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Specifying Carbon Ion Doses for Radiotherapy: The Heidelberg Approach

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Carbon/Radiotherapy/Prescription/Reporting.

There are currently no guidelines for prescribing and reporting radiation therapy (RT) with ion beams. In this paper an overview over some technical aspects and their implication on ion RT are reported. This includes a discussion of the difference in the treatment planning systems currently used for active and passive beam shaping systems, aspects of patient positioning and target definition and dose prescription. Special emphasis is put on the questions arising from the use of the beam scanning methods in combination with biological treatment plan optimization, which is used in the German heavy ion therapy facility at GSI and will also be introduced at the hospital based facility in Heidelberg. Furthermore, the Heidelberg approach for the clinical dose prescription is compared with the methods developed at HIMAC in Chiba, Japan.

INTRODUCTION

Within the last two decades radiotherapy (RT) with protons and heavy ion beams has gained increasing interest. Currently the availability of heavy ion RT is limited, as worldwide only 3 facilities offer carbon ion RT: two hospital based facilities in Japan (HIMAC/Chiba and HIBMC/Hyogo) and a physics research facility at Gesellschaft für Schwerionenforschung (GSI) in Darmstadt in Germany. There is, however, an increasing interest in ion radiotherapy especially in Europe and Japan. New facilities are being built in Germany, Italy and Japan or are in an advanced planning phase like in Austria and France.[1)]

At the research laboratory GSI, a therapy unit began its clinical operation in 1997.[3)] Until the end of 2006, about 330 patients have been treated with carbon ions at GSI. Only one treatment room is available that is equipped with a treatment couch.

The beam delivery system at GSI is completely active and allows 3D scanning of arbitrarily shaped volumes with a spatial resolution of 2 mm in all three directions.[5)] Using a magnetic deflection system, the intensity controlled raster scanner can deliver a monoenergetic pencil beam over an arbitrarily shaped area. To do so, a beam of 4–10 mm full-width half-maximum is scanned over a regular grid of points with typically 2–3 mm spacing. After completion of a scan, the accelerator energy can be switched from pulse to pulse and another scan can be performed with a different radiological depth. In total, 252 accelerator energies are available.

A feedback loop from the intensity control to the scanner moves the beam to the next beam spot, when a predefined number of particles is reached. The online monitoring of the beam position and the feedback loop keep the beam extremely stable at each scan spot.

In order to obtain the energy levels and particle numbers required for each scan point in a treatment field, a radiobiological optimization procedure is performed for each individual treatment plan. The modeling is used to calculate the radiobiological effectiveness of the ions at each point in the irradiated volume.

The new beam delivery method in combination with the radiobiological treatment planning procedure poses a number of questions on the prescription of radio-therapeutic doses for ion therapy. Not only the beam application and treatment planning deviates substantially from the methods used at HIMAC and HIBMC, but also differences in dose prescription between both facilities arise.

MATERIALS AND METHODS

Beam delivery systems and treatment planning

Since the demands on the treatment planning system (TPS) are very much connected to the beam production and delivery system that is used, the differences in the techniques

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for passive and active beam shaping will be outlined briefly.

At all existing ion RT facilities, synchrotrons are used to accelerate the ion beam up to energies of around 400MeV/u. Synchrotrons offer the unique possibility to change the extracted beam energy from pulse to pulse, i.e. a variation of the penetration depth is possible without any further hardware. This in turn has the advantage that the contamination with other ions due to nuclear fragmentation is extremely small as compared to a passive range shifting methods. It should also be kept in mind, that ion beams with same energy, but produced with active and passive energy variation can differ somewhat in the delivered particle spectrum. This may have some impact on the resulting beam quality in terms of the biological effectiveness of the beam.

The high momentum of ions at therapeutic energies furthermore leads to much higher magnetic beam rigidity as compared to proton beams. At 400MeV/u, the beam rigidity of a carbon beam is roughly three times higher as compared to a proton beam of the same range. To achieve a reasonable bending radius, much higher field strengths and thus larger and heavier magnets are necessary for ions.[6)]

Passive Beam Shaping

Concerning the beam shaping methods, passive beam shaping still is most commonly used in proton and heavy ion therapy. In this case, modulators, range shifters, compensators, collimators and a double scattering system are typically introduced in the beam, in order to shape the individual fields of a treatment plan (see[10)] for a detailed description of the HIMAC system).

