STATE – OF – THE – ART AND THE FUTURE OF PARTICLE THERAPY (Perspectives for the SEE countries)

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ABSTRACT

Radiation therapy (RT) is aimed to treat cancer cells with a radiation dose sufficient to stop their growth and simultaneously to spare the surrounding healthy tissue. Hadron Therapy (HT) alternatively called Particle Therapy (PT) involves accelerating hadrons (charged particles such as protons or heavier ions) to almost the speed of light, then "painting" the tumour's volume precisely with the radiation beam. Advances are continuously being made with the developments of new and more accurate technologies. In this work, we intend to show the advancement in the PT and the prospective advancements beyond the-state-of-the-art in (1) accelerator technologies that provide higher intensity ion beams, improvement in the ion-beam "optics" and detection technologies, (2) new gantry design, (3) radiobiology innovative research of the lethal and DNA recovery effects on different accelerated ions species on radioresistant cancer cell lines, and also an examination of possibilities of FLASH PT treatments (using higher doses at a reduced number of treatments), (4) detection and imaging improvements and (5) performances of the profound clinical studies with a big-data approach, in which a comparison between the conventional RT and the PT on large groups of patients that suffer from some types of cancer was made.

Cancer is a critical societal issue and currently, it is the second leading cause of death and radiation therapy (RT) is a fundamental component of effective cancer treatment. The main goal of RT is to maximise the damage to the tumour while minimising the damage to the surrounding healthy tissue. The most frequently used modalities of RT use high-energy (MeV) photon or electron beams. Conventional X-ray radiation therapy is characterised by almost exponential attenuation and absorption, and consequently delivers the maximum energy near the beam entrance but continues to deposit significant energy at distances beyond the cancer target.

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Hadron therapy or Particle therapy (PT) (protons and other light ions) can overcome the limitations of X-rays since hadrons/particles deposit most of their energy at the end of their range and these beams can be shaped with great precision. Hence it allows for a more accurate treatment of the tumour destroying the cancer cells more precisely with minimal damage to surrounding tissue, therefore, sparing the healthy surrounding tissue. The use of protons and carbon-ions for treating cancer has grown over the last 20 years. However, despite the efforts made on compactness and cost reduction, the equipment is still relatively large and expensive, making such facilities economically challenging for most hospitals.

To achieve more cost-efficient facilities and thereby give improved access to patients globally, research needs to be strengthened, broadened and combined in several fields including (1) accelerator technologies that provide higher intensity ion beams and improvement in the ion-beam "optics" (2) new gantry design, (3) radiobiological innovative research including the possibilities of using FLASH PT (using high doses in very short irradiation times), (4) detection and imaging improvements and (5) extensive clinical trials with a larger number of patients, in which comparisons between the conventional RT and the PT can be made.

Keywords: Particle Therapy, Hadron therapy, Proton, Ion, Accelerator.

INTRODUCTION

Cancer is a critical societal issue. Worldwide, in 2018 alone, 18.1 million cases were diagnosed, 9.6 million people died and 43.8 million people were living with cancer (Figure 1). Current projections anticipate an increase with approximately 24,6 million newly diagnosed patients and 13 million related deaths by 2030. Cancer imposes an enormous economic burden worldwide—around 2 trillion dollars in 2010 and these costs are rising and putting a major burden on public healthcare budgets. In the EU where over 3.7 million new cases per year are diagnosed and total costs over 120 billion EUR were reported for the EU in 2012. Combating cancer is considered to be a priority research challenge by the European Commission, this is particularly relevant in the Balkan region where mortality rates from cancer are on average 40% higher compared to the rest of Europe [1].

Ever since the discovery of X-rays in 1895, they played a key role in cancer treatment. RT became a fundamental component of effective cancer treatment and control. It is estimated that about half of all cancer patients would benefit from radiotherapy for treatment of localised disease, local control, and palliation. However, conventional photon RT is characterised by almost exponential attenuation and absorption, and consequently delivers the maximum energy near the beam entrance, but continues to deposit significant energy at distances beyond the cancer target, which at times can be as high as 50% of the dose to the target resulting in considerable damage to healthy tissue.

RT with heavier charged particles also called **hadron therapy** (HT) with protons and other ions species has also been proposed and offers several ballistic advantages over the classical RT with X-rays. Thirty years after the design of the initial generation of such facilities [2], the time is ripe for a breakthrough in accelerator technology and treatment modalities that will

make cancer treatment with heavy-ion beams accessible to a larger fraction of the European population. After years of experimentation and clinical trials, the use of particle beams for radiotherapy of cancer, with particle beams leaving a low dose of radiation in the healthy tissues surrounding the tumour, has proven its advantages over conventional X-ray radiation therapy (RT) for many types of cancer [3]. The ion beam therapy, or hadron therapy (HT) or, more commonly called Particle Therapy, is an RT modality characterized by highly conformal dose distributions and integral dose sparing. Possible ideas to improve the performance of a novel gantry could include fixed structures that deliver beams from many directions; structures that combine patient movement and magnets with large momentum acceptance.
Using an active beam energy variation and magnetic scanning of narrow pencil-like ion beams over the target, a further improved dose shaping in three dimensions is possible. 60 years after they were first proposed to cure cancer, there has been a revival of interest in this subject in the context of high precision radiation therapy since the high energy protons suffer little angular deflection and have a well-defined penetration range, with a sharp increase in the energy loss at the end of their trajectories, namely the Bragg peak. Also, it was found that for high energy proton beams the amount of escaped energy by neutrons is almost 10 times larger than that by photons [4].

