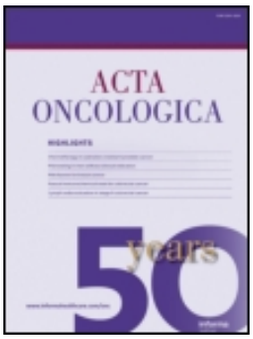

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ORIGINAL ARTICLE

Proton and carbon ion radiotherapy for primary brain tumors and tumors of the skull base

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Abstract

To analyze clinical concepts, toxicity and treatment outcome in patients with brain and skull base tumors treated with photons and particle therapy. *Material and methods.* In total 260 patients with brain tumors and tumors of the skull base were treated at the Heidelberg Ion Therapy Center (HIT). Patients enrolled in and randomized within prospective clinical trials as well as bony or soft tissue tumors are not included in this analysis. Treatment was delivered as protons, carbon ions, or combinations of photons and a carbon ion boost. All patients are included in a tight follow-up program. The median follow-up time is 12 months (range 2–39 months). *Results.* Main histologies included meningioma (n = 107) for skull base lesions, pituitary adenomas (n = 14), low-grade gliomas (n = 51) as well as high-grade gliomas (n = 55) for brain tumors. In all patients treatment could be completed without any unexpected severe toxicities. No side effects > CTC Grade III were observed. To date, no severe late toxicities were observed, however, for endpoints such as secondary malignancies or neurocognitive side effects follow-up time still remains too short. Local recurrences were mainly seen in the group of high-grade gliomas or atypical meningiomas; for benign skull base meningiomas, to date, no recurrences were observed during follow-up. *Conclusion.* The specific benefit of particle therapy will potentially reduce the risk of secondary malignancies as well as improve neurocognitive outcome and quality of life (QOL); thus, longer follow-up will be necessary to confirm these endpoints. Indication-specific trials on meningiomas and gliomas are underway to elucidate the role of protons and carbon ions in these indications.

The treatment of brain and skull base tumors is challenging from various perspectives. On the one hand, some are characterized by aggressive histology, such as high-grade gliomas and meningiomas, while on the other hand, the close vicinity to organs at risk (OAR) especially in skull base lesions requires high-end treatment planning and delivery to optimally spare these radiation sensitive structures. To optimize this therapeutic window, individual choice of photons, protons and carbon ions can help increase dose and spare normal tissue.

Technical development in radiation oncology has continuously improved dose delivery to defined target volumes: For tumors such as gliomas in the primary treatment situation, three-dimensional (3D)-conformal radiotherapy delivers acceptable treatment plans and allows for safe and effective treatment, alone, or in combination with systemic treatment; stereotactic radiotherapy, either as single-dose radiosurgery (SRS) or within fractionated regimens produces highly conformal dose plans, and offers excellent options for low-grade tumors such as benign meningiomas, acoustic neuromas, or low-grade gliomas [1–6]. Moreover, these techniques have enabled the radiation oncologist to perform re-irradiations with convincing efficacy, while with older techniques indication for re-irradiation had to be weighted diligently against potential side effects [7–9]. For complex-shaped tumors, and tumors in the skull base region in close vicinity to OAR, intensity-modulated radiotherapy (IMRT) leads to improved dose distributions [1].

Particle therapy is unique due to the physical properties of the ion beams. The inverted dose profile results in low-dose deposition in the entry channel of the beam, and a steep dose deposition in the tumor

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region, followed by a sharp dose-falloff. Especially regions of low and intermediate doses can be significantly reduced leading to an overall reduction of integral dose. Especially in benign lesions, the hypothesis is that the risk for side effects, predominantly long-term effects such as neurocognitive sequelae, secondary malignancies can be diminished as shown by several studies and calculations [10–13]. However, to date, no prospective randomized data have shown this clinical improvement. High-LET particle beams, such as carbon ions, are associated with an increased relative biological effectiveness (RBE); for a number of indications, a benefit of carbon ions has been shown, however, again, no randomized studies exist to date compared to modern photon or proton treatment. Especially for glioblastomas, which are highly treatment resistant, this increase in RBE has been shown in the preclinical setting, and initial Phase I/II data from Japan showed convincing results [14].

Since 2009, treatment of patients with brain tumors and skull base lesions has been performed at the Heidelberg Ion Therapy Center (HIT). The aim of the present study was to analyze clinical concepts, toxicity and treatment outcome in patients with brain and skull base tumors treated with particle therapy using the active raster scanning technology.

