Tumor Therapy with Heavy Ions at GSI Darmstadt

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Abstract. In comparison to conventional photon therapy heavy-ion beams offer favourable conditions for the treatment of deep-seated local tumors. The physical depth-dose distribution in tissue is characterized by a small entrance dose and a distinct maximum (Bragg peak) near the end of range with a sharp fall-off at the distal edge. The well-defined range and the small lateral beam spread make it possible to deliver the dose with millimetre precision. In addition, heavy ions have an enhanced biological effectiveness in the Bragg peak region, which is caused by the dense ionization and the resulting reduced cellular repair rate. Furthermore, heavy ions offer the unique possibility to apply Positron Emission Tomography (PET) techniques for an in-vivo range monitoring of positron-emitting isotopes like ^{11}C which are formed in nuclear fragmentation reactions. The pilot therapy unit at GSI started operation in December 1997 using ^{12}C ions with energies of 80-430 MeV/u from the heavy-ion synchrotron SIS-18 and a novel fully active rasterscan system for beam delivery. So far more than 260 patients were treated with very promising clinical results. The indications comprise mainly inoperable and radio-resistant tumors of the skull base (chordoma, chondrosarcoma and others) which are located near sensitive organs such as the brain stem or the optical nerve. The treatments with a median tumor dose of 60 Gye delivered in 20 fractions were well tolerated and no significant side effects occurred. Local tumor control rates after three years follow-up time were 100% for chondrosarcomas and 81% for chordomas. The construction of a new dedicated proton/ion treatment centre (HIT) at the Radiological Clinic in Heidelberg with a planned capacity of more than 1000 patients per year has started in spring 2004. It will be equipped with one 360° isocentric Gantry system and two additional treatment rooms with horizontal beam lines. Clinical operation is expected to begin in 2007.

1. Introduction

Radiotherapy (with photons or particles) plays an important role in the treatment of cancer. Nowadays it is the most frequently and most successfully applied form of therapy after surgery and more than 50% of all patients with localized malignant tumors are treated with radiation. In radiotherapy the key problem is to deliver the dose in such a way that ideally the intended target volume receives 100% of the planned dose needed to kill all cancer cells in the tumor, while the surrounding normal tissue does not receive any dose. This can not be achieved in practice because of the unavoidable dose deposited in the entrance channel of the irradiation but in the past 50 years much progress has been made to improve the dose deposition towards the ideal and to increase thereby the tumor control rate for potentially curable cases. The contribution of GSI Darmstadt presented in this paper is the development of highly tumor-conform irradiation techniques using ^{12}C ions from the accelerator SIS-18. These achievements would not have been possible without the strong and fruitful interdisciplinary collaboration of scientists in the fields of oncology and radiation medicine, radiation biology, accelerator technology and engineering, as well as atomic and nuclear physics.
The application of high-energy beams of **heavy charged particles** to radiotherapy was first considered in 1946 when Robert R. Wilson investigated the depth dose characteristics of proton beams (primarily for shielding purposes). He recognized the potential benefits of proton beams and predicted "...that precision exposures of well defined small volumes within the body will soon be feasible" [1]. Two years later the 184 inch synchrocyclotron at LBL Berkeley became available for experiments and the physical and radiobiological properties of proton beams were thoroughly investigated by Tobias and co-workers [2]. Patient treatments

started in 1954 at LBL Berkeley, first with protons and later with helium beams. Radiotherapy with heavier ions was initiated by Tobias et al. [2,3] at the BEVALAC facility at LBL. There most of the patient treatments (1975-1992) were performed with beams of ^{20}Ne (670 MeV/u) which at that time appeared to be most attractive because of their high relative biological effectiveness (RBE) combined with a low oxygen enhancement ratio (OER) in the treatment target volume. The beams were delivered to the patient by passive beam shaping systems, including scattering devices and wobbler magnets for broadening the beam and a number of passive elements like ridge filter, range modulator, collimator and bolus [4]. Until its closure in 1992 the BEVALAC was the only facility worldwide using heavy ions for the treatment of localized deep-seated tumors. In 1994 the heavy-ion medical accelerator HIMAC [5] dedicated to radiotherapy started with carbon ions at NIRS Chiba (Japan), using similar technical concepts as those pioneered at Berkeley.