CANCER IN THE SEE REGION AND EUROPE

More than every fourth death in the EU is caused by cancer, making it the second leading cause of death, second only to cardiovascular diseases [5]. In Horizon Europe, the commission gives the fight against cancer even more priority by considering it to be one of the greatest world challenges and specifically placing the mission against cancer as a top priority in its mission-oriented policy [6]. **Error! Reference source not found.** shows the mortality-to-incidence ratio (MIR) in Europe and SEE countries in 2018. The data were extracted from Globocan[2]. The SEE region consists of the countries that are EU Member States (Bulgaria, Croatia, Greece and Slovenia), as well as of the countries that are aspiring for membership soon (Albania, 2 This is a provisional file, not the final typeset article SEEIIST project Bosnia and Herzegovina, Kosovo, Montenegro, North Macedonia and Serbia). Due to recent turbulent times in South-East Europe, all scientific and economic activities have slowed down. As a consequence, the region also suffered from an extensive brain drain of the young and prosperous scientists [7]. The figure highlights a higher mortality-to-incidence ratio in the SEE region (shown in red) compared to selected Western European countries. One can notice that the MIR for Bosnia and Herzegovina is almost double in Switzerland. One factor causing the higher mortality rate in SEE countries is the lack of modern, advanced imaging and treatment equipment. All the SEE countries except for Slovenia and Greece reveal MIR higher than the European average.

[2] https://gco.iarc.fr/

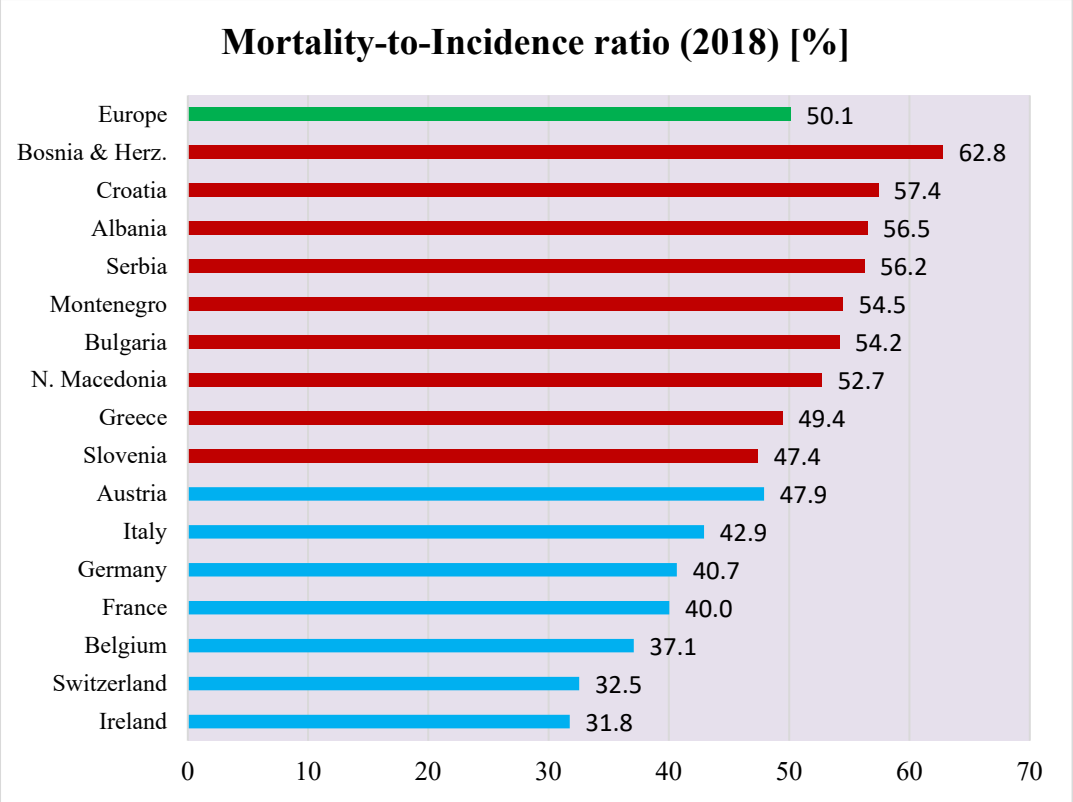


Figure 1. Cancer statistics – mortality-to-incidence ratio (all cancers, excl. non-melanoma skin cancers). Red bars indicate SEE countries, blue (Western European countries). The green bar pertains to an average of Europe.

Around 10% of the patients who have been referred to RT can benefit the most from proton therapy and a minimum of 3-5% can benefit the most from the heavy ion therapy. This translates to at least 7000 people annually in the SEE region who have either radio-resistant tumours or tumours close to sensitive organs and would benefit from the use of heavy-ion therapy. Without PT, those patients are likely to have major challenges from the X-irradiation of healthy tissues nearby [8]. Presently, X-ray RT technology is mainly used for the treatment of cancer patients in the SEE region (including 3D conformal X-ray RT and Intensity Modulated RT). In the entire SEE region covering about 43 million inhabitants, there is no treatment facility using either proton and/or heavy ion beams. If patients from SEE countries need this type of specialized treatment, their only option, at a high cost to the national health systems, is to travel to one of the 28 proton centres or one of the 4 heavy ion centres in operation in Europe (Figure 2) or travel to centres beyond Europe.

The principle of the PT relies on accelerated particles (hadrons), delivering their energy at the end of the pathway where they stop in the living matter, releasing a high amount of energy (so-called Bragg peak). This fundamental feature allows very little damage to occur to normal tissue as the beam traverses the body and thus the killing power is focused on the tumour. In comparison, the traditional RT causes damage before and after the tumour.

