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Boron neutron capture therapy and add-on bevacizumab in patients with recurrent malignant glioma

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Abstract

Background: Although boron neutron capture therapy has shown excellent survival data, previous studies have shown an increase in radiation necrosis against recurrent malignant glioma. Herein, we proposed that bevacizumab may reduce radiation injury from boron neutron capture therapy by re-irradiation. We evaluated the efficacy and safety of a boron neutron capture therapy and add-on bevacizumab combination therapy in patients with recurrent malignant glioma.

Methods: Patients with recurrent malignant glioma were treated with reactor-based boron neutron capture therapy. Treatment with bevacizumab (10 mg/kg) was initiated 1–4 weeks after boron neutron capture therapy and was administered every 2–3 weeks until disease progression. Initially diagnosed glioblastomas were categorized as primary glioblastoma, whereas other forms of malignant glioma were categorized as non-primary glioblastoma.

Results: Twenty-five patients (14 with primary glioblastoma and 11 with non-primary glioblastoma) were treated with boron neutron capture therapy and add-on bevacizumab. The 1-year survival rate for primary glioblastoma and non-primary glioblastoma was 63.5% (95% confidence interval: 33.1–83.0) and 81.8% (95% confidence interval: 44.7–95.1), respectively. The median overall survival was 21.4 months (95% confidence interval: 7.0–36.7) and 73.6 months (95% confidence interval: 11.4–77.2) for primary glioblastoma and non-primary glioblastoma, respectively. The median progression-free survival was 8.3 months (95% confidence interval: 4.2–12.1) and 15.6 months (95% confidence interval: 3.1–29.8) for primary glioblastoma and non-primary glioblastoma, respectively. Neither pseudoprogression nor radiation necrosis were identified during bevacizumab treatment. Alopecia occurred in all patients. Six patients experienced adverse events ≥grade 3.

Conclusions: Boron neutron capture therapy and add-on bevacizumab provided a long overall survival and a long progression-free survival in recurrent malignant glioma compared with previous studies on boron neutron capture therapy alone. The add-on bevacizumab may reduce the

detrimental effects of boron neutron capture therapy, including pseudoprogression and radiation necrosis. Further studies of the combination therapy with a larger sample size and a randomized controlled design are warranted.

Key words: bevacizumab, boron neutron capture therapy, glioblastoma, malignant glioma, re-irradiation

Introduction

No effective treatment currently exists for recurrent malignant glioma (MG) following standard treatment with temozolomide concomitant with 60-Gy radiation therapy. Bevacizumab is a useful agent for recurrent MG, which has been found to extend survival time by 3 months compared with other treatments in a small study with recurrent glioblastoma (1). In contrast, a randomized trial revealed that bevacizumab could improve progression-free survival (PFS) without extending the overall survival (OS) rates for recurrent glioblastoma (2). Hence, many novel therapies are under development for clinical use. Re-irradiation is among the treatment options for recurrent MG. However, stereotactic radiosurgery (SRS)/stereotactic radiotherapy (SRT) after 60-Gy external beam radiation therapy results in radiation necrosis in various rates up to 40% of patients (3–5). Our institute has evaluated the feasibility and efficacy of boron neutron capture therapy (BNCT) as a treatment for MG (6). Our previous research has shown a marked prolongation of survival in patients with MG treated with BNCT. In particular, BNCT tended to provide survival benefit for patients classified into recursive partitioning analysis (RPA) classes 3 and 7, who had poorer prognostic factors (7) compared with other RPA classes. BNCT is a tumor-selective particle radiation therapy in which boron-10, a stable isotope, is subjected to thermal neutron capture and divides into high linear-energy-transfer α and Li particles. These particles are released with a short range of 5–9 μm, which is shorter than the diameter of a cell. Hence, cells containing boron-10 are selectively damaged and killed by these particles. Boronophenylalanine (BPA) is accumulated in cells through an L-amino acid transporter-1 (8). L-amino acid transporter-1 is upregulated in glioma cells (9). BNCT is, therefore, able to irradiate glioma cells at a higher dose compared with normal cells in the tumor center or just around the tumor tissue.

