
Heavy Ion Therapy at GSI¹ M. Durante²

INTRODUCTION

Heavy-ion beams produced in accelerators are essential for space research. There is, however, another important application of accelerator-based heavy-ion beams and that is for the radiation therapy of cancer patients. For therapy the properties which represent the major problem for radiation protection in space are used for a biologically very effective and physically very precise irradiation of deep seated tumors¹ (Amaldi and Kraft, 2005).

The main advantage of heavy ion beams is an inverse depth dose profile, with maximum dose at the end of the range in contrast to photon profiles with maximum dose at or close to the surface. This was recognized in 1946 by R. Wilson² (Wilson, 1946), when measuring depth dose profiles at the Berkeley cyclotron. Patients were treated about 10 years later, first at Berkeley and then at Harvard. The use of heavier ions like He-ions followed at Berkeley. Treatment of patients with very heavy ions followed nearly 20 years later. The world's first carbon and neon patients were treated at the Lawrence Berkeley Laboratory (LBL) in 1977. Radiobiological findings in the laboratory indicated that resistant cells of hypoxic tumors could be very effectively destroyed with even heavier high LET³ beams such as silicon and argon. However, clinical results with a few patients with argon in 1979 and silicon in 1982 demonstrated disadvantageous physical dose distributions and adverse late tissue results, and the use of these beams was discontinued.

Today, carbon ions are used for large numbers of patients with heavy ion beam therapy at three cities in Japan (Chiba, Hyogo, and Gunma) and in Heidelberg, Germany. Modern therapy units having both protons and carbon ions are planned and are under construction at many places in the world³ (Jermann, PTCOG, 2010). At each of the European therapy facilities underway, close to 2,000 patients need to be treated per year to reach a fair price of 20K € per patient.

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³ LET – Linear Energy Transfer

PHYSICAL BASIS OF HEAVY ION THERAPY⁴

Physical basis of heavy ion therapy

The main advantage of ion beams compared to conventional photon irradiation (x-rays, gamma rays, high energy photons) is the different depth dose distribution, illustrated in Figure 1⁴.

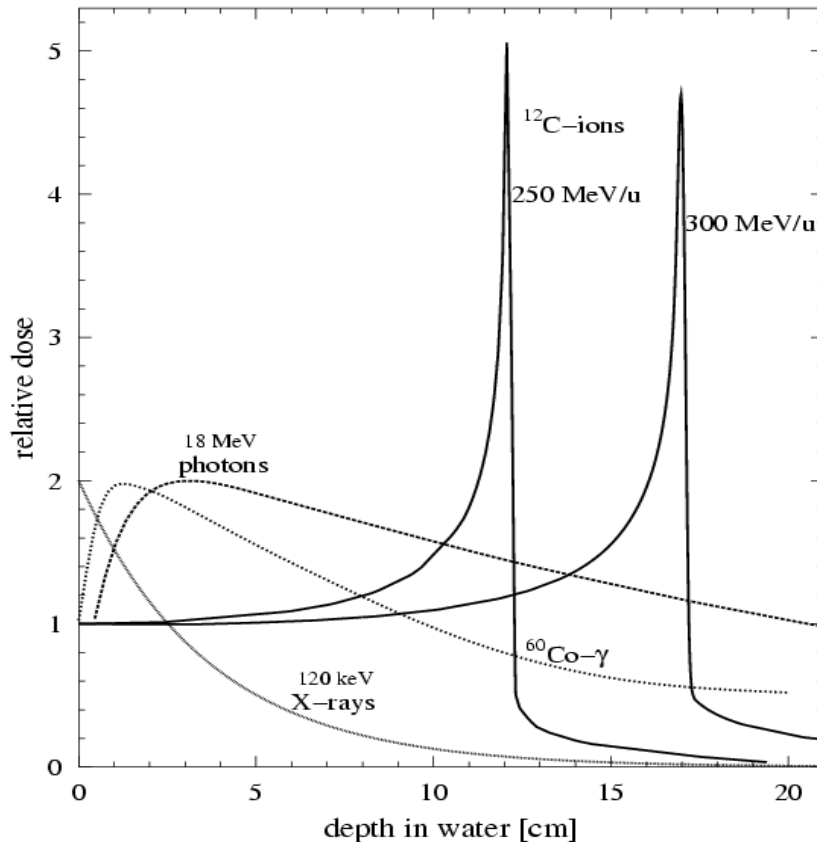


Figure 1. Depth-dose distribution of photons and particle beams. In the case of photons the dose decreases exponentially after a maximum in the beginning. In contrast, particle beams have a dose maximum at the end of the range. This maximum can be guided over the tumor. (Krämer and Durante, 2010.)

For photons, the dose decreases exponentially after an initial maximum increase in dose located a few centimeters below the skin. Hence, for a single field irradiation tumor, the dose to tissues in front of the tumor would be larger than the dose in the target volume. In order to reach a high dose in the tumor without too much damage in the normal tissue, many entrance channels are used to irradiate the tumor in a “crossfire” technique. Using this technique, the undesired integral dose is not reduced, but is distributed over a larger volume of normal tissue. With Intensity Modulated Radiotherapy (IMRT) beam delivery methods that can be used with conventional photons, protons, or carbon ions, 6 to 10

⁴ Protons, neutrons, and heavy ions respond to nuclear force fields (“strong interactions”) that are not dependent on electric charge. The common character of these particles is often indicated by reference to them as hadrons.

entrance channels are used. The intensity and the contours of each channel can be modulated using special multileaf collimators, in such a way that the target volume is finally exposed to a homogeneous dose⁵ (Kraft, 2000). However, the doses to normal tissue can be very different depending on which of these radiation types is used in this comparison.

In general, IMRT produces excellent dose distribution over the target volume but at the cost of a high integral dose in the normal tissue. By using heavy ion beams, the dose to the normal tissue can be decreased dramatically. Ion beams have different physical interactions than photons and a more favorable depth dose distribution in the tissue in Figure 2.

