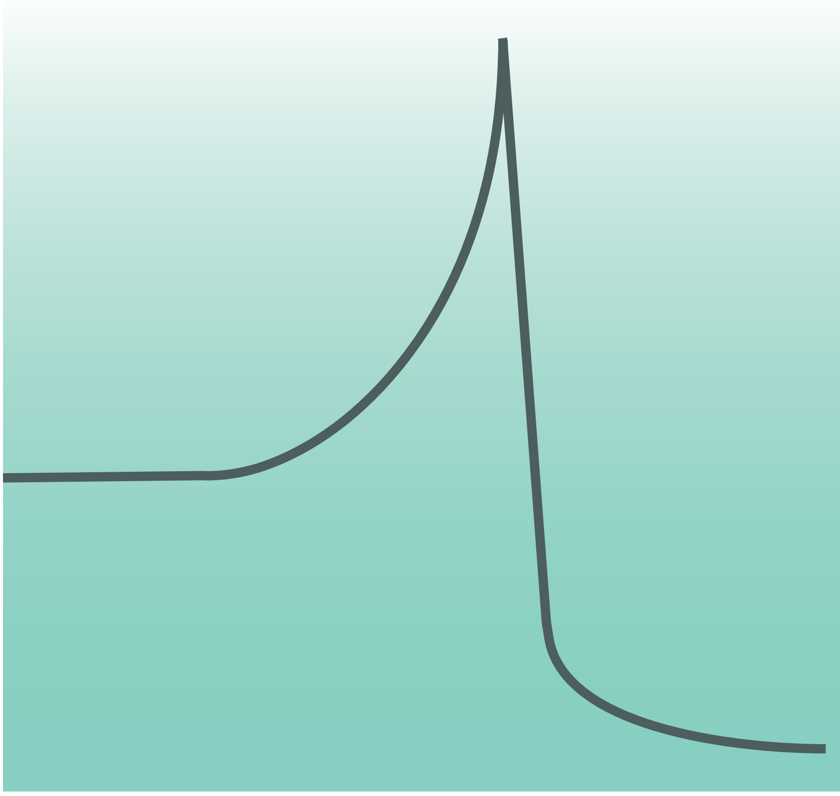
Construction of a Clinical Therapy Facility for Cancer Treatment with Ion Beams



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A PROJECT PROPOSAL

by the Radiologische Universitätsklinik Heidelberg (project leader), the Deutsches Krebsforschungszentrum Heidelberg (DKFZ) and the Gesellschaft für Schwerionenforschung, Darmstadt (GSI) in cooperation with the Forschungszentrum Rossendorf (FZR).

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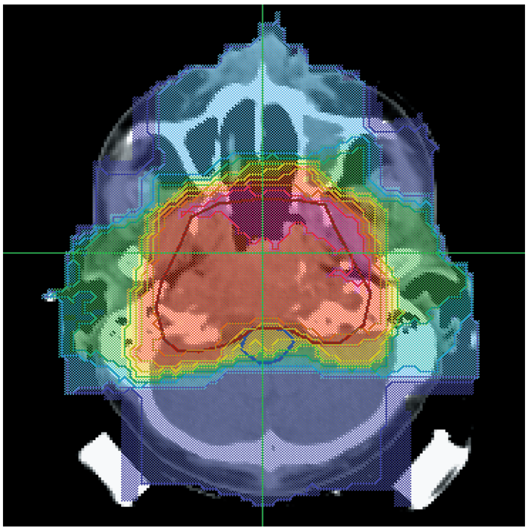
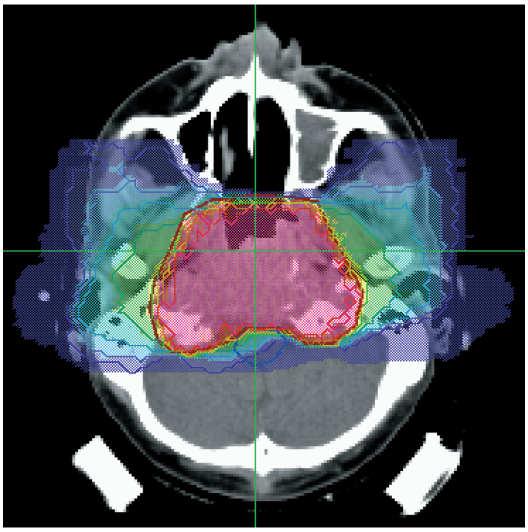
Advantages of Therapy Using Protons and Ions

The physical advantage

In the history of radiation therapy there are many examples of how cure rates have been increased through improvements in physical dose distribution and the resulting increase in feasible tumor dose. These examples include brachytherapy in gynecological tumors, stereotactic radiotherapy, and proton therapy in intraocular tumors. In deep-seated tumors, the change from orthovoltage x-ray therapy to high-energy electron accelerators has yielded a significant improvement in therapeutic results. In many cases, however, an exact fit of the irradiated volume to the target volume is impossible due to the physical characteristics of the gamma rays or electron-bremsstrahlung used in therapy: After a short build-up, the dose progressively decreases at greater depth. In a deep-seated tumor, the integral dose is therefore always lower than in the adjacent healthy tissues.

