Current Status and New Developments in Ion Therapy

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Background: Worldwide, encouraging clinical results of ion radiotherapy led to planning and construction of several new treatment facilities.
Material and Methods: The main technical and biological aspects of ion therapy are reviewed. The current status and future developments are discussed.
Results: The use of ions in radiotherapy results in highly conformal dose distributions. The degree of conformality is higher for active than for passive beam delivery techniques. Applying ion therapy, uncertainties in the range and the biologically effective dose have to be considered. For heavy ions, the clinical value of the increased biological efficiency has to be investigated.
Conclusion: Although the principal methods for clinical application of ion therapy are available, the development must be continued to explore its full potential.

Key Words: Radiotherapy · Protons · Heavy ions · Heavy charged particles

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Aktueller Stand und neue Entwicklungen in der Ionentherapie

Hintergrund: Vielversprechende klinische Ergebnisse der Ionentherapie führten weltweit zu Planung und Aufbau zahlreicher neuer Therapieeinrichtungen.
Material und Methodik: Die wichtigsten technischen und biologischen Aspekte der Ionentherapie werden zusammengefasst. Der momentane Status und künftige Entwicklungen werden diskutiert.
Ergebnisse: Die Anwendung von Ionen führt zu hochkonformen Dosisverteilungen (Abbildungen 2 und 3). Die Konformität ist für aktive Feldformungstechniken größer als für passive (Abbildung 1). Die Anwendung von Ionen in der Strahlentherapie muss Unsicherheiten in der Reichweite und der biologisch effektiven Dosis berücksichtigen. Für schwere Ionen muss die klinische Wertigkeit der erhöhten biologischen Effektivität untersucht werden.
Schlussfolgerung: Obwohl die wesentlichen Methoden für den klinischen Einsatz der Ionentherapie vorhanden sind, muss die Entwicklung fortgeführt werden, um ihr Potential voll auszuschöpfen.

Schlüsselwörter: Strahlentherapie · Protonen · Schwerionen · Schwere geladene Teilchen

Introduction

Ion therapy is a worldwide strongly evolving treatment modality in radiation therapy [17, 19, 45, 50, 51]. This development is mainly driven by the special physical properties of ions, which exhibit a finite range in matter together with an "inverted" depth dose profile, the so-called Bragg peak [24]. For clinical application, several monoenergetic Bragg curves are superimposed to result in a spread-out Bragg peak (SOBP), which covers the tumor homogeneously with dose, while sparing the adjacent normal tissue. These special characteristics may be used to increase the dose to the tumor and hence improve local control rates, without increasing complication probability.

While these physical properties are shared between protons and heavy ions, e.g., carbon ions, heavy ions exhibit an increased biological efficiency in the Bragg peak as compared to the entrance region (plateau) [24]. This differential effect increases the biologically effective dose in the tumor further without raising the dose to the adjacent normal tissue. In addition, the dependence of the tumor response on biological parameters such as oxygenation and cell cycle is reduced.

These advantages make ions attractive for conformal radiotherapy and it is expected that patients will benefit considerably from further development of this radiation modality. This paper reviews the main technical and biological aspects

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of ion radiotherapy with special focus on heavy ions. The current status and future developments are discussed.

Material and Methods

Worldwide, around 30 facilities are [13, 34, 47, 55] or have been [4, 5] treating patients with protons or heavy ions [50]. Most of these facilities are still operating. While proton radiotherapy is quite well established and has been used for more than 42,000 patients, treatments with heavy ions were only applied in about 5,000 cases. About 20 additional facilities for protons and heavy ions are planned or already under construction [50]. Currently, all heavy ion facilities are using carbon ions. The next heavy ion facilities which will be brought into clinical operation are the Heidelberg Ion Therapy facility (HIT, Germany) [10, 12], the CNAO facility in Pavia (Italy) [1], and a facility in Gunma (Japan).

Beam Delivery

Currently, two principally different techniques are used to generate the treatment field for a specific tumor. These techniques are referenced as active and passive beam delivery techniques, respectively [24].

