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Particle therapy in the future of precision therapy

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ABSTRACT

The first hospital-based treatment facilities for particle therapy started operation about thirty years ago. Since then, the clinical experience with protons and carbon ions has grown continuously and more than 200,000 patients have been treated to date. The promising clinical results led to a rapidly increasing number of treatment facilities and many new facilities are planned or under construction all over the world. An inverted depth-dose profile combined with potential radiobiological advantages make charged particles a precious tool for the treatment of tumours that are particularly radioresistant or located nearby sensitive structures. A rising number of trials have already confirmed the benefits of particle therapy in selected clinical situations and further improvements in beam delivery, image guidance and treatment planning are expected. This review summarises some physical and biological characteristics of accelerated charged particles and gives some examples of their clinical application. Furthermore, challenges and future perspectives of particle therapy will be discussed.

BACKGROUND

Only a few decades after the first patient treatment with X-rays, another type of radiation has slowly found its way into cancer treatment: particle beams. Back in 1929, Ernest Orlando Lawrence and M.S. Livingston picked up the idea of linear particle accelerators already described by Rolf Widerøe and extended it to a more compact and powerful circular accelerator: the cyclotron.¹ In 1934, E.O. Lawrence patented the first cyclotron at the University of California in Berkeley.² Together with his brother John Lawrence, who was both a physicist and a physician, he conducted first experiments on rats with accelerated particles in 1936. They used fast neutrons, produced by shooting a beryllium target with accelerated deuterons.³ Two years later, in 1938, fast neutrons were used for the first time to treat patients with malignant disease.⁴ However, treatment with fast neutrons will only gain limited acceptance in the following decades, since the biological advantages are accompanied by heavier side-effects, due to unfavourable depth-dose distributions. This ultimately led to a significant decrease of clinical application since the 1990's.⁵⁻⁷

In 1946, R.R. Wilson suggested for the first time to use accelerated protons in radiotherapy. He investigated the

depth-dose profile of protons produced at the cyclotron in Berkeley and observed a steep increase of energy deposition at the end of the particle range, known as Bragg peak.⁸ In the same year, simultaneous descriptions of phase stability by Veksler and McMillan enabled further improvements in accelerator technology with the introduction of synchrocyclotrons, isochronous cyclotron and finally synchrotrons. The first proton synchrotron was designed in 1952 by Sir M. Oliphant.⁹

Proton and deuteron beams were used for the first time on animal tissue at the Lawrence Radiation Laboratory in Berkeley.¹⁰ In 1958, the same group reported on the first clinical use of accelerated protons: 26 patients with advanced breast cancer received 340 MeV proton beam therapy to the pituitary gland for hormone suppression in a palliative intention.¹¹ In the following decades, several proton therapy programs expanded and clinical application was further investigated, notably at the Harvard Cyclotron Laboratory in Boston and at the Gustaf Werner Institute in Uppsala, Sweden. The accelerator facilities used had initially been developed for nuclear physics programs, therefore they only had little beam time dedicated to medical purposes and the beam lines were not ideal for

Figure 1. Plan of the HIT Center in Germany. This hospital-based facility can treat patients with protons and heavy ions. Particles are accelerated in a synchrotron (at the back left) and three rooms are available for patient treatment (red arrows). The third treatment room on the right features a heavy ion gantry, enabling flexible positioning of the beam delivery system. HIT, Heidelberg Ion Beam Therapy.

patient treatment. With the construction of the proton cyclotron at the Clatterbridge Oncology Center in 1989 and the proton synchrotron at Loma Linda University in 1990, the first dedicated treatment facilities for proton therapy started operation.¹² In the meantime, radiotherapy with heavier charged particles, including Helium-, Carbon-, Argon- and Neon-ions, had also been implemented into pre-clinical and clinical trials from the 1970's on, notably at the BEVALAC in Berkeley.¹³ Nevertheless, it took some other 20 years, until 1994, for the first dedicated treatment facility for carbon ion radiotherapy, the HIMAC in Chiba (Japan), to start with patient treatment.¹⁴

As of December 2018, over 200,000 patients have been treated with particle therapy, mainly protons and carbon ions. The number of treatment facilities has increased rapidly in the last years, especially for proton therapy, and spreads throughout the USA, Europe and Asia.¹⁵ To date, only 13 institutions are treating patients with carbon ion beams and there is an ongoing discussion whether the potential benefits can justify higher costs for construction and maintenance of heavy ion facilities (Figure 1).

