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Roadmap: helium ion therapy

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Abstract

Helium ion beam therapy for the treatment of cancer was one of several developed and studied particle modalities in the 1950's, leading to clinical trials beginning in 1975 at the Lawrence Berkeley National Laboratory. The trial shutdown was followed by decades of research and clinical silence on the topic while proton and carbon ion therapy made debuts at research facilities and academic hospitals worldwide. The lack of progression in understanding of principle facets of helium ion beam therapy in terms of physics, biological and clinical findings persist today, mainly attributable to its highly limited availability.

Despite this major setback, there has been an increasing focus on evaluating and establishing clinical and research programs using helium ion beams, with both therapy and imaging initiatives to supplement the clinical palette of radiotherapy in the treatment of aggressive disease and sensitive clinical cases. Moreover, due its intermediate physical and radio-biological properties between proton and carbon ion beams, helium ions may provide a streamlined economic steppingstone towards an era of widespread use of different particle approaches to light and heavy ion therapy. With respect to the clinical proton beams, helium ions exhibit superior physical properties such as reduced lateral scattering and range straggling with higher relative biological effectiveness (RBE) and linear energy transfer (LET) ranging ~4 keV/μm to ~40 keV/μm. In the frame of heavy ion therapy using carbon, oxygen or neon ions, where LET increases beyond 100 keV/μm, helium ions exhibit similar physical attributes such as a sharp lateral penumbra, however, with reduced biological uncertainties and without potentially spoiling dose distributions due to excess fragmentation of heavier ion beams, particularly for higher penetration depths.

This roadmap presents an overview of the current state-of-the-art and future directions of helium ion therapy: understanding physics and improving modeling, understanding biology and improving modeling, imaging techniques using helium ions and refining and establishing clinical approaches and aims from learned experience with protons. These topics are organized and presented into three main sections, outlining current and future tasks in establishing clinical and research programs using helium ion beams — A. Physics B. Biological and C. Clinical Perspectives.

Contents

1. Introduction to the Helium Ion Therapy Roadmap

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The role of particle therapy in cancer treatment continues to expand, with protons and carbon ions as the leading therapies (1). The clinical potential of high-energy charged particle beams was first identified in the early 20th century, demonstrating dosimetric superiority compared to conventional radiotherapy. Their physical characteristics such as the finite beam range exhibited were well understood, leading to extensive clinical trials using various particle species from protons and helium ions up to neon and argon ions at the Lawrence Berkeley National Laboratory (LBNL). With a relatively narrow range of biological effect variation, protons were quickly adopted as the leading particle therapy modality in the US, while Japanese and German facilities further developed carbon ion therapy for its improved dose conformity and higher LET for enhanced biological effect. Since then, technological advances in beam acceleration and delivery using scanning-beam technology and intensity-modulation for high-precision dose localization continue to improve tumor targeting and reduce normal tissue dose.

To date, clarity on the cost-benefit of particle therapy remains rather subtle. More indication-specific data are needed to better understand efficacy and clinical outcome, e.g., overall survival (OS), progression free survival (PFS) and/or overall response rate (ORR) endpoints, compared to conventional therapies. However, the main attributes of particle beams at therapeutic energies can be beneficial in treating tumors in close proximity to critical structures/organs-at-risk and in patients where integral dose minimization is a high priority. In theory, particle therapy has, compared to intensity modulated photon therapy, the potential for increased overall survival, reduced risk of secondary cancers and improved quality of life of the patient. That said, neither protons or carbon ions can be considered the “perfect” particle — and for the moment, ion species selection is based on availability and/or facility/physician preference for particular indications.

To this end, interest in helium ion beams is growing, with several studies exploring their unique biophysical attributes intermediate of the two clinical modalities. For instance, preparations to begin the first raster-scanning helium ion beam therapy program are underway at the Heidelberg Ion-beam Therapy Center (HIT) with other centers in planning phase (2). Despite their favorable physical and biophysical characteristics, i.e., qualities intermediate of the major clinical beams, helium ions are used solely for experimentation and have remained clinically unexploited worldwide since the shutdown of the LBNL trials using passive scattering technology in the early 1990’s (3–5). Given their intermediate properties compared to protons and carbon, helium ions are suspected to provide clinically beneficial distributions with tradeoffs between protons and carbon ions – for instance, enhanced linear energy transfer (LET) and targeting compared to protons. Moreover, their anticipated clinical revival will present numerous untapped medical and

monetary advantages, considering the reduced fragmentation tail / variability in biological effect compared to carbon ions coupled with the potential for a compact facility design (6). Moreover, helium ions exhibit reduced lateral scattering and penumbra close to carbon ions, with a significantly decreased fragmentation tail (7). Relative biological effectiveness (RBE) values for helium ions range between ~1.3 and ~3. With such characteristics, helium ion beam therapy has the potential to improve clinical efficacy of several treatment sites such meningioma and in pediatrics (8, 9).

Compared to its scientifically matured predecessors, helium ion therapy is in an elementary state and substantial ground level work towards development and study of helium ions is required for optimal future practice. For example, prior to the first patient, selection of an appropriate dose level, fractionation scheme, tissue radio-sensitivity (α/β_x) assignment, algorithm for dose calculation, and model for relative biological effectiveness (RBE) are essential – issues which call for consensus both locally within an operating facility and among the particle therapy community at large. Recent works take the steps towards evaluating biophysical phenomena of ^{4}He (10), developing models for RBE (11, 12) and assessing associated models from a clinical standpoint (13, 14). Inter- and intra-model dependencies both *in silico* were observed and subsequently benchmarked *in vitro*. Depending on the case study, clinically relevant differences in RBE prediction as a function of the various endpoints (dose, LET and tissue type) can be observed.

Helium ion beams produce their own distinctive energy and particle species spectra. Similar to proton beams, the helium ion spectra composed mainly of proton, deuteron, triton, helium-3, helium-4 and neutrons afford a unique physical dose distribution and, in turn, biological effect. Physics simulation methods such as Monte Carlo are the predominant means to model and predict mixed radiation fields in ion-beam therapy. Proper characterization of mixed radiation fields for various particle species is important to establish a simulation framework and predict both physical dose prediction and effective dose prediction in complex geometries like patients. Recently, the FLUKA (15, 16) and MonteRay Monte Carlo codes (17) are under development for improved modeling of helium ion beam radiation and updated with cross-section measurements for fragmentation of helium ions (17).

Recent efforts perform comprehensive dosimetric characterizations (7, 18) and develop in-house dose engines for helium ions, both analytical and Monte Carlo (19–22), with both research and/or clinical investigations, such as *in vitro* study, treatment plan comparisons or clinical TPS development and validation. Regarding dose calculation, several published works outline a novel approach to the pencil beam algorithm (PBA) for helium ions (19, 21), demonstrating excellent agreement with Monte Carlo simulation and measurements in both homogenous and heterogeneous settings (23). Such systems support RBE calculation and integration of the first commercial TPS for helium ion therapy, currently underway at HIT in collaboration with RaySearch (Stockholm, Sweden).

For imaging and treatment monitoring, helium ions are a promising candidate for their reduced lateral scattering compared to protons, and reduced imaging dose (with comparable image quality) compared to carbon ions. (24–26). Examples of novel systems to reduce delivery

uncertainties by properly locating/verifying the delivered Bragg peak *in vivo* for particle beams include prompt gamma spectroscopy (27–30) and ion-beam radiography (31–33)

For protons, clinical treatment planning assumes a constant relative biological effectiveness (RBE) of 1.1, a conservative estimate, while for carbon, more intricate models are implemented to consider the multi-dimensional variability of RBE. With over a decade of clinical indication in particle therapy, what have we learned from these delivered hadrontherapy treatment techniques, assuming a constant RBE for protons and variable RBE for carbon ions to best practice future modalities? What are the aims/primary treatment sites for helium ions in place of the status quo? Prior to clinical application of helium ions, we address the prospective tasks and challenges that will direct the clinical introduction of active scanning helium ions (Figure 1.1). These efforts call for interdisciplinary collaboration between physicians, physicists and radiobiologists within the scientific community to realize the full clinical potential of this technology.

Considering these discussion points, much work remains to understand various aspects of therapeutic helium ion beams. In this roadmap, key topics and questions related its applications in medicine are presented, categorized into three sections (“Physics”, “Biology” and “Clinical Perspectives”). Given the applied nature of helium ion therapy, the discussed topics are highly associative and collaborative. Therefore, connection and consideration between the different themes and subsections is critical (Figure 1.1).

Primary aims involve establishing physical, biological and clinical basis for treatment with helium ion beams and determining/quantifying unknowns. Once identified and concepts are implemented and/or considered in subsequent R&D and clinical practice, the main objectives should aim to improve efficacy and accuracy while reducing uncertainties of these “knowns” as currently underway with clinical proton beams, for example, outlined in the AAPM 256 task report and proton therapy roadmap (35, 36). It is impractical and, in some form, futile to present a comprehensive roadmap specific to only helium ions, i.e., without mentioning concepts which are certainly applicable to other ions and particle therapy as a whole. Therefore, readers may approach this roadmap as both an outline for future endeavors with helium ion beams, assessment of helium ions and their potential roles in radiotherapy as well as a scientific exploration of novel ion beams.

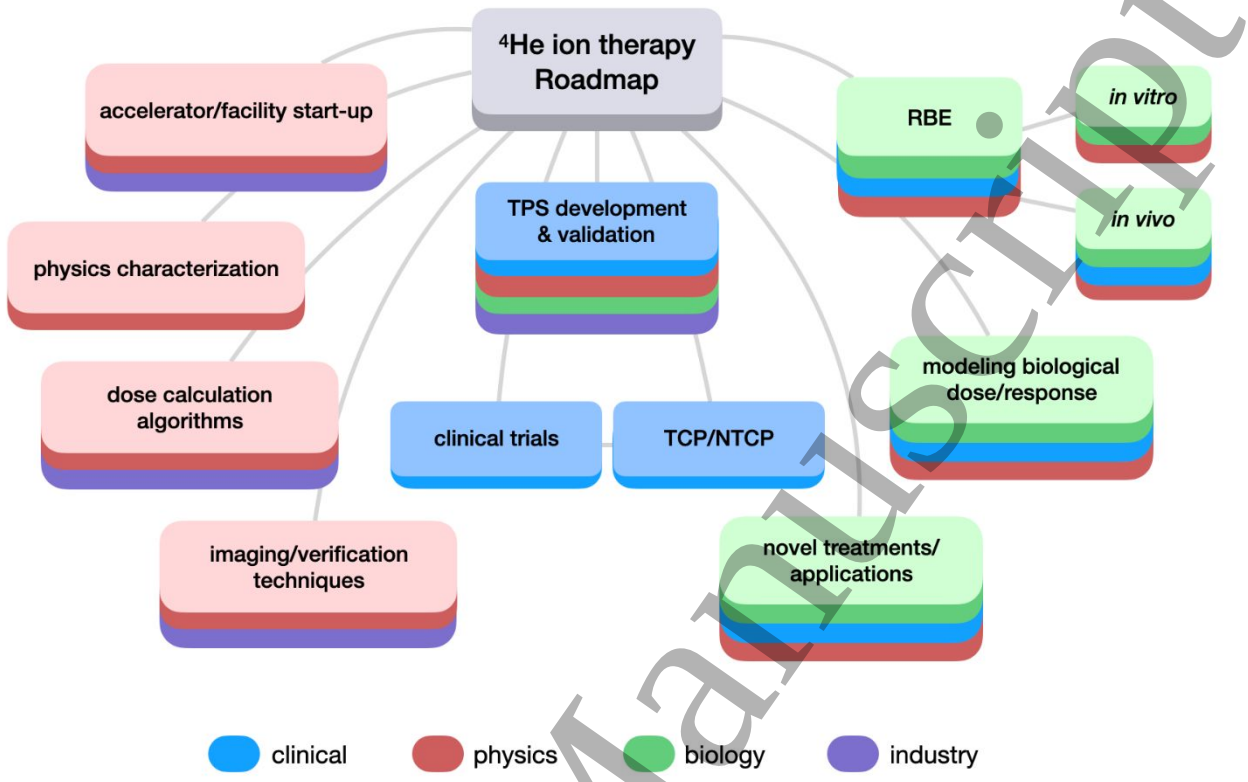

Figure 1.1 Roadmap for development, investigation and clinical translation of helium ion beams. Topics include the following: past and future clinical trials, physical characterization of helium ions, accelerator/facility start-up, imaging/verification techniques, dose calculation algorithms, TPS development and validation, biological effects (*in vitro* vs. *in vivo*), clinical modeling and novel novel applications.

Physics

Widespread adoption of particle therapy, especially for novel and/or ions like helium, is hindered by the substantial facility start-up costs. Fewer centers host high energy helium ion beams within the therapeutic range for key measurements necessary to develop/test novel delivery and detection systems and improve physics models. With this paucity of infrastructure, our understanding of helium ion beam transport and interactions in various materials needs refinement. Lastly, reliable dose calculation and treatment planning engines are needed for both preclinical evaluations of helium ions and trial start-up. Correspondingly there are five roadmap contributions in this topic: “Considerations for ^{4}He ion beam facility/accelerator start-up and beam delivery development”, “Experimentation and improved modeling of ^{4}He nuclear interactions”, “Modeling and Monte Carlo simulation of helium ion beam interactions with matter” , “Dose calculation development and treatment plan comparisons: preparations and investigations towards optimal clinical practice with ^{4}He” and “Helium ion beams for imaging and treatment verification techniques”

Biology

Better understanding and predicting the variations in biological response when exposed to particle beams compared to photons is a critical scientific point of interest and arguably the main source of uncertainty in treatment efficacy for particle therapy. An overwhelming majority of experimental biological data applicable to helium ion beams pertains to radioactive isotopes with alpha-emitters of low energy/high LET and minimal range (on the order of a few millimeters). Existing data from LBNL and facilities currently operating with helium ions in research mode provide foundational benchmarks however further data is urgently needed not only to address scarcity of *in vitro* and *in vivo* data but to quantify cell characteristics beyond standard endpoints based on survival/cell-kill. With these data, expansion and validation of intricate biophysical modeling is made possible. For instance, measurable and immeasurable genomic/cell/tumor micro-environment characteristics when exposed to high-energy helium ion beams will further distinguish the role of multiple particles in radiotherapy and facilitate clinical outcome interpretation of site-specific treatment. There are four roadmap contributions in this topic: **"**Key experiments for benchmarking a helium ion program: the LBNL experience", "Radiobiological phenomena of helium ions: fundamentals, features and clinical potential", "*in vitro* and *in vivo* biological readouts and indications for guiding clinical practice with helium ions", "Effective dose and RBE modeling for ^{4}He: progress and recommendations towards patient-specific treatment planning"

Clinical Perspectives

Establishing clinical standards in treatment planning and approaches to randomized clinical trials for determination of efficacy of helium ion beam therapy compared to standard clinical modalities is a main priority. Consequently, proper consideration and/or translation of advances in physics and radiobiology of helium ion beams is paramount to improve standard of care given current capabilities and limitations. With more advanced treatment delivery and reliability/robustness in particle radiobiology, future uses of helium may involve more personalized treatment regimes, such as advanced delivery techniques (e.g., ultra-high dose-rate, hypo-fractionation, multi-ion therapy, arc, etc.) and combined therapies (e.g., radio-sensitizer/repair inhibition, immunotherapy/response modulation, etc.). There are five roadmap contributions in this topic: "Challenges and remarks on the proton therapy experience with constant RBE", "Clinical directions with helium ions", "Clinical medical physics and treatment planning", "Future perspectives on helium ions", "Multi-ion therapy and the role of helium ions" and "Concluding remarks on biology and physics considerations in the clinic."

Summary

This Physics in Medicine and Biology roadmap is written for readers with clinical, industry and/or research backgrounds in radiation oncology, radiation physics and radiation biology. Many of the topics discussed focus on foreseeable scientific developments needed to best establish the future of helium ion beam therapy in the context of what is learned from experiences with the clinical modalities in particle therapy. Here, the status of helium ion beam therapy and future directions are surveyed toward establishing novel ion beam therapy programs, which categorizes the articles into three different themes, "Physics", "Biology", "Clinical Perspectives". For example, in "Physics" – measurements, modeling understanding, accuracy in the TPS, LET/RBE considerations during clinical practice, and applications in imaging/treatment verification and

monitoring. “Biology” – what are the anticipated differences in biophysical and clinical endpoints from using passive delivery at LBNL to state-of-the-art active scanning during trials, key endpoints of interest, how to approach and model biological-phenomena and trends, and how to best measure and implement bio-effect considering existing treatment approaches proton and carbon ions. “Clinical Perspectives” – establishing a clinical program using helium ions, defining clinical parameters and settings following existing schemes for dose escalation studies, prospective treatments techniques and what is learned from decades with protons to best practice helium ions.

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Part A: Physics

2. Considerations for ^{4}He ion beam facility/accelerator development and start-up

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Introduction

During the pioneering era of ion beam therapy at LBNL (Berkeley, USA), more than 2000 patients were treated with relativistic helium ion beams. Just one year after the shutdown of the clinical program at the Bevalac in 1993 clinical trials for carbon ion radiation therapy (CIRT) started at HIMAC (Chiba, Japan), followed by a 1997 pilot project at GSI (Darmstadt, Germany) for the hospital-based particle therapy facility at the University of Heidelberg [1]. While the clinical beamline at GSI was designed to transport oxygen beams, the final decision in favor of carbon ions for clinical translation at the Heidelberg Ion-beam Therapy center (HIT) a decade after clearly represents a compromise to balance radiobiological and physical characteristics as well as the comparability with the clinical trials conducted in Japan.

Today, the state of affairs for facility design and start-up is not comparable to what it was in the 90's during the initial surge in proton or carbon ion therapy post-LBNL shut down. At the time of program development at HIMAC and GSI, there were no established vendors for particle therapy and a major milestone was met by instituting the know-how-transfer into the industry which our growing field benefits from today with +50 facilities. Several reputable vendors now exist which have experience in design, assembly and operation of charged particle accelerators, beam lines, active delivery and monitoring systems of various types and sizes. With that said, how should we best proceed with helium ion facility start-up? What are the primary considerations and current limitations for centers using helium ion beams in the present day?

This contribution touches on viewpoints specific to helium and is best suited for readers with prior knowledge in fundamental aspects of particle therapy. A dedicated section of recent roadmap for proton therapy physics and biology (Paganetti et al 2021) provides an outlook for optimizing accelerator technology and facility specifications for delivery efficiency / cost reduction, such as treatment room design/operation, delving into topics such as recommended improvements for synchrotron vs cyclotrons, scanning systems and energy switching mechanisms [2]. These topics are mostly applicable to all charged particle modalities and we recommend reviewing these sections for more fundamental outlooks of improving per se the current state, accelerator/delivery technology and facility design/operation for particle therapy as a whole.

Status

Since the clinical inauguration of HIT in 2009, Europe's first hospital-based ion beam therapy facility, the mission was (and still is) twofold: to run clinical trials and to conduct biophysical studies to better understand which indication benefits most from what particle therapy modality. As of 2021, HIT is configured to offer two lower LET beams, protons for clinical and helium (see figure 2.1) for pre-clinical applications, and two higher LET beams, carbon for clinical and oxygen for pre-clinical applications [3]. Even though more than 7000 patients at HIT were successfully treated using proton or carbon beams our analysis shows [4] that improved clinical protocols are achievable once helium is fully commissioned and approved. Since installation of the helium ion source in 2015, fundamental work began to understand physical and radio-biological properties of helium ion beams to achieve a final quality suitable for safe and effective patient treatment. This year, HIT is set to begin the first helium ion beam therapy treatment program using raster-scanning technology.

With the start of the clinical program at HIT in 2009 a government grant became available that triggered the development of a third ion source branch. As a first step a commercially available ion source [5] was installed at HIT's injector test bench, optimized for the production of helium ions and combined with a mass spectrometer to guarantee the purity of the beam (2011/2012). Summer 2013 two mini-shutdowns of 4 days each were used to install the tested ion source / low-energy beam transfer components at the HIT's regular injector and to integrate this section into the accelerator control system. By the end of 2013 the status of technical commissioning allowed the first raster-scans using ^{4}He at the research cave (see figure 2.1) which was the starting point of a broad biophysical program to establish the base data for the treatment planning and modelling platforms [6]–[12] and to study the radiobiological properties in detail [4], [13]–[16]. In 2018 an additional fund could be raised to realize upgrades of the medical product in the treatments rooms (IONTRIS, Siemens Healthineers) and the upcoming treatment planning system (RayStation, RaySearch, Stockholm, Sweden). The close collaboration of these vendors with HIT's experts enabled the first raster-scanning dose delivery of treatment plans suitable for clinical use in summer 2020.

Apart from HIT, other facilities are either using helium ion beams for research purposes, gearing up for clinical-use or planning future treatment centers. Given facility specifications and on-going research/clinical efforts at National Center of Radiological Sciences (NIRS) in Chiba, a japan-based helium ion treatment program either as a standalone particle or integrated in a multi-ion therapy program has been proposed (see "Section 15"). Additionally, other Asian and European based carbon ion facilities, such as SPHIC (Shanghai, China), MedAustron (Vienna, Austria), and CNAO (Pavia, Italy), to list a few, are readily equipped for accelerator adaptation and helium ion source integration. With the absence of vendors offering helium treatment options, how can we adapt existing accelerators or develop novel systems that are simultaneously cost-effective and yielding high clinical performance?

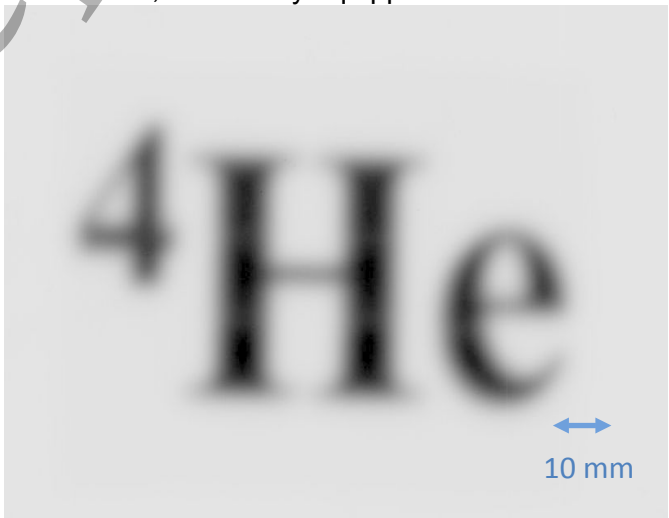

Figure 2.1. Raster-scan of the helium isotope symbol recorded in a radiochromic film at HIT (^{4}He@HIT, 220.5 MeV/u).

Current and Future Challenges

With respect to existing accelerators for helium ion beams, existing technology in the proton and carbon ion world should be considered for initial design and first we must identify the modification required specifically for adapting to helium ions.

In principle, several operational carbon ion facilities can be adapted for acceleration of helium ion beams. Similarly existing sources can also be adapted for helium in a relatively short time span. That said, the mission of adapted carbon ion facilities is to generate initial experience in terms of pre-clinical (physical and biological data) and clinical results for helium ions. If results look promising, development of dedicated solutions using helium ions could be particularly valuable. It may turn out to be a very attractive solution for the future. Adding auxiliary higher-LET beams alongside protons and not being as costly as carbon ions could be interesting in terms of properties like scattering, mild RBE increase and OER aspects (see “Section 9” and “Section 11”).

