

Specification of Carbon Ion Dose at the National Institute of Radiological Sciences (NIRS)

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HIMAC/RBE/Carbon ion radiotherapy.

The clinical dose distributions of therapeutic carbon beams, currently used at NIRS HIMAC, are based on *in-vitro* Human Salivary Gland (HSG) cell survival response and clinical experience from fast neutron radiotherapy. Moderate radiosensitivity of HSG cells is expected to be a typical response of tumours to carbon beams. At first, the biological dose distribution is designed so as to cause a flat biological effect on HSG cells in the spread-out Bragg peak (SOBP) region. Then, the entire biological dose distribution is evenly raised in order to attain a RBE (relative biological effectiveness) = 3.0 at a depth where dose-averaged LET (linear energy transfer) is 80 keV/μm. At that point, biological experiments have shown that carbon ions can be expected to have a biological effect identical to fast neutrons, which showed a clinical RBE of 3.0 for fast neutron radiotherapy at NIRS.

The resulting clinical dose distribution in this approximation is not dependent on dose level, tumour type or fractionation scheme and thus reduces the unknown parameters in the analysis of the clinical results. The width SOBP and the clinical / physical dose at the center of SOBP specify the dose distribution.

The clinical results analysed in terms of TCP were found to show good agreement with the expected RBE value at higher TCP levels. The TCP analysis method was applied for the prospective dose estimation of hypofractionation.

INTRODUCTION

Many studies in the field of radiobiology have revealed that RBE, the biological effectiveness of heavy ions relative to Megavoltage photons, depends on various physical parameters. Primarily, RBE of a heavy ion beam gradually increases as the LET by the beam increases, reaches its maximum and then decreases. In addition, the RBE curve is known to show a different behavior for different ion species, fractionation schedules, or even dose levels. Even if these physical conditions are identical, RBE also varies as a function of biological parameters such as the type of tissue or cell, oxygenic conditions, endpoint of interest, and so on. The enormous complexity of the RBE determination hinders itself from being understood even at this moment.

Under these circumstances, clinical trials at HIMAC were

initiated following pioneering studies at Lawrence Berkeley Laboratory.¹⁾ One of the objectives of the HIMAC project is to understand the RBE of heavy ions. Clinical dose distribution is designed in order to cope with this objective: only the LET dependency is taken into account while the other factors are stayed as open questions that should be derived through the results of clinical trials. In this respect, our approach is in contrast to German one, which is trying to include those factors into their RBE model.²⁾ The details of our designing and specifying the clinical dose as well as verification of our method are described in this article.

DOSE DISTRIBUTION DESIGN³⁾

Boundary Conditions

Physical Beam Model

In a first approximation, the patient's body is regarded as a mixture of water with various local densities. Then we calculate the depth-dose and LET distributions of a monoenergetic heavy ion beam including fragmentation effects, using the code HIBRAC⁴⁾ developed by Sihver *et al.* The one-dimensional propagation of incident particles, as well as secondary and tertiary fragment particles originating from a

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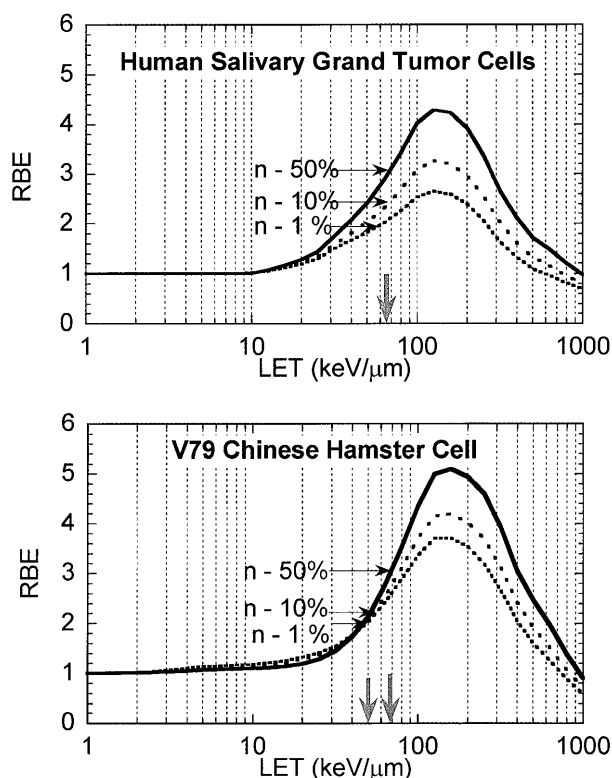


Fig. 1. RBE of HSG and V79 cells' colony formation for the incidence of C-135 MeV/n beams. The arrows correspond to RBE obtained using the neutron beam at the survival levels.

projectile are simulated in water by the code. LET or dose is deduced at each depth by recording energy deposition from each particle at that depth. The results of the calculations were verified through comparisons with experimental results.

