Survival Benefit of Cytoreductive Surgery prior to Bevacizumab for Patients with Recurrent Glioblastoma: A Single-center Retrospective Analysis

Shigeru Yamaguchi (yama-shu@med.hokudai.ac.jp)
Hokkaido University https://orcid.org/0000-0003-3710-5888
Hiroaki Motegi
Department of Neurosurgery, Faculty of Medicine, Hokkaido University
Yukitomo Ishi
Department of Neurosurgery, Faculty of Medicine, Hokkaido University
Michinari Okamoto
Department of Neurosurgery, Faculty of Medicine, Hokkaido University
Ryosuke Sawaya
Department of Neurosurgery, Faculty of Medicine, Hokkaido University
Hiroyuki Kobayashi
Kashiwaba Neurosugical Hospital
Shunsuke Terasaka
Kashiwaba Neurosurgical Hospital
Kiyohiro Houkin
Department of Neurosurgery, Faculty of Medicine, Hokkaido University

Research article

Keywords: Bevacizumab, Cytoreductive surgery, Glioblastoma multiforme, Recurrence

Posted Date: June 18th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-36402/v1

Abstract

Background

Bevacizumab (BEV) is a key anti-angiogenic agent in the treatment for recurrent glioblastoma multiforme (GBM). The aim of this study was to investigate whether cytoreductive surgery prior to treatment with BEV contributes to prolongation of survival for patients with recurrent GBM.

Methods

We retrospectively analyzed the treatment outcomes of 124 patients with recurrent GBM who were initially treated with the Stupp protocol in our institution between 2006 and 2019. Given that BEV has only been available in Japan since 2013, we grouped the patients into 2 groups according to the time of first recurrence: the pre-BEV group (N = 51) included patients who had a recurrence before BEV approval, and the BEV group (N = 73) included patients with recurrence after BEV approval. The overall survival after first recurrence (OS-R) according to treatment strategy was analyzed. In addition, multivariate analysis using Cox's proportional hazards model was used to evaluate the impact of clinical factors on OS-R after cytoreductive surgery in the patients with recurrent GBM.

Results

Among 124 patients, 27 patients (19.4%) received cytoreductive surgery: 9 cases in the pre-BEV group and 18 cases in the BEV group. Although the mean extent of resection of both groups was almost equal (92.2% pre-BEV group and 93.3% BEV group), OS-R was significantly different: median OS-R was 8.1 m in the pre-BEV group and 16.3 m in the BEV group, respectively ($P = 0.007$). Multivariate analysis revealed that the unavailability of BEV postoperatively ($P = 0.03$) and decreasing performance status caused by surgery ($P = 0.01$) were significant poor prognostic factors for survival after cytoreductive surgery in the patients with recurrent GBM.

Conclusions

With the advent of BEV, cytoreductive surgery might provide superior survival benefit at the time of GBM recurrence, especially in cases where surgery can be performed without deteriorating the patient's condition.

Introduction

Although several promising drugs have come to the forefront recently, glioblastoma (GBM) is still a dismal disease because the majority of cases eventually experience tumor recurrence. Since there is no standard therapeutic regimen, treatment options for patients with recurrent GBM are usually

individualized and diverse. A previous randomized clinical trial found that the median overall survival (OS) after recurrence was only 6.2 months [1].

The Food and Drug Association in the United States approved Bevacizumab (BEV), a humanized monoclonal antibody that inhibits vascular endothelial growth factor (VEDF), in 2009 for recurrent GBM. BEV was approved in 2013 for malignant glioma, including newly diagnosed glioblastoma, in Japan. BEV is frequently given to patients with recurrent GBM despite its limited efficacy for prolongation of OS in these patients [2–5]. Although patients sometimes experience rapid regression of recurrent lesions after short courses of BEV, median OS after recurrence was still 9.2 months with BEV monotherapy [5].

One of the treatment options for recurrent GBM is repeated surgery, however, the efficacy of surgery remains controversial. Several retrospective analyses showed that surgical resection had a survival benefit [6–8], whereas other retrospective analyses demonstrated that resection of recurrent lesions was not significantly associated with increased post-progression survival [9, 10]. In particular, the role of the cytoreduction of recurrent glioma prior to treatment with BEV remains unclear.

In our institution, we always consider repeated surgery when a patient with GBM suffers from recurrent disease during or after maintenance temozolomide (TMZ) treatment. Therefore, since BEV has been approved in Japan, we have used BEV to treat every patient with recurrent GBM who has undergone the maximum possible tumor resection. In this study, we hypothesized that for selected cases of recurrent GBM, cytoreductive surgery before treatment with BEV may comprise a more effective salvage treatment and improve OS. The aim of this investigation was to evaluate whether cytoreductive surgery for recurrent lesion prolongs survival in the BEV era.

Materials And Methods

Patient Selection

Local Institutional Review Boards in Hokkaido University Hospital approved this retrospective study. We retrospectively reviewed the medical records of adult patients with GBM treated in our institution by conventional radiotherapy concomitant with TMZ according to the Stupp protocol [11] between 2006 and 2019, with June 2013 representing when BEV was first used to treat GBM in Japan. We identified 212 adult patients with GBM during this period.

