FIRST PATIENTS' TREATMENT AT GSI USING HEAVY-ION BEAMS

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Abstract

Beams of heavy-charged particles of high energy like carbon ions are superior to any other type of radiation conventionally used in external radiotherapy. In contrast to photons and neutrons, the dose for the ions increases with penetration depth and culminates in a sharp maximum at the end of range. Due to the microscopic track structure this region of high energy deposition has an increased biological efficiency. In addition, a small amount of positron emitting isotopes is produced by the projectile and makes it possible to trace the beam inside the patient's body by PET techniques. At GSI an experimental heavy-ion therapy started with patient treatment. It is based on a totally active beam delivery and a biology-oriented treatment planning system in order to exploit the favourable particle properties to a maximum extent.

Introduction

In the 100 years' history of radiation therapy two ways for better tumor control have been successfully applied [1]. The first was the use of higher photon energies in order to improve the dose localisation and to shape the irradiated volume according to the tumor contours: Some decades ago the low voltage x-ray machines were replaced by the megavolt therapy using Co-gamma radiation, that is now replaced by the Röntgen Bremsstrahlung from high energy electron linear accelerators (Fig. 1). These high energy photons combined with inverse treatment planning using multiple ports produce extremely well defined dose contours even for deep-seated tumors. However, due to the physical nature of an exponential dose decay with growing penetration depth the integral dose to the healthy tissue mostly exceeds the target dose and limits the tumor dose because of severe complications.

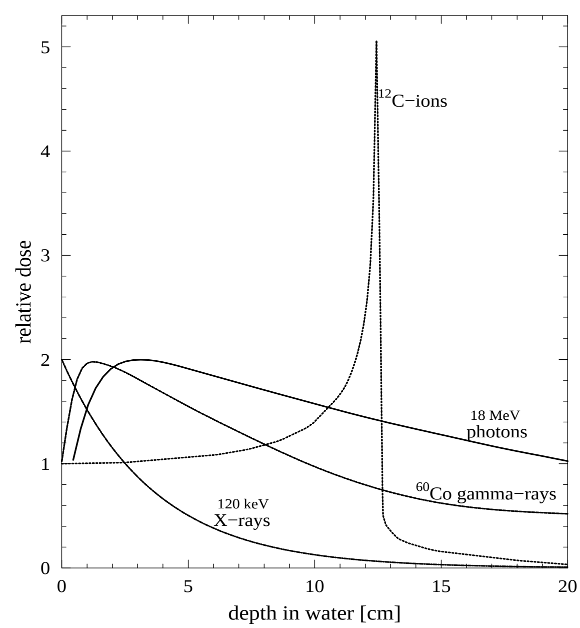

Fig.1 *Comparison of depth dose profiles of X-rays, Co-gamma-rays and electron Bremsstrahlung with a carbon beam showing an inversed dose profile with the maximum energy deposition at the end of the range.*

The second way to improve radiotherapy was the change of the radiobiological interaction mechanisms. Neutron beams are densely ionizing radiation because of the high Linear Energy Transfer (LET) of the reaction products and are able to kill radioresistant cells with high efficiency. Therefore, the local tumor control by neutron irradiation is drastically improved, especially for radioresistant tumors. Unfortunately, neutron beams show a similar dose depth curve like Co-gamma radiation, thus producing a high amount of biologically