Passive beam delivery techniques use double-scattering systems or wobbling magnets in combination with scatterers to produce large ion fields [2, 20, 24]. The fields are then confined to the tumor by individually manufactured collimators or multileaf collimators. To generate the SOBP, a rotating modulator wheel is used [21]. This device introduces material of varying thickness into the beam in order to modulate the range. Alternatively, a static filter of varying thickness may be applied [20]. This so-called ridge filter produces different ranges at different lateral positions within the treatment field, which are then smeared out over the treatment field by lateral scattering of the particles. Each modulator wheel or ridge filter is connected to a specific SOBP and is selected according to the extension of the tumor in depth. To adjust the SOBP to the distal edge of the tumor, additional material is brought into the beam using so-called range shifters. Individually manufactured compensators may finally be used to adjust the dose distribution to the distal edge of the tumor. As the extension of the SOBP remains constant over the tumor cross section, the dose conformation at the distal edge is connected to high doses in the normal tissue at the proximal edge of the tumor (Figure 1a) [6].

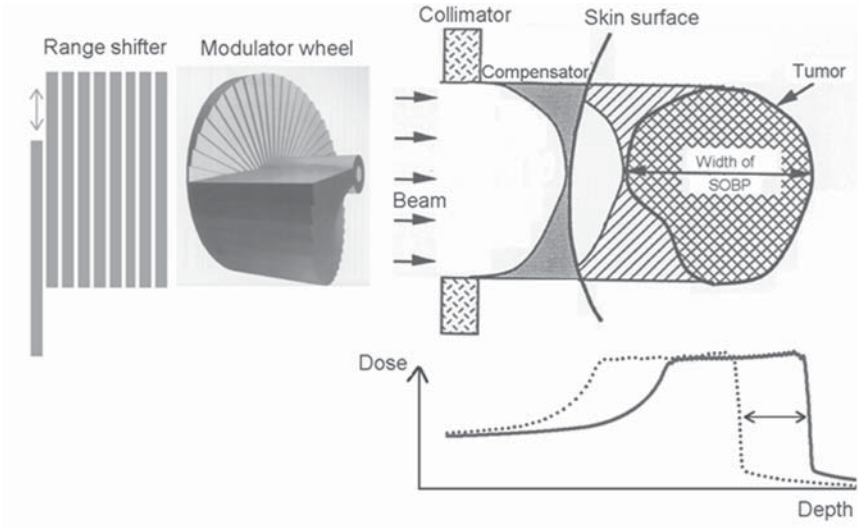

Figure 1a – Abbildung 1a

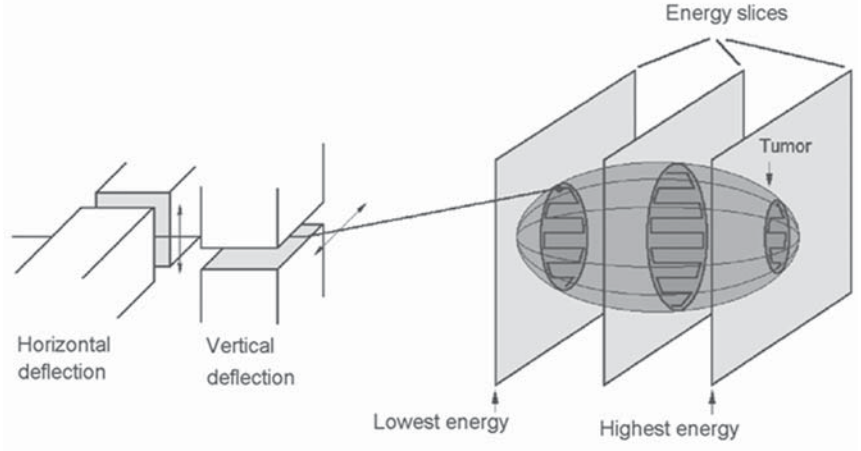

Figure 1b – Abbildung 1b

Figures 1a and 1b. For passive beam delivery (a), the dose distribution is shaped by four components: the range shifter, the modulator wheel (or alternatively a ridge filter), the collimator, and the compensator. The modulation depth is constant over the tumor cross section. For active beam delivery (b), a monoenergetic pencil beam is scanned over the tumor cross section. After one slice is irradiated, the energy of the beam is switched actively (or passively in case of a range shifter) to the next energy.

Abbildungen 1a und 1b. Für passive Feldformungstechniken (a) wird die Dosisverteilung durch vier Komponenten geformt: den Range-Shifter, das Modulatorrad (oder alternativ den Ridge-Filter), den Kollimator und den Kompensator. Die Ausdehnung der Tiefenmodulation ist über den gesamten Tumorquerschnitt konstant. Für aktive Feldformungstechniken (b) wird ein Bleistiftstrahl über die Querschnittsfläche des Tumors gescannt. Nachdem eine Schicht bestrahlt ist, wird die Energie des Strahls aktiv (oder passiv im Fall eines Range-Shifters) auf die nächste Energie umgeschaltet.