Basic Treatment Strategy for GBM in Our Institution

Patients diagnosed with GBM during primary surgery underwent 60Gy/30Fr localized radiotherapy concomitant with TMZ according to the Stupp protocol. From June 2013, patients whose tumors continuously progressed during radiotherapy received add-on BEV as intensive consolidation therapy. Otherwise, patients underwent adjuvant TMZ chemotherapy (150–200 mg/m^2, 5 days, every 4 weeks) up to 12–24 courses. Patients also underwent contrast-enhanced MRI every 3 months during and after adjuvant TMZ chemotherapy.

Tumor recurrence was revealed by MRI findings or clinical deterioration. In cases where it was difficult to distinguish tumor recurrence from radiation necrosis, ^{11}C-methioinine (MET) Positron emission tomography was performed [12].

Once recurrent tumor was observed, we considered resection of recurrent lesions as often as possible. BCNU wafers (Gliadel®), available in Japan since January 2013, were occasionally implanted after tumor resection at the discretion of the surgeons. After cytoreductive surgery for recurrent tumor, patients resumed or continued adjuvant TMZ until second recurrence. Since June 2013, patients who underwent gross total resection of recurrent tumor received TMZ continuously at second recurrence, then; BEV was added to intensify consolidation therapy. Patients who did not undergo gross total resection of recurrent tumors received BEV with or without TMZ. The patients with unresected recurrent lesions would receive BEV in combination with second-line chemotherapy or best supportive care (BSC) depending on their clinical condition.

Inclusion Criteria

In this study, we focused on the overall prognosis after first recurrence in patients with primary GBMs treated by the Stupp regimen. Therefore, we excluded patients with GBM from this analysis as follows; 1) patients that did not have radiotherapy (N = 24); 2) patients that did not receive TMZ (N = 14); 3) patients that received add-on BEV chemotherapy during or just after radiotherapy because of continuous progression (N = 17). Eventually, we analyzed 157 patients with primary GBM in this study.

Assessment

According to treatment at the first recurrence, we classified patients into 3 groups: 1) the cytoreductive surgery group, who received maximum safe resection of recurrent tumor with or without chemotherapy, 2) the second-line chemotherapy group, who received chemotherapy without cytoreductive surgery for recurrent tumor, and 3) the BSC group, who did not receive any anti-tumor treatment after recurrence. The prognosis was assessed by overall survival after first recurrence (OS-R). Duration of OS-R was defined as the interval between the date of the MRI study on which the first recurrence was detected and the date of death or last follow-up.

Tumor volumes and extent of resection were calculated by the planimetry method using 5-mm slice axial T1WI with contrast enhancement, as described previously [13]. The extent of resection was defined as the percentage of resected tumor volume in the preoperative tumor volume. In the cytoreductive surgery group, each patient's performance status was assessed by the Karnofsky Performance status (KPS) before and 1 month after operation.

Statistical Analysis

All statistical analyses were carried out using R statistical software version 3.4.2. The distribution of categorized data was compared by Pearson's chi-squared test. The means of continuous variables were

compared using Welch's t-test, and the medians of continuous variables were compared using the Wilcoxon rank-sum test. The Kaplan-Meier method was used to estimate survival curves, and the log-rank test was used for the comparison. To analyze clinical factors for the risk of survival after cytoreductive surgery, Cox proportional hazards regression models were applied. A hazard ratio and 95% confidence intervals (CIs) were calculated using multivariate Cox models. In multivariate analysis, clinical factors with *P*-value < 0.20 in univariate analysis were selected. Graphic designs were created by PRISM ver. 8.0. All statistical significance was defined as *P*-value < 0.05.

Results

Patient Demographics

This study included 157 primary patients with GBM (90 males and 67 females). Median age of onset was 64 years (range, 25–85 years). As concerns the extent of resection at primary surgery, 18 (11.5%) patients underwent only biopsy, 27 (17.2%) patients underwent partial tumor resection with less than 90% resection, 43 (27.4%) patients underwent subtotal resection (90–98% resection), and 69 (43.9%) patients underwent gross total resection (more than 98% resection) before treatment by the Stupp protocol. Of these 157 patients, 124 (79.0%) experienced tumor recurrence and 98 patients (62.4%) died at the time of this analysis. Median OS was 20.4 months and 2-year OS was 39.3% (Supplement Fig 1).

