Carbon ion radiotherapy

Carbon ion radiotherapy performed as re-irradiation using active beam delivery in patients with tumors of the brain, skull base and sacral region

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A B S T R A C T

Introduction: To assess carbon ion radiation therapy (RT) performed as re-irradiation in 28 patients with recurrent tumors.

Materials and methods: Twenty-eight patients were treated with carbon ion RT as re-irradiation for recurrent chordoma and chondrosarcoma of the skull base (n = 16 and n = 2), one chordoma and one chondrosarcoma of the os sacrum, high-risk meningioma (n = 3), adenoid-cystic carcinoma (n = 4) as well as one SCCHN.

All patients were treated using active raster scanning, and treatment planning was performed on CT- and MRI-basis.

All patients were followed prospectively during follow-up.

Results: In all patients re-irradiation could be applied safely without interruptions. For skull base tumors, local tumor control after re-irradiation was 92% at 24 months and 64% at 36 months. Survival after re-irradiation was 86% at 24 months, and 43% at 60 months. In all three meningiomas treated with C12 for re-irradiation, the tumor recurrence was located within the former RT-field. Two patients developed tumor progression at 6 months, and in one patient the tumor remained stable for 67 months. In patients with head-and-neck tumors, three patients developed local tumor progression at 12, 24 and 29 months after re-irradiation. Median local progression-free survival was 24 months.

For sacral tumors, re-irradiation offered palliation with tumor control for 24 and 36 months.

Conclusion: Due to the physical characteristics particle therapy offers a new treatment modality in cases with tumor recurrences. With carbon ions, the additional biological benefits may be exploited for long-term tumor control. Further evaluation in a larger patients’ cohort will be performed in the future.

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In the past, a second course of radiation therapy (RT) was applied only reluctantly and independently of tumor site since conventional methods of RT did not enable the radiation oncologist to spare normal tissue. Especially in locations where tumors are directly adjacent to sensitive normal tissues, such as the skull-base region, radiation tolerance of OAR is exhausted by the previous course of RT. Developments in photon RT including stereotactic treatment and intensity modulated radiotherapy (IMRT) offered the possibility to generate steep dose gradients [1–5]; therefore, high local doses could be applied while sparing normal tissue therefore enabling the radiation oncologist to perform second courses of RT for tumor control with low rates of side effects.

Over the last few decades the value of re-irradiation has been demonstrated in a number of indications such as malignant gliomas, ependymoma, gastrointestinal tumors as well as tumors of the skull base [6–13]. Especially in recurrent glioma and in tumors of the head-and-neck region re-irradiation has been analyzed in numerous institutions. For local recurrences of nasopharyngeal cancer (NPC) or squamous-cell carcinomas of the head and neck (SCCHN) local re-irradiation has been evaluated and local control rates of up to 50% with 5-year survival rates of about 20% could be observed in selected cases [14–19]. Stereotactic treatments have been established for subgroups of patients with recurrent gliomas using different fractionation schemes, with median overall survival times of over 8 months in patients with glioblastoma histology [9,20].

The physical advantages of particle therapy offer even more pronounced sparing of normal tissue. With protons as well as carbon ion RT, energy deposition in the entry channel of the beam is very low, while a high local dose deposition called the “Bragg Peak” can be directed into the defined target area. Therefore, the dose deposited to normal tissue is very low as compared to photon beams. The particle range is determined by the energy of the incoming particles, which can be varied quickly during treatment.
application to enable optimal coverage of the defined treatment volume. Additionally, carbon ion beams are characterized by a higher biological efficiency, especially in the end of the beams’ range; the values for this relative biological effectiveness (RBE) range between 3 and 5 depending on the tissue analyzed, and may depend on a variety of different factors [21,22]. For a number of indications, clinical superiority of carbon ion RT has been shown [23].

Carbon ion radiation therapy has been available since 1997 by the Department of Radiation Oncology at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt, Germany. Over 450 patients were treated using active beam delivery with mainly chordomas (CH) and chondrosarcomas (CS) of the skull base, adenoid-cystic carcinomas (ACC), meningiomas as well as sacral chordomas (CH) and chondrosarcomas (CS) [24–29]. Out of these patients, 28 patients were treated with carbon ion RT as re-irradiation which was addressed in the present analysis with respect to treatment outcome and toxicity.

Materials and methods

Between December 1997 and February 2008, we treated 28 patients with carbon ion radiotherapy as re-irradiation. All recurrences were confirmed by repeat imaging and/or histological confirmation after surgical intervention. Patients were treated for recurrent CH and CS of the skull base (n = 16 and n = 2), one CH and one CS of the os sacrum, high-risk meningioma (n = 3), ACC (n = 4) as well as one squamous-cell carcinoma of the head-and-neck-region (SCCHN).

