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Tumortherapy with ion beams

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For the Heavy Ion Therapy collaboration[1]

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Abstract

Beams of heavy-charged particles like protons or carbon ions represent the optimum tool for the treatment of deep-seated inoperable tumors: in contrast to the conventionally used photons the dose increases along with the penetration depth through the body, culminating in a sharp maximum at the end of the particle range. In order to achieve a precisely conform irradiation of the selected target volume, this maximum can be shifted in depth by energy variation and distributed laterally through magnetic deflection of the particle beam. Because carbon ions have a lateral scattering of only about 1 mm at 10 cm depth they offer the most conform irradiation. In addition to this excellent physical selectivity the biological efficiency concerning cell killing increases towards the end of the carbon ions' range. Therefore, the increase in dose is potentiated by an increase in biological efficiency. Finally, the stopping of the carbon ions can be monitored by tracing a small amount of β^+ active ^{10}C and ^{11}C ions which are produced in nuclear reactions with atoms of the penetrated tissue. This β^+ distribution can be visualized by applying PET-techniques, thus allowing a good control of the beam distribution. At GSI Darmstadt a heavy-ion therapy unit has been designed and constructed in collaboration with the Radiological Clinic and the DKFZ Heidelberg and the FZR Dresden. The layout of this facility as well as the treatment of now more than 30 patients will be reported on. The proposal for the layout of a dedicated medical facility at Heidelberg will be presented

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1. Motivation for particle therapy

Since December 1997 patients with radioresistant tumors in head and neck are treated at GSI with high-energy carbon ions. Carbon therapy has a large advantage of an extreme precision in the dose application and of a high biological efficiency in the malignant tissue. This therapy is the result of a long-standing radiobiological research and a very sophisticated technical development.

As early as at the beginning of the experiments at GSI the radiobiological experiments had been carried out by the Biophysics group in parallel to the physics experiments. Their goal was a better understanding of the biological action of ion beams as well as the development of a more precise beam application procedure for large volumes. However, the final reason that this development reached an experimental therapy is the clinical demand for a high-precision therapy. Almost half of the 380 000

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cancer incidents every year in Germany can be cured in the long run. These patients predominantly have a single solid tumor in the beginning that could be removed through surgery or sterilized through high radiation doses. However, also in this group of patients almost 20% cannot be cured permanently with conventional therapy because the tumor can neither be removed completely nor be radiated with a sufficiently high dose. In principle, it is possible to sterilize any tissue in the body if a sufficient radiation dose can be applied. In the radiological practice the maximum dose is always limited by the tolerance of the healthy tissue around.

Therefore, it has always been the goal throughout the 100 years of radiation therapy to increase the precision of the irradiation in order the concentrate the dose in the target volume and to reduce the dose in the healthy tissue or distribute this inevitable dose over a larger tissue area. Using variable collimators like multi-leaf collimators and intensity-modulated Bremsstrahlung from linear electron accelerators, radiation therapy in the last years has reached a significantly better dose distribution and in consequence improved clinical results. However, a further increase in precision and biological action is only possible with the use of particle beams as was postulated by Wilson [1] in 1946. Yet, ion beam therapy got started rather slowly at Berkeley where the first patients were treated with protons in 1954, with helium in 1957 and with heavy ions – mostly neon – in 1975. From there, ion beam treatment spread all over the world and until today more than 20 000 patients have been treated successfully – mostly with protons [2]. Four hundred and thirty patients have been treated with neon ions at Berkeley and another 400 with carbon, almost all of them at NIRS; Chiba, Japan. Harvard University played a pioneering role in the development of proton therapy, treating nearly one-third of all patients, while Loma Linda later on installed the first dedicated medical therapy center where today 1000 patients a year can be treated.

2. The physical basis

At high energies, heavy-charged particles like carbon ions interact very weakly with the penetrated tissue. Thus, in the beginning the energy loss is small and the dose is low. At the end of the particle range the interactions becomes stronger and the energy loss increases steeply. This enhanced interaction has two significant consequences for particle therapy: First, a better dose profile and second the increased relative biological efficiency inside the target volume [3].

