are also produced through interactions with neutron-proton pairs (quasi-deuterons);
- Intranuclear cascade and pion production (above 140 MeV): at even higher energies, pion production becomes possible. These pions can generate secondary neutrons through interactions with nuclei, though this mechanism peaks at around 300 MeV, beyond the likely energy range used in VHEE radiotherapy[75] [5].

Early research on VHEE beams estimated the neutron yield to be about 0.03 neutrons per electron at 150 MeV. The contribution of induced radioactivity to the overall dose was found to be minimal—approximately 0.01% of the primary electron dose. Importantly, the neutron dose is considerably lower at energies below 50 MeV, particularly due to the predominant contribution from giant-resonance processes occurring below 30 MeV. Monte Carlo simulations further suggest that the total body neutron dose from VHEE irradiation with pencil beam scanning is 1 to 2

orders of magnitude lower than that produced by proton therapy or 15–18 MV photon IMRT [43]. However, these initial estimates may vary significantly depending on the future beam delivery methods employed, such as different types of collimation or scanning techniques, as more realistic conditions have yet to be incorporated into shielding calculations.

5.2 Prototype characteristics and layout

The prototype currently under construction as part of the SAFEST project is a scaled-down version of the proposed VHEE LINAC, and it is designed to accelerate electron beams up to 24 MeV. While the final version of the LINAC aims to reach higher energies (up to 130 MeV), this intermediate prototype serves multiple crucial purposes. Primarily, the 24 MeV demonstrator will be used to validate and test the various components of the machine. These components must be optimized to ensure smooth beam acceleration and high transmission efficiency before scaling up to higher energies. Beyond component testing, the 24 MeV electron beam also holds significant potential for in vitro experiments in the field of radiobiology. Such beam energy is particularly useful for studying the biological effects of electron radiation on cell cultures and tissue samples, helping researchers investigate cellular responses to radiation, such as DNA damage and repair mechanisms. This energy range is well-suited for evaluating dose deposition in thin biological samples, allowing precise control over the radiation dose delivered to cells. Moreover, in vitro studies at this energy can provide insights into the mechanisms behind the FLASH effect, as well as optimal conditions for maximizing therapeutic benefits while minimizing side effects. The layout of the prototype is displayed in Fig. 5.2: as previously mentioned, the prototype includes the SW injector, where the electron source is a thermionic klystron operating in DC mode at 15 kV, and a TW section.

Designing and testing an accelerating structure involves several critical steps. First of all, detailed

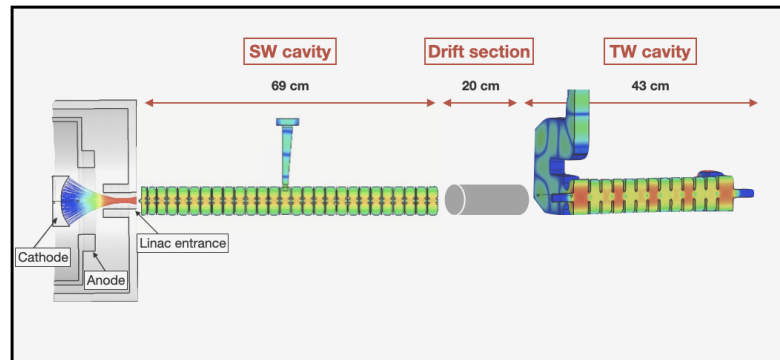


Figure 5.2: Layout of the VHEE LINAC prototype with the injector and one TW high-gradient accelerating structure. The maximum expected beam energy is about 24 MeV.

electromagnetic simulations to optimize the geometry of the accelerating cells, ensuring efficient energy transfer to the particle beam, were carried out. This step included analyzing all relevant parameters, such as *Shunt impedance*, *quality factor*, and phase velocity of the proposed setup, to achieve the desired acceleration gradient. The key specifications of the injector are summarized in Table 5.1. A schematic of the design of the individual Standing Wave (SW) accelerating cell is presented in Fig. 5.3. Connected to the injector via a drift section approximately 20 cm in length is the high-gradient Traveling Wave (TW) section. This section consists of a series of asymmetrical

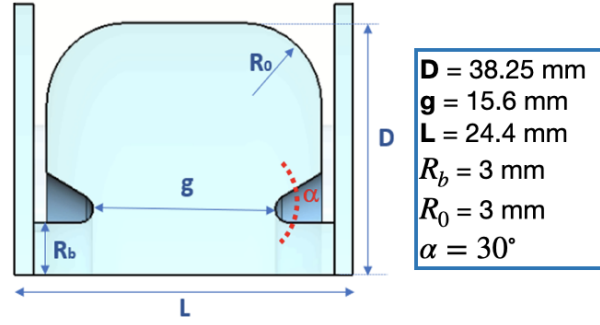


Figure 5.3: Layout of the SW single cell of the injector structure with its dimensions.