In an existing facility like HIT, the integration of a third ion source branch into the production is a challenge in terms of the limited space in the injector area and the upgrade must be realized at an almost zero downtime budget as a facility like HIT is operated in a 24/7 mode during 335 days per year. In principle, two different isotopes could be used for helium ion-beam therapy, namely ^{3}He and ^{4}He [17]**.** In the original proposal of the HIT facility, the use of the more exotic ^{3}He isotope was foreseen instead of ^{4}He. However, for the final realisation at HIT the preferred helium isotope was ^{4}He in order to maximize the sharpness of the lateral dose fall-off. But as a result of HIT’s risk management a technical solution was required that safely identifies and solely accelerates $^4He^{2+}$. As a potential ion mixture in the ion source plasma chamber having a mass-to-charge ratio A/Q = 2 ($^{12}C^{6+}$, $^{14}N^{7+}$, $^{16}O^{8+}$, $^{20}Ne^{10+}$) could be the result of a leakage, at HIT the residual gas is permanently monitored using a mass spectrometer coupled to the accelerator interlock system [19]. The first phase of the permanent establishment of a new ion species is the physical and radiobiological characterization of the beam to provide the information for the base data generation and the definition of the pencil beam library shared by the accelerator controls and the treatment planning and modelling platforms [4, 5]. As for helium the underlying cross sections are

not precisely known, these data-taking campaigns require a relevant amount of beamtime typically allocated during the nights. A quasi-parallel operation of all ion sources with very short changeover times optimally supports the commissioning of the new ion species. The technical challenge consists in finding a solution for a compact low energy transport line equipped with two ECR ion sources that can be switched within minutes [18], [19].

The challenging integration of a third ion source branch could be accomplished by developing a very short low energy beamline from the ion source to the analyzing dipole magnet. The source was positioned in the optical focus of the spectrometer magnet. This analyzing magnet serves two purposes: it is used to select between the carbon and the helium ion source and it allows for the selection of the appropriate ion species to be transported into the first linear accelerator section, the RFQ (see figure 2.2). The original three-electrode design of the ECR ion source was upgraded to a four-electrode set-up resulting in an increased beam brilliance [7].

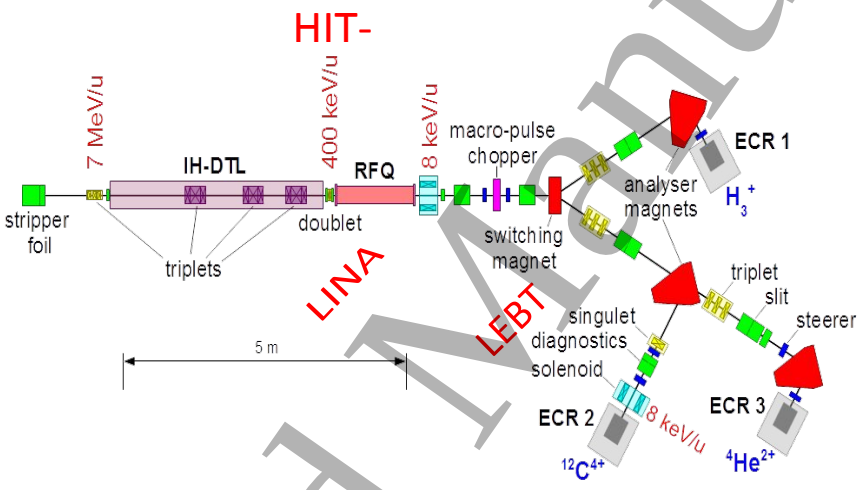

Figure 2.2 The HIT-injector upgraded with a compact third ion source branch dedicated for the production of ^{4}He ions (lower right).

Not every facility can readily implement helium ions as described above. The HIT system may be considered one of the more flexible accelerator types in terms of adding novel particle beams but it's not the solution for every clinical site. In general, a system designed for carbon ions will not be challenged by adding helium beams. Neither the space charge limit nor the transport efficiency pose critical problems. Moreover, developments in R&D for novel treatment and delivery techniques in particle therapy are foreseen which will ultimately require tech upgrades for existing heavy ion facilities within the next decades. Therefore, the next generation design for accelerator/delivery tech for helium ions must consider increasing demand for high performance, flexible and cost-effective systems.

Advances in Science and Technology to Meet Challenges

Upgrading an existing hospital-based proton therapy facility typically is not a realistic option. Whereas a phased installation that starts with protons and helium ions produced in a compact cyclotron and adds carbon ions accelerated to clinically relevant energies by a booster cyclotron

at a later stage was proposed already one decade ago [35]. Facilities being designed for carbon ion production and delivery may consider adding helium functionality or switching one particle species to helium. Seeing the enormous progress in the field of accelerator technology, image guidance and computing dedicated and very compact helium systems could be realized. Industry in cooperation with experts in the field can tailor single or multi-room systems meeting the customer's requirements.

One can also consider clever accelerator technology such as variable energy cyclotrons [20], [21] as an interesting starting point. For instance, compact, cooled superconducting cyclotron models with variable energy and possibly two particles (protons and helium or C/He) could be particularly advantageous to offer almost table-top sized accelerators for helium. Implementation of short beamlines with no degeneration systems could make possible a two-room facility option for helium with mitigated radiation protection issues.

For instance, recent proposals describe a helium ion therapy system based on "classical concept of injector linac and synchrotron", but incorporate modernized developments for various components [22]. Other initiatives like the HEATHER (HElium ion Accelerator for radioTHERapy) project design dedicated accelerators for helium ion therapy [23]. Using non-scaling fixed field alternating gradient (nsFFAG) accelerators, which take benefits from both the synchrotron and the cyclotron [24]. However, these works may be questionable for two reasons: FFAG typically needs very large and heavy magnets. This concept seems to be of special interest for accelerator developers whereas a cost-efficient, hospital-based system may not benefit from FFAG. A conventional carbon cyclotron (as it was or still is planned for the French-based ARCHADE project [25]) is extremely heavy and will be seriously challenged by synchrotron systems. That said, compact cyclotron solutions for heavy ions (eg, helium and carbon) are under development and could bring the two room facility option for helium + carbon to clinical fruition [26].

Aside from these works, there is little information about upcoming dedicated helium ion accelerator tech. Lastly There's a growing interest in novel treatment delivery approaches like MR-guidance, uHDR, multi-ion, and arc delivery where helium ions may prove clinically advantageous. Future facility design and features should address the limitations of existing accelerator and delivery tech to enable potentially transformative treatments:

- p/He^4 ion Gantry: Based on the experience gathered while treating more than 7000 patients at HIT it can be clearly stated that a rotating gantry is mandatory. Downscaling HIT's pioneering conventional carbon gantry technology to meet the requirements of helium ion treatment would result in an only moderate reduction of about 25% concerning the radius as well as the building space. Nowadays superconducting (SC) carbon gantries can be realized that are characterized by a massive reduction in weight and very compact dimensions hence reduced building and operational costs. Already the 3rd generation of a SC gantry based on combined function magnets is under development [27] that aims at B_{max} ~ 5 Tesla. The overall dimension of such a design will be relevantly smaller than a conventional proton gantry. Combining an energy-variable compact accelerator that delivers scanning-ready pencil beams with such a 3rd generation SC-gantry will allow for almost tennis court size single room systems for helium [28].

- MR-guidance: Daily MR-imaging would offer superior soft-tissue contrasts in combination with volume-of-interest monitoring and potentially allow for an on-table adaption of treatments plans. While in conventional radiotherapy MR-linac systems are in clinical use for particle therapy, due to the additional complexity caused by the interaction of the charged particles with the imaging field [29] the development has just started. At HIT within the ARTEMIS-project, a demonstrator for MR-guided dose delivery is under development. Design and application of on-board MR-guidance with helium ion therapy will require specific physics considerations. One can imagine that a relevant fraction of gantry-patients may be treated at an MR-guided system once the workflow for imaging, treatment planning and verification gets sufficiently fast (see “Section 5” on dose calculation).
- FLASH dose-rate delivery: according to recent studies, FLASH irradiation requires dose rates somewhere in the range of >50-100 Gy/s (see “Section 8” on radiological phenomena). Assuming a treatment volume of several hundred cubic centimeters such a dose rate is not compatible with the space charge limit of a compact synchrotron even if the dose delivery is realized by a passive spreading system. Cyclotrons or synchro-cyclotrons have the potential to treat clinically relevant volumes using passive dose delivery methods. As of today the potential therapeutic window for FLASH irradiations appears to be small whereas the superior dose conformation of scanning beam delivery is obvious and in broad use. FLASH dose-rate helium ion beams have recently entered the lime-light [30].
- Arc Delivery: Studies have shown that arc delivery would allow for improved OAR and normal tissue sparing [31]. But combining beam scanning dose delivery with the gantry rotation into a continuous irradiation procedure requires sophisticated control mechanisms not only for the scanning system but for the energy and angle dependent settings of the beamline elements. A “rotate-and-scan procedure” using a sufficient number of pre-defined and quality-assured ports represents an excellent option at this point. Several works have outlined optimization and delivery procedures for protons but dedicated solutions for heavy ion gantry are required [32], [33]. CERN’s innovative GaToroid.concept [36] may become a highly attractive beam delivery system to deliver a large number of fields not needing a complex and costly rotational structure.
- Multi-ion Therapy: Mixing ions in a single fraction can already be done at HIT; however, the workflow may be cumbersome but manageable, which may call for specific developments (see “Section 13 and “Section 15”). The role of helium and the other ion species of interest should be investigated further.in multi-ion therapy.

Concluding Remarks

The revival of helium ion therapy that is envisaged for 2021 at HIT using state of the art imaging, dose delivery and planning methods will mark a new chapter in ion beam therapy. The very promising properties of helium beams hopefully can be transformed into better treatments and exciting ideas like mixed beam protocols already came to life [34].

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3. Helium ion beam physics: experimentation and improved modelling of ^{4}He nuclear interactions

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Status

Like carbon ions, helium ions undergo various interactions when penetrating a patient's body: electronic energy loss, multiple coulomb scattering and nuclear fragmentation alter the composition, energy and direction of the radiation field before hitting the target volume. In contrast to heavier ions, however, the possible projectile fragmentation channels for ^{4}He are extremely limited (Figure 3.1). Moreover, nuclei within the patient's body – mainly oxygen nuclei in the water molecules of the tissue will break up into target fragments and further alter the beam composition and radiation quality.

During the initial preparation of ^{4}He therapy at HIT, inconsistencies between measured and calculated 1D-depth dose distributions were found (Tessonnier2017). Therefore, HIT and the GSI Helmholtzzentrum für Schwerionenforschung started a dedicated measurement program (Horst2017, Horst2019) to improve the total nuclear reaction cross section models for ^{4}He ions used to calculate the basic data (e.g., Bragg curves) for treatment planning systems (see "Section 5" on treatment planning). Discrepancies between theoretical models and measured cross sections could be identified and the models in the FLUKA Monte Carlo code (see "Section 4" on Monte Carlo modeling) were adjusted appropriately (Arico2019) (Figure 3.2 left), leading to an improved accuracy of recalculated ^{4}He depth dose distributions. In previous experiments, angular distributions of fragments produced by ^{4}He ions in water targets were also studied (Rovituso2017) (Figure 3.2 right).

When calculating 3D dose and particle distributions, considering not only the longitudinal but also lateral dimension, total reaction cross sections alone are not sufficient to describe fragmentation processes in detail and need to be supplemented with additional isotopic single and double differential cross sections to reach the full predictive power of the theoretical models (Figure 3.1). The quality of transport calculations, a fundamental part of treatment planning, as well as the prediction of the Relative Biological Effectiveness (RBE) are directly linked to the goodness of these underlying models (see "Sections 7-10" on radiobiology). For an accurate prediction of 3D dose distributions produced by ^{4}He ion beams in water, including the wide halo from light secondary fragments, more nuclear cross section data is necessary. Furthermore, a precise knowledge of the creation of fragments and secondary particle yields is a necessity for treatment verification techniques (see "Section 6" on imaging and treatment verification), including Positron Emission Tomography (PET) or experimental online monitoring techniques using prompt gammas or charged fragments. Besides their direct application in therapy, ^{4}He ions are also a prime candidate for radiography applications (Martisikova2018) and are part of novel beam delivery techniques like the simultaneous mixing of carbon and ^{4}He beams (Volz2020).

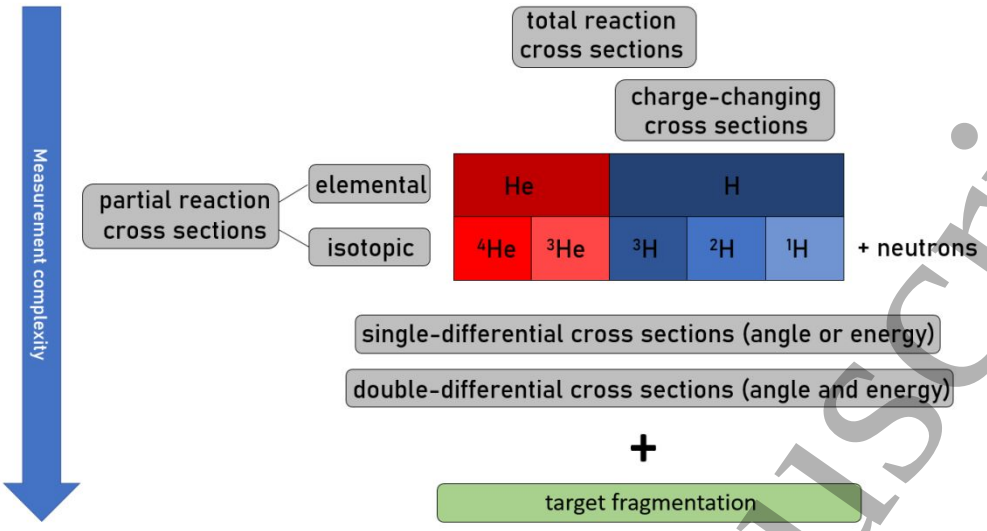

Figure 3.1. Schematic representation of the cross section hierarchy for ^{4}He beams. The experimental complexity and beam time requirements increase drastically for single- and even more for double-differential measurements.

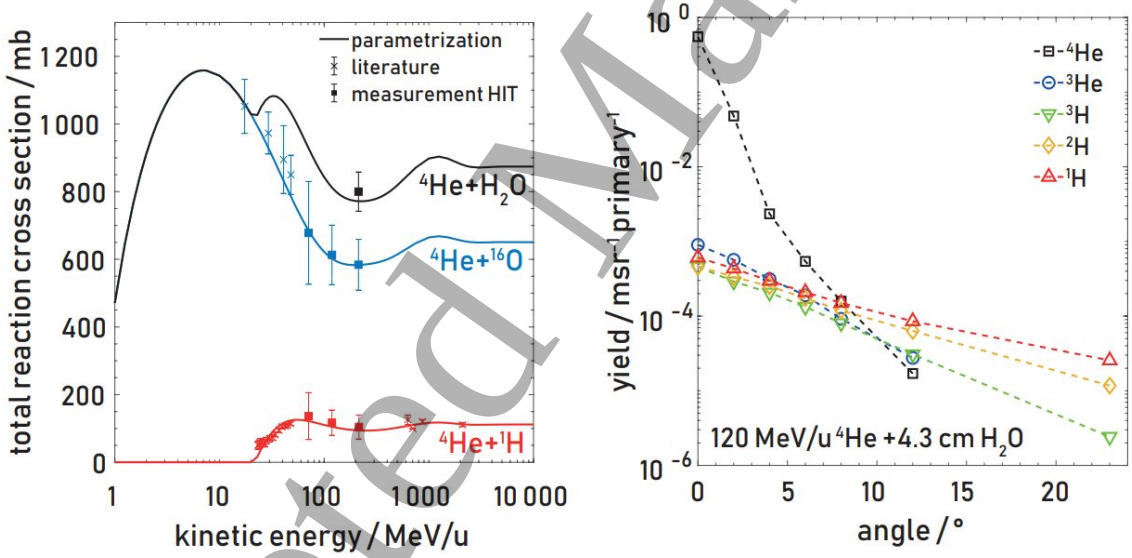

Figure 3.2. Left: Updated parametrizations of Tripathi96/99 (lines – Horst2019) compared to available experimental total reaction cross section data (symbols – Norbury2020). The cross section of ^{4}He + H_2O (black line) was calculated by adding the cross sections of H (red line) and O (blue line) and compared to a direct measurement on a water target (black symbol). **Right:** Angular distribution of primary ions and fragments produced by 120 MeV/u ^{4}He on a 4.3 cm thick water target (Rovituso 2017).

Current and Future Challenges

To fully exploit all the potential benefits of ^{4}He ions, highly functional and benchmarked interaction models and transport codes, which can accurately describe a pencil beam traversing a patient's body, are a necessity. This directly translates to a high demand on the quality of the available

cross section data, while the use of Monte Carlo methods and geometries with realistic material compositions not only drastically increases the demand on the quantity of total cross section datasets but also the demand for full double differential measurements. As mentioned previously, these demands are not fully met by the available experimental data (Norbury2020).

While sufficient datasets are available for ^{4}He total reaction cross sections in the most important materials (Norbury2020, Figure 2), high quality isotopic single- and double-differential datasets in the appropriate energy range and for targets of interest are especially sparse. Additionally, available data points show comparably large uncertainties and, therefore, are not always directly useful for modeling. Thus far, target fragmentation, a relevant effect in proton therapy was not investigated in detail for ^{4}He and might strongly influence the initial build up in the first few centimeters of material (Pfuhl2018). Overall, the existing gaps can be explained with several peculiarities of applied nuclear physics research for particle therapy:

Firstly, the use of the traditional radiotherapy reference material, water, in a nuclear physics context, complicates the production of pure and well-defined (e.g. thickness, composition, etc.) interaction targets, directly increasing the measurement uncertainty in thin target cross section measurements.

Secondly, in contrast to most other research fields at high-energy particle accelerators, therapy related research is typically not backed by large collaborations, but spread over numerous smaller independent research groups located at different accelerators. While often highly useful to tackle smaller research projects that are common in applied medical physics, the lack of collaboration often limits the achievable quality and type of the measured cross section data. This also limits the available manpower, the development of dedicated detector technology, the available budget and the beam time of extensive cross section measurement campaigns.
As also pointed out in “Section 4”, a closer collaboration between experimentalists and theoreticians/code developers would be highly desirable.

Lastly, the availability of facilities offering high purity ^{4}He beams and the necessary infrastructure to enable complex cross section measurements is limited. The only medical accelerator in Europe that currently fulfils all necessary requirements for complex fundamental physics experiments with ^{4}He beams is HIT. On the other hand, acquiring reasonable amounts of beam time at dedicated research accelerators, like GSI/FAIR, is highly competitive and difficult to achieve without strong political support of a large community.

Advances in Science and Technology to Meet Challenges

To partially mitigate the aforementioned problems, the biophysics community established a **Cross Section Working Group** during the first **International Biophysics Collaboration**, meeting in 2019 (Durante 2019). The aim of the collaboration is to offer the necessary political support to identify and tackle large-scale biophysical problems. The aim of the working group is specifically to identify missing cross section data for particle therapy and space radiation protection necessary for precise theoretical modeling. Due to the resurgence of interest in particle therapy using helium beams, the first focus of the working group was to study fragmentation of light ions (Norbury 2020).

Additionally, the Italian led FOOT (**F**ragmentati**O**n **O**f **T**arget) experiment promises high quality double-differential measurements for medical and space radiation protection purposes in the near future (Valle 2019). To enable these high precision measurements, the FOOT collaboration designed a medium-scale and travel-ready nuclear physics experimental setup, which employs full vertex (interaction point) reconstruction and a magnetic spectrometer and was optimized to operate under typical infrastructure constraints present at medical particle accelerators.

Furthermore, additional dedicated experimental rooms in clinical facilities (CNAO, Med-Austron) have been recently commissioned and will be able to offer ^{4}He beams in the future (see table 3, Norbury 2020), strongly reducing the current beam time constraints for cross section measurement campaigns.

It is important to note that smaller scale experiments are still useful and necessary. Due to their reduced complexity, small scale experiments can be optimized to measure specific systems or quantities with high precision in a comparably short timeframe. Furthermore, their data is highly useful to complement and validate the data of larger experiments. Nevertheless, small-scale fundamental physics experiments need to adjust to utilize their impact fully. The fast adaption of state-of-the-art electronics, dedicated detector developments, like the TIMEPIX (Llopart, 2007) system, or the fast translation of particle physics detectors, like MIMOSIS (Deveaux 2019), are a necessity. These technologies will not only increase the precision of smaller scale applied nuclear physics experiments, while limiting the amount of necessary beam time, but also offer new opportunities in other relevant topics for particle therapy, like beam monitoring or imaging.

Lastly, it should be emphasized, that larger scale experiments, like FOOT, should focus on the measurement of cross sections on relevant elemental targets to fully exploit their high precision, whereas dedicated smaller experiments should continue to additionally measure using optimized water-targets or other compounds to guaranty proper validation.

Concluding Remarks

Although thousands of patients were treated decades ago using ^{4}He beams at Berkeley, radiation transport calculations are still not able to accurately describe all helium interactions – especially the lateral distribution of a pencil beam – with the precision necessary for state-of-the-art particle therapy. To support the start of ^{4}He ion therapy at HIT, extensive measurements campaigns were performed and the cross section working group of the international biophysics collaboration identified literature gaps within the cross section database. Additionally, large-scale experiments, like FOOT, promise to provide missing high quality, double differential datasets and smaller-scale experiments are already in preparation to further help with providing missing data. Though substantial work remains, reliable and precise transport calculations of ^{4}He ions in clinical quality are tangible and will guarantee safe treatments in the near future.

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4. Modeling and Monte Carlo simulation of helium ion beam interactions with matter

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Status

The paucity of experimental data, as described in the previous section is a natural hindrance factor for the development of accurate Monte Carlo modeling of ^{4}He interactions in the human body. This applies particularly to nuclear elastic and non-elastic interactions, where the peculiarity of ^{4}He ions with respect to other nuclear species is source of uncertainties, i.e., its small number of nucleons, very high binding energy and no excited levels. These attributes make the models developed for heavy ion interactions inapplicable without specific modification for helium ions. Conversely, ionization and multiple scattering processes can be safely assumed to be as well described as in the case of all other proton and ion beams.

Nevertheless, comparisons of FLUKA simulations with experimental data (Tessonnier2017, Tessonnier2017a) on dosimetric measurements in water show a remarkable level of agreement, within 2-3% on all quantities except some underestimation of tails in the lateral dose distributions. Nonetheless, in phase of FLUKA developments for therapeutic helium ion beams, internal assessments find that slight disagreement in the dose levels just before the Bragg peak and model improvements are needed. That said, to our knowledge, there are no published works which present predictions from other codes like PHITS and GEANT4 against experimental data for helium ion beams.

Both discrepancies, despite small, require improvements in the nuclear interaction models for ^{4}He. Furthermore, a better understanding of nuclear interactions will improve the predictions on different observables, such as the production of β^+ emitters, or prompt photons, or far-reaching neutrons. In part, experimental data is urgently needed on this subject, and data on elemental thin targets would be even more valuable.

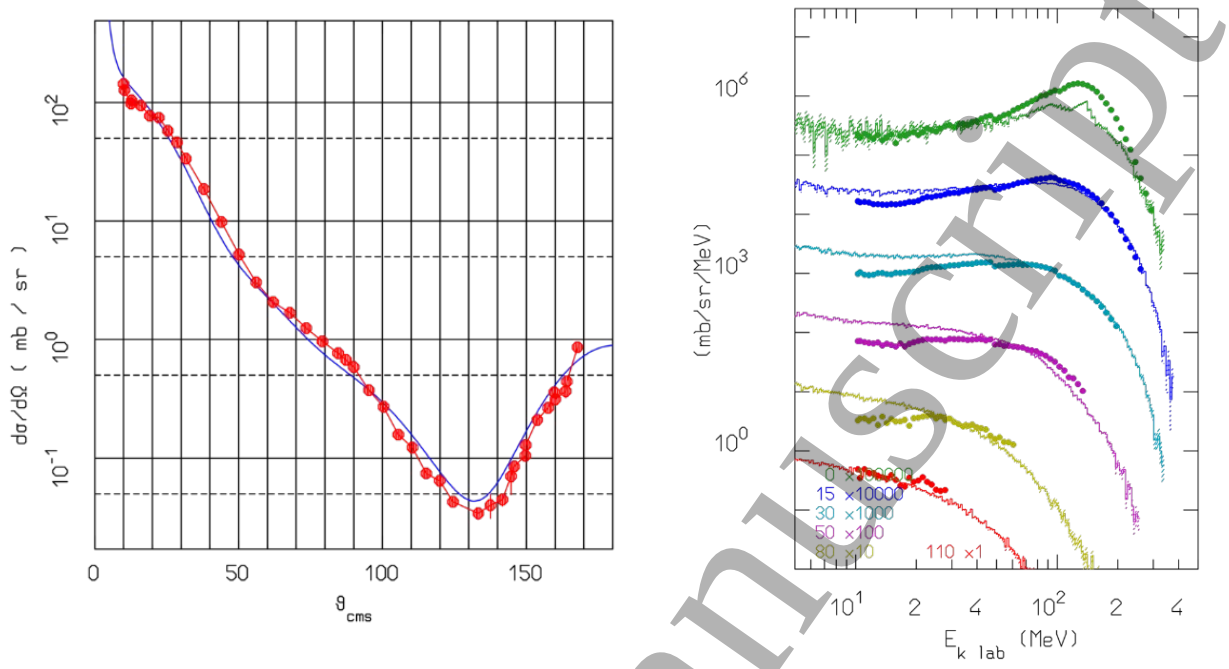

Figure 4.1. Left: simulated (blue curve, FLUKA) and experimental (red dots) cross section for elastic scattering of protons on alphas at 85 MeV. Exp. Data from Votta1974. Right: neutron spectra at selected angular values from ^{4}He interactions on carbon at 135 MeV/nucleon (experimental data from Sato2001).