Patients’ characteristics are summarized in Table 1.

Previous radiation treatment

All patients had been treated with a previous course of radiation therapy. Details regarding the previous treatment concepts and doses are shown in Table 2.

In most patients, photon radiotherapy had been applied as a fractionated regimen. Three patients had been treated with gamma knife radiosurgery for a clivus CH with doses of 11 Gy/80% isodose, 16 Gy/40% isodose and 17.5 Gy/80% isodose.

Six patients had been treated with carbon ion RT at GSI during the first course of radiotherapy up to 60 Gy E in single doses of 3 Gy E, of which 5 were skull base tumors (4 CH and one CS) and 1 patient had been treated with carbon ion radiotherapy up to 18 Gy E in single fractions of 3 Gy E in combination with precision photon IMRT for locally advanced ACC with a total dose of 50.4 Gy. One patient had been treated for a skull base CH at a proton therapy center in the USA with a total dose of 79.2 Gy E.

Three patients have been treated with 3 courses of radiation therapy during the course of their disease. Treatment characteristics of these patients are summarized in Table 3.

Re-irradiation with C12

All 28 patients were treated at GSI for recurrent tumors using carbon ions delivered by active raster scanning as published

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years of age</td>
<td>24</td>
</tr>
<tr>
<td>≥65 years of age</td>
<td>4</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
</tr>
<tr>
<td>Female</td>
<td>11</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Chordoma</td>
<td>17</td>
</tr>
<tr>
<td>Chondrosarcoma</td>
<td>3</td>
</tr>
<tr>
<td>Adenoid-cystic carcinoma</td>
<td>4</td>
</tr>
<tr>
<td>Meningioma</td>
<td>3</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Skull base</td>
<td>19</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>3</td>
</tr>
<tr>
<td>Os sacrum</td>
<td>2</td>
</tr>
<tr>
<td>Head-and-neck area</td>
<td>4</td>
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</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Diagnosis (n)</th>
<th>Technique</th>
<th>Median dose previous RT (range)</th>
<th>Median time between RT and re-RT (months; range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chordoma and chondrosarcoma of the skull base (n = 18)</td>
<td>Radiosurgery (n = 3)</td>
<td>16 Gy/40%</td>
<td>60 (30–108)</td>
</tr>
<tr>
<td></td>
<td>Radiosurgery (n = 3)</td>
<td>17.5 Gy/80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Photons (n = 10)</td>
<td>60 Gy (50.4 Gy–66 Gy)/1.8–2 Gy</td>
<td>52 (8–144)</td>
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<tr>
<td></td>
<td>Proton (n = 1)</td>
<td>79.7 Gy E (1.8–2 Gy E)</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Carbon ion (n = 4)</td>
<td>60 Gy E/3 Gy E</td>
<td>42 (8–61)</td>
</tr>
<tr>
<td>Meningioma (n = 3)</td>
<td>Photon</td>
<td>57.6 Gy (1.8 Gy)</td>
<td>57</td>
</tr>
<tr>
<td>Adenoid-cystic carcinoma (n = 4)</td>
<td>Photon (n = 3)</td>
<td>66 Gy (50–66 Gy)/2 Gy</td>
<td>67 (59–89)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma of the head-and-neck area (n = 1)</td>
<td>Photon + C12 (n = 1)</td>
<td>50.4 Gy + 18 Gy E</td>
<td>79</td>
</tr>
<tr>
<td>Sacral chordoma/chondrosarcoma (n = 2)</td>
<td>Photon</td>
<td>50 Gy/2 Gy</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Photon</td>
<td>59.4 Gy/1.8 Gy</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>Photon</td>
<td>50.4 Gy/1.8 Gy + 18 Gy E/3 Gy E</td>
<td>17</td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Diagnosis</th>
<th>1. RT</th>
<th>2. RT</th>
<th>3. RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Skull base/cervical spine chordoma</td>
<td>60 Gy E C12</td>
<td>48.6 Photon + 18 C12 field border recurrence</td>
<td>50 Gy Photon outfield metastasis</td>
</tr>
<tr>
<td>2</td>
<td>Skull base chordoma</td>
<td>16 Gy/40%</td>
<td>16 Gy/60% (outfield contralateral)</td>
<td>45 Gy E C12</td>
</tr>
<tr>
<td>3</td>
<td>Skull base/cervical spine chordoma</td>
<td>65.5 Gy photons</td>
<td>54 Gy E C12 outfield recurrence</td>
<td>45 Gy E C12 clivus in-field recurrence</td>
</tr>
</tbody>
</table>
Cast™ as described previously [26,27]. For patients with sacral tumors with skull base infiltration, immobilization was performed with an individually manufactured head mask made of Scotch Cast™ as described previously [26,27]. For patients with sacral tumors, a body cast made of Scotch Cast™ was used for treatment planning and carbon ion RT. Target volume definition was performed on the basis of contrast-enhanced CT- and MRI-imaging. The target volume depended on the histology of the tumor and the location as well as the previously performed radiation therapy. In most cases, the gross tumor volume (GTV) was contoured as the macroscopic tumor visible on imaging, and the clinical target volume (CTV) included the GTV as well as a histology-depending margin to account for potential microscopic spread.

