



# New Ions for Therapy

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## Abstract

**Purpose:** Charged particle therapy (CPT) is currently based on the use of protons or carbon ions for the treatment of deep-seated and/or radioresistant tumors, which are known to return poor prognosis in photon treatments. A renovated interest has recently been observed in the possibility of extending the spectrum of ions used in CPT. The potential and limitations of different particle species will be discussed in this work, with special regard to <sup>1</sup>H, <sup>4</sup>He, <sup>12</sup>C, and <sup>16</sup>O, that is, those presently available in the most advanced particle therapy clinical centers.

**Materials and Methods:** Literature information has been screened, as well as additional analysis has been performed, aimed at the comparison of basic physical and biological properties of several ions. The research treatment planning system TRiP98 is also employed to compare the dose distribution resulting from exposure to the different ions in different configurations, including the irradiation of hypoxic targets.

**Results:** Particles of intermediate charge, such as helium and lithium, offer an increased physical selectivity compared with protons, while having reduced biological effectiveness compared with carbon. The latter aspect translates into a less sensitive biological optimization of CPT treatments, though still more effective than protons in killing cancer cells. At the same time, in view of their increased linear energy transfer, heavier ions, like oxygen, are considered attractive, especially for the treatment of hypoxic tumors. While the higher biological dose released in the entrance dose represents in general a drawback for ions heavier than carbon, for oxygen beam this effect may be balanced by the lower dose increase requested to overcome hypoxia.

**Conclusions:** The possibility of delivering radiation quality-optimized CPT treatments seems to be the new challenge in heavy ion therapy. The potential and limitations of different particle species, according to different sensitivity and morphological scenarios, makes combined treatments of different ions an intriguing option. New ions could open new scenarios in cancer therapy, but would represent as well an opportunity for the treatment of specific non-cancer disease such as atrial fibrillation.

Submitted 04 Jul 2015  
Accepted 19 Aug 2015  
Published 09 Feb 2016

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## Original Article

DOI  
10.14338/IJPT-15-00027.1

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Particle Therapy

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**Keywords:** charged particle therapy; RBE; OER; Bragg peak; light ions; heavy ions

## Introduction

Since the early days of radiation therapy, research efforts have always been directed toward obtaining improved dose distributions (ie, high dose to target volume, dose as low as possible to healthy tissues), possibly increasing at the same time the selectivity in biological effectiveness, and thus enhancing the therapeutic ratio. The idea proposed by Robert Wilson to use charged particles for cancer therapy [1] seemed to immediately

present accelerated ion beams as natural candidates to improve dose conformity in light of the peculiar characteristics of their inverse depth-dose profile, the so-called Bragg peak (BP). In parallel, it was soon evident that the physics of radiation-matter interaction (eg, increasing linear energy transfer [LET] toward the end of range) would offer the possibility coupling the spatial selectivity of charged particles with enhanced biological effectiveness. After preliminary radiobiological experiments confirmed these hypotheses, the development and diffusion of charged particle therapy (CPT) started.

According to recently published statistics, there has been a continuous increase in the number of patients treated with charged particles in the past decade [2]. By the end of 2013, more than 120 000 patients had received CPT, mostly with protons (87.5%) and with carbon ions (10.8%). Even though they represent minor fractions, other particles have been employed as well, for example, neutrons, helium, and neon ions in the old trials carried out in Berkeley [3–6].

A gradual shift in thinking of the radiation therapy community seems to have occurred, from the pioneer questions *if* CPT might produce actual clinical benefit to current discussions of *how and when* it may be possible to best exploit the therapeutic potential offered by CPT [7] (eg, which particle species, dose, and fractionation scheme as well as which cancer type, anatomic site, depth position, normal tissue radiosensitivity). Use of CPT still draws criticism, however, mostly because of its debated cost-effectiveness, scarcity of data showing clinical superiority (always claimed to be necessary to fulfill evidence-based medicine requirements), increased technical and clinical complexity, and enhanced biophysical uncertainty compared with photons [8]. This is also related to the difficult and controversial possibility of making comparisons based on randomized clinical trials [9].

Despite these worries, it is now generally recognized that accelerated ions represent a possible alternative to low LET photon radiation for the treatment of radioresistant, deep-seated and/or hypoxic cancers [10]. This is especially true for pediatric patients, for whom the induction of secondary cancers is definitely an issue; therefore, the reduced integral dose delivered makes CPT particularly attractive. Current estimations suggest that overall about 10% of cancer patients would benefit from ion therapy [11]. As the awareness of such advantages for CPT is increasing in the clinical community, new opportunities appear for CPT.

Protons are certainly the charged particles most frequently used and for which the largest clinical experience has been acquired, despite the improved physical properties offered by heavier ions. However, the biological effectiveness of other ions is offset by large uncertainties, which concern clinicians. However, in addition to several centers in Japan and China, carbon ions are now available in Europe, and the first carbon ion therapy facility will likely start construction in the United States in the next few years. Indeed, an intense discussion has once again arisen in the literature in recent years concerning the possibility of optimizing the clinical potential of CPT by extending the spectrum of therapeutic ions beyond protons and carbon ions. While this was hindered in the past by technical issues, recent progress (eg, the diffusion of raster scanning) has made it possible to better exploit the peculiarities of different ion species. For instance, helium and lithium ions have been proposed in light of their improved lateral dose distributions compared with protons; at the same time they have a relative biological effectiveness (RBE; ie, ratio of photon to charged particle dose producing a same biological effect) lower than that of carbon, and thus, they are easier to adopt for clinical use. Oxygen is also considered a good candidate, especially due to its high LET distribution, which makes it particularly attractive for the irradiation of hypoxic tumors [12, 13].

