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Research needed for improving heavy-ion therapy

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Abstract. The large interest in heavy-ion therapy is stimulated from its excellent clinical results. The bases of this success are the radiobiological and physical advantages of heavy-ion beams and the active beam delivery used for an intensity-modulated particle radiotherapy (IMPT). Although heavy-ion therapy has reached a high degree of perfection for clinical use there is still large progress possible to improve this novel technique: in order to extend IMPT to more tumor entities and to tailor the planning more individually for each patient in an adaptive way, radiobiological work is required both experimentally and theoretically. It is also not clear whether the neighboring ions to carbon could have a clinical application as well. For this extension basic biological studies as well as physics experiments have to be performed. On the technical side, many improvements of the equipment used seem to be possible. Two major topics are the extension of IMPT to moving organs and the transition to more compact and therefore cheaper particle accelerators. In the present paper, these topics are treated to some extent in order to give an outline of the great future potential of ion-beam therapy.

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Contents

1. Introduction	2
2. Radiobiological research	3
2.1. General strategies for RBE-weighted treatment planning	3
2.2. Extension of the biology-based treatment planning to new beams and new tumor entities	4
2.3. Development of patient-specific predictive assays of radio sensitivity	5
2.4. Long-term effects and secondary tumors	6
2.5. Dose modulation inside the target: adaptive treatment planning	7
2.6. Radiobiological properties of ions other than carbon	8
3. Physical data for an extension to ions other than protons or carbon	9
3.1. Gross properties of the new beams	9
3.2. Future developments of ‘in-beam PET’	9
3.3. Basic atomic physics data for track structure calculations	9
4. Irradiation of moving targets	10
5. New accelerator concepts	11
5.1. Laser-driven ion acceleration (LDIA)	12
5.2. Dielectric wall accelerators	14
6. Summary	14
Acknowledgments	15
References	15

1. Introduction

It is the final goal of any external radiotherapy to expose the tumor to a lethal dose and to spare the normal tissue to a maximum extent. Beams of accelerated ions like protons or carbon ions represent a major step in this direction: firstly, a higher dose can be applied to the tumor compared with the dose to the normal tissue because of the inverse dose profile of particles with the Bragg maximum at the end of the particle range. Secondly, a millimeter precision is reached everywhere in the human body due to the small spatial scattering of carbon ions. Thirdly, radio-resistant tumors are inactivated with greater probability because of the increase of the relative biological effectiveness (RBE) for carbon ions with penetration to maximum values in the target volume. Finally, the range and location of the primary beam can be tracked inside the patient without creating additional radioactivity by monitoring positron-emitting isotopes via positron emission tomography techniques (PET) [1, 2].

All these properties are presently known to an extent that allows a safe and successful treatment of patients at the heavy ion facilities: National Institute for Radiological Science (NIRS) and Gesellschaft für Schwerionen Forschung (GSI) at Chiba and Darmstadt and represent a basic set of information for the upcoming centers at Heidelberg, Pavia, Marburg, Kiel and other places. In a comprehensive review, the large variety of tumors treated up to now with particles and the clinical outcome is discussed [3]. It shows that the most successful heavy-ion treatment is given for slowly growing and therefore radio-resistant tumors. Because of the limited access to carbon beams the patient numbers for the different tumor entities are small and thus smaller differences in the clinical results become less prominent. For these cases, more

clinical research has to be done to optimize ion treatment, which shall not be subject of the present paper.

In addition, for the application of beam scanning as planned in the new centers, all tumors have to be subjected to a rigid fixation from outside because of the very conformal treatment and a potential interplay between organ motion and scanning. External fixation is only possible in the head and neck areas, along the spinal cord and to some extent in the pelvis. In future, the treatment should also be extended to moving organs in the thorax and abdomen and aim for a fully three-dimensional (3D) adaptive treatment for all relevant tumors at any location in the body. It would be favorable to include more tumor entities, especially tumors that are more common like lung, prostate and gliomas, for instance. The treatment should be more individualized and based on the individual radio tolerance as well as on the variation in the radio resistance in the target volume. Therefore, it is important to improve the knowledge on the biological reaction of both tumor and normal cells concerning inactivation and late effect, respectively. On the physicochemical side, the properties of light ions other than protons and carbon have to be explored and possibilities for novel acceleration techniques less expensive than the existing high-energy accelerators have to be studied.

According to these problems, the present paper is divided into four main parts. In the first section, the biological problems are discussed. In particular, we want to address the ion-specific treatment planning, the long-term effects and possible advantages of ion species other than protons and carbon ions. Section 2 covers physical data, e. g. PET measurements and microscopic track structure. Section 3 describes the possibility of irradiating moving targets, and in section 4 we want to introduce new accelerator concepts.