Beams of charged particles (protons or ions) produce a much more favorable dose distribution: For protons and ions, the delivered dose increases at greater depth, and then declines abruptly beyond a sharply defined maximum known as the Bragg peak. The location of this maximum in the patient's body can be precisely determined by the energy of the particles. In addition, protons and ions exhibit a small lateral and range scattering, which is another prerequisite for achieving a tumor conform treatment. These physical properties of charged-particle beams make it possible to substantially increase the tumor dose while at the same time reducing the integral dose in healthy tissues. This increase in tumor dose is the essential prerequisite for the improvement of curative success rates





Comparison of treatment plannings for photons with four treatment fields (top) and for ions with two treatment fields (bottom). The target area lies within the red outline. With ion irradiation, the dose distribution can be matched much more accurately to the tumor volume.

The sparing of healthy tissues is especially relevant in radiotherapy of children and adolescents, in whom successful therapeutic results are presently being achieved, and whose long life expectancy mandates that the risk of late sequelae and radiation-induced tumors be minimized.

Differences in physical dose distribution between protons and ion beams (helium, carbon, oxygen, neon and argon) result from two effects having opposite consequences: As the atomic number increases, both lateral scattering and range dispersion decrease, resulting in a more precise dose distribution. At the same time, however, the quantity of nuclear reactions in the tissue, in which mainly light fragments with a somewhat longer range are created, increases. As a result, the steep dose drop-off at the end of the range becomes unsharp. An optimum in overall dose distribution occurs between helium and oxygen.

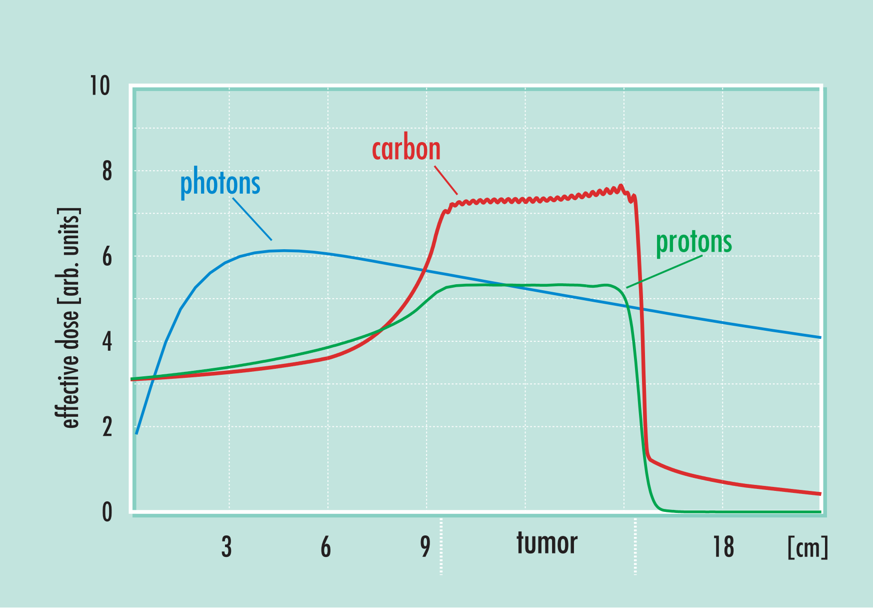
The biological advantage

In addition to the favorable physical dose distribution, a specific high-LET effect (as is also encountered with neutrons) becomes effective in the case of ions as distinct from protons: As the atomic number increases, the linear energy transfer (LET) in the cell increases sharply. In areas of especially high energy transfer, the biologically effective mechanisms are thereby changed.

This manifests itself by an increase of the relative biological effectiveness (RBE) that in turn allows higher curative success rates for well defined indications. Amongst these indications are hypoxic tumors, slowly growing tumors, and tumors being less or almost non-responsive to conventional photon therapy.

With lighter ions such as carbon or oxygen, this high-LET effect occurs mainly in the Bragg peak, while the repair capacity of cells in the entry zone—the so-called plateau—remains nearly unchanged, i.e. as is the case with low-LET irradiation (x-rays, gamma rays, electrons, protons).

Biologically effective doses for photons, protons and carbon ions. The increased energy deposition at the end of the particle track and the increased biological effectiveness render ions an outstanding tool for irradiating deep-seated tumors.



Compared to conventional radiation, protons and ions deposit a higher physical dose at the end of their range, i.e. within the tumor volume. In addition, ions exhibit an increased biological effectiveness. The advantage of protons compared to conventional radiation therapy has already been clinically proven for specific types of tumors. For selected indications, an additional increase in cure rates resulting from the high-LET effect is beeing expected, and has in part been clinically substantiated. These and other indications for the use of high-LET particle beams need to be evaluated in systematic clinical studies.