Patients and methods

Between November 2009 and February 2013, 260 patients with brain tumors and tumors of the skull base were treated at the HIT. Patients enrolled in and randomized within prospective clinical trials as well as cartitageous, bony or soft tissue tumors are not included into this analysis. Main histologies included meningioma (n = 107) for skull base lesions, pituitary adenomas (n = 14), low-grade gliomas (n = 51) as well as high-grade gliomas (n = 55) for brain tumors (Table I). All patients were seen by a specialized clinical team and interdisciplinary discussion decided upon the indication for treatment.

Table I. Distribution of histologies/tumor entities treated with particle therapy.

Indication	Number (%)
Pituitary adenoma	14 (5)
Pilocytic astocytoma	20 (8)
Low-grade glioma	31 (12)
Anaplastic glioma	26 (10)
Glioblastoma	29 (11)
Vestibular schannoma	2 (1)
Atypical/anaplastic meningioma	36 (14)
Low-grade meningioma	71 (27)
Craniopharyngioma	5 (2)
Other	26 (10)

A total of 176 patients were treated with protons (67%), 84 patients with carbon ions (33%); of the latter, 36 patients (43%) with photon radiotherapy and a carbon ion boost. One hundred and eighty-six patients were treated as primary radiotherapy (72%), and 74 with a second course of radiotherapy (28%). Median age was 48 years (range 1–85 years). Thirty patients were children younger than 18 years of age; of these, five were treated with anesthesia.

For each patient individually manufactured head masks were used with Scotch Cast™ or thermoplast masks as described previously [15,16]. For treatment planning the system by Siemens Oncology Care Systems (Syngo PT Planning, Siemens, Germany) was used, and target delineation was performed using the Siemens Oncologist Software (Siemens, Germany). For planning, a CT without and with contrast enhancement was acquired. A recent contrast-enhanced MRI was used for target volume delineation, additionally molecular imaging based on PET was used depending on the indication. For meningiomas, target definition enhanced by ^{68}Ga-DOTATOC-PET and ^{18}FET-PET, for gliomas, ^{18}FET-PET was added for planning. All imaging was co-registered with the planning CT for target delineation.

We defined all OAR, as well as the tumor depending on tumor site and histology according to the ICRU criteria: The gross tumor volume (GTV) for any macroscopic tumor, the clinical target volume (CTV) for any microscopic spread depending on histology, and a planning target volume (PTV) for setup deviations which was defined depending on the location and the fixation device used.

Treatment planning based on the local effect model (LEM) was used as published in detail previously [17–20]. For carbon ions, the optimization is based on this radiobiological model, which takes into account the variations of RBE within the radiation field and as a function of tissue type and fraction dose. This model allows the inclusion of organ and tumor specific RBE values. We adhered to the constant α/β value of 2 for intracranial lesions. Generally for protons, an RBE of 1.1 is used.

Patient positioning was evaluation prior to each fraction using orthogonal x-ray imaging position correction was performed using re-positioning of the treatment couch as well as using the pitch-and-roll feature of the robotic table system in some patients.

The median follow-up time is 12 months (range 2–39 months). All patients are seen for regular follow-up initially 4–6 weeks after completion of treatment, thereafter in three months intervals for the first year, or as needed clinically. Usually after the first year follow-up intervals are extended depending on the histology and the overall performance status of the patient. Follow-up examinations include a

thorough clinical and neurological assessment, as well as contrast-enhanced MRI. Additional examinations are scheduled as needed clinically.

Follow-up assessment included thorough analysis of toxicities according to the Common Terminology Criteria CTCAE Version 4.1. Treatment response on imaging was based on the RECIST criteria.

Results

In all patients treatment could be completed without any unexpected severe toxicities; mild acute side effects included alopecia, fatigue, headaches as well as conjunctivitis and skin erythema. No side effects > CTC Grade III were observed. Table II (middle column) summarizes clinical symptoms, patients' complaints and symptoms reported within the first months after treatment.

Of all patients, 157 (60%) were followed for more than six months. Thus late toxicity was scored in these patients. To date, no severe late toxicities were observed, however, for endpoints such as secondary malignancies or neurocognitive side effects follow-up time still remains too short. In Table I, patients' complaints reported after six months of follow-up are documented.

Local recurrences were mainly seen in the group of high-grade gliomas or atypical meningiomas; for benign skull base meningiomas, to date, no recurrences were observed during follow-up.