Choice of Particle Species

Preceding the heavy ion radiotherapy project at HIMAC, we have 20 years of clinical experience using another high LET modality – fast neutrons. It was thus planned to first determine the particle species that possesses similar LET characteristics as the neutron beam, and then start heavy ion radiotherapy to make use of the same treatment schedule found effective in fast neutron radiotherapy. In those terms, carbon ion beams were considered most suitable.

Through biological experiments with a C-135 MeV/n beam (Fig. 1), it was found that the neutron RBE of different survival levels coincided with the RBE of the carbon beam at a dose-averaged LET of around 65 keV/μm. It can thus be assumed that the neutron beam is nearly equivalent to a 65-keV/μm carbon beam. In case of fractionated irradiation, the survival curves of crypt cells for neutron irradiation coincided with the survival curves for the irradiation of the proximal peak of the SOBP carbon beam with both single and fractionated irradiations.⁵⁾ The dose-averaged LET of the proximal peak of the SOBP was about 65 keV/μm. Even

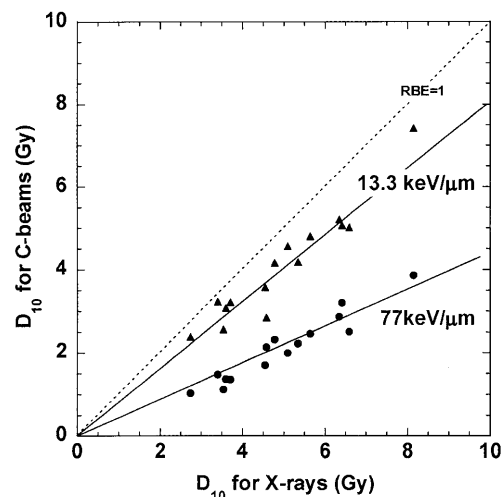


Fig. 2. D_{10} of various cell lines for X-rays and carbons.

though the biological effects for the SOBP beam should be slightly different from those for the monoenergetic beam of the same LET, these results of the effects of single and fractionated irradiations on crypt cells have supported the assumption that the NIRS neutron beam is nearly equivalent to a mono-energetic 65-keV/μm carbon beam. Consequently, we decided to select a carbon beam as the first heavy-ion beam to start clinical trials of heavy-ion radiotherapy.

Biological Endpoint

Referring to the work of Lyman *et al.* in the design of their ridge filter⁶⁾ and the work by Ito *et al.* at the RIKEN ring cyclotron,⁷⁾ we found that the response of HSG (human salivary gland) cells is representative for a variety of biological species. The response of HSG cells has a small shoulder in their survival curve, and belongs to early-responding tissues. In addition, RBE at D_{10} was found to be independent of cell types,⁸⁾ as shown in Fig. 2. Therefore, we selected HSG cells to be representative of a typical tumour response. RBE of HSG cells at the endpoint of D_{10} as a function of LET was applied for designing flat biological dose distributions. Here, a linear-quadratic (LQ) model was chosen as a biological model to describe the HSG response as a function of the given dose.

Clinical Endpoint

The clinical RBE of the carbon beam was determined based on the RBE for the neutron beam at NIRS. In neutron therapy, the clinically determined RBE for the neutron beam was 3.0 when the total number of irradiation fractions was 16 and the dose level of each fraction was 0.9 Gy. The clinical RBE value at the neutron-equivalent position of the carbon spread-out Bragg peak (SOBP) was then determined to be 3.0. In this respect, it is regarded that the clinical dose distributions calculated in our TPS primarily reflects the extent of acute reactions.

Design of SOBP

In the design of SOBP, we needed data concerning the LET dependence of the coefficients (α and β) in the LQ model of the survival curve for HSG, for the most common beam energy. The survival curves were experimentally investigated for various monoenergetic carbon beams in order to tabulate the coefficients.