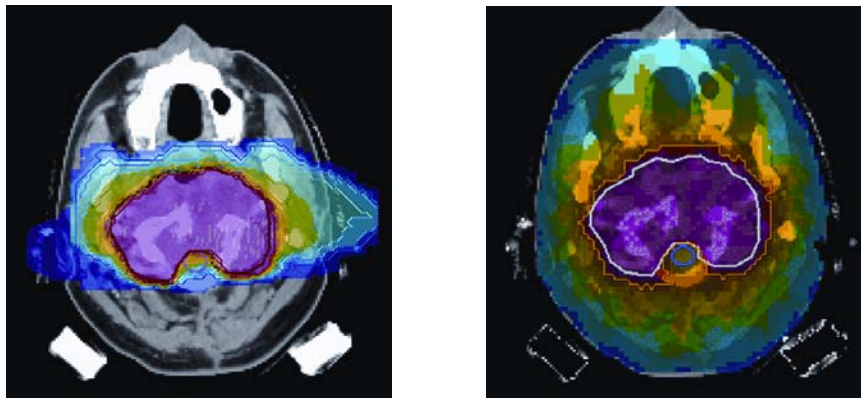


Figure 2. Comparison of carbon irradiation (left) and photon irradiation (right). For photon IMRT nine channels are used to distribute the dose to the normal tissue. For carbon scanning therapy the dose in the only two entrance channels is much smaller than for IMRT.

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 a patient. Because ions are charged particles, they interact mainly with the electrons of the penetrated tissue. At high initial particle velocities, this interaction is small and only a little energy is transferred to the tissue. With increasing depth the ions are slowed down and the local interaction becomes greater, transferring a higher dose to the tissue. Then the dose increases at the end of the ion-range to very high values where the primary ions stop. This is the so-called Bragg peak of ionization⁴ (Figure 1). After the Bragg peak, the dose decreases to zero when the primary ions come to rest. This yields an ideal depth-dose distribution and is optimal for therapy: with a low dose at the entrance channel in the normal tissue, and a large dose at the end of the penetration in the tumor volume. Beam fragmentation, however, contributes additional doses along the depth and beyond the stopping region of the primary ions.

In 1946, R. Wilson² recognized the great advantage of the depth dose distribution of protons compared to conventional irradiation and proposed the use of the Bragg peak for radiotherapy. LBL developed simple, but very efficient,

procedures for patient treatment in order to adapt the very sharp Bragg maximum to the target volume⁶ (Chu et al., 1993). Using increasing sophistication beam delivery methods, from scattering foils to magnetic sweeping, and finally to raster scanning, the beam was enlarged in width, and with variable ridge filters, it was modulated in depth. With these techniques, a higher dose to the target volume could be applied, but at similar or smaller doses to the normal tissue than in conventional photon therapy. At that time this was a very efficient step for the improvement of therapy of deep seated tumors.

Intensity modulated particle therapy using the raster scan technique

Ions are charged particles and can be deflected with magnetic fields. Therefore, it is possible to replace the passive modulation systems that were initially used by active systems in Figure 3 where the beam is laterally deflected by magnets and modulated in depth by an energy variation in the accelerators⁷ (Haberer et al., 1993). For the irradiation, the target volume is dissected in slices of equal ion energy and the beam is scanned in lines over each slice.

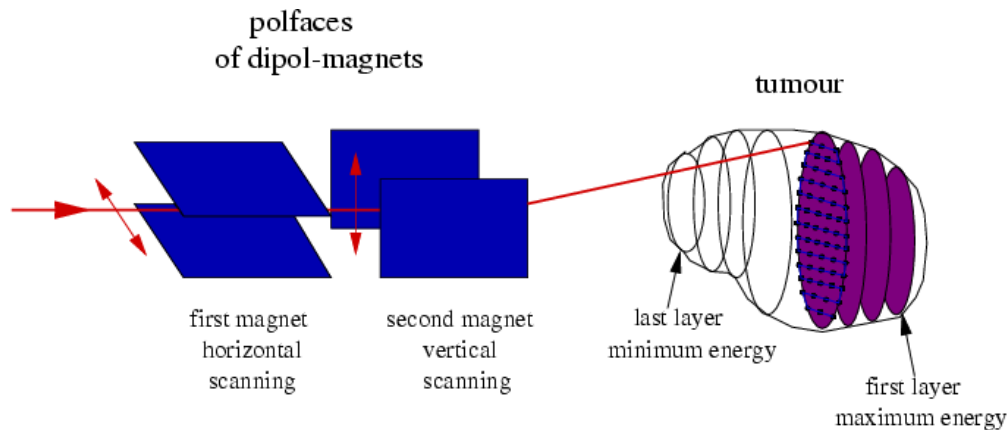


Figure 3. Active beam modulation systems. The tumor is dissected in slices and each iso-energy slice is covered by a net of pixels for which the number of particles has been calculated previously. The beam is then guided by the magnetic system in a raster-like pattern from pixel to pixel. (Durante and Loeffler, 2010)

When irradiation some deeper, more distal, layers with the Bragg maximum, the more proximal layers are partly pre-irradiated. This has to be corrected for and results in an inhomogeneous dose distribution for all individual layers.

In addition, the variation of the relative biological effectiveness (RBE) of the particle beams has to be taken into account in treatment planning, which results in an even larger variation in effective particle dose covering per slice. This is necessary in order to obtain a homogenous distribution of the biological effect over the complete tumor volume.

The novel technique of beam scanning is in principle the same as the production of a TV picture image using an electron beam in a TV set (Figure 4). There, the

picture is divided in lines and separate picture points (pixels) and the beam is guided to modulate the intensity from pixel to pixel (Figure 5).