High-grade gliomas

For WHO Grade III gliomas and glioblastomas treated for primary diagnosis, treatment consisted of 50 Gy E photons and a carbon ion boost of 18 Gy E, with concomitant and adjuvant temozolomide, according to the CLEOPATRA protocol. Of 34 patients, 12 patients developed a recurrence during follow-up with a median progression free survival time of 5.8 months. For re-irradiation (n = 21 patients), carbon ion radiotherapy alone was applied according to the CINDERELLA protocol; during follow-up, 13 patients developed tumor recurrences.

Table II. Patients' complaints recorded within the first 6 months of particle radiotherapy (middle column). Of 260, 157 patients were followed more than 6 months (right column).

Characteristic	< 6 months	≥ 6 months
Pain	22 (8%)	14 (9%)
Skin toxicity	21 (8%)	4 (3%)
Nausea	29 (11%)	9 (6%)
Fatigue	70 (27%)	8 (5%)
Motor deficits	72 (27%)	31 (20%)
Sensory deficits	41 (16%)	32 (20%)
Cognitive dysfunctioning	40 (15%)	32 (20%)
Hair loss	95 (37%)	13 (8%)
Hearing impairment	37 (14%)	33 (21%)
Dizziness	40 (15%)	21 (13%)
Headache	69 (27%)	54 (34%)
Seizures	22 (8%)	15 (9%)
Visual deficits	74 (28%)	45 (28%)

Meningiomas

After primary radiotherapy, for low-grade meningiomas treated with proton radiotherapy with a median dose of 57.6 Gy E, local control over the follow-up time was 100%. Figure 1 shows a typical treatment plan of a skull base benign meningioma treated with protons, as well as a significant treatment response during follow-up. No recurrences were observed, and patients remained alive until the last included follow-up visit.

For high grade meningiomas, 17 of 36 patients developed a tumor recurrence after primary

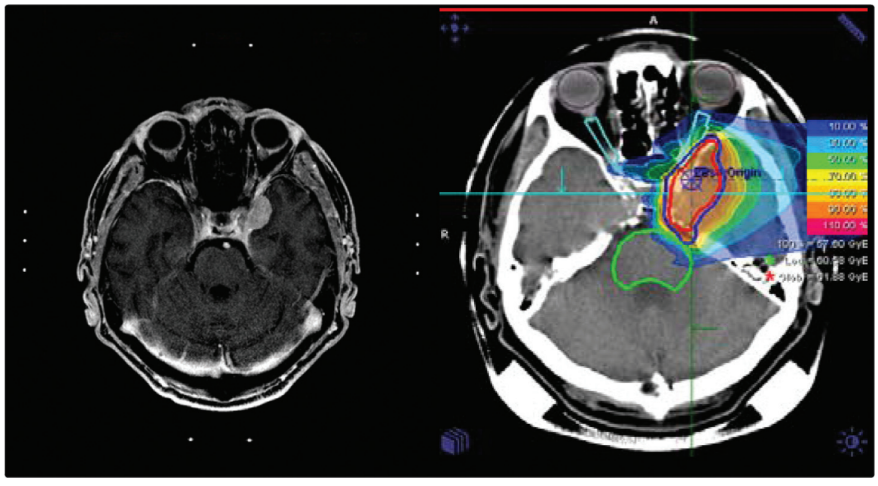

Figure 1. Typical treatment plan for a benign skull base meningioma treated with protons.

radiotherapy consisting of photon radiotherapy and a carbon ion boost. Local control was 54% at one year and 33% at two years.

Other histologies

For benign histologies such as craniopharyngioma or pituitary adenomas, local control was 100% after primary radiotherapy, delivered at a dose of 50.4–54 Gy E, depending on size, volume, shape or pre-existing symptoms of the patients.

Discussion

Clinical results after proton and carbon ion radiotherapy for primary brain tumors and certain tumors of the skull base region show promising outcome with very low side effects. Compared to photons, acute side effects such as hair loss or fatigue seem to be reduced, however, not completely absent. Combination with chemotherapy as performed in high-grade gliomas is well tolerated without any complications. Clinical workflow, especially with combined photon and particle boost treatment, require strict organization and streamlined treatment planning.

To date, clinical evidence of the superiority of particle beams is scarce. The optimized dose distributions with significant reduction of integral dose suggest a clinical benefit, however, long-term sequelae such as neurocognitive side effects of even rates of secondary malignancies in the adult population are difficult to assess and require very long-term standardized follow-up.

The indication for particle therapy may be set for two reasons, one being reduction of unwanted effects, the other a potential use of dose escalation due to the beneficial dose distributions, or the use of the higher RBE of carbon beams for certain high-grade histologies.

