

# Proton beam therapy for intracranial and skull base tumors

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**Abstract:** Radiotherapy is widely used for treating malignant and benign intracranial or skull base tumors because of the difficulty in performing wide or complete tumor resection due to the involvement of eloquent areas, vital vessels, or cranial nerves. Similarly, local radiotherapy with conventional methods may sometimes be inefficient for treating brain tumors because the tolerance doses for the optic nerves, eyes, and brainstem are strictly limited. Under the circumstances, particle radiotherapy with proton or carbon ion beams has excellent dose localization to the target volume owing to the sharp Bragg peak ionization in the human body. With this property, it is possible to deliver higher doses to tumors of various shapes while preserving the surrounding critical brain structures. Although the efficacy of proton beam therapy (PBT) has been suggested for skull base chordoma and unresectable meningioma, further clinical evidence is required for optimization and standardization of the therapy. In refractory tumors such as glioblastoma multiforme and anaplastic meningioma, it is necessary to deliver high doses to improve tumor control. Under these circumstances, protons or carbon ions have potential to deliver sufficient doses to the target while keeping the healthy brain intact. In this context, we focus on the current status of proton beam radiotherapy for treating intracranial and skull base tumors.

**Key Words:** Proton beam therapy (PBT); brain tumor; glioma; meningioma; chordoma



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## Introduction

Surgical resection is the most fundamental treatment for brain tumors; however, it is sometimes difficult to put wide surgical margins because of damage in the surrounding normal brain tissues such as the cranial nerves, the brainstem, and others. This renders the roles of postoperative radiotherapy (PORT) important or even essential. Particle radiotherapy such as proton beam therapy (PBT) and carbon ion therapy has better dose distribution than photon radiotherapy owing to a narrow energy peak called Bragg peak. Because of this excellent physical property, particle radiotherapy is suitable for treating brain tumors because high doses can be delivered to the target while preserving the surrounding normal tissue. In addition, because it is possible to make irregular target fields, particle radiotherapy can enable us to deliver uniform doses to irregularly shaped tumors.

Proton beams are categorized as low linear energy transfer (LET) radiation with a biological effect of 1.1 times that of photon beams (1). In contrast, carbon ions have a higher biological effectiveness than protons or photons; their effectiveness is almost 2-3 times that of photon beams (2,3), and they may be effective for treating highly radioresistant tumors. In this review, we describe current findings, particularly on PBT for brain tumors, including glioblastoma (GBM), low-grade glioma (LGG), chordoma, and meningioma.

## PBT for low-grade glioma

Sequential PORT is recommended in some cases of LGG, depending on the tumor location, extent of residual disease, and proliferative potency. However, the significance of PORT for LGG is still not very clear (4-6). In the EORTC 22845 trial, progression-free survival (PFS) was significantly

better in patients who received early PORT at a dose of 54 Gy in 30 fractions compared with that in patients who did not receive radiotherapy ( $P < 0.0001$ ); however, there was no significant difference in the overall survival (OS) ( $P = 0.872$ ) (5). The current recommended dose is 50-55 Gy in conventional fractions (1.8-2 Gy per fraction). Fitzek *et al.* used PBT in combination with photon beams at doses of 68.2 and 79.7 GyE for glioma of grades 2 and 3, respectively, with dose escalation. However, they were not able to improve the outcome significantly (7). In contrast, Hug *et al.* reported an improved visual status in 27 pediatric patients with LGG treated with PBT at a median dose of 55.2 Gy (RBE) at 1.8 Gy per fraction (8). With the use of PBT for adult LGG at a median dose of 54 Gy (RBE) at 1.8 Gy per fraction, Hauswald *et al.* found that tumor progression was noticed in only 1 patient and there was no severe toxicity (9).