In this review, physical and biological properties of particle beams in clinical use today, *i.e.* carbon ions and protons, will be summarised. Some of the clinical results will be presented and future perspectives of particle therapy will be discussed. In this context, the authors would also like to refer to a recently published special issue dedicated to proton therapy, which summarises clinical findings and current developments and points out future challenges and opportunities.¹⁶

THE PRINCIPLE OF PARTICLE THERAPY

Physical aspects

The observations R.R. Wilson made in the 1940's already revealed essential characteristics of particle beams. The energy deposition in irradiated tissue and therefore the dose distribution differs

much from conventional radiotherapy with photons. The main difference is an inverted depth-dose profile leading to sharply increasing energy deposition in narrowly defined areas at the end of the particle's range. This phenomenon, also called Bragg peak, was first described by Sir William H. Bragg in 1904 on a particles originating from radium salt.¹⁷ Charged particles are slowed down in matter and lose energy due to interactions with electrons and nuclei. The probability for these interactions increases as particles get slower, leading to a sudden increment in energy and dose deposition just before the particle stops in a depth defined by its energy. This results in a characteristic Bragg curve, as illustrated for carbon ions in Figure 2. This figure also sketches the main difference when compared to the depth-dose profile of photons (red curve). The low energy deposition in the entrance path and beyond the target volume seem to make charged particles particularly interesting for the means of radiotherapy.

A three-dimensional target volume can generally not be covered by a single monoenergetic particle beam, even when considering a broadened Bragg peak resulting from energy and thus range straggling of different particles.¹⁸ Thus, during treatment planning, a set of beams with decreasing energies needs to be superimposed to produce a so-called spread-out Bragg peak (SOBP) (Figure 2). In this way, complex shaped target volumes can receive the prescribed dose with high conformality and homogeneous dose distribution.

Furthermore, charged particles undergo coulomb interactions with nuclei and electrons that cause lateral deviation and consequently beam-broadening. This lateral scattering is more important for lighter ions such as protons, especially for lower energies and deeper penetration depths. For heavier particles such as carbon ions, the lateral scattering is almost negligible.¹⁹ In clinical practice and during treatment planning, this difference has meaningful consequences when striving sharp

Figure 2. Schematic diagram of depth–dose distributions of different radiation modalities.

dose gradients in order to spare tissue at risk. A more detailed discussion and comparison of physical properties of protons and carbon ions are provided for instance by Weber et Kraft²⁰ and Durante et al.^{21,22}

Biological aspects

Radiotherapy generally attempts to achieve high dose depositions in a target volume while sparing surrounding healthy tissue. The physical dose distribution of charged particles is particularly well suited for this purpose, as described previously. The density of this dose deposition and the resulting biological effects can be quantified by the linear energy transfer (LET), defined as the amount of energy loss per unit of length of the particle's track. Higher LET radiation can produce more severe damage on a biomolecular scale. Direct interactions of accelerated heavy charged particles (*e.g.* carbon ions) with a cell's DNA can cause cluster lesions with single-strand breaks, cross-links or double-strand breaks that occur close to each other in time and space.²³ This disables the tumour cell's capacity to repair the lesions, resulting in a greater potential for tumour cell inactivation.

To account for the different biological effects of higher-LET radiation, the relative biological effectiveness (RBE) has been introduced. It is the dose ratio of a reference beam (250 keV X-rays) to a particle beam producing the same biological effect. The physical dose of a particle beam needs to be multiplied with a specific RBE in order to obtain the biologically effective dose in Gy (RBE). The RBE depends on several factors, most importantly the LET of the particle, the position within the Bragg peak, dose levels, fractionation, oxygenation, cell lines, cell position within the cell replication cycle and chosen clinical endpoints.²⁴

For protons, the LET stays relatively low and rises only a little towards the end of the SOBP.²¹ In clinical practice, it is common

to define a constant RBE of 1.1 for treatment planning with protons. However, this represents an average value deduced by *in vivo* measurements, eventually underestimating a local "hot spot" in the distal millimetres of the SOBP, where the RBE can increase steeply.²⁵

For carbon ions, the RBE increases in function of LET within the SOBP while staying low in the entrance path of the beam. Depending on several factors, as mentioned previously, the RBE of carbon ion beams can reach values up to 3–5 in the distal parts of the SOBP.^{19,26} This selective increase of RBE within the SOBP represents a significant advantage of heavier charged particles in radiotherapy, as the therapeutic ratio of high dose to a target volume and low dose to surrounding tissues can be enhanced by higher biological effects. Also, the oxygen enhancement ratio (OER), *i.e.* the ratio of doses required to produce the same clinical effect in hypoxic and normoxic conditions, is lower for high LET radiation,²⁷ potentially increasing the cell killing effect in hypoxic and generally radioresistant tumour areas. Furthermore, carbon ion beams might be able to generate stronger immunological responses, although this is still subject to preclinical research at this point in time.²⁸

Beam delivery

Two main beam delivery systems can be distinguished in particle therapy: passive scattering and active scanning.