Therapeutic Approach for Primary Recurrent GBM

Among the 124 patients with recurrent disease, 51 recurred before March 2013 (the pre-BEV group). They were unable to receive BEV in combination with second-line chemotherapy after recurrence; however, 3 out of 51 cases eventually received BEV after its approval in Japan. The remaining 73 patients had tumor recurrence after May 2013, when BEV was available for clinical use (the BEV group). Table 1 shows patient demographics at time of recurrence. The median duration between primary surgery and recurrence was 8.2 months in the pre-BEV group and 9.6 months in the BEV group. Although the duration of the BEV group was longer than that of the pre-BEV group, this difference was not statistically significant (*P* = 0.22). The therapeutic approach for first recurrence of tumor was cytoreductive surgery, second-line chemotherapy, and BSC, for 9 (17.6%), 7 (13.7%), and 35 patients (68.6%) in the pre-BEV group, respectively, and for 18 (24.7%), 34 (46.6%), and 21 patients (28.8%) in the BEV era, respectively. Second-line chemotherapy included add-on Interferon-β (N = 3), repeat course of TMZ (N = 2), BEV after available (N = 2), in the pre-BEV group, while all 34 patients received BEV in combination with second-line chemotherapy in the BEV group. The inclusion chart of this study is described in Fig 1.

Median OS-R was 6.9 months in the pre-BEV group and 8.1 months in the BEV group. OS-R in the BEV group was significantly longer than in the pre-BEV group regardless of the therapeutic approach (*P* = 0.032) (Supplement Fig 2).

Impact of Cytoreductive Surgery for Primary Recurrent GBM on OS-R Before and After BEV Approval

As described above, cytoreductive surgery for primary recurrent GBM was performed in 27 patients, 9 patients from the pre-BEV group and 18 from the BEV group. Table 2 shows the characteristics of the 2 groups. There were no significant differences between the 2 groups in age of recurrence, duration between onset and recurrence, and recurrent tumor volumes. In addition, almost all patients achieved subtotal resection or gross total resection of recurrent tumors, and the mean extent of cytoreductive surgery was 92.9% in the pre-BEV group and 93.3% in the BEV group. Postoperatively, 8 patients (53%) were given BEV after recurrent surgery in the BEV group, because residual lesions were observed in postoperative MRI.

Eventually, only 1 patient was given BEV at second recurrence in the pre-BEV era group after BEV approval. In the BEV group, 15 out of 18 cases were treated with BEV; 7 patients were given BEV at the second recurrence. Two patients without BEV application did not have second recurrence at the time of this analysis. One patient could not receive BEV because of decreasing clinical status caused by surgery. Median OS-R in the pre-BEV group was 8.1 months, while that in the BEV group was 16.3 months (Fig 2). OS-R of the BEV group was significantly longer than that of the pre-BEV group ($P = 0.007$).

In addition, we investigated whether other clinical factors influenced survival after cytoreductive surgery. Table 3 shows the univariate and multivariate analyses of candidate clinical factors. In addition to postoperative BEV availability ($P = 0.03$), the most significant poor prognostic factor affecting OS-R was decreased KPS score after cytoreductive surgery ($P = 0.01$)

Impact of Cytoreductive Surgery in BEV Group

As a second set of analyses, we evaluated whether cytoreductive surgery before treatment with BEV contributes to prolongation of patient prognosis in the BEV era. There were 73 patients with recurrent GBM in the BEV group, as described above. The median OS-R of patients who received cytoreductive surgery (N = 18), BEV combined with second-line chemotherapy (N = 34), and BSC (N = 21) was 16.3 months, 7.4 months, and 4.6 months, respectively (Fig 3). Cytoreductive surgery of recurrent GBM before BEV application shows remarkable prolongation of OS after first recurrence in the BEV group.

Discussions

Once patients with GBM experience recurrence, there is no established standard treatment approach. Therapeutic options for recurrent GBM have to be carefully weighed taking into consideration tumor location, performance status, and prognostic factors [14]. Although repeated cytoreductive surgery is one of the effective therapeutic options for improving survival in patients with recurrent GBM [6, 15], it is provided for only 10%–30% of patients with recurrent GBM [16–20]. According to Harvey-Jumper *et al*, predictors of improved survival after re-operation for high-grade glioma are younger age (< 50 years), preoperative better performance status (KPS score ≥ 70), longer interval between operations, smaller tumor volume, and greater extent of resection [21]. However, these factors were not significant predictors of OS post-surgery in our study; rather, decreased KPS after cytoreductive surgery was one of the

strongest clinical factors affecting OS after recurrence. If done carefully, repeated cytoreductive surgery for recurrent GBM does not negatively affect the patient's clinical condition.

To date, the majority of previous studies show that median interval between repeated surgery and death was less than 12 months in patients with recurrent GBM who were initially treated with the Stupp protocol [17, 22]. Brandes *et al* reported that the median survival from second surgery for recurrent GBM treated by the Stupp protocol was 11.4 months, and survival time was influenced by the extent of resection and 06-Methylguanine-DNA Methyltransferase (MGMT) methylation status [22]. In our study, cytoreductive surgery for recurrent GBM treated by the Stupp protocol was only 8.1 months before BEV approval though almost all patients achieved gross total resection. This prognosis corresponds with prognoses in previous studies, suggesting that cytoreductive surgery makes only a limited contribution to the prolongation of prognosis and appropriate palliative chemotherapy after cytoreductive surgery should be available.