Then, SOBP was designed to achieve a flat survival probability (10%) on the HSG cells of the entire SOBP region. It is regarded that cell survival for combined high- and low-LET beams could also be expressed by the LQ model, with new coefficients (α_{mix} and β_{mix}) for a mixed radiation field. The parameters were obtained by dose-averaging of the coefficients α_i and β_i for monoenergetic beams over the spectrum of the SOBP beam with f_i as a weight in dose of the i -th beam component,⁹⁾ as below:

$$\alpha_{\text{mix}} = \sum f_i \alpha_i \quad (1)$$

$$\sqrt{\beta_{\text{mix}}} = \sum f_i \sqrt{\beta_i} \quad (2)$$

The biological responses for the energy-modulated beam were validated for quite different biological samples, such as HSG cells,¹⁰⁾ MG 63 human osteosarcoma cells,¹¹⁾ and crypt cells of mouse jejunum.³⁾ Also, it was shown that the survival level of V79 Chinese hamster cells is successfully uniform throughout SOBP.

The RBE of HSG cells as a function of dose-averaged LET of SOBP shows that, around 80 keV/ μm , the carbon beam is equivalent to the NIRS neutron beam in terms of biological responses (Fig. 3) for the incidence of 290 MeV/n beam, which is the most commonly used one in radiotherapy at NIRS. It was found here that the neutron-equivalent LET of the spread-out beam was higher than in the case of a monoenergetic carbon beam of 135 MeV/n. This may be because a spread-out beam using C-290 MeV/n contained a large amount of low-LET components, and the LET spectrum of the beam spread over a very wide range.

The experimental results of an early reaction of mouse skin also showed that around 80 keV/ μm beams of carbon SOBP were equivalent to the NIRS neutron beam given in four fractions. Flat responses were observed within the SOBP for various cell lines (Fig. 4).

The relationship between biological- and physical dose distributions, estimated from the responses of the HSG cells, were assumed to be held even in the clinical situation. Then the clinical dose distribution was finally deduced by equally multiplying a fixed factor, the ratio between the clinical and biological RBE value at the point where the dose-averaged LET is 80 keV/ μm , with the entire biological SOBP. The scheme described above is summarized below.

Prescription of clinical dose

1. The dose level of the flat top of the biological dose dis-

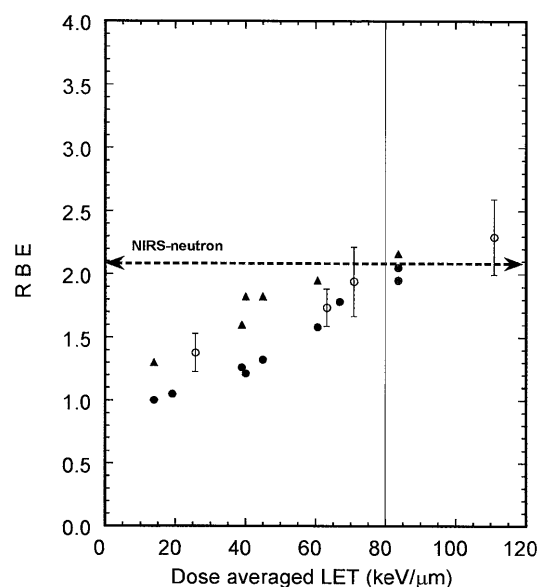


Fig. 3. LET dependency of RBE for colony formation of HSG cells at the 10% survival level. The data of RBE were obtained by exposures of a HIMAC carbon beam of 290 MeV/nucleon. The dashed line shows RBE for the NIRS neutron beam for HSG cells.