The passive scattering technique, at first, modulates a monoenergetic beam to different energy levels, *e.g.* with a rotating modulator wheel, producing the depth–dose distribution of a SOBP. The thin pencil beam is then spread laterally after passing through scattering material. Finally, the beam is shaped by collimators and compensators in order to adapt to the three-dimensional target volume.²⁹

In active scanning techniques, the penetration depth of the beam can be modulated actively by modifying the output energy of the accelerator. The target volume is then split up into isoenergetic slices that are scanned voxel wise by a pencil beam with predefined energy. During the scanning process, the thin pencil beam is deflected by fast moving magnetic dipoles.³⁰ The result is a very flexible, intensity modulated particle therapy with highly conformal three-dimensional dose distributions, also for complexly shaped target volumes. Active scanning techniques offer some other advantages, including sparing of normal tissue in the entrance path, absence collimators and compensators and reduced secondary radiation resulting from particle interaction with scattering material.³¹

More compact accelerators and beam delivery systems have been developed in the past decades and single-room solutions are available now for proton beam therapy, integrating a synchrocyclotron, a gantry and image guidance systems.^{32,33} But also for heavy ion treatment facilities, a more compact gantry solution has been designed and started operation in 2017 at the HIMAC in Chiba, Japan.³⁴

CLINICAL RESULTS

The true impact of particle therapy on local tumour control (LC) or overall survival (OAS) can only be determined by clinical trials. The following section will briefly review some of the results of particle beam therapy in use today, *i.e.* carbon ion

beam RT (CIRT) and proton beam RT (PRT), in selected clinical situations.

Chordoma and chondrosarcoma of the skull base

Tumours growing at the skull base are challenging, both for surgery and radiotherapy. Because of vicinity to sensitive organs at risk such as the optical system, cranial nerves, the brainstem, the carotid arteries or the inner ear, surgery is often incomplete or not feasible, requiring definitive or additional radiotherapy.

Chordomas are rare bone tumours, most likely arising from notochordal remnants and therefore generally located at the midline along the spinal axis. About 30% are located at the skull base.³⁵ Tumour growth is generally slow but locally invasive with high recurrence rates. Additional radiotherapy is therefore recommended, even after macroscopic complete resection.³⁶ As suggested by Schulz-Ertner *et al.* in 2007 and later by McDonald *et al.*,^{37,38} there is a strong dose–response relationship for chordomas. However, dose escalation with conventional radiotherapy has physical boundaries and is often not sufficient. A selection of studies analysing particle beam therapy after partial resection or biopsy of skull base and cervical spine chordoma are summarised in Table 1. Results with both, CIRT and PRT are promising, yielding LC in 70% and more after 5 years, with only few or no Grade 3 or higher toxicities. For 106 patients treated in a combined protocol with photons and protons, Fung *et al* have found LC rates of 75% after 5 years with Grade 3 or higher

Table 1. Selected studies of outcome after particle therapy for skull base/cervical spine chordoma

Reference	Study design	Modality	n	Median age (range)	Median dose in Gy (RBE) (range)	Fx	Gy (RBE)/Fx	Follow-up in months (range)	LC	OAS
Schulz-Ertner <i>et al.</i> , 2007 ³⁷	R	CIRT	96	47 (11–80)	60 (60–70)	20	3	31 (3–91)	81% (3y) 70% (5y)	92% (3y) 89% (5y)
Mizoe <i>et al.</i> , 2009 ³⁹	P	CIRT	34	47 (16–76)	60.8 (48.0–60.8)	16	3–3.8	53 (8–129)	85% (5y) 64% (10y)	88% (5y) 67% (10y)
Uhl <i>et al.</i> , 2014 ⁴⁰	R	CIRT	155	48 (15–85)	60 (60–70)	20	3	72 (12–165)	82% (3y) 72% (5y) 54% (10y)	95% (3y) 85% (5y) 75% (10y)
Noel <i>et al.</i> , 2005 ⁴¹	R	PhRT + PRT	100	53 (8–85)	45 (29–55) PhRT +22 ^{12–38} PRT	30–39	1.8–2.0	31 (0–87)	86% (2y) 54% (4y)	94% (2y) 81% (5y)
Weber <i>et al.</i> , 2016 ⁴²	R	PRT	151	43.3a (18,1 SD)	72.5 ± 2.2a/b	35–40	1.8–2.0	50 (4–176)b	76% (5y) 71% (7y)	73% (7y)
McDonald <i>et al.</i> , 2016 ³⁸	R	PRT	39	52 (17–78)	77.4 (70.2–79.2)	35–40	2	51 (2–106)	70% (5y)	81% (5y)
Fung <i>et al.</i> , 2018 ⁴³	R	PhRT + PRT	106		72 (68.4–73.8)	38–41	1.8	61 (11–119)	89% (2y) 78% (4y) 75% (5y)	99% (2y) 90% (4y) 88% (5y)

CIRT: carbon ion beam radiotherapy; Fx, Fractions; LC, local control; OAS, overall survival; P, Prospective; PRT, proton beam radiotherapy; PhRT, conventional radiotherapy with photons; R, Retrospective.

