Tumor Therapy with Ion Beams: From Cell Experiment to Treatment Planning

Carbon ions have a decisive advantage: high tumor dosage, yet low effects on normal tissue. Furthermore, they have an increased biological effectiveness in the tumor. These particular characteristics are successfully implemented into treatment planning at the 'Gesellschaft für Schwerionenforschung' (GSI) in Darmstadt, Germany.

By Wilma Weyrather, Ph.D., Associate Professor Michael Scholz, Ph.D., Michael Krämer, Ph.D., GSI, Darmstadt, Germany

The most important objective in radiation therapy is to apply an optimal dose to the tumor and spare normal tissue as well as radiation-sensitive organs as much as possible.

Photon beams used in conventional radiation therapy show a less favorable distribution of the dose in depth (Figure 1) which is especially adverse when treating deep-seated tumors. Although it is possible to keep the maximum dose away from the radiation-sensitive skin, due to the exponential decrease behind the maximum, the dose in front of the tumor is greater than inside the tumor. In addition, radiation-sensitive organs in front of and beyond the target volume are affected by the radiation as well.

Beams of accelerated ions have a different depth dose distribution, which is more favorable for therapy. Within the entrance channel, which usually consists of normal tissue, the energy and velocity of the particle are still very high, while the absorbed dose is quite low. The particle dose begins to increase very steeply shortly before the particle comes to a halt in the 'Bragg peak.' This inverted depth dose distribution is a characteristic of all ions. The range of the particles and therefore the location of the Bragg peak are defined by the initial energy of the ions. By superimposing several Bragg peaks of adequate beam energies, large tumors can be irradiated at a uniform dose level.

Factors for the Choice of Ions

Apart from these physical characteristics, biological factors, such as the reaction of cells and tissue to radiation, play a role when selecting ions that are heavier than protons, such as carbon. In order to verify this statement in a cell culture experiment, the survival of CHO-K1 cells (Chinese hamster ovary) was measured at different depths after irradiation with carbon ions of 195 MeV/u (Figure 2). The green curve in the upper image of Figure 2 shows the applied dose as a

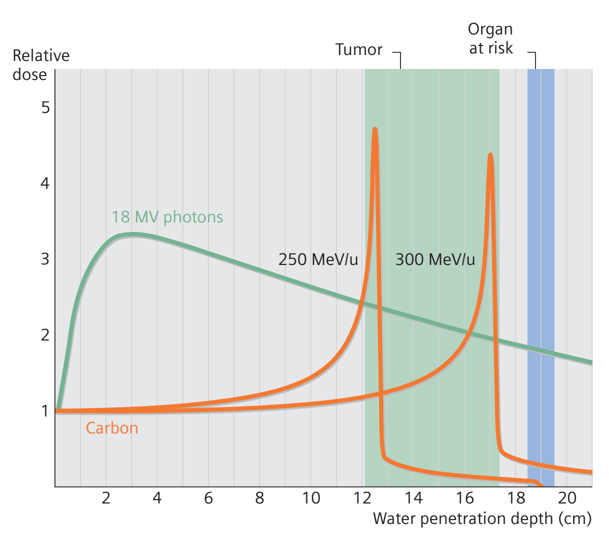

FIGURE 1: The depth dose distribution of carbon ions, more favorable than for photons, allows for a tumor-conform irradiation while simultaneously sparing healthy tissue.

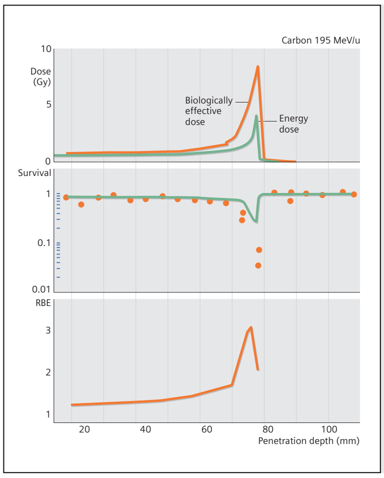

FIGURE 2: The higher biological effectiveness of carbon in the Bragg maximum leads to an increased biologically effective dose in the tumor volume.