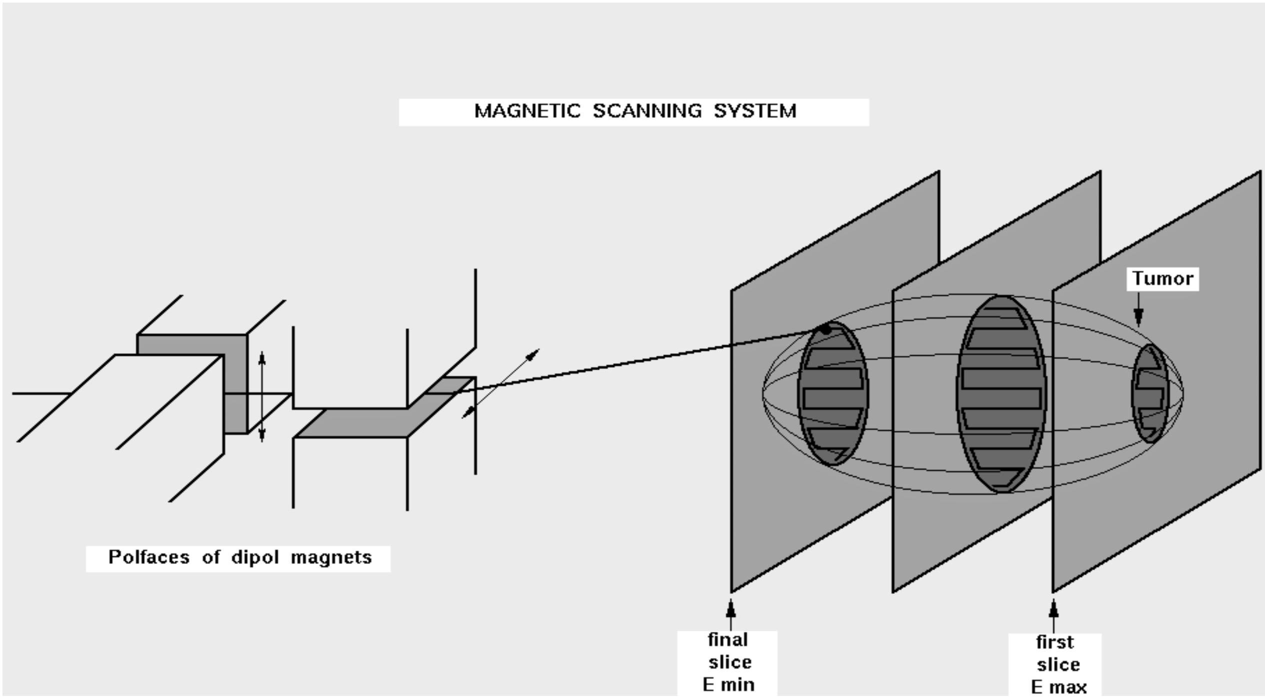

Fig 2. *Principle of the rasterscan technique: the target volume is dissected in slices of equal particle range and each slice is painted with a pencil beam in a rasterlike procedure.*

very effective damage in the healthy tissue arround the tumor. In consequence, neutron therapy has been terminated in most cases because of its severe side effects in spite of the good tumor control.
For further development of radiotherapy, beams of heavy-charged particles like protons or carbon ions yield a better dose distribution than any other modality and have an increased relative biological efficiency RBE like neutrons but restricted to the target volume [2].

1 Physical properties of heavy ion beams

The main physical advantage of ion beams is the inversed dose profile i.e. the increase of energy deposition with increasing penetration depth that culminates in a sharp maximum - the Bragg peak - just before the particles stop (Fig.1). Beyond the Bragg maximum the dose drops sharply to very small values. In addition, carbon beams experience only a small angular deflection when penetrating the tissue in front of the tumor. For a penetration depth of 10 cm the beam widening due to scattering effects is less than 1 millimeter [2]. In consequence, very complex target volumes can be precisely covered when using a fine carbon beam that is carefully guided over the target volume.

2. The rasterscan system

At GSI, a novel technique of beam delivery has been developed: the intensity-controlled rasterscan system [3]. In the rasterscan technique the target volume is dissected in slices of equal particle range and each slice is painted with a dose using a small pencil beam having a diameter of a few millimeters only (fig. 2). For this procedure each slice is covered by lines of picture points i.e. pixels and the beam is sweeped from pixel to pixel using two pairs of fast deflection magnets. For each pixel the number of particles has been calculated to achieve later on the desired biological effect. The resulting particle distribution is normally not homogeneous over the treated field because planning corrections have to be made for density inhomogeneities as well as for the effects of previous dose depositions when more distal layers are treated before and in addition for variations in the RBE. With the rasterscan technique these inhomogeneous particle covering can be followed to a large extend in the same way as a TV is able to produce images of various contours and intensities. But in contrast to the TV imaging the rasterscan produces a 3-dimensional ‘volume-picture’ by reducing the beam energy and accordingly the penetration depth from slice to slice.

