

REVIEW ARTICLE

Treatment with heavy charged particles: Systematic review of clinical data and current clinical (comparative) trials

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Abstract

Background. To analyze relevant data on carbon ion radiotherapy for different tumor indications and to review current clinical trials. **Material and methods.** All published data on carbon ion radiotherapy were searched for with specific criteria in PUBMED. The terms for search were ‘carbon ion and (radiotherapy OR radiation therapy) and (nirs OR chiba OR japan OR iiep OR st. petersburg OR PSI OR dubna OR uppsala OR clatterbridge OR loma linda OR nice OR orsay OR itemba OR mpri OR himac OR triumph OR GSI OR HMI OR NCC OR ibmc OR pmrc OR MGH OR infn-lns OR shizuoka OR werc OR zibo OR md anderson OR fpti OR ncc ilsan OR boston OR heidelberg OR tsukuba) NOT in vitro NOT cell culture NOT review[Publication Type] Filters: Humans, English’. The search delivered 273 hits, of which only articles in English including 20 or more patients were included. Case reports were not considered. We subdivided into disease- and site-specific groups. **Results and conclusion.** To date, several studies have been performed, however, no randomized trials have been conducted. Therefore, carbon ion radiotherapy must be considered an experimental treatment, and randomized trials comparing modern photon as well as proton treatments are necessary.

Treatment of patients with particle therapy remains a promising alternative, although to date no randomized data have proven a significant clinical benefit in any patient subgroup. Especially in patients with radiation-resistant tumors which are located in close vicinity to organs at risk (OAR), the intricate biology of the carbon beam has been shown to enhance radiation response in vitro and in vivo, as well as to potentially lead to an improved clinical outcome [1–5]. The physical properties of particle beams lead to a reduction in integral dose due to the inverted dose profile with an energy-dependent deposition of the Bragg Peak into the defined tumor volume. While proton beams have been shown to be associated with an almost comparable biological efficacy with a relative biological effectiveness (RBE) of about 1.1, heavier charged particles produce radiation damage within the cell nuclei contributing to an increased RBE; depending on the cell line, the dose and fractionation, the endpoint and many other factors, this RBE can be between approximately 2 and 5 [6–12].

Worldwide, a number of centers are currently treating patients with proton therapy, and due to the

comparable RBE to photons, proton therapy is seen to be comparable to photons when applying the same single and total doses; however, for protons, evidence of superiority is currently lacking. Carbon ion radiotherapy remains available at only a few centers worldwide. The first to treat patients were in Japan at the National Center for Radiation Sciences (NIRS), followed by Heidelberg University treating patients at the Gesellschaft für Schwerionenforschung (GSI) in Darmstadt and since 2009 at the Heidelberg Ion Therapy Center (HIT) [1]; additionally, Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia has started treatment with protons and carbon ions, and few other clinically operating centers are found in Japan. The HIT facility poses the unique opportunity to perform randomized clinical trials comparing actively scanned protons with carbon ions, as well as all modern techniques of photon radiotherapy. The center is directly attached to the Department of Radiation Oncology at the University Hospital of Heidelberg, thus enabling the radiation oncologist to choose the most appropriate technique available for the single patient. Within the disease- and site-specific working groups, several prospective

clinical trials comparing different treatment modalities are currently recruiting patients.

To date, no randomized clinical trials are available to demonstrate the real benefit of high-LET radiotherapy. Several phase I and II trials have been performed in Japan, and special indications such as chordomas and chondrosarcomas as well as adenoid cystic carcinomas (ACCs), atypical meningiomas or prostate cancer have been treated within the limited beamtime available at GSI [13–22]. In the past, some groups have pooled the data found in the literature, however, most are limited either to protons, or the Japanese results published on carbon ions. Currently, a large number of prospective studies evaluating the potential of the carbon beam are recruiting patients. Thus, the present work summarizes the currently available data on carbon ion radiotherapy, puts the data into perspective with modern photon and proton treatments, and elucidates the role of novel study concepts and summarizes the currently available protocols as a comprehensive review.

Methods and results

We performed a literature research in PubMed on the clinical results of carbon ion radiotherapy. All published data on carbon ion radiotherapy were searched for with specific criteria in PUBMED. The terms for search were ‘*carbon ion and (radiotherapy OR radiation therapy) and (nirs OR chiba OR japan OR itep OR st. petersburg OR PSI OR dubna OR uppsala OR clatterbridge OR loma linda OR nice OR orsay OR itemba OR mpri OR himac OR triumph OR GSI OR HMI OR NCC OR ibmc OR pmrc OR MGH OR infn-lns OR shizuoka OR werc OR zibo OR md anderson OR fpti OR ncc ilsan OR boston OR heidelberg OR tsukuba) NOT in vitro NOT cell culture NOT review[Publication Type] Filters: Humans, English*’. The search delivered 273 hits, of which only articles in English including 20 or more patients were included. Case reports were not considered. The selected data were discussed and when available put in context with recent conference data which are not yet available on PubMed, however, contribute significant information. However, overview tables with clinical data include only published literature found during the PubMed search.

We subdivided into disease- and site-specific groups of brain and skull base, head and neck, lung, gastrointestinal malignancies including liver tumors, esophageal cancer, pancreatic cancer, sarcomas and prostate cancer, gynecologic malignancies as well as pediatric tumors.

Brain and skull base

Due to the intricate anatomy of the skull base the use of particle beams allows high doses to be applied

while sparing normal tissue structures. Especially in radioresistant histologies this enables necessary dose escalation without risking high rates of side effects. Moreover, keeping in mind the rationale of the higher RBE in carbon ions, the close vicinity of radioresistant tumors and radiation sensitive structures offer an optimal anatomical and biological scenario to fully exploit the potential of the carbon beam.