Based on this principle of operation, BNCT can be possibly applied in recurrent MG previously treated with 60-Gy radiation therapy. However, our previous research found radiation necrosis to be a significant risk for recurrent MG following BNCT. This is because normal brain tissue, including vasculatures, is still irradiated with a small dose by BNCT, despite the greater focus on tumor cells. Moreover, we experienced rapid tumor responses after BNCT, including pseudoprogression, sometimes with acute phase symptoms (6, 10, 11). Bevacizumab is effective not only as a treatment for MG but also in reducing radiation necrosis and pseudoprogression (11–13). The combination therapy of re-irradiation and bevacizumab results in significantly less frequent radiation necrosis compared with re-irradiation alone (14). Our previous preliminary report indicated that early treatment with bevacizumab after BNCT could prevent and control radiation necrosis, stabilize the neurological state and prolong survival time in patients with recurrent MG (15). Here, we report the results of treatment with BNCT and add-on bevacizumab for recurrent MG with further treated patients to elucidate the effects of this combination therapy.

Patients and methods

Eligible patients

Patients aged between 15 and 75 years had histologically confirmed MG and had experienced more than one relapse after first-line therapy. Patients were required to have a Karnofsky performance status (KPS) $\geq$ 60%, normal bone marrow, liver, kidney and lung functions, and a life expectancy greater than 3 months. Kyoto University research reactor was used as the neutron source for BNCT. The reactor was required to suspend operation for several months a year for regular maintenance. Therefore, patient enrollment was suspended temporarily during these periods. The inclusion criterion for BNCT was a supratentorial single tumor located in the ipsilateral hemisphere without leptomeningeal dissemination. The exclusion criteria were as follows: active infection, diabetes, pregnancy and severe comorbidities, such as cardiovascular diseases, pneumonia, coagulopathy and uncontrollable hypertension. Patients with phenylketonuria, current bleeding, thromboembolism within the past 6 months, unstable control of anticoagulant therapy and allergies to BPA or bevacizumab were also excluded.

This study was approved by the institutional ethical committee of Osaka Medical and Pharmaceutical University (No. 1386). Written informed consent was obtained from all patients.

BNCT and add-on bevacizumab

The clinical regimen of BNCT has been described previously (15). Briefly, intravenous administration of BPA began at 2 h before neutron irradiation and continued at a rate of 200 mg/kg/h until neutron irradiation and at a rate of 100 mg/kg/h during neutron irradiation. BPA concentration in tumor tissue was estimated using the blood concentration of BPA and a tumor/blood (T/B) concentration ratio of 3.5. If patients underwent ^{18}F-BPA-PET before BNCT, the T/B ratio was calculated from PET data. As mentioned, the Kyoto University research reactor was used as the neutron source. The patient's head was held in place with a collimator. Neutron irradiation was planned using the simulation environment for radiotherapy applications software (Idaho National Engineering and Environmental Laboratory, Idaho Falls, ID) and was performed so that the maximum dose to normal brain tissue was less than 13 Gy-equivalent.

Bevacizumab treatment was initiated 1–4 weeks after BNCT; 10-mg/kg Bevacizumab were administered every 2–3 weeks until disease progression. In addition to disease progression, bevacizumab administration was discontinued when adverse events precluded it, physicians decided that bevacizumab should be discontinued, or at the patient's request.

Efficacy and safety assessments

Clinical and radiological assessments were performed every 2–3 months. Most patients were referred to our institute from other provinces. In such cases, patient data, including radiological images and patient status, were provided to our institute by

physicians from those provinces. Tumor responses were assessed by two neurosurgeons (MF, S-IM) using response assessment in neuro-oncology (RANO) criteria (16). In clinical practice, pseudoprogression and radiation necrosis were fundamentally defined as follows: pseudoprogression referred to an enhanced lesion and/or perifocal edema that was enlarged within 12 weeks after BNCT and spontaneously resolved on subsequent magnetic resonance imaging (MRI). In contrast, radiation necrosis was defined when the enhanced lesions were enlarged with a soap bubble-like appearance, a Swiss cheese appearance and periventricular enhancement. When radiation necrosis could not be differentiated from tumor progression on MRI, we recommended amino acid positron emission tomography if possible. The primary endpoint was 1-year survival rate after BNCT. The secondary endpoints were OS and PFS after BNCT, and safety. In our previous report on the use of BNCT for recurrent MG, the 1-year survival rate for glioblastoma was 26.3% (6). The predicted 1-year survival rate for BNCT and add-on bevacizumab was 50%. With an α error of 0.05 in a two-sided binomial test and a power of 0.9, the required sample size was estimated to be 41 patients. Considering the inclusion of patients with grade 3 glioma, 50 patients were set as the required sample size for this study. Tumor diagnosis for our cohort was primarily morphological. Information on molecular diagnosis was insufficient because many patients were initially diagnosed with MG before or around 2016. Therefore, initially diagnosed (*de novo*) glioblastoma was categorized as primary glioblastoma (pGBM), whereas other forms of MG, including secondary glioblastoma and grade 3 glioma, were categorized as non-pGBM. Equivalent dose in 2 Gy (EQD2) of BNCT was calculated based on the Linear Quadrantic model. The $\alpha\beta$ ratios for tumor and normal brain were 10 and 3, respectively. Statistical analyses were performed using the JMP® Pro 15.1.0. software (SAS, Cary, NC). Survival estimates were determined using the Kaplan–Meier method. Graphs were constructed using GraphPad Prism v. 6.03 J software (GraphPad, La Jolla, CA). The Cox proportional hazards model was used to calculate the hazard ratios for risk of death. In the Cox proportional hazards model, continuous variables were categorized using RPA.