^aMean values.

^bWeber *et al* analysed 222 patients with chordoma (151) or chondrosarcoma (71) of the skull base. Characteristics marked with b refer to the whole patient group.

toxicities in seven patients (6.6%).⁴³ A metanalysis conducted by Zhou et al. in 2018 compared overall survival after conventional radiotherapy, stereotactic radiotherapy or particle therapy for skull base chordomas after surgery, suggesting long term survival benefits after particle therapy.⁴⁴

Low-grade chondrosarcomas are similarly known to be relatively radioresistant, causing the same dilemma of required high doses in a highly sensitive region when located at the skull base. Nevertheless, evidence of safety and high efficacy for particle therapy has been continuously growing, making them indispensable in the multidisciplinary treatment approach for these tumours. Matke et al. for instance analysed 101 patients with residual tumour at the skull base who had received either CIRT (median 60 Gy(RBE) at 3 Gy (RBE)/fraction) or PRT (median 70 Gy (RBE) at 2 Gy (RBE)/fraction). Control rates were high, with 100% after 1, 2 and 4 years for PRT and 100%, 98.5% and 92.9% after 1, 2 and 4 years for CIRT. No Grade 3 or higher toxicity was observed.⁴⁵

There is growing evidence demonstrating that particle therapy is beneficial for the treatment of skull base chordomas and chondrosarcomas, although prospective analyses remain sparse. Two ongoing prospective randomised controlled trials are comparing CIRT and PRT for the treatment of skull base chordomas and chondrosarcomas.^{46,47} The results will also be important to clarify whether the higher RBE of CIRT can further improve the effectiveness of the treatment.

Meningioma

Meningioma are generally benign and slow growing tumours, over 90% classified WHO Grade I.⁴⁸ Surgery is the treatment of choice, but especially when located at the skull base, e.g. in the petroclival region, resection is often incomplete or not feasible. Postoperative or primary conventional or stereotactic radiotherapy is well established for meningioma of the skull base, achieving promising local control rates of more than 90% after 10 years, a frequent relief of cranial nerve affections and acceptable complication rates.^{49–51} However, the vicinity to vital structures such as the brain stem or cranial nerves requires steep dose gradients in many situations. Furthermore, reduction of possible late side-effects is indispensable, considering the very good prognosis of these patients. PRT offers high conformality and steep dose gradients, reducing the integral dose exposure of surrounding tissues. Dosimetric treatment plan comparisons confirmed possible advantages over conventional radiotherapy.^{52,53} The clinical outcome after particle therapy of skull base meningioma has been reported in several studies, some of them are summarised in Table 2. Results were promising, with high local control rates and low toxicities. Besides conventional fractionation, stereotactic radiosurgery with protons has also been used in analogy to modern hypofractionated RT or SRS with photons, suggesting feasibility and good tolerance.⁵⁵

Atypical and anaplastic meningioma (WHO Grade II + III) are less frequent, but treatment is complicated by high local recurrence rates and necessity of high radiation dose to achieve local control. In fact, McDonald et al showed that dose escalation to

Table 2. Selected clinical studies of particle beam therapy for meningioma of the skull base

Reference	Study design	Histology	% located at skull base	Median/Mean Follow up (range)	Modality	n	Median/Mean age (range)	Median dose in Gy (RBE) (range)	Number of Fx	Gy(RBE)/Fx	LC in % (years)	OAS in % (years)
Noel et al., 2005 ⁵⁴	R	WHO°I	100	21 (1–90)	PhRT +PRT	51	56 (11–75)	60.6 (54–64) 30.6 Gy +30 Gy(RBE)	30–32	1.8–2	98% (4y)	100% (4y)
Halasz et al., 2011 ⁵⁵	R	WHO°I	69	32 (6–133)	PRT	50	60 (33–85)	13 (10.0–15.5)	1	13 (10.0–15.5)	94% (3y)	n.s.
El Shafie et al., 2018 ⁵⁶	R	WHO°I–III	100	47	PRT (WHO°I) PhRT +CIRT (WHO°II/III)	104/6	52 (45–59)	54 Gy(RBE) / (50 Gy)+18 Gy (RBE)	28–30/25–28+6	1.8/3	100% (3y) 97% (5y)	96% (5y)
Vlachogiannis et al., 2017 ⁵⁷	R	WHO°I	91	84	PRT	170	54 (22–85)	21.9 (14–46)	4–23	2–6	93% (5y) 85% (10y)	n.s.
Murray et al., 2017 ⁵⁸	R	WHO°I–III	67	57 (12–207)	PRT	96 (64 skull base)	53 (3–77)	WHO°I: 54 (50.4–64) WHO°II/III: 62.0 (54–68)	28–34	1.8–2	86% (5y)	88% (5y)

CIRT, carbon ion beam RT; LC, local control; OAS, overall survival; PRT, proton beam RT; PhRT, conventional radiotherapy with photons.

