

1. Heavy Ion Radiotherapy

OLIVER JÄKEL, PHD

DEUTSCHES KREBSFORSCHUNGSZENTRUM

Abteilung für Medizinische Physik in der Strahlentherapie

INF 280, Heidelberg, 69120, Germany

Introduction

Within the last two decades not only photon radiotherapy has rapidly developed, but also particle therapy with protons, Helium and Carbon ions has gained increasing interest (Jäkel et al. 2003). The term *heavy ions* is used here for ions heavier than Helium ions. The primary rationale for RT with heavy charged particles is the sharp increase of dose in a well defined depth (Bragg peak) and the rapid dose fall-off beyond that maximum. The ratio of Bragg peak dose vs. dose in the entrance region is larger for heavy ions than for protons. Due to their larger mass, angular and energy straggling is becoming negligible for heavy ions as compared to protons or even Helium ions. Heavy ions therefore offer an improved dose conformation as compared to photon and proton RT with better sparing of normal tissue structures close to the target. In addition, heavy ions exhibit a strong increase of the linear energy transfer (LET) in the Bragg peak as compared to the entrance region. The radiobiological advantages of high LET radiation in tumor therapy is well known from neutron therapy. Unlike in radiotherapy with neutron beams, in heavy ion radiotherapy the high LET region can also be conformed to the tumor.

Between 1977 and 1992, first clinical experiences have been made, especially with Helium and Neon ions at the Lawrence Berkeley Laboratory and many encouraging results (esp. in skull base tumors and paraspinal tumors) were achieved (Castro et al. 1994, Castro et al., 1997).

While Helium ions are very similar to protons in their biological properties, heavy ions exhibit an increased relative biological effectiveness (RBE) in the Bragg peak as compared to the entrance region (see Fig. 1). This advantage is lost for very heavy ions (above oxygen), because here, the RBE is already high in the entrance region and does not increase much further in the Bragg peak.

Another disadvantage of very heavy ions for radiotherapy is the increase of nuclear fragmentation processes, which leads to a fragment tail in the depth dose distribution that extends beyond the Bragg peak (see Fig. 2).

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 GSI, Darmstadt in Germany. There is, however, an increasing interest in ion radiotherapy especially in Europe, where new facilities are being built in Germany and Italy or are in an advanced planning phase like in Austria, France and Sweden (Sisterson, 2003).

Treatment Techniques

Beam production and beam delivery systems

One of the basic features of heavy ions is their strongly increased energy loss or linear energy transfer (LET) as compared to protons, which is responsible for their RBE characteristic. Consequently, the ion energy required to treat deep seated tumors is much higher: while a proton beam of 150 MeV can penetrate 16cm in water, the same radiological depth is achieved with carbon ions of 3000MeV or 250MeV/u (energy per nucleon). To accelerate particles to such high energies, synchrotrons are better suited than cyclotrons, which are a standard in proton radiotherapy. Particle acceleration in synchrotrons is, however, much more complicated and hence cost intensive than in cyclotrons.

Also ion sources for heavier ions are more difficult to design than for protons, where simple hydrogen gas targets of high purity are available. To inject the ions into a synchrotron ring, they have to be accelerated first in a linear accelerator (Linac) injector to several MeV/u. Such a Linac consists of a radiofrequency cavity and a drift tube and has several meters length. All these components make ion beam production considerably more costly than proton beams.

The high momentum of ions at therapeutic energies furthermore leads to a much higher magnetic beam rigidity as compared to proton beams. The rigidity is defined as the product of the bending radius and the required magnetic field strength. The maximum energies used for heavy ions are around 400MeV/u. At this energy the beam rigidity is 6.3 Tm as compared to 2.2 Tm for a proton beam

of same range. To achieve a reasonable bending radius, much higher field strengths and thus larger and heavier magnets are necessary for ions. While the weight of a proton gantry is already around 100 tons (at a diameter of 10m), an isocentric gantry for carbon ions is expected to have weight of about 600 tons at a diameter of 13m.

The enormous size and weight of such a gantry together with the high spatial accuracy required for the beam position at the isocenter is probably the reason why no such gantry has been built up to now. Instead of flexible beam delivery systems, fixed inclined beam lines have been realized at the two operating clinical ion facilities in Japan, where vertical beams and beams with 45° inclination are available together with horizontal beams. Another possibility is to move the patient rather than the beam. At some proton as well as heavy ion facilities, treatment chairs are available or moulds that can be rotated (see patient positioning for details).

It should be mentioned that size and weight of a gantry could be reduced by the use of superconducting magnets. The cryogenics involved, however, requires considerable space and is more delicate to handle in terms of stability and patient safety.

Beam application systems

There exist two principle methods to shape the beam and thus to tailor the dose to the target volume, which will be described in the next sections.

Passive beam shaping

Passive beam shaping, was the first method to be developed and still is most commonly used in proton and heavy ion therapy. In a first step, the depth dose of the monoenergetic beam from the accelerator is modulated by a variable degrader. This degrader may be a rotating wheel with varying thickness or a wobbling plate with wedge shaped engravings (ridge filter). In both cases the modulator is designed such that a predefined depth dose profile is resulting. To cover different depth modulations in tissue, several different modulators are available.

In order to move the modulated Bragg peak (or spread-out Bragg peak, SOBP) to the desired radiological depth, an additional range shifter is needed. It consists

typically of a number of homogeneous plastic plates of different thickness, that can be moved into the beam.

Finally, the small sized beam has to be spread out laterally to cover the whole target homogeneously. This is achieved either by a double scattering system, or by a magnetic wobbling system that moves the beam over a defined area (Fig. 3 schematically shows the design of a passive beam delivery system).