The State of Clinical Research

History and international development

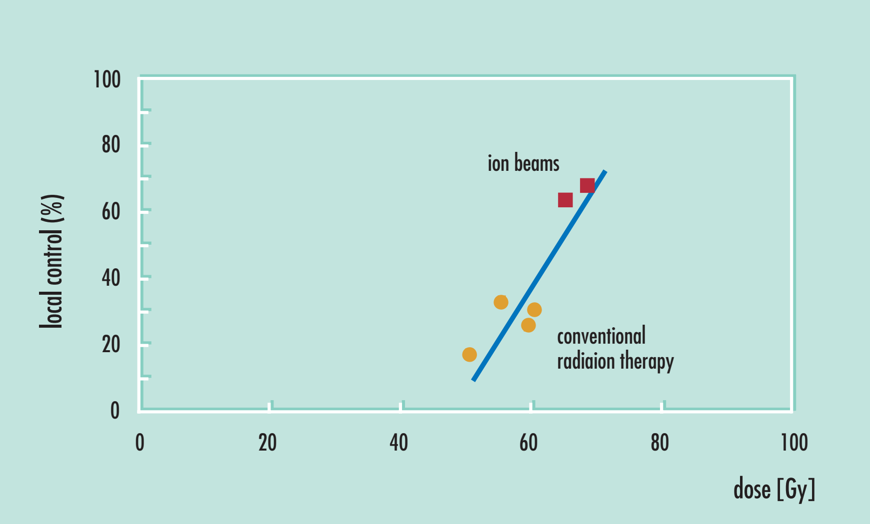
The use of protons and ions in radiation therapy of cancer patients is an approach that has been pursued since the mid-1950s. The pioneers in radiation therapy with protons and ions include the Lawrence Berkeley National Laboratory in Berkeley (protons, 1954, helium ions, 1957, carbon and heavier ions, 1975), the Harvard Cyclotron Laboratory (HCL) in Boston (protons, 1961), and the Institute of Theoretical and Experimental Physics (ITEP) in Moscow (protons, 1969). The clinical studies were initially conducted exclusively at research institutes for nuclear and particle physics, due to the availability there of suitable accelerator systems. In many locations this is still true today. In such facilities, logistical problems are common, as the environment is not primarily designed for medical requirements. Furthermore, availability of the ion beam for medical applications is not unrestricted, making it difficult to evaluate various indications with statistically significant numbers of patients.

To-date, approximately 25,000 patients have been treated worldwide with proton beams, and about 850 with ion beams. Particle therapy has been used especially in patients with inoperable tumors of the head and neck, or with pelvic tumors.

Harvard University in Boston plays a leading role in proton therapy. More than 7,500 patients have been treated there with a high degree of success using an old nuclear-physics cyclotron. A new, dedicated therapy facility is currently under construction in Boston.

At the Loma Linda University Medical Center in California, the first proton therapy system directly integrated into a hospital setting has been in use since 1990. This arrangement has worked out exceedingly well. At present, about 1000 patients per year are being treated with protons at Loma Linda. Because of the highly successful clinical results in both centers (for example, in treating prostate carcinomas) three additional centers for proton therapy are currently under construction in the U.S.A.

The cure rates of patients with tumors of the base of the skull are higher following irradiation with ions compared to conventional photon therapy, since a higher dose can be applied to the tumor. This has been demonstrated by clinical studies in the U.S.A. and Japan.



From 1975 through 1992, a total of 433 patients have been treated with ions—mainly neon—at LBL in Berkeley. Despite the non-perfect radiation treatment techniques, available at that time the clinical results were very promising. For specific indications, the tumor control rate was improved by a factor of two or even three, compared to conventional therapy. In 1994, the National Institute for Radiological Sciences (NIRS) in Chiba, Japan, started treating patients at the first dedicated facility for ion therapy. Here too, the concept of integrating the treatment unit and the hospital under one roof has been applied. To-date, some 400 patients have been treated with carbon ions. The resulting data concerning local tumor control (after 12 months) were so convincing that the construction of a second ion therapy facility has now been started in Hyogo. In addition, three proton facilities are in operation or being planned in Japan. A total of five particle therapy centres each will be in operation in the U.S.A. and Japan within a few years.

In Europe, a number of studies and activities concerning particle therapy of deep-seated tumors have been undertaken since the early 1990s. Since 1996, a modern proton machine has been in operation at the Paul Scherrer Institute in Villigen, Switzerland. And since late in 1997, the ion-beam therapy unit has been in operation at GSI in the context of

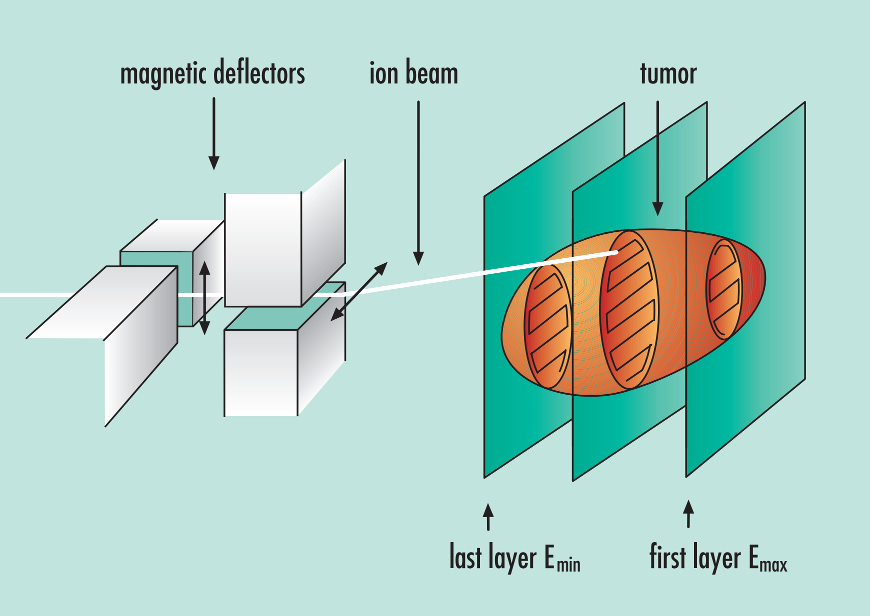
Overview of existing therapy facilities for treating deep-seated tumors with protons and ions. Worldwide there are more than 10 therapy systems for protons but only two facilities for ions. Only the U.S.A. and Japan have dedicated facilities integrated into hospital settings. Based on the good results of radiation therapy with protons and ions, additional facilities are scheduled to start operating this year in both countries. As yet there are no dedicated clinical facilities for particle therapy in Germany and Europe.

