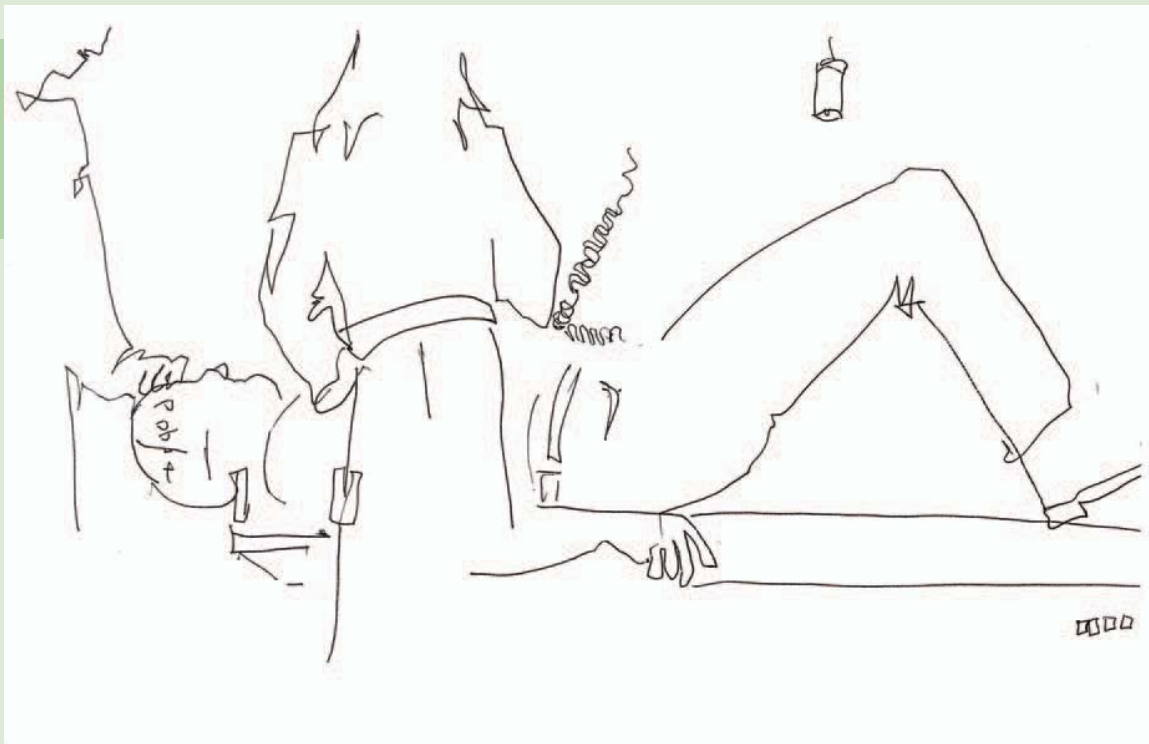


Tumor Therapy with Heavy Ions

Physical and biological basis

Technical realization at GSI

Clinical results



Information for physicians, students, and patients

Association
for the Promotion
of Tumor Therapy
with Heavy Ions

Preface

The field of „heavy ion tumor therapy“ covers a broad scientific and technical spectrum. It is a challenge to write a booklet on this topic for physicians, students, patients as well as other interested scientists.

To help make the content more transparent, we divided it in several chapters and indicated the importance of the text by using different fonts.

The reader should get a first impression by looking at the figures and reading the titles. The main text provides for a more detailed description of the subject matter. Finally, some special topics are explained which are frequently asked after lectures. Without getting involved in heavy ion therapy as such, these sections focus on readers who show a special interest in particle therapy.

This booklet is not a scientific publication. For this reason, it does not include a detailed list of publications. A more complete list of references is provided at the end of the review papers. These reviews are recommended for physicians and students with a greater than normal interest.

Finally the booklet includes photographs of the therapy and the biology labs at GSI to illustrate the text. In

addition, the booklet shows 15 drawings by Sofia Graff. These drawings were made during therapy sessions and vividly display the impressions made during these sessions.

The therapy sections of this booklet describe the principles and technical realization of heavy ion therapy at GSI, the so called "pilot project". It was realized in the years from 1993 – 1997 in collaboration with the FZR-Dresden, the Radiological Clinic and the German cancer research center in Heidelberg.

I would like to thank all the people who were involved in the construction of the project and who are now running the facility. To our great satisfaction the pilot project and its results had a positive effect on the field of external tumor therapy. Meanwhile a Heidelberg Ion Therapy HIT is under construction and a second project was started at the University of Marburg. Other projects in Germany and Europe are coming up as well. HIT will start its' operation at the beginning of 2008. Then the pilot project at GSI will be terminated after 10 years of very successful operation, successful for many patients but also successful in developing and implementing new ideas to the field of ion beam therapy.

Gerhard Kraft
May 2007

Text (Copyright): Gerhard Kraft

Drawings: Sofia Greff

Layout: Sabine Knorr

Photographs: Gabi Otto / A. Zschau

Figures: see references

Publisher: Verein zur Förderung der Tumorthherapie mit schweren Ionen e.V.
Planckstraße1
64291 Darmstadt
Germany
www.gsi.de/informationen/verein-tuthe/

Print: Frotscher Druck GmbH

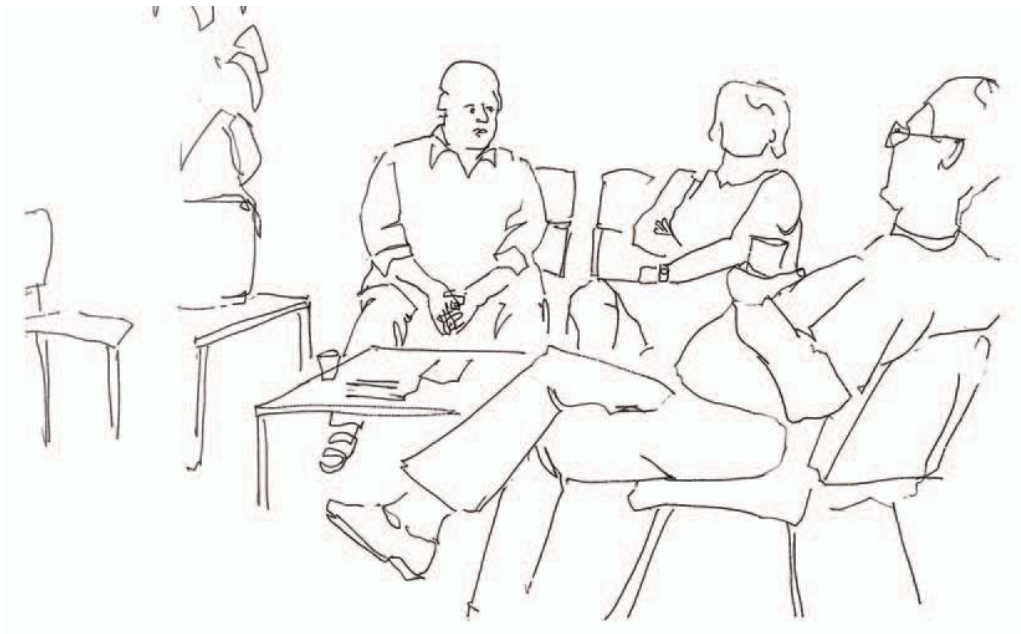
ISBN: 3-9811298-2-2
978-3-9811298-2-3

2007

Heavy ion therapy is a novel technique of high precision external radiotherapy. It yields a better perspective for tumor cure of radio-resistant tumors. Heavy ion therapy is not a general solution for all types of tumors. As compared to conventional radiotherapy, heavy ion radiotherapy has the following advantages:

- Higher tumor dose and improved sparing of normal tissue in the entrance channel
- More precise concentration of the dose in the target volume with steeper gradients to the normal tissue
- Higher radiobiological effectiveness for tumors which are radio-resistant during conventional therapy

These properties make it possible to treat radio-resistant tumors with great success - including those in close vicinity to critical organs.



On December 13, 1997, the first patient was treated with heavy ions at GSI, the German Heavy Ion Research Center. This was the first tumor therapy with carbon ions in Europe and the first Intensity Modulated Particle Ion Therapy IMPT worldwide. The heavy ion irradiation was the result of four years of constructing the therapy unit at GSI and 20 years of research in radiobiology and physics. In addition, a prototype of the intensity modulated beam scanning had been constructed and tested at GSI's heavy ion accelerator SIS from 1988 to 1991.

Radiobiological research showed that carbon ions represent the ideal beam for the treatment of deep-seated and radio-resistant tumors: first, the low dose in the entrance channel causes mostly repairable damage. Second, the high dose at the end of the beam combined with the high radiobiological effectiveness guarantees a very effective inactivation of radio-resistant tumors. Minimal lateral scattering results in millimeter precision at the target. In addition, the use of carbon beams made it possible to localize the beam inside the patient for the first time: carbon beams produce a small amount of instable isotopes during their passage through the tissue of the patient. Some of these isotopes such as ^{10}C and ^{11}C are positron emitters. Using a camera for positron emission tomography PET, the decay of these isotopes can be measured from the outside of the patient. This allows reconstructing their position and hence the monitoring of particle delivery. As a result, the beam in radiotherapy can be controlled for the first time inside the patient during the course



Fig.1: Preparing a patient for heavy ion precision therapy.

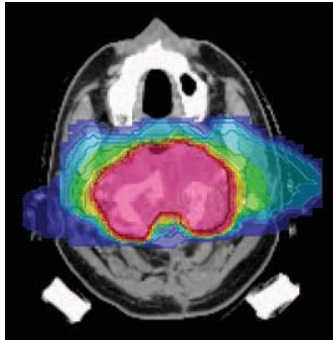


Fig.2: Treatment plan for carbon therapy of a large target volume in the base of the skull. The linear dose-scale ranges from red 100% of the prescribed dose to magenta (10%).

of therapy. From the beginning PET imaging of the beam inside the patient was a very important quality assurance. It allowed applying the novel scanning system to patients after a very short test phase. Up to now more than 340 patients have been irradiated at GSI with great success. First, patients with tumors in the head and neck area were irradiated. Although, the geometry of this target volume is very complex at these sites, masks can be used for precise alignment of the head with respect to the beam to allow precise irradiation of complex target volumes. Later on treatment was extended to tumors along the spinal cord. Patients with prostate tumors are treated since 2006. For spinal cord and prostate irradiations, a body cast is used for patient positioning.

At present, it is not possible to treat tumors with the scanning system in the thorax or abdomen because organs and target volumes move according to the patient's breathing and heart beat. In combination with a scanned beam, movement of the target volume destroys the homogeneity and precision of the irradiation. However, the scanning process is quick enough to follow the breathing motion and hence to compensate for tumor movement. First experiments showed feasibility, but it will take additional time to transfer this technique to clinical routine. At present, irradiation of moving organs is one of the main points of the biomedical research and development in the GSI biophysics department. Another radiobiological research area is the extension of carbon ion therapy to other, more frequent tumors, such as gliomas or lung carcinomas.

In parallel to the research mentioned above and the pilot project in progress, GSI is responsible for the technical construction of a heavy ion therapy unit at Heidelberg HIT. For a similar project in Pavia, Italy GSI has delivered the injector. Recently, GSI has transferred exclusive patent licenses for all therapy know-how to Siemens Medical Solutions. In addition, a contract for the transfer of know-how between these partners has been signed. Based on this transfer of know-how and the longstanding expertise of Siemens, Siemens Medical Solutions is now able to offer the leading heavy ion therapy system all over the world. A first unit will be constructed by Siemens Particle Therapy at Marburg, Germany. Other German universities as well as other European and Asian countries plus the US have shown strong interest in particle therapy. For many projects, the necessary investment of more than 100 Mio € presented a hurdle with respect to timely realization.

In the following pages, the physical and radiobiological basis, the technical realization and possible future developments are described. These pages are considered to be the basic information for physicians, patients, and students. Literature for the specialist is listed at the end of this brochure.



Physical basis of heavy ion therapy

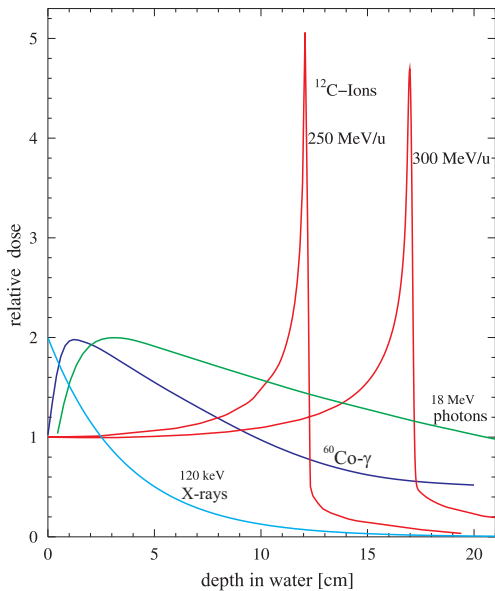


Fig. 3: Depth-dose distribution of photon and particle beams. In the case of photons, the dose decreases exponentially after a maximum in the beginning. In contrast, particle beams have a dose maximum at the end of the range. This maximum can be shifted across the tumor.

The maximum advantage of ion beams compared to conventional photon irradiation (x-rays, gamma rays, high energy photons) is the different depth-dose distribution (Fig. 3). For photons the dose decreases exponentially after an initial maximum located a few centimeters under the skin. In consequence, for irradiations of a deep seated tumor with a single entrance channel, the dose before the tumor is larger than the dose in the target volume. In order to reach a high dose in the tumor with tolerable damage in normal tissue, many entrance channels are used to irradiate the tumor in a "crossfire" technique. Using this technique, the unwanted integral dose is not reduced but rather distributed over a larger volume. In modern Intensity Modulated Radiotherapy IMRT, up to 10 entrance channels are used. Using special multileaf collimators, the intensity and the contours of each channel are modulated in such a way that the target volume is finally exposed conformal with a homogenous dose (Fig. 4).

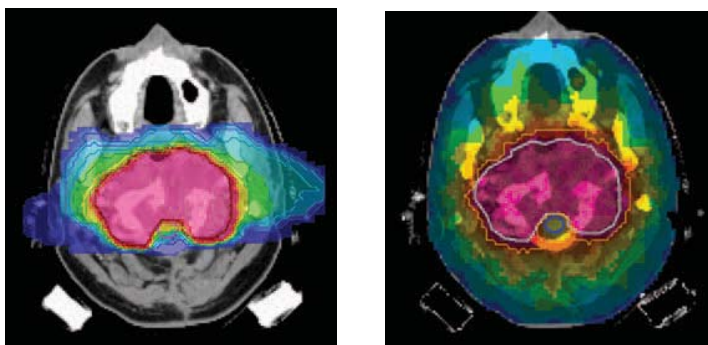


Fig. 4: Comparison of carbon irradiation (left) and photon irradiation (right). For photon IMRT, nine channels are used which distribute the dose to the normal tissue. For carbon therapy with a scanned beam, the dose in the only two entrance channels is much smaller than for IMRT.

In general, IMRT produces excellent dose distribution over the target volume, however, at the cost of a high integral dose in normal tissue.

Ions have different physical interactions than photons and a more favorable depth-dose distribution in the tissue. Only by using heavy ion beams is it possible to dramatically reduce the dose to normal tissue.

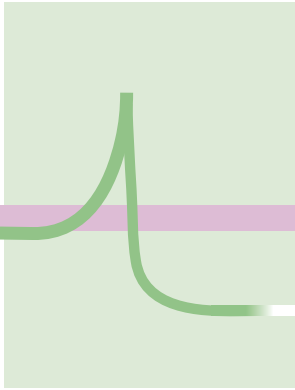
At present, light hydrogen ions (protons) or the heavier carbon ions are used in therapy. They are produced in ion sources and accelerated up to 50% of the speed of light in order to reach the necessary depth in the patient. A typical therapy beam consists of 1 million to 10 million carbon ions per second or 100 times more proton ions.

Ions

Ions are positive charged atoms. These are atoms where one or many negative electrons are removed. In daily life, we find ions, for instance, in neon light tubes. There a few electrons are accelerated by an electrical field. In collisions these few electrons produce other electron-ion pairs. During this process UV radiation is emitted, which produces some visible light during interactions with the phosphorus that has been deposited at the glass tube. For tumor therapy, ions are produced in a similar way in an ion source and injected in the accelerator.

Because of their charge, the ions interact mainly with the electrons of the penetrated tissue. At the high initial speed, this interaction is short and only little energy is transferred to the tissue. With increasing depth, the ions are slowed down and the local interaction becomes longer, transferring a higher dose to the tissue. Therefore, the dose increases at the end of the ion range to very high values, the so called Bragg maximum. After the Bragg peak, the dose decreases to zero when the ions come to rest. All together this yields a depth-dose distribution optimal for therapy: a low dose in the entrance channel in normal tissue and a large dose at the end of penetration in the tumor volume.





In 1946, the great advantages of heavy particle depth-dose distributions compared to conventional irradiation have been recognized by R. Wilson, when he measured the depth-dose profiles of protons and carbon ion beams at the Berkeley cyclotron. But it took almost 10 years from his first publication until particles were applied to the first patient. In these years, LBL Berkeley and in parallel Harvard Cyclotron/MGH at Boston developed a simple, but very efficient procedure for patient treatment that allowed adaptation of the very sharp Bragg maximum to the target volume.

In a first step scattering foils enlarge the beams laterally to the extension of the target. Then variable ridge filters and patient-specific compensators are used to modulate the range of the beam so that Bragg maxima cover the target's extension in depth. With this technique, a higher dose to the target volume could be applied at similar or smaller doses to the normal tissue than in conventional photon therapy. This was a very efficient step for tumor therapy of deep-seated tumors at this time and is still used at most centers today.

