

# 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), Boscios *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 Grade I: 47 NP*: 21 Grade II: 4	50.4-66.6 (G1+NP) 54-70.2 (G2)	1.8	74	96 (5 y) G1+NP: 99 G2: 50	72 (5 y)

**Table 1 (continued)**

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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		1.8-2.0	59	38 (5 y)	89 (5 y)
		Atypical: 15	62.5 [50.4-68.4]				
		Malignant: 16	58 [40-72]				
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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Review

## Bevacizumab for Glioblastoma—A Promising Drug or Not?

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**Abstract:** Two double blind, placebo-controlled, and randomized phase III studies were conducted, and the results including OS's were reported at the ASCO Meeting in June 2013, which was the beginning of confusion surrounding this topic. This is a review article not only summarizing the previous evidence, but also looking beyond.

**Keywords:** bevacizumab; glioblastoma; chemotherapy

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### 1. Introduction

Studies have confirmed angiogenesis as a complex and dynamic process occurring during the growth of all solid tumors beyond 2–3 mm in size and that tumors are angiogenesis dependent [1]. Vascular endothelial growth factor (VEGF) is one of the most important factors regulating angiogenesis in the most aggressive malignant brain tumor, glioblastoma (GBM) [2]. Bevacizumab is a humanized form of a mouse monoclonal antibody against human VEGF, which binds to and neutralizes mainly VEGF-A. The interaction between GBM stem cells located in their perivascular niche and endothelial cells may also be disrupted by anti-VEGF agents such as bevacizumab, contributing to eventual cell death [3].

Bevacizumab was first reported as a treatment for recurrent GBMs in 2005 [4]. The results showed significant improvement in radiological scans as well as in the patients' symptoms and neurological function. In a retrospective analysis of 29 patients treated with a combination of bevacizumab and irinotecan, a topoisomerase-1 inhibitor, an overall response rate of 43% was observed, with one complete response (CR), eight partial responses (PR), and eleven patients with stable disease (SD).

There was one death that occurred secondary to intracranial hemorrhage and one due to gastrointestinal perforation [4]. This initial efficacy of bevacizumab led to a phase II trial by Vredenburgh *et al.* in a total of 35 patients with recurrent GBMs, using also bevacizumab and irinotecan [5]. The overall results of this trial included a PFS at 6 months (PFS-6m) of 46% (95% confidence interval [CI]; 32%–66%). A PR was observed in 20 of 35 patients (57%. 95% CI; 39%–74%), with the median OS in the study being 10.5 months. A historical comparator of PFS-6m for recurrent GBM should be the data of temozolomide by Yung *et al.* that was 18% [6]. The adverse events in this bevacizumab study included one intracranial hemorrhage and four patients who developed thromboembolic events. Thus, bevacizumab was seen as a promising new therapeutic for treating patients with gliomas. A subsequent study conducted by Friedman *et al.*, an open-label randomized phase II study, evaluated bevacizumab with and without irinotecan in 167 recurrent GBM patients (BRAIN study) [7]. A response rate of 37.8% and 28.2% in the bevacizumab plus irinotecan ( $n = 82$ ) and the bevacizumab alone ( $n = 85$ ) groups, respectively, and PFS-6m of 50.3% and 42.6%, respectively, was seen in this study.

## 2. Bevacizumab as a Single Agent vs. Combination Therapy for Recurrent GBM

One of the practical issues in treating recurrent GBM with bevacizumab is that combination with other chemotherapeutic agents has not been proved to increase efficacy of bevacizumab monotherapy. This is distinct from other malignancies where bevacizumab is approved and used in combination with cytotoxic agents, due to the fact no appreciable benefit is observed by using bevacizumab alone. For recurrent GBM, similar rates of response (20%–40%) and PFS-6m (23%–50%) were reported for bevacizumab plus chemotherapy (including irinotecan, carboplatin, nitrosoureas such as carmustine [1,3-Bis(2-chloroethyl)-1-nitrosourea; BCNU], lomustine [1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; CCNU] and fotemustine, temozolomide (TMZ), erlotinib, etoposide, and enzastaurin) relative to bevacizumab monotherapy [7–12], having argued that it is unclear whether additional agents contribute to enhance the benefit of bevacizumab in the treatment of recurrent GBM. Among those, irinotecan showed a slight increase in efficacy, albeit with limited single-agent activity in the recurrent setting [7,13–17].