institution	particles	therapy since	patient number
LBL Berkeley, USA	protons helium heavy ions, mainly neon	1954 - 1957 1957 - 1987 1975 - 1993	30 2054 433
GWI Uppsala, Sweden	protons	1957	220
HCL Cambridge, Boston USA	protons	1961	7694
JINR Dubna, Russia	protons	1967	124
ITEP Moscow, Russia	protons	1969	3039
PINP St. Petersburg, Russia	protons	1975	1029
PMRC Tsukuba, Japan	protons	1983	576
LCUMC - Loma Linda, USA	protons	1990	3433
NAC Faure, South Africa	protons	1993	263
UC Davis, USA	protons	1993	162
NIRS Chiba (HIMAC), Japan	carbon ions	1994	389
PSI Villigen, Switzerland	protons	1996	11
GSI Darmstadt, Germany	carbon ions	1997	20

a pilot project for the presently proposed clinical facility. In addition to the new project proposed here—the construction of a clinical therapy facility in Germany—two other project proposals are currently underway in Europe: the TERA project in Italy and the MED-AUSTRON project in Austria. All European activities in particle therapy are being coordinated within PIMMS (Particle Ion Medical Machine Study) Study Group at CERN.

The results to-date of cancer treatment with protons and ions prove without doubt the superiority of particle therapy to conventional methods for specific indications. As a result of its high precision and the specific high-LET effect, radiation therapy with ions is recognized as the treatment of choice for slow-growing, inoperable, radiation-resistant tumors (e.g., chordomas and chondrosarcomas), especially in the vicinity of high-risk organs like the brain stem, optic nerve or spinal chord. To provide optimal treatment of these clinical indications and also to evaluate additional indications, Germany urgently needs a dedicated therapy facility for protons and ions that is directly integrated into a hospital setting.

The Pilot Project at GSI



Developed and first used in radiation therapy at GSI, the raster scan method makes it possible to irradiate tumors of any shape, however complex, while sparing the surrounding normal tissues.

To lay the groundwork for a clinical facility, a pilot project for tumor therapy using ion beams has been conducted since 1994 in the context of a joint project of the Radiologische Universitätsklinik, Heidelberg, the Gesellschaft für Schwerionenforschung, Darmstadt, and the Deutsches Krebsforschungszentrum, Heidelberg, in cooperation with the Forschungszentrum Rossendorf. During four years of construction, a radiation therapy unit was installed at the GSI heavy-ion synchrotron. In December 1997, the first two patients were treated with ion beams at this facitlity—the first such treatments in Europe.

Several innovations were implemented during the course of this project. These include the intensity-controlled raster scan method for tumor-conform dose delivery, the use of positron emission tomography (PET) for the direct monitoring of the beam in the patient, and the development of a treatment planning system adapted to the special properties of particle beams.

The intensity-controlled raster scan method

Tumor-conform irradiation can be achieved with protons and ion beams by steering the charged-particle beam laterally by means of magnetic fields, and by adjusting the penetration depth through the energy of the ions. The irradiation method developed at GSI is unique worldwide, and represents a key technology for the optimal use of proton and ion beams. In this method, the tumor volume is subdivided into layers of equal depth. By varying the energy of the ions, the penetration depth of the beam is adjusted. The individual layers are scanned line by line, similar to the image on a TV screen. The lateral deflection of the beam is achieved by means of rapidly controllable dipole magnets. To control the intensity, each line is subdivided into pixels. The beam remains in a given pixel until the calculated target dose has been reached. As a result, this method of intensity-controlled raster scans allows a precise three-dimensional scanning of the target volume defined by the physician. This approach represents a significant improvement over conventional treatment methods with photons, as well as over passive beam application techniques previously used in proton and ion beam therapy.

