History of the Heavy Ion Therapy at GSI

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Introduction

Space exploration and ion therapy have a common interest - the locally ionizing action of energetic ions. In space exploration the ionizing power of heavy ions represents a major risk for both humans and electronic equipment, because ions are accelerated in space to relativistic energies. Therefore, spacecraft are penetrated by a large flux of heavy ions that can modify and destroy the information stored in the computers and also in the DNA molecules of the astronauts. These effects place both the astronauts and the space vehicle at risk. Energetic ions can influence the spacecraft control system and the astronaut's health. Interestingly, the cross sections for cell effect are very similar to the cross sections for electronic failure. They are different in their absolute magnitude but they parallel each other in their dependence on atomic number or energy.

In cancer therapy, however, the situation is more complex: in order to kill all tumor cells a maximum of biological effectiveness is wanted at the tumor cells, but the normal tissue should not be affected by the radiation. This is not entirely possible to achieve in practice, but a dose application using scanning of particle beams, where a high dose is delivered at the end of the ion flight path in the Bragg peak, can come close to this requirement and reduce the exposure of the normal tissue to a minimum, while the tumor may be eradicated by a lethal dose.

In both cases - space research and tumor therapy - the biological action of ions should be known very precisely. This ambiguity in biological ion research was a driving force in the development of ion radiobiology at the Gesellschaft fur Schwerionenforschung (GSI),Darmstadt, Germany. With the installation of the Universal Linear Accelerator UNILAC, radiobiological research started in 1976 with the main focus being on space research. But when the next accelerator stage - a high energy synchrotron (SIS) - became operational in 1988 the focus in research changed completely to therapy, and a clinical therapy project was installed at GSI in the years 1993 -1997. During the time of patient treatment 1997 - 2008, the focus of research was clearly dominated by therapy related topics. Now, after 10 years of patient treatment and after the successful installation of a dedicated medical facility at the Heidelberg University Hospital in 2009, the GSI biophysics research again changed its direction back to space related problems. In the following, the history of the GSI therapy project will be given in more detail.

Preparations and New Concepts

The GSI tumor therapy program originated from the heavy ion therapy work at Lawrence Berkeley National Laboratory (LBNL), and in 1978 the first discussions started about the future developments of the GSI facility. At that time the GSI UNILAC accelerator was limited to a final energy of 20 MeV/n, and the scientific reasons for the construction of a heavy ion synchrotron (Schwerionen Synchrotron, SIS) were documented in a proposal by R. Stock. His booklet summarized mainly nuclear physics experiments in the energy region up to 15 GeV/n,

but it contained also a small chapter on heavy ion radiobiology and tumor therapy (authors: H. Dertinger and G. Kraft) which was a adaption of the Berkeley medical activities at the Bevalac to the proposed SIS including radiobiological experiment, with a purpose of determining the relative biological effectiveness (RBE) using different cell lines, physics experiments on energy loss and beam fragmentation. The main topic was the construction of a therapy cave where a horizontal beam line would be directed towards a patient in a supine position and where the beam was shaped to fit the contours of the target volume inside the patient using passive modulators like ridge filters, absorbers and boli, apertures and range shifters.

One year later, in July 1979, an official proposal ”SIS 100, an accelerator for relativistic ion beams” was submitted to the German government where the former proposal was complemented by the design layout of a heavy ion synchrotron capable of accelerating all ions He…U up to energies of 14 GeV/n(corresponding to a magnetic rigidity of 100 Tm and a ring radius of 125m) with intensities close to the space charge limit, maximum for such a machine.

Because it turned out that this proposal was too ambitious and too expensive, it was modified in several stages. Finally a two-step solution of SIS 12 and SIS 65 was accepted where the small SIS 12 should be built first and the bigger accelerator some time later. Finally in 1984, the construction of SIS 18 began with a final energy of 1.4 GeV/n and started operation in October 1988 with many experiments, including radiobiology but without a therapy facility.
The time before SIS18 became operational was used intensively by the radiobiology group of GSI to learn more about ion beam therapy and particle radiobiology. In 1979 two scientists (G. Kraft and W.K. Weyrather) were sent by GSI´s director G. zu Putlitz as visiting scientists to the LBL group of C. A. Tobias and E.A. Blakely where radiobiology experiments for the heavy ion therapy were being performed. This was a very useful time and helped to accelerate the radiobiology at GSI after their return. First an exposure setup for high sample throughput was installed at the UNILAC facility where a hundred samples could be exposed within a few hours. This increased the statistical data and consequently the precision in the measurements as well, but it also allowed one to extend these measurements to many end points and energies.

A main topic of these experiments was to measure the relative biological effectiveness, as a function of the energy, of the different light ions. In these measurements all the individual RBE curves were measured for each atomic number from protons to neon ions. The most important result was that for carbon ions the RBE maximum coincides with the energy loss maximum or Bragg peak in the range curves. But for lighter ions the RBE maximum occurred at the distal side of the Bragg peak, while for the heavier ions, the RBE maximum was at the proximal side. The fact that energy loss and RBE peaked at the same position was the major reason to choose carbon ions for therapy instead of the heavier neon ions used at LBNL and the lighter protons used in all other facilities.