Figure 4. Reproduction of the famous photograph of Albert Einstein produced with the GSI raster scan system as a heavy ion beam TV using a 430 MeV/u carbon beam of 1.7 mm width (FWHM). The picture consists of 105 x 120 pixels filled by $1.5 \cdot 10^{10}$ particles given in 80 spills (5 sec. each) of the SIS accelerator. Original size of the picture: 15 cm x 18 cm. (Courtesy GSI.)

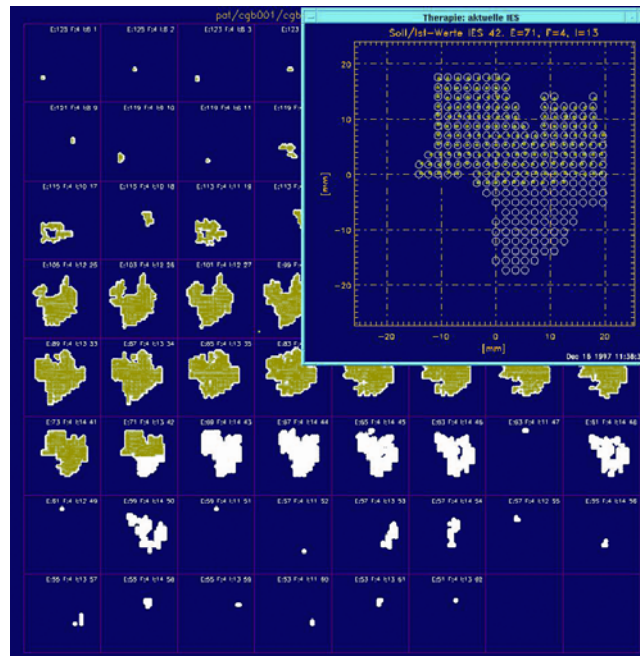


Figure 5. Iso-energy-slices of a tumor. The target volume was dissected into 60 slices which are covered with a net of about 10 000 picture points (pixels). One slice is shown enlarged (upper right corner). The circles correspond to the position where the beam should be and the green points are the centers of the measured beams. However, the beam has a diameter of about 6 mm and covers more than three beam positions normally in each direction. (Courtesy GSI.)

However, the tumor treatment system has three dimensions, so the “pictures” can be stacked by varying the beam energy. Subsequently, a 3-dimensional target volume can be exactly “painted” with the beam. Even critical organs that are enclosed partly or completely by the tumor can be spared in the intensity modulated ion therapy, and the dose to critical organs can be drastically reduced. This is often necessary in the case of tumors in the brain stem region at the base of the skull. Using raster scanning, the dose to the brain stem can be reduced below the normal tissue tolerance.

If critical structures are completely or partially enclosed by a tumor, it is important that the particle tracks do not pass through the critical organ to reach the distal parts. Then it is useful to apply the beam from two sides and to avoid penetration of the organ. In general, two or three entrance channels can be extremely inhomogeneous, but all together they produce a homogeneous biological effect. Using Intensity Modulated Particle Therapy (IMPT), an optimal agreement between the irradiated volume and the target volume can be reached combined with a maximal sparing effect of critical structures also inside the target volume.

Another important parameter for treatment planning in many cases is the dose gradient between the target volume and critical organs. In Figure 6, a single patient MRI is used to design a treatment using carbon (which was indeed applied later on) and proton beams. Carbon ions have a gradient that is three times steeper than protons. This ratio between gradients for protons and heavy ions holds for approximately all penetration depths. Therefore, tumors close to critical organs can be effectively treated with high carbon doses, with only rare cases of tumor recurrence.

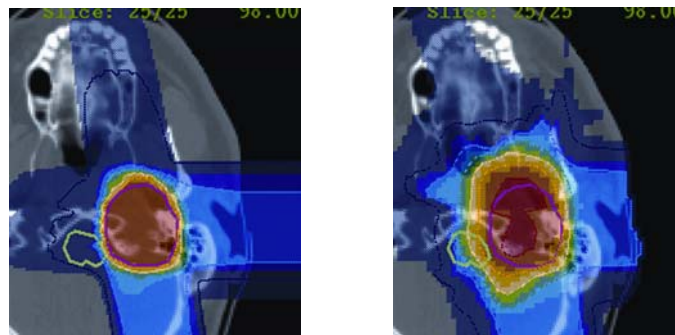


Figure 6. Comparison of a treatment plan with carbon ion on the left side and a proton plan on the right side. The carbon plan shows a very steep dose gradient. With such a steep dose gradient the irradiation can be closer to the brain stem, which is a critical structure shown outlined in green at the left side. In addition, the proton plan was implemented using a passive beam application system which leads to a less precise covering of the target volume (courtesy of O. Jäkel, DKFZ).

BIOLOGICAL BASIS OF RADIOTHERAPY

Experiments related to the biological effectiveness

Heavy ions, such as carbon, produce a better depth dose profile than protons in therapy and also create an efficient *in situ* control using the PET technique⁸ (Enghardt, 1996). The advantage of a carbon beam is the higher relative biological effectiveness at the end of the range of the beam. At the entrance channel, the RBE is only slightly elevated. This together with the low dose in the entrance channels produces less and more reparable damage than the more significant and less reparable damage in the target volume. An essential goal for the development of heavy ion therapy was to maximize the difference in the biological effectiveness between entrance channel and tumor area.