At GSI Darmstadt (Germany) a new concept [6] was developed, differing significantly in two aspects from the previous designs at the BEVALAC and HIMAC: (i) moving a narrow pencil beam with controlled intensity over the target volume (intensity-modulated raster scan) a tumor conform treatment can be achieved to a high degree, restricting the biologically most effective ions to the target volume and minimizing the dose to the surrounding normal tissue. A similar method for proton irradiations has been developed at PSI (Switzerland) [7]. In spite of the demanding technical concept the fully active raster scan system has proven to operate reliably since the first patient treatment in December 1997. (ii) The unique treatment planning system TRiP [8,9] developed at GSI takes into account individually for each voxel the large variation of biological effectiveness of the carbon ions across the irradiated volume (biological dose optimization).

Within the **Heavy-Ion Therapy Collaboration** three other institutes take care of various parts of the project: The Radiological Clinic University Heidelberg (all clinical aspects such as patient selection, diagnostic, dose calculation), the German Cancer Research Center DKFZ Heidelberg (patient immobilization, treatment planning, dosimetry), and the Research Center FZ Rossendorf near Dresden (PET irradiation monitoring). Up to date more than 260 patients, most of them with tumors in the skull base region, were treated with carbon beams at GSI.

2. Physical and Radiobiological Aspects

The major physical advantage of heavy charged particles as compared to photons is their characteristic depth-dose profile – the well known Bragg curve – named after Sir William Henry Bragg who investigated the energy deposition of α-particles in air in the beginning of the last century. Whereas the photon dose decreases exponentially with penetration depth according to the absorption law for electromagnetic radiation, the depth-dose profile of charged particles exhibits a flat plateau region and a distinct peak near to the end of range of the particles. This is a consequence of the interaction mechanism of the particles in the slowing-down process as described by the Bethe-formula which shows a $1/\beta^2$ dependence of the specific energy loss dE/dx. At high velocities $\beta\ (\equiv v/c)$ the projectiles loose small amounts of energy in a large number of quasi-continuous inelastic collisions with atomic electrons of the absorber material. The specific energy loss is at a maximum (Bragg peak) when the projectile reaches the Bohr velocity $v_B = e^2/\hbar$. Carbon ions applied for the treatment of deep-seated tumors have initial energies of about 80 – 400 MeV/u corresponding to velocities β = 0.4 to 0.7. Depth-dose profiles of ^{12}C ions in water measured at various entrance energies are shown in Fig.1.

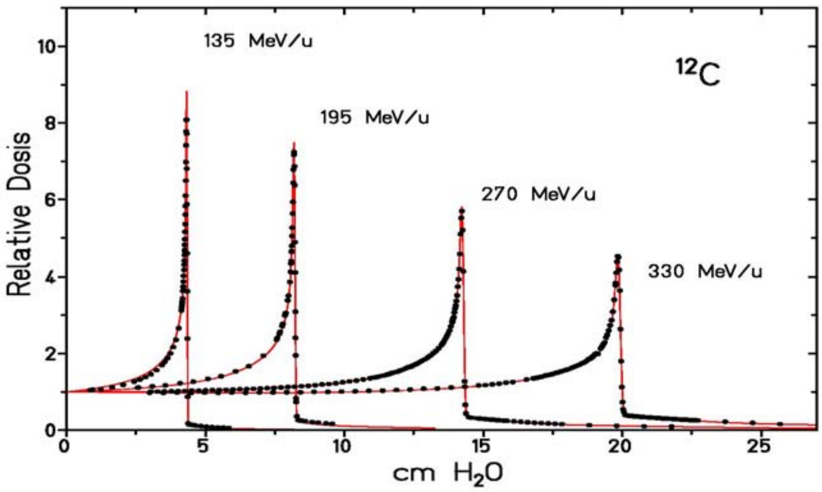

FIG. 1. Measured depth-dose profiles of high-energy carbon beams in water [10].

The peak-to-entrance dose ratio is highest for low energies and decreases towards higher energies. This is partly due to straggling effects which cause a broadening of the sharp Bragg peak at larger depths. Another important effect is nuclear fragmentation along the penetration path which may cause a significant alteration of the radiation field. The most frequent nuclear interactions are peripheral collisions where the beam particles may loose one or several nucleons. The projetile-like fragments continue travelling with nearly the same velocity and direction. Fragmentation reactions lead to an attenuation of the primary beam flux and a build-up of lower-Z fragments with increasing penetration depth. As the range of the particles scales with A/Z^2 the depth-dose profile of heavy-ion beams shows a characteristic fragment tail beyond the Bragg peak (Fig.2).

