State-of-the-art and future prospects of ion beam therapy: physical and radiobiological aspects

Michael Scholz

Abstract— **The number of facilities offering radiotherapy with protons or heavier ions is continuously increasing; worldwide, more than 160000 patients have been treated with protons, and more than 25000 with heavier ions. Despite this substantial clinical experience, there is still a need for further developments and improvements which are specific to the properties of particle beams. This contribution briefly summarizes the main physical and radiobiological properties of ion beams which make them favorable for application in tumor therapy. In addition, major challenges that are currently addressed in different research areas are reviewed. These comprise the fields of biophysical modelling, treatment planning, mitigation of target motion and novel approaches based on particular spatio-temporal beam delivery techniques.**

Index Terms— **Biomedical applications of radiation, protons, ion beams, radiotherapy.**

I. INTRODUCTION

Ion beam therapy represents a rapidly developing branch of radiotherapy, mainly using proton beams and - to a lower extent - also heavier ions like e.g. carbon ion beams. After the proposal by Wilson [1] to use ion beams for medical applications, first clinical applications were implemented with proton beams at Berkeley in 1954 [2] and in 1957 at Uppsala [3]; treatments with He beams were initiated in 1957 and with heavier ions in 1975 also at Berkeley [2].

Until the establishment of a dedicated, clinically based proton therapy in Loma Linda with first patient treatments in 1990, therapeutic applications were restricted to accelerator facilities generally built for fundamental physics research purposes. In the following decades, the number of dedicated proton and since 1994 also carbon ion therapy facilities is continuously rising; currently 68 proton facilities and 12 carbon ion facilities are in operation [4]. But in addition, the number of facilities under construction or planned is still substantially increasing.

The main motivation for application of ion beams in radiotherapy is their advantageous depth dose profile, allowing maximizing the dose to the tumor by simultaneously

M. Scholz is with the GSI Helmholtzzentrum für Schwerionenforschung GmbH, D-64291 Darmstadt, Germany (email: m.scholz@gsi.de).

sparing the surrounding normal tissue as compared to conventional photon radiation. Whereas this property is shared by all ion species, in particular heavier ions like carbon ions show an additional advantage with respect to their biological effectiveness. They exhibit an increased biological effectiveness in particular towards lower energies, i.e. in the region where they come to rest when penetrating tissue (the so-called "Bragg peak"). These main characteristics are depicted in a schematic way in Figs. 1. In addition, lateral scattering of heavier ions is substantially reduced as compared to protons, thus allowing to spare normal tissue at the side of treatment fields.
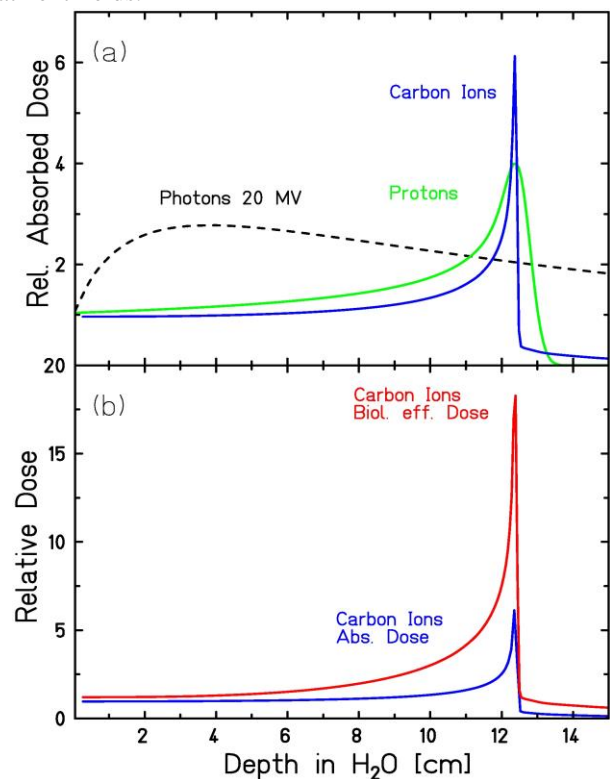

Fig. 1. (a) Schematic comparison of absorbed depth dose profiles for protons and carbon ions with high energetic photons. (b) Comparison of absorbed depth doses profiles and effective dose for carbon ions.

Since the longitudinal extension of a Bragg peak is only in the order of a few mm and thus much smaller than the typical extension of a tumor, several Bragg peaks at different positions in depth have to be superimposed in order to achieve a homogenous coverage of the target volume in depth (see Fig.

2). This variation in depth can be either achieved by passive methods, e.g. using ridge filters, or by active energy variation.

Furthermore, also lateral shaping of the treatment field can be achieved by passive as well as active methods. Passive methods are based on collimators, whereas active methods exploit the possibility of magnetic deflection of a narrow pencil beam. Combining active energy variation with magnetic lateral scanning of a pencil beams allows the optimal conformation of the dose also to almost any irregular shaped target volume [5].

Although already in clinical use, the full potential of ion beams in therapy has not yet been exploited. This review will thus briefly describe the state-of-the-art and the fields of ongoing research, addressing major important challenges in ion beam therapy. As a quite broad range of aspects is covered in this review, it is not intended to be exhaustive, but rather pointing to a selection of topics that are considered to be relevant from a biophysicists point of view.
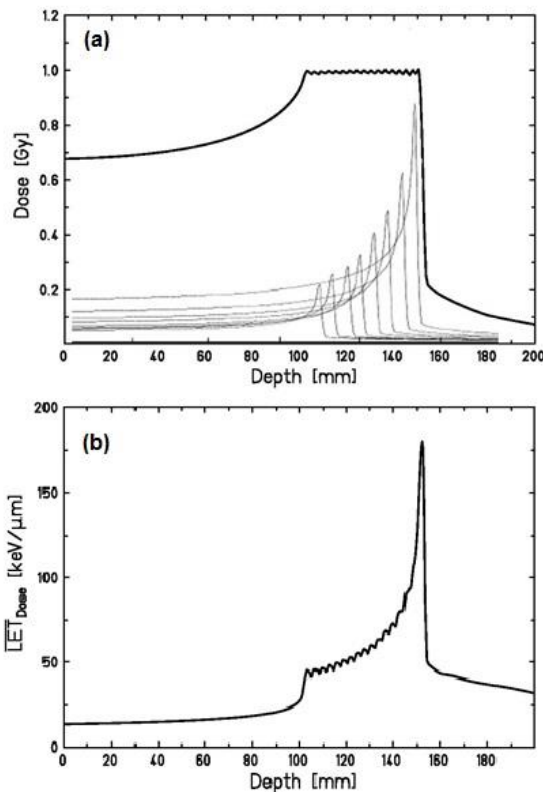

Fig. 2. (a) Production of spread-out Bragg-peaks (SOBP) for irradiation of extended volumes by superposition of individual Bragg peaks with different depth. Appropriate weighting of individual beams allows shaping of the corresponding depth dose profile. (b) Corresponding distribution of linear energy transfer (LET) values, which are indicative of the increased biological effectiveness.

II. BIOLOGICAL EFFECTS OF ION BEAMS

A. Definition of the relative biological effectiveness

In general, ion beams exhibit an increased biological effectiveness as compared to conventional photon radiation, i.e. a lower dose is required to achieve a desired biological effect, e.g. a given level of cell killing. In terms of typical dose response curves depicting the fraction of surviving cells after radiation this is reflected in the steeper slope of survival curves as schematically shown in Fig. 3.

INSERT FIGURE 3 ABOUT HERE

The relative biological effectiveness is defined by the doses required to achieve a given survival level with photons and ion beams, respectively:

$$RBE = \frac{D_{Photon}}{D_{Ion}}\bigg|_{Isoeffect}$$

However, the curves for ion irradiation are not only steeper, but at the same time also the shape of the dose response curves changes, as they typically get straighter as compared to the shouldered shape of survival curves observed after conventional photon radiation.

The dose response curves are characterized in general in terms of the linear-quadratic (LQ) model:

$$S(D) = e^{-(\alpha D + \beta D^2)}$$

$$\alpha_{Ion} \geq \alpha_{Photon}$$
$$\beta_{Ion} \leq \beta_{Photon}$$

The changes primarily result from the increase of the linear term α, whereas the impact on the quadratic term is less pronounced and subject to larger uncertainties. As a consequence of the more linear dose response curves after ion irradiation, the RBE depends on the effect level for which it is determined. In general, RBE is maximal at low doses and decreases towards higher doses and correspondingly lower cell survival levels. Furthermore, the RBE varies with energy and thus with the stopping power of the ions as characterized by the linear energy transfer (LET).

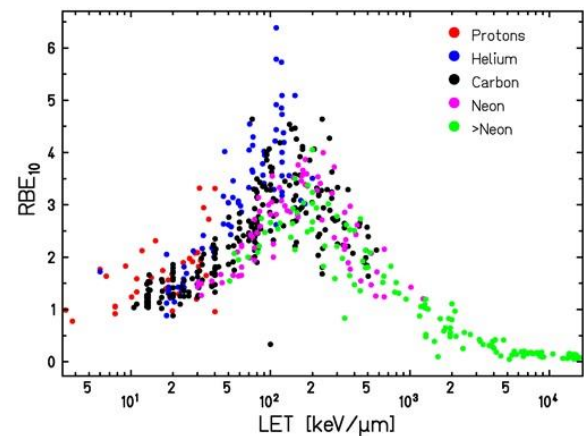Fig. 3. Schematic comparison of dose response curves for cell survival after photon and ion irradiation.

Fig. 4. RBE at 10% survival level as a function of the linear energy transfer for different ion species; compilation based on the PIDE data base (Friedrich et al. 2012; for details see text).

B. In-vitro studies of RBE

In order to study these systematic dependencies, numerous *in-vitro* studies have been performed to determine the RBE for a wide panel of different cell lines, ion beam species and irradiation conditions. Friedrich et al. [6] have compiled these data in the PIDE (Particle Irradiation Data Ensemble), which contains more than 1000 published cell survival curves obtained with a wide variety of different ion beams and cell types and is continuously updated with new data[1].

Based on these *in-vitro* studies, the fundamental characteristics of ion beam radiation as compared to photon radiation can be summarized as follows (see Fig. 4):

1. RBE rises with LET up to a certain maximum and drops toward higher LET values
2. The RBE(LET) curves are shifted towards higher LET values with increasing particle mass
3. RBE decreases with increasing dose and thus decreasing survival level
4. RBE in general is higher for cells that are radioresistant against conventional photon radiation as compared to cells that are sensitive against photon radiation.

The LET dependencies can be interpreted based on the microscopic features of the energy deposition pattern of individual ions. With increasing LET, the local energy deposition within the particle tracks increases, leading to more complex damages and thus an increasing biological effectiveness [7][8].

At very high LET values, however, saturation effects occur, leading to a corresponding decrease of the biological effectiveness. The cell line dependence can be explained by the corresponding differences in the photon dose response curves: whereas radioresistant cell lines are typically characterized by a pronounced shoulder of the photon dose response curve, very sensitive cell lines exhibit a steeper and straighter photon dose response curve. Therefore, for resistant cell lines a higher gain in effectiveness is expected when comparing high doses to low doses; combining this information with the more pronounced contribution of high local energy deposition for ion beam radiation, a higher RBE can be expected in the case of radioresistant cell lines [9]. The dose dependence, as mentioned above, can be traced back to the differences in the general shape of the dose response curves.

For the dose prescription in ion beam therapy, the increased effectiveness needs to be adequately taken into account. As a consequence of the above mentioned complex dependencies of RBE, this obviously is not a trivial task, and the strategies developed in that direction will be addressed in more detail in sections 1.3 and 1.4.

As a result of the inverted depth dose profile and the resulting sparing of the normal tissue surrounding the tumor, higher doses per fraction to the tumor are feasible in ion beam therapy as compared to conventional treatment modalities without enhanced side effects. The accurate understanding of the high-dose portion of the dose response curves is thus of high importance. Concerning the photon dose response curve there is clear evidence that the pure linear-quadratic model that is generally used to characterize the dose response curves is valid only in the low and intermediate dose range, and a transition to a more straight shape is observed towards higher doses (approx. 5-10 Gy) [10][11][12][13]. This deviation from the LQ-shape might also affect RBE values at high doses; the

---

[1]   PIDE is freely available upon registration at https://www.gsi.de/work/forschung/biophysik/forschungsfelder/radiobiological_modelling/pide_project.htm

corresponding analysis of the high-dose part of high-LET dose response curves is therefore of utmost importance for applications of hypofractionation in ion beam therapy [14]. Limitations of the LQ-model might also occur at very low doses (< 1Gy), if cell lines exhibit the so-called "low dose hypersensitivity", which is characterized by a steep initial slope, followed by a transition to the normal LQ-shape. However, this effect is not observed in all cell lines, and the deviation is less critical with respect to RBE determination as the contribution to the overall effect of such low doses is still small.

