

What we can learn from heavy ion therapy for radioprotection in space

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Abstract

A major problem in manned space flight is the impact of cosmic radiation, especially that of heavy charged particles since they have an elevated biological efficiency (RBE). The RBE estimation determines the potential exposure for man. It is one of the limiting factors for space flight and should be known very precisely. The same is true for heavy-ion tumor therapy where beams of carbon ions are used to treat deep-seated tumors. There, RBE values determine the dose distribution and are estimated using the Local Effect Model (LEM). The clinical results confirm the correctness of LEM and suggest to use the same theoretical approach to assess the impact of cosmic rays.

KEYWORDS: Heavy ion therapy, relative biological efficiency, track structure models, scanned beams.

1. Introduction

The prerequisite for a successful application of heavy ions like carbon in tumor therapy is the precision of dose delivery and the knowledge of the relative biological efficiency in the target volume as well as in the healthy tissue affected by radiation mostly in the entrance channel.

The problem of tumor-conform delivery of carbon ions to the target volume has been solved with the introduction of the intensity-controlled raster scan technique. There, the target volume is dissected into layers of equal particle range and each layer is covered by a net of pixels. For each pixel the number of particles has been calculated before and the beam is moved from one pixel to the next after this number has been reached. When one layer has been painted, the energy is reduced for the next layer which is then painted in the same way. Using this technique, target volumes of any shape can be filled very precisely with a precalculated dose. However, the number of particles to be delivered to a pixel significantly depends on the relative biological efficiency (RBE) of the particles traversing or stopping in the pixel. Because RBE depends on physical parameters like atomic number and energy and on biological parameters like repair capacity and on the different endpoints like cell killing in the target volume and late effects in the normal tissue, RBE determination is the most important task for ion therapy.

In view of this complexity it is not possible to determine the RBE distribution over the treatment field for each individual patient experimentally. In practice, the RBE is calculated using the local effect model (LEM) that is able to predict RBE values on

the basis of the track structure of the different particles and energies, the size of the cell nuclei as target and the dose effect relationship for sparsely ionizing radiation. Using these input parameters RBE for cell killing as well as for late effects can be calculated and optimized in the treatment planning. Up to now, clinical experience fully confirms the RBE estimation of LEM for more than 50 patients treated so far.

In consequence it might be worthwhile for radiation protection in space to analyze the results of LEM for its application to radioprotection in space because it is the only model that is subjected to the most critical test, the radiotherapy.

2. Motivation for particle therapy

Almost half of one million cancer incidents every year in Europe 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 frequently 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 to 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 R.R. Wilson [1] in 1946. Ion beam therapy started 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]. 430 patients have been treated with neon ions at Berkeley and another 700 with carbon, most of them at NIRS, Chiba, Japan. At GSI more than 50 patients have been treated up to now, using beam scanning and a biology based therapy planning.

3. The physical basis

At high energies, heavy-charged particles like carbon ions interact very weak 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 (Fig. 1). 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 energy variation is generated using passive absorber systems [4]. The lateral distribution is reached by scattering foils and the spread beam is limited with collimators. This procedure leads to a better dose distribution than was possible with the conventional photon therapy ten years ago. However, in the meantime a similar dose distribution can be produced using intensity-modulated photon application. For the first time ever it was possible at GSI to produce a range modulation for heavy ions by an 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.