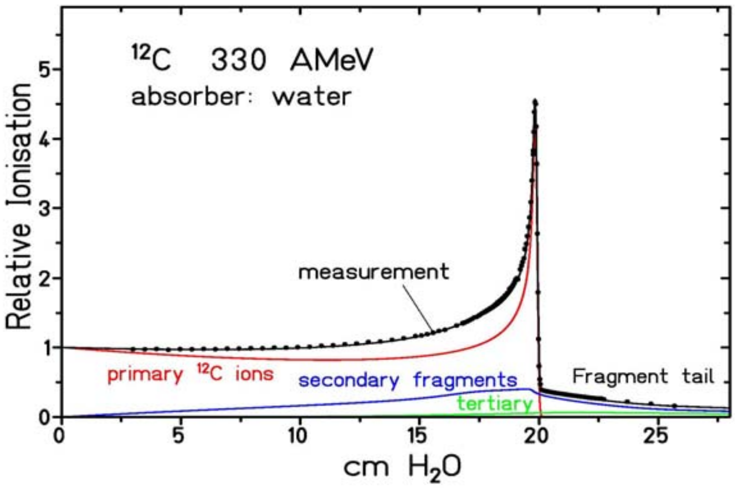

FIG.2. Bragg curve for 330 MeV/u ^{12}C ions in water measured at GSI with large parallel-plate ionization chambers. The data points are compared to a model calculation [11] (solid line). The calculated contributions from the primary particles (red line) and from nuclear fragments (blue line) are also shown.

The production of nuclear fragments as a function of penetration depths in water and their angular and velocity distributions were experimentally investigated for ^{20}Ne beams at LBL Berkeley [12] and for various primary beams (^{10}B, ^{12}C, ^{14}N, ^{16}O, ^{20}Ne) [13-15] at GSI. Similar studies were performed at HIMAC/Chiba [16].

The composition of the particle field at a given penetration depth is important for the estimation of the biological effect as an essential requirement for treatment planning. The radiobiological effectiveness of charged particles is mainly characterized by their local ionization density which can be directly correlated to the local density of DNA damage. As a result of extensive irradiation experiments with cell cultures at LBL, NIRS and GSI it was found that carbon beams meet the therapy requirements best possible [17,18]. At high energies in the entrance region carbon ions have a sufficiently low ionization density and act like photons, producing mostly repairable DNA damage. Towards the Bragg peak the ionization density increases significantly, resulting in irreparable damages and high cell killing power. These findings were confirmed by measuring cellular and molecular damage and repair along therapeutic beams [19]. As an example, cell survival curves measured at GSI are shown in Fig.3 for ^{12}C ions at various energies and in comparison with X-rays [18].