The passive beam shaping technique for ions has three major disadvantages: first, the modulation depth, given by the maximum extend of the target, is constant throughout the field. Therefore, the high dose region is can not be tailored to the proximal end of the target. This is due to the fact, that the compensator shifts the SOBP towards the entrance region. A considerable amount of the high dose region (and high LET region) is therefore located in the normal tissue upstream of the target volume, especially at the lateral field borders. Secondly, the amount of material in the beam line is considerable, leading to an increase in nuclear fragments produced by nuclear interactions with the material of the beam modifiers. The beam therefore has a higher component of light fragments and neutrons when it enters the patient. This effect is most important for cyclotron facilities, which operate at a fixed energy level and need a range shifter for the full depth modulation. A third aspect is the large number of patient specific beam modifiers which have to be manufactured (a compensator and a collimator for each treatment field) and the necessity to produce a number of modulators which may have to be exchanged for different patients.

Using the passive depth dose shaping system at HIMAC, the depth dose profile is fixed by the modulator hardware throughout the irradiation field and no further optimization is necessary. The modulators were designed in order to achieve a prescribed homogeneous biological effective dose for a single field. The design of the modulators reflects a fixed dependence of the RBE with depth for a certain dose level.

As a consequence, there is no biological optimization needed during the treatment planning process for a passive beam shaping system. Furthermore, a passive system is considered to be less subject to dose errors resulting from organ movement, as in the case of a moving beam.

The algorithms needed to calculate absorbed dose for a passive beam shaping system are very similar to those used in conventional photon therapy. The beam transport models are relatively simple, as lateral scattering of carbon is very small as compared to protons and the lateral penumbra of the primary beam is preserved almost completely in depth. The modeling of nuclear fragmentation is not a serious problem, because treatment planning can rely on measured depth dose data that include fragmentation. These measurements for the various depth modulators are performed in water and sum up the dose contribution of all fragments.

The calculation of relative biological effectiveness (RBE) of an ion beam in tissue applied with a passive system can be reduced to a fixed depth dependent RBE factor for practical applications,[11)] as long as the fractionation scheme and dose per fraction are kept fixed and only one modulator yielding a certain depth dose is used for each treatment field. This is possible, as several fields of a treatment plan are applied on different treatment days. Thus, the treatment fields can be considered to be independent and the effective dose values can simply be added up.

Active Beam Shaping

Active beam shaping takes advantage of the possibility of scanning a small pencil beam (around 5 mm full width half maximum) over the treatment field. Moreover, the energy from a synchrotron can be switched from pulse to pulse in order to adapt the range of the particles in tissue. This way, a target volume can be scanned in three dimensions and the dose distribution can be tailored to any irregular shape without any passive absorbers or patient specific devices, like compensators or collimators. Therefore, the high dose region can also be conformed to the proximal end of the target volume and the integral dose as well as the volume receiving high LET radiation is minimized.There is, however, considerable effort necessary in order to monitor on-line the position and intensity of the beam and to enable a safe and accurate delivery of dose to the patient. (We would like to stress, that we use the term *intensity* here, since it was introduced by the developers of the scanning system, although the term *flux* may be more appropriate.)

It should be stressed, that the beam scanning method used at GSI does not rely on a continuous beam extraction with a constant intensity. Instead, any fluctuation in the beam intensity (which can be very large for a synchrotron) is mon-

itored online and compensated for by the time period, during which the beam delivers ions to a single spot. Between two neighboring spots, the extraction is not switched off, but the beam is moved quickly to the next spot, with a velocity of typically 10m/s. This is very different from the approach followed by most proton beam scanning systems, where a continuous extraction is aimed for and the intensity at each spot is controlled by the scan speed, or by discrete spot scanning, where the beam is switched off after delivery of each spot.

For an active beam shaping system for ions, a research TPS was developed for the GSI facility. The system is a combination of a versatile graphical user interface for RT planning, called VIRTUOS (Virtual radiotherapy simulator,[2]) and a program called TRiP (Treatment planning for particles), which handles all ion specific tasks.[14,15,8] VIRTUOS features most tools used in modern RT planning, while TRiP handles the optimization of absorbed as well as biological effective dose and the optimization of the machine control data.

The introduction of a 3D scanning system has some important consequences for the TPS.

A modulator for passive beam shaping is designed to achieve a prescribed homogeneous biological effective dose for a single field. A 3D scanning system, however, can produce nearly arbitrary shapes of the spread out Bragg peak (SOBP). The shape of the SOBP therefore has to be optimized separately for every scan point in the irradiation field.

The resulting new demands on the TPS for an active system are:

- The beam intensity of every scan point at each energy has to be optimized separately, in order to obtain a homogeneous biological effect.
- As the system is able to apply any complicated inhomogeneous dose distribution, the capability for intensity modulated radiotherapy with ions should be taken into account.
- All fields of a treatment plan are applied at the same day to avoid uncertainties in the resulting dose due to setup errors.
- The dose per fraction should be variable for every patient.
- The scanner control data (energy, beam position, particle number at every beam spot) have to be optimized for each field of every patient.
- An RBE model has to be implemented, that allows the calculation of a local RBE at every point in the patient depending on the spectrum of particles at this point.