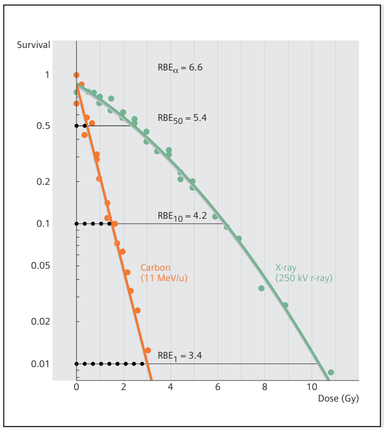

FIGURE 3: The dose dependence of RBE using X-rays and low-energy (0.5-mm range) carbon beams. The index refers to the respective survival rate.

function of the penetration depth. The green curve in the center figure shows the expected survival, assuming a dose response as for photon irradiation. The red dots show the actually measured survival rate after carbon irradiation. While only a minor difference of survival is found at the entrance channel, the survival at the Bragg maximum was much lower than expected. The red curve in the upper figure shows the photon dose that would have been necessary to apply to obtain the same effect as found with ions. This dose is called the 'biologically effective dose.' The lower figure shows the ratio of both doses. The ratio of photon and ion doses, leading to the same biological effect is known as the 'relative biological effectiveness' (RBE). The RBE is explained in detail in Figure 3, based on cell survival experiments. As shown in Figures 2 and 3, the RBE is not a constant value, but depends on a variety of factors:

1. *Dose:* The RBE is at its maximum with small doses (i. e., at high survival rates); it decreases in proportion to higher doses.
2. *Energy:* With high particle energies, that is, in the entrance channel, the RBE is initially low; however, it increases steeply with larger penetration depths and begins to rapidly decrease after a maximum value.
3. *Type of ions:* The position of the RBE maximum of carbon ions coincides with the Bragg maximum. This leads to an especially effective tumor dose. For protons, the increased RBE values are limited to the last few micrometers of their maximum penetration depth and play a secondary role in clinical application. For ions that are heavier than oxygen, this maximum shifts away from the Bragg maximum and moves towards the entrance channel and therefore into normal tissue, where it can later lead to undesirable damage.
4. *Repair capacity of the cells:* The RBE strongly depends on the cells' ability to repair. An irradiated cell tries to repair the radiation damage to its DNA and is usually very successful in doing so. The repair capacity varies with different cell and tissue types as well as from individual to individual. But it is nearly impossible for the cell to repair radiation damage caused by carbon in the range of the Bragg maximum.
5. *Oxygen supply:* The RBE is higher in hypoxic tissue, that is, in tissue with low oxygen supply.
6. *Clinical effect:* The RBE in the same tissue may differ with respect to clinical effects, e. g., acute or late damage.

Biophysical Model for the Calculation of Higher Effectiveness of Ion Beams

Considering this multitude of dependencies, the RBE values required for tumor irradiation can not be determined experimentally, mainly because it is impossible to directly transfer results from cell experiments to the organism – even using the same cell types. To accurately determine the necessary