Intensity Modulated Particle Therapy using the rasterscan technique

Ions are charged particles and can be deflected with magnetic fields. Therefore, it is possible to replace the initially used passive modulation systems with active systems where the beam is laterally deflected by magnets and modulated in depth by an energy variation in the accelerator. In clinical application, the target volume is dissected into layers of equal ion energy produced by different energies of the heavy ion

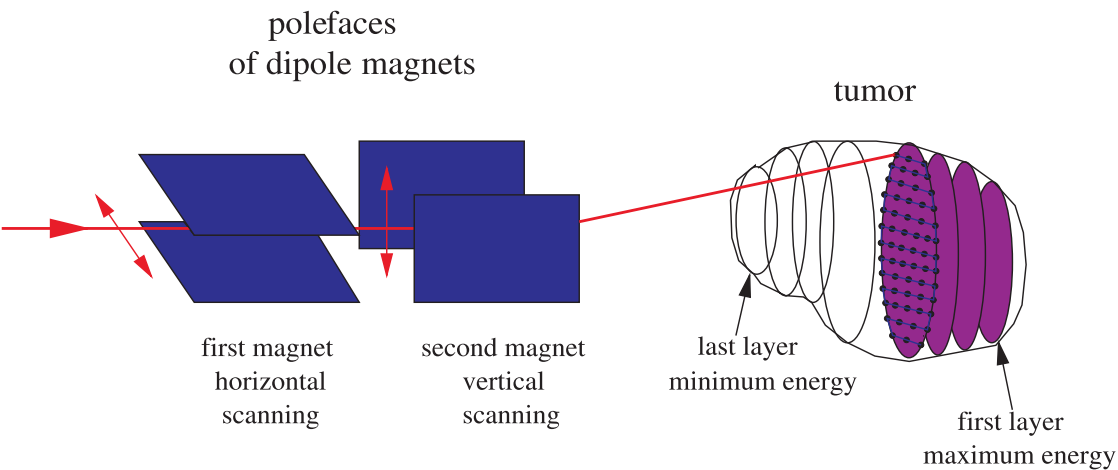


Fig. 5: The tumor is dissected in slices. Each isoenergy slice is covered by a grid of pixels for which the number of particles has been calculated before hand. During irradiation, the beam is guided by the magnetic system in a row-by-row pattern from pixel to pixel (Fig. 7).



Fig. 6: The rasterscan principle is the same technique as used with electrons in TV sets. The figure shows the reproduction of the famous photograph of Albert Einstein using a GSI's rasterscan system as an ion TV. The image of Albert Einstein is produced using a 430 MeV/u carbon beam of 1.7 mm width (FWHM). The picture consists of 105x120 pixel filled by $1.5 \cdot 10^{10}$ particles given in 80 spills (5 sec. each) of the accelerator. Original size of the picture: 15 cm x 18 cm.

synchrotron. For irradiation, each layer is covered by a grid of pixels and the beam is scanned in a row-by-row pattern over these pixels.

During irradiation of the deeper, more distal layers with the Bragg maximum, the proximal layers are partly pre-irradiated. This has to be corrected for and yields in general an inhomogeneous particle distribution for all individual layers.

In addition, the variation of the relative biological effectiveness RBE has to be taken into account in heavy ion treatment planning. This results in an even larger variation of particle coverage in each slice, however, it is necessary for a homogenous distribution of the biological effect over the complete tumor volume.

The novel technique of beam scanning is in principal the same technique as producing a picture using an electron beam in a TV set. The picture is divided into lines and separate picture points (pixels) and the beam is guided intensity modulated from pixel to pixel (Fig. 6).

In addition, the tumor treatment system is able to produce a 3-dimensional "image". Using the beam energy variation, the "pictures" can be stacked in depths. Therefore a 3-dimensional target volume can be exactly painted with the beam. Even critical organs that are enclosed partly or completely by a tumor can be spared by using intensity modulated ion therapy. This is frequently necessary for tumors in the brain stem at the base of the skull. With rasterscanning the dose to this organs at risk can be drastically reduced. Using rasterscanning, the dose to the brain stem can be reduced far below normal tolerance limits for tissue.

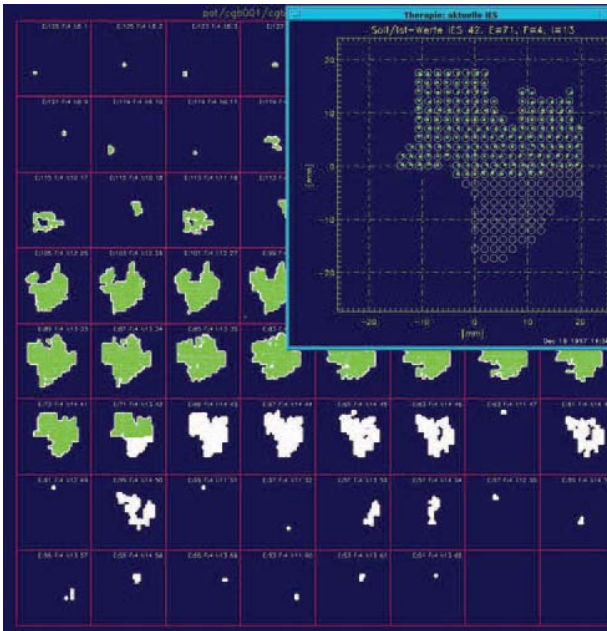
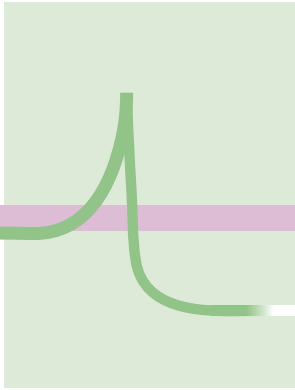


Fig. 7: Isoenergy slices of a tumor. The target volume was dissected into about 60 slices which are covered with a grid of about 10 000 picture points (pixels) in total. At the right corner, one slice is shown enlarged. The circles correspond to the position where the beam should be, the green points are the centers of the measured beams. Since the beam has a diameter of about 6 mm, the beam at one pixel typically covers more than three pixels in each direction.

If a critical organ, such as the brain stem, is completely or partially enclosed by a tumor it is important that the particle tracks are not passing through the critical organ. This is achieved by applying the beam from multiple channels in combination with advanced treatment planning algorithms. In the clinical practice two or three entrance channels are sufficient to reach an optimal sparing effect. However, the dose distributions for the different entrance channels can be extremely inhomogeneous to reach a homogenous biological effect in total.

Using Intensity Modulated Particle Therapy (IMPT), an optimal agreement between irradiated volume and planned target volume can be reached combined with a maximal sparing effect of critical structures, also inside the target volume.

In many cases the dose gradient between target volume and critical organs is an important

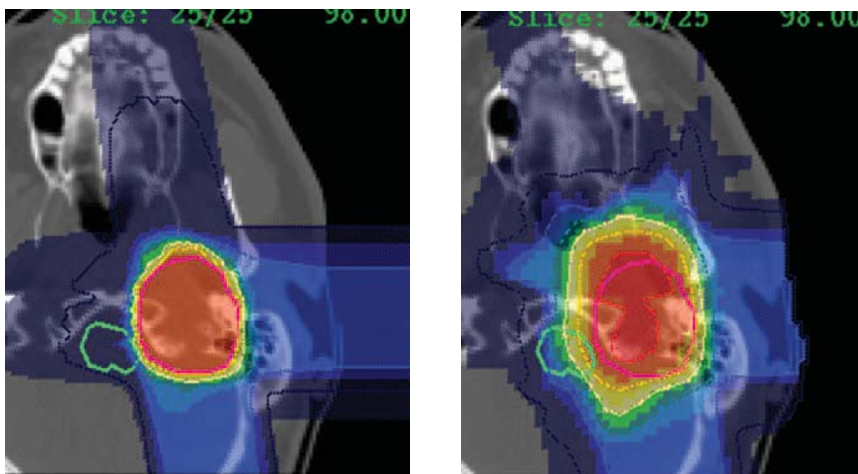


Fig. 8: Comparison of a treatment plan for carbon ions (left) and for protons (right). The carbon plan shows a very steep dose gradient. With such a steep dose gradient, the high dose area can be closer to the brain stem which is a critical organ shown in green at the left side. In addition, the proton plan was performed using a passive beam application system which allows a less satisfactory conformation to the target volume.

parameter for treatment planning. In Fig. 8 the planned dose distribution for carbon therapy (which was executed later on) and for proton treatment is shown. Both dose distributions were planned with the same treatment planning system based on the same patient data. Carbon ions have a three times steeper gradient for approximately all penetration depths. Therefore, tumors close to critical organs can be treated with higher doses with carbon beams yielding a very low tumor recurrence rate.

The high precision of carbon beams and the low dose in the entrance channels allow for dose escalation in the tumor without increasing side effects. Therefore radio resistant tumors can be inactivated and the patient can be cured.

Quality assurance of the beam application

Safe beam application in the patient requires precise knowledge of the irradiation geometry and an accurate positioning of the patient (Fig. 9).

In tumor diagnosis screening procedures are used, such as computer tomography CT or nuclear magnetic resonance (called: magnetic resonance imaging, MRI). In order to define size and position of a tumor, CT imaging is mostly sufficient. However, MRI is more suitable in defining the border of active tumor cells. Therefore MRI is used to produce the target volume for treatment. From CT data (Hounsfield units) without contrast-enhancing drugs, the density of the different tissues can be calculated and used to determine the carbon ion range.

Dose in radiotherapy

The energy which is deposited per kilogram mass in a body is called dose. The dose is given in Gray:

$$1 \text{ Gy} = 1 \text{ Joule / kg}$$

The daily dose in an conventional radiation treatment is approx. 2 Gy, the total dose of a complete therapy between 60-70 Gy. Compared to other energies, these are small amounts of energy. For instance a dose of 2 Gy causes only a very small rise in temperature of a few thousands of a degree. This is far below a daily temperature cycle in our body. The action of ionizing radiation is not correlated with any temperature effect. Ionizing radiation destroys chemical bounds directly and afflicts very heavy damage to the biological system. For instance if the DNA is hit, the complete genetic information is destroyed locally.

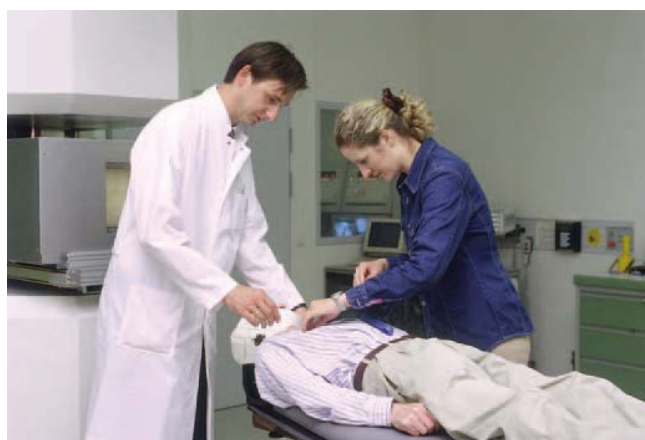


Fig. 9: Preparing a patient.

For the irradiation itself it is important that the beam hits exactly the target volume in the patient.

Incorrect irradiation with a shift of only 1-2 mm would also destroy a part of the normal tissue, but much more important, it leaves part of the tumor cells without any dose. These cells survive and very rapidly cause a recurrent tumor.

In order to guarantee the precision of the irradiation procedure, a thermoplastic mask is manufactured for each patient at the Radiological Clinic Heidelberg (Fig. 10). The patient's mask is permanently attached to the patient couch, the patient is positioned, and the mask is attached, allowing for precise alignment. Under X-ray control, the necessary accuracy of 1 mm for the head and 2-3 mm along the entire spinal cord and in the pelvic region is ensured. The thorax and the abdominal region cannot be sufficiently immobilized through external means because of breathing and heart beat. There the target volume can move even though the body is immobilized from the outside. The possibility for treating moving tumors will be discussed later.

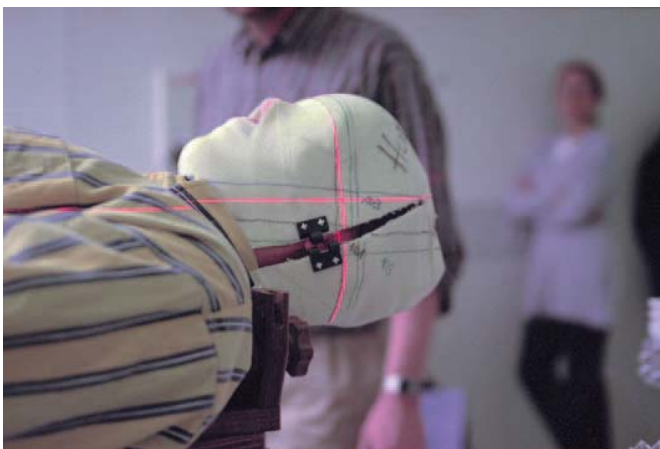


Fig. 10: Immobilizing the head with a thermoplastic mask.

For most patients the immobilization mask is the most stressful part of heavy ion therapy. The mask covers the head very tightly and does not allow any movement. It is the purpose of the mask to ensure exact positioning the target volume. Because the mask fits very tightly and immobilizes the patient, some patients feel helpless, especially during the first irradiation which is often experienced as extreme psychological stress.

After a few irradiations, the patient gets used to the rigid mask. Nevertheless, the immobilization procedure is by far the most unpleasant part of all treatment sessions. The action of the ion beam in the body cannot be felt by the patient. However, a few patients see light flashes when the target volume is close to the optical apparatus. This "phosphen effect" is also known from space research, when cosmic rays impinge on the optical nerves or the retina of an astronaut. The phosphen effect is very weak and seen only in complete darkness.

Also external immobilization should be sufficient. The position of the patient is controlled by at least two X-ray images of the target volume (taken perpendicular to each other). By detecting significant structures, such as bones or other anatomical landmarks, the position of immobilization is controlled. In case of deviations greater than 1 millimeter, the patient will be repositioned and recontrolled.

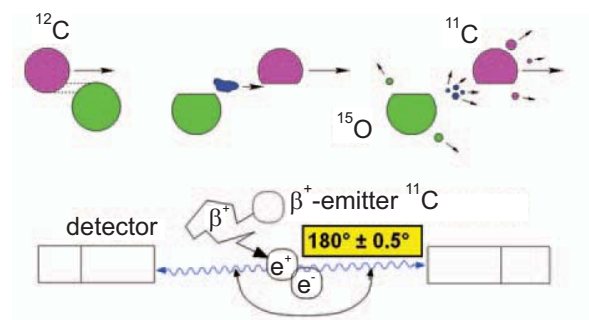


Fig. 11: The collision of a carbon nucleus with an atom of the tissue can lead to an unstable carbon isotope that emits a positron (β^+). The annihilation of these positrons produces two gamma-rays that can be detected from the outside with appropriate detectors. In this way the range of the original carbon beam in the patient can be visualized.

The PET analysis

Besides these indirect methods of quality assurance the irradiation with ion beams offers for the first time the possibility of following and controlling the beam inside the patient.

During the passage of an ion beam through the patient's tissue, a small percentage of the primary beam is transferred to lighter fragments by nuclear reactions (Fig. 11). The fragments with smaller atomic numbers, which are the lighter elements between hydrogen and carbon, have a longer range than the primary carbon beam and cause a long dose tail beyond the target volume (see Fig. 3). However, a few of these nuclear reactions do not change the atomic number, because only one or two neutrons are lost. In this way, carbon isotopes, such as carbon-10 and carbon-11, are produced. These isotopes are not stable and decay with a half-time of 19 seconds and 20 minutes, respectively under the emission of a positron and a neutrino that later leaves the body of the patient. These unstable carbon isotopes ^{10}C and ^{11}C are stopped nearly at the same position in the patient as the primary stable carbon beam and decay. The decay of the positrons can be monitored via the two emitted gamma-quanta from outside the body, using a positron emission tomography PET-camera (Fig. 12). With this method, the range of the primary beam inside the patient can be measured without any additional dose to the patient and presently with an accuracy of 2 millimeters.

The PET range control was developed by the FZ Rossendorf, Dresden and is very important for irradiations where a longer range could hit

critical organs. PET control also helps to detect even small changes inside the irradiated area. Many patients undergo surgery before irradiation. After the operation, swollen parts of the tissue decrease slowly in volume during the course of the radiation treatment. In addition, tissue-vacuoles -occurring after an operation- can be filled with water or mucus. These processes change the geometry of the target volume and reduce the precision of the irradiation. Using the PET analysis, all these changes are measured from day to day. In case of larger deviations, treatment planning has to be repeated based on a new CT.



Fig.12: Patient positioned in front of the exit-window before irradiation. The X-ray equipment is removed and positioned at the ceiling. The two heads of the PET-camera are above and below the patient's head.

At the GSI therapy, a PET analysis is performed regularly for each patient treatment. The PET analysis visualizes the irradiation inside the patient. Based on the measured PET data, the accuracy of irradiation can be improved. In addition, - because of the PET analysis - the question of the fate of the carbon ions in the patient can be answered.

The analysis of the measured PET data showed that the implanted carbon ions combine with oxygen ions, which are present everywhere to form CO_2 . CO_2 is exhaled over the lungs in the usual breathing cycle. The biological half time, i.e. the absorption of C-12 to CO_2 , of the carbon is about 100 sec and much shorter than the physical half time of about 20 min. The decrease to the measured PET signal reflects the biological recycling process of the oxygen.

However, the transport of the CO_2 molecule depends on the blood flow in the tissue. Tissue which has a normal blood flow is free from ^{11}C ions in a very short time. In tissues with reduced blood flow, the implanted ^{11}C ions stay longer. PET can measure this washout process of the carbon and determine the blood flow in the tissue as well as provide information on tissue reaction in response to irradiation. However, at present we have not quantified these data and do not know what information we are able to obtain. Whether we can use these data to optimize the irradiation procedure has to be shown in future research.