Figure 2. Countries in Western Europe with PT Centers (yellow, orange and red) and in SEE region with no PT Centers (green).

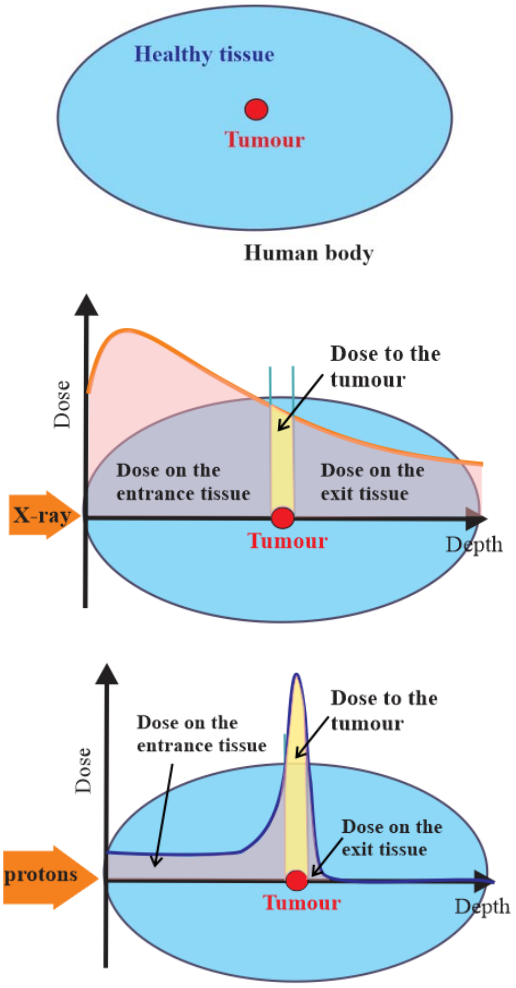
Protons are the easiest ions (H^+) to produce and accelerate. Proton therapy has been continuously growing since the opening of the first medical centre dedicated to proton therapy in 1990 in Loma Linda University, California, USA. The accelerator is the key component to the overall performance of the facility and the main avenue to improving the access to heavy ion therapy. In radiation therapy, gantries represent the parts that move the beamlines which are used to precisely direct the beam on the tumours from different angles, while the patient is usually lying on a couch.

The principle of the HT relies on accelerated particles (hadrons) delivering their energy at the end of the pathway where they stop in the living matter releasing a high amount of energy (so-called Bragg peak). This fundamental feature allows very little damage to occur to normal tissue as the beam traverses the body and thus the killing power is focused on the tumour. In comparison, the traditional RT causes damage before and after the tumour. As the particles stop in the tumour, they release the major part of their energy and cause targeted damage to the DNA of the cells which are hit, resulting in cell death in case their DNA is not repaired, similarly to X-rays [9]. Relative stopping power tells us the water equivalent thickness for a given thickness of material to allow us to plan the beam range [10]. Scanning modalities fully integrated with gantry geometry represent possibilities to move the beam across the tumour's volume. Being the lightest ions (H^+) protons are easiest to produce and accelerate. The accelerator is the key component to the overall performance of the facility and the main avenue to improving the access to heavy ion therapy. In radiation therapy, gantries represent the parts that move the beamlines which are used to precisely direct the beam on the tumours from

different angles, while the patient is usually lying on a couch. The huge dimensions of the ion-gantries implied the necessity of research for new, more compact design.

STATE-OF-THE-ART RADIOTHERAPY

X-rays (photons) radiotherapy (RT) is a widely used treatment modality to fight various types of cancer, exploiting the damage made by radiation to the cells' DNA when the radiation dose is concentrated on the tumour. X-rays have a dose distribution in tissues characterized by an almost exponential attenuation and absorption, delivering large energy near the beam entrance, reaching a maximum at few cm depths, and then continuing to deposit significant amounts of energy beyond the cancer target. Figure 2 puts some light on the difference between the dose distribution on the healthy tissue and the tumour in classical RT with X-rays and particle therapy (PT).



(a) Transversal cross-section of a model of a human body: healthy tissue (blue ellipse) with a tumour inside (red circle)

(b) Dose distribution vs. the depth at the classical RT treatment with X-rays. Orange area on the left- dose delivered to the healthy tissue at the entrance of the radiation in the human body, yellow area – dose to the tumour, orange area on the right – dose to the healthy tissue on the exit.

(c) Dose distribution vs. the depth at particle therapy (PT) with protons. Orange area on the left- dose delivered to the healthy tissue at the entrance, yellow area – dose to the tumour, orange area on the right – dose to the healthy tissue on the exit.

Figure 3. Comparison between the dose distribution in the targeted tumour and the healthy tissue in a model of a human body.