Compared to photons, particle beams show an inverse dose profile: with increasing penetration depth the dose increases up to a sharp maximum. Beyond this so-called Bragg maximum the dose decreases within a few millimeters to a small value which consists of nuclear fragments of the carbon beam. Through energy variation the dose maximum can be shifted over the depth of the target volume. Today, in most of the particle therapies – predominantly proton therapies – the necessary

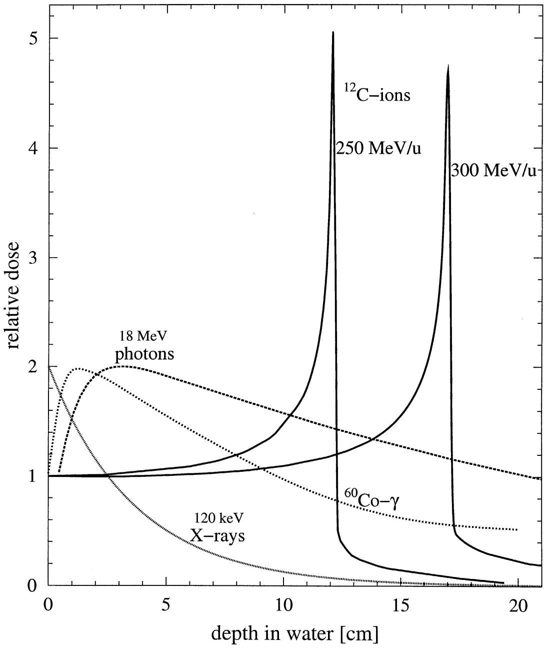

Fig. 1. Comparison of the depth-dose distribution of photons (conventionally used) and carbon ions. With photons the dose decreases exponentially with increasing depth, i.e. the dose in the target volume of deep-seated tumors is smaller than the dose delivered to the healthy tissue around. Carbon ions dispose of an inverse dose profile, i.e. the dose increases with increasing penetration depth. This profile can be shifted by energy variation over the target volume, leading to a much higher dose deposition inside the tumor than outside in the healthy tissue.

energy variation is generated using passive absorber systems [4]. The lateral distribution is reached by scattering foils and the spread beam limited with collimators. This procedure leads to a better dose distribution than was possible with the conventional photon therapy 10 years ago. However, in the meantime a similar dose distribution can be produced through proton beams using intensity-modulated applications. For the first time ever it was possible at GSI to produce a range modulation for heavy ions by a computer-controlled energy variation of the heavy-ion accelerator SIS and to use fast magnetic lateral deflection. This system allows to perform an extremely tumor conformal irradiation.

In order to translate the optimum physical properties in adequate irradiation procedure the raster-scanning system has been developed at GSI in the last 10 years [5]. During this three-dimensional (3D) procedure, the target volume as delineated by the physician is divided into different layers of equal particle range and each layer is irradiated with a pencil beam in a raster-like pattern. The big advantage of this system is the possibility to adapt the irradiated volume to the irregular shape of the target volume. Yet, the central problem of this procedure consists in the pre-irradiation of the layers in front when the deeper layers are treated (Fig. 1). In consequence, except for the most distal layer all the proximal layers have to be irradiated with an inhomogeneous dose pattern in order to produce a homogeneous dose distribution or a homogeneous biological effect in the complete target volume. To produce the necessary complex particle distribution, a conventional technique – normally used in TVs – was adjusted for the use of heavy ions. In each TV set the picture is divided into lines with distinct picture points (pixels). For each pixel the beam's intensity is controlled in order to achieve the correct brightness of the picture. In analogy, in the ion beam scanning, each layer of the target volume is dissected in different pixels and the beam will be moved from one pixel to the next after the necessary number of particles has been reached (Fig. 2). With this method individual dose distribution can be achieved for each layer.