Not any optimized scan pattern may be feasible to deliver with a given scanning system. E.g. there is a lower threshold for the particle number at each scan spot, which can be resolved accurately by the monitoring system. The feasibility of each plan has to be checked also with regard to the delivery time, if exceedingly many spots of a low intensity are used.

The dose calculation for active beam shaping systems is very similar to the pencil beam models used for conventional photon therapy and also relies on measured data like for the passive systems. Instead of the measured depth dose data for the SOBPs resulting from the modulators, data for the single energies are needed. If the applied dose is variable, it is necessary to base the calculation of absorbed dose on absolute particle numbers rather than on relative values. For the calculation of absorbed dose, the integral data including all fragments are sufficient.

Before the actual dose calculation starts, the target volume is divided into slices of equal radiological depth. The scan positions of the raster scanner are then defined as a quadratic grid for each beam energy. Then, the particle number at each scan point is optimized iteratively until a predefined dose at each point is reached.

Concerning the biological effectiveness, a more sophisticated biological model is needed, as compared to a passive system. Such a model was developed *e.g.* at GSI.[16] Its main idea is to transfer known cell survival data for photons to ions, assuming that the difference in biological efficiency arises only from a different pattern of local dose deposition along the primary beam.

The model takes into account the different energy deposition patterns of different ions and is thus able to model the biological effect resulting from these ions. An important prerequisite for this is, however, the detailed knowledge of the number of fragments produced as well as their energy spectrum. The calculated RBE shows a dependence on the dose level and cell type, if the underlying photon survival data for this respective cell type are known. In the TPS, a prescribed biological effective dose within the target volume is then optimized.[14,8] At each iteration step, however, the RBE has to be calculated anew, as it is dependent on the particle number (or dose level). Since this includes the knowledge of the complete spectrum of fragments, the optimization is rather time consuming. Again, it has to be pointed out, that the dose dependence of the RBE demands the use of absolute dose values during optimization. As a consequence, the dose levels and depth modulation is varying for each treatment field.

Aspects of patient positioning

Due to the high spatial accuracy that is achievable with ion beams, patient fixation and positioning require special attention. Patient fixation is currently achieved with an individually prepared mask systems developed at DKFZ. This system allows only very small movements of 1–2 mm of the skull within the mask. Highest possible accuracy during the initial positioning is achieved by the use of stereotactical imaging and positioning techniques. Prior to every fraction the position is verified using X-ray imaging in treatment position. The X-ray images are compared against digitally reconstructed radiographs obtained from the treatment plan-

ning CT. On the X-ray images the isocenter of the treatment room is visualized by thin steel wires placed in front of the image intensifiers. Given the magnification of the obtained images, deviations of the position of bony landmarks of above 1 mm relative to the isocenter can clearly be detected and corrected for prior to the first treatment.[12)]

For the treatment of tumors in the pelvic region a cast system of the same material as for the head mask is used to fix the bony structures of the pelvis. In addition a modified head mask is used to limit movements of the patient in craniocaudal direction. In combination with the X-ray position verification, the accuracy of the position of bony structures in the pelvis is less than 3 mm.

To achieve additional freedom, treatment chairs were developed at HIMAC and GSI to treat patients in a seated position. In this case, patient movement plays an important role, since the patient tends to relax and move downward in the chair with time. The treatment time therefore has to be minimized and means to control the patient position during therapy are advisable. Additional uncertainties are introduced, if the treatment planning is performed on a conventional horizontal CT scan, with the patient in supine position. The best way to exclude this uncertainty is to perform the treatment planning CT in seated position, using dedicated vertical CT scanners.[9)]

Target definition and dose prescription

For the treatment of skull base tumors at GSI, the PTV is defined by adding a margin of 1–2 mm around the CTV. The margin accounts for target movement, uncertainties in the set-up during the treatment course and uncertainties in the beam delivery and range calculation.

Setup errors in the direction longitudinal to the beam are not very important, as the scanned ion beam has a very small divergence (about 1 milli-steradian) and can be considered parallel. This is due to the fact that the virtual source point is about 8m upstream of the isocenter. Lateral setup errors are much more important.

The uncertainty due to the scanning beam delivery system amounts to approximately 0.5 mm in lateral direction. This is ensured by the online monitoring of the beam position used to control the scanning magnets. The uncertainty in the beam energy is extremely small since the GSI synchrotron represents a very efficient spectrometer. Range uncertainties due to energy variations can therefore be neglected. The calculation of ion ranges in tissue, however, is the largest source of uncertainty. It depends strongly on the type and homogeneity of the traversed tissue. For a beam path through cranial bone and brain tissue without large inhomogeneities the uncertainty is around 1 mm. For a beam path through the auditory channel or paranasal cavities range uncertainties of up to 5 mm may occur.