Currently, innovative treatment-planning studies that allow simultaneous optimization of different particle beams are needed [14] and the practical implementation of multi-ion CPT treatments still requires additional technological development. At the same time, experimental data are needed to consistently describe the physical and biological properties of ions other than protons and carbon ions to a level of accuracy high enough to allow their clinical use. There is renewed interest in identifying scenarios in which each particle species shows its maximum therapeutic potential. Extending the therapeutic spectrum of clinical ions appears to be the new challenge in CPT, which will require experimental effort and technology development. Selection and delivery of radiation quality optimized treatments would be in keeping with the era of biomedical research devoted to finding strategies to personalize cancer treatments.

## Other Ions: Particles Sitting on the Bench

The same physical and biological aspects that are responsible for differentiating photon radiotherapy and CPT (namely increased target conformity coupled with an enhanced biological effectiveness in inactivating tumor cells) can actually be adopted to discuss more in detail the properties of different particle species. Actually, a number of studies can be found in the

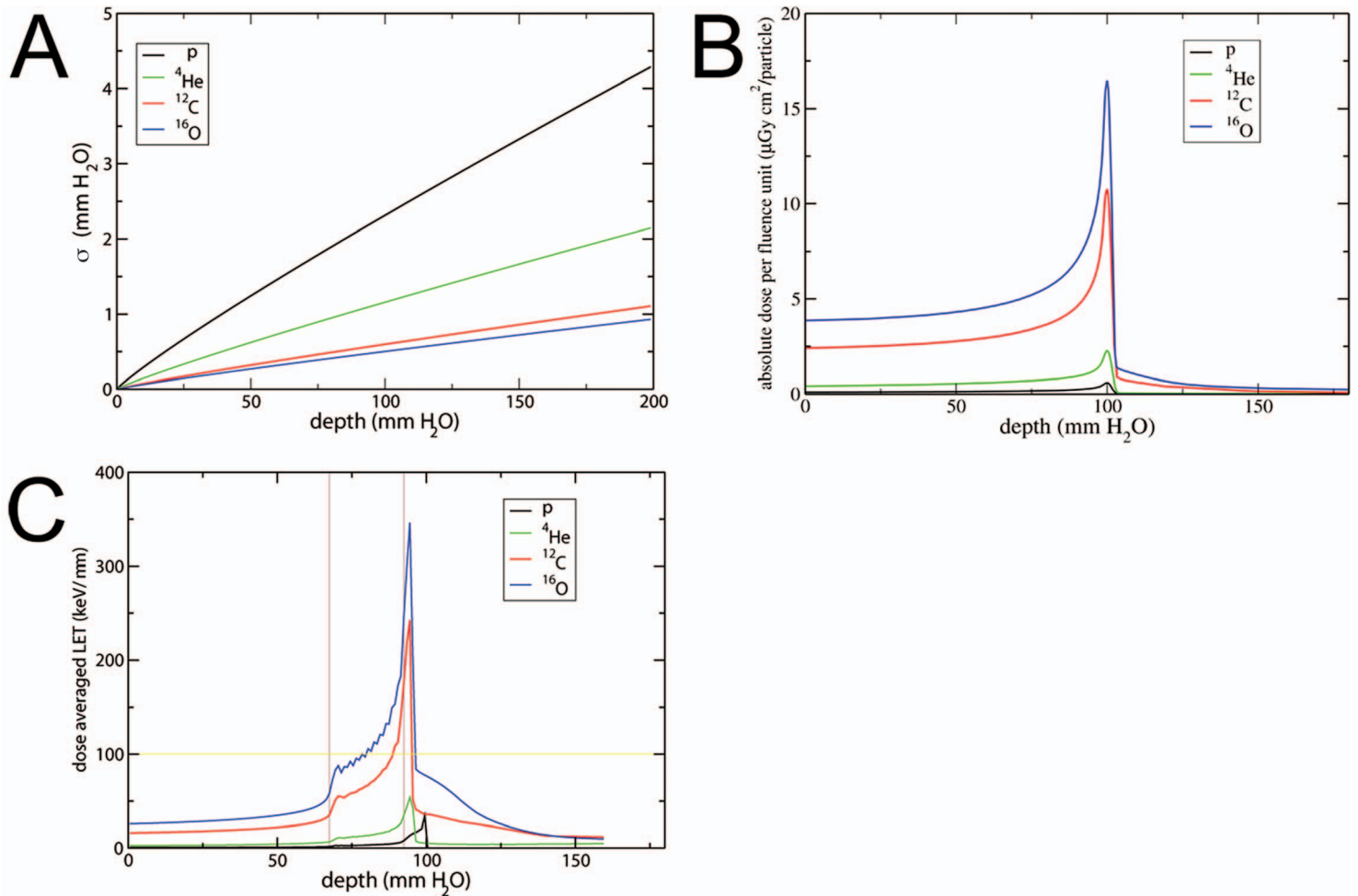
literature investigating physical properties for a spectrum of charged particles, with focus on their clinical potential [15–18]. These studies are mainly based on radiation transport simulations through analytical or Monte Carlo methods, while experimental data are largely missing for particles other than protons and carbon ions. This represents a limit in the reliability of the beam models that are normally adopted for these particles. Up to now, only a few studies were directed to improve the description of helium [19] and oxygen [20] beams for clinical use on the basis of experimental data.