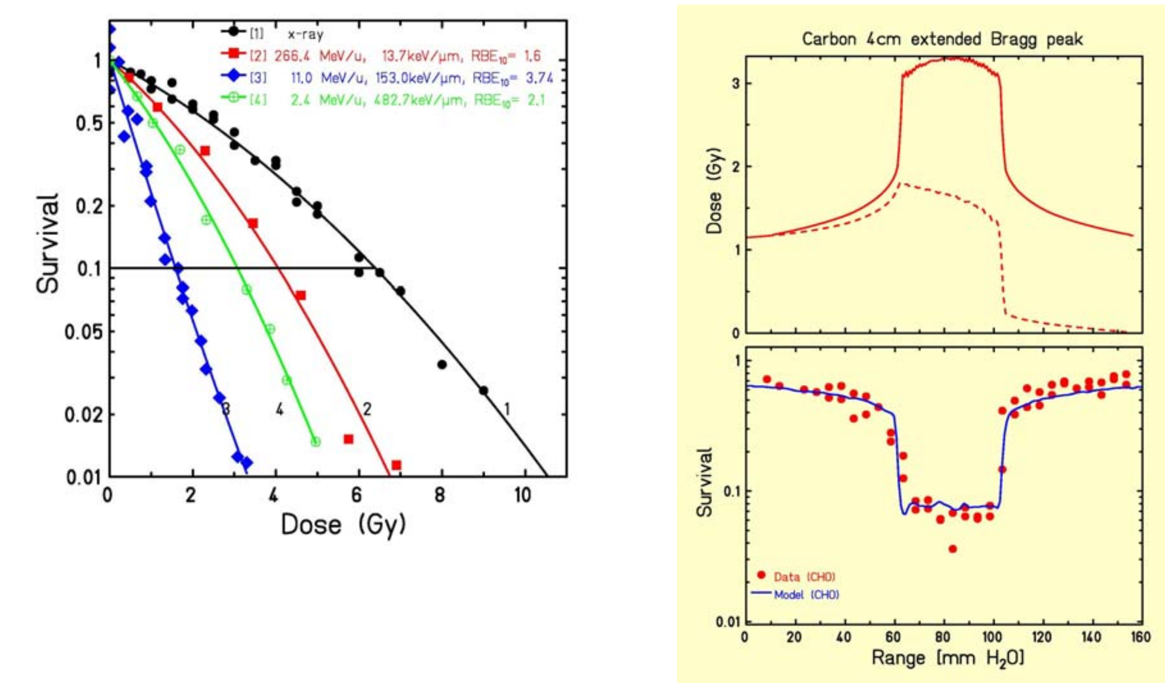

FIG.3. Left: Measured survival curves of CHO cells irradiated with ^{12}C ions at different energies and with X-rays. The relative biological effectiveness (RBE) is defined as ratio of particle dose and X-ray dose producing the same effect (here the same survival level of 0.1). Right: Comparison of calculated and measured cell survival for a two-port irradiation aiming at a constant biological effect in the extended Bragg peak [20].

The radiobiological effectiveness (RBE) is defined as the dose ratio D_p/D_X, where D_p is the particle dose and D_X the X-ray dose producing the same biological effect. RBE is a very complex quantity, depending on the local ionization density (which includes depencies on the particle charge and velocity), survival level (see Fig.3), but also the repair capacity of the irradiated tissue. In radiobiological experiments it was found that repair-proficient cells show a small RBE value in the plateau region of the Bragg curve but a steeply increasing RBE in the Bragg peak, whereas repair-deficient cells do not show such an increase. From this finding the highest therapeutic gain can be expected for radio-resistant tumors where the normal repair capacity is large but heavy ions have an increased biological effectiveness.

Keeping in mind the various dependencies of RBE and the complex radiation field (including fragmentation), the treatment planning which should take into account the biological effects to the best knowledge becomes a difficult task. The treatment planning program [8,9] developed at GSI and DKFZ Heidelberg is based on an advanced track structure model [21,22] which is able to reproduce the correlation between the α/β-ratio (which defines the shoulder of survival curves in the linear-quadratic model) and the RBE. The good agreement between model prediction and measured cell survival can be seen in Fig.3 for an opposing-field irradiation where the treatment planning aimed at a constant biological effect in the extended Bragg peak.

3. The GSI treatment unit

In May 1993 the proposal for the construction of an experimental radiotherapy unit at GSI Darmstadt was submitted to the Department of Research and Technology of the German Federal Republic. The construction phase started right after proposal submission in 1993 and in parallel the extensive paper work necessary to obtain the authorisation for the radiation treatments according to the German radiation laws had to be tackled. In December 1997, shortly after receiving the authorisation, the first patient was treated. Since then the facility is routinely operated with about 40 treatments per year and without any major technical problems. The basic data of the GSI Pilot Project are summarized in table 1.

TABLE 1. Basic data of the radiotherapy unit installed at GSI Darmstadt.

Carbon Ion Therapy Pilot Project at GSI Darmstadt

GSI-Darmstadt – Radiol. Clinics University Heidelberg – DKFZ Heidelberg – FZ Rossendorf

Time Table		**Technical Data**	
May 1993	Proposal submission	Beam:	^{12}C ions 80 - 430 MeV/u from Synchroton SIS-18
1993 – 1997	Construction phase Investment cost: 6 Million €	Beam delivery:	Intensity-controlled **rasterscan system** Active energy variation On-line PET monitoring Biological dose optimization
Dec. 1997	First patient treatment		
		Operation:	3 Treatment blocks per year each 20 d
1998 – 2007	Treatment of ~ 40 patients per year with malignant tumors in the skull base or pelvic region	⟹	Time sharing with physics experiments (during patient positioning)

Future: Heidelberg Ion Therapy HIT → Clinical facility

In order to have a maximum benefit of the physical and biological advantages of heavy-ion beams for the treatment of deep-seated tumors the concept of the GSI treatment unit includes a fully active beam delivery system [23]. A pencil beam (typically 5 mm half-width) with well-defined energy and corresponding depth of the Bragg peak is moved by fast horizontal and vertical scanning magnets slice-by-slice over the target volume. By choosing appropriate steps in the beam energy the whole target volume is irradiated (Fig.5). In order to ensure that each pixel of the target slices receives the desired dose, the scanning system has to be intensity controlled and needs a feedback from a fast beam monitor. This implies great demands on the control and safety systems as well as strong requirements on the accelerator performance such as stability and reproducibility of the absolute beam position. In comparison with passive beam delivery, the active system has a clear advantage as there are no restrictions in shaping the target volume and any prescribed 3-dimensional dose distribution can in principle be generated. Furthermore, beam losses and contamination by nuclear fragmentation in passive beam shaping elements in front of the patient are minimized in active systems.