In the technical realisation of this concept the energy variation is achieved by the accelerator. The complete particle range between 2 and 30cm corresponding to 80MeV/u to 430MeV/u carbon energy is dissected into 255 steps. According to the tumor geometry a subset of 30-60 energies is usually needed to fill the volume and is available on request from pulse to pulse within 2 seconds [4]. In order to facilitate the irradiation of large and small volumes and to reduce the irradiation time it was necessary to have flexibility in the choice of the beam spot size as well as in the beam intensity. The changes of energy, focus and intensity (EFI) have to be available on request i.e. from pulse to pulse from the accelerator. Under the very stringent condition the spatial stability of the beam at the target is maintained. In other words. the center of the beam spot has to stay constant within 1mm whatever EFI combination is selected out of more than 20,000 possible combinations.

Accelerator Requirements

energy range	85...430 MeV/u corresponding to: 20...300mm H_2O
energy stepping	255 steps variable step size: 0.3...2.6% cycle time: 5s
energy definition	0.05%
extraction mode	slow: 2s flat top
extraction interrupt	fast: < 1ms
intensity range	maximum 15 steps $2 \times 10^6 ... 2 \times 10^8$ particles/spill
beam spot size	maximum 7 steps FWHM: 4...10mm no variation within the treatment
beam spot stability	< 20% FWHM achromatic seting

A complete treatment of a large tumor in the basis of the skull using 60 energy slices took 12 minutes altogether. These short treatment times are made possible by the high speed of the scan in order of 10m/sec. The overall treatment time is also determined by the speed of the safety system

3. Safety system

The basic issue of the safety system is to protect the patient against any possible failure. In such a complex machinery like a heavy-ion accelerator many components have to be controlled for a correct beam delivery [5]. For the safety system only components that could cause an irradiation at a false position or a false intensity are important. Malfunction that could cut off the beam but will not influence the beam precision like vacuum problems appear on the screen as warning signals. The inhibitive signals of the safety system are mainly created by the beam diagnostics at the treatment area. There, the beam localisation and intensity is measured just in front of the patient. For this purpose a pair of intensity and localisation counters i.e. ionisation chambers and multiwire proportional counters are installed that compare the beam status with the precalculated values every 120 μsec. Intensity deviations of a single pixel up to 5 % yield warnings, larger deviations cause interrupts. Spatial deviation of the beam position of more than 30 % of the halfwidth of the beam cause interruptions, too. From the experience with many phantom irradiations and the first patient treatments it is obvious that these extremely strict conditions can be fullfilled. During the daily course of patient treatments only a few beam interrupts occured. This demonstrates that the synchrotron beam can achieve a very high stability although no passiv modules like slits etc are used for beam shaping.

4. In vivo beam localisation by PET

Due to nuclear reactions a small fraction of the stable carbon ions is converted to ^{11}C and ^{10}C. Both isotopes are radioactive and decay with a half life of 20 min and 19sec, respectively under the emission of a positron [6]. The positron annihilates with a target electron and emits two 511 keV gamma rays coincidently under 180°. A large fraction of these coincident quanta can be detected by two gamma cameras on opposite sites of the patient and their origin i.e. the region of the stopping carbon ions can be reconstructed after each treatment session. Using this techique of positron emission tomography (PET) it is possible to verify with a precision of two millimeters whether the target volume was irradiated correctly. The use of PET for the localisation of stopping ions was developed by the FZ Rossendorf and represents a completely new techique of in vivo monitoring. It is only possible for heavy ions like carbon but not for proton beams.