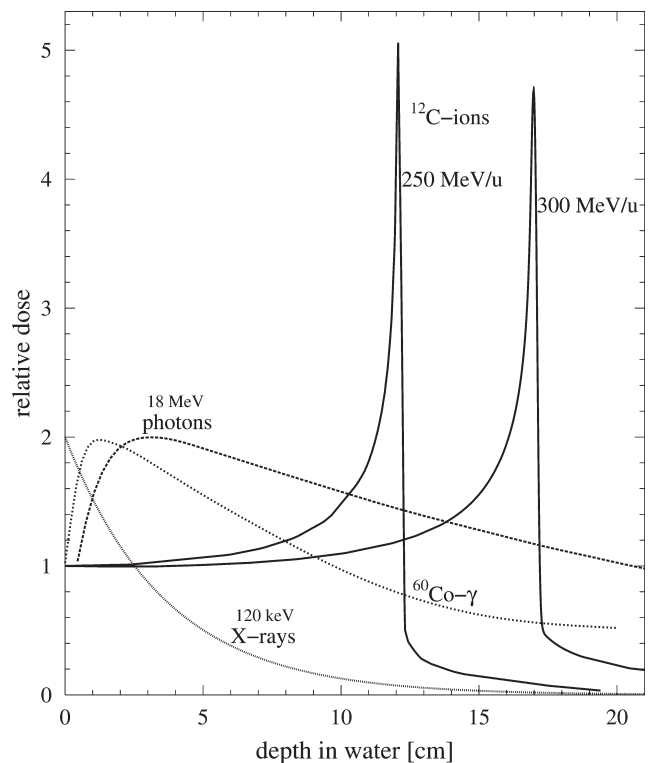


Fig. 1 – Comparison of the depth dose distribution of photons (conventionally used) and carbon ions. With photons the dose decreases exponentially with increasing depth, i.e. the dose in the target volume of deep-seated tumors is smaller than the dose delivered to the healthy tissue around. Carbon ions 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.

4. Target conform treatment by scanning

In order to translate the optimum physical properties in adequate irradiation procedure the rasterscanning system has been developed at GSI in the last 10 years [5]. In this three-dimensional 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. The central problem of this procedure consists in the pre-irradiation of the layers in front when the deeper layers are treated. 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

