The Prognostic Improvement of Add-on Bevacizumab for Progressive Disease during Concomitant Temozolomide and Radiation Therapy in the Patients with Glioblastoma and Anaplastic Astrocytoma

Shigeru Yamaguchi[1)], Yukitomo Ishi[1)], Hiroaki Motegi[1)], Michinari Okamoto[1)], Hiroyuki Kobayashi*[1)], Kenji Hirata[2)], Yoshitaka Oda[3)], Shinya Tanaka[3)], Shunsuke Terasaka[1)], Kiyohiro Houkin[1)]

Department of Neurosurgery[1)], Nuclear Medicine[2)], and Cancer Pathology[2)], Faculty of Medicine, Hokkaido University, N-15, W-7, Kita-Ku, Sapporo, 060-8638, Japan

Corresponding author: Hiroyuki Kobayashi, M.D.

Department of Neurosurgery, Hokkaido University Graduate School of Medicine,

North 15 West 7, Kita-ku, Sapporo 060-8638, JAPAN

Tel: +81-11-706-5987 Fax: +81-11-708-7737

E-mail: hiro-ko@med.hokudai.ac.jp

Abstract

BACKGROUND: Although newly diagnosed high-grade glioma patients in Japan can receive bevacizumab (BEV) as first-line chemotherapy, randomized clinical trials have not shown a survival benefit for BEV for these patients. In this study, we investigated whether selective add-on BEV for patients with newly diagnosed glioblastoma (GBM) and anaplastic astrocytoma (AA) improves prognosis, in cases where tumors were continuously growing during radiotherapy concomitant with temozolomide (TMZ).

METHODS: We conducted a retrospective survey of the overall survival (OS) of patients with GBM/AAs who were treated in our institution between 2006 and 2016. Patients whose tumors were continuously growing regardless of radiotherapy were categorized as the “progressive” group; remaining patients were categorized as the “non-progressive” group. Since 2013, patients in the “progressive” group received add-on BEV therapy with the Stupp regimen during or just after radiotherapy.

RESULTS: Of 151 GBM/AA patients, 34 (22.5%) were categorized in the “progressive” group. Median OSs of the “progressive” and “non-progressive” groups were 13.2 months and 25.3 months, respectively ($P < 0.001$). Twelve patients in the “progressive” group received add-on BEV therapy, and their median OS was 20.2 months; whereas for the remaining 22 patients in the “progressive” group who were treated before the BEV era, their median OS was 10.5 months. In the “progressive” group, add-on BEV significantly extended OS ($P = 0.018$) and was the lone clinical factor of better prognosis.

CONCLUSIONS: We found that, for patients with GBM/AAs whose tumors were continuously growing during radiotherapy, add-on BEV treatment resulted in survival benefits.

Key words: Astrocytoma – Bevacizumab – Glioblastoma – Radiotherapy – Temozolomide

Introduction

Because of some promising results in uncontrolled clinical trials [1, 2], Bevacizumab (BEV) - a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEGF) - has been approved in Japan since 2013 for the treatment of primary high-grade glioma. However, for newly diagnosed glioblastoma (GBM) patients who received BEV as first-line chemotherapy with the ordinary Stupp regimen [3], two large-scale international phase III clinical trials failed to demonstrate an improvement in overall survival (OS) [4, 5]. Therefore, in patients with high-grade glioma, the effect of angiogenesis inhibition on OS is probably limited, and it is disputable whether BEV should be administered to all patients with primary high-grade glioma. In our institution, we do not currently administer BEV as first-line chemotherapy to patients with high-grade glioma; but patients whose tumors were continuously growing despite radiotherapy concomitant with temozolomide (TMZ) were selectively treated with add-on BEV during or immediately after radiotherapy. In this study, we retrospectively investigated whether this “selective” add-on BEV chemotherapy improved the prognosis of patients with aggressive high-grade astrocytoma, as compared to the prognosis of patients in the pre-BEV era.

Materials and Methods

Patients

In this retrospective study, we analyzed 151 adult patients with newly diagnosed GBM and anaplastic astrocytoma (AA) who were treated in our institution between 2006 and 2016 with conventional radiotherapy and concomitant TMZ according to the Stupp regimen. Patients with anaplastic oligodendroglioma and oligoastrocytoma, which was defined based on World Health Organization 2007 criteria, were excluded. Also excluded were patients with clinical secondary GBM, patients with pediatric glioma who were under 18 years of age, and patients whose tumors were not histopathologically confirmed. Additionally, patients who received hypofractionated radiotherapy (34 Gy/10 Fr) were excluded as well, even if they also received TMZ chemotherapy.