However, in contrast to the two-dimensional (2D) TV the third dimension can be added in the ion scanning system with a depth modulation by energy variation form the accelerator. In a

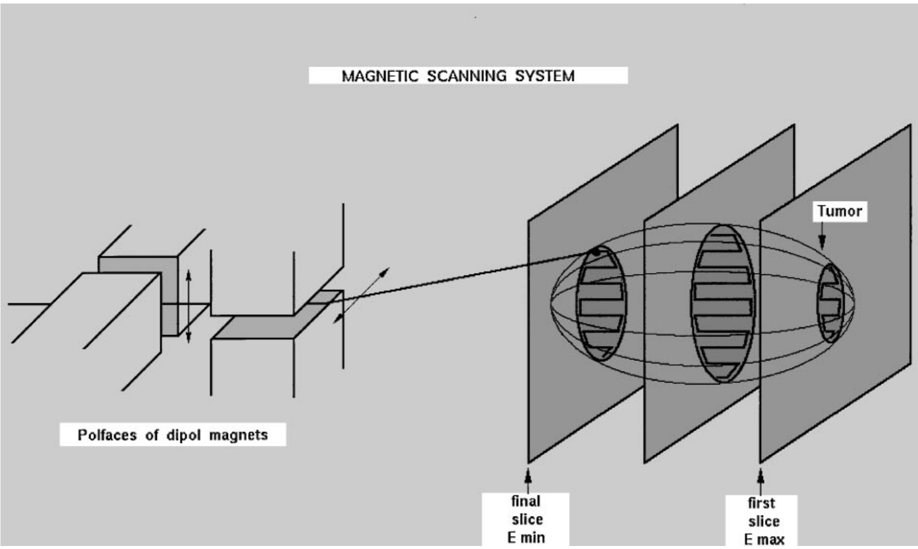

Fig. 2. Principle of the rasterscan technique: the target volume is dissected into slices of equal particle range and each slice is painted with a pencil beam in a rasterlike procedure. The velocity of the scanning procedure is controlled by the beam intensity in such a way that any homogeneous or inhomogeneous particle distribution within a layer becomes feasible.

synchrotron this can be done from pulse to pulse, i.e. within 1 s or less. This way it is possible to irradiate irregularly shaped volumes with a very high precision and without excessively damaging the healthy tissue around the tumor. Therefore, ion scanning therapy is most adequate for tumors with irregular geometries in head and neck because there are often critical structures like brain stem and spinal cord in close neighbourhood to the target volume, which should as far as possible be spared from radiation damage. A similar method of target-conform proton irradiation has been developed at PSI, Switzerland [6].

3. Treatment planning

In a typical treatment of a patient at GSI (Fig. 3) a large target volume in the base of the skull situated close to the brain stem and the optical nerve was irradiated. The same was true for many of the other GSI patients where the target volume was close to critical and sensitive structures. In order to execute these treatments the particle range has to be calculated according to the density of the structures to be penetrated. If the ion beam has to pass an extremely dense structure such as bones, the energy has to be increased. But when passing