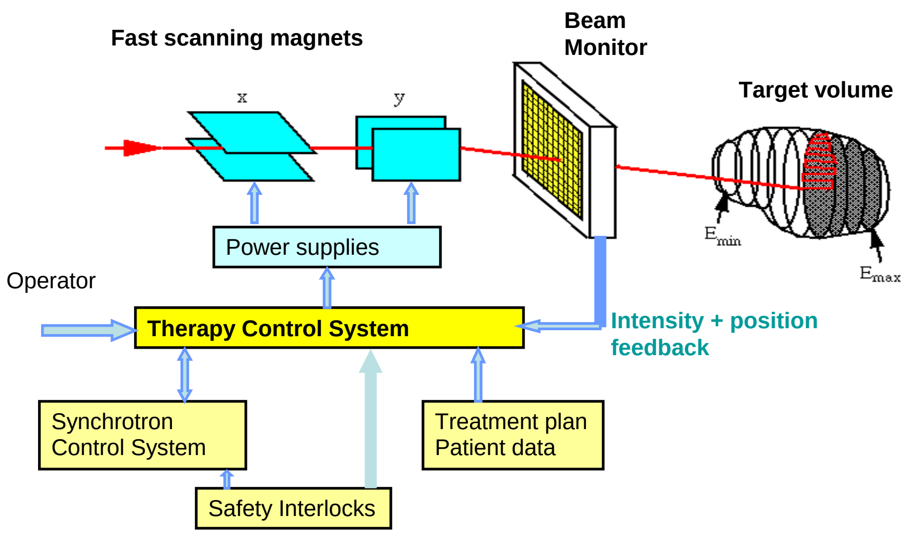

FIG.5. Principle of the intensity-controlled magnetic scanning system [23] at GSI. The target volume is irradiated by moving the ion beam (80-430 MeV/u ^{12}C) with fast magnets over each slice. The required beam energies - corresponding to the depth of the Bragg peak for each slice - are supplied on a pulse-to-pulse operation by the synchrotron (SIS) control system.

The therapy unit includes a dedicated beam line, the treatment room and local control room (Fig.4), and a medical annex building. The treatment room is equipped with a patient couch and a patient chair [24] both isocentric. In combination with the horizontal beam this allows irradiations within a frontal plane (couch) or transversal plane (chair) of the patients head. The treatments are performed in a so-called stereotactic setup, where two Cartesian coordinate systems – the patient system and the room system – have to be exactly matched. The fixation of the patient system is accomplished by an individually shaped full mask which is rigidly attached to the patient couch. An orthogonal laser system defines the origin of the room coordinate system. Special care has to be taken that the rotation axis of the patient couch is exactly vertical and matches with the laser crossing point which also is the reference point for the central beam position. Furthermore, an orthogonal X-ray system with image intensifiers and digital image acquisition provides an independent verification of the patient position with high accuracy [25]. For each individual treatment plan the physical dose distribution has to be verified by measurements of the local dose at many different positions using a water phantom and a special array of 24 air-filled thimble-type ionization chambers [26]. Correct performance of all sub-systems has to be checked within an extensive quality assurance programme before treatments can be delivered.