Table 3. Selected studies analysing side-effects of PRT vs photon IMRT in head and neck cancer

Reference	Location	n/modality	Endpoint	Outcome for protons (%)	Outcome for photons (%)	p value
Sio et al., 2016 ⁶⁴	Oropharynx	35 PRT +CHT 46 IMRT +CHT	Subacute mucus symptoms Subacute appetite symptoms Chronic appetite symptoms Subacute Dysgeusia	62% 4.68a 2.12a 5.76a	84% 6.37a 4.14a 7.70a	0.038 0.048 0.036 0.01
Blanchard et al., 2016 ⁶⁵	Oropharynx	50 PRT 100 IMRT	Xerostomia°II-III (patient reported, 3 months after RT) Gastrostomy tube or weight loss (>20%) (1 year after RT)	42% 8%	61% 24.7%	0.009 0.01
Romesser et al., 2016 ⁶⁶	Major salivary gland or cutaneous SCC (unilateral)	18 PRT 23 IMRT	Acute Mucositis >= °II Acute Dysgeusia >= °II Acute Nausea >= °II	16.7% 5.6% 11.1%	52.2% 65.2% 56.5%	0.019 <0.001 0.003

CHT, Chemotherapy; IMRT, intensity modulated radiotherapy; PRT, proton beam RT.

^aScore of the MD Anderson Symptom Inventory-Head and Neck Module (MDASI-HN).

>60 Gy (RBE) for high-risk meningioma significantly increases local control rates.⁵⁹ This dose escalation in highly sensitive regions such as the skull-base is difficult, even with modern IMRT techniques or photon SRS. CIRT has the potential to increase dose without threatening organs at risk (OAR) due to favourable dose distributions and enhanced biological effects. Safety and feasibility of CIRT combined with photons has been shown in a Phase I/II trial by Combs et al.⁶⁰ and the efficacy of this bimodal approach after incomplete resection of atypical meningiomas is currently being investigated in the prospective MARCIE-Trial at HIT in Heidelberg.⁶¹

Head and neck cancer

Postoperative or primary radiotherapy is one of the central pillars in the treatment of advanced head and neck cancer (HNC). Nevertheless, morbidity associated with chemoradiotherapy or radiotherapy alone is high, even though the past decades have shown significant improvements with the introduction of intensity modulated radiotherapy (IMRT).⁶² But even with IMRT, integral dose to normal tissue remains high, due to physical limitations of photon beams in complex shaped target volumes. In 2014, Patel et al. have reviewed 43 cohorts treated with either protons or photons (incl. IMRT) for malignant disease of the nasal cavity and paranasal sinuses. Disease free survival after 5 years and locoregional control at longest follow-up differed significantly in favour of PRT, HR 1.44 (CI 1.01–2.05) and 1.26 (1.05–1.51).⁶³ Other, although retrospective, analyses report lower toxicities after PRT. Some of them are summarised in Table 3. Dosimetric analyses in those trials showed reduced dose maxima to the brainstem and spinal cord as well as reduced mean dose to the contralateral salivary glands and oral cavity.⁶⁶ Considering the growing interest in individualised target volume delineation and identification of low-risk patients, *e.g.* HPV-positive oropharyngeal cancer, PRT might be an important asset to further reduce acute and late toxicities. Numerous prospective

trials are planned or already recruiting in order to generate reliable data on patient outcome after PRT.⁶⁷

Heavier charged particles can be beneficial when dose escalation is required but not feasible with low LET radiation due to adjacent OAR. This is the case for instance for sinonasal malignancies, where dose escalation with IMRT alone is limited by adjacent eyes, optical nerves or the brain stem.^{68,69} First results on CIRT alone (median dose 64 Gy (RBE)) for advanced HNC were published at NIRS in Chiba, Japan.⁷⁰ Specific results for advanced sinonasal malignancies have been published by Koto et al. in 2014 and 2018, yielding promising local control rates of 84% after 2 years, although visual impairment remained the most common Grade 3 or higher toxicity.^{71,72} A prospective trial analysing safety and effectiveness of a combination of CIRT+IMRT has finished recruiting in Heidelberg and first results are to be expected soon.⁷³

A particular challenge in the head and neck region are salivary gland tumours with low radiosensitivity. A typical example is adenoid cystic carcinoma (ACC), an uncommon salivary gland tumour with high recurrence rates and perineural spread towards the skull base. As shown in the late last century with fast neutrons, higher LET radiation can achieve higher local control rates.^{74–76} Based on this rationale, a combination treatment of IMRT and carbon ion boost was tested, yielding promising results and comparing favourably to historical cohorts of IMRT only.⁷⁷ Subsequently, dose escalation up to 24 Gy (RBE) CIRT followed by 50 Gy IMRT was tested in the COSMIC-Trial, resulting in local control rates of 82% after 3 y with moderate toxicity.⁷⁸ CIRT has also been used alone to treat salivary gland tumours in Japan, with a median dose of 64 Gy (RBE) in 16 fractions.⁷⁹ Other retrospective analyses confirmed the good results of CIRT for ACC of different localisations, with or without previous surgery. Some of them are summarised in Table 4.

