Radiation Therapy With Charged Particles
Daniela Schulz-Ertner, MD,* Oliver Jäkel, PhD,† and Wolfgang Schlegel, PhD‡

Charged particle beams can offer an improved dose conformation to the target volume as compared with photon radiotherapy, with better sparing of normal tissue structures close to the target. In addition, beams of ions heavier than 4He exhibit a strong increase of the linear energy transfer in the Bragg peak as compared with the entrance region. These physical and biological properties are much more favorable than in photon radiotherapy. As a consequence, particle therapy with protons and heavy ions has gained increasing interest worldwide, and many clinical centers are considering introducing radiation therapy with charged particles. This contribution summarizes the physical and technical principles of charged particle therapy with protons and heavy ions. It briefly reviews the clinical experience gathered so far with proton therapy and gives a more detailed summary of the recent results in carbon ion therapy of skull base tumors, head and neck tumors, non–small-cell lung cancer, hepatocellular carcinomas, bone and soft-tissue sarcomas, and prostate cancer.

Dr. Robert R. Wilson, a physicist who had worked on developing particle accelerators, was the first to propose the medical use of protons for cancer therapy in 1946.1 Less than 10 years later, protons were used to treat cancer patients for the first time.

Between 1977 and 1992, the first clinical experience took place, especially with helium, carbon, and neon ions at the Lawrence Berkeley Laboratory, and encouraging results (especially in skull base tumors and paraspinal tumors) were achieved.2,3

Today, particle therapy with protons, helium, and carbon ions has gained increasing interest.4 Worldwide, there are about 25 therapy units for treating patients with protons. Therapy with particles heavier than protons is currently available at 3 centers. The majority of the particle therapy centers are located in physics research laboratories, and only a few are in a hospital environment. This situation is changing; there are more then 20 centers under construction or in the planning phase that will start to treat patients within the next 5 years,5 and nearly all those installations will be hospital based. This contribution gives an overview of the physical and technical background and of the clinical experience that has been gathered in charged-particle therapy.

Physical Properties of Charged-Particle Beams
Because the physical and biological properties of proton beams differ significantly from those of heavier particles, particle therapy is now divided into 2 categories: “proton-therapy” characterized by low linear energy transfer (LET) and “heavy-ion therapy” with high LET properties. The term heavy ions is used here for ions heavier than helium ions. The expression charged particle therapy will be also used and covers both proton therapy and heavy ion therapy. (In principle, “particle therapy” also covers radiation therapy (RT) with electrons, pions and neutrons. In this contribution, we would like to restrict particle therapy to charged particles with masses equal to or heavier than protons.)

Charged particles passing through tissue slow down losing energy in atomic or nuclear interactions. This reduces the energy of the particles, which in turn causes increased interaction with electrons. Maximum interaction occurs at the end of range causing maximum energy transfer and thus maximum dose deposition within the target area. The primary rationale for RT with charged particles is this sharp increase...
of dose in a well-defined depth (Bragg peak) and the rapid
dose falloff beyond that maximum (Fig 1).

Bragg peaks are usually not wide enough to cover most
treatment volumes. By superimposing a set of beams with
decreasing energies and weights, a “spread out break peak”
(SOBP) is generated, which delivers the desired dose to the
whole treatment volume (Fig 2).

The ratio of Bragg peak dose versus dose in the entrance
region is larger for heavy ions than for protons. Because of
their larger mass, angular and energy straggling becomes
negligible for heavy ions as compared with protons. Heavy
ions therefore offer an improved dose conformation as com-
pared with proton and proton RT, with better sparing of
normal tissue structures close to the target. In addition, heavy
ions exhibit a strong increase of the LET in the Bragg peak as
compared with the entrance region. The radiobiological ad-
vantage of high LET radiation in tumor therapy is well known
from neutron therapy. Unlike radiotherapy with neutron
beams, in heavy ion radiotherapy the high LET region can be
conformed to the tumor.

Technical Aspects of
Charged-Particle Therapy

Beam Production With
Cyclotrons and Synchrotrons

Compared with photon beams, charged particles have the
basic difference that they are slowed down when passing
through tissue and thus have a finite range. The energy re-
quired to treat a tumor thus depends on the depth of the
target volume within tissue. For protons, energies between
80 and 250 MeV are required. In most proton facilities, cy-
clotrons are used to produce proton beams with sufficient
energy and beam intensity. Cyclotrons produce continuous
beams with a fixed energy that makes the design quite simple:
the accelerator operates at a fixed radiofrequency and all
the settings of the beam lines are predetermined. No sophisti-
cated controls are needed, which makes operation easy.6

The energy required to treat deep-seated tumors with
heavy ions is much higher; although a proton beam of 150
MeV can penetrate 16 cm in water, the same penetration
depth is achieved with carbon ions of 3,000 MeV or 250
MeV/u (energy per nucleon).