For tumors in the neck region or paraspinal tumors larger setup errors are expected and the margin has to be increased to 3 mm for extracranial tumor sites. Moreover, in critical cases the robustness of the treatment plan is assessed by simulating various setup errors and their effect on the dose distribution.

The dose prescription is always given to the whole target volume and the dose optimization is done in such a way, that the dose in each volume element of the target volume is varying by not more that 2–3% from the prescribed dose. The quantity used for optimization is always the biological effective dose, i.e. in the TPS the absorbed dose is optimized so that the product of dose and relative biological effectiveness is homogeneous throughout the target volume.

It is intended that the whole target volume is covered with at least 90% of the prescribed dose. The minimum diameter of hot and cold spots is intended to be below 2–3 mm. Deviations of this rule are only acceptable, if an OAR is involved (leading to cold spots) or a patch field technique is unavoidable (leading to hot spots). The homogeneity of dose distributions is typically much better than in conventional therapy or IMRT. (Here it should be stressed, that currently only tumors are treated at GSI, where internal organ movement plays a minor role. For moving organs, beam scanning can lead to severe hot and cold spots, when the movement is not corrected for.)

The fractionation scheme used for carbon ion treatments at GSI is also part of the prescription. Typically, for a fully fractionated treatment, 20 fractions are delivered on 20 consecutive days. The dose per fraction and the total dose are reported. Only the fraction dose enters the TPS, as complete repair is assumed to take place in one day. For a fully fractionated treatment, a sequential boost is delivered typically during the last 5 days of the treatment course. This is obtained by optimization of a second treatment plan optimized for the PTVII (the GTV plus a 1–2 mm margin), usually with the same dose per fraction as the treatment of PTVI.

The fraction dose (as well as the radiation tolerances of the normal tissue) has to be specified in terms of the biological effective dose, rather than in terms of absorbed dose. This procedure has the advantage that the experience gained in the application of X-rays for radiotherapy can directly be translated to carbon ions, using the radiobiological model.

When defining the prescribed dose per fraction, however, it is important to specify also the endpoint for which the RBE is optimized. With the biological model used at GSI, it is the α- and β-values for X-rays that have to be specified in order to allow for an optimization of the RBE. Basically it's the α/β-ratios that enter the calculation, since the dependence of RBE on α and β alone is rather weak as long as the ratio is constant. (Other model parameters, like the target size and cut-off dose D_t,[16)] are less important and therefore kept constant.) Since the applied doses are limited by the surrounding normal tissues, it is the α/β-ratio for late effects in the normal tissues that are used for the optimization of

RBE. If α/β-ratios for the dose limiting toxicity and for the tumor are assumed to differ substantially, the biological treatment optimization can be done for both, the α/β for the OAR and the tumor, respectively. It is also possible to choose an α/β-ratio for each different organ, by assignment to a volume of interest (VOI).

In principle, dose distributions might also be optimized with α/β-ratios assumed for the specific tumor, but the α/β-ratios are not well known for most of the tumors and a large variability between patients or even within a single tumor can be expected.

Within clinical phase I/II trials, the toxicity of the dose-limiting OAR is to be assessed very carefully. The prospectively collected clinical data has to be used to retrospectively validate the planning data and the biological model and to allow the correlation of the clinical data with the estimated α/β-ratios for a specific tumor.

Planning of combination therapies

In case of adenoidcystic carcinoma and pelvic tumors, carbon ion treatment at GSI is delivered as a boost treatment given in addition to a conventional 3D conformal RT or an IMRT treatment. Typically a carbon boost of six fractions is given on six consecutive days prior to the IMRT treatment. Both treatment modalities are planned using the same patient CT data and volume definitions and are integrated in the treatment planning platform VIRTUOS.

First the carbon ion treatment plan is optimized to yield a homogeneous biological effective dose to the PTVII. The calculated carbon ion dose distribution is assessed in the TPS in order to derive the constraints for the OARs for the IMRT optimization. The KonRad software is used for the optimization of the photon dose distribution.

The weighted sum of the resulting photon dose and carbon ion dose distribution is then calculated on a voxel by voxel basis. Before the summation, the IMRT treatment plan is normalized to the median dose. The carbon dose may not be normalized since it is optimized to an absolute value of absorbed dose, or absolute particle numbers. Then both dose distributions are added up using the fraction of dose delivered with each modality. In obtaining these fractions, the total biological effective dose is taken into account, rather than the biological equivalent doses (BED), which may be even more appropriate due to the different fraction doses and fractionation schemes (6 consecutive fractions of carbon ions vs. 5 fractions per week of photon RT).