Table 4. Selected clinical studies of CIRT for ACC in the head and neck region

Reference	Type	Location	n	modality	Dose prescription	LC in % (years)	PFS in % (years)	OAS in % (years)
Jensen et al., 2015 ⁷⁷	R	Paranasal sinus Parotid gland Nasopharynx	58 37	CIRT + IMRT IMRT/FSRT	18Gy (RBE)+54 Gy 66 Gy	59.6% (5y) 39.9% (5y)	48.4% (5y) 27% (5y)	76.5% (5y) 58.7% (5y)
Jensen et al., 2015 ⁷⁸	P	Paranasal sinus, submandibular gland, palate	53	CIRT + IMRT	24Gy (RBE)+50 Gy	81.9% (3y)	57.9% (3y)	78.4% (3y)
Lang et al., 2018 ⁸⁰	R	Oral cavity	67 (postoperative RT)	CIRT + IMRT	24Gy (RBE)+50 Gy	85.5% (5y)	57.4% (5y)	74.9% (5y)
Akbaba et al., 2019 ⁸¹	R	Paranasal sinuses	137 (primary RT) 90 (postoperative RT)	CIRT + IMRT	18–24 Gy (RBE)+48– 56 Gy	79% (3y) 82% (3y)	67% (3y) 74% (3y)	64% (3y) 79% (3y)

ACC, adenoid cystic carcinoma; CIRT, carbon ion beam RT; FSRT, Fractionated stereotactic radiotherapy; IMRT, intensity-modulated radiotherapy; LC, local control; OAS, overall survival; RBE, relative biological effectiveness.

Based on the rationale of enhanced LC with high LET radiation and given that local recurrence of ACC is often in-field, a prospective randomised controlled trial has been launched at the HIT in Heidelberg, comparing CIRT alone (cumulative dose of 66 Gy(RBE)) with the established bimodal concept (50 Gy +24 Gy (RBE)) (NCT04214366, www.clinicaltrials.gov).

Re-irradiation

Locoregional recurrence of HNC after primary or postoperative (chemo-)radiotherapy is a challenging situation. Local treatment options with potential curative intent are sparse, surgery is often not feasible and re-irradiation is limited by cumulative dose constraints for surrounding OAR. However, local control of the recurrent disease is of major importance in terms of overall survival but also to preclude uncontrolled tumour growth in the head and neck region, causing significant morbidity and quality of life impairment. Retrospective analyses of re-irradiations in the head and neck region with PRT showed acceptable toxicity and reasonable local control rates.^{82–84} For instance, Romesser et al. analysed 92 patients with recurrent HNC, treated with a median dose of 60.6 Gy (RBE). Locoregional failure, OAS and distant PFS at 12 months were 25.1%, 65.2% and 84.0% respectively. Major acute toxicities Grade 3 included mucositis, dysphagia, esophagitis and dermatitis (all <10%). Two bleeding-related deaths occurred. Dysphagia and skin toxicity were the only other Grade 3 or higher toxicities, observed in 7.1 and 8.6% respectively.⁸²

CIRT might be of particular use in the treatment of recurrent disease. The rationale are steep dose gradients but also a higher biological effectiveness, potentially valuable in overcoming lower radiosensitivity of recurrent tumour disease. In 2011, Combs et al. analysed first results of re-irradiation with active raster scanning CIRT at GSI in Darmstadt, Germany. In 28 patients with mostly chordoma or chondrosarcoma of the skull base or sacral bone and few cases of other head and neck malignancies, re-irradiation was generally well tolerated with no severe acute or late toxicity, yielding an OAS rate of 86% after 2y.⁸⁵ Gao et al. have recently analysed 141 patients with recurrent HNC after primary treatment involving radiotherapy, in most cases IMRT. Patients underwent re-irradiation with CIRT in Shanghai, China with a median dose of 60 Gy (RBE). After a median follow-up of 14.7 months, LC and OAS rates 1 year after re-irradiation were 84.9% and 95.9%, respectively. Grade 3 or higher late toxicities were observed in 10.6% of the patients, most common toxicity being mucosal necrosis. The death of four patients was related to haemorrhage after mucosal necrosis.⁸⁶ In 32 patients treated with CIRT for recurrent HNC with a cumulative dose of 128.6 Gy (RBE; EQD2), Held et al. found local control rates of 66% after 1 y, no Grade 3 or higher toxicities were observed.⁸⁷ El Shafie et al. have analysed re-irradiation of recurrent intracranial meningioma with CIRT ($n = 34$) and PRT ($n = 8$). Local control was promising with 71 and 56.5% after 1 and 2 y, especially considering that 74% were classified high-risk, *i.e.* WHO Grade II or III. No Grade IV or higher toxicities were observed.⁸⁸