On the other hand, our study found that after BEV approval, the prognosis of patients who received cytoreductive surgery significantly improved. As in our study, several retrospective studies reported survival prolongation achieved by the combination of cytoreductive surgery and palliative chemotherapy in the patients with recurrent GBM [23, 24]. De Bonis P *et al* showed that patients treated with surgery and adjuvant chemotherapy had a median OS after recurrence of 14 months, compared with patients treated with chemotherapy alone who had OS after recurrence of only 8 months [24]. Azoulay *et al* showed that the median survival from time of progression was 10 months in patients with repeat surgery followed by salvage chemotherapy, compared to 6.56 months in patients with salvage chemotherapy alone [23]. Both studies demonstrated the survival benefit of combination cytoreductive surgery with salvage chemotherapy. However, salvage chemotherapies in these studies were not uniform including TMZ, lomustine, procarbazine, irinotecan, etc, as well as BEV. In our study, the median OS-R of patients who received cytoreductive surgery followed by BEV treatment was 16.3 months. Compared with a previous similar investigation of repeated craniotomy for recurrent GBM, survival in our series appears to be better. We consider cytoreductive surgery followed by BEV application to be one of the best available therapeutic options at present.

To the best of our knowledge, there are few studies that focus on the impact that cytoreductive surgery has on the prognosis for recurrent glioma prior to BEV. Clark *et al* compared the survival of patients with recurrent GBM who received repeated craniotomy during BEV treatment with patients who received repeated craniotomy without BEV treatment in a UCSF study [25]. Since patients that received BEV preoperatively had a worse postoperative OS and a higher perioperative morbidity rate than patients not receiving preoperative BEV, they concluded that the indication of repeat surgery in patients in whom BEV treatment failed must be carefully weighed against the intended benefit and risk of surgery. Considering their conclusions together with our study, BEV should be considered as an actual last-line chemotherapy for patients with recurrent GBM [26, 27].

Conclusion

As compared to survival contribution of surgery in the pre-BEV era, cytoreductive surgery prior to BEV for recurrent GBM might contribute to survival prolongation. If effective resection without neurologic deterioration is feasible, patients with recurrent GBM should be considered for maximum cytoreduction before treatment with BEV.

Abbreviations

BEV: Bevacizumab; BSC: Best supportive care; GBM: Glioblastoma multiforme; MRI: Magnetic resonance imaging; OS: Overall survival; OS-R: Overall survival after first recurrence; TMZ: Temozolomide

Declarations

Ethics Approval and Consent to Participate

This study was performed with the approval of the Internal Review Board (IRB) on ethical issues of Hokkaido University Hospital, Sapporo, Japan (IRB No: 017-0075). The IRB waived the requirement for obtaining informed consent.

Consent for Publication

Not applicable

Availability of Data and Materials

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

Competing Interests

The authors declare that they have no competing interests.

Funding

None

Authors' Contributions

SY analyzed and interpreted the patient data and was major contributor in writing manuscript. HM, YI, MO, and RS collected patient data, HK and ST refined the concept of this study, and KH supervised this study. All authors read and approved the final manuscript.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the English language review.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459–66.
2. Erdem-Eraslan L, van den Bent MJ, Hoogstrate Y, Naz-Khan H, Stubbs A, van der Spek P, Bottcher R, Gao Y, de Wit M, Taal W, et al. Identification of Patients with Recurrent Glioblastoma Who May Benefit from Combined Bevacizumab and CCNU Therapy: A Report from the BELOB Trial. Cancer Res. 2016;76(3):525–34.
3. Taal W, Oosterkamp HM, Walenkamp AM, Dubbink HJ, Beerepoot LV, Hanse MC, Buter J, Honkoop AH, Boerman D, de Vos FY, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomised controlled phase 2 trial. Lancet Oncol. 2014;15(9):943–53.
4. Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, Brandes AA, Taal W, Domont J, Idbaih A, et al. Lomustine and Bevacizumab in Progressive Glioblastoma. N Engl J Med. 2017;377(20):1954–63.
5. Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2009;27(28):4733–40.
6. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, Berger MS, Parsa AT. Impact of extent of resection for recurrent glioblastoma on overall survival: clinical article. Journal of neurosurgery. 2012;117(6):1032–8.
7. Perrini P, Gambacciani C, Weiss A, Pasqualetti F, Delishaj D, Paiar F, Morganti R, Vannozzi R, Lutzemberger L: **Survival outcomes following repeat surgery for recurrent glioblastoma**: **a single-center retrospective analysis**. *Journal of neuro-oncology* 2017, **131**(3):585–591.
8. Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, Weyerbrock A, Westermaier T, Senft C, Schucht P, et al. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neurooncology. 2016;18(1):96–104.
9. Sastry RA, Shankar GM, Gerstner ER, Curry WT. The impact of surgery on survival after progression of glioblastoma: A retrospective cohort analysis of a contemporary patient population. J Clin Neurosci. 2018;53:41–7.