Results

Patient enrollment was suspended temporarily between June 2014 and July 2017 because of renovating the reactor for earthquake resistance. Enrollment was also discontinued in February 2019 because the Kyoto University research reactor stopped irradiation for clinical use, and the clinical trial of BNCT using the accelerator as the neutron source was launched for recurrent MG. Twenty-five patients were treated with BNCT and add-on bevacizumab between June 2013 and February 2019. Patient demographics are shown in Table 1. There were 16 male and 9 female participants, with a median age of 53 years (range: 20–68 years), and 14 patients were classified with pGBM and 11 with non-pGBM. The histological diagnoses of non-pGBM were secondary GBM in two patients, anaplastic astrocytoma in two patients, anaplastic oligodendroglioma in two patients and anaplastic oligoastrocytoma in five patients. KPS at tumor recurrence was 100% in five patients, 90% in seven patients, 80% in four patients, 70% in seven patients and 60% in one patient, and 8 patients relapsed in the first pre-BNCT period, 10 patients in the second and 7 patients in the third. The median gross tumor volume was 35.1 ml (range: 6.6–83.6). The median period between the initial diagnosis and BNCT was 18.5 months (range: 8.8–161.8). The median values of maximum and minimum tumor doses were 75.6 Gy-equivalent (range: 35.9–151) and 39.4 Gy-equivalent (range: 16.0–83.1), respectively. The median value of the maximum normal brain dose was 11.2 Gy-equivalent (range: 5.67–13.7). In terms of EQD2, the maximum and minimum tumor doses were 539.28 Gy (range: 137.32–2025.92) and 162.2 Gy (range: 34.67–409.76), respectively. The maximum normal brain dose by EQD2 was 31.81 Gy (range: 9.83–45.67).

The median follow-up period was 17.4 months [95% confidence interval (CI): 16.1–31.8]. The median OS and PFS for all patients after BNCT were 24.7 months (95% CI: 11.4–73.6) and 12.1 months (95%CI: 8.0–15.1), respectively. The 1-year survival rate for pGBM and non-pGBM was 63.5% (95% CI: 33.1–83.0) and 81.8% (95% CI: 44.7–95.1), respectively. The median OS was 21.4 months (95% CI: 7.0–36.7) for pGBM and 73.6 months (95% CI: 11.4–77.2) for non-pGBM (Fig. 1a; log-rank test, $P = 0.0428$). The median PFS values for pGBM and non-pGBM were 8.3 months (95% CI: 4.2–12.1) and 15.6 months (95% CI: 3.1–29.8), respectively (Fig. 1b; log-rank test, $P = 0.0207$). Complete and partial responses were obtained from 6 to 12 patients, respectively [Fig. 2; objective response rate (ORR) 72%; 95% CI: 52.4–85.7]. The median time to the maximum decrease in the sum of perpendicular diameters from BNCT was 2.3 months (95% CI: 0.8–5.9). There were no statistically significant differences between the ORR of patients with pGBM and non-pGBM.

Regarding pGBM, correlations between clinical factors and OS were analyzed using the Cox proportional hazards model. Age, KPS, the number of relapses, gross tumor volume, the period between the initial diagnosis and BNCT and BNCT doses were categorized by RPA into two groups. Table 2 shows the univariate analysis of OS for pGBM. Only gross tumor volume <44 ml was significantly associated with longer survival in patients with pGBM (hazard ratio 0.10; 95% CI: 0.01–0.88; $P = 0.0382$). An illustrative case is shown in Fig. 3.

