Boron Neutron Capture Therapy and Add-on Bevacizumab in Patients with Recurrent Malignant Glioma

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Research Article

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

Posted Date: September 27th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-930901/v1

Version of Record: A version of this preprint was published at Japanese Journal of Clinical Oncology on January 1st, 2022. See the published version at https://doi.org/10.1093/jjco/hyac004.

Abstract

Introduction: Boron neutron capture therapy (BNCT) has shown excellent survival data but increases in radiation necrosis against recurrent malignant glioma (MG) in previous studies. We proposed that bevacizumab may reduce radiation injury from BNCT by re-irradiation. We evaluated the efficacy and safety of a combination therapy of BNCT and add-on bevacizumab in patients with recurrent MG.

Methods: Patients with recurrent MG were treated with reactor-based BNCT. Treatment with bevacizumab (10 mg/kg) was initiated 1–4 weeks after BNCT irradiation and was re-administered every 2–3 weeks until disease progression. Initially diagnosed glioblastomas were categorized as primary glioblastoma (pGBM) and other forms of MG were categorized as non-pGBM.

Results: Twenty-five patients (14 with pGBM and 11 with non-pGBM) were treated with BNCT and add-on bevacizumab. 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) and 73.6 months (95% CI, 11.4–77.2) for pGBM and non-pGBM, respectively (p = 0.0428). The median PFS was 8.3 months (95%CI, 4.2–12.1) and 15.6 months (95% CI, 3.1–29.8) for pGBM and non-pGBM, respectively (p = 0.0207). Alopecia occurred in all patients. Six patients experienced adverse events ≥ grade 3.

Conclusions: BNCT and add-on bevacizumab were found to provide both a long OS and a long PFS, compared to the previous studies of BNCT alone for recurrent MG. The add-on bevacizumab may reduce the detrimental effects of BNCT radiation, including pseudoprogression and radiation necrosis.

Introduction

The standard treatment for malignant glioma (MG) is temozolomide concomitant with 60-Gy radiation therapy. This extends overall survival (OS) by 2.5 months in patients with newly-diagnosed glioblastoma [1]. However, no effective treatment currently exists for the treatment of MG recurrence after this first-line treatment. Bevacizumab is a useful agent for recurrent MG, but the extended survival time is about 3 months, compared to other treatments in patients with 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 about 40% of patients.[3] Our institute has evaluated the feasibility and efficacy of boron neutron capture therapy (BNCT) as a treatment for MG [4]. Our previous research has shown a marked prolongation of survival in patients with MG treated with BNCT. These patients had poor prognoses and were classified into recursive partitioning analysis classes 3 and 7 [5]. 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 [6]. L-amino acid transporter-1 is

upregulated in glioma cells [7]. BNCT is, therefore, able to irradiate tumor cells at a higher dose than normal cells in MG.

Based on this, BNCT has possible applications in recurrent MG previously treated with 60-Gy radiation therapy. However, our previous research found radiation necrosis to be a significant risk following BNCT for recurrent MG. This is because normal brain tissue 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 [4, 8, 9]. Bevacizumab is effective not only as a treatment for MG itself but also in the reduction of radiation necrosis and pseudoprogression [9–11]. The combination therapy of re-irradiation and bevacizumab results in radiation necrosis significantly less frequently than re-irradiation alone [12]. Our previous preliminary report indicated that early treatment with bevacizumab after BNCT can prevent and control radiation necrosis, stabilize the neurological state, and prolong survival time in recurrent MG [13]. 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.

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) ≥ 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 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.

Boron Neutron Capture Therapy and Add-on Bevacizumab

The clinical regimen of BNCT has been described previously [13]. Briefly, intravenous administration of BPA was begun 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. The 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, 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 performed so that the maximum dose to the scalp and normal brain tissue was less than 13 Gy-equivalent.

Bevacizumab treatment was initiated 1–4 weeks after BNCT. Bevacizumab of 10 mg/kg was administered every 2–3 weeks until disease progression. Bevacizumab administration was discontinued if adverse events precluded it, if 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.[14] The primary endpoint was 1-year survival rate after BNCT. The secondary endpoints were overall survival (OS) and progression-free survival (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%.[4] 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. 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 2016. Therefore, initially diagnosed (de novo) glioblastoma was categorized as primary glioblastoma (pGBM) and other forms of MG, including secondary glioblastoma and grade 3 glioma, were categorized as non-pGBM. Statistical analyses were performed using 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 recursive partitioning analyses.