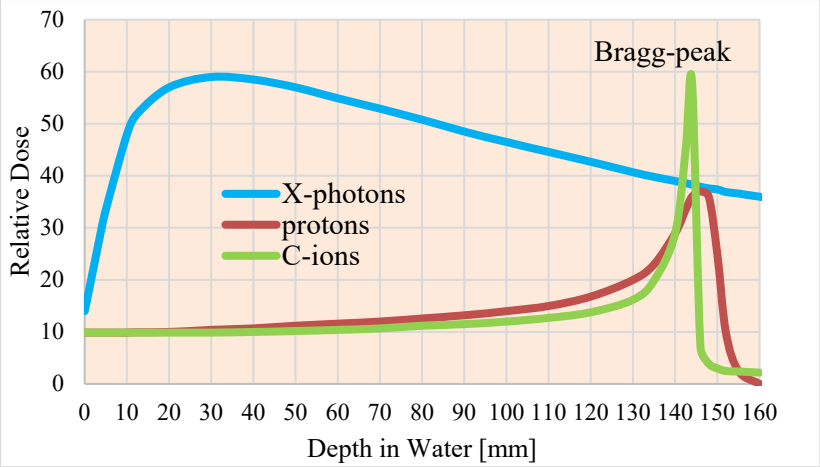
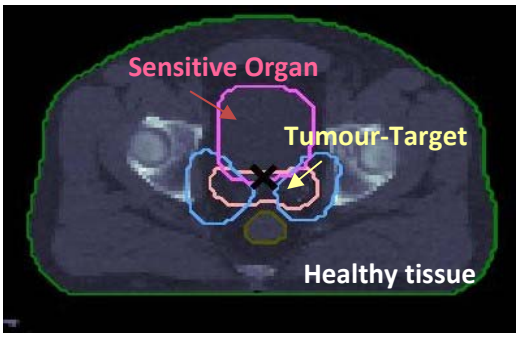
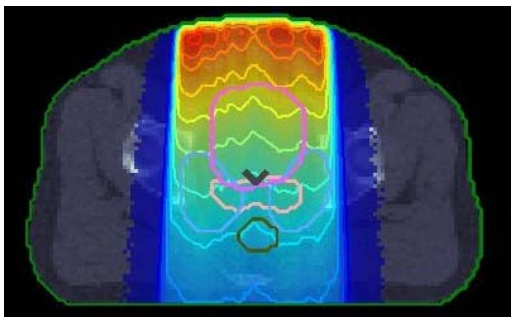


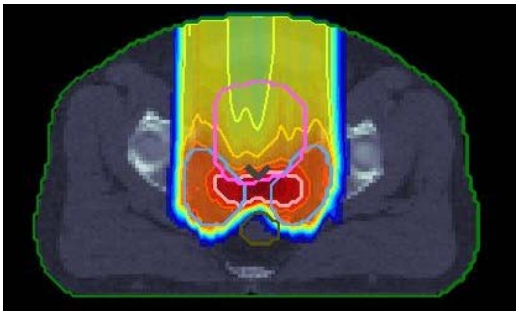
Figure 4. Dose distributions in water with depth for X-ray photons, protons and C-12 ions.



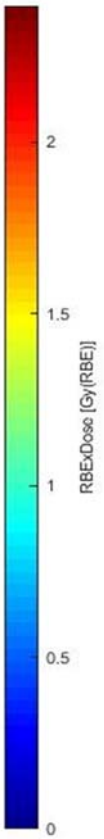
(a) Prostate tumour. Grey mass - healthy tissue, yellow line -the border of the targeted tumour. Purple line – border of the sensitive organ.

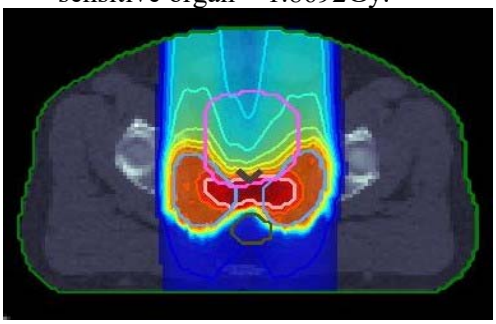


(b) Dose distribution upon optimized RT with X-photons. Dose to the healthy tissue=0.3145 Gy; Dose to the Target Tumour = 2.1216 Gy; Dose to the sensitive organ = 1.8692Gy.



(c) Dose distribution upon optimized proton therapy. Dose to the healthy tissue= 0.1593 Gy; Dose to the Target Tumour = 2.2628 Gy; Dose to the sensitive organ = 1.3359 Gy





(d) Dose distribution upon optimized Carbon-12 therapy. Dose to the healthy tissue= 0.1434 Gy; Dose to the Target Tumour = 2.2578 Gy; Dose to the sensitive organ =1.1165 Gy.

Figure 5. (a) Prostate cancer treatment planning with MatRAD[3], a software dedicated to educational/training purposes, (b) X-ray photons, (c) protons and (d) C-12 ions. Pictures show the effect of the lesser dose distributed to the sensitive organs by protons and C-ions compared to X-rays. The list dose to the healthy tissue is induced by C-ions therapy.

[3] https://link.springer.com/chapter/10.1007/978-3-319-19387-8_391

Because they are the lightest ions, protons are easy to produce and accelerate, and proton therapy is continuously growing ever since the opening of the first dedicated clinical facility in Loma Linda, California, the USA in 1990.

At the end of 2019, we counted 96 particle therapy facilities worldwide in clinical operation[4], treating patients with tumours where the reduced damage to healthy tissues is particularly beneficial for example at the base of the skull, or tumours in children. Another 37 particle therapy centres are under construction or in the planning stage. By end of 2019, about 260'000 patients have been treated worldwide with particle radiotherapy, more than 220'000 with protons, about 34'000 with C-ions and about 3'500 with He-ions, pions and other particles. Presently, there are no proton or hadron centres in the SEE region. The necessity of a particle therapy facility in SEE is highly justified due to the over 40 million inhabitants and possible patients who would benefit from this more targeted treatment. However, the major limitations to having PT is the cost of such a facility and treatment cost, presently about a factor of 4 higher than X-ray RT and the lack of expertise and associated technologies such imaging equipment etc. The planned SEEIIST PT facility will be located in one of the SEE countries. The project is currently in a technical design phase. According to the SEEIIST's project timeline, the first patient will be treated in 2029. The task of the SEEIIST facility is twofold: the cancer treatment and the associated ion therapy research programme, which should ultimately become an integral part of the PT field [7].