These results indicate that particle therapy might be a safe and effective option, widening the therapeutic window for this

heavily pre-treated patient group that is often not suitable for other local treatments. Nevertheless, those findings need to be validated in prospective trials with meticulous documentation of early and late side-effects.

Younger patients and integral dose reduction

In younger patients and children, exposure of healthy tissue to ionising radiation must be reduced to a minimum, not only because of acute toxicities, but also because they are more likely to experience long-term sequelae and secondary malignancies. Furthermore, damage to organs with central functions in child development, *e.g.* the pituitary gland, can cause developmental delay and long-term deficiencies. The results of a Phase II trial published by Yock *et al.* in 2016, analysing ototoxicity, neurocognitive and neuroendocrinological function in young patients with Medulloblastoma, suggest that PRT is a safe modality for craniospinal irradiation, with no difference in PFS (80%) and OAS (83%) after 5 years compared to photon IMRT. After a median follow-up of 7 years, no late cardiac, gastrointestinal or pulmonary toxicities were observed, comparing favourably to historical photon RT studies.^{89,90} The same group prospectively compared health-related quality of life in paediatric patients with brain tumours after PRT ($n = 57$) and RT with photons ($n = 63$), finding significantly higher scores in the psychosocial and physical domains for PRT.⁹¹ Tabrizi *et al.* have recently updated the results of their prospective cohort of 20 patients with low-grade glioma treated with PBRT (54 Gy (RBE)). No overall decline in neurocognitive functioning was observed after a median follow-up of 6.8 years.⁹² The contralateral hippocampus could be successfully spared (median Dmean: 0 Gy (RBE)), comparing favourably to doses with photon IMRT after hippocampal sparing (median Dmean 23.5 Gy).⁹³ These results are in line with the analysis of 74 young patients and adults with low-grade glioma who underwent PRT at the HIT in Heidelberg. 3D-CRT plans were generated and dosimetric comparison showed significantly lower maximum and mean doses to critical neurological

structures and areas of neurogenesis with PRT.⁹⁴ Figure 3 illustrates the potential benefits of particle therapy, comparing treatment plans of different modalities in an 8-year-old boy with craniopharyngioma. Integral dose can be reduced with PRT and surrounding structures, *e.g.* the brainstem, are more likely to be spared.

DISCUSSION AND PERSPECTIVES

Particle therapy has the strength of producing highly conformal dose distributions while reducing integral doses to surrounding tissue. But this potential can only be fully exploited when limiting factors concerning beam delivery and target motion are reduced. Especially, active scanning techniques are particularly sensitive to intra- or interfractional anatomical variations within the beam's path. The scanning process has a time and space dimension and can therefore interfere with time-dependent target motion, also known as the interplay effect.⁹⁵ As a result, small subvolumes might not receive the prescribed and intended dose. Although this can be partly prevented by optimising treatment plans, some target motions and anatomical changes are unpredictable, requesting better motion control or compensation. A common approach is to predict motion patterns during treatment planning with 4D-computed tomography in order to define an internal target volume (ITV) that accounts for target motions.⁹⁶ However, this often leads to larger target volumes and correspondingly higher doses to surrounding tissue. Gating techniques compensate organ motion by enabling beam delivery only within predefined thresholds (*e.g.* end of expiration). Nevertheless, some downsides remain, as for instance uncertainties of external surrogate parameters (respiratory sensors or skin surface monitoring) or required implantation of fiducial markers when using internal surrogates.⁹⁷ Another method to mitigate interplay effects is rescanning, *i.e.* repeated irradiation of isoenergetic layers or whole target volumes with smaller doses in order to statistically reduce dose inhomogeneities.⁹⁸

Figure 3. Exemplary treatment plan comparison in a young patient with craniopharyngioma. A: 3D-CRT with photons, B: IMRT (VMAT) with photons, C: PRT with two opposing beams. Highlighted OAR: Brain stem. IMRT, intensity modulated radiation therapy; OAR, organ at risk; PRT, proton beam radiotherapy; VMAT, volumetric modulated arc therapy

Newer approaches, *e.g.* respiratory-correlated rescanning, can adapt to cyclic organ motion and further increase precision of particle beam delivery.⁹⁵ However, a drawback of these methods is the extended treatment time. Tumour tracking could therefore be an effective approach to account for target motion and mitigate interplay effects.⁹⁹ A major challenge that will need to be addressed in the future is the tracking speed of beam delivery systems. Although fast lateral displacements are already feasible with fast scanning dipole magnets, adaptation of the beam's range is still too slow in most particle accelerators. Some solutions combining superconducting cyclotrons with linear accelerators have already been proposed.¹⁰⁰ Also, future improvements in computational power to extrapolate and predict organ motion as well as image guidance that is sensitive to soft tissue, *e.g.* 4D-MRI, will help moving towards a real 4D-conformal dose distribution.