C. In-vivo studies of RBE

Most of the systematic studies that have been performed to characterize the radiobiological properties of ion beams are based on *in-vitro* cell culture experiments, in particular on measurements of cell survival using the so called "clonogenic assay". In this assay, the continuous proliferative capacity of individual cells and their ability to build colonies with more than 50 daughter cells is used to define the survival of cells. This continuous cell division, however, more resembles the situation of tumor like tissues, but is considered to be less relevant to mimic normal tissue response. In that respect, to distinguish between e.g. rodent and human cell lines might be less important, as in general the systematic dependencies on LET, dose etc. do not qualitatively differ between these cell lines.

A more relevant aspect to be considered is that in general *in-vitro* assays based on single cells do not reflect the high complexity of biological processes, e.g. cell-cell interactions, underlying the radiation response of tissues and are thus of limited value with respect to a direct quantitative translation to the clinical situation. *In-vivo* animal experiments thus represent the next important step to validate the systematic dependencies described above for other biological endpoints more closely related to the clinical situation.

One important aspect that can be better addressed with *in-vivo* experiments is related to therapeutic benefit of different ion species, where the therapeutic benefit is defined by the balance between tumor RBE and surrounding tissue RBE. If the RBE in the tumor is low, but high in the surrounding tissue little advantage is expected for heavier ions compared to protons, whereas in the opposite case of a high tumor RBE and low normal tissue RBE the highest benefit is expected. Strategies for application of ion beams thus should always be based on consideration these differential RBE effects.

The Japanese facilities have chosen e.g. skin response or intestinal crypt cell survival as normal tissue response to determine the therapeutic ratio / gain of carbon ion irradiation and conclude that larger doses per fraction might be beneficial in carbon ion treatments to maximize the therapeutic benefit [15][16][17]. For the treatment of tumors in the head and neck region, the central nervous system represents another particularly relevant normal tissue system that needs to be spared in radiotherapy treatments. Therefore, in the framework of the pilot project with carbon ions performed at GSI, an extended series of measurements of tolerance doses for the rat spinal cord has been performed, comprising 1 Fx, 2 Fx, 6 Fx and 18 Fx irradiations [18][19]. These studies thus cover a broad range of fractionation schemes that come very close to the 20 Fx scheme that was applied in the framework of the pilot project for carbon ion treatments at GSI. Apart from the clinical relevance of this endpoint, the system is particularly suitable for accurate RBE determinations due to the small cross section of the animal's spinal cord. The target can thus be precisely positioned in the radiation field, and differential measurements with varying radiation quality along the penetration depth of a treatment field can be performed with high resolution. More recently, these studies have been substantially extended to a wider range of radiation qualities [20][21][22], and studies are ongoing also with other ion species like e.g. protons [23], He ions and O ions. Despite the much more complex biological endpoint, in general these studies qualitatively confirm the systematic dependencies with respect to dose- and LET dependencies as described above for *in-vitro* cell culture studies.

Comparably few studies have been performed concerning the tumor response in the framework of carbon ion therapy. Ando et al.[16] report a combined study to determine the biological gain of carbon-ion radiotherapy for the early response of tumor growth delay and against early response of skin reaction in mice. Sørensen [24] compare tumor control, acute skin reactions and late radiation induced fibrosis in a mouse model. Brownstein et al. [25] analyze the response of primary sarcomas in a mouse model after carbon ion irradiation. Systematic studies using different sublines of a syngeneic prostate carcinoma model have been reported in [26][27][28][29]. Three different sublines of this tumor model are available, characterized by different radiosensitivities. As observed also *in-vitro*, the most resistant tumor showed the highest RBE value, whereas the most sensitive tumor is characterized by the lowest RBE value. It is, however, important to note that this variation in RBE is a consequence of the large variation of sensitivity against photon radiation, whereas after ion beam irradiation the variations were much less pronounced [28][29] (see Fig. 5). This again is compatible with results from *in-vitro* studies, showing that in general the range of variation in radiosensitivity observed after low-LET radiation is substantially compressed after high LET radiation [9]. This aspect is also relevant with respect to the heterogeneity of tumor cells, which is expected to affect the overall survival of tumor cells after photon radiation more pronounced as after ion beam irradiation. This results in a steeper TCP curve for ion irradiation, i.e. a larger incremental control probability per percent increase in dose [30].
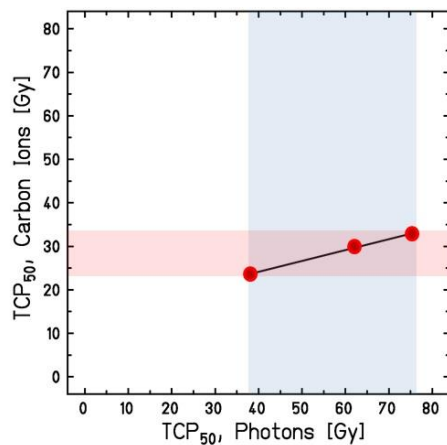
Fig. 5. Variation of doses to achieve 50% tumor control probability for a panel of three tumor types showing a very broad range of different sensitivities against photon radiation, indicated by the light blue band. In contrast, the variation of sensitivities is largely suppressed after carbon ion irradiation, as indicated by the much smaller light red band. Based on data reported by Glowa et al. (2017).

Another important aspect of high-LET radiation is the reduced dependence of the effectiveness on the oxygen concentration in the surrounding medium. In general, about 3-times higher doses are required to kill fully anoxic cells as for killing of well oxygenated cells. This is described by the Oxygen Enhancement Ratio (OER), defined by the ratio of doses required to kill the same fraction of cells under hypoxic and oxic conditions, respectively. The OER drops with increasing LET, and approaches values close to 1 at very high LET (>100-200 keV/µm) [31][32][33][34], reflecting the independence of the biological response to the oxygen concentration in this case and indicating an advantage of high-LET radiation in particular in the case of hypoxic tumors.

D. Specific aspects for protons

For protons, in general the differences in biological effectiveness as compared to photon radiation are less pronounced due to their lower LET [35]. This motivates simplified approaches to take RBE into account in treatment planning; currently it is thus recommended to simply multiply the absorbed dose by a constant RBE of 1.1 [36]. Nevertheless, *in-vitro* experiments clearly show a significant rise of RBE towards the end of a SOBP, and at the distal edge typically RBE values substantially higher than the clinically applied value of 1.1 are observed [35][37]. However, reports about unexpected effects in patient treatment that can uniquely be attributed to such an increased RBE are scarce. For example, Peeler et al. [38] report about the first clinical evidence for a correlation between normal tissue damage and LET in proton treatments of ependynoma. Gensheimer et al. [39] analyzed an overshoot of the proton beam visible in MR images; this overshoot effect might be attributable to an increased RBE at the distal edge [37]. But it remains to be elucidated how the apparent discrepancy between *in-vitro* and clinical results can be resolved, and the debate about whether variable RBE values larger than 1.1 need to be used in treatment planning is still ongoing [40][41][43][44]. Additional in-vivo experiments to determine tolerance doses of late responding tissues, e.g. spinal cord, after proton irradiation could help to bridge the gap between in-vitro systems and clinical data. Saager et al. [42] have reported first measurements; however, these experiments were restricted to 1F and 2F irradiations involving very high doses per fraction, and therefore further experiments with fraction doses in the therapeutically relevant regime are highly desirable here.

One potential explanation of this apparent discrepancy might be due to the small volumes in which typically enhanced RBE values are expected in proton therapy. Although partial volume dependent tolerance doses have been analyzed [45][46], there is still substantial lack of data to estimate tolerance doses particularly for the case that only very small subvolumes of an organ are irradiated. This urgently calls for experiments to better understand the mechanisms relevant for recovery from tissue damage and their role in partial volume irradiation, similar to those reported e.g. in [47][48][49].

E. Combined treatments

Finally, with respect to clinical applications the understanding of combined treatments, e.g. chemotherapy + Rx and immunotherapy + Rx are of great interest, and several studies have been reported in this direction. For example, Melzig et al. [50] have combined external carbon ion beam therapy in combination with radioactive labeled antibodies against a cell surface receptor involved in cell growth; they report an activation of the immune-response by carbon ions that markedly enhanced the antibody based therapy. Ohkubo et al. [51] analyzed the antimetastatic efficacy of a combination of carbon ion radiotherapy and immunotherapy by use of an in vivo murine model; they report the effective inhibition of distant metastasis after this combination therapy. Durante et al. [52][53] discuss potential mechanisms that are involved in the radiation induced activation of immune pathways.

III. BIOPHYSICAL MODELLING

As a consequence of the complex RBE dependencies discussed above, RBE values e.g. will vary across the tumor and depend on the fractionation scheme used, and in general they can therefore not adequately be represented by a single number for conversion of absorbed dose to RBE-weighted dose. To fully exploit the advantageous properties of ion beams, the systematic dependencies of the RBE have to be considered adequately in treatment planning in ion beam therapy, allowing taking advantage of the vast experience made with conventional photon therapy.

8/12/2019 MS_IEEE_20190812_CameraReady.docx

Biophysical models can represent an important tool for treatment planning in that respect. However, the transition from the initial energy deposition to the final observable biological effect after a radiation insult includes numerous complex biological processes and pathways, from which many are still unknown or at least not yet accurately quantified, and any model thus can represent an approximation to reality only. One of the major challenges of modeling in the framework of treatment planning therefore is to find the right balance between accuracy and model complexity, i.e. number of different processes and mechanisms to be taken into account. A higher level of detail corresponds to an increasing number of degrees of freedom by introduction of additional parameters. If, however, the number of degrees of freedom is too high, no significant parameter values can be expected any more when fitting the model to experimental data. In contrast, if a model has too few degrees of freedom, the model is incomplete, corresponding to a reduced predictive power of the model. One has to keep in mind that as a consequence of the required approximations different ways of approximation might be feasible, which may lead to similar predictions, even if assumptions about the underlying mechanisms are different.

At present, two different models are actually used in treatment planning for carbon ion beam therapy: the Microdosimetric-Kinetic Model (MKM) is used in the Japanese facilities, whereas the Local Effect Model (LEM) is used in the European facilities. In both approaches, the characterization of the microscopic energy deposition pattern represents a major ingredient, although the details how this energy deposition pattern is translated into a biological response substantially differs. The characterization of the dose response curve after low-LET radiation represents the second pillar of these models.

The MKM makes use of characterization of energy deposition in micrometer sized volumes. Its original version has been developed by Hawkins [54][55][56], and subsequent further developments have been implemented in the framework of the Japanese heavy ion therapy projects. For example, a correction related to the overkill effect at very high LET has been introduced [57] and implemented in a treatment planning environment [58]. In the meantime, it serves as a replacement for the former experimentally based approach used to optimize the shape of SOBPs in the Japanese treatment planning approach (for details see section IV).

The LEM is in its original version (LEM I; [59]) is used for treatment planning in the European carbon ion facilities. It resembles the MKM approach in that it directly translates the microscopic energy deposition pattern into an observable biological effect, i.e. cell killing. The model had been further developed and improved to achieve better agreement with experimental data [60][61]. In the most recent version (LEM IV; [62][63]), the major change as compared to the LEM I is the introduction of an intermediate step, where first the microscopic distribution of DNA damages is calculated, and based on the evaluation of the clustering properties of these DNA damages the final observable effect is determined. LEM IV has been demonstrated to accurately represent experimental

data *in-vitro* over a larger range of different ion species from protons to oxygen ions [64][65][66]. Furthermore, besides *in-vitro* experiments also RBE for *in-vivo* experiments, e.g. the tolerance of the rat spinal cord, can be modelled with LEM IV [21][22]. Interestingly, the concept of damage classification that had been developed for the LEM IV has been demonstrated to be applicable also to other radiation qualities, and several key aspects like LQ-shape of survival curves, rejoining kinetics, dose rate effects and cell cycle effects can be correctly modeled by this approach [67][68][69][70].