Photon data for chordomas have shown in the past that using conventional radiotherapy dose escalation exceeding 60 Gy E is rarely possible, and local control remained around 50% at five years using highly conformal radiotherapy, such as stereotactic treatment; developments in photons, such as intensity-modulated radiotherapy (IMRT), perhaps allow higher dose depositions, however no long-term clinical data on outcome for these skull base tumors are currently available [23–25]. In general, for carbon ion radiotherapy, smaller series of skull base lesions are available from Japan, including chordoma, chondrosarcoma, olfactory tumors or meningiomas. Mizoe published 39 patients in 2009 with chordomas of the skull base and upper cervical spine, with local control of 82% at five years; dose range was between 48 and 60.8 Gy E in 16 fractions; long-term follow-up is still being awaited, as the median follow-up was 4.8 months [26]. Updated results on 76 patients including 44 chordoma, 14 chondrosarcoma and several other indications at the skull base revealed five-year local control of 88% [27]; specifically for chordoma, a recent report showed local control of 88% at five and 79% at 10 years after treatment with 60.8 Gy median dose in 16 fractions [28,29].

At GSI, local control after carbon ion radiotherapy for chordomas was 70% at five years, with severe late toxicity under 5%; this study showed a significant benefit of higher doses (66 Gy E compared to 60 Gy E), and higher doses had been applied in patients where dose escalation was possible due to the anatomy and the calculated dose distribution [30]. For chondrosarcomas, local control was 87% at four years, with comparably low rates of side effects [18]. Overall treatment time was three weeks, due to a seven-day treatment schedule based on the availability of the carbon beam within the research-based GSI facility, and single fraction size was 3 Gy E in both reports. Based on these data, prospective randomized trials are underway in both indications comparing protons (74 Gy E total dose according to the established prescription concept from MGH) and carbon ions (60–66 Gy E), with primary endpoints including toxicity analyses as well as local control [31,32].

For skull base chordomas and chondrosarcomas, treatment with proton radiotherapy may be considered the gold standard due to the clinical data available; however, main criticism may be that

photon radiotherapy evolved over time, and with modern IMRT/image-guided radiotherapy (IGRT) it is possible to deliver comparable doses with optimal sparing of normal tissue structures. This might result in comparable clinical data to proton therapy. The subtle clinical benefits with respect to toxicity, quality of life (QOL) or neurocognitive functioning are long-term endpoints difficult to assess, but, however, treatment planning studies comparing the two radiation modalities are in favor of particles. Additionally, long-term data have shown a decrease in local control beyond five years, and the biology of carbon ions might contribute to more long-term local control.

For primary brain tumors, both low-grade gliomas as well as high-grade gliomas have been treated successfully with carbon ion beams. Only recently, a study published by Hasegawa et al. from Japan showed excellent tolerability and convincing outcome in patients with low-grade gliomas treated with carbon ion radiotherapy [33]; this study included 14 patients, and carbon ion radiotherapy was administered in 24 fractions over a time frame of six weeks; dose was escalated from 46.2 to 50.4 Gy E, and up to the highest dose group of 55.2 Gy E. No grade 3 toxicities were observed; the median progression-free survival was 18 months for the low-dose group and 91 months for the high-dose group. Median overall survival was 28 months for the low-dose group, and the high-dose group had not yet reached the median at publication date. Dose significantly influenced both progression-free and overall survival.

For high-grade gliomas, a prospective study by Mizoe et al. performed between 1994 and 2002 included WHO grade III ($n = 16$) and IV ($n = 32$) patients with a carbon ion boost in combination with photon radiotherapy up to 50 Gy, with nimustine hydrochloride (ACNU) administered at a dose of 100 mg/m² concurrently in weeks 1, 4, or 5 of XRT. The carbon ion dose (8 fractions) was increased from 16.8 to 24.8 Gy E in 10% incremental steps (16.8, 18.4, 20.0, 22.4, and 24.8 Gy E). There was no grade 3 or higher acute reaction in the brain; late sequelae included four cases of grade 2 brain morbidity and four cases of grade 2 brain reaction among 48 cases. The median survival time in anaplastic astrocytoma patients was 35 months and that of glioblastoma patients 17 months. The median progression-free survival and median survival time of GBM showed four and seven months for the low-dose group, seven and 19 months for the middle-dose group, and 14 and 26 months for the high-dose group. Outcome compares favorably with standard chemoradiation for glioblastoma, especially when keeping in mind that only patients after biopsy or

incomplete resection were included [26]. Moreover, no addition of temozolomide was performed as which is the treatment standard today. To further elucidate the value of a carbon ion boost in glioblastomas the CLEOPATRA-trial, randomizing a carbon ion boost to standard 60 Gy E low-LET radiotherapy is currently recruiting patients. Initial clinical data have shown safety and promising responses, however, full recruitment of the trial must be awaited [1,34,35].

Meningioma is the second most common primary brain tumor and represents approximately 15–26% of all intracranial neoplasms [36]. About 5–10% of meningiomas are of non-benign histology (atypical or anaplastic) and are associated with less favorable outcome; high-risk meningiomas commonly show aggressive growth patterns, and recur early after surgery alone [37]. Radiation therapy is the most effective adjuvant treatment available, although meningiomas are classified as relatively radioresistant tumors [38–41]. For non-benign meningiomas, a number of small and non-controlled series have reported superior outcome after postoperative radiotherapy as compared to surgery alone [42–47].

Outcome after proton as well as advanced photon radiotherapy are comparable for the treatment of benign meningiomas, with high local control rates and low rates of treatment-related side effects; in benign meningiomas, total doses of 50–60 Gy are recommended [48]. For anaplastic and atypical meningiomas, doses of 60 Gy are known to be not sufficient for long-term tumor control; therefore, strategies of dose escalation could play an important role for treatment optimization. With particle therapy, dose escalation required for long-term control of atypical or malignant meningiomas is feasible while adhering to normal tissue tolerance constraints. Preliminary results after carbon ion radiotherapy obtained within a phase I/II trial performed at GSI could show safety and feasibility in patients with high-risk meningiomas treated with a carbon ion boost to the macroscopic tumor [gross tumor volume (GTV)] in combination with precision photon radiotherapy delivered as IMRT FSRT to the clinical target volume (CTV) [49]. No severe acute or long-term toxicity could be observed, and treatment outcome with overall survival rates of 75% and 63% at five and seven years is promising; all patients had macroscopic tumors at the timepoint of radiotherapy.