Concerning biological effects of particle therapy, a better understanding of the variability of RBE is required to further improve homogeneity of the biological effective dose distribution. The use of a fixed RBE of 1.1 for protons seems to be too simplistic. Numerous *in vitro* trials have detected greater RBE values, especially at the end of the SOBP.^{101–103} The consideration of this RBE variability during treatment planning could further increase effectiveness of PRT and reduce potential side-effects. For CIRT, biological dose computation and treatment planning is more complex and time-consuming. Different calculation models accounting for different parameters that influence the RBE have been developed and are continuously improved and adapted: *e.g.* the local effect model (LEM) and the Microdosimetric Kinetic Model (MKM) for active scanning techniques.^{104,105} However, the model used is still choice of the treating institution and a consensus is required to achieve better comparability throughout all CIRT-facilities.¹⁰⁶

Since the pioneer work in the 1970–1980s on different particles including Helium (⁴He) and Neon (²⁰Ne) at the LBL in California,¹⁰⁷ mainly protons and carbon ions have been used for particle therapy to date. Nevertheless, there is a growing interest in widening the spectrum of particles used in radiotherapy and preclinical research has led to a better understanding of other particles.¹⁰⁸ Helium ions exhibit radiobiological characteristics similar to protons but have some physical benefits such as reduced lateral scattering. First treatment plan comparison studies have shown the potential clinical benefit of ⁴He ions for selected tumour geometries and localisations.^{109,110}

The use of heavier ions such as oxygen (¹⁶O) might seem tempting, considering that increased LET can enhance tumour cell inactivation, especially for hypoxic areas with low radiosensitivity.¹¹¹ But this gain in RBE within the target volume comes along with higher RBE values in the entrance path of

the beam, potentially increasing toxicity. Nevertheless, heavier charged particles might still be beneficial, especially when their attributes of higher LET can be exploited while minimising drawbacks of higher LET in surrounding tissue. A strategy that is currently subject of investigations is dose painting, or LET painting with multiple ions.¹¹² A combination of heavy ions and lighter ones, *e.g.* ¹⁶O and ⁴He, can result in conformal and uniform high LET distributions in the target volume, as shown *in silico* by Sokol et al.¹¹³ The combination of multiple ions for particle therapy has a great potential to further improve biological dose distribution while sparing surrounding tissue.

CONCLUSION

There is growing evidence for safety and effectiveness of particle therapy for a variety of clinical situations. Especially for protons, the development of more compact treatment solutions integrating superconducting synchrocyclotrons, gantries and image guidance systems led to a rapidly increasing number of hospital-based treatment facilities.¹¹⁴ About 200,000 patients have been treated with PRT to date. However, there is still a lack of high-level evidence directly comparing PRT with modern conventional radiotherapy techniques. These trials are underway, *e.g.* for low-grade glioma, oropharyngeal cancer, lung cancer, prostate cancer and liver cancer.¹¹⁵

CIRT has been used in the past three decades in Asia and Europe based on the rationale of favourable dose distribution and higher biological effectiveness. Expansion of heavy charged particle therapy has been much slower, as it demands large investments, sufficient space for bigger accelerators and a team of specialists who are familiar with the physical and biological peculiarities. About 30,000 patients have been treated with CIRT so far, most of them at the NIRS in Japan.¹¹⁶ For some entities such as chordomas, chondrosarcomas and salivary gland tumours, CIRT has proven to be highly effective. For many other tumour entities such as early stage lung cancer, oesophageal cancer, hepatocellular carcinoma, pancreatic cancer or prostate cancer, treatment with CIRT is being investigated.¹¹⁷ Comparing CIRT with conventional radiotherapy remains difficult due to unconventional fractionation regimens and heterogeneous biological dose calculation models. This needs to be addressed in future clinical trials and improved understanding of RBE variability is required. Early data suggest high effectiveness of CIRT for selected tumour entities, but the full potential of heavy charged particles remains unclear and must be determined by further preclinical and clinical research. This should be considered when outweighing costs and benefits of the construction of a heavy ion facility. To our knowledge, new heavy ion facilities are planned or under construction in the USA, France, Taiwan, South Korea, Japan and China.¹¹⁸

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