2. Radiobiological research

2.1. General strategies for RBE-weighted treatment planning

The major reason to use ions heavier than protons is the increase in RBE with penetration depth. This is the case for all charged particles from protons to the very heavy ions; however, there are two competing processes that determine the effectiveness: the higher local ionization densities toward lower velocities yield first an increase of more complex and therefore less repairable DNA damage. Later on at further increasing ionization density saturation processes take over and decrease the RBE drastically. This yields a shift of the RBE maximum in comparison with the Bragg maximum depending on the ionic species of the projectiles: for protons the RBE maximum is at the distal side of the Bragg maximum, whereas for argon ions it is shifted about 2 cm toward the entrance point. In the first ion therapy at Berkeley this broad RBE maximum extending over a large range was the reason to choose argon ions in order to kill radio-resistant tumor cells with great efficiency (figure 1). The argon and later on silicon beams yielded good tumor control rates at the expense of nontolerable side effects. Therefore neon ions were used as a compromise between biological effectiveness and tolerable side effects [4]. For carbon ions the RBE maximum coincides with the Bragg maximum, thus the high dose is combined with high effectiveness. The facilities at Chiba and Darmstadt follow a different strategy: carbon ions are used to maximize the difference of the RBE between the tumor and normal tissues in order to reduce side effects. This seems to be a better approach, especially when the tumors are irradiated extremely conformally using scanning techniques [3].

Although it is now evident that the therapeutic window for optimal ionic species are ions with a mass close to or below carbon ions, no systematic research both experimentally and in

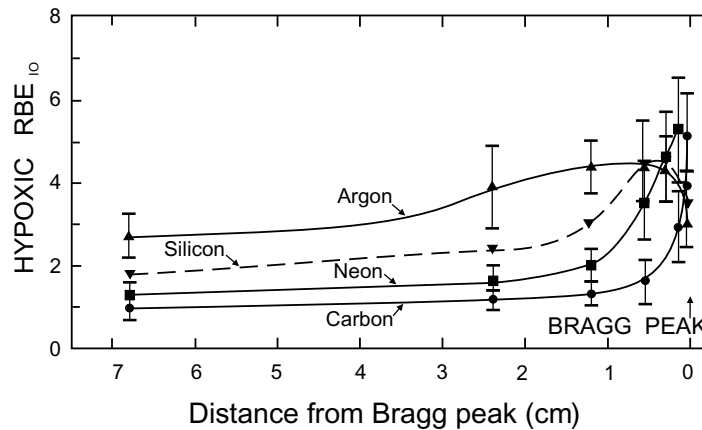


Figure 1. RBE as a function of penetration depth for different projectiles from carbon to argon ions. Very heavy argon ions show saturation effects already at the end of the range in the Bragg maximum in the target volume and large RBE values in the normal tissue before (adapted from [5]).

modeling has been performed for the ions from oxygen to protons. In the following section, different aspects of this future research in biology and physics are outlined.

2.2. Extension of the biology-based treatment planning to new beams and new tumor entities

To calculate the dose distribution for scanned irradiation, the local RBE values for each irradiated pixel are needed. In the GSI pilot project, these RBE data were not transferred directly from *in vitro* experiments to the clinical planning situation [6]. Therefore, a greater theoretical understanding of the RBE was necessary to calculate the RBE values pixelwise for the target volume. This knowledge has been achieved with the development of the local effect model (LEM) at GSI that enables to calculate the RBE values for all pixels of the target volume and for the radiation-affected normal tissue outside the target volume independent of the tumor type [7].

The basic inputs of the LEM are physical and biological parameters: in physics, the microscopic track structure of the ions and the beam fragmentation both depending on energy, atomic number and penetration depth are most important. The biological inputs for the LEM are the size of the cell nuclei and the general radio sensitivity as given by the α to β ratio of cell inactivation for the specific tumor type or of the sensitivity for late effects of the normal tissue. These values have to be taken from published photon data or specific designed experiments (figure 2).

At present, α to β ratios are well known for some slowly growing tumors like chordomas, chondrosarcomas and benign meningiomas that are already acknowledged as medical indications for particle therapy. The sensibility of prostate tumors has been evaluated and is used presently for experimental studies. In order to extend the particle therapy to other more frequent tumor entities the clinical α to β ratios for photon therapy have to be evaluated from published data and if possible confirmed in animal experiments in order to calculate the local RBE values needed in treatment planning. These data represent the basis for a general application of the LEM in treatment planning and replace to some extent the classification of tumor tissue by inactivation doses.