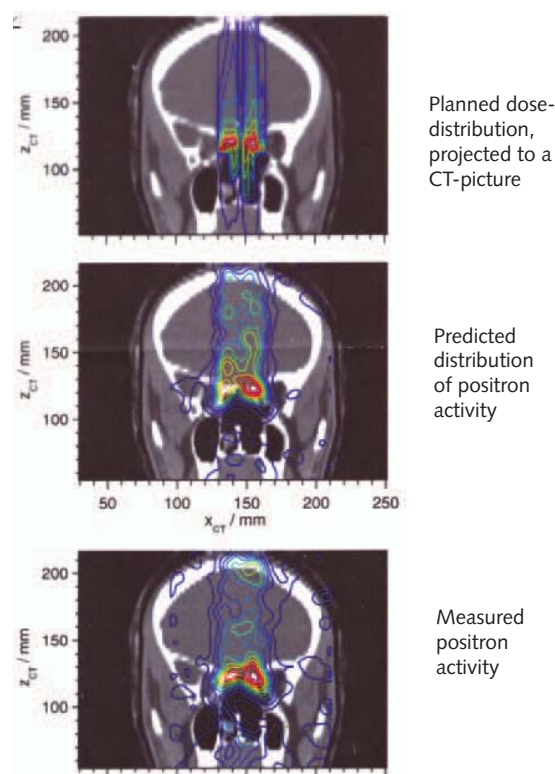


Fig.13: In this comparison, the dose distributions and the expected distribution are compared to measurements. The comparison shows that no critical regions, such as the brain stem, were hit.

Moving tumors: influence of breathing

For high precision irradiation with the rasterscan technique, patients have to be immobilized with millimeter precision in order to irradiate the target volume as planned. Despite external immobilization, tumors in the thorax and pelvic region are moving because of the heart beat and breathing.

For therapy of moving targets in the thorax region, two techniques are frequently proposed: synchronization of irradiation and breathing (gating) and repeated irradiation (multi-painting).

For gating, the breathing cycle is measured and the target is irradiated only when the lungs are empty in the short exhaled phase which is about 15 – 20 percent of the overall cycle. The rest of the time cannot be used for irradiation. This extends the irradiation time and makes the gating procedure less time efficient. The other technique, multi-painting of the same volume increases the homogeneity compared to a single irradiation, however, not to the extent required for a few paintings. The periodicity of scanning,

using a pulsed beam from the synchrotron can interfere with the breathing frequency. Even when irradiation is repeated a few times inhomogeneities of more than 5% are found that cannot be tolerated for therapy. A more frequent repetition increases the treatment time again. In addition, with this technique, the steep gradients at the border of the irradiation volume are lost. Most gradients are then determined by the amplitude and can reach values of a few centimeters. Accordingly, the treatment volume has to be extended into the normal tissue. For example, for 1 cm³ large lung tumor, the treatment volume has to be enlarged to more than 30 cm³ for a peak-to-peak breathing amplitude of approx. 3 cm.

A very efficient possibility to conserve precision and homogeneity for irradiation of moving targets consists of fast motion correction using the rasterscan system itself.

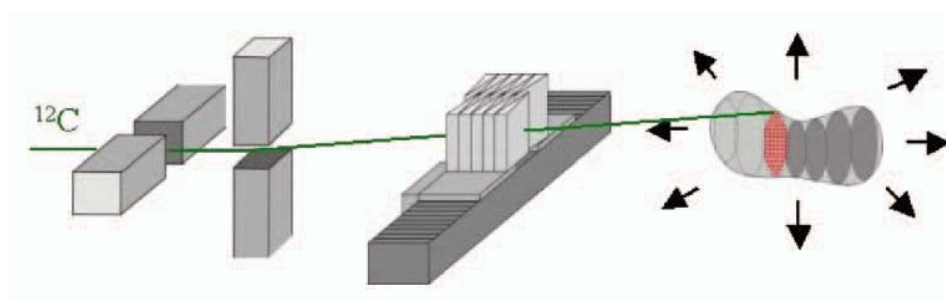


Fig.14: Breathing causes tumor movement. In order to irradiate moving tumors, the beam has to be corrected in the lateral direction and in depth. For lateral correction, the scanner can be used, for correction in depth a double wedge system has been developed, which is connected to a fast linear motor. When the two wedges move towards each other, the absorber gets thicker and the path length gets shorter.

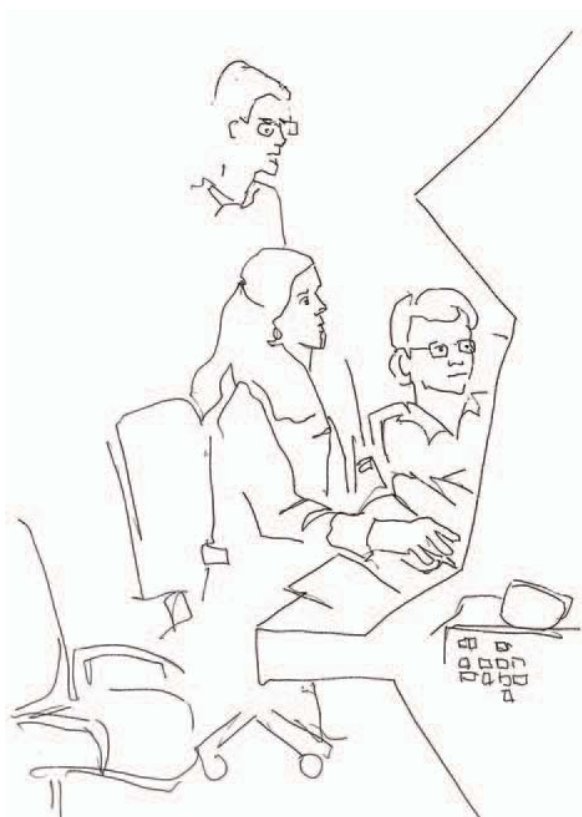


Fig. 15: This figure shows the dose distribution inside a sphere of 5 cm in diameter, which was submerged in water. On the left side the sphere is not moving, in the middle, the sphere is simulating the breathing movement without any correction of the scanning system. At the right side, the online correction as described in the text has been applied and the original precision of the static case can be reproduced.

In the thorax region, organs are moving with a velocity of 3 cm per second and with maximum amplitude of 2–3 cm. In contrast, the magnetic scanning system has a lateral velocity in the patient of about 10 m/sec and is therefore 300 times faster than organ movement. Hence it is possible to correct the beam online in a lateral direction. The movement in depth would correspond to a fast correction in ions energy which is at present not possible from the accelerator. The corresponding energy correction has to be produced in less than one millisecond. Therefore a fast passive system

was designed for energy correction. The energy is corrected by the energy loss in a double wedge system made of Plexiglas. These two wedges are mounted on linear motors and can be moved with high velocity against each other. Then the absorber thickness and, accordingly, the residual range can be varied.

The double wedge system combined with the rasterscan system has shown in test experiments that it is possible to reach a fast online correction for moving targets (Fig. 15). However, to use this system for patient treatment, it has to be integrated into the control system and the data of the actual movement inside the patient have to be transmitted to the control system. In addition, treatment planning has to be extended for the different phases of movement which are then requested by the control system. These completions to our existing therapy are at present a main topic of the technical developments at the GSI. The developments are performed together with the radiology department of the Heidelberg University, the DKFZ, and in collaboration with Siemens Medical Solutions.



Biological basis of heavy ion therapy

Radiation quality and relative biological effectiveness RBE

Radiation of different qualities can produce a different biological effect for the same physical dose. In radiation therapy sparsely ionizing radiation such as electrons, gamma, and X-rays (often called photons) are distinguished from densely ionizing radiation such as neutrons, alpha-particles, and heavy ions. The same dose of sparsely ionizing radiation produces the same biological effect. This is not true for heavy ions: different biological effects can occur for the same dose depending on the energy and atomic number of the ions. Ions produce along their trajectories a track of electrons and ionizations of high local dose up to a few thousand gray. Between these tracks, large areas of the nucleus are not hit by the beam (Fig. 20). The damage inside such a track is frequently not repairable and the biological action does not correlate with the macroscopic dose, because it also depends on the quality of radiation. In order to take care of these differences, the relative biological effectiveness, RBE, was introduced.

The relative biological effectiveness is first an empirical factor and can be calculated from measured data as the ratio between X-ray dose and ion dose which is necessary to produce the same effect. For heavy ion therapy at GSI, a theory of RBE was developed: the so called *local effect model LEM*.

Experiments related to the biological effectiveness

In tumor therapy, heavy ions, such as carbon produce a better depth-dose profile than protons. However, the essential advantage of carbon ions is the higher biological effectiveness at the end of their range in the tumor. In the entrance channel the RBE is only slightly elevated. In combination with the low dose in the entrance channel, less as well as more easily repairable damage is produced in normal tissue. An essential goal of the development of heavy ion therapy at GSI was to maximize the difference in the biological efficiency between entrance channel and tumor area.

The goal of the former heavy ion therapy at Berkeley was to maximize the absolute effects in the tumor area while taking into account greater side effects in normal tissue. Therefore Argon ions were chosen first and followed later on Neon ions. Both ions produce an extremely high tumor control rate but also many late effects in normal tissues.

This clinical response of ion heavy beams can be explained with cell experiments: cells that are irradiated with carbon ions in different depths within a water tank as a tissue equivalent produce a cell survival that differs from the one known from experiments with sparsely ionizing irradiation, such as photons (Fig. 16, mid panel). For carbon ions, the measured cell survival in the entrance channel is close to that of photons. But in the range of the Bragg maximum, carbon survival (red curve)

is much lower. It corresponds to an about 3 times higher dose than absorbed in the Bragg peak. This corresponds to a relative biological effectiveness of 3 (RBE=3) (Fig. 3, low panel).

In Fig. 16 the RBE in the entrance channel is close to 1.5 and reaches at the end, before and in the Bragg maximum values of about 3.5.

Similar behavior of the RBE is found for all ions. But for protons, the range of an elevated RBE is restricted to the last micrometers of the range, i.e. elevated RBE values are only found at the very distal parts of the Bragg maximum. Consequently, in clinical application the slightly elevated RBE values of protons are not important for therapy and are taken into account with a global factor of 10% – 15%, (RBE = 1.10 to 1.15). For very heavy ions -such as Argon- the increase of RBE starts very early in the entrance channel. This leads to the observed but unwanted side effects in normal tissue. For carbon ions, however, the increase of RBE is restricted to the last 2 cm. This last part of the range can ideally be used in clinical application to very effectively destroy tumor cells in the target volume.

The reason for the difference in RBE can be explained by the microscopic structure of particle tracks and their interaction with DNA.

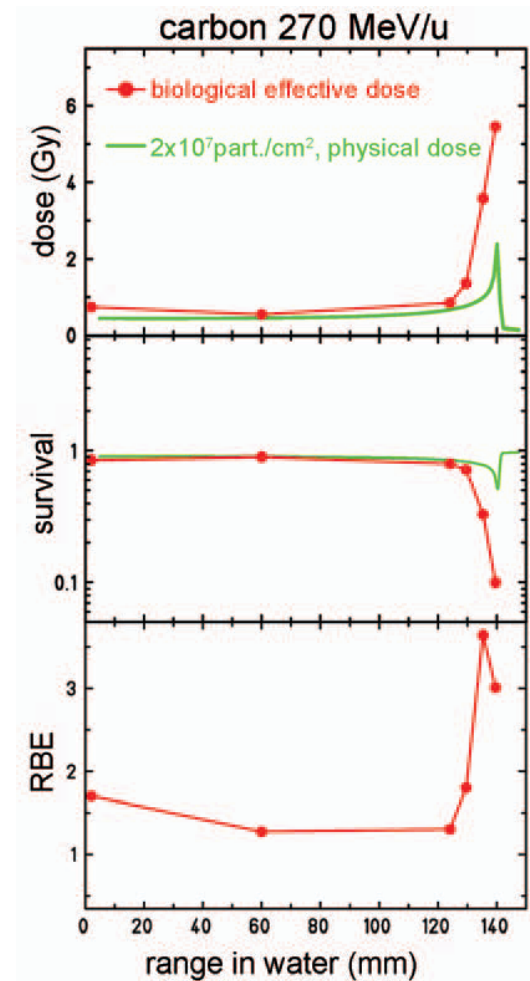


Abb.16: As a function of penetration-depth the dose, the survival, and the relative biological effectiveness RBE are compared for a carbon beam. In the top panel, the absorbed physical dose, i.e. the Bragg curve (in green) is compared with the biological effective dose BED (in red). BED results from the absorbed dose multiplied by the RBE (lower panel). RBE is determined by comparing the expected survival based on photon sensitivity (green, middle panel) with the measured survival (red).

Microscopic understanding of RBE

During the slowing down process of heavy ions, energies between 10 eV and to a few 100 eV are transferred to the electrons of the tissue. These energies are small compared to the total energy of the carbon ion which is in the range of a few million electron volts (MeV). But they are big compared to the binding energy of the electrons of a few electron volts. Therefore, the electrons are liberated and leave the atoms with large kinetic energies. The energy of the liberated electrons is transmitted to secondary ionizations and excitations. The ionizations destroy chemical compounds and, as a result, biologically important molecules. The most important target for the action of ionizing radiation in the cell is the DNA molecule which contains the complete genetic information. Because the integrity of DNA is essential for survival of the cell and the complete organism, a very efficient repair system protects the integrity of the DNA.

In daily life DNA lesions are produced continuously in all tissues. Base-damage, single strand-breaks and most of the double strand-breaks are repaired fast and with high reliability. This is also true for most of the lesions which are produced by ionizing radiation. Only if a high local ionization density produces many DNA-lesions close to each other (clustered lesions), the repair may be frequently unsuccessful and the cell loses its ability to divide (clonogenic death) or the cells are forced to destroy themselves (apoptotic death). For sparsely ionizing radiations, the necessary high ionization density can only be reached with an increase in overall dose.

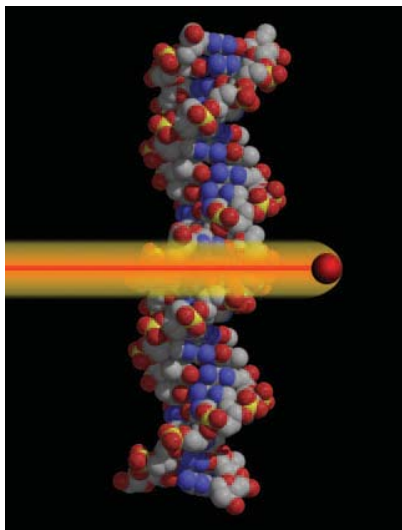


Fig.17: Schematic presentation of a DNA molecule exposed to a particle traversal.



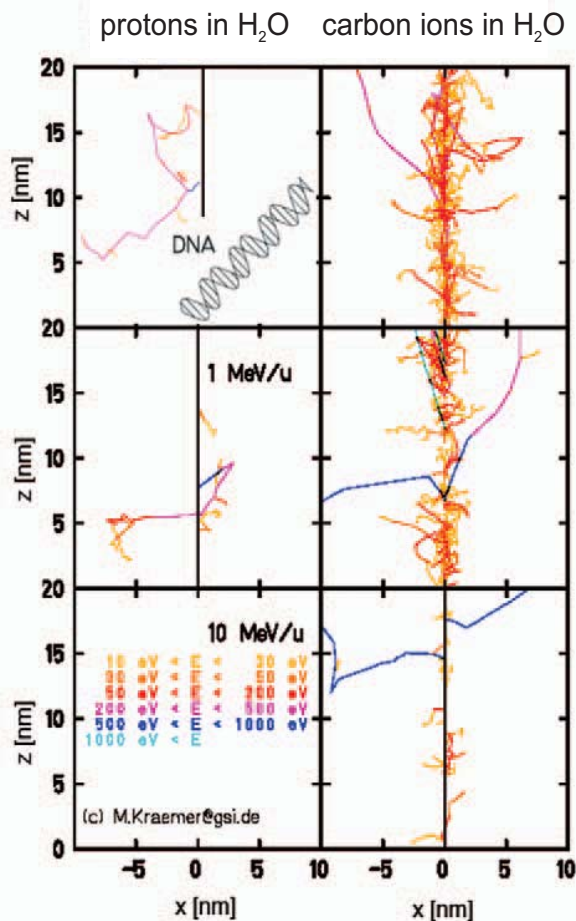


Abb.18: The structures of proton and carbon tracks are compared to a schematically shown DNA molecule. Sections of tracks are given at energies before, at, and behind the Bragg maximum. From the trajectory of the primary ion, the electrons that produce the biological damage are starting. For a carbon ion, a clustered damage can be produced that cannot be repaired by the cell and causes cell death.

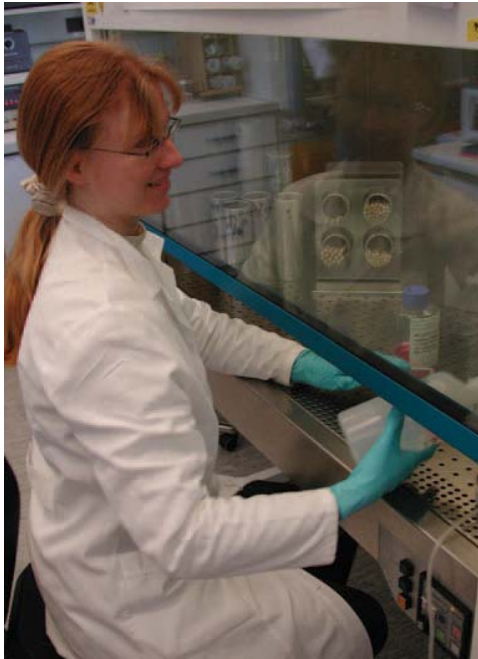
For carbon ions, high local ionization densities are reached in the center of each single track when the particle energy loss reaches values of a few 100 keV per micrometer or more.