Carbon ion RT was applied using active beam delivery with the raster scanning technique developed at GSI by Haberer et al. [30]. Treatment planning was performed using biologic treatment planning optimization with the treatment planning software TRiP which taking into account local values of the relative biological effectiveness (RBE); to calculate these RBE values, the local effect model (LEM) developed by Scholz et al. is integrated into the TRiP software [21,22,31–34]. An α/β value of 2 for the endpoint late toxicity to the normal tissue was used for treatment planning.

In 7 patients, carbon ion radiotherapy was combined with high-precision photon radiotherapy performed as FSRT or IMRT. Carbon ion RT was delivered in 7 fractions per week in single doses of 3 Gy E. Prior to each treatment, patient positioning was evaluated and corrected with the patients immobilized in their Scotch cast head mask of body cast using orthogonal X-rays. In most patients, 2 treatment portals were used for plan delivery from the horizontal beam. The median follow-up time after carbon ion radiotherapy was 41 months (range 10–72 months). The first follow-up visit was scheduled 6 weeks after completion of treatment, thereafter in 3 months intervals for the first year. Subsequently, follow-up visits were scheduled twice per year for additional 2 years, thereafter in yearly intervals. All visits included contrast-enhanced MRI-examinations including thorough clinical assessment. Regular endocrinological check-up examinations were recommended after RT for patients treated in the skull-base region.

Results

In all patients re-irradiation could be applied safely and no interruptions due to side effects or clinical deterioration were necessary. Therefore, treatment was completed in all patients without any interruptions.

Side effects

Skull base tumors

Treatment-related side effects included mucositis grade I and II in 5 patients, conjunctivitis in 1 patient, local skin erythema in 1 patient and intermittent hearing impairment in 1 patient. In one patient local glial changes in the temporal lobe were observed in MRI during follow-up without any clinical manifestations. No other severe acute or long-term side effects developed.

Head-and-neck tumors

Treatment-related side effects included Grade II mucositis, local alopecia and local grade II erythema; in one patient mild trismus developed. However, no severe high-grade acute or long-term RT-related side effects could be documented.

Outcome

Meningiomas

Acute side effects included focal alopecia in all three patients, mucositis in one patient, fatigue and in one patient with a fronto-centrally localized meningioma dysaesthesias of the left side.

Sacral tumors

Acute side effects were limited to skin erythema Grade I; no other acute or long-term side effect could be observed.

Skull base tumors

Sixteen out of 18 patients (89%) were treated with carbon ion RT alone. The median dose applied was 51 Gy E (range 42–60 Gy E), in single fractions of 3 Gy E.

In two patients, a combined treatment of stereotactic photon RT with 39.6 Gy and 48.6 Gy in single doses of 1.8 Gy was applied with a carbon ion boost to the macroscopic tumor with 15 Gy E and 18 Gy E in 3 Gy E single fractions. In both patients the tumor recurrence was along the upper cervical spine. Local tumor control after re-irradiation was 92% at 24 months and 64% at 36 months (Fig. 1).

Survival after re-irradiation was 86% at 24 months, and 43% at 60 months.

Meningiomas

In all three meningiomas treated with C12 for re-irradiation, the tumor recurrence was located within the former RT-field. In one patient, carbon ion radiotherapy was performed alone with a total dose of 42 Gy E in 3 Gy E single doses. In the two other patients, carbon ion RT was performed as a boost to the macroscopic tumor with 18 Gy E in 6 fractions, and photon radiotherapy was performed with 36 Gy and 22 Gy using stereotactic photon radiotherapy.

Two patients developed tumor progression at 6 months after follow-up, and in one patient the tumor recurrence remained stable for 67 months until local progression developed. This patient had been treated with the highest dose of 18 Gy E carbon and 18 Gy photon RT.

All patients died of tumor progression during follow up at survival times of 10, 12 and 67 months after RT.

Head-and-neck tumors

In three patients, carbon ion RT was performed alone with a median total dose of 45 Gy E in single doses of 3 Gy E. In two pa-
tients carbon ion RT was applied as a boost to the macroscopic tumor: A recurrent adenoid-cystic carcinoma was treated with a boost of 6 × 3 Gy E, and photon RT was applied with 45 Gy in 1.8 Gy single doses. The recurrent SCCHN was also treated with combined treatment, with 4x3 Gy E carbon ions and 12.8 Gy photon RT.