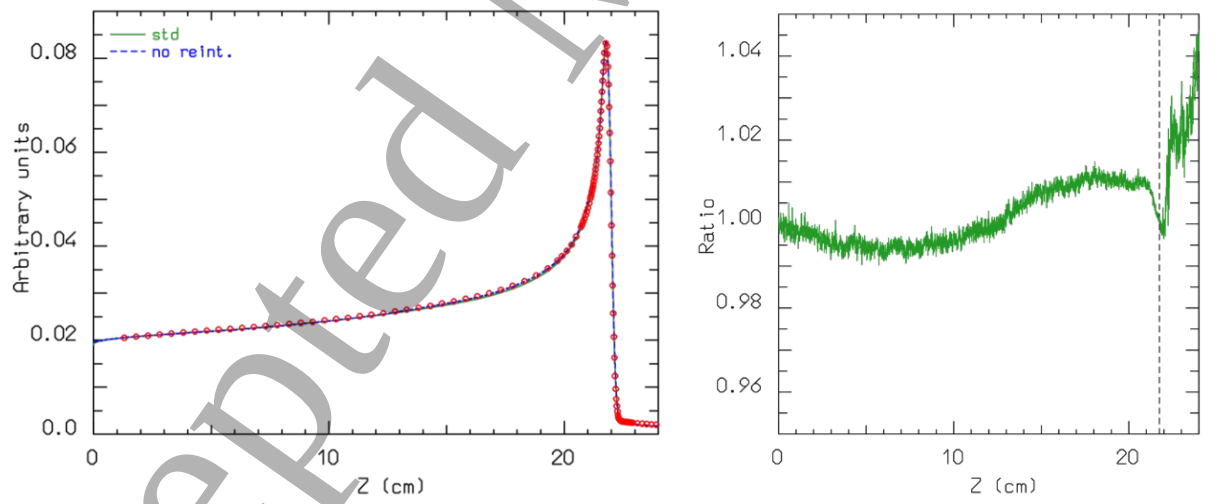

Figure 4.2 Left: Depth-dose distribution for a 182.5 Mev/nucleon ^{4}He beam in water, with ripple filter, full simulation of HIT setup. Data from HIT (dots, private communication), line is FLUKA simulation (std = standard version, no reint. = without fragment reinteraction) Right: ratio of depth-dose distributions with and without fragment reinteractions.

Current and Future Challenges

Besides electronic energy loss, helium ions in human body undergo elastic and non-elastic nuclear interactions, most of them on hydrogen and oxygen nuclei. Elastic scattering on hydrogen is well described, in inverse kinematic, by fits to experimental data applying the nuclear-optical model (Votta1974). An example is shown in Figure 4.1. This process is important mainly because of the production of recoiling protons. Elastic scattering on heavier targets could impact the interpretation of experimental data.

Non-elastic interactions on hydrogen are a particular case of the description of proton interactions on nuclei. However, ^{4}He is a very peculiar nucleus, with a small number of nucleons, a very high binding energy and no excited levels. Thus, standard models might fail in reproducing proton-alpha interactions. It is worthwhile to mention that the neutron-proton asymmetry of the alpha-proton system favors the production of ^{3}He, both from fragmentation of the compound nucleus and from stripping of one neutron, with respect to ^{3}H.

Non-elastic interactions of alpha particles on Carbon, or Oxygen, are generally treated in the framework of intranuclear cascade plus pre-equilibrium codes (in codes like FLUKA (Battistoni2016), GEANT4 (Allison2016), PHITS (Sato2018)). Quantum molecular dynamics is also applicable, although not really suited for such light systems.

The reliability of these models for ^{4}He should be assessed through comparison with experimental data. Unfortunately, available experimental data are limited, in some cases contradictory or not complete, and too often on composite thick targets. Comparisons on neutron emission from thin targets (Figure 4.1) show satisfactory agreement except for forward-emitted neutrons

Conversely to the hydrogen case, one is dealing here mostly with isospin symmetric systems. The Coulomb barrier can be deemed negligible above a few tens of MeV/nucleon. Therefore, the expectation is for symmetry in the emission of ^{3}He and ^{3}H, as well as for p and n. It is difficult to verify this assumption on recent data concerning interactions in water phantoms, due to the coexistence of alpha-H and alpha-Oxygen interactions. Furthermore, at the same energy per nucleon, ^{3}He ions experience four times larger energy losses with respect to ^{3}H, making any conclusion about their initial production spectra particularly hard.

Peripheral interactions can lead to ***target*** excitation and fragmentation, with angular deflection and energy loss of the incoming ^{4}He ion, but without ***projectile*** fragmentation. This leads to several consequences:

- All non-elastic cross section measurements for ^{4}He on C and O are actually measurements of the projectile fragmentation cross section. The actual non-elastic cross section is surely larger due to the contribution of target excitation/fragmentation processes. Available Monte Carlo models vary wildly in predicting this contribution, with estimations ranging from a few % to 20%. The actual value of the non-elastic cross section has a direct influence effect on the height of the Bragg peak;

- Deflected ^{4}He could be misinterpreted as ^{3}He, see for example the details of the analysis in (Horst2017);
- High-LET target fragments are important for biological dose estimations;
- Target fragmentation is important for dose monitoring through prompt photons and β^+ emitters.

To the knowledge of the authors, no experimental data is available about target excitation/fragmentation with the ^{4}He ion surviving. Re-interaction of fragmentation products plays a small role (see figure 4.2).

Advances in Science and Technology to Meet Challenges

As discussed in the previous section, atomic processes and elastic scattering on Hydrogen are well understood and described. A better knowledge and modeling of elastic scattering on nuclei would be important. However experimental data on ^{4}He nuclear elastic scattering are sparse at energies of relevance for hadrontherapy. A few examples for Carbon and Oxygen targets can be found in Michel1983, Wiktor1981, Wakasa2007, Itoh2011, Chaumeaux1976 and references therein. Theoretical approaches are usually based on optical model calculations, however available optical models are usually reliable up to 200 MeV total kinetic energy; also optical models tend to be less reliable for light nuclei. An alternative approach could be a low-energy extension of the Glauber model. Additional data are needed in order to tailor the implementation of these models.

Non-elastic interactions are where Monte Carlo codes still need to be validated and improved. The Intranuclear Cascade and preequilibrium models that have proven to be reliable for heavier systems will undergo modifications to consider the peculiarity of the helium ion system. To guide terse improvements, experimental data on thin elemental targets is necessary. Moreover, thin target data should be as complete as possible, i.e. include double differential measurements of both proton and neutron emission, as well as 3He and 3H emission, so that isospin symmetry can be checked. Thick target experiments and experiments on water target are a valuable check, but introduce too many variables to be the primary source of information.

Progress in knowledge will only profit from a deeper collaboration between Monte Carlo developers and experimentalists. Full simulation of experiments and raw data comparison with Monte Carlo could help in disentangling processes and resolve ambiguities, such as the possible misidentification of quasi-elastically scattered helium ions. Comparing predictions of different Monte Carlo codes against experimental data is warranted.

Concluding Remarks

The description of ^{4}He interactions in the human body in its present status allows to reproduce dose distributions from therapeutic beams with a reasonable level of accuracy, better than a few percent on most observables. Residual discrepancies need refinement of already deployed

models, in close collaboration with experimental groups who are already planning a wealth of new measurements.

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5. Dose calculation development and treatment plan comparisons: preparations and investigations towards optimal clinical practice with 4He

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Status

Due to their physical and biological characteristics between proton and carbon ions, helium ions have great potential for radiation oncology. After clinical studies have been conducted with Helium ions during the pioneering phase of particle therapy based on rather simple algorithms, their revival is conducted with sophisticated dose calculation.

The higher mass of Helium compared to protons reduces beam broadening by a factor of two and provides a sharper Bragg peak, consequently enabling more conformal dose depositions. In addition, fragmentation effects are less pronounced than for Carbon, reducing unwanted dose after the target region.

Two major dose calculation methods are currently used in clinical practice, i.e. pencil beam (PB) algorithms and Monte Carlo (MC) dose calculation engines. PB algorithms model the passage of particles through matter via a semi-empirical approach on a per beam basis, enabling fast dose calculations. Typically, the beam shape is determined by a superposition of beams, each modeling empirically different physical effects (see Fig. 5.1). Their accuracy is good, unless used in overly complex heterogeneous geometries such as lung [1]. Due to their calculation speed and reasonably high accuracy, they still remain the clinical workhorse in particle radiation therapy.

MC based dose calculation engines on the other hand, model the passage of single particles through matter based on physical models. Although being slower, MC dose engines provide increased accuracy compared to PB algorithms also in the presence of heterogeneities [1]. Recently, MC based dose calculation engines are becoming available for protons in clinical treatment planning systems. In clinical routine MC is used in tandem with PB algorithms, using PB algorithms as fast dose calculation during optimization, while relying on the increased accuracy of MC for final dose computation. PB algorithms are still the main dose calculation methods in clinical treatment planning systems for other ions, due to their more complex physical interactions.

PB algorithms, due to the semi-empirical approach, need to be specifically optimized for an ion species. Using look-up tables, they can then be fine-tuned to match the specific beam line. There is still research on potential refinements to increase accuracy ongoing, but overall PB algorithms have reached a mature state [1,2]. In 2012 the first dedicated helium ion PB was created which was later included in a research treatment planning system [3,4]. Another established research TPS was soon also adopted to allow dose calculation with helium ions [5], shortly followed by a Monte Carlo based TPS, which was also validated experimentally [6,7]. Recently a GPU based Monte Carlo calculation platform became available [8].

After the calculation frameworks became available, first treatment planning studies started (see Fig. 5.2) [5,9,10], paving the way for an in-depth validation and future clinical application [6,11,12].

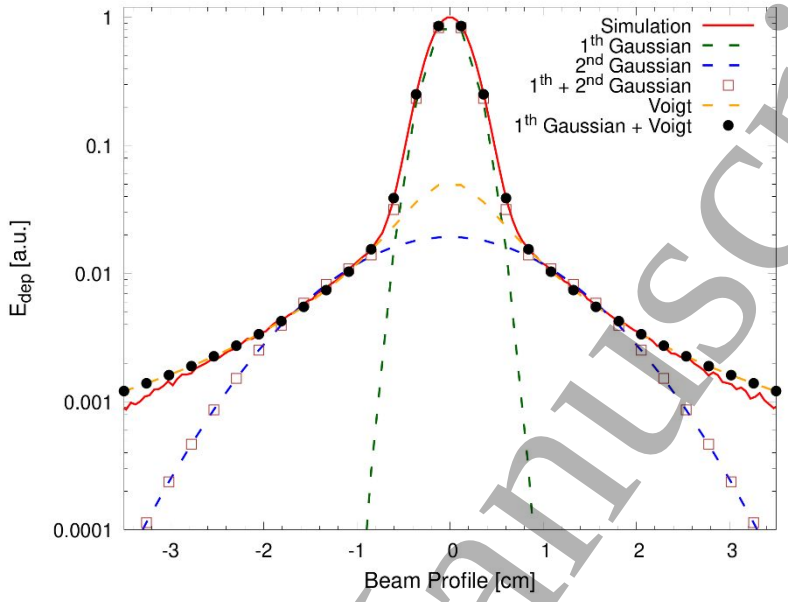
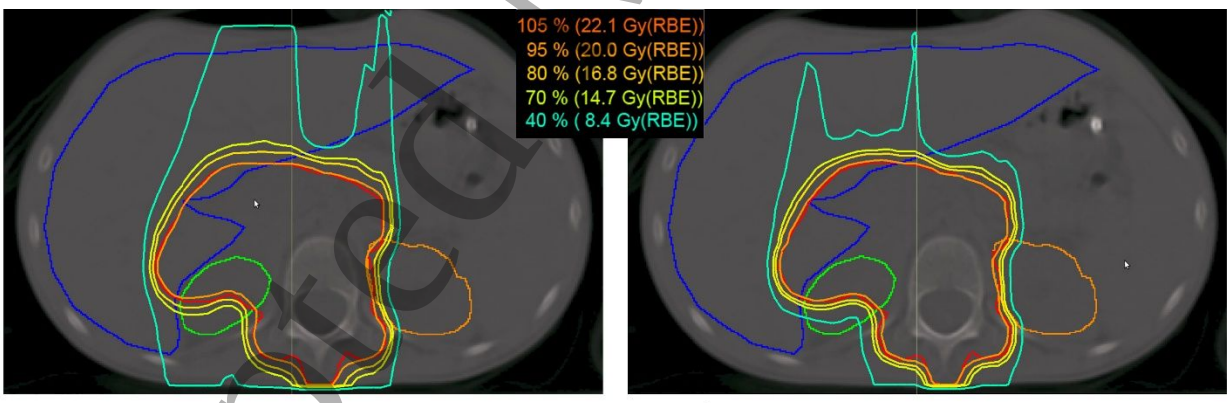


Figure 5.1. Beam profile of a helium ion beam in water with an initial energy of 150 Mev/A at a depth of 10 cm. Calculated using the Monte Carlo toolkit GATE. Different analytical functions are employed to match the profile. Note that two Gaussians are not sufficiently accurate at larger distances from the beam center.



(a) p^+ (b) ^4He

Figure 5.2. Isodose distributions (left: protons, right: 4He) of a representative Neuroblastoma patient. Note the differences in beam entrance and dose fall-off regions around the PTV between protons and Helium ions. The red structure defines the PTV, while the organs at risk liver and kidneys are indicated by the blue, brown and green structures.

Current and Future Challenges

Although PB algorithms enable fast and reasonably precise dose calculations, MC codes provide more detailed and comprehensive physics information, such as fragmentation data as well as linear energy transfer (LET) values on voxel or sub-voxel basis. This is in turn necessary for

predicting biological effects in clinical dose calculation and/or for research purposes. Unfortunately, most currently available MC codes are extensive multi-purpose codes (e.g. Geant4, FLUKA, PHITS…), which are too slow for clinical routine but provide reference class quality.

Recently it was observed and described in several clinical proton papers, that higher dose averaged LET values might lead to detectable changes in tissues [13]. The currently used single and constant RBE value of 1.1 for protons is thus intensively discussed. Consequently, with the advent of readily available helium ion beam therapy additional or at least revised concepts on RBE modelling for low LET particles need to be established. In Europe synchrotron-based ion therapy facilities are commissioned for helium ion therapy and research, and will provide research platforms for physics, biophysics and radiobiological research. It needs to be underlined that high quality biological data require in the first-place high quality macroscopic and microscopic dosimetric quantities.

MR guidance paves the way for next level image guidance and real time adaptive radiotherapy (ART). A necessary precursor is the development of fast dose calculation methods, where changes of patient anatomy need to be incorporated into the treatment plan. Motivated by ART, more efficient assurance and patient specific dose verification methods are currently being implemented for proton beam therapy, which need to be tackled for helium ions in a similar manner. A related topic is the development of 3D accumulation, not only with respect to dose, but also including other physical parameters, such as LET.

Existing treatment planning guidelines for protons will most likely need to be adapted for helium ions. The most notable difference to protons will be the higher LET values and the presence of a fragmentation tail, e.g. excess dose after the Bragg-peak. Although this dose contribution will be small compared to carbon ions, it will nevertheless need to be accounted for. Taking advantage of MC supported dose calculation, LET driven rather than dose-based optimisation is an important upcoming topic, with large potential for Helium ions.

Finally, multi-particle treatments including helium will be enabled by synchrotron-based facilities, which requires extensive further research and treatment planning comparisons, as this concept is rather in its infancy.

Advances in Science and Technology to Meet Challenges

To be able to complement the standard physics quantity absorbed dose, with parameters such as LET or fragmentation specific data, PB algorithms need to be extended to provide the necessary data for RBE calculation, as currently done for carbon ions.

Another and certainly more versatile solution is to develop MC codes for Helium ions optimized for clinical routine, such as the ones becoming available for protons. This is certainly feasible with the increasing amount of calculation power of multi core CPUs and advanced GPUs. Such developments are currently ongoing for carbon ions. Increased effort must be invested to enable 3D data accumulation, which is not limited to dose and one particle species.

One possibility to reduce the overall planning time would be the use of machine learning approaches. So far, first studies are focusing on predicting the optimal dose distribution without performing an optimization procedure. A deliverable plan is then created by determining the required particle energies, spot positions, and weighting, retrospectively but knowledge based. Especially the last step still involves conventional dose calculation methods. Further improvements may be possible by also performing dose calculation itself by novel machine learning approaches. So far only limited development was performed in this regime [14].

With the advent of scanned beam delivery and thus more conformal treatment plans, patient and organ motion become an even more important factor. The upcoming CT based but potentially also MR based in-room imaging technology in particle therapy opens the gate for adaptive ion therapy approaches. Consequently, efficient patient specific quality assurance procedures need to be established, such as log-file based beam delivery verification that can be linked with independent dose calculation [16]. Furthermore, fast dose accumulation will be of utmost importance in an on-line adaptive setting. For all these reasons pencil beam-based dose calculation is expected to remain as established dose calculation means for the next decade, i.e. during the clinical exploration phase of Helium ions.

For exploratory research and/or clinical implementation of methods that are already explored for proton therapy, such as prompt gamma imaging for range verification, Monte Carlo methods for dose calculation are expected to dominate. Examples of special research topics that cannot proceed without MC are mini-beam therapy, FLASH therapy, particle imaging or multi-particle treatments.

Concluding Remarks

Helium ions, combining elements from protons and carbon ions, may provide a promising additional treatment modality. However, before wider clinical exploration can take place, several development steps need to be undertaken. Dose calculation is the hub for clinical and biological research; it is the Achilles heel in the context of primary treatment planning and its role in secondary (patient specific) quality assurance procedures will increase in the context of image guided adaptive ion therapy. European synchrotron-based ion beam facilities will play leading roles in research endeavors for Helium ion therapy, especially in experimental benchmarking studies.

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6. Helium ion beams for imaging and treatment verification techniques

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Status

Already in the pioneering phase of experimentation with energetic helium ion beams, ground-breaking studies were carried out to illustrate the abilities of these beams for transmission tomographic imaging (Goitein 1972) and visualization of the actual irradiation via tissue β^+-activation (Maccabee et al 1969). However, the wider availability of proton therapy facilities and the clinical interest in carbon ion radiation of higher linear energy transfer (LET) slowed down for many decades the research activities around helium ion beams, with the exception of dedicated low-energy applications of microbeams for radiation research (e.g., Radners-Pehrson et al 2001) and high-resolution microscopy (Joens et al 2013). Nevertheless, in the last one and a half decade the renewed interest in transmission ion imaging, along with the preparatory work at few synchrotron-based facilities toward clinical translation of helium ion beams, motivated a revival on applications of helium ions to imaging and treatment verification techniques. However, most of these studies either entirely relied on in-silico computations, without the opportunity to benchmark the underlying beam model assumptions with experimental data, or exploited instrumentation originally tailored to proton or carbon ion beams, thereby not yet fully optimized for application to helium ions, as addressed in the following.

Current and Future Challenges

Helium ions for pre-treatment transmission imaging

The potential superiority of helium ions for transmission imaging in comparison to protons and even heavier carbon ions was already postulated by Hansen et al (2014). Their purely Monte Carlo simulation phantom study showed that at the same clinical dose level (evaluated via a quality factor weighted computed tomography dose index) helium ions gave the best spatial resolution for tomographic imaging with an ideal detector setup registering position and momentum of each ion before and after the imaged object. This is because helium ions offer a very promising trade-off between reduced scattering compared to protons, with still a sufficient number of tracks compared to carbon ions at the same level of dose, corresponding to a considerably different particle fluence for different ion species. However, Hansen et al also acknowledged that the minimum equivalent dose yielding an acceptable image quality in terms of stopping power ratio (SPR) reconstruction accuracy was about five times larger for helium ions than for protons for their considered imaged objects, when relying on a not yet validated Monte Carlo computational framework and employing their weighted quality factor calculation. Similar findings were obtained by Meyer et (al 2019), who used an experimentally benchmarked Monte Carlo computational engine to generate ion computed tomography (iCT) images of patients' heads with beam scanning, again for an ideal single-particle tracking detector setup, given then in input to a research treatment planning system for quantitative evaluation of the implications on dose calculation (figure 1). For the sake of convenience, for particle transport in the patient anatomy, the underlying patient X-ray CTs were imported in the Monte code and converted to the ground truth SPR by forcing the code to follow a monotonic, bijective and error-free clinical-like

HU-SPR conversion curve (Meyer et al 2019). This way, the exact SPR distribution of the simulated patient anatomy in the Monte Carlo code code is known, and the only remaining uncertainty originates from the energy dependency of SPR, which can be considered negligible in the considered energy range (Meyer et al 2019). Moreover, their computational framework integrated a mechanistic radiobiological model for quantifying the biological effectiveness (in terms of cell death and DNA double-strand break induction as relevant biological endpoints) of iCT for protons, helium and carbon ions relative to low-energy diagnostic X-rays, hereafter denoted as RBE_X. For the considered realistic clinical scenarios, helium CT showed the overall lowest error in SPR reconstruction at the same physical imaging dose, while only a ~3-5% increase of RBE_X in comparison to the proton case, however remaining still well below the value of 1, thus suggesting a lower risk compared to low-energy diagnostic X-rays. However, also this study acknowledged the need for radiobiological experiments to understand the effects of low-dose imaging and the postulated lower risk of iCT compared to currently used X-ray spectra for frequent imaging in treatment planning and adaptive therapy. Experimental confirmation of the superior spatial resolution of ^{4}He ions compared to protons for radiographic imaging, without disadvantages in terms of contrast-to-noise-ratio at the same dose level, was shown by Gehrke et al (2018). Their dedicated setup featured a small-scale, single-particle tracking system consisting of five parallel Timepix detectors of small (14mm × 14mm) sensitive area, with two pairs acting as trackers before/after the object followed by an energy loss detector. The findings of this comprehensive study are in line with the first results obtained with larger imaging prototypes, including a single-particle tracking system optimized for proton tomography (Volz et al 2017) and, to some extent, an integrating range telescope tailored to carbon ion imaging (Kopp et al 2020), thus motivating optimization of large scale setups for helium ion imaging.