The prognosis of patients with LGG is better compared with that of patients with high-grade glioma. The 5- and 10-year OS rates have been reported to be 58% and 32%, respectively, for astrocytoma (10) and 88% and 85%, respectively, for low-grade oligodendroglioma (11). Therefore, the quality of life after treatment is an important consideration for patients with LGG, particularly younger patients. The advantages of PBT in the preservation of the healthy brain and in the reduction of risk for secondary cancer in patients with pediatric brain tumors have been widely suggested (12-19). Further clinical analyses of not only neuro-functional preservation but also secondary cancer prevention are required to establish the efficacy of PBT in younger patients with LGG.

### **PBT for high-grade glioma**

PORT improves OS of patients with high-grade glioma (HGG) (20). Postoperative photon radiotherapy of approximately 60 Gy in conventional fractions with concomitant and adjuvant temozolomide is currently the standard therapy (21). However, the prognosis is still not satisfactory, and it has shown little improvement in patients with GBM over the past decades. The median survival times (MSTs) of patients with HGG have been reported to be 11-18 months, and the 5-year survival rates have been reported to be less than 10% (20-24). Outcomes were not improved even high linear-energy transfer (LET) radiations were applied. MSTs of 13.9 and 9 months were reported using radiation with carbon, helium, and neon (25) and pions, respectively (26). In contrast, dose escalation has

yielded favorable results. Fitzek *et al.* found that accelerated fractionation of 90 Gy (RBE) using conformal protons and photons improved local control and survival in GBM, with MST of the 23 cases being 20 months (27). In their report, tumor recurrence occurred most commonly in areas that received doses of 60-70 Gy (RBE) or less, and only 1 case showed recurrence within areas that received 90 Gy (RBE).

In patients with GBM, Tanaka *et al.* reported MSTs of 16.2 (12.8-19.6) and 12.4 (10.0-14.8) months and 2-year survival rates of 38.4% (23.5-53.3%) and 11.4% (0.0-25.3%) after treatment with high-dose conformal X-ray radiotherapy of 80-90 Gy and 60 Gy, respectively. The patients who received 60 Gy did not develop radiation necrosis (RN), whereas 9 patients who received higher doses (80-90 Gy) developed RN. In addition, Mizumoto *et al.* also found a survival benefit of hyperfractionated concomitant boost PBT with nimustine hydrochloride (ACNU) in patients with GBM (28). In this study, radiotherapy was conducted for 20 patients with GBM twice a day as follows: 1.8 Gy (RBE) for the tumor and surrounding edema in the morning and 1.65 Gy (RBE) for the gross tumor on gadolinium-enhanced MRI in the afternoon (6 h later) over 28 days; a total dose of 96.6 Gy (RBE) in 56 fractions was delivered to the tumor. Only 1 of 20 patients had recurrence within the 96.6 Gy (RBE) volume. The MST was 21.6 months and the 1- and 2-year PFS was 45.5% and 15.5%, respectively. RN occurred in 6 cases, and probable leukoencephalopathy was observed in 1 patient. Although dose escalation may be associated with an increased risk of RN, the development of RN might be inevitable in patients with GBM when considering its refractoriness. The findings of Fitzek *et al.* and Mizumoto *et al.* indicate that a total dose  $\geq 90$  GyE has the potential to control GBM. However, because the accurate evaluation of the area of tumor infiltration was difficult with MRI or CT, recurrence mainly occurred in the marginal area. This fact may indicate that the use of methionine positron emission tomography facilitates the evaluation of exact tumor invasion and improves the outcome.

Carbon ions are also of interest for the treatment of HGG. Mizoe *et al.* conducted a phase I/II study in 48 patients with HGG (16 with anaplastic astrocytoma and 32 with GBM) using photon and carbon ion therapy with ACNU (29). The radiation dose with photon beams was 50 Gy in 25 fractions, followed by carbon ion therapy. The doses of carbon ions were escalated in 10% incremental steps from 16.8 to 24.8 Gy, and a high dose was associated with good prognosis with MST of 26 months.