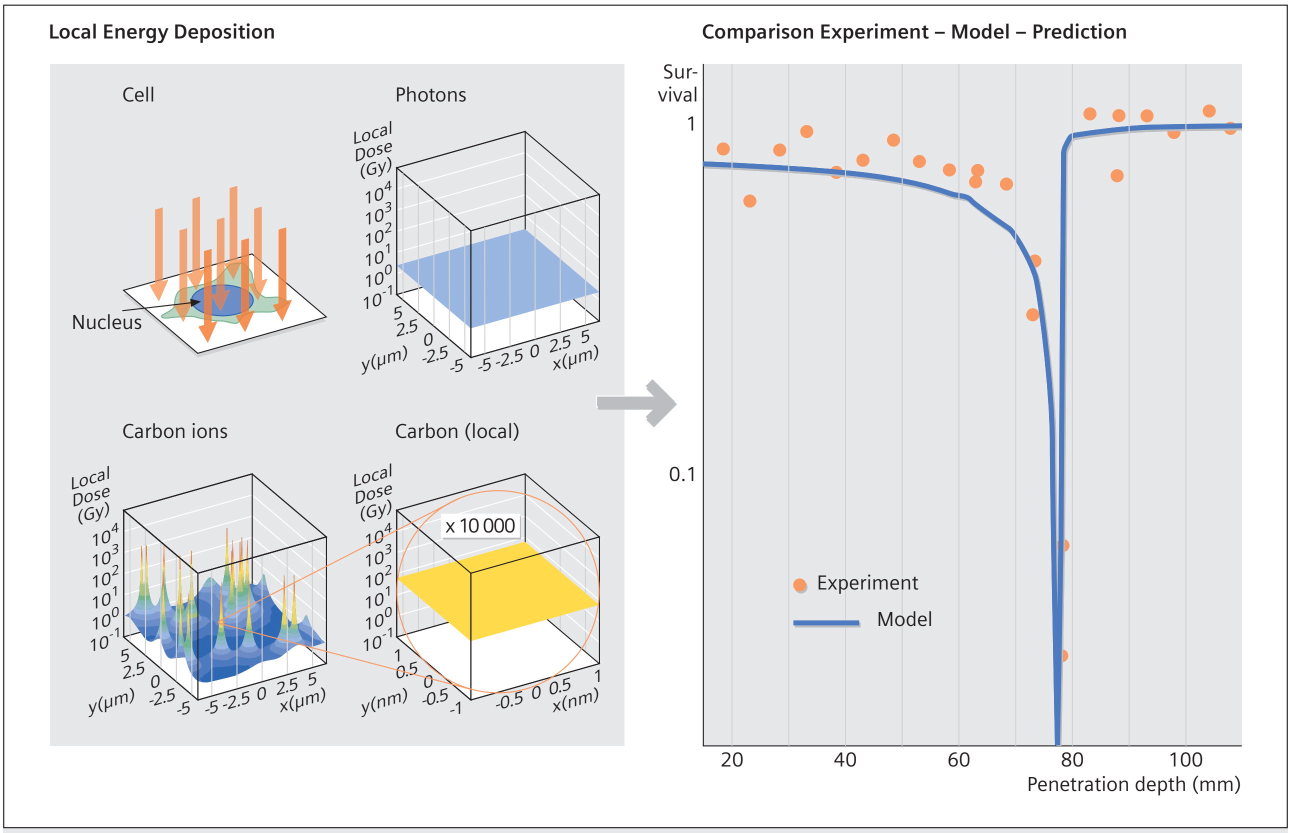

FIGURE 4: Modeling the effectiveness of ion beams with LEM.

irradiation dose, a biophysical model was developed, the local effect model (LEM). As the name indicates, the calculation of the biological effectiveness is based on the local energy deposition inside the cell nucleus as displayed in Figure 4. The left half of the figure shows the expected dose distribution after the ion rays have passed through the cell nucleus. Noteworthy are the high dose peaks at the location where ions pass through the cell. In comparison, only relatively low doses are expected in intermediate areas. After irradiation with conventional photon beams, however, the distribution appears to be highly uniform, even at microscopic dimensions (Figure 4, top center).

These differences in the local dose distribution are the reason why a higher biological effectiveness is observed for ions. While uniform distribution of the photon dose, especially at low doses, allows extensive repair of radiation damage, the high local doses of the ions reaching up to 10^6 Gy do not allow significant repair. Therefore, a higher effectiveness of ion beams can be expected.

The basic idea of LEM calculation is to compute the biological effects in very small subareas of the cell nucleus: when looking at a small, greatly magnified subarea, distribution for this subarea appears nearly uniform for ion beams similar to photon beams (Figure 4, lower center). This is why the biological effect in this volume should correspond to the one expected for photon beams at the same dose level. By dividing the cell nucleus into small local subareas with a homogeneous dose, for all subareas the biological effect of ion beams can be calculated from the photon dose response curve. The overall effect is the result of integration across these local effects.