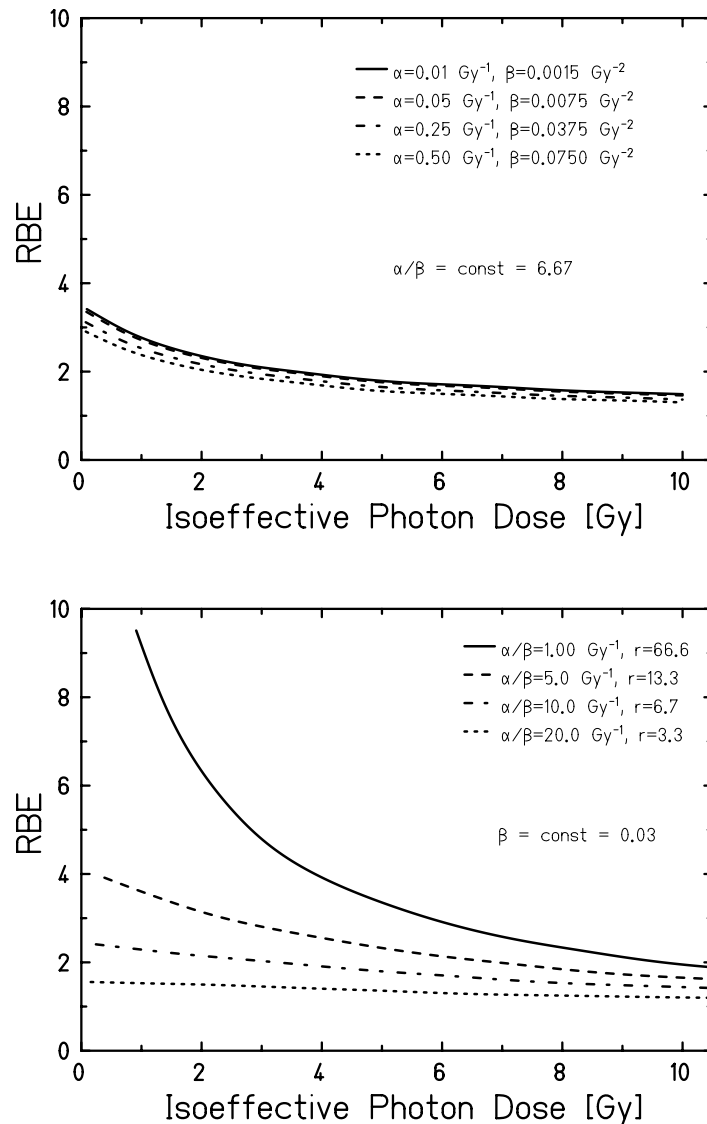


Figure 2. With the LEM model RBE values are calculated as function of dose. Compared are values where the ratio of the slope parameters α to β is fixed but the absolute numbers are different with a set of data where the ratio of α to β is varied but one parameter is kept constant. The data clearly indicate that the variation of the α to β is the determining parameter for the RBE calculation that has to be known on the biological side (adapted from [8]).

2.3. Development of patient-specific predictive assays of radio sensitivity

Up to now the LEM calculations are based on the mean values of sensitivity of a specific tumor entity averaged over all published data of photon therapy without any corrections for the individual patient. This is the same approach as used in conventional radiotherapy where general protocols are used for the various tumor types without individual corrections.

A precise knowledge of the individual radio sensitivity for each patient would be very helpful to improve treatment planning again for both conventional treatment as well as ion

irradiation: for patients with greater tolerance of the normal tissue the dose applied to the tumor could be increased in order to reach a greater tumor control probability with tolerable side effects. For more sensitive patients, lower doses would be given in order to reduce the incidence of side effects [9].

Attempts are made to determine the radio sensitivity response from biopsies and from lymphocytes using inactivation as cellular endpoint; furthermore, the usage of molecular markers is discussed [10]. However, to our knowledge, up to now no stringent correlations have been found that could be used to adapt therapy individually. For instance, the radiation sensitivity of external lymphocytes of one individual can vary by more than a factor of two over a few months. So far, it is not clear whether this variation is paralleled by the same variations of the radio sensitivity of the tissue. In addition, it seems to be a problem whether measurements of external samples such as lymphocytes or cultured cells from biopsies can be predictive for *in vivo* tissue: when samples are taken out of their original environment such as trypsinated biopsies, the cell properties, especially gross properties like radio resistance or tolerance, can be different.

Recently, it has been reported that it is feasible to culture thin slices of tumor tissue over a few weeks [11]. This culturing technique combined with appropriate markers quantified at cellular level could give a powerful tool for future research. In these tissue slices the cellular effect after irradiation could be studied for instance with fluorescent microscopy on an intracellular level. This technique could use tissue from various types of tumors under conditions more realistic to patient treatment than *in vitro* culture. It should also be used to test the possibility to influence the radiation response by modifying ingredients such as sensitizing, protecting drugs or simply to test the residual oxygen effect for particle radiation.

2.4. Long-term effects and secondary tumors

In order to extend ion therapy to young patients having a longer life expectancy it is necessary to investigate the long-term effects of particle irradiation such as the induction of secondary tumors and genetic mutations in greater detail. In recent publications, the influence produced by neutrons during therapy on secondary tumor induction was analyzed for intensity-modulated radiation therapy (IMRT), conventional therapy and particle therapy using active and passive beam preparation [12]. The general potential of ionizing radiation to produce cell transformation is well known but poorly quantified for the different radiation modalities because of the experimental difficulties [13]. Since the transformation probability is normally in the range of a few per mille per applied Gray, it is very difficult to obtain solid data other than in *in vitro* cell experiments. For x-rays a few classical experiments are reported [12] whereas for particle irradiation the database is even more scarce [13].