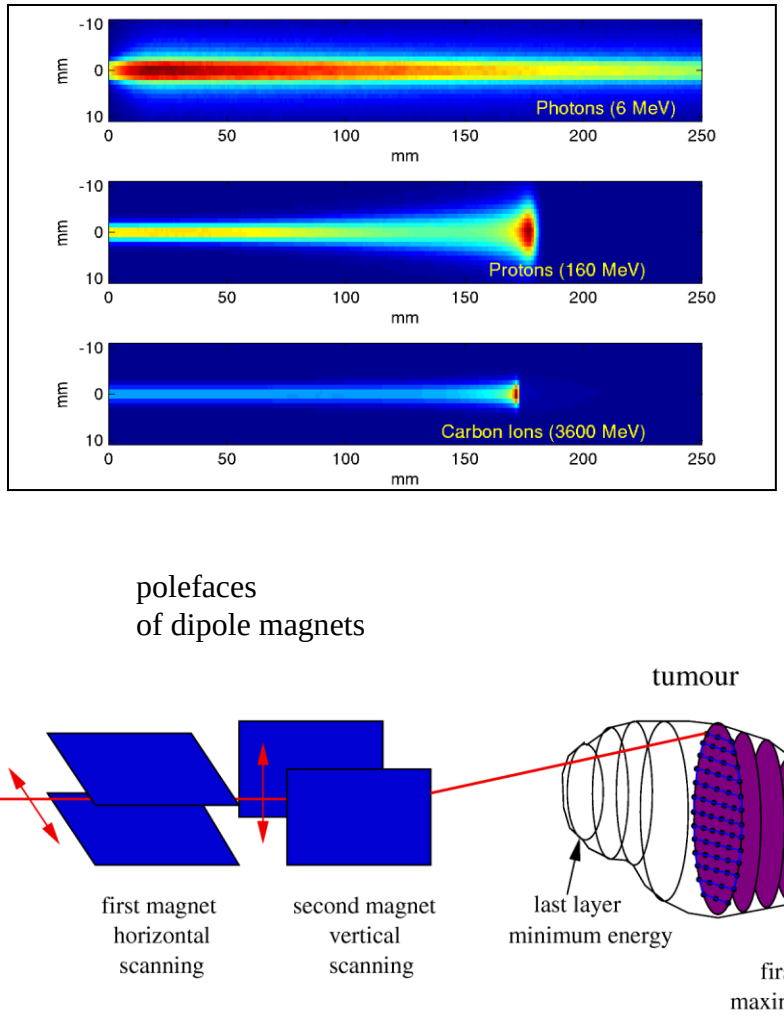

Figure 1. Top: Comparison of the beam profiles of photons, protons and carbon ions (courtesy of K.Parodi, LMU Munich))
Bottom : Principles of raster scanning

Another major change from the former paradigms was the preparation of an active beam scanning system instead of passive range and scattering modulators, Figure 1. At GSI, Bernd Fischer had managed to set up a micro beam where he directed single ions with a spatial precision of 1 µm. Translating this technology from the micrometer scale to the dimension of a focused ion beam, the complex volume of a tumor could be irradiated with a resolution of a few millimetres as shown with the image of A. Einstein in Figure 2.

Figure 2
Picture of Albert Einstein produced with a scanned carbon beam

In the later therapy pilot project the target volume of a deep-seated tumor was divided in up to 60 iso-energy layers where each of them was filled in a raster-like pattern with a few hundred pixels each representing the stopping points of the ion beam. In order to achieve a fast irradiation, the beam was moved from one pixel to the next without turning off the beam when the pre-calculated coverage was reached. Critical problems were the fast and stepwise ramping of the power supplies and the online monitoring of the intensity of the beam and its actual position at the beam line exit in front of the patient. The new technique of fast scanning was regarded as being very challenging; therefore the quality of the exposure was a major issue for patient treatment.

In addition to the beam monitoring in front of the patient, an online positron emission tomography (PET) system was proposed by G. Beyer and W. Enghardt and colleagues from Dresden, at that time East Germany. They were working on a new type of gamma detector with high resolution, but as it turned out later, the efficiency was too low for a double head PET camera. Therefore, it was replaced later on by a commercial available set up of sliced BGO crystals. At that early time a collaboration with the Dresden laboratory was difficult, because a direct transfer of scientists and equipment across the inner German border was not allowed. The alternative, a planned transfer of the PET camera via the common partners in Dubna, Russia, could not be accomplished either after the sudden German reunification.

When SIS18 started in 1988 the technology of beam scanning and its monitoring could be tested with a prototype magnetic scanner, and European Union money supported two collaborators - a Ph.D. student, T. Haberer, and an engineer, W. Becher.

Setting up the Pilot Project 1988 -1997

From the beginning of the discussions of ion therapy at GSI, there was a strong connection to the radiology department at the Heidelberg University Hospital, because of the good relations between GSI´s zu Putlitz and Klaus zum Winkel, former director of university radiology at Heidelberg. This was continued later on by Michael Wannenmacher who took over the university-radiology and simultaneously the experimental radiotherapy unit at the German cancer research center (DKFZ) at Heidelberg under the directorship of Harald zur Hausen.Such a interaction is normally difficult because of the two different "languages" of physicists and physicians. But in this case it was very easy to discuss complex physical processes because of the Heidelberg tradition that most of the physicians had also studied physics and obtained a PhD, like Guenther Gademann who was initially responsible for ion beam therapy at Heidelberg. The first attempt to formulate a therapy proposal before the start of the SIS construction failed. In 1988 a first proposal - "Construction of an experimental heavy ion therapy at GSI Darmstadt" (authors G.Gademann, G.Hartmann, G.Kraft) - was submitted by the three cooperating institutes to the German government - but never acted upon by the ministry.