There were no cases of pseudoprogression and radiation necrosis identified by MRI during bevacizumab treatment. All patients experienced grade 2 alopecia. Moreover, other adverse events were reported in 15 patients (60%). Adverse events ≥grade 3 were grade 3 proteinuria in four patients, grade 5 meningitis in one patient and grade 5 acute myocardial infarction in one patient. Here, grade 5 AEs are as follows. Chest pain occurred suddenly to the patient who experienced myocardial infarction that was followed by cardiopulmonary arrest 13 days after the last dose of bevacizumab administered. The patient underwent percutaneous cardiopulmonary support and coronary intervention, and intra-aortic balloon pumping. However, the patient did not recover and died 3 days after the onset of myocardial infarction (21.4 months after BNCT). In contrast, bacterial meningitis occurred at 4 months after BNCT in the other patient with a grade 5 adverse event. Although meningitis was found to be improved in response to antibiotics, the patient recurred following their discontinuation. The source of infection was unknown. Cisternography showed no evidence of cerebrospinal fluid leakage. The patient suffered from disturbed consciousness and died 65 days post-admission for meningitis.

Discussion

Treatment of recurrent MG after the first-line therapy, especially in cases of glioblastoma, is an ongoing challenge. Re-irradiation has been considered a treatment option for recurrent MG. Clinical practice guidelines recommend re-irradiation to improve local tumor control without concurring survival benefits (class III evidence) (17).

Table 1. Patient demographics

	All patients ($n = 25$)	pGBM ($n = 14$)	Non-pGBM ($n = 11$)
Median age, years (range)	53 (20–68)	59.5 (20–68)	48 (36–66)
Sex, *n* (%)			
Male	16 (64.0)	10 (71.4)	6 (54.5)
Female	9 (36.0)	4 (28.6)	5 (45.5)
Karnofsky performance status, *n* (%)			
100	5 (20.0)	2 (14.3)	3 (27.3)
90	7 (28.0)	4 (28.6)	3 (27.3)
80	4 (16.0)	3 (21.4)	1 (9.1)
70	8 (32.0)	4 (28.6)	4 (36.4)
60	1 (4.0)	1 (7.1)	0 (0.0)
Number of relapsing times, *n* (%)			
First	8 (32.0)	7 (50.0)	1 (9.1)
Second	10 (40.0)	6 (42.9)	4 (36.4)
Third	7 (28.0)	1 (7.1)	6 (54.5)
Median gross tumor volume, ml (range)	35.1 (6.6–83.6)	37.5 (6.6–83.6)	35.1 (7.1–46.8)
Median period between initial diagnosis and BNCT, months (range)	18.5 (8.8–161.8)	14.0 (8.8–53.7)	58.1 (10.7–161.8)
BNCT dose, Gy-equivalent (range)			
Maximum tumor dose	75.6 (35.9–151)	72.5 (35.9–96.2)	77.9 (61.2–151)
Minimum tumor dose	39.4 (16.0–65.3)	41.6 (16.0–65.3)	36.8 (23.0–63.9)
Maximum normal brain dose	11.2 (5.67–13.7)	11.4 (5.67–13.7)	11.1 (9.18–12.0)

BNCT, boron neutron capture therapy; pGBM, primary glioblastoma.