The LET is usually seen as a key parameter to explain the modulation of biological effects induced by heavy ions (high LET) compared with x-rays or  $\gamma$ -rays (low LET), and has been the primary subject of investigation. In the classic picture, a strong advantage offered by the physics of charged particles is the increasing LET in the BP region, which allows high RBE to be obtained corresponding to the tumor. However, the LET variation along the depth-dose profile of different ions deserves a discussion. In fact, it has been shown that the portion of the depth-dose curve where high LET is released is strongly influenced by the particle type [15, 16]. While light particles like protons and helium produce high LET only at the very distal part of the BP, in carbon ions the high LET region corresponds to the entire BP; high LET is released in the proximal part of the BP and therefore in healthy tissues. Intermediate ions from lithium to beryllium may represent a valid compromise [15–17]. At the same time, very high LET radiation is effective in killing hypoxic cells that are normally radioresistant. The oxygen enhancement ratio (OER), defined as the ratio of doses under hypoxia to normoxic conditions needed to obtain the same biological effect, becomes close to one only at LET values for ions heavier than carbon. From the perspective of measuring efficacy in hypoxic tumors, oxygen and neon ions might be promising tools. However, due to their increased charge, such heavy ions release a comparably high LET along the whole peak, thus increasing the risk of normal tissue damage. This suggests that they might be used as a boost treatment for the irradiation of a restricted volume where hypoxic cells are present [7]. This aspect will be analyzed in more detail later. Monte Carlo data also show that the number of fields delivered influences the actual LET distribution. Generally speaking, when multiple fields are considered, a decrease is observed in the maximum LET obtained in the target, but a larger fraction of target volume is covered by high LET [16].

Target conformity is strongly correlated with lateral and longitudinal straggling. It has been shown that lateral straggling of helium, due to multiple Coulomb scattering, is roughly half that of protons [15]. It has also shown that the lateral penumbra obtained with protons for deep targets can be worse than what is achievable with modern photon techniques [21]. However, some of the effect can be mitigated by adopting active scanning instead of passive beam delivery systems [22]. Similarly, range straggling is also maximal for protons and then reduced for increasing atomic mass. Despite that, nuclear interactions also have to be considered, resulting in the production of projectile (for  $A > 1$ ) and target fragments that worsen the quality of the depth-dose profile. For instance, fragmentation is responsible for the tail dose observed in the BP curves. Thus, for particles of increasing mass, fragmentation counterbalances the positive effect of a narrower beam. The tail dose contribution is dependent on the particle range, becoming more pronounced for deep-seated targets. This suggests that at small penetration depths the dose profiles of heavy ions are not largely affected by the tail dose, but become more pronounced with increasing beam energies [17].

**Figure 1** summarizes what has been discussed in terms of physical properties for protons, helium, carbon, and oxygen ions, which are considered the most relevant candidates for advancing particle therapy. These ions are presently available at the HIT facility (Heidelberg, Germany) and will likely be considered soon in MedAustron (Wiener Neustadt, Austria) and CNAO (Pavia, Italy). Concerning the multiple scattering effect (**Figure 1A**; calculated according to the formula proposed by Tobias et al [23]), the latter 2 ions exhibit a similar lateral spreading of the beam, while the difference with helium, and especially with proton, is remarkable. Beside absolute differences in LET and dose delivered by a single particle (**Figure 1B** and **1C**), the relative contribution of the fragmented tail dose is similar for oxygen and carbon, while at the entrance dose the differences obtained with the 2 ions are more pronounced. On the other hand, helium and protons are substantially less effective at the entrance and exit dose.

As mentioned, these considerations are based essentially on simulations performed with different transport codes (analytical or Monte Carlo) and show good general agreement. Nevertheless, these studies should be complemented by measurements of dose profiles and fragmentation cross sections because, apart from protons and carbon ions, little clinical data are available to support simulations. Moreover, this would help to benchmark and improve the beam models adopted in Monte Carlo codes for the alternative ions. For example low charge fragmentation cross-section models (eg, for helium and proton target fragments) are affected by several uncertainties, and the scarcity of experimental data still does not allow for a reliable assessment of the resulting fragmentation spectra. Considering the complexity and the many aspects involved in a thorough comparison, the community would clearly benefit from such efforts.

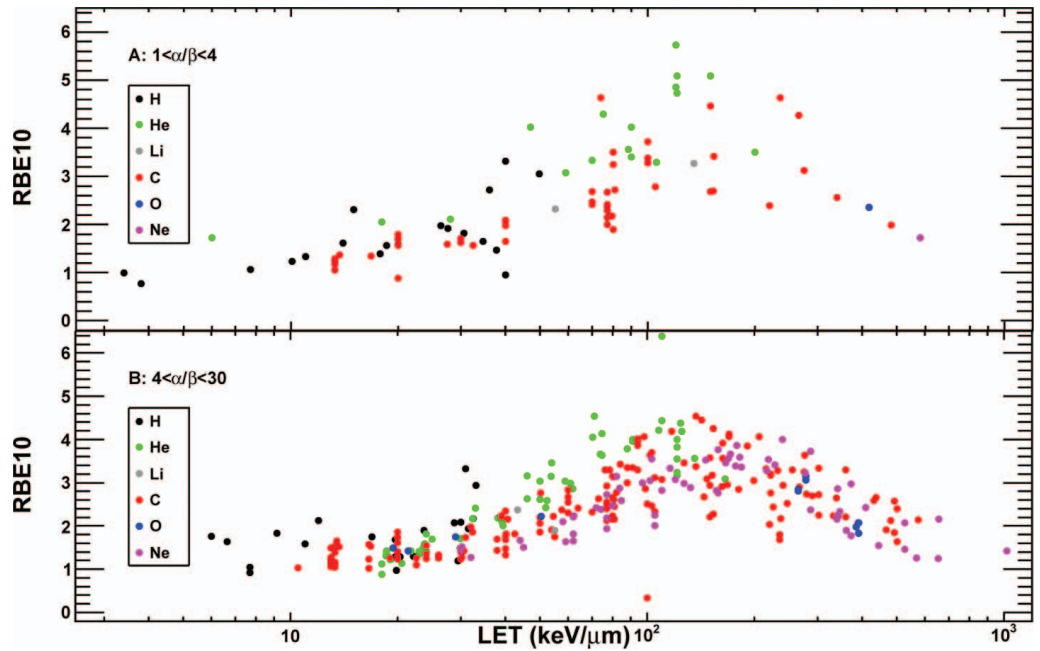


**Figure 1.** Physical properties of different ion beams propagating in water. (A) Width of lateral dose falloff ( $\sigma$ ) due to multiple scattering, (B) Absolute dose per unit fluence. (C) Profiles of dose-averaged linear energy transfer for the irradiation of an extended target of  $2.5 \times 2.5 \times 2.5 \text{ cm}^3$  centered at 8 cm depth in water, with a field optimized on a uniform physical dose (2 Gy). The horizontal line in (C) indicates a linear energy transfer level that can be associated to a significant reduction in the oxygen enhancement ratio. (See also **Figure 5A**.)