Online therapy monitoring

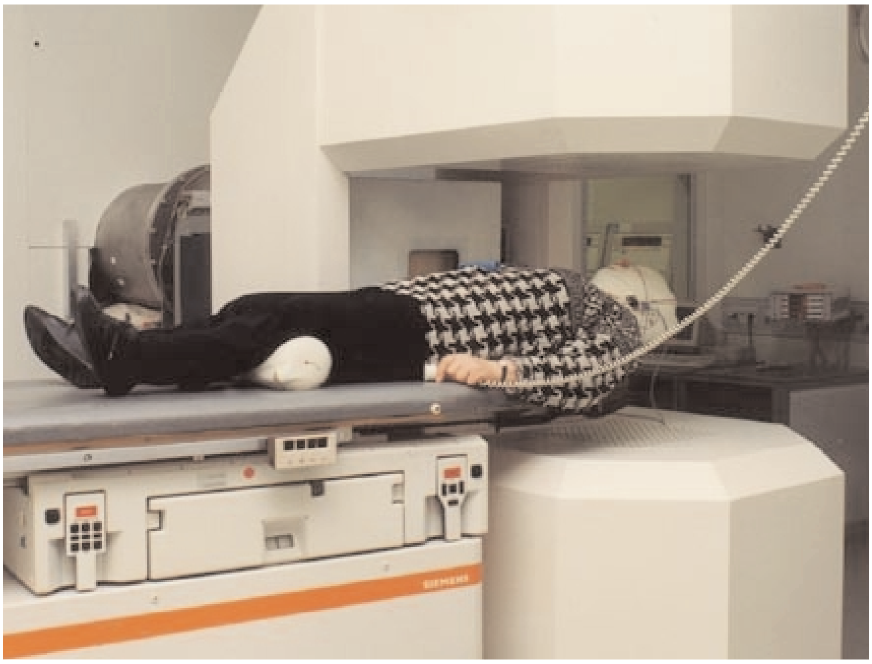
A special feature of therapy using ions is the possibility to check the position of the delivered beam within the patient's body “online”—i.e. directly during the treatment. To exploit this possibility, the technique of positron emission tomography (PET) was further developed at the Forschungszentrum Rossendorf for use in ion therapy. On its path through the tissues, a small proportion of the ion beam is converted into positron-emitting isotopes. In the case of carbon as a therapeutic beam, mostly lighter carbon isotopes having practically the same range are generated. The positrons emitted by these isotopes have a very short range of only a few millimeters, and upon encountering an electron they emit two characteristic gamma quanta at an angle of 180° with respect to each other. These gamma rays are imaged by a special PET camera, providing information about the position of the delivered beam within the body. By reconstructing the PET signals, the activity distribution can be compared with target values established in the treatment plan, which further enhances the safety of the patient. Also this direct monitoring of the therapeutic beam using PET is a worldwide first in particle therapy.

Patient positioning and safety

In addition, the stereotactic methods developed at the DKFZ for patient positioning have been adapted to meet the requirements of particle irradiation. To achieve highly reproducible positioning throughout the entire course of therapy of twenty treatment sessions, an individual head mask with characteristic reference lines is fashioned for each patient. This mask is firmly mounted to a patient couch which can be rotated and translated in all three coordinate directions. Once immobilized by this system, the patient is then positioned on the moveable table into the treatment position as defined by a stationary laser coordinate system. The accuracy of positioning is verified by means of x-ray images in two orthogonal projections. Only when the position is exact to a millimeter the treatment will start.

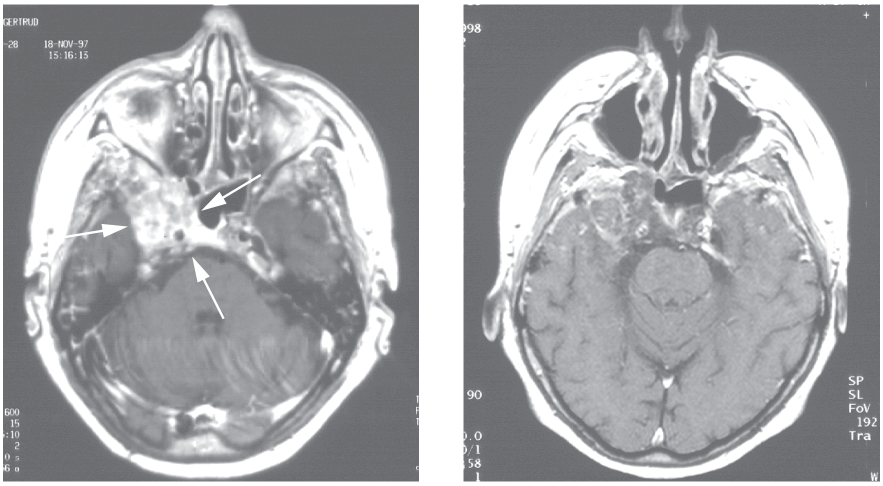
The monitoring and control system of the entire facility meets the highest safety standards. The position and intensity of the beam, for example, are measured 10,000 times per second. In the event of a deviation from the planned values, the radiation treatment is terminated within half a millisecond—a small fraction of the fastest possible human response time. All monitoring and checking devices are redundant and operated independently of each other. Even during a total failure of all beam transport and deflection systems, the ion beam would never strike the patient, but pass harmlessly above.

Within the pilot project at GSI, the first patients were irradiated with carbon ions in December 1997. During the treatment the patient's head is positioned exact to a millimeter by a mask mounted to the patient couch.



The newly developed intensity-controlled raster scan method allows for proton and ion beams a dose application with a previously unattainable degree of precision. This facility allows an optimal utilization of the physical and biological advantages of heavy charged particles. For ion beams, the use of PET provides the additional opportunity of monitoring the beam position and dose distribution during the treatment. The new radiotherapeutic technique moreover includes very precise patient positioning systems as well as comprehensive control and monitoring systems to guarantee the patient's safety throughout the entire treatment.