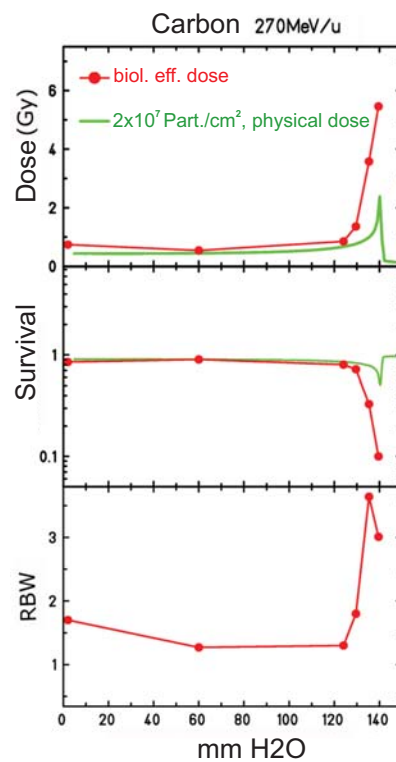


Figure 7. Survival and RBE as a function of penetration depth dose for a carbon beam. In the top panel the lower curve is the physical dose, (Bragg curve); the upper curve is the biological effective dose BED. The BED is calculated as the dose multiplied by the RBE shown in the bottom panel (RBW in the German original), calculated using the local effect model⁹. (Weyrather et al., 1999). Cell survival corresponding to the physical dose and the biological dose, respectively, is shown in the middle panel as discussed in the text.

The goal of the pioneering heavy-ion therapy work at Berkeley was to maximize the effects in the tumor area while taking into account higher side effects in the normal tissue. A large number of ion beams were investigated, including protons, helium, carbon, neon, silicon, and argon. Carbon and neon ion beams demonstrated the most optimal physical and radiobiological features. Silicon and argon ion beams provided an extremely high tumor control rate for superficial tumors, but also many late effects in the normal tissues. This clinical response

can be explained with cell experiments: Cells are irradiated in a water tank as a tissue equivalent in different depths of the ion beam, and the cell survival does not correspond to sparsely ionizing radiation like photons⁹ (Figure 7, green curve in the middle). For carbon ions, the experimental cell survival in the entrance channel is close to the calculated survival rate based on photons. But in the range of the Bragg maximum, the survival⁹ (Figure 7, red curve) is very much reduced, corresponding to a dose about three times higher than measured in the Bragg peak. Therefore, the ratio of the photon and ion doses that yield the same cellular survival, which is the relative biological effectiveness (RBE), in this case is three.

A similar behavior of the RBE is found for all ions. But for protons, the range of an elevated RBE is restricted to the last fractions of a millimeter of the range; i.e., elevated RBE values are only found with the distal part of the dose maximum. Consequently, in the clinical application the slightly elevated RBE values of protons are only slightly increased and are taken into account with the global factor of up to 10%, (RBE = 1.1) for the 2 Gy dose fraction. For very heavy ions like argon, the RBE is already high in the entrance channel adversely affecting normal tissue overlying the tumor, and then is less effective in the tumor region. This leads to the observed undesirable outcome. For carbon ions, however, the increase of RBE is restricted to the last 2 cm, depending on the initial beam energy. This range can be used clinically in an optimal way, in order to destroy the tumor cells in the target volume very effectively. The reason for the difference in RBE can be explained by the microscopic structure of particle tracks and their interactions with DNA.

Microscopic understanding of RBE

During the slowing down process of heavy ions, the particle energies are transferred to the electrons of the absorbing tissue. These energy transfers are small compared to the total energy of the carbon ion, which is in the range of a few million electron volts. But they are big compared to the binding energy of the electrons of a few electron volts. Therefore, the liberated electron leaves the atoms with large kinetic energies. This energy is transferred to secondary ionization and excitations. The ionizations can destroy chemical compounds and consequently destroy the biological molecules. The most important target for the action of ionizing radiation in the cell is the DNA molecule, which contains the genetic information of the cell and the organism. Because the integrity of DNA is essential for the further life of the cell and of 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- and most of the double-strand breaks are repaired fast and with high fidelity. This is also true for most of the lesions that are produced by ionizing radiation. However, if a high local ionization density produces many lesions on the DNA in close proximity (clustered lesions), the repair may not be successful, the cells may have lost their ability to divide (clonogenic death), or the cells are

forced to dissolve themselves (apoptotic death). For sparsely ionizing radiations, the necessary high ionization density can only be reached by increasing the dose. For carbon ions, the high local ionization densities are reached in the center of the track when the energy loss reaches values of a few 100 keV per micrometer or more even within one particle track. This means the two radiation types cause fundamentally different types of damage per unit dose.

In Figure 8, proton and carbon tracks are compared with a schematic DNA molecule. For proton ions, the energy loss is small, and the ionization events are far from each other. This results in DNA damage that can be repaired.

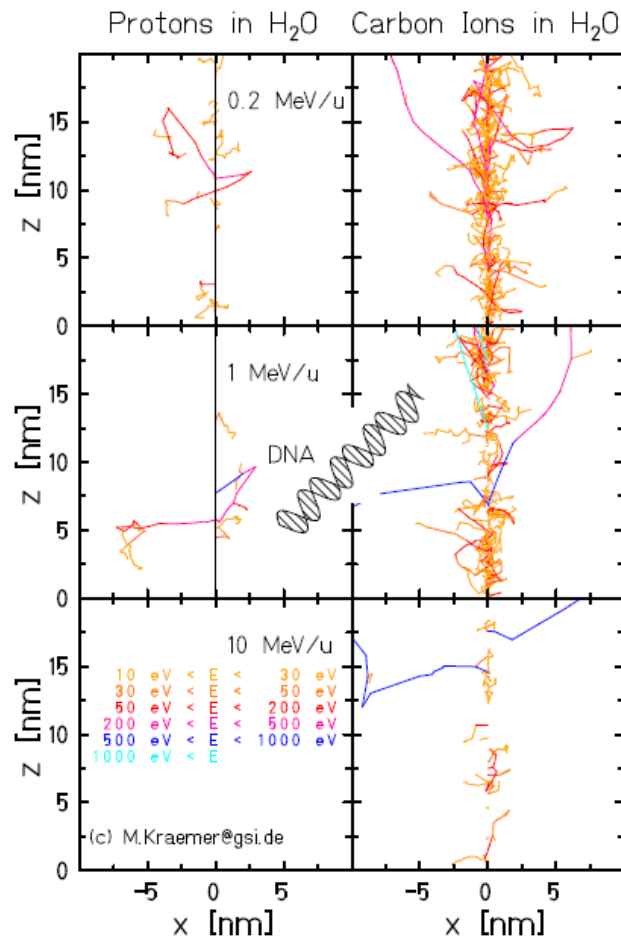


Figure 8. Simulated paths of δ -electrons created by ions of various energies in water. (Courtesy Krämer, GSI).