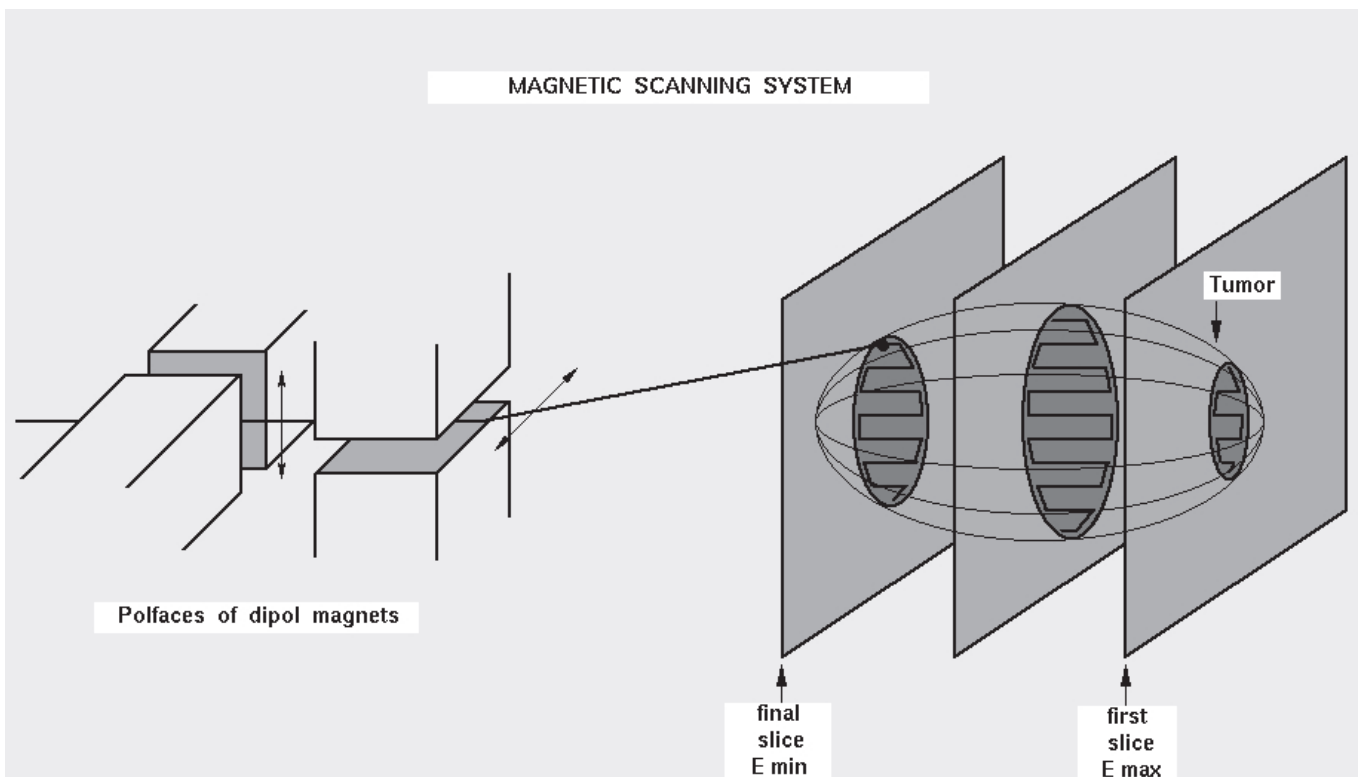


Fig. 2 – Principle of the rasterscan technique: the target volume is dissected into slices of equal particle range and each slice is painted with a pencil beam in a rasterlike procedure. The velocity of the scanning procedure is controlled by the beam intensity in such a way that any homogeneous or inhomogeneous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

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 TV the third dimension can be added in the ion scanning system with a depth modulation by energy variation from the accelerator. In a synchrotron this can be done from pulse to pulse, i.e. within one second or less. This way it is possible to irradiate irregularly shaped volumes with a very high precision and without excessively damaging the normal 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 called Voxelscan [6].

5. Beam monitoring and PET-control

On the one side the rasterscan system is very effective producing precise target contours, on the other

side 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 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. At the GSI system 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 microseconds while the position of the beam center is recorded once every 120 microseconds 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 coordinates can be visualized directly on the control panel as shown in Figure 4. This offers a very precise on-line status control.