Three patients developed local tumor progression at 12, 24 and 29 months after re-irradiation within the former high-dose irradiation field. In all three cases, local progression was associated with metastases of the lung, liver or meningeal enhancement. Median local progression-free survival was 24 months.

All patients died during follow-up of tumor progression or of disease-related complications.

**Tumors of the sacrum**

Two patients were treated for recurrent sacral tumors, which were one CH and one CS. Re-irradiation could achieve tumor control for 36 and 24 months without severe treatment-related side effect and patients and without uncontrollable pain due to the tumor.

The chondrosarcoma patient had been treated with photon IMRT up to 50.4 Gy with a carbon ion boost up to 18 Gy E in 3 Gy E single fractions at GSI. He was treated with carbon ion RT for 16 months after primary treatment for tumor progression with a dose of 30 Gy E in 10 fractions. During follow-up, this patient developed pulmonary metastases 22 months after re-irradiation treated with chemotherapy including adriamycin and ifosfamide. Local tumor progression developed with severe pain 36 months after re-irradiation and was treated with a palliative resection.

The second patient with a sacral tumor suffered from chordoma that had been treated previously with 59.4 Gy in 1.8 Gy single doses of photon radiotherapy, and recurred locally 63 months thereafter. Carbon ion RT was delivered with a dose of 18 Gy E in 3 Gy E fraction in combination with photon IMRT up to a dose of 40 Gy in 2 Gy single fractions; massive local and locoregional tumor recurrence developed 24 months after re-irradiation with nearly incontrollable pain, and a further neurosurgical debulking was performed.

**Discussion**

In the present manuscript we report our clinical results of 28 patients treated with carbon ion radiation therapy as re-irradiation for tumor recurrences. Patients with the main histologies treated at GSI including skull base CH and CS, meningioma, ACC as well as sacral CH and CS were treated for tumor recurrence after initial RT. In spite of the heterogeneous group and small patient population, the data strongly document that the risk for side effects was not only associated with the dose to the brainstem but also with the volume of brainstem receiving doses greater or equal than 50, 55 and 60 Gy E, of which the dose exceeding 60 Gy E remained significant after multivariate analysis [37]. For carbon ions, the radiation tolerance of the spinal cord was evaluated in preclinical experiments, and showed distinct differences: It could be shown by observing the endpoint “symptomatic myelopathy” in rats treated with single fraction and fractionated photons as well as Bragg Peak and plateau carbon ions that the repair processes known for fractionated photon treatments could be demonstrated for plateau carbon ions, but were significantly reduced in the Bragg peak carbon ions [38]. For fractionated carbon ion treatments with 6 and 18 fractions, it could be confirmed that Bragg Peak carbon ions are significantly more associated with radiation induced side effects to the rat spinal cord than in the plateau region [39].

In spite of these data, it is unknown for most clinical situations to what extent experimental data can be transferred to the clinical setting. This holds true especially when patients remain alive for many years after re-irradiation, and very long-term side effects may occur in these patients.

However, novel radiation techniques such as IMRT or particle therapy together with advanced imaging identifying local areas of tumor recurrence or even areas of more aggressive tumors which can be targeted selectively with modern radiation techniques might improve overall outcome. With these techniques, the substantial rates of side effect as stated above might be reduced through sparing of normal tissue. Therefore, also patients with tumors in very close vicinity to OARs such as the patients included into this analysis can be offered a second course or radiotherapy exploiting the physical characteristics of ion beams. In the present manuscript we could show effectiveness of carbon ion RT performed as re-irradiation in a small group of patients. Individual dose prescription and target volume definition were
performed according to the tumor histology, the size and location of the tumor, prior treatments especially prior radiation treatment. In several patients carbon ion RT was performed as a boost treatment to the macroscopic tumor in combination with photon RT to areas of microscopic spread. Therefore, no clear dose–response-relationship can be shown by these results, and further evaluation in larger groups of patients remains warranted. However, taking into account the critical locations in all 28 patients included into this analysis, the data strongly support the application of ion beams for the treatment of patients with recurrent tumors of certain indications.

Conclusion

The present data support the hypotheses that the physical (and also biological) characteristics of particle beams offer new treatment options for patients with recurrent tumors after radiation therapy also in regions critical for treatment-related side effects. In spite of the heterogeneous population, the data clearly show that for different anatomical regions carbon ions offer even enduring tumor control after re-irradiation, depending on the histology of the tumor. Moreover, severe treatment-related side effects can be avoided due to the beneficial dose distributions. Further studies should evaluate larger patient groups and potential combination treatment with systemic treatments depending on the tumor type.

Conflict of Interest

The authors declare that they have no conflict of interest.

References


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