SW structure parameters	
N of cells	27
R	103 M Ω /m
Q	10178
Operation mode	Bi-periodic $\pi/2$
E_{beam}	10 MeV
I_p	100 mA

Table 5.1: Key specifications of the injector section of the prototype under construction. All parameters symbols have been already defined in Table 3.1 and section 3.1.2.

cells specifically designed to facilitate in-house fabrication. The layout of a single TW cell is shown in Fig.5.4, while the characteristics of the entire TW section are summarized in Table 5.2. Once

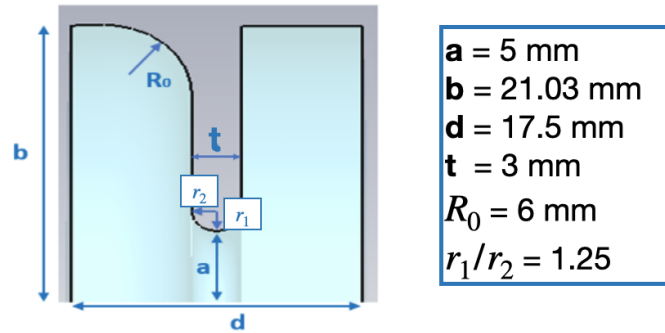


Figure 5.4: Layout of the TW single cell of the high-gradient structure with its dimensions.

the design was finalized, the next step involved selecting the fabrication method for the various structures, typically requiring precision machining. The prototype, that has already been built, is currently undergoing RF testing to verify its performance, including measuring the reflection coefficient to ensure proper impedance matching and minimize power losses. In Fig. 5.5, images related to the ongoing testing phase are shown. High-power RF testing follows, where the structure is exposed to high-power RF pulses to assess breakdown limits and conditioning. After successful RF testing, the final step is to integrate the structure with other accelerator components and conduct beam tests to validate its performance with real particles, evaluating parameters such as beam quality, energy gain, and stability. This will be done by the end of 2025.

TW structure parameters	
R	107 M Ω /m
Q	10127
Operation mode	Bi-periodic $2/3\pi$
E_{beam}	24 MeV
I_p	100 mA

Table 5.2: Key specifications of the high-gradient section of the prototype under construction. All parameters symbols have been already defined in Table 3.1 and section 3.1.2.

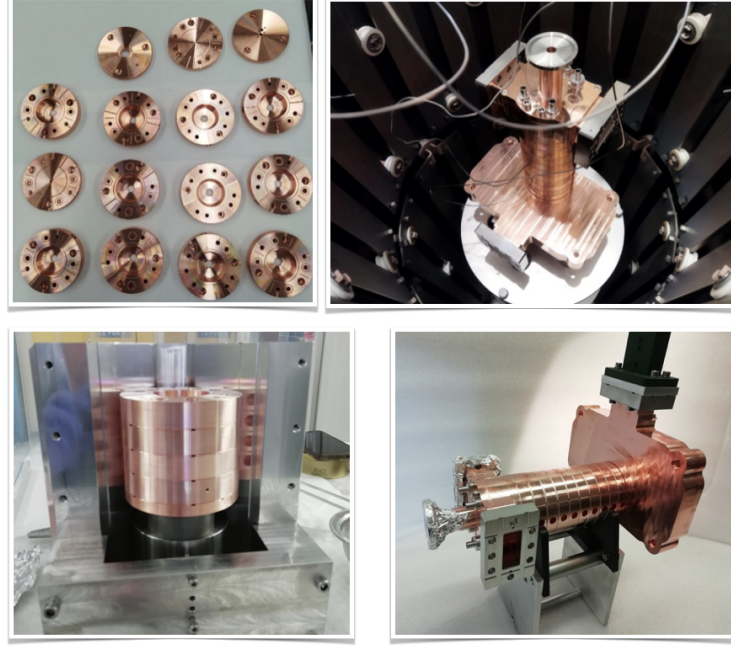


Figure 5.5: Images of the accelerating cells, both as individual units and fully assembled, during the RF testing phase.

5.3 Dispersed flow simulations

The objective of the radioprotection study I have carried out is to evaluate and quantify the scattered radiation flux generated by the accelerator during its normal operation, in order to determine the appropriate shielding thickness and composition required to protect the surrounding environment. To achieve this, I analyzed electromagnetic simulations performed using the software Parmela [82]. Parmela is specifically designed to simulate the electromagnetic fields (both electric and magnetic) that influence particle beams, but it does not account for the particles interactions with the materials. Therefore, while it provides detailed insights into the beam dynamics, it does not simulate the interactions between primary particles and the accelerator structure itself. From the Parmela output files, I extracted information I needed regarding the position, direction, and energy of each individual particle as it moves through the accelerator. Each primary electron is tagged with a unique ID, and the data for each particle is provided at discrete points along the z-axis (i.e., along the beam direction), ideally at the end of each accelerating cell. By reconstructing the trajectory of each primary particle based on this information, it is possible to trace its path within the simulated electric field. Fig. 5.6 left shows the spatial distribution of primary beam particles in the x and

y directions, as read from the Parmela output file, while on the right, an energy histogram of the primary beam is presented. To determine which of these electrons remained focused within the beam