To accelerate particles to such high energies, synchrotrons
are better suited than cyclotrons. Synchrotrons produce
pulsed beams, and the energy can be varied from 1 cycle to
the next in steps of a few MeV. Hence, modulation of the
Bragg Peak to scan a target in depth can be achieved without
absorbers, avoiding scattering and degradation of sharpness
in energy. Particle acceleration in synchrotrons is, however,
much more complicated and hence more cost intensive than
in cyclotrons.

Beam-Delivery Systems (Gantries)

Experience with charged-particle therapy has been acquired
in the past mainly in research laboratories using horizontal
beam lines. In RT, however, the success of a treatment is
strongly related to the possibility of applying the beam to the
target volume using multiple fields. The freedom to apply the
beam on a gantry that rotates around the patient is expected
to offer significant advantages. To validate the outcome of
charged particles as compared with conventional radiation, it
is necessary to apply both modalities at the same level of
complexity.

The major drawback of gantries for charged particles is the

Figure 1 Relative depth dose of monoenergetic-charged particle
beams (protons and $^{12}$C-ions). Characteristic is the Bragg peak,
which is more pronounced for heavy ions (in this case $^{12}$C-irradia-
tion). The distal dose gradient is steeper for 12C-ions as well, and
the ratio of dose of the plateau to the peak is more favorable com-
pared with protons. A disadvantage of heavy ions is the extension of
a small portion of dose behind the Bragg peak (the so-called frag-
mentation tail). This is because of nuclear reactions induced by the
$^{12}$C-ions leading to nuclear fragments with higher ranges. In most
clinical situations, however, the dose in the fragmentation tail is not
higher than 10% of the dose to the target and thus causes no severe
restrictions to the treatment plan.

Figure 2 SOBP (dashed line) as composed of a number of Bragg
peaks with different energies. The depth modulation is either per-
fomed by a set of absorbers of different thickness (eg, by using a
modulator wheel or a ridge filter as range shifter) or by active scan-
ning using charged-particle beams from a synchrotron that is able to
change the energy between the beam spills.
size and weight of the rotating structure supporting the beam. Although the weight of a proton gantry is around 100 tons and has a diameter of 10 meters, an isocentric gantry for carbon ions is expected to have a weight of about 600 tons and a diameter of 13 meters.

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 2 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 and molds that can be rotated around the patient’s longitudinal axis by about ± 15° are available.

Beam-Application Systems

There exist 2 principal 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 to yield a predefined depth-dose profile (Fig 2).

To move the modulated Bragg peak (or SOBP) to the desired radiologic 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. By using a collimator, the lateral extent of each treatment field is adapted to the beam’s eye view of the target volume. Additionally, a compensator is used to account for tissue inhomogeneities and the curvature of the patient’s 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 charged-particle beams has 3 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 because of the fact that the compensator shifts the SOBP toward 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. Second, the amount of material in the beam line is considerable, leading to an increase in nuclear fragments (including neutrons) 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.

Active-beam shaping

Another method of beam delivery is called active-beam shaping. This system takes advantage of the electric charge of the particles to produce a tightly focused pencil beam that is then deflected laterally by 2 magnetic dipoles to allow a scanning of the beam over the treatment field. When the beam is produced with a synchrotron, the energy can be switched from pulse to pulse to adapt the range of the particles in tissue. This way, a target volume can be scanned in 3 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 nontarget volume receiving high LET radiation is minimized. Figure 4 shows the principle of the active-beam delivery system. There are only 2 facilities in which beam scanning is already applied clinically: the German heavy ion facility at the Gesellschaft für Schwerionenforschung, GSI, where a fully active system including energy variation of the synchrotron is used, and the proton facility at the Paul-Scherrer Institute, PSI, Switzerland, where a 1-dimensional beam scanning is combined with a 1-dimensional patient movement and a variable range shifter.
Problem because treatment planning can rely on measured depth. The modeling of nuclear fragmentation is not a serious scattering of carbon ions is very small and the lateral penum- 
tration models are relatively simple because lateral similar to those used in conventional photon therapy. The beam- 
ticles therapy for a passive-beam–shaping system are very sim- 
ilar to those used in conventional photon therapy.