For carbon ions, the ionization density at the end of the track at low energies is high, and multiple DNA damage sites are very likely (Figure 9).

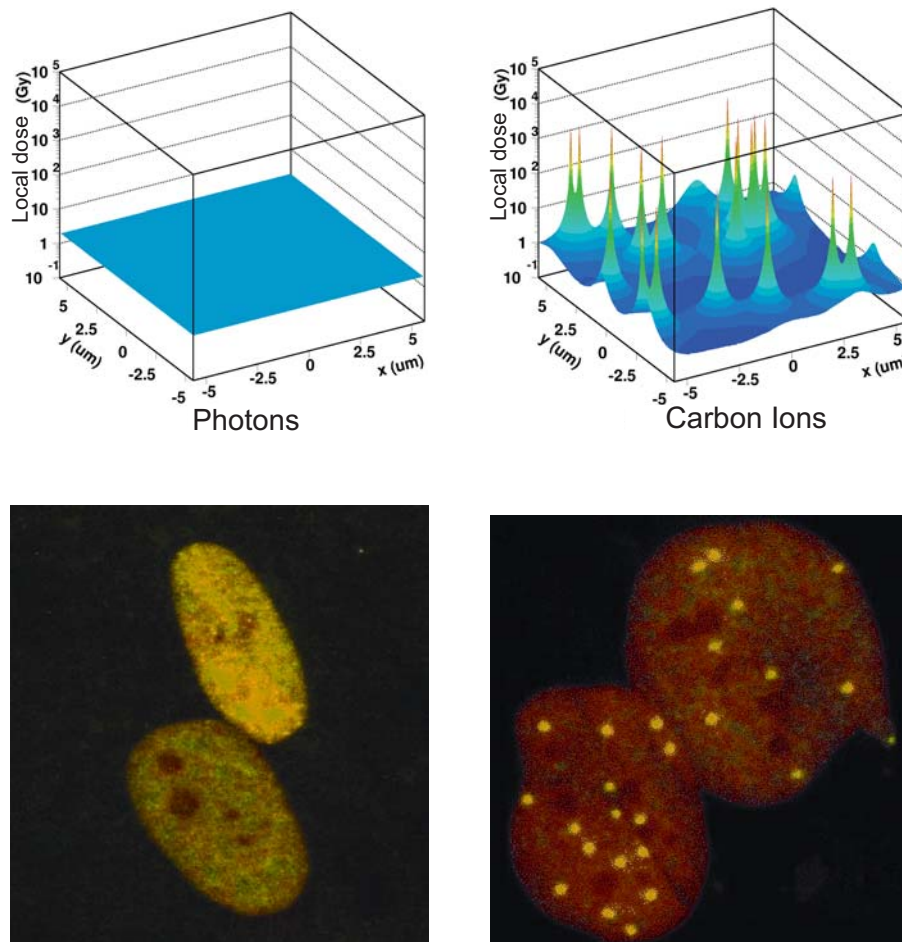


Figure 9. Comparison of energy deposition of x-rays and particles in the dimension of micrometers within cell nuclei. For x-rays the dose is homogeneously distributed in the cell nucleus. For particles at the same microscopic scale, a large fraction of the cell nucleus is not hit, and the dose is concentrated in a few very sharp needles. This can also be seen in the distribution of the DNA damage (lower row). For x-rays, the damage (yellow color) is homogeneously distributed over the cell nucleus. For ions (right panel), the damage represented by large diameter yellow foci is concentrated in the path of particle traversals and is resistant to repair. (Jakob *et al.*, 2000¹⁰, 2003¹¹).

These complex DNA damages overcome the repair system, and the cells die after many attempts at repair. This is true also for cells having an extremely large repair capacity, which are otherwise very radio-resistant. Because of the high density of local damage, the repair capacity is not sufficient and the survival probability is drastically reduced after irradiation with heavy ions. Cell cultures that are resistant to the sparsely ionizing radiation show the largest increase in radio-sensitivity; i.e., the highest RBE values if they are irradiated with carbon

ions. This behavior of cell cultures can be directly extrapolated to tissues and tumors of a patient.

In survival measurements where the cell inactivation is measured as a function of the dose of X-rays, 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 more steeply. This non-linear behavior in the form of a shoulder in the survival curve is mathematically expressed in a linear quadratic function where the fraction of surviving cells S is related to the absorbed dose D by:

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

The coefficient α describes the linear component, 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 of the repair capacity. Cells or tissues with high repair potential exhibit a large shoulder with small α / β ratio between 1 and 3. Cells with small repair capacity have a large α / β ratio close to 10.

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

The Local Effect Model

For treatment planning, but also for prediction of late effects, the Local Effect Model (LEM) has been developed at GSI¹² (Scholz and Kraft, 1994). The basic principle of the LEM is to convolute the non-homogeneous dose distribution in the particle track with a non-linear photon dose effect curve. With this method, the effect of the particles can be calculated on the basis of the photon dose-effect curve for any system for which the photon dose-effect curve is known.

In the calculation, the cell nucleus is covered with a particle density corresponding to the macroscopic dose (Figure 10). The physical parameters like particle energy and atomic number determine the radial dose distribution of the particle tracks and the absolute dose. According to the radial dose of the tracks, an inhomogeneous dose distribution over a cell nucleus is split into areas within which the dose variation is small compared to the absolute value of the dose. For each of these small areas, the number of lethal lesions is calculated according to the photon dose-effect curve and weighted with 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 N .