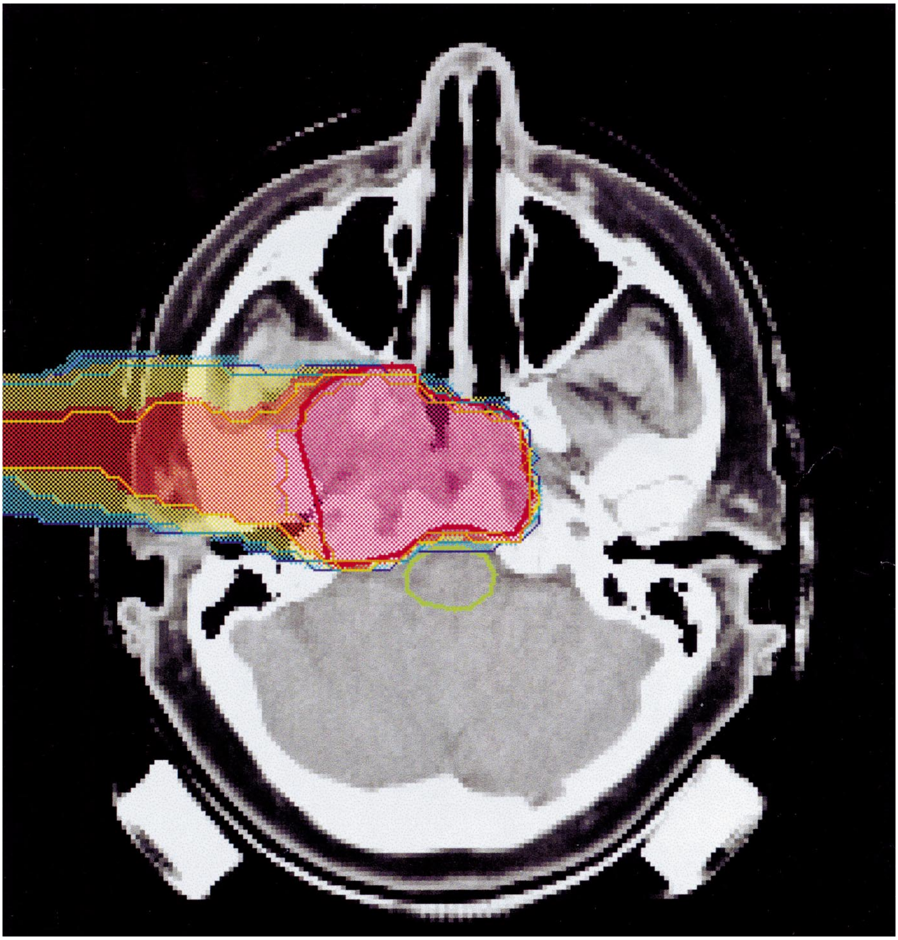

Fig. 3. Treatment plan for a GSI patient having a large tumor in the base of the skull. The target volume is very close to the brain stem which can be spared due to a steep dose fall-off.

air-filled gaps as in nose or ear smaller energies have to be applied in order to place the Bragg peak in the correct position in the target volume.

In Fig. 4 the different energy layers are shown with their very complex contours. During the irradiation the layer being irradiated is shown in enlargement. The requested positions of the beam are displayed as circles and are compared with the measured value as produced by the control system which is installed directly in front of the patient.

4. Beam monitoring and PET-control

On the one hand, the rasterscan system is very effective producing precise target contours, on the other malfunctions of the system signify an enlarged risk because a high-intensity beam like the very narrow pencil beam is applied very close to critical organs and malfunctions could produce serious damage in these structures.

Therefore, one has to make sure that the beam is not misplaced at any moment during irradiation.