Patient Positioning
Because of the high spatial accuracy achievable with charged- 
particle beams, patient fixation and positioning requires special attention. Patient fixation is usually achieved with individually prepared mask systems or whole-body molds. The highest accuracy during the initial positioning can be achieved by the use of stereotactical methods. Before every fraction, the position is verified by using radiograph imaging in the treatment position. The radiograph images are compared against digitally reconstructed radiographs obtained from the treatment-planning computed tomography (CT) scan. Another possibility for position control, which is used at the Heavy Ion Medical Accelerator in Chiba, is to do a CT scan of the patient in the 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 because 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.

Treatment Planning

Treatment Planning Systems (TPS) for Passive-Beam Shaping
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 algorithms to calculate absorbed dose in charged particle therapy for a passive-beam–shaping system are very similar to those used in conventional photon therapy. The beam-transport models are relatively simple because lateral scattering of carbon ions is very small and the lateral penum- 
bra 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 radiologic depth of a proton or ion beam in tissue is calculated by using an empirical relation between radiograph CT numbers and measured particle ranges, which is valid for all tissues but not for material with high Z values, such as metal implants.

By 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.

TPS for Active-Beam Shaping
With a 3-dimensional scanning system, nearly arbitrary shapes of the SOBP can be produced. The shape of the SOBP therefore has to be optimized separately for every scan point in the irradiation field.

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 each of the energies are needed. If the applied biological effective 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 Cartesian grid with quadratic grid elements 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.

Biological Modeling
Charged particles differ from photons in their radiobiological properties. They are biologically more effective than photons; in other words, lower dose is required to achieve the same biological effect. The relative biological effectiveness (RBE) of a charged-particle beam is defined as a dose of a photon beam divided by the dose delivered by the charged particle beam to achieve the same biological effect. The RBE adjusted dose (or effective dose) is defined as the product of the physical dose and the respective RBE describing the radiosensitivity of the tissue after ion irradiation compared with photon irradiation at a given level of effect.

In general, the RBE of a charged particle beam in tissue depends on the type of the particle, underlying LET spectrum, the cell type, and the dose level.

Protons
Although the RBE depends on many different parameters as mentioned previously, it was concluded that for proton ther-
apy the magnitude of RBE variation with treatment parameters in clinical situations is only on the order of 10% to 20%. The average value at mid SOBP overall dose levels was shown to be $RBE = 1.1$. At almost all institutions, proton therapy is based on the use of a single RBE value ($RBE = 1.1$), which is applied to all proton-beam treatments independent of dose/fraction, position in the SOBP, initial beam energy, or the particular tissue.

**Heavy Ions**

For heavy ions, the dependence of RBE on the various physical and biological properties are much stronger and cannot be disregarded. For passive-beam–delivery systems, this problem was solved by a number of pragmatic steps and assumptions: 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.

If the fractionation scheme and dose per fraction are kept fixed, only 1 modulator yielding a certain depth dose is used for each treatment field and several fields of a treatment plan are applied on different treatment days. The treatment fields can be considered to be independent, and the effective dose values can simply be added.

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.

To fulfill the demands of an active-beam delivery on the TPS concerning the biological effectiveness, a more sophisticated biological model is needed. 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. 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 by using the same iterative optimization algorithm as for the absorbed dose. At each iteration step, however, the RBE has to be calculated anew because it is dependent on the particle number (or dose level).

**Clinical Experience With Charged-Particle Therapy**

About 43,000 patients have up to now been treated with protons. The experience with carbon ions is much more limited. At the National Institute of Radiological Sciences (NIRS)/Chiba, more than 2,000 patients have been treated with carbon ions since 1994; the Hyogo Ion Beam Medical Center (HIBM/C) has operated since 2002 and has treated about 40 patients up to now. At GSI, almost 300 patients have been treated since December 1997. Both proton and carbon ion RT enable dose escalation and sparing of surrounding sensitive normal tissue structures.

**Protons**

The main advantage of protons in comparison to photons is the reduction of the integral dose to healthy tissue outside the planning target volume, which is because of the “inverse depth-dose profile” (ie, Bragg peak) of proton beams. Radiation-induced side effects including the risk for secondary malignancies can thus be reduced. This point is of major importance when children, adolescents, and young adults are treated. This advantage is especially pronounced in comparison to modern photon IMRT. Although photon IMRT achieves almost comparable target coverage and sparing of adjacent normal tissue from the high-dose region of the dose distribution, the volume of normal tissue outside the planning target volume receiving low doses is much larger with IMRT.