Imaging

Each patient underwent magnetic resonance imaging (MRI) with T1-weighted, T2-weighted, fluid-attenuated inversion recovery (FLAIR) and T1-weighted with contrast enhancement preoperatively, within 48 hours postoperatively, at the midpoint of the radiotherapy, and the end of radiotherapy. Tumor volumes and extent of resection

were calculated by the planimetry method using 5-mm slice axial T1WI with contrast enhancement, as described previously [6]. In cases of tumors without obvious contrast enhancement, tumor volumes were assessed in the hyperintense area of the FLAIR images. Extent of tumor resection was estimated by the volumetric change between preoperative and postoperative tumor volume. Resection rate was defined as the percentage of resected tumor volume in the preoperative tumor volume. In needle biopsy cases, extent of resection was defined as 0%. Evaluation of imaging was conducted independently by a neuroradiologist who was blinded to the clinical course. The calculations of extent of tumor resection rate were performed by a neurosurgeon (Y.I.) who was blinded to the course of the operation.

Treatments

After histopathologic confirmation, patients received conventional localized radiotherapy (54-60Gy) concomitant with TMZ according to the Stupp regimen [3] within 21 days postoperatively. Beginning in June 2013, BEV was approved for malignant glioma, if the contrast-enhanced tumor and/or hyperintense area in T2/FLAIR images appeared to evidently increase compared to postoperative MRI. In these cases, patients also received BEV (10 mg/kg every 2 weeks) as add-on chemotherapy with the Stupp

regimen. Patients who received BEV during radiotherapy were continuously treated with TMZ and BEV in the maintenance phase after irradiation.

Evaluation and statistical analysis

R statistical software, version 3.0.3, was used to conduct all statistical analyses and create graphical images. We evaluated clinical information including age at onset, sex, tumor volume, extent of resection, preoperative Karnofsky performance status (KPS) score, and isocitrate dehydrogenase (IDH) mutation. IDH mutation was assessed by direct sequencing for IDH-1 codon 132 and IDH-2 codon 172. O^6-methylguanine DNA methyltransferase (MGMT) expression status was evaluated by immunohistochemical (IHC) analysis at the diagnosis, as described previously [7, 8]. Chi-square tests, Welch's tests, and Wilcoxon rank-sum tests were applied for comparison between groups. Study endpoint was OS, which was measured from the day of the first surgery. Survival curves were described using the Kaplan-Meier method and compared by the log-rank test. Cox proportional hazards models were also applied for survival analysis. All patients were followed in our institution until death or last visit.

Results

Patient characteristics

Since 2006, 151 patients with GBM (N = 111) and AA (N = 40) were treated in our institution according to the Stupp regimen, of whom 34 (22.5%) progressed during the period of radiotherapy. Table I shows the characteristics of these 34 patients, who were categorized as the “progressive” group; the remaining 117 patients were categorized as the “non-progressive” group.

In the “progressive” group, 26 GBMs and eight AAs were initially diagnosed, and no statistical significance was observed histopathologically between the “progressive” group and the “non-progressive” group (P = 0.66; chi-square test). Additionally, no statistical significance was observed among each group in age at onset, sex, or preoperative tumor volume. Conversely, some differences were observed between the two groups in terms of preoperative clinical performance status and extent of tumor resection. Preoperative KPS scores of the “non-progressive” group were better than the scores of the “progressive” group (P = 0.02). Moreover, median values of extent of tumor resection were clearly different between two groups: 36.4% in the “progressive” group and 93.0% in the “non-progressive” group (P < 0.001). Gross total resection, defined as more than 98% resection, was achieved in 47 of 117 patients (40.2%) in the “non-progressive” group, whereas in only 4 of 34 patients (11.8%) in the

“progressive” group. Conversely, only biopsy, which extent of resections were less than 25 %, were performed in 15 patients (13.2%) in the “non-progressive” group and in 15 patients (44.1%) in the “progressive” group. Extent of tumor resection was apparently associated with the risk of progression during radiotherapy.

In 115 patients, IDH mutation could be investigated. In the “non-progressive” group, 10 of 90 patients (10%) were identified as having IDH mutation, whereas IDH-mutated astrocytoma was not included in the “progressive” group. In addition, 101 of 151 cases were evaluated by MGMT expression status in this series. In the “non-progressive” group, approximately half of cases showed negative expression of MGMT, and the other half showed positive expression. Conversely, in the “progressive” group, 18 of 24 assessed cases (75%) showed positive expression of MGMT.