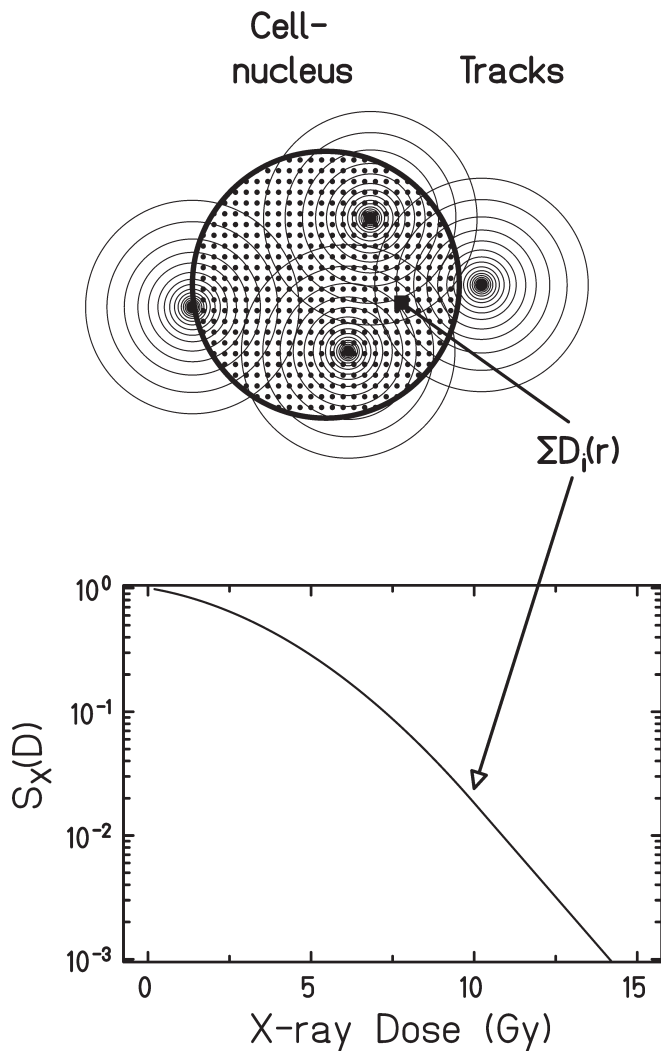


Fig. 3 – Principle of the Local-Effect-Model: The radial dose distribution of the track is divided into zones of nearly equal dose and the probability to produce a lethal lesion in each zone is calculated according to the X-ray dose effect curve [11].

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 the 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 gamma emission. The γ -rays are simultaneously emitted within 180° to each other. Because a fraction of these gamma rays leaving the patient can be measured in two gamma cameras from outside, the stopping region of the primary beam can be traced back. However, the reconstruction of the PET image can be performed after irradiation. Possible deviations can therefore be corrected in the next irradiation fraction by changing the treatment plan. But 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.

6. 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 main target for the attack of ionizing radiation. 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. 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 of the local ionization density shows that can directly be correlated with the local density of the DNA damage. Many experiments showed that for lighter ions an optimum for therapy exists at atomic number six, i.e. for carbon ions [9]: For 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 normal tissue in front of the tumor. For very light ions like protons no clinically significant damage potentiation can be observed in the target volume. Carbon ion beams therefore represent an optimum in biological efficiency in tumor therapy – also on the molecular level of DNA damage and repair along a therapeutic beam [10].

The increased RBE represents the greatest advantage of the carbon ion therapy. However, this advantage is also linked to some complications since the increase of RBE mainly depends on the differences in repair. Tissues that are radiosensitive due to their reduced repair capacity do not exhibit an enlarged biological effect when irradiated with carbon ions. 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.

7. The Local-Effect-Model (LEM)

In order to incorporate repair and more detailed physical information into the RBE calculations the Local-Effect-Model LEM has been developed [11]. The basic idea of this model is to cover the cell nucleus by individual tracks in a Monte Carlo simulation and divide the tracks into concentric