This first proposal was followed by later attempts to obtain funding from national and international sources. These failed too, partially because of the unusual structure of the project with a very artificial separation between beam production by GSI on one side and all the topics such as the medical tasks of diagnosis, treatment planning, and also beam transport, beam application, monitoring, etc. being the responsibility of the Heidelberg partners. At that time GSI did not want to be involved in the project except for beam production. The great fear was that ion therapy would be too successful and could overshadow the nuclear and atomic physics programs at GSI.

This view changed completely in the spring of 1993 when Hans Specht took over the directorship of GSI. He wanted to see the first patient to be treated within the first four years of his directorship. He was willing to support the project with the highest priority in all technical, physical and radiobiological details, in whatever areas GSI had the necessary experience. Independent from the preparation of a new proposal for the government, the construction of a medical exposure facility started immediately in May 1993.
The intention was to construct a high technology heavy ion therapy based on:

- Raster-scanning as the active beam delivery system, including
  - Fast energy variation by the accelerator
  - Online quality control including *in situ* PET diagnosis

- Single beam-spot treatment planning including
  - Local RBE assignment according to the tissue and the radiation field

The very short time of only 4 years to realize this novel technology was a great challenge. (The technical data are given in Table 1.) Dieter Böhne became general project leader, and as the head of the accelerator division, he had strong experience in the realization of complex projects. The different sub-projects were coordinated by a committee KAT (Koordinations Ausschuss Therapie) chaired by Gerhard Kraft, which met normally once a month, but more frequently in

the last phase just before patient treatment. The whole project was supervised by an external Advisory Committee Therapy ACT chaired by Edward Alpen, LBNL, Berkeley.

For the beam delivery system, a prototype of the raster scan system (T. Haberer) was already successfully operating, including prototypes of beam monitor systems (B.Voss). But there was no previous experience for all the new accelerator-control technologies. The active energy variation were not used at the Bevalac or at the Heavy Ion Medical Accelerator Center (HIMAC) at the National Institute for Radliological Sciences (NIRS) in Chiba, Japan, because the time required could be several minutes., With that limitation in mind, the capability to change all machine settings after the injector and obtain active energy variation within seconds was requested at GSI. The energy library had 250 discrete steps and with reproducible accuracy of 0.1 % that could be deliverd from pulse to pulse. In addition the extraction had to be smooth without intensity-spikes that would be intolerable for the scanner system. It was the great success of Hartmut Eickhoff and his team that the SIS was the first accelerator to fulfill all these conditions.

Although these technical achievements were necessary for a successful operation of the new therapy, novel solutions had to be found for other tasks, including fast scanner control, beam quality control, treatment planning, and dose verification. Most importantly, the relative biological effectiveness, RBE, had to be predicted and verified to be accurate for the mixed beam in a complex target volume of different tissues including the malignant tissue.

A major challenge was the fast beam control system i.e, the monitors in front of the patient that guarantee the precise position and intensity of the particle fluence for each pixel. For the high granularity of several times 10 000 pixels in the scanned area, a position sensitive ionization chamber having a spatial resolution of 2 mm or less was not feasible. Therefore, the functions of the monitor system were separated: wire chambers were used for the position measurement, and ionization chambers for the intensity measurement which were read in 120 µsec and 10 µsec respectively. This separation of functions is possible because one did not expect to have two beams at two different locations at the same time. The beam monitoring system is one of the most critical components of the therapy unit because the speed of the control system is the limiting factors of the overall treatment time and consequently for the number of patients that can be treated per year.

Table I. Parameters of the GSI therapy system

Ion	**Carbon**
Range in tissue	20…300 mm H_2O
Field size	200 mm x 200 mm
Dose range	Treatment volume 0.75 – 4.0 Gye
	Normal tissue < < 2Gye
Treatment time	< 5 min / fraction
Raster Scanner	
Deflection angle	Horizontal 1.45° vertical 3.30°
Radius	12.0 m
Field size	20cm x 20 cm
Scan speed	Horizontal: 2.0 cm/ms vertical 1.0 cm/ms
Field ramp rate	Horizontal: 38.0 T/sec vertical: 9.5 T/sec
Max current	410 A
Rise time	Horizontal:10 ms vertical 40 ms
Accelerator	
Energy range	85- 430 MeV/u (range 20- 300 mm water equivalent)
Energy stepping	255 steps, cycle time 5 sec
Energy definition	0.5 %
Extraction mode	Slow > 2 sec flat top
Extraction interrupt	< 1msec
Intensity range	10** 6 to 10**8 particle / spill
Beam spot size	7 steps: FWHM 4- 10 mm
Beam spot stability	< 20% FWHM, achromatic focusing

For the irradiation of an extended target of 50,000 pixels, these features would result in a minimum irradiation time of approximately 5 seconds for an average target of one liter exposed to 2 Gy.
But a realistic exposure time is longer because based upon Poisson statistics at least 3 measurements have to be done at each pixel to make a decision. Additional time is needed for: (1) The data transfer between the control systems of the accelerator and the application system, (2) For the acceleration to the various energies, and (3) At the end of the extraction cycle when all magnets have to be ramped up into saturation to overcome hysteresis effects.