Suit *et al.* suggested 2 directions for future radiotherapy, i.e., the shrinkage of the irradiation field and expansion of a gap between radiosensitivity of tumor and normal tissues (30). In this regard, PBT or carbon ion therapy has considerable potential to achieve the shrinkage of the irradiation field, in particular, by developing intensity-modulated particle therapy (IMPT). A recent study on radiosensitivity showed the feasibility of radiotherapy in combination with not only temozolomide but also other molecular-targeted agents (31,32). Therefore, high-dose particle therapy in combination with recently developed molecular-targeted or radiosensitizing agents should be tried as a promising multimodal treatment for GBM. In addition, boron neutron capture therapy (BNCT) may permit the expansion of the radiosensitivity gap. This approach is based on a nuclear capture reaction that occurs when boron ( $^{10}\text{B}$ ) is irradiated with neutrons of thermal energy to yield high-energy short-range  $\alpha$  particles ( $^4\text{He}^{2+}$ ) and recoiling lithium ( $^7\text{Li}$ ) nuclei. Because  $^{10}\text{B}$  is selectively taken up by cancer cells, theoretically, only cancer cells are destroyed by this treatment. The outcomes of patients with GBM treated with BNCT have been found to be favorable, with MSTs of 13-27 months (33-36).

### **PBT for skull base chordomas and chondrosarcomas**

Chordomas are rare low-grade malignancies that often develop in the clival region. Because metastasis and dissemination are uncommon, local control by aggressive treatment is important for long-term survival. Although surgical resection is the first treatment choice, gross total resection is often difficult because of difficult access and proximity to critical structures. Therefore, adjuvant radiotherapy is almost essential for tumor control. The control of skull base chordomas or chondrosarcomas requires doses more than 56-70 Gy (37-39) that are beyond the tolerance of critical structures such as the optic nerve, chiasma, and brainstem. This makes the treatment with photon beams difficult, it has been reported that 5-year PFS with X-ray treatment remained 17-39% (40-43). In this regard, particle radiotherapy was shown to be superior to photons for delivering higher doses to the tumor while keeping lower doses to normal tissues in the clival region in the 1990s (29,44-50).

The use of PBT for treating chordoma dates back to the 1990s. In early studies, PBT was often conducted in combination with photon radiotherapy. For example,

Munzenrider *et al.* treated 519 patients with skull base tumors, including 290 chordomas and 229 chondrosarcomas, with photon and proton radiotherapy at a total dose of 66-83 Gy (RBE) at 1.8-1.92 Gy per fraction, and 10-year local control rates (LCRs) for chordoma and chondrosarcoma were 54% and 88%, respectively. Similarly, Hug *et al.* treated 58 patients (33 with chordomas and 25 with chondrosarcomas) with a median total dose of 71.9 Gy (RBE) and 69.3 Gy (RBE) for chordoma and chondrosarcoma, respectively, at 1.8 Gy (RBE) per fraction and found that 5-year LCRs for chordoma and chondrosarcoma were 59% and 75%, respectively, with symptomatic late toxicities being observed in only 3 of the 58 patients.

Ares *et al.* reported the outcomes of 42 patients with skull base chordomas and 21 patients with chondrosarcomas treated with only PBT. The dose for chordoma and chondrosarcoma was 73.5 Gy (RBE) and 68.4 Gy (RBE), respectively, at 1.8-2.0 Gy (RBE) dose per fraction. The 5-year LCR was 81% and 94% for chordoma and chondrosarcoma, respectively, and severe toxicities were observed in 4 patients, resulting in 94% 5-year freedom from severe toxicity (44). In addition, Fuji *et al.* obtained a 3-year LCR and OS of 100% in 8 patients with skull base chordomas using a prescribed dose of 70 Gy (RBE) at 1.8 Gy (RBE) per fraction (51). In 96 patients with chordomas treated with carbon ion therapy at a median dose of 60 Gy (RBE) delivered in 20 fractions within 3 weeks, Shulz-Ertner *et al.* obtained a 5-year LCR of 70%. Meanwhile, grade 3 optic nerve neuropathy and fat plumb necrosis occurred in 4 patients and 1 patient, respectively (48). Mizoe *et al.* conducted a phase I/II study of carbon ion therapy for skull base chordoma with dose escalation in 4 steps of 4.8 Gy from 48 to 60.8 Gy (RBE) in 16 fractions and obtained a 5-year LCR of 100% without severe toxicities (52).