Intensity modulated ion therapy

Although any treatment field applied with the beam scanning method is intrinsically modulated in intensity, intensity modulation (IM) is usually referred to as a simultaneous optimization of several treatment fields, each delivering an inhomogeneous dose to the target. A first prototype allowing the optimization of a homogeneous biological effective dose for two or three fields of carbon ions is available and is currently being evaluated.[4] There are a number of questions that have to be clarified, however, before IM for ions can be introduced clinically.

Since ion therapy is often applied using only 2 or three beams, a significant increase of the dose in the entrance region of one of the beams may not be avoided. Similarly, range uncertainties may become more important, since automatically the IM will try to make use of the finite range of the particles (unless the range uncertainty itself is introduced into the optimization procedure).

The distribution of absorbed doses and LET will become much more inhomogeneous as compared to single field optimization. Consequently, the uncertainty of the RBE calculation may be larger in this case and has to be validated in radiobiological experiments.

Documentation and Reporting

There are two different types of documentation produced for every patient: German laws require a printed documentation of all relevant aspects of the treatment plan, prescription, dosimetric verification and the delivery of radiotherapy which has to be kept for 30 years. Due to the limitations of the amount of data in the printed documentation an electronic record of each treatment is also produced, to allow full access to all relevant parameters of a treatment.

The printed documentation contains all relevant information on the diagnostic data, the dose prescription, target volume definition, treatment plan, plan verification and a treatment record.

The prescription includes all relevant parameters like fraction dose, weekly fractionation, tumor type, α/β-ratios used for various organs and relevant CT and MR images used for target volume definition. The doses are specified as biological effective doses and are not converted into BED (corresponding to a conventional fractionation of 2Gy per fraction in 5 fractions per week).

The treatment plan documentation includes printouts of the CT images including all slices of the target volumes and contours of all OARs receiving a relevant dose. Isodose lines are included in this printout. Furthermore, the dose volume histograms and histogram statistics is included. The histogram statistics gives information on the minimum, maximum and mean dose and standard deviation for each VOI, as well as the volume receiving more than 30% and less than 90% of the prescribed dose and the absolute volume of each VOI. The biological effective dose is used for the documentation of the DVH and isodose lines.

To be able to assess also the RBW distribution, an isodose plot in a sagittal, transversal and coronal plane through the isocenter is added for the biological effective as well as for the absorbed dose. The α/β-ratios of the dose-limiting biological normal tissue endpoints used for biological treatment plan optimization are documented as well.

The 3D beams eye-views of all treatment fields are included as well as DRR for position verification and a printout of the transversal CT image including the target point and stereotactic fiducials in order to allow for a simple check of the stereotactic target coordinates. Finally the version of the TPS and data base for biological and physical parameters is included.[7)]

Data from the dose verification include a complete record of the measurements done for dosimetric plan verification. This includes data on the planned and measured se values for each chamber position, the position of the chambers in the water phantom and the statistical evaluation of these data. Furthermore a radiochromic film image of the treatment field is added, which can be compared to the BEV and a calculated film response using the treatment plan.

The treatment record includes a detailed report on the daily treatments, including a list of the treated fields, eventual interruptions, X-ray images done for position verification as well as the image parameters (tube current, time and kV setting).

The electronic record includes all data used and generated during treatment planning like CT- and MR-images, calculated dose distributions and optimized machine control data. Furthermore an electronic treatment record generated by the monitoring system is stored. This record contains the measured actual position of the beam at every beam spot, as well as the measured intensity at each spot, as well as the deviation from the planned values. Also the PET images gained during the irradiations for each fraction are stored electronically.

The most important data are the machine control data, since they document the position, energy and particle number used for each beam spot in a treatment field. Given this information, it is always possible within the TPS to calculate the absorbed dose and biological effective dose using any available model. This is of special importance if changes in the models or data base are performed, in order to check the influence of these changes on the applied doses. The electronic treatment record is also of great importance to reconstruct the applied dose after an interlock, if the treatment can not be resumed the same day. In principle a resumption of a treatment is possible at any beam spot in a treatment plan. In case of an interlock the systems stores the last treated spot.

The data are stored in an archiving system based on tape robots. All data are regularly copied to new storage media and two copies are stored in different places.

RESULTS AND DISCUSSION

Beam delivery and treatment planning

The beam, delivery using active beam scanning together with a radiobiological optimization in treatment planning was introduced clinically 10 years ago at GSI. It has been shown to be a feasible and safe technique and the clinical results also showed the effectiveness of this technique (see [17,18,19, 20)] for a review of the clinical results).