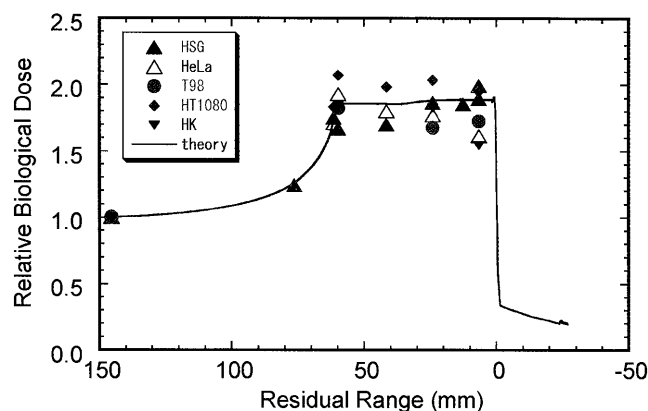


Fig. 4. Biological dose distribution of a therapeutic carbon beam. The Bragg peak of a monoenergetic carbon beam of 290 MeV/n was spread out to 60 mm.

tributions, which corresponds to the prescribed clinical dose to the target, is first given by a radiation oncologist.

2. The physical dose at the neutron-equivalent position is determined using the RBE value of 3.0.
3. The physical dose distribution of the SOBP beam is then normalized at the neutron-equivalent position.
4. The physical dose at the center of the SOBP is obtained and the RBE values at the center of the SOBPs are then obtained by dividing the biological dose by the physical dose.

Figure 5 schematically shows the method of determining the RBE at the center of the SOBP for clinical situations.

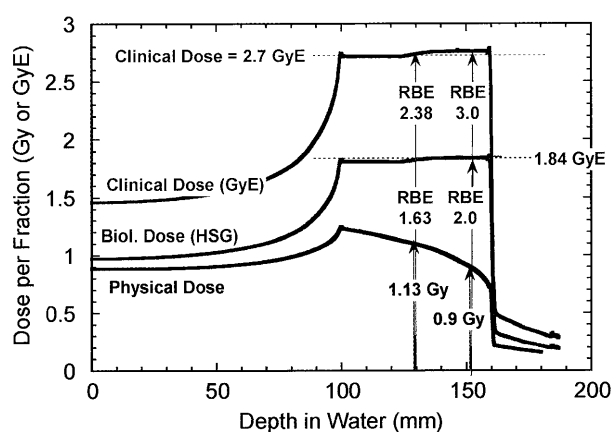


Fig. 5. Schematic method used to determine RBE at the center of SOBP for the clinical situation.

Strictly speaking, this approach is valid for a single field irradiation in one day, however, it is assumed that the each single field distribution could be addible in case of multi-port irradiation in one day.

This scheme is used to apply universal depth-dose distributions to all patients, independent of tumour type or dose level. The universal use of these depth dose distributions is considered to be adequate for clinical applications within clinical trials aiming at clarification of the clinical effectiveness of carbon ion RT in situations where the dependency or differences in radiosensitivity among tumour types are not yet proven. It is assumed that this contributes to a reduction of the number of free parameters.

During the first decade of clinical trials at HIMAC, we performed dose escalation studies on various tumour types to find the optimum dose using a universal shape of the SOBP. In other words, the differences in radiosensitivity between tumour types are at first attributed to the total dose in order to achieve a certain clinical result.

DOSE REPORTING

Dose Prescription and Individual Calibration

At this moment, a passive beam delivery method is considered to be advantageous to realize homogenous dose distribution over a moving organ in somatic region in contrast to an active beam delivery method (raster- or spot scanning). The irradiation system at HIMAC is based on the passive beam delivery method in order to cover tumours in moving organs by respiration, such as liver or lung, in clinical trials. The drawback of the passive beam delivery is its dose conformity, *i.e.*, a part of normal tissues proximal to the target is suffered from the high dose region. The layer-stacking broad beam irradiation¹²⁾ has been applied for some cases in order to reduce the high dose region in the normal tissues.

A pair of wobbler magnets together with a metal foil (as a scatterer) broadens the therapeutic carbon beam laterally.

An appropriate universal ridge filter is selected among discrete variation in width in order to shape the planned SOBP. The system fits to our dose-designing scheme: once the width of the SOBP is selected, the entire dose distribution is automatically settled independently of dose level or tumour type. Here, it is implicitly expected that the beam possesses a uniform biological or clinical effect over the entire target region.

A radiation oncologist determines the clinical dose to the tumour based on a certain protocol. Then the physical dose at the center of the SOBP, which corresponds to the clinical dose specified by the radiation oncologist, is derived using an RBE table in our treatment planning system in order to characterize the dose distribution. Table 1 shows the clinical RBE of carbon beams at the center of various sizes of the SOBP.