Recent development of photon radiotherapy has enabled us to achieve a confocal and precise dose distribution. Debus *et al.* performed stereotactic radiotherapy (SRT) in 37 patients at a dose of 66.6 Gy with a median fraction size of 1.8 Gy, whereas Foweraker *et al.* treated 9 chordoma patients with radiotherapy at a dose of 65 Gy in 39 fractions (53). In meta-analysis of these recent studies, most of which are small and retrospective, Maio *et al.* found that 5-year PFS and OS were 50.8% and 78.4%, respectively, and no significant differences in 5-year OS were observed among photon radiotherapy, gamma-knife surgery, PBT, and carbon ion therapy, but 5-year PFS was lower in gamma-knife surgery (54). Although doses of photons delivered were lower than those of protons

and carbon ions, these results suggest that chordoma may possibly be controlled when a sufficient dose is delivered, regardless of the radiation quality. Further progress both in photon and particle radiotherapy is definitely required to overcome this radioresistant and invasive tumor that develop at the very complicated location.

Medial temporal lobe injury is another risk in particle radiotherapy of the middle and upper clival region, which results in amnesia with a specific memory impairment profile (55-57). Ten of 96 patients (10.4%) reportedly developed clinical symptoms or MRI changes in the temporal lobe after PBT at doses of 63-74 Gy (RBE) (58). Although a correlation between the occurrence of temporal lobe toxicities and tissue volume that received high doses has been suggested (58), a threshold dose for temporal lobe toxicity has not been clarified till date.

Collectively, at present, the treatment modality is selected on the basis of not only the tumor location, size, and shape but also the experiences of each institute. Although it takes at least 5 years to draw a meaningful result in chordomas and chondrosarcomas, clinical evidence with higher grades is highly desirable.

### **PBT for meningioma**

Meningiomas are classified into 3 grades in the WHO classification. Most are benign or WHO grade I with an indolent course or a low rate of local recurrence. The first treatment choice for meningiomas is complete surgical resection. Condrao *et al.* found that 5- and 10-year LCRs after gross total resection (GTR) were 93% and 80%, respectively (59). However, complete resection with Simpson G-I or II is sometimes difficult owing to the location, size, and involvement of vital vessels or cranial nerves. In addition, it has been reported that subtotal resection (STR) is associated with a higher recurrence rate of 45-60% (60,61). In these patients, PORT significantly improves local control, although meningiomas are less sensitive to radiotherapy (61-64). Taylor *et al.* found that 69% of patients had recurrence after STR alone, compared with only 15% after PORT (P=0.01) (63).

As for atypical meningiomas, the role of PORT is not sufficiently proven; however, at present, PORT is recommended for all patients, regardless of GTR or STR (65-68). Since the revision of WHO grading criteria in 2000, there has been a significant increase in the number of meningiomas diagnosed as grade II (69,70). Among 114 patients diagnosed with WHO grade II meningioma, Mair *et*

*al.* found a benefit of PORT only for patients who underwent STR (68). In contrast, Komotar *et al.* suggested that PORT improved local control even after GTR. They mentioned that recurrence was noticed only in 1 of 13 patients who received PORT, while it was noticed in 13 of 32 patients who did not receive PORT (P=0.085) (71). The typical dose for PORT is 50-54 Gy and 60 Gy for benign and atypical meningiomas, respectively. In addition, dose escalation may improve local control, particularly for atypical meningioma (72-74), and SRT is reportedly effective for treating small and unresectable meningiomas (75-79).