The question of whether the high local energy transfer (LET) of particle radiation induces a greater rate of secondary tumors has not yet been answered. From patients presently treated at NIRS or GSI no increased amount of secondary tumors has been reported. The question of the transforming power of ion beams is normally raised in radioprotection, where the critical tissues are exposed to a low dose of high LET radiation. In radiotherapy, however, the target volume will be exposed to a high dose leading to an inactivation of all cells, hence mutation and transformation cannot be expressed. Therefore, the relevant issues for particle therapy are the long-term effects of the tissue in the entrance channel that is exposed to intermediate LET values at moderate doses.

First cell experiments indicate that there is no larger RBE for transformation than for inactivation in this range of intermediate LET in contrast to high LET. In these *in vitro* experiments, it has been observed that the transformation and the induction of secondary tumors are not larger than for x-ray treatment [14]. These data have to be systematically extended to other model systems and to animal tissues. However, it is nearly impossible to perform as many animal experiments as are needed to obtain significant results. Therefore the same strategy as used for the inactivation RBE should be performed: the LEM or any other model should be extended from inactivation to transformation. After this the fidelity of the calculation has to be verified at some significant amount of cell experiments before it can be extended to the risk estimation.

2.5. Dose modulation inside the target: adaptive treatment planning

In particle therapy as in radiotherapy in general, the biological effect is planned to be uniform over the target volume that means killing of all tumor cells independent of their sensitivity. In conventional therapy using photons and in proton therapy a homogeneous dose is planned [15], whereas in heavy-ion therapy an inhomogeneous RBE distribution is taken into account based on the variations of the physical parameters but assuming a homogeneous cell sensitivity. However, it is known that in many cases the sensitivity of the tumor cells shows some variation over the tumor volume, for instance in the less blood circulated areas, hypoxia increases the radio resistance.

Although the different sensitivities are starting to be taken into account in conventional 'adaptive' radiotherapy by increasing the local dose, it is not clear to what extent these corrections have to be incorporated in heavy-ion therapy. Because the RBE is larger for radio-resistant tissue, the variation in radio sensitivity is compensated to a large extent by the opposite RBE variation of high LET radiation.

In the ideal case when only low-energy carbon ions with a high effectiveness hit the tumor cells, the areas of greater photon radio resistance do not have to be exposed to a higher carbon dose because the greater hypoxic RBE will correct automatically for the greater resistance. This argumentation can be adapted to all effects changing the repair characteristic.

In all real target fields mixtures of different carbon energies are superimposed. While for the stopping carbon ions the corrections would be minimal, the ions with higher energies having lower RBE need a larger correction. In the treatment planning the elevated RBE will yield for these resistant areas a dose correction to a lower extent than for photons or protons. Up to now we do not know whether and to what extent local corrections for an adaptive treatment planning will be necessary for carbon. The present treatment planning systems are capable of modeling the RBE distribution over the target field and of modifying the local doses accordingly as shown in figure 3.

For the detection of different radio sensitivities as well as of the local proliferation status, several imaging techniques have been proposed such as functional magnetic resonance imaging (MRI) and PET combined with immune labeled drugs. In carbon therapy there seems to be a more direct way to gain information of the intrinsic proliferation of the tissue in the target field: in-beam PET measurements have shown that the implanted carbon projectiles combine with oxygen when stopped, forming CO₂ [16].

The decrease of this carbon dioxide PET signal has two different sources: the physical half-life of 20 min and a faster biological washout of about 100 s. Thus the detection of the time

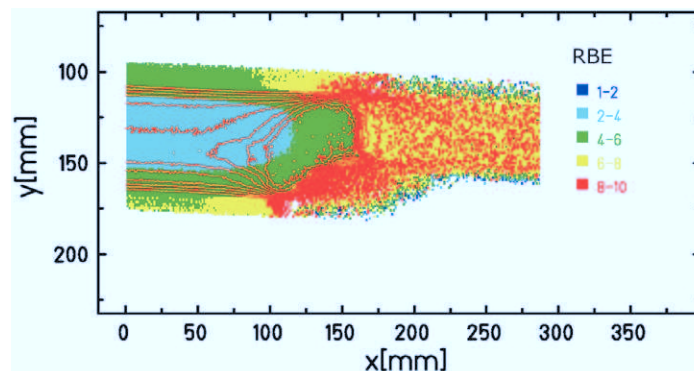


Figure 3. RBE distribution for a single field optimized for one fraction only. The RBE varies over a factor of ten having the highest values in the normal tissues beyond the distal border of the field. Because of the inverse RBE dependence on dose, the extreme low doses correspond to large RBE values but also in the target field the RBE changes from two to four. It is also possible for an adaptive planning to change this RBE according to the local radio sensitivity (adapted from [6]).

kinetics of the PET signal enables the internal status, at least of the oxygenation of the tissue, to be monitored online. A more quantitative measurement would allow the measured sensitivity variations in adaptive particle radiotherapy to be corrected for immediately.