Assuming Poisson statistics, from the total number of lesions N the survival S can be calculated as $S = \exp(-N)$; i.e., different doses. A dose-effect curve can then be calculated for many different particle fluences. The RBE is then

calculated as the point-by-point ratio between the x-ray dose and the particle dose for the same effect on the dose-effect curves. The main biological parameter of this calculation is the shape of the photon dose-effect curve (the shoulder); i.e., the α / β ratio. In calculations the LEM model yields good agreement with experimental data and shows that large RBE values are associated with small α / β values and vice versa.

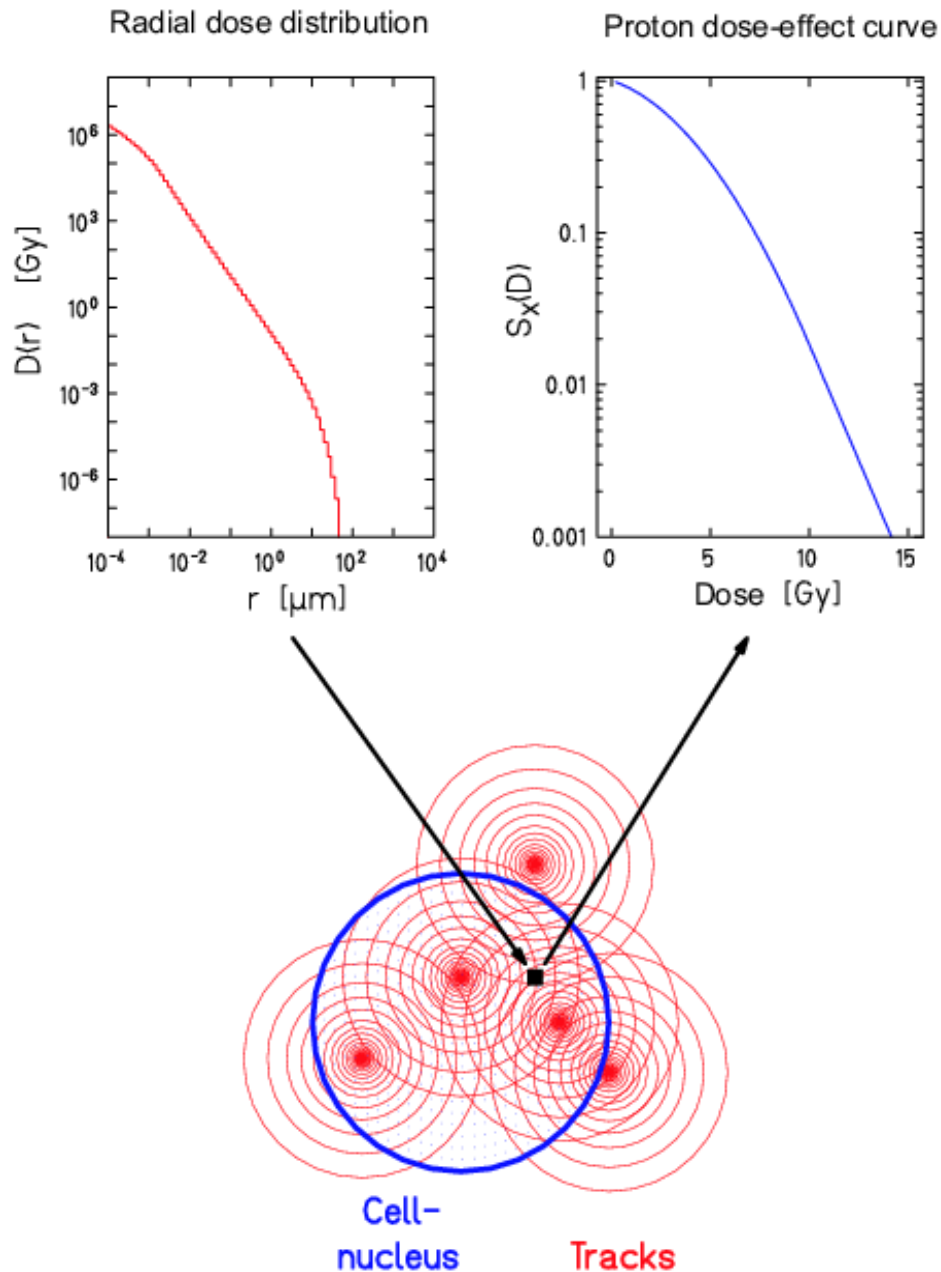


Figure 10. The basics of the local effect model are the radial dose distribution of a particle track and the photon dose-effect curve. In the calculation the radial dose distributions are overlaid to the cell nucleus and according to the local doses in small areas the effect is taken from the photon dose-effect curve.

The fidelity of the LEM model was confirmed in many cell survival experiments and in animal experiments⁴ (Krämer and Durante, 2010). LEM was also confirmed in non-biological systems like thermo-luminescent detectors (TLD's) of photographic emulsions, which have a non-linear dose response curve against sparsely ionizing radiation.

This fact can be used to optimize patient treatment. Using the local-effect model for each different composition of the radiation field, the RBE can be calculated point by point for treatment planning⁴ (Krämer and Durante, 2010). This calculation yields a large variation of RBE over the treatment according to the radio-resistance of the tumor or other tissues and the local dose. However, LEM does not contain any time-dependent parameters. In protracted irradiation where many biological lesions are repaired, the biological effect is overestimated.

CLINICAL RESULTS AND INTERNATIONAL SITUATION

In 1994 the National Institute for Radiological Science (NIRS) in Chiba, Japan started carbon ion therapy. As of now over 5,000 patients have been treated very successfully. In 1997 carbon therapy was started at GSI in collaboration with the German Cancer Research Center DKFZ Heidelberg as well as the Institute of Ion Beam Physics and Materials Research FZR Dresden. From December 1997 until the end of 2008, a total of 440 patients have been treated with carbon ions at GSI.

A typical result of these treatments is given in Figure 11.

