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ACCELERATORS FOR HEALTH:

FROM CURRENT TO DREAM MACHINES

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Any kind of sculpted particle beams from high-energy photons (X-rays and gamma rays), electrons, protons, neutrons to various atomic nuclei and more exotic species have been used to treat cancer. The development of a next generation of accelerators to face the challenges and issues of Particle Therapy is crucial. What are the most promising accelerator techniques, particles or dose delivery modes?

▲ Layout of SEEIIST (South East Europe International Institute for Sustainable Technologies) facility

The potential of accelerator-based Radiotherapy (RT) has increased considerably over the past decades, playing an increasingly important role in identifying and curing affections, such as cancer. Energetic particles of any kind have been used in the past, but nowadays photons (X-rays), low-energy electrons, protons and carbon ions are the most common types of irradiation (Figure 1).

X-rays are the most common method of RT for cancer treatment. Even if the X-rays therapy is a mature technology there is room for improvement. The current challenges are related to the accurate delivery of X-rays to tumours involving sophisticated techniques to combine imaging and therapy. Hadron (*i.e.* proton and ion) beam therapy has growing potential in dealing with tumours close to organs at risks, because the irradiation dose (Figure 1) is mainly deposited at a specific longitudinal position, the Bragg peak, which depends on the energy of the particles. Also, some treatments may benefit from the use of ions that deliver doses with a greater radiobiological effectiveness (RBE), notably Carbon. Helium and Oxygen are also promising candidates for therapy and in particular techniques combining irradiation with multiple ions are getting more interest, to exploit the advantages of the different species[1]. With the recent developments of high-gradient normal conducting (NC) Radio Frequency (RF) linear accelerator (linacs) technology (Figure 2) or even the novel acceleration techniques such as the Laser-Plasma Accelerator (LPA), Very High-Energy Electrons (VHEE) with energies between 50-200 MeV offer a very promising option for anticancer RT.

Whatever RT particle used, the treatment is limited by the toxicity introduced in the healthy tissues surrounding the tumours. A novel paradigm-shifting method for delivering ultra-high doses within an extremely short irradiation time (tenths of a second), known as FLASH-RT is now under study. The technique has recently been shown to preserve normal tissue in various species and organs while still maintaining anti-tumour efficacy equivalent to conventional RT at the same dose level. The "FLASH effect" has been shown to take place with electron, photon and more recently for proton beams. For details we refer to [2, 3].

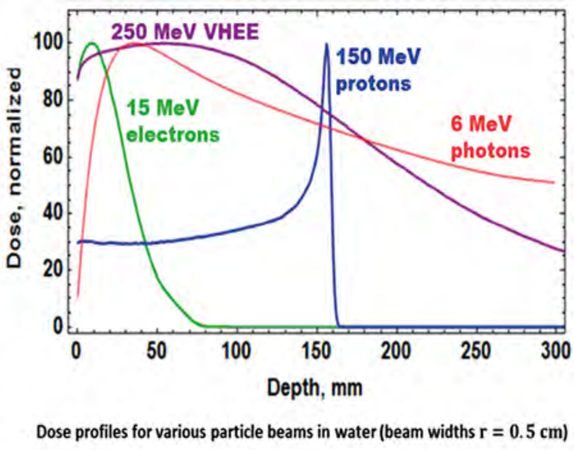
Towards a compact and flexible Hadron Therapy facility

For proton therapy, compact accelerator systems are nowadays available on the market: mostly cyclotrons in Europe and America and synchrotrons in Japan. The irradiation is mainly done via 3D beam-scanning.

Cyclotrons have the advantage that they are very compact and have only a few tuning parameters, thus are simple to operate in a hospital environment. However, scaling to the energies needed for Carbon-ions, which have a factor 3 higher beam rigidity (*i.e.* the resistance to deflection by a magnetic field) is challenging. Another limitation of conventional cyclotrons is their fixed extraction energy, which implies the use of degraders, with associated transmission losses and radioprotection constrains. Current R&D goes in the direction of energy-variable cyclotrons and the use of high-field superconducting (SC) iron free magnets [3].