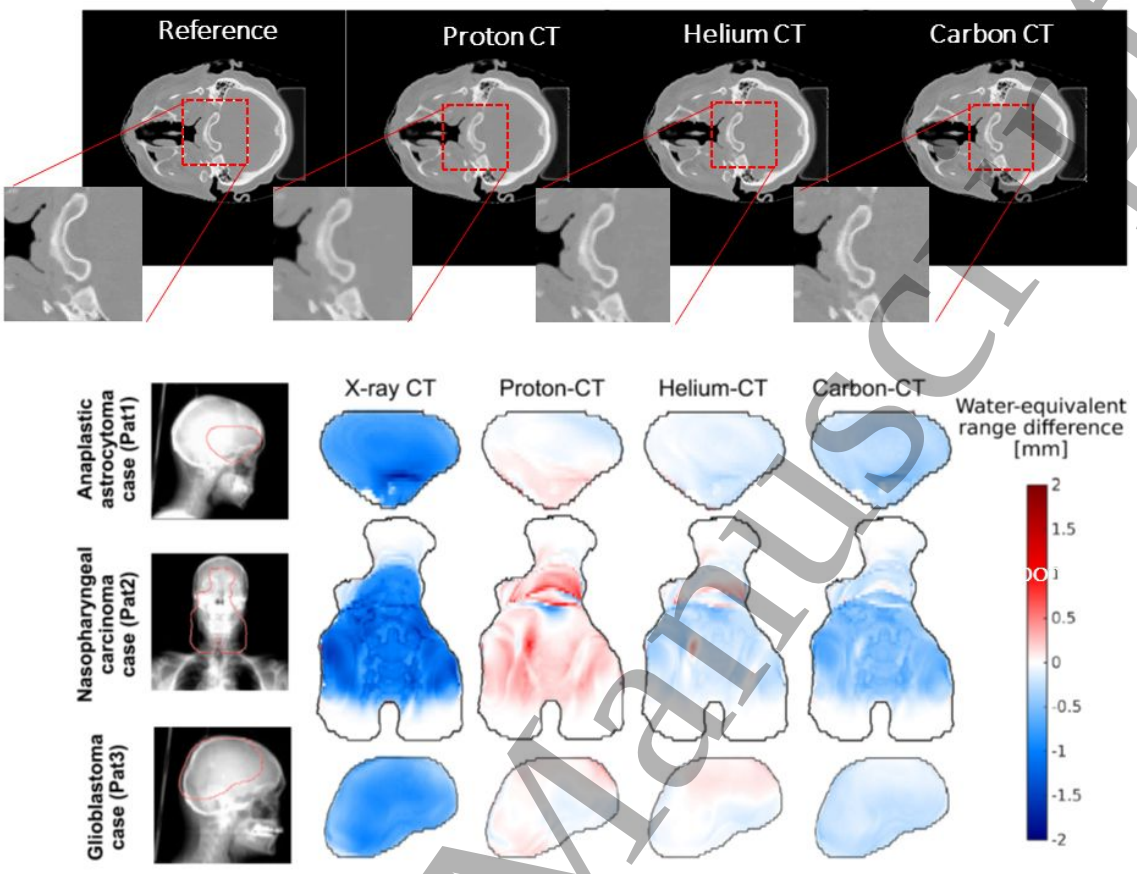

Figure 6.1. Top: Comparison of reconstructions of simulated proton, helium and carbon iCTs against the reference ground truth SPR image used in the Monte Carlo calculations. The insets enable to appreciate the different image quality in highly heterogenous regions (Courtesy of S. Meyer). Bottom: Beam's-eye view water-equivalent proton range variations for treatment recalculation based on the SPR distributions coming from the different iCTs of the upper panel and randomly sampled errors according to known SPR uncertainties of X-ray CT, with respect to the optimized dose of the reference plan obtained on the ground truth SPR image. The left column shows the 80% isodose contours overlaid with the ground truth radiographies for illustrating the considered indications. Taken from Meyer et al 2019.

Helium ions for treatment verification

The currently mostly investigated methods for in-vivo range verification rely on the detection of energetic photons produced either as a consequence of the transient β^+-activation of patient tissue, first studied by Maccabee et al (1969) for ^{4}He ion irradiation, or as fast de-excitation of nuclei excited in nuclear reactions, as first measured by Min et al (2006) for proton irradiation. Hence, already during the preparatory phase at GSI Darmstadt toward helium ion clinical translation in Heidelberg, characterization of positron emitter yields in different phantoms of known composition was carried out with the dedicated in-beam positron emission tomography (PET) scanner, however back then focusing on ^{3}He ions (Fiedler et al 2006) (see "Section 2" on facility start-up). More recent experimental studies were performed at a commercial PET/CT

scanner after ^{4}He ion irradiation at the Heidelberg Ion Beam Therapy center (figure 6.2), to compare the absolute production yield and activity spatial distribution for different ion species (Bauer et al 2019). Despite the improved quantification accuracy and different helium isotope used in the latter campaign, the results consistently showed the potential but also the challenges of PET verification for helium ion beams. Such challenges are mainly due to reduced amount of formed β^{+}-activity per given dose from the lower particle fluence and less straightforward correlation of activity fall-off with range because of a tail of target activation from long ranging projectile fragments compared to protons, along with the lack of peaked activity signal close to the Bragg peak compared to carbon ions. Moreover, comparisons with predictions of general-purpose Monte Carlo codes highlighted the challenges to properly reproduce the details of the nuclear reaction channels leading to β^{+}-activation, even when being able to capture the general shape of the dose distribution and of the secondary heavy charged particle spectra (Rohling et al 2013). Similar challenges are also expected for helium ion range monitoring based on the detection of so-called prompt gamma (PG), despite the first encouraging experimental studies and extrapolations to clinical use reported by Mattei et al 2017. Relevant questions yet to be fully answered include the amount of PG signal for a given dose, expected to be lower than for protons, its correlation with the beam range, considering the background signal produced by secondaries even beyond the Bragg peak, and the ability of nuclear reaction models to correctly reproduce all such emissions in available computational engines.

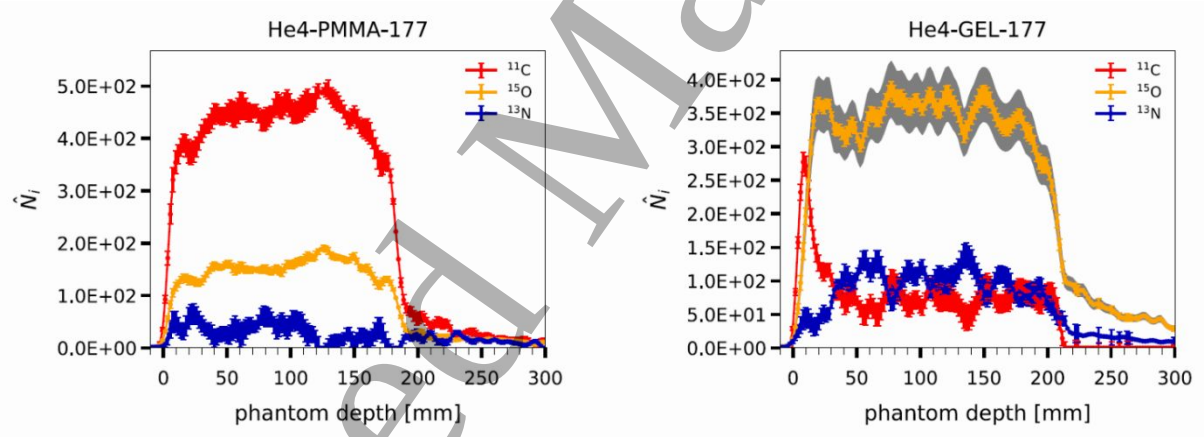

Figure 6.2. Radionuclide-specific production yield per 10^{6} primary beam particles as a function of phantom penetration depth, as estimated from a mathematical model and dynamic analysis of PET/CT acquired data after 176.68 MeV/u helium ion irradiation of PMMA (left) and gelatine (right), according to Bauer et al 2019. The beam range is expected at 181 mm (left) and 209 mm (right).

Advances in Science and Technology to Meet Challenges

Helium ions for pre- and even in-treatment transmission imaging

The major challenge for application of proton imaging prototypes to helium ions is the production of light projectile fragments in the object and the detector, which leads to a mixing of information (e.g. from ^{3}He fragments exhibiting a similar energy loss as the primaries) that needs being disentangled for proper interpretation of the imaging data. However, it has been already shown for an advanced proton computed tomography scanner that such events can be effectively eliminated by applying custom-made filters optimized on the basis of extensive simulation studies, making full use of the measured signal for each individual event (Volz et al 2018). Although the

proposed solution was especially tailored to the multistage energy detector of the considered scanner, adapted to function as a $\Delta E - E$ telescope, it points to the relevant considerations to be made when designing dedicated imaging setups, particularly the energy detector, for helium ions. In such dedicated systems, projectile fragmentation in the detector itself should be also minimized to prevent the loss of usable events, which would in turn increase the required imaging dose for a certain image quality. To this end, reliable and well-benchmarked Monte Carlo codes will be needed to study the impact of nuclear fragmentation in different materials and optimize the detector design along with the data processing for optimal imaging. For reliable considerations on imaging dose, more radiobiological data will be indispensable to better understand the effects and associated risks of low-dose irradiation of energetic (i.e., low LET) ions, to open the prospects of frequent and safe use of helium ion transmission imaging. Additional dose reduction possibilities could be achieved based on the recently proposed scheme of fluence field modulated imaging (Dickmann et al 2020), successfully demonstrated for scanned proton beams acquired with the same above-mentioned advanced proton CT scanner already tested in helium ion beams. The superior spatial resolution at similar SPR accuracy of helium compared to proton imaging, along with the more promising SPR accuracy compared to X-rays (and even to carbon ions at the same imaging dose), may open very interesting prospects not only for providing the initial patient model for accurate treatment planning, but also for frequent in-room imaging for adaptive therapy. In particular, given the approximate independence of the SPR for different therapeutic ion species, helium ion imaging could become the imaging modality of choice at synchrotron-based facilities providing a large variety of therapeutic ion species. Here, both tomographic and radiographic helium ion imaging could be exploited to substitute or complement the widely established X-ray modalities of treatment planning diagnostic CT imaging and in-room cone beam CT acquisitions. Depending on field size and acquisition speed, especially the radiographic mode could enable fast imaging of regions of interest, e.g., to track uncertainties of integral SPR in moving anatomies by requesting for short periods of time energetic transmitted helium ions in-between the therapeutic beam delivery. This approach could even benefit from the intriguing possibility of mixing a small amount of helium ions with a therapeutic carbon ion beam. As experimentally shown (still in sequential irradiation mode) in Volz et al (2020), this recently revived old idea could open the prospects of detecting online changes in the treated anatomy with a very minor increase of the dose delivered to the patient, being most of the low-fraction (ca. 1:10 ratio) helium ion beam stopped in a detector outside the patient.

Helium ions for treatment verification

Although the ideal treatment monitoring approach for helium ions still remains to be assessed, it can be anticipated that detector solutions tailored to PET and PG imaging of proton (as well as carbon ion) beams will likely work also for helium ions. The issue of decreased counting statistics for the same therapeutic dose in comparison to protons could be mitigated with recently proposed strategies, which already in the planning process boost the number of ions to be delivered to selected spots for reliable range verification of a few beam locations at the beginning of the treatment session (Tian et al 2020). Moreover, new detector technologies able to exploit both PET and PG signatures during the beam-on time and from the decay of pure β^+-emitters as well as triple γ-PET events in the pauses of synchrotron beam delivery have been recently proposed and are currently under development. In this context, also more recently proposed approaches of

"real-time PET", i.e., PET imaging of produced ms-short-lived emitters (Ozoemelam et al 2020) or PG spectroscopy for tracking variations in elemental compositions as surrogate of treatment response (e.g., in relation to hypoxia, Martins et al 2020) should be considered. Development of dedicated single- or multi-modal detector technologies will have to be accompanied by extensive experimental campaigns to enable validation of computational approaches based e.g., on Monte Carlo, for correct modelling of the dosimetrically less relevant nuclear reaction channels underlying the production of the PET and PG signals along with their relevant features. Moreover, both experimental and simulated data will be essential to further develop PET and PG data analysis tools, primarily explored in the context of proton therapy monitoring, to infer reliable range information, despite the increased background signal originating from long ranging secondary fragments. The latter increased production of projectile fragments might also open the prospects of additional monitoring techniques based on the detection of charged secondary emissions (e.g., protons), for which initial basic investigations have been already carried out with helium ions (Rucinski et al 2017) and a first prototype system is starting clinical evaluation for irradiation with proton and carbon ion beams at the Centro Nazionale Adroterapia Oncologica in Italy. Depending on the accelerator technology and beam pulsing structure, additional methods currently under vivid investigation like ionoacoustics could become also of relevance for helium ion beams, owing to their favourably sharper Bragg peak (both in the longitudinal and lateral direction) and elevated energy loss compared to protons, which may thus enhance the instantaneous energy density deposition and associated thermoacoustic emissions.

Concluding Remarks

Although only a couple of facilities equipped with powerful synchrotron accelerators are currently able to provide helium ions in the clinically relevant energy range, the topic is attracting more and more attention in the community, where helium ions are often perceived as a potential candidate to replace on the long run the lighter protons. Considering the prospects of additional small footprint accelerator technologies able to provide energetic helium ion beams, it can be foreseen that their very attractive features for transmission imaging, where they are anticipated to outperform protons and carbon ions, will further motivate the ongoing developments toward clinical translation of helium ion therapy. In this context, also unconventional solutions of mixed ion beams for simultaneous imaging and therapy, or for a wider degree of freedom in LET/RBE modulation, are expected to receive increasing interest. And while the situation for in-vivo range monitoring might be less advantageous than for clinically established ions, there are no apparent showstoppers on the translation of range verification technologies largely explored in the context of proton and carbon ion therapy, such as PET and PG, to helium ion beams. Here, other emerging techniques should also be carefully evaluated, as they might even result more suitable for helium ion beams than for protons, e.g. due to the penetrating light fragment production for secondary charged particle detection and the locally more concentrated pencil beam dose deposition for ionoacoustics. In all cases, despite the possibility to adapt systems initially conceived for the lighter protons, it will be very beneficial to devise detector solutions specifically tailored to applications with helium ion beams. Moreover, extensive experimental campaigns at the accessible beams will be urgently needed to support the refinement of helium ion transport and interaction models, particularly in terms of nuclear interactions, for providing reliable computational engines to guide the above-mentioned detector optimizations and the proper

development of data processing pipelines for the envisioned application. Finally, to enable full exploitation of the image guidance opportunities offered by helium ions, deeper understanding of the biological implications and risks of low-dose, high-energy transmission irradiation will be required, thus calling for complex biological experiments again complemented by the development of appropriate computational models.

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Part B: Biology

7. Key experiments and foundations for benchmarking a helium ion therapy program

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Status

Current interest in rekindling the use of helium-ion beam radiotherapy for noninvasively targeting cancer or other disease has sparked critical re-evaluations of what is actually known about the effects of accelerated helium ions that were successfully used for radiosurgery, as determined by long-term follow-ups of only 2,045 patients in Berkeley, California between 1957-1992. After more than 4-decades of emphasis on protons and carbon ions world-wide, helium ions have basically been overlooked as a particle modality for the future. However, that is changing now, spearheaded by international reports of helium-ion preclinical treatment planning physics [1-3], imaging [4]; radiobiology [5-9], and theoretical modelling of biological effects [10-16]. It is now essential that we define what key experiments and foundations are still required to benchmark a roadmap to a new helium-ion therapy program.

Historically, the 184" cyclotron at the University of California, Berkeley/Lawrence Radiation Laboratory was completed by Ernest Orlando Lawrence in 1947 to accelerate protons, deuterons, and helium ions [17]. An upgrade to convert the cyclotron to a synchrocyclotron in 1954 permitted the acceleration of up to 230 MeV/u alpha particles for preclinical research by Tobias et al., 1952 [18] on the effects of helium ion beams on the brains of rodents. John Lawrence had previously reported on the effects of 180 kV X-rays on the pituitaries of several animal species [19] before he began his medical studies treating acromegaly and other disorders of the human pituitary [20, 21].

Long-term follow-ups of up to 20-years for helium patients treated for acromegaly [22], intracranial arteriovenous malformations (AVM) [23, 24], and uveal melanoma [25-29] have now established the long-term success of helium radiotherapy for radiosurgery in the cranium. However, at the time these studies were conducted, clinical particle research interest became quickly focused on the "heavier" higher atomic number ions with the demonstration of much greater enhanced biological effectiveness. In fact, helium ions became the "control", low ionization density radiation reference modality for the pioneering heavy charged particle clinical studies of Castro et al. [30-32].

The high-energy entrance helium beam is similar in biological effectiveness to reference electrons, X-rays or protons but scatters dose less laterally. The dosimetry of helium ion beams allowed simplified dose comparisons and facilitated treatment planning and pilot studies with the heavier ions. Not to be overlooked however, the biological effect of helium ions at the Bragg peak is similar to that of the entrance channel of ion beams of higher atomic number and energy (see comparison of Table 5-1 and Fig. 6-16 in [9]). The clinical safety helium may afford pediatric patients, or adult tumors adjacent to sensitive organs at risk has been heavily weighted in the decision radiation oncologists must make selecting which radiation in their tool-box is most appropriate for an individual to spare the patient normal tissue toxicities. As a consequence of the focus on protons

and heavy ions, the helium-ion field and database are currently understudied and are experiencing a resurgence in interest as an acceptable alternative treatment option. This endeavor will require an international effort to effectively confirm that stopping helium ions in the distal Bragg peak pack enough “intermediate” high-LET punch to eradicate resistant tumors, or to trigger immune responses to eliminate microscopic disease.

Current and Future Challenges

The most significant research challenges for acquiring additional *in vitro* and *in vivo* radiobiological information on the effects of helium ion beams are access to beam time among the few facilities capable of providing these beams without competing with the ongoing clinical programs, and the resources required (including well trained staff) to complete the detailed protocols. The existing helium-ion physics, biology and 20-yr clinical follow-up data from Berkeley may help guide the experimental design and establishment of upcoming and future clinical trials ([33]).

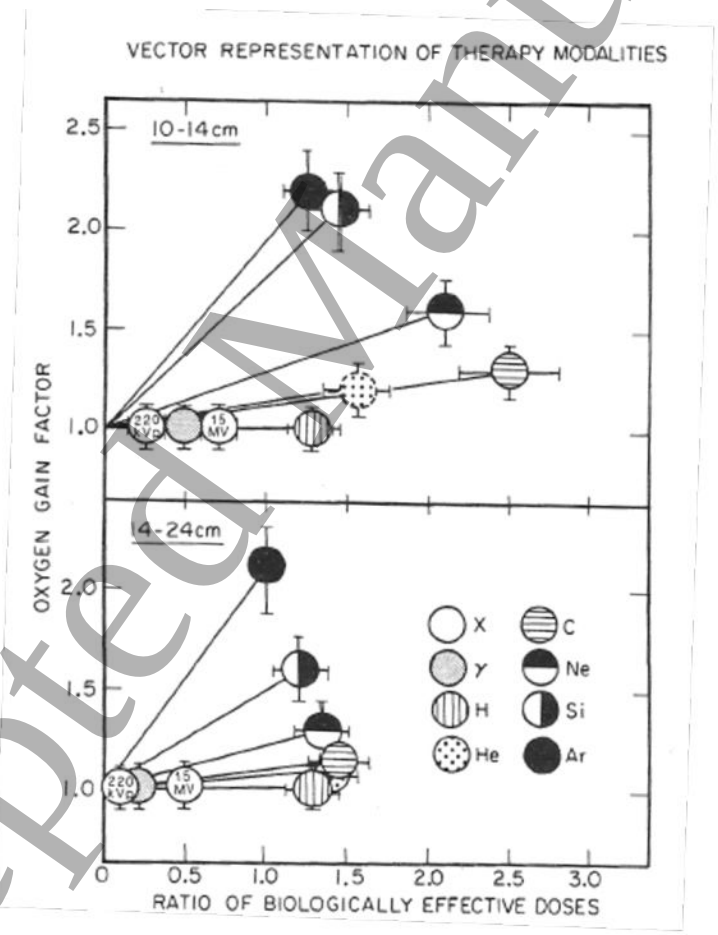

Figure 7.1. Composite vector representation of low-LET and high-LET particle therapy modalities for treatment of a small, shallow field (upper panel) and a large, deep field (lower panel). Reprinted from Blakely et al., [5] with permission from Elsevier.

Early studies at Berkeley were focused on comparing the quantitative and qualitative features of particle beam modalities. Figure 7.1 presents a vector representation of low- and high-LET radiation therapy modalities plotting published *in vitro* radiobiology data for Oxygen Gain Factor (OGF= the ratio of the OER obtained with the reference low-LET source to the OER of the test radiation modality), versus the ratio of the Biologically Effective Dose (BED) in the Bragg peak to that in the plateau. Comparisons of OGF values eliminate differences in the efficiency of oxygen removal between experimental techniques. The most therapeutically advantageous positions on the Figure are located closer to the upper right quadrant. The data indicate that for smaller, shallow target volumes, carbon is superior. For larger, deeper tumors, the 187 MeV proton beam, and the 225 MeV/u helium beams are quite similar.

Some of the questions which are pertinent to helium ions, and even all high-LET ions include: Why do two particle beams of different atomic numbers with the same ionization density or LET, show different biological effectiveness for the same biological endpoint, and even more differences for different tissue endpoints? Are there differences in clustered DNA damage and tissue radiation repair processes and immune responses in laboratory experimental model systems compared to human systems that might contribute to unexpected clinical outcomes based on treatment planning with only experimental data from the model systems? What is the role of tissue-dependent stem cell radiosensitivity? Why do three different human glioblastoma cell lines demonstrate different biological effectiveness in their LET response? Why is hypofractionation of high-LET particle beams with larger dose/fraction and lower RBE so beneficial? Once these and other issues are answered, it will be more straightforward to choose the beams most pertinent to assuring the goal of tumor eradication without collateral damage to surrounding normal tissues. The current task at hand is to decide which experiments must be accomplished with an appropriate number of replicates to answer the questions with statistical significance, despite the inherent biological variabilities between individuals. It may be that treatment plans involving more than one ion will be the most optimal.

Advances in Science and Technology to Meet Challenges

To meet the challenge of broadening the use of helium-ion radiotherapy, future research is required to elucidate more explicit information about the cell type-, tissue-, and species- specificity of the radiosensitivity, and their dependences on the ion beam, energy, dose fraction, total dose, dose rate and LET (for example see recent papers by Beyreuther et al 2019, and Suckert et al 2021, which describe modern approaches to these important challenges [34, 35]). Automation of the analysis of experimental assays and endpoints would also be useful to accomplish faster through-put of data.

Concluding Remarks

Helium-ion radiotherapy has many potential advantages as one of the most conservative particle beams, and yet effective tools in the arsenal of the radiation oncologist. To effectively make use of helium ions for human therapies it is important, even critical to expand what is known about the ion beam energy-, dose-, dose-fractionation- and dose-rate-dependent effects of helium ion beams in the entrance and spread-out Bragg peak on various normal human and animal tissues and tumour targets. This will require an expansion of both *in vitro* and *in vivo* experiments, with

selected model systems and acute and late-appearing endpoints including evaluation of the risk of second cancers, as well as theoretical modelling to inform clinicians and treatment planning physicists of the potential range of biological variability of the response to helium ion beams. Fortunately, some of this outstanding work is already ongoing at the few international facilities with access to helium ion beams, and by some of the authors contributing to this roadmap.