In Fig. 18, proton and carbon tracks are compared with a schematic representation of a DNA molecule. For protons, the energy loss is small and the individual ionization events are far from each other. This leads mostly to repairable DNA damage.

For carbon ions, the ionization density at the end of the track at low energies is high and local multiple damage sites of DNA (clustered damage) are very likely.

The induction of these complex DNA damages overrules the repair system and the cells die after many trials to repair. This is also true for cells having an extreme large repair capacity which are otherwise very radio-resistant. However, because of the high local density of damage, even their repair capacity is not sufficient and the survival probability is drastically reduced after irradiation with heavy ions. Therefore cell cultures that are resistant against sparsely ionizing radiation show the largest increase in radio-sensitivity, i.e. the highest RBE values if irradiated with carbon ions. This behavior of cell cultures can be directly transferred to tissue and tumors of a patient.

In the clinical trials at GSI, preferentially slowly growing and therefore extremely radio-resistant tumors were irradiated with carbon ions. They showed the expected fast regression of tumors at low physical doses corresponding to a significantly elevated relative biological effectiveness.



In survival experiments, cell inactivation is measured as a function of the X-ray dose. In these experiments radio-resistant cells show normally shouldered survival curves: at low doses, the radio-sensitivity is small because most of the damage can be repaired. At higher doses, the sensitivity increases and the dose effect curves decrease much more steeply. This non-linear behavior in form of a shoulder of the survival curve is mathematically expressed in a linear-quadratic function where survival is given as:

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

The coefficient α describes the linear fraction which is the slope at very small doses and gives the initially produced irreparable damage. The coefficient β describes the quadratic part, the influence of repair which is important for higher doses. The ratio α/β is therefore a measure for the repair capacity. Cells or tissues of high repair potential exhibit a large shoulder with small α/β ratios between 1 and 3 Gy. Cells with small repair capacity have a large α/β ratio close to 10 Gy.

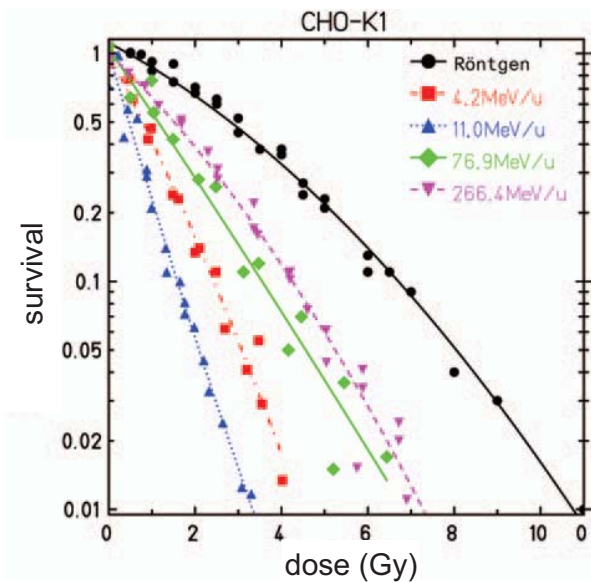


Fig.19 Cell survival is given as a function of the absorbed dose of X-rays or Carbon ions. For small carbon energies corresponding to the end of the range, the survival curves become steeper, indicating a greater effectiveness of the particles.

For clinical application of carbon ions, radio-resistant tumors having small α/β ratios are the best candidates.

These are, for example, chordomas, chondrosarcomas, meningiomas, and of the more frequent tumors, prostate carcinomas, and non-small cell lung carcinomas, for instance.

Calculation of the relative biological effectiveness RBE

RBE is a complex function of many parameters, such as dose, particle energy, and atomic number and, on the biological side, it is a function of repair capacity and size of the cell nucleus of the affected tissue.

For correct treatment planning, these dependencies have to be implemented in the calculation of local RBE values. This is extremely important when the beam is scanned and the composition of the radiation field and therefore the RBE changes from pixel to pixel. At GSI, the local effect model was developed for calculating the correct RBE values in the irradiation field. With this model, the particle action can be calculated on the basis of measured photon data. The reason for the elevated RBE is the different pattern of energy deposition of ions compared to sparsely ionizing radiation. Comparing the dose distribution in small subspaces of the cell nucleus, i.e. in the sub-micrometer region, the dose deposited by photons is more or less homogeneously distributed over the cell nucleus. For ions, the dose is concentrated in the tracks of each particle hit. For low energy ions, a large fraction of the cell nucleus is not covered with dose at all. Also inside the particles' track, the dose is not homogeneously distributed. It decays from very high doses in the center of the track according to a $\frac{1}{r^2}$ law to the border of the track (where r is the distance from the center). This law holds across several orders of magnitude corresponding to a central dose of many kilo-Grays (kGy) up to a fraction of Grays (Gy) at the border of the track. But in the center of the track below a few nanometers the dose radial dose distribution has a flat top.

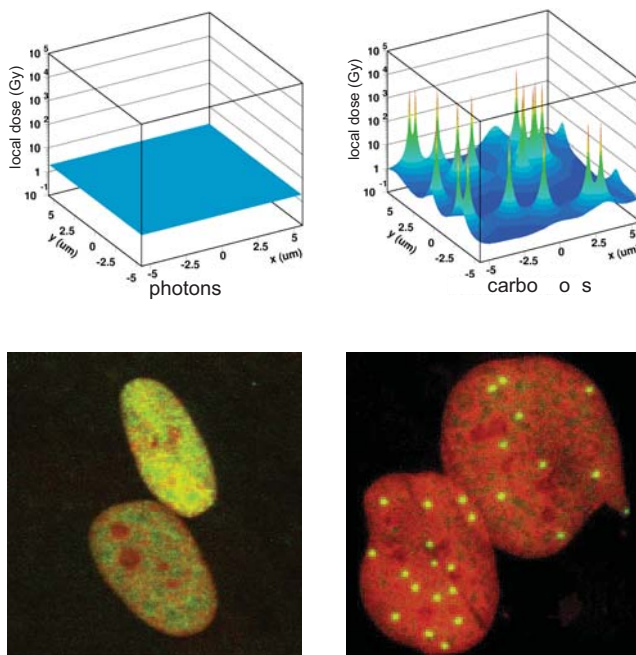


Fig.20: Comparison of energy deposition for particles and X-rays in the frame of micrometers, i.e. in the frame of the cell nucleus: for x-rays, the dose is homogeneously distributed over the cell nucleus. For heavy particles, a large fraction of the cell nucleus is not hit and the dose is concentrated in a few very sharp spikes. This can also be seen in the distribution of the DNA damage (lower row). For X-rays, the damage (yellow) is homogeneously distributed over the cell nucleus. For ions, the damage is concentrated at the location of particle traversals. Areas of such high local dose resist DNA repair.

The local effect model LEM

The basic principle of the local effect model LEM is to convolute the non-homogeneous dose distribution in the particle track with the non-linear photon dose effect curve. With this procedure the effects of the particle can be calculated on the basis of the photon dose effect curve.

In the calculations, the cell nucleus is covered with a particle density corresponding to the macroscopic dose (Fig. 21). The physical parameters, such as particle energy and atomic number, determine the radial dose distribution inside the particle tracks and the absolute dose. According to the radial dose distributions of the tracks, an inhomogeneous dose distribution across the complete cell nucleus is produced. Then the inhomogeneous dose distribution is dissected in submicrometer areas where the dose variation in each area is small compared to the absolute value of the dose. For each of these small areas, the number of lesions is calculated according to the photon dose effect curve and weighted according to the size of the area in relation to the total size of the cell nucleus. The total sum of lesions inside a cell nucleus is called N . Assuming Poisson statistics, the survival S can be calculated as $S = \exp(-N)$. A dose effect curve can be deduced by using many different particle coverings, i.e., different doses. In comparison to the X-ray dose-effect curve, the RBE is calculated. The main biological parameter of this calculation is the shape (the shoulder) of the photon dose effect curve i.e. the α/β ratio. The LEM calculations yield good agreement with experimental data and show that large RBE values are correlated to small α/β values and vice versa.

The fidelity of the LEM model was confirmed in many cell experiments and animal experiments. At the same time, LEM predictions were confirmed in non-biological systems, such as thermo-luminescent detectors (TLDs) and photographic emulsions which have a non-linear dose response curve for sparsely ionizing radiation. In general, LEM has the power to calculate the particle dose effect curves of any system when the photon dose effect curve is known.

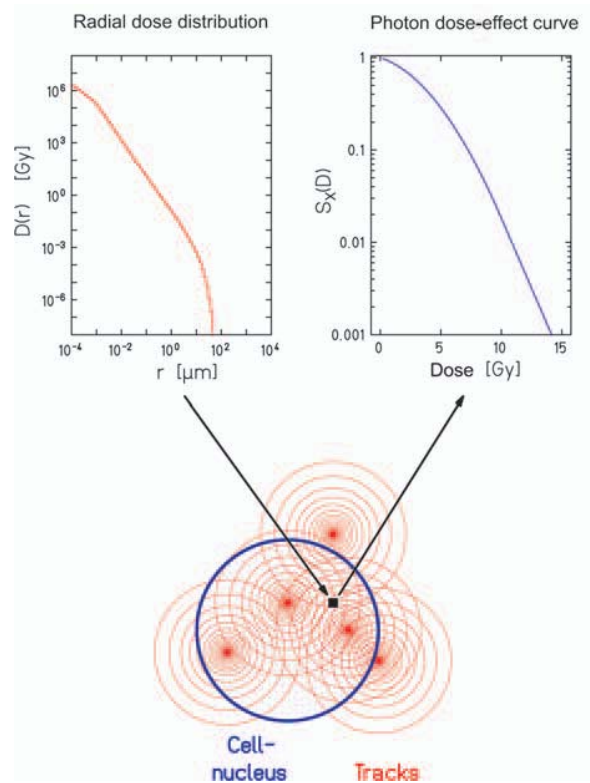
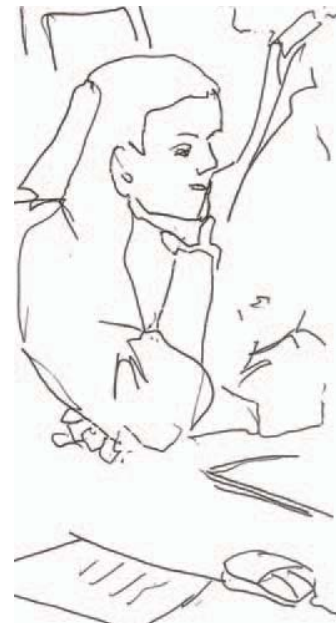



Abb.21: Principles of the *Local Effect Model* LEM (see text).

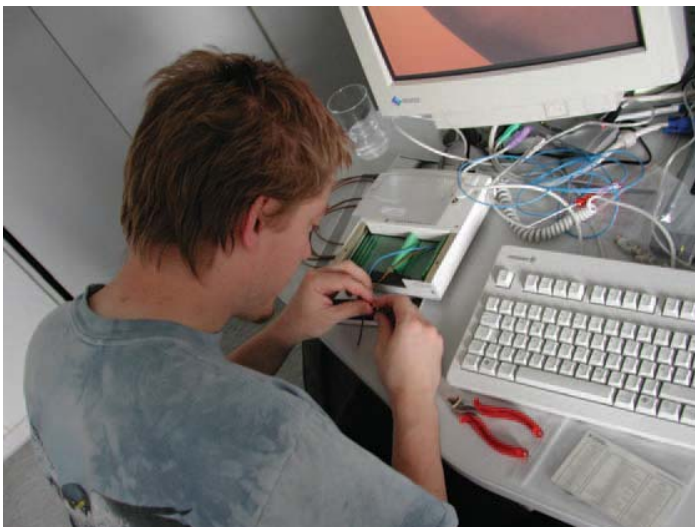




This generality of the LEM can be used for a biologically optimized treatment planning. For each different composition of a radiation field, the RBE can be calculated point by point and used for treatment planning. This calculation yields large variations of RBE over the treatment volume according to the radio-resistance of the tumor or other tissues and the local dose. However, LEM does not contain any time parameters. In a protracted irradiation many lesions are repaired. There LEM overestimates the biological effect in the entrance channel. But this means that the tissue there is in reality less affected by the radiation than predicted in treatment planning.

Comparison to micro-dosimetry:

Radiation oncologists who are used to work with neutrons propose to calculate the RBE for the physical doses using micro dosimetric response functions. This procedure is in principle not impossible but very difficult. First, the response functions are not known, but they could be in principle measured for each tumor. However, this response function depends also on particle energy and atomic number. This means that for complex irradiation fields, not only one but many response functions should be measured. In addition, the response function depends on the dose. This means that the set of response functions has to be enlarged according to the number of possible doses. Without discussing now the possibility to measure all these data, it is evident that the procedure of micro-dosimetry does not reduce the data according to one simple dependence as it is possible in the case of LEM. In contrary, for each point of the target volume, a complete set of micro-dosimetric data is necessary for the different functional dependencies. Therefore the micro-dosimetric RBE distribution for treatment planning and documentation with heavy ion seems not to be practical because it requests an effort much larger than can be done. This is supported by the simple fact that up to now it was not possible to predict a single survival curve of an in vitro experiment according to micro-dosimetric calculations.



Biological optimized treatment planning using RBE values

The elevated relative biological effectiveness RBE is the most important advantage to use heavier ions, such as carbon for therapy. Only with heavier ions, is it possible to overcome the repair capacity of resistant tumor cells. However, RBE values have to be integrated correctly into treatment planning. As shown before, RBE is a complex function of many physical and biological parameters and it cannot be taken into account using one global factor for one tumor type.

According to the increased knowledge of recent years and the possibility to use larger and faster computers, the medical physicists are now able to calculate complex RBE distributions at any point of the irradiation field. This was not possible at the beginning of particle therapy at Berkeley. Therefore approximations had to be used there. With the construction of newer therapies, treatment planning of heavy ion therapy was improved step by step. For proton therapy, this improvement did not take place to this extent.

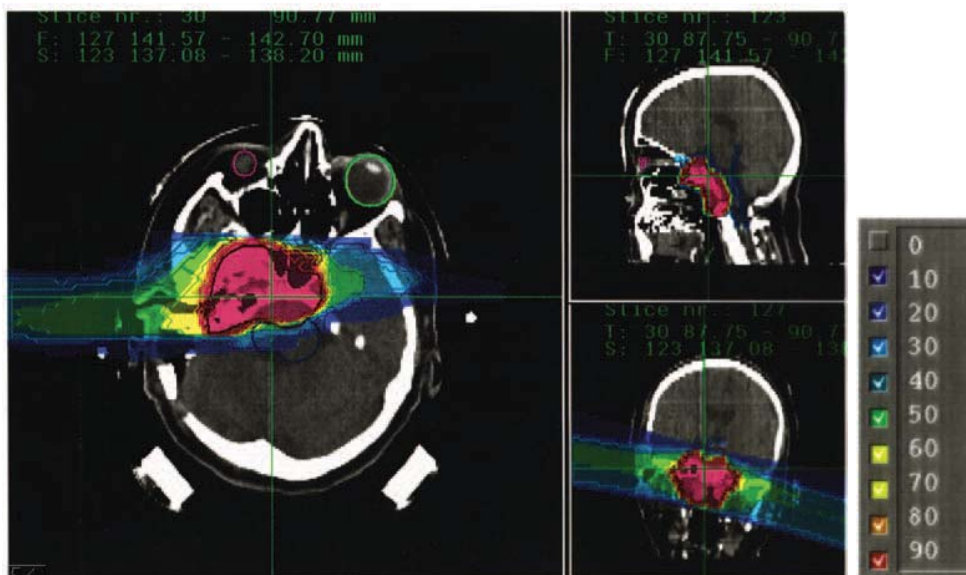


Fig.22: Three-dimensional treatment planning for carbon ions for a patient having a large tumor at the base of the skull. The dose can be focused exactly to the tumor. Normal tissues, such as eye balls, optical nerves, chiasm, and brain stem, are spared to a large extent.

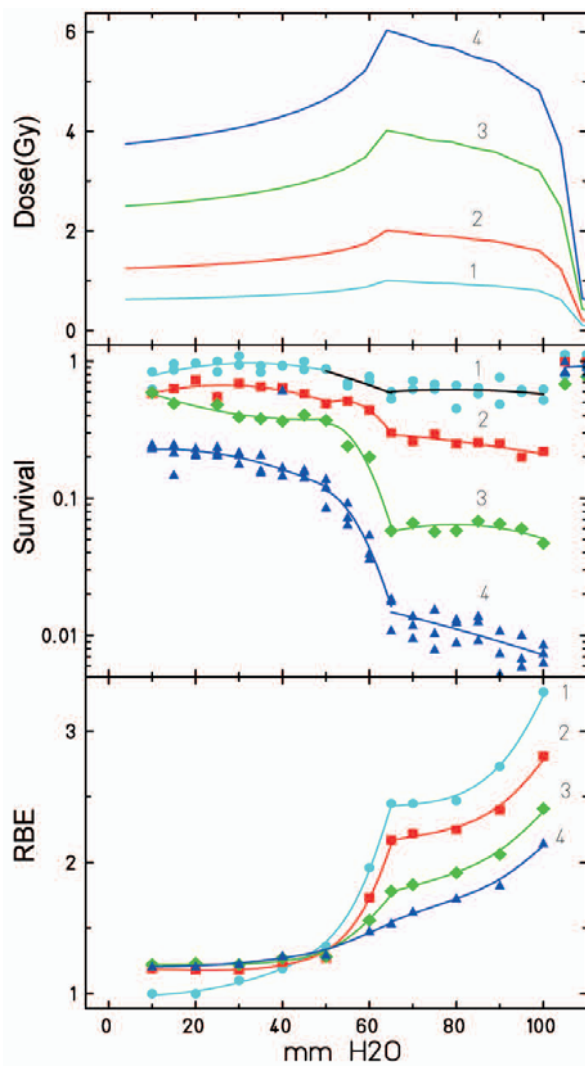


Fig.23: Comparison of measured RBE values in an extended volume as a function of penetration depth. A simulated tumor volume was exposed to different doses as shown in the upper row. The dose is modulated such that a homogenous cell death should be reached across the complete tumor region (middle curve). From the measured cell survival the relative biological effectiveness RBE was determined (lower curve). The results show that the RBE increases with depth and is largest for small carbon doses.

