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REVIEW ARTICLE

Particle Radiation Therapy Using Proton and Heavier Ion Beams

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A B S T R A C T

Particle beams like protons and heavier ions offer improved dose distributions compared with photon (also called x-ray) beams and thus enable dose escalation within the tumor while sparing normal tissues. Although protons have a biologic effectiveness comparable to photons, ions, because they are heavier than protons, provide a higher biologic effectiveness. Recent technologic developments in the fields of accelerator engineering, treatment planning, beam delivery, and tumor visualization have stimulated the process of transferring particle radiation therapy (RT) from physics laboratories to the clinic. This review describes the physical, biologic, and technologic aspects of particle beam therapy. Clinical trials investigating proton and carbon ion RT will be summarized and discussed in the context of their relevance to recent concepts of treatment with RT.

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INTRODUCTION

The use of protons and heavier ions was first proposed by Robert Wilson in 1946.[1] Since then, more than 48,000 patients have been treated with particle beams around the world. Most of these treatments were delivered with proton radiotherapy (RT). Currently, there are 25 operating proton therapy facilities, whereas carbon ion RT is provided at three facilities. More than 3,000 patients have been treated with carbon ions at the National Institute of Radiological Sciences (NIRS) in Chiba, Japan, since 1994, and more than 300 patients have undergone carbon ion therapy at the Gesellschaft für Schwerionenforschung (GSI) in Germany since 1997. A third carbon ion therapy facility started operation in Hyogo, Japan, in 2004.

Much interest was generated when large companies became involved in the further technologic development of particle therapy and medical insurance companies included proton therapy into their services as a reimbursable treatment modality. More than 20 hospital-based facilities are planned to be built within the next 10 years, and most of them will be based in university hospitals with a long-standing experience in modern photon RT. These facilities will be equipped with state-of-the-art technology and will set the stage for an intensification of preclinical and clinical research into this emerging field of activities.

This review aims at describing the physical and biologic properties of particle beams as well as some additional important technologic aspects. It also summarizes the results of clinical trials available so far and discusses their relevance in the context of the treatment results obtained with modern photon RT techniques.

PHYSICAL, BIOLOGIC, AND TECHNICAL ASPECTS OF PARTICLE THERAPY

Physical Aspects

Particle beams, such as proton and heavier ion beams, show an increase in energy deposition with penetration depth up to a sharp maximum at the end of their range to form the so-called Bragg peak. Almost no dose is deposited in the normal tissue beyond the Bragg peak. The particle range is determined by the energy of the incoming particles (Fig 1). Favorable dose distributions with a steep dose fall-off at the field borders and, thus, more precise dose localization can be achieved with these beams compared with photon beams. As a consequence, it seems likely that dose escalation can be performed without aggravating toxicity in surrounding normal tissues.

Biologic Aspects

The rate at which charged particles lose energy when penetrating material increases with the mass of the particle and can be quantified as linear energy transfer (LET). Protons have a higher LET than photons, but their radiobiologic properties do not differ substantially from those of photons. For clinical

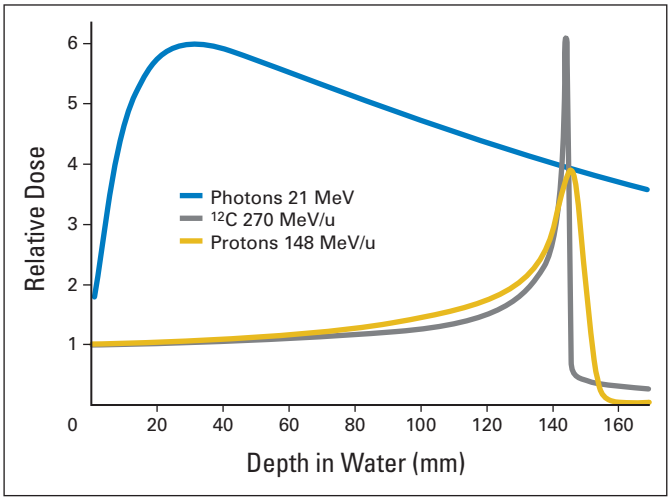

Fig 1. Depth dose profiles of photons, protons, and carbon ions.

applications, the absorbed dose is multiplied by a factor of 1.1 to express the biologic effective proton dose in cobalt gray equivalents (CGE). Heavier ions such as carbon ions share the favorable physical properties of protons but also have a biologic advantage. Their biologic efficiency increases at the end of the beam's range, whereas it is low along the entrance channel. When different clinical situations are considered, the biologic advantages of carbon ions over protons are expected to be most pronounced for tumors that demonstrate low radiosensitivity when treated with photons. This is particularly true when the tumor is surrounded by radiosensitive normal tissue. Local values for relative biologic effectiveness (RBE) can be as high as 4 for carbon ion RT and depend on many factors, which have to be addressed during treatment planning. Experiments conducted with fast neutrons and carbon ions have demonstrated that increasing the dose per fraction tends to lower the RBE of both the tumor and normal tissues. The RBE of the tumor, however, did not decrease as rapidly as the RBE of the normal tissue.[2,3] These experiments corroborate the assumption that the therapeutic ratio increases if short-course hypofractionation schemes are used in carbon ion RT. At the NIRS in Chiba, Japan, hypofractionated carbon ion RT has been investigated systematically for a variety of tumor entities, and it seems that a significant reduction of overall treatment time can be accomplished for many tumor entities without enhancing toxicity.[4]

One of the most important disadvantages of particle therapy is the high cost of its technical realization and operation. Large cyclotrons or synchrotrons are needed to accelerate protons and heavier ions to the required energy levels for the treatment of deep-seated tumors. Furthermore, high precision and reproducibility of patient positioning coupled with high-quality imaging for treatment planning are prerequisites for this type of treatment.