To adapt the dose individually for each patient, patient specific hardware is necessary. Using a collimator, the lateral extend of each treatment field is adapted to the beams-eye-view of the target volume. An additional compensator is used to account for tissue inhomogeneities and the curvature of the patients surface. The compensator is designed such that the distal end of the modulated Bragg peak matches the distal end of the target volume. In doing so, the depth dose profile can only be shifted to smaller depths.

The passive beam shaping technique for ions has three major disadvantages: first, the depth dose can only be tailored to the distal end of the target, but not to the proximal end. 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 in front 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. These nuclear fragments have lower energies and lead to a higher LET and thus an increased biological effective dose of the beam already in the entrance region. 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.

Active beam shaping

Another way of beam delivery is called active beam shaping. This systems takes advantage of the electric charge of ions, in order to produce a tightly focused pencil beam that is then deflected laterally by two magnetic dipoles to allow a scanning of the beam 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. Fig. 4 shows the principle of the active beam delivery system.

Patient positioning

Due to the high spatial accuracy that is achievable with ion beams, patient fixation and positioning requires special attention. Patient fixation is usually achieved with individually prepared mask systems or whole body moulds. Highest accuracy during the initial positioning can be achieved by the use of stereotactical methods. 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 planning CT. Another possibility of position control, which is used at HIMAC, is to do a CT scan of the patient in treatment position and compare it with reference images used for treatment planning.

To achieve additional freedom, treatment chairs may be used 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 lying on the table. Then the assumption has to be made, that organ movement is negligible, when moving the patient from lying to seated position, which is commonly believed to be reasonable for tumors within the cranium. The best way to exclude this uncertainty, is certainly, to perform the treatment planning CT in seated position, using dedicated vertical CT scanners (Kamada et al., 1999).

At HIMAC an additional degree of freedom was introduced, by rotating the patient in a mould around its longitudinal axis. Using this method, the problem of organ movement has to be carefully considered and rotation angles are limited to 15 degrees at HIMAC.

Treatment Planning

Since the details of the treatment planning system (TPS) are very much connected to the beam delivery system that is used, TPS for passive and active beam shaping will be dealt with separately.

TPS for passive beam shaping

Treatment planning systems (TPS) for the passive systems at Berkeley and HIMAC facilities were developed as research tools within the corresponding institutions, since no commercial products were available at that time (Chen et al., 1979 and Endo et al. 1996). In the meantime, the HIBMC treatment planning system is available as a fully certified medical product (FOCUS-M by Computerized Medical Systems Inc. St. Louis and Mitsubishi, Kobe). Furthermore, it is embedded in a modern graphical user interface for 3D conformal radiotherapy planning including all up to date available features. For the passive depth dose shaping system, 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 the fixed dependence of the RBE with depth for a certain dose level.

ABSORBED DOSE CALCULATION

The algorithms 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 or even neon ions is very small 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 radiological depth of the beam in tissue is calculated using an empirical relation between X-ray CT numbers and measured particle ranges (Minohara et al., 1993 and Jäkel et al., 2001).

Using this procedure, the design of necessary patient specific devices like bolus, compensators and collimators can be optimized by computer programs. Similar to photon therapy, only relative values of the absorbed dose may be used, because the absorbed dose scales with the number of monitor units.

BIOLOGIC MODELING

The situation is more complicated for the calculation of biological effective dose because the relative biological efficiency (RBE) of an ion beam in tissue is depending on the underlying LET spectrum, the cell type, the dose level and some other quantities. This problem was solved by a number of pragmatic steps and assumptions for passive beam delivery systems (Kanai et al., 1999):

The clinical RBE is replaced by an LET dependent RBE for in vitro data under well defined conditions and then linked to clinical data by an empirical factor. At HIMAC, e.g. the RBE value for the 10% survival level of human salivary gland (HSG) cells was chosen and then linked to the existing clinical data gained in fast neutron radiotherapy at the corresponding LET level (see also the chapter on “Biological Models for Treatment Planning”).

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.

Under these conditions, the resulting RBE can be approximated to be only a function of depth. If this function is determined, a corresponding ridge filter can be designed in such a way, that the resulting depth dose curve leads to a constant biological effective dose. Consequently, no further biological modeling or optimization is necessary once the ridge filters are designed.

TPS for active beam shaping

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, Bendl et al., 1993), and a program called TRiP (Treatment planning for particles), which handles all ion specific tasks (Krämer et al., 2000a,b). 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 are:

- The beam intensity of every scan point at every energy has to be optimized separately 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.

ABSORBED DOSE CALCULATION

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 (Here the same empirical methods of range calculation as for passive systems are used). Each slice then corresponds to the range of ions at a certain energy of the accelerator. The scan positions of the raster scanner are then defined as a quadratic grid for each energy. In the last step, the particle number at each scan point is optimized iteratively until a predefined dose at each point is reached.

BIOLOGIC MODELING

To fulfill the demands of an active beam delivery on the TPS concerning the biological effectiveness, a more sophisticated biological model is needed. Such a model was developed e.g. at GSI (Scholz et al., 1997). 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 (see also the chapter on “Biological Models for Treatment Planning”).

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.

The model allows the optimization of a prescribed biological effective dose within the target volume (Krämer and Scholz 2000; Jäkel et al. 2001b) using the same iterative optimization algorithm as for the absorbed dose. 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.