This concept is currently further investigated in the prospective MARCIE-trial treating patients with atypical meningiomas with macroscopic tumor with photons up to 50 Gy, followed by a carbon ion boost with 18 Gy E in 6 fractions [50].

Trials in the skull base and brain region are summarized in Table I. Taken together, however, to date, no randomized trials have shown superiority of carbon ions over protons or photons for any histology, thus only level II evidence is available.

Head and neck

For several tumor types in the head-and-neck region, concepts including particle therapy have been applied. Most of them combine photon treatments with particles as a boost to regions of high risk, such a tumor remnants or regions of R1/Rx resections. Main indications included mucosal melanoma, salivary gland tumors including adenoid cystic histology or mucoepidermoid tumors, adenocarcinomas, but also sarcoma types located in the head-and-neck region.

The most extensive data available is on ACCs. Due their growth pattern and spread along perineural routes, microscopic spread has been shown to extend to around 5 cm beyond any macroscopically visible tumors, along nerves or blood vessels. Thus, CTVs are commonly large and include large volumes of normal tissue at risk for microscopic invasion. In contrast, lymph node involvement is usually comparably low and between 5% and 10%, depending on extension and location of the lesion [51–53]. ACCs mostly develop in the head-and-neck region, and they are usually within the salivary glands, as they arise from glandular tissues. Due to their

radioresistant histology, local dose escalation strategies, at least in incompletely resected lesions, has been shown to increase local control [54].

Clinical data from proton centers, mainly from MGH in Boston, have set a goalpost with high local control of 93% at five years, with five-year overall survival of 77% [55]; more severe side effects of CTCAE grade III or higher were seen in 17% of the patients. With neutrons, toxicity was actually comparable in the series published by Huber et al., and local control was 75% at five years with overall survival at five years of 59% [56]. Due to the metastatic potential associated with ACC histology, any means of dose escalation, either neutrons, protons or carbon ions, have increased local control, but OS was unaltered due to distant spread. For carbon ions, data from GSI/HIT as well as NIRS in Japan are available. The concepts of treatment between both centers differ with respect to target volumes, dose and radiation modality. While carbon ions were applied as a boost of 18 Gy E in combination with 50 Gy of photon IMRT in the German group, the Japanese physicians applied carbon ions alone. Target volumes for the photon CTV were considerably larger including regions of potential perineural spread, as compared to the more focused carbon ion dose to the macroscopic tumor adding a safety margin in the Japanese series.

In the GSI-group of patients, late severe side effects were below 5%, in the Japanese series no late effects were reported. Local control was 78% at four years with a carbon boost compared to 25% at four

Table I. Carbon ion radiotherapy for brain and skull base tumours.

Publication	Number of patients	Tumour	Treatment	Median follow-up	Local control	Overall survival
Combs et al., 2013	70	Meningioma	Proton; Carbon ion; Photon + Carbon boost	6 (range 2–22 months)	92% local control at 17 months (high-risk meningioma; Carbon boost for primary RT)	100%
Rieken et al., 2012	26 Carbon	Glioma, meningioma	50 Gy Photon, Carbon ion boost 18 Gy E/6 fractions	Not reported	–	–
Schulz-Ertner et al., 2007	54	Skull base chondrosarcoma	60 Gy E, 20 fractions	33 (range 3–82 months)	96.2% at 3 and 89.8% at 4 years	98.2% at 5 years
Schulz-Ertner et al., 2007	96	Skull base chordoma	60 Gy E, 20 fractions	31 (range 3–91 months)	70% at 5 years	91.8% at 3 and 88.5% at 5 years
Tsujii et al., 2012	47	Skull base chordoma	60.8 Gy E, 16 fractions	3.7 years	88% at 5 and 80% at 10 years	87% at 5 years
Mizoe et al., 2009	33	Skull base chordoma	Dose escalation: 16 fractions/4 weeks, 48–60.8 Gy E	4.7 years	85.1% at 5 years, 63.8% at 10 years	87.7% at 5 years, 67% at 10 years
Mizoe et al., 2007	48	Anaplastic glioma; Glioblastoma	50 Gy E Photons; Carbon boost 16.8–24.8 Gy E	Not reported	Median progression-free survival: 7 months for glioblastoma, 15 months for anaplastic astrocytoma	Median overall survival: 17 months for glioblastoma, 35 months for anaplastic astrocytoma

years after IMRT alone; in the carbon-only patients local control at five years was 96% in T1–T3 tumors, and 71% in T4 lesions [57].

For mucosal melanoma, local control is much of an issue due to the radioresistant histology of the tumors, and the difficulty of applying local dose; advanced photon treatments such as IMRT offer excellent dose distributions, however, significant dose escalation still remains limited due to a feared risk of side effects [58]. At NIRS, a large series reported on 198 patients with malignant melanoma of the head-and-neck region treated with carbon ion radiotherapy, mostly with concomitant chemotherapy [59–62]; initially. In total 57.6 Gy E were prescribed in 16 fractions, delivered over four weeks. In this group, overall survival at five years was 35% [63]. Although results compared favorably to the literature, outcome improvement was aimed at by adding chemotherapy with dacarbazine, nimustine and vincristine (DTIC). This was explored in 96 patients, and chemotherapy was applied before radiotherapy, after completion of radiotherapy, and then followed by another three courses as adjuvant treatment [59]. Five-year survival improved to 58% from 35%, while local control, however, remained comparable. Recently, updated results reported local control of 75% at five years [61].

Besides melanoma, several other histologies were treated within the head-and-neck region, which was recently summarized by Mizoe et al. [61]. Doses were commonly 64 Gy E in 16 fractions, in patients were large areas of normal tissue, especially skin, were within the treatment fields, dose was reduced to 57.