Technical Aspects

The physical advantages of particle beam therapy can only be properly exploited when it is possible to use multiple fields at the same level of complexity that is commonly used for modern photon treatments. Although gantries for proton therapy have been installed at several proton therapy facilities, carbon ion RT is still delivered with fixed beam lines. The particle therapy facility under construction at the Heidelberg University (Heidelberg, Germany) will be the first to be equipped with a rotating gantry for proton and carbon ion RT. The optimal design of a modern particle therapy facility, however, is actively being discussed, and future improvements in accelerator technology are very likely to influence this discussion.

Beam delivery is performed with passive methods using modulators, collimators, and compensators at most of the centers. The advantage of passive beam delivery systems is that the treatment planning for this system is simple. This approach has already been applied in many clinical situations including the treatment of moving targets. The major disadvantage is that a significant amount of the dose is also delivered along the entrance path, which often includes nontarget normal tissue. As an alternative to passive beam delivery, active beam delivery techniques, such as spot scanning or raster scanning, have been developed. At the Paul Scherrer Institute in Villigen, Switzerland, one-dimensional spot scanning is combined with the movement of the patient couch during treatment. At GSI in Darmstadt, Germany, a raster scan method is used.[5] Focused pencil beams produced in a synchrotron are deflected laterally by two magnetic dipoles, whereas the energy of the incoming beam is varied during the treatment. Thus, three-dimensional, intensity-modulated carbon ion RT can be accomplished, and the dose distribution can be tailored optimally to any irregular tumor shape without adding passive absorbers, compensators, or collimators. The dose distribution can also be conformed to the proximal edge of the target volume, and normal tissue that resides along the entrance channel of the beam can thus be spared. For both passive and active beam delivery techniques, patient immobilization and its day-to-day reproducibility need to be consistent with the high spatial accuracy achievable with particle beams. Precision head and body immobilization systems, stereotactic target localization, and image guidance with pretreatment correction of even small interfractional set-up deviations are commonly used at modern particle therapy centers. However, active beam delivery is extremely sensitive to movements of the target during treatment. Using passive beam delivery, interfractional and intrafractional movements are addressed by adding a safety margin to ensure that the clinical target volume is fully covered during treatment. For active beam delivery, adding a safety margin around the clinical target volume is not sufficient because movement of the target during the scanning process can cause regions already irradiated to again move into the path of the beam, whereas regions that have not been irradiated can escape the path of the beam. Different strategies of tumor tracking are currently being explored.[6-8] The use of an active beam delivery system also has implications in terms of the treatment planning procedure. This is because treatment planning becomes more complex, and biologic plan optimization has to be undertaken. A more detailed summary of all physical, biologic, and technologic aspects of particle therapy is given in Schulz-Ertner et al.[9]

INDICATIONS FOR PROTON AND CARBON ION RT

Proton facilities offering low-energy protons are only suited for the treatment of eye tumors, whereas deep-seated tumors need higher energies. Most of the proton therapy facilities have focused their clinical programs on pediatric tumors, skull base tumors, and head and neck tumors. In addition, some of the proton facilities in the United States have an extensive expertise in treating patients with localized prostate cancer and inoperable early-stage lung cancer. Given the

availability of beam time, tumor entities such as paraspinal tumors and other tumors in difficult-to-treat regions are sometimes accepted.

The suitability of carbon ion RT may be similar to proton therapy except for benign tumors, where expected local control rates are equally high with both protons and carbon ions. Because the main goal is to minimize the risk for secondary malignancies, proton RT is preferable compared with high-LET beam RT in most of the patients with benign lesions. Most of the patients treated with carbon ion RT have been included in prospective clinical phase I to II and phase II trials. The clinical trials were accompanied by extensive radiobiologic research programs.

Uveal Melanoma

Accepted treatment modalities for uveal melanomas include surgical eye enucleation, brachytherapy with iodine-125 (^{125}I) and rhodium-106 plaques, and RT with charged particles such as protons and helium ions. RT of uveal melanoma aims at local tumor control and eye retention. Brachytherapy is an accepted function-preserving alternative to surgery in medium-sized choroidal melanomas because episcleral plaque brachytherapy has been found to be superior to eye enucleation in the randomized Collaborative Ocular Melanoma Study[10] and in a retrospective nonrandomized comparative trial.[11]

Particle therapy with protons or helium ions has been investigated especially for tumors of the posterior segment. These tumors are often not suitable for episcleral brachytherapy. Helium ion RT improved local control and eye retention rates compared with brachytherapy with ^{125}I plaques in medium to large tumors of the posterior segment and in tumors close to the optic nerve in a prospective randomized phase III trial. However, there were more anterior segment complications.[12] In a subsequent nonrandomized dose search study, dose was progressively reduced from 80 CGE to 48 CGE.[13] After termination of the helium therapy program, proton therapy was investigated at several proton facilities. Using protons, 5-year local control rates in the range of 96% and eye retention rates between 75% and 92% were observed in prospective case series.[14-20] At most proton centers, a total dose of 60 CGE was delivered in 4 fractions. Secondary enucleations caused by radiation-induced complications, such as glaucomas, were reported in approximately 6% of the patients. To further reduce toxicity, dose reduction from 70 CGE to 50 CGE has been investigated in a prospective randomized phase III trial in patients with small- to medium-sized choroidal melanomas near the optic disc. Although local control rates did not differ, less visual field loss was observed after 50 CGE.[21] The results from two prospective nonrandomized trials investigating stereotactic photon irradiation have also been published.[22,23] In both series, local control rates of 100% were achieved with only mild subacute toxicity in the anterior eye segment. Both series had a short follow-up time, and patient numbers were small. Long-term studies are needed to confirm these results. Additionally, the effectiveness of carbon ion RT was demonstrated in a recent dose-escalation trial for large-size uveal melanomas.[24]

The results obtained from these trials (Table 1) justify the recommendation of particle therapy with protons or helium ions for uveal melanomas that cannot be treated satisfactorily with episcleral plaque