Existing and Planned Facilities

The Bevalac Facility

Pioneering work in the field of radiotherapy with heavy ions was performed at the University of California, Berkeley. The Bevalac provided the scientific and technological basis for many of the current developments in the field of ion radiotherapy. Between 1977 and 1992, in total 433 patients have been treated here with ions heavier than Helium. The majority of patients received neon ion treatments, although some patients were also treated with carbon, silicon and argon beams (Castro and Lawrence, 1978 and Castro et al., 1994).

At the Bevalac, two treatment rooms, both equipped with a fixed horizontal beam-line, were available. The majority of the patients was treated in a sitting position. For treatment planning, a CT scanner was modified to scan patients in a seated position.

The modulation of depth dose was performed using a fixed accelerator energy and passive range modulators, like ridge filters and patient specific compensators. The lateral width of the beam was produced using a double scattering system and was improved to a beam wobbling system in the 80ies. Patient specific field collimators were used to confine the beam to the target volume. A magnetic beam scanning system was installed in combination with a passive range modulator, that was used, however, for the treatment of a single patient only.

The HIMAC Facility

The Heavy Ion Medical Accelerator HIMAC started its clinical operation at Chiba, Japan, in 1994. Until February 2002, 1187 patients have been treated with carbon ions (Tusijii et al., 2002). Two redundant synchrotrons deliver carbon ion beams at energies of 290, 350 and 400 MeV/u.

Patients are treated in three different treatment rooms, which are equipped with a vertical beam-line, a horizontal beam-line and the third with a vertical and a horizontal beam-line, respectively.

For more flexibility, treatment chairs are used additionally to conventional treatment couches. In addition, a tub-like system may be mounted on the treatment table, to allow a small angle rotation of the patient around the longitudinal axis. For treatments in seated position, special horizontal CT scanners are available for treatment planning (Kamada et al., 1999).

The beam delivery uses passive range modulation by bar ridge filters to achieve a fixed modulation depth. The lateral field width is obtained by a wobbler system and beam shaping is achieved by patient specific collimators (Kanai et al., 1999).

The GSI Facility

At the research laboratory Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, a therapy unit began its clinical operation in 1997 (Eickhoff et al, 1999 and Debus et al., 2000). Until spring 2004, more than 220 patients have been treated with carbon ions. Only one treatment room is available that is equipped with a treatment couch. An additional treatment chair will come into clinical operation in the near future.

The beam delivery system is completely active and allows 3D scanning of arbitrarily shaped volumes with a spatial resolution of 2mm in all three directions. Using a magnetic deflection system, the intensity controlled raster scanner can deliver a monoenergetic pencil beam over an arbitrarily shaped area (Haberer et al., 1993). To do so, a beam of 4-10mm full-width half-maximum is scanned over a regular grid of points with typically 2-3mm 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 moves the beam to the next beam spot, when a predefined number of particles is reached. An online monitoring of the beam position and a feedback loop to the scanner is used to keep the beam extremely stable at each scan spot.

The HIBMC Facility

The Hyogo Ion Beam Medical Center (HIBMC) started operation with protons in 2001 and with carbon ions in 2002 at Harima Science Garden City, Japan. It is the first facility offering carbon ion and proton treatment at the same facility. Until

mid of 2002, 28 patients have received carbon ion therapy (Itano et al., 2003). Six therapy rooms are available with seven treatment ports. Three rooms are dedicated to carbon ion beams: one with a vertical beam line, one with a horizontal and one with a 45 degree oblique beam line, respectively. Two proton treatment rooms are equipped with commercially designed gantries. The beam delivery system is based on the HIMAC system.

New facilities

There is currently an increasing interest in heavy ion radiotherapy especially in Europe and Asia (Sisterson, 2003). There are proposals for hospital based heavy ion facilities in Lyon (France), Pavia (Italy), Stockholm (Sweden) and Vienna (Austria). Only two facilities (in Italy and Germany) , however, have by now reached the phase of construction or call for tenders. In Lanzhou (China) an existing heavy ion research facility is preparing for clinical patient treatments with ions. The therapy facility will be installed within the environment of a research laboratory, similar to the GSI facility. It features only a horizontal beam-line. The Italian project is driven by the CNAO (Centro Nazionale Adroterapia) and will set up the facility in Pavia near Milano. It will exhibit a synchrotron of about 25m diameter that is capable of accelerating protons and Carbon ions up to energies of 400MeV/u. It features three treatment rooms equipped with horizontal beam lines, one of them with an additional proton gantry. Beam scanning will be available at all beam lines. The construction of this first phase should start at the beginning of 2004 and the first patient is planned to be treated at the end of 2007. Then in a second project phase, the construction of two additional treatment rooms equipped with superconducting isocentric ion gantries is foreseen. The currently most ambitious and advanced project is the Heavy Ion Therapy accelerator HIT which will be installed at the Heidelberg university hospital (Heeg et al., 2004; Eickhoff et al., 1998). The facility will be equipped with three treatment rooms, which host 2 horizontal beam lines and one room with a fully rotating isocentric gantry (Spiller et al., 2000). When completed, this gantry will be the first ion gantry worldwide. The facility will use much of the know-how developed at the GSI facility. The beam delivery in all three treatment rooms, e.g. will rely on the active 3D beam scanning method together with the active energy variation of the synchrotron.

One of the biggest technological challenges is the construction of the isocentric ion gantry with an integrated beam scanning system. The scanning magnets will be placed upstream of the last bending magnet in order to reduce the diameter of the gantry to about 13m. The last bending magnet therefore needs a very large aperture and contributes much to the total weight of the gantry of roughly 600 tons. A very rigid mechanic framework is therefore mandatory to guarantee a sufficient stability of the gantry. The total length of the gantry will be about 20m. Furthermore, the design of the synchrotron and beam line will enable the use of Carbon ions as well as protons, Helium and Oxygen ions for radiotherapy. One of the major research goals is thus to evaluate which ion beam modality is best suited for the treatment of a certain type of tumor.