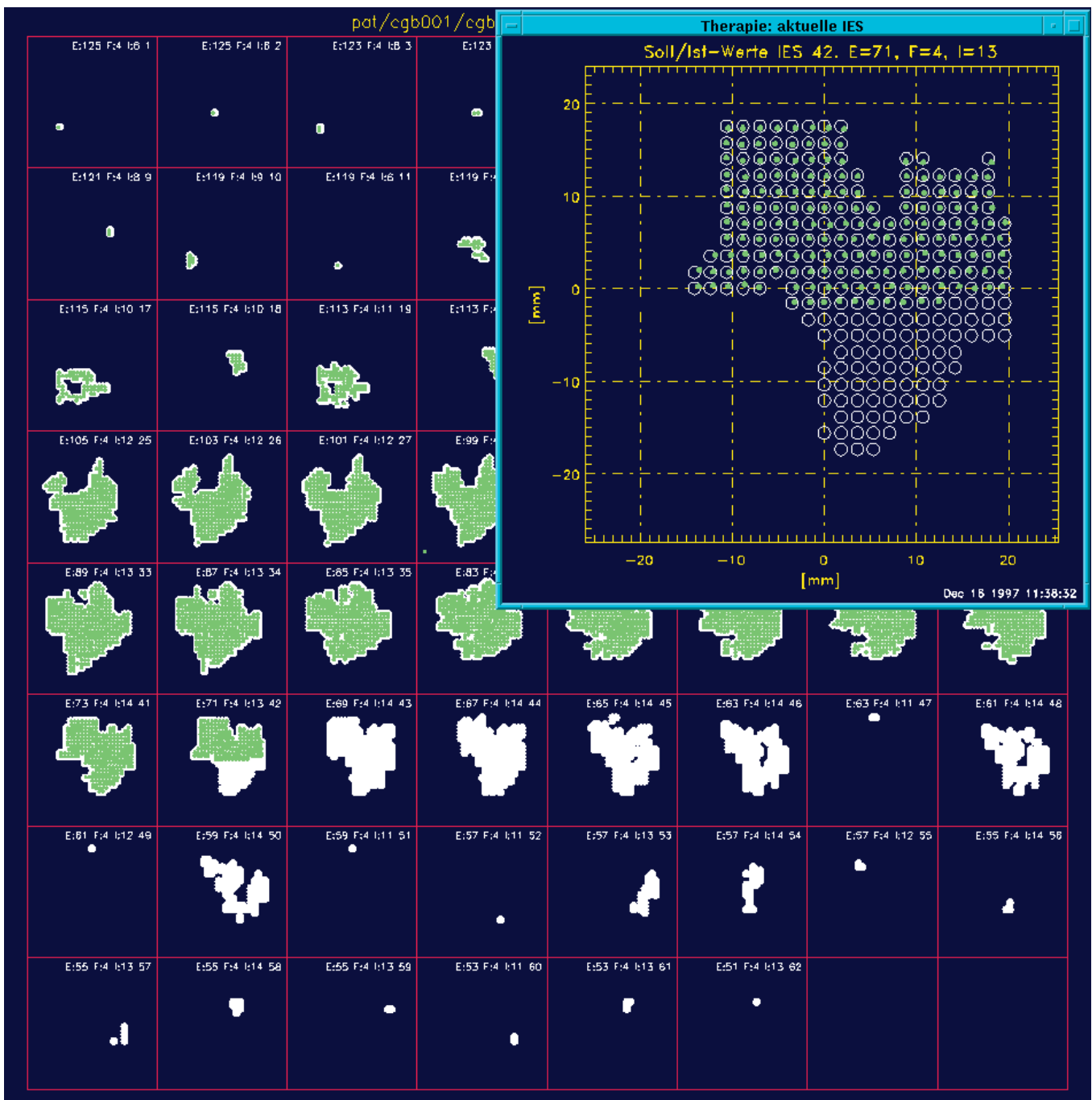


Fig. 4 – Irradiation layers in the tumor. Due to density inhomogeneities, such as bones or air-filled holes, a large variety of energies has to be used in order to get to the same depth level, leading to very complicated irradiation patterns of individual layers. Within every layer, the individual target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

zones of equal doses. Then the probability to produce lethal events in the cell nucleus separately is calculated for the local dose in each zone (Fig. 3). This is done by comparing the measured effect for the same X-ray dose to the local dose inside the track. The probability is then scaled in accordance with the volume of overlap between cell nucleus and track zones. Finally, all local probabilities are integrated over the volume V of the cell nucleus. The survival probability for an

individual cell is calculated to be:

$$S_{\text{Ion}} = e^{-N_{\text{lethal}}}$$

where N_{lethal} , the average number of lethal events, is given by

$$N_{\text{lethal}} = \int \frac{-\ln S_x(D(x, y, z))}{V} dV$$

Because in the X-ray response curve $S(D)$ the cellular repair is expressed in the shoulder, the use of this shouldered curve as template introduces repair into the track structure model. The non-linear X-ray curve explains the increase in RBE for high LET particles: In the local zones where the local dose in the track is low the produced effects correspond to low X-ray doses where repair is largely present. If the local dose is greater, the correspondence at the X-ray curve moves over the shoulder and the same dose increment becomes more efficient than at lower doses. Consequently, RBE increases, when a large fraction of the dose inside each track produces non repairable damage. This explains also that biological tissues having large shoulders in the X-ray curve produce large RBE maxima, while no shouldered X-ray do not show a marked RBE maximum, because there is no change in the increment for linear X-ray effect curves.