In radiobiology, the **relative biological effectiveness** (shortly **RBE**) is the ratio of biological effectiveness of one type of ionizing radiation relative to X-ray radiation, given the same amount of absorbed energy. The RBE is an empirical value that varies depending on the type of ionizing radiation, the energies involved, the biological effects being considered such as cell death. However, there are still unsolved questions regarding the RBE of protons [11]. In general, RBE in particle therapy depends on the following factors: (1) fractionation scheme; (2) biological endpoint; (3) radiation quality; and (4) tissue type. The biological system has a remarkable influence on the RBE values because of the radiosensitivity of different tissues. Radiation quality includes the type of radiation and its energy and is often characterized by the quantity, linear energy transfer (LET). LET is a descriptor of the energy deposited from the beam to the irradiated material per unit path length (in units of keV mm) of the particle.

ACCELERATOR DESIGN

The accelerator is the key to the overall performance of the facility and the main avenue to improving access to heavy ion therapy. In the past decades, Europe had a prominent role in the development of heavy-ion therapy systems thanks to the pioneering work done at GSI (Germany) in 1993-2008 and the PIMMS (Proton Ion Medical Machine Study) collaboration lead by CERN (Switzerland) in 1996-2000 to adapt the design of scientific ion synchrotrons to the requirements of PT [12] The focus of GSI design was set on compactness and reduced complexity of the machine, while PIMMS was focused on flexibility. Both European designs, even if

[4] https://www.ptcog.ch/index.php

the lattices are different, share similar characteristics and in particular, they all provide only up to a maximum of 10^9 Carbon ions per cycle, have a similar circumference size, the same linac and source design. These initiatives resulted in the construction of four heavy ion therapy facilities, two in Germany following the GSI design, one in Italy (CNAO[5]) and one in Austria (medAustron[6]) following the CERN PIMMS[7] design. All these facilities are based on warm-magnet synchrotrons with different features and share the same design for the injector Linac. In 2018, a design study along the CERN-CNAO line was proposed for the SEEIIST RI. The accelerator is a warm-magnet synchrotron of 78 m circumference supplied by a 60 m long injector, located in an accelerator hall of about 3000 m^2. After 20 years since the PIMMS study was completed, it is now time to imagine a technology leap based on this progress that has taken place in High Energy Physics technology and with the successful running of LHC that could extend the reach of heavy ion therapy and bring to the society as a whole the benefits of technologies developed for basic research. This is what is envisaged for the HITRI design for SEEIIST. The main needs and specifications for a novel accelerator design were defined in a Workshop organized in June 2018 to identify common ground between accelerator scientists, medical physicists, and medical doctors.

Figure 5 shows a schematic comparison of the size of a compact superconducting (SC) synchrotron-based facility equipped with a gantry [13], to the layout of the CNAO and MedAustron facilities, neither of which operates a gantry. Laser production of heavy ion beams for therapy is only at a very early development stage [14] and it is not possible to imagine any sufficient advance over the time duration of this Design Study.

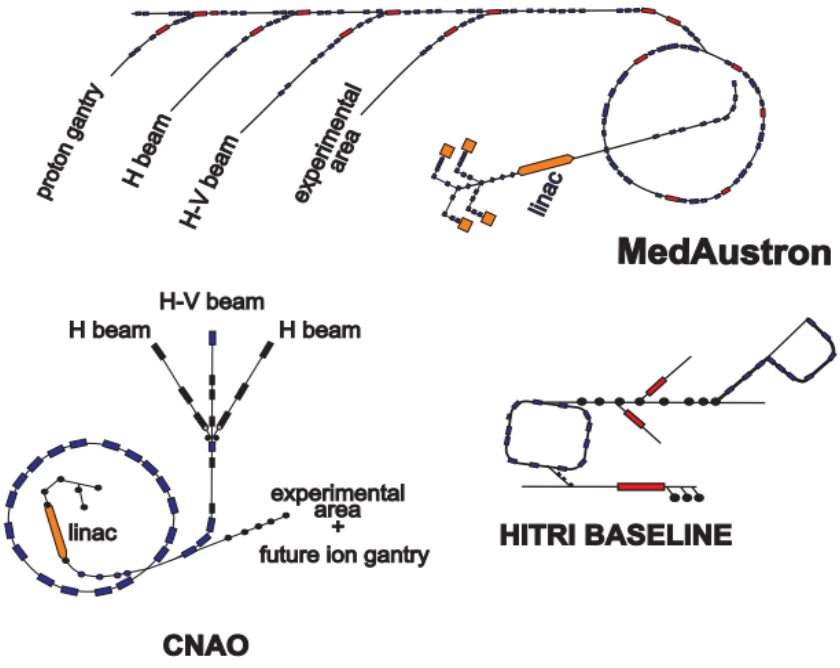


Figure 5. Overall size of the SEEIIST (HITRI) footprint compared to CNAO and MedAustron ion treatment facilities. HITRI baseline based on superconducting synchrotron - drastic reduction in the footprint (area).