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8. Radiobiological phenomena of helium ions: fundamentals, features, and clinical potential

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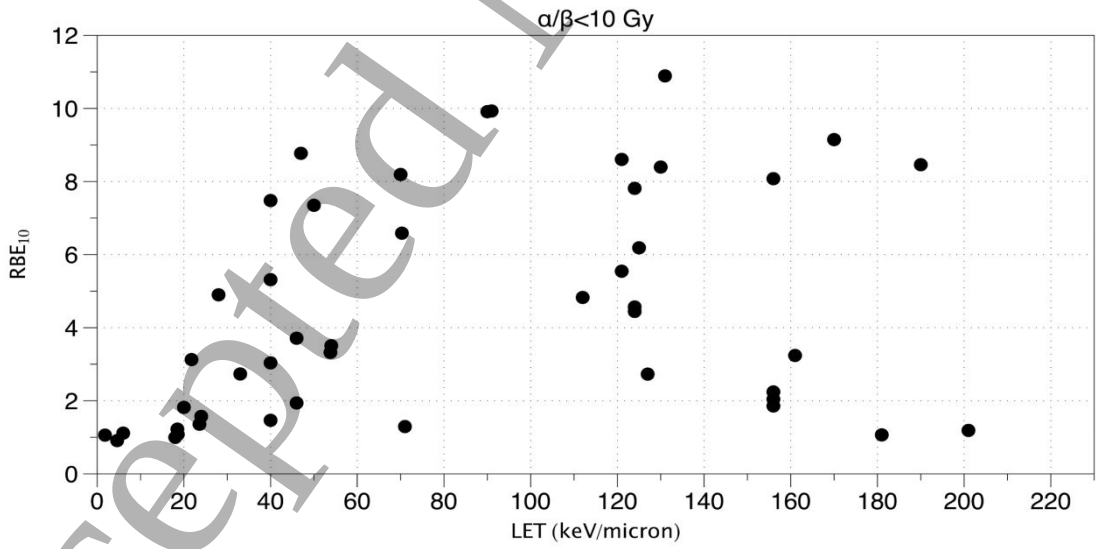
Status

Radiobiology of low-energy He-ions has been studied for about a century. In fact, α-particles sources were easily available and were largely used to measure the response of simple biological targets [1]. The literature on biological effects of α-particles is therefore enormous. Decades of experiments have convincingly demonstrated that α-particles are among the most effective radiation types in the induction of early and late biological effects. However, α-particles have an energy around 1.3 MeV/u, and therefore represent only the final microns of the path in tissue of a typical therapeutic beam that is accelerated up to around 250 MeV/u. Moreover, most studies are confined to relatively low doses, because they are relevant for radiation protection (exposure to radon and its progeny), while for radiotherapy the relative biological effectiveness (RBE) at high doses is necessary. In Figure 8.1 we have summarized the in vitro RBE data for cell killing of ^{3}He- and ^{4}He-ions available in the literature, using the PIDE database developed at GSI [2]. The RBE is calculated at 10% survival (RBE_{10}). The data for radiosensitive cells (α/β>10 Gy) are plotted separately from radioresistant cells (α/β<10 Gy) as a function of the particle LET. The results show that, similarly to the studies at low doses, the RBE can reach very high values in the α-particle range (80-200 keV/μm), especially for tissues with low α/β ratio. However, at higher energies (lower LET) the RBE_{10} is generally <2.



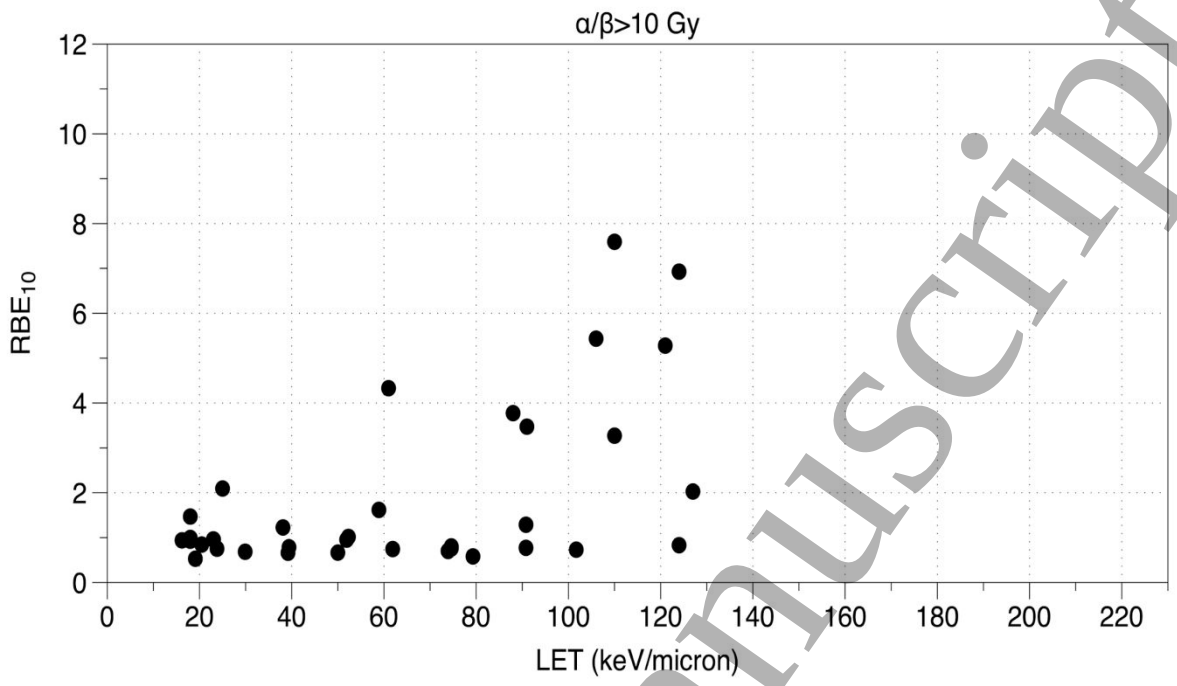


Figure 8.1. RBE calculated at 10% survival for cells irradiated in vitro with He-ions at different LET. Upper panel, radioresistant (a/b<10 Gy) cells; lower panel, radiosensitive (a/b>10 Gy) cells. Same scale is used to ease comparison of the plots. Experimental data extracted from the PIDE database, available online at www.gsi.de/bio-pide.

From the radiobiology point of view, He-ions at therapeutic energy are therefore intermediate between protons [3] and C-ions [4], the only two ions currently used in clinical practice. This should apply not only the RBE for cell killing but to the other radiobiological properties as well, such as oxygen enhancement ratio (OER), dependence on fractionation, cell-cycle stage etc.

Current and Future Challenges

Currently treatment planning in particle therapy takes little into account radiobiology. Only the RBE is included. For protons, tumors are exposed to a constant dose calculated as D(Gy)xRBE, using a constant RBE=1.1 along the spread-out-Bragg-peak (SOBP) [5]. For ^{12}C-ions, the variation of the RBE along the SOBP is taken into account modifying the physical dose with appropriate RBE models to achieve a uniform RBE-weighted dose in the target volume [6]. The use of a constant RBE in proton therapy is generally acknowledged to be a rough approximation, because it is well known that low-energy protons have an RBE higher than 1.1 [7], actually even higher than He-ions at the same LET values [8]. A constant RBE approximation may be even more problematic, considering that at the distal edge of the SOBP the energies are those of α-particles. This can be an advantage even compared to C-ions, where at the distal SOBP edge the LET is so high to enter in an overkill region, whilst for He it will reach the maximum radiobiological effectiveness. For the radiobiology of helium ions in therapy the challenges will be to:

a) develop a good RBE model;

b) develop appropriate normal tissue complication (NTCP) models, possibly including radiogenomics data;
c) verify the OER of the He-beams;
d) study the combination of helium with targeted therapy and immunotherapy;
e) optimize the LET distribution of helium in beam delivery.

About the point a), it has been already shown that TRiP98 [9], the treatment planning system used in Europe for C-ion therapy, shows a good agreement with the experimental in vitro cell survival data along the SOBP [10] (Figure 8.2). The stochastic microdosimetric kinetic (SMK) model [11], a modified version of the microdosimetric kinetic model (MKM) used for C-ion therapy in Japan [12], also carefully reproduce in vitro experimental survival data after exposure to He-ions [13]. Therefore, RBE modelling frameworks for He-ions with reasonable accuracy are already available. The other points mentioned above are more challenging and require more research.

Advances in Science and Technology to Meet Challenges

As noted above, the assessment of the biological effectiveness of He-ions can be done quite safely with the current models already used on C-ion therapy. The main issue with He-ions will be to assess their biological properties beyond the RBE, a modern issue shared with particle therapy using other ions [3,4]. A second challenge will be to test whether the approach of a uniform RBE-weighted dose (Figure 8.2), currently used in C-ion therapy, is the best choice for He-ion therapy. In fact, a constant target dose is not necessary in modern radiotherapy. Many protocols with stereotactic body radiotherapy (SBRT) result in a strong overdosage in the target center, and some clinical studies are using partial-tumor irradiation [14]. A recent retrospective analysis on the C-ion treatment plans at NIRS suggest that the LET is positively associated to local control of pancreas tumors. In particular, patients with higher minimum dose-averaged LET values in the gross tumor volume had lower probability of local failure compared to those with minimum LET values below 40 keV/μm [15]. Considering that Bragg peak He-ions have LET around the maximum effectiveness (Figure 8.1), characteristic of α-particles, we may lose biological advantages of He-ion therapy using a constant dose rather than a high-LET all over the target volume.

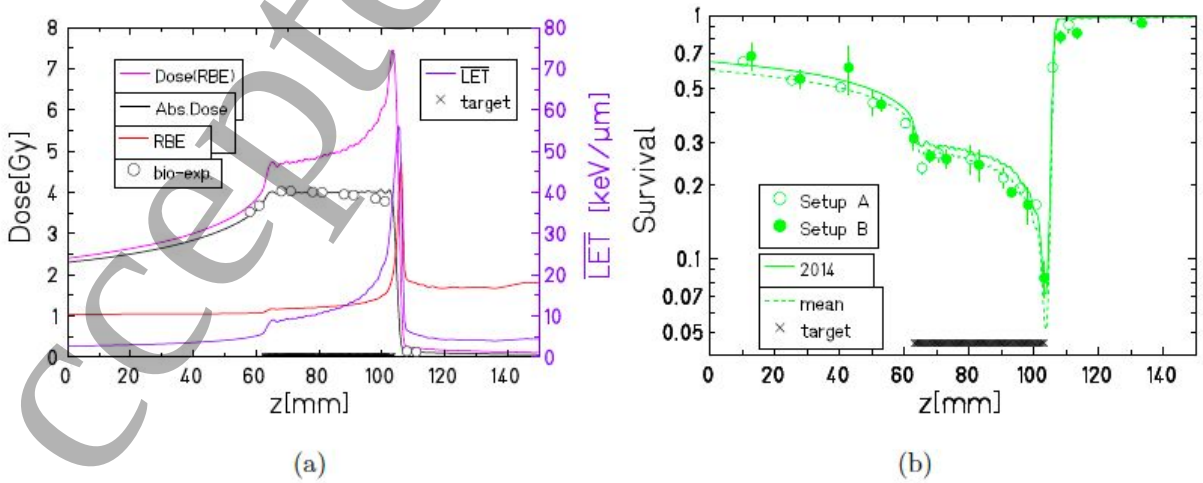


Figure 8.2. Depth profiles for the biological verification of a ^{4}He-ion beam accelerated at HIT

(Heidelberg) using a Chinese hamster ovary (CHO) cell phantom. The target volume is cantered at 82 mm depth, and covers a depth range of 40 mm. (a) Calculated absorbed dose, RBE-weighted dose, RBE, and dose-averaged LET depth profile. The symbols represent absorbed dose measurements performed with a set of 24 pin-point ionization chambers. (b) Depth survival profile of CHO cells in the phantom. Circles are clonogenic survival measurements and standard errors from two different experiments. The two curves are predictions of the LEM model using different a/b ratios of the reference radiation. Plot from ref. [10], reproduced with permission of the American Association of Physicists in Medicine and John Wiley & sons ltd. under creative commons attribution license (CCBY 4.0).

Concluding Remarks

Radiobiology of low-energy He-ions is very well known, and it has been shown many times that α-particles are the most effective natural radiation in causing biological effects. At high, therapeutic energies, it is expected that He-ions will have biological properties somewhere in between protons and carbon ions. However, unlike protons, He-ions can reach significantly high-LET values; and, unlike C-ions, the distal part of the SOBP is not reaching LET values in the overkill region. In other words, the He-ions Bragg peak is somewhat ideal to exploit high-LET radiobiology. This will require a different concept of beam delivery, aiming to increase the dose-averaged LET and dropping the dogma of a uniform RBE-weighted dose along the SOBP. Current models used in C-ion therapy seem to accurately describe the RBE of therapeutic beams of He-ions, within the high biological uncertainties. Far less is known about other radiobiological properties such as OER, effects in the microenvironment, fractionation dependence, and interaction with drugs such as those used in targeted therapy or immunotherapy.

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9. In vitro and in vivo biological readouts and indications for guiding clinical practice with helium ions

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Status

As discussed in the previous sections, clinical experience with helium ions has been gained at LBNL in 2054 patients (www.ptcog.ch) and promising results have been obtained for some indications (1) (see "Section 7" on LBNL experience). Similar to other ions, dose prescription in helium ion treatments requires assumptions about the RBE and at LBL, the applied RBE was 1.3 for most tissues and 1.6 for tissues of the late responding central nervous system (1). During the LBL project, RBE-measurements for helium ions have been performed in various cell lines (2), mammary and rhabdomyosarcoma tumor models (3,4), normal tissues such as skin and spinal cord (5), intestinal crypt cells, testis and for various endpoints in other *in vivo* systems (4).

Due to the shutdown of the accelerators, clinical studies at LBL had to be terminated. However, ion beam radiotherapy accompanied by radiobiological studies were pursued at various other institutions focusing on protons as low- and carbon ions as high-LET radiation modality. Since then, a large number of *in vitro* and *in vivo* studies have been published for these ions. With increasing clinical experience, however, the question initially addressed at LBL, which ion is best for radiotherapy, was raised again and the Heidelberg Ion Beam Therapy Center (HIT) was explicitly designed to investigate different ion beams including helium (6). In addition, HIT and the National Center of Radiological Sciences (NIRS) investigated the possibility of multi-ion irradiations including helium beams (7,8) and also other researchers are exploring helium ions (9). Especially the improved treatment planning and beam delivery techniques are considered as a possibility to improve the early results from LBL. Addressing the renewed interest in helium ions, systematic RBE-measurements in cell lines and comparison with model predictions have been performed at HIT (8,10). In addition, radiation response studies in the rat spinal cord were extended to helium (unpublished data). In spite of these preparatory experiments, the available experimental data and the attempts to validate the RBE-models are still very limited. To better understand the biological effectiveness of helium ions, additional preclinical studies especially in normal tissues and tumors are required.

Current and Future Challenges

Although some clinical experience as well as experimental data are available, there are still a number of limitations posing challenges for clinical use of helium ions:

(i) Previous clinical and experimental data at LBL have been obtained with passively modulated beams while contemporary facilities use beam scanning. This may alter beam quality and introduce uncertainties in the transfer of biological data.

(ii) As the experiments at LBL were not designed to benchmark RBE-models, which were not available at this time, relevant input parameters such as the fluence distribution of primary and secondary particles are not available. The data from LBL are therefore not suited for retrospective RBE-calculations and testing current RBE-models.

(iii) Since the early experiments focused on the comparison of different ion types using single representative positions in the plateau and SOBP, systematic studies of the RBE-dependence on treatment parameters like LET and doses are lacking. These data, however, are important to empirically optimize treatment schedules as well as for comparisons with model predictions.

(iv) While some peak-to-plateau ratios for RBEs (and OERs for tumors) were measured at LBL, these studies focused on heavier ions such as carbon, neon and argon rather than helium and the differential biological effectiveness between tumors and normal tissues has only rarely been addressed.

(v) Naturally, the early data do not reflect recent advances in experimental *in vitro* and *in vivo* models, dosimetry, treatment planning, RBE-modeling and beam delivery as well as in molecular biological analysis methods.

Recent technical advancements do not only allow for a better planning of the experiments and a more accurate delivery of absorbed dose and the obtained results can also be closer connected with treatment planning and RBE-modeling procedures. In contrast to the early studies at LBL, new and well-designed studies with helium ions especially enable for developing and testing of RBE-models, for prescribing the RBE-weighted dose more accurately and in the long term also to improve TCP/NTCP calculations, the latter being still an important research topic also for other ions. With the new studies, a comprehensive data basis for the effectiveness of helium ions has to be established covering the range of all relevant treatment parameters, different cell lines as well as normal tissue and tumor models similar to the efforts that have been and are still being taken for protons (see “Section 11” on proton RBE) and carbon ions (11,12).

While *in vitro* and normal tissue data may be used to benchmark RBE-models, data from experimental tumors may serve to identify tumor-associated factors that impact the RBE, but which are not considered in RBE-models. Important examples are tumor hypoxia or radioresistant cellular subpopulations, which both may compromise tumor control. A better understanding of these factors may help to determine patient eligibility for helium treatments relative to established clinical indications for carbon ions or protons, or even to improve RBE-models by including these parameters. With this respect, the existing data from LBL may be used as valuable guidance for the experimental design as well as for dose finding.

Advances in Science and Technology to Meet Challenges

Given the goal of clinical introduction of helium ions and the present limitations of the available radiobiological data, research on the biological effectiveness of helium ions needs to be strengthened and intensified. To promote this process, several organizational, technical as well as scientific challenges have to be met. As the required amount of radiobiological data is largely independent of the number of institutions that plan to use helium ions, the availability of sufficient facilities providing helium ion beams is important. These helium beams have to be commissioned at least in terms of beam delivery, dosimetry and physical treatment planning [see Weber, Ferrari and Fuchs sections] to enable accurate dose delivery in radiobiological studies. In addition, equipment for accurate and efficient positioning of cellular samples and animals is required. For high-throughput cell experiments, a dedicated robot is advantageous (13). As radiobiological studies are usually performed by specialized experimenters, helium facilities should provide access to external researchers and support their experiments logistically by lab space or animal

housing, dosimetry as well as planning and execution of the experiments. For comparison of measurements with model-based RBE-values (see “Section 10” on RBE modeling), the spectral fluence of primary and secondary particles (see “Section 3” on physics measurements and “Section 6” on helium ion imaging) has to be provided in a readable format. Regarding the type of experiments, it is most important that studies are performed in a systematic way to cover especially the clinical range of the LET- and dose-dependence of the RBE. The aim should be to build-up a comprehensive and consistent dataset. To reflect also the dependence on biological factors, different cell-lines should be employed. As *in vitro* experiments reflect the radiation response only under rather artificial conditions, neglecting the interaction of different cell types in real tissue, supplementing dose response experiments in early- and late-reacting normal tissues are inevitable. Both types of experiments are necessary to determine the main dependencies of the RBE as well as to benchmark model predictions. Besides this, experiments in tumor models are required to assess the expected clinical efficiency of helium ions and to stratify patients with different tumors to treatments with different ion beams. While only the very early experimental tumor studies from LBL are available for helium (3,4), the response of different prostate tumor sublines has been systematically investigated after single and fractionated carbon ion doses (14). Further tumor studies are required for all ion species including helium. In this context, also OER-measurements are of high clinical importance. Ideally, the design of these experiments will be the same as for previous and upcoming experiments with carbon ions to allow direct comparisons. Finally, combination of normal tissue and tumor data should allow analyzing the differential RBE between both tissue types.

Concluding Remarks

Since early patient treatments and radiobiological studies at LBL, treatment planning and delivery techniques, dosimetry and RBE-models for helium ions have advanced significantly. Re-establishing ion beam irradiation nowadays in patients requires a comprehensive RBE dataset as a function of LET and dose in different cell lines as well as in different normal tissue and tumor models. Besides availability of facilities with commissioned helium beams, this requires access as well as logistic and scientific support of external experimenters to carry out experiments. Measurements should allow a characterization of the RBE-dependencies, comparison with model predictions and assessment of tumor response and its dependence on biological parameters. The acquired data will help to establish the model-based RBE-depth profile and to estimate the prescribed dose level for patient treatments. Altogether, this will improve our knowledge on the biological effectiveness of helium in comparison to carbon ions and protons.

Acknowledgements

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10. Effective dose and RBE modelling for helium-ion radiotherapy treatment planning: progress and recommendations

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Status

Biological effectiveness of helium-ion beams is higher than that of conventional photon radiations [1]. To optimally use their biologic advantage in clinical practice, a clinically relevant dose, i.e., effective dose, which is defined as the product of the absorbed dose and the RBE, should be calculated in treatment planning of helium-ion radiotherapy. In pioneering studies performed at the LBNL, more than 2000 patients of various tumor sites were treated with helium-ion beams using a passive beam delivery [2, 3]. In their works, constant RBE values across the target volume ranging from 1.2 to 1.4 were used for the tumor sites independent of beam configuration, target depth, and dose level [2, 4]. The constant RBE assumption was appropriate at the time, since little was known about the clinical effectiveness of helium-ion beams, primarily due to the complexity of the RBE mechanism. However, this assumption of a constant RBE is questionable even for low LET proton beams [5]. In the case of helium-ion beams with higher LET, significant variations of the RBE with depth in the SOBP region have been reported for several cell lines such as Chinese hamster ovary cells (CHO-K1) [6] and human alveolar adenocarcinoma cells (A549) [7]. The depth-survival and depth-RBE distributions of A549 cells exposed to the SOBP helium-ion beam are shown in figure 10.1. The RBE value increased with depth, taking the maximum of about 4 at the distal region of the SOBP. The constant RBE assumption is thus no longer appropriate, and spatial variations of RBE have to be considered in helium-ion radiotherapy treatment planning for individual clinical cases based on RBE models.

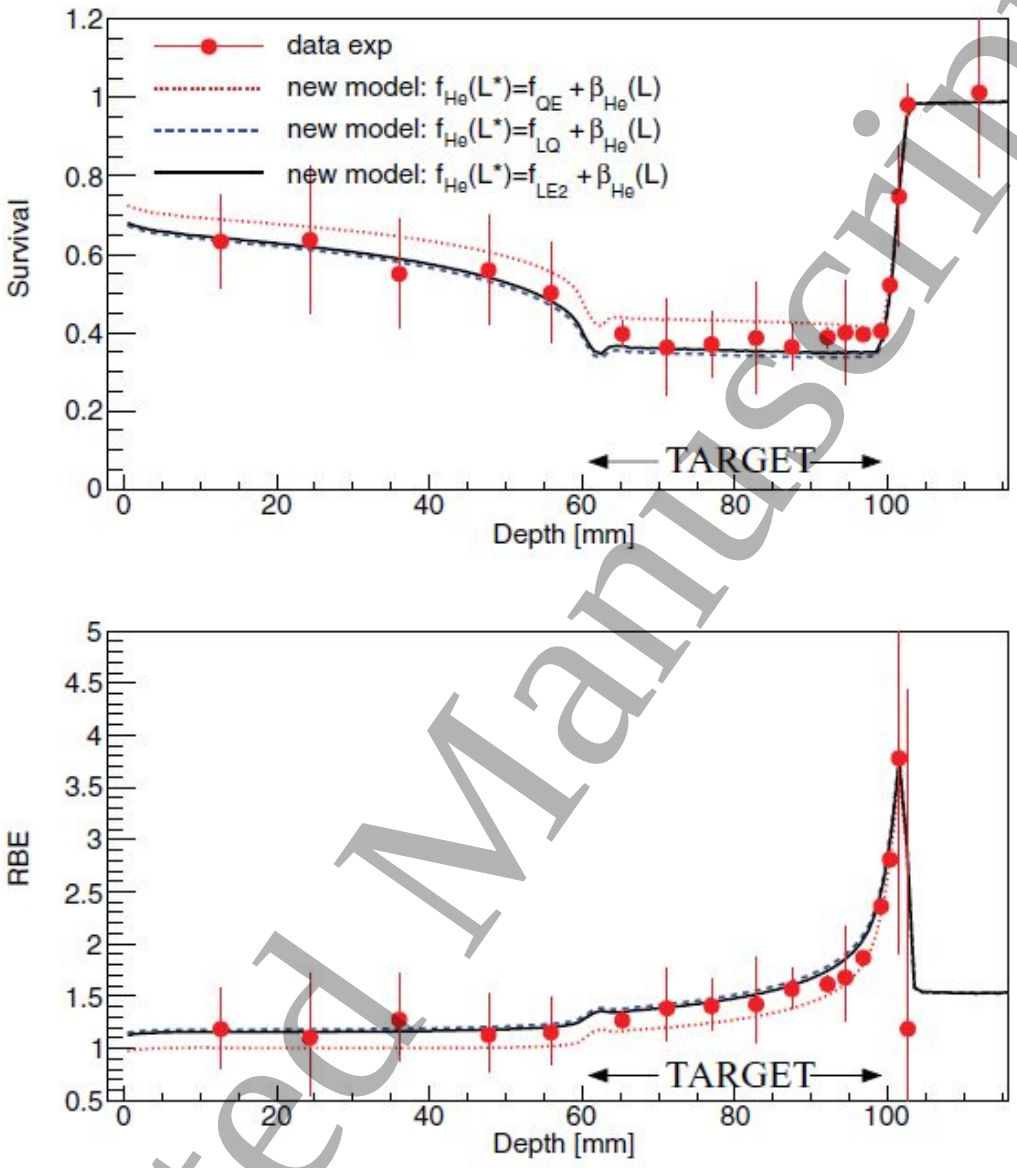

Figure 10.1. Cell survival (upper panel) and RBE (lower panel) values of A549 cells exposed to a SOBP helium-ion beam as a function of depth in water. The black solid curve is the calculated survival and RBE values with the data-driven phenomenological model (DDM) developed by Mairani et al (2016) [7].