Gy E in 16 fractions. In 6% of the patients grade 3 skin and 10% mucosal reactions were skin, late skin reactions were 3% and 2% in mucosal toxicity, however, not grade 3 or higher. The five-year local control was 69% for ACC (see above), 73% for adenocarcinoma, 61% for papillary adenocarcinoma, 61% for squamous cell carcinoma, and 24% for sarcomas.

In HIT, within a prospective trial a carbon ion boost in combination with induction chemotherapy with TPF and concomitant application of cetuximab is recruiting for patients with locally advanced tumors of the oro-, hypopharynx and larynx, a trial for sinusal tumors with photon IMRT and a carbon ion boost, as well as a trial for recurrent head-and-neck tumors [64,65].

Table II summarizes published data of carbon ion radiotherapy in the head-and-neck region.

Lung cancer

Depending on tumor stage, outcome in patients with non-small cell lung cancer (NSCLC) can be excellent after surgery or high-dose radiotherapy alone, however, in subgroups of patients with advanced disease treatment optimization remains necessary.

Data on carbon ion radiotherapy are summarized in Table III. At NIRS, lung tumors were treated according to the anatomical region, i.e. peripheral tumors and centrally located lesions. For the first group, a regimen reducing fraction number has been conducted from 18 fractions applied in six weeks to eventually single-fraction treatment [66–71]. No serious side effects were observed over time, and in

Table II. Carbon ion radiotherapy for tumors in the head-and-neck region.

Publication	Number of patients	Tumour	Treatment	Median follow-up	Local control	Overall survival
Jingo et al., 2012	27	Head-and-neck sarcoma	70.4 Gy E/16 fractions	37 months (range 4.1–73 months)	91.8% at 3 years	74.1% at 3 years
Schulz-Ertner et al., 2005	29	Adenoid-cystic carcinoma	Photon 50 Gy E, Carbon Boost 18 Gy E/6 fractions	16 months (2–60 months)	78% at 5 years	76% at 5 years
Yanagi et al., 2009	102	Mucosal melanoma	Carbon ions	49.2 months (range 16.8–108.5)	84.1% at 5 years	27% at 5 years
Mizoe et al., 2012	236	Malignant melanoma, adenocarcinoma, squamous cell carcinoma, adenoid-cystic carcinoma	Carbon ion radiotherapy	54 months (mean; range 3–162 months)	5-years: 75% for malignant melanoma, 73% for adenoid cystic carcinoma, 73% for adenocarcinoma, 61% for papillary adenocarcinoma, 61% for squamous cell carcinoma and 24% for the 14 with sarcomas	5-years: 68% for adenoid cystic carcinoma, 56% for adenocarcinoma, 35% for malignant melanoma

Table III. Carbon ion radiotherapy for lung cancer.

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Miyamoto et al., 2003	81	NSCLC	Carbon ion 59.4–95.4 Gy E/18 fractions/6 weeks 68.4–79.2 Gy E/9 fractions	52.6 months (minimum 30 months)	59% at 5 years	42% at 5 years
Miyamoto et al., 2007	50	NSCLC	Carbon ion 72 Gy E/9 fractions/3 weeks	59.2 months (range 6–83 months)	95% at 5 years	50% at 5 years
Miyamoto et al., 2007	79	NSCLC	Carbon ion T1: 52.8 Gy E/4 fractions/1 week T2: 60 Gy E/4 fractions/1 week	38.6 months (range 2.5–72.2 months)	T1: 98% at 5 years T2: 80% at 5 years	45% at 5 years
Iwata et al., 2013	27	NSCLC	60 Gy E/10 fractions; 52.8 Gy E/4 fractions; 66 Gy E/10 fractions; 80 Gy E/20 fractions	51 months (range 24–103 months)	75% at 4 years	58% at 4 years
Yamamoto et al., 2012	91	Metastatic lung tumors	40–80 Gy E, 1–16 fractions	2.3 years (range 0.3–13.1 years)	91.9% at 2 years	71.2% at 2 years

the group treated with 9 or 4 fractions local control rate at five years was 95% and 90%, respectively. Depending on stage I NSCLC, local control for T1 was 95.8% and for T2 92.9% after 9 fractions [72]. In the 4-fraction group, local control was 97.5% for T1 and 79.8% for T2 lesions. In both groups, no side effects above CTCAE grade II were seen.

Within the subsequent protocol, a single-dose schedule was evaluated in 218 patients [72]. Patients with stage I NSCLC after PET-staging were included into a dose escalating regimen from 28 to 50 GyE. All patients were treated with respiratory gating, with markers implanted for motion monitoring. Again, no side effects exceeding CTCAE grade II were observed. Dose was a significant prognostic factor. Local control after ≥ 36 Gy E was 79.2% at five years, compared to 54.5% in patients receiving ≤ 34 Gy E [72]. Failures after treatment included local progression, lymph node involvement as well as distant spread in 26, 26 and 39 of 151 patients, respectively.

For centrally located lesions, larger fraction sizes are applied at NIRS to be cautious about radiation-induced side effects. Successful local control has been observed after 9 fractions applied over three weeks up to total doses of 57.6 Gy E.

A pooled analyses has shown long-term outcome after proton and carbon ion radiotherapy in large (T2a–T2bN0M0) NSCLC [73]; with a median follow-up of 51 months, 34-year local control was 75% (70% for T2a, 84% for T2b), with overall survival at 58% (53% for T2a, and 67% for T2b). Grade III pulmonary toxicity was rare and only observed in 2/70 patients. Plans for a next study include addition of chemotherapy in these subgroups of patients.

Further investigation is currently under way, also for a third group of patients with chest wall infiltration. The latter will be the first group of lung cancer patients addressed at HIT within a prospective clinical trial.

A new concept is the treatment of oligo-recurrent lesions in the lung, which is currently under further evaluation [74].