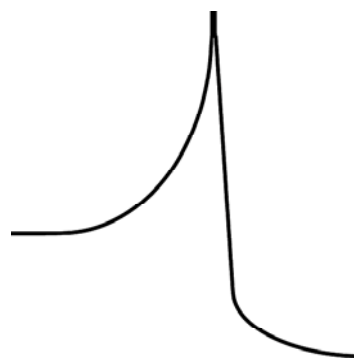
Protons

For protons, the RBE is increased only for the last fraction of a millimeter of the range. This has been shown in cell experiments after clinical trials of protons had been started. For clinical use, RBE has been determined for extended volumes and an increase of 10 – 20 % was found. Therefore, in treatment planning for proton irradiations, the absorbed physical dose is currently multiplied with the global factor RBE = 1.1 to RBE = 1.2. This dose is then called the biological effective dose and is given in GyE (Gray equivalent). For tumor conform irradiations using a raster scan system, this approximation might not be always appropriate. For this technique, RBE variations should be implemented at least at the proximal part of the planning.

Heavy ions

Heavy ions, such as carbon exhibit much larger RBE values and a greater variation over a larger area of the range. This has to be taken into account in the entire planning procedure. The essential dependencies of RBE on physical parameters can be understood from an experiment shown in Fig. 23. For an extended tumor volume the RBE increases to the distal part, i.e., to the maximal range because there Bragg peak ions contribute mostly to the dose. In the region closes to the surface, i.e., the proximal part of the target volume, the fraction of plateau ions is large and consequently the RBE is small. In order to achieve a homogeneous biological effect across the complete tumor, the physical dose has to be decreased to the distal end. This is shown in Fig. 23 for all dose levels. However, by comparing the RBE and the survival curves, it is evident that the RBE depends strongly on the dose: for high doses RBE is small, for a low dose RBE is large.

Association for the Promotion of Tumor Therapy with Heavy Ions



Foundation declaration November 25 1997

Beams of heavy ions deposit a high and biologically very effective dose with great precision in the tumor. They represent the ideal tool for treating inoperable radio-resistant tumors combined with maximum sparing of the surrounding normal tissue.

The objective of the association is to promote and contribute to the activities of the research project: "Heavy Ion Tumor Therapy" at GSI with the final objective to develop and improve the design for an advanced clinical heavy ion therapy unit for the tumor patients. As a result the following topics are supported:

- Physical and biological research as the basis of heavy ion therapy.
- Construction and operation of exposure areas at GSI/SIS.
- Research and development for the beam application system.
- Improvement of the raster-scan system of GSI and its extended application to moving organs.
- Biophysical experiments.
- Design of advanced therapy units including an accelerator for clinical use.
- Scientific conferences, publications, and information distribution to the scientific community and public regarding ion beam therapy and its application.
- Promotion of the education of young scientists.
- Awards young scientists with the Christoph Schmelzer Prize.

All these activities are non-profit activities.

For membership and further information please contact:

**Dr. Helmut Zeitträger, e-mail: H.Zeittraeger@gsi.de
www.gsi.de/informationen/verein-tuthe/**

The Heidelberg Ion Therapy HIT



The gantry room during the assembling of the gantry structures.



View of the accelerating synchrotron. Dipole magnets (in red) at the left and right held the beam on its duty cycle while the quadrupoles (yellow) focus the beam.

Treatment room with the „patient“ robot at the floor and the „imaging robot“ at the ceiling. The patient robot will carry the patient couch and position the patient before the beam exit window. The imaging robot carries a X-ray tube and an image amplifier that are rotated around the patient to verify the position of the patient in relation to the treatment coordinates.



Control panel of the HIT facility.

Pictures courtesy of HIT, Universitätsklinikum Heidelberg

<http://www.klinikum.uni-heidelberg.de/Heidelberger-Ionenstrahlen-Therapie-HIT.1165.0.html>



Christoph Schmelzer Award

1999 - 2006



- 1999 Dr. Caterina Brusasco, Univ Gesamthochschule Kassel
Dr. Kathrin Lauckner, Technical University Dresden
- 2000 Dr. Claudia Fournier, Technical University Darmstadt
Dr. Marco Pullia, Université Claude Bernard, Lyon
- 2001 Dr. Akifumi Fukumura, Tohoku University Chiba, Japan
Dr. Konstanze Gunzert, Technical University Darmstadt
- 2002 Yvonne Borgiel, Technical University Darmstadt

- 2003 Dr. Nina Tilly, Karolinska Institute and
Stockholm University, Schweden
- 2004 Dr. Sven Oliver Grözinger, Technical University Darmstadt
- 2005 Dr. Katia Parodi, FZ Rossendorf/Technical University Dresden
Dr. Sairos Safai, ETH Zürich
- 2006 Carola Gübitz, Technical University Darmstadt
Cläre Hanna Freiin von Neubeck, University Darmstadt

The Christoph Schmelzer Prize is named after the first scientific director of GSI, and given on an annual basis to young scientists for outstanding master's or Ph.D. theses in the field of heavy ion tumor therapy. The pictures show the laureates and the chairmen of the Association for the Promotion of Tumor Therapy with Heavy Ions who handed out the certificates (Dr. Niewodniczanski, 1999, since then Stephan von der Heyde and the vice chairman, Dr. Zeittraeger or Mr. Jaeger, 2004).

From the last chapter it is evident that RBE depends heavily on the repair capacity of the affected tissue cells. In general, radio-resistant cells having a small α/β ratio in the X-ray dose effect curves show extremely high RBE values. In treatment

planning for heavy ions, the dependency on dose, on particle energy, on the particle's atomic number, and on the repair capacity of the cells has to be taken into account very precisely. To do so, the different therapies have used different strategies.

The Berkeley strategy (1975 – 1993)

In the experimental therapy at Berkeley, the ion beam was adjusted to the target volume with passive elements, such as slits, apertures, range modulators, and compensators (Fig. 24). For the range modulators, ridge filters were used which are saw-tooth like absorbers. The absorption in the thicker part of the teeth corresponds to a range in the proximal area and the absorption in the thinner part of the teeth corresponds to a range in the distal part of the target volume. When the ridge filter is moved very fast over the irradiated area, the beam is modulated in depth at each position. The transition from thick to thin areas of the saw tooth determines the frequency with which the different

ranges are realized and consequently the shape of the decrease of the dose to greater depth. For a given shape of the mechanical ridge filter, the RBE weighting in depth is therefore fixed. It can neither be changed for different patients nor for fractionation schedules. For the ridge filters used at Berkeley, RBE depth-dose distributions and absolute values of the RBE have been adjusted to experimental data from in vitro experiments to human T1-cells. This was independent of the tumor to be irradiated and independent of the fractionation scheme. The analysis of clinical data yielded in some cases deviation from the planned values in tumor reaction. In these cases, the absolute RBE values and

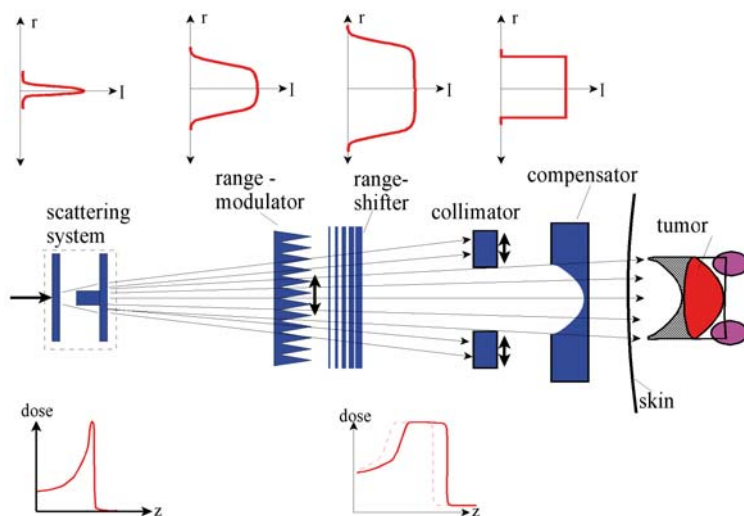


Fig.24: The passive beam shaping systems have two tasks: lateral scattering of the beam across the tumor volume and depth modulation. For lateral scattering, sophisticated sets of combined absorber foils are used to reach a homogeneous dose across the target volume. The outer contours are then defined by apertures. The depth modulation is more difficult, because the depth distribution has to contain also the information of the depth-RBE dependence. Therefore, the shape of the teeth of the ridge filters determines the depth-dose distribution. Finally, compensators in front of the patient can be used to shape the distal fall off.

the physical dose were changed correspondingly, however, the shape of the depth-dose distribution could not be fine-tuned. At the Berkeley therapy, many different sets of ridge filters were used for different tumor extensions and depths and for different RBE dependencies. But a correction of the depth-dose profiles to the radio-resistance of the

tissue could not be achieved at Berkeley with the mechanical filter systems. For this purpose an even a larger number of tumor-specific absorber systems would have been required. In cell experiments, these problems of the biological effective dose have been measured and discussed.

The strategy at Chiba (since 1993)

The heavy ion medical accelerator at Chiba, HIMAC was designed at "the peak" of the Berkeley neon therapy and was conceived as a technology transfer from California to Japan. Therefore, in the beginning the concept and many technical details were identical with the Berkeley unit. For historical reasons, the accelerator at Chiba is a double ring synchrotron where all ions from carbon to argon can be accelerated to a maximum

energy of 800 MeV/u. This choice of particles was determined based on the Berkeley experience. Also for beam application a passive system is used that was changed in time to a semi-active system where the lateral scattering of the beam can be performed by a magnetic wobbler system. Ridge filters are used for depth variation. The variation of RBE is integrated into treatment planning similar to Berkeley.

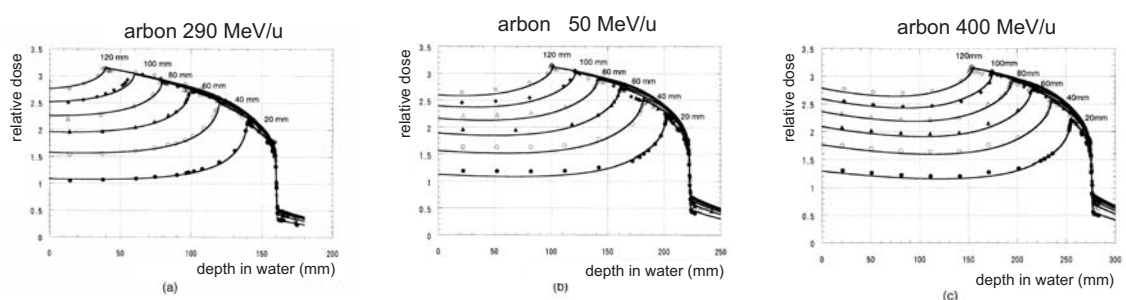


Fig.25: Depth-dose profiles of the physical dose for different primary carbon energies. With human salivary gland cells, the shape of the RBE curve in depth was measured and transferred to an absorber design curve for different energies. For each of these energies a different ridge filter was produced (width of each SOBP indicated in the graph). These filters were used for all irradiations independent of tumor histology and fractionation scheme.

Using Human Salivary Gland cells (HSG cells), RBE values were determined in cell experiments. For a spread out Bragg Peak (SOBP) the dose was corrected accordingly and verified in experiments. However, to transfer the RBE data to actual clinical application, the absolute RBE values of these in-vitro measurements were not used. Instead these data were compared to clinical neutron data.

The cell experiment showed that in the middle of the extended Bragg maximum the RBE values of carbon ions for HSG cells showed the same RBE values as for neutrons. Therefore it was concluded in the same way that the RBE values from clinical experiments with neutrons could be transferred to the carbon therapy.

As shown in Fig. 25, the RBE value for HSG cells was 1.6 in the middle of a 3 cm SOBP of carbon ions. The same value was found for neutrons in a HSG experiment at an LET of 80 keV/um. For clinical application of the carbon beam, the data from neutrons showing RBE values of 3 are also used for the carbon ion in the middle of a 3 cm SOBP.

In a radiation field produced by a passive absorber, the RBE depends only on the depth and there is no lateral RBE variation. Therefore the method used at Chiba is a very practical way for passive systems. The clinical experience shows agreement with treatment planning and very good clinical results could be achieved at Chiba.



The Darmstadt strategy (since 1997)

In contrast to Berkeley and Chiba, a strict tumor-conform irradiation system was developed at GSI that completely avoided passive beam-forming elements. The purpose of the irradiation system is to individually adapt the beam intensity to the patient at each point of the irradiated volume. Using this intensity modulated particle therapy (IMPT), it is possible to adapt the dose distribution to any complex form of the target volume and also individually for any patient plan without producing always new patient-specific hardware, such as apertures and absorbers.

Using the local effect model LEM, the local RBE at each pixel can be calculated for any radiation field. This requires not only knowledge of the local dose for each volume element. Instead it also requires the composition of the radiation field with respect to the physical parameters, i.e., the energy spectrum of the primary carbon ions and their fragments.

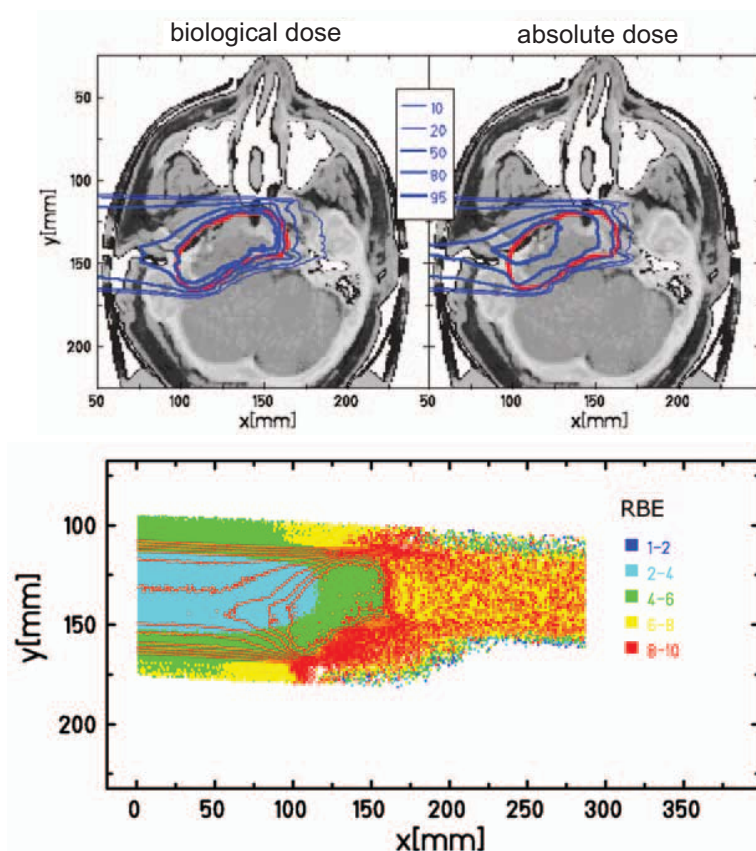


Fig.26: Shows the biological dose, the physical dose, and the RBE distribution of a treatment plan. The biological effective dose (top left) is a function of the physical dose (top right) which has to be multiplied with the relative biological effectiveness RBE (bottom).

Physical optimization of the treatment plan

Treatment planning starts with a pure physical planning procedure just as it does in conventional therapy. The physician defines the outer contour of the target volume and the entrance channels for each CT slice which should not collide with critical structures such as the brain stem. For planning the target volume is transformed into the beam's direction (beam's eye view). In contrast to conventional therapy, planning starts with the optimization of the most distal slice of the target volume.

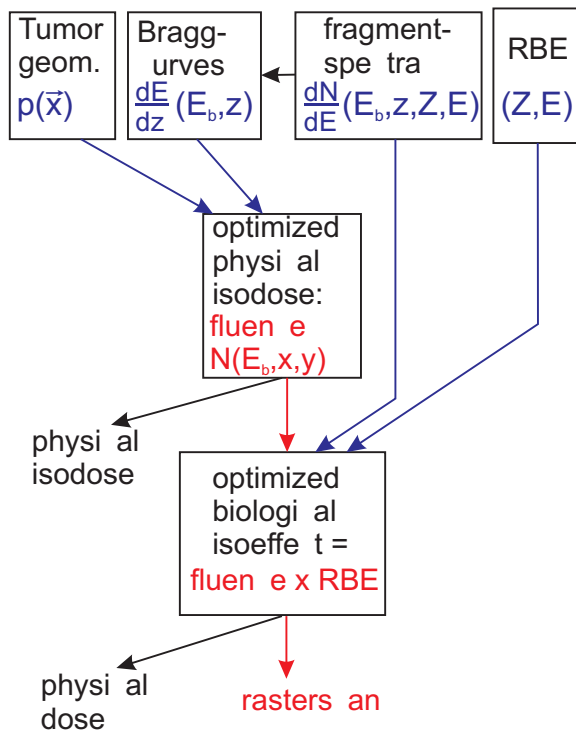


Fig.27: Schematic representation of treatment planning: in the first pure physical procedure the physical dose is optimized. In a second step the relative biological effectiveness RBE for each pixel of the target volume is calculated and the biological effective dose is optimized. Finally, after some iteration, the control files for the scanner system are calculated.