Synchrotrons are easily scalable to ion operation, even if this implies an increase of their footprint, and allow acceleration of different type of ions. The preferred choice for carbon-ions today is a rather large synchrotron (of >20-m diameter compared to the 6-m size for protons). Most important, synchrotrons are flexible with respect to the extraction energy, which can be easily changed between one cycle to the next. A limitation of today synchrotrons, though, is the length of each cycle, of the order of 1s. In Europe, and following what was recently implemented in National Institute of Radiological Sciences (NIRS) in Japan [5], the tendency is to operate synchrotrons with the so-called multi-energy extraction (MEE) scheme, to deliver beams at different energies within the same cycle, thus saving time.

Ultimately, if one could accelerate the total number of ions needed for a treatment session within one cycle (thus a factor 10-20 times higher intensity, accumulated by multi-turn injection), the full dose will be delivered significantly faster. Moreover, this mode of operation will make the use of SC magnets feasible, thus allowing a significant reduction of the dimensions of the ion synchrotron (indeed the SC magnets ramping time is much longer than for NC magnets). The R&D in this sense focus on ions sources to reliably deliver a higher current, on advanced injection and extraction schemes and on strongly curved SC magnets. The development of a SC-magnet carbon-ion synchrotron is precisely one of the main objectives of the Heavy Ion Therapy Research Integration (HITRIplus) [6] and what is being studied by the SEEIIST (South East Europe International Institute for Sustainable Technologies) [7] and the CERN NIMMS (Next Ion Medical Machine Study) initiative [8].



◂ **FIG. 1:** Dose profile for various particle beams in water (beam widths r=0.5 cm)

Accelerators other than cyclotrons and synchrotrons are also under study, in particular Fixed Field Alternating gradient (FFA) and linacs. After several years of R&D and developments in research and international laboratories environment, the first linac based proton therapy facilities is under construction and commissioning in Europe. With the use of high-frequency high-gradient copper structures, designed to achieve relatively compact solution and high repetition rate operation, linacs will allow the production of beams with fast energy variation as well as small emittance beams that are potentially suited for the further development of mini-beams dose delivery techniques. Detailed information in [9, 10].

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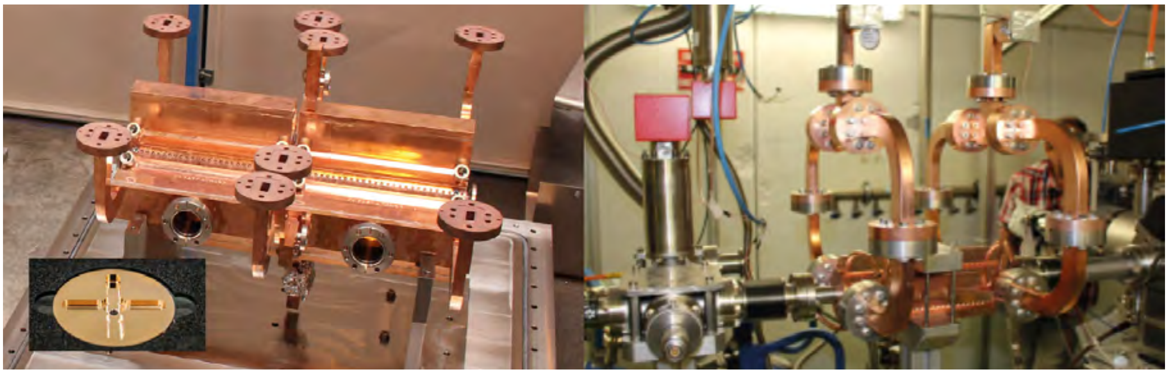

▸ **FIG. 2:** CLIC RF X-band cavity prototype (12 GHz, 100 MV/m)

Towards a VHEE RT facility

Low-energy electrons have historically been used to treat cancer for more than five decades, but mostly for the treatment of superficial tumours given their very limited penetration depth. However, this limitation can be overcome is VHEE (50-200 MeV, Figure 1) are used. Theoretically, VHEE beams offers several benefits. The ballistic and dosimetry properties of VHEE provide small-diameter beams that could be scanned and focused easily, enabling finer resolution for intensity-modulated treatments than is possible with photons beams. Electron accelerators are more compact and cheaper than proton therapy accelerators. Finally, VHEE beams can be operated at very high-dose rates and fast electromagnetic scanning providing a uniform dose distribution throughout the target and allowing for unforeseen RT modalities in particular the FLASH-RT.