Poor prognosis of patients with progressive disease during radiotherapy

Figure 1 shows the differences in OS of all 151 patients with AA/GBM according to tumor progression during radiotherapy concomitant with TMZ. Overall prognosis of patients in the “progressive” group was significantly worse than that of patients in the “non-progressive” group ($P < 0.001$). Median OS of the “progressive” group and the “non-progressive” group was 13.2 months and 25.3 months, respectively. Indisputably,

the prognosis of the “progressive” group was dismal.

Prognostic effect for add-on BEV application for progressive tumor during radiotherapy concomitant with TMZ

As described above, 34 patients had tumor progression during radiotherapy and were categorized as the “progressive” group; of these, 12 patients could be applied BEV. Of these 12 patients, two were histologically diagnosed with AA and 10 were histologically diagnosed with GBM. Five patients started BEV in the middle of radiotherapy; the other seven started BEV just after radiotherapy. In 11 of 12 patients, contrast-enhanced and T2/FLAIR hyperintensity lesions were decreased after BEV administration (Fig. 2); however, one patient did not have an observable response despite BEV administration and died at 4.7 months. Before the BEV era, 22 patients in the “progressive” group were treated; of these, six had AA and 16 had GBM. In this group, six patients (27%) did not receive adjuvant TMZ maintenance therapy after irradiation because of poor performance status.

Figure 3 shows the prognostic differences of the “progressive” group according to chemotherapy. The prognosis of patients who received add-on BEV was significantly better than that of patients who were treated before BEV approval (P = 0.018). The

median OS of the former group and the latter group were 20.2 months and 10.5 months, respectively. Furthermore, Cox proportional hazards models showed that add-on BEV was the lone clinical factor for improved prognosis in the “progressive” group (Table II).

Discussion

The management of GBM and AA remain enormously challenging. Despite the development of several promising molecular target drugs, including BEV, currently no drugs verifiably improve the survival of patients with GBM and AA. Nonetheless, BEV has been met with hopeful anticipation because it can cause a rapid decrease in contrast-enhancing tumors and in perifocal tumor edema [9]. Our study showed that selective add-on BEV during radiotherapy for “progressive” GBM and AA has a reasonable treatment strategy and could extend patient OS. After BEV is approved outside Japan for the treatment of primary high-grade glioma, many other institutions may adopt this strategy; however, to our knowledge, ours is first retrospective survey to show the efficacy of “selective” BEV administration for primary GBM/AAs.

Since BEV as first-line chemotherapy for primary GBM did not show a significant improvement in OS [4, 5], we recommend against administering BEV as

first-line chemotherapy for all patients with GBM/AAs. Therefore, it is very important to select the appropriate patients who could likely benefit from first-line BEV therapy. Several studies investigated the efficacy of first-line chemotherapy for unresectable malignant glioma [10-12]. In 2014, a phase II trial in France (TEMAVIR) was performed to determine whether neoadjuvant and/or adjuvant BEV and irinotecan could improve prognosis for unresectable GBM [11]. In 2016, phase II trial in Spain (GENOM 2009) studied the efficacy of add-on BEV on radiotherapy concomitant with TMZ for unresected GBM [10]. Unfortunately, neither of these trials showed extension of OS with first-line BEV. Although a single retrospective study from Japan reported improved OS for patients with malignant glioma without cytoreductive surgery [12], we should consider that first-line BEV cannot always improve patient outcomes even if residual tumor is observed before chemo-radiotherapy. However, in this series, the extent of resection and resection rate were strong clinical factors between the “progressive” group and the “non-progressive” group. Therefore, the existence of residual tumor should be a particularly noticeable factor to watch out for early progression during radiotherapy.

Patient selection by molecular aspects should also be considered. Based on the phase III AVAglio trial, subsequent translational research showed that G-CpG island methylator phenotype (CIMP)-“proneural” GBMs benefitted from BEV and TMZ

chemotherapy [13]. It will be potentially valuable if patients likely to benefit from add-on BEV can be selected according to these morphologic subgroups. However, such detailed morphologic information on tumors is rarely available before radiotherapy. Although Methyl-Guanine-Methyl-Transferase (MGMT) methylation status is another strong biomarker for GBM, especially under the Stupp regimen [14], no survival benefit of add-on BEV was observed, even for unmethylated MGMT GBMs [4]. In our series, we did not evaluate MGMT methylation status, but we did evaluate MGMT expression status by IHC. Although the IHC approach to evaluate the expression level of MGMT is still controversial [15], MGMT positive expression theoretically corresponds to unmethylated MGMT [16]. We previously demonstrated good correlation between MGMT expression status and survival of GBM patients and proposed evaluation procedure[7]. In this series, among the assessed cases, the "progressive group" contained a large population of GBM/AAs with positive expression of MGMT. However, although a small population, some GBM/AAs with negative expression of MGMT showed progression during primary radiotherapy concomitant with TMZ. Presently, it would be difficult to select patients with primary GBM/AAs who are likely to benefit from add-on BEV. Therefore, patients whose tumors are continuously growing during radiotherapy with the Stupp regimen might be selectively administered add-on BEV

treatment. Notably, no cases with IDH-mutated GBM/AAs were observed in the "progressive" group; therefore, IDH mutation status might be an important factor to predict clinical course in the early-stage treatment of GBM/AAs.