Table 1. Particle RT of Uveal Melanomas

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Egger et al[17]	2003	PSI, Switzerland	P	2,645	Proton RT	5-/10-year eye retention: 88.9%/86.2%; after optimization of technique: 100% small, 99.7% medium, 89.5% large tumors
Courdi et al[19]	1999	Nice, France	R	538	Proton RT, 57.2 CGE	LC: 89%; OS: 73.8%; metastases rate: 8%
Char et al[12]	1993	San Francisco, CA	Phase III	184	Helium-ion RT *v* ^{125}I BT; maximum diameter < 15 mm; thickness < 10 mm	Recurrence/eye enucleation rate higher after BT, but more anterior segment complications after helium-ion RT
Fuss et al[18]	2001	LLUMC, United States	R	78	Proton RT; medium and large tumors	5-year LC: 90.5%
Dendale et al[14]	2006	CPO, France	R	1,406	Proton RT, 60 CGE	5-year LC: 96%; 5-year OS: 79%
Gragoudas et al[21]	2000	MGH, Boston, MA	Phase III	188	Proton RT, 50 CGE *v* 70 CGE; small- and medium-sized tumors, near optic disc or macula	No difference for LC, less visual field loss after 50 CGE
Desjardins et al[20]	2003	Paris, France	R, 2 arms	1,272	^{125}I BT for small anterior tumors; protons for tumors at equator and posterior equator < 12 mm	5-year LC: 96% (protons) *v* 96.25% (^{125}I)
Castro et al[13]	1997	San Francisco, CA	P	347	Helium-ion RT, 48-80 CGE; dose search trial	5-year LC: 96%; 5-year OS: 80%; at 48 CGE, 5-year LC: 87%
Damato et al[15]	2005	Liverpool, United Kingdom	P	88	Proton RT, 53.1 CGE; iris melanoma	4-year LC: 96.7%
Hocht et al[16]	2004	Berlin, Germany	P	245	Proton RT, 60 CGE	3-year LC: 95.5%; 3-year eye retention: 87.5%
Tsujii et al[24]	2006	NIRS, Japan	P	57	Carbon RT, 60-85 GyE; dose-escalation trial; large tumors	3-year LC: 97.4%; 3-year eye retention: 91.1%; 3-year OS: 88.2%

Abbreviations: RT, radiotherapy; PSI, Paul Scherrer Institut; P, prospective nonrandomized; R, retrospective nonrandomized; CGE, cobalt gray equivalents; LC, local control; OS, overall survival; phase III, prospective randomized phase III trial; ^{125}I, iodine-125; BT, brachytherapy; LLUMC, Loma Linda University Medical Center; CPO, Centre de Protontherapie d'Orsay; MGH, Massachusetts General Hospital Boston; NIRS, National Institute of Radiological Sciences, Chiba, Japan; GyE, gray equivalents.

brachytherapy because of their thickness or vicinity to the optic nerve. Results with precision photon and carbon ion RT are preliminary.

Pediatric Tumors

The reduction in integral dose to normal tissue achieved with proton RT is assumed to be most beneficial for the treatment of pediatric tumors because the risk for secondary malignancies is expected to be reduced compared with photon RT. The physical advantages of proton beams in minimizing the dose to normal tissue have been demonstrated in a number of plan intercomparisons.[25,26] Furthermore, proton RT has been investigated in a prospective phase I to II trial and a number of retrospective case series for different pediatric tumors[27-32] (Table 2). Outcomes after proton RT compare favorably with the results reported for precision photon RT, but follow-up periods were not sufficient to completely assess late toxicity after both RT modalities. However, randomized clinical phase III trials comparing proton RT versus precision photon RT are not considered reasonable because it is unlikely that photon RT will achieve better outcomes or a reduction in toxicity. Marginal misses are not expected to occur more often after proton RT as long as the clinical target volume concepts are not altered, safety margins included in the planning target volume are appropriate with respect to target movement, and patient alignment is checked and optimized before each irradiation. As long as modern delivery techniques are used, intensity-modulated actively delivered proton RT will always deliver less dose to normal nontarget tissue than photon intensity-modulated RT (IMRT) for most of the indications in pediatric radiation oncology.[33] The question is whether sparing of normal tissue from medium- to low-dose exposure will lead to a measurable clinical benefit. A long follow-up period should be considered a necessary component of any trial investigating this end point, and the continuous medical and technologic progress with particle therapy makes it unlikely that such trials will be organized.

Skull Base and Intracranial Tumors

Skull base chordomas and low-grade chondrosarcomas. Surgery is the mainstay for treatment of skull base chordomas and chondrosarcomas. Complete resections are, however, rarely achieved in the skull base region because of the vicinity to vulnerable normal tissue structures. After incomplete resection, adjuvant high-dose RT is recommended because a dose-response relationship has been proposed. Prospective randomized phase III trials comparing protons or carbon ions with precision photon RT have never been conducted because the needed high tumor doses cannot be reached with acceptable toxicity using photons. Colli and Al-Mefty[34] published a retrospective analysis of nonrandomized treatment groups treated with protons or photons and found that chordoma patients treated with protons had a significantly higher local control probability. The applicability of this article to 2006, however, is limited because the comparison did not include patients treated with precision photon RT. Consistent data are available from a number of retrospective case series for chordomas and chondrosarcomas[35-44] (Tables 3 and 4). The variance of local control rates between the different proton centers is significant and might be a result of patient bias and differences in the proton therapy techniques used. Although improvements have been achieved with proton RT, it has been pointed out that long-term outcome in the case of chordoma is quite unsatisfactory, with a number of local recurrences occurring even after 5 years of treatment.[45]

Carbon ion RT showed good effectiveness in patients with skull base chordomas and chondrosarcomas as well. At GSI, cumulative local control and overall survival rates at 4 years were 74% and 86%, respectively, for chordomas and 87% and 100%, respectively, for chondrosarcomas. Severe late toxicity was observed in less than 5% of all patients, whereas overall treatment time could be significantly reduced to 3 weeks (Tables 3 and 4).[43,44]

Taking into consideration the available data on proton and carbon ion RT in patients with chordomas and chondrosarcomas and the limited effectiveness of modern photon RT, postoperative high-dose particle therapy is considered to be the treatment of choice for these tumors. Randomized phase III trials comparing proton and carbon ion RT are not available.