The lack of significant enhancement of efficacy by bevacizumab combinations might be partially attributable to the brain-specific microenvironment constituted with the blood-brain barrier (BBB), as compared to other organs. One of the hypothetical mechanisms for therapeutic effects by bevacizumab is normalization of VEGF-induced dysregulated vascular structure causing excessive increase in fluid leakiness from vessels, resulting in high interstitial pressure and low perfusion in the tumor tissue, thereby hampering sufficient drug delivery. A consequence of bevacizumab action is neutralization of vascular permeabilizing effects of VEGF and reducing interstitial edema, thus it is postulated that perfusion within tumor tissue is normalized, leading to improved drug delivery to tumor cells. However, in the brain, this process may be accompanied with repair of disrupted BBB function as well, which in turn would restrict penetration of most chemotherapeutic agents into the brain parenchyma [18,19]. One example was shown in a mouse xenograft model where TMZ was effective in inducing apoptosis and eradication of tumors derived from human glioma U87 cells, but the addition of a multitargeting anti-angiogenic inhibitor vandetanib to TMZ conversely resulted in a decrease in apoptosis rate and tumor suppression compared to TMZ monotherapy [20].

To explore this issue directly, randomized comparator trials of bevacizumab have been initiated in patients with recurrent GBM by a Dutch study (BELOB) and European Organisation for Research and Treatment of Cancer (EORTC; EORTC 26101). Both studies use lomustine (CCNU) as the standard comparator to bevacizumab, either as a single agent or in combination with bevacizumab, to evaluate whether bevacizumab alone is superior in improving survival to lomustine that has served as the standard therapy at progression in Europe, and whether the combination has a higher activity than bevacizumab monotherapy as well. The phase II three-arm Dutch study BELOB has recently closed with 140 patients randomly allocated to either bevacizumab alone, lomustine alone, or combination of these two agents using the RANO criteria for response assay. The primary endpoint, OS at 9 months, was 38%, 43%, and 59%, and PFS-6m was 16%, 13%, and 41%, respectively, demonstrating better activity for bevacizumab/lomustine combination therapy [21]. While PFS-6m in the bevacizumab/lomustine arm (41%) was consistent with other bevacizumab combination studies, considerably lower PFS-6m in the bevacizumab single arm (16%) in this study than in historical data (25%–43%) appears to correlate with the number of cycles administered before progression determined by Response Assessment in Neuro-Oncology (RANO) criteria. Here, the median number of cycles was two, with 28% of patients in the bevacizumab arm deemed PD after the first cycle. This data contrasted strikingly with the previous phase II studies of bevacizumab as a single agent where the median number of bevacizumab doses was nine (BRAIN trial, NCT00345163) and six (JO22506) [7,22]. Whether this difference comes from different methods in measuring progression or other more complex reasons, remains to be elucidated.

An Australian randomized phase II trial (CABARET) compared bevacizumab with or without carboplatin to determine whether addition of another commonly used cytotoxic agent to bevacizumab may benefit survival in 122 patients with recurrent GBM. PFS-6m was 26% (combination) and 24% (bevacizumab monotherapy), and mOS was 6.9 months and 6.4 months, respectively, failing to result in clinical benefit with the combination [23].

A German randomized phase II trial (GLARIUS, NCT00967330) aimed to improve survival of patients with newly-diagnosed GBM having unfavorable unmethylated MGMT promoter, by treating with bevacizumab and radiotherapy followed by combination of bevacizumab plus irinotecan instead of TMZ. The primary endpoint of PFS-6m was 79.6% in the bevacizumab/irinotecan arm and 41.3% in TMZ arm ( $p < 0.0001$ ). mPFS was 9.7 months (bevacizumab/irinotecan) vs. 6.0 months (TMZ), and mOS was 16.6 months (bevacizumab/irinotecan) vs. 14.8 months (TMZ). Among patients in the TMZ arm who had progressed or died (85%), the crossover rate (second line with bevacizumab/irinotecan) was 63% [24]. These results suggest that substitution of TMZ with irinotecan in combination with upfront bevacizumab use may benefit the survival of patients with MGMT-unmethylated newly diagnosed GBM, in contrast to the Radiation Therapy Oncology Group (RTOG) 0825 study (see below) where addition of bevacizumab to TMZ showed no survival benefits in this unfavorable prognostic population. These studies warrant further phase III trials investigating bevacizumab/irinotecan combination in the patients with MGMT-unmethylated newly diagnosed GBM.