Apart from the LEM and the MKM, other approaches are discussed for potential applications in ion beam therapy, as e.g. reported in [71][72][73]. However, a conceptual comparison of the models has revealed substantial differences e.g. with respect to the impact of overkill at very high LET and the change of the quadratic component with LET (Fig. 6, see also [74]), suggesting the need for more detailed validation of the models by means of experimental data in order to assess the impact of these model differences on the accuracy of the model prediction.

The demand for RBE modelling is clearly more relevant in the case of heavier ions as for protons, since RBE values are substantially greater for heavy ions, and it is still under discussion in how far a variable RBE instead of using a constant RBE=1.1 could be beneficial in proton therapy. The MKM and LEM are models applicable over a broad range of particles, covering protons as well. However, numerous simplified, empirical models have been also proposed which are applicable solely to the case of protons, as they are based on certain simplified assumptions that are not valid for heavier ions. A common concept behind many of these models is the characterization of RBE in terms of LET_d. Despite this similarity, depending on the datasets that have been used for calibration of the model parameters, the models lead to quite different predictions. For example, Rorvik et al. [75] have compared 13 models that are based on a parametrization of RBE as a function of LET_d and other biological parameters like e.g. the photon α/β-ratio; they report differences for RBE-weighted dose in the Bragg peak region of more than a factor of 1.5, thus highlighting substantial uncertainties in RBE predictions of these models. However, no direct comparisons to experimental data have been performed in this study.
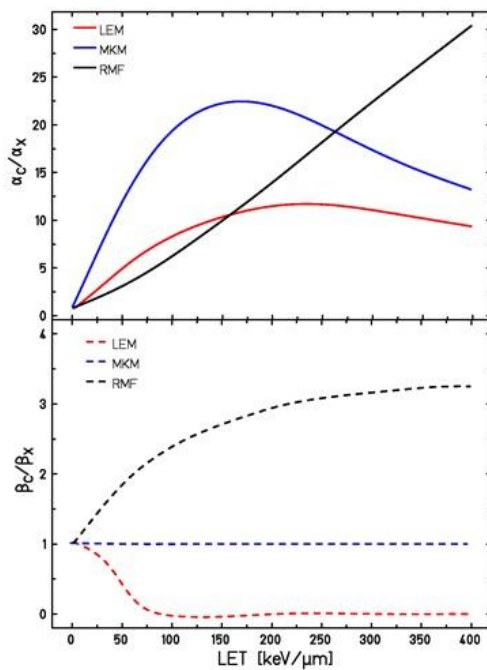
Fig. 6. Comparison of model predictions of the linear-quadratic parameters α (upper panel) and β (lower panel) after carbon ion irradiation at different LET in relation to the underlying photon parameters for three different models. LEM: Local Effect Model; MKM: Microsdosimetric-Kinetic Model; RMF: Repair-Misrepair Fixation Model. Modified after Stewart et al. (2018)

With increasing number of models, comparisons and systematic tests / validations against experimental data are of increasing importance in order to allow the choice of an appropriate model for treatment planning. It would be extremely helpful here to agree on a common set of experimental data which are most relevant for model testing. As a minimum requirement for a general purpose model, simultaneous prediction of RBE(LET) dependencies in-vitro for p, He and C ions and for RBE_α and RBE_{10} for different cell lines covering a broad range of sensitivities might be a starting point. Furthermore, applicability to predict RBE values *in-vivo* can be considered as prerequisite for clinical application. However, the choice of the relevant endpoints will largely depend on the specific clinical application, and therefore guidance from a clinical perspective would be highly desirable here. This also includes the definition of potential gaps and limitations in experimental data as well as in the modelling approaches, which are needed in order to determine the strategy for potential model improvements.

IV.   TREATMENT PLANNING

A. *Physical aspects*

Both physical and biological aspects represent an important challenge for treatment planning in ion beam therapy. Accurate stopping power determination is an extremely relevant issue to determine the range of ions in tissue, as success of ion beam therapy will largely depend on the accuracy with which the potential precision of ion beams can be actually exploited in patient treatments. Ion beam therapy is thus much more sensitive to all aspects of range uncertainty and positioning errors [76][77][78]. Dual-energy CT, ion computed tomography and ion beam radiography are discussed as potential solutions to substantially reduce uncertainties in range estimation [79][80][81][82][83][84][85]. With respect to range verification, prompt gamma imaging is one of the promising new approaches discussed as alternative to e.g. PET based methods [86][87][88][89]. Due to the timing, prompt gammas are particularly suitable for online imaging, and a major advantage compared to PET is that distortions resulting from wash-out effects can be avoided. First clinical installations have demonstrated the feasibility and the particular benefits of prompt gamma imaging and its potential for improving the accuracy of particle therapy [90][91].

Accurate planning is specifically challenging for complex treatment situations, involving large heterogeneities or metal implants [92]. With respect to the physical characterization of the radiation field, Monte-Carlo algorithms have proven to represent an accurate tool in treatment planning also in ion beam therapy [93][94][95]. In combination with the appropriate nuclear physics approaches, they are particularly suitable to represent the complex nuclear fragmentation and scattering processes that are indispensable for an accurate description of the radiation field [96]. Monte-Carlo calculations also represent an important tool to characterize microscopic energy deposition features e.g. in novel treatment approaches aiming at the enhancement of effectiveness by combining ion beam irradiation with nanoparticles [97][98][99].

More general aspects of treatment planning developments refer e.g. to advanced automization techniques, multicriteria optimization and/or aspects of plan robustness [100]. For example, the optimal choice of beam angle directions at present typically requires manual interventions and thus offers high potential for further improvements based on automization. Multicriteria optimization - aiming at the right balance between eradicating the cancer and avoiding unacceptable injury to normal tissues – inherently includes trade-offs: more conformal dose to the target comes at a cost of higher normal tissue complications, and sparing of one organ at riske gives increased dose to another. The aim of multi-criteria optimization is to manage the inherent multidimensional trade-offs better, and to present these trade-offs in a transparent way, thus enabling a more efficient planning process [101][102][103]. Furthermore, comparably small uncertainties in patient positioning, stopping power calculations and anatomical changes might have significant consequences like hot or cold spots in the resulting dose distribution in the patient. A major topic in treatment planning therefore is the plan robustness against these uncertainties [104][105][106][107]. This also includes the impact of a variable RBE in proton treatment planning, which could be

related to hot spots in the RBE-weighted dose distribution at the distal egde of the field or in general in regions characterized by an increased LET [108][109][110].

B. Biological aspects

With respect to biological aspects, the major goal of biologically optimized treatment planning is to achieve a homogenous RBE-weighted dose coverage of the target volume. This requires the reduction of the absorbed dose towards the distal end of an SOBP in order to compensate for the increased biological effectiveness as a consequence of the increase of LET with depth (see Fig. 2). The models described in section III represent important tools to determine RBE in treatment planning for ion beam therapy, although different strategies are followed in the Japanese and the European approach in that respect. The basic idea of the Japanese approach is based on a hybrid approach, combining aspects of the model based characterization of RBE for cell killing with clinical experience in neutron therapy [111]. This approach exploits the fact that under certain conditions carbon ion beams and neutron beams exhibit similar radiobiological properties. The European approach based on the LEM, in contrast, is solely based on biophysical modelling directly linking photon dose response curves to ion beam response curves [112][113].

RBE modeling is frequently considered to be subject to large uncertainties, depending on the accuracy with which the model input parameters are known [114]. However, one has to keep in mind that similar uncertainties need to be considered in conventional photon therapy when e.g. α/β-values are used to determine dose corrections in the case of changing fractionation schemes. Actually, in particular at lower doses as they are clinically applied the impact of uncertainties can expected to be less pronounced after ion beam irradiation as compared to photon irradiation [115]. This is a consequence of the less pronounced differential, e.g. cell line specific, effects after high-LET radiation [9][28]. Nonetheless, attempts have been reported to circumvent biological modelling and refer to LET distributions as a surrogate for RBE distributions. This approach is particularly promoted for proton therapy [116][117][118], as in this case actually due to the low RBE values uncertainties of RBE might be higher than the value itself. It has, however, been demonstrated that LET is not an accurate estimator of RBE [119], because for a given dose-mean LET value both the width of the LET distribution as well as the particle species will affect the RBE [119][120].

In order to get less dependent on uncertainties in RBE and thus on potential hot spots in the RBE-weighted dose distribution, strategies have been proposed to more homogenously distribute the high-LET components throughout the target region [121][116][117][122][123]. This is of interest also for avoiding high-LET components in critical structures of the surrounding normal tissue, since

taking into account safety margins, the distal edge of a treatment field and thus the region with highest LET and RBE values is typically located in the normal tissue.
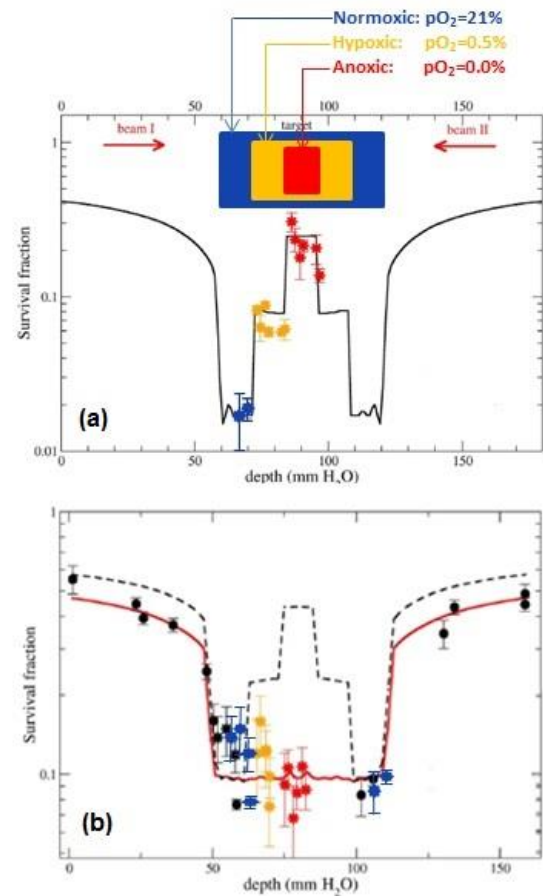

Fig. 7. Example of kill painting approach. (a) The typical structure of a tumor with a hypoxic core is simulated by combination of cell culture samples at fully oxic conditions,(blue), an anoxic region (yellow) and a completely anoxic core (red). Standard treatment plan optimization based on only well oxygenated cells leads to underdosage of the hypoxic regions and correspondingly high cell survival. (b) Adaptation of the dose optimization to the specific sensitivity allows to achieve almost homogenous cell killing throughout the whole target volume. Modified after Tinganelli et al. (2015)

Another approach aims at specifically distributing the high-LET component to the most resistant regions of a tumor, e.g. to the hypoxic region (so called LET-painting) [124][125][126]. As LET alone is not an accurate descriptor of RBE and thus of the expected biological effectiveness, more advanced approaches aim at directly optimizing the biological effect, e.g. the so called "kill-painting" approach [127][128] (see Fig. 7). In order to optimally apply these approaches, the accurate characterization of the spatial distribution of sensitivities is required. This includes e.g. the delineation of hypoxic regions and the quantification of the level of hypoxia; advanced imaging techniques will therefore play a crucial role in this respect. In order to further optimize ion beam treatment, also mixed irradiation with multiple ion species has been proposed, where heavier ions are used to specifically treat the most resistant parts of the tumor, and lighter ions to

treat the more sensitive regions. This approach requires highest flexibility in treatment planning as well [128].

A specific aspect of ion beam treatment planning that needs to be considered in particular for intercomparison of treatment plans of different institutions are the different strategies to take into account the increased biological effectiveness of ion beams. Steinsträter et al. [129] and Molinelli et al. [130] have reported e.g. intercomparison of plans based on the approach developed at HIMAC and at GSI/HIT, respectively, to determine RBE-weighted doses. Although at RBE-weighted doses of 3...5 Gy / fraction both approaches are similar, at lower as well as at higher doses per fraction substantial differences are expected; at doses relevant e.g. for single fraction treatments, estimated RBE values can differ by approximately a factor of 2. Therefore, if the same values of prescribed RBE-weighted doses are reported by the Japanese and European centers, the underlying absorbed doses might considerably differ as a consequence of the different RBE values. This finally will lead also to different clinical outcome for the same prescribed dose.