Normal Conducting RF linac is the technology being used for most of the VHEE research. The main advantages of the linacs are the flexibility and the compactness. Regarding the linac design in the energy range of interest for VHEE applications there are different possibilities offering the desired performances and compactness with different degrees of technology matureness. The S-band (~3 GHz) technology is the most mature one, High-Gradient compact linacs of this type are already available from various industrial partners. The C-band (~5 GHz) and X-band (~12 Ghz) RF linacs still less mature and are mainly constructed in accelerator laboratories with the help of industries for the machining. Lately a considerable effort is being made from the industrialization point of view [11]. A limited number of accelerators in Europe and USA are available for VHEE R&D. The majority based in NC RF linacs, few of them are based on Super Conducting (SCRF) linac technology at L-band (~1.3 GHz). Finally, a VHEE-FLASH RT facility based on a Compact Linear Collider (CLIC) X-band 100 MeV linac is being designed at CERN in collaboration with *Centre Hospitalier Universitaire Vaudois* (CHUV) to treat large, deep-seated tumours in FLASH conditions. The facility is as compact as to fit on a typical hospital campus.

Recent advances in the high-gradient RF structures, mainly in the material domain (origin, purity, surface treatment) and manufacturing technology in one side and the consistency and reproducibility of the test results in the other side, are transforming the landscape for VHEE RT. Some promising R&D in the next decade are: the distributed coupling accelerator and the use of cryogenic copper that is transforming the linac design offering a new frontier from beam brightness, efficiency and cost-capability. Another approach for the next generation of compact, efficient and high performance VHEE accelerator is the use of higher frequencies millimetric waves (~100 GHz) and higher-repetition rates using THz sources. An important R&D effort to apply these accelerator technologies in the medical has to be made in the next decade to make VHEE RT a clinical reality [2].

Therapy facilities based on Laser-Plasma-Acceleration

As high-performance lasers took big increased enhancements in the last years concerning power and repetition rate their use for particle therapy may be possible in future. The actual limit of about 100 MeV achieved for the highest proton energies driven by ultra-intense lasers using Target Normal Sheath Acceleration (TNSA) depicts a major milestone on the way to the needed energies. But still the broad energy spread of the accelerated protons is not feasible for treatment modalities. The reached energies for laser accelerated ions is still a magnitude lower and thus far from necessary values. The very short dose peaks may be attractive for FLASH therapy, but then the repetition rate of the Petawatt lasers should reach 100 Hz and more, which is not the case nowadays. In addition, the target configuration has to resist this high load on a long-time basis – a therapy facility runs several 1000 hours a year. Furthermore, the reliability of a laser-based proton or ion accelerator must reach 98% or more to be of practical use in a medical facility. But this technique should be explored with high effort in the next decade to identify the long-term potential. Concerning the VHEE there is an intense R&D effort in LPA for being applied in the next generation of VHHE-RT facilities. The major challenge for the LPA technique is the beam quality, reproducibility and reliability needed for RT applications. This R&D is being carried out in some LPA facilities in Europe, Japan and USA, where dedicated beamlines provide stable experimental conditions for radiobiology and dosimetry R&D. A wide international R&D programme, in particular we highlight the role of the EU network: EUPRAXIA (Compact European Plasma Accelerator with Superior Beam Quality) [12], will be needed in the next decade in order to convert these “dream" facilities into reality.

Final remarks

To enhance the coverage of particle therapy in Europe and worldwide and to enlarge the number of patients, which can profit from this special treatment, the investment costs of such facilities should be reduced as much as possible, which requests smaller and simpler machines to save manufacturing and operating effort. Especially the size of the accelerator has important influence on the building costs. And the amount of beam losses demands more or less concrete for radiation shielding, therefore they should be minimized by design. In addition, the operating and maintenance team needed should be small, but adequate and well-trained, sustained by a modern control system, which predicts pre-emptive maintenance measures through Artificial Intelligence algorithms and thus guarantees highest availability. ■

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