In the procedure of dose calibration, the physical dose is measured with an ionization chamber at the center of SOBP according to the IAEA protocol. Dose monitors in the beam line are calibrated with the physical dose at the center of SOBP for all patients once selected for the first course of the therapy. The ratio between the physical dose measured at the center of the SOBP and the output of the main dose monitor (monitor count) is stored as a calibration factor as the unit Gy/monitor count.

On the other hand, the standard depth-dose profile (60 mm SOBP for beams of 290, 350 and 400 MeV/n and 20 mm SOBP for those of 140 and 170 MeV/n) is measured daily. Fluctuation of the calibration factor is then compensated for on the basis of a daily trend in the standard depth-dose profile.

Table 1. SOBP width and clinical RBE at the center

SOBP width (mm)	Clinical RBE
30	2.8
40	2.6
60	2.4
80	2.3
100	2.2
120	2.1

Items Recorded in a Report

Our clinical depth dose distribution can be represented only with the width of the SOBP. In treatment planning, nominal and uniform dose is prescribed to the target volume. Due to this unique scheme, only the prescribed clinical dose and the corresponding physical dose at the center of SOBP calculated in treatment planning are recorded together with the width of the SOBP for each irradiation. After the irradiation, the actual physical dose that was given to the center of SOBP is deduced based on the preset monitor count and

the measured monitor count. This information is also stored in the report. In case of multi-port irradiation, the additive law in terms of clinical dose is assumed and the information is stored for each port.

VERIFICATION AND APPLICATION OF THE RBE MODEL

TCP Analysis for Non-small Cell Lung Cancer¹³⁾

The clinical validation of the underlying RBE model needs to be performed systematically using the clinical data derived from the dose escalation studies. We present here the tumour control probability (TCP) analysis for non-small cell lung cancer (NSCLC) as an example for the validation of the clinical results in terms of the above-mentioned clinical RBE prescription scheme.

Miyamoto *et al.* analyzed the clinical results of NSCLC treated by HIMAC beams.¹⁴⁾ They depicted a very conspicuous dose dependency of the local control rate. A dose escalation study was performed with a treatment schedule of 18 fractions in 6 weeks. Hayakawa *et al.* reported the local control rate for NSCLC using photons. In order to compare the two results, dose dependency of TCP with the photon beam was fitted by the following formula:

$$TCP = \sum_i \frac{1}{\sqrt{2\pi}\sigma} \left\{ -\frac{(\alpha_i - \alpha)^2}{2\sigma^2} \right\} \cdot \exp \left[-N \exp \left\{ -nad(1 + d/(\alpha + \beta)) + \frac{0.693(T - T_k)}{T_p} \right\} \right] \quad (3)$$

α and β are coefficients of the LQ model of the cell survival curve. In the analysis, α and β values of HSG cells were used. σ is a standard deviation of the coefficient α , which reflects patient-to-patient variation of radiosensitivity. N is the number of clonogens in tumour (fixed value of 10^9 was used). n and d are total fraction number and the fractionated dose, respectively. T (42 days), T_k (0 day) and T_p (7 days) are overall time for treatment, kick-off time, and average doubling time of tumour cells, respectively. Values used in the analysis are shown in brackets. The result is shown in Fig. 6.

The same analysis was carried out to determine the TCP using carbon ion RT. Here, the width of SOBP and dose-averaged LET in the SOBP region were both fixed at 60 mm and 50 keV/ μ m, respectively, for simplicity. The result is also shown in Fig. 6. It is clear from the figure that the TCP curve of the carbon beam is much steeper than that of the photon beam. The value of σ in eq. (3) was 0.18 for the photon beam, while that for the carbon beam was reduced to 0.11. The result implies that carbon beam provides equally excellent local tumour control regardless of the individual radiosensitivity.

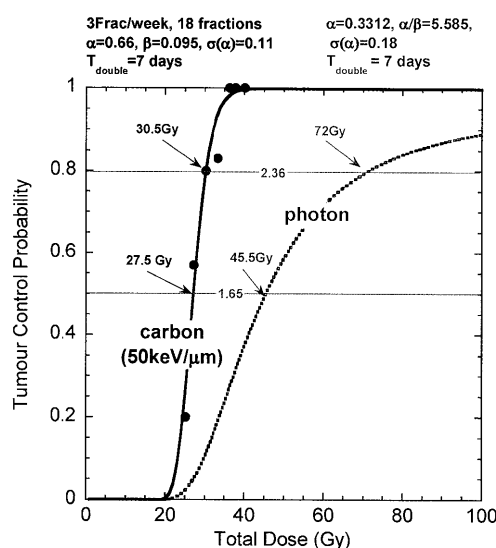


Fig. 6. TCP of NSCLC with photon (dashed, red line) and carbon (black line) beams. Circles show clinical results at HIMAC. For carbon TCP, the width of SOBP and LET were fixed at 60 mm and 50 keV/ μ m, respectively.