Other skull base and brain tumors. Proton RT has also been investigated for other malignant and benign tumors of the brain and

Table 2. Proton RT in Pediatric Tumors

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Yock et al[27]	2005	MGH, Boston, MA	R	7	Proton RT + standard chemotherapy; orbital rhabdomyosarcoma	LC comparable to photon trials, but dose to normal tissue can be reduced
McAllister et al[28]	1997	LLUMC, United States	R	28	Proton RT; pediatric brain, head, and neck tumors	Low acute toxicity
Habrand et al[29]	1999	CPO, France	R	8	Proton RT; pediatric CNS tumors	4 of 8 patients had treatment-related late toxicity
Yuh et al[30]	2004	LLUMC, United States	P	3	Proton RT; craniospinal RT; medulloblastoma	Elimination of exit dose, reduction of toxicity in children with a history of myelosuppression
Hug et al[31]	2002	LLUMC, United States	R	27	Proton RT, 50.4-63 CGE; low-grade astrocytoma	Mean follow-up: 3.3 years; control rates comparable to photon RT; mild toxicity
Hug et al[32]	2002	MGH, Boston, MA	R	29	Proton RT or photons + protons; chordoma, n = 10; chondrosarcoma, n = 3; RMS, n = 4; other sarcoma, n = 3; benign tumors, n = 9	Mean follow-up: 40 months; 5-year LC: 72%; 5-year OS: 56%; severe late effects: 7%

Abbreviations: RT, radiotherapy; MGH, Massachusetts General Hospital Boston; R, retrospective nonrandomized; LC, local control; LLUMC, Loma Linda University Medical Center; P, prospective trial; CPO, Centre de Protontherapie d'Orsay; CGE, cobalt gray equivalents; RMS, rhabdomyosarcoma.

Table 3. Particle Therapy of Skull Base Chordomas

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Colli and Al-Mefty[34]	2001	Sao Paulo, Brazil	R	53	Protons *v* conventional RT	4-year LC: 90.9% *v* 19.4%
Noel et al[35]	2005	CPO, France	P	100	Photons + protons, 67 CGE	4-year LC: 53.8%; 5-year OS: 80.5%
Weber et al[36]	2005	PSI, Switzerland	R	18	Proton RT, 74 CGE	3-year LC: 87.5%; 3-year OS: 93.8%; 3-year complication-free survival: 82.2%
Igaki et al[37]	2004	Tsukuba, Japan	R	13	Proton RT or protons + photons,72 CGE	5-year LC: 46%; 5-year OS: 66.7%
Castro et al[38]	1994	LBL, United States	R	53	Helium/neon ions, 65 CGE	5-year LC: 63%
Terahara et al[39]	1999	MGH, Boston, MA	R	115	Proton RT, 68.9 CGE	5-year LC: 59%; 10-year LC: 44%
Hug et al[40]	1999	LLUMC, United States	R	33	Proton RT, 70.7 CGE	5-year LC: 59%
Schulz-Ertner et al[43]	2004	GSI, Germany	P	44	Carbon ion RT, 60 CGE	4-year LC: 74%; 4-year OS: 86%

Abbreviations: RT, radiotherapy; R, retrospective nonrandomized; LC, local control; CPO, Centre de Protontherapie d'Orsay; P, prospective trial; CGE, cobalt gray equivalents; OS, overall survival; PSI, Paul Scherrer Institute; LBL, Lawrence Berkeley Laboratory; MGH, Massachusetts General Hospital Boston; LLUMC, Loma Linda University Medical Center; GSI, Gesellschaft für Schwerionenforschung.

skull base such as pituitary adenomas, vestibular schwannomas, gliomas, and craniopharyngiomas (Table 5).[46-59] Most of the available data was retrospectively analyzed, and local control rates achieved with proton RT were comparable to rates achieved with modern photon RT modalities such as fractionated stereotactic RT. The observation times in almost all case series are too short to rule out late toxicity. Although the advantage of minimizing low-dose exposure to normal tissue seems likely to be important for the pediatric population, the issue of finding a measurable benefit in adult patients remains controversial.

Prostate

Proton RT was investigated in a prospective phase III trial at the Massachusetts General Hospital in Boston for 202 patients with locally advanced stage T3-4N0-2M0 prostate cancer. Patients were randomly assigned to receive a total dose of 77.2 CGE with a combination of photons and protons (arm 1) or 67.2 Gy with photon RT alone (arm 2). A significant improvement in local control by dose escalation could only be identified for poorly differentiated tumors.[60] Another randomized phase III trial was initiated to investigate dose escalation with proton RT for T1-2b tumors. Results of this study are still being awaited and will have to be measured against results obtained most recently with modern photon IMRT.[61] The main question is whether proton RT permits higher radiation doses to the prostate at the same toxicity level as photon IMRT. Taking into consideration that the safety margin around the prostate has to account for possible movements of the prostate during RT, dose escalation to the prostate will be associated with dose escalation to the anterior rectal wall. It is obvious that the advantage of proton RT, if there is any, is very small, and high patient numbers will be needed to prove a clinical benefit in a randomized phase III trial comparing proton RT with photon IMRT.