In contrast to passive techniques, active beam delivery uses a pencil beam which is scanned magnetically over the tumor cross section [6, 9, 24, 25, 39, 40] (Figure 1b). For this, the tumor is virtually divided into slices of equal range and is then irradiated slice by slice selecting the corresponding energy. Between two slices, the energy is switched either actively [9] by the synchrotron or passively [39, 40] by a range shifter. Since the lateral borders of the treatment field can be selected independently in each energy slice, the depth modulation may be adjusted to the tumor extension for each position of the pencil beam. Consequently, the dose distribution can be adjusted at the distal as well as the proximal edge of the tumor. The degree of dose conformation is therefore higher for active than for passive beam delivery techniques. In addition, no patient-specific hardware such as collimators or compensators are required.

Calculation of the Absorbed Dose

To calculate the range of the ions in the patient, an empirical relation between the Hounsfield units of the CT images and the ranges has to be established in a set of tissue-equivalent materials [15, 22, 43]. By integrating the ranges along the path of the particles, the required energies of the monoenergetic Bragg peaks composing the SOBP are determined.

For passive beam delivery techniques, the SOBP is fixed by the selected modulator wheel, which implicitly defines the weights of the underlying monoenergetic Bragg peaks. Additional use of a range shifter only modifies the depth of the SOBP without changing its shape. By contrast, active beam delivery techniques can produce arbitrary depth dose profiles and the modulation depth is generally varying with the lateral position of the pencil beam. As the weight of each beam spot can be independently selected, active techniques are ideally suited for intensity-modulated beam delivery.

The beam delivery technique also determines the complexity of the dose optimization algorithms. As scanning systems dramatically increase the number of degrees of freedom, an inverse dose optimization algorithm is required [26, 35, 41]. During optimization, the fluence has to be optimized for each beam energy and scan point.

Calculation of the Biologically Effective Dose

The increased biological effectiveness of ions is considered by introducing the relative biological effectiveness (RBE), which is defined as the ratio of a photon dose to the corresponding isoeffective ion dose [24]. The RBE is a rather complex quantity as it depends on linear energy transfer (LET), dose per fraction, the amount of projectile fragmentation, the cell or tissue type irradiated as well as on the selected biological endpoint.

For protons, a global RBE value of 1.1 is adopted. Although there are experimental data showing that the RBE may increase up to 2 at the distal edge of the Bragg peak, this is not considered to be clinically relevant [37, 38]. As the RBE for protons is assumed to be a constant factor, it has no impact on the dose optimization algorithm.

For heavy ions, the RBE increases strongly with LET and hence depth [20, 21, 24, 25]. A more detailed RBE model is therefore required. To arrive at a homogeneous biologically effective dose within the target volume, the absorbed dose must decrease with increasing depth. Due to the nonlinear dependence of the RBE on absorbed dose, this optimization process is more difficult than for protons [27, 28], especially for the simultaneous optimization of multiple fields.

For passive beam delivery, the modulation depth and hence the RBE depth profile remain constant over the treatment field [20, 21]. The RBE profile can therefore directly be considered in the design of the modulator wheel. For active beam delivery, however, the modulation depth depends on the lateral beam position. Moreover, the absorbed dose profile may be arbitrarily selected (e.g., for producing intensity-modulated fields) and the fragment spectra may therefore differ from one field to another. Consequently, the RBE is calculated separately for each point within the treatment field [44].

Results and Discussion

It is generally accepted that the application of ions rather than photons leads to improved dose distributions, especially if active beam delivery techniques are used. It is therefore believed that the dose in the tumor may be escalated and hence local control may be improved, without increasing the risk of normal tissue complication. Although many of the current facilities still use passive beam delivery techniques, scanning techniques are considered to be state of the art and most new facilities are planned to be equipped with this delivery technique.

Conformality

Due to the depth dose profile of ions, the required number of treatment fields is generally smaller than for photons. In addition, the dose distributions delivered with ions exhibit a higher degree of conformality (Figure 2). Although the dose distributions of photon intensity-modulated radiotherapy and ions may be comparable on the 90% isodose level, the surrounding organs at risk are better spared by ions at the intermediate dose level [33] and the integral dose in normal tissue is significantly reduced. Due to scattering of protons in larger depths, the lateral dose gradients achieved with heavy ions are steeper than for protons.