V. MOVING TARGETS & MOTION MITIGATION STRATEGIES

The treatment of moving targets represents a challenge in ion beam therapy in particular for active beam delivery methods, as the interplay between beam scanning and target movement might lead to undesired interference patterns, finally resulting in inhomogeneous dose distributions. In addition to intra-fractional movements, inter-fractional movements are of interest here, justifying the strong interest in in-room imaging and range verification.

Different strategies like e.g. re-scanning, gating and tracking are discussed as potential motion mitigation techniques, each having their specific advantages and disadvantages [131][132][133][134]. Re-scanning is the option easiest to implement, since the dose per fraction only needs to be split into the appropriate number of smaller doses which are then applied multiple times at a given treatment day. This method is thus based on the statistical averaging of positional errors, since dose errors are smoothed out by irradiating the target volume multiple times. Gating is expected to be more accurate in that respect, as the target is irradiated only in defined motion phases characterized by a much smaller residual motion. Tracking theoretically is the most elegant and accurate method, as magnetic scanning can in principle be corrected for the movement of the tumor on-line [135]. However, in this case the determination of the actual tumor position with high accuracy represents the major challenge, and at present no method seems accurate enough to follow that strategy, since in general the tumor cannot be tracked directly, but usually sampling is based on an external motion surrogates. In order to partially circumvent the interplay between active scanning and target motion, also hybrid techniques combining passive elements with active scanning have been proposed [136].

Precise motion mitigation techniques require quantification of the motion, for example by time resolved computed tomography (4DCT), sampling periodical motion in several motion phases, and the corresponding adaptations of the treatment planning procedures. Individual motion phases can be identified with quasi-static 3D volumes, e.g. standard CT volumes, for which individual plans are optimized. Treatment then requires the fast switching between the different plans, depending on the particular motion phase [137][138][139].

VI. ION SPECIES OTHER THAN PROTONS AND CARBON IONS

Both the Japanese as well as the European facilities have chosen carbon ions as the first high-LET modality for comparison with proton and photon treatments. Having in mind the impact of the ion species on almost all RBE dependencies, it is frequently discussed which ion species would be optimal for therapy. However, as indicated above, the judgement concerning the potential benefit will critically depend on the differential RBE effect in the tumor and the surrounding normal tissue. It will thus primarily depend on the specific radiobiological characteristics of the tissues involved in the treatment field, and thus no general answer can be given to this question, but rather treatment plan comparisons need to be performed for the specific cases in order to allow for a thorough assessment. Nonetheless, some general remarks will be compiled here in order to indicate potential areas of interest for future improvements of ion beam therapy

Heavier ions than carbon will particularly be interesting in the case of hypoxic tumors, where reduction of the OER is of importance. Several approaches have been reported to characterize the decrease of OER values with increasing LET [31][33][140][141], indicating a drastic reduction of OER values with LET higher than 100 keV/m. Recent studies [142][143][144][127] indicate the possible role for 16O beams in this respect. An important aspect here is the accurate characterization of the hypoxic region, which typically is located in the central region of the tumor. The development of appropriate imaging methods will be crucial in that respect [145][146]. As for heavier ions also the RBE in the entrance channel / healthy tissue in front of tumor might be undesirably high, also combined treatments with light and heavier ions might be feasible. In this case, the heavier ions are solely used to treat the central / hypoxic part of the tumor, and the lighter ions for the treatment of the remaining part of the tumor, so that the dose delivered to the proximal normal tissue by high-LET ions can be kept to a minimum [142]. Mixed radiation are also discussed by Brahme [147] and Inaniwa [148].

Lighter ions like e.g. He are also discussed for therapeutic application [64][149]. From the physical point of view, they might be advantageous since projectile fragmentation is less pronounced for He ions as compared to carbon ions, and

lateral scattering is less pronounced as compared to protons. This is further confirmed by the results reported by Tessonier et al. [150][151], indicating that helium ions could afford a more conformal treatment and in turn, increased tumor control.

From the radiobiological point of view, the RBE of He is closer to protons, which is considered to be beneficial e.g. in the treatment e.g. of pediatric patients, where the potential risk of increased secondary cancer induction resulting from elevated RBE needs to be kept minimal.

As the interplay between the physical and biological properties depends on different parameters like the ion species, dose level, tissue characteristics and beam configuration, idealized treatment planning studies are expected to represent an appropriate guide for preselection of cases and choice of the optimal ion species. For example, Grün et al. [152] report about such treatment plan comparisons using simple target volume and beam angle configurations. The comparison of p, He and C ions suggests a strong dependence of the advantages of the three ions on the dose-level, tissue type, and field configuration. In terms of conformity, i.e., dose to the normal tissue, a clear gain is expected using carbon or helium ions compared to protons.

These results are in line with the conclusions drawn by Remmes et al. [153] that no single ion is optimal for all treatment scenarios. The heavier ions are superior in cases in which the α/β ratio of the target tissue is low and the α/β ratio of normal tissue is high, and protons are superior in the opposite circumstances. Lithium and beryllium appear to offer dose advantages similar to carbon, with a considerably lower normal tissue dose when the α/β ratio in the target tissue is high and the α/β ratio in the normal tissue is low.

Simultaneous acceleration of He + C has been proposed by Mazzucconi et al. [154] for combined imaging and treatment: Fully stripped nuclei of ^{12}C and ^{4}He have the same magnetic rigidity; therefore, the two species can be accelerated together and a mixed particle beam delivered to the patient. With the same energy per nucleon, the range of ^{4}He is about three times the ^{12}C one. Therefore, carbon ions stopping in the tumor can be used for tumor cure, while helium, emerging from the patient, can be used for imaging by detecting and measuring the residual range and position of He.

VII. NOVEL TREATMENT APPROACHES

In recent years, two treatment modalities that are related to a specific spatio-temporal characteristics of the dose delivery – although already discussed for conventional photon radiation - have attracted substantial attention and triggered a series of investigations to better characterize their potential advantages in tumor therapy. They are based either on ultrahigh dose-rates (so called FLASH irradiation), or on radiation fields focused to narrow regions (so called grid-, microbeam- or minibeam therapy) in the entrance region of the treatment field.

A. Minibeam therapy

The basic idea of the latter has been exploited already decades ago [155][156]. By focusing or collimating the beam to regular grids or spots at the entrance of the beam to the body (see Figure 8) certain regions e.g. of the skin remain undamaged, thus resulting in an enhanced recovery in the superficial layers of the normal tissue in front of the tumor. With increasing depth, scattering of the beam leads to increased filling of the dose valleys in between the grid structure, leading to a more homogenous irradiation of the deep-seated locations, i.e. the tumor. The particular role of small, unirradiated regions interlacing with high dose regions has been demonstrated to be beneficial also in the above mentioned studies of the rat spinal cord [47][48], but is considered to be a generally valid principle also for other tissues. The corresponding increase of the normal tissue tolerance has been demonstrated for a variety of different dose delivery patterns, using different geometries as e.g. parallel lines, grids and point patterns with different beam width.

Although grid / sieve therapy have been originally proposed for conventional radiation like X-rays and high energy photon radiation, it has been recognized that the use of ion beam radiation in combination with grid therapy might show additional advantages [157][158][159][160][161][162][163] [164][165] (see Fig. 8). In particular the less pronounced scattering of heavier ions like e.g. carbon ions might have advantages here since it allows to preserve the grid pattern and with that the sparing effect also in regions close to the target. On the other hand, it requires additional techniques like interlaced irradiation with multiple fields in order to assure the homogenous irradiation of the target region [166][167]. Since these interlacing techniques require extremely accurate positioning of the target, it remains to be clarified in how far this accuracy can be achieved in the clinical practice.

Also in general, a need is seen to specify ideal dosimetry parameters and to formulate robust clinical indications and guidelines for optimal standardized care using grid and minibeam therapy [168].
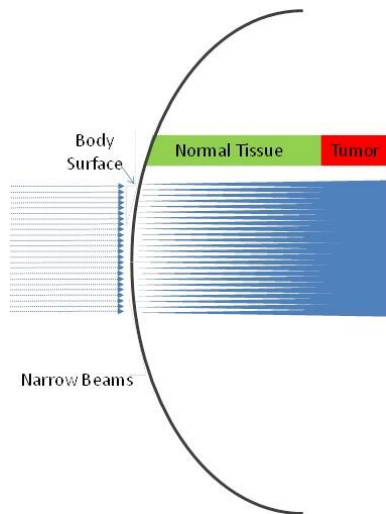
Fig. 8. Principle of grid therapy: A (regular) pattern of narrow beams enters the body; with increasing depth, scattering processes lead to widening of the beams and thus to superposition and consequently a more homogeneous irradiation in depth, i.e. in the target region.

B. Ultrahigh dose rates

The second approach makes use of extremely high dose rates, which have been reported to also lead to an increased tolerance of the normal tissues surrounding the tumor without compromising the reduction of tumor growth [169][170][171][172][173]. Also here, the detailed mechanisms need to be clarified, as e.g. in general *in-vitro* no significant difference between pulsed irradiation with ultrahigh dose rates and continuous irradiation with lower, conventional dose rates (~Gy/min) have been found [174][175]. Combination of ion beam therapy with FLASH therapy is also discussed, and studies are ongoing to demonstrate the potential synergy between the two radiation modalities [176].

Ultrahigh dose rates are also discussed in the framework of laser generated particle beams, where ions are accelerated by shooting thin foils with extremely short (fs) laser pulses [177]. In line with the results reported above, Zlobinskaya et al. [178] found no difference in the tumor growth response between conventional irradiation and pulsed proton irradiation of human tumor xenografts in nude mice. However, these authors do not analyze the corresponding normal tissue effects.

In general, more detailed studies related not only to tumor growth delay, but also to tumor cure would be highly desirable here to complement the existing studies, as the endpoint "growth delay" may not be sensitive enough to detect differences in the response that finally determine tumor cure, being the most relevant endpoint for the determination of the therapeutic window.

C. Treatment of non-cancer diseases

Another research area of growing interest is related to the application of ion beams for the treatment of non-cancer diseases. Also the early clinical trials included already e.g. the treatment of non-cancer diseases like arteriovenous malformations (AVM). More recently, the treatment of heart arrhythmia with carbon ion beams has been discussed, taking advantage of the extremely localized energy deposition of carbon ions in a small, mm-sized Bragg peak region. This makes ion beams particularly suitable to damage small sub-areas of the heart with very high doses, allowing to create chronic lesions that locally interrupt cardiac conduction and therefore enable treatment of heart rhythm disorders completely noninvasively while sparing surrounding tissues [179][180][181][182].

The principle of using external radiation for the treatment of heart arrhythmia has been also reported for highly conformal photon therapy (SBRT) [183][184][185]. However, ion beams allow a substantially better focusing of the high dose area and thus a potentially higher effectiveness in achieving the desired effect without exceeding the tolerance doses in the surrounding normal tissue.

A particular challenge for this type of application represents the movement of the target region as a consequence of the heart beat as well as of the breathing and corresponding movement of the whole heart. Appropriate measures have thus to be taken to compensate / mitigate these motion effects.

VIII. SUMMARY AND CONCLUSION

Despite considerable experience with both protons and ion beams in radiotherapy applications, still the potential of these radiation modalities is not yet fully exploited. Therefore, both on the physical/technical as well as radiobiological side a lot of research activities are ongoing, which have been briefly addressed in this contribution. Major aims of these research activities should e.g. be:

- Technical improvements to enhance conformity of the treatment even in challenging situations, e.g. for moving targets;
- A better understanding of the radiobiological properties of ion beams in particular for the case of partial volume irradiations;
- Investigations of the role of the immune response and the potential impact of high-LET radiation modalities to optimally exploit the immune response;
- Preclinical experiments to elucidate the potential advantage of FLASH and minibeam irradiation techniques using ion beams;
- Combination of imaging techniques to accurately characterize resistant subvolumes (e.g. hypoxic areas) with

advanced treatment planning strategies to appropriately adapt the prescribed dose in these regions accordingly;
- Extension of application to non-cancer diseases.

These research activities then will help to accurately define and identify patient groups that will mostly benefit from the different treatment options.

IX. REFERENCES

[1] Wilson RR. Radiological use of fast protons. Radiology 1946;47:487–491.