As an example of the flexibility of the described active beam delivery and treatment planning system, a number of differently modulated depth doses are shown in Fig. 1. The modulations of the absorbed dose result from different penetration depths and different field weights. Fig. 1a shows typical data for a single field treatment plan, where the resulting RBE is around 3.4 in the SOBP. If two fields are combined in a treatment plan, the resulting dose per field is reduced and the RBE for each single field increases to around 4, as seen from Fig. 1b. The situation changes, however, if the two fields are applied within the same treatment session. In this case, the total dose will be increased and the resulting overall RBE will be decreased to around 3 in the SOBP. The dose shown in 2b is optimized to 1.9Gye in order to achieve a prescribed dose of 3.0 Gye in the tumor. The

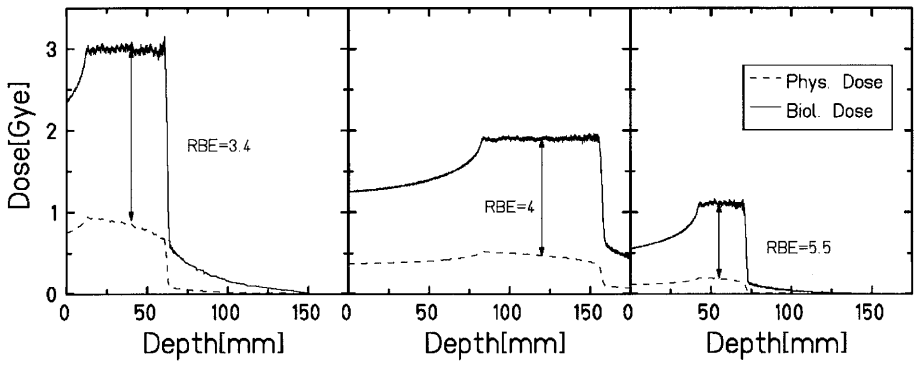

Fig. 1. Variable depth modulation of absorbed and biological effective dose for the treatment of chordoma patients using a scanned carbon ion beam. Shown is the absorbed (physical dose, dashed line) for various modulation depths and dose levels. Due to the increase of the RBE with depth, the resulting biological effective dose (full line) is homogeneous throughout the target volume. It can be seen that the RBE is higher for lower dose levels and that the depth modulation is not constant.

RBE of 4 (as shown in 2b) would only be valid, if the two fields were applied on different days (as it is generally done at the HIMAC facility, with the exception of single fraction treatments).[11]

Finally, if the beam weights are not uniformly distributed, the doses and RBE levels are changing accordingly, as seen in Fig. 1c. Here, the field weight was reduced and consequently the RBE increases to over 5 for that treatment field.

Relative biological effectiveness and fractionation

The RBE values calculated for the GSI facility can not easily be compared to the RBE values used at HIMAC, since they do not refer to the same endpoint. At HIMAC, the RBE was chosen in such a way, that the clinically applied neutron doses could be translated into carbon ion doses (at a given LET). Probably due to the passive beam delivery system, the endpoint chosen for carbon RT at HIMAC are acute reactions of the skin.[11] In this region, the high dose extends proximal to the target volume and limits the applicable doses. Consequently, great care has to be taken, when clinical results from the different facilities are compared.

Another important factor when comparing clinical results are the differences in the fractionation schemes. When comparing results from different facilities, it is advisable to calculate first the BED, which is equivalent to an X-ray RT given in a conventional fractionation scheme (2Gye per fractions and 5 fractions per week). To avoid misunderstandings, it seems useful, that the BED be reported and documented in all future clinical trials with ions and protons. Since not only the number of fractions, but also the time course of the treatment may vary (*e.g.* 5 vs. 7 fractions per week, one vs. several fields per day) this should also be accounted for in the calculation of the BED.

When different α/β-ratios are used to optimize different treatment plans, there are generally only very minor differences in the calculated isodose lines and biological effective dose distributions. It is therefore extremely important to perform a dosimetric verification that aims at absolute values of the absorbed dose in order to verify, if the correct doses are applied. If *e.g.* the α/β-ratio is raised from 2 to 4, the RBE is decreased and consequently the number of particles needed for the same treatment can be increased by about 40% and the absorbed dose by about 16%, respectively. Fig. 2a shows an example of the dose distribution resulting for prostate treatment using 2 horizontally opposing fields and a dose of 3 Gye per fraction. The relative differences in the absorbed doses can be seen in the dose volume histogram of both treatment plans (Fig. 2b).

If a varying α/β-ratio is chosen in the optimization, there are a number of points that have to be regarded. First, if the α/β-ratio varies at the border of a VOI, the same level of absorbed dose will lead to different levels of biological effective dose. In other words there will be discontinuities in the dose distribution, which are not only unfamiliar in radiotherapy planning but also appear to be artificial.