Gastrointestinal (GI) malignancies

Data on carbon ion radiotherapy is mainly available for liver tumors, pancreatic cancer as well as rectal cancer, but also other smaller studies have been published in other indications. Table IV shows recent results on carbon ion treatment.

A smaller study reported on carbon ion radiotherapy for esophageal cancer [75]; 31 patients with thoracic esophageal cancer at NIRS were treated with dose escalation from 28.8–36.8 Gy E. After treatment, clinical evaluation and surgery was followed 4–8 weeks later. No late toxicities were observed, and acute toxicity was only seen in one patient (3.2%). Twelve of 21 patients demonstrated complete clinical response (38.7%), and 13 patients (41.9%) partial response. Pathological complete remission was found in 12/31 patients (38.7%). Overall survival at one-, three-, and five-years rates in stage I patients were 91%, 81%, and 61%, and was 100%, 85%, and 77% for stage II, and 71%, 43%, and 29% for stage III cases, respectively.

The attempt of using the carbon beam has been focused on several histologies in the lower GI-tract, including pancreatic cancer as well as hepatocellular cancer (HCC; Table V).

Previously, HCC was rarely seen in Western countries, however, in Asian countries there was a high incidence due to the wide spread of Hepatitis B and C in China and Japan, respectively. Over the last years the incidence has increased also in Western countries, so presentation of patients with HCC within GI-tumor boards has increased worldwide. Surgery remains the treatment of choice in these patients, either local resection or liver transplantation,

Table IV. Carbon ion radiotherapy for gastrointestinal tumors.

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Akutsu et al., 2012	31	Thoracic oesophageal cancer	28.8–36.8 Gy E	Not reported	38.7%: clinical complete response (CR); 41.9% a partial response, 38.7% pathological CR	Stage I: 81% at 3 years and 61% at 5 years Stage II: 85% at 3 years and 77% at 5 years Stage III: 43% at 3 years and 29% at 5 years
Shinoto et al., 2013	26	Pancreatic cancer	Carbon ion 30–36.8 Gy E	33.8 months (survivors)	–	42% at 5 years; 52% at 5 years after surgery

for multiple lesions or systemic spread treatment with sorafenib has been established [76]. The physical properties of ion beams have led several proton centers including Loma Linda, Tsukuba and NCCHE to treating HCC patients, with local control being between 80% and 90% at five years depending on the dose, fractionation schedule and tumor diameter [77–79].

Most patients treated with carbon ion radiotherapy to date have been treated at NIRS; early reports have focused on a 4-fraction treatment with a total dose of 52.8 Gy E, with local control of 94% at three and 81% at five years [80]; subgroup analysis have shown safety and efficacy for tumors in close vicinity or with direct infiltration of the porta hepatis, however, local control is this subgroup was lower with 87.8% compared to 95.7% in the non-porta-hepatis-group [81]. Subsequent strategies have focused on more hypofractionated regimens, including a dose escalation up to 45 Gy in 2 fractions. Currently, at NIRS, two fractions applied at two days using respiratory-gated carbon ion radiotherapy with total doses of 32–45 Gy E (i.e. 16–22.5 Gy E per fraction) are applied using 2–3 ports. Tumor size (≤ 5 cm versus > 5 cm) seems to influence local control, however, does not reach significance level. However, dose has an impact with doses beyond 42.8 Gy E significantly enhancing local control. Toxicity mainly is limited to CTCAE grade 1 and 2 for early and late toxicity, only very few patients developed grade 3 toxicity to the liver only.

At HIT using a scanned ion beam, treatment of HCC within a clinical protocol (PROMETHEUS-1 trial) has started and initial results have been published recently [82]. Using either patient positioning with an abdominal press or active gating based on an Anzai-Belt signal is applied for motion monitoring. The trial is designed as dose-escalation trial starting at 4×10 Gy E and moving up to 4×14 Gy E [83]. Feasibility and safety have been confirmed, as well as promising local control.

The dismal prognosis of locally advanced pancreatic cancer argues for exploiting the biology of high-LET particle beams in these patients. The idea to bring locally advanced tumors into a resectable status has been addressed explicitly in several studies [84–90]. Therefore, there is evidence that the rate of margin-free resection can be increased by preoperative chemoradiation [91].

In Japan, several clinical trials have been performed to evaluate carbon ion radiotherapy for pancreatic cancer, either alone or in combination with chemotherapy. In a first step, between 2000 and 2003, 22 patients with localized, resectable adenocarcinoma of the pancreas were treated with preoperative carbon ion radiotherapy. Doses between 44.8 Gy E and 48 Gy E in single doses of 2.8 Gy E and 3.0 Gy E were applied. Local control rate was 100%, and overall survival was 59% at one year. A subgroup of patients did not receive post-radiotherapeutic resection, which showed a significantly lower outcome (one year overall survival of 3%) as compared to patients receiving surgery (86%

Table V. Carbon ion radiotherapy for hepatocellular carcinoma (HCC).

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Kato et al., 2004	69	HCC	Carbon ions 52.8 Gy E/4 fractions	71 months (range 63–83 months)	94% at 3 and 81% at 5 years	33% at 5 years
Imada et al., 2010	40	HCC	Carbon ions 42.8–45 Gy E/2 fractions	34 months (range 6–90 months)	87.8% at 5 years (porta hepatis) 95.7% at 5 years (non-porta hepatis)	22.2% at 5 years (porta hepatis) 34.8% at 5 years (non-porta hepatis)

Table VI. Carbon ion radiotherapy for prostate cancer, gynaecological malignancies and recurrent rectal cancer.