Finally, the number of ions requested for a pixel can vary by a factor of 20. But the particle flux could not be changed during the extraction and was fixed to low values in order to serve the low

fluence pixels correctly. Accordingly, longer extraction was requested to fill high dose points. All together, typical exposure times range between 2- 6 minutes for a target volume of 20, 000 – 50, 000 pixels but also depending on the geometry, i.e. how many energy slices are needed. The time needed to treat one fraction of about 10 minutes on average plays an important role for the estimation of the number of patients that can be treated in general at such a heavy ion therapy unit and consequently for the costs for each complete patient treatment of 20 fractions.

It was essential for the success of the GSI therapy project that all the different components for beam monitoring and application were developed and integrated into a unique control system that could be handled by the clinical crew who were accustomed to conventional therapy.*

Another critical point in preparing for patient treatment was the development and installation of an appropriate treatment planning system, which had two major components: (1) The dose shaping and (2) The determination on the biological effect in the different tissues.

At DKFZ, significant experience in treatment planning existed for precision therapy with photons such as Intensity Modulated Radio Therapy IMRT (W.Schlegel). From this all the "conventional" components of the planning like the segmentation of the target volume, etc. could be used. But because of the different physical interaction of ions compared to photons, a new dose kernel had to be developed at GSI (M. Kraemer). This treatment planning system for ion therapy (TRIP) was based on measured depth dose distributions, including beam fragmentation (D. Schardt) and the physical scattering both lateral and longitudinal (U. Weber). In order to obtain the local density in a complex target such as the head of a patient, the Hounsfield numbers of a corresponding CT image were converted into density maps using appropriate calibration curves measured with animal tissue (O.Geiss).

With these data the proposed dose distribution in the target volume could be optimized, but in contrast to conventional therapy or proton treatment, the same absorbed carbon dose can produce different biological effects when originating from ions of different energies or atomic numbers. Therefore, instead of absorbed dose for each penetrating ion, the biological effective dose has to be calculated, which is the absorbed dose multiplied by the relative biological effectiveness (RBE). For Bragg peak- carbon ions, the RBE can vary by a factor of two to four depending on the ions' kinetic energy and atomic number, but also on the tissue that is being irradiated. But the RBE stays close to one in the entrance channel at high velocities.

With decreasing energy the RBE increases towards the end of the ions' range in the Bragg peak. But the magnitude of the RBE depends on the biological characteristic of the cells. Cells that have a strong repair capacity and which are therefore very resistant against X-rays lose their repair advantage when irradiated with Bragg peak carbon ions yielding high RBE values. This behavior was the basis of the Local Effect Model LEM (M.Scholz) where the X-ray dose-response curve of specific cells or tissue is taken as a template on which the local doses inside a particle track are mirrored (see Figure 3). Thus a response curve to particle irradiation can be constructed and compared to the original X-ray response curve yielding the RBE.

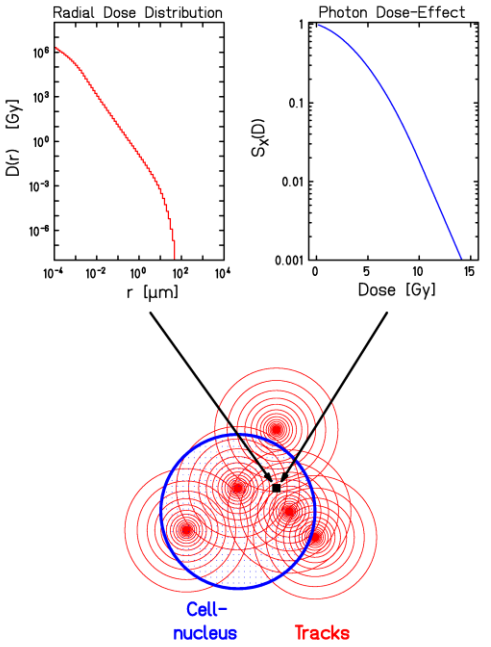

Figure 3. Principle of the Local effect model LEM: The cell nucleus is overlaid by a particle track according to the macroscopic dose wanted. The cell nucleus is divided in small compartments and the cell killing probability is calculated for each spot according to the measured dose effect curve of the same type of cells. Finally all probabilities are summed.

In the earlier ion therapies at LBNL and NIRS a fixed RBE value for the complete target field was used, which was taken from cell experiments or from the clinical experience of other high LET response like neutrons. At GSI, for the scanned carbon therapy a 3-D map of RBE values over the complex target volume is calculated using the LEM, where the template is the X-ray response of the specific tumor under treatment. In addition it is also possible to calculate in such a treatment field the expected normal tissue response in the entrance channel. In Figure 4 such an example of a dose distribution and the associated RBE map is given.

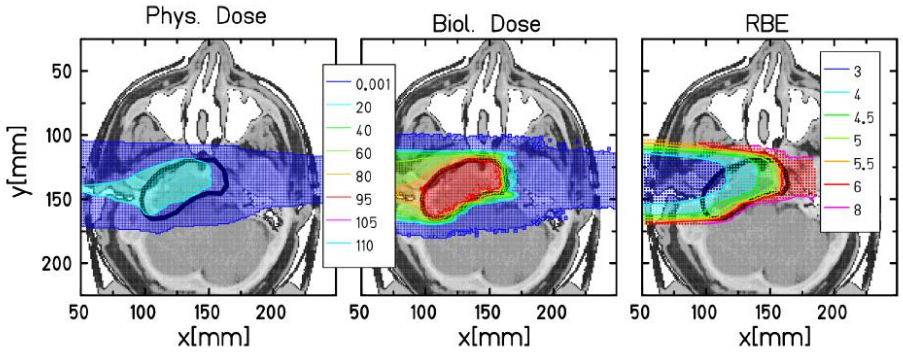

Fig.4 The biological effective dose (center) is the product of the physical absorbed dose (left) with the relative biological effectiveness (right)(courtesy Michael Kraemer, GSI)