Particle Range

In ion radiotherapy, the uncertainty of the range calculation must be considered. Based on the uncertainty in the empirical relation between Hounsfield units and range, this uncertainty is considered to be 2–3% [15, 43]. Setup errors of the patient, however, may significantly increase this uncertainty as the ions may traverse along a different path as intended in treatment planning [16]. Underdosage of the tumor or overdosage of normal tissue may be the consequence. Additional uncer-

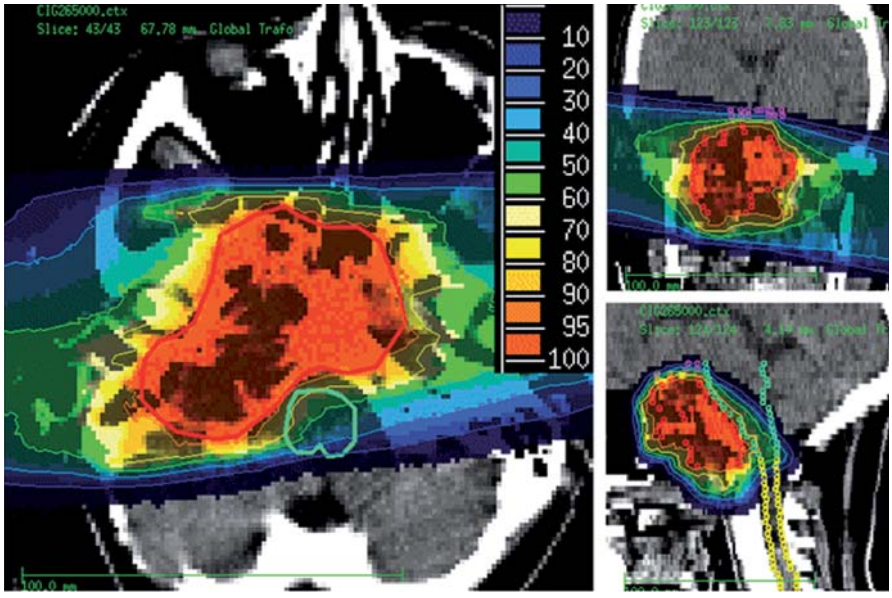

Figure 2. Biologically effective dose distribution obtained with carbon ions for the treatment of a chondrosarcoma of the skull base (3 GyE/fraction, total dose: 60 GyE).

Abbildung 2. Biologisch effektive Dosisverteilung, wie sie mit gescannten Kohlenstoffionen für die Behandlung eines Chondrosarkoms an der Schädelbasis erreicht wird (3 GyE/Fraktion, Gesamtdosis: 60 GyE).

tainties may arise, if the patient has metal implants [14, 18]. While the uncertainty due to the related artifacts may be acceptable or may be reduced by correction of the underlying CT images, the range calculation in the implants is completely wrong. Irradiations through the implants should therefore be avoided. As the presence of iodine contrast agent also influences the range calculation, only native CTs should be used for dose calculation [57].

RBE

As the RBE of protons may well be approximated by a global value of 1.1, only the distribution of the absorbed dose has to be optimized. For heavy ions, however, the biologically effective dose has to be optimized. As the RBE of heavy ions shows large variations within the treatment field and, moreover, also depends on biological parameters of the irradiated tissue, the biologically effective dose intrinsically contains a significant uncertainty. Experimental data support the use of the applied RBE models to optimize the biologically effective dose distribution within the target volume [21, 23]. Nevertheless, the uncertainty of the absolute value is still expected to be in the range of ±20% [23]. This uncertainty has to be considered by careful selection and escalation of the prescribed dose. This dose-finding process is an intrinsic part in the introduction of new treatment modalities of not exactly known efficiency.

Besides the uncertainty in the RBE, it has to be considered that normal tissue within or nearby the tumor is also exposed to a high LET and hence receives a high biologically effective dose. Whether this limits the dose in the tumor has to be evaluated clinically. In contrast to neutron radiotherapy, however, the geometric accuracy of ions offers the possibility to minimize the volume of normal tissue exposed to a high dose.