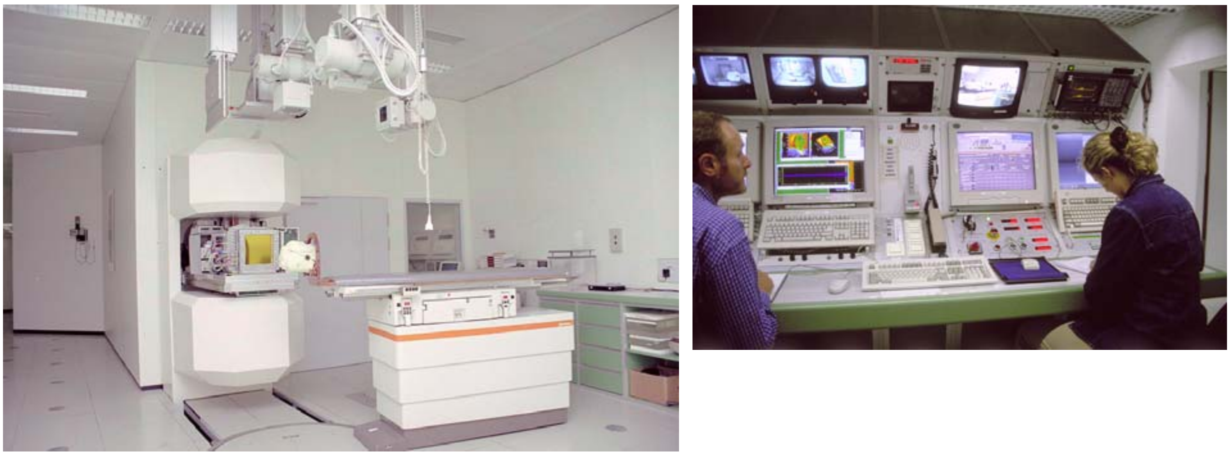

FIG.4. Treatment room and local control room of the GSI treatment unit.

4. Irradiation monitoring with PET-techniques

An interesting positive aspect of the nuclear fragmentation effect discussed above is the formation of short-lived positron-emitting isotopes which can be utilized for an in-situ monitoring of their stopping points by applying Positron Emission Tomography (PET) techniques [27,28]. This yields an independent experimental verification of correct treatment planning and beam delivery, especially the monitoring of the penetration depths which is invaluable for treating tumors near critical structures. This feature is unique to heavy-ion beams as here a significant fraction of the induced β^+-activity in tissue stems from positron-emitting **projectile-like fragments** which have nearly the same end-of-range as the primary particles.

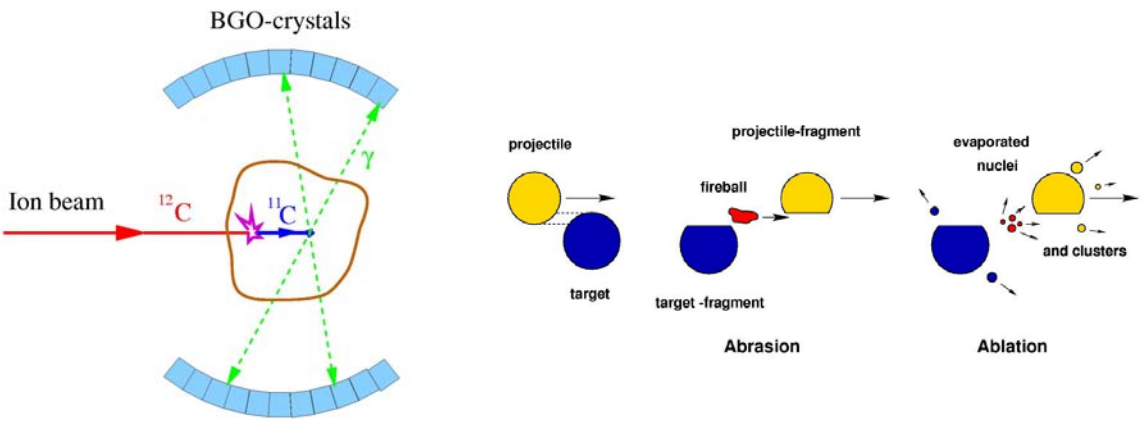

FIG.6. Principle of the in-situ range verification by PET techniques. Positron-emitting istopes like ^{11}C are formed most frequently in peripheral nuclear collisions as described by the two-step abrasion-ablation model of Serber [29]. They have nearly the same range as the primary ions and their stopping locations can be monitored by coincident detection of the two annihilation quanta.

The principles of the measurement are sketched in Fig.6. Along the penetration path in tissue the primary ^{12}C ions may undergo a nuclear reaction and continue travelling as ^{11}C fragments with about the same velocity and direction. As they have the same nuclear charge they reach almost the same depth as the primary ions (slightly less because of the lower mass number). The spatial distribution of the β^+-activity of the ^{11}C ions can be obtained by coincident recording of the annihilation radiation in two opposite detector heads. The PET-scanner installed at GSI was built of components of the commercial PET-Scanner ECAT EXACT (CTI PET Systems Inc. Knoxville, TN). Each detector head consists of 8 x 4 position sensitive BGO-scintillation detectors which are subdivided into an 8 x 8 crystal matrix and readout by 4 photomultipler tubes. Considerable effort has been put into the development of powerful tomographic reconstruction algorithms taking into account the limiting-angle restriction and low counting statistics of the data [30]. The reconstructed β^+-activity distribution (Fig.7) is compared to the expected distribution which is calculated based on the patient CT-data, the treatment plan and the actual irradiation conditions. Superposition of the measured and calculated β^+-activity distributions then reveals possible differences with an accuracy of about 2.5 mm. This method has proven to be a valuable tool for the quality assurance of heavy-ion therapy and is routinely applied in all patient irradiations at GSI [31].