Results

Patient enrollment was suspended temporarily between June 2014 and July 2017 because of the renovation of the reactor for earthquake resistance. Enrollment was discontinued in February 2019 because Kyoto University research reactor stopped irradiation for clinical use and the 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 nine female participants, with a median age of 53 years

(range, 20–68 years). Fourteen patients were classified with pGBM and 11 with non-pGBM. At tumor recurrence, the KPS was 100% in five patients, 90% in seven patients, 80% in four patients, 70% in seven patients, and 60% in one patient. Eight patients relapsed in the first pre-BNCT period, ten patients in the second, and seven patients in the third. The median gross tumor volume was 35.1 mL (range, 6.6–83.6 mL). The median period between the initial diagnosis and BNCT was 18.5 months (range, 8.8–161.8 months).

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 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, boron neutron capture therapy; pGBM, primary glioblastoma

The median OS and PFS for all patients after BNCT were 24.7 months (95% confidence interval [CI], 11.4–73.6) and 12.1 months (95%CI, 8.0–15.1) and, 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 for six and twelve 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, and the period between the initial diagnosis and BNCT were categorized into two groups by recursive partitioning analysis. 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.

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
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

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. In the patient who experienced myocardial infarction, chest pain occurred suddenly, followed by cardiopulmonary arrest 13 days after the last bevacizumab administration. 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 onset. In the other patient with a grade 5 adverse event, bacterial meningitis occurred 4 months after BNCT. The meningitis improved in response to antibiotics, but recurred after 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 after admission.

Discussion

The treatment of recurrent MG, especially in glioblastoma, after the first-line therapy is an ongoing challenge. Re-irradiation was considered a treatment option for recurrent MG. Clinical practice guidelines recommend re-irradiation to improve local tumor control, not accompanying survival benefits (class III evidence) [15]. However, a recent systematic review of re-irradiation research yielded encouraging results in terms of both disease control and survival rates [16]. 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 [17]. 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 existing chemotherapies, a bevacizumab-based regimen improves PFS, but not OS in patients with recurrent glioblastoma [18]. 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 [19]. A systematic review of radiotherapies, including fully or hypo fractionated SRT and SRS with or without bevacizumab for recurrent MG 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 [20]. 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).

In addition to the antitumor effect, bevacizumab can control brain radiation necrosis, reducing perilesional edema, and contrast enhancement [11, 21]. Brain radiation necrosis, with or without symptomatic brain edema, occurred at 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 than in patients treated with re-irradiation alone (1-year risk rates of 23.9% and 54.1%, respectively) [12]. SRS with bevacizumab also had a lower incidence of radionecrosis (5%) than SRS without bevacizumab (19%) [19]. Therefore, the 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 [22].

We have previously reported a retrospective study of BNCT for patients with recurrent MG using the same reactor used in the current study as the neutron source [4]. 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. 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%, and 0.9 and 18.9 months, respectively [23]. The acute tumor response to irradiation may explain the long median OS but short median PFS. This trial prohibited the use of bevacizumab until disease progression 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 [14]. In this study, bevacizumab was initiated within 4 weeks of BNCT. 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. Recently, a Taiwanese research group reported on BNCT of lower tumor dose (range, 8.51–25.09 Gy-equivalent) than other reports in treatment of recurrent MG with life-threatening, end-stage status [24]. Their median PFS and OS were 4.18 and 7.25 months, respectively. They reported no adverse reactions, including no radiation necrosis. Although lower-dose BNCT prevented the occurrence of radiation injury, the dose reduction decreased the survival benefits provided by BNCT seen in the regimen of the Taiwanese study. 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 [25]. Even in this study, however, a small tumor volume (< 44.0 mL) was significantly associated with longer OS in patients treated with BNCT. Hence, small tumors respond better to re-irradiation than large tumors, even with BNCT.