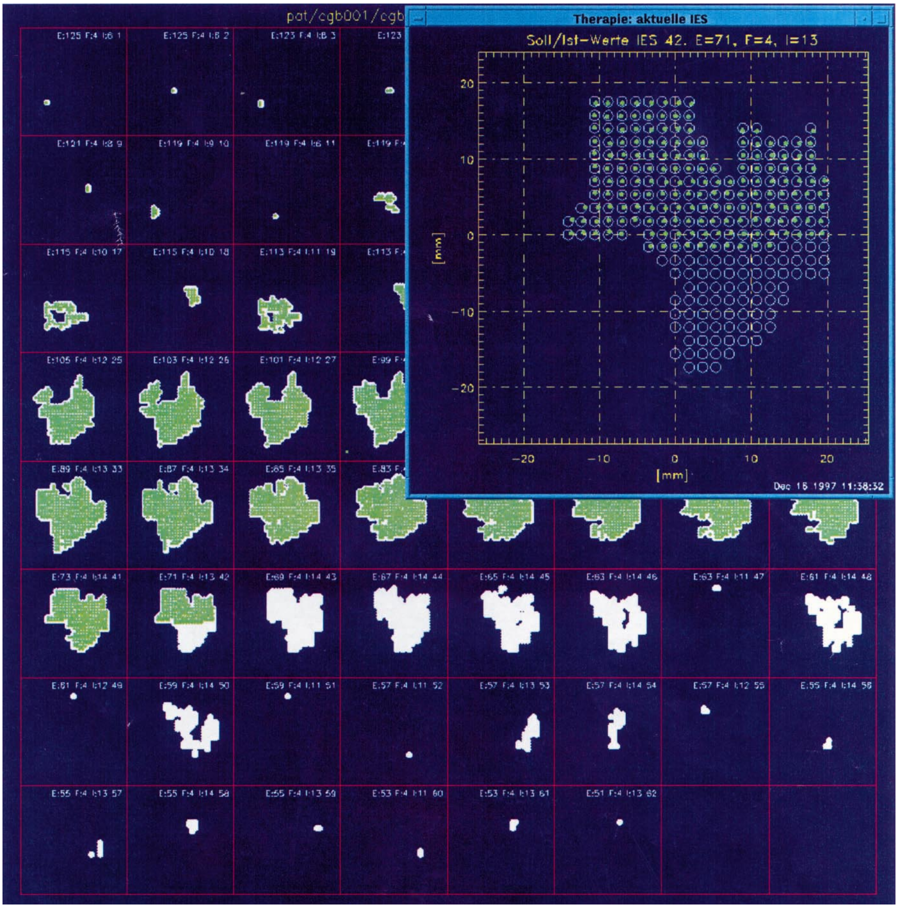

Fig. 4. Irradiation layers in the tumor from Fig. 2. Due to density inhomogeneities, such as bones or air-filled holes, a large variety of energies has to be used in order to get to the same depth level, leading to very complicated irradiation patterns of individual layers. Within every layer, the individual target points are displayed and filled during irradiation with the precalculated number of particles.

At the GSI system this control is performed with detectors, that were predominantly developed for high-energy physics. The precision is assured at different levels. First, the position and the intensity of the beam is measured during irradiation and compared to the desired values.

For this purpose multiwire and ionization chambers are mounted directly in front of the patient. In the ionisation chambers the intensity is measured approximately once every 12 μs while the position of the beam center is recorded once every 120 μs in the multiwire detector. Both values are then combined and compared with the requested values. For each pixel at least four measurements are sequentially performed and only one of these measurements is allowed to deviate from the requested values. If more than one measurement differs the beam will be shut off in the accelerator within less than half a millisecond. Only the use of such a detector system, that was originally developed for high-energy physics, guarantees the necessary security which cannot be assured by manual control. In addition, the measured position and intensity co-ordinates can be visualized directly on the control panel as shown in Fig. 4. This offers a very precise on-line status control [14].

A second and also novel control system is the PET-control for the localisation of the beam inside the patient during irradiation. It was developed by the FZR Dresden [7]. Stable carbon ions of a primary beam are fragmented inside the patient to a small percentage into ^{10}C and ^{11}C isotopes which both decay under positron emission and subsequent γ-emission. The γ-rays are simultaneously emitted within 180° to each other. Because a large fraction of these γ-rays leaving the patient can be measured with the help of two γ cameras from outside, the stopping region of the primary beam can be traced back. However, the reconstruction of the PET image can only be performed after irradiation. Possible deviations can therefore only be corrected in the next irradiation fraction by changing the treatment plan. Yet, PET imaging of volumes under irradiation is of major use since with no additional dose the quality of the irradiation can be monitored with an accuracy of 2.5 mm. This is of immense importance for dose gradients close to critical structures.

5. Increased biological efficiency

Apart from precision in dose application the increased biological efficiency in the target volume is the second main advantage of carbon therapy [8, 9]. In all biological systems the DNA represents the target for the attack of ionizing radiation. The DNA contains all the information that is needed for an organism to live, reproduce and function. The DNA of single chromosomes represents the largest molecules in a cell and is therefore most sensitive to radiation. In order to guarantee the integrity of DNA, cells developed a system of redundant information and repair throughout evolution. The redundancy mainly consists in the fact that the DNA molecule has two strands containing identical information. An information loss in one strand can be repaired on the basis of the information in the other strand. Only when both strands are hit at the same time and have been damaged to a major extent, repair becomes impossible.