The facility will be completely integrated into the radiological clinic of the Heidelberg university and is designed to treat 1000 patients per year when in full operation. The construction of the facility is scheduled to be finished in 2006 and clinical operation is planned to start at the beginning of 2007.

Clinical application of ion beams

Considering the physical and biological properties of carbon ions, a potential benefit for carbon ion RT can be assumed for all tumors with a low α/β ratio and which are surrounded by critical structures. A low α/β ratio has been shown for chordomas, low grade chondrosarcomas and malignant salivary gland tumors such as adenoid cystic carcinomas and other head and neck tumors. Further potential indications are bone and soft tissue sarcomas, lung cancer and prostate cancer. For these tumor entities higher control rates and an improved quality of life can be expected if heavy ion RT is performed (Griffin et al., 1988 and Debus et al., 2000).

Clinical trials at Berkeley

At the time, when ion RT in Berkeley started almost no clinical information was available about the biological effectiveness of ions for various tumors and normal tissues. The studies were basically defined as dose-finding studies. Moreover, most of the patients were irradiated with Helium ions, which do not show a significantly increased LET and in total only 433 patients have been treated with heavy ions (mainly with Neon). Moreover, the heavy ion treatment was mainly

applied in combination with Helium ions and/or conventional photon therapy. 299 patients have received a minimum neon ion dose of 10 Gy. Only few patients (e.g. with malignant glioma, pancreatic cancer and salivary gland tumors) were irradiated solely with heavy ions. For many tumors at the base of skull (SB) pure Helium beams were used and Neon ions (used only for advanced salivary gland tumors) were avoided because of their large fragmentation tail and the high RBE in normal tissue of the central nervous system.

The five year actuarial disease specific survival (DSS) and local control (LC) rates suggested that Helium and Neon ions improved the outcome for a number of tumor types given in table I as compared to historical results.

For some other tumor types like malignant glioma, pancreatic, gastric, esophageal, lung and advanced or recurrent head and neck cancer, however, the outcome was not significantly better than for low LET irradiation. Also a large number of patients suffered from severe radiation induced toxicity, which was attributed to the high LET of Neon ions and the drawbacks of the passive beam delivery system. A significant improvement in outcome was, however, observed for patients treated between 1987 and 1992, which is attributed to improvements in 3D treatment planning, patient immobilization and availability of MRI. A review of the clinical data can be found in (Castro et al., 1997, Castro et al., 1994, Linstadt et al., 1991).

Table I: Clinical results from Berkeley according to (Castro et al., 1997, Castro et al., 1994 and Linstadt et al., 1991). DSS and LC are the disease specific survival and local control after 5 years.

Doses refer to median total doses. Neon ion doses are given in parentheses.

Indication	DSS	LC	Patients	D_{total}(D_{Ne}) in Gye
Chondrosarcoma (SB)	83%	78%	27	65 (-)
Chordoma (SB)	72%	63%	53	65 (-)
Meningioma (SB)	82%	85%	27	65 (-)
Advanced salivary gland ca.	50%	50%	18	65 (>10)
Advanced soft tissue sarcoma	42%	59%	32	60 (14)
Bone sarcoma	45%	59%	17	69.6 (16.8)
Locally advanced prostate ca.	90%	75%	23	76.9 (11.2)
Biliary tract carcinoma	28%	44%	28	60 (17.8)

Clinical trials and routine treatments at GSI

Since December 1997, more than 220 patients have been treated with Carbon ion RT at GSI. An overview over the results is found in (Schulz-Ertner et al., 2003a). Patients with chordomas (n=44) and low grade chondrosarcomas (n=23) of the skull base were treated within a clinical phase I/II trial with Carbon ion RT only. Median dose was 60 GyE (20 fractions each 3Gye). In February 2003, the median follow-up was 20 months. Actuarial 3-year local control rate was 100% for chondrosarcomas and 81% for chordomas of the skull base, respectively. Actuarial 3-year overall survival was 91%. Toxicity correlated with radiobiological model estimations. Late toxicity greater than common toxicity criteria (CTC) grade 3 was not observed (Schulz-Ertner et al., 2003a). Local control rates after carbon ion RT are at least comparable to the results after proton RT (Noel et al., 2001), which is currently considered the treatment of choice in chordomas and low grade chondrosarcomas. Therefore, carbon ion RT is offered at GSI as a routine treatment to patients suffering from these tumors as an alternative to proton RT since January 2002.

Figure 5 shows an example of a treatment plan for patient with a chondrosarcoma close to the brain stem. The excellent dose conformation of the 90% isodose to the target is clearly demonstrated, although only two horizontal treatment fields were used here. The dose sparing of the relevant organs at risk can be seen in the dose volume histogram (Fig. 5b).

A clinical phase I/II study of combined photon RT plus a Carbon ion boost for sacral / spinal chordomas and low grade chondrosarcomas is ongoing. Treatment consists of combined photon IMRT (weekly fractionation 5 x 1.8 Gy, median dose 50.5 Gy) and a Carbon ion boost (weekly fractionation 6 x 3.0 GyE) to the macroscopic tumor residual after surgery (median total dose was 68.4Gye). In December 2002, local control was achieved in 8 of 9 patients with cervical spine tumors. Mucositis CTC grade 3 was observed in 3 patients with chordomas of the cervical spine, but none of the patients developed severe late effects to the spinal cord.