[2] Boone ML, Lawrence JH, Connor WG, et al. Introduction to the use of protons and heavy ions in radiation therapy: historical perspective. Int J Radiat Oncol Biol Phys. 1977;3:65–9.

[3] Falkmer S, Fors B, Larsson B, Lindell A, Naeslund J, Stenson S. Pilot study on proton irradiation of human carcinoma. Acta radiol. 1962 Feb;58:33-51.

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

[5] Schardt D, Elsässer T, Schulz-Ertner D. Heavy-ion tumor therapy: Physical and radiobiological benefits. Rev. Mod. Phys. 82 (2010), 383-425

[6] Friedrich T, Scholz U, Elsässer T, Durante M, Scholz M. Systematic analysis of RBE and related quantities using a database of cell survival experiments with ion beam irradiation. J Radiat Res. 2013 May;54(3):494-514.

[7] J. Kiefer: The physical basis for the biological action of heavy ions New J. Physics 10, 2008, 075004

[8] T. Elsässer, R. Cunrath, M. Krämer, M. Scholz: Impact of track structure calculations on biological treatment planning in ion radiotherapy. New J. Physics 10, 2008, 075005

[9] Weyrather WK, Ritter S, Scholz M, Kraft G. RBE for carbon track-segment irradiation in cell lines of differing repair capacity. Int J Radiat Biol. 1999 Nov;75(11):1357-64.

[10] Astrahan M. Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. Med Phys. 2008 Sep;35(9):4161-72..

[11] Park C, Papiez L, Zhang S, Story M, Timmerman RD. Universal survival curve and single fraction equivalent dose: useful tools in understanding potency of ablative radiotherapy. Int J Radiat Oncol Biol Phys. 2008 Mar 1;70(3):847-52.

[12] Andisheh B, Edgren M, Belkić D, Mavroidis P, Brahme A, Lind BK. A comparative analysis of radiobiological models for cell surviving fractions at high doses. Technol Cancer Res Treat. 2013 Apr; 12(2):183-92.

[13] Guerrero M, Li XA. Extending the linear-quadratic model for large fraction doses pertinent to stereotactic radiotherapy. Phys Med Biol. 2004 Oct 21;49(20):4825-35.

[14] Friedrich T, Scholz U, Durante M, Scholz M. RBE of ion beams in hypofractionated radiotherapy (SBRT). Phys Med. 2014 Jul;30(5):588-91.

[15] Koike S, Ando K, Uzawa A, Takai N, Fukawa T, Furusawa Y, Oohira C, Aoki M, Monobe M, Lee R, Suzuki M, Nojima K. Significance of fractionated irradiation for the biological therapeutic gain of carbon ions. Radiat Prot Dosimetry. 2002;99(1-4):405-8.

[16] Ando K, Koike S, Uzawa A, Takai N, Fukawa T, Furusawa Y, Aoki M, Miyato Y. Biological gain of carbon-ion radiotherapy for the early response of tumor growth delay and against early response of skin reaction in mice. J Radiat Res. 2005 Mar;46(1):51-7.

[17] Yoshida Y, Ando K, Ando K, Murata K, Yoshimoto Y, Musha A, Kubo N, Kawamura H, Koike S, Uzawa A, Takahashi T, Ohno T, Nakano T. Evaluation of therapeutic gain for fractionated carbon-ion radiotherapy using the tumor growth delay and crypt survival assays. Radiother Oncol. 2015 Nov;117(2):351-7.

[18] Debus J, Scholz M, Haberer T, Peschke P, Jäkel O, Karger CP, Wannenmacher M. Radiation tolerance of the rat spinal cord after single and split doses of photons and carbon ions. Radiat Res. 2003 Nov;160(5):536-42.

[19] Karger CP, Peschke P, Sanchez-Brandelik R, Scholz M, Debus J. Radiation tolerance of the rat spinal cord after 6 and 18 fractions of photons and carbon ions: experimental results and clinical implications. Int J Radiat Oncol Biol Phys. 2006 Dec 1;66(5):1488-97.

[20] Saager M, Glowa C, Peschke P, Brons S, Scholz M, Huber PE, Debus J, Karger CP. Carbon ion irradiation of the rat spinal cord: dependence of the relative biological effectiveness on linear energy transfer. Int J Radiat Oncol Biol Phys. 2014 Sep 1;90(1):63-70.

[21] Saager M, Glowa C, Peschke P, Brons S, Grün R, Scholz M, Huber PE, Debus J, Karger CP. The relative biological effectiveness of carbon ion irradiations of the rat spinal cord increases linearly with LET up to 99 keV/μm. Acta Oncol. 2016Dec;55(12):1512-1515.

[22] Saager M, Peschke P, Welzel T, Huang L, Brons S, Grün R, Scholz M, Debus J, Karger CP. Late normal tissue response in the rat spinal cord after carbon ion irradiation. Radiat Oncol. 2018 Jan 11;13(1):5.

[23] Saager M, Peschke P, Brons S, Debus J, Karger CP. Determination of the proton RBE in the rat spinal cord: Is there an increase towards the end of the spread-out Bragg peak? Radiother Oncol. 2018 Jul;128(1):115-120.

[24] Sørensen BS, Horsman MR, Alsner J, Overgaard J, Durante M, Scholz M, Friedrich T, Bassler N. Relative biological effectiveness of carbon ions for tumor control, acute skin damage and late radiation-induced fibrosis in a mouse model. Acta Oncol. 2015;54(9):1623-30.

[25] Brownstein JM, Wisdom AJ, Castle KD, Mowery YM, Guida P, Lee CL, Tommasino F, Tessa C, Scifoni E, Gao J, Luo L, Campos LDS, Ma Y, Williams N, Jung SH, Durante M, Kirsch DG. Characterizing the Potency and Impact of Carbon Ion Therapy in a Primary Mouse Model of Soft Tissue Sarcoma. Mol Cancer Ther. 2018 Apr;17(4):858-868.

[26] Peschke P, Karger CP, Scholz M, Debus J, Huber PE. Relative biological effectiveness of carbon ions for local tumor control of a radioresistant prostate carcinoma in the rat. Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):239-46.

[27] Karger CP, Peschke P, Scholz M, Huber PE, Debus J. Relative biological effectiveness of carbon ions in a rat prostate carcinoma in vivo: comparison of 1, 2, and 6 fractions. Int J Radiat Oncol Biol Phys. 2013 Jul 1;86(3):450-5.

[28] Glowa C, Karger CP, Brons S, Zhao D, Mason RP, Huber PE, Debus J, Peschke P. Carbon ion radiotherapy decreases the impact of tumor heterogeneity on radiation response in experimental prostate tumors. Cancer Lett. 2016 Aug 10;378(2):97-103.

[29] Glowa C, Peschke P, Brons S, Neels OC, Kopka K, Debus J, Karger CP. Carbon ion radiotherapy: impact of tumor differentiation on local control in experimental prostate carcinomas. Radiat Oncol. 2017 Nov 9;12(1):174.

[30] Scholz M, Matsufuji N, Kanai T. Test of the local effect model using clinical data: tumour control probability for lung tumours after treatment with carbon ion beams. Radiat Prot Dosimetry. 2006;122(1-4):478-9.

[31] Wenzl T, Wilkens JJ. Modelling of the oxygen enhancement ratio for ion beam radiation therapy. Phys Med Biol. 2011 Jun 7;56(11):3251-68.

[32] Wenzl T, Wilkens JJ. Theoretical analysis of the dose dependence of the oxygen enhancement ratio and its relevance for clinical applications. Radiat Oncol. 2011 Dec 15;6:171.

[33] Scifoni E, Tinganelli W, Weyrather WK, Durante M, Maier A, Krämer M. Including oxygen enhancement ratio in ion beam treatment planning: model implementation and experimental verification. Phys Med Biol. 2013 Jun 7;58(11):3871-95.

[34] Strigari L, Torriani F, Manganaro L, Inaniwa T, Dalmasso F, Cirio R, Attili A. Tumour control in ion beam radiotherapy with different ions in the presence of hypoxia: an oxygen enhancement ratio model based on the microdosimetric kinetic model. Phys Med Biol. 2018 Mar 16;63(6):065012

[35] Paganetti H. Relative biological effectiveness (RBE) values for proton beam therapy. Variations as a function of biological endpoint, dose, and linear energy transfer. Phys Med Biol. 2014 Nov 21;59(22):R419-72.

[36] ICRU. Prescribing, Recording, and Reporting Proton-Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements. 2007;Report No. 78.,

[37] Grün R, Friedrich T, Krämer M, Scholz M. Systematics of relative biological effectiveness measurements for proton radiation along the spread out Bragg peak: experimental validation of the local effect model. Phys Med Biol. 2017 Feb 7;62(3):890-908.

[38] Peeler CR, Mirkovic D, Titt U, Blanchard P, Gunther JR, Mahajan A, Mohan R, Grosshans DR. Clinical evidence of variable proton biological effectiveness in pediatric patients treated for ependymoma. Radiother Oncol. 2016 Dec;121(3):395-401. First report of RBE-related toxicity

[39] Gensheimer MF, Yock TI, Liebsch NJ, Sharp GC, Paganetti H, Madan N, Grant PE, Bortfeld T. In vivo proton beam range verification using spine MRI changes. Int J Radiat Oncol Biol Phys. 2010 Sep 1;78(1):268-75. Overshoot at distal edge; no toxicity. Authors claim that RBE effect not sufficient for explanation, but Grün et al. can explain.based on shallower dose gradient, leading to a more pronounced extension

[40] Jones B. Why RBE must be a variable and not a constant in proton therapy. Br J Radiol. 2016 Jul;89(1063):20160116.

[41] Jones B, McMahon SJ, Prise KM. The Radiobiology of Proton Therapy: Challenges and Opportunities Around Relative Biological Effectiveness. Clin Oncol (R Coll Radiol). 2018 May;30(5):285-292.

[42] Saager M, Peschke P, Brons S, Debus J, Karger CP. Determination of the proton RBE in the rat spinal cord: Is there an increase towards the end of the spread-out Bragg peak? Radiother Oncol. 2018 Jul;128(1):115-120.

8/12/2019 MS_IEEE_20190812_CameraReady.docx

[43] Paganetti H. Proton Relative Biological Effectiveness - Uncertainties and Opportunities. Int J Part Ther. 2018 Summer;5(1):2-14.

[44] Paganetti H, Blakely E, Carabe-Fernandez A, Carlson DJ, Das IJ, Dong L, Grosshans D, Held KD, Mohan R, Moiseenko V, Niemierko A, Stewart RD, Willers H. Report of the AAPM TG-256 on the relative biological effectiveness of proton beams in radiation therapy. Med Phys. 2019 Mar;46(3):e53-e78.

[45] Bentzen SM, Constine LS, Deasy JO, Eisbruch A, Jackson A, Marks LB, Ten Haken RK, Yorke ED. Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific issues. Int J Radiat Oncol Biol Phys. 2010 Mar 1;76(3 Suppl):S3-9.

[46] Emami B, Lyman J, Brown A, Coia L, Goitein M, Munzenrider JE, Shank B, Solin LJ, Wesson M. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991 May 15;21(1):109-22. Review.

[47] Bijl HP, van Luijk P, Coppes RP, Schippers JM, Konings AW, van der Kogel AJ. Unexpected changes of rat cervical spinal cord tolerance caused by inhomogeneous dose distributions. Int J Radiat Oncol Biol Phys. 2003 Sep 1;57(1):274-81..

[48] Bijl HP, van Luijk P, Coppes RP, Schippers JM, Konings AW, van der Kogel AJ. Dose-volume effects in the rat cervical spinal cord after proton irradiation. Int J Radiat Oncol Biol Phys. 2002 Jan 1;52(1):205-11

[49] van Luijk P, Bijl HP, Konings AW, van der Kogel AJ, Schippers JM. Data on dose-volume effects in the rat spinal cord do not support existing NTCP models. Int J Radiat Oncol Biol Phys. 2005 Mar 1;61(3):892-900.

[50] Melzig C, Golestaneh AF, Mier W, Schwager C, Das S, Schlegel J, Lasitschka F, Kauczor HU, Debus J, Haberkorn U, Abdollahi A. Combined external beam radiotherapy with carbon ions and tumor targeting endoradiotherapy. Oncotarget. 2018 Jul 6;9(52):29985-30004.