In our study, 11 of 12 patients (92%) in the "progressive" group with BEV achieved tumor regression after BEV administration, and all 12 received maintenance TMZ and BEV therapy after irradiation. In contrast, six of 22 patients (27%) in the "progressive" group without BEV did not receive maintenance TMZ therapy after irradiation because of poor clinical status. Selective add-on BEV therapy might sustain patient conditions during and/or just after irradiation, leading to improved OS in the "progressive" group.

It is important to note that, in this study, pseudo-progression cases might be included in the "progressive" group. The existence of pseudo-progression cases is a potential limitation. Pseudo-progression may occasionally develop at a relatively early stage after radiotherapy and it is sometimes difficult to distinguish pseudo-progression from true recurrence. In addition, some previous reports demonstrated the efficacy of BEV for the treatment of symptomatic pseudo-progression [17, 18]. In this series, we applied add-on BEV for radiologically progressive disease during radiotherapy; therefore, some cases might be pseudo-progressions rather than true early progressions.

This retrospective survey showed that BEV can potentially improve the OS of patients with GBM/AAs who have very poor prognoses. Additionally, from an economic standpoint, selective administration of BEV for primary GBM/AAs should be considered. This strategy should be verified by prospective trials or multi-center, large-scale retrospective surveys.

Conclusions

Our retrospective survey showed that patients with GBM and AA whose tumors were continuously growing during radiotherapy concomitant with TMZ might obtain survival benefits from the administration of add-on BEV.

REFERENCES

1. Lai A, Tran A, Nghiemphu PL, Pope WB, Solis OE, Selch M, et al. Phase II study of bevacizumab plus temozolomide during and after radiation therapy for patients with newly diagnosed glioblastoma multiforme. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2011 Jan 10;29(2):142-8. PubMed PMID: 21135282. Pubmed Central PMCID: 3058273.

2. Vredenburgh JJ, Desjardins A, Reardon DA, Peters KB, Herndon JE, 2nd, Marcello J, et al. The addition of bevacizumab to standard radiation therapy and temozolomide followed by bevacizumab, temozolomide, and irinotecan for newly diagnosed glioblastoma. Clinical cancer research : an official journal of the American Association for Cancer Research. 2011 Jun 15;17(12):4119-24. PubMed PMID: 21531816. Pubmed Central PMCID: 3117928.

3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987-96. PubMed PMID: 15758009. Epub 2005/03/11. eng.

4. Chinot OL, Wick W, Mason W, Henriksson R, Saran F, Nishikawa R, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. N Engl J Med. 2014 Feb 20;370(8):709-22. PubMed PMID: 24552318. Epub 2014/02/21. eng.

5. Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014 Feb 20;370(8):699-708. PubMed PMID: 24552317. Pubmed Central PMCID: 4201043. Epub 2014/02/21. eng.

6. Ishi Y, Terasaka S, Yamaguchi S, Yoshida M, Endo S, Kobayashi H, et al. Reliability of the Size Evaluation Method for Meningiomas: Maximum Diameter, ABC/2 Formula, and

Planimetry Method. World neurosurgery. 2016 Oct;94:80-8. PubMed PMID: 27381669.

7. Miyazaki M, Nishihara H, Terasaka S, Kobayashi H, Yamaguchi S, Ito T, et al. Immunohistochemical evaluation of O6 -methylguanine DNA methyltransferase (MGMT) expression in 117 cases of glioblastoma. Neuropathology : official journal of the Japanese Society of Neuropathology. 2014 Jun;34(3):268-76. PubMed PMID: 24397721.

8. Sasai K, Nodagashira M, Nishihara H, Aoyanagi E, Wang L, Katoh M, et al. Careful exclusion of non-neoplastic brain components is required for an appropriate evaluation of O6-methylguanine-DNA methyltransferase status in glioma: relationship between immunohistochemistry and methylation analysis. The American journal of surgical pathology. 2008 Aug;32(8):1220-7. PubMed PMID: 18580490.

9. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007 Oct 20;25(30):4722-9. PubMed PMID: 17947719.

10. Balana C, De Las Penas R, Sepulveda JM, Gil-Gil MJ, Luque R, Gallego O, et al. Bevacizumab and temozolomide versus temozolomide alone as neoadjuvant treatment in unresected glioblastoma: the GENOM 009 randomized phase II trial. J Neurooncol. 2016 May;127(3):569-79. PubMed PMID: 26847813.

11. Chauffert B, Feuvret L, Bonnetain F, Taillandier L, Frappaz D, Taillia H, et al. Randomized phase II trial of irinotecan and bevacizumab as neo-adjuvant and adjuvant to temozolomide-based chemoradiation compared with temozolomide-chemoradiation for unresectable glioblastoma: final results of the TEMAVIR study from ANOCEFdagger. Ann Oncol. 2014 Jul;25(7):1442-7. PubMed PMID: 24723487.

12. Yonezawa H, Hirano H, Uchida H, Habu M, Hanaya R, Oyoshi T, et al. Efficacy of

bevacizumab therapy for unresectable malignant glioma: A retrospective analysis. Molecular and clinical oncology. 2017 Jan;6(1):105-10. PubMed PMID: 28123740. Pubmed Central PMCID: 5244831.

13. Sandmann T, Bourgon R, Garcia J, Li C, Cloughesy T, Chinot OL, et al. Patients With Proneural Glioblastoma May Derive Overall Survival Benefit From the Addition of Bevacizumab to First-Line Radiotherapy and Temozolomide: Retrospective Analysis of the AVAglio Trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2015 Sep 01;33(25):2735-44. PubMed PMID: 26124478. Pubmed Central PMCID: 5015426 online at www.jco.org. Author contributions are found at the end of this article.

14. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med. 2005 Mar 10;352(10):997-1003. PubMed PMID: 15758010.

15. Karayan-Tapon L, Quillien V, Guilhot J, Wager M, Fromont G, Saikali S, et al. Prognostic value of O6-methylguanine-DNA methyltransferase status in glioblastoma patients, assessed by five different methods. J Neurooncol. 2010 May;97(3):311-22. PubMed PMID: 19841865.

16. Everhard S, Tost J, El Abdalaoui H, Criniere E, Busato F, Marie Y, et al. Identification of regions correlating MGMT promoter methylation and gene expression in glioblastomas. Neuro Oncol. 2009 Aug;11(4):348-56. PubMed PMID: 19224763. Pubmed Central PMCID: 2743215.

17. Khasraw M, Ameratunga M, Grommes C. Bevacizumab for the treatment of high-grade glioma: an update after phase III trials. Expert opinion on biological therapy. 2014 May;14(5):729-40. PubMed PMID: 24655021.

18. Miyatake S, Furuse M, Kawabata S, Maruyama T, Kumabe T, Kuroiwa T, et al. Bevacizumab treatment of symptomatic pseudoprogression after boron neutron capture therapy for recurrent malignant gliomas. Report of 2 cases. Neuro Oncol. 2013 Jun;15(6):650-5. PubMed PMID: 23460324. Pubmed Central PMCID: 3661101.

NOTES

Conflicts of interest.—

The auhotrs certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Funding.—

The research was partly supported by a Grant-in-Aid for Young Scientists from the Japan Society for the Ministry of Education, Culture, Sports, Science and Technology (#16K19991). The funding body played no role in the design of the study, collection, analysis, and interpretation of data, or in writing the manuscript.

Authors' contributions.—

Shigeru Yamaguchi designed this study, acquired clinical data, performed statistical analyses. Shigeru Yamaguchi and Shunsuke Terasaka wrote the manuscript. Yukitomo Ishi and Kenji Hirata performed experimental mutational analysis and assessed radiographical imaging. Hiroaki Motegi and Hiroyuki Kobayashi provided clinical perspective and contributed to the drafting of the manuscripts. Yoshitaka Oda and Shinya Tanaka provided MGMT IHC information. Michinari Okamoto corrected and summarized MGMT IHC data. Hiroyuki Kobayashi and Kiyohiro Hukin participated in the critical review and approval of the final version for publication. All authors read and approved the final manuscript.

Acknowledgements.—

The authors would like to thank the staff at the Departments of Radiology, Neurosurgery,

and Cancer Pathology of Hokkaido University Graduate School of Medicine, and Department of Surgical Pathology of Hokkaido University Hospital.