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Okada et al., 2012	740	Prostate cancer	57.6 Gy E, 16–20 fractions	59.3 months	89.7% at 5 years (biochemical-relapse free): 16 fractions – 88.5%; 20 fractions – 90.2%	95.2% at 5 years
Shimazaki et al., 2012	728	Prostate cancer	Protocol 9402: 54–72 Gy E; Protocol 9703: 60–66 Gy E; Protocol 9903-1.2; fixed dose 66 Gy E; Protocol 9904-03: fixed dose 57.6 Gy E	87 months (range 16–153 months)	Biochemical failure rates: 12%, 6%, and 15% in low-, intermediate- and high-risk patients	–
Ishikawa et al., 2012; Tsujii et al., 2011	855	Prostate cancer	Carbon + Hormones: 66.63 Gy E/20 fractions; 57.6 Gy E/16 fractions	Minimum 6 months	–	87–99% at 5 years (Group 2–4)

overall survival at one year [92]). Subsequently, a more hypofractionated regimen was evaluated in patients with comparable inclusion criteria, increasing applied dose from 30 to 35.2 Gy E in 8 fractions. Still, no local tumor recurrences were observed, and overall survival at one and five years in patients treated with surgical resection after pre-operative carbon ion radiotherapy was 89% and 51% [92]. Moreover, patients with locally advanced and in the first step inoperable pancreatic cancer were included into a phase I/II trial. Patients with histologically confirmed ductal carcinoma of the pancreas with a treatment volume of 14 cm or less in diameter, inoperable after evaluation by specialized surgeons, were included and treated with increasing doses from 38.4 to 52.8 Gy E in 12 fractions. Overall survival at one year was 60% with a local control rate of 81%, and patients receiving higher doses showed a clear benefit with respect to local control as well as overall survival [92]. In analogy to treatment schedules with photons, also the combination of chemotherapy with gemcitabine and carbon ions was placed in a clinical study protocol at NIRS in Japan and is currently still in the recruitment phase. In the first part of the trial a carbon ion dose of 43.2 Gy E in 12 fractions was set as constant, and weekly gemcitabine was increased from 400 mg/m² to 1000 m². Acute hematological toxicity as well as non-hematological side effects were low, no grade 4 and 5 toxicities were

observed. Only in the 700 mg/m² and 1000 mg/m² gemcitabine arm, 3/6 (50%) and 8/12 (75%) developed grade III hematological toxicity. Local control was basically identical over time between all three treatment arms, however, survival was higher with increasing chemotherapy doses. Currently, this regimen is being performed with constant gemcitabine at 1000 mg/m² and the carbon ion dose is being escalated to 50.4 Gy E [92].

Therefore, in the PHOENIX-01 trial, carbon ion radiotherapy using the active rasterscanning technique will be evaluated in patients with advanced pancreatic cancer in combination with weekly gemcitabine and adjuvant gemcitabine.

For rectal cancer, an initial phase I/II trial with 16 fractions of carbon ion radiotherapy over four weeks was performed as a dose escalation trial from 67.2 to 73.6 Gy E, which was followed by a phase II trial at the dose level of 73.6 Gy E [93]. All patients presented with recurrent rectal cancer, however, had not been previously treated with radiotherapy. Local control was clearly dependent on dose, with local control at five years being 35% for the lowest dose group, 84.2% for the intermediate group, and 92.8% for the high-dose group. In 202 lesions treated in 189 patients, toxicity was low and late side effects were only seen in seven patients, of which three were grade III (skin, GI and GU tract), and three were grade IV (skin, GI-tract). To reduce toxicity to the intestine, cooperation with surgical teams were initiated in

Table VII. Carbon ion radiotherapy for soft-tissue sarcomas as well as chordomas and chondrosarcomas of the trunk and the extremities.

Publication	Number of patients	Tumor	Treatment	Median follow-up	Local control	Overall survival
Matsunobu et al., 2012	78	Osteosarcoma of the trunk	Carbon ion	Minimum follow-up: 14 months	–	32% at 5 years
Imai et al., 2009	95	Sacral chordoma	Carbon ion	42 (range 13–112)	88% at 5 years	86% at 5 and 74% at 10 years

Japan implanting spacer devices to separate the tumor from normal tissue. With spacer, 73 cases have been treated, with local control of 88% at five years. No grade IV toxicities were seen, and late grade III was only seen in four patients which was an infection, no other GI or GU toxicity. Further analysis showed that patients with spacer implantation did show a survival benefit [93,94].

For recurrent rectal cancer after initial radiotherapy, the use of particle beams was also exploited [93,94]. At NIRS, 23 patients with mainly pre-sacral, but also lymph node or perineal involvement, were treated with a median time interval between primary radiotherapy and re-irradiation of 25 months (range 4–66 months). A dose of 70.4 Gy E was applied, toxicities were slightly higher for re-irradiation, however local control was above 90% during follow-up.

At HIT, a prospective phase I/II trial is evaluation the use of scanned carbon ion beams as re-irradiation in recurrent rectal cancer [95].

Prostate cancer

Substantial improvement of the therapeutic window with advanced photon radiotherapy has been achieved in patients with prostate cancer; thus, the use of proton radiotherapy has been discussed highly controversially due to a lack of sound evidence of a clinical benefit [96]. The radioresistant histology, slow growth pattern and presumably low α/β of prostate cancer tissue however provides a strong rationale for hypofractionation, as well as for the use of high-LET beams with enhanced RBE. Thus, particle therapy using heavier ions might convert into a clinical benefit compared to advanced photons or protons alike (Table VI). A hypofractionated trial in 20 fractions over five weeks was initially started, then moving on to 20 and 12 fractions in three weeks at NIRS. Late toxicity to the lower urinary tract after 63 Gy E in 20 fractions was comparable to IMRT, however, rectal toxicity was lower.