The right part of Figure 4 shows that LEM allows for excellent prognosis. The calculated survival probability and the experimental data are demonstrated as a function of the penetration

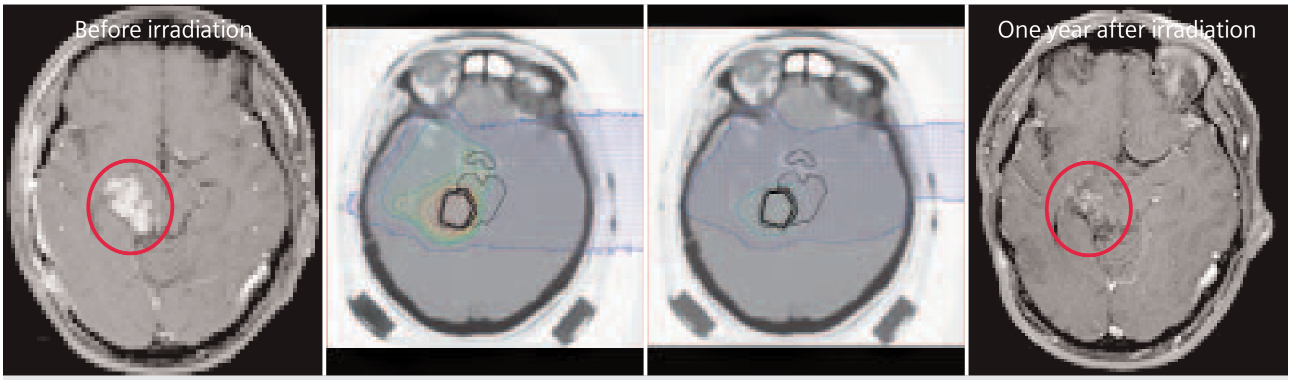

FIGURE 5: Example of an irradiation plan. A low inhomogeneous physical dose distribution generates a high biologically effective dose limited to the tumor.

depth of a carbon beam. The low effectiveness of the first centimeters as well as the drastic increase in the area of the Bragg maximum are correctly described by the RBE calculations with LEM.

Integration Into Treatment Planning

In addition to our own measurements, measurements of additional research groups were applied to test the model. The comparison to animal experiments was especially important, since tissue might react differently to irradiation than cell cultures. These cases showed a good correlation as well. As a result, clinical application of the model for therapy planning seemed to be reasonable.

The necessary physical dose distribution for this purpose, generally consisting of primary ions of different energies as well as additional nuclear fragments, is known from experiments and computations. The response of the respective tissue to photon radiation needed for calculation results from previous clinical experience with conventional types of radiation. To convert the strategy explained so far into real radiation therapy planning for tumor patients, several additional steps are required. The geometric prerequisites, location of the target volume, the organs at risk, and – particularly important due to the defined ion range – the density distribution of the tissue in the irradiated volume are usually obtained with 3D computer tomograms, frequently combined with magnetic resonance tomograms.

Irradiation as such is performed with a raster scan. For this purpose, the tumor is divided into small-volume elements. After the radiation oncologist has determined the 3D target specifications, the required ion energies, positions, and intensities are calculated first via the computer program TRiP98, developed at GSI. The biological effectiveness for each irradiated volume element is calculated simultaneously for the tumor as well as for normal tissue that is inevitably irradiated as well. Depending on the size of the target volume, up to 50 000 individual raster scan points are required to fully irradiate a tumor.

Successful Irradiation

The image sequence in Figure 5 shows the treatment over time: the tumor is localized with MRI, but irradiation is planned based on a CT scan, the difference between the purely physical dose (to the right) and the biologically effective dose (left), which is the relevant one for treatment success, is indicated by the color scale. The homogeneous high-dose range (red) is limited to the target volume, the physical dose is extremely reduced due to the RBE. The last partial figure shows the irradiation success in an MR image: even for tumors, which are relatively resistant to photons, good control rates with only minor toxicity can be achieved.

Literature

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