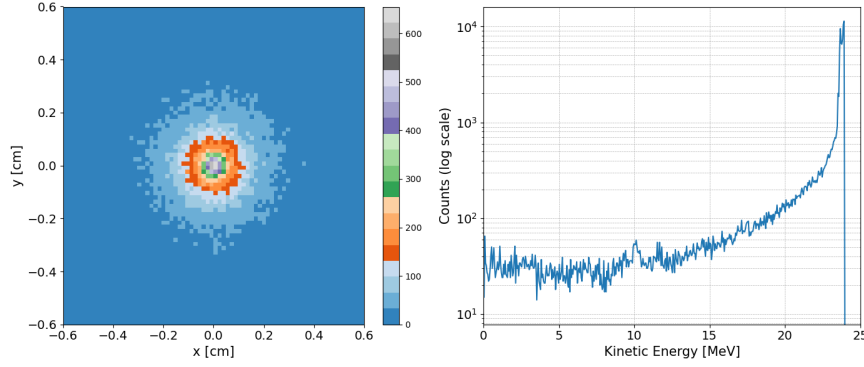


Figure 5.6: In the left panel the the spatial distribution of primary beam particles in the x and y directions, as obtained from the Parmela output file, with a color scale indicating the number of particles in each spatial bin. In the right panel a logarithmic-scale energy histogram of the primary beam, highlighting the energy distribution of the particles.

pipe throughout their journey to the exit window, and which diverged and struck the copper walls of the accelerating cells, I carried out a geometrical analysis. My goal was to identify the exit positions from the iris of the accelerator and the energy gained by the primary particles that contributed to the scattered flux. Fig.5.7 illustrates the rationale behind this analysis, while the distributions in z (beam axis) and kinetic energy of the particles exiting the LINAC beam pipe are presented in Fig.5.8. By examining the energy spectrum, it is possible to observe that while the primary beam

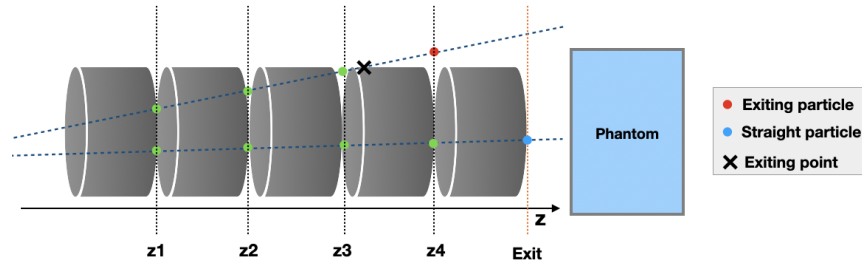


Figure 5.7: Scheme of the geometric analysis used to determine the exit point from the beam pipe for particles constituting the scattered flux. At each discrete z-position where particle information is available, a check is performed: if a particle (red dot) is found outside the beam aperture (iris), its trajectory is back-projected to identify the exit point on the pipe (marked with an **X**) and this information is saved. For particles following a straight trajectory within the pipe (green dots), their geometric and energy values are updated as they progress through the beam pipe. The exit coordinates and energy of these particles are recorded when they exit the accelerator (blue dot).

in Fig. 5.6 have a peak at 24 MeV, as expected, the electrons exiting the iris in Fig. 5.8 showed energy peaks at both a few keV and approximately 8 MeV. The presence of low-energy peaks in the spectrum can be attributed to electrons that underwent significant scattering events or lost energy through interactions with the accelerator structure, such as collisions with the copper walls of the accelerating cells. These electrons are more likely to have lower kinetic energies due to inelastic interactions, which result in energy dissipation. The peak at around 8 MeV, on the other hand, likely corresponds to electrons that still retained a significant fraction of their initial energy but experienced partial deceleration or energy loss after grazing interactions or scattering from surfaces

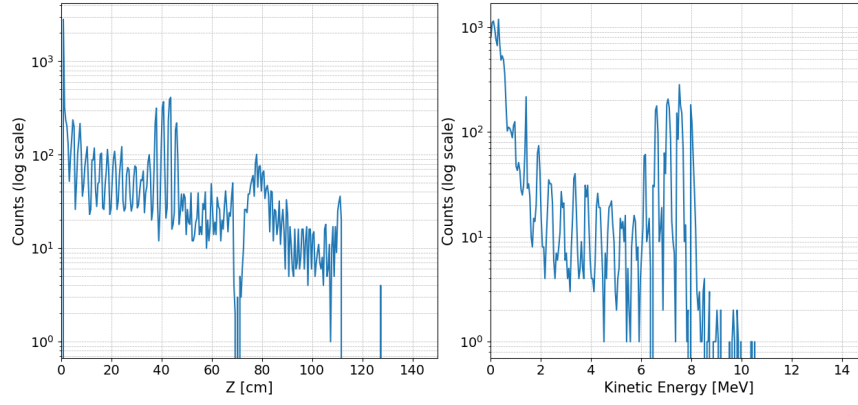


Figure 5.8: In the left panel the the spatial distribution of the exiting particles in the z direction, as obtained from the geometrical analysis (in logarithmic-scale). In the right panel a logarithmic-scale energy histogram of the exiting particles, highlighting the energy distribution of the particles.