Treatment planning included the prostate and seminal vesicles, adding a 10 mm margin (5 mm posterior to the rectal wall). Starting from the 63–66 Gy E in 20 fractions, fractionation was reduced to 57.6 Gy E in 16 fractions, and then 51.6 Gy E in 12 fractions. Dose constraints to the rectum included a $D_{\max} \leq 66$ Gy E with V50 of < 8 cm³; for the bladder, $D_{\max} \leq 66$ Gy E and V50 below 50 cm³. Androgen deprivation was recommended depending on staging, i.e. for low risk only carbon ion radiotherapy ($T \leq T2a$ and $PSA < 20$ and $Gleason \leq 6$), for intermediate risk ($PSA < 20$ and T -stage = $T2b$ or $Gleason = 7$) short-term androgen deprivation, and 24 months or more of androgen deprivation in

high-risk tumors ($T3$ or $PSA \geq 20$ or $Gleason \geq 8$; [97]). Late radiation toxicity was low and included mainly Grade 1 and 2 side effects to the GI and GU tract. Biochemical relapse-free survival was 95.1% in 1479 patients, and hypofractionated patients (12 fractions) seem to show a benefit, however, follow-up in this group is only short. Biochemical failure was in detail described by Shimizaka et al. after carbon ion radiotherapy. In total 728 patients were analyzed, treated with carbon ions at NIRS within prospective clinical protocols including dose escalation. Independently from dose or hormone therapy, this study could confirm the known influence on histology and stage on outcome [98].

Depending on the clinical situation, randomized trials with advanced photon IMRT/IGRT and with proton radiotherapy should be performed, especially since proton radiotherapy is being discussed controversially for prostate cancer. At HIT, two trials in prostate cancer are currently recruiting, comparing protons to carbon ions. In one setting, prostate cancer patients with a lymph node involvement risk below 15% receive either proton or carbon ion radiotherapy (20 fractions, 3.3 Gy E single dose). The other study evaluates the role of proton therapy in biochemical recurrence after prostatectomy (18 fractions of protons, 3 Gy single fractions).

Gynecological malignancies

Few data is available to date for these tumor types, however, some patients have been treated with carbon ions for cervical cancer as well as uterine sarcoma. In total 57 patients with cervical adenocarcinoma were treated, most of them with stage IIIb or IVa disease, with local control at five years of 53.3%. However, prospective data and especially comparison with photon and brachytherapy data are required for further analysis and evaluation [4].

Sarcomas

The probably strongest rationale for the use of carbon beams exists for sarcoma-type tumors, including osteosarcomas, soft-tissue sarcomas as well as chordomas and chondrosarcomas. Carbon ions in Japan were applied as carbon-only treatments, in patients not amenable to surgical resection (Table VII). Only recently, the data on over 500 lesions in 495 patients were reported including several histologies, with local control at two and five years of 85% and 69% [28]. Side effects, especially grade 3 and 4, were rare, and included only skin and soft tissue reactions in nine patients. For head-and-neck tumors, local control was 91.8% at three years; in this dose-escalation

trial, a strong correlation of outcome and dose could be shown. With a dose of 70.4 Gy E in 16 fractions, local control and survival were improved compared to 57.6 Gy E or 64 Gy E, including bone and soft tissue sarcoma in adults [99]. Again, for extremity sarcomas a comparable influence of dose was shown, and local control was 76% at five years [100].

For sacral chordomas, which commonly occur in the elderly population, complete surgical resection is rarely possible without severe impairment in functioning after hemipelvectomy, and local control remains around 50–60% at five years depending on the surgical series [101]. In Japan, sacral chordomas was one of the largest groups of patients treated with carbon ions, and a study including 95 patients reported 88% local control at five years; only two patients developed severe side effects in terms of skin and soft tissue reactions; 15 patients reported severe damage to the sciatic nerve requiring medication, however, 91% of all patients remained ambulatory with overall good QOL. Updated results after a follow-up time of 68 months show local control of 78% at five years in 185 patients [28]. Late morbidity in this follow-up population remains low, with most toxicities developing at the skin; 176 patients of 185 developed grade 1 and 2 late morbidity of the skin, but only three patients complained of grade 3 and 4 side effects; again, damage to peripheral nerves grade 3 and 4 were seen in six patients, however, the majority of patients remained without any treatment-related adverse events.

At GSI, a small subgroup of patients within the prospective trials was treated with a carbon ion boost in combination with photon IMRT for sacral chordoma. Patients are currently under follow-up and final results are awaited. However, based on the observed clinical outcome as well as the data from Japan a prospective trial at HIT has been initiated treating sacral chordomas in a hypofractionated setting with 4 Gy E single doses in 16 fractions.

For chondrosarcomas of the trunk, 71 patients treated with carbon ions between 1996 and 2009 showed local control at five years of 60%; again late toxicities were rare but included mainly skin reactions in four patients [59].

Osteosarcomas represent the most common type of bone cancer and are mostly located in the extremities. Again surgical resection may lead to severe function impairment, however, surgery in combination with chemotherapy is considered the treatment of choice. Dose escalation strategies with protons have led to local control rates of 82% at three and 67% at five years, after a combination of photons and a proton boost (mean total dose 68.4 Gy E; [102,103]). However, late toxicities were observed in 30% of the patients' grade 3 and 4. For osteosarcoma, recently

updated results from NIRS in 78 patients with osteosarcomas of the trunk after a follow-up time of 70 months demonstrated local control of 73% at two and 61% at five years; tumor volume did have a significant impact on outcome (volumes $< 500 \text{ cm}^3$ local control 87%, $\geq 500 \text{ cm}^3$ 31% [28]). No patients developed grade 3 and 4 toxicities. Currently, locally unresectable osteosarcomas are treated at HIT within a clinical trial [104] in combination with chemotherapy; this represents the only group of pediatric patients treated with carbon ions, due to the dismal prognosis and the potentially enhanced possibility of cure (see below).

Pediatric patients

In spite of the biological benefits associated with the carbon ion beam, and the clinical benefits potentially associated therewith, radiobiology also shows that carbon beam could lead to an increased induction of secondary malignancies. Preclinical evaluations conducted at GSI indicate that outside the target volume there may be a risk of enhanced radiation-induced secondary malignancy induction [105].