Obviously, the differential clinical properties of charged particles cannot be explained based on LET and straggling aspects alone. This is also evident when considering that the RBE associated with charged particles is dependent on many parameters. A nonexhaustive list includes LET, dose and dose fractionation, oxygenation, cell cycle phase, and endpoint considered. This is reflected by the large uncertainties usually affecting RBE measurements. Notwithstanding the limitations of RBE studies, RBE data for endpoints like cell inactivation and crypt cells regeneration still represent the basis for considering biological effects in CPT. Survival of jejunal crypt cells was used to study the RBE of different ions (namely helium, carbon, neon, and argon), not only in the peak region but also in the entrance dose in the 1980s in Berkeley [24, 25]. This allowed researchers to estimate a positive therapeutic ratios for helium, carbon, and neon, which were then used in CPT trials. With argon ions, an inversion was observed with an RBE higher in the plateau than in the peak region as a consequence of the high LET and overkill effects. Thus, argon appears to not be a good candidate for CPT. The RBE was also evaluated and compared for normoxic and hypoxic cells, resulting in increased effectiveness of ions compared with photons under hypoxic conditions due to the reduced OER. This is in line with recent studies that suggest the use of charged particles for boost treatments of hypoxic tumors [13, 26]. This study thus presents an effective and intuitive comparison of the properties of different charged particles, highlighting the therapeutic potential and the relevance of damage in the normal tissue, which is often a limiting factor in clinical practice.

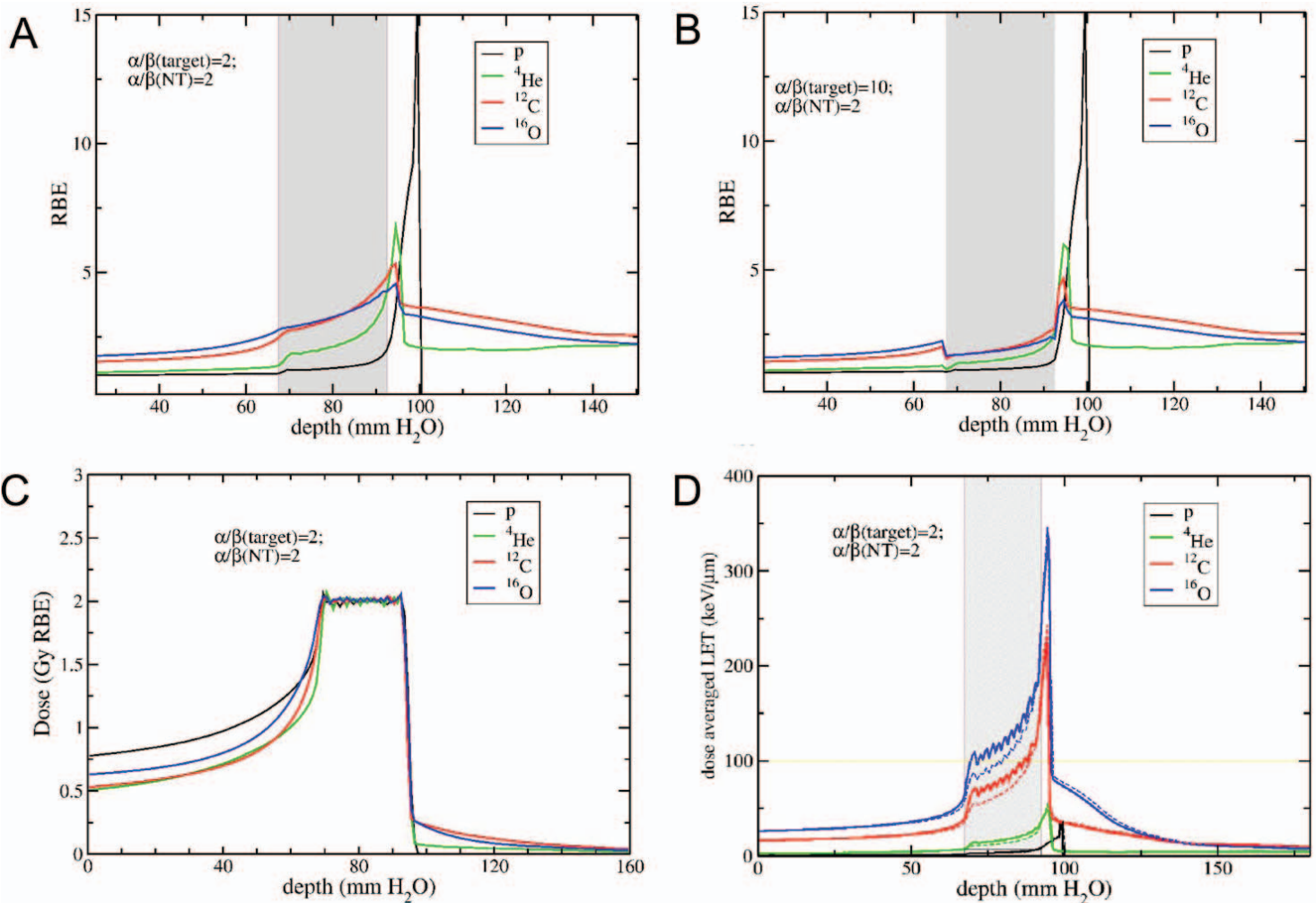
**Figure 2** shows RBE for 10% survival as a function of LET for protons, helium, lithium, carbon, oxygen, and neon. Calculations are based on experimental information (in vitro) extracted from the Particle Irradiation Data Ensemble