The increase of energy loss with decreasing velocity is characteristic for all ions, from protons to uranium. On a molecular scale, this increase means the increase of the local ionization density, which can directly be correlated with the local density of the DNA damage (Fig. 5). Very extensive experiments, that were carried out at LBNL, NIRS and GSI throughout many years, revealed that regarding lighter ions carbon is the optimum for therapy [9]: For the high energies in the entrance region the low ionization density mostly produces repairable damage. But with an increased energy loss towards the Bragg Peak a significant increase in irreparable damage is observed which yields a higher relative biological efficiency (RBE). For heavier ions like neon or argon the fraction of irreparable damage in the entrance channel is already significant thus damaging the healthy tissue in front of the tumor. For very light ions like protons no damage potentiation can be observed in the target volume. Carbon ion beams therefore represent an optimum in biological efficiency in tumor therapy – also in the molecular level, measuring DNA damage and repair along a therapeutic beam [10].

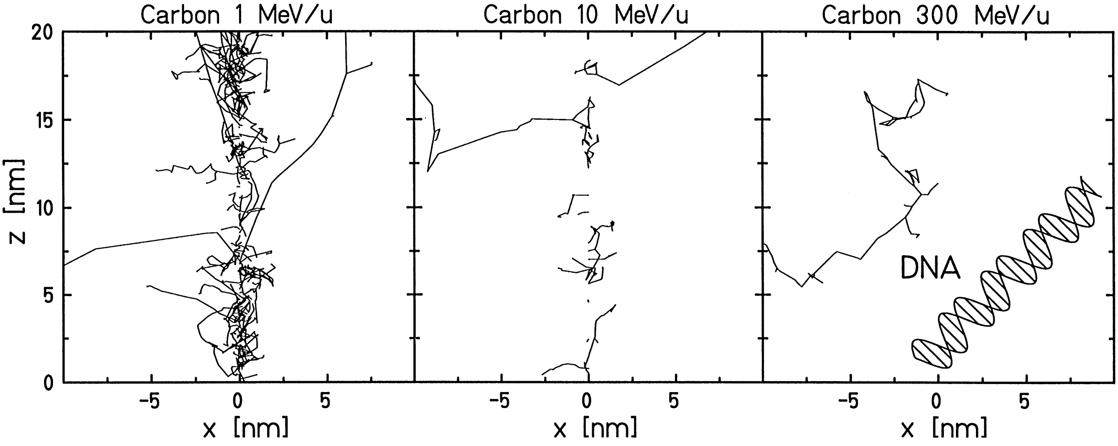

Fig. 5. Comparison of the microscopic structure of carbon tracks at different energies with a simplified depiction of a DNA molecule. Ionisation and consequently the damage to the DNA is low at high particle energies but increases significantly at lower particle energies yielding clustered damage that is difficult to repair.

6. RBE and treatment planning

The increased RBE represents one of the greatest advantages of the carbon ion therapy. However, this advantage is also linked to some complications since the increase of RBE mainly depends on the different repair capacity. Tissues that are radiosensitive due to their reduced repair capacity do not exhibit an enlarged biological efficiency when irradiated with carbon ions. Yet, tissues being very radioresistant due to a high repair capacity show a drastically increased RBE when irradiated with carbon ions. This yields a significantly higher chance of cure for the conventionally difficult to treat tumors.

To include the variance of RBE in therapy planning, it was necessary to develop a quantitative model of the biological action of particle beams [11]. The model is based on the long-term experience of radiobiological research at GSI and describes the radiobiological action of particle beams on the basis of physical data of particle tracks, the X-ray sensitivity of cells and the morphology of cells. Using this model the RBE is calculated in the different voxels of the target volume and the dose is adjusted to this RBE in order to reach a homogeneous biological effect in the complete target volume [12]. The experience with patients who were irradiated at the GSI facility has confirmed the correctness and soundness of this procedure in every aspect.