Example of the course of disease in a cancer patient after carbon ion therapy. It can be seen that the tumor diagnosed before the treatment (left) at the base of the skull (histology: chordoma) has rapidly responded following ion irradiation (right).



Successful start of clinical studies

In December, 1997, the first two patients with radiation-resistant tumors in the brain stem region were treated with four or five fractions of carbon ion radiation respectively, integrated into a course of conventional photon therapy. These radiation treatments were completed successfully and demonstrated both the applicability of the new irradiation method and the precision and reliability of the overall system. The clinical results of both treatments are exceedingly favorable and promising. Although only a portion of the therapy was conducted with ion beams, a surprisingly rapid tumor regression was noted in both patients.

Since August, 1998, clinical studies have been formally started in the context of the overall project. To-date, a total of twenty patients have been treated with ion beams at GSI. In the next five years, several hundred patients with inoperable tumors of the brain and at the base of the skull are scheduled to be treated with ion beams, to conduct clinical studies with the new irradiation method and to verify ion therapy as the method of choice for specific indications, over conventional radiation therapy. In addition, the experience gained in the pilot project—both with respect to apparatus and the clinical aspects—is intended to flow directly into the presently proposed project of a dedicated therapy system in a hospital setting.

The applicability of the newly developed radiation therapy method has been successfully demonstrated by the clinical studies started at GSI. The treatment results to-date are impressive. However, no more than 50 to 70 patients per year can be treated at the GSI facility. The proposed therapy facility integrated into a hospital setting represents the logical extension of this work, with the aim of creating a clinical base in Germany for therapy with particle beams.

The Clinical System

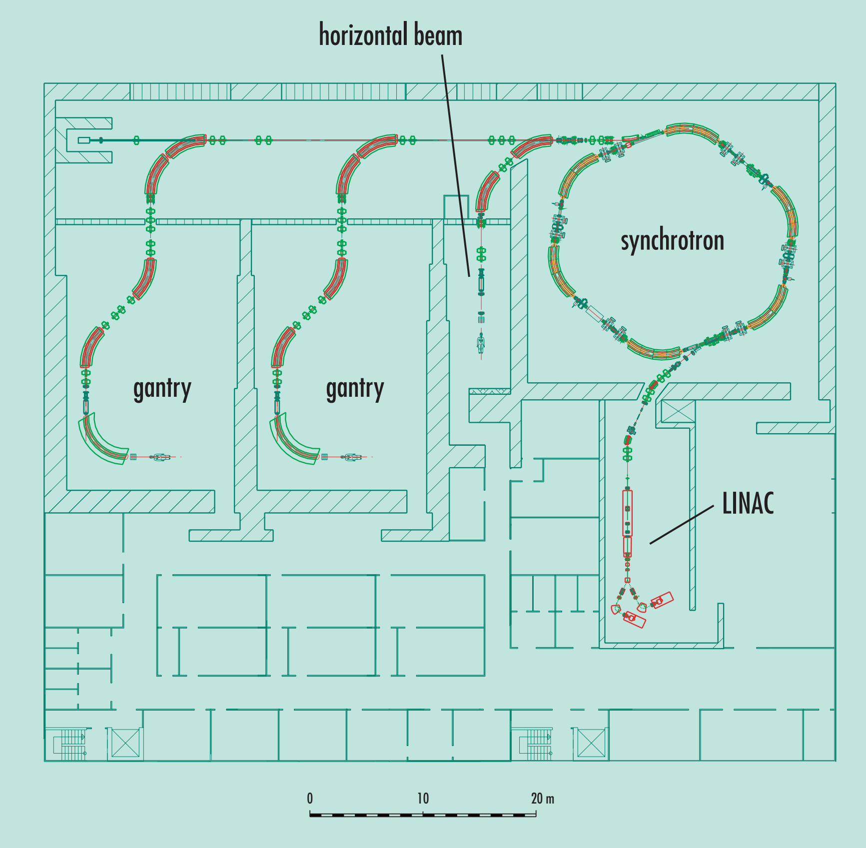
From the very start, the pilot project at GSI included a design study for a dedicated therapy accelerator intended to evolve into the present project proposal for a clinical facility. The plan for this clinical machine is detailed in a separate Technical Proposal. The following is an overview of its basic design and essential specifications.

The intent is to build a therapy facility capable of providing protons as well as a variety of clinically interesting ions (helium, carbon, oxygen). This flexibility will allow comparative clinical studies in the field of particle therapy, i.e. of the role of ions versus protons for well defined indications. The facility is intended to accommodate about 1,000 patients per year.

The intent in the medical use of the therapy facility is to focus on treating mainly those tumors where no satisfactory treatment has been available to-date. These especially include inoperable tumors of the base of the skull and of the brain, soft-tissue sarcomas, and prostate carcinomas. In addition, the intent is to treat those conditions in which the risk of late effects is very high, for example in tumors among children and adolescents. Such complex therapeutic strategies, some of them in the context of multimodal therapy regimens, absolutely mandate the integration of the system into a hospital environment.

Thereby, the proposed therapy facility will be a first important step in closing the gap existing in Germany and Europe concerning the use of particle beam therapy in patient care. In addition, the attainable patient throughput permits the rapid and efficient completion of statistically valid studies of potential additional indications.