Locoregional control was yielded in 7/8 patients treated for tumors of the sacrum. Two out of 8 patients with sacral chordoma developed distant metastases. Combined photon RT and carbon ion boost of sacral chordomas is very well tolerated, and no side effects were observed up to now.

A clinical phase I/II study for combined photon RT with a carbon ion boost in locally advanced adenoid cystic carcinomas is ongoing. Therapy consists of combined stereotactically guided photon RT to the clinical target volume (CTV) (CTV dose 54 Gy) and a Carbon ion boost to the macroscopic tumor residual (boost dose 18 GyE). A typical treatment plan for this combination therapy is shown in Figure 6.

An interim analysis on 21 patients in December 2002 (median follow-up 14 months) showed an actuarial locoregional control rate of 62% at 3 years, disease-free survival and overall survival were 40% and 75% at 3 years, respectively. Acute severe side effects CTC grade 3 were observed in 9.5% of the patients, but no RT related late effects greater than CTC grade 2 occurred up to now (Schulz-Ertner et al., 2003b). These results are encouraging as locoregional control rates are better than in most photon trials and comparable to neutron RT (Huber et al., 2001 and Laramore et al., 1993), however, with minimized toxicity.

Treatments at HIMAC

At HIMAC a number of studies are ongoing using ion RT for the treatment of tumors of the head and neck, prostate, lung, liver as well as sarcomas of soft tissue and bone and uterine carcinomas. Between 1994 and February 2002, 1187 patients have been treated within clinical trials using carbon ion therapy and performing dose escalation studies. Table II gives an overview over the most important results (Tsujii et al., 2002). Ion radiotherapy of the prostate was given in combination with hormone therapy and for uterine tumors in combination with conventional photon therapy. The fractionation scheme used is generally 16 fractions in 4 weeks for head and neck tumors as well as for sarcomas of bone and soft tissue. It was significantly shortened for lung cancer (9 fractions in 3 weeks) and liver tumors (12 fractions in 3 weeks) and is being further shortened to 4 fractions in 1 week for both indications.

The latest results are from dose escalation studies in lung tumors and soft tissue sarcoma.

In two phase I/II trials for stage I non-small cell lung cancer (NSCLC), using different fractionation schemes (18 fractions in 6 weeks and 9 fractions in 3 weeks), a dose escalation was performed from 59.4 to 94.5 Gy and from 68.4 to 79.2 Gy, respectively (Miyamoto et al., 2003, Koto et al., 2004). The resulting

overall control rates for the 6- and 3-week fractionation were 64% and 84%, respectively. The total recurrence rate was 23.2%.

For unresectable bone and soft tissue sarcomas, a further phase I/II trial was performed with doses between 52.8 to 73.6 Gye (Kamada et al., 2002), applied in 16 fractions over 4 weeks. The observed overall control rates were 88% and 73% at 1 year and 3 years, respectively.

Table II: Results from HIMAC (Tsuji et al., 2002). Local control (LC) and overall survival (OS) is given for 2 and 3 years and refers to the latest completed trial (patient numbers in brackets).

Indication	LC(2y)	OS(3y)	Patients	D(C₁₂) in Gye
Locally advanced head & neck tumors	61%	42%	170(134)	52.8-64
Lung cancer (stage I)	100%	73%	161(50)	72
Hepatocellular Ca. (stage T2-4N0M0)	83%	45%	122(86)	49.5-79.5
Prostate Carcinoma (stage T1-3N0M0)	100%	97%	143(61)	60-66
Squamous cell Carcinoma (uterus; stage T2-4N0M0)	67%	36%	67(14)	68.8-72.8
Unresectable bone and soft tissue sarcoma	77%	50%	95(64)	52.8-73.6

Outlook

In the last decade, valuable clinical experience has been gained in heavy ion therapy at HIMAC and GSI. Together with the development of new technologies especially for beam application and treatment planning there will certainly be a broader implementation of ions in clinical settings that allow for an optimal exploitation of the physical and biological potential of protons and heavy ions. Among these technologies are inverse treatment planning for particles (Oelfke and Bortfeld, 2000 and 2001), gating for breath dependent targets (Minohara et al, 2000; Shirato et al., 2000 and Ford et al., 2002), the raster scan system for tumor conform beam application (Haberer et al., 1993) and biologic plan optimization for carbon ion RT (Scholz et al., 1997 and Krämer et al., 2000a,b). Further research is still required to clarify what indications benefit most from heavy ion therapy and what is the ideal ion species and fractionation scheme.

These questions can be answered only in clinical studies performed at dedicated ion facilities, like the HIMAC, HIBMC or the upcoming Heidelberg facility. For tumors with proven effectiveness of carbon ion RT such as chordomas and low grade chondrosarcomas of the skull base, clinical phase III trials are necessary to determine the advantages of carbon ion RT over other RT modalities such as modern photon techniques (like IMRT) or proton RT which is currently considered to be the treatment of choice. Toxicity, quality of life and socio-economic aspects have to be investigated as study endpoints besides local control probability.

The encouraging results from HIMAC especially for bone and soft tissue sarcomas as well as for lung tumors warrant further clinical investigation of carbon ion RT in the treatment of these tumors. Clinical phase III studies will have to be conducted and will not only have to compare different RT modalities but will have to include a control arm of surgically treated patients.

New immobilization techniques with rigid immobilization devices and pre treatment control and correction of the patient alignment together with the development of faster dose calculation and optimization algorithms and better knowledge of the complex biology of carbon ions will help to enlarge the spectrum of possible indications for carbon ion RT. The development of a gantry for carbon ion RT will facilitate the safe treatment of paraspinal tumors by allowing posterior beam directions.