within the accelerator. These intermediate energy levels highlight the complexity of the energy transfer processes taking place as the electrons exit the beam pipe and interact with surrounding materials. After identifying the coordinates at which the electrons exited the accelerator, both for the straight and scattered electrons, further simulations were conducted using FLUKA to model the radiation transport and secondary particle production. In FLUKA, the accelerator geometry was accurately reproduced to simulate the interactions between the primary beam and the accelerator's components. Figure 5.9 shows the reproduced geometry (top) and a schematic of the photon and electron (both primary and secondary) trajectories generated during the simulation. All simulations have been performed with a statistics of 10^8 primary particles. Analyzing the FLUKA output

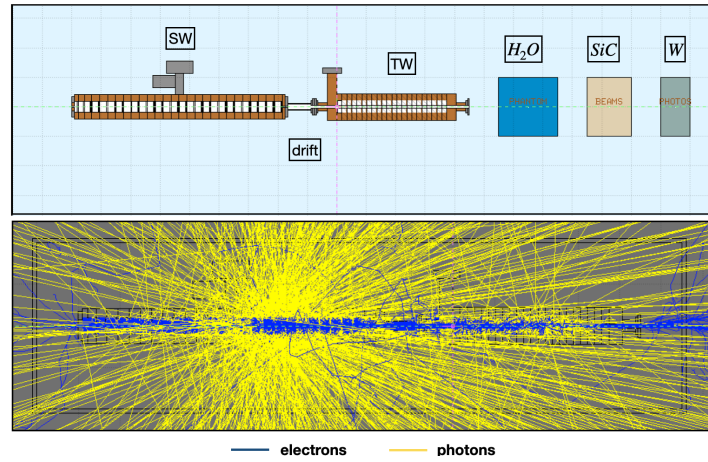


Figure 5.9: Representation of the LINAC geometry simulated in FLUKA. At the top, the SW section, drift tube, and TW section of the accelerator are clearly distinguishable. Downstream, there is a water phantom ($20 \times 20 \times 20$ cm), a silicon carbide beam stopper ($20 \times 20 \times 15$ cm) designed to absorb the primary electrons, and a tungsten block ($20 \times 20 \times 10$ cm) to shield against bremsstrahlung photons generated by the primary beam. Below, the tracks of the interaction products between the outgoing primary beam and the accelerator materials are displayed: yellow tracks represent photons, blue tracks represent electrons, and gray tracks indicate neutrons, which are not always visible due to their low quantity.

allowed us to characterize the different types of radiation produced by various interactions within the accelerator. The electrons that struck the accelerator structure contributed to the production of a variety of secondary particles, including photons, neutrons, and other scattered electrons. Figure

5.10 presents energy histograms for the four main radiation products of interest: electrons (panel A), photons (panel B), positrons (panel C), and neutrons (panel D). These histograms are displayed on a logarithmic scale, normalized per primary electron simulated with FLUKA, and include the average energy for each distribution. These histograms reveal how the interactions of lower-energy

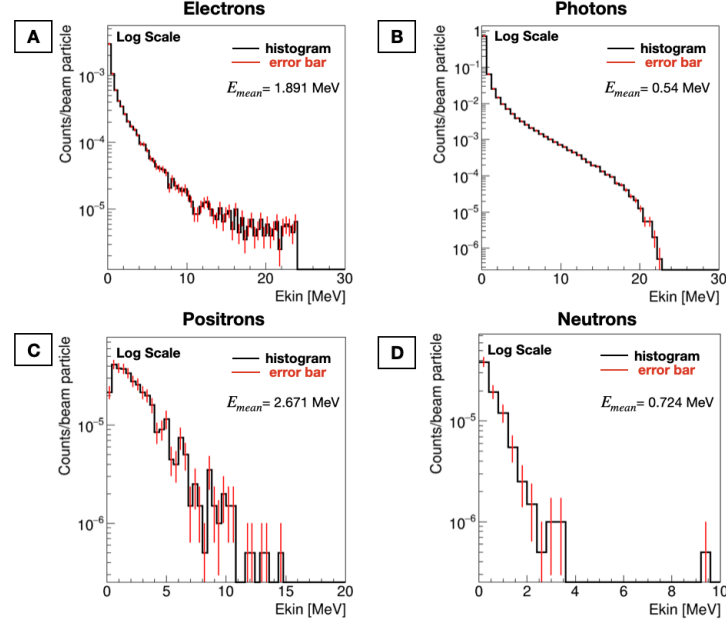


Figure 5.10: Energy histograms for the four primary radiation products of interest, displayed across four panels: electrons (Panel A), photons (Panel B), positrons (Panel C), and neutrons (Panel D). These histograms are presented on a logarithmic scale and normalized per simulated primary electron using FLUKA. Each distribution includes the average energy value, providing insight into the energy profiles of the radiation products. The red bars indicate the statistical uncertainty associated with the Monte Carlo simulations for each respective bin, reflecting the inherent variability due to random sampling within the simulation process.

scattered electrons can generate a wide range of secondary particles, underscoring the importance of comprehensive shielding and mitigation strategies in minimizing exposure to both primary and secondary radiation. Additionally, the simulation results provided insights into the dose delivered to the surrounding air by the particles exiting the accelerator, as well as the dose deposited by the focused primary beam in the region beyond the exit window. For this region, I modeled a setup consisting of a water phantom, a silicon carbide beam stopper (positioned to absorb the primary electrons), and a tungsten block to shield against the bremsstrahlung photons produced by the primary beam. The water phantom, positioned 10 cm from the end of the accelerator, has dimensions of $20 \times 20 \times 20$ cm. The beam stopper measures $20 \times 20 \times 15$ cm, and the tungsten block is $20 \times 20 \times 10$ cm. The dose distribution as a function of position z along the LINAC, plotted as a slice integral representing the cumulative dose along the beam direction, is shown in 5.11.