There were several limitations to this study. Most of the patients were referred to our institute for BNCT from other provinces in Japan. Therefore, follow-up data were obtained mainly from the local physician's reports. Under these circumstances, some data were missing, and follow-up periods were irregular. Although serious adverse events were reported properly, mild adverse events did not appear to be, based on their lower frequency than that seen in other clinical trials with bevacizumab. Most of the 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 to those seen with 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 was ended 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 of BNCT has shown it to be a promising alternative treatment for recurrent MG. However, BNCT resulted in shorter PFS because of pseudoprogression or radiation necrosis in our previous research. Add-on bevacizumab resolved this effect, resulting in high ORR, and an extension of PFS. Accelerator-based BNCT is currently under review, pending approval for clinical use as an alternative to reactor-based BNCT. Further research with a larger sample using accelerator-based BNCT and add-on bevacizumab is required to elucidate the efficacy and safety of this combination therapy.

Declarations

Funding

This work was partly supported by Grants-in-Aid for Scientific Research (B) (16390422 and 19390385) from the Japanese Ministry of Education, Science and Culture and Kenzo Suzuki Memorial Medical Science Applications Foundation, the Takeda Science Foundation, to S-IM.

Conflicts of interest

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

Availability of data and material

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

Code availability

Not applicable.

Author contribution

Conception and design: Miyatake SI. Operation of BNCT: Kondo N, Tanaka H, Sakurai Y, Suzuki M, Ono K. Data acquisition: Takeuchi K, Shiba H. Analyses and interpretation of data: Furuse M, Kawabata S, Miyatake SI. Manuscript drafting: Furuse M. Study supervision: Wanibuchi M, Miyatake SI.