These data have made radiation oncologists hesitant in treating pediatric patients or even young adults with carbon ion radiotherapy. Children are treated, when available, with proton therapy, ideally with a scanned proton beam due to the reduced neutron dose delivered to out-of-target locations [106,107]. However, radiation resistant tumors with poor prognosis such as inoperable osteosarcomas, or chordomas/chondrosarcomas in critical locations without availability of a proton beam might be treated with a carbon beam within clinical study protocols in patients when curative resection is not possible, and when dose escalation or the higher RBE of carbon ions seem to have a promising impact on outcome. At GSI, a group of children and young adults was treated with carbon ion radiotherapy in cases where a proton beam treatment slot was not available, and the tumors were in critical locations and complete oncological resection was not possible [15]. Between 1997 and 2007, 394 patients were treated with carbon ion RT at GSI. Of these patients, 17 patients were aged ≤ 21 years. Seventeen of these young patients were treated for chordoma or low-grade chondrosarcoma of the skull base and were analyzed in this study. Irradiation was performed after primary diagnosis in 14 patients (82%) and for recurrent tumors in three patients (18%). A median total dose of 60 Gy E (range 60–66.6 Gy E) in a fractionation of 7×3 Gy E per week of carbon ion RT using the raster scan technique was applied. All patients were observed prospectively on a regular basis after carbon ion RT. After a median follow-up

time of 49 months, one patient with chordoma developed tumor progression at 60 months after carbon ion RT. All other patients demonstrated no signs of tumor progression during follow-up. No long-term high-grade side effects, especially no secondary malignancies, were observed [14,108].

Thus, for locally inoperable osteosarcoma, due to the dismal prognosis, this indication is currently being treated with a carbon ion boost within a prospective trial [104] at the HIT.

Discussion

Clinical data from carbon ion radiotherapy demonstrate intriguing responses depending on tumor type. Local control for several indications seems to be enhanced, while toxicity is comparably low. For some indications, the responses are directly convincing, for others, however, the benefit may be only marginal. Thus, prospective clinical trials will be required in the future to move from individual treatment decisions to real evidence-based oncology in particle treatments. The present manuscript reviews the available literature on carbon ions in various tumor regions, for several histological tumor subtypes. Taken together, however, to date, no randomized trials have shown superiority of carbon ions over protons or photons for any histology, thus only level II evidence is available. Carbon ion radiotherapy should be considered an experimental treatment, and the role in specific indications must be defined in prospective clinical trials. For example, the prototype indications are skull base chordomas and chondrosarcomas, for which several institutions have generated convincing data with proton radiotherapy. Over time, advances in photon treatments have significantly improved dose distributions in such regions. Moreover, for carbon ions, only single-institution series on outcome is available, of which some are only focused on small groups of patients. These data necessitate direct comparison of protons with carbon ions, and, perhaps, depending on the indication, also with advanced photons. Such randomized trials focusing on disease- and site-specific endpoints, such as brain stem toxicity, bowel toxicity, local control, overall survival or neurocognitive function should be initiated, specifically with respect to the individual clinical situation.

Independently of that, analysis of normal tissue toxicity, as well as molecular responses and reactions to high-LET beams must be addressed to further enhance the knowledge and broaden the clinical use of ion beams.

On the road to defining clinical indications for particle therapy, several important factors also in the field of physics and technology must be addressed.

Issue of motion management

In modern facilities, scanned particle beams are applied offering clear advantages with respect to hardware necessity, reduction of neutron dose, as well as dose distribution and application [107]. However, with moving targets, substantial interaction with the particle beam leads to disrupted dose distributions [109–111]; this interplay effect may have a detrimental impact on moving targets, and means of motion management, motion compensation or innovative treatment planning approaches are required. Technical approaches such as gating, tracking or re-scanning are being investigated; gating has been applied with scanned particle beams, and at HIT, the first patients treated with this techniques are HCC patients within the Prometheus-01 trial [82,83].

Radiobiology, patient stratification and biomarkers

Although deep insights into the biology of particle beams have been undertaken, the full potential has not been understood as yet. Therefore, analysis of radiation response in normal tissue as well as tumor tissue is required. Moreover, in the 21st century “individualized radiotherapy” based on biology and molecular characteristics is in focus. Besides modulated biology by using high-LET beams, perhaps identification of risk or stratification factors based on the individual patient could improve patient selection and subsequently outcome in the future.

Intelligent clinical trials and multicenter collaboration

Many agree that clinical trials are necessary, however, in some indications such as pediatrics randomization may not be fully feasible. Additionally, classical trial designs including many hundreds of patients may need re-thinking and modern re-design including new statistical models and calculations for smart assessment of novel radiation modalities. This might include matched pairs analyses, pooled data acquisition, or mathematical calculations based on smaller patient numbers. Joint approaches including multi-institutional concepts may help recruit sufficient numbers of patients, and bring together expertise in all required fields. With this intent, currently, several European and other projects are underway, including ULICE and the ENLIGHT consortium.

Cost and argumentation

Today, the investment cost and size of particle facilities is enormous, and some discussion on indications, especially for proton therapy, are driven by this fact. Perhaps, if facilities were smaller and

proton therapy would be more widely available, and the cost of treatment would also be lower or only slightly higher than with advanced photons, perhaps some critical issues would not be addressed in the way they are today. This holds true especially for protons, where the RBE is considered around 1.1 and thus the effects are comparable to photons. For carbon ions, however, the biological differences are somewhat more prominent and should be considered an experimental treatment, until further evidence is available. This lack of clinical evidence is fostering the generation of clinical trials of all stages; prospective ideally randomized trials are under way to elucidate these questions. This, together with advances in technology, may lead to more widespread distribution of particle therapy. In the near future particle therapy will be smaller, more cost-effective and available to more patients worldwide.

Conclusion

To date, convincing data exists showing excellent clinical results for carbon ion radiotherapy. However, no randomized trials have been conducted. This is mainly due to the lack of availability of the carbon ion beam, as well as due to the lack to randomize in one institution between high-LET particle therapy, low-LET particle therapy and advanced photon radiotherapy. The task of the future will be to perform such clinical trials in different indications, and to consolidate the knowledge about the underlying biology of high-LET beams.

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