Plan of the proposed clinical ion beam facility, which comprises a synchrotron feeding three treatment rooms, two with a gantry and a third with a horizontal beam pipe.



The planned therapy system will be housed in a building covering an area of 70 x 60 meters. The heart of the facility is the therapy accelerator, comprising a compact linear accelerator as injector and a synchrotron for the acceleration to the desired final energy, which is variable from pulse to pulse. On the injector side, state-of-the-art developments are being exploited in the areas of ion sources and accelerator structures (ECR ion sources and RFQ/IH Linac). After acceleration to the synchrotron injection energy of 7 MeV per nucleon, the ions pass through a stripper foil where the entire electron shell is stripped off. In the synchrotron—which has a diameter of about 18 m and a magnetic rigidity of $B \cdot \rho = 1.0$ to 6.6 Tm—the particles are accelerated to the desired therapeutic energy, from 50 to 430 MeV per nucleon. This corresponds to a penetration depth of the particle beams from 2 to 30 cm.

The synchrotron feeds into a beam transport system which guides the ion beam into three different treatment rooms. One room provides a horizontal beam, the two others will be equipped with a gantry system allowing rotation of the therapeutic beam about the patient. The gantry systems allow further optimization of treatment planning, especially for patients with tumors in the trunk. Their construction is a new area of technology. Special challenges are posed by the integration of the raster scan method—which is indispensable for a precise dose application—within the gantry, and by the adaptation of the PET method of beam monitoring to a rotational beam transport system. With the exception of the gantry system, for which in the meantime a complete design has been developed at GSI, the know-how for all other systems already exists among the project partners or has been developed in the context of the pilot project. This applies in particular to the raster scan method, PET beam monitoring and patient positioning as well as to safety and monitoring systems.

particles	protons, $^{4}\mathrm{He}^{2+}$, $^{12}\mathrm{C}^{6+}$, $^{16}\mathrm{O}^{8+}$
accelerator type	synchrotron
beam energy	50 - 430 MeV per nucleon
beam intensity (ions per synchrotron pulse)	protons : 4×10^{10} helium ($^{4}\mathrm{He}^{2+}$) : 1×10^{10} carbon ($^{12}\mathrm{C}^{6+}$) : 1×10^{9} oxygen ($^{16}\mathrm{O}^{8+}$) : 5×10^{8}
treatment rooms	two rooms with gantry systems; one room with firmly installed horizontal beam transport system
beam application method	active energy and intensity variation from the accelerator plus rasterscan process
gantry	isocentric geometry, barrel-type gantry, can be rotated 360°, with integrated rasterscan in front of the last deflection magnet
online PET control	yes
patient number per year	1000

Technical specifications of the proposed therapy facility

Implementation and schedule

The technical specifications are summarized in a separate Technical Proposal. The implementation and commissioning will be undertaken in cooperation with competent industrial partners. A site in the immediate vicinity of the Radiologische Universitätsklinik and the DKFZ has been proposed for the location of the clinical facility.

Project management will be the responsibility of the Radiologische Universitätsklinik, Heidelberg, which will also coordinate the implementation of the construction.

The DKFZ will be responsible for treatment planning, dosimetry, patient positioning, and patient safety. GSI has developed a complete design for the therapy facility, comprising the accelerator, beam transport and attached gantry systems, and will be responsible for its implementation in cooperation with industrial partners.

The Forschungszentrum Rossendorf will be in charge of adapting the PET system used for beam monitoring to the requirements of the gantry system.

Five years must be allowed for the construction of the system up to the first patient treatment. This period contains a one-year planning and development phase, a three-year construction phase, and a one-year commissioning phase including all safety checks and required approvals. Assuming a start of the development work in 1999, Germany’s and Europe’s first clinical facility for particle therapy could begin treating patients in 2004.

Costs and financing

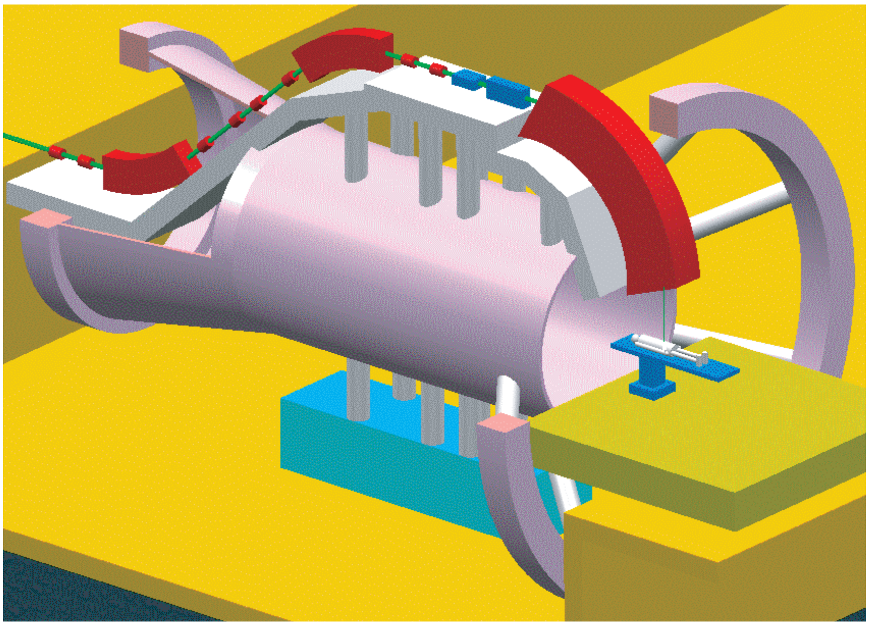
The construction of the clinical facility will require DM 110 million in funds for capital expenditures. About DM 77 million of this will be needed for the accelerator complex including beam transport system and treatment rooms, and DM 33 million for the building including furnishings.