[5] https://fondazionecnao.it/en/
[6] https://www.medaustron.at/en/home
[7] https://cds.cern.ch/record/449577/?ln=en

It is clear from the cost-footprint analysis that the superconducting synchrotron and gantry would provide the most promising option, concerning its performance. Footprint, however, the actual cost and time needed are still being established. Its ambitious design parameters will give HITRI-plus Design, being developed under an EU funded project, the lead medical accelerating technology among the heavy ion therapy facilities together with Japan who is also well advanced in using superconductivity for the future heavy ion therapy facilities, they already have a functioning superconducting gantry. The final parts of the facility are the beam transfer lines to the patient and the experimental hall. The transfer lines should transport stable beams of various sizes to the patient. This is complicated by the particular shape of the beam produced by the slow extraction process. The state-of-art dose delivery systems rely on 3D beam scanning and the last part of the beamlines contain fast scanning magnets which allow for the application of this 3D technique [7].

GANTRY DESIGN

In radiation therapy, rotating gantries provide moving beamlines used to precisely direct the beam on the required position on the patient lying on a couch. The conventional rotating gantry for Heavy ion therapy equipment is massive because of the cost, size, and complexity, gantries currently represent another limiting factor for the widespread adoption of ion therapy. Presently, there is one and the very first conventional carbon gantry in the world for ions at HIT, Heidelberg, in Germany, it measures 25 m in length, 13 m in diameter and weighing more than 600 tons. In Chiba Japan, NIRS and Toshiba jointly developed which became operational in 2017. This SC gantry has a reduced size measuring 13 m in length, 13 m in diameter and weighing 300 tonnes, but has the added challenge of a rotating cryogenic system. The size and weight are being further reduced in the next generation design [15].

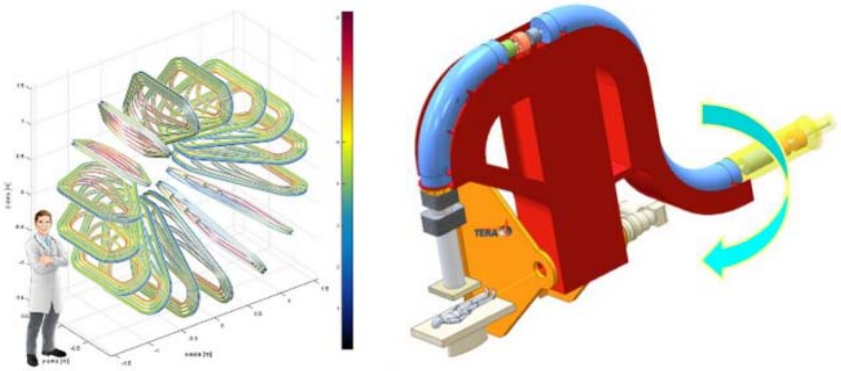


Figure 6. (left): schematic of the coils of the Ga-Toroid (the beam would pass in between the coils) (source CERN), (right): schematics of the compact 1800 rotating gantry (source TERA Foundation).

Possible ideas to improve the performance of a novel gantry could include fixed structures that deliver beams from many directions; structures that combine patient movements and magnets with large momentum acceptance. Scanning modalities fully integrated with gantry geometry represent possibilities to move beyond the present state-of-the-art. Among the gantry options

that will be studied by the HITRI-Plus project partners, there is a light-weight rotating design fixed to a vertical wall, based on the same SC magnets to be developed for the synchrotron [16] (Error! Reference source not found. right), and the recently proposed GaToroid [17] (**Figure 6** left), based on a non-rotating toroidal magnet. Both designs promise a significant reduction in weight (almost an order of magnitude concerning existing ion gantries). The toroid gantry could also be interesting for fast beam delivery treatments, for use in FLASH treatment.

DETECTION AND IMAGING ADVANCEMENTS

One of the main motivations for the use of proton and light ion beams in radiation therapy is the possibility of delivering a highly conformed dose deposition using the Bragg peak [18].
In ion beam radiotherapy, the final dose distribution in the patient exhibits strong susceptibility to patient alignment and inter-and intrafractional displacements [19]. A slab head phantom was used to simulate proton therapy in brain tissue. In this study, simulation was carried out using the Monte Carlo MCNPX code.
Several imaging and image guidance reviews are presently available in the literature for both photon and proton (ion) beam therapy. Here, we discuss imaging technology presently available for proton and ion therapy in a three-stage approach that can guide the application of new/old imaging technology to proton and carbon ion centres: Stage 1: Pre-treatment imaging Stage 2: In-room image-guidance; Stage 3: Post-treatment imaging. The three stages are represented by three numbers “1”, “2” and “3” to represent the overall impact the imaging procedures can have on the quality of the treatment, where “1” has the highest impact while “3” has the lowest impact. Imaging in protons and ion therapy is vital to guarantee that the dose is delivered correctly and accurately to the tumour, where a small shift in the Bragg peak can have led to large variations in the final delivered dose.

Table 1. Present and future imaging technology used in proton and ion therapy centres.

Present	Future
Pre-treatment imaging	
Single energy CT (SECT), PET, MRI, SPECT	Dual-energy CT (DECT), PET/MRI
In-room image-guidance	
2D x-ray radiograph, CBCT, PET	Prompt gamma, implantable dosimeters
Post-treatment imaging	
CT, MRI for standard follow-up imaging	MRI or PET/MRI for dose/range imaging to evaluate proton/ion therapy and patient response

RADIOBIOLOGY RESEARCH

Among numerous DNA damaging factors, ionizing radiation produces the damage showing a very unique structure. Since ionizing radiation passes through a target DNA as a beam, the respectively induced lesions locate close together around the track. Such damage aggregation on target DNA called "clustered DNA damage" is thought to be a major cause of the specific

and serious effect of ionizing radiation. Currently, we have less knowledge about the structure of clustered DNA damage, which seems very important in its biological impact [20].