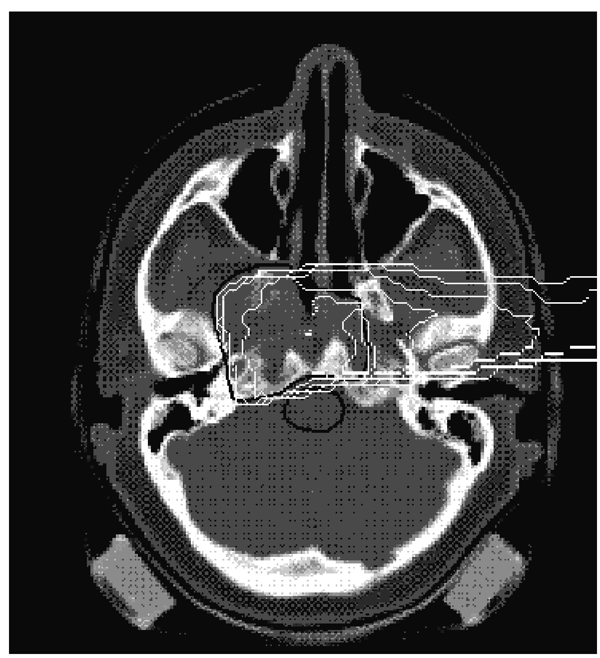

Fig.3 *Physical dose as restulting from the biological optimization for a single field used for the first patient. The Idodose lines correspond to 20, 40. 60, 80, 90, 100% of the maximum dose.*

5.Radiobiological advantages of heavy ions

In addition to the physical selectivity, superior to any other kind of radiation including protons, the heavier ions supply a greater biological efficiency because of their increased LET and consequently increased RBE at the end of range. DNA experiments measuring the fraction of irrepairable double strandbreaks after heavy ion exposure revealed that at the end of the range of the carbon ions the rate of repair drops from 80% to 20% or even less in experiments using cultured cells [7]. However, the relative biological efficiency RBE is no parameter that can be measured in *in vitro* experiments and then transferred as a fixed number to the exposed tissues in patient treatment. As increased RBE is caused by reduced repair, the repair capacity of the different tissues determines the RBE. Generally, slowly growing tumors are therefore very radioresistant to photon irradiation, and show the largest effect in RBE when exposed to carbon beams. For radiosensitive and fast proliferating tumors the gain in biological efficiency is smaller. But the extreme tumor-conform dose delivery always remains a strong argument for carbon ions.

6. RBE and treatment planning

Because of the different radiosensitivities of the tissues involved in patient treatment it is neither possible to determine experimentally the RBE distribution over the treatment fields for each individual patient nor for typical treatment scenarios. Therefore, it was a fundamental condition for the heavy-ion therapy to develop a theory that allows to calculate the RBE. The local effect model (LEM) explains the RBE on the basis of the X-ray sensitivity of the tissue and the radial dose distributions within the particle tracks and their dependence on energy and atomic number of the particles [8]. LEM has successfully been tested in numerous cell and animal experiments before it was applied to treatment plans.

In treatment planning LEM is combined with the dose optimization using a physical beam model that includes beam fragmentation, energy loss angular scattering, etc. and optimizes the distribution of the biological effect (Fig. 3). The treatment planning system is an adaption of the Voxelplan system (DKFZ-Heidelberg) to the modalities of heavy particles [9]. Apart from the biology the major problem of heavy particles are the density inhomogeneities caused by very different types of tissue like skin, fat, bone, muscles and air. In order to correct the particle ranges regarding these inhomogenities the gray values i.e. Hounsfield numbers of the CT scan are transformed to density values that are taken into account in the planning procedure. The physical optimization of the treatment field takes only a few seconds of computer time while the biological optimization that takes into account all the different tissue sensitivities as well as the dose levels takes hours. However, for the first time in radiation therapy the treatment planning is based on biology and not only on the physical dose optimization.

7. Heavy-ion therapy at GSI

In the therapy project at GSI all the radiobiological and physical advantages of carbon beams are exploited to a maximum. The new technique of tumor-conform irradiation using carbon ions represents a quantum leap in radiothearpy: The target volume can be shaped excactly to the tumor.