10. Ortega A, Sarmiento JM, Ly D, Nuno M, Mukherjee D, Black KL, Patil CG. Multiple resections and survival of recurrent glioblastoma patients in the temozolomide era. J Clin Neurosci. 2016;24:105–11.
11. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
12. Okamoto S, Shiga T, Hattori N, Kubo N, Takei T, Katoh N, Sawamura Y, Nishijima K, Kuge Y, Tamaki N. Semiquantitative analysis of C-11 methionine PET may distinguish brain tumor recurrence from radiation necrosis even in small lesions. Annals of nuclear medicine. 2011;25(3):213–20.
13. Ishi Y, Terasaka S, Yamaguchi S, Yoshida M, Endo S, Kobayashi H, Houkin K. Reliability of the Size Evaluation Method for Meningiomas: Maximum Diameter, ABC/2 Formula, and Planimetry Method. World neurosurgery. 2016;94:80–8.
14. Tosoni A, Franceschi E, Poggi R, Brandes AA. Relapsed Glioblastoma: Treatment Strategies for Initial and Subsequent Recurrences. Curr Treat Options Oncol. 2016;17(9):49.
15. Quick J, Gessler F, Dutzmann S, Hattingen E, Harter PN, Weise LM, Franz K, Seifert V, Senft C. Benefit of tumor resection for recurrent glioblastoma. Journal of neuro-oncology. 2014;117(2):365–72.
16. Barbagallo GM, Jenkinson MD, Brodbelt AR. 'Recurrent' glioblastoma multiforme, when should we reoperate? Br J Neurosurg. 2008;22(3):452–5.
17. Montemurro N, Perrini P, Blanco MO, Vannozzi R. Second surgery for recurrent glioblastoma: A concise overview of the current literature. Clinical neurology neurosurgery. 2016;142:60–4.
18. Park CK, Kim JH, Nam DH, Kim CY, Chung SB, Kim YH, Seol HJ, Kim TM, Choi SH, Lee SH, et al. A practical scoring system to determine whether to proceed with surgical resection in recurrent glioblastoma. Neurooncology. 2013;15(8):1096–101.
19. Park JK, Hodges T, Arko L, Shen M, Dello Iacono D, McNabb A, Olsen Bailey N, Kreisl TN, Iwamoto FM, Sul J, et al. Scale to predict survival after surgery for recurrent glioblastoma multiforme. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2010;28(24):3838–43.
20. Ryken TC, Kalkanis SN, Buatti JM, Olson JJ, Committee ACJG: **The role of cytoreductive surgery in the management of progressive glioblastoma**: **a systematic review and evidence-based clinical practice guideline**. *Journal of neuro-oncology* 2014, **118**(3):479–488.
21. Hervey-Jumper SL, Berger MS. Reoperation for recurrent high-grade glioma: a current perspective of the literature. Neurosurgery. 2014;75(5):491–9. discussion 498–499.
22. Brandes AA, Bartolotti M, Tosoni A, Poggi R, Bartolini S, Paccapelo A, Bacci A, Ghimenton C, Pession A, Bortolotti C, et al. Patient outcomes following second surgery for recurrent glioblastoma. Future oncology. 2016;12(8):1039–44.
23. Azoulay M, Santos F, Shenouda G, Petrecca K, Oweida A, Guiot MC, Owen S, Panet-Raymond V, Souhami L, Abdulkarim BS: **Benefit of re-operation and salvage therapies for recurrent glioblastoma multiforme**: **results from a single institution**. *Journal of neuro-oncology* 2017, **132**(3):419–426.

24. De Bonis P, Fiorentino A, Anile C, Balducci M, Pompucci A, Chiesa S, Sica G, Lama G, Maira G, Mangiola A. The impact of repeated surgery and adjuvant therapy on survival for patients with recurrent glioblastoma. Clinical neurology neurosurgery. 2013;115(7):883–6.
25. Clark AJ, Lamborn KR, Butowski NA, Chang SM, Prados MD, Clarke JL, McDermott MW, Parsa AT, Berger MS, Aghi MK. Neurosurgical management and prognosis of patients with glioblastoma that progresses during bevacizumab treatment. Neurosurgery. 2012;70(2):361–70.
26. Wenger KJ, Wagner M, You SJ, Franz K, Harter PN, Burger MC, Voss M, Ronellenfitsch MW, Fokas E, Steinbach JP, et al. Bevacizumab as a last-line treatment for glioblastoma following failure of radiotherapy, temozolomide and lomustine. Oncology letters. 2017;14(1):1141–6.
27. Heiland DH, Masalha W, Franco P, Machein MR, Weyerbrock A: **Progression-free and overall survival in patients with recurrent Glioblastoma multiforme treated with last-line bevacizumab versus bevacizumab/lomustine**. *Journal of neuro-oncology* 2016, **126**(3):567–575.