The rationale to use carbon ion RT for the treatment of prostate cancer patients is that prostate cancer cells are assumed to have a low radiosensitivity against photon RT represented by relatively low α/β values in the range of 1.5 Gy, whereas a somewhat higher radiosensitivity is assumed for dose-limiting late reactions of the rectal wall.[62] At NIRS, hypofractionated carbon ion RT has been evaluated, and the optimal dose for carbon ion RT of prostate cancer has been determined to be 66 CGE in 20 fractions over 5 weeks.[63,64] A subsequent prospective phase II trial provided evidence that carbon ion RT at this dose level is highly effective in the treatment of prostate cancer patients with high risk for local recurrence, and late toxicity rates were low.[65] However, a comparison with photon IMRT data must be drawn with caution because regular hormone therapy was not administered in most of the modern photon IMRT series published so far. Detailed information on published retrospective and prospective proton and carbon ion RT trials is listed in Table 6.[60,63-70]

Lung

Surgical resection is the treatment of choice for localized non–small-cell lung cancer (NSCLC). Primary photon RT is considered in medically inoperable patients, and dose escalation within the target volume might improve local control probability. Fractionated proton

Table 4. Particle Therapy of Skull Base Chondrosarcoma

Study	Year	Institute	Study Type	No. of Patients	RT Modality	LC Rates (%)
Weber et al[36]	2005	PSI, Switzerland	R	11	Proton RT, 68 CGE	3 years: 100
Hug et al[40]	1999	LLUMC, United States	R	25	Proton RT, 70.7 CGE	5 years: 75
Rosenberg et al[41]	1999	MGH, Boston, MA	R	200	Protons + photons, 72.1 CGE	5 years: 98
Castro et al[38]	1994	LBL, United States	R	27	Helium and neon ions, 65 CGE	5 years: 78
Noel et al[42]	2003	CPO, France	P	18	Protons + photons, 67 CGE	3 years: 85
Schulz-Ertner et al[44]	2007	GSI, Germany	P	54	Carbon ion RT, 60 CGE (BED, 75 CGE)	4 years: 89.8

Abbreviations: RT, radiotherapy; LC, local control; PSI, Paul Scherrer Institute; R, retrospective nonrandomized; CGE, cobalt gray equivalents; LLUMC, Loma Linda University Medical Center; MGH, Massachusetts General Hospital Boston; LBL, Lawrence Berkeley Laboratory; CPO, Centre de Protontherapie d'Orsay; P, prospective trial; GSI, Gesellschaft für Schwerionenforschung; BED, biologic equivalent dose.

Table 5. Particle Therapy in Meningiomas, Vestibular Schwannomas, Craniopharyngiomas, Pituitary Adenomas, and Gliomas

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Meningioma						
Noel et al[48]	2005	CPO, France	R	51	Photons + protons, 60.6 CGE	4-year LC: 98%; 4-year OS: 100%; 2 of 51 patients had grade 3 late toxicity
Noel et al[51]	2002	CPO, France	R	17	Photons + protons, 61 CGE	4-year LC: 87.5%; 4-year OS: 88.9%
Vernimmen et al[52]	2001	Tygerberg, South Africa	R	27	Proton RT	LC: 88%; 13% permanent neurologic deficits
Wenkel et al[53]	2000	MGH, Boston, MA	R	46	Protons + photons, 59 CGE	10-year OS: 77%; 10-year LC: 88%; 10-year severe toxicity free: 80%
Hug et al[54]	2000	MGH, Boston, MA	R; historical control arm	31	Protons + photons; 62 CGE for AM; 58 CGE for MM	8-year LC: AM 19%, MM 17%; significantly better outcome for proton RT dose $\geq$ 60 Gy
Weber et al[56]	2004	PSI, Switzerland	R	16	Proton RT, 52.2-64 CGE	3-year LC: 91.7%; 3-year OS: 92.7%; 3-year toxicity-free survival: 76.2%; 3 of 16 patients had grade 3-4 late toxicity
Gudjonsson et al[59]	1999	Uppsala, Sweden	R	19	Proton RT, 24 CGE, 4 fractions	3-year LC: 100%
Vestibular schwannoma						
Weber et al[50]	2003	MGH, Boston, MA	R	88	Stereotactic proton radiosurgery, 12 CGE	5-year LC: 93.6%; 5-year normal facial/trigeminal nerve function rate: 91.1%/89.4%; 33.3% serviceable hearing
Bush et al[57]	2002	LLUMC, United States	R	31	Proton RT, 54-60 CGE	LC: 100%; 31% useful hearing maintained; no toxicity to facial and trigeminal nerves
Craniopharyngioma						
Luu et al[58]	2006	LLUMC, United States	R	16	Proton RT, 50.4-59.4 CGE	LC: 14 of 15 patients; late toxicity: panhypopituitarism, cerebrovascular accident, out-of-proton field meningioma
Fitzek et al[46]	2006	MGH, Boston, MA	R	15	Photons + protons, 56.9 CGE	10-year LC: 85%; 10-year OS: 72%
Pituitary adenoma						
Ronson et al[47]	2006	LLUMC, United States	R	47	Protons, 54 CGE	Local progression in 3 of 47 patients; $<$ 10% severe late toxicity
Glioma						
Fitzek et al[55]	1999	MGH, Boston, MA	P	23	Photons + protons, 90 CGE; glioblastoma multiforme	2-/3-year OS: 34%/18%; radiation necrosis in 7 of 23 patients
Fitzek et al[49]	2001	MGH, Boston, MA	P	20	Protons + photons; dose escalation; glioma WHO stage II, 68.2 CGE; glioma WHO stage III, 79.7 CGE	5-year OS: 71% for WHO stage II, 23% for WHO stage III; high rate of radionecrosis

Abbreviations: RT, radiotherapy; CPO, Centre de Protontherapie d'Orsay; R, retrospective nonrandomized; CGE, cobalt gray equivalents; LC, local control; OS, overall survival; MGH, Massachusetts General Hospital Boston; AM, atypical meningioma; MM, malignant meningioma; PSI, Paul Scherrer Institute; LLUMC, Loma Linda University Medical Center; P, prospective trial.

and carbon ion RT was evaluated for localized lung cancer in three prospective nonrandomized case series[71-73] and in two retrospective analyses published more recently.[74,75] After proton RT, 5-year in-field control rates of 89% and 39% were observed for stage IA and stage IB NSCLC, respectively; overall survival rates for these two groups were 70% and 16%, respectively.[74] Similar results were found in the other proton trials (Table 7). In a prospective phase I to II dose-escalation trial, the optimal dose fractionation scheme for carbon ion RT in stage I NSCLC was determined to be 68.4 to 79.2 CGE administered in 9 fractions. Five-year local control rate was 84%, and three of 81 patients developed grade 3 pneumonitis.[72] Respiratory gating and image-guided RT are currently being integrated into modern photon RT and particle therapy to allow for further sparing of normal lung tissue.[7,8] So far, there are no data available comparing proton and carbon ion RT with modern stereotactic photon RT. A comparative study is particularly warranted in the treatment of large T2 tumors.