### 3. Controversies

Following the results of the various trials in recurrent GBMs, there has been considerable interest in evaluating the benefit of bevacizumab in untreated newly diagnosed GBMs. There are two randomized phase III trials evaluating the role of bevacizumab in combination with TMZ and radiation therapy for newly diagnosed GBMs. RTOG 0825 is a large phase III trial targeting 720 patients and the other trial is the Effectiveness of Avastin in GBM (AVAglio) study targeting over 900 patients and sponsored by Hoffman-LaRoche (Basel, Switzerland). In November 2012 at the Society of Neuro-Oncology Meeting in Washington, D.C., Chinot *et al.* presented the interim results of the AVAglio study that included final PFS data and interim OS data. The result was positive for an improved PFS, with other promising outcomes in secondary endpoints such as quality of life (QoL). Specifically, the Investigator-Assessed PFS, that was one of the co-primary endpoints, had a 10.6 months median survival in the bevacizumab arm compared to median survival of 6.2 months for standard therapy with a hazard ratio (HR) of 0.64 (95% CI: 0.55–0.74,  $p < 0.0001$ ). The central Independent Review Facility Assessed PFS (a secondary endpoint) demonstrated a median survival in the bevacizumab group as 8.4 months compared with 4.3 months in the standard therapy group; again statistically significant with stratified HR of 0.61 (95% CI: 0.53–0.71,  $p < 0.0001$ ). The interim OS analysis demonstrated a small non-statistically significant benefit in the bevacizumab group with a one year survival rate of 72% (68–76) compared with 66% (62–71) with  $p = 0.052$ ; with 254 events in the bevacizumab arm compared with 263 events in the standard therapy arm, with a stratified HR of 0.89 (0.75–1.07),  $p = 0.2135$ . In the arm receiving up-front bevacizumab, there were statistically significant benefits in the five pre-specified domains of health-related quality of life (HRQoL) (secondary endpoints), namely global health status, physical functioning, social functioning, motor functioning, and communication deficit; with longer median duration that patients were stable/improved from baseline. The median duration these patients maintained was a KPS higher than 70, with 9 months in the bevacizumab arm *vs.* 6 months in the standard arm. In the bevacizumab arm, 66% of patients who were on steroids at baseline discontinued their steroids compared with 47% in the standard arm. The time to steroid initiation for patients who had been off steroids at baseline was 12.3 months in the bevacizumab arm *versus* 3.7 months in the standard arm with a HR of 0.71 (95% CI; 0.57–0.88,  $p = 0.0018$ ). Overall, patients receiving bevacizumab had a diminished steroid requirement. There was no significant increase in intracranial hemorrhage (2.6% *vs.* 2.2% for all WHO tumor grades, I–IV, 1.5% *vs.* 0.7% for grade 3 or higher). There was more mucocutaneous bleeding in the bevacizumab arm (26.7% *vs.* 8.9%), but only 0.4% was grade 3 or higher. There were slightly more wound-healing complications (3.7% *vs.* 2.2%), as well as an increase in arterial thromboembolic events (5% *vs.* 1.6%) and a slightly lower incidence of venous thromboembolic events (7.8% *vs.* 9.6%). The incidence of hypertension was higher in the bevacizumab arm; 37.5% *vs.* 13.0%, and 10.3% *vs.* 2.0% for grade 3 or higher). Proteinuria was also higher (14% *vs.* 4%). There was a slight excess of gastrointestinal perforation at 1.7% *vs.* 0.2%; with abscesses or fistulae of 0.6% *vs.* 0.4%.

The other phase III study, RTOG 0825, also reported a longer PFS in the bevacizumab arm compared to the standard therapy; 10.7 months, and 7.3 months, respectively, HR = 0.79 (95% CI; 0.66, 0.94,  $p = 0.007$ ), which actually did not reach the pre-specified statistical endpoint of  $p = 0.004$ . The mOS could not achieve the pre-specified statistical endpoint of  $p = 0.046$ , as that in the bevacizumab arm was 15.7 months and that in the placebo arm was 16.1 months (HR = 1.13, 95% CI; 0.93, 1.37). One of the

striking differences between the two phase III trials was in the analyses of HRQoL data. In the RTOG 0825 trial, patients on the bevacizumab arm experienced significant worsening in cognitive function, motor dysfunction, and communication deficits measured by EORTC/BN20 QoL scale. Global symptom burden, interference and multiple factor groups measured by MDASI-BT were also significantly worse with bevacizumab compared to placebo. If longer PFS but equal OS compared to placebo, rather worse HRQoL (if the analyses of HRQoL for RTOG 0825 was appropriate), and some side effects are realistic, it would suggest no room for bevacizumab to be used in an upfront GBM treatment setting.