Current and Future Challenges

Currently, there is no consensus as to which RBE model is best suited for the treatments with helium-ion beams. Ideally, the RBE model is established and tuned to *in vivo* and clinical data of helium-ion beams. However, such data for helium-ion beams are scarce. Therefore, it seems a practical way is to establish and tune the RBE model so as to reproduce relatively abundant *in vitro* data, and then to validate the established RBE model against *in vivo* and clinical data (reference to Karger section), as has been done in carbon-ion radiotherapy [8]. Three existing

RBE models have been tested to predict *in vitro* cell responses exposed to mono-energetic and clinically-relevant SOBP helium-ion beams [9]. The models were a data-driven phenomenological model (DDM) [7], the local effect model (LEM, version IV) [9], and the modified microdosimetric kinetic model (MKM) [10, 11]. The DDM parameterizes *in vitro* experimental data of protons and helium ions available in the literature as a function of LET, and predicts the RBE of therapeutic helium-ion beams using the parameterizations. Both LEM and MKM are mechanistic models based on the microscopic dose distribution patterns. Mechanistic differences between the models have been discussed elsewhere [12].

The three RBE models could reasonably reproduce the *in vitro* experimental data of helium-ion beams [9]. This may imply that the accuracy in the prediction of RBE for therapeutic helium-ion beams is not primarily influenced by the choice of the RBE model, but instead influenced by the choice of the *in vitro* dataset and the methodology used for tuning the RBE model parameters. These models, however, differ greatly from the viewpoints of applicability to other ion species as well as capability for tissue-dependent RBE calculations. As the DDM is parameterized specifically to protons and helium ions, this model cannot be used to predict the RBE of other ion species. On the other hand, the LEM and the MKM with no ion-species-specific parameters are, in principle, applicable to the RBE prediction of other ion species. This is particularly important in future developments of multi-ion therapy, where two or more ion species including helium ions are delivered in a treatment session to maximize the therapeutic effects of ion beams [13, 14]. In carbon-ion radiotherapy treatment planning, for simplicity, a single-tissue approximation has been applied for RBE calculations. The RBE of ion beams should be ideally calculated for respective tissues in accordance with their radiation sensitivities. The DDM and the MKM can reflect the tissue-dependent radiation sensitivities into the RBE calculations in terms of the linear and quadratic parameters of the LQ model for photon radiation, α_x and β_x, without any cell-specific tuning of the model parameters [11]. In the LEM, contrarily, an explicit tuning of one model parameter, namely a transition dose D_t, is required for each cell line to reproduce *in vitro* data with sufficient accuracy. These characteristics of the three RBE models are summarized in table 1.

Table 1. Characteristics of the RBE models, i.e., the DDM, the LEM, and the MKM.

	DDM	LEM	MKM
Accuracy in RBE prediction of helium-ion beams	Accurate	Accurate	Accurate
Applicability to other ion species	Inapplicable	Applicable	Applicable
Tissue-dependent RBE prediction	Easy to do	Not easy to do	Easy to do

Advances in Science and Technology to Meet Challenges

So far, the MKM seems to be the best RBE model for helium-ion radiotherapy from the perspective of accuracy and extensibility. The MKM exhibited better agreement to *in vitro* and *in vivo* experimental data of carbon-ion radiotherapy as compared to the LEM [8]. Microdosimetric measurements using a tissue equivalent proportional counter (TEPC) or a silicon-on-insulator

(SOI) detector combined with the MKM allow the verification of the RBE and/or effective dose distributions [15]. These factors may also justify the selection of the MKM for upcoming treatment programs, e.g., helium-ion radiotherapy and multi-ion radiotherapy. However, it is still challenging to make definitive statements about the best RBE model for helium-ion radiotherapy due to the lack of experimental data. Collecting additional *in vitro* and *in vivo* experimental data for helium-ion beams under various conditions is essential in the future, in addition to the accumulation of clinical data.

The RBE of helium-ion beams depends on various physical and biological parameters such as radiation quality, dose level, dose-rate, irradiation geometry, type of tissue or cell, oxygen conditions, and endpoints of interest. Ideally, these parameters should be incorporated into the RBE models. Recently, some studies tried to incorporate the effects of hypoxia into RBE models [16, 17]. However, none of the RBE models including the MKM can perfectly deal with all these parameters, resulting in uncertainties in the RBE predictions. In addition, systematic uncertainties in RBE predictions must arise from the difference between *in vivo* and *in vitro* responses. Consecutive efforts must be paid to reduce these uncertainties. The choice of the RBE model and tissue type for effective dose calculation is ultimately a clinical decision to ensure the safest and most effective patient treatments. However, assessments of the clinical data as well as the continuous refinements of the RBE models are essential even after initiation of the clinical practice of helium-ion radiotherapy.

Besides the developments of accurate RBE models, high quality macroscopic and microscopic dosimetric quantities are requisite for accurate RBE predictions. The developments of accelerated and accurate calculation codes of these dosimetric quantities in patient are important as discussed in section 5. Developments of imaging modalities providing noninvasive means to quantify the spatial and temporal distributions of radiosensitivity in tumor are also indispensable to realize biologically driven personalized treatments.

Concluding Remarks

Spatial variations of RBE have to be considered in helium-ion radiotherapy treatment planning for individual clinical cases based on RBE models. The RBE model should be selected from the perspective of accuracy and extensibilities. In this regard, the MKM seems to be the best RBE model among three existing RBE models, i.e., DDM, LEM, and MKM. However, none of the RBE models can perfectly deal with all parameters affecting the RBE of therapeutic helium-ion beams, resulting in uncertainties in the RBE predictions. The choice of the RBE model and endpoint for effective dose calculation is ultimately a clinical decision to ensure the safest and most effective patient treatments. Collection of additional *in vitro* and *in vivo* experimental data, assessment of the clinical data as well as continuous refinements of the RBE models are essential even after initiation of the clinical practice of helium-ion radiotherapy.

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Part C: Clinical Perspectives

11. Challenges and remarks on the proton therapy experience with constant RBE

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Status of RBE considerations in proton therapy

In proton therapy both tumor prescription doses as well as constraints to organs at risk are based on scaling photon doses with a constant RBE of 1.1. The value is based on average RBE values measured in-vivo relative to Co^{60} in the center of a spread-out Bragg peak for various endpoints such as skin reaction or LD_{50} (Paganetti, Niemierko et al. 2002). It was chosen as a lower boundary because the main goal was to ensure that patients would receive the desired prescription dose based on experience with photon therapy. Elevated RBE values are expected particularly at the end of range where the linear energy transfer (LET) is increasing when protons decelerate. Consequently, it is likely that most tumors will experience a higher RBE at the distal part of a spread-out Bragg peak (SOBP) field. Furthermore, organs at risk close to the distal edge might experience elevated RBE values. In intensity-modulated proton therapy using multi-field uniform dose optimization, regions of elevated RBE are not as easy to predict but would still be predominantly in the periphery of the target. The magnitude of RBE variations depends on the biological endpoint. As a rule of thumb, for cell survival in vitro at 2 Gy, the estimated average RBE is about 1.15 and 1.35 in the center and distal edge of a typical SOBP increasing further in the distal fall-off (Paganetti, Niemierko et al. 2002, Paganetti 2014).

One reason why treatment planning in proton therapy neglects RBE variations is because our current knowledge on variations in RBE is largely based on measurements of clonogenic cell survival in vitro. However, while these data may not be suitable for treatment plan optimization, they may be employed in retrospective data analysis to estimate potential magnitude of RBE effects. Figure 11.1 shows RBE values using an empirical model based on parameterized fits of published experimental data on clonogenic cell survival (McNamara, Schuemann et al. 2015). Various RBE values for endpoints other than cell survival have also been measured in vitro and in vivo but results are sparse and inconsistent. RBE studies based on patient data are in its infancy due to limited data sets and generally low incidents of toxicities. Even variations of 20% might be hidden under patient specific radiosensitivity if treatment scenarios involve mainly the shallow upper and lower regions in the dose response curves for tumor control probability and normal tissue complication probability, respectively. There is increasing concern that proton RBE for normal tissue injuries may be underestimated significantly, leading to some unexpected toxicities (Haas-Kogan, Indelicato et al. 2018). There is anecdotal evidence that toxicities seen with protons might be more severe but not more frequent compared to photon therapy. A potential explanation might be that patient variability is magnified by RBE effects (Paganetti 2017).

In recent years, particularly brain and brainstem necrosis in proton therapy patients have been the focus of numerous studies, some of them suggesting a significant dependence of toxicity occurrence with regions of elevated LET (Peeler, Mirkovic et al. 2016, Eulitz, Troost et al. 2019, Bahn, Bauer et al. 2020). Unfortunately, these studies are inconclusive because of the small sample size, because the correlation of voxels from the same patient is not considered, and because high LET regions are typically in the periphery of the target where high doses will also increase the likelihood of toxicities. In a recent study analyzing 50 adult patients individually, no correlation of elevated RBE in necrotic regions was seen (Niemierko, Schuemann et al. 2020). This may not be surprising considering that necrotic regions evolve and expand over time so that correlations with LET might be weakened. Most importantly, it seems as if RBE variations in proton therapy are smaller than patient variations in radiosensitivity. On the other hand, retrospective qualitative and quantitative analyses of late-phase asymptomatic lung-density changes (indicative of asymptomatic fibrosis) for a small cohort of breast cancer patients irradiated to the chest wall suggested proton RBE values potentially even exceeding 3.0 (Underwood, Grassberger et al. 2018) for 2 Gy/fraction but an RBE on the order of 1.1 in a cohort of hypofractionated patients suggesting significant dose dependency (Li, Dykstra et al. 2019). Interestingly, there were differences in the time course of the inflammatory response after proton compared to photon SBRT indicating differences in inflammatory response even if the RBE might be close to 1.1.

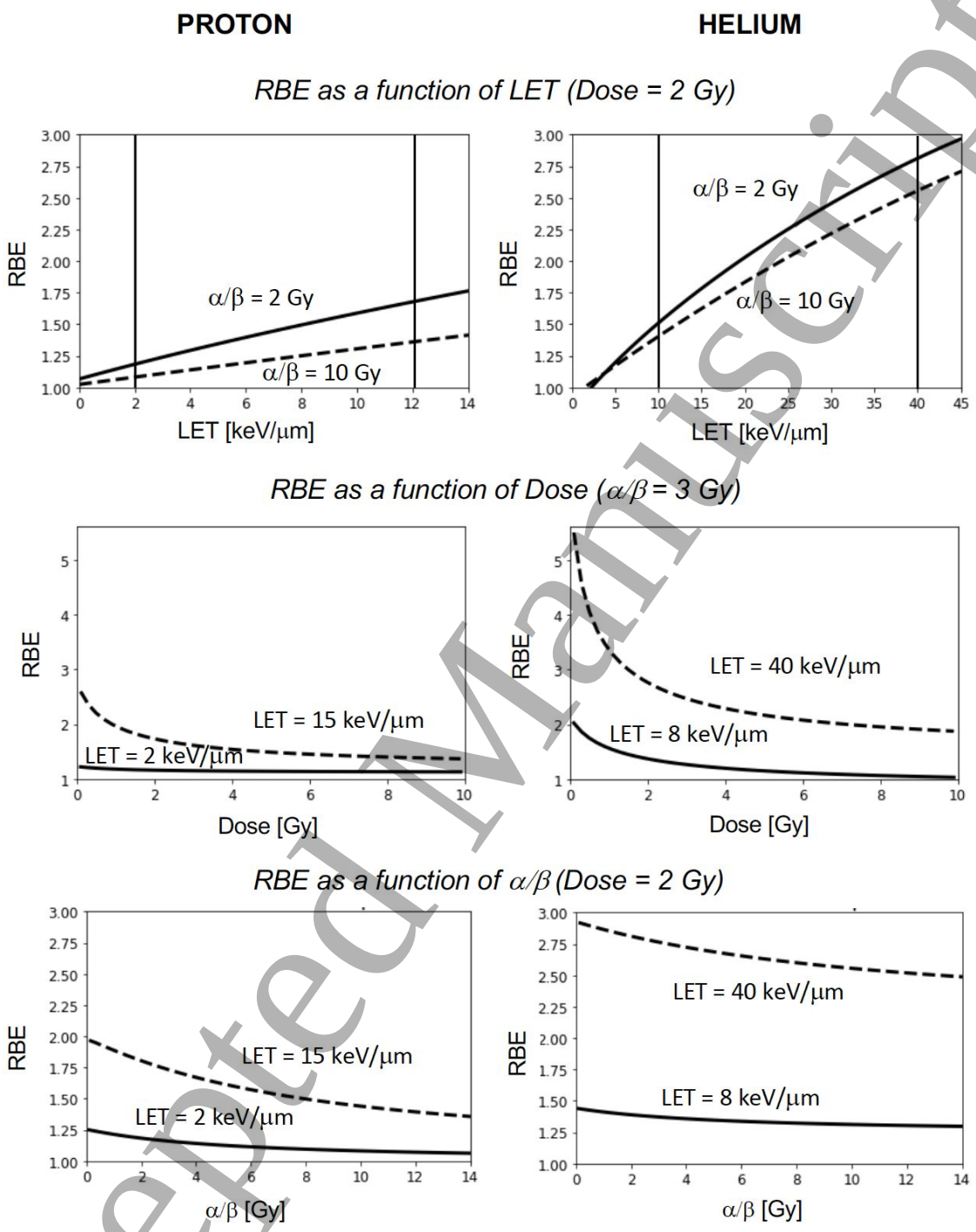

Figure 11.1: RBE values for proton (left column) and Helium ions (right column) for clonogenic cell survival as predicted by empirical models (McNamara, Schuemann et al. 2015, Mairani, Magro et al. 2016). Upper: RBE as a function of LET_d at 2 Gy for two different $(\alpha/\beta)_x$ values. The vertical lines indicate most likely values in the entrance and exit region of an SOBP. Middle: RBE as a function of dose for $(\alpha/\beta)_x$=2 Gy for two different LET_d values corresponding to entrance and exit regions of an SOBP. Lower: RBE as a function of $(\alpha/\beta)_x$ for a photon dose of 2 Gy for two different LET_d values corresponding to entrance and exit regions of an SOBP.

As more patients are being treated, assessing RBE effects in patients will be feasible with higher level of statistical significance. This will likely result in a revision of current clinical practice. Whether this will be done based on empirical models or simply by adjusting photon-based dose constraints and prescriptions remains to be seen. Since we do except RBE values to increase in areas of elevated LET and since we are capable of predicting LET maps in patients, the short term strategy in treatment planning should be to avoid elevated LET values in critical areas of organs at risk by including LET in treatment optimization. Feasibility has been demonstrated in intensity modulated proton therapy (Unkelbach, Botas et al. 2016).

Current and Future Challenges for Helium Ion Therapy Based on Proton Experience

The experience from proton therapy can only to some extend help guide the consideration of RBE in Helium ion therapy as the magnitude of RBE effects differs. Other than in proton therapy, the use of a constant RBE seems clinically unreasonable. The current knowledge of RBE from Helium beams is more limited compared to protons (and even Carbon ions). Despite uncertainties, similar to empirical modeling approaches in proton therapy, fits have been applied to Helium ion data. Figure 11.1 shows the results from such an empirical model (Mairani, Magro et al. 2016). The overall trend of RBE for clonogenic cell survival in vitro is very similar as with protons, albeit with significantly higher absolute values. Noteworthy, as in proton therapy, RBE as a function of LET in the region of interest seems to be monotone and not reaching the overkill region as with Carbon ions. The RBE as a function of LET shows an increase in RBE across a typical spread-out Bragg peak of ~25-40% for protons compared to about a factor of 2 for Helium ions. Interestingly, the percentage change in RBE as a function of α/β at the distal fall-off is somewhat smaller in the case of Helium but this would likely be offset by the much stronger dose dependency. More experiments are needed to improve our understanding of RBE in vitro and in vivo aiming at minimizing uncertainties for well-defined tumor types and critical structures. In proton therapy, patient variability might be in the same order of magnitude as RBE variations and uncertainties (Niemierko, Schuemann et al. 2020). For Helium ions, variations might go beyond patient variability due to the overall higher RBE values. These estimations assume treatments with 2 Gy per fraction. The future will likely see more treatments using hypofractionation, particularly for sites such as liver or lung (Laine, Pompos et al. 2015). Considering that more aggressive hypofractionation schedules might be applied with heavier ions, this might slightly decrease the relative RBE effects between the two modalities.

Proton therapy is currently mainly employing empirical models. This is different, for instance, in Carbon ion therapy because complex radiation fields require models that go beyond simply characterizing the radiation at a given voxel by the LET. Consequently, Carbon ion therapy employs models such as the LEM model, which has also been used for Helium ions (Elsasser, Weyrather et al. 2010). The radiation field with Helium ions is less complex than with Carbon ions, involving mostly Helium and protons (Kempe, Gudowska et al. 2007). While there are different RBE-LET relationship of alpha particles and protons with protons having higher biological effect than alpha particles of the same LET (Mairani, Dokic et al. 2016), it seems feasible to use an empirical model such as shown in Figure 11.1, at least as an estimate to guide treatment

optimization. This would allow considering Helium RBE as a function of a single LET value. Furthermore, other than with Carbon ions, Helium ions do not reach the overkill at high LET values in regions of significant dose so that an increasing RBE with LET can be safely assumed.

Advances in technology to meet challenges

Obviously, in proton as well as Helium ion therapy one would ideally incorporate RBE models in treatment planning optimization (see “Section 10” on RBE modeling). This has been realized in Carbon ion therapy with models such as the LEM. As models are not fully mechanistic, their uncertainties have to be balanced against overall RBE variations. Because in proton therapy RBE variations for most scenarios are believed to be in the same order as patient specific radiosensitivity variations and uncertainties in model predictions, RBE models have so far not been used. In order to develop more accurate models we not only need more experimental data for relevant cell lines, it is also desirable to develop these models towards a more mechanistic implementation and consideration of patient specificity (Ingram, Warmenhoven et al. 2019). Also, measurements on more fundamental endpoints are needed and potentially incorporated in more mechanistic models (see “Section 7”, “Section 8” and “Section 9” on key experiments, radio-biological phenonema and read-outs).

Most patients worldwide are treated with conventional radiation therapy, even in most centers that have proton or ion therapy facilities. The limited capacity asks for stratification and identifying patients that benefit most from protons, Helium or Carbon ions. While this depends on many factors, RBE considerations may play a role as well. Biomarkers have to be developed to identify individual patients with, for example, high tumor RBE. RBE depends not only on dosimetric factors such as fractionation and LET, but also on genomic characteristics of cells. For instance, a subset of human cancers have defects in DNA repair pathways that may influence RBE (Rostek, Turner et al. 2008, Grosse, Fontana et al. 2014, Liu, Ghosh et al. 2015). Predictive biomarkers of RBE could thus be helpful to predict RBE variations amongst patients and could identify patients that will benefit most from ion therapy (Willers, Allen et al. 2018). More studies on genomically characterized human cancer cell lines and normal human tissue are desirable using, for example, human tumor cells implanted in immune-deficient animals.

To increase our understanding of RBE values in patients, the analysis of outcome data using blood and imaging biomarkers is urgently needed. Particularly for healthy tissue, retrospective investigations on toxicity are currently based on a limited number of patients. Independent of RBE considerations between treatment modalities, dose-response relationships should not be solely analyzed based on organ contours but on sub-regions (Palma, Monti et al. 2019). It is known that classical NTCP models based on contoured structures may work well for photon treatments but may have less predictive power in proton or ion therapy with sharper dose gradients and many critical structures only partly in the irradiated field. For outcome modeling, the inhomogeneous dose distributions with proton or ion therapy will allow sub-region analysis based on a voxel-based approach in order to identify sensitive areas in organs independent from drawn contours (Palma, Monti et al. 2019, Palma, Monti et al. 2020). This will not only benefit outcome modeling for ion therapy but also conventional therapy. Moving forward, machine learning techniques will be increasingly used in this context (Ibragimov, Toesca et al. 2020).

Another challenge to the RBE concept in protons, Helium as well as Carbon ion treatments are the increasing number of treatment modalities being used in the adjuvant or neoadjuvant setting. Particularly drugs targeting specific tumor sub-populations or repair pathways can impact RBE (Konings, Vandevoorde et al. 2020). Immune therapies may require not only to understand RBE in tissues but also RBE for circulating lymphocytes. In the future it will become more important to understand these synergies and not perform dose scaling based on RBE values alone.

Concluding remarks

A constant RBE of 1.1 is an appropriate average value for ensuring tumor control in proton therapy but it likely underestimates RBE in regions of normal tissue. In the near future, LET based optimization is expected to account for variations in RBE mostly in normal tissues. In contrast, due to more significant variations in RBE, biological optimization based on RBE models is being conducted in Carbon ion therapy. The latter is certainly necessary in Helium ion therapy as well. However, some lessons can be learned from proton therapy. For instance, as an approximation, treatment optimization based on LET might be feasible in Helium ion therapy considering the limited complexity of the radiation field. In the long term, more mechanistic models are desired for proton as well as ion therapy.

In the meantime, retrospective and prospective outcome studies have to be prioritized in proton, Helium and Carbon ion therapy. In vitro studies are certainly valuable if focused on understanding biological mechanisms.

Treating patients with helium ions in addition to proton and Carbon ion therapy will increase the variety of dose and RBE distributions in patients. Furthermore, it will certainly lead to increasing efforts using laboratory systems. While this increase in variety might hamper statistically significant findings it also presents a chance to utilize different probes to assess mechanisms of RBE.

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12. Clinical directions with helium ions

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Status

According to the latest patient statistics published by the Particle Therapy Co-Operative Group (PTCOG) approximately 260.000 patients have been treated with (heavy) charged particles until December 2019. The predominant portion of treatments was performed with protons (approx. 220.000) – and the number is significantly increasing [1]. That is because the rationale for the use of proton radiotherapy (PRT) with their advantageous physical properties is widely accepted. Currently, there are roughly a hundred particle therapy facilities operational with several more under construction or in planning, but there are only 12 facilities capable of treating with carbon or other ions. Radiotherapy with carbon ions (CIRT) has in addition to the dosimetric properties in particular biological advantages such as an increased relative biological effectiveness (RBE). However, the use of CIRT especially for pediatric patients is disputed especially for pediatric patients. Main concern against it is the fragmentation tail of carbon ions. Of particular importance are secondary neutrons and their potential negative influence on the risk for treatment related secondary malignancies.