2.6. Radiobiological properties of ions other than carbon

Carbon ions were chosen for radiotherapy because the ratio of the RBE in the entrance channel—compared to the target volume—seems to be optimal for a radio-resistant tumor. However, this ratio depends on physical parameters such as projectile fragmentation and scattering [17, 18]. For the more superficial tumors, ions heavier than carbon could be more efficient because the absolute amount of the fragments is lower due to a shorter penetration.

This would result in a greater RBE in the target as compared to the RBE for a treatment with carbon ions. In future research, the neighboring ions of carbon like nitrogen or oxygen should be examined. Especially the RBE dependence from depth has to be measured for therapeutic situations and compared with the corresponding model calculation, to find out whether the heavier ions would yield a significant benefit for superficial tumors. In contrast, it should also be studied whether lighter ions like boron would be appropriate for tumors that are deeper seated.

Another question related to ion beams of different atomic numbers is the treatment of infiltrating tumors. Up to now particle therapy has had its greatest success for tumors with well-defined boundaries: a high dose is given to the target and normal tissue outside the target volume is spared. Because of the compact target geometry little normal tissue is affected. For tumors with less pronounced borders or tumors that grow infiltrating the normal tissue it has to be studied whether there is a benefit for treatment using particles of different atomic numbers or even mixtures of different ion beams: for instance, when the cells differ in the size of the cell nuclei the tumor cell and normal tissue will experience a different biological effective dose even when bombarded with the same physical dose. In this case, mixtures of ion beams combined in sophisticated fractionation schedules might help to achieve tumor inactivation combined with

reasonable normal cell survival. The idea of using various ions in one treatment field is further discussed in [19].

3. Physical data for an extension to ions other than protons or carbon

3.1. Gross properties of the new beams

To extend ion-beam therapy to different ionic species, basic physical data are needed with an absolute precision below 1% for treatment planning. This accuracy cannot be reached by theoretical estimations or Monte Carlo simulations. Most important are exact LET determinations, range measurements with submillimeter error, the lateral scattering of the primary ions and the lateral scattering of the fragments in order to provide a physical beam model of sufficient accuracy. In a first attempt, these data can be obtained roughly by scaling of the basic carbon data to the neighboring nuclides such as boron, nitrogen and oxygen, but finally these calculations have to be confirmed in precision experiments.

3.2. Future developments of 'in-beam PET'

At the very beginning one major advantage of carbon ions was the possibility to monitor the ion range inside the body by measuring the decay of the positron emitting ^{10}C and ^{11}C isotopes with a PET camera. In this case, the interpretation of the PET data is relatively simple because there are only two carbon lines and a broad background in the energy spectrum. The background signal arises from the decay of ^{15}O that forms a flat continuum extending over nearly the full range of the signal caused by carbon ions.

For oxygen or nitrogen the situation becomes more complex because more isotopes can contribute to the PET signal. Enghardt and colleagues have already started to measure the spectra of all the positron emitting isotopes produced by light ion impact. These measurements have to be extended to all ions of interest for future ion-beam therapy.

At present, the application of carbon beams is safe because of the large amount of physical and clinical data acquired with carbon beams at Chiba and Darmstadt. But when it is planned to extend particle therapy to other ions or to perform radio surgery with single fractions then it would be very helpful to develop new setups of in-beam PET connected to the ion-beam facilities. Currently, the GSI pilot project only uses an in-beam PET analysis for a fixed horizontal beam. Due to external constraints such as the space needed for the beam nozzle and the patient couch the acceptance angle of the cameras is very limited, reducing the number of measurable decay events. This problem becomes even more prominent for applications using oblique beams and gantries. Cameras with a larger acceptance angle would have a higher resolution, since more photons could be detected, enhancing the precision of the reconstructed image [20]. Furthermore, it has to be investigated whether commercial PET units could be used for a nearly online operation when the patient is immobilized on a platform carried by a robot. In this case, it would be possible to move the patient from the irradiation position into the PET camera within 1 min.

3.3. Basic atomic physics data for track structure calculations

Basic track structure parameters form another class of data needed for a better understanding and calculation of the RBE. According to a general understanding, the difference of particle

RBE compared with x-rays is due to the different spatial patterns of energy deposition in a microscopic scale. For ion beams, the energy released by the primary projectile is translated mostly into kinetic energy of emitted δ electrons. Their energy is transported by multiple scattering from the center of the track to the outer parts and yields the radial dose distribution. The very frequent low-energy electrons have a short range and therefore determine the inner part of the track that is of special importance because the applied doses of the electrons are in the order of kilo Gray and cause irreparable damage to DNA.

The primary electron spectra used for track structure calculations are obtained from measurement of electron emission in gas targets. No data exist for condensed matter although it is known that in a condensed target the energy spectrum differs from gas targets. The low-energy part of the electron spectrum will change strongly in solids: in a classical picture these low-energy electrons are created in distant collisions with large impact parameters that become less probable in condensed matter because of the increasing shielding of the atoms in between. In addition to the electron emission process, the electron transport in solids can be different from that in gas. Therefore, the knowledge of the track structure formation should be improved and extended to condensed material for better RBE calculations [21].