Further investigation is needed in the field of multimodal treatments. There is almost no clinical data available about adjuvant chemotherapy or hormone therapy, although interdisciplinary treatment of patients with tumors that tend to metastasize seems to be warranted. In this connection, major attention has to be drawn to the proper definition of clinical trials for head and neck malignancies, gynecological tumors and prostate cancer in order to obtain comparability with up-to-date oncological standard therapy regimes.

A combination of different RT modalities such as photon IMRT plus carbon ions or protons might be favorable for a number of indications. Combined RT offers the possibility for risk-adapted treatment of different target volumes in one patient dependent on the oncological concept based on risk estimation. Furthermore, the combination of carbon ion RT or protons with photon RT will guarantee that a higher number of patients will benefit from the advantages of particle RT despite

the still limited availability. Possible indications are head and neck malignancies, malignant primary brain tumors and prostate cancer. For patients with unfavorable localized prostate cancer a clinical phase I/II trial of combined photon IMRT with a carbon ion boost, which is a project of the European hadrontherapy network „ENLIGHT“, is in preparation (Nikoghosyan et al. 2004).

Due to the biologic properties of carbon ion RT, hypofractionation might be considered for a number of tumor entities. The accelerated fractionation scheme used at GSI for chordomas and low grade chondrosarcomas of the skull base corresponds to a reduction of treatment time by about 50% compared to conventional photon RT. First clinical hypofractionation trials for lung cancer are underway at HIMAC and further studies are in preparation. These studies investigate outcome and toxicity of hypofractionation as endpoints, as well as quality of life and economic aspects. Carbon ion RT might even turn out to be an optimal treatment option from the economic point of view, as hypofractionation leads to substantial reduction of overall treatment time and hospitalization.

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Figure 1: Cell inactivation cross section as a function of LET for various ions. The decrease at very high LET values indicates that further increase in LET does not lead to higher biological effectiveness.

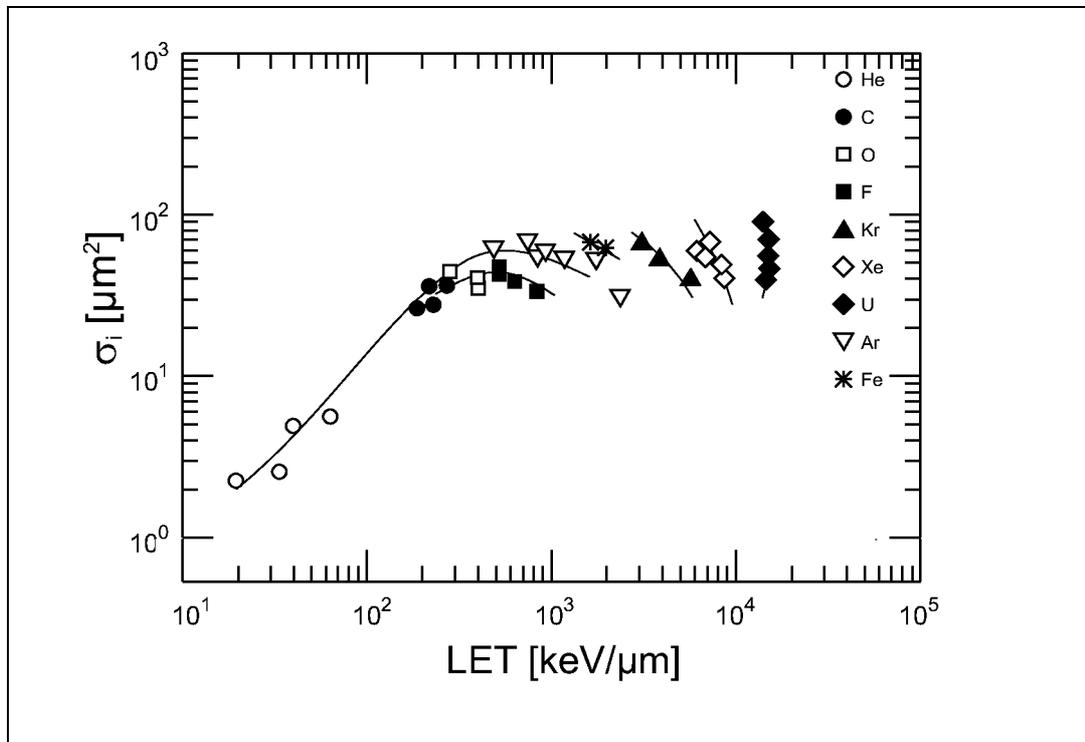


Figure 2: Depth dose distribution for various photon beam qualities and monoenergetic Bragg curves for C-12 ion beams. The dose beyond the sharp fall-off is due to nuclear fragments with larger range than the primary ions.