Hence, there is a constantly growing interest to introduce or rather re-introduce another ion into clinical routine: helium. Helium ions have already been used for treatment very successfully several decades ago. Between 1957 and 1992 more than 2054 patients have been treated with helium ions. Starting 1975, several phase I/II trials were conducted to evaluate the potential use of other heavy charged particles including helium, carbon, neon, argon and silicon ions [2-4].
At Berkeley (see “Section 7” on LBNL and key experiments), more than 810 patients received pituitary gland radiosurgery with high energy plateau helium ions. Levy et al. published an 18-year follow-up on that cohort documenting both efficacy and tolerability. The low complication rate – focal temporal lobe necrosis or cranial nerve injury occurred in only 1% of the cohort – combined with the achieved tumor control and successful reduction of growth hormone secretion is impressive evidence for the potential of helium ions [5]. Saunders and Castro successfully implemented helium ion high dose irradiation for uveal melanoma, resulting in 97% tumor control [3, 6] and pathed the way for the first randomized phase III trial conducted in charged particle radiotherapy investigating the results of helium ion radiotherapy for uveal melanoma compared to ^{125}Iodine plaques in 184 patients. The long-term analysis confirmed the excellent results with significantly improved local control and eye preservation for helium irradiation [7, 8].

These remarkable results form a solid foundation that warrant further clinical evaluation of helium ions in radiotherapy. The physical properties of helium have been characterized in detail.

Especially at larger depths the penumbra of protons is considerably large due to lateral scattering (and in fact sometimes larger than high energy photons). A helium beam offers significantly reduction of lateral penumbra which can become clinically relevant as figure 12.1 demonstrates.

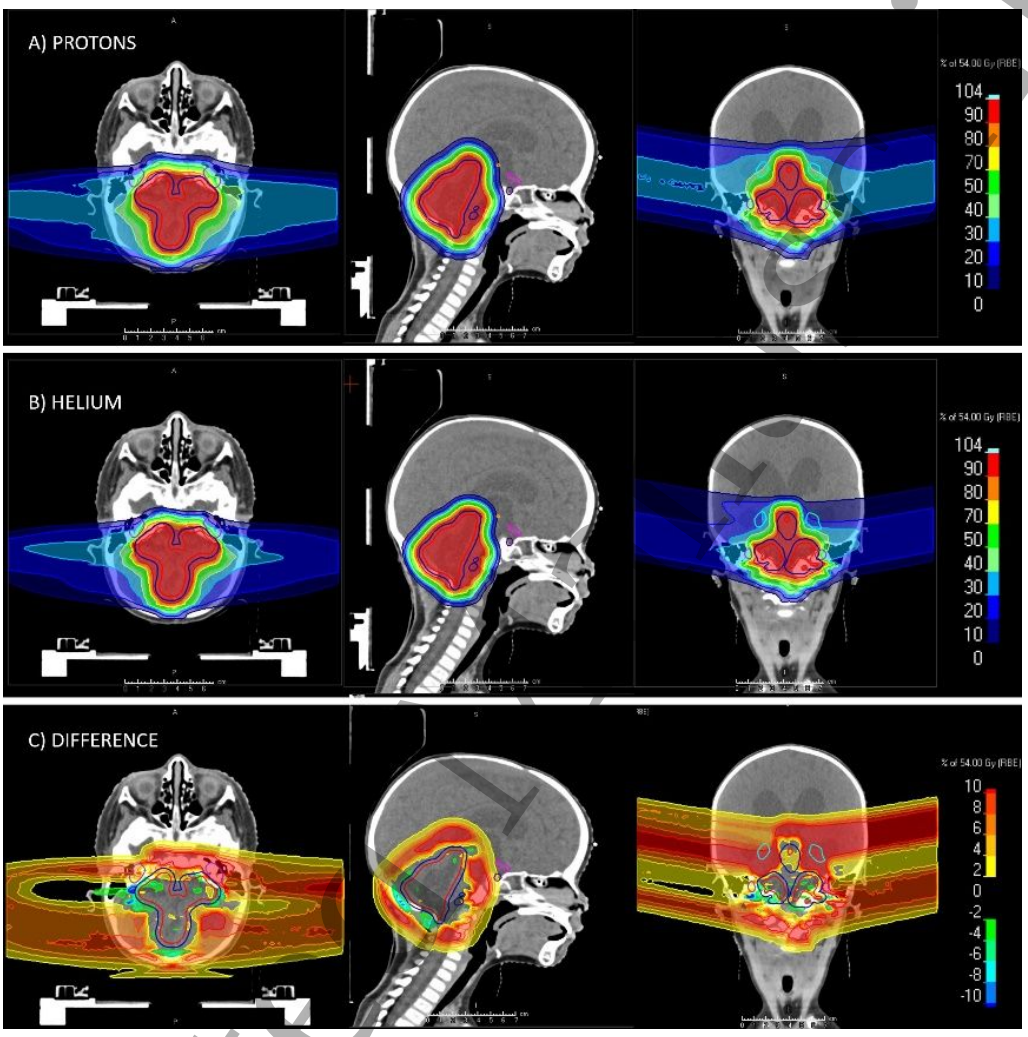

Figure 12.1. Comparison of treatment plans for a pediatric patient with posterior fossa ependymoma optimized with the same beam geometry for protons (A) and helium ions (B). Due to less lateral scattering the dose absorbed by the brainstem, cochleae, pituitary and hippocampi is significantly reduced (C).

Treatment-related sequelae are frequent – especially in pediatric brain tumor patients where the developing brain tissue is vulnerable to radiation damage. Over the decades, the prognosis for pediatric cancer patients in general and particularly for those with tumors of the central nervous system has significantly improved. Pediatric cancer patients are expected to become long-term survivors. Therefore, it is essential to minimize the burden of treatment-related side effects. Recent studies could clearly demonstrate that the dosimetric advantage of protons compared to photon based treatment translates into a measurable clinical benefit [9]. Given the dose response relationship of critical organs at risk (such as the pituitary [10]) preliminary results of dosimetric

in-silico study provide a strong rationale that the use of helium ions has the potential to even further reduce the risk for treatment related sequelae.

Current and Future Challenges

Despite evidence for a considerable variability of the relative biological effectiveness (RBE) of protons a fixed value of 1.1 has been accepted as a reasonable approximation worldwide (see "Section 11" on proton therapy experience with constant RBE). Both for Helium and CIRT however, the RBE increases as a function of the linear energy transfer (LET). Provided that the underlying biological model is correct, this selective increase of RBE can be used to optimize the therapeutic window delivering high doses to the tumor while the low dose to the healthy tissue is minimized. However, depending on the necessary input variables of the RBE model used its prediction is subject to substantial uncertainties. Since the current operational ion facilities pursue different approaches in terms of RBE model, fractionation and scheduling the respective clinical results must be interpreted cautiously. It remains to be seen which path will be taken for treatment with helium ions. A major challenge will be to find common ground, limit the uncertainties and standardize dose calculation for helium, hopefully allowing for future inter-institutional comparisons.

The fragmentation tail of carbon ions is discussed critically. While the secondary particle spectrum of protons consists mainly of secondary protons and neutrons with a very low residual range the fragmentation of carbon ions leads to a spectrum of secondary particles with a range that might be higher than the initial primary particle. Although the relative number of secondary neutrons might be higher for a carbon ion beam, when adjusted for the same RBE weighted dose the absolute number might be not because the number of particles needed to deliver the same RBE weighted dose is about two orders of a magnitude lower [11]. Thus, the risk for developing a CIRT related secondary malignancy might be overestimated. However, the risk for radiation induced subsequent neoplasm is of major concern, especially in pediatric patients or other patients who are expected to become long-term survivors. Treatment with helium ions might even further reduce the risk because it is expected that the number of secondary neutrons is very low and the resulting neutron dose might be even lower than in protons. However, further investigations into neutron dose of clinically used helium beams are required to quantify the effect.

Particular attention should be paid when it comes to patient selection. Since normal tissue sparing and hence reduction of normal tissue complication probability is a major goal for treatment with helium ions in principle all patients eligible for protons would be suitable candidates for helium as well. Although dosimetric advantages might determine largely the potential benefit, the selection should not only be based on dosimetric criteria. An improved understanding of biological effects allowing for an optimized LET- and RBE-distribution might also increase tumor control probability. Furthermore, patient specific individual biological marker are not yet sufficiently characterized but could have a major impact on treatment effectiveness.

Advances in Science and Technology to Meet Challenges

Currently available RBE models that are used in the daily routine need to be carefully evaluated and where necessary adapted for the purpose of RBE based treatment planning for helium (see

"Section 10" on RBE models). Since clinical experience is still limited, in silico, in vitro and in vivo experiments offer urgently needed and valuable input and will help minimizing the uncertainties. Establishing inter-institutional collaborations allowing for collection of large data sets for both preclinical and clinical data is necessary and requires significant funding to be successful in overcoming the challenge.

In addition to biological uncertainties related to RBE models one hast to keep in mind that there is also an inherent uncertainty and heterogeneity in the biological response of both the individual normal tissue of the patient as well as the tumor. To refine the understanding of treatment outcome not only classic endpoints and risk factors should be analyzed but also further biomarkers such as molecular tumor information, blood samples, genetic information or radiomics should be taken into consideration. Incorporating these variables would advance treatment planning of radiotherapy with ions one step closer towards truly individualized radiotherapy.

There is a paucity of facilities able to accelerate ions other than protons. While a carbon ion facility that yields for the same range as a proton facility needs significantly larger accelerators and is thus more expensive, the initial energy (per nucleon) needed for helium is comparable to protons and can also be produced by a cyclotron rather than a synchrotron. Nevertheless, availability of facilities capable of treatment with helium ions will be limited for a foreseeable time. Therefore, trial design, choice of endpoints and patient selection are crucial to learn which patient cohorts benefit most. Ultimately, prospective clinical evidence is indispensable.

Concluding Remarks

Radiotherapy with helium ions is not only due to superior physical properties a promising treatment option but also because the radiobiological behavior is still similar to that of protons. While the LET of helium is only slightly increased and still in the range of protons, helium offers an increased RBE and oxygen enhancement ratio nevertheless [12, 13].Furthermore, treatment with helium ions is also interesting for its economic aspects since the technical effort needed to accelerate helium ions is less compared to CIRT and deliverable with a cyclotron.

In summary, radiotherapy with helium promises to combine the best properties of both protons and carbon ions providing the means of high precision dose deposition and optimized sparing of normal tissue and making it a very suitable candidate to re-introduce into clinical routine.
Just recently, the Heidelberg Ion-Beam Therapy Center (HIT) was able to overcome the obstacles and treated worldwide the first patient with an active scanned helium beam within the framework of a compassionate use.

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13. Clinical medical physics and treatment planning

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Introduction

The primary mission of clinical medical physics in radiation oncology is to ensure that the planned dose is correctly delivered to the patient. More specifically, the patient must receive at each radiotherapy session the correct dose validated on the treatment planning system (TPS). For both photon and particle-based therapies, this involves measuring, managing and reducing the various uncertainties from treatment planning to delivery. These uncertainties are inherent throughout the entire treatment chain, such as beam/dose calibration, patient simulation/set-up, treatment planning physics, biological considerations in planning and daily delivery. However, there are several uncertainties intrinsic to particle therapy and must be considered for preparation of helium ion therapy.

In terms of management, clinical physics for helium ion therapy won't be vastly different from treatment with protons and carbon ions. Their use will present a similar level of uncertainty with unique magnitudes for aspects of physics and biology. Knowing where the community stands with proton and carbon ions in the clinic, how can we best practice clinical physics for helium ion beam therapy? From treatment over the last decades with protons and carbon ions, what has clinical medical physics learned about potential uncertainty and their impact on patient treatment? A recent proton therapy roadmap touches on various topics of medical physics considerations for proton therapy, including uncertainties in proton therapy, treatment planning, active beam scanning delivery, robust planning, adaptive therapy for variations in patient anatomy and beam range, live range verification, 4D planning/delivery and RBE [1]. In many cases, these concerns apply to all ion types and for sake of avoiding redundancy, here we focus on key aspects of clinical physics specific to helium ion therapy.

Current and Future Challenges

Physics and dosimetry: Beginning with center beam/facility start-up, physics for helium ion beam therapy must meet the same clinical standards/tolerances demonstrated with protons and carbon ions. As with any novel radio-therapy modality, the first challenge will involve establishing ideal beam physics and dosimetry for helium ions. For the HIT facility this occurred for years following ion source installation as outlined in prior section (see "*Section 2"* on facility start-up). Medical physics focused on acquisition of beam data and development/implementation for facility specific beam models in collaboration with the TPS vendor. More specifically, beam data must include all relevant characteristics (akin to proton and carbon ion therapy beam models), i.e., integral depth dose, lateral profiles in air, absolute dosimetry in water for monogenetic layers for various energies in the clinical range [2], [3].

Subsequently, comprehensive validations should involve dose measurements in various simple homogeneous scenarios (SOBPs in water), in heterogeneous geometries (i.e., anthropomorphous phantoms) and for oblique field delivery. Within these conditions, relevant sources of uncertainties must be identified such as beam range uncertainties, stemming from SPR prediction and/or anatomy changes in the patient; other beam delivery uncertainties such as beam width, spot position (daily fluctuations between planned and delivered beam physics settings, often recorded in system log-files); TPS beam modeling; dose calibration from the primary standards dosimetry laboratory applied to a specific center. By dedicated QA procedure, optimization and/or in vivo verification/imaging techniques (see “Section 6” on helium ion imaging), medical physics works to manage, mitigate and measure these uncertainties.

***Absolute dosimetry*:** Absolute dose calibration and corrections factors must also be considered for proper use of ionization chambers for helium ions, yielding precise conversion of coulomb to Gray for the reference radiation in water to the beam quality of interest [4]. While saturation, polarity, pression/temperature correction factors are more straightforward to derive, the beam quality correction factor can be more subtle to determine. The latter is associated with the larger uncertainty level compared to the other correction factors (on the order of a few percent) and the use of different factors between particle therapy modalities is still unclear and must be resolved, especially for lower beam energies <100 MeV/u [4]. One way to overcome this correction is to have correction factors directly linked to beam quality that could be derived from calorimetry measurements [5]. Helium ions are by default affected by this technical hurdle and while correction factors might be between the range of protons and carbon ions, it must be properly assessed to reduce uncertainties.

***Treatment planning*:** Introducing helium ions into clinical practice will initially not require exceptionally new techniques in terms of pure implementation and workflow for clinical medical physics. In other words, clinical physics procedures will be largely unchanged from protons and carbon ions, aside from additional helium dedicated QA routines. That said, we must still recognize both similarities and minute differences with respect to protons and carbon ions. For instance, what are the capabilities and limitations of analytical (standard for carbon ions) and Monte Carlo (standard for protons) dose engines for treatment planning for helium ions? Is the TPS able to model reliably using analytical methods? Do the clinically applied biological model applied for helium ions predict in vitro and in vivo data benchmarks and at which level of agreement? What is the impact of different treatment schemes on RBE and biological sensitivity within clinical tissue types?

Especially for heavier ions, it can be particularly challenging to assess/account for the RBE and associated radio-biological uncertainties during clinical practice (see “Section 7” and “Section 8”). Even for proton therapy, the assumption of constant RBE of 1.1 can be considered a safe estimate but neglects known variations at distal end [6], [7]. For carbon ions, the severity of RBE enhancement is unavoidable via such approximations and must be explicitly modeled during

treatment planning. For a specific tissue type, classic endpoints for variable RBE include particle species, dose and LET; however, greater complexity is known depending on indication and patient-specificity for all ion types [8], [9]. On the contrary with protons, evidence in the literature suggests variable biological enhancement should be considered for helium ions and should follow a similar approach to that of carbon ions with variable RBE consideration in treatment planning. Thus, one must validate the definition of "effective dose" against available measured endpoints, which are particularly scarce for helium ions, and potentially, recently developed bio-mechanistic models supported by literature data.

Advances in Science and Technology to Meet Challenges

Ultimately, the main challenges in clinical medical physics and radiobiology for helium ion therapy will aim to diminish the compounding physical /biological uncertainties and improve confidence in treatment planning and delivery methods. This can be done through a variety of avenues. First, we should continue to improve reliability and flexibility of the TPS by introducing new features and metrics for helium ion therapy. Most recently at our institution, development and validation of the RayStation took place in collaboration between industry and medical physics groups. Ongoing and future areas for TPS development for helium ion include the following:

Fast Monte Carlo: So far, while Monte Carlo tends to remain as the gold standard reference for proton therapy dose predictions, analytical pencil beam algorithms remain the standard for heavy ions, like carbon ions. While PB algorithms could lead to good dosimetric agreement with measurement in many clinical scenarios for helium ions, the mathematical formalisms themselves are simplified and propagate beam transport from homogeneous to heterogeneous anatomy applying lateral heterogeneity handling. Therefore, the PB algorithms may still yield unsatisfactory clinical performance in certain cases that have yet to be investigated. One of them is modeling beam modifiers and handling dose kernel distortion in settings with substantial lateral heterogeneity. For instance, studies suggested for thorax treatments, analytical commercial systems are unsuitable for proton therapy [10]. In addition, biological planning with PB algorithms may be susceptible to calculation uncertainties due to limitations in accuracy in handling lateral evolution of the mixed radiation spectra [11].

That said, computational performance using large costly clusters may soon be outpaced by fast MC codes on GPU, which are becoming standard for the proton therapy TPS [12]. Therefore, we must determine whether analytical approaches to dose calculation are sufficient and for which treatment sites are Monte Carlo approaches required. It's possible that eventually, development and integration of Monte Carlo computational methods will make their way to the clinic even for heavier ions. This will be mostly beneficial for challenging treatment sites and MR-image guidance where the magnetic field will impact the dose distribution (see "Section 5" on dose calculation). Before clinical integration of fast MC codes, application as secondary dose engines for treatment development and support is foreseen, especially for novel ions.

RBE model: One of the main sources of uncertainty in planning is related to the relation and translation of biological effect for a particular ion species to photons. That said, a major milestone will be establishing consensus between clinicians and medical physics teams between centers on the selected RBE model and appropriate inputs. Initial selection of variable RBE model, input parameters and tissue-specific inputs for mechanistic models are, for a lack of better words, an initial best guess, based on limited in vitro and in vivo data in the literature. It is important to collectively analyze data as it becomes available if indications point to specific changes in understanding helium RBE which may be clinically relevant. For helium ions, the optimal RBE model and inputs for clinical indications and specific treatments could be hinted at via analysis of already existing and ongoing clinical trial data for photons, protons and carbon ions.

As mentioned in the previous section (see “Section” 10 on RBE modeling and “Section 12” on clinical directions with helium ions), mMKM was selected for biological dose modeling during treatment planning and defining input parameters at the HIT facility. For instance, tissue-specific α/β values (and corresponding absolute values) are largely based on in vitro data which may alone be insufficient in the long run. Nevertheless, novel measurements from in vivo study/patient follow up and advanced biophysical models for effective dose prediction may provide further insight. That said, it will be our job as research and clinical scientist to determine how to best make use of them during clinical practice without jeopardizing tumor control or increasing risk of toxicity. Furthermore, for improving biological dose prediction in the clinic, we need involvement from physics and biological disciplines for precise measurement (“Section 3”) and modeling of the mixed radiation spectra (“Section 4”), in vitro/ in vivo readouts (“Section 9”), algorithm development (“Section 5”) and model mechanics (“Section 10”).

LET consideration/optimization**:** To date, there is still no widespread LET consideration or optimization during clinical practice with light and heavy ions. This is an ongoing challenge for proton therapy where variable RBE is not considered. For heavier ions like carbon, converging high LET within the target volume and away from normal tissues would be largely beneficial due to inherently large uncertainty in bio-effect at the distal end. However, this is currently not implemented in any commercial TPS even if proton LET optimization may be on the horizon. Therefore, citing the previous point regarding clinical value of secondary dose engines, LET-optimization for helium ion beam therapy could be one potential approach for combating biological uncertainties within organs at risk [13], [14].

Robust planning**:** If not properly managed, known range and position uncertainties of particle therapy may adversely affect biologically weighted dose [15], especially for multi-field IMPT. In turn, this may lead to potential mistreatment via under or over dosage, and elevated dose/LET levels in organs at risk. Thus, robust optimization [16] could be a primary and practical mitigator of biological uncertainty stemming from variations in range and patient positioning for helium ion therapy.

Multi ion therapy: Introducing helium ions at existing particle therapy facilities can potentially enable transformative treatment approaches such as multi-ion therapy (MIT) for biologically robust delivery (see “Section 15”). MIT has been shown to substantially reduce biological dose

uncertainty by homogenizing physical and biophysical distribution like RBE and LET within the target volume [17], [18]. TPS features currently do not allow treatment planning with multiple particle beams within each fraction and should be developed for pre-clinical testing outside of in-house developed beyond in-house systems. Even at our multi-particle facility, the HIT framework (from calculation in TPS to delivery in treatment room) does not yet allow for delivery of multiple particle species within the same patient plan, which should be addressed in future re-structuring of the global delivery system. Of course, within a standard TPS, the physical dose distribution of multiple particle treatments could technically be summed together, however, the multi-dimensional dependencies of variable RBE for helium and carbon ions, per say, would require dedicated biological optimization and calculation platforms for correct biological weighted dose. So far, multiple particles cannot be associated within the same treatment plan — nonetheless, these issues are somewhat trivial and involve revamping technical infrastructure.

Arc delivery: Proton arc techniques are gaining attention and still require further scientific development before clinical translation. But several technical studies have worked on feasibility of optimization and robust delivery for proton arc, which may be beneficial for several treatment indications [19]. Arc delivery with particle beams still needs further development and evaluation prior to clinical use, however, considering its physical /biophysical properties, helium ions may present numerous advantages over protons in arc delivery [20]. Despite range concerns in arc delivery techniques, arc combined with robust planning and energy switching optimization procedures may yield biological robust treatments. Capabilities of helium arc delivery with gantry or rotational treatment chairs would require further study and development.

Concluding Remarks

One of the largest remaining uncertainties in clinical treatment planning involves RBE modeling for ion therapy in general and to effectively resolve, may take substantial time, dedicated research and interpretation of clinical trials/derivation of in vivo RBE using helium in large patient cohorts. In contrast, many uncertainties can be practically handled and/or mitigated via techniques such as eventual introduction of fast MC codes in TPS, novel calibration procedures and new treatment optimization techniques. While these physical and biological uncertainties will be present in the short term, attributes of helium ion beam therapy remain in the same range as other clinical beams and are therefore mature enough to exploit in cancer treatment.

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14. Future Perspectives on Helium Ions

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Status

Other than the cost, the choice of a hadron species has largely been dictated by dose distribution characteristics (see “Section 3” and “Section 4” on physics and modeling), crude estimates of the hadron relative biological effectiveness (RBE) and oxygen enhancement ratio (OER) (see “Section 7”, “Section 8”, “Section 9” and “Section 10”, on biological response and modeling). Among the heavier hadrons, carbon has become the de facto standard because it was the first to be adopted clinically in the modern era in Japan, which was in part because its RBE was estimated to be similar to that for neutrons.

Until the recent helium ion program based in Heidelberg (see “Section 12” and “Section 13”), helium has not been used for RT since the LBNL experience, although hadron facilities in Japan, Europe and China now have the required capability. Compared to protons, helium beams have sharper distal and lateral falloffs, and thus can produce more conformal dose distributions. Helium dose distributions are only slightly less conformal than those for carbon, yet produce a considerably smaller number of secondary particles and fragments that contribute dose outside the field laterally and beyond the end of range.

In general, the relationship of RBE with linear energy transfer (LET) for hadrons is a complex function of dose and biological factors and generally not well-understood. The high RBE of carbon ions has been cited as a primary driver for their use in radiation resistant tumours. However, the distal regions of helium beams may have similarly high biologic effectiveness, without the “over-kill effect” seen with high LET carbon ions. Perhaps equally as important, the moderate LET values of helium beams may be more sparing of normal tissues adjacent to the tumours, potentially enabling the treatment of many tumour types, including tumours in paediatric patients (discussed in “Section 12” on Clinical Directions), if appropriate treatment planning and delivery techniques were to be used. With regard to these issues, recently, there have been numerous *in-silico* investigations to design helium radiation treatment plans and compare their potential with that of other modalities [2-4]. In addition, since the initial clinical experience, the delivery technology has advanced considerably with the development of scanning beam-based systems. Moreover, there have been numerous experimental and theoretical (simulation) studies to investigate the biological effects of helium ions [5-8] and develop RBE models for helium therapy.