Additionally, a further study was conducted on the particles that are accelerated in a backward direction. Inside a SW structure, approximately half of the particles within the first cell will experience a decelerating electric field, which causes these particles to be transported backward toward the cathode. Their energy distribution is, at most, comparable to that of the particles that are accelerated forward starting from the second cavity onward. This phenomenon occurs due to the interplay between the standing wave fields and the dynamics of particle acceleration, leading to a unique situation where a subset of particles, instead of being accelerated forward, are effectively

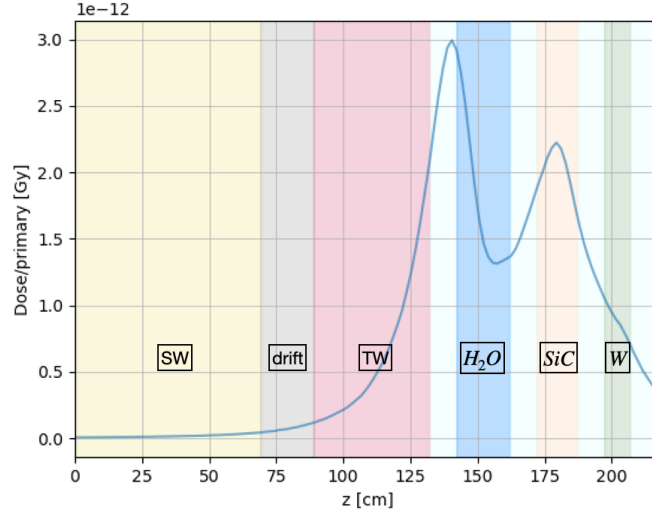


Figure 5.11: Integrated dose (in Gy per primary particle) along the length of the accelerator, providing insights into radiation exposure in various sections. The background colors denote different geometric regions along the LINAC: yellow for the SW section, gray for the drift tube, pink for the TW section, blue for the water phantom, beige for the silicon carbide beam stopper, and green for the tungsten parallelepiped. These color-coded regions enhance the visualization of dose variation with respect to position, facilitating a clearer understanding of how the dose is distributed throughout the accelerator's components.

decelerated and redirected. To illustrate this phenomenon, Fig. 5.12 schematically represents the behavior of the electric fields within the standing wave structure.

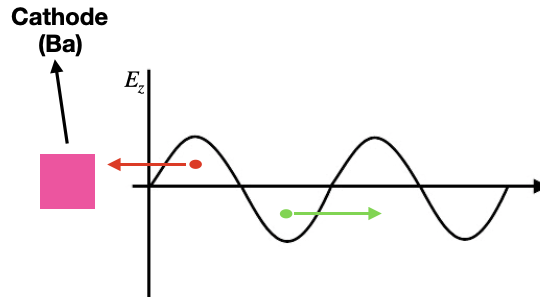


Figure 5.12: Schematic representation of the electric field distribution within the standing wave structure. The field orientation alternates across the cavities, resulting in both forward-accelerated particles and backward-directed particles within the first cell. The backward motion is due to particles experiencing a decelerating field, redirecting them toward the cathode.

Additionally, Fig. 5.13 shows two histograms: one on the left depicting the angular distribution and the other on the right showing the energy distribution of the particles moving backward. Notably, the angular distribution exhibits a peak at 0 radians, while the energy distribution reveals a peak energy of 0.3 MeV for these backward particles. Given this information, we can infer that these particles are likely to be completely absorbed by the cathode, which is made of Barium in our case. Thanks to the simulation results, radiation protection experts are able to design the shielding barriers effectively, accurately assessing the secondary particle production and optimizing the shielding to meet stringent dose constraints for both controlled and supervised areas, which is essential.

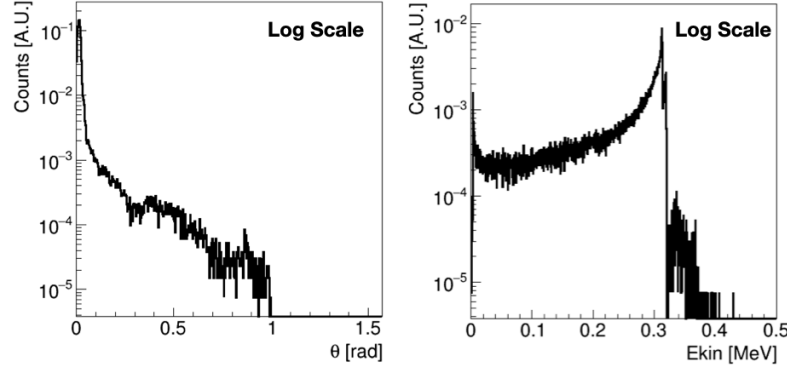


Figure 5.13: Angular and energy distributions of particles accelerated backward towards the cathode. Left: Angular distribution of backward particles, showing a peak at 0 radians, indicating their alignment with the beam axis. Right: Energy distribution with a peak at 0.3 MeV, suggesting that these particles possess low enough energy to be fully absorbed by the Barium cathode.