The treatment of pediatric tumors is one of the most important indications for proton therapy because a clear clinical benefit by means of reduced toxicity is assumed. Advantages for proton RT were found for tumors of the head and neck region, the skull base, the orbit, the brain, and extracranial sites. Proton RT is therefore preferred in children and adolescents whenever available, although clinical phase III trials are lacking. The treatment of children, which has to be performed with sedation or general anesthesia in the very young, requires a close collaboration between the radiation oncologist and the pediatric oncologist and RT has to be intercoordinated within multimodal treatment protocols.

Besides the treatment of childhood tumors and the treatment of benign skull-base tumors and arteriovenous malformations in adolescents and young adults, the effectiveness of proton RT has been proven in large patient series for uveal melanomas, chordomas, and low-grade chondrosarcomas of the skull base. Egger and coworkers report on 2,645 patients with uveal melanoma treated with proton RT at PSI, Villigen, Switzerland. Eye-retention rates were between 89.5% and 100% at 5 years for all patients treated with an optimized proton RT technique. In 375 chordomas of the skull base, 5-year local control rates of 73% at 5 years have been obtained with protons at Massachusetts General Hospital.

In most proton centers, proton therapy is offered to localized non–small-cell lung cancer (NSCLC) patients and prostate cancer patients as well. A clinical phase II trial of proton RT in stage I NSCLC has been performed at the Loma Linda University Medical Center (LLUMC). Sixty-eight patients received a target dose between 51 and 60 centigray equivalent (CGE) in 10 fractions. Locoregional control rates at 3 years were 87% for T1 tumors and 49% for T2 tumors, respectively. The overall survival rates at 3 years were 27% after a total dose of 51 CGE versus 55% after 60 CGE, respectively. An ongoing trial investigates further dose escalation of proton
RT in stage 1 NSCLC. However, stereotactic photon irradiation using 3 × 10 Gy has been applied in 27 patients with localized tumors of the lung by Wulf and coworkers in Wuerzburg, Germany. They yielded a 2-year locoregional control rate of 76% and an overall survival rate of 21%. Similar results with 2-year locoregional control and overall survival rates of 71.1% and 64%, respectively, were obtained by Hof and coworkers with stereotactic single-dose photon irradiation of 19 to 26 Gy in 10 stage 1 NSCLC patients in Heidelberg. To fully exploit the advantages of high precision techniques in the treatment of localized lung cancer, movements of the target caused by breathing have to be minimized. In the case of a scanned beam, interference effects between the movement of the beam and the internal organ movements may cause significant problems and need special attention. Although respiratory gating and image-guide RT are currently being integrated into modern photon RT as well as into proton RT, tracking of the tumor motion with the scanned beam is currently being experimentally investigated and not yet in clinical application.

Eight-year disease-free survival rates obtained with proton RT in localized prostate cancer were 81% for patients presenting with prostate-specific antigen (PSA) values between 4.1 and 10 ng/mL, 62% for PSA values between 10.1 and 20 ng/mL and 43% for PSA values between 20.1 and 50 ng/mL at the Loma Linda University Medical Center. These rates are very similar to those obtained with modern photon IMRT, which is not surprising because the doses are very similar. Dose escalation with proton RT is being investigated in an ongoing trial at the Massachusetts General Hospital, Boston, MA. A randomized clinical trial investigating high-dose proton RT versus high-dose photon IMRT is still needed to determine whether the physical advantage of proton RT translates into a measurable benefit in quality of life.

Heavy Ions

Carbon ions have similar physical properties as protons but additionally offer a higher biological effectiveness in specific tumor types. Because RBE is different for different biologic endpoints and for different tissues, radiobiological aspects are of high relevance for the choice of potential indications. Carbon ion RT offers the highest ratio of RBE values between the Bragg peak and the plateau for tumors with a low intrinsic radiosensitivity against conventional photon RT, characterized by low α/β ratios in the cell-survival curves and a pronounced shoulder of the curves indicating a high repair capacity. RBE values for carbon ion RT might also be high for normal tissue structures in close vicinity to the irradiated tumors that fulfill the same biological criteria and have to be included into the target volume for oncologic reasons. On the other hand, low RBE values for carbon ion RT are assumed in tumor cells showing good response to photon RT indicated by high α/β ratios of the cell-survival curves. Taking into account radiobiological aspects, the highest benefit of carbon ion RT in the form of increased biological effect and minimized toxicity can be expected for tumors relatively radioresistant to photon RT, which are located within sensitive normal tissues. Carbon ion RT might, on the other hand, be disadvantageous in the treatment of radiosensitive tumors located in relatively radioresistant normal tissue. Potential indications for carbon ion RT are therefore chordomas and chondrosarcomas and malignant salivary gland tumors for which high RBE values have been determined. Furthermore, carbon ion RT may be advantageous in prostate cancer, lung cancer, and specific bone and soft-tissue sarcomas. However, clinical data proving the benefit of carbon ion RT in the treatment of these tumors are very limited and will be summarized in the following.