The decrease of the RBE maxima follows the same pattern as in the older track structure models: Overkill caused by much too high ionization densities waste a major part of the dose in the thin down region of the track. The calculations of local ionization densities are performed as Monte Carlo calculations. However, the tracks overlaid to the critical target do not have to be identical. Mixed radiation fields as created by neutrons or in an extended Bragg peak in heavy-ion radiotherapy can be treated in this model with great success [12].

For the application of the local effect model, the basic features that have to be known are the radial dose distribution of the tracks, depending on the energy and on the atomic number; secondly, the size of the critical target i.e. the cell nucleus and finally, the X-ray dose effect curve for the endpoints under consideration.

The dependence of the model on measurable quantities makes it more transparent and accessible to direct tests. Before used in therapy LEM has been tested extensively in cell and animal experiments. It has been found that the results of inactivation measurements can be predicted with reasonable accuracy including mixed radiation modalities like neutrons or extended Bragg peaks.

8. Treatment planning

For the therapy, RBE is calculated for the complete irradiated volume i.e. the target volume and the affected volume in the entrance and tail region according to the local effect model LEM for small volume points (voxels). Basis of these calculation is – as mentioned before – the radial dose distribution of the tracks depending on energy and atomic numbers, the size of the critical target i.e. the cell nucleus and the X-ray sensitivity. These calculations are very accurate in case of cultured cells. For tissues, irradiated during patient treatment, frequently the last part, the X-ray sensitivity is not available in form of dose response curves. However, from the

known fractionation response of the tissues in conventional therapy, a hypothetical dose effect curve can be calculated [13] and used for the RBE calculation [12]. With this method also the biological response for fractionated carbon treatment can be calculated and used to modulate the physical dose distribution in order to achieve a homogeneous biological effect [14]. Because RBE can be calculated for the different voxels, the difference in RBE between early effects in the tumor and late effects in the normal tissue can be built in in these calculations giving the probability of cell killing in the target volume and possible late complications in the normal tissue.

In a typical treatment plan of a patient at GSI (Fig. 5) 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 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 Figure 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.

9. Results

Up to now 57 patients with radioresistent tumors in the base of the skull, in neck and sacrum have been treated with great success. In all cases the patient could be treated as planned and no major delay occurred due to technical problem. PET analysis was performed in most of the cases and yielded mostly good agreement with the expected β^+ -distributions. In all but 3 cases an efficient tumor control could be reached, in a large fraction a rapid tumor regression was observed. From the three patients having recurrent tumors was one out of field and the other two at the border of the treatment field.

Two patients died from other deceases, but showing good tumor control before.

The excellent tumor control rate is a strong indication for the correctness of the RBE values obtained from LEM calculations. In addition early side effects like erythema, hairloss and muscosa were mild and did not exceed grade II.

Finally no late effects have been observed also the observation time after exposure is now long enough for the expression of late effect.