Table I.— *Patient characteristics*

		"Progressive" group (n=34)	"Non-progressive" group (n=117)	p-values
Age	mean	58.6	58.5	0.95
Sex	Women/Men	15/19	60/57	0.46
tumor volume	mean (ml)	38.0	45.2	0.12
Preoperative KPS	≦70%	17	33	0.02
	80-100%	17	84	
Extent of resection	Gross total (>98%)	4	47	<0.001
	Subtotal (90-98%)	5	27	
	Partial (25-90%)	10	28	
	Biopsy (<25%)	15	15	
Resection rate	Median (%)	36.4 %	93.0 %	<0.001
Histopathology	GBM	26	85	0.66
	AA	8	32	
IDH mutation		0/25 (0%)	9/90 (10%)	
MGMT expression	positive	18	39	

	negative	6	38	
	not analyzed	10	40	

AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Status; MGMT, O^6-methylguanine DNA methyltransferase

Table II.— *Cox proportional hazards model on overall survival in the "progressive" group*

		Hazard Ratio	95% CI	P-value
Age		1.02	0.989 – 1.054	0.196
Sex	Men	1.892	0.833-4.295	0.128
Preoperative KPS	>80%	1.418	0.659-3.052	0.372
Extent of resection		1.003	0.993-1.013	0.547
Malignancy	Grade IV	1.576	0.592-4.195	0.363
Add-on BEV	yes	0.345	0.138-0.866	0.023

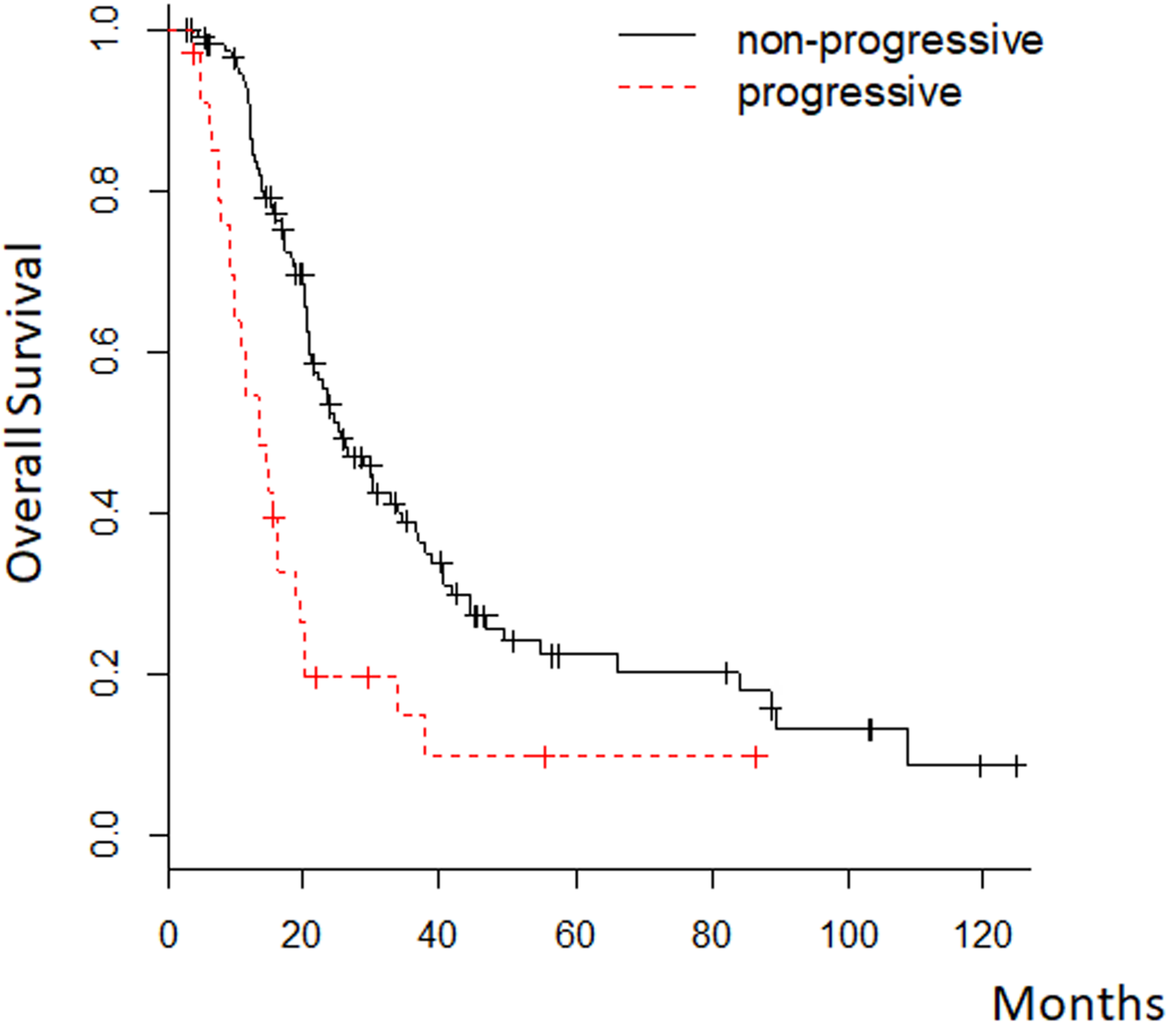
BEV, bevacizumab; CI, Confidence Interval; KPS, Karnofsky Performance Status