This distal slice is planned for the prescribed dose by ions of an energy which produces a Bragg maximum at that range. The dose contribution of these ions in the more proximal slices is calculated and subtracted from the dose prescribed there. In the next step, the second distal slice is covered again with Bragg maximum ions of the corresponding lower particle range and this dose is subtracted from the proximal slices as well. The same procedure is repeated with the residual target volume until the complete target volume is filled with dose. After this procedure, additional optimization for the total volume has to be performed because nuclear fragmentation causes scattering of a small dose fraction in forward direction and always affects the previous slice (Fig. 27). During this physical optimization procedure, it is important that the information of the particle distribution of the primary ions having different energies and the corresponding fragments is maintained, because RBE depends on these parameter.

Biological optimization

In the second, more time-consuming step, the biological effective dose is optimized: for each small volume element (voxel) the actual RBE is calculated. For this procedure, the RBE values of the carbon ions of the different energies in the irradiation field and their fragments are calculated separately. Therefore, it is important that in the previous step of physical optimization not only the dose fractions are optimized but also the origin of these fractions, i.e., the complete particle field in each voxel is known.

After the local RBE values are calculated, the biological effective dose BED is calculated point by point:

$$\text{BED} = \text{RBE} \cdot \text{Dose}$$

The biological effective dose distribution exceeds the planned physical dose. First it is remarkable that the highest RBE values are beyond the target volume (Fig. 26). There RBE values up to 10 are reached. The reason for these high RBE values is the RBE dependence on dose. RBE increases with decreasing dose and reaches a tissue-specific limit. Beyond the distal part of the target volume, the dose is very small and therefore RBE values are high. However, from the distribution of the biological effective dose (Fig. 26 upper right) it is obvious that multiplication of the low physical dose with these high RBE values still yields small BED values and consequently small inactivation probabilities and steep dose gradients. In addition, two usually opposing fields are used in clinical routine. As a result, the distal dose of one side matches the entrance channel of the other and the high RBE values of one side are partially compensated for the RBE values of the opposite side.

Important for treatment planning is the RBE distribution in the target volume and the resulting distribution of the biological effective dose, BED. After the first computational step, higher BED values are obtained than the prescribed dose. Therefore the particle covering in the target field is gradually reduced along with the point-by-point recalculation of RBE until the new distribution of the biological effective dose corresponds to the nominal dose prescribed by the physician. Fig. 26 shows the distribution of absorbed dose, of RBE value, and of biological effective dose for an optimized single field.

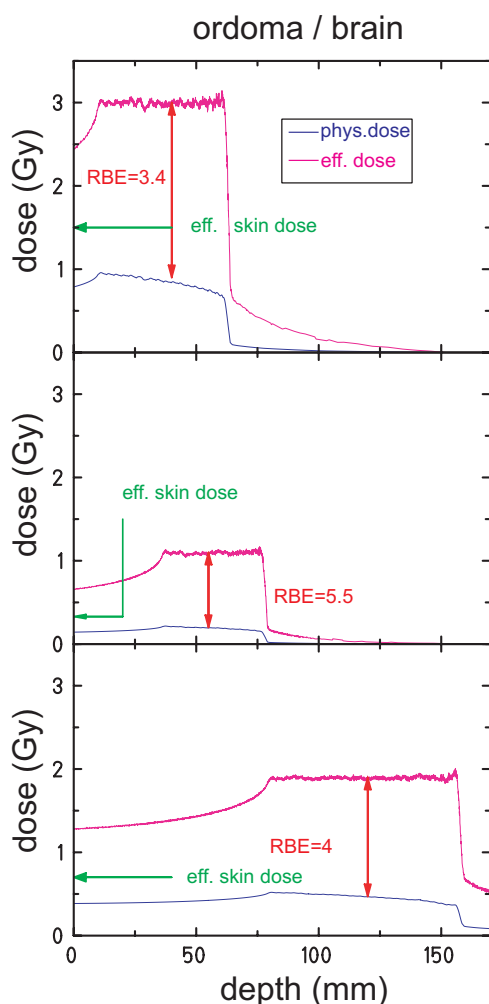


Fig.28: Comparison of treatment plans for three patients with same tumor histology. The tumors were located at different depths and were irradiated with different doses (single field optimization). Shown is the physical dose, the biological effective dose, and the RBE in the middle of the target volume. Depending on depth and dose value, the RBE varies even though it is the same tumor histology. This shows that the RBE is not a fixed parameter, but instead it has to be calculated on an individual basis. A similar effect occurs for the biological effective dose for the skin (arrow). The skin effective dose varies significantly from the tumor effective dose, although the physical dose remains the same.

Fig. 29 compares treatment plans of the same clinical case for different modalities indicating that carbon ions yield the best distribution when given with an active scanning system.

In these optimization procedures the tumor dose is maximized. It is also possible to define tolerance limits for the organs at risk. Then the physical dose deposited in the organs at risk can be weighted with the typically very different RBE for organs at risk to yield a minimal biological effective dose. In general, however, maximization of the effective dose in the target volume is mostly sufficient.

With these procedures an optimal BED distribution across the complete irradiated field can be achieved: maximal dose to the tumor

and minimal dose to the organs at risk which frequently can be spared completely.

All patients at GSI have been treated according to this treatment planning procedure. Very good tumor control with minimal side effects in normal tissue justifies the elaborate procedure.

From the RBE dependence on dose it is evident that it is not efficient to distribute the dose over too many entrance channels. Because RBE increases with decreasing dose the sparing effect is not proportional to the dose reduction. In addition very small particle fluences are difficult to monitor in the ionisation and wire chambers.

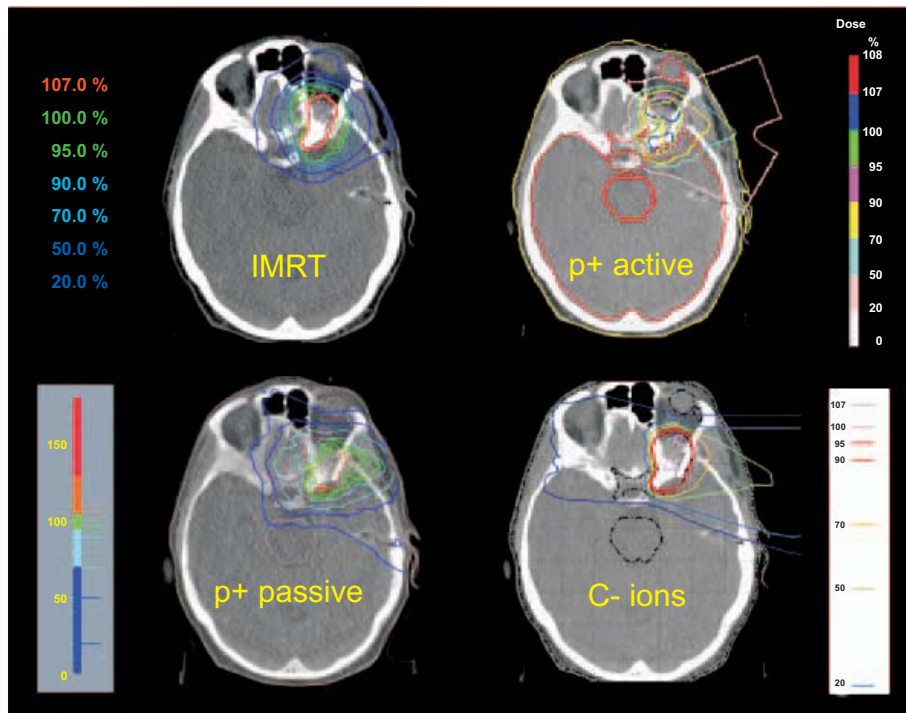


Fig.29: Comparison of the planned dose distributions of a carcinoma in the front part of the head. Upper left: IMRT planning with high energy photons. Lower left: passive proton application. Upper right: active application of protons. Lower right active application of carbon ions which yields the best dose distribution. (These figures are supplied by Dr. M. Kreggli, CNAO, Italy.)

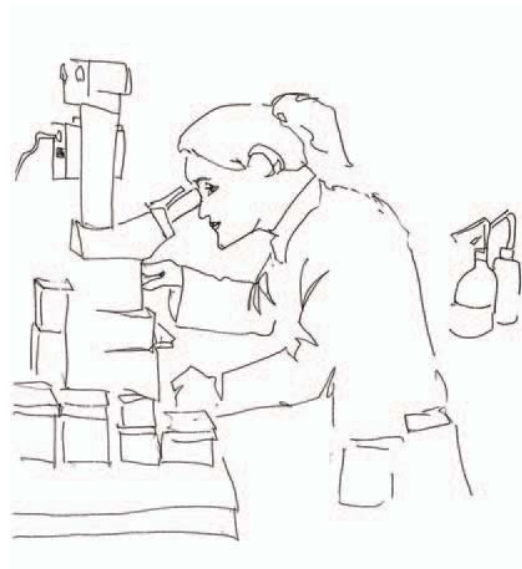
Documentation of the treatment

In heavy ion therapy, the medical prescription of the dose and documentation of the irradiation become difficult because of the inhomogeneous distribution of the physical absorbed dose.

In conventional therapy, the given dose correlates in a unique way with the biological effect. Therefore the prescription of a certain dose and the documentation of the given dose is unique and sufficient. In proton therapy and in the former neutron therapy, the increase of biological effectiveness was a constant factor across the complete irradiated volume. Therefore the absorbed physical dose was multiplied with a fixed RBE value which is approximately 1.15 for protons and approximately 3 for neutrons in order to document the biological effective dose. For heavy particle therapy it is not possible to use this simple approximation: the RBE is not constant across the target volume, because it depends on particle distribution and dose. This means that different RBE values have to be used for the same type of tumor irradiated in different patients when the size and depth of the tumor position are different or when a different fractionation scheme is used.

This is a very important fact: in heavy particle therapy the clinician is not able to justify an absolute value of RBE in a certain patient based on clinical experience. When he treats a new tumor with the same histology in another patient who shows a different tumor size and position, the old RBE values cannot be used. However, the physician can very much determine the re-

sponse of the tumor: it is the radio-resistance in form of α/β ratios from which new RBE values for the next irradiation can be calculated according to the local effect model LEM. For the documentation of the irradiation in daily practice, this means that first the desired value of the biological effective dose, BED has to be documented. In addition, the physical dose distribution and the radio-sensitivity in form of the α/β ratio for the corresponding sparsely ionizing radiation have to be documented. From these data, the treatment planning and the actual treatment can always be reconstructed in a unique way.



Technical construction of the therapy at GSI

In spring 1993 the installation of tumor therapy at GSI was started. First the shielded patient irradiation area (medical treatment room) was constructed and the beam lines including the scanning and monitor system were installed. In parallel the necessary changes of the accelerator and the control system were initiated. In order to guarantee the quality of patient irradiation, a novel quality assurance system had to be developed and tested. In addition, the complete accelerator control system had to be adapted to the new task: in physics experiments the beam is optimized by hand and then the accelerator is running for a long time (days or weeks) without any parameter change. The new therapy demands a completely different strategy: energy changes from second to second and from pulse to pulse with the same beam quality at the target are a must. In addition, it has to be assured that during patient treatment no parameter of the accelerator could be changed by other users or from the outside. In December 1997 the first patient could be irradiated at GSI.

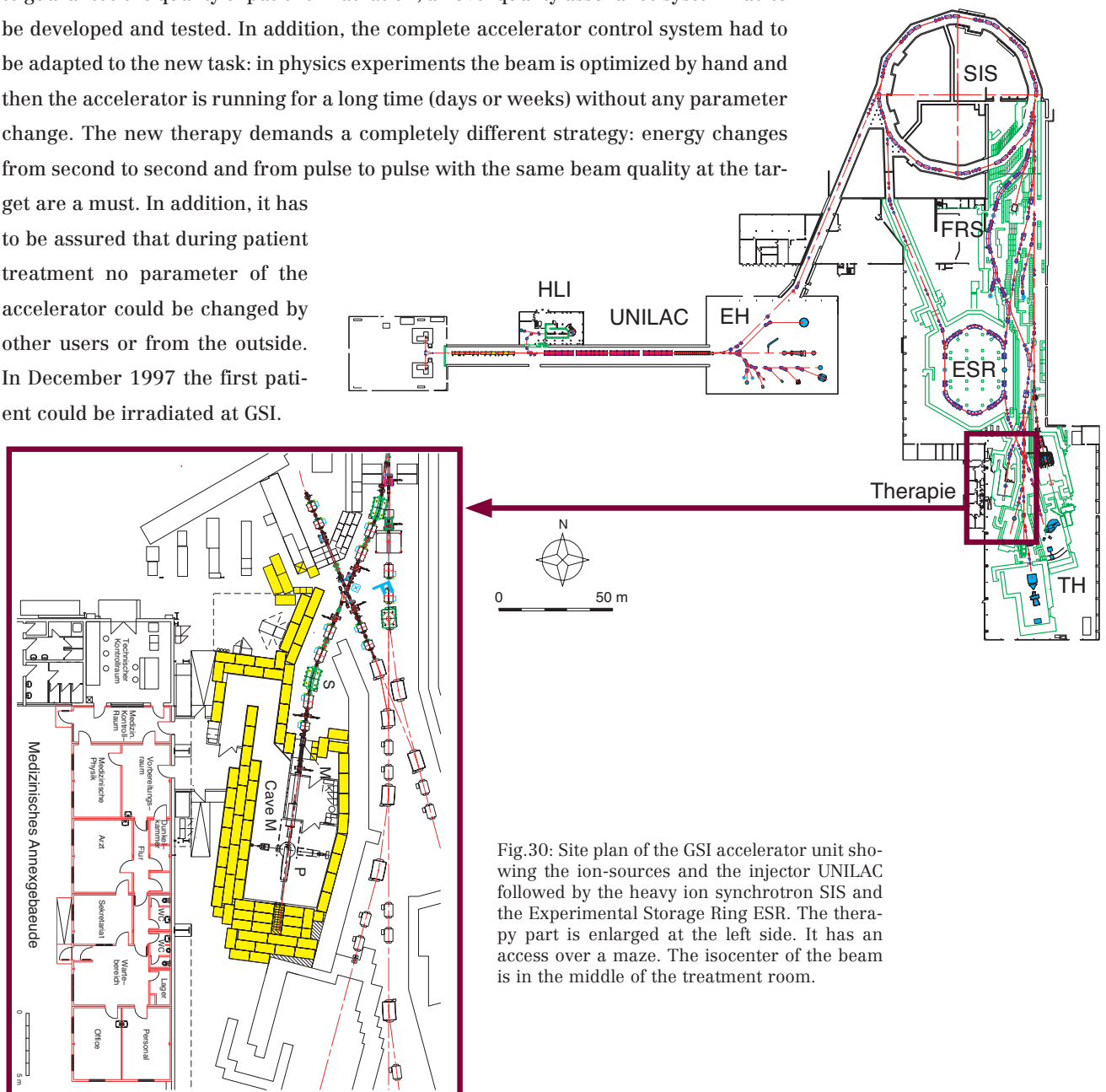


Fig.30: Site plan of the GSI accelerator unit showing the ion-sources and the injector UNILAC followed by the heavy ion synchrotron SIS and the Experimental Storage Ring ESR. The therapy part is enlarged at the left side. It has an access over a maze. The isocenter of the beam is in the middle of the treatment room.

In the new control system, the energy range relevant for therapy (80 MeV/u to 430 MeV/u, which corresponds to a range of 2 – 30 cm in tissue) is divided into 255 energy intervals that can be demanded from the therapy control system in any arbitrary sequence. Also the beam spot size and beam intensity can be changed. For the spot size 7 steps between 2.5 and 10 millimeters are possible. Beam intensity covers a range from $2 \cdot 10^6$ to $2 \cdot 10^8$ particles per pulse (15 steps). Only this type of flexibility was it possible to perform patient treatments in a safe and quick way to ensure that the patient has to stay only a very short time in the patient immobilization system.

In addition, a waiting area for the patients and rooms for the physicians for meetings as well as computer terminals for the PET system and for the treatment delivery control were provided.

The complete control system of the rasterscan and the accelerator merges into the technical control room (TKR, Fig. 31). There the patient data, i.e., the control data of the rasterscan systems are loaded into the computers and the irradiation progress is controlled and monitored. For this purpose the different tumor slices are shown at the Therapy Online Monitor, TOM. A slice which is just under irradiation is shown in greater detail (see Fig. 7).



Fig.31: View of the control desk in the therapy control room TKR with the main control monitor in the center.

With the beam monitors in front of the patient, the beam positions are read out every 100 micro-seconds (i.e. 10 000 times per second) and compared with the planned data. The beam intensity is measured 10 times more frequently in ionization chambers. In case of deviations more than 5% of the dose in one pixel, irradiation is stopped and the error is shown. Also for other possible errors, irradiation can be stopped within half a millisecond at the accelerator and the error is shown at the control monitor. In case of an error that does not influence the quality of the complete irradiation, the dose application is continued at the same pixel where it was stopped.

From the TKR console it is possible to talk to the patient and to see him on the monitor (Fig. 31). He can be informed about the irradiation progress. One irradiation takes a few minutes in total. For the first sessions, the time for set-up is longer. However, it becomes shorter when the patient is more experienced in this procedure.

During irradiations at GSI, the patient is immobilized on the couch with a mask. The immobilization as such is controlled via X-ray images. For this purpose, three X-ray systems are mounted to the ceiling of the irradiation area. They can be lowered down to the patient (Fig. 12). With three X-ray systems and the corresponding image processors, two images of the patient's position are taken

for control. In case of deviations of more than 1 mm, the patient is repositioned. When positioning is correct the patient couch is turned to the planned angle with respect to the beam and the X-ray system is moved to the parking position at the ceiling. Before irradiation starts, the PET camera is moved into position for therapy. The PET camera consists of two heads each containing 32 scintillation detectors. In this camera the decay of the positron emitters, mainly ^{11}C atoms, is measured from which the range of the beam in the patient can be extracted. The PET images are reconstructed after each treatment fraction.