5.4 Results and shielding proposal

In designing radiation shielding for medical and research accelerators, ensuring a balance between dose limits and radiation protection objectives is of paramount importance. The guiding principle, *ALARA* (As Low As Reasonably Achievable), summarize all aspects of optimization. The shielding design goal must account for various occupational zones, each with different levels of radiation exposure risk, ensuring that doses remain well below annual effective dose limits of 20 mSv for workers and 1 mSv for the general public. In this analysis, the aim is to determine the necessary shielding for the FLASH Lab that will host the VHEE LINAC, focusing on ensuring compliance with dose constraints in both controlled and supervised areas. The accelerator area will be classified as a "Controlled Area" due to the potential for higher radiation levels, restricting access to personnel specifically trained and monitored for occupational exposure. Surrounding areas will be classified as "Supervised Areas," where dose constraints are more restrictive. The required attenuation factor (B) for the shielding was calculated using the following formula:

$$B = \frac{P}{T} \cdot \frac{d^2}{WUT} \quad (5.3)$$

where P is the shielding design goal, which represents the maximum allowable dose rate beyond the shielding barrier, W is the beam workload, expressed in terms of the number of beam particles or operating hours per week or year, and it reflects how frequently the machine is in use, U is the use factor, representing the fraction of time the primary beam is directed towards the specific barrier being considered, T is the occupancy factor, which accounts for the fraction of time individuals are present in the area adjacent to the shielding, and d is the distance between the radiation source and the point beyond the shielding where the dose is being evaluated. Given the radiation field, the ceiling was identified as the critical area requiring additional protection. The calculations indicated that a 20 mm thick concrete shield with a density of 2350 kg/m³ was necessary to adequately attenuate the radiation in the bunker area. In other cases, the shielding design goal is met by using standard partition walls. After completing the analytical studies on the appropriate shielding design, another simulation was conducted, similar to the previous one, to evaluate the dose at four key positions, in air, of interest for radiation protection protocols: along the beam axis at a distance

of 180 cm (point A) from the tungsten block, laterally at the phantom position 170 cm from the beam axis (points B and C), placing oneself 30 cm beyond the bunker wall, and at 230 cm above the beam axis (point D), positioned 40 cm from the floor of the upper level. These points are graphically represented in Fig. 5.14. At these spatial positions, the dose was calculated in two

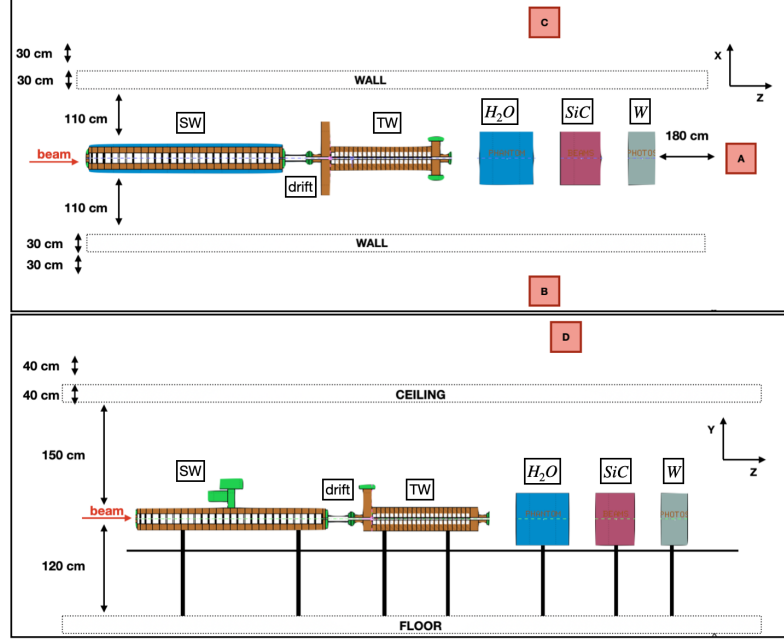


Figure 5.14: Representation of the LINAC geometry simulated in FLUKA, indicating the four points where the dose was calculated for the purpose of designing the shielding walls required by radiation protection protocols. Point A is positioned along the beam axis at 180 cm from the tungsten block; Point B and Point C are placed laterally at the phantom position, 170 cm from the beam axis and 30 cm beyond the bunker wall; Point D is at 230 cm above the beam axis, positioned 40 cm from the floor of the upper level.

configurations: without any type of shielding around the accelerator walls and assuming three 3 cm thick lead plates, as an additional precaution, on the lateral walls and the top of the accelerator, as well as in the region comprising the phantom, beam stopper, and tungsten block. Also in this case all simulations have been performed with a statistics of 10^8 primary particles. The results of the simulations in both cases were compared to verify the actual dose attenuation with shielding. As