Tables

Table 1 Patient Characteristics in 124 recurrent GBMs according to timing of recurrence

	Recurrence before BEV approval (pre-BEV era group)	Recurrence after BEV approval (BEV era group)	P-value
Patient No.	51	73	
Age (median)	62 y	66 y	0.01
Duration from primary surgery to recurrence (median)	8.2 months	9.6 months	0.22[a]
Treatment after first recurrence			
Cytoreductive surgery	9 cases (17.6%)	18 cases (24.7%)	
2nd line chemotherapy	7 cases (13.7%)	34 cases (46.6%)	
Best supportive care	35 cases (68.6%)	21 cases (28.8%)	
Median OS-R	6.9 months	8.1 months	0.032[a]

[a] *P* values were calculated by Log-rank test

BEV: Bevacizumab, GBM: Glioblastoma multiforme, OS-R: overall survival after recurrence

Table 2 Characteristics in 27 patients with recurrent GBM who underwent cytoreductive surgery

	Pre-BEV era group	BEV era group	P-value
Patient No	9	18	
Age (median)	67 y	61 y	0.33
Duration from primary surgery to recurrence (median)	16.9 months	22.0 months	0.11[a]
Recurrent tumor volume (mean)	8.93 ml	16.3 ml	0.25
Extent of resection (mean)	92.9 %	93.3 %	0.96
BCNU wafer implantation	1 case (11%)	12 cases (67%)	
Postoperative Bevacizumab	-	8 cases (53%)	

[a] *P* values were calculated by Log-rank test

BEV: Bevacizumab, GBM: Glioblastoma multiforme,

Table 3 Univariate and multivariate analysis of clinical factors for survival after cytoreductive surgery by the proportional hazard model

		Univariate analysis			Multivariate analysis		
		Hazard ratio	95% CI	*P* values	Hazard ratio	95% CI	*P* values
Age at recurrence	(continuous variable)	1.001	0.97–1.03	0.96	-	-	-
Interval between surgeries	(continuous variable)	0.993	0.97–1.01	0.47	-	-	-
Preoperative KPS	<80%	1			1		
	80–100%	0.43	0.14–1.35	0.15	1.20	0.31–4.54	0.78
KPS change after surgery	decrease	1			1		
	stable	0.24	0.09–0.66	0.005	0.22	0.07–0.71	0.01*
Extent of Resection (%)	(continuous variable)	0.98	0.95–1.02	0.37	-	-	-
BCNU wafer implantation	no	1			1		
	yes	0.48	0.19–1.17	0.11	1.12	0.37–3.46	0.84
BEV available after surgery	yes	1			1		
	no	3.19	1.27–7.98	0.013	3.34	1.11–10.1	0.03*