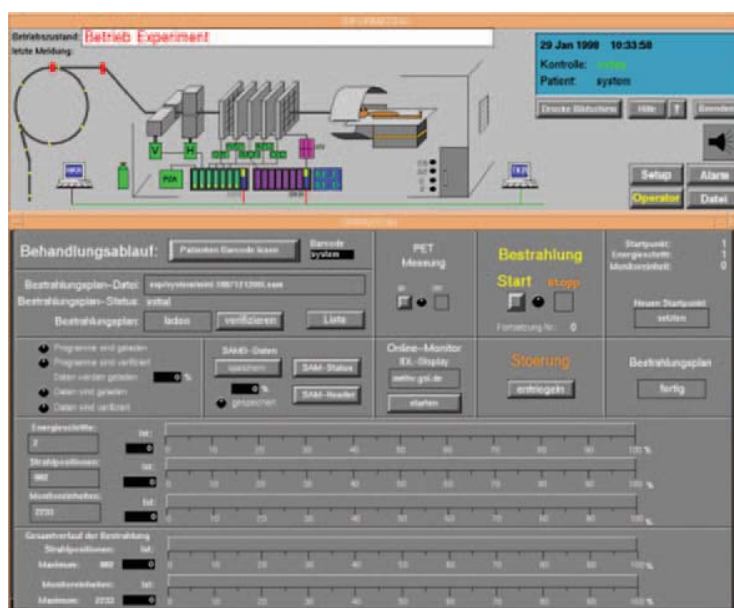
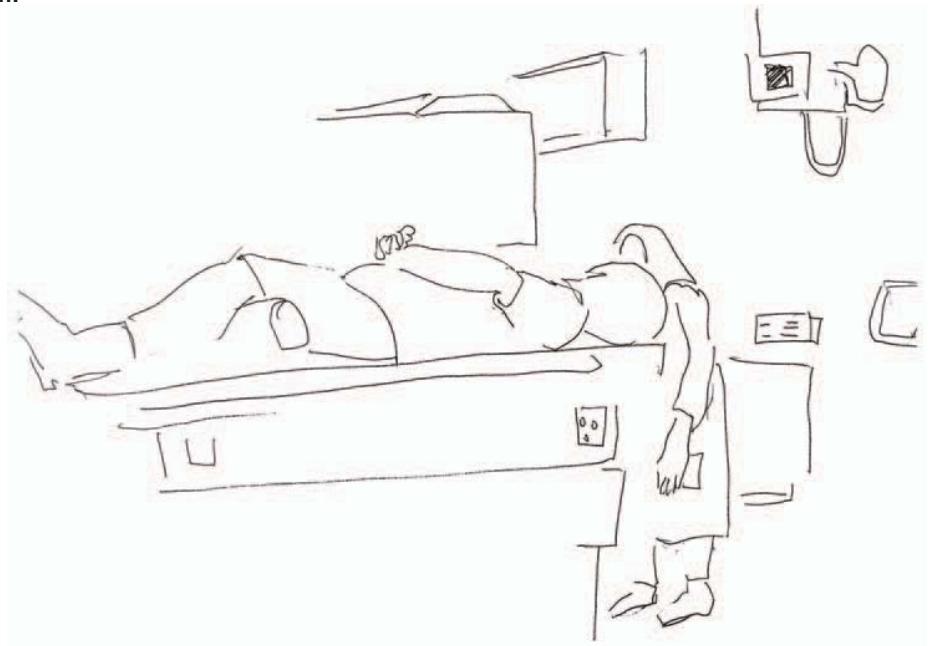


Fig.32: The upper part of the main control monitor shows a schematic representation of beam line (synchrotron, beam line, and raster scan system), monitor system, and patient (resting on the couch and being covered by the PET system). The lower part contains the interface to handle treatment plans and a display that shows the irradiation progress.

For online control of the primary beam position, three ionization chambers and two position-sensitive wire chambers are mounted at the beam exit window in front of the patient. The ionization chambers are read out every 12 microseconds, the wire chamber is read approx. every 100 microseconds. They produce the data for the control system and the therapy online monitor TOM (Fig. 7). Finally in each therapy room several laser systems are installed to position the patient. The online beam control is extremely important for the quality of the irradiation, but it is the speed of these monitors that determine the time of the patient exposure.

During the design of the complete therapy unit, care was taken to ensure a comfortable environment for the patient. The patient cannot see the large technical effort located ahead of the irradiation room.





Workflow of patient irradiation

Diagnosis and planning

The medical responsibility for the therapy pilot project at GSI lies with the Radiological University Clinic in Heidelberg. All patients are examined there and the necessary diagnostic images are generated. These are normally CT and MRI images used to delineate the size and position of the tumor as well as measure functionality.

Prior to radiation therapy, many patients undergo surgery where a large part of the primary tumor is removed. For the residual tumor, the physician delineates the target volume in each CT slice. In addition, the physician defines organs at risk and the entrance channels of the beam.

To calculate particle range, the different densities of the different tissue have to be taken into account in treatment planning. For this purpose, the gray values (Hounsfield numbers) of a calibrated CT image acquired without a contrast medium are used. These densities are transferred to energy loss values of carbon ions and used in the planning. However, for the diagnostic imaging a separate CT image may be made using a contrast agent.

Based on this input data, the medical physicist at the DKFZ, Heidelberg calculates a treatment plan which is first optimized only according to the physical dose without taking into account the different biological effectiveness. The physical dose plan already allows for very good judgement of the treatment geometry and the dose to the organs at risk.

After the physical optimization the plan is transferred to GSI where the RBE values are calculated and the biological effective dose, BED is optimized for each voxel of the target volume.

The optimization procedure is iterated until the desired dose in the target volume is reached. For this optimized particle distribution, the control data for the rasterscan system are calculated.

However, prior to patient treatment, the control data have to be verified. For this procedure the target field is transferred to a water phantom and the critical parts, i.e., the gradients close to the brain stem are measured with thimble ionization chambers. Their positions in the target volume are first transferred from the patient's inhomogeneous density distribution into the density distribution of a water phantom. In this transformed "water equivalent" target, the size of the target volume is changed, however the sharp contours in areas which could be reached in case of overrange of particles are maintained and can be examined. The successful examination of the control data of the raster system is a pre-requisite for using the data for the patient.

While diagnosis and physical planning are made at Heidelberg, biological planning, treatment plan verification, and the treatment itself have to be done at GSI in Darmstadt. However, in the new HIT facility in Heidelberg the workflow will be improved, because all these steps will be performed within one group at Heidelberg.

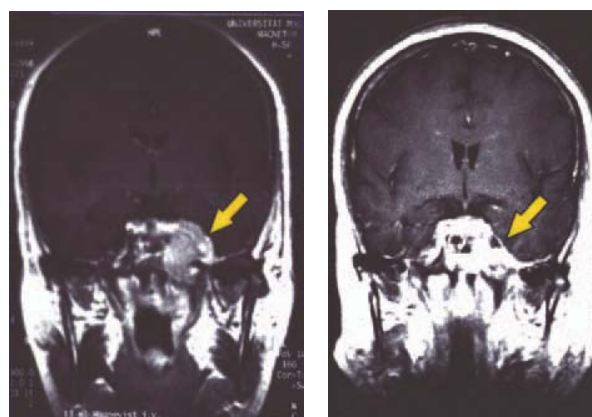


Fig.33: CT-image of a patient before (left) and 6 weeks after (right) carbon therapy. In many cases the tumor disappears within a few weeks and so do the secondary symptoms of the disease (see Fig. 34).



Logistics of the treatment procedure and quality assurance

GSI is mainly an institute for basic research. Only 20% of the total beam time is dedicated to therapy in 3 blocks a year at 4 weeks each. Each block treats 12 to 16 patients. The treatment of one patient is distributed in 20 single fractions over 20 successive days, including weekends.

Each block starts with a preparation phase of 4 to 5 days during which all accelerator settings and the rasterscan system are verified. This very elaborate quality assurance phase is necessary because the accelerators at GSI are used between treatment blocks for very different experiments and the accelerator system at GSI is rapidly developing. For a dedicated therapy accelerator with continuous patient throughput, this quality assurance phase can be reduced.

The essential points of quality assurance are first the accelerator functions. The carbon beam is checked to ensure that it is free of

contaminations from different ions, that energy and intensity steps match the nominal values used for treatment planning, and that the beam spot sizes are independent of all other beam parameters.

For the rasterscan system, the quality assurance affects mostly the position of the beam and the parallax, size, and stability of the beam spots in the target area. Of further interest is the accuracy of intensity and position monitors for a pristine beam as well as the quality of the calibration patterns produced by the scanner system.

These parameters are adjusted at the beginning of each treatment block. Part of this quality assurance is also performed each morning before patients are treated. With respect to the patient, correct patient positioning relative to the isocenter in the room coordinates has to be checked.

For irradiation, the patient is immobilized in his individual mask which is adjusted using the laser system in relation to the coordinates of the treatment room. This adjustment, especially the exact positioning of the patient in the mask, is controlled with two X-ray images taken perpendicular to each other. In case of deviations by more than 1 mm in the head area and 2 mm in the body, the patient is readjusted. This happens very seldom, except at the beginning of a series of irradiations while the patients are not used to the system. After one or two days, the patients experience less stress because the process has become routine and consequently the patients remain relaxed and introduce less misalignments.

After the adjustment, the patient couch is turned into the treatment angle and the PET camera is moved over the patient. Irradiation can now begin. The irradiation of one field, this means the irradiation of the target volume from one side, takes about 3 – 5 minutes. Even this time will be reduced with the optimized system at HIT. After that, the couch is turned to the second treatment angle and patient irradiated again. Only in very rare cases irradiation with 3 fields is necessary.



In the technical control room TKR, the different slices of the treatment volume are shown during irradiation. In addition, the individual pixels of the area which is just under treatment are shown in greater detail (Fig. 7). The course of irradiation is fully automated and proceeds without any manual interruptions or manual control from the control desk. Manual control would not be possible because of the high speed of the scan system of 10 meter per second. The human reaction time is at best in the order of 1 tenth of a second which would correspond to misirradiation of more than 1 meter, a value that lies far outside the tolerance limit.

The monitors of the control system measure the beam position every 100 microsecond, this means 10 000 times per second. It is therefore 1000 times faster than any manual intervention. An irradiation outside the given intensity tolerance limits of maximal 5 % per pixel leads automatically within a few milliseconds to a beam stop in the extraction of the synchrotron. The status of the error is shown at the irradiation desk and the physician and the technical assistant have to decide whether this error in one of the approx. 10 000 pixels justifies an interruption of the entire irradiation or whether irradiation can be continued. This is usually the case and irradiation is continued at the pixel where it was interrupted. Another reason for interrupting irradiation is an incorrectly functioning accelerator. In addition, the beam can always be interrupted manually. In case of any larger problem at the accelerator that requires a longer repair time, patient treatment has to be stopped for hours. However, the majority of patient treatments are not interrupted.

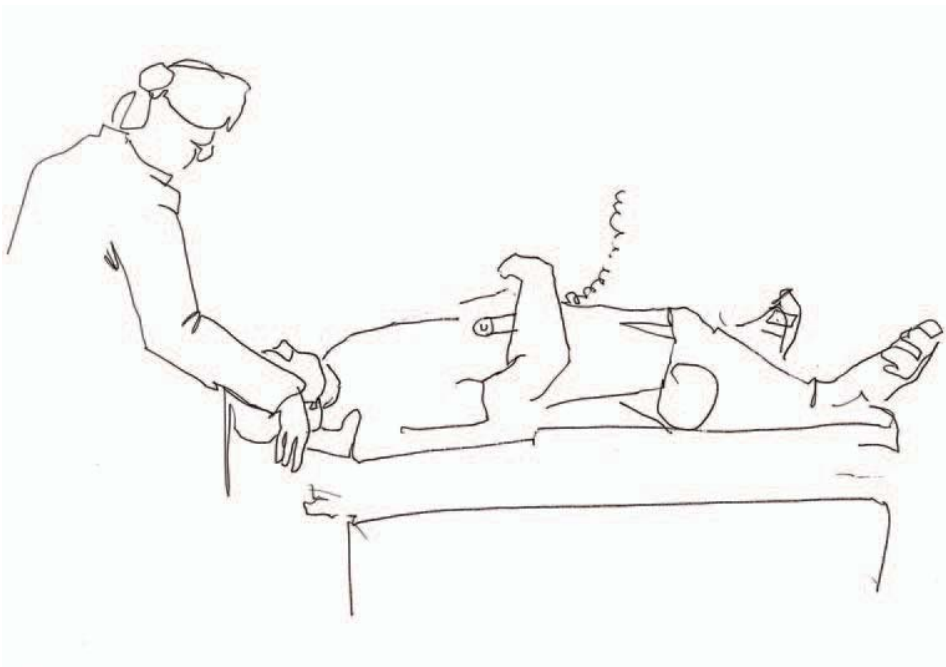
The general experience made with the therapy provided by GSI therapy shows that up to now the heavy ion accelerator provides the same reliability (more than 95%) as clinical electron linacs. Almost all irradiations at GSI were performed without any interruptions. In a clinically-based system which is optimized for particle therapy only and does not have the complexity of the GSI accelerator, the interruption rate should be even lower.



After irradiation, the patients are released from their immobilization and can leave the irradiation area. In one day, a total of up to 15 patients with at least 2 fields can be treated. At GSI a large fraction of the total time, however, is not due the irradiation time itself but rather due to the time required for patient immobilization and positioning.

In a future clinical unit, 3-4 irradiation rooms will be operated in parallel. At least part of the patient immobilization will be performed outside the treatment room. There the accuracy of immobilization can be controlled using X-ray or ultrasound imaging. In total, patient throughput is determined to a greater extent by optimal patient preparation than by irradiation itself. Optimization of patient throughput is not only a question of economy. It is more important that the time spent by the patient in the unpleasant immobilization system is minimized as much as possible.

Using improved methods of patient preparation and having 3 – 4 exposure rooms, a clinical unit will be possible to irradiate 1 500 – 2 000 patients per year with 20 fractions each.



Clinical results

From December 1997 until the end of 2006, more than 340 patients have been treated with carbon ions at GSI. The results of these irradiations can be analyzed in different ways:

The acute effects of irradiation, the tumor control rate, and finally the patient survival rate are the important criteria.

In the following comparison, mostly the first two points are used because the time span for closely evaluating the survival rate of most patients is too short. In addition, the tumor control rate is the most important factor for a comparison of different conforming methods.

Heavy ion therapy is a very localized therapy and the success of this local application can be taken as the main criteria: a therapy which has better local control is superior to a therapy which has less local control. In addition, the occurrence and intensity of side effects play a very

important role, because the dose can only be escalated to a level with tolerable side effects.

The side effects depend very strongly on maximal and integral dose in normal tissue. High local doses inactivate normal tissues and organs in the same way as tumors. Large integral doses which are below inactivation level favor the incidence of secondary tumors. As shown before, the dose and also the biological effective dose is much more precisely distributed in heavy ion therapy as compared to conventional therapy and also IMRT.

Correspondingly less significant are also the observed side effects. It was also speculated that for heavy ion therapy the late effects such as the incidence of secondary tumors would be greater. It is too early to answer this question clinically. However we can make some projections.



Fig.34: This tumor patient shows severe paralysis of the right side of the face caused by a large tumor in the skull. 6 weeks after heavy ion irradiation, these symptoms disappeared.

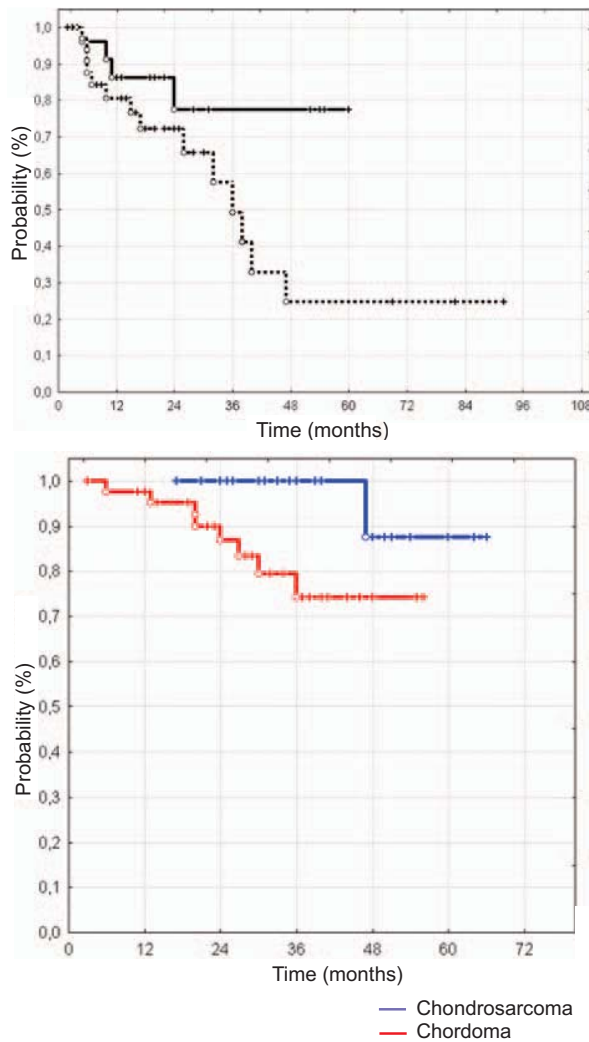


Fig.35: Top – Local tumor control rate of patients suffering from an advanced carcinoma of the salivary gland. 29 patients are treated with a photon IMRT radiation combined with a carbon boost (upper curve). The lower curve shows the result of 35 patients treated with IMRT only. The boost irradiation with carbon ions increases the local control rate after 60 months from about 25 percent to 75 percent. Lower panel – Local tumor control rate for 44 chondroma patients (lower curve) and for 23 chondrosarcoma patients (upper curve).