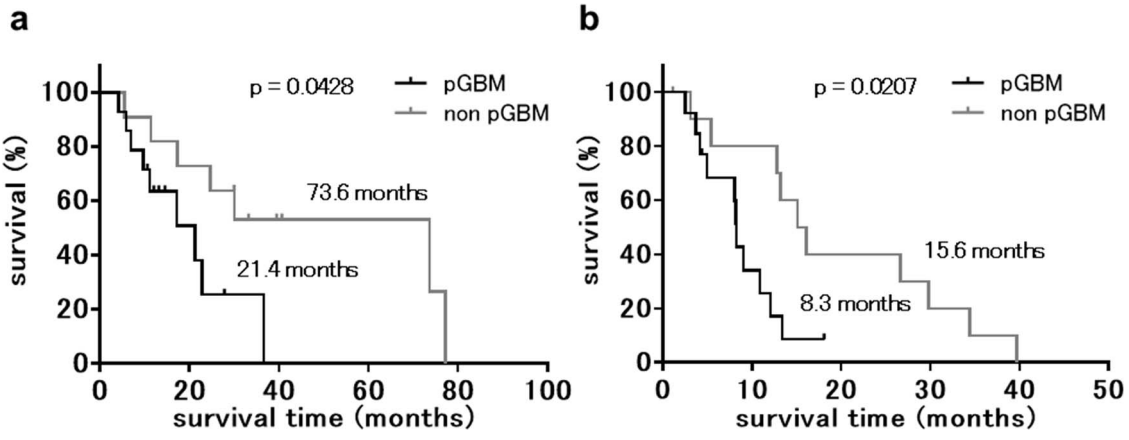

Figure 1. Kaplan–Meier estimates of (a) overall survival and (b) progression-free survival from boron neutron capture therapy (BNCT) in patients with recurrent malignant glioma.

However, a recent systematic review of re-irradiation research yielded encouraging results in terms of both disease control and survival rates (18). With regard to radiation modality, SRS or fractionated SRT is usually utilized in the treatment of recurrent MG. In a recent meta-analysis of CyberKnife treatment for recurrent MG, the median OS values after CyberKnife were 11 and 8.4 months for grade 3 and grade 4 gliomas, respectively (19). A comparison between single-session SRS and fractionated SRS revealed no statistical differences between PFS and OS for MG (PFS, 4.5 and 4.6 months; OS, 12.7 and 12.6 months, respectively) (3).

Re-irradiation combined with chemotherapy, especially using bevacizumab, has been found to produce better outcomes than re-irradiation alone in patients with recurrent MG. In current chemotherapy regimens, a bevacizumab-based regimen has been found to improve PFS but not OS in patients with recurrent glioblastoma (20). Linear-accelerator SRS with adjuvant bevacizumab results in significantly longer PFS and OS (5.2 and 11.2 months, respectively) than SRS alone (2.1 and 3.9 months, respectively) for recurrent glioblastoma (21). A systematic review of radiotherapies, including fully or hypo fractionated SRT and SRS with or without bevacizumab, for recurrent MG has also found that a combination of radiotherapy and bevacizumab results in longer PFS and OS (5.6 ± 1.0 and 11.2 ± 2.1 months, respectively) than radiotherapy alone (5.2 ± 1.6 and 9.9 ± 2.1 months, respectively), but the difference was not statistically significant (22). In a sub-analysis of radiation modalities, only fractionated SRT showed significantly longer OS in the bevacizumab group than in the non-bevacizumab group (11.3 ± 1.6 and 9.4 ± 1.6 months, respectively), but not PFS (6.4 ± 0.9 and 5.2 ± 1.4 months, respectively).

Bevacizumab can control brain radiation necrosis, reducing perilesional edema and contrast enhancement (13, 23). Brain radiation necrosis, with or without symptomatic brain edema, occurred at

Table 2. The univariate analysis with Cox proportional hazards model

Variables	Category	*n*	Hazard ratio	*P* value
Age	<56 years	5	0.52 (0.11–2.44)	0.4089
Sex	Male	10	1.55 (0.31–7.78)	0.5920
Karnofsky performance status	90–100%	6	0.42 (0.10–1.83)	0.2482
Number of relapsing times	1st relapse	5	1.17 (0.29–4.75)	0.8218
Gross tumor volume	<44.0 ml	7	0.10 (0.01–0.88)	0.0382
Period from initial diagnosis	<12.7 months	3	0.13 (0.02–1.14)	0.0660
BNCT dose				
Maximum tumor dose	≥73.2 Gy-equivalent	5	0.51 (0.12–2.22)	0.3656
Minimum tumor dose	≥45.9 Gy-equivalent	5	0.15 (0.02–1.28)	0.0829
Maximum normal brain dose	≥10.6 Gy-equivalent	9	0.47 (0.09–2.39)	0.3600

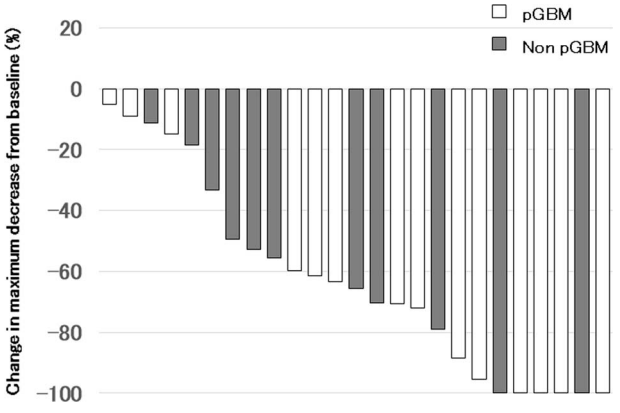

Figure 2. Changes in the maximum percentage decrease of the sum of the perpendicular diameters of tumors from the baseline. The white bar represents primary glioblastoma; the gray bar represents non-primary glioblastoma.