Figures

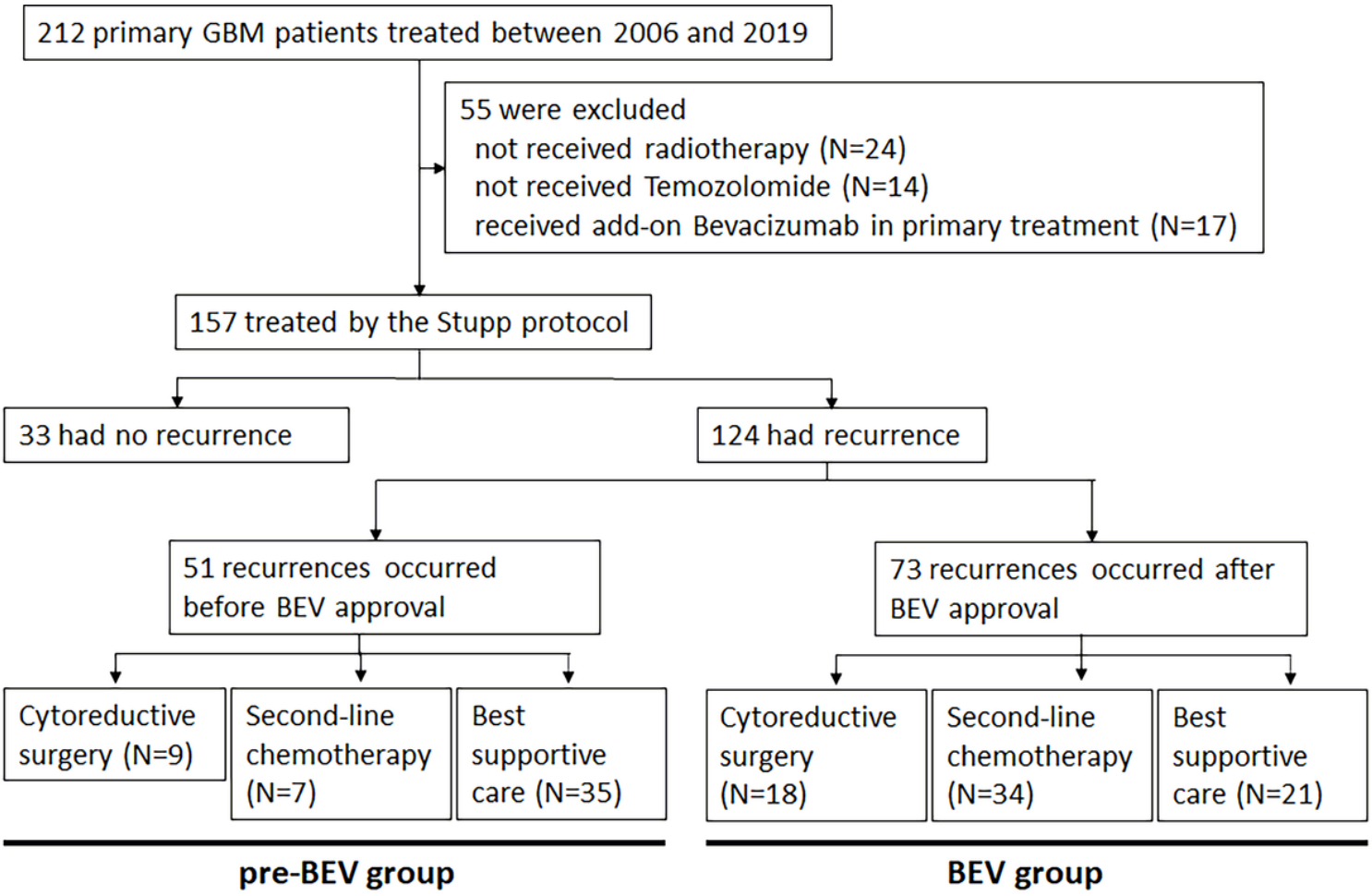

Figure 1

Inclusion chart and treatment flow of this study according to Bevacizumab availability

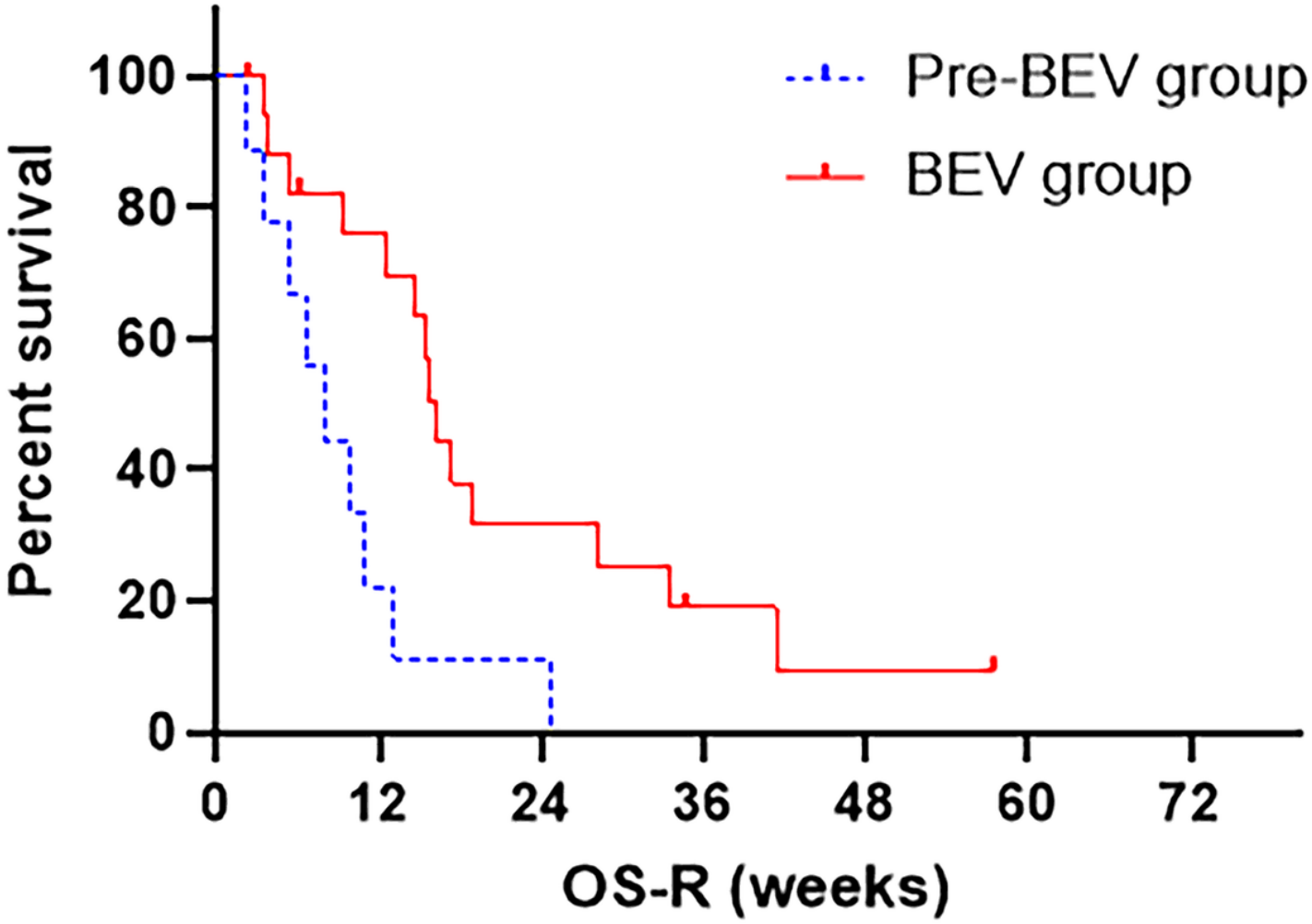

Figure 2

Overall survival after recurrence (OS-R) in patients who underwent cytoreductive surgery at recurrence were shown according to the timing of recurrence before BEV approval (pre-BEV) or after BEV approval (BEV). Median OS-R of the BEV group (16.3 months) was significantly better than that of the pre-BEV group (8.1 months) (P=0.007).