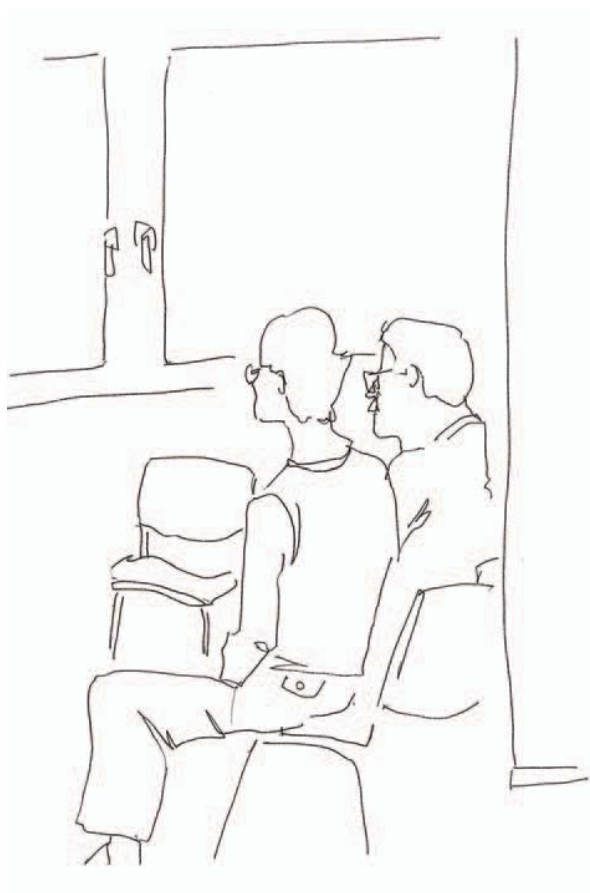
Secondary tumors have a latency period of some years. But radiobiological cell experiments measuring cell transformation, i.e., the induction of cancer cells by carbon beams, are much faster and do not show a largely elevated RBE in the entrance channel. It was also speculated that using carbon ions, more neutrons would be produced, which could also lead to very severe late effects. During carbon therapy, the dose produced by fast neutrons in normal tissue was found to be much lower than 1% of the dose in the target volume. This is comparable to the neutron dose of a proton therapy with beam scanning. But it is much lower than the neutron dose produced in proton therapy with passive scattering methods. The low neutron production is due to the raster scan system where no materials, such as collimators and compensators are in the beam in front of the patient, which would produce large amounts of neutrons in the direction of the patient.

Therefore, for heavy ion therapy less late effects are expected in normal tissue compared to conventional therapy.

The second criterion is the tumor control rate: this is defined as observing no tumor growth up to 5 years after treatment. There are not enough patients treated at GSI to make statistically correct statements on 5 year tumor control rates for all tumor entities treated at GSI. In all cases, however, for the first 152 patients over the first 5 years very positive results were reached (Fig. 35).

In these patients slowly growing and consequently radio-resistant tumors, such as chordoma and chondrosarcoma and malignant tumors of the salivary gland have been irradiated. Because it is possible to immobilize the head in a very simple way using masks, the first tumors treated were in the skull base, even though the geometry in the head is very complex. In the head, very different tissue densities, such as bones, soft tissue, and vacuoles are found very close together. Using the immobilization technique with a mask, sufficient accuracy of 1 mm or better could be reached. For patients treated at GSI, the first study of chordoma tumor patients revealed a tumor control rate of 74% after 5 years, 23 chondrosarcoma patients showed a tumor control rate of 87% (Fig. 35). At NIRS in Japan, more patients have been treated than at GSI. Their results are listed together with the GSI data in the table on page 50.

In general, these data show a better tumor control rate for all patients treated with carbons. For patients treated at GSI, the very precise irradiation technique using the raster-scan system yielded, in addition, a much smaller incidence of side effects as would be possible with conventional therapy.



indication	end point	results, photons	results, ions -NIRS-	results, ions -GSI-
Nasopharynx carcinoma (advanced state)	5y-S	40 - 50 %	63 %	
Chordoma	LCR	30 - 50 %	65 %	70 %
Chondrosarcoma	LCR	33 %	88 %	89 %
Glioblastoma	AST	12 month	16 month	
Choroid melanoma	5y-S	95 %	96 % preservation of eyesight	
Paranasal sinuses tumors	LCR	21 %	63 %	
Pancreatic carcinoma	AST	6.5 month	7.8 month	
Liver tumors	5y-S	23 %	100 %	
Salivary gland tumors	LCR	24 - 28 %	61 %	77.5 %
Soft-tissue carcinoma	5y-S	31 - 75 %	52 - 83 %	


LCR: local control rate
5y-S: 5 year survival

PFSR: survival without tumor growth
AST: average survival time

International situation

Therapy with ion beams started at Berkeley with protons (1954) and with helium ions (1958). Beginning in 1975 heavy ions were also tested at Berkeley: first argon beams were used because radiobiological experiments showed that radio-resistant hypoxic tumors could be eliminated with argon ions. However, due to large side-effects in normal tissue, argon irradiation was stopped after a few patients. Also silicon irradiations were stopped because due to considerable side-effects. Finally, the lighter neon ions did show tolerable side effects and approx. 420 patients have been treated at Berkeley with neon ions. In 1993, the Berkeley accelerator was closed and therapy ended.

In 1994, the National Institute of Radiological Sciences NIRS in Chiba, Japan started with carbon ion therapy. There, approx. 2 500 patients have been treated very successfully. In 1997, carbon therapy started at GSI in collaboration with the University of Heidelberg (Department of Radiation Oncology), the DKFZ, Heidelberg, and the FZR Dresden. The Darmstadt Therapy has the great advantage that an active application system was installed and an extreme target-conform irradiation could be performed.



The highly satisfactory tumor control rates at Chiba and Darmstadt together with the low rate of side effects for conformed application were the reasons to start other carbon therapy projects. In Hyogo, Japan, a unit for carbon ions and protons started in 2002. The construction of a third Japanese unit in Gunma is under-way.

In 1992 an initiative for hadron therapy TERA was founded in Italy which first propagated a center for all hadrons, this means protons, neutrons, pions, and heavy ions. After a short time, this proposal was reduced to proton and carbon therapy only. In 2004, construction of a therapy unit was financed by the Italian government. The Centro Nazionale Adroterapia Oncologica CNAO was founded to build and operate this project. The TERA foundation accompanied this project with research. In Austria, Med-AUSTRON, a project for the construction of a carbon-proton therapy was initiated. In the beginning this project was combined with a Spallation Neutron Source, using the same fast cycling synchrotron. However, after a short time it became evident that different accelerators, one for therapy and another for neutron production would be more efficient and as a consequence Med-AUSTRON was designing its own dedicated therapy system. After the termination of the neutron spallation project, Med-AUSTRON continued separately. The construction of a therapy unit was decided by the government in January 2005. In spring 2007 the State of Lower Austria provided 120 million € for construction.

In 1995 under the umbrella of CERN, the European high energy nuclear research center in Geneva, a collaboration of different European institutes for an accelerator study, was started which was called Proton Ion Medical Machine Study, PIMMS. The goal was a European layout that would produce modules for all national European projects. Parallel to this, the design of the Heidelberg therapy HICAT unit was produced at GSI.

The PIMMS collaboration and the increasing interest of the different projects resulted in a common discussion forum: the European Network for Light Ion Therapy, ENLIGHT – under the umbrella of the European Society for Therapeutic Radiology and Oncology (ESTRO) at the European Union at Brussels.

The workshops on Heavy Charged Particles in Biology and Medicine (HCPBM) started in 1982 were used as a discussion platform for ENLIGHT and for the future development of heavy ion therapy. This workshop is now continued as conference Ion beams in Biology and Medicine, IBIBAM with a meeting at Heidelberg in September 2007.

In 2003, the construction of heavy ion therapy at the Heidelberg clinic was started. In 2005 in Pavia, close to Milano, the foundation stone for the Italian CNAO unit was laid and clinical operation is expected to start 2008. In May 2005 funds were given by the French government for the design of the ETOILE project in Lyon.

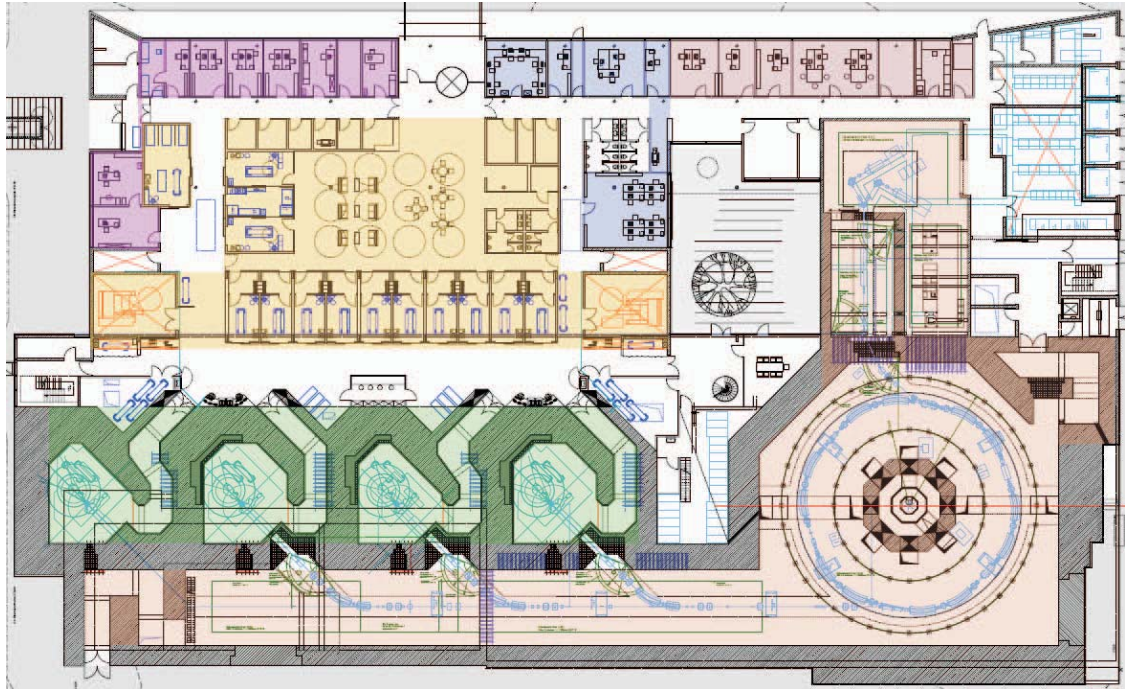
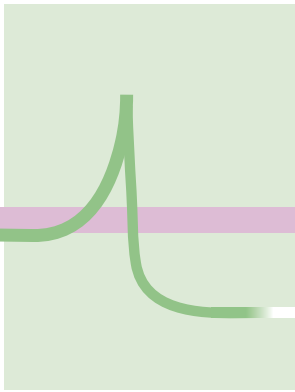


Fig.36: Layout of the Marburg Heavy Ion Therapy of the Rhön Klinikum AG. The ion source and the synchrotron on the right produce the beam for three irradiation areas having a fixed horizontal beam similar to GSI. In the fourth treatment room far left, the beam is injected at 45° degrees which allows for additional entrance channels. These treatment rooms are marked in green. The patient area (marked yellow) contains examination-immobilisation rooms and two CT rooms (left and right). Room for the physicians (magenta) and medical physicists (blue) are in the upper front followed by radiobiological laboratories and rooms for radiobiologists (pink). The Marburg facility will be constructed and operated by Siemens Medical Solutions.

Meanwhile in 2007, a second project at Marburg, Germany was started by a private hospital supplier, the Rhön-Klinikum AG, RKA (Fig. 35). The investment in the Marburg ion beam unit was a part of the developing plan of RKA when buying the University clinics of Giessen/Marburg. In the next years, 5 units will be constructed in Europe the interest outside Europe is large as well. For an estimated need of about 1 unit per 10 million inhabitants these first 5 units are not sufficient. How many heavy ion therapies will be in operation in the end depends essentially on the clinical success also in comparison to pure proton units which are about 30% cheaper in their investment costs.

In the end, as is true for any big medical system, success will determine the number of units. In the European market Siemens Medical Solutions has taken over GSI know-how and GSI patents. The Belgian company Ion Beam Application IBA, as well as the German company ACCEL, are producing and offering heavy ion therapy. In Japan, Mitsubishi is selling heavy ion therapy systems.

The large interest of these companies shows that an important market for heavy ion therapy is expected to benefit many patients and increase their chances for a cure.



Contents

Preface	3
Physical basis of heavy ion therapy	7
Biological basis of heavy ion therapy	19
Physical optimization of the treatment plan	33
Biological optimization	34
Technical construction of the therapy at GSI	37
Clinical results	47
Further reading	53
Source references plus acknowledgements	54
Impressum.....	2

More general references:

Amaldi U., Kraft G.: Recent applications of Synchrotrons in cancer therapy with Carbon Ions.
europhysics news, Vol. 36, No. 4, pp.114-118, 2005

Schulz-Ertner D. et al.: Results of Carbon Ion Radiotherapy in 152 Patients.
Int. J. Radiation Onc. Biol. Phys., Vol. 58, No. 2, pp. 631-640, 2004

Nikoghosyan A., Schulz-Ertner D., et al.: Evaluation of Therapeutic Potential of Heavy Ion Therapy for Patients with locally advanced Prostate Cancer.
Int. J. Radiation Onc. Biol. Phys., Vol. 58, No. 1, pp. 89-97, 2004

Kraft G.: Tumor Therapy with Heavy Charged Particles.
Progress in Part. and Nucl. Phys., 45, pp. S473-S544, 2000

Acknowledgements:

Heavy Ion Tumor Therapy at GSI was a joint venture of many scientists and engineers of GSI in Darmstadt, the Research Center Rossendorf FZR, the German Cancer Research Center DKFZ and the University of Heidelberg, Department of Radiation Oncology. I want to thank all persons involved who worked with great enthusiasm on the completion and operation of the therapy unit. My special gratitude goes to Dr. D. Schulz-Ertner, Radiotherapy Heidelberg and Dr. D. Schardt, Dr. M. Scholz and Dr. H. Zeitträger for their proofreading and many helpful suggestions. Thanks also go to Mrs. S. Knorr for the layout and Angela Phalen-Weiss for editing the manuscript. Gabi Otto and Achim Zschau contributed with photographs and Sofia Greff made the beautiful drawings. I also want to thank the Association for the Promotion of Heavy Ion Tumor Therapy and Siemens Medical Solutions who made the print of this booklet possible.

For the new English edition I would like to thank again Angela Phalen-Weiss and Dipl. Mathe. Svetlana Ktitareva for editing the English version.

Finally I would like to thank the following persons and institutions who contributed with figures:

H.Brand	Fig. 7, 32
J. Debus	Fig. 33, 34
W. Enghardt	Fig. 13
S. Grözinger	Fig. 14, 15
K. Gunzert-Marx	Fig. 11
O. Jäkel	Fig. 2, 4, 8, 22
M. Krämer	Fig. 18, 26, 27
M. Krengli	Fig. 29
D. Schulz-Ertner	Fig. 35
M. Scholz	Fig. 20a, 21
G. Taucher-Scholz	Fig. 20b
U. Weber	Fig. 3, 5, 6, 24
W. K.-Weyrather	Fig. 16, 19, 23, 28
<i>NIRS, Chiba</i>	Fig. 25
<i>Rhön Klinikum AG, Marburg</i>	Fig. 36
<i>Universitätsklinikum Heidelberg</i>	Fig. 37, 38 and HIT pictures

We thank the following sponsors:

**Canberra Eurisys GmbH,
Rüsselsheim**

**Eckelmann AG,
Wiesbaden**

**Jäger Elektrotechnik,
Eppstein**

**Metronom Automation GmbH,
Mainz**

**PINK GmbH
Vakuumtechnik,
Wertheim**

**SIEMENS AG,
Medical Solutions,
Erlangen**

**Thales Suisse SA,
Turgi, Schweiz**

**HSE HEAG
Südhessische Energie AG/
ENTEKA, Darmstadt**



Fig.37: Model of the HIT Facility with the entrance area in front and in the center the gantry housing that determines the height of the building.

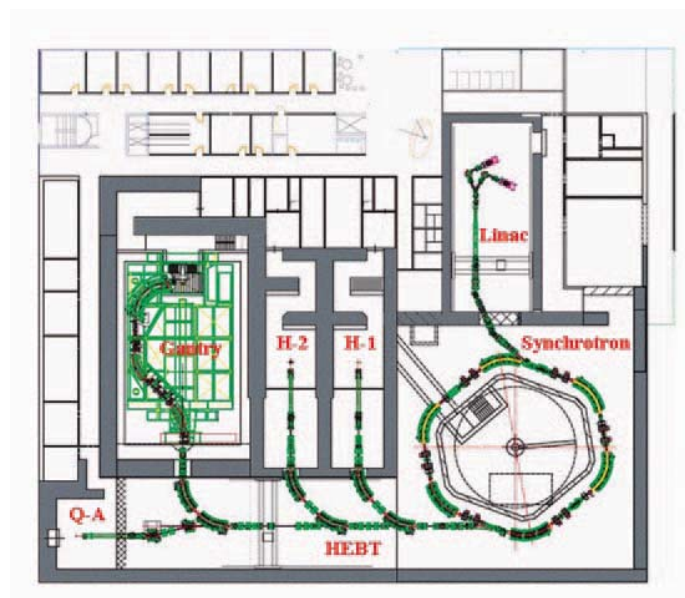


Fig.38: Ground plan of the layout of the HIT facility showing the ion source and the synchrotron from where the beam is guided to the two medical areas with fixed horizontal beam and to the gantry room.

[www.klinikum.uni-heidelberg.de/
Heidelberger-Ionenstrahlen-Therapie-HIT.
1165.0.html](http://www.klinikum.uni-heidelberg.de/Heidelberger-Ionenstrahlen-Therapie-HIT.1165.0.html)



ISBN: 3-9811298-2-2
978-3-9811298-2-3