Special care when using varying α/β has to be taken also in the case of moving organs. E.g. in the case of prostate tumors, the target volume exhibits a volume, that encloses the prostate at all possible positions. The enclosed tissue therefore also includes surrounding normal tissue. The resulting dose distributions may thus be rather artificial. The application of organ specific α/β-ratios does at the moment

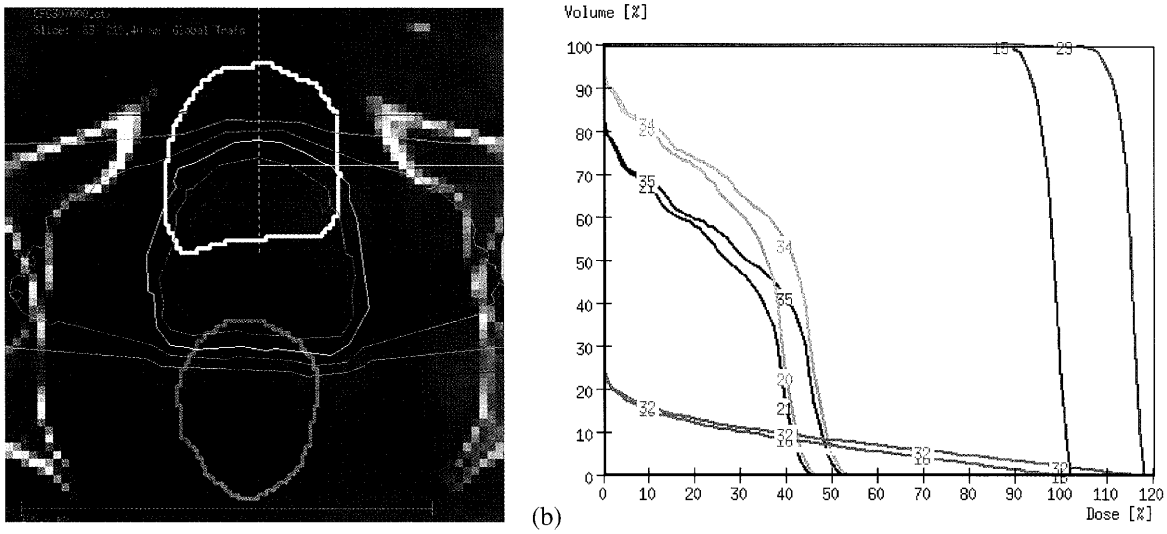

Fig. 2. The biological effective dose distribution for a patient with prostate carcinoma is shown in (a). Shown are the contours of the GTV (red line), the rectum (purple line) and the bladder (yellow line) together with isodose lines for 10% (dark blue), 30% (light blue), 50% (green), 70% (yellow) and 90% (red), respectively. The absorbed dose distributions resulting from various α/β-ratios are compared in the dose-volume histogram in (b). For each organ the upper and lower line represents a value of $\alpha/\beta = 4$ and $\alpha/\beta = 2$, respectively. The biological effective dose for both treatment plans is identical and was optimized to be 3.0 Gye in the target volume.

not appear to be a reasonable option. It is rather a method to be used during the process of optimization of the treatment plans and planning parameters. Fig. 3 shows an example of a treatment plan that was optimized with varying α/β-ratios (while we generally used a value of $\alpha/\beta = 2$ for the prostate, somewhat higher values for the bladder and rectum are discussed in the literature).

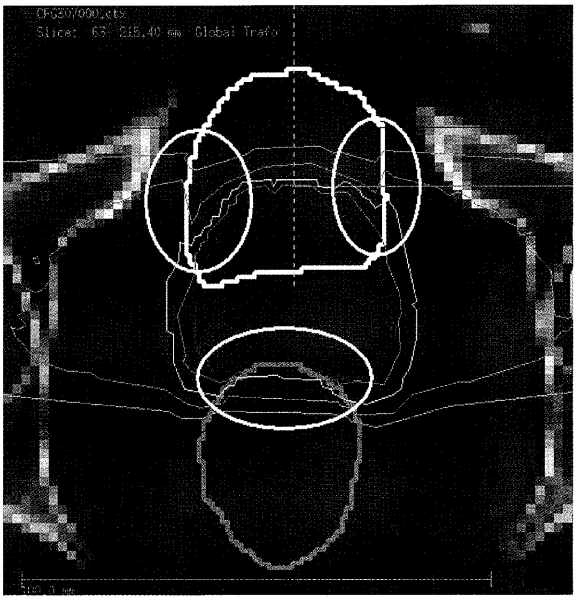

Fig. 3. Biological effective dose distribution for the same prostate case as in Fig. 2, however, different values for the α/β -ratio were chosen for different tissues. For the prostate, rectum and bladder α/β values of 2, 4 and 5 were chosen, respectively. The surrounding tissue was set to $\alpha/\beta = 2$. The white circles indicate the discontinuities that arise at the boarder of the various organs, due to the various RBE values resulting in the various tissues.