	Without shielding	With shielding
	Dose [Gy/primary]	
Point A	$9.73 \cdot 10^{-18} \pm 3.06 \cdot 10^{-19}$	$3.75 \cdot 10^{-18} \pm 1.76 \cdot 10^{-19}$
Point B	$7.28 \cdot 10^{-18} \pm 3.28 \cdot 10^{-19}$	$5.99 \cdot 10^{-19} \pm 7.61 \cdot 10^{-20}$
Point C	$7.82 \cdot 10^{-18} \pm 3.48 \cdot 10^{-19}$	$8.49 \cdot 10^{-19} \pm 9.31 \cdot 10^{-20}$
Point D	$3.86 \cdot 10^{-18} \pm 2.27 \cdot 10^{-19}$	$3.48 \cdot 10^{-19} \pm 4.63 \cdot 10^{-20}$

Table 5.3: Dose values dispersed in the space surrounding the accelerator at various locations in point A, B, C, D (as described above). In the second column the values for the scenario without any shielding around the accelerator, while the third column presents the simulated values with 3 cm thick lead plates surrounding the accelerator.

summarized in Table 5.3, the simulations demonstrate a significant attenuation of radiation dose

when appropriate shielding is applied. These findings confirm that the proposed shielding, consisting of three 3 cm thick lead plates on the lateral walls and ceiling, is effective in minimizing radiation exposure at critical locations. The significant reduction in dose values demonstrates compliance with radiation protection protocols, ensuring that both operational personnel and the general public remain within acceptable exposure limits. The results I have obtained have been used, with the help of the RadioProtection service of Sapienza University to define the structural work that will be done, prior of the installation and test of the VHEE accelerator in the Sapienza LAB that will host the machine.

Conclusions

In my thesis, I have studied how critical advancements in Very High Energy Electron (VHEE) therapy, especially in the context of ultra-high dose rate (UHDR) or FLASH radiotherapy, can be studied to assess the feasibility of their use for treating deep-seated tumors and what are the essential challenges that have to be still addressed before their clinical implementation.

In my research work I have developed a customized Treatment Planning System (TPS) and used it to plan VHEE treatments and compare them against the state-of-the-art therapies that are currently being delivered in the clinical centres. The results I have obtained confirm the competitiveness of lower-energy (70-130 MeV) VHEE beams in multi-field configurations even without FLASH mode, showing performance comparable to proton therapy (PT) and conventional radiotherapy (RT). These VHEE configurations, due to their unique dose distribution characteristics as charged particles, can achieve precise dose delivery with reduced treatment times and minimal integration impact in hospital environments. This flexibility, and the natural easiness in delivering VHEE beams at FLASH intensities allows VHEE therapy to re-enter the field of external beam radiotherapy (EBRT) as a viable treatment option, meeting the energy requirements within clinical and hospital settings without extensive modifications to existing infrastructure. In my thesis, I have also shown how VHEE beams can provide FLASH doses with excellent precision, eliminating the need for a 3D range modulator with the potential to significantly change the landscape of treatment delivery. The VHEE option, either in conventional or FLASH mode, opens the door to new treatment strategies, particularly for radioresistant tumors or anatomical regions where the toxicity of Organs at Risk (OARs) limits therapeutic efficacy. In the intracranial lesion study, for instance, VHEE's dose conformity allows for optimized PTV coverage while preserving critical structures such as the cochlea. Similarly, in the pancreatic tumor case, VHEE beams demonstrate effective dose distribution and a unique ability to reduce OAR exposure in FLASH mode, providing high tumor coverage while sparing critical structures like the stomach and intestines. This precision is particularly beneficial for treating pancreatic cancer, where surrounding sensitive organs have often made effective dose delivery challenging, and underscores VHEE's potential for broad clinical applicability.

In the last part of my thesis I have addressed the radioprotection challenge associated with VHEE technical implementation in a research or hospital facility, essential for ensuring safe clinical integration. Through radiation shielding studies, effective solutions were identified for containing radiation exposure around the VHEE LINAC prototype. Simulating secondary particle emissions and dispersed radiation within the experimental setup led to a proposed shielding design that meets regulatory standards in both controlled and supervised environments, adhering to the ALARA principle. This outcome confirms that it is feasible to incorporate VHEE facilities within medical environments while maintaining necessary safety protocols, demonstrating a clear path toward secure

clinical adoption.

In conclusion, this thesis provides a robust framework for VHEE radiotherapy: starting from a technical solution to implement VHEE in a clinical environment, I have addressed the planning challenge and studied a shielding solution for the implementation in research facilities, marking a substantial step toward clinical viability. Notably, this work enabled the initial phases of installation and safety protocols for a VHEE accelerator at Sapienza, a critical step toward the operation of the first demonstrator for FLASH radiobiology studies. The clinical potential of VHEE, particularly when integrated with FLASH mode, presents promising possibilities for elevating the precision, safety, and therapeutic impact of radiotherapy. These advancements are especially significant for complex cases like pancreatic cancer, where conventional techniques often face limitations. Going forward, further experimental validations and refinements of both the TPS and shielding designs will be essential to fully harness the clinical applications of VHEE therapy.