Hepatocellular Carcinoma

RT of hepatocellular carcinoma (HCC) is a treatment option for inoperable tumors. Damage to the liver parenchyma is considered to be the dose-limiting toxicity. Effectiveness of proton RT in HCC has been demonstrated in two retrospective case series[76,77] and in one prospective nonrandomized case series.[78] Five-year local control and overall survival rates obtained with proton RT were in the range of 86.9% to 87.8% and 23.5% to 55.6%, respectively. Toxicity was low, but coexisting liver cirrhosis was found to affect overall survival.[76,77]

Table 6. Particle Therapy for Prostate Cancer

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Slater et al[66]	2004	LLUMC, United States	R	1,255	Proton RT, 74-75 CGE; localized prostate cancer	DFS comparable with other forms of local therapy, minimal morbidity
Yonemoto et al[67]	1997	LLUMC, United States	P; phase I/II	106	Photons, 45 Gy pelvis + protons, 30 CGE prostate	2-year grade 1-2 toxicity: 12%; no grade 3-4 toxicity; 2-year PSA normalization: 96% (PSA 4-10 ng/mL), 97% (PSA 10-20 ng/mL), 63% (PSA > 20 ng/mL); 2.8% local recurrence
Nihei et al[68]	2005	NCCHE, Japan	P; phase II, one arm	30	Photons, 50 Gy prostate/vesicles + proton boost, 26 CGE; T1-3N0M0 prostate cancer	Late grade 2 toxicity; GU: 10%; GI: 10%; no late toxicity > grade 2; biochemical relapse in six of 30 patients
Zietman et al[69]	2005	MGH, Boston, MA	P; randomized phase III	393	Photon RT, 70.2 Gy *v* photon + proton RT, 79.2 CGE; T1b-2b, PSA < 15 ng/mL	5-year bDFS: 61.4% (photons) *v* 80.4% (photons + protons); late toxicity > grade 2: 2% *v* 1%
Slater et al[70]	1999	LLUMC, United States	R	119	Protons or protons + photons, 74-75 CGE; prostate cancer T1-2b, PSA < 15 mg/mL	5-year bDFS: 88%; no severe toxicity; biochemical control rates comparable to radical prostatectomy; no significant toxicity
Shipley et al[60]	1995	MGH, Boston, MA	P; randomized phase III trial	202	Photons, 67.2 Gy *v* photons, 50.4 Gy + perineal proton boost, 25.2 CGE; T3-4 prostate cancer	Median follow-up: 61 months; improved LC only in patients with poorly differentiated tumors treated with high-dose RT; grade 1-2 rectal bleeding rate significantly higher in the high-dose arm (32% *v* 12%) as well as urethral stricture (19% *v* 8%)
Akakura et al[63]	2004	NIRS, Japan	P; nonrandomized dose-escalation trial; phase I/II	96	Carbon ion RT, 54-72 CGE; T1b-3 localized prostate cancer ± hormonal treatment	5-year bDFS: 82.6%; optimal dose level: 66 CGE
Tsuji et al[64]	2005	NIRS, Japan	Summary of results from phase I/II and phase II trials (1995-2003)	201	Hypofractionated carbon ion RT, 66 CGE; localized prostate cancer, hormonal therapy in high-risk patients	5-year bDFS: 83.2%; no toxicities > grade 2; grade 2 GU toxicity: 6%; grade 2 GI toxicity: 1%
Ishikawa et al[65]	2006	NIRS, Japan	P; phase II (2000-2003)	175	Carbon ion RT, 66 CGE; low-risk PC (stage < T2b + PSA < 20 ng/mL, Gleason score < 7), n = 33; high-risk PC (PSA ≥ 20, Gleason score ≥ 7, stage ≥ T2b), n = 142; androgen deprivation therapy	4-year bDFS: 87% overall; low risk, 87%; high risk, 88%; 4-year OS: 91%; late toxicity grade 2: GI, 2%; GU, 6%; no grade 3 late toxicity

Abbreviations: RT, radiotherapy; LLUMC, Loma Linda University Medical Center; R, retrospective; CGE, cobalt gray equivalents; DFS, disease-free survival; P, prospective; PSA, prostrate-specific antigen; NCCHE, National Cancer Center Hospital East, Chiba, Japan; GU, genitourinary; MGH, Massachusetts General Hospital Boston; bDFS, biochemical disease-free survival; LC, local control; NIRS, National Institute of Radiological Sciences, Chiba, Japan; PC, prostate cancer; OS, overall survival.

Carbon ion RT yields local control with overall survival rates comparable to proton RT.[79] Experience in the treatment of HCC has been accumulated mainly in Japanese centers, but there is increasing interest at other institutes as well.

Head and Neck Tumors

Two retrospective analyses[80,81] (Table 8) investigated the use of proton RT as a boost technique delivered in combination with photons to treat patients with locally advanced head and neck cancer. The role of proton RT in relation to modern photon IMRT in the treatment of locally advanced head and neck tumors still remains undefined. Dose escalation within the macroscopic tumor can also be achieved with photon IMRT using an integrated boost concept.