Finally, a quality assurance (QA) system for the applied beam had to be developed and implemented. Because there was no template which one could copy and because beam delivery by scanning was so different from conventional practice, one had to develop a completely new QA system and to identify which parameters were critical to guarantee correct long-term results of the therapy. As outlined below, the QA program was based on a number of physical and biological measurements. Ultimately, however, a regime of frequent patient examinations was defined (daily, weekly and monthly) to observe and track response to the treatments. And finally we had to convince the administrative people in the government - mostly lawyers - that these QA procedures were adequate and sufficient. This convincing of the lawyers took two years to complete.

The physical measurements of the QA program had three principal topics:

- The measurement of the absorbed dose in a water phantom,
- The PET control of the stopping carbon inside the patient and
- The measurement of the biological effect in a biology target.

But there were also many additional measurements from the ion source to the gas pressure in the detectors that are not reported here.

The first part of the 3-D measurement of the absorbed dose in a water-phantom was a straightforward translation of techniques used by O.Jäckel, P. Heeg and C.Karger (DKFZ) to verify dose distributions of conventional precision therapy. In a water tank 24 thimble-ionization chambers were distributed over the target volume. The measured non-uniform density distribution inside a patient was converted into an equivalent water distribution and a complete irradiation field was generated to match the scaled water volume. The dose in each ionization chamber was then integrated over the irradiation time of a complete treatment. The main attention was given to the homogeneity inside the field and the field gradients to sensitive targets adjacent to the target. This method produces very solid information on the dose distribution but it always requires the irradiation of a complete field to obtain the information at each spot, so takes as long as the actual patient treatment. In addition, it yields information on the dose only, and not on the biological effect in the tissue.

In order to measure the biological effective dose distribution and to verify the RBE corrections that have been applied in the treatment planning, a biological test chamber was developed. In a 1- D version, Petri dishes were immersed in a tank filled with nutrient cell medium that keeps the cells alive. In a 2-D version, rods covered with cells replaced the Petri dishes. The treatment plan was then delivered to the tank and the survival of the different cell populations was measured with a colony-forming assay. These experiments are very difficult and time consuming because after irradiation, 50 - 100 cell samples have to be processed simultaneously under exactly the same condition. Secondly, cells have to grow after irradiation for one week before the

experiment can be analyzed. Thirdly, RBE is tissue-specific and therefore with this method the RBE calculation for specific cell types can be confirmed but not for the clinical situation. But if tests with many different cell lines and with animals confirm the validity of the RBE calculations, one can assume that LEM produces reliable RBE data for the clinical case. In general W.K. Weyrather and her group could reach an absolute accuracy of 10-20 %, which is within the experimental errors. The 10 year experience with patients has confirmed the correctness of these measurements.

The most innovative quality control was established by the Dresden / Rossendorf center under the leadership of W. Enghardt. For the first time, in situ PET measurements of the stopping beam distribution were performed on a routine clinical basis. A small fraction of the primary carbon 12 beam undergoes nuclear fragmentation yielding the lighter carbon 11 and 10 isotopes. These are positron emitters that decay with lifetimes of 20 min and 19 sec respectively, mostly stopping close to the Bragg peak of the primary beam.(Figure. 5). During treatment a PET-camera was placed over the treatment area and the location of the positron decay inside the patient could be monitored externally without applying an extra dose to the patient. The PET camera measured, at each fraction during the beam application and in the access time after the irradiation, the location of the stopping carbon isotopes. From this information, the quality of each fraction could be judged and possible errors in the beam application corrected. The in situ PET control quickly became a central approach in this experimental therapy, because after the end of each patient irradiation, one could determine the accuracy of the dose distribution.

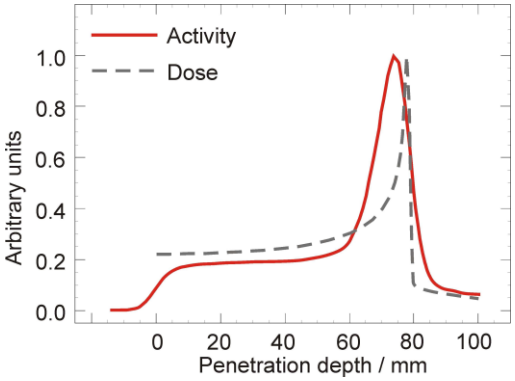

Figure 5 The dose distribution of a stopping carbon beam (dashed line) is compared to the ß+ activity (red) induced by the carbon ions. (Courtesy W. Enghardt , FZ Dresden)

In the very short time between May 1993 and December 1997 all these innovations for the therapy pilot project were developed and installed at GSI. From the beginning it was understood that therapy at GSI would operate for a maximum time of 5 years. In this time, a few hundred patients would be treated in order to evaluate and confirm the clinical advantage of carbon therapy. The agreement was that prolonging the project after this number of years would only occur if a clinical construction project at Heidelberg were underway.