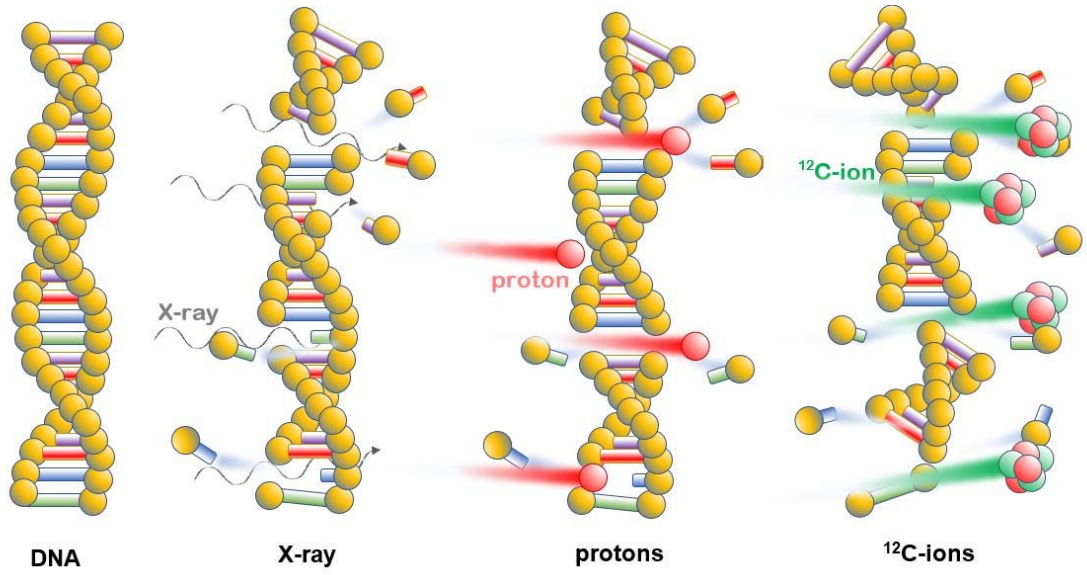


Figure 7. Illustration of the damage to DNA induced by radiation with X-rays, protons and C-12 ions. The damage with protons and even more with C-12 ions provide breakage of the double chain of DNA.

As could be seen in the illustration in **Figure 7**, presenting the damage to DNA induced by radiation with X-rays, protons and C-12 ions, the damage with protons and even more with C-12 ions provides breakage of the double chain of DNA. Hence, the likelihood of recovery of the damaged DNA is much smaller compared to the case with the X-ray radiation. However, biological effects of proton therapy, in particular the potential impact of their increased effectiveness, are much less well understood than those of photons [21]. The main results of the international expert workshop ‘‘Radiobiology of Proton Therapy” that was held in November 2016 in Dresden were summarized in a report that addresses the major topics (1) relative biological effectiveness (RBE) in proton therapy, (2) interaction of proton radiobiology with radiation physics in current treatment planning, (3) biological effects in proton therapy combined with systemic treatments, and (4) testing biological effects of protons in clinical trials.

The clinical distribution of radiobiological effectiveness of protons alone or in combination with systemic chemo or immunotherapies as well as patient stratification based on biomarker expressions are key to reach the full potential of proton beam therapy.

The physical description of the transport of heavy ions through the tissue and shielding materials is of interest in radiobiology, cancer therapy and space exploration, including a human mission to Mars. For example, Galactic cosmic rays (GCRs) consist of a large number of ion types and energies. Energy loss processes occur continuously along the path of heavy ions and are well described by the linear energy transfer (LET), due to straggling and multiple scattering algorithms. Nuclear interactions lead to much larger energy deposition than atomic-molecular collisions and alter the composition of the heavy-ion beams while producing

secondary nuclei often in high multiplicity events [22]. A goal of future research in radiobiology would be to utilize the stochastic physical descriptions of ions and energy deposition events in the application of stochastic models of the biological responses in the targeted tissue [23].

The NASA-funded Space Radiation Health Program [24] is built upon the capabilities of the NASA Space Radiation Laboratory at the Brookhaven National Laboratory (Upton, New York, USA), and has produced experimental data in the past few years of great relevance for reducing uncertainty on risk assessment. To foster European research in the field, the European Space Agency (ESA) has also recently initiated a ground-based radiobiology program [25], which will be located at the high-energy synchrotron of the Gesellschaft für Schwerionen for stung in Darmstadt, Germany. Research in this field is also essential for heavy-ion cancer therapy (hadron therapy) on Earth, in which beams of high-energy carbon ions have been utilized for solid cancers sterilization [26]. One major problem related to this treatment is the risk of occurrence of secondary cancer, especially within the population of pediatric patients [27]. Heavy-ion cancer risk is being sought by researchers among the space mission's personnel. Research of the impact of space radiation is also essential for estimating the incidence of secondary malignancies in these patients, and therefore the two research fields share many common issues and concerns [28].

Proton therapy revealed significant potential in cancer treatment but must be used carefully with respect given to the underpinning physics and radiobiology. Further preclinical research and model development must aim to employ digital tools to predict the optimal treatment for proton therapy so that their full potential can be realized in the advancing era of personalized medicine.

Experiments with restriction enzymes indicated that double-strand breaks in DNA can trigger events in adaptation. Also, preliminary experiments on the survival of whole-body irradiated mice have shown that multiple exposures to a low adapting dose can have profound effects on survival, and other experiments have shown that adaptation can induce thymic lymphoma in irradiated mice [29]. The EPTN reports add to a significant amount of recent papers published in Radiotherapy & Oncology within the field of PT [30]. Particle therapy (PT) offers both new opportunities for improvements in cancer care and new opportunities for high-quality research.