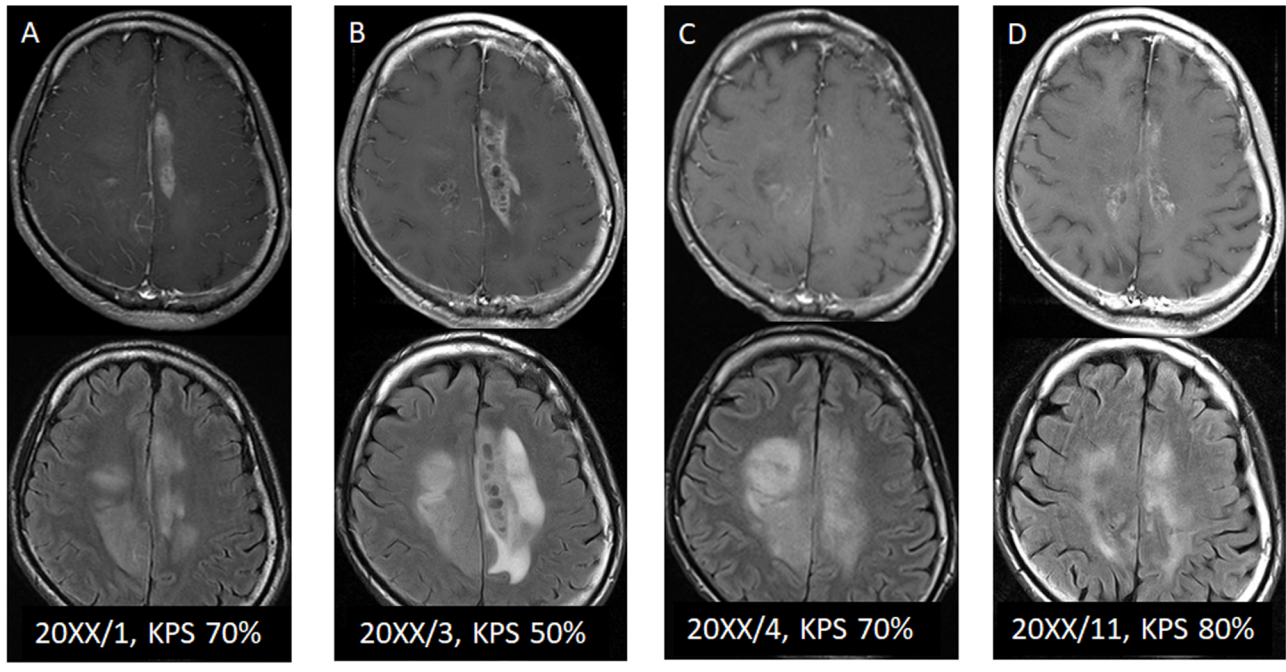
TITLES OF FIGURES

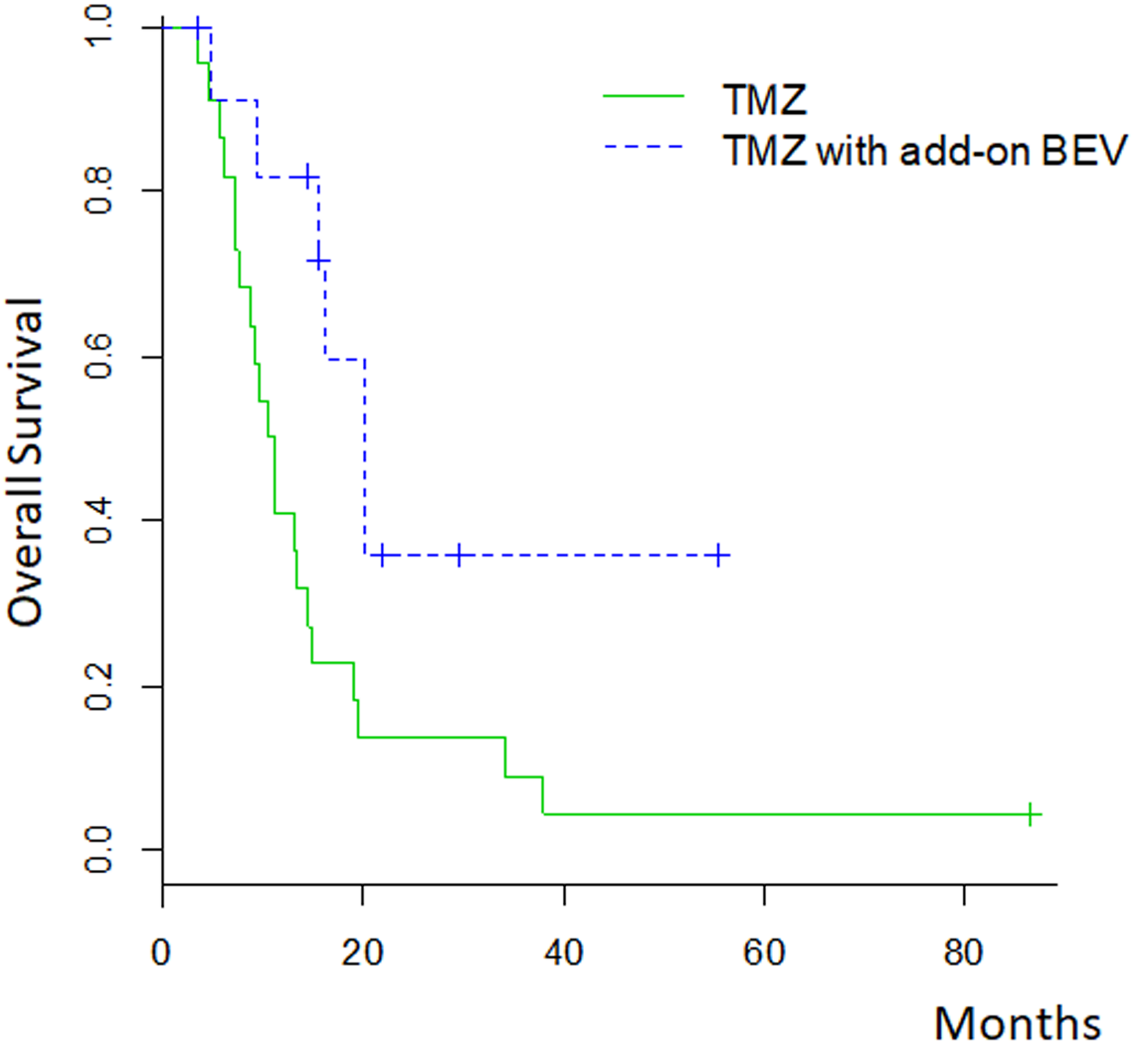
Figure 1.— Kaplan-Meier curve of overall survival according to tumor progression during radiotherapy for patients with glioblastoma and anaplastic astrocytoma ($P < 0.001$).

Figure 2.—Representative case of the “progressive group” treated by add-on BEV. A 36-year-old man presented with right hemiparesis. Serial MRIs were laid out (uppers are T1-weighted images with contrast enhancement; lowers are FLAIR images). (A) MRI at onset. Tumor is mainly located in the left cingulate gyrus and invaded to the corpus callosum and the contralateral deep frontal lobe. He underwent open biopsy and was diagnosed with anaplastic astrocytoma, IDH wild. (B) MRI shows apparent progression in the midpoint of radiotherapy concomitant with TMZ. His clinical status also got worse. He received add-on BEV from this point. (C) MRI conducted 1 month after add-on BEV treatment. Tumor clearly decreased in size, and the patient’s neurological condition also improved. (D) MRI conducted 10 months after onset; treatment with maintenance TMZ and BEV therapy. Tumor size remained stable.

Figure 3.—Kaplan-Meier curve of overall survival in the “progressive” group according to first-line chemotherapy. The prognosis of patients who received add-on BEV therapy (blue line) was significantly better than that of patients who did not receive BEV therapy (green line) ($P = 0.018$).


non-progressive
progressive
Overall Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
Months


A
B
C
D
20XX/1, KPS 70%
20XX/3, KPS 50%
20XX/4, KPS 70%
20XX/11, KPS 80%


TMZ
TMZ with add-on BEV
Overall Survival
0.0
0.2
0.4
0.6
0.8
1.0
0
20
40
60
80
Months