[51] Ohkubo Y, Iwakawa M, Seino K, Nakawatari M, Wada H, Kamijuku H, Nakamura E, Nakano T, Imai T. Combining carbon ion radiotherapy and local injection of α-galactosylceramide-pulsed dendritic cells inhibits lung metastases in an in vivo murine model. Int J Radiat Oncol Biol Phys. 2010 Dec 1;78(5):1524-31.

[52] Durante M, Brenner DJ, Formenti SC. Does Heavy Ion Therapy Work Through the Immune System? Int J Radiat Oncol Biol Phys. 2016 Dec 1;96(5):934-936.

[53] Durante M, Formenti SC. Radiation-Induced Chromosomal Aberrations and Immunotherapy: Micronuclei, Cytosolic DNA, and Interferon-Production Pathway. Front Oncol. 2018 May 29;8:192.

[54] Hawkins RB. A microdosimetric-kinetic model for the effect of non-Poisson distribution of lethal lesions on the variation of RBE with LET. Radiat Res. 2003 Jul;160(1):61-9.

[55] Hawkins RB. A microdosimetric-kinetic model of cell death from exposure to ionizing radiation of any LET, with experimental and clinical applications. Int J Radiat Biol. 1996 Jun;69(6):739-55.

[56] Hawkins RB. The relationship between the sensitivity of cells to high-energy photons and the RBE of particle radiation used in radiotherapy. Radiat Res. 2009 Dec;172(6):761-76.

[57] Kase Y, Kanai T, Matsumoto Y, Furusawa Y, Okamoto H, Asaba T, Sakama M, Shinoda H. Microdosimetric measurements and estimation of human cell survival for heavy-ion beams. Radiat Res. 2006 Oct;166(4):629-38.

[58] Inaniwa T, Furukawa T, Kase Y, Matsufuji N, Toshito T, Matsumoto Y, Furusawa Y, Noda K. Treatment planning for a scanned carbon beam with a modified microdosimetric kinetic model. Phys Med Biol. 2010 Nov 21;55(22):6721-37.

[59] Scholz M, Kellerer AM, Kraft-Weyrather W, Kraft G. Computation of cell survival in heavy ion beams for therapy. The model and its approximation. Radiat Environ Biophys. 1997 Feb;36(1):59-66.

[60] Elsässer T, Scholz M. Cluster effects within the local effect model. Radiat Res. 2007 Mar;167(3):319-29.

[61] Elsässer T, Krämer M, Scholz M. Accuracy of the local effect model for the prediction of biologic effects of carbon ion beams in vitro and in vivo. Int J Radiat Oncol Biol Phys. 2008 Jul 1;71(3):866-72.

[62] Elsässer T, Weyrather WK, Friedrich T, Durante M, Iancu G, Krämer M, Kragl G, Brons S, Winter M, Weber KJ, Scholz M. Quantification of the relative biological effectiveness for ion beam radiotherapy: direct experimental comparison of proton and carbon ion beams and a novel approach for treatment planning. Int J Radiat Oncol Biol Phys. 2010 Nov 15;78(4):1177-83.

[63] Friedrich T, Scholz U, Elsässer T, Durante M, Scholz M. Calculation of the biological effects of ion beams based on the microscopic spatial damage distribution pattern. Int J Radiat Biol. 2012 Jan;88(1-2):103-7.

[64] Krämer M, Scifoni E, Schuy C, Rovituso M, Tinganelli W, Maier A, Kaderka R, Kraft-Weyrather W, Brons S, Tessonnier T, Parodi K, Durante M. Helium ions for radiotherapy? Physical and biological verifications of a novel treatment modality. Med Phys. 2016 Apr;43(4):1995.

[65] Grün R, Friedrich T, Krämer M, Zink K, Durante M, Engenhart-Cabillic R, Scholz M. Assessment of potential advantages of relevant ions for particle therapy: a model based study. Med Phys. 2015 Feb;42(2):1037-47.

[66] Sokol O, Scifoni E, Tinganelli W, Kraft-Weyrather W, Wiedemann J, Maier A, Boscolo D, Friedrich T, Brons S, Durante M, Krämer M. Oxygen beams for therapy: advanced biological treatment planning and experimental verification. Phys Med Biol. 2017 Sep 20;62(19):7798-7813.

[67] Friedrich T, Durante M, Scholz M. Modeling cell survival after photon irradiation based on double-strand break clustering in megabase pair chromatin loops. Radiat Res. 2012 Nov;178(5):385-94.

[68] Tommasino F, Friedrich T, Scholz U, Taucher-Scholz G, Durante M, Scholz M. A DNA double-strand break kinetic rejoining model based on the local effect model. Radiat Res. 2013 Nov;180(5):524-38.

[69] Herr L, Friedrich T, Durante M, Scholz M. A model of photon cell killing based on the spatio-temporal clustering of DNA damage in higher order chromatin structures. PLoS One. 2014 Jan 2;9(1):e83923

[70] Hufnagl A, Herr L, Friedrich T, Durante M, Taucher-Scholz G, Scholz M. The link between cell-cycle dependent radiosensitivity and repair pathways: a model based on the local, sister-chromatid conformation dependent switch between NHEJ and HR. DNA Repair (Amst). 2015 Mar;27:28-39.

[71] Carlson DJ, Stewart RD, Semenenko VA, Sandison GA. Combined use of Monte Carlo DNA damage simulations and deterministic repair models to examine putative mechanisms of cell killing. Radiat Res. 2008 Apr;169(4):447-59.

[72] Frese MC, Yu VK, Stewart RD, Carlson DJ. A mechanism-based approach to predict the relative biological effectiveness of protons and carbon ions in radiation therapy. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):442-50.

[73] Kamp F, Cabal G, Mairani A, Parodi K, Wilkens JJ, Carlson DJ. Fast Biological Modeling for Voxel-based Heavy Ion Treatment Planning Using the Mechanistic Repair-Misrepair-Fixation Model and Nuclear Fragment Spectra. Int J Radiat Oncol Biol Phys. 2015 Nov 1;93(3):557-68.

[74] Stewart RD, Carlson DJ, Butkus MP, Hawkins R, Friedrich T, Scholz M. A comparison of mechanism-inspired models for particle relative biological effectiveness (RBE). Med Phys. 2018 Nov;45(11):e925-e952.

[75] Rørvik E, Fjæra LF, Dahle TJ, Dale JE, Engeseth GM, Stokkevåg CH, Thörnqvist S, Ytre-Hauge KS. Exploration and application of phenomenological RBE models for proton therapy. Phys Med Biol. 2018 Sep 13;63(18):185013.

[76] Schaffner B, Pedroni E. The precision of proton range calculations in proton radiotherapy treatment planning: experimental verification of the relation between CT-HU and proton stopping power. Phys Med Biol. 1998 Jun;43(6):1579-92.

[77] Paganetti H. Range uncertainties in proton therapy and the role of Monte Carlo simulations. Phys Med Biol. 2012 Jun 7;57(11):R99-117.

[78] Yang M, Zhu XR, Park PC, Titt U, Mohan R, Virshup G, Clayton JE, Dong L. Comprehensive analysis of proton range uncertainties related to patient stopping-power-ratio estimation using the stoichiometric calibration. Phys Med Biol. 2012 Jul 7;57(13):4095-115.

[79] Hünemohr N, Paganetti H, Greilich S, Jäkel O, Seco J. Tissue decomposition from dual energy CT data for MC based dose calculation in particle therapy. Med Phys. 2014 Jun;41(6):061714

[80] Möhler C, Wohlfahrt P, Richter C, Greilich S. Range prediction for tissue mixtures based on dual-energy CT. Phys Med Biol. 2016 Jun 7;61(11):N268-75.

[81] Meyer S, Kamp F, Tessonnier T, Mairani A, Belka C, Carlson DJ, Gianoli C, Parodi K. Dosimetric accuracy and radiobiological implications of ion computed tomography for proton therapy treatment planning. Phys Med Biol. 2019 Mar 14.

[82] Bär E, Lalonde A, Royle G, Lu HM, Bouchard H. The potential of dual-energy CT to reduce proton beam range uncertainties. Med Phys. 2017 Jun;44(6):2332-2344.

[83] Lo Presti D, Gallo G, Bonanno DL, Longhitano F, Bongiovanni DG, Reito S, Randazzo N, Leonora E, Sipala V, Tommasino F. An Innovative Proton Tracking System for Qualification of Particle Beam in Real-Time IEEE Trans Rad Plasma Med Sci ,2017 Vol 1(3), 268 - 274

[84] Johnson RP. Review of medical radiography and tomography with proton beams. Rep. Progress Phys., 2018, vol. 81, no. 1, Art. no. 016701.

[85] Bashkirov VA et al., Novel scintillation detector design and performance for proton radiography and computed tomography. Med. Phys. 2016, vol. 43, no. 2, 664–674.

[86] Moteabbed M, España S, Paganetti H. Monte Carlo patient study on the comparison of prompt gamma and PET imaging for range verification in proton therapy. Phys Med Biol. 2011 Feb 21;56(4):1063-82.

[87] Hueso-González F, Fiedler F, Golnik C, Kormoll T, Pausch G, Petzoldt J, Römer KE, Enghardt W. Compton Camera and Prompt Gamma Ray Timing: Two Methods for In-vivo Range Assessment in Proton Therapy. Front Oncol. 2016 Apr 12;6:80.

[88] Hueso-González F, Pausch G, Petzoldt J, Römer KE, Enghardt W. Prompt Gamma Rays Detected With a BGO Block Compton Camera Reveal Range Deviations of Therapeutic Proton Beams. IEEE Trans Rad Plasma Med Sci, 2017, vol 1(1), 76 - 86

[89] Huisman BF, Létang JM, Testa É, Sarrut D. Accelerated prompt gamma estimation for clinical proton therapy simulations. Phys Med Biol. 2016 Nov 7;61(21):7725-7743.

[90] Richter C, Pausch G, Barczyk S, Priegnitz M, Keitz I, Thiele J, Smeets J, Stappen FV, Bombelli L, Fiorini C, Hotoiu L, Perali I, Prieels D, Enghardt W, Baumann M. First clinical application of a prompt gamma based in vivo proton range verification system. Radiother Oncol. 2016 Feb;118(2):232-7.

[91] Xie Y, Bentefour EH, Janssens G, Smeets J, Vander Stappen F, Hotoiu L, Yin L, Dolney D, Avery S, O'Grady F, Prieels D, McDonough J, Solberg TD, Lustig RA, Lin A, Teo BK. Prompt Gamma Imaging for In Vivo Range Verification of Pencil Beam Scanning Proton Therapy. Int J Radiat Oncol Biol Phys. 2017 Sep 1;99(1):210-218.

[92] Chetty IJ, Curran B, Cygler JE, et al. Report of the AAPM Task Group No. 105: Issues associated with clinical implementation of Monte Carlo-based photon and electron external beam treatment planning. Med Phys. 2007;34:4818–53.

[93] Paganetti H, Jiang H, Parodi K, et al. Clinical implementation of full Monte Carlo dose calculation in proton beam therapy. Phys Med Biol. 2008;53:4825–53.

[94] Böhlen TT, Bauer J, Dosanjh M, Ferrari A, Haberer T, Parodi K, Patera V, Mairani A. A Monte Carlo-based treatment-planning tool for ion beam therapy. J Radiat Res. 2013 Jul;54 Suppl 1:i77-81.

[95] Tessonnier T, Böhlen TT, Ceruti F, Ferrari A, Sala P, Brons S, Haberer T, Debus J, Parodi K, Mairani A. Dosimetric verification in water of a Monte Carlo treatment planning tool for proton, helium, carbon and oxygen ion beams at the Heidelberg Ion Beam Therapy Center. Phys Med Biol. 2017 Jul 31;62(16):6579-6594.

[96] Robert C, Dedes G, Battistoni G, Böhlen TT, Buvat I, Cerutti F, Chin MP, Ferrari A, Gueth P, Kurz C, Lestand L, Mairani A, Montarou G, Nicolini R, Ortega PG, Parodi K, Prezado Y, Sala PR, Sarrut D, Testa E. Distributions of secondary particles in proton and carbon-ion therapy: a comparison between GATE/Geant4 and FLUKA Monte Carlo codes. Phys Med Biol. 2013 May 7;58(9):2879-99.

[97] Wälzlein C, Scifoni E, Krämer M, Durante M. Simulations of dose enhancement for heavy atom nanoparticles irradiated by protons. Phys Med Biol. 2014 Mar 21;59(6):1441-58.