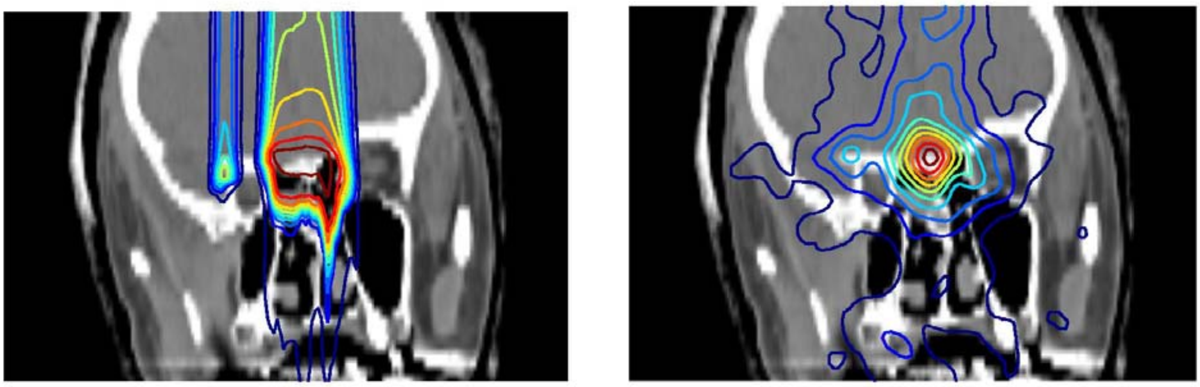

FIG.7. Treatment plan showing the dose distribution in a frontal slice of the patient's head (left) and the corresponding measured β^+-activity distribution (right).The carbon beam entered from the top. The PET-detector heads were located vertically above and below the patient table.

5. Clinical results

The treatment of radioresistant skull-base tumours with carbon ion beams seemed to be most promising because conventional radiotherapy with photons is often not applicable due the limited tolerance of neighbouring radiosensitive structures. As can be seen from a typical treatment plan shown in Fig.8, the target volume for such tumors is close to the brain stem or the optical nerves that can be spared very well by the precision irradiation with ion beams. In addition, the enhanced biological effectiveness (RBE) of heavy ions ensures that a sufficiently high dose can be delivered to the target volume.

Since December 1997 more than 180 patients were treated at GSI within clinical pase I/II trials. First results were reported for 45 patients with chordomas, chondrosarcomas and other skull base tumors [32,33]. Most of these patients received a fractionated carbon ion irradiation in 20 consecutive days with a median total dose of 60 GyE which was well tolerated without severe side effects. No local recurrence within the treatment volume was observed. Local control rates at 3 years of 81% for chordomas, 100% for chondrosarcomas and 62% for adenoid cystic carcinomas were found. Ongoing clinical studies of patients including skull base tumors and sacral/spinal chordomas and chondrosarcomas show a good effectiveness and no severe toxicity [34].

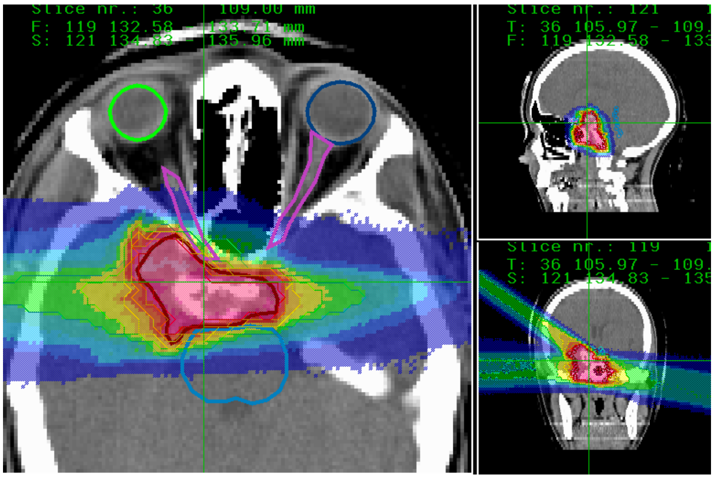

FIG.8. Carbon-ion treatment plan for a large tumor in the skull base. The target volume is close to the brain stem and optical nerve which can be spared very well by the carbon ion irradiation.