a significantly lower rate in patients with recurrent MG treated with re-irradiation using intensity-modulated radiation therapy or volumetric-modulated arc therapy plus bevacizumab compared with patients treated with re-irradiation alone (1-year risk rates of 23.9 and 54.1%, respectively) (14). SRS with bevacizumab also revealed a lower incidence of radionecrosis (5%) than SRS without bevacizumab (19%) (21). Therefore, addition of bevacizumab to SRS permits an increase in the median prescription dose up to 22 Gy without significant adverse events associated with SRS alone in recurrent glioblastoma (24).

We have previously reported a retrospective study of BNCT in patients with recurrent MG using the same reactor for neutron source as in the current study (6). The 1-year survival rate for glioblastoma was 26.3%. The median OS was 10.8 months for all cases and 9.6 months for recurrent glioblastoma cases. Table 3 shows patient characteristics in both the present and our previous studies to allow a comparison between the background of patients treated with combination therapy of BNCT and bevacizumab, and BNCT alone. It is shown that there is no significant difference in the distribution of RPA classes and BNCT doses between the two groups. In non-pGBM, however, the BNCT group had a significantly higher rate of grade 4 tumor (secondary GBM) compared with the combination group (Pearson's Chi-square test, $P = 0.0408$). Moreover, there was a significant difference in the population of patients undergoing temozolomide treatment prior to BNCT between the two groups. (Pearson's Chi-square test, pGBM, $P = 0.0007$; non-pGBM, $P = 0.0001$). Therefore, the survival outcome in this study should not be directly compared with the findings of our previous BNCT study because these factors could be associated with patient survival.

Our recent phase II trial of BNCT using a cyclotron-based neutron generator showed that the 1-year survival rate, and the median PFS and OS for recurrent glioblastoma were 79.2%, 0.9 and 18.9 months, respectively (25). The acute tumor response to irradiation may explain the long median OS but the short median PFS. This trial prohibited the use of bevacizumab until disease progression was assessed on MRI after BNCT. Pseudoprogression and radiation injuries, such as radiation necrosis and brain edema in the acute phase, were regarded as disease progression based on the RANO criteria (16). In contrast, in this current study, bevacizumab was initiated within 4 weeks of BNCT, and there was no pseudoprogression or radiation necrosis identified by MRI during bevacizumab treatment. Therefore, the median PFS of 8.3 months was longer than that for BNCT without bevacizumab. The early induction of bevacizumab treatment could suppress radiation toxicity after BNCT, as with other radiation therapies. To evaluate the survival benefit of BNCT and add-on bevacizumab more clearly, we compared the OS in this combination therapy with our historical control, which was treated with bevacizumab in recurrent pGBM (without BNCT). Among 14 pGBM patients, 12 patients were matched to patients in our bevacizumab group using a propensity score matching model. The median OS were 17.2 months (95% CI: 5.9–36.7) for the combination group and 11.3 months (95% CI: 1.4–17.4) for the bevacizumab group, respectively, but there was no statistically significant difference (Fig. 4; log-rank test, $P = 0.3248$). A larger sample size could be required to draw the conclusion.

Recently, a Taiwanese research group reported a lower tumor dose on BNCT (range: 8.51–25.09 Gy-equivalent) compared with other reports focusing on the treatment of recurrent MG with life-threatening, end-stage status (26). Their median PFS and OS were 4.18 and 7.25 months, respectively. The authors reported no adverse reactions, including no radiation necrosis. Although lower-dose BNCT might prevent the occurrence of radiation injury, this lower dose reduced the survival benefits provided by BNCT seen in the regimen of the Taiwanese study in comparison with our current series. Compared with other radiation therapies, BNCT can be applied to recurrent MG in larger volumes. The median gross tumor volume was 35.1 ml in this cohort. The median treated volume for SRS ranged from 2 to 20.1 ml in re-irradiation of glioblastoma (27). Even in this study, however, a small tumor volume (<44.0 ml)