[98] Lin Y, McMahon SJ, Scarpelli M, Paganetti H, Schuemann J. Comparing gold nano-particle enhanced radiotherapy with protons, megavoltage photons and kilovoltage photons: a Monte Carlo simulation. Phys Med Biol. 2014 Dec 21;59(24):7675-89.

[99] McKinnon S, Guatelli S, Incerti S, Ivanchenko V, Konstantinov K, Corde S, Lerch M, Tehei M, Rosenfeld A. Local dose enhancement of proton therapy by ceramic oxide nanoparticles investigated with Geant4 simulations. Phys Med. 2016 Dec;32(12):1584-1593.

[100] Wedenberg M, Beltran C, Mairani A, Alber M. Advanced Treatment Planning. Med Phys. 2018 Nov;45(11):e1011-e1023. doi: 10.1002/mp.12943.

[101] Chen W, Unkelbach J, Trofimov A, Madden T, Kooy H, Bortfeld T, Craft D. Including robustness in multi-criteria optimization for intensity-modulated proton therapy. Phys Med Biol. 2012 Feb 7;57(3):591-608.

[102] Kamal-Sayed H, Ma J, Tseung H, Abdel-Rehim A, Herman MG, Beltran CJ. Adaptive method for multicriteria optimization of intensity-modulated proton therapy. Med Phys. 2018 Dec;45(12):5643-5652.

[103] Kurz C, Süss P, Arnsmeyer C, Haehnle J, Teichert K, Landry G, Hofmaier J, Exner F, Hille L, Kamp F, Thieke C, Ganswindt U, Valentini C, Hölscher T, Troost E, Krause M, Belka C, Küfer KH, Parodi K, Richter C. Dose-guided patient positioning in proton radiotherapy using multicriteria-optimization. Z Med Phys. 2018 Nov 5. pii: S0939-3889(18)30062-X.

[104] Ammazzalorso F, Jelen U, Engenhart-Cabillic R, Schlegel W. Dosimetric robustness against setup errors in charged particle radiotherapy of skull base tumors. Radiat Oncol. 2014 Dec 5;9:279.

[105] Eley JG, Newhauser WD, Richter D, Lüchtenborg R, Saito N, Bert C. Robustness of target dose coverage to motion uncertainties for scanned carbon ion beam tracking therapy of moving tumors. Phys Med Biol. 2015 Feb 21;60(4):1717-40.

[106] Batista V, Richter D, Combs SE, Jäkel O. Planning strategies for inter-fractional robustness in pancreatic patients treated with scanned carbon therapy. Radiat Oncol. 2017 Jun 8;12(1):94.

[107] Graeff C. Robustness of 4D-optimized scanned carbon ion beam therapy against interfractional changes in lung cancer. Radiother Oncol. 2017 Mar;122(3):387-392.

[108] Ödén J, Eriksson K, Toma-Dasu I. Incorporation of relative biological effectiveness uncertainties into proton plan robustness evaluation. Acta Oncol. 2017 Jun;56(6):769-778.

[109] Ödén J, Toma-Dasu I, Eriksson K, Flejmer AM, Dasu A. The influence of breathing motion and a variable relative biological effectiveness in proton therapy of left-sided breast cancer. Acta Oncol. 2017 Nov;56(11):1428-1436.

[110] Resch AF, Landry G, Kamp F, Cabal G, Belka C, Wilkens JJ, Parodi K, Dedes G. Quantification of the uncertainties of a biological model and their impact on variable RBE proton treatment plan optimization. Phys Med. 2017 Apr;36:91-102.

[111] Inaniwa T, Kanematsu N, Matsufuji N, Kanai T, Shirai T, Noda K, Tsuji H, Kamada T, Tsujii H. Reformulation of a clinical-dose system for carbon-ion radiotherapy treatment planning at the National Institute of Radiological Sciences, Japan. Phys Med Biol. 2015 Apr 21;60(8):3271-86.

[112] Krämer M, Scholz M. Treatment planning for heavy-ion radiotherapy: calculation and optimization of biologically effective dose. Phys Med Biol. 2000 Nov;45(11):3319-30.

[113] Krämer M, Scholz M. Rapid calculation of biological effects in ion radiotherapy. Phys Med Biol. 2006 Apr 21;51(8):1959-70.

[114] Kamp F, Wilkens JJ. Application of variance-based uncertainty and sensitivity analysis to biological modeling in carbon ion treatment plans. Med Phys. 2019 Feb;46(2):437-447.

[115] Friedrich T, Grün R, Scholz U, Elsässer T, Durante M, Scholz M. Sensitivity analysis of the relative biological effectiveness predicted by the local effect model. Phys Med Biol. 2013 Oct 7;58(19):6827-49

[116] Giantsoudi D, Grassberger C, Craft D, Niemierko A, Trofimov A, Paganetti H. Linear energy transfer-guided optimization in intensity modulated proton therapy: feasibility study and clinical potential. Int J Radiat Oncol Biol Phys. 2013 Sep 1;87(1):216-22.

[117] Unkelbach J, Botas P, Giantsoudi D, Gorissen BL, Paganetti H. Reoptimization of Intensity Modulated Proton Therapy Plans Based on Linear Energy Transfer. Int J Radiat Oncol Biol Phys. 2016 Dec 1;96(5):1097-1106.

[118] McMahon SJ, Paganetti H, Prise KM. LET-weighted doses effectively reduce biological variability in proton radiotherapy planning. Phys Med Biol. 2018 Nov 9;63(22):225009.

[119] Grün R, Friedrich T, Traneus E, Scholz M. Is the dose-averaged LET a reliable predictor for the relative biological effectiveness? Med Phys. 2019 Feb;46(2):1064-1074.

[120] Furusawa Y, Fukutsu K, Aoki M, Itsukaichi H, Eguchi-Kasai K, Ohara H, Yatagai F, Kanai T, Ando K. Inactivation of aerobic and hypoxic cells from three different cell lines by accelerated (3)He-, (12)C- and (20)Ne-ion beams. Radiat Res. 2000 Nov;154(5):485-96. Erratum in: Radiat Res. 2012 Jan;177(1):129-31.

[121] Grassberger C, Trofimov A, Lomax A, Paganetti H. Variations in linear energy transfer within clinical proton therapy fields and the potential for biological treatment planning. Int J Radiat Oncol Biol Phys. 2011 Aug 1;80(5):1559-66.

[122] An Y, Shan J, Patel SH, Wong W, Schild SE, Ding X, Bues M, Liu W. Robust intensity-modulated proton therapy to reduce high linear energy transfer in organs at risk. Med Phys. 2017 Dec;44(12):6138-6147.

[123] Cao W, Khabazian A, Yepes PP, Lim G, Poenisch F, Grosshans DR, Mohan R. Linear energy transfer incorporated intensity modulated proton therapy optimization. Phys Med Biol. 2017 Dec 19;63(1):015013.

[124] Bassler N, Jäkel O, Søndergaard CS, Petersen JB. Dose- and LET-painting with particle therapy. Acta Oncol. 2010 Oct;49(7):1170-6. doi: 10.3109/0284186X.2010.510640. Erratum in: Acta Oncol. 2013 Feb;52(2):458.

[125] Bassler N, Toftegaard J, Lühr A, Sørensen BS, Scifoni E, Krämer M, Jäkel O, Mortensen LS, Overgaard J, Petersen JB. LET-painting increases tumour control probability in hypoxic tumours. Acta Oncol. 2014 Jan;53(1):25-32.

[126] Malinen E, Søvik Å. Dose or 'LET' painting--What is optimal in particle therapy of hypoxic tumors? Acta Oncol. 2015;54(9):1614-22.

[127] Tinganelli W, Durante M, Hirayama R, Krämer M, Maier A, Kraft-Weyrather W, Furusawa Y, Friedrich T, Scifoni E. Kill-painting of hypoxic tumours in charged particle therapy. Sci Rep. 2015 Nov 24;5:17016

[128] Sokol O, Krämer M, Hild S, Durante M, Scifoni E. Kill painting of hypoxic tumors with multiple ion beams. Phys Med Biol. 2019 Feb 8;64(4):045008.

[129] Steinsträter O, Grün R, Scholz U, Friedrich T, Durante M, Scholz M. Mapping of RBE-weighted doses between HIMAC- and LEM-Based treatment planning systems for carbon ion therapy. Int J Radiat Oncol Biol Phys. 2012 Nov 1;84(3):854-60.

[130] Molinelli S, Magro G, Mairani A, Matsufuji N, Kanematsu N, Inaniwa T, Mirandola A, Russo S, Mastella E, Hasegawa A, Tsuji H, Yamada S, Vischioni B, Vitolo V, Ferrari A, Ciocca M, Kamada T, Tsujii H, Orecchia R, Fossati P. Dose prescription in carbon ion radiotherapy: How to compare two different RBE-weighted dose calculation systems. Radiother Oncol. 2016 Aug;120(2):307-12.

[131] Bert C, Grozinger SO, Rietzel E. Quantification of interplay effects of scanned particle beams and moving targets. Phys Med Biol. 2008;53:2253–2265.

[132] Mori S, Knopf AC, Umegaki K. Motion management in particle therapy. Med Phys. 2018 Nov;45(11):e994-e1010. doi: 10.1002/mp.12679.

[133] Bert C, Herfarth K. Management of organ motion in scanned ion beam therapy. Radiat Oncol. 2017 Nov 6;12(1):170.

[134] Kubiak T. Particle therapy of moving targets-the strategies for tumour motion monitoring and moving targets irradiation. Br J Radiol. 2016 Oct;89(1066):20150275.

[135] Eley JG, Newhauser WD, Lüchtenborg R, Graeff C, Bert C. 4D optimization of scanned ion beam tracking therapy for moving tumors. Phys Med Biol. 2014 Jul 7;59(13):3431-52.

[136] Simeonov Y, Weber U, Penchev P, Ringbæk TP, Schuy C, Brons S, Engenhart-Cabillic R, Bliedtner J, Zink K. 3D range-modulator for scanned particle therapy: development, Monte Carlo simulations and experimental evaluation. Phys Med Biol. 2017 Aug 11;62(17):7075-7096.

[137] Richter D, Schwarzkopf A, Trautmann J, Krämer M, Durante M, Jäkel O, Bert C. Upgrade and benchmarking of a 4D treatment planning system for scanned ion beam therapy. Med Phys. 2013 May;40(5):051722.

[138] Knopf AC, Stützer K, Richter C, Rucinski A, da Silva J, Phillips J, Engelsman M, Shimizu S, Werner R, Jakobi A, Göksel O, Zhang Y, Oshea T, Fast M, Perrin R, Bert C, Rinaldi I, Korevaar E, McClelland J. Required transition from research to clinical application: Report on the 4D treatment planning workshops 2014 and 2015. Phys Med. 2016 Jul;32(7):874-82.

[139] Graeff C. Robustness of 4D-optimized scanned carbon ion beam therapy against interfractional changes in lung cancer. Radiother Oncol. 2017 Mar;122(3):387-392.

[140] Carlson DJ, Stewart RD, Semenenko VA. Effects of oxygen on intrinsic radiation sensitivity: A test of the relationship between aerobic and hypoxic linear-quadratic (LQ) model parameters. Med Phys. 2006 ep;33(9):3105-15.

[141] Antonovic L, Lindblom E, Dasu A, Bassler N, Furusawa Y, Toma-Dasu I. Clinical oxygen enhancement ratio of tumors in carbon ion radiotherapy: the influence of local oxygenation changes. J Radiat Res. 2014 Sep;55(5):902-11.

[142] Sokol O, Scifoni E, Tinganelli W, Kraft-Weyrather W, Wiedemann J, Maier A, Boscolo D, Friedrich T, Brons S, Durante M, Krämer M. Oxygen beams for therapy: advanced biological treatment planning and experimental verification. Phys Med Biol. 2017 Sep 20;62(19):7798-7813.

[143] Bassler N, Jäkel O, Søndergaard CS, Petersen JB. Dose- and LET-painting with particle therapy. Acta Oncol. 2010 Oct;49(7):1170-6.

[144] Bassler N, Toftegaard J, Lühr A, Sørensen BS, Scifoni E, Krämer M, Jäkel O, Mortensen LS, Overgaard J, Petersen JB. LET-painting increases tumour control probability in hypoxic tumours. Acta Oncol. 2014 Jan;53(1):25-32.