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Appendix A

Appendix

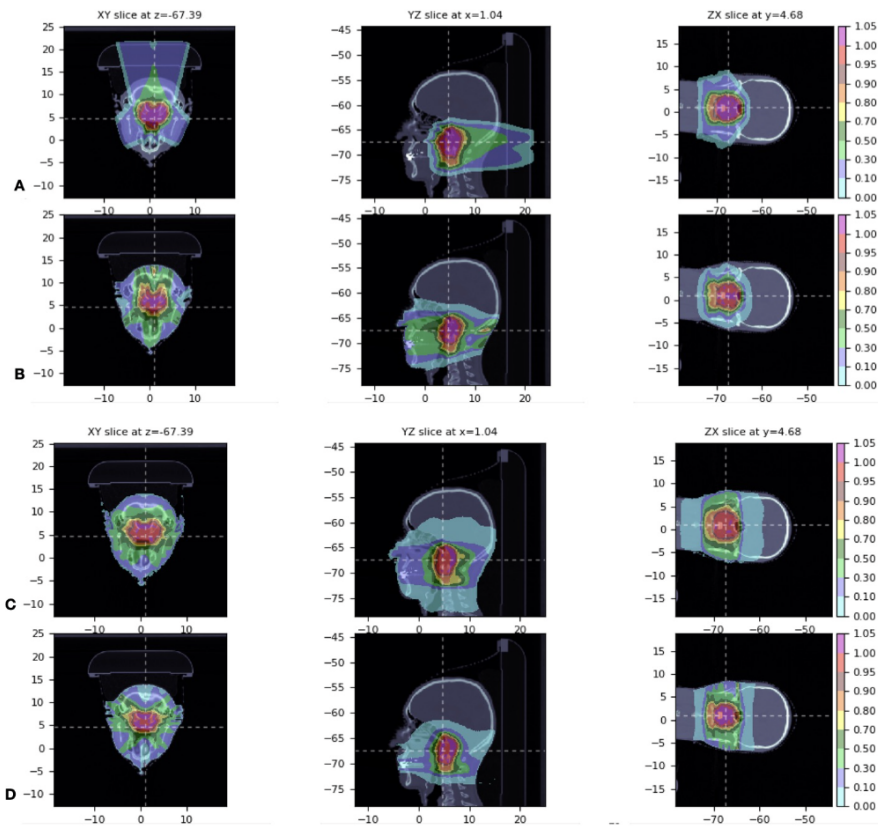


Figure A.1: Patient C1 isodose maps: a) PT, b) VHEE 4 fields, c) IMRT, d) VHEE 7 fields. The distributions are shown for the optimised plans in which no FLASH effect was included.

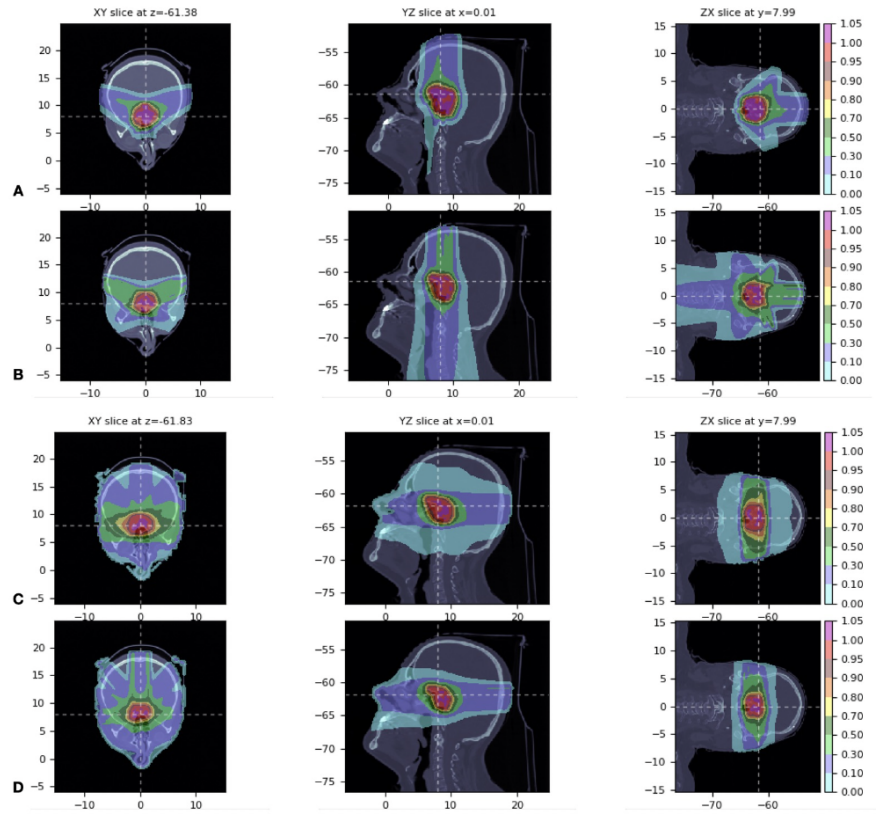


Figure A.2: Patient M1 isodose maps: a) PT, b) vhee 3 fields, c) IMRT, d) VHEE 7 fields. The distributions are shown for the optimised plans in which no FLASH effect was included.