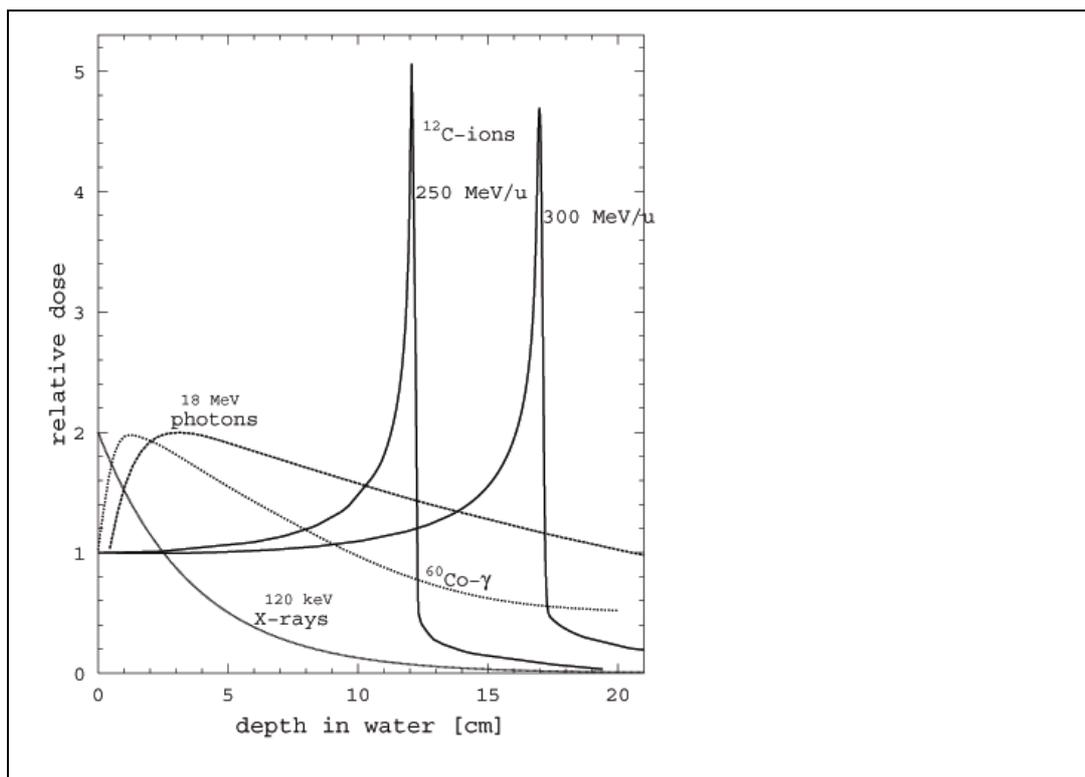


Figure 3: Principle of the passive dose delivery system used for proton and ion beams. Shown is the incoming broadened beam that is modulated in depth. The variable range shifter has to shift the modulated depth dose to the desired depth, while collimator and compensator are patient specific devices. The lines in the body represent the distal dose fall-off that can be shifted in depth with the range shifter.

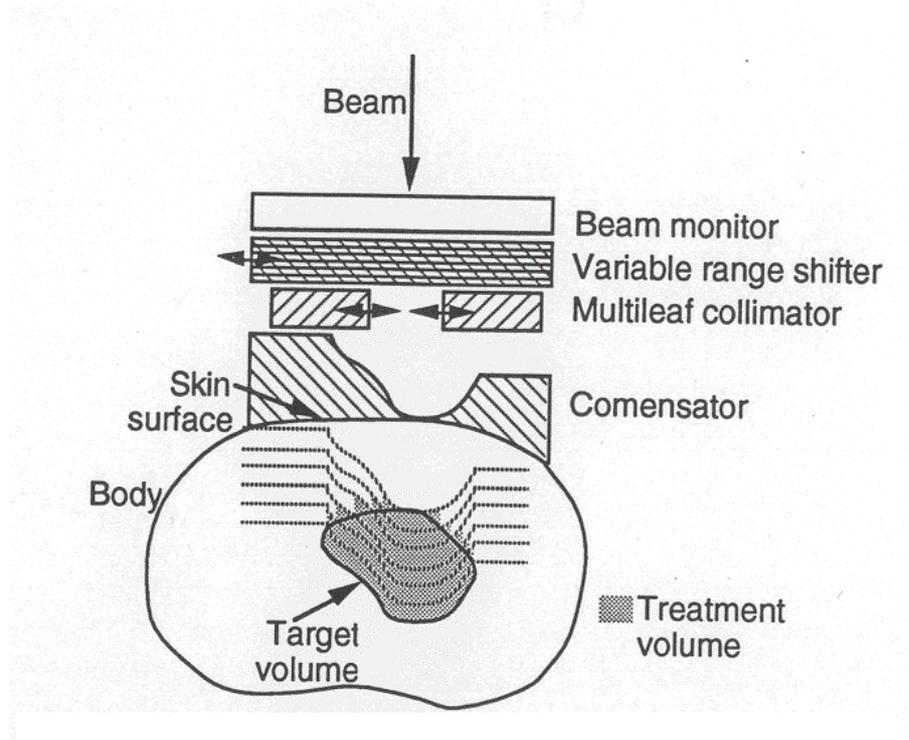


Figure 4: Principle of the active rasterscan system used at GSI for carbon ions. A small pencil beam is scanned in vertical and horizontal direction, using two pairs of scanner magnets. By switching the energy of the synchrotron, the position of the Bragg peak can be chosen so that each scanned area is adapted to the extend of the target in depth.