Therapy in the Pilot Project 1998- 2008

On December 13, 1997, heavy ion therapy started at GSI and T. Haberer , head of therapy project group pressed the button for the first treatment A Saturday was selected to start with a boost treatment of five fractions for the first two patients, because one did not want to deal with the routine experimental and administrative rush at GSI. But when the first treatment of a patient was over, the space around the therapy cave filled with all the people who had worked so hard to make this treatment possible, and we celebrated this first success. The complete set of the planned five treatment days went well, but the next day one of the main transformers failed, causing a long break after this very first treatment. A few months later, therapy started again and was continued over 10 years with three therapy blocks each year of four weeks each. One week was needed for setting up the therapy mode parameters at the accelerator and three weeks for patient treatment. During all the 10 years the system ran very reliably and patients never needed to be sent home for a long period due to a machine failure.

During the treatment process, the patients either made the daily 60 km bus trip from Heidelberg or they stayed in a nearby hotel. But some of them used the time of treatment at GSI as a vacation in the nearby recreation areas or continued working in the afternoon after the daily treatment. In a very extreme case, one patient came by bicycle a few 100 km from Switzerland, stayed here during treatment and, after 20 fractions, returned home again on his bicycle. These examples illustrate that the patients supported the treatments extremely well.

The medical responsibility for the project was in the hands of the Heidelberg Radiology Department (M. Wannenmacher), and the patients were selected by Juergen Debus and his team from Radiology and DKFZ, who also provided medical care during and after the treatment. At Heidelberg the diagnosis was performed with CT and MRI scans, and if necessary with PET imaging. The treatment planning started in the conventional way with target segmentation and the designation of the possible entrance ports and organs of risk. This planning was done by the responsible physician and medical physicist at Heidelberg. Then these plans were completed at GSI with the biological optimization programs and translated into steering files for the scanner system (See Figure 6).

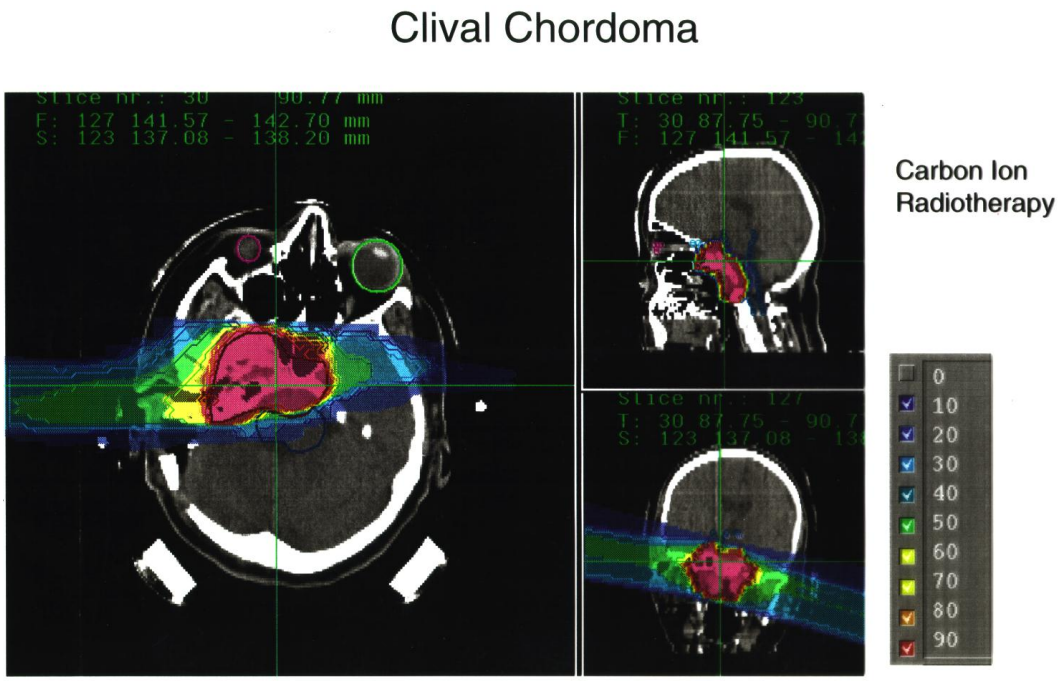

Figure 6. Treatment plan of two-field treatment in the head

Before the start of the pilot therapy project the question of the clinical fractionation scheme had been discussed in a workshop with leading experts from all over the world. From a hyper-fractionation scheme of 40 fractions to a hypo-fractionation scheme of less than five fractions, and all possible variations in between were proposed. Finally a slightly accelerated hypo-fractionation scheme of 18-20 fractions on 20 consecutive days, including weekends, was accepted and carried out for most of the patients. A small number of patients received a carbon boost treatment of 5-6 fractions during their conventional treatment at Heidelberg. For adenoid cystic carcinoma the carbon boost had a very significant effect and increased five-year tumor control from approximately 30% to 80%.

Patient treatment at GSI was focussed, in general, on slowly growing tumors of the head and neck, because a large benefit of carbon therapy compared to conventional therapy was expected. For these tumors the RBE for carbon treatment was calculated to increase by a factor of two to three in the tumor volume but not in the entrance channel. Accordingly, the total dose could be lowered, thus yielding a smaller dose in the entrance channel where the RBE increase stays close to one. The geometrical condition in the head is very complex and treatment planning was therefore difficult, but the head is easy to immobilize by using a thermoplastic mask technique developed at Heidelbergs DKFZ..

In all irradiations the PET analysis was applied routinely and discrepancies in the order of 2-3 mm could be detected in a few cases. For these very first treatments, the 3-D PET analysis of the field distribution was extremely valuable. Small misalignments or changes of tissue density due to local inflammations could be detected and corrected either with a better alignment or by applying a new treatment plan based on a new CT.