Skull-Base Tumors

Thirty-five percent of all chordomas have their origin in the skull-base region. Complete resection is rarely possible, and local recurrences are common. Results after conventional photon RT are poor with local control rates between 17% to 23% at 5 years. With modern stereotactic photon techniques allowing for higher tumor doses, a 5-year local control rate of 50% has been obtained. Local control probability increases with dose leading to favorable results in patients treated with tumor doses exceeding 65 Gy. In concordance with the finding of a dose-response-relationship, best results have been reported in chordomas with proton RT using doses up to 83 CGE. Five- and ten-year local control rates were 73% and 54%, respectively, for 375 patients with skull-base chordomas treated at Massachusetts General Hospital. Somewhat lower rates have been reached at other proton centers (Table 1).

Although proton RT is considered the treatment of choice for patients with base of skull chordomas, carbon ion RT has been shown to yield similar results. Between 1997 and 2001, a clinical phase I/II study has been performed at GSI investigating the feasibility and effectiveness of carbon ion RT in chordomas and chondrosarcomas of the skull base. Sixty-seven patients with chordomas (n = 44) and low-grade chondrosarcomas (n = 23) were treated with carbon ion RT to a median total tumor dose of 60 CGE (range 57-70 CGE) in a weekly fractionation of 7 × 3.0 CGE. An example of a dose distribution is shown in Figure 5. Local control rates for chordomas and low-grade chondrosarcomas of the skull base were 74% and 87% at 4 years, respectively. Overall survival at 4 years was 86% and 100% for chordomas and chondrosarcomas, respectively. Three patients developed a com-

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**Table 1 Treatment Results After Charged Particle RT for Skull-Base Chordomas**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Patients (n)</th>
<th>RT Modality</th>
<th>Tumour-Dose (GGE)</th>
<th>Local Control</th>
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<tbody>
<tr>
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<td>375</td>
<td>Protons + Photons</td>
<td>66–83</td>
<td>73%/5 y</td>
</tr>
<tr>
<td>Hug, 1999</td>
<td>58</td>
<td>Protons</td>
<td>64.8–79.2</td>
<td>59%/5 y</td>
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<tr>
<td>Noel, 2003</td>
<td>67</td>
<td>Protons + Photons</td>
<td>67 (median)</td>
<td>71%/3 y</td>
</tr>
<tr>
<td>Schulz-Ertner, 2004</td>
<td>67</td>
<td>Carbon ions</td>
<td>60 (median)</td>
<td>74%/4 y</td>
</tr>
</tbody>
</table>
mon toxicity criteria (CTC) grade 3 mucositis, but acute toxicities greater than CTC grade 3 were not observed. Comparing the local control rates and toxicity rates obtained in chordoma patients with different RT modalities, RBE values of carbon ion RT in chordoma cells appear to be higher than RBE values for the biological endpoint late effects in normal brain tissue, which is the biological endpoint to which the dose distributions have been normalized during biological plan optimization at GSI.

Head and Neck Tumors
In locally advanced head and neck tumors, RT is an established part of multimodal treatment. Most of the patients treated for locally advanced head and neck tumors have squamous-cell carcinomas. Carbon ion RT has been considered especially for the less common histological subtypes such as adenocarcinomas, adenoid cystic carcinomas, and malignant melanomas because these histological subtypes are considered to be relatively resistant to conventional photon RT. Squamous-cell tumors were also eligible for the clinical trials performed in Chiba, Japan.

Between 1994 and 1997, 36 patients with locally advanced head and neck tumors have been treated within a dose escalation trial with carbon ion RT at the NIRS in Chiba. Eleven patients had squamous-cell carcinomas, 5 had malignant melanomas, 9 had adenoid cystic carcinomas, 4 had adenocarcinomas, and 7 patients had other histologies. Total doses between 52.8 and 70.2 CGE were given in 16 or 18 fractions within 4 to 6 weeks. Five-year local control rates were 100% for malignant melanoma, 50% for adenoid cystic carcinoma, and 34% for squamous-cell carcinoma. Although these results await validation with a higher patient number, local control rates appear favorable in comparison to conventional photon RT, especially in malignant melanoma, adenoid cystic carcinoma, and adenocarcinoma.