Combination therapy and Intensity modulated RT

The delivery of combined treatments of *e.g.* IMRT and carbon ions can be very successful, as shown by the clinical results for patients treated for adenoidcystic carcinoma at GSI.[20] While there are good clinical reasons to apply this technique, there is in addition a potential to increase the number of patients that can be treated at a facility and thus contribute to a more economical operation of the facility. The combination of X-rays with carbon-RT can also reduce the uncertainty in the delivered dose, resulting from uncertainties in the alignment of the patient. This was shown in a dosimetric phantom study.[13] Fig. 4 shows an example of a treatment plan for a combination of an IMRT treatment with a carbon ion boost. The large difference between PTVI and PTVII is clearly visible. Again, since the fractionation used for IMRT and Ion RT are different in this case, this has to be accounted for in the calculation of the overall BED of a combined RT.

Using the flexible active beam delivery, the introduction of intensity modulation is not related to any further technical or QA effort. Only the TPS needs the capability optimize several fields simultaneously. The introduction of IMRT for ions further increases the possible sparing of normal tissue further, while at the same time improving the dose conformity.[4]

The introduction of IMRT puts further demands on the reporting and recording practices, as it will lead to subtle changes in the LET distribution (depending on the applied constraints) and may have consequences on the RBE and finally the clinical outcome.

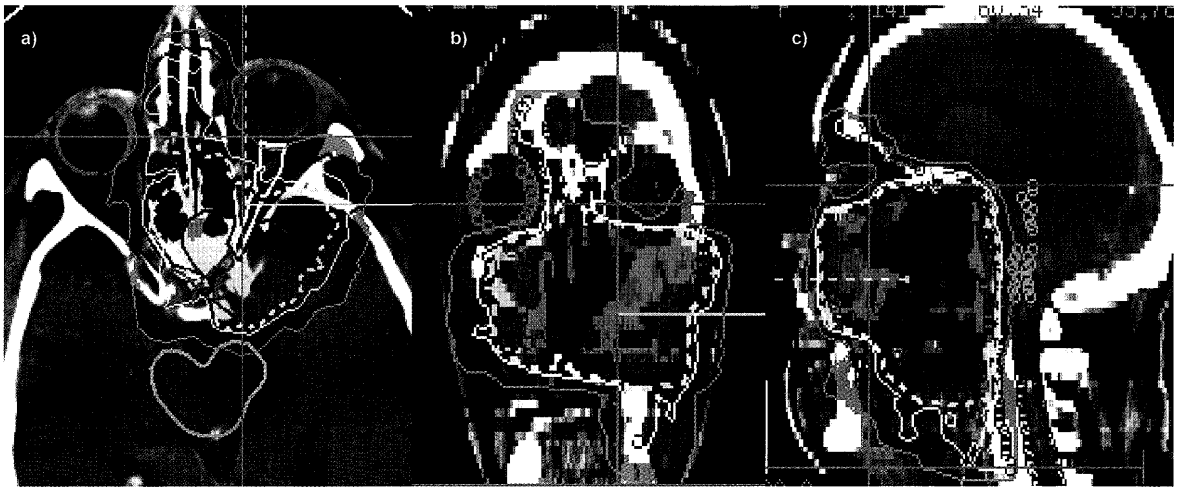

Fig. 4. Treatment plan for patient treated for an adenoidycystic carcinoma, where photon IMRT was applied to the CTV (outer red contour) and carbon ion therapy was applied as a boost to the GTV (inner purple contour) only. Shown are the axial (a), coronal (b) and sagittal views (c). IMRT was applied up to a total dose of 54 Gy (30 fractions, 1.8 Gy each) and an additional dose of 18 Gye (6 fractions, 3Gye each) was delivered with carbon RT. The dotted and fine yellow lines correspond to the 60 and 54 Gye isodose line; respectively. The fine green line represents the 39Gye isodose line.

CONCLUSION

The introduction of an active beam scanning system offers great flexibility and in the beam delivery and achieves highest degrees of dose conformation, which even exceed the capabilities of IMRT. In addition with the radiobiological treatment plan optimization, this technique, however, also requires additional efforts in patient positioning, target contouring, but especially dose prescription, reporting and dosimetric verification. The additional biological parameters that have to be specified within such an approach offer new possibilities to optimize the treatment, but also put new demands on the reporting. Especially when clinical results are compared between various facilities and modalities, there are many potential pitfalls connected to the radiobiological specification of the applied doses. Even today, with only three ion facilities in operation, the comparison of clinical results is complicated by different RBE models, differences in the dose limiting clinical endpoints, different fractionation schemes, etc. In view of the upcoming new ion facilities, it is very important to introduce common guidelines for the dose prescription and reporting in ion beam therapy.

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