**Figure 2.** Biological characteristics (relative biological effectiveness at 10% survival level) of different particles as a function of the linear energy transfer, grouped in different sensitivity ranges. All data are extracted from the Particle Irradiation Data Ensemble [27] database and refer to monoenergetic beam irradiation.



database [27]; data referring to both normal and tumor cell lines are pooled together, and only monoenergetic beams are considered. The data shown in the figure for different ion species are divided in 2 groups depending on the ratio (linear quadratic model parameters). This suggests that, on the one hand, similar RBE values are obtained for both groups and, on the other hand, that a dependence on particle species is observed, with the maximum RBE shifting toward higher LET for increasing particle charge (see also Sorensen et al [28] and Friedrich et al [29] for an in-depth discussion and debate about RBE-LET dependence). This is mostly evident for high ratios because more data are available and the trend is better defined. In fact, the majority of data are measured with cell lines showing a high ratio, which is generally a good representation for cancer cells. In **Figure 2**, we recognize that the data set is really extensive only for carbon ions. A reasonable amount of data is also available for protons and for helium and neon ions. Remarkably, for these particle species a lack of data at high energies is observed as well as only a small amount of data corresponding to low ratio. Despite the potential clinical interest, data are very poor for oxygen and lithium ions. Obtaining basic RBE data over a wide spectrum of energies and cell lines is an essential step for implementing other ions in treatment-planning software. Therefore, it is evident that further experimental effort is needed to fill the current information gaps. Future experiments should include the investigation of RBE at high energies with helium, lithium, and oxygen because of the importance of obtaining an accurate evaluation of side effects in the entrance dose when comparing different ions.

Concerning the balance between cell killing and normal tissue sparing, several *in silico* studies have appeared recently, where treatment-planning software is used to compare the effectiveness of different particle species in terms of tumor control probability and normal tissue complication probability [30, 31]. What clearly emerges from those studies is that no ion species will be superior to the others in every circumstance. There are, rather, specific cases in which the physical and biological properties of one charged particle type can result in the best outcome. Having considered the dependence of the RBE on LET for different particle species, we can now more closely examine the clinical impact of this dependence in treatment planning. For this purpose, we refer to the irradiation of a box-shaped target with dimensions of  $2.5 \times 2.5 \times 2.5 \text{ cm}^3$ , centered at 8 cm depth in water, as simulated with TRiP98 [14, 32]. Active scanning was adopted as the beam delivery method. Irradiation is performed with a single field of alternatively protons and helium, carbon, or oxygen ions; the biological dose to the target is optimized to 2 Gy (RBE), assuming the local effect model for RBE description (LEM IV [33, 34]). Two different tissue types were simulated, assuming a photon ratio of 2 ( $\alpha = 0.1 \text{ Gy}^{-1}$ ,  $\beta = 0.05 \text{ Gy}^{-2}$ ,  $D_t = 8 \text{ Gy}$ ) and of 10 ( $\alpha = 0.5 \text{ Gy}^{-1}$ ,  $\beta = 0.05 \text{ Gy}^{-2}$ ,  $D_t = 14 \text{ Gy}$ ). Two configurations were considered, namely uniform sensitivity—  $\alpha/\beta$  (target) =  $\alpha/\beta$  (normal tissue) = 2 (**Figure 3A**)—and sensitive target—  $\alpha/\beta$  (target) = 10,  $\alpha/\beta$  (normal tissue) = 2 (**Figure 3B**). Target position is highlighted in the figures by the shadowed region. RBE is computed here as the ratio between biological (RBE-weighted) and physical (absorbed) dose. The results nicely show that despite the biological optimization, because of the variable LET profile, RBE is not constant in the target. This is mostly evident in the isosensitivity configuration (**Figure 3A**), while the difference becomes less pronounced



**Figure 3.** Single-field extended target irradiation of an idealized geometry resembling a head and neck tumor ( $25 \times 25 \times 25 \text{ mm}^3$ ) centered at 80-mm depth; the plan was calculated with a relative biological effectiveness (RBE)-weighted dose optimization in the target. RBE profiles for 2 different sensitivity scenarios are shown in (A) and (B). For the first configuration, the resulting biological dose profile (C) is also shown for a better understanding, and the dose average linear energy transfer profiles (D) are compared with those resulting from a physical dose optimization (dashed, from **Figure 1C**).

when a higher value is assigned to the tumor (**Figure 3B**). In any case, the highest RBE is obtained with carbon and oxygen ions, while protons produce the lowest RBE, and helium is in between. Similar behavior, as expected, is obtained in both entrance and exit doses for the 2 configurations. Carbon and oxygen release higher RBE in healthy tissue before the tumor, especially proximal to the target. At the same time, all the ions show a peak in RBE at the distal falloff. This is the result of combined high LET and low doses released behind the tumor. This behavior is especially pronounced for protons, and this can be explained with the very low local doses (as seen in **Figure 3C** at the distal falloff). Thus, despite the very high RBE, consequent biological effects are not obvious but might deserve consideration, for example, in extending the effective range of the irradiation [35]. Finally, **Figure 3D** shows the corresponding dose-averaged LET profile compared with those ones arising from a physical dose optimization. The RBE values obtained with the different ions at different positions along the irradiation field are reported in the **Table** for both configurations.