Hug *et al.* reported the outcomes of 31 patients with WHO grade 2 and 3 meningiomas treated with photon or combined proton-photon irradiation. The total doses ranged from 50 to 68 Gy (RBE) and 40 to 72 Gy (RBE) for grades 2 and 3 meningiomas, respectively. Local control was significantly improved with PBT compared with that with photon radiotherapy alone (P=0.025), and the survival rates for WHO grade 2 meningiomas were significantly improved by PBT and radiation doses >60 Gy (RBE) (74). Similarly, in a study of 24 patients with WHO II and III meningiomas treated by proton and photon beams with a median dose of 65.1 Gy (RBE), Boscos *et al.* found that survival was significantly associated with the total dose (72). In a recent report on the outcomes of 6 patients with WHO II and III meningiomas treated at doses of 68.4 Gy (RBE) and 72.0 Gy, respectively; Chan *et al.* observed local recurrence in 1 patient with WHO grade 3 meningioma but found no severe toxicity (73).

With regard to the use of SRT for meningiomas, Selch *et al.* found that 3-year PFS was 97.4% in a study of 41 cases of benign cavernous sinus meningioma (median tumor volume, 14.5 cc) treated with SRT (median dose, 50.4 Gy) after incomplete resection (77). In addition, in 12 cases of high-grade meningioma (tumor volume, 4.4 cc) treated with SRT at a mean marginal dose of 12-20 Gy, Kano *et al.* found that a marginal dose <20 Gy was a significant predictor (P=0.0139) of short-term tumor progression (5-year PFS, 29.4% *vs.* 63.1%) (79).

PBT is advantageous for treating tumors that are large or have a complex shape or for those adjacent to critical regions (80-85). Thus, in 46 patients with partially resected, biopsied, or recurrent meningiomas treated with a combination of photon and protons at median doses of 59 Gy (RBE), Wenkel *et al.* found that 5- and 10-year LCRs were 100% and 88%, respectively (84). IMRT also gives excellent dose distribution with the avoidance of surrounding organs (86). Kosaki *et al.* reported that