A main problem of these irradiations was to keep the fixation by the mask very tight in order to achieve high positioning precision. For the patients, the face mask is the major downside of the treatment. They normally did not experience any feeling of the beam, even in the brain. But there was one exception when stray ions entered the retina of the eye, and the patient saw optical artifacts, similar to those seen by astronauts in space. This phenomenon could be localized with a special setup. When the patients saw a retinal light flash they pushed a button and the scanner calculated the position of the beam spot inside the patient assuming a reasonable reaction time .

A similar technique helped to test the electronics for the Alpha Mass Spectrometer (AMS) installed later at the International Space Station(ISS). Many parts of the control system were irradiated at GSI by D. Schardt- some with a broad beam but some electronic components were exposed in Fischer´s micro-beam in order to correlate beam position and failures. The correlation between electronic failures like single event upsets and the actual irradiated pixel helped to localize weak points in the electronic control of the AMS spectrometer.

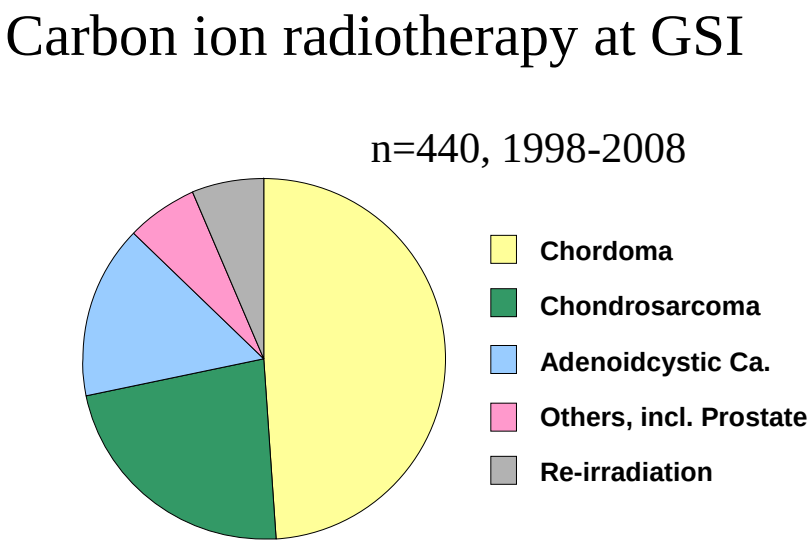

Figure 7. Distribution of the patients treated at GSI

During the 10 years of operation, the list of tumor types and locations was enlarged: from head and neck tumors to tumors along the spinal cord and to some prostate treatments. Because of biological reasons, but also because of the limited access to the beam, mainly slowly growing tumors like chordomas, chondro-sarcomas and meningiomas were treated. The distribution of the tumor types for all patients treated is given in Figure 7.

Since ion therapy was using very new and unconventional techniques, the first patients were treated as “test participants” not as real patients. They had to be included in studies and an insurance contract over 1 million DM had to be arranged individually for each patient. As no

insurance wanted to take over these risks, finally the German government had guaranteed the patients insurance for 30 years after treatment.

For all new tumor types clinical studies had to be performed. Usually a patient study consisted of two modalities, carbon and conventional irradiation with approximately 30 patients for each mode. Five years after treatment the studies were terminated and the carbon treatments of chordomas and chondro-sarcomas in head and neck became a medical standard in radio-oncology in Germany, and are reimbursed by the health insurance system.

Other treatments are still in the observation phase; 15 new studies have been started now at the Heidelberg Ion-beam Therapy HIT.
In the 10 years of operation many details of the carbon therapy were improved:

- The scanner system got an internal feedback loop which reduced the jitter for the beam spots < 0.2mm,
- PET analysis became faster and more precise,
- The treatment planning became faster and all the fields of one fraction are optimized together.
- This intensity modulated therapy (IMPT) reduced the radiation burden of critical structures that are partially surrounded by the target volume.
- In the LEM calculations of the RBE, radical interactions and diffusion as well as the interaction of strand breaks were included which taken together improved the dose accuracy for the normal tissue in the entrance channel.

In parallel the operation of the accelerator was improved dramatically. The beam quality and the time needed to produce high quality beams was improved, the beam extraction was smoothed and spikes reduced, the energy variation was accelerated, etc. GSI is an accelerator laboratory where after each treatment block the accelerator had to rapidly and reliably return to the stable treatment conditions (H. Eickhoff, U.Scheeler, P. Schütt). In addition new possibilities to improve the scanning speed by an intensity variable extraction or energy variation during the extraction were proposed and patented (K. Blasche). But it was not possible to include these novel features in the pilot project.