FLASH

Very high-dose radiotherapy (>40 Gy/s) is generally acknowledged as a promising, and potentially evolutionary, the pathway for radiotherapy. Pre-clinical data in animal models have indeed shown that at high-dose-rate normal tissue toxicity is significantly reduced, while tumour control is not modified [31], [32] and [33]. The potential advantages in terms of widening the therapeutic windows are enormous. The first patient has been treated with electrons under FLASH conditions in Lausanne Switzerland and the first one using proton therapy by increasing the cyclotron intensity to reach the FLASH regime in Cincinnati, USA. Heavy-ion FLASH, the high intensity has to be achieved probably using synchrotrons. This is one of the goals of the new SEEIIST accelerator.

Particle therapy holds great promise to improve the therapeutic outcome of cancer patients treated with this modality. Therefore, with the opening of a considerable number of particle centres in Europe and worldwide, there is a great opportunity to collaborate across institutions and countries to secure evidence-based implementation of particle therapy. The need to generate clinical evidence for PT is extremely important for the radiation oncology community. With high initial capital investment and personnel costs, with the costs of servicing the hardware, the introduction of PT has been slow and difficult globally. Most European countries have a high degree of public health care coverage, and thus have also a regulated evidence-based system for investments in new and emerging sometimes costly technology. Collaboration between PT-centers between scientific and clinical evidence is thus of critical importance. European particle therapy centres are active members of the global Particle Therapy Co-Operative Group (PTCOG[8]). Also, there are currently two active European networks working in complementary fields of particle therapy: the European Network for Light Ion Hadron Therapy (ENLIGHT[9]), and the European Particle Therapy Network (EPTN; www.estro.org/Science/ EPTN) [34]. INSPIRE[9] is an EU Infrastructure project for Proton facilities similar to HITRI-plus which is targetting heavy ions.

The clinical trials were initiated by conducting Phase 1/11 dose-escalation studies on various types of tumours, aiming at verification of the safety of carbon ion radiotherapy and to evaluate its anti-tumour effects. Since then, all patients have been treated with carbon ion radiotherapy according to the clinical protocols (phase 1/11 or phase li) that were approved by the Ethics Committee of the NIRS. You should perhaps also add something about clinical trials in Europe and the USA.

The clinical applications of each method, however, are still limited to selected tumours and the therapeutic eligibility of both methods has not been fully explored. Despite such limitations, the recent development of dedicated machines for ion beam therapy has shown that in many situations the dose distributions of ion beams would be superior to that of IMRT (intensity-modulated radiotherapy), leading to higher tumour control probability and reduced frequency of radiation-induced morbidity [35]. Therefore, PT can potentially deliver a higher dose to the primary tumour, leading to improved local tumour control, while simultaneously decreasing the irradiated volume and doses delivered to the surrounding critical organs such as normal lung tissue, heart, oesophagus, spinal cord, and mediastinum. The treatment protocols have been evaluated by the committee every other year and are perpetually subjected to minor modifications whenever it appears to be necessary. The patient number was expected to be at least 35 for each protocol to evaluate toxicity and efficacy. **Table 2** below shows an example of how many patients are currently treated as a part of ongoing clinical studies [36].

[8] www.ptcog.ch
[9] https://enlight.web.cern.ch

Table 2. Ongoing clinical studies of PT treatment according to the tumour site.

Tumour Site	No. of studies	No. of Patients
Head and neck tumours	2	62
Prostate Cancer	3	1,562
Ocular tumours	9	9,522
Gastrointestinal cancer	5	375
Lung Cancer	3	125
CNS tumours	10	753
Sarcomas	1	47
Other sites	3	80
Total	36	12,606

The clinical practice proved that for certain kind of tumours PT represents a better treatment option than X-ray stereotactic radiotherapy. The comparison among these treatment modalities should be performed concerning physical dose distribution and biological effectiveness, and finally with vast clinical studies applying big data analysis.

CONCLUSION

Scanning modalities fully integrated with gantry geometry represent possibilities to move beyond the present state-of-the-art. The accelerator is the key to the overall performance of the facility and the main avenue to improving access to heavy ion therapy. In radiation therapy, gantries are movable beamlines used to precisely direct the beam to the required position on the patient, who is usually lying on a couch. Due to their cost, size, and complexity, gantries currently represent another limiting factor for the widespread adoption of ion therapy. Scanning modalities fully integrated with gantry geometry represent possibilities to move beyond the present state-of-the-art.

Besides experimental research with cell lines, the radiobiology research could be also theoretical by applying models and using the biophysical Monte Carlo Particle Transport Code for simulating and DNA damage upon a wide range of ion energies relevant in radiation therapy, assessing the effects systematically, on a detailed mechanistic basis. The simulations made so far showed that protons and helium ions induce more DNA damage than other heavier ions do at the same Linear Energy Transfer values (LET). Ion-beam therapy with protons or carbon ions is recognized globally since it is offering a transformative new modality in cancer treatment for numerous specific tumour types and sites, such as head and neck, pancreas, liver, lung, breast and prostate. In their research programme, SEEIIST will include the possibility of performing a heavy-ion therapy for pets (such as dogs) which already have been diagnosed with kinds of cancers that are relevant for humans. The clinical applications of each method, however, are still limited to selected tumours and the therapeutic eligibility of both methods has not been fully explored. Despite such limitations, the recent development of dedicated machines for ion beam therapy has shown that in many situations the dose distributions of ion beams would be superior to that of IMRT (intensity-modulated radiotherapy), leading to higher tumour control probability and reduced frequency of radiation-induced morbidity.

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