7. The facility at GSI

GSI operates the only accelerator throughout Europe which is capable of delivering the energies and intensities required for therapy. Thus, the construction of a therapy unit was started in summer 1993 and the operation began in December 1997 (Fig. 6) [13]. There are several institutions taking care of the various parts of the therapy project. The Radiological Clinic Heidelberg takes the responsibility for all medical aspects such as patient selection, diagnosis and dose calculation. The DKFZ (German Cancer Research Center) Heidelberg is responsible for the patients' immobilization through masks, the treatment planning and quality control by appropriate dosimetry. The FZ Rossendorf (Research Center Rossendorf) near Dresden installed the PET camera and developed the analysis which is applied during patient irradiation. But the irradiation itself actually takes place at GSI Darmstadt. Here, the treatment plans are biologically optimized and converted into coordinates for the

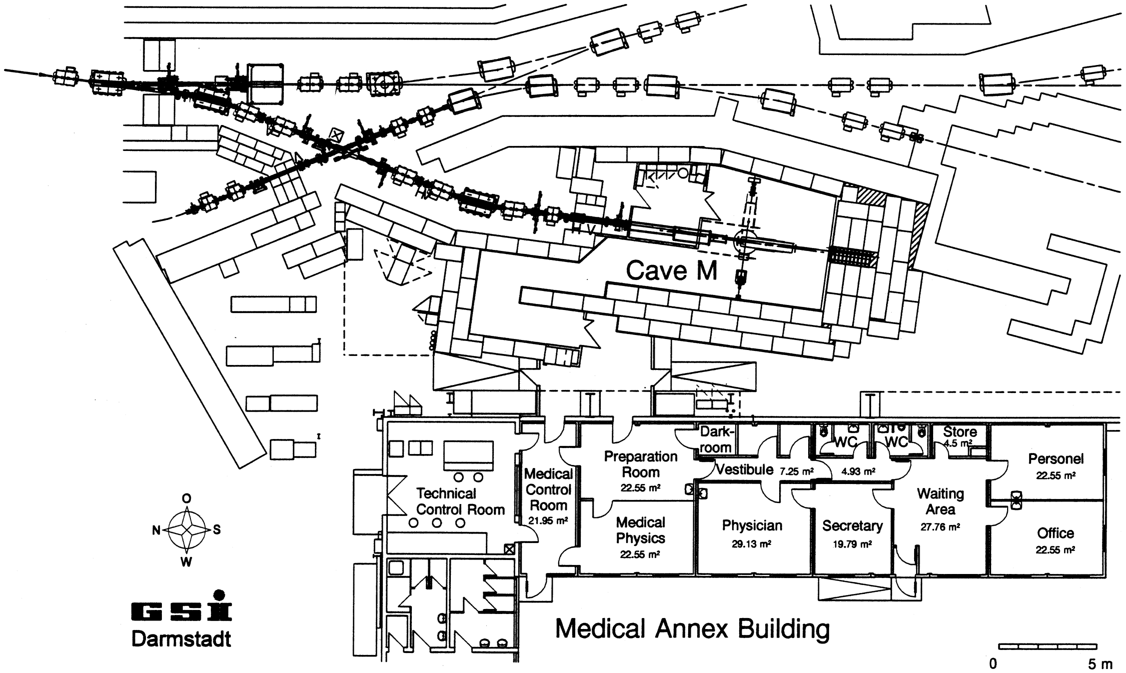

Fig. 6. Groundplan of the GSI therapy facility and the adjacent building for the physicians, the patients and the control room.

accelerator and the rasterscan system and here the beam is generated.

The patients (Fig. 7) are out-patients from Heidelberg or come directly from home. A patient may receive up to 20 fractions on 20 days running, including week ends, and generally receives no other treatment. But for a small number heavy-ion therapy is applied as a boost to a conventional radiation therapy, i.e. part of the photon dose is substituted by a carbon ion dose. Until September 1999, a heavy-ion treatment was given to 48 patients, who were suffering from slowly growing tumors such as chordomas, chondrosarcomas or adenoid-cystic carcinomas in head or neck region. Three of the patients treated had pelvic tumors very close to the spinal cord. Medicalwise as well as technicalwise, these treatments were very successful.

Although the coordination of the accelerator and the rasterscan system during irradiation is rather demanding, patient treatment was carried out smoothly with only some minor interruptions. The reliability of the system proved to be as good as that of the technically much simpler hospital-based linear electron accelerators and thus the system is perfectly fit for use in clinics, too.