#### 4. Treatment Options after Progression on Bevacizumab

It is also challenging to determine treatment options for patients with recurrent GBM who progress after bevacizumab treatment. Currently there is no active regimen in this setting, since previous studies that employed continuing bevacizumab plus another agent, for example irinotecan, carboplatin, etoposide, or dose-intensified TMZ, or discontinuing bevacizumab and treating with an alternative agent failed to show efficacy: mPFS was 1.0–2.6 months, PFS-6m was 0–16%, and mOS was 3–6 months [9,25–27].

There is a concern that discontinuation of bevacizumab after failure in patients with recurrent GBM, may give rise to rapid tumor re-growth with accelerated clinical deterioration, which is recognized as a rebound phenomenon [28]. Mikkelsen and his colleagues reported that 28% of patients who did not respond to bevacizumab showed rebound progression and mOS was only 7 weeks [28]. Some of these patients exhibited a partial response to re-administration of bevacizumab post rebound progressive disease (PD). It is, however, argued that the incidence of rebound phenomenon after bevacizumab discontinuance is relatively rare in other studies, and it may be a matter of interpretation as to the definition [29–31].

Another critical issue that has been addressed is whether continuation of bevacizumab beyond progression (BBP) could enhance survival of patients with recurrent GBM, although its net benefit appears limited as described above. This therapeutic approach has been exploited and proved meaningful in metastatic colorectal cancer in ML18147 randomized phase III study [32]. Patients who received bevacizumab plus standard first line chemotherapy (either oxaliplatin or irinotecan) and exhibited PD were randomly allocated to standard second line chemotherapy either with or without bevacizumab until PD. OS from randomization, the primary endpoint, was significantly longer in patients with bevacizumab continuation than those without, with HR = 0.81 and  $p = 0.0062$ . PFS was also longer in the bevacizumab group (HR = 0.68,  $p < 0.0001$ ) [32]. According to the positive results in colorectal cancer, and the fact that outcome after bevacizumab failure remains dismal, BBP has also drawn attention for recurrent GBM [22,25]. Reardon *et al.* analyzed outcome among patients with recurrent GBM who received subsequent therapy after initial progression on bevacizumab regimens of one of five consecutive, single-arm phase II trials; the bevacizumab partners were either irinotecan, daily TMZ, etoposide, bortezomib, or erlotinib [33]. mOS and OS at 6 months for patients who continued bevacizumab therapy beyond progression ( $n = 55$ ) were 5.9 months and 49.2%, compared with 4.0 months and 29.5% for those treated with a non-bevacizumab regimen ( $n = 44$ ;  $p = 0.014$ ), and bevacizumab continuation was an independent predictor of improved OS (HR = 0.64;  $p = 0.04$ ) [33]. OS for patients who did not receive further therapy after initial PD was only 1.5 months. To confirm whether BBP strategy is beneficial in recurrent GBM, a phase IIb randomized trial (MO28347) has been planned

to initiate in 2013 with estimated enrollment of 510 patients (NCT01860638). Patients with newly diagnosed GBM who are treated with standard TMZ and radiotherapy plus upfront bevacizumab will be randomized upon PD to receive second line therapy either with bevacizumab continuation vs. placebo, which will further proceed to the third line therapy. The primary endpoint is OS from randomization.