In the present practice of the LEM application, the necessary track parameters describing the inner part of the tracks are fitted from basic biological measurements and then transferred to treatment planning, but it is important to replace this empirical procedure by measured data. Since the track structure parameters play an important role in most other applications of ion beams, this is not only relevant for radiobiology or therapy but also for many other particle applications such as material and space research.

4. Irradiation of moving targets

At present, the passive beam shaping system used in most particle therapies has been out-dated by the much cheaper IMRT using photons [15]. Only active particle scanning systems produce a dose conformity of ions superior to IMRT. In addition, the active scanning systems have no material in the beam except the beam monitor and the exit window. Therefore less neutrons are produced and consequently a much lower rate of secondary tumors is expected [12]. Up to now beam scanning has been limited to nonmoving target volumes since the internal target movement caused by breathing interferes with scanning. Methods able to mitigate target motion have to be developed in order to extend the indications for particle therapy into the thorax and abdomen areas (figure 4).

To cope with the motion-induced dose inhomogeneity and nonconformity, two methods are used in photon therapy: multiple painting and synchronization (gating) of the exposure.

It has been demonstrated that the multiple painting or rescanning technique is not an appropriate method for scanned beams because of the remaining poor homogeneity and the dramatic loss of sharp dose gradients at the field borders [23]. Gated exposure yields better results but prolongs the exposure time by a factor of two to four and still has a residual in field inhomogeneity [24, 25].

Therefore a 3D online correction of the scanning procedure is presently being developed at GSI utilizing the setting of the scanning magnets for lateral corrections. Fast degraders have to be used for the range correction because the corresponding energy variation is not possible using the accelerator. In the system, the whole motion cycle is divided into small increments.

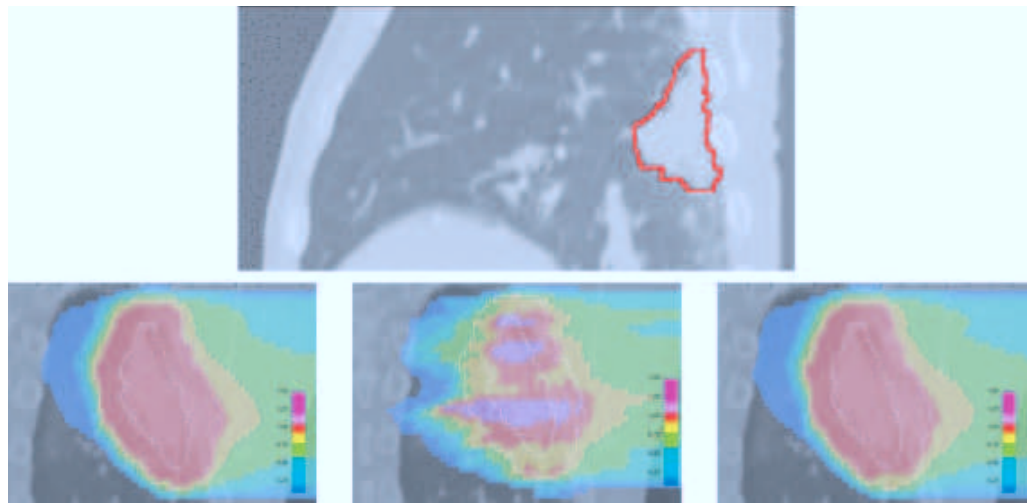


Figure 4. In the upper panel the motion of a tumor at the distal side of the lung is given. In the lower panel the result of treatment planning for such a tumor is given for the case without motion (left) and for a treatment with a scanned beam and a moving target (middle). At the right side the motion is corrected online and the accuracy of the static irradiation is restored (adapted from [22]).

Because breathing is a cyclic motion, the increment of the translation caused by the motion can be predicted to a large extent according to the previous motion and the expected course of a breathing cycle that can be measured in a time-resolving CT [26]. Consequently, the location of a certain pixel at a given time in the breathing cycle is based on the expected motion according to 4D CT measurements performed before. In reality, the breathing can be different and the pixel is at a slightly different position than expected. In this case the next step is used to correct between predicted and real motion. This strategy has been partially confirmed in phantom experiments [22].

A major and still remaining problem is the online detection of the inner motion of the organs around the tumor and of the target area itself. Ultrasound techniques seem to be feasible to some extent in the abdomen but fail in the lung because of its low density. Up to now no method has been developed that allows a fast and precise detection of the position changes of the target volume. Research and development on target tracking is not only mandatory for heavy-ion therapy but also for any other extreme target conforming irradiation.