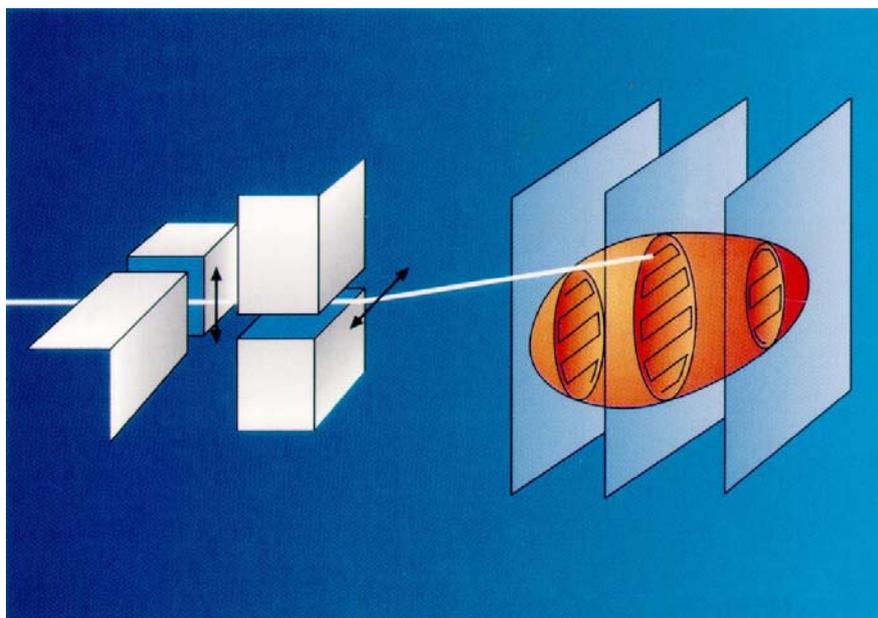


Figure 5: Example of a treatment plan for fully fractionated radiotherapy using 2 nearly opposing fields of carbon ions, as it was performed at GSI. In (a) the dose distribution at isodose levels of 10%, 30%, 50%, 70% and 90%V is shown, respectively. 100% dose corresponds to 60Gye, that where applied in 20 consecutive fractions of 3Gye. The GTV and CTV is shown as a red and blue line, respectively. The organs at risk (OAR) are the brain stem (green line), optical nerves (blue lines), eyes (light purple) and optic chiasm (purple; seen in the right image only). In (b) the dose volume histogram for the target and these OAR is shown.

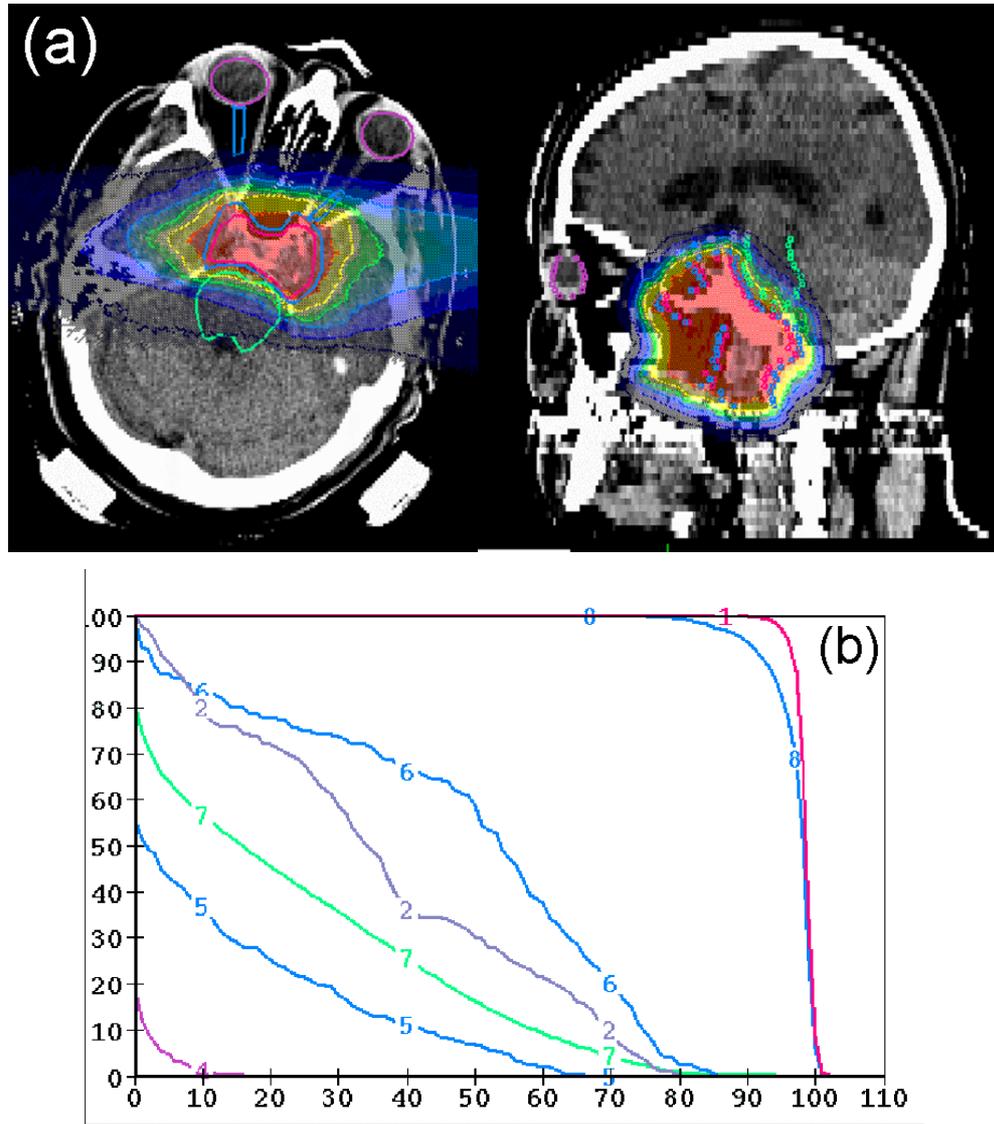


Figure 6: Example of a combination therapy for a patient with adenoid cystic carcinoma, where the larger CTVI (including microscopic spread of the tumor) was treated with photon IMRT in conventional fractionation up to 54Gy and only the CTVII (defined as GTV plus a margin) was treated with carbon ions in 6 fractions with a total dose of 18Gye.