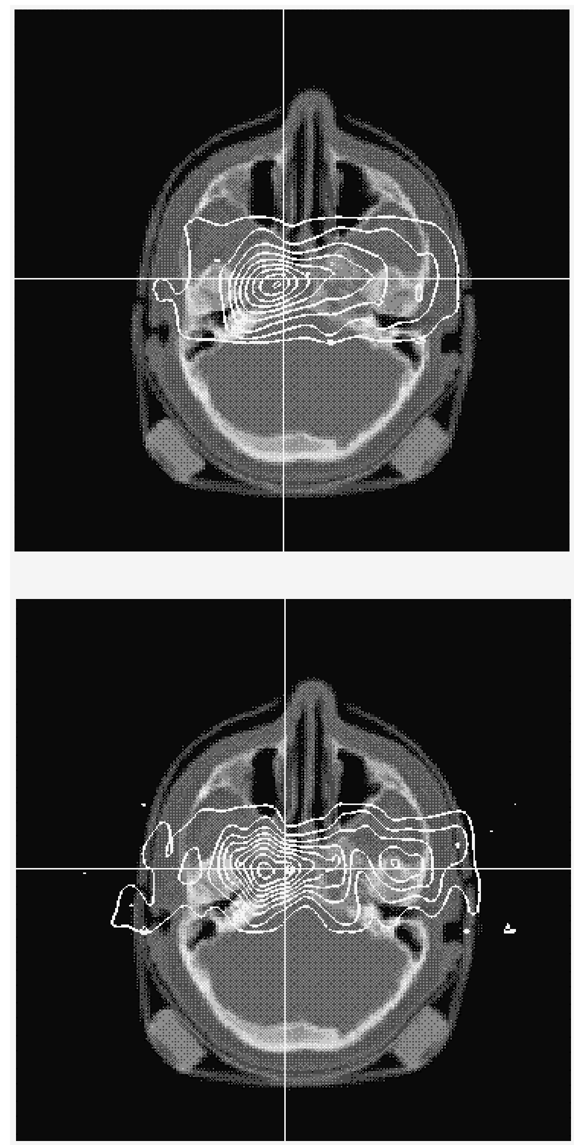

Fig. 4 *X-ray computed tomograms of a patient that has been irradiated with* ^{12}C *in Dec. 1997. the upper contour plot shows the precalculated* ß$^{+}$*-activity distribution, the lower contour plot shows the measured* ß$^{+-}$*activity distribution. The isodose and isoactivity lines are spaced by 10% of the maximum value.*

The variation in RBE of different tissues are included in the planning. During irradiation the control of the beam in front of the patient is visualized online. After each fraction the result of the treatment in the patient is measured with the non-invasive PET technique.

Alltogether, the GSI system is more reliable and more flexible than any other system used up to now.

On Saturday, December 13, 1997, the first patients were treated with a carbon ion boost after the legal approval procedure for the therapy unit had been finalized two days before. During five consecutive days of operation two patients were treated with two opposing fields per fraction summing up to a total of 18 applied fields. The systems's performance proved extremely stable and the patient monitor data as well as the PET reconstruction did not reveal any critical aspect (Fig. 4). The extremely successful start of the patient treatment was the consequence of an intense and careful preparation phase of all subsystems in the project. These initial patient treatments at GSI demonstrated for the first time in the world the feasibility of an extreme tumor-conform carbon beam application using the methods of active beam delivery i.e. the intensity-controlled rasterscan in combination with the fast energy variation by the accelerator.

8. Future Developments

The therapy project at GSI is presently limited to five years during which a few hundred patients with tumors in the base of the skull and in the brain are going to be treated. It is the purpose of this project to test the clinical feasibility of the novel beam application and the biology-based treatment planning system. The final goal of our project, however, is to transfer this technology to the clinic in order to serve the tremendous demand of many thousand patients who could profit from heavy-particle therapy. For this puropose the design of a dedicated clinical therapy unit is under way in a joint effort of the TERA-project (Italy) and Austron project (Austria) in a common study group at CERN, Geneva.

We hope that these efforts will be successful and that the clinical machine can be put in operation by the time the GSI project is supposed to have come to its end.

Acknowledgement

The heavy-ion therapy was only possible because of the enormous support of our colleagues at GSI, cutting back their own scientific programs to allow more beam time for therapy. We would like to thank them for their sympathy. We owe special thank to Prof. H.J. Specht for his generous support. His enthusiasm was one of the driving forces that got the project started in such a short time.

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