### 5. Should Bevacizumab Be Used at First Indication of PD?

Another issue in treating recurrent GBM with bevacizumab that has not been treated with bevacizumab upfront is whether to apply it at the first relapse or to defer until other second line therapies have failed. As discussed above, despite its potent and rapid antitumor or anti-edema effects, tumors will eventually regrow and, at the time of bevacizumab failure, survival expectation is quite limited because of lack of effective follow-up therapies [9,25,26,33]. In the BRAIN trial (bevacizumab vs. bevacizumab + irinotecan), 85 patients in the bevacizumab alone arm comprised 69 (81%) at the first relapse and 16 (19%) at the second. mOS after initiation of bevacizumab was similar in both settings, 9.1 months and 9.2 months, respectively [7]. Omuro *et al.* performed a clinical trial of protracted TMZ regimen in patients with recurrent TMZ-pretreated GBM with or without a history of bevacizumab use. Patients with previous bevacizumab exposure (18 cases) survived significantly less than bevacizumab-naïve patients (19 cases; nine of them received bevacizumab after progression on protracted TMZ) (mOS was 4.3 months vs. 13 months, HR = 3.2;  $p = 0.001$ ) [34], suggesting that bevacizumab may benefit patients with recurrent GBM given even at the second relapse. Piccioni *et al.* analyzed retrospectively patients with recurrent GBM treated with bevacizumab (388 cases) to determine whether the timing of bevacizumab initiation would affect time to progression (TTP) and post-bevacizumab survival after initiation of bevacizumab. Analysis of this data showed that there were no significant differences in any survival periods as median TTP was 4.1, 4.2, and 3.4 months for those treated with bevacizumab at the first recurrence ( $n = 264$ ), at the second recurrence ( $n = 88$ ), and at the third recurrence ( $n = 36$ ), respectively ( $p = 0.165$ ), and median post-bevacizumab survival was 8.5, 8.9, and 6.2 months, respectively ( $p = 0.330$ ) [35]. Since these studies are not intended to evaluate this issue primarily, efficacy and its duration of chemotherapy may be reduced with an increase in number of recurrence. Prospective studies are warranted to address this question. Nonetheless, these results may pose a potential strategy to withhold bevacizumab until further recurrence occurs by applying novel exploratory therapeutics in front at the initial recurrence prior to bevacizumab to benefit survival in cases with good performance status.

### 6. Recurrence with Diffuse Infiltrative Pattern after Bevacizumab Therapy

It has been postulated that anti-angiogenic therapy, such as bevacizumab treatment of GBM, results in an increased incidence of distant and diffuse patterns of radiographic recurrence. One of the potential explanations for this phenomenon is that antiangiogenic therapy only targets the angiogenic-dependent contrast-enhancing components of tumor, but does not target the angiogenic-independent, highly-infiltrating glioma cells at the leading edge demonstrated by FLAIR image [29,36]. Another reason is that after normalization of VEGF-induced abnormally developed tumor vasculature and interstitial edema, remaining glioma cells migrate through preexisting vessels by vessel cooption [37]. Iwamoto *et al.* reported on patterns of relapse in 37 adult patients with recurrent GBM treated with

bevacizumab [38]. Following progression on therapy, 35% of patients showed non-enhancing tumor progression. Norden *et al.* retrospectively evaluated 28 patients with high-grade gliomas treated with bevacizumab and irinotecan with respect to the pattern of disease progression after bevacizumab failure; 18% were diffuse and 18% were distant. However, they also found similar patterns of radiographic recurrence (18% diffuse and 6% distant) in those not treated with bevacizumab [27,39]. Pope *et al.* retrospectively analyzed the data of the prospective BRAIN trial of 167 patients with recurrent GBM treated with bevacizumab and with or without Irinotecan. There were 17% diffuse and 2.4% distant patterns of recurrence after the Stupp regimen prior to bevacizumab. Following bevacizumab treatment, 82% of patients maintained the same in disease pattern, and 16% of patients in the baseline local disease group were converted to a diffuse pattern [40]. Chamberlain *et al.* retrospectively reviewed 80 patients with GBM who were treated with the Stupp regimen initially, followed by bevacizumab monotherapy at first recurrence as for patterns of radiographic presentation. At initial diagnosis, 87.5% of GBM were local and 2.5% were diffuse. At first recurrence after the Stupp regimen, 80% were local and 6.25% were diffuse. At second recurrence following progression on bevacizumab, 71% were local and 11.25% were diffuse, and at third recurrence, they were 71% and 14%, respectively, suggesting that the majority of patients with GBM manifest local disease and maintain the same pattern regardless of multiple recurrence and use of bevacizumab [41]. This issue has been addressed in a prospective manner in a large international phase III AVAglio trial for patients with newly diagnosed GBM as discussed earlier. Patterns of radiographic progression were assessed in 65% of patients enrolled in the study as compared to the baseline. At baseline, a diffuse pattern was observed in 60% of placebo arm and 70% of bevacizumab arm. Non-diffuse tumors (placebo arm 40%; Bev arm 30%) changed to a diffuse pattern at progression in 22.8% and 24.7% cases, respectively, indicating no significant increase in induction of an invasive pattern of recurrence following upfront bevacizumab treatment [42]. Based on these data from clinical trials and experiences, it does not seem a universal phenomenon that anti-angiogenic therapies induce preferentially diffuse invasive progression in GBM, although a number of basic research studies have implicated it through several distinct mechanisms including a shift of major pro-angiogenic factors from VEGF to others, such as c-Met or SDF (discussed later), and it is still challenging to define response and progression radiographically following bevacizumab treatment which may result in different interpretation of patterns of recurrence.