Taking into account the difference between the TCP slopes shown in Fig. 6 when TCP is regarded as an endpoint, the RBE value is found to be dependent on the TCP level. Furthermore, the biological RBE value coincided with the RBE at 50% TCP, whereas the clinical RBE value corresponded to that at 80% TCP. This agreement of the designed clinical RBE at higher TCP level is considered to be justified from the therapeutic point of view.

Application to Hypofractionation

Hypofractionation is generally not preferred in conventional radiotherapy, as the increase in fraction dose gives rise to anxiety concerning possible severe complications to surrounding normal tissues. However, the excellent dose localization realized by heavy ions may keep the dose level to the normal tissues below the threshold while delivering sufficient dose to the tumour with even smaller fractions. A reduction in fraction number would obviously be beneficial from the viewpoint of reducing the cost of this therapy modality.

At HIMAC, hypofractionation studies with carbon ions have been carried out for different tumour entities. Among them, a clinical trial for NSCLC was designed with a single fraction. By applying the α , β and σ values deduced from the actual clinical results into eq. (3), it is possible to estimate the TCP of different fractionation schedules. The expected TCP curves in the case of fractionation schemes employing 9, 4, and 1 fractions coincide well with the preliminary clinical local control rates obtained in the clinical trial.

Single dose irradiation was also investigated within clinical trials for liver metastasis from colorectal cancer. Before activation of new protocols, we estimated the expected clin-

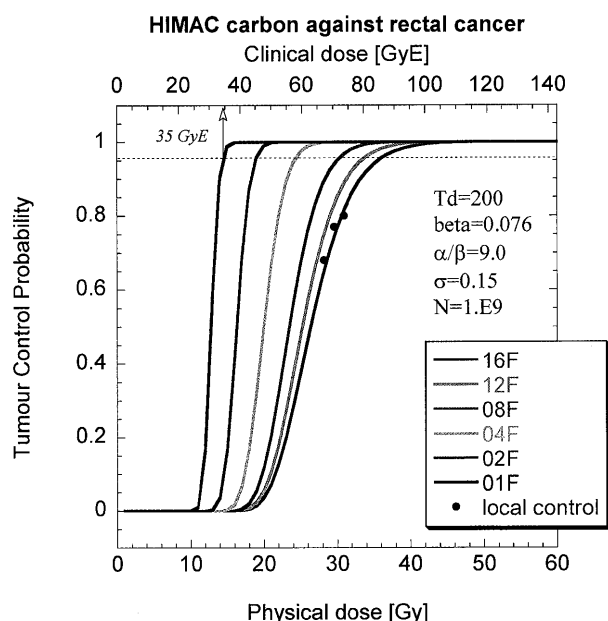


Fig. 7. TCP estimation for hypofractionated RT of liver metastasis from colorectal cancer. In the case of a single fraction, 96% of TCP is expected by a clinical dose of 35.0 GyE.

ical results corresponding to the prescribed dose level.

A prospective estimation was performed for liver metastasis from colorectal cancer in order to determine the appropriate starting dose. TCP analysis was performed using the clinical data in terms of local control derived from a clinical trials investigating carbon ion RT for rectal cancer (Yamada S, NIRS, personal communication). The resultant σ and α/β were 0.15 and 9.0, respectively when $T_p = 200$ days. The single fraction dose corresponding to an expected TCP level of 96% was estimated to be 35.0 GyE (Fig. 7). Based on this estimation, the single fraction dose was determined to be 36.0 GyE including the other clinical aspects.

This approach can be applied for other tumours to identify the tumour-specific radiosensitivity for carbon ion radiotherapy.

CONCLUSION

More than 2,500 patients have been treated at HIMAC with carbon ions. The designed universal clinical dose distribution has been found to be appropriate after verification with the clinical results.

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