At GSI, experience with carbon ion RT is limited to the treatment of locally advanced adenoid cystic carcinomas. This histological subtype of high-grade malignant salivary gland tumors was chosen for a study at GSI because of the relatively high RBE values of up to 8 reported for high LET RT. Complete surgical removal of the tumor is attempted whenever possible, and adjuvant RT is recommended for high-grade tumors irrespective of the extent of surgery. Inoperable tumors with infiltration of the skull base are considered unfavourable because gross tumor residuals require high target doses, which are rarely deliverable with conventional photon RT in the skull base region. The best results for locally advanced adenoid cystic carcinomas have been obtained with neutrons. A randomized phase III trial showed a significantly better locoregional control for neutron RT as compared with photon RT (56% v 17% at 10 years).

Through September 2003, 29 patients with locally advanced adenoid cystic carcinoma have been treated with a combination of photon RT and a carbon ion boost to the macroscopic tumor within a clinical phase I/II study at GSI. Only patients with histologically proven, inoperable, incompletely resected or recurrent adenoid cystic carcinoma were included. The clinical target volume (CTV) covered the course of the involved cranial nerves up to their entry into the base of skull, and the treatment of regional lymph nodes was omitted since occult lymph node metastases are rare. The GTV included the macroscopic tumor with a safety margin of 1 to 2 mm, taking into account the precision of the immobilization device and the beam delivery. The median gross tumor volume was 184.5 mL. Patients were treated with combined stereotactic photon RT (fractionated stereotactic RT or intensity-modulated stereotactic RT) to the CTV and a carbon ion boost to the gross target volume (GTV). Treatment planning for carbon ion RT included a biologic plan optimization using the TRiP treatment-planning software developed at GSI. A target dose of 18 CGE of carbon ion RT was applied in 6 fractions of 3.0 CGE. At a median follow-up of 16 months, the 4-year locoregional control and overall survival rates were 77% and 76%, respectively. Severe late toxicity grade 4 was observed in 1 patient. Locoregional control rates and overall survival rates were comparable to his-
torical neutron data, but toxicity seems to be less severe after carbon ion RT.

**NSCLC**

Surgery is the standard treatment for localized NSCLC, but about 5% to 10% of all stage I patients are considered inoperable for medical reasons or refuse surgery. For some of these patients, radiotherapy is an alternative treatment option. Because of the high radiosensitivity of the lung parenchyma and the reduced lung function in most of these patients, the benefit of RT has to be weighed against the risk of further impairment of lung function. Carbon ion RT represents a RT modality that can be focused very precisely to the tumor.

At the NIRS, several study protocols for carbon ion RT in stage I NSCLC have been implemented since 1994. In the first phase I/II trials, carbon ion doses were escalated from 59.4 CGE to 95.4 CGE, and fractionation was altered as well to determine the optimal target dose and fractionation schedule. In the first dose-escalation trial, carbon ion RT was delivered in 18 fractions within 6 weeks; in the subsequent trial, 9 fractions were given within 3 weeks. Treatment consisted of 2 to 4 portals, and a respiratory gating system and high-precision patient alignment according to implanted iridium clips were used to reduce the necessary safety margins. The overall local control rate obtained with carbon ion RT was 76%, and a clear dose-response dependency was revealed. The 5-year overall and cause-specific survival were 42% and 60% for 81 patients, respectively (64.4%/82% for stage IA and 22%/40% for stage IB patients). Nine out of 81 patients (9.9%) developed isolated regional lymph node recurrences of which 7 were treated with another course of RT. Grade 3 radiation pneumonitis was observed in only 3.7% of the patients. A total dose of 72.0 CGE given in 9 fractions within 3 weeks was found to be the optimal dose fractionation scheme with respect to tumor control and toxicity. Between April 2000 and February 2003, a clinical phase II trial was performed to test a 4 fraction design. A total dose of 52.8 CGE was delivered in 4 fractions within 1 week to stage IA tumors; stage IB tumors received a total dose of 60 CGE using the same fractionation schedule. A 3-year survival rate of 63% was reported for 71 patients; locoregional lymph node metastases occurred in 10% to 15% of the stage I patients treated to the primary tumor. A clinical phase II trial investigating carbon ion RT for stage I NSCLC using a single dose of 28.0 CGE is ongoing. A randomized trial comparing single dose irradiation with carbon ions to single-dose irradiation with photons is warranted to determine the RBE and the efficacy of carbon ion RT for early lung cancer.