All expectations regarding the medical success of the treatment were met or even exceeded by reality. No patient showed more than very slight side effects like hair loss and reddening of the skin was rare. Other side effects occured hardly, a fact that confirmed the very advantageous properties of the carbon ions' inverse dose profile: the low-dose deposited in the entrance channel and the high-dose deposited in the target volume.

Also the PET analysis after the treatments revealed a very good agreement between the target volume and the actually irradiated volume. In the follow-up of patient treatment a very satisfying tumor control in the target volume could be observed, sometimes even an unexpected and fast tumor regression. This backs two general ideas of radiation therapy, that a better dose distribution leads to better results and that an enhanced biological efficiency multiplies the radiation impact.

Fig. 7. A patient is prepared for a carbon ion treatment. In order to get an exact positioning of the target volume the head of the patient is fixed with an individually manufactured mask. The end of the beam pipe with ionization and multi-wire chambers for the beam control is visible at the left side. During irradiation, the PET cameras above and below the ionization chambers are placed over the patient.

8. Future plans for a medical dedicated heavy-ion accelerator

Although it is too early to speak of curing the patients, i.e. a five-year survival without recurrent tumors, the clinical success of the GSI facility is so convincing, that it has prompted plans for a center that will be dedicated to medical purposes alone [14] and will serve 1000 patients a year (Fig. 8). It is estimated that the costs for a patient's treatment will correspond more or less to those of surgery and will be much less than those caused by a failed treatment. These advantages have also been recognized elsewhere, resulting in the construction of similar facilities in France, Italy and Austria. Japan, already disposing of a large medical heavy-ion unit, is building another one. The US favors proton centers, due to the lack of know-how in extremely tumor-conform dose application which is indispensable for heavy-ion therapy. Construction and operation of the GSI facility demonstrate the immense advantage of a tumor-conform treatment with heavy-ions beams, a

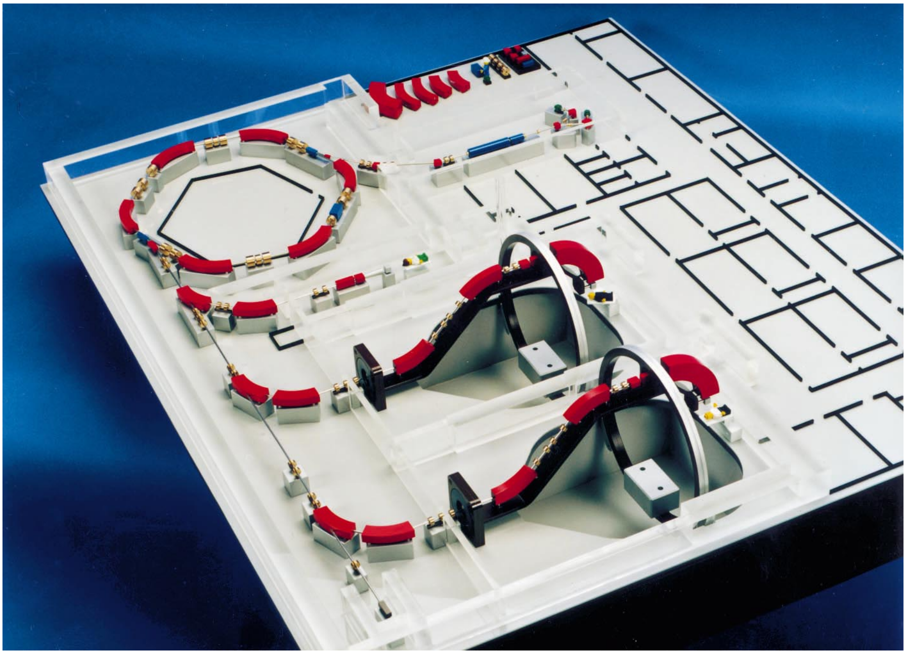

Fig. 8. Model of a medical accelerator consisting of a synchrotron (up left) and three treatment areas, two of which dispose of a mobile beam delivery device (gantry). With a gantry the beam can be applied from any angle.

treatment that only became possible through the transfer of many a technique originally developed for high-energy physics.

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