A frequent incidence of severe late effect has

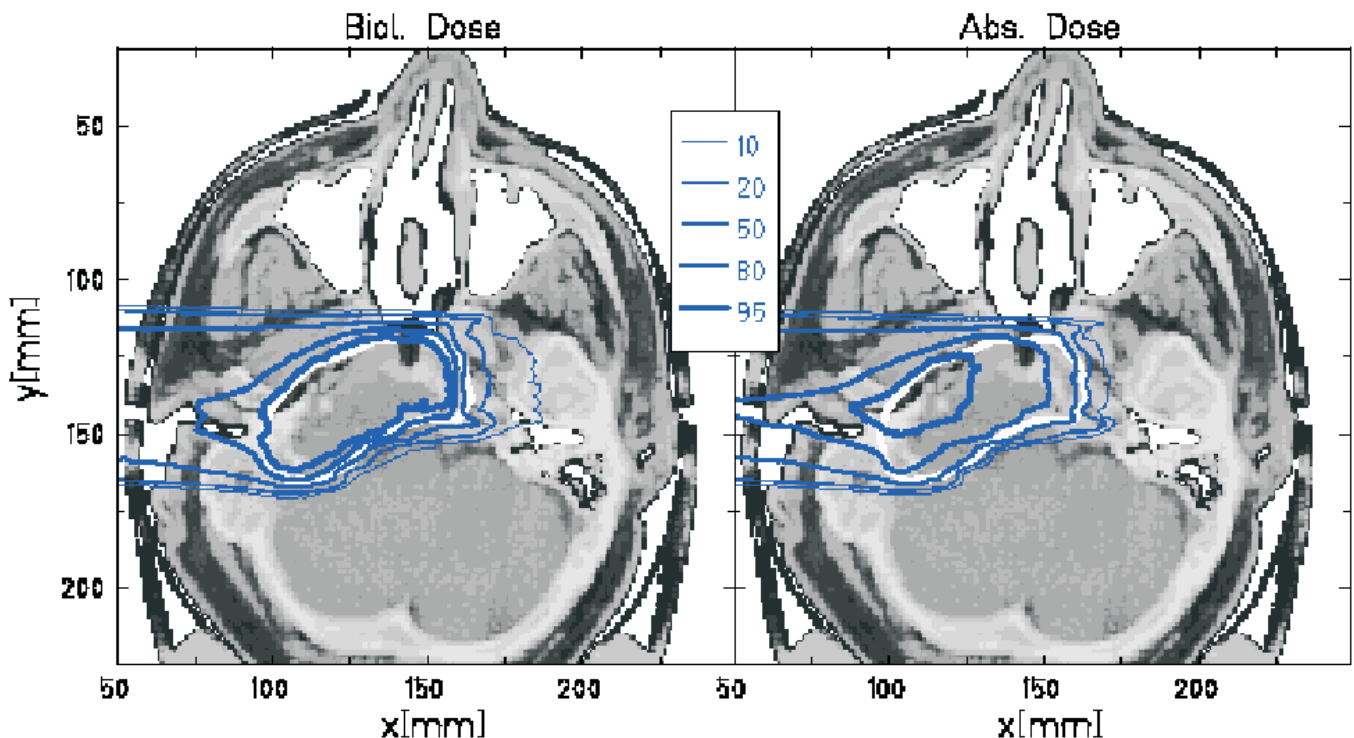


Fig. 5 – Comparison of the absorbed dose with the biological effective dose for a tumor in the base of the skull. The biological effectiveness is increasing towards the distal end in the target volume. Therefore, a lower absorbed dose yield the same biological effect.

been proposed on the basis of a simpler track structure model as developed by the coworkers of R. Katz (see the report on “ion kill dosimetry” in this conference). The disagreement between the predictions and the reality shows again very clearly the limitations of the older model calculations.

The clinical results of the carbon therapy using target conform beam delivery by scanning beam application based on realistic RBE values are very convincing.

Therefore a carbon therapy is presently planned at the Heidelberg hospital where thousand patients could be treated per year. In addition, in other European countries most of the proposed facilities include both, carbon and proton treatment [2].

10. Conclusions

The successful application of the Local-Effect-Model for the calculation of RBE value has been demonstrated clinically. The LEM is basically a mathematical convolution of the non linear dose response curve as measured with sparsely ionizing radiation with the dose distribution inside the particle track. Because the dose response curve contains the biological properties of tumor response, this response is translated into the efficiency of carbon irradiation. The same procedure can also be successfully applied to other effects like the induction of

DNA breaks by heavy ions (see S. Brons et al. this report).

LEM has also been applied successfully to effects of film blackening by heavy ions [15] and for the heavy ion dosimetry of thermoluminescent detectors [16].

In consequence this LEM should also be used to analyze the genetic effects of ion exposure that are important for space research.

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Parts of this manuscript have also been used for proceedings of other conferences.

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