A different analysis is shown in **Figure 4**. Still based on the same target described earlier, irradiation is now performed with 2 opposing fields. In **Figure 4A**, the physical dose released by the different charged particles is compared for the delivery of 2 Gy homogeneous doses to the target. In this case, for the same dose to the target, a higher dose to the surrounding normal tissues is released by carbon and oxygen compared with protons and helium. Biological optimization was also performed, for the 2 configurations of target and normal tissues described earlier. Results obtained for the ratio equal to 2 for target and normal tissue are shown in **Figure 4B**, while **Figure 4C** refers to the ratio equal to 10 for the tumor and 2 for

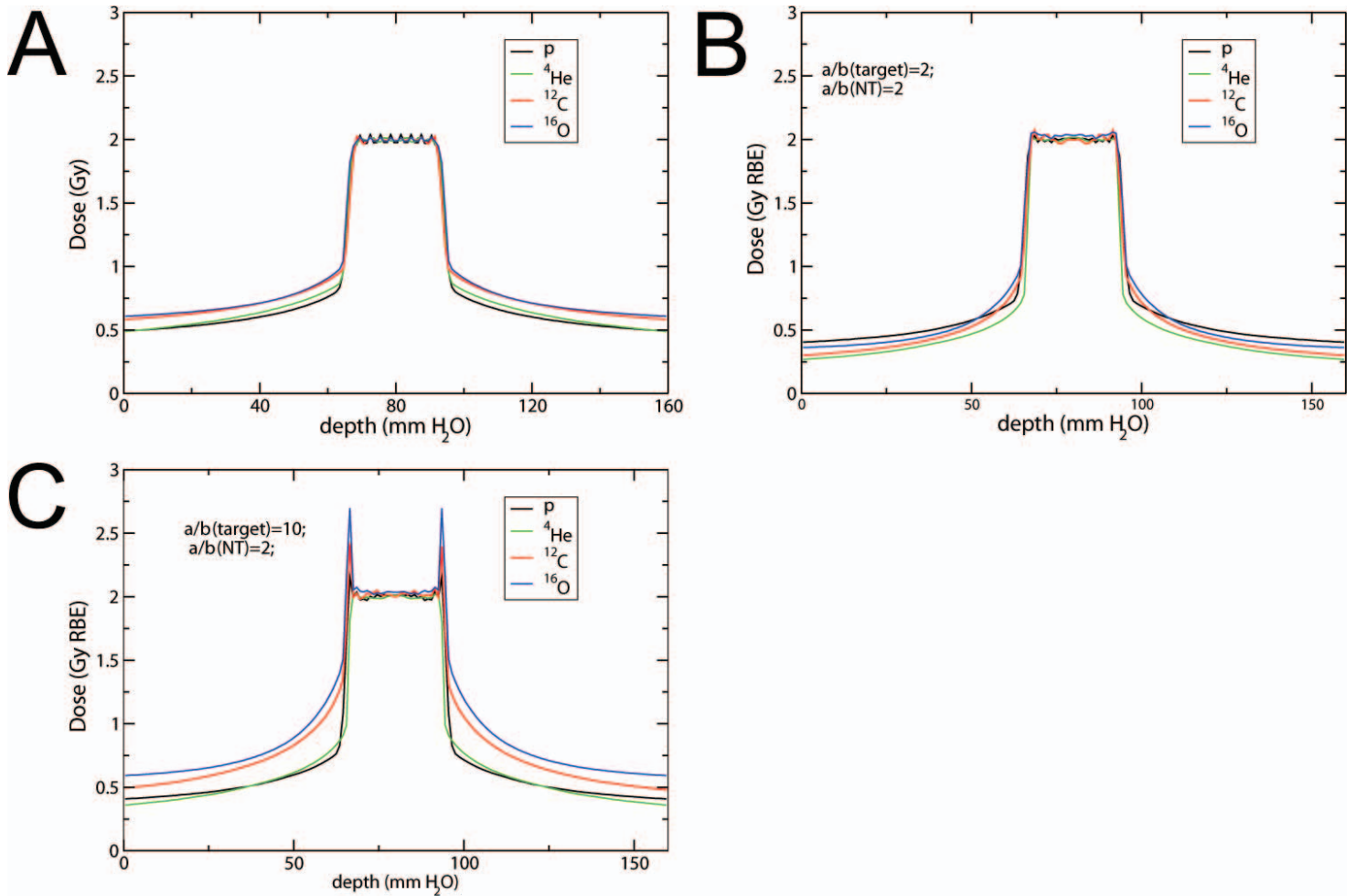
**Table 1.** Relative biological effectiveness (RBE) at different depth positions for the extended target irradiation shown in **Figure 3**. Two different sensitivity scenarios were considered, with different RBE ratios assigned to target (T) and normal tissue (NT).

Ion species	RBE, $(\alpha/\beta)_T = (\alpha/\beta)_{NT} = 2\text{Gy}$				RBE, $(\alpha/\beta)_T = 10; (\alpha/\beta)_{NT} = 2\text{Gy}$			
	Entrance (0 mm)	Proximal (67.5 mm)	Mid (80 mm)	Distal (92.5 mm)	Entrance (0 mm)	Proximal (67.5 mm)	Mid (80 mm)	Distal (92.5 mm)
Proton	1.00	1.13	1.27	2.00	1.00	1.06	1.14	1.51
Helium	1.07	1.52	2.11	4.26	1.06	1.22	1.50	2.57
Carbon	1.44	2.61	3.24	4.82	1.36	1.63	1.92	2.70
Oxygen	1.68	2.83	3.28	4.26	1.55	1.68	1.86	2.31