5. New accelerator concepts

A clear disadvantage of the acceleration concepts implemented in ion therapy so far are the huge dimensions and hence the high costs of the apparatus. A major contribution to these costs arises from the accelerator and the eventually needed heavy gantry necessary for treatment with ion beams. This fact leads to the search for new accelerator concepts. The final goal would be the development of an accelerator small enough to be rotated around the patient. This would replace the bulky heavy gantry and hence reduce the costs dramatically. At present, there are two upcoming concepts to overcome these problems.

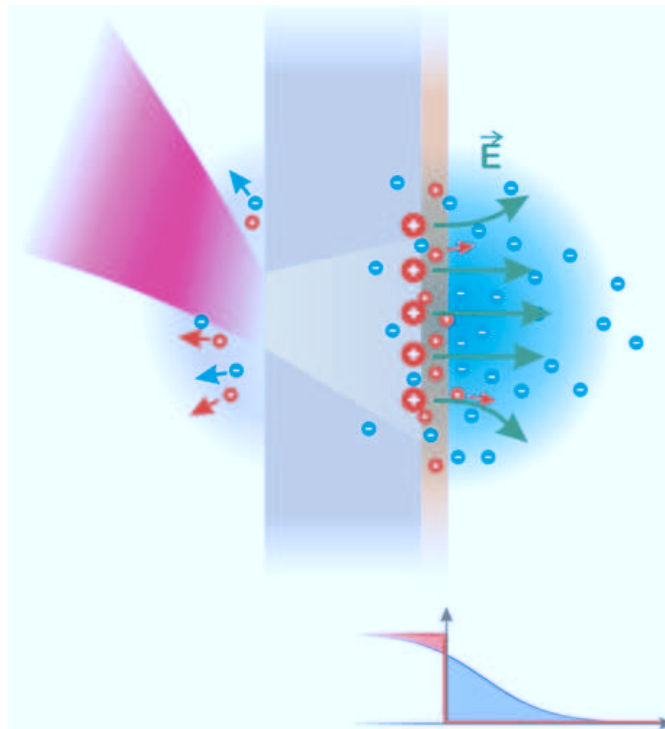


Figure 5. Acceleration of protons from the back side of a thin foil. A focused laser beam heats the electrons in the foil. Therefore some of the electrons leave the foil and create a strong electric field that accelerates the ions. The lower picture shows the electron density distribution.

5.1. Laser-driven ion acceleration (LDIA)

In LDIA ion beams are produced by focusing the beam of a high-power laser onto a thin foil. The experiments on LDIA utilize high-power lasers with very short pulses. Present systems running at repetition rates of up to 10 Hz have pulse lengths between ten and a few hundred femtoseconds with energies of a few Joules per pulse resulting in maximum powers of 0.1–1 PW. In recent years there has been rapid development in lasers of this power rating, so that they are meanwhile small enough to fit into a normal laboratory. To produce fast ions the laser beam is focused to a small spot of a few micrometers diameter onto a thin foil leading to peak intensities of up to $10^{21} \text{ W cm}^{-2}$ (figure 5). Because of the high electric field a plasma is produced and electrons in the foil are heated to temperatures of a few megaelectronvolts. The hot electrons can penetrate through the foil, the escape from the back side forming a cloud of negative charges around it. This negative space charge creates a huge electrical field on the order of 10^{12} V m^{-1} , six orders of magnitudes higher than in common RF accelerators, which accelerates ions located at the foil. Though this mechanism works for any ionic species, in first experiments protons and carbon ions originating from a contamination layer on the target were observed most often.

First spectra reported in the literature had a thermal energy distribution showing ions with energies up to 5–55 MeV [27]–[31]. These spectra show a lot of low energetic and only a few high energetic ions and are therefore not favorable for patient treatment. The form of the spectra has two main reasons: only a small spot of the target gets heated by the laser beam resulting in an

inhomogeneous electron density and therefore a spatially varying electric field at the backside. Due to this, ions positioned at different lateral positions experience different electric fields. In addition, the field collapses after a few picoseconds leading to different acceleration times of ions with different starting times in the foil.

The energy spectra changed during the last two years. In two experiments, it was shown independently that a preparation of the foil backside can lead to monoenergetic ion beams [32, 33].

Both experiments reported quasi-monoenergetic ion beams, although with low energies below 5 MeV and still relatively broad energy distributions (10–20%). One way to improve the ion energy is to increase the laser power. Fuchs *et al* [34] have compared published data and derived scaling laws for the proton number as well as the proton energy. They conclude that it should be possible to produce 200 MeV proton beams with lasers available in the near future; nevertheless, up to now it was not possible to examine this regime experimentally.