Ethics approval/ Consent to participate

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

Consent to publication

Not applicable

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Figures

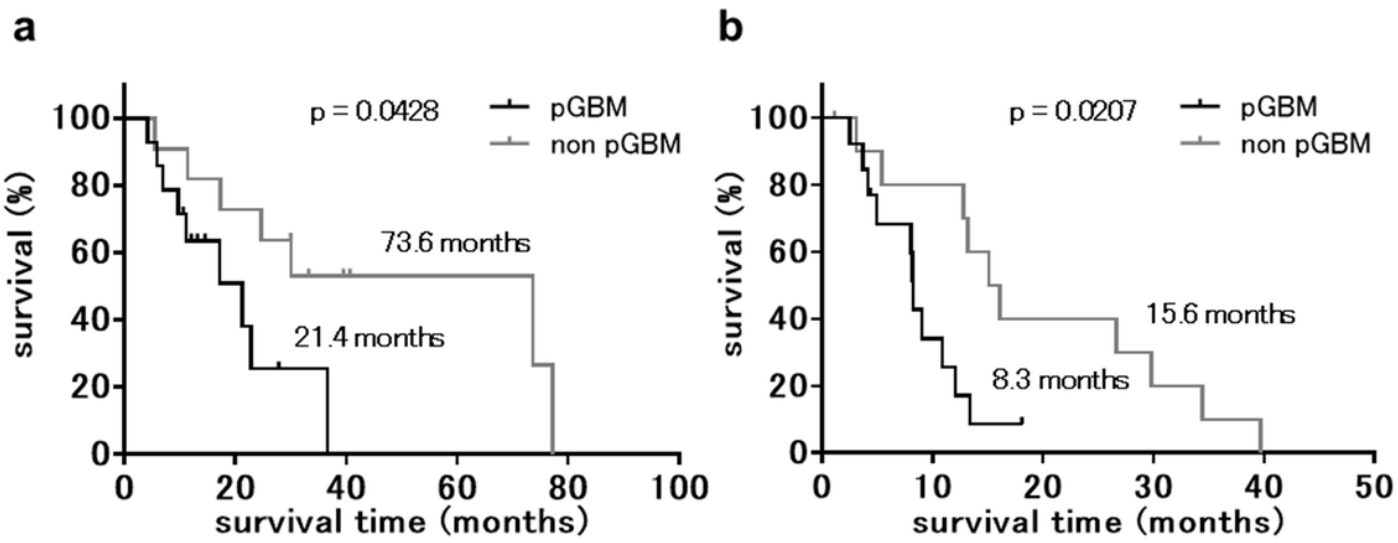

Figure 1

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

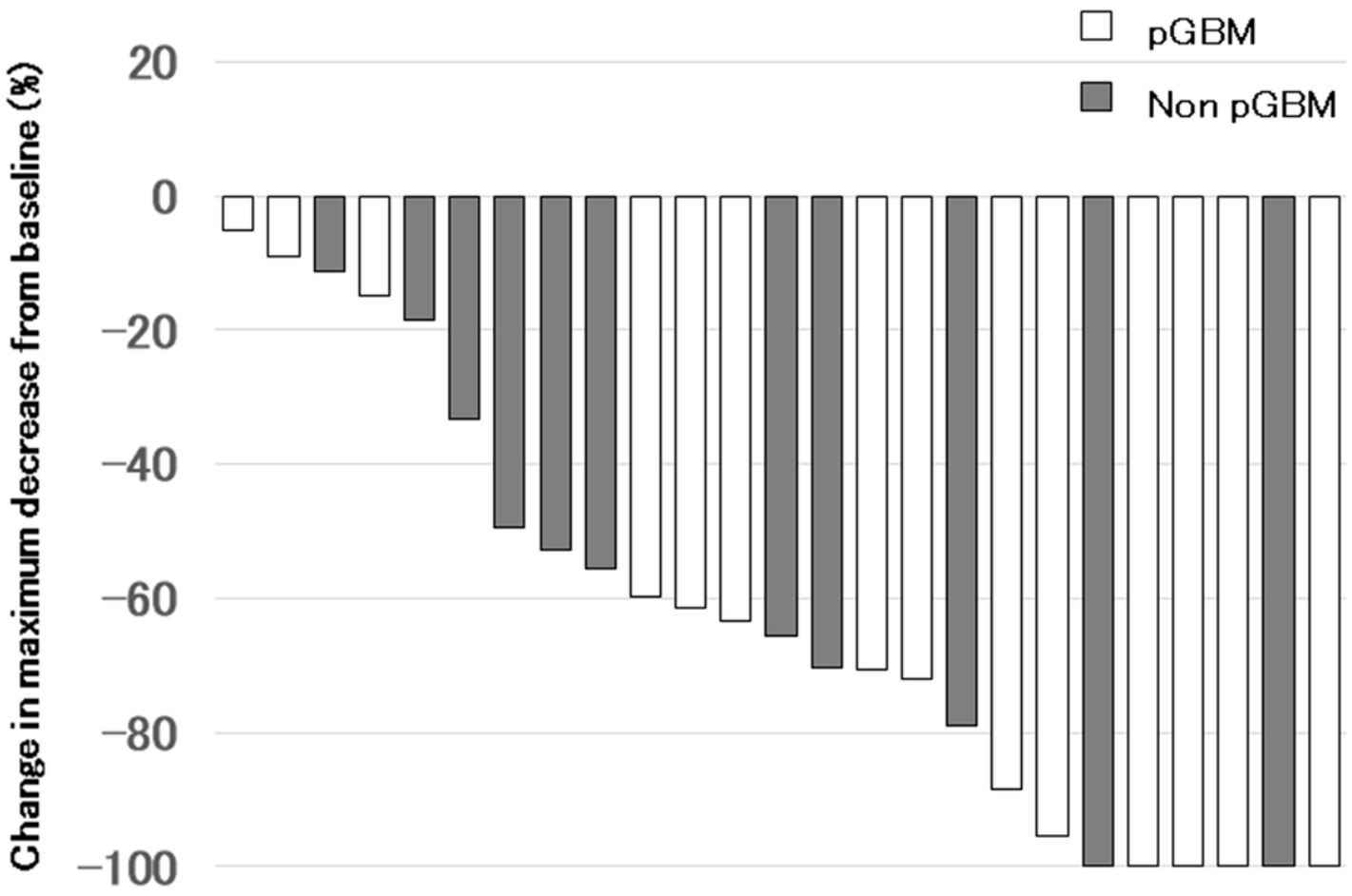

Figure 2

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

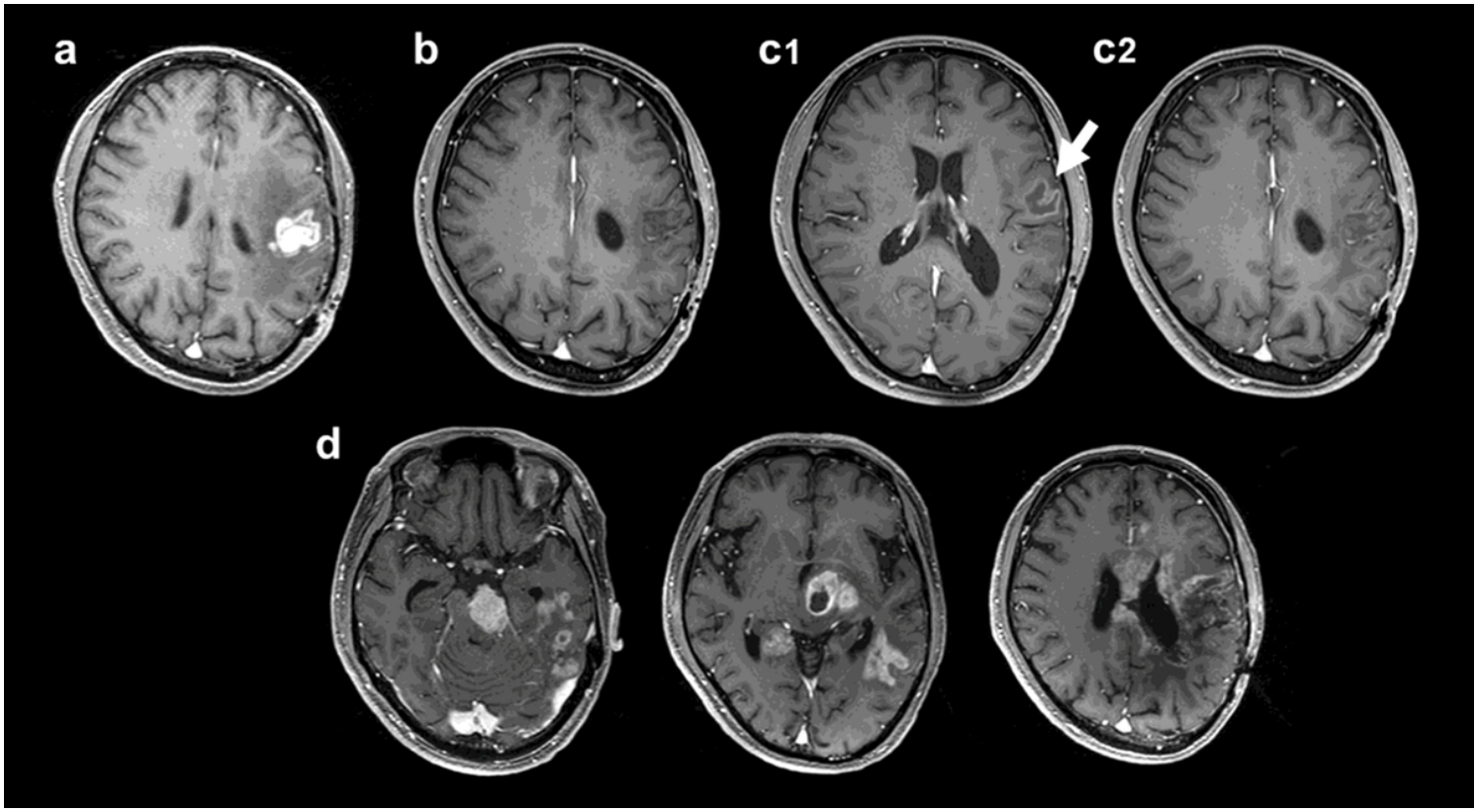

Figure 3

An illustrative responsive case with a long survival time. (a) A 44-year-old man with primary glioblastoma had his first recurrence 8.8 months after the operation. Boron neutron capture therapy (BNCT) and add-on bevacizumab treatment was applied to a recurrent tumor with a gross tumor volume of 16.8 mL; (b) the tumor shrank and 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) the patient died, with dissemination, 36.7 months after BNCT.