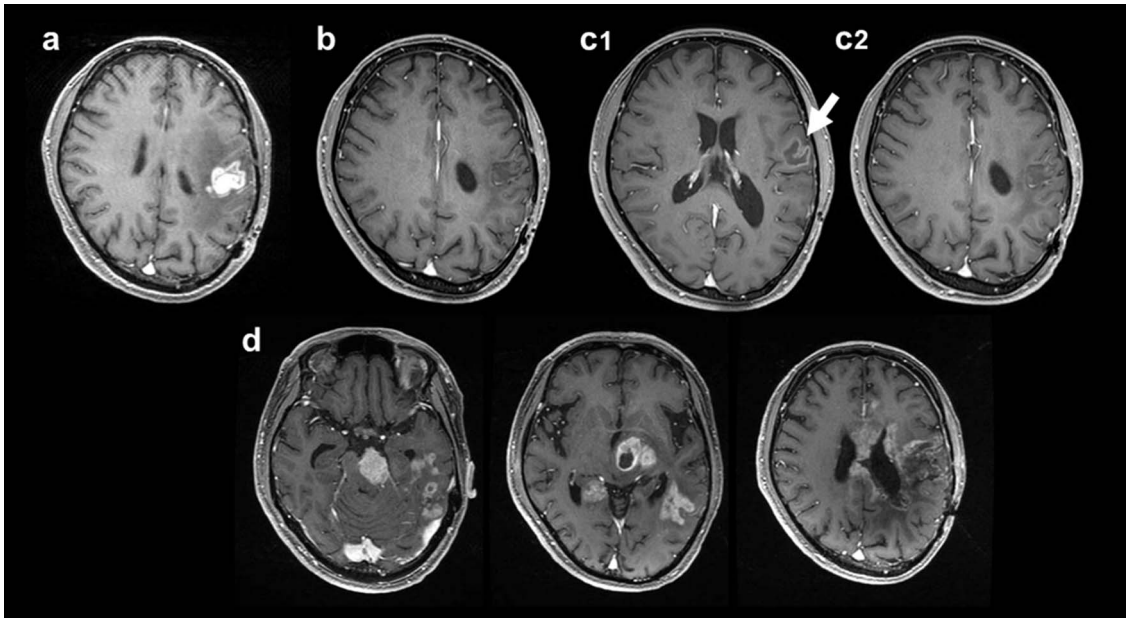

Figure 3. An illustrative responsive case with a long survival time. (a) A 44-year-old man with primary glioblastoma had his first recurrence at 8.8 months after the operation. BNCT and add-on bevacizumab treatment were applied to a recurrent tumor with a gross tumor volume of 16.8 ml; (b) the tumor shrank was completely remitted 3 months after BNCT; (c) the tumor recurred (c1, white arrow), although the original tumor volume targeted by BNCT was well-controlled (c2) 8.2 months after BNCT; (d) chemotherapy was continued beyond progression, but the patient died 36.7 months after BNCT.

Table 3. Comparison of patient characteristics treated with combination of BNCT and bevacizumab, and BNCT

	pGBM			Non-pGBM		
	BNCT and bevacizumab ($n = 14$)	BNCT alone ($n = 11$) (Ref. 6)	*P* value	BNCT and bevacizumab ($n = 11$)	BNCT alone ($n = 11$) (Ref. 6)	*P* value
RPA class, *n* (%)						
Class 1				4 (36.4)	2 (18.2)	0.5134
Class 2				2 (18.2)	4 (36.4)	
Class 3				5 (45.5)	5 (45.5)	
Class 4	2 (14.3)	3 (27.3)	0.5309			
Class 5	1 (7.1)	2 (18.2)				
Class 6	1 (7.1)	0 (0.0)				
Class 7	10 (71.4)	6 (54.6)				
Tumor histology						
Primary glioblastoma	14 (100.0)	11 (100.0)				
Secondary glioblastoma				2 (18.2)	8 (72.7)	0.0408
Anaplastic astrocytoma				2 (18.2)	2 (18.2)	
Anaplastic oligodendroglioma				2 (18.2)	0 (0.0)	
Anaplastic oligoastrocytoma				5 (45.5)	1 (9.1)	
TMZ prior to BNCT, n (%)	13 (92.7)	3 (27.3)	0.0007	10 (90.9)	1 (9.1)	0.0001
BNCT dose, Gy-equivalent						
Minimum tumor dose	41.6 (16.0–65.3)	34.9 (19.7–59.0)	0.6416	36.8 (23.0–63.9)	29.3 (12.7–73.9)	0.2786
Maximum normal brain dose	11.4 (5.67–13.7)	11.7 (7.5–13.8)	0.4272	11.1 (9.18–12.0)	9.9 (3.7–14.2)	0.5326
Overall survival, months	21.4 (7.0–36.7)	10.3 (6.0–12.3)	0.0072	73.6 (11.4–77.2)	10.8 (4.4–32.4)	0.0237

pGBM, primary glioblastoma; RPA, recursive partitioning analysis.
Note: Reference (6).