**Hepatocellular Carcinoma**

RT of hepatocellular carcinoma is considered in tumors that are not suitable for surgery because of the location and size of the tumor or in patients with poor general medical condition. However, RT is also very limited in most cases because of the high radiosensitivity of the liver parenchyma. In the past, precision techniques such as stereotactic irradiation delivered in 1 to 3 fractions have been investigated. Herfarth and coworkers report a locoregional control rate of 81% at 18 months for 60 liver lesions (37 patients) treated with total doses between 14 and 26 Gy delivered in 1 to 3 fractions, but only 4 patients with primary liver tumors were included. Although target volumes included a small safety margin of 1 to 2 cm, the development of acute focal liver reactions was a common finding in postradiotherapeutic CT scans, and the median threshold dose was determined to be 13.7 Gy for single-dose irradiation. This implies that toxicity to the liver does play a role in the treatment of larger lesions.

In a carbon ion dose-escalation trial performed in Chiba, the total dose was escalated from 49.5 to 79.5 CGE given in 15 fractions. In subsequent phase II trials, the fractionation schedule was shortened from 15 fractions to 4 fractions given within 1 week. A total dose of 52.8 CGE given in 4 fractions of 13.2 CGE each within 1 week was determined to be safe and effective. This regimen was then investigated in a clinical phase II trial in 44 further patients. The local control rate was reported to be 90% at 3 years in this clinical phase II trial. The incidence of serious adverse liver acute reactions grade 3 requiring inpatient treatment was 3%; other severe toxicities were not observed.

**Bone and Soft-Tissue Sarcomas**

For bone and soft-tissue sarcomas of the trunk, a poor survival rate of 15% has been reported after incomplete resection and adjuvant photon RT. The poor results are because of the inability to achieve a R0/I resection and to deliver a sufficient dose to the tumor while adhering to the tolerance doses of normal-tissue structures in close vicinity to the tumor. Particle therapy with protons and carbon ions has mainly been used for chordomas, chondrosarcomas, and osteosarcomas in the past because these histological subtypes can be characterized as being very unresponsive to conventional RT and high tumor doses are needed. Hug and coworkers reported a 5-year actuarial local recurrence-free survival rate of 53% in chordomas and 100% in chondrosarcomas of extracranial origin with proton RT. Schoenthaler and coworkers reported a local control rate of 55% at 5 years for 14 patients with sacral chordoma treated with helium and neon ions to a median dose of 75.65 CGE at the Lawrence Berkeley Laboratory, Berkeley, CA, between 1977 and 1989.

At NIRS, 57 patients with inoperable bone and soft-tissue sarcomas were treated within a phase I/II dose escalation trial. Carbon ion beams were applied passively using compensators and collimators, whereas the RBE value of carbon ions was estimated to be 3.0 at the distal part of the SOBP. Total doses between 52.8 to 73.6 CGE were given in 16 fractions within 4 weeks. The overall local control rate was 73% at 3 years; the overall survival rate was 46%. Results were promising especially for 15 patients with inoperable osteosarcoma of the trunk for which an overall survival rate of 45% at 3 years was obtained. Seven out of 17 patients treated with a total dose of 73.6 CGE developed Radiation Therapy Oncology Group (RTOG) grade 3 toxicity to the skin, which was considered the maximum tolerated dose.

Imai and coworkers report a 5-year local control rate of 96% for a subset of 30 patients with unresectable sacral chordomas treated with carbon ion RT between 1996 and 2003 at
NIRS. Total doses between 70.4 and 73.6 CGE were delivered in 16 fractions within 4 weeks.

At GSI, 20 patients with spinal and sacral chordomas and low-grade chondrosarcomas have been treated with carbon ion RT alone or with a combination of photon IMRT and a carbon ion boost within a clinical phase I/II trial completed in July 2005. Although patients with tumors of the upper cervical spine might be treated with a full course of carbon ion RT delivering 60 GyE in a safe manner, patient misalignment may be more pronounced in more caudal regions. To ensure a safe treatment in extracranial tumor sites, patients included into the trial received 50.4 Gy of photon IMRT (5 × 1.8 Gy / week) plus a carbon ion boost of 18 CGE (6 × 3.0 CGE) to the macroscopic tumor. Preliminary analysis showed good tolerance to the treatment. No severe late reactions have been observed so far. For evaluation of local control and survival rates, follow-up is still too short. However, given the high local control rates obtained with a full course of carbon ion RT in skull-base chordomas and chondrosarcomas with a relatively low total dose of 60 CGE at GSI and taking into account the favorable control rates obtained at NIRS with 70.4 to 73.6 CGE for sacral chordomas, the RBE values in chordoma and chondrosarcoma cells can be assumed to be higher than for the biological endpoint of normal tissue toxicity to the relevant normal tissue structures close to the tumors. To fully exploit this biological advantage, it seems to be reasonable to test the use of a full course of carbon ion RT for extracranial tumors of this histology.