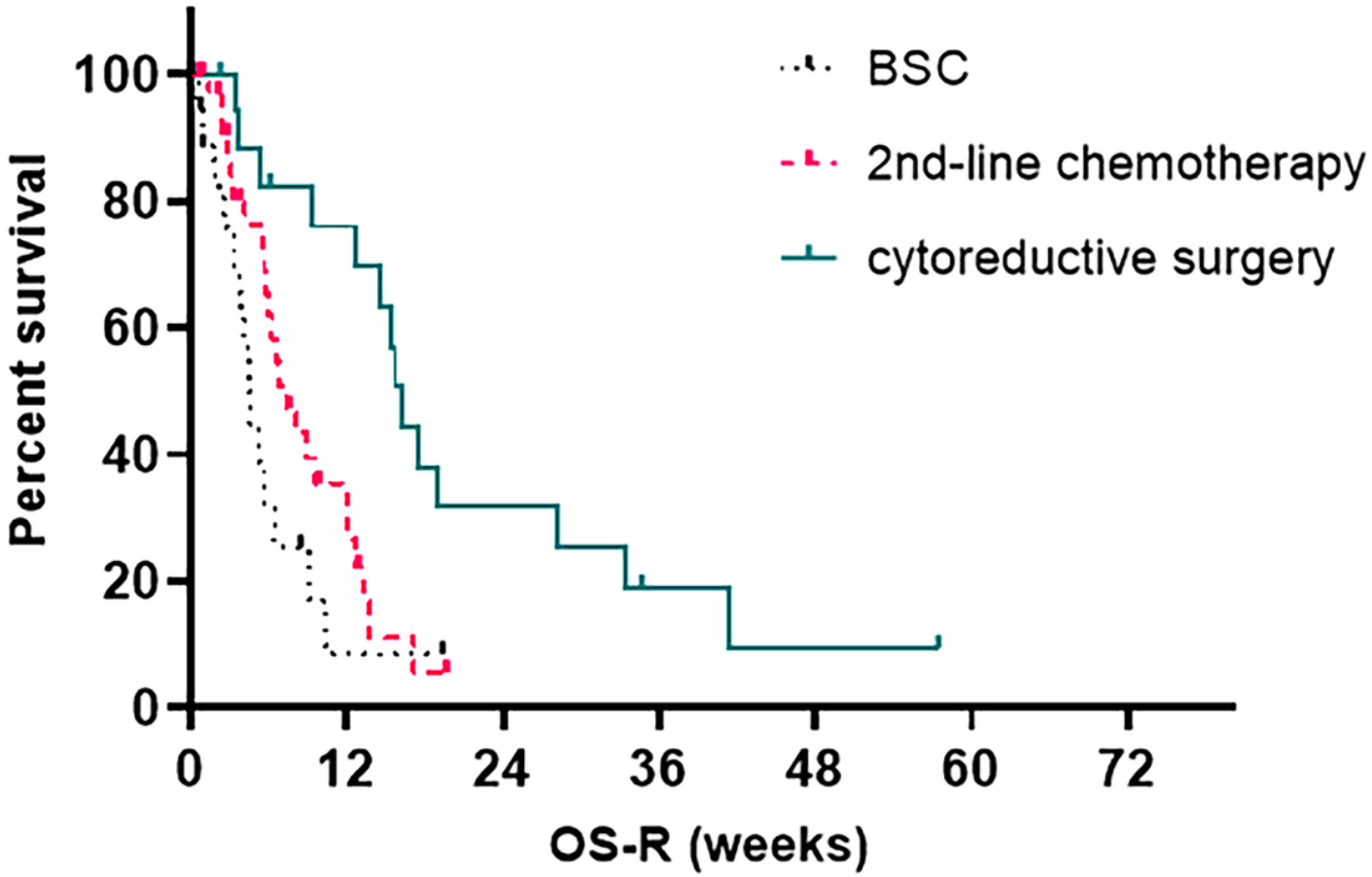

Figure 3

Overall survival after recurrence (OS-R) in the BEV group according to treatment strategy at recurrence. The median OS-R of cytoreductive surgery, second-line chemotherapy without cytoreductive surgery, and best supportive care was 16.3 months, 7.4 months, and 4.6 months, respectively.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementFigv2.pptx