healthy tissues. In the first case, we observe that the optimal sparing of normal tissues is obtained with helium ions. Protons release the highest biological dose in the entrance, while in the region proximal to the target we observe carbon and oxygen curves crossing with the protons' profile and resulting in a higher biological dose. The situation changes quite drastically when considering the second configuration (**Figure 4C**). In this case, similar results are obtained with protons and helium, showing the highest peak to entrance ratio. On the contrary, a higher dose is clearly released to normal tissues by carbon and oxygen. Our results suggest that not only the physics of the different ion beams but also the biological aspects strongly influence the resulting dose profiles. Therefore, the choice of the optimal ion depends on the specific tumor configuration. This is in agreement with findings recently published in other works [30, 31]. Indeed, a thorough comparison should also consider the different physical aspects discussed earlier (eg, straggling and fragmentation), which were shown to have a different impact according to target depth and extension. Remarkably, TRIP98 was recently shown to be suitable for performing simultaneous optimizations for different ion species, realizing a proof of principle plan combining proton and carbon, exploiting the advantages of both particles for a specific target, but allowing in principle the use of other ions, namely helium, carbon, and oxygen [14]. This is a critical step toward possible future clinical implementations of multi-ion treatments. A large-scale study performed on realistic treatment plans rather than on simplified geometries would also be of great benefit. The discussion up to now has mostly been based on *in silico* studies, which may now guide dedicated radiobiological experiments (possibly conducted *in vivo*) directly comparing the effects of different particles.

## Targeting Hypoxia

While conventional research in treatment-planning studies with ion beams was always based on RBE-weighted dose optimization, a further step in a biological based treatment is accounting for effects related to the local microenvironment, as, for instance, in tumor hypoxia. In **Figure 5A** we show the OER as a function of the dose-averaged LET for monoenergetic beams of different ion species, combining published experimental data [36, 37] with a fit analysis for carbon and neon [12]. The results show a drastic change in OER inside the therapeutic LET range. This is well defined for carbon, thanks to the data available. On the contrary, wide experimental information is not available for oxygen, even though this ion species, given its physical properties, is the favorite candidate for the treatment of hypoxic tumors (see earlier discussion). However, when comparing the fitted profiles it clearly emerges that, apart from the contribution of dose-averaged LET, very weak particle dependence (if any) is present for quite a broad variation of ion type (from  $Z = 6$  to 10). Therefore, from the single oxygen point lying exactly on the carbon curve, it could be assumed that using the same OER (LET) dependence for these 2 ions can be considered a very good approximation. As seen in **Figure 3D**, the LET profile of a field is also extremely skewed after an RBE-weighted dose optimization. Thus, approaches based on crafting the LET distribution were proposed for the treatment of tumor hypoxia; these were based on the adoption of specific beam shapes (ie, dose ramps) able to focus the maximum LET in a defined region (ie, LET painting [13, 26]). More recently, researchers have introduced the possibility of directly including oxygenation levels in the treatment planning for ion beams, thus aiming to restore a flat survival level across the whole target (so-called kill-painting) [12]. According to this method, in **Figure 5** we consider the effects of carbon and oxygen irradiation for a box-shaped target ( $4 \times 4 \times 6 \text{ cm}^3$ ) with different oxygenation, composed by CHO cells (used for biological dosimetry). Specifically, the normoxic case (**Figure 5B**) is compared with the case when the target is divided in regions of different oxygenation (**Figure 5C**), presenting the highest level of hypoxia (0% oxygenation) in its center (orange) and 0.5% around it (yellow). In the second case, both ions are optimized, including RBE and OER, in order to obtain the prescribed survival level, with the minimum increase in the entrance dose. Remarkably, we observe a clear inversion in the resulting profiles when comparing the 2 configurations, with oxygen showing clear advantages over carbon ion in the case of hypoxic target.