5. Outlook

Encouraged by the positive clinical results obtained from the GSI pilot project a new dedicated ion beam facility was proposed [35] by the Radiological University Clinics Heidelberg (project coordinator), the German Cancer Research Centre (DKFZ Heidelberg) and GSI Darmstadt in cooperation with FZ Rossendorf. The new facility HIT (Heidelberg Ion Therapy) located at the Radiological Clinics is presently under construction and is expected to be operational in 2007. A layout of the facility is shown in Fig.9. It will be the first clinical heavy-ion treatment centre in Europe and is planned for the treatment of more than 1000 patients per year. The new machine is able to deliver protons, helium, carbon, and oxygen ions at energies ranging from 50 to 430 MeV/u, but will be used routinely with proton and carbon ion beams. Its main components are two ECR-type ion sources, an RFQ-type linear accelerator injecting into a synchrotron and the high-energy beam lines transporting the ion beams to the three treatment rooms. One of them will be equipped with a rotating isocentric gantry system, the other two rooms will be supplied with horizontal beam lines and robot based patient positioning devices. With a gantry device the ion beam can be delivered from any angle to the patient table. The gantry system with a total weight of about 600 tons and a full 360° rotation is being manufactured by MAN-Technologies and will be the first gantry for heavy-ion beams worldwide. The ion optical design includes a two-dimensional scanning system and incorporates the experiences gained in seven years scanning beam operation in the GSI pilot project. A prototype of the final section of the beam delivery system, including a large 90° bending magnet which will be later mounted on the gantry was successfully tested on-line at GSI in spring 2004.

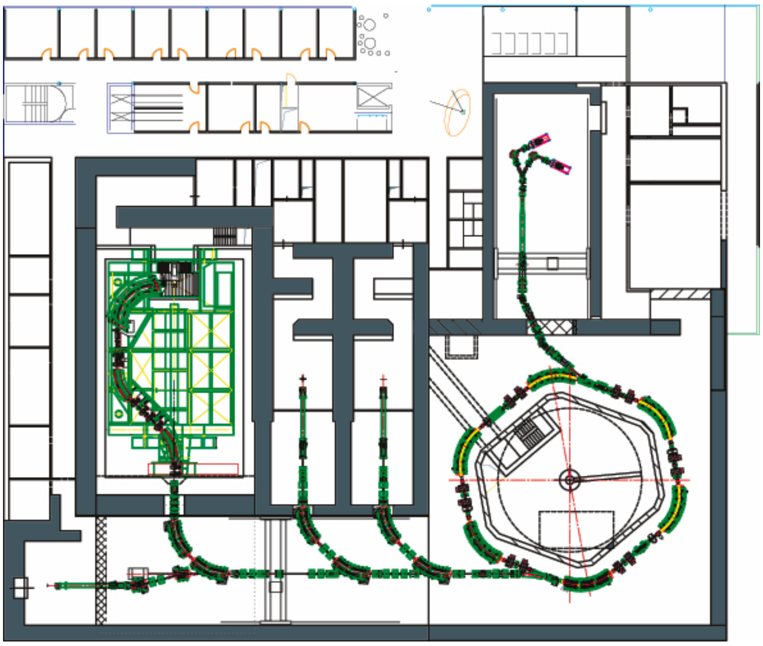

FIG.9. Layout of the heavy-ion clinical facility HIT with a total size of 60 m x 70 m. The main components are the LINAC with two ion sources, the synchrotron accelerator, and three treatment rooms. One room is equipped with a 360° rotating gantry, the two other rooms with horizontal beam lines.

In the remaining time until start-up of the new HIT-facility the pilot project at GSI will continue with patient treatments, but also investigate further developments. The irradiation of moving targets (such as the lung) by active motion-compensating systems [36] appears to be the most challenging technical problem. The clinical research will be continued with planned studies of prostate treatments with carbon ion beams. The combination of an excellent localisation of the dose deposition and the increased effectiveness of carbon ions is supposed to substantially improve the results in patients with advanced prostate cancer.

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