Carbon ion RT has been found to offer radiobiologic advantages in non–squamous cell tumors such as adenocarcinomas, adenoid cystic carcinomas, and malignant melanomas in prospective dose-escalation trials.[82] At GSI, a clinical phase I to II trial investigated combined photon IMRT and a carbon ion boost in the treatment of locally advanced adenoid cystic carcinomas. Locoregional control rates for the combined photon IMRT and carbon ions were better than the locoregional control rates observed in a historical series of patients treated with photon IMRT alone. However, the difference was not statistically significant at the time of analysis.[83]

Bone Tumors

Patients with bone tumors, mainly osteosarcomas, chondrosarcomas, and chordomas, were treated within a dose-escalation trial at the NIRS. Cumulative local control and overall survival rates were 73% and 46%, respectively, at 3 years, but patient numbers (especially for the soft tissue sarcoma subgroup) were small, and these results do not allow for definitive conclusions.[84] Imai et al[85] retrospectively analyzed the subgroup of sacral chordomas treated with carbon ion RT. A high local control rate of 96% was found, and recurrences developing more than 2 cm away from the planning target volume were

Table 7. Particle Therapy in Localized NSCLC

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Shioyama et al[74]	2003	Tsukuba, Japan	R	51	Proton RT, median dose: 76 CGE; NSCLC stage I-IV	5-year OS: overall, 29%; IA, 70%; IB, 16%; 5-year in-field control: IA, 89%; IB, 39%
Bush et al[71]	1999	LLUMC, United States	P	37	Photon RT mediastinum, 45 Gy + proton boost to gross tumor, 28.8 CGE, or proton RT alone; NSCLC stage I-IIIA, inoperable and patients refusing surgery	Two of 37 patients had pneumonitis; 2-year DFS: 63%; 2-year DFS: 86% in stage I patients; 2-year LC: 87%; results comparable to conventional photon data
Miyamoto et al[72]	2003	NIRS, Japan	P; 2 phase I/II dose-escalation trials	81	Carbon ion RT: 59.4-95.4 CGE, 18 fractions in first trial; 68.4-79.2 CGE, 9 fractions in second trial; NSCLC stage I	Grade 3 pneumonitis with full recovery in three of 81 patients; 5-year OS: 42%; local recurrence rate 23.2%; local control: 64% (18 fractions) and 84% (9 fractions)
Nihei et al[75]	2006	NCCHE, Japan	R	37	Proton RT, 70-94 CGE (20 fractions); NSCLC stage I	2-year OS: 84%; 2-year locoregional control: 80% (stage IA: 79%; stage B: 60%); late grade 2-3 pneumonitis in six of 37 patients
Miyamoto et al[73]	In press	NIRS, Japan	P	50	Carbon ion RT, 72 GyE in 9 fractions	5-year LC: 94.7%; 5-year OS: 50% (cause-specific: 75.7%)

Abbreviations: NSCLC, non-small-cell lung cancer; RT, radiotherapy; R, retrospective; CGE, cobalt gray equivalents; OS, overall survival; LLUMC, Loma Linda University Medical Center; P, prospective; DFS, disease-free survival; LC, local control; NIRS, National Institute of Radiological Sciences, Chiba, Japan; NCCHE, National Cancer Center Hospital East, Chiba, Japan.

defined as distant failures. This definition makes it difficult to compare the data with other sacral and spinal chordoma series using high-dose proton RT and other charged particles[84-88] (Table 9). Nevertheless, the results obtained with carbon ions alone provide evidence that carbon ion doses between 70.4 and 74 CGE are highly effective in controlling chordoma cells within the target volume. Further investigation into carbon ion RT in the treatment of sacral chordomas is therefore warranted.

Other Malignant Tumors

Carbon ion RT was also found to be effective in locally advanced carcinomas of the uterine cervix in initial dose-escalation trials. Local control rates were encouraging, especially in patients with stage IVA tumors,[89] but simultaneous chemotherapy has not been delivered, and patient numbers are still small.[90] Effectiveness of dose escalation with proton RT in the treatment of esophageal cancer has been shown in two retrospective case series,[91,92] but prospective trials and randomized trials are missing.

Other Benign Lesions

Radiosurgery is an accepted treatment option for inoperable intracranial arteriovenous malformations with a high risk of bleeding. Radiosurgery with photon beams or gamma knife radiosurgery is

Table 8. Particle Therapy of Head and Neck Tumors

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Slater et al[80]	2005	LLUMC, United States	R	29	Accelerated photon + proton radiation, 75.9 CGE; stage II-IV oropharyngeal cancer	5-year locoregional control: 84%; late grade 3 toxicity in three of 29 patients
Tokuuye et al[81]	2004	Tsukuba, Japan	R	33	Proton RT or protons + photons, 76 CGE; primary RT of head and neck tumors	5-year LC: 74%; 5-year OS: 44%; acute grade 3 toxicity: 3%; late grade 3 toxicity: 18%
Mizoe et al[82]	2004	NIRS, Japan	P; phase I/II dose escalation	36	Carbon ion RT; group A: 48.6-70.2 CGE, 18 fractions, 6 weeks; group B: 52.8-64 CGE, 16 fractions, 4 weeks; locally advanced head and neck tumors	5-year LC: 100% in malignant melanoma, salivary gland tumors and ear; 50% in adenoid cystic carcinoma; 34% in squamous cell carcinoma
Schulz-Ertner et al[83]	2005	GSI, Germany	Nonrandomized; comparison of results of 2 prospective phase I/II trials	63	Arm A: combined photon IMRT, 54 Gy + carbon ion boost, 18 CGE; arm B: photon IMRT alone, 66 Gy; locally advanced adenoid cystic carcinomas of the skull base, macroscopic tumor	4-year locoregional control: 77.5% in arm A *v* 24.6% in arm B; 4-year OS: 75.8% in arm A *v* 77.9% in arm B; severe late toxicity $< 5\%$ in both groups

Abbreviations: RT, radiotherapy; LLUMC, Loma Linda University Medical Center; R, retrospective; CGE, cobalt gray equivalents; LC, local control; OS, overall survival; NIRS, National Institute of Radiological Sciences, Chiba, Japan; P, prospective; GSI, Gesellschaft für Schwerionenforschung, Darmstadt, Germany; IMRT, intensity-modulated radiotherapy.