The proposed system design allows the acceleration of protons as well as ions. Because of their high precision and increased biological effectiveness, however, ions are of special therapeutic importance. Compared to a machine for protons only, the ion option calls for a more costly configuration of the accelerator system and the downstream beam transport system. In the proposed system, these requirements amount to additional costs of about 25 percent in terms of capital investments. In the subsequent operating costs, which will decisively influence per-patient treatment costs, the difference amounts to 10 percent to 15 percent. Thus, a large gain in therapeutic and scientific possibilities from a configuration for both proton and ion therapy, is achieved for a low additional cost.

The financing of the facility will be obtained largely through bank credits that will be paid back from subsequent patient revenues. To get the project started, an application has been submitted to the Strategiefonds of the Helmholtz-Gemeinschaft deutscher Forschungszentren (HGF) for DM 10 million for capital expenditures, and for 15 scientific and engineering positions. These funds will allow important R&D work for the new project to go forward. The focus of this work will be on the development and clinical implementation of multifield ion therapy, comprising a gantry system with integrated raster scan and PET, as well as the associated, biologically optimized treatment planning.

The treatment cost per patient should be set so as to cover the personnel costs for about 75 positions to be newly created plus all operating costs including payback of the credits obtained for the financing. Given a capacity of 1,000 patients per year, this amounts to an average treatment cost per patient of about DM 40,000. This is comparable to the costs entailed by major surgical or pharmaceutical treatment methods. The figure is far lower than the amounts reimbursed by health insurance companies for costs arising from referral of cancer patients to radiation clinics in the U.S.A. or Japan. Consequently, the project not only closes a healthcare gap; given the relatively moderate treatment costs and especially in view of the attainable increase in cure rates for a group of conventionally untreatable patients, the project contributes to a reduction rather than a further increase in healthcare costs.

The new project also includes the development and implementation of a gantry system for ion beams that allows rotation of the beam application system about the patient. This is particularly important in tumors of the trunk. The gantry system can be rotated 360° about the patient, and has a radius of nearly 6 meters and a total weight of 160 metric tons.



The object of the new project is the construction of a clinical ion beam therapy system that will be an international technological trendsetter. This facility will close a medical care gap in Germany for established indications and will also allow the evaluation of new indications in large-scale clinical studies. The clinical therapy facility can be constructed in five years by the participating institutions in cooperation with industry. The required funds for capital expenditures in the amount of DM 110 million can be refinanced through the subsequent patient revenues. To operate the facility at a break-even level, average treatment costs are set at DM 40,000 per patient.

The Project Partners

The implementation of the project will be managed by the Radiologische Universitätsklinik through the participating institutes in close cooperation with industrial partners.

The Radiologische Universitätsklinik, Heidelberg, Department of Clinical Radiology (Schwerpunkt: radiation therapy), is one of Germany's largest radiation therapy centers, with about 2,800 new patients per year. In addition to patient care, a broad research program in the area of radiation oncology is pursued at Heidelberg. The clinical studies of ion beam therapy in the context of the pilot project are also being conducted under its management.

The Deutsche Krebsforschungszentrum in Heidelberg, with a focused program on radiological diagnostics and therapy, is the center of internationally renowned research and development in the field of leading-edge techniques in radiation therapy. Here, major scientific achievements have been made in the field of three-dimensional treatment planning and precision radiotherapy, including dosimetry and quality assurance. The new therapeutic methods are developed and clinically tested in the Clinical Cooperative Unit for Radiotherapeutic Oncology, in conjunction with the Radiologische Universitätsklinik.

The Gesellschaft für Schwerionenforschung in Darmstadt is among the internationally leading centers of heavy-ion research. More than 1000 scientists from over 30 countries currently conduct research at its accelerator facility. Since its establishment, GSI has also been conducting studies in radiation biology, especially concerning the radiobiologic effects of ions. In addition, there is abundant expertise in the areas of accelerator technology and the development of highly precise irradiation methods. With the SIS heavy-ion synchrotron, GSI currently has at its disposal the only accelerator system in Europe where patients with deep-seated tumors can be treated with ions.

The Forschungszentrum Rossendorf near Dresden conducts basic and applied research in the fields of materials research, biomedicine and biochemistry, environmental research, as well as nuclear, hadron and radiation physics. The planned clinical facility will especially benefit from this institute's in-depth expertise in the biomedical application of positron emission tomography (PET).

Within of the pilot project, the project partners have developed new, trendsetting methods that represent key technologies for the proposed therapy system as well as future projects. This groundwork—in combination with the expertise of the participating institutes in various areas of particle therapy—represents an ideal basis for a successful completion of the new project, jointly with industrial partners. In view of the European and international demand level for such therapy systems, the project represents a substantial business opportunity for industry.