For gliomas, few data are available on particle therapy. For protons, dose escalation studies performed earlier and published by Fitzek and colleagues demonstrated a clear dose-response relationship for high-grade gliomas with patients treated with higher doses showing significantly increased survival, however, the rate of severe treatment-related toxicity, mainly symptomatic necrosis was relatively high. However, patients with necrosis showed a significantly increased overall survival, stressing the dose-response relationship of gliomas [21]. With carbon ion radiotherapy, at NIRS, patients with glioblastomas and WHO Grade III astrocytomas were treated within a prospective trial with dose escalation; higher dose was significantly associated with increased outcome, and median survival of 17 months for glioblastoma is promising. To further elucidate the role of carbon ion radiotherapy, studies on primary and recurrent glioblastomas are currently recruiting patients at the HIT [22,23]; for primary glioblastomas, combination with temozolomide according to the present treatment standard is applied. Early data has shown promising responses and low rates of unwanted effects [24,25]. In the future, advances in imaging, such as identification of high-risk regions with amino acid-PET, potentially help direct high doses to only precisely defined areas, thus exploiting the potential of dose escalation with particle therapy, but minimizing the risk for treatment-associated side effects [26–29].

Studies implementing comparable doses of radiation for high-grade gliomas have yet not been reported, and data from low-grade gliomas have shown comparable outcome to photon treatment [30]. However, in these patients the main benefit of protons may be in reduction of neurocognitive sequelae, and from most series no long-term follow-up has been reported, or may not include prospective assessment of neurocognitive scores. In the present series, we see promising local control rates, and no severe treatment-related side effects. Acute toxicity may be reduced compared to photons regarding fatigue, etc., however, hair loss is also present in the majority of the patients. In Japan, a smaller series of patients was treated with carbon ion radiotherapy for low-grade gliomas; progression free survival was at a median of 18 months in patients treated with lower doses (50.4 Gy E), and 91 months in the higher dose group (55.2 Gy E); it could be shown that dose had a significant impact on outcome local control. Toxicity was acceptable, no Grade III side effects were observed during the follow-up time [31]. However, due to the biology of carbon ions and the natural behavior of low-grade gliomas, a clear rationale for carbon ions might be difficult, however, when available, potentially the superior dose distribution compared to protons and the RBE might convert to a clinical benefit, especially in patients with tumors close to OAR, or with adverse prognostic factors.

Meningiomas have been a target for proton centers in the past; again, for low-grade meningiomas the rationale is most likely reduction of long-term side effects, while high-risk meningiomas may benefit from dose escalation with particles. For this purpose, we treated 10 patients with high-grade meningiomas with photon radiotherapy up to 50 Gy E with a carbon ion boost of 18 Gy E to the macroscopic tumor [32]. Two patients of 10 developed tumor recurrence after re-irradiation, six and 67 months after treatment. Local control rates after primary RT was 86% and 72% at five and seven years, respectively, which compared favorably to data

in the literature. However, it is not clear whether this is due to the biology of carbon ions, or the dose escalation compared to conventional series treated commonly up to 60 Gy E; for high-grade meningiomas, again, a dose-response relationship is known, and doses exceeding 60 Gy E are anticipated to further increase local control [33–36]. For low-grade meningiomas, again, studies to date have not shown superior results to photons, however, long-term assessment is still to be awaited. Currently, a prospective trial on high-risk atypical meningiomas is further assessing the role of a carbon ion boost [37]. Target volume definition is based on molecular imaging using e.g. 68-Ga-DOTATOC-PET, which has been shown to have significant impact on identification of target lesions, as well as on target volume definition [38,39].

For recurrent tumors, the benefit or particle dose distributions underline the rationale for re-irradiations. Within our GSI experience, we could demonstrate safe and effective re-treatment using carbon ion radiotherapy in different anatomical regions [40]. Currently, the value of carbon ion radiotherapy is compared to FSRT in a randomized controlled trial for recurrent glioblastomas [23].

In conclusion, the data presented in the present manuscript add valuable information on patients treated with particle therapy within the brain and skull base region. Optimization in particle beam technology as well as advances in treatment planning can help improve outcome, especially in those patients with dismal prognosis such as glioblastomas or high-risk meningiomas. Currently, prospective trials are under way, thus the data on the value of particle therapy is enlarged continuously. Until these data are available, information on treatment concepts, toxicity and outcome as reported in the present analysis provide useful information for treating and referring physicians, and especially for those setting up a particle therapy service.

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