On July 16, 2008 the pilot project for tumor therapy was terminated at GSI and the last patient was irradiated. That young man suffered from a tumor in the brain, but the tumor underwent carbon treatment, expecting a 100% control. Figure 8 . That was an excellent result for this young man. Now 15 years after the start of therapy, the first group of 8 patients that received a full course of carbon treatment in July 1998 is still alive and healthy. According to conventional experience their 5 year life expectation was at approx. 50%

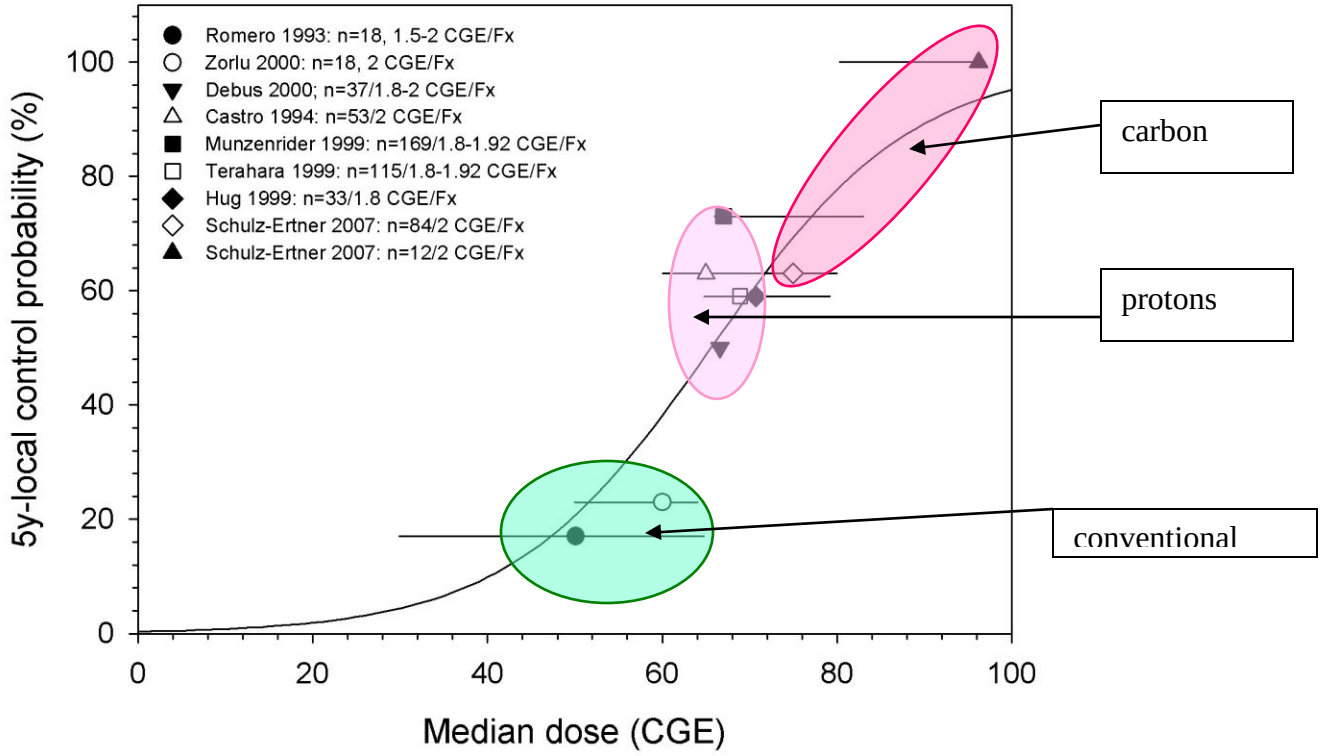

Figure 8. Comparison of the tumor control rates of chordomas for X-rays, protons and carbon

The Future Outlook

The GSI pilot project successfully introduced three new features into carbon therapy:

- Target conforming beam scanning
- Biology based treatment planning
- In vivo dose-control using PET techniques

Using these techniques it was possible to significantly improve the tumor control rates, even to 100% in some cases. (See Figure 8).

In 1998, parallel to the start of the Darmstadt pilot project, a proposal for the Heidelberg Ion-beam Therapy (HIT) was submitted to the government and was approved in 2003. HIT started operation in 2009 with both proton and carbon beams. Other projects in Europe were initiated: The Centro Nazionale Adrontherapia Oncologica CNAO, Pavia, Italy, which went into operation in 2012 and the MedAustron project in Wiener Neustadt which is under construction at this time.

In order to commercialize the innovations, GSI transferred know-how and the exclusive licenses of all GSI patents to the Siemens Company. Siemens wanted to develop and sell a standardized particle therapy system and was first involved in the HIT project with the construction of the beam application system (scanner and beam monitoring system at the patient) and the development of a unique treatment planning system. Siemens contracted for construction of combined proton/ carbon units for hospitals in Marburg(Rhoen-Klinikum-Ag.RKA) and Kiel (University Hospital), Germany and in Shanghai, (Fudan University)China. In 2011 when the Marburg machine should have been transferred to the RKA hospital, projections of patient flow through the unit were much smaller than anticipated (less than that was realized at GSI)Therefore ,RKA could not operate the system and Siemens decided to leave the field of radiotherapy completely. The already running accelerator at Kiel was to be dismantled, the Marburg unit is presently used as a prototype and test and development unit for the Shanghai project, which should go into operation in 2014.

However, the GSI innovations are included in all these facilities, especially beam scanning, which became a standard procedure not only for the Siemens accelerators. Also the Japanese heavy ion therapy community, which has three carbon units in operation and two in preparation, started to use beam scanning. But one has to admit that their system is more advanced than the GSI version.

Finally, the NIH has recently started tendering an offer for the optimal design of a carbon therapy facility, however as yet no construction projects have been initiated in the United States.

In summary, carbon- ion therapy using the advanced technique of beam scanning had a break-through in many countries, which was initiated by GSI, but growth of carbon facilities is much slower than initially expected.

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[*] The clinical crew was composed of the detector lab and electronics groups who worked on the pilot therapy project (K. Badura, H. Brand, H. Essel, J.Hoffmann, N. Kurz, M. Richter, K. Popensieker, W. Ott et al.)