was significantly associated with longer OS in patients treated with BNCT. Hence, small tumors respond better to re-irradiation compared with large tumors, even with BNCT. A trend emerged in that the minimum tumor dose was correlated to longer OS; however, this correlation was not statistically significant.

There were several limitations to this study. Most of the BNCT patients included were referred to our institute from other provinces in Japan and even from abroad. Therefore, follow-up data were obtained mainly from local physicians' reports. Under these circumstances, some data were missing, and follow-up periods were

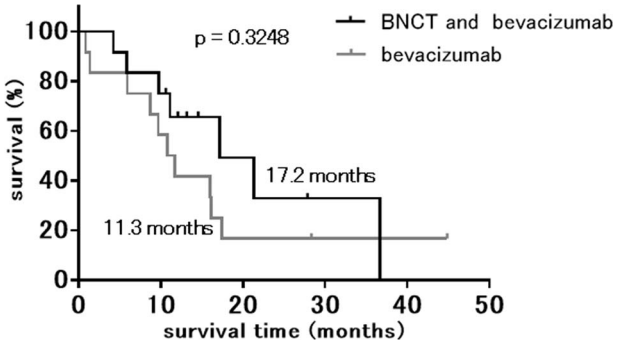

Figure 4. Kaplan–Meier estimates of overall survival in patients with primary glioblastoma. The survival curves of the combination of BNCT and add-on bevacizumab, and bevacizumab treatment in our institute were compared. Twelve patients with combination therapy were matched to patients treated with bevacizumab after recurrence by a propensity score matching model.

irregular. Contrary to serious adverse events, mild adverse events were not reported properly, something that can be deduced from their lower frequency than that experienced in other clinical trials with bevacizumab. The majority of patients were diagnosed with MG histologically rather than molecularly. As IDH wild- and mutant-type tumors are biologically different, information on the molecular status of MG should be obtained to compare treatment effects with the results of other recent therapies. This study included a small number of patients. The reactor required inspection for several months, and its operation was suspended for earthquake-resistant renovation for 3 years. Therefore, it was not always possible to enroll candidates for this study. Finally, this study was discontinued midway through because the use of the Kyoto University research reactor for clinical irradiation ceased in order to launch clinical trials with accelerator-based BNCT. This study was designed with a single arm of BNCT and add-on bevacizumab. The efficacy of add-on bevacizumab to BNCT would have been demonstrated more clearly by a two-arm study comparing BNCT and add-on bevacizumab to treatment with bevacizumab alone.

Conclusions

Our experience has shown that BNCT is a promising alternative treatment for recurrent MG. However, our previous study demonstrated that BNCT results in shorter PFS because of pseudoprogression or radiation necrosis. Add-on bevacizumab can resolve this effect and result in high ORR and extended PFS. Accelerator-based BNCT is currently under review for on-label use, pending approval for clinical use as an alternative to reactor-based BNCT. Further research with a larger sample and randomized controlled design using accelerator-based BNCT and add-on bevacizumab is required to elucidate the efficacy and safety of this combination therapy.

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Authors' contribution

Conception and design: S.I.M. Operation of BNCT: N.K., H.T., Y.S., M.S., K.O. Data acquisition: K.T., H.S. Analyses and interpretation of data: M.F., S.K., S.I.M. Manuscript drafting: M.F. Study supervision: M.W., S.I.M.

Availability of data and material

The datasets analyzed in the current study are available from the corresponding author on reasonable request.

Code availability

Not applicable.

Ethics approval/Consent to participate

All patients signed a written informed consent, and the study was approved by the Ethics Committee of Osaka Medical and Pharmaceutical University (No. 1386).

Consent to publication

Not applicable.

Conflicts of interest statement

There are no conflicts of interest concerning the materials or methods used in this study.

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