An alternative route to higher proton energies was investigated more recently [35, 36]. Both groups examine the dependence of the maximum energy of protons on the target thickness. Ceccotti and coworkers compared the spectra obtained with two different laser beams. The first beam is focused to an intensity of 10^{19} W cm⁻² and has a contrast, i.e. the ratio of the intensity during the pulse and in the pedestal before the pulse, of 10^6 . The second beam has only half the intensity but a much higher contrast of 10^{10} . For the low contrast measurements, the proton energy increases as the thickness of the target decreases until it reaches a maximum value of 1.8 MeV at 20 μ m. With target thicknesses below 10 μ m it was not possible to detect any protons at all because the energy in the pedestal of the laser pulse destroys the foil before the pulse arrives. In the high contrast measurements the results look different. Here, the energy rises up to 5 MeV at 0.1 μ m, even for a laser focus with a relatively low intensity. Numerical simulations from Yin *et al* [37] suggest that this enhancement is even stronger for lasers with a higher intensity.

For the new ion-beam therapy systems, intensity-modulated beam application is the standard where the target volume is in more than 10 000 pixels and irradiated sequentially. This technology of beam scanning requires a high ion spill repetition rate in order to complete the treatment within a reasonable time. Although conventional accelerators have repetition rates of some kilohertz, nowadays high-power lasers run with 10 Hz at maximum. If one does not want to drop the concept of scanning, new lasers must have a repetition rate of at least a few hundred hertz. An important research direction will be the development of new laser materials appropriate to high pulse repetition rates. A further challenge is the collimation and stirring of the beam on the short distance between the accelerator and the patient. First attempts of beam focusing have been investigated in two different groups during the last year showing promising results [38, 39]. In addition, new scanning concepts dividing the tumor in columns or sheets rather than in pixels should be explored.

The reported results show that LDIA is a good way to control beam parameters such that it can be used in medical applications. Besides the need of higher ion energies, particularly the control of the energy spectrum and beam direction has to be improved [40]. Even if the control over the ion-beam parameters is not sufficient to place a foil in front of the patient, still clinical therapy could benefit in the near future: in a first step, the laser driven accelerator could be used as an injector for an RF accelerator. This would solve the most frequent problems of particle acceleration, which occur at the low-energy part, but the big advantage of a cheap acceleration and of the replacement of the gantry would be lost as well. As soon as it is possible to produce sufficient energy and intensity for therapy but without the necessary beam quality, energy filters

and beam forming elements could bring the beam to a quality necessary for application to the patient [41]. If these accelerators are less expensive than a conventional accelerator it would be possible to install separate small and cheap accelerators in each treatment room.

5.2. Dielectric wall accelerators

An alternative approach toward a small accelerator was proposed by Caporaso *et al* [42]. In their proposal a linear RF accelerator is used with two main differences: in contrast to existing devices they propose insulators with higher dielectric constants and higher bulk breakdown strength. Consequently, much higher electric fields would be feasible which allow to shrink the whole accelerator to a length of 3–4 m. The higher breakdown voltage in the accelerator cells is achieved by filling the gaps between the electrodes with a dielectric isolator instead of vacuum. Secondly, the accelerating structures would be triggered using for instance SiC (silicon carbide) switches that can be fired optically using sufficient laser power. Pulse lengths of 15 ns have been achieved experimentally.

Until now voltage gradients of up to 100 MV m^{-1} have been demonstrated in acceleration cells of 0.3 cm, i.e. for a total gradient of 300 kV. Caporaso *et al* could combine four cells resulting in a total voltage of 1.2 MV. Nevertheless, no proton acceleration has been reported so far. In addition, it should be noted that this compact setup is not designed for 3D active scanning. Because of the small dimensions, no magnetic lateral deflection is possible in this design and mechanic movements of the patient are proposed. Because of these difficulties distal edge tracking has been proposed as a beam application strategy, a technique where the particle dose is not distributed over the target volume and instead only the distal edges of the treatment volume are irradiated with high doses from many entrance ports. The distal edge tracking exposes large volumes of normal tissue and is supposed to produce dose inhomogeneities essentially larger than the required 3% limit. It is therefore expected that in the upcoming development this will be a point of intense research [43].

6. Summary

Although ion-beam therapy has now been in clinical use for many years and has produced excellent results there is a need for further research in specific areas as shown in the sections above. There are definitely also many smaller improvements that would make ion-beam therapy more reliable and effective: physical research and technical developments should be focused on the improvement of detectors for the control of the beam in front of the patient and inside the human body. At present, the speed of the treatment is limited by the read-out velocity of the position-sensitive monitors in front of the patient. Faster position-sensitive transmission monitors could reduce the treatment time. Online PET allows the measurement of the position of the stopping particles after each treatment fraction. This PET reconstruction of the beam position should be complemented by a direct reconstruction of the dose deposition. In addition, a direct observation of the promptly emitted gamma rays during the treatment by means of position-sensitive photon detectors should control the beam in real time.

There are also many other improvements possible that have not been mentioned in this paper. However, it is very difficult to predict what the next steps are because this is not only a question what is most urgent for the clinical point of view but also from the skills of the people that are available and from some industrial interest. At present there are four companies

offering ion-beam therapy units. The technology of all four providers is well covered by patents and there is also large interest to overcome the patents of the competing companies with new developments. This will also result in pressure for new research for instance for completely new treatment planning systems etc. So it is very challenging to provide a perspective for future research as we have tried to do in this paper.

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