**Prostate Cancer**

For locally advanced prostate cancer with a serum PSA >10 ng/mL and a Gleason Score of at least 7, biochemical control probability after conventional photon RT is poor. Recent studies showed that dose escalation to doses exceeding 76 Gy leads to improved local control and biochemical relapse-free survival in patients with locally advanced prostate cancer of the intermediate and high-risk group (PSA 10-20 ng/mL and PSA >20 ng/mL). Five-year no-evidence-of-disease (NED) rates were 51% after conventional RT with doses <76 Gy versus 82% for doses ≥76 Gy. With such high doses, severe radiation-induced reactions of the rectum have to be considered after conventional RT. Modern RT techniques such as intensity-modulated stereotactically guided RT help spare the rectum and at the same time escalate the dose to the prostate. First results for photon IMRT are available and show high biochemical disease-free survival rates and low toxicity rates at 3 years.

Given the relatively high doses needed to control prostate cancer, prostate cancer cells can be assumed to be relatively radioresistant to conventional photon RT, and the α/β ratio was found to be very low. Therefore, the delivery of higher single doses is currently under discussion. High-LET beams such as carbon ions not only provide the physical advantage of an inverted dose profile, which enables a steep dose gradient toward the anterior rectal wall, but also offers biological advantages by means of an enhanced biological effectiveness in tumors with low α/β ratios. Planning intercomparison studies have been performed at the German Cancer Research Center (DKFZ) Heidelberg to investigate different treatment concepts. A clinical phase I/II trial of combined photon IMRT plus a carbon ion boost in patients with locally advanced prostate cancer has recently been activated at GSI Darmstadt.

At NIRS, 201 patients with T1 to 3 localized prostate cancer were treated with carbon ions within a clinical phase II trial. High-risk patients received neoadjuvant hormonal therapy for 2 to 6 months. The patients received a total dose of 66.0 CGE in 20 fractions within 5 weeks, which had been proven effective in dose-escalation trials before. Although anterior and lateral safety margins of 10 mm and a posterior margin of 5 mm were added to the CTV for the initial planning target volume, the posterior margin was reduced to fit the anterior rectal wall for the latter half of the carbon ion RT series to reduce rectal toxicity. The 5-year biochemical disease-free survival rate was 83.2% for all patients. A 5-year biochemical disease-free survival rate of 100% was observed in 37 low risk patients, whereas a rate of 80.5% was observed in 164 high-risk patients. No patient developed RTOG/EORTC [me]grade 3 toxicity. High biochemical disease-free survival rates after carbon ion RT appear higher than with modern photon IMRT and proton RT especially for patients with high-risk prostate cancer. Slater and coworkers report a 5-year NED rate of 57%, and a 5-year NED rate of 51% was reported for conventional RT with photons. As shown, combined photon IMRT yields a biochemical disease-free survival rate of 81% at 3 years, whereas severe toxicity rates to the genitourinary system and the rectum are higher as compared with the rates reported by Akakura and coworkers (10% v 4.1%). However, high-risk patients treated with carbon ions at NIRS received neoadjuvant hormonal therapy. The promising results obtained with carbon radiotherapy need confirmation in controlled clinical trials with large patient numbers comparing carbon RT with photon IMRT and proton RT. Taking also into account toxicity and quality of life. Further hypofractionation of carbon ion RT appears attractive and might be realized with further optimization of the beam delivery and in combination with new methods for tumor tracking in the future.

**Outlook**

In the last decade, in 30 centers worldwide, valuable clinical experience has been gained in charged particle therapy. Together with the development of new technologies, especially for beam application and treatment planning, there will likely 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, improved patient positioning systems, gating for breathing-dependent targets, raster scan systems conformal beam delivery, and biological plan optimization for carbon ion RT.

From the clinical point of view, further research is still required to clarify which indications benefit most from therapy with protons and heavy ions and which are the ideal ion species and fractionation scheme. These questions can be
answered only in clinical studies performed at hospital-based ion facilities.

References

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