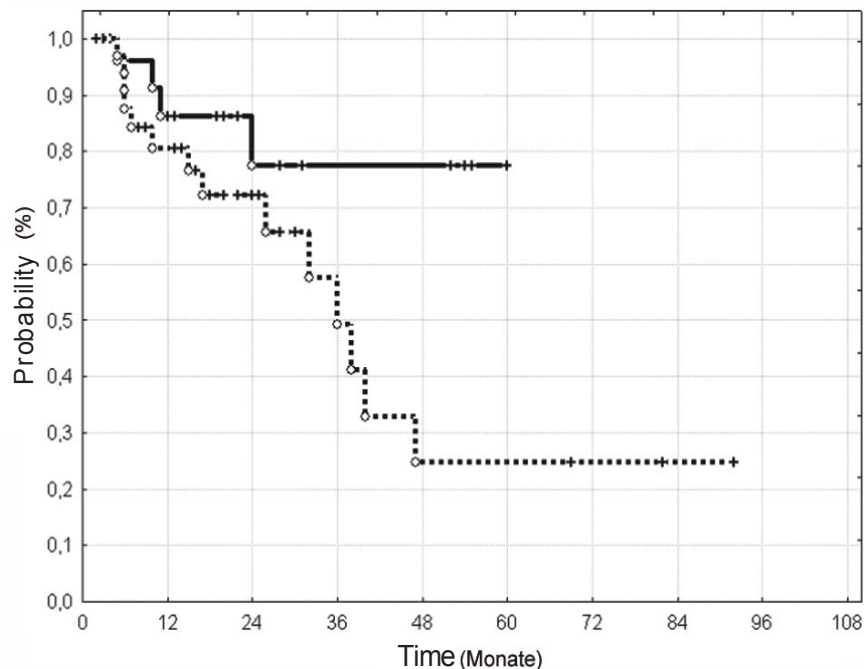


Figure 11. Local tumor control rate (fraction of patients with no evidence of tumor recurrence within a given time interval) of patients with advanced adenocarcinoma. Twenty-nine

patients were treated with photon IMRT combined with a carbon boost (upper curve). The lower curve shows the result of 35 patients who were treated with IMRT only. The boost irradiation with carbon ions increases the local control rate after 60 months from about 25 percent to 80 percent.¹³ (Schulz-Ertner *et al.*, 2005)

For the patients treated at GSI, the very precise irradiation technique using the raster scanning system yielded, in addition to the good tumor control, a much smaller incidence of side effects than would be possible with conventional therapy. A tumor control rate of 80% is a typical figure for all radioresistant tumors at GSI.

The number of patients treated in hadron therapy centers worldwide may be found at the website of the Particle Therapy Co-Operative Group (PTCOG): http://ptcog.web.psi.ch/patient_statistics.html

In 2003, construction of the Heavy Ion Therapy facility (HIT) at the Heidelberg clinic was started. The first carbon patients were treated at HIT in 2009.

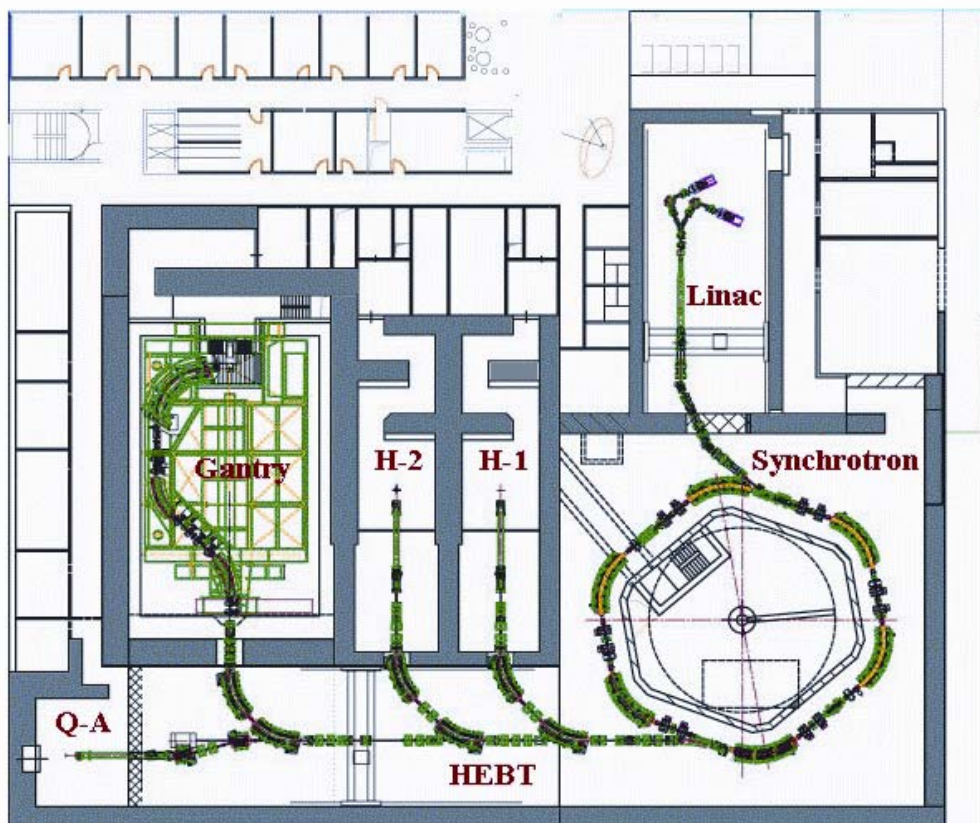


Figure 12. Layout of the Heidelberg Heavy Ion Therapy (HIT). Ion source and the synchrotron at the right side produce the beam for two irradiation sources having a fixed horizontal beam similar to GSI and for one beam that can be rotated around the patient. Gantry is shown at the left side.

The good tumor control rate in Chiba together with the low rate of side effects at Darmstadt in Germany were the reasons to start other carbon therapy projects. At Hyogo in Japan, a unit for carbons and protons started in 2002. The construction of a third Japanese unit in Gunma prefecture has just recently started its first carbon patients in 2010.