**Table 1** Series of intracranial and skull base tumors treated by proton beam therapy

Authors [year]	Histology	Number of Patients	Mean dose (range) [Gy (RBE)]	Dose per fraction [Gy(RBE)]	Mean follow up (Month)	Local control (%)	Overall survival (%)	
Fitzek <i>et al.</i> [2001]	Low grade glioma (Grade II)	7	68.2	1.92	61	N/A	71 (5 y)	
Hug <i>et al.</i> [2002]	Low grade glioma	27	55.2	1.8	39.6	87	93	
Hauswald <i>et al.</i> [2012]	Low grade glioma (Grade I/II)	19	54.0 [48.6-54]	1.8	N/A	N/A	N/A	
Fitzek <i>et al.</i> [1999]	Glioblastoma	23	93.5 [81.6-94.2]	1.8-1.92 (2 Fx/day)	33	N/A	34 (2 y), 18 (3 y)	
Mizumoto <i>et al.</i> [2010]	Glioblastoma	20	96.6	1.8 & 1.65 (2 Fx/day)	21.6	15.5 (2 y)	45.3 (2 y)	
Hug <i>et al.</i> [1999]	Chordoma	33	71.9 [66.6-79.2]	1.8	33.2	59 (5 y)	79.0 (5 y)	
	Chondrosarcoma	25	69.3 [64.8-72]			75 (5 y)	100 (5 y)	
Munzenrider <i>et al.</i> [1999]	Chordoma	290	66-83	1.8-1.92	41	73 (5 y), 54 (10 y)	80 (5 y), 54 (10 y)	
	Chondrosarcoma	229				98 (5 y), 94 (10 y)	91 (5 y), 88 (10 y)	
Noel <i>et al.</i> [2001]	Chordoma	34	66.7 [60-73]	1.8-2.0	31 (median)	83.1 (3 y)	91.2 (4 y)	
	Chondrosarcoma	11				90 (3 y)	60 (4 y)	
Igaki <i>et al.</i> [2004]	Chordoma	13	72.0 [63-95]	2.0-3.5	69.3 (median)	66.7 (5 y)	44.2 (5 y)	
Ares <i>et al.</i> [2009]	Chordoma	42	73.5 [67-74]	1.8-2.0	38	81 (5 y)	62 (5 y)	
	Chondrosarcoma	22	68.4 [63-74]			94 (5 y)	91 (5 y)	
Fuji <i>et al.</i> [2011]	Chordoma	8	63 [50-70]	1.8	42 (median)	100 (3 y)	100 (3 y)	
	Chondrosarcoma	8				86 (3 y)	100 (3 y)	
Yasuda <i>et al.</i> [2012]	Chordoma	40	68.9 [55-74]	N/A	62.3	70 (5 y)	83.4 (5 y)	
Vernimmen <i>et al.</i> [2001]	Meningioma	18	20.3 [17.3-24.3] (ICRU reference dose)	3 fractions	40	88 (5 y)	N/A	
Halasz <i>et al.</i> [2011]	Meningioma (benign)	50	10.0-15.5 (90% line)	10.0-15.5 (radiosurgery)	32 (median)	94 (3 y)	N/A	
Weber <i>et al.</i> [2004]	Meningioma (benign+atypical)	16	56 [52.2-64]	1.8-2.0	34.1	91.7 (3 y)	92.7 (3 y)	
Slater <i>et al.</i> [2012]	Meningioma (benign+atypical)	Total: 72		1.8	74	96 (5 y)	72 (5 y)	
		Grade I: 47	50.4-66.6 (G1+NP)					G1+NP: 99
		NP*: 21						
	Grade II: 4	54-70.2 (G2)	G2: 50					

**Table 1 (continued)**

**Table 1** (continued)

Authors [year]	Histology	Number of Patients	Mean dose (range) [Gy (RBE)]	Dose per fraction [Gy(RBE)]	Mean follow up (Month)	Local control (%)	Overall survival (%)
Hug <i>et al.</i> [2000]	Malignant meningioma	Total: 31 Atypical: 15 Malignant: 16	62.5 [50.4-68.4] 58 [40-72]	1.8-2.0	59	38 (5 y) 52 (5 y)	89 (5 y) 51 (5 y)
Boskos <i>et al.</i> [2009]	Malignant meningioma	24	68	1.8-2.0	48	46.7 (5 y)	53.2 (5 y)
Chan <i>et al.</i> [2012]	Malignant meningioma	6	68.4 for Grade II 72.0 for Grade III	1.8	145	N/A	N/A

\*NP, No pathology

the difference in dose distribution between IMRT and PBT for complex-shaped skull base meningiomas was very small. However, they mentioned that PBT allowed almost complete avoidance of the brainstem, while this region received 10-30% of the dose in IMRT (87). In an evaluation of the risk of a secondary tumor after radiotherapy for benign meningiomas, Arvot *et al.* found that PBT reduced this risk to less than half of that with photon radiotherapy (81). In addition, they also mentioned that PBT could significantly reduce the risk of neurocognitive, visual, and auditory complications. A summary of proton beam therapy for intracranial and skull base tumors is reported in *Table 1*.

## Conclusions

The role of particle beam radiotherapy for intracranial and skull base tumors has not been fully established. However, it is clear that this method has 2 important advantages compared with photon radiotherapy. First, particle beam radiotherapy makes it possible to deliver a high dose to refractory tumors such as high-grade gliomas and anaplastic or atypical meningiomas, which can improve control rates of these tumors. Second, PBT can reduce the irradiated volume of normal brain tissues, thereby significantly reducing neurotoxicity. Therefore, particle beam radiotherapy is particularly advantageous for childhood brain tumors, low-grade gliomas, and benign meningiomas that require a long-term follow-up.

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