[145] Toma-Dasu I, Uhrdin J, Antonovic L, Dasu A, Nuyts S, Dirix P, Haustermans K, Brahme A. Dose prescription and treatment planning based on FMISO-PET hypoxia. Acta Oncol. 2012 Feb;51(2):222-30.

[146] Cheney MD, Chen YL, Lim R, Winrich BK, Grosu AL, Trofimov AV, Depauw N, Shih HA, Schwab JH, Hornicek FJ, DeLaney TF. [18F]-Fluoromisonidazole positron emission tomography/computed tomography visualization of tumor hypoxia in patients with chordoma of the mobile and sacrococcygeal spine. Int J Radiat Oncol Biol Phys. 2014 Dec 1;90(5):1030-6.

[147] Brahme A. Recent advances in light ion radiation therapy. Int J Radiat Oncol Biol Phys. 2004 Feb 1;58(2):603-16.

[148] Inaniwa T, Kanematsu N, Noda K, Kamada T. Treatment planning of intensity modulated composite particle therapy with dose and linear energy transfer optimization. Phys Med Biol. 2017 Jun 21;62(12):5180-5197.

[149] Knäusl B, Fuchs H, Dieckmann K, Georg D. Can particle beam therapy be improved using helium ions? - a planning study focusing on pediatric patients. Acta Oncol. 2016 Jun;55(6):751-9.

[150] Tessonnier T, Mairani A, Brons S, Sala P, Cerutti F, Ferrari A, Haberer T, Debus J, Parodi K. Helium ions at the heidelberg ion beam therapy center: comparisons between FLUKA Monte Carlo code predictions and dosimetric measurements. Phys Med Biol. 2017 Aug 1;62(16):6784-6803.

[151] Tessonnier T, Mairani A, Chen W, Sala P, Cerutti F, Ferrari A, Haberer T, Debus J, Parodi K. Proton and helium ion radiotherapy for meningioma tumors: a Monte Carlo-based treatment planning comparison. Radiat Oncol. 2018 Jan 9;13(1):2.

[152] Grün R, Friedrich T, Krämer M, Zink K, Durante M, Engenhart-Cabillic R, Scholz M. Assessment of potential advantages of relevant ions for particle therapy: a model based study. Med Phys. 2015 Feb;42(2):1037-47.

[153] Remmes NB, Herman MG, Kruse JJ. Optimizing normal tissue sparing in ion therapy using calculated isoeffective dose for ion selection. Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):756-62.

[154] Mazzucconi D, Agosteo S, Ferrarini M, Fontana L, Lante V, Pullia M, Savazzi S.Mixed particle beam for simultaneous treatment and online range verification in carbon ion therapy: Proof-of-concept study. Med Phys. 2018 Nov;45(11):5234-5243.

[155] Haring W. Siebstrahlung. Strahlentherapie. 1934;51:154–163.

[156] Marks H. Clinical experience with irradiation through a grid. Radiology. 1952;58:338–342.

[157] Dilmanian FA, Eley JG, Krishnan S. Minibeam therapy with protons and light ions: physical feasibility and potential to reduce radiation side effects and to facilitate hypofractionation. Int J Radiat Oncol Biol Phys. 2015 Jun 1;92(2):469-74.

[158] Dilmanian FA, Eley JG, Rusek A, Krishnan S. Charged Particle Therapy with Mini-Segmented Beams. Front Oncol. 2015 Dec 1;5:269.

[159] Prezado Y, Jouvion G, Guardiola C, Gonzalez W, Juchaux M, Bergs J, Nauraye C, Labiod D, De Marzi L, Pouzoulet F, Patriarca A, Dendale R. Tumor Control in RG2 Glioma-Bearing Rats: A Comparison Between Proton Minibeam Therapy and Standard Proton Therapy. Int J Radiat Oncol Biol Phys. 2019 Jan 29. pii: S0360-3016(19)30171-3.

[160] Prezado Y, Jouvion G, Patriarca A, Nauraye C, Guardiola C, Juchaux M, Lamirault C, Labiod D, Jourdain L, Sebrie C, Dendale R, Gonzalez W, Pouzoulet F. Proton minibeam radiation therapy widens the therapeutic index for high-grade gliomas. Sci Rep. 2018 Nov 7;8(1):16479.

[161] Girst S, Greubel C, Reindl J, Siebenwirth C, Zlobinskaya O, Walsh DW, Ilicic K, Aichler M, Walch A, Wilkens JJ, Multhoff G, Dollinger G, Schmid TE. Proton Minibeam Radiation Therapy Reduces Side Effects in an In Vivo Mouse Ear Model. Int J Radiat Oncol Biol Phys. 2016 May 1;95(1):234-41.

[162] Farr JB, Moskvin V, Lukose RC, Tuomanen S, Tsiamas P, Yao W. Development, commissioning, and evaluation of a new intensity modulated minibeam proton therapy system. Med Phys. 2018 Jul 15.

[163] Gao M, Mohiuddin MM, Hartsell WF, Pankuch M. Spatially fractionated (GRID) radiation therapy using proton pencil beam scanning (PBS): Feasibility study and clinical implementation. Med Phys. 2018 Apr;45(4):1645-1653.

[164] Martínez-Rovira I, González W, Brons S, Prezado Y. Carbon and oxygen minibeam radiation therapy: An experimental dosimetric evaluation. Med Phys. 2017 Aug;44(8):4223-4229.

[165] Tsubouchi T, Henry T, Ureba A, Valdman A, Bassler N, Siegbahn A. Quantitative evaluation of potential irradiation geometries for carbon-ion beam grid therapy. Med Phys. 2018 Mar;45(3):1210-1221.

[166] Henry T, Bassler N, Ureba A, Tsubouchi T, Valdman A, Siegbahn A. Development of an interlaced-crossfiring geometry for proton grid therapy. Acta Oncol. 2017 Nov;56(11):1437-1443.

[167] Henry T, Ödén J. Interlaced proton grid therapy - Linear energy transfer and relative biological effectiveness distributions. Phys Med. 2018 Dec;56:81-89.

[168] Billena C, Khan AJ. A Current Review of Spatial Fractionation: Back to the Future. Int J Radiat Oncol Biol Phys. 2019 Jan 23. pii: S0360-3016(19)30154-3.

[169] Favaudon V, Caplier L, Monceau V, Pouzoulet F, Sayarath M, Fouillade C, Poupon MF, Brito I, Hupé P, Bourhis J, Hall J, Fontaine JJ, Vozenin MC. Ultrahigh dose-rate FLASH irradiation increases the differential response between normal and tumor tissue in mice. Sci Transl Med. 2014 Jul 16;6(245):245ra93.

[170] Montay-Gruel P, Petersson K, Jaccard M, Boivin G, Germond JF, Petit B, Doenlen R, Favaudon V, Bochud F, Bailat C, Bourhis J, Vozenin MC. Irradiation in a flash: Unique sparing of memory in mice after whole brain irradiation with dose rates above 100Gy/s. Radiother Oncol. 2017 Sep;124(3):365-369

[171] Harrington KJ. Ultrahigh Dose-rate Radiotherapy: Next Steps for FLASH-RT. Clin Cancer Res. 2019 Jan 1;25(1):3-5.

[172] Durante M, Bräuer-Krisch E, Hill M. Faster and safer? FLASH ultra-high dose rate in radiotherapy. Br J Radiol. 2018 Feb;91(1082):20170628.

[173] Vozenin MC, De Fornel P, Petersson K, Favaudon V, Jaccard M, Germond JF, Petit B, Burki M, Ferrand G, Patin D, Bouchaab H, Ozsahin M, Bochud F, Bailat C, Devauchelle P, Bourhis J. The Advantage of FLASH Radiotherapy Confirmed in Mini-pig and Cat-cancer Patients. Clin Cancer Res. 2019 Jan 1;25(1):35-42

[174] Beyreuther E, Karsch L, Laschinsky L, Leßmann E, Naumburger D, Oppelt M, Richter C, Schürer M, Woithe J, Pawelke J. Radiobiological response to ultra-short pulsed megavoltage electron beams of ultra-high pulse dose rate. Int J Radiat Biol. 2015 Aug;91(8):643-52.

[175] Buonanno M, Grilj V, Brenner DJ. Biological effects in normal cells exposed to FLASH dose rate protons. Radiother Oncol. 2019 Mar 5. pii: S0167-8140(19)30076-3.

[176] Patriarca A, Fouillade C, Auger M, Martin F, Pouzoulet F, Nauraye C, Heinrich S, Favaudon V, Meyroneinc S, Dendale R, Mazal A, Poortmans P, Verrelle P, De Marzi L. Experimental Set-up for FLASH Proton Irradiation of Small Animals Using a Clinical System. Int J Radiat Oncol Biol Phys. 2018 Nov 1;102(3):619-626.

[177] Karsch L, Beyreuther E, Enghardt W, Gotz M, Masood U, Schramm U, Zeil K, Pawelke J. Towards ion beam therapy based on laser plasma accelerators. Acta Oncol. 2017 Nov;56(11):1359-1366.

[178] Zlobinskaya O, Siebenwirth C, Greubel C, Hable V, Hertenberger R, Humble N, Reinhardt S, Michalski D, Röper B, Multhoff G, Dollinger G, Wilkens JJ, Schmid TE. The effects of ultra-high dose rate proton irradiation on growth delay in the treatment of human tumor xenografts in nude mice. Radiat Res. 2014 Feb;181(2):177-83.

[179] Lehmann HI, Richter D, Prokesch H, Graeff C, Prall M, Simoniello P, Fournier C, Bauer J, Kaderka R, Weymann A, Szabó G, Sonnenberg K, Constantinescu AM, Johnson SB, Misiri J, Takami M, Miller RC, Herman MG, Asirvatham SJ, Brons S, Jäkel O, Haberer T, Debus J, Durante M, Bert C, Packer DL. Atrioventricular node ablation in Langendorff-perfused porcine hearts using carbon ion particle therapy: methods and an in vivo feasibility investigation for catheter-free ablation of cardiac arrhythmias. Circ Arrhythm Electrophysiol. 2015 Apr;8(2):429-38.

[180] Lehmann HI, Graeff C, Simoniello P, Constantinescu A, Takami M, Lugenbiel P, Richter D, Eichhorn A, Prall M, Kaderka R, Fiedler F, Helmbrecht S, Fournier C, Erbeldinger N, Rahm AK, Rivinius R, Thomas D, Katus HA, Johnson SB, Parker KD, Debus J, Asirvatham SJ, Bert C, Durante M, Packer DL. Feasibility Study on Cardiac Arrhythmia Ablation Using High-Energy Heavy Ion Beams. Sci Rep. 2016 Dec 20;6:38895.

[181] Richter D, Lehmann HI, Eichhorn A, Constantinescu AM, Kaderka R, Prall M, Lugenbiel P, Takami M, Thomas D, Bert C, Durante M, Packer DL, Graeff C. ECG-based 4D-dose reconstruction of cardiac arrhythmia ablation with carbon ion beams: application in a porcine model. Phys Med Biol. 2017 Aug 4;62(17):6869-6883.

[182] Graeff C, Bert C. Noninvasive cardiac arrhythmia ablation with particle beams. Med Phys. 2018 Nov;45(11):e1024-e1035. doi: 10.1002/mp.12595.

[183] Zei PC, Soltys S. Ablative Radiotherapy as a Noninvasive Alternative to Catheter Ablation for Cardiac Arrhythmias. Curr Cardiol Rep. 2017 Sep;19(9):79.

[184] Cuculich PS, Schill MR, Kashani R, Mutic S, Lang A, Cooper D, Faddis M, Gleva M, Noheria A, Smith TW, Hallahan D, Rudy Y, Robinson CG. Noninvasive Cardiac Radiation for Ablation of Ventricular Tachycardia. N Engl J Med. 2017 Dec 14;377(24):2325-2336.

[185] Lehmann HI, Deisher AJ, Takami M, Kruse JJ, Song L, Anderson SE, Cusma JT, Parker KD, Johnson SB, Asirvatham SJ, Miller RC, Herman MG, Packer DL. External Arrhythmia Ablation Using Photon Beams: Ablation of the Atrioventricular Junction in an Intact Animal Model. Circ Arrhythm Electrophysiol. 2017 Apr;10(4). pii: e004304.