In 1992 an initiative for hadron therapy (TERA) was founded in Italy, intended to provide beams of protons, neutrons, pions and heavy ions. After a short time, this proposal was reduced to proton and carbon therapy only. In 2004 the construction of a therapy unit was financed by the government and the Centro Nazionale Adroterapia Oncologica (CNAO) was founded to operate that project.

In 1994, Med-AUSTRON, a project for the construction of carbon-proton therapy, started in Austria. In the beginning this project was combined with a spallation-neutron source, using the same synchrotron. However, after a short time it became evident that different accelerators, one of therapy and another for neutron production, would be more effective and consequently, Med-AUSTRON designed its own dedicated therapy system. After the termination of the spallation project, the construction of the therapy unit was decided by the government in January 2005.

In 2005 in Pavia, close to Milan, the foundation stone for the Italian unit was laid. At the beginning of 2005 the Med-AUSTRON project was funded by the Austrian government and in May 2005 money was given by the French government for the ETOILE project in Lyon.

Meanwhile in Germany, a second project at Marburg was started by a private hospital supplier, the Rhoen Klinikum AG (RKA). According to this company, in the next several years, five units will be built in Europe. At an estimated need of about one unit per 10 million inhabitants, the first five units are not sufficient for Germany. For the European Union approximately 30 units are necessary to provide good care for all patients. How many additional heavy ion therapy units will be constructed in the end depends on the clinical success, especially in comparison to the proton units, which are about 25% cheaper. In the end, as for any significant medical investments, the clinical success will determine the number of units. In the European market, Siemens Medical Solutions has taken over the GSI technology and patents. In addition the Belgian company Ion Beam Application (IBA) and the Japanese Hitachi company, as well as the German Company ACCEL, are offering heavy-ion therapy units.

Lists of current and planned particle therapy facilities may be found at the website of the Particle Therapy Co-Operative Group (PTCOG):

Facilities in Operation: <http://ptcog.web.psi.ch/ptcentres.html>

Planned Facilities: <http://ptcog.web.psi.ch/newptcentres.html>

The large interest of these companies shows that an important market for heavy ion therapy is expected. This will be beneficial for many patients for whom heavy ion therapy provides a higher chance for the cure of their cancer.

Many of the radiobiological and physical data necessary for tumor therapy are also of interest for space research. This is especially true for the evaluation of long-term effects like the induction of secondary tumors, genetic mutations, or transformations. Experiments investigating these topics could be shared by both communities. But it is very clear from the onset that the clinically dedicated accelerators will not have much free time for these experiments, and it is also likely that the most relevant beams for space research, like Fe-ions, will not be produced at the clinical machines. Therefore, a separate, dedicated research program must be carried out according to the needs and requirements of research to provide space radiation protection.

¹ U. Amaldi and G. Kraft, Recent applications of synchrotrons in cancer therapy with Carbon Ions, *Europhysics News* **36**(4), 114-118 (July-August 2005). <http://dx.doi.org/10.1051/eprn:2005402>

² R. Wilson, Radiological use of fast protons. *Radiology* **47**, 487-491 (1946).

³ M. Jermann, Particle therapy facilities in a planning stage or under construction, Particle Therapy Co-Operative Group, <http://ptcog.web.psi.ch/newptcentres.html> 31 July 2010.

⁴ M. Krämer and M. Durante, Ion beam transport calculations and treatment plans in particle therapy. *Eur. Phys. J. D.* **60**(1), 195-202 (2010). <http://dx.doi.org/10.1140/epjd/e2010-00077-8>

⁵ G. Kraft, Tumor Therapy with Heavy Charged Particles, *Prog. Part. Nucl. Phys.* **45**, 473-544 (2000).

⁶ W. Chu, B. Ludewigt, and T. Renner, Instrumentation for treatment of cancer using protons and light-ion beams, *Rev. Sci. Instrum.* **64**(8), 2055 (1993). <http://dx.doi.org/10.1063/1.1143946>

⁷ T. Haberer, W. Becher, D. Schardt, and G. Kraft, Magnetic scanning system for heavy ion therapy, *Nucl. Instrum. Meth. Phys. Res. Section A: Accelerators, Spectrometers, Detectors and Associated Equipment*, **330**(1-2), 296-305 (1993).

⁸ W. Enghardt, Positronen-Emissions-Tomographie bei Schwerionentherapie, *Phys. Bl.* 52(874) (1996).

⁹ W. K. Weyrather, S. Ritter, M. Scholz, and G. Kraft, RBE for carbon track segment irradiation in cell lines of differing repair capacity. *Int. J. Radiat. Biol.* **75**(11), 1357-1364 (1999).

<http://dx.doi.org/10.1080/095530099139232>

¹⁰ B. Jakob, M. Scholz, G. Taucher-Scholz, Immediate localized CDKN1A (p21) radiation response after damage produced by heavy-ion tracks, *Radiat. Res.* Oct. **154**(4), 398-405 (2000).

¹¹ G. Taucher-Scholz, B. Jakob, G. Becker, M. Scholz, Microscopic visualization of a biological response to charged particle traversal, *Nucl. Instr. Meth. Phys. Res. Section B: Beam Interactions with Materials and Atoms* **B 209**, 270-276 (2003).

¹² M. Scholz and G. Kraft, Calculation of heavy ion inactivation probabilities based on track structure, X-ray sensitivity and target size, *Radiat. Prot. Dosim.* **52** 29-33 (1994).

<http://rpd.oxfordjournals.org/content/52/1-4/29.abstract>

¹³ D. Schulz-Ertner, A. Nikoghosyan, B. Dinger, M. Mütner, O. Jäkel, Ch. P. Karger, J. Debus, Therapy strategies for locally advanced adenoid cystic carcinomas using modern radiation therapy techniques, *Cancer* July 15; **104**(2), 338-344 (2005).

<http://dx.doi.org/10.1002/cncr.21158>