Table 9. Particle Radiation Therapy in Paraspinal and Sacral Bone Tumors

Study	Year	Institute	Study Type	No. of Patients	RT Modality	Results
Kamada et al[84]	2002	NIRS, Japan	P	57	Carbon ion RT, 52.8-73.6 CGE, 16 fractions; dose-escalation trial; unresectable bone and soft tissue sarcomas (osteosarcoma, chordoma, chondrosarcoma, MPNST, MFH, liposarcoma, and others)	3-year LC: 73%; 3-year OS: 46%; maximum-tolerated dose: 73.6 CGE
Imai et al[85]	2004	NIRS, Japan	R	30	Carbon ion RT, 52.8-73.6 CGE; unresectable sacral chordoma	5-year LC: 96%; 5-year OS: 52%
Schoenthaler et al[86]	1993	LBL, United States	R	14	Helium and neon ion RT, 75.65 CGE; sacral chordoma	5-year LC: 55%; 5-year OS: 85%
Park et al[87]	2006	MGH, Boston, MA	R	27	Protons + photons; sacral chordoma	LC after surgery + RT: 12 of 14 patients with primary tumors; one of seven patients with recurrent tumors; LC after RT alone: three of four patients who received $\geq$ 73 CGE
Hug et al[88]	1995	MGH, Boston, MA	R	47	Protons + photons, 55.3-82 CGE; osteogenic and chondrogenic tumors of the axial skeleton	5-year LC: 100% chondrosarcoma, 53% chordoma, 59% osteogenic sarcoma, 76% other bone tumors; 5-year OS: 50% chordoma, 100% chondrosarcoma, 44% osteogenic sarcoma, 87% other bone tumors

Abbreviations: RT, radiotherapy; NIRS, National Institute of Radiological Sciences, Chiba, Japan; P, prospective trial; CGE, cobalt gray equivalents; MPNST, malignant peripheral nerve sheath tumor; MFH, malignant fibrous histiocytoma; LC, local control; OS, overall survival; R, retrospective nonrandomized; LBL, Lawrence Berkeley Laboratory; MGH, Massachusetts General Hospital Boston.

associated with a low rate of late toxicity as long as the normal brain tissue contained within the high-dose region is minimized. The rationale for using protons instead of photons or gamma knife radiosurgery is that normal brain volume can be better spared, thus allowing higher total doses to the target volume. For targets of similar size, obliteration and toxicity rates obtained with hypofractionated proton RT[93,94] are comparable to the results reported for photon radiosurgery.[95] Long-term toxicity data and randomized studies comparing proton and photon radiosurgery are not available.

The effectiveness of proton RT in the treatment of age-related macular degeneration is being discussed but remains controversial. Although single proton doses between 8 and 14 CGE were found to be effective in preserving visual acuity in three prospective nonrandomized case series,[96-98] the effectiveness of proton RT has never been proven in a randomized trial. Negative results from four of five prospective, double-masked, randomized trials comparing photon RT with observation or sham treatment constitute a high grade of evidence.[99-102] Preservation of visual acuity was found to be significantly better only in one randomized trial comparing photon RT (4×6 Gy) with observation.[103] However, the follow-up period in this trial was too short to be sure that the initial effect will not be neutralized by radiation-induced toxicity at a later time. A randomized phase III trial comparing results after proton RT with observation and sufficient follow-up would be needed to prove the effectiveness of proton RT in preserving visual acuity in patients with age-related macular degeneration.

DISCUSSION AND FUTURE DIRECTIONS

Particle therapy with protons and heavier ion beams offers physical and, in the case of carbon ions, biologic advantages compared with photon RT. Particle therapy, however, is more complex and cost intensive, and trained staff is needed to ensure high quality and safety of its clinical application. To transfer this new RT modality from the physics laboratory to routine clinical use, it is necessary to prove the superiority of particle RT over photon RT in terms of direct patient benefit. For particle therapy to gain widespread applicability, recent and future achievements and developments in the fields of molecular biology, targeted therapy, imaging, and radiation technology must be fully integrated into the particle therapy process before any meaningful comparison can be made with photon therapy. One example is the use of online image guidance for daily adjustment of the patient's setup. The potential of particle therapy can only be exploited if a full integration of particle therapy into clinical environments and interdisciplinary treatment strategies is sought and if new medical and technologic advances are properly incorporated into the total treatment process.

Several prospective trials with high patient numbers, as well as one prospective randomized phase III trial comparing helium RT with brachytherapy, provide scientifically sound evidence that proton RT is superior to conventional RT in the treatment of uveal melanomas not manageable with brachytherapy. Pediatric tumors are considered a clear indication for proton RT because a reduction of dose deposition in nontarget tissue is believed to reduce the risk of secondary malignancies. If prospective trials with small patient numbers and retrospective trials with large patient numbers are included and a reduction in evidence quality is accepted, effectiveness of proton RT can be postulated for specific skull base tumors such as chordomas, chondrosarcomas, and malignant and atypical meningiomas. Carbon ion RT yielded at least comparable results in chordomas and chondrosarcomas of the skull base in a prospective nonrandomized trial.

The role of proton RT in the treatment of prostate cancer, early-stage lung cancer, arteriovenous malformation, HCC, paraspinal tumors, and skull base tumors not mentioned earlier remains unclear because similar treatment results have been reported for modern photon techniques such as IMRT or stereotactic photon RT. The same holds true for carbon ion RT, which was found to be effective in a number of prospective nonrandomized trials for non–squamous cell head and neck tumors, locally advanced adenoid cystic carcinomas, prostate cancer, lung cancer, HCC, and locally advanced bone and soft tissue tumors.

Controlled clinical trials comparing particle therapy with modern photon RT are strongly needed. However, these trials must be planned very carefully and should also assess toxicity and cost parameters.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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