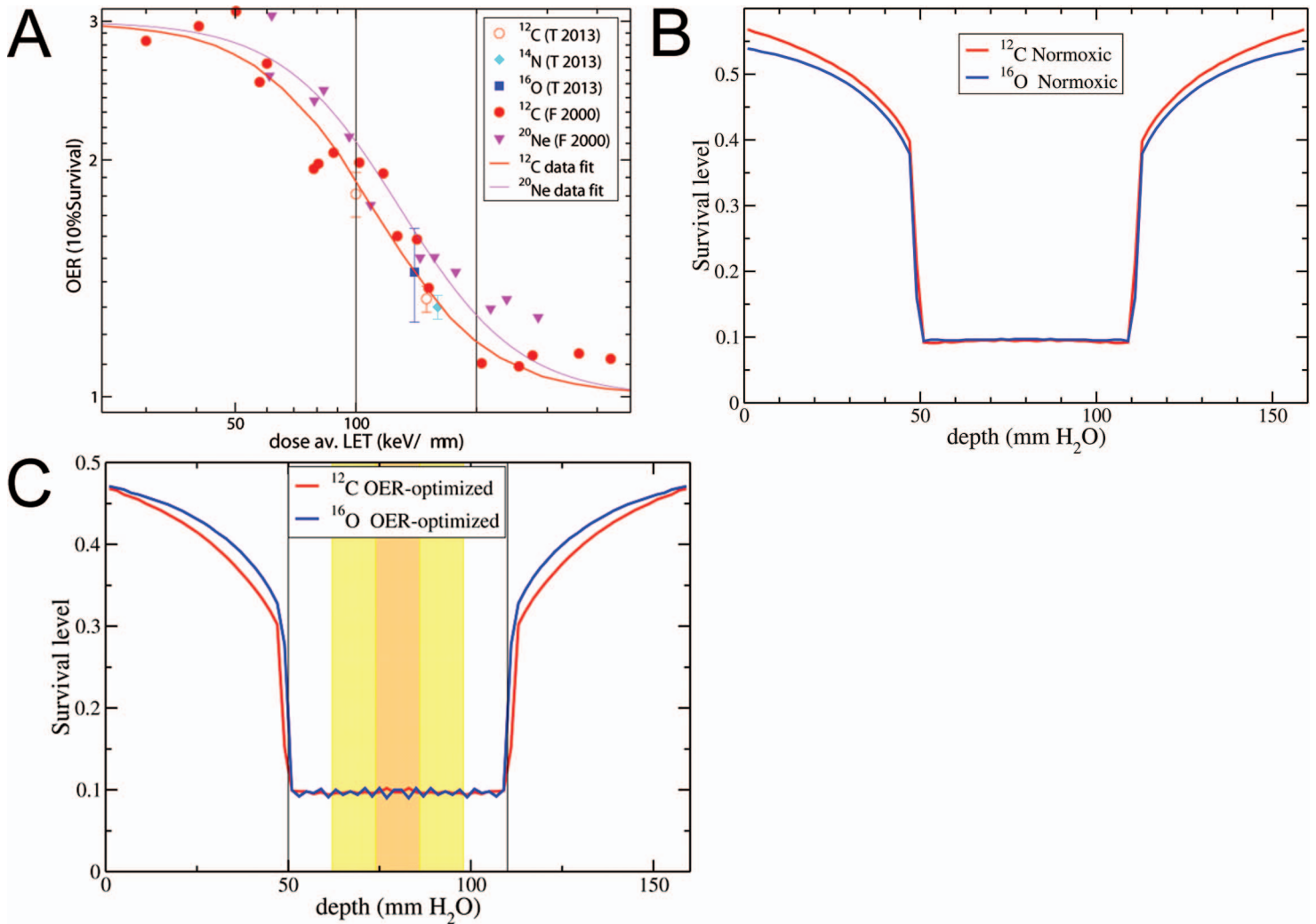
**Figure 4.** Double opposed field irradiation of an idealized geometry simulating a typical case of head and neck cancer. The tumor ( $25 \times 25 \times 25 \text{ mm}^3$ ) is centered in an irradiation volume of 16-cm length. Physical dose optimization was performed (A), as opposed to relative biological effectiveness–weighted dose optimization for different sensitivity scenarios in (B) and (C).

### Other Applications

Recent advances in biological sciences have made it possible to extend our understanding of genetic aspects of cancers. Thus, it is no longer unrealistic to hypothesize that in the future it could be possible to select patients for radiotherapy based on the effectiveness expected according to their genetic background. At the same time, it is increasingly clear that different radiation qualities elicit different biological response at different levels, from the subcellular to the tissue level [38–40]. Importantly, this seems to be dependent mostly on the ionization density rather than on the dose delivered. This opens new interesting scenarios for exploiting different charged particle types in CPT and for evaluating associated risks [41, 42].

Interest is also increasing toward possible applications of charge particles to the treatment of diseases other than cancer [43]. This is also triggered by the improved conformity made possible by active scanning techniques. Atrial fibrillation, renal denervation, trigeminal neuralgia, epilepsy, and macular degeneration are among the illnesses for which photon radiation therapy has been already applied. In all these cases, the increased ballistic precision offered by ions could enhance the therapeutic outcome compared with photons. Limited clinical studies have already been performed with protons for the treatment of arteriovenous malformations. Importantly, new scenarios might be opened by the possibility of optimizing the choice of the charged particle according to a given disease and based on the physical and biological properties of the different radiation qualities. However, some issues have to be considered, first of all the implementation of adequate motion mitigation techniques. Present estimations suggest that charged particles might find practical application for the cure of noncancer diseases in the next 10 years. Preliminary in silico studies are needed to identify diseases most likely to benefit from charged particle irradiation, which should be followed by dedicated in vitro and in vivo studies.





**Figure 5.** (A) Oxygen enhancement ratio (OER) in full anoxia (0%  $\text{O}_2$ ) and 10% survival as a function of dose averaged linear energy transfer for mono-energetic irradiation with different ion species, as measured in Furusawa et al [36] and Ma et al [37] for CHO and V79 cell lines, and including experimental data fit for carbon and neon with the formula in Scifoni et al [12]. (B) double opposed field irradiation for a fully normoxic and (C) partially hypoxic idealized tumor of  $4 \times 4 \times 6 \text{ cm}^3$  with oxygen and carbon beams. In the hypoxic case, the plan accounts for OER in the different regions with different oxygen concentrations and optimizes the fields accordingly.

## Conclusions

Broadening the spectrum of ions to be used in clinical applications might open new frontiers in CPT. When looking at the exquisite physical and biological properties offered by different ion species, this statement appears obvious. However, up to now several technical issues made impractical the use of ions other than protons and carbon ions. With the spread of active scanning techniques in charged particle facilities, it is possible to conceive a therapeutic scenario where the characteristics of different radiation qualities are optimally exploited. In silico studies on a larger scale are necessary to support the promising indications coming from first investigations. Dedicated radiobiological experiments should follow to confirm the outcome of simulations. In parallel, additional technical effort is needed to improve the robustness and feasibility of motion mitigation techniques. This would be an important step for extending the use of charged particles to the treatment of noncancer disease, for which precision is also critical.

In the next years, the final goal of following this road map should be the clinical implementation of radiation-quality optimized treatments based on adapting the selection of particle species to the specific patient and disease characteristics, an important step toward personalized medicine.

## ADDITIONAL INFORMATION AND DECLARATIONS

**Conflicts of interest:** The authors have no conflicts to disclose.

**Acknowledgments:** We thank Michael Krämer and Rebecca Grün for fruitful discussions during preparation of this manuscript. This work was partly funded by Portfolio Technologie und Medizin (Helmholtz Gemeinschaft), TIFPA-INFN Trento and by the EU FP7 programme ITN-ARGENT, grant agreement 608163.

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