Clinical Application

Ion radiotherapy is currently applied for a variety of tumors. These include head-and-neck [13, 34, 36, 46, 48, 49, 52, 53, 56], but also extracranial tumors [11, 54, 55]. The treatment may be applied solely with ions [46, 49] or as a combined treatment with photons and ions (Figure 3) [48]. Such combination therapies are often used due to the limited availability of the facilities, but may nevertheless be more effective than a pure photon treatment.

It has been shown that the dose escalation realized with protons and carbon ions may increase local control for some indications [45, 46, 48]. For carbon ions, it is an open question whether this effect results from improved conformality or from the increased biological effectiveness. As the specification of the biologically effective dose contains the uncertainty of the RBE, this has to be

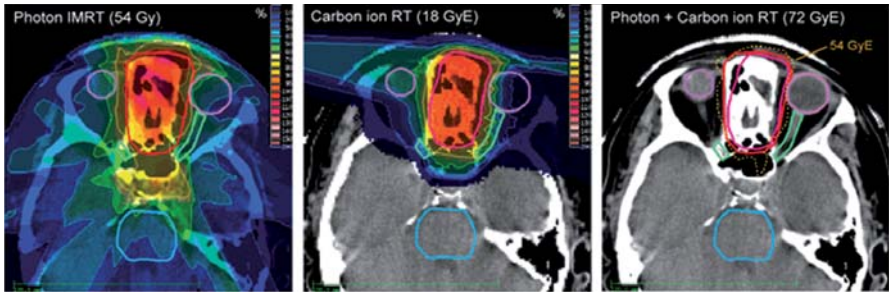

Figure 3. Combined treatment with photons (1.8 Gy/fraction, total dose: 54 Gy) and carbon ions (3 GyE/fraction, total dose: 18 GyE to the reduced boost volume). The optic nerves and the eyes were kept outside the 54 GyE isodose.

Abbildung 3. Kombinierte Behandlung mit Photonen (1,8 Gy/Fraktion, Gesamtdosis: 54 Gy) und gescannten Kohlenstoffionen (3,0 GyE pro Fraktion, Gesamtdosis: 18 GyE auf das verkleinerte Boostvolumen). Sehnerven und Augen liegen außerhalb der 54-GyE-Isodose.

investigated clinically by comparing local control data of carbon ions and protons at the same toxicity level. Comparison of carbon and helium ions may also be of interest, since helium beams exhibit similarly steep dose gradients as carbon ions, however, are comparable to protons with respect to their biological properties. Such comparisons have to be performed within randomized clinical trials separately for different tumor types. Moreover, the same planning and beam delivery techniques have to be used. The HIT facility will be the first facility, which will be able to perform such clinical trials.

Further Developments

Although radiotherapy with protons and heavy ions has already achieved impressive clinical results, further improvements are expected. Scanning techniques may be used to apply intensity-modulated ion (particle) therapy (IMPT). This technique improves sparing of organs at risk and is already clinically applied for protons [30, 52]. For carbon ions, intensity-modulated techniques are developed and will be clinically applied in the near future.

It is anticipated that implementation of IMPT will lead to the optimal spatial dose distribution. For the treatment of thoracic or abdominal tumors, however, these distributions may be compromised by respiratory motion. To explore the full potential of ion therapy also for moving targets, respiratory motion has to be compensated by applying gating or tracking techniques, which require online monitoring of the patient, e.g., by fluoroscopy, breathing belts or surface monitoring. Currently, only gating in combination with passive beam delivery is realized for ion radiotherapy [32]. The increase in treatment delivery time expected for gating of a scanned beam may be minimized by additional gating of the beam extraction from the accelerator. Although tracking may in principle be feasible [8, 29, 42], if the trajectory of the tumor can be acquired, it has to be considered that a lateral shift of the tumor may also change its radiologic depth, i.e., the required range of the ions [31]. Currently, tracking techniques appear to be far from clinical realization.

Using IMPT together with gating or tracking techniques, the best possible spatial-temporal dose distribution will be delivered. This dose distribution would consider the tumor as a biologically homogeneous structure defined on the basis of morphological images. The treatment, however, may be further improved by incorporating also biological information from functional and molecular imaging [3, 7, 58]. A detailed biological characterization of the tumor and the surrounding normal tissue may be used to refine the planning target volume, to monitor the treatment response and, in the ideal case, to optimize the dose and LET distribution to achieve a homogeneous response within the tumor. These developments are still at the very beginning, and it has to be considered, that the biological response especially to heavy ions may be different from that to photon or proton irradiation.

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