Current and Future Challenges

At the most basic level, the physical properties of helium (and other hadrons), e.g., energy, ionization density or LET, determine the achievable dose distribution patterns, normal tissue sparing potential as well as the biological effectiveness. Ultimately, the clinical effectiveness of a specific radiotherapy modality depends on our ability to clearly understand and relate biological effect to physical parameters. However, our knowledge of the biologic effects of helium and other

ions and even the appropriate physical factors to use are lacking. This severely limits the development of appropriate models for use in treatment planning.

Extensive in-vivo and in-vitro preclinical experiments and, in many cases, in silico simulations need to be conducted to investigate the response of tumours and normal tissues and various cell lines as a function of dose and LET (or lineal energy). With the data thus accumulated, reliable biophysical models as a function of beam quality (LET or microdosimetric quantities) can be developed for clinical use. The models developed may be initially validated with experimental in-vitro and in-vivo data. However, ultimate validation of models will require clinical response data (e.g., tumour control, toxicities, survival, etc.). Such clinical data will only be available if well designed clinical trials with detailed follow-up are implemented. For helium ions, in addition to radiation resistant tumours where high RBE would be preferred, clinical trials could include multiple disease sites, potentially even paediatric tumours.

New areas of helium radiation biology also need to be explored both pre-clinically and through initial clinical trials. For example, only recently have the profound immunosuppressive effects of radiation and the potential of particle therapy to mitigate them been appreciated. This is especially important as the use of immunotherapy spreads across multiple tumour types. Initial evidence, obtained mostly with proton therapy, indicates that particle therapy, due to its compact dosed distributions, may be less immunosuppressive in comparison to photon therapy. which may improve survival [9-11]. Moreover, the greater sparing and preservation of the immune system with particle therapy is critical for the effectiveness of adjuvant immunotherapy. Furthermore, preclinical studies with carbon ions suggest greater immunogenic cell death and the increased release of inflammatory cytokines lead to greater immune system stimulation [12-14]. Up until now, clinical immunoradiotherapy has been studied with photons only. However, a combination of heavy ion therapy with immunotherapeutic agents may be considerably more effective as evidence indicating that high LET particles may promote an immunogenic response accumulates. While the current data come from carbon ions, it is likely that the response to helium ions will be as robust.

There is also growing interest in ultra-high dose rate (FLASH) radiotherapy and its potential normal tissue sparing effects. Hadron therapy may be ideally suited for the clinical delivery of FLASH treatments to deep seated tumours. However, it would be important to investigate how FLASH effects are different among protons, helium or carbon ions through modelling and preclinical studies. A recent publication suggested that the mechanism of FLASH effect of high LET radiation may be due to the production of oxygen within the target that sensitized the tumour cells [15]. This is in contrast with the FLASH effect for lower LET radiation, which is hypothesized to be due to the depletion of oxygen in normal tissues resulting in their sparing.

Lastly, one cannot ignore the issue of cost. It is quite plausible that helium offers the highest value (clinical effectiveness / cost) as a dedicated helium centre would potentially require more compact equipment and hence lower upfront investment. Helium therapy may also be more amenable to hypofractionated therapy than proton therapy. These factors, along with the potential of lower treatment-induced toxicities, may make helium to be no more costly than protons.

Advances in Science and Technology to Meet Challenges

While progress is already being made, much remains to be done. There is an urgent need for better preclinical data regarding the biological effects of helium ions. Carefully designed biological studies must be carried out collaboratively among radiation oncologists, physicists and biologists in order to clearly relate the physical factors of the beam to biological effects. This will enable the development of novel models for use in treatment planning and delivery. We believe that these models should be incorporated into the criteria of optimization of multi-field intensity-modulated ion therapy approaches, in which high LET helium ions preferentially deposit dose within target volumes.

Early phase clinical trials for selected disease sites to assess the safety and tolerability of helium therapy can begin as soon as appropriate treatment planning and delivery systems are available. Initially such trials may be for adults before extending them to paediatric patients. Simultaneously, in-vitro and in-vivo experiments can be initiated to generate the biological response data. These, along with the clinical response data, can then be used to reparametrize biophysical models or develop new models (see “Section 10” on biological models). Most treatment planning models to date have been based on the averaged value of beam quality (LET or lineal energy) and the in-vitro experimental data such as clonogenic cell survival and DNA damage. However significant improvement in accuracy may be achievable if they were to be based on the in-vivo or ex-vivo experimental data (for example tissue organoids grown along with patient derived cancerous cells) and microdosimetric spectra (e.g., the biological weighting function of lineal energy) [16].

As large clinical response data sets are accumulated, their analyses could yield TCP and NTCP models. Traditionally, such models have been based primarily on simple dosimetric indices, e.g., mean dose or volumes receiving specified doses or higher, and their predictions are population averages. Considering the heterogeneity in intrinsic sensitivity among patients and the variability of diseases characteristics and treatment planning techniques, it is likely that the predictions of such models may have high degrees of uncertainty. Thus, treatment response modelling should consider patient-specific factors along with the dosimetric factors so that the models can more precisely predict an individual patient’s risk of toxicity or treatment failure. Such models, when incorporated into the criteria of optimization of dose distributions, could lead to improved therapeutic ratio. Without such improvements, the potential of helium vs. other ions may be obscured by the data noise.

It cannot be expected that the first clinical trials will offer definitive evidence of the superiority of helium ions (as has been the case with proton therapy). Instead, as the knowledge base grows and the predictive models are improved, more sophisticated clinical trials can be undertaken to generate additional high-quality data to be fed back for further refinement of the state of the art. Biological and clinical data can be combined with in-silico simulations of physical, biological and immunological effects to further improve understanding of the underlying mechanisms of these effects of helium relative to other ions.

In addition, to make helium therapy cost effective, there is a need to develop compact gantries and accelerators. A helium-only treatment delivery system may be substantially less costly than a carbon ion facility and yet may be equally as effective clinically. Future development of helium therapy (or any heavy ion therapy) may be influenced by recent advances in superconductivity and associated technologies. Such a delivery system may be widely affordable, especially with the increased use of hypofractionated treatments.

Concluding Remarks

Use of helium ions for radiotherapy has not yet been explored in the modern era. Considering their physical and biological characteristics, it is plausible that helium ions offer a superior alternative to carbon ions and, certainly, to protons. Considerable additional biophysical research is needed to guide the development of high-quality clinical trials using state-of-the-art models of biological and immunological effects, and normal tissues and tumour responses to make this modality optimally effective. Some such research is already occurring across the globe, mainly in Europe and Japan where facilities with ions heavier than protons, including helium, are available. In United States, currently there are no heavy ion facilities, though a plan has been announced by Mayo Clinic to establish one on their campus in Jacksonville, Florida.

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15. Multi-ion therapy and the role of helium ions

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Several sections of this roadmap have mentioned or briefly discussed helium ions in the context of an emerging topic known as multi-ion therapy (MIT). As the name suggests, this potential treatment concept involves combining multiple ion species into a single treatment fraction. MIT offers additional degrees of freedom in treatment design, planning and optimization otherwise not attainable with the use of a single radiation quality. Naturally MIT delivery would require that a facility hosts several ion sources and delivery system capable of efficiently delivering different ion species to the same treatment room (see Section 2 on facility start-up). Furthermore, dedicated treatment planning and optimization systems must handle the mixed radiation field of multiple primary particle beams to accurately predict effective dose (see Section 5 on dose calculation and Section 13 on clinical medical physics).

For the moment, MIT remains in a state of research and development and prior to clinical investigations, extensive development and validation at existing clinical heavy ion centers is required. There are several published approaches and in-depth studies of MIT from separate facilities, each differing in its primary aim and method. In all cases, helium ions are applied in MIT as the 'lower' LET particle. More specifically, the role of helium ions in these studies could be described as the application of a lower LET particle to balance dosimetric and biophysical features compared to other ions within the mixture, e.g., carbon, oxygen or neon ions.

The initial MIT optimization strategy developed at HIT was inspired by efforts to investigate robustness of carbon ion therapy in light of the relatively sizeable biological uncertainty associated with applied models and clinical/experimental observation (1). It was suspected that mixing ion beams and appropriately optimizing dosimetric and biophysical planning features could mitigate undesirable gradients in distribution (dose and LET) while harmonizing biophysical attributes inter- and intra-patient (2). By introducing multiple particle species within a single fraction, initial works demonstrated that optimization goals for physical dose, RBE and in turn biological dose uniformity could be achieved with MIT, specifically for parallel opposed beam configurations. MIT was further extended and validated for single field delivery both dosimetrically and biologically in vitro. Dosimetric comparisons with reference single ion plans showed benefits of various MIT mixtures (p + C and He + C) in different clinical cases (3). Figure 15.1a presents single field uniform dose (SFUD) plans using a single ion species (He or C) and a proposed MIT technique, combined ion-beam with constant RBE (CICR) using He and C mixtures. The CICR plan generates more homogenous physical dose, RBE and LET distributions than the SFUD single ion plans, with biophysical attributes intermediate of helium and carbon ions.

Other works from GSI in Darmstadt, Germany present MIT techniques combining helium and oxygens ions to improve tumor control rates for hypoxic tumors. (4) Current treatment planning for carbon ion therapy makes use of mechanistic variable RBE models which account for main dependencies of biological response: dose, LET, tissue type and ion species (see Sections 8 and 10). It is well known that the tumor oxygen status can impact the elicited bio-damage and should be considered during planning, however, measuring and incorporating patient-specific pO2 levels is challenging and remains a key area of research in radiotherapy (5). The GSI approach to MIT employs particle-specific LET-painting making use of oxygen ions in the hypoxic tumor regions while allocating helium ion beams for dose coverage in remaining normoxic or physoxic regions (Fig 15.1b). This approach involves biologically informed planning, i.e., spatial mapping of pO2 levels within the tumor volume, however given assumptions of a reasonable measured pO_2 value could provide means to combat hypoxia-related tumor resistance.

At NIRS in Chiba, Japan, research groups are developing their own MIT technique for potential clinical translation. These MIT works began with an LET-optimization approach known as intensity modulated composite particle therapy (IMPACT) (6) mixing helium and other available ion species at their facility. As opposed to conventional carbon ion therapy, IMPACT affords highly homogenous LET_d distributions in the target volume. Alongside retrospective analyses of carbon ion therapy have been conducted to investigate the impact of LET_d on local control (7) or on side effects (8). For instance, Hagiwara *et al* (2020) revealed that the minimum LET_d within GTV has a significant association with local control of pancreatic cancers (7). Meanwhile, an adapted stochastic microdosimetric kinetic (SMK) model to improve agreement between measured and predicted survival (and in turn RBE) for high-dose and high-LET conditions in vitro, multi-ion therapy treatments combining various mixtures with helium, carbon, oxygen and neon ions were presented (9, 10). More recently, SMK was further expanded to include RBE dependencies with oxygen status for developing standard and hypo-fractionation treatment regimens (11). Neon and helium ion beams are mixed in a single field arrangement to target hypoxic tumor volumes (e.g., GTV for pancreatic adenocarcinoma tumors) with higher LET beams (neon ions) and the 'non-hypoxic' target regions with lower LET beams (helium ions) (Fig 15.1c). Future efforts may consider further development and investigating techniques like hypo-fractionated multi-ion therapy (HFMIT) to predict/measure potential gains in TCP and impact on NTPC in various treatment sites.

Similarly, on-going works at HIT develop and investigate combining multi-ion with other promising treatment approaches like particle arc (12, 13). MIT mixtures with helium and oxygen or neon ions with SHArc delivery may afford additional treatment benefits such as LET-redistribution, LET-painting and/or target RBE/LET uniformity.

Since helium ions exhibit more ideal physical characteristics for high-precision delivery compared to proton, like a lateral penumbra / multiple coulomb scattering, similar to the heavier ions in the clinical energy range, they may be the most ideal candidate as a "lower-LET" particle for MIT. In other words, implementation of helium ions as the lower LET particle during MIT treatment optimization with mixtures of higher-LET particles like carbon, oxygen or neon may be the most

appropriate approach dosimetrically. For instance, as demonstrated in the HFMIT study (11), MIT mixtures using helium can help for maintain a high-level of dose conformity to the tumor in regions for cases where high LET may not be required (target boundaries) outside hypoxic GTV. However, further works should investigate dosimetric and biophysical features of MIT which include helium and other ion species.

That said, the multi-ion therapy concept is young and substantial efforts lie ahead to reach clinical maturity and to understand its applicability and clinical function. Nonetheless, it is evident from the existing works that helium ions may play a critical role in MIT. For now, however, clinical practice continues to make use of a single radiation quality each fraction. Clinics equipped with photons, protons and carbon ions do deliver treatments which make use of different radiation qualities inter-fractionally. For example, several particle facilities implement treatment regimens which involve an initial course of photon RT followed by a short course ('boost plan') of carbon ions often with a smaller delineated target volume than initial course (14, 15). Future works may consider investigating the potential for 'boost planning' using helium ions. Related works investigate and develop a biophysical model for joint optimization of combined proton-photon or carbon-photon treatments (16, 17), which could similarly be performed with helium ions.

Several key questions regarding MIT must be formally addressed in future works and in the context of helium ion applications: what are the principal drivers for clinical translation of MIT? In which indications and clinical scenarios will MIT techniques be most profitable? Which ion combinations using helium and other particles are most ideal for improving TCP and/or reducing NTCP? Can we design and build accelerator systems and particle therapy facilities to enable MIT delivery without substantial financial costs associated with heavy ion therapy?

With development and benchmarking of RBE models which accurately predict cell survival in vitro for a wide dose and LET range for various particle species (see Section 10 on RBE models), future investigations may continue to explore RBE various cell lines and in vivo models for both tumor and normal tissues (see Section 9 on biological readouts) in both the context of standalone use for helium ions and MIT applications. It is unclear whether MIT mixtures of helium ions and protons would provide any clinical benefit, however it is worth systematically examining various mixtures with 2 or more ion species with various MIT techniques to determine the ideal mixtures for specific clinical scenarios. Moreover, MIT optimization techniques have been developed using in-house optimization and calculation systems. Prior to clinical translation, collaborations with industry to make MIT optimization techniques both plannable and deliverable using the clinical TPS and delivery system are necessary.

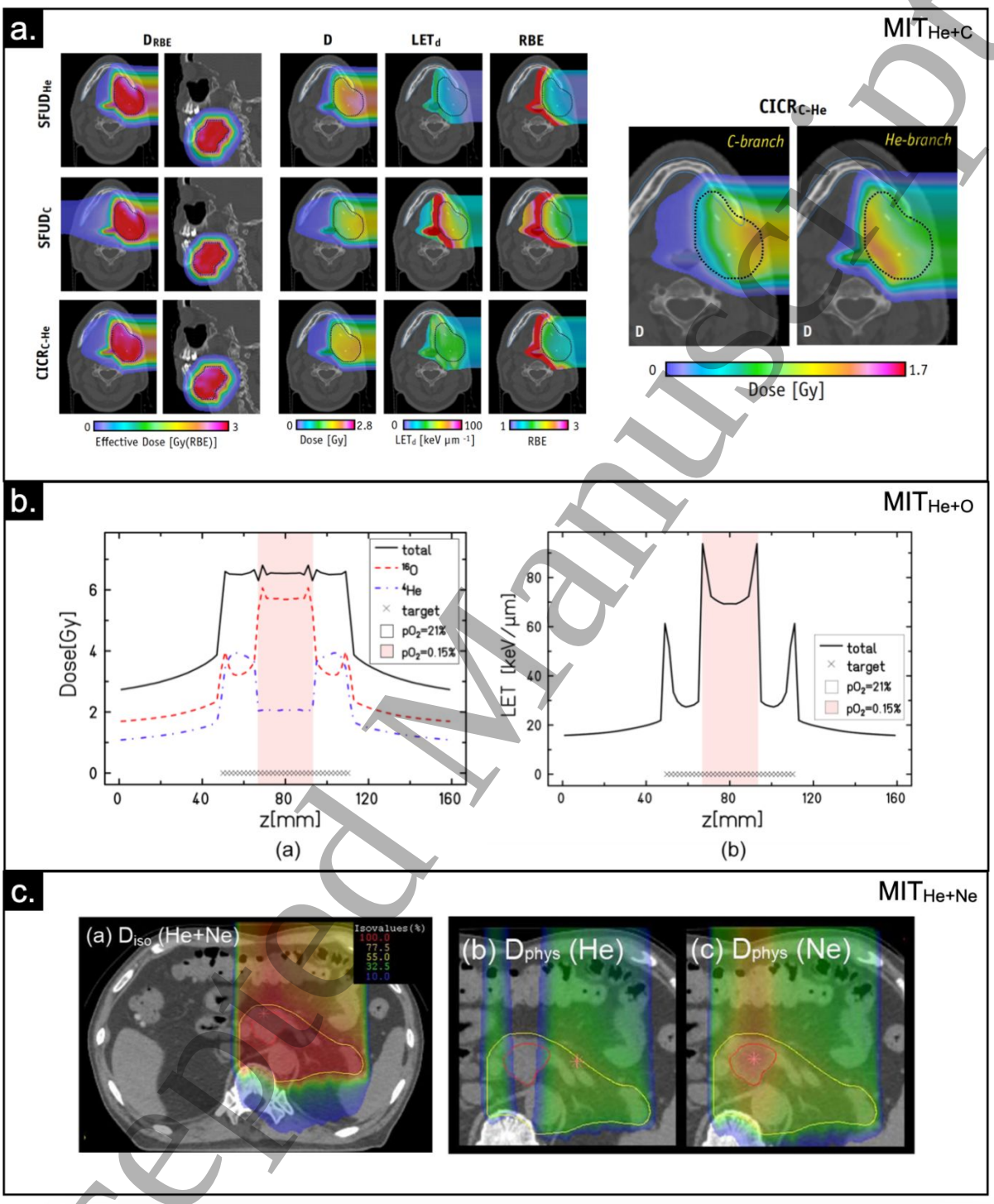

Figure 15.1. Multi-ion therapy optimization approaches which combine helium ions with higher-LET particle beams like carbon, oxygen and neon. a) Combined ion-beam with constant RBE (CICR) optimization using He+C, b) multi-ion LET painting using He+O and c) hypo-fractionated multi-ion therapy (HFMIT) using He+Ne. Figures were adapted from Kopp et al. 2019, Sokol et al 2018 and Inaniwa et al. 2021.

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16. Concluding remarks on biology and physics considerations in the clinic

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The roadmap comprises current and future endeavors in establishing helium ion beam therapy with physics, biology and clinical considerations. With recent and ongoing advances in accelerator technology, developments are expected to continue and could help lower facility start-up costs through compact treatment room/gantry design (*Section 2*). By mitigating economic burden with modern facility design for helium ion therapy, accessibility will further drive the extensive measurements campaigns and large-scale experiments ongoing for characterizing helium ion beam physics (*Section 3*). Through expansion and enrichment of the physics data like cross-sections, collaboration between experimentalists and physics model developers (e.g., Monte Carlo simulation and clinical treatment planning systems) can lead to more accurate descriptions of ^{4}He interactions in the human body, paving the way for advanced delivery and treatment verification/monitoring techniques (*Sections 5 & 6*). For instance, beyond therapy applications, helium ion uses in transmission imaging provide further motive for clinical translation (Section 6). Several institutional efforts are establishing MR-guided particle therapy beginning with proton beams which could open up ions to daily adaptive planning, efficient gating and other advanced live online onboard imaging and treatment control, particularly advantageous of treatment sites which are problematic currently with particle beams or controversial like thorax and abdominal based treatments with substantial organ motion. Interaction of accelerated charged particles with the MR-field would increase complexity of necessary physics characterization, simulation and validated treatment planning approaches (Section 5).

For clinical trials using helium ions, it is important to frame clinical questions in the context of and in relation to experience and results from the LBNL studies (*Section 7)*. For example, how are local control and toxicity prevalence altered using high-precision raster scanned delivery compared to passively scattered beam? How well does the in vitro tuned RBE modeling approach handle variations in bio-damage in vivo as opposed to constant RBE assumptions? With such inferences, experimental characterization and modeling of biological phenomena of helium ions can be approached systematically for not only the primary end points like dose, LET and tissue type, but also more elusive quantities which impact the RBE like dose-rate, the role of dynamic oxygen concentration, characteristics of the microenvironment, fractionation dependence, and interaction with drugs such as those used in targeted therapy or immunotherapy via in vitro, in vivo and patient settings (Sections 8, 9 & 10). Despite these circumstances, biological uncertainty for carbon ion therapy remains one of the most pertinent unknowns/clinical challenges which hinders full potential of the high LET beams (~20-30% uncertainty in bio-response). As performed with carbon ions, translation of clinical constraints and prescription doses from one bio-effect paradigm in Europe for example LEM to the Japanese experience using various updated MK

models may be necessary if more centers arise installing and applying helium ions for clinical practice [1], [2]. This should be avoided, and biological model updates could inevitably be agreed upon and recommended by an overseeing body or task groups within the International Atomic Energy Agency (IAEA), American Association of Physicists in Medicine (AAPM), etc. This could help streamline interpretability of helium ion beam therapy clinical outcome between centers internationally.

By illuminating the learned experiences in terms of physical, biological and clinical challenges for protons (Section 11), a clear clinical approach helium ions radiotherapy can be defined (*Sections 12 & 13*). Helium ions may present numerous advantages for clinicians in substitution for protons or photons in pediatrics for instance. And in the case of carbon ions, conservative approaches to handling the unknowns of biological impact may reduce normal tissue toxicity at the expense of local control and/or recurrence. Clinical trials will, in time, guide future directions through development and translation of personalized treatment schemes and combined therapies using helium ion beams (*Section 14*).

As indicated in *Section 11*, diversity of particle species selection for treatment may, to some degree, slow down the collection of patient statistics for the other established particle beams; however, this impact is suspected to be minimal compared to gains in understanding physical and biological interactions, in which helium is ubiquitous for both proton and carbon ion beams within the mixed radiation field, in addition to added degrees of freedom for treatment design and future delivery techniques. Particularly, the PRECISE concept introduced in the context of multi-ion therapy, could gain traction. This would involve expansion of particle therapy treatment planning concepts to multiple particles for selection of best plan not only dosimetrically but based on tumor-type indications, considering patient-specific factors, etc.

It is with these considerations that helium ions and particle therapy at large may need to pivot towards machine learning based approaches to treatment selection or more technically advanced delivery methods using single or multiple ions [3], [4]. As touched on in previous sections, helium ions will begin use in clinical trials at the HIT facility and others are anticipated to follow given recent press releases and academic/industry collaboration with companies like RaySearch to establish the first clinical treatment planning system for helium ions. Ultimately, considering the need to reduce biological uncertainty and intra/inter patient RBE variability, multiple ion treatment advanced optimizations should be considered including helium as well as other heavy ions. In principle, by conducting clinical trials in combining helium ions with other low and high LET particle species, robustness and reliability of interpreting outcome could greatly improve, particularly for tumor control and honing/defining tissue-specific prescription doses in the context of particle therapy. However, several technical developments are required to enable novel delivery techniques such as MIT as outlined in prior sections (*Sections 2, 13 & 15*)

Moreover, several sections in this roadmap discuss topics of tumor microenvironment factors and biological informed treatment planning for helium ions, such as taking more consideration of oxygen status of hypoxic tumors (*Sections 7, 8, 9, 10 & 14*). There is of course a limit to how much time-efficient screening and patient-specific planning can be practically involved within the

treatment chain, but such concepts for treatment are headed in this direction. Multi-ion or arc delivery techniques may provide unique avenues here in reducing influence of hypoxic related radio-resistance by LET enhancement (*Sections 13 & 15*). This alone may not be completely sufficient since there is of course a reasonable limit to how high LET can be delivered in the tumor as well as saturation effects [5]. Development and discovery of potent biological, drug or agent-based treatments with helium ion therapy has great potential for improving clinical outcome and understanding fundamental biological features of particle beams in these settings is highly warranted (Sections 8 & 14). Regardless of the approach to therapy, helium ions can bring several clinical benefits, as either its own modality or as a component of upcoming advanced delivery techniques/hybrid treatment strategies.

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