## 7. Bevacizumab Dosing

As bevacizumab is usually administered at 10 mg/kg, every 2-week interval, it is still unclear which dosing schedule is the most optimal for bevacizumab monotherapy in recurrent GBM. To analyze its dose-response effect, Wong *et al.* performed a meta-analysis of 15 studies published from 2005 to 2009, involving 548 patients treated with bevacizumab for recurrent GBM and showed that there was no difference in bevacizumab dose-response benefit between 5 mg/kg and 10 to 15 mg/kg [43]. If the dosing could be lowered to 5 mg/kg, reduced bevacizumab use results in a substantial savings of medical cost. The cost-effectiveness of 5 vs. 10 mg/kg of bevacizumab dose in GBM patients needs to be prospectively examined.

## 8. Next Steps and Future Directions

Disease progression, as reflected by tumor growth and, probably enhanced, metastasis/invasion during treatment with inhibitors of VEGF signaling, is attributed to multiple interacting mechanisms. Among them are activation of pathways that favor epithelial-mesenchymal transition, promotion of invasiveness, and induction of tolerance and activation of cancer stem cells. Disease progression during treatment with bevacizumab paired with chemotherapy does not necessarily mean that the inhibitor has lost efficacy [44]. The resistance could be due to the chemotherapy. Evidence of better OS in metastatic colorectal cancer, when bevacizumab is continued beyond progression in the presence of diverse types of chemotherapy, reflects the continued involvement of VEGF as mentioned before [45].

However, some effects of VEGF inhibitors that slow tumor growth can still promote invasion and metastasis in certain models [46,47]. Tumors with high MET expression or activating mutations of MET are generally more aggressive and have a less favorable prognosis [48]. The activation of MET can promote epithelial-mesenchymal transition and tumor invasiveness [49,50], partly by increasing the activity of transcriptional repressors, such as snail homolog 1 (*SNAIL*; also known as *SNAIL*), *ZEB1* and *TWIST1*, that reduce E-cadherin expression, increase N-cadherin expression and turn on the expression of other mesenchymal markers [51]. Inhibition of VEGF signaling can result in decreased expression of epithelial markers and increased expression of mesenchymal markers such as *SNAIL1*, *TWIST1* in preclinical models [52,53]. The expression of the mesenchymal marker fascin increases in GBMs after treatment with bevacizumab [54].

Targeting angiogenesis and tumor progression/invasion/metastases together has recently shown promise as a strategy for preventing escape from inhibitors of VEGF signaling [54]. One approach is the inhibition of MET and VEGF signaling together, either by concurrent administration of selective inhibitors or by single agents that block both receptors [cabozantinib (also known as XL184) or foretinib (also known as XL880)] [55,56]. Concurrent inhibition of MET and VEGF signaling can slow tumor growth, decrease invasion and metastasis, and change invasive tumors into a shape with a ball-like appearance in certain models. The therapeutic benefit of this approach is currently being evaluated in clinical trials of multiple tumor types.

Cabozantinib, which inhibits MET, AXL and VEGF receptors, as well as multiple other receptor tyrosine kinases, is a potent inhibitor of invasion and metastasis in spontaneous and xenograft tumors in mice [55,56]. Cabozantinib has better effects on tumor angiogenesis and survival than those found with combinations of selective inhibitors of MET and VEGF signaling in the same model, suggesting that AXL or other targets (such as RET, KIT and TIE2) contribute to the efficacy of cabozantinib [57]. Cabozantinib is showing promising results in clinical trials of castration-resistant metastatic prostate cancer, medullary thyroid cancer, breast cancer, NSCLC, malignant melanoma, liver and ovarian cancers [58,59]. It remains to be determined if clinical trials with such dual or multiple inhibitors will effectively impact GBM recurrence and invasion. Blocking both angiogenesis and escape pathways is now an attainable step in the evolution of the use of agents that inhibit VEGF signaling together with other targets. The current knowledge of tumor vascular biology and mechanisms of tumor growth, invasion and metastasis, will enable these approaches. Steps that still need to be taken include learning more about escape mechanisms, identifying additional targeted drugs that act synergistically with angiogenesis inhibitors. Predictive biomarkers to identify patients who will have benefit from such approaches is also important.

## Conflicts of Interest

Motoo Nagane has received honoraria from Chugai Pharmaceutical Co. Ltd. and MSD KK. Ryo Nishikawa has received honoraria from Chugai Pharmaceutical Co. Ltd., MSD KK., Eisai Co., Ltd., and Hoffmann-La Roche.

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