Role of Bevacizumab in High-grade Meningiomas

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Research Article

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Abstract

Background: To explore the role of bevacizumab (BV) in High-grade Meningiomas (HGMs) undergoing surgical treatment.

Methods: Review the clinical data of 139 patients with HGMs and divide them into BV group and non- BV group according to whether they receive BV treatment. Then we compared the progression-free survival (PFS) and overall survival (OS) of the two groups.

Results: The Chi-square test showed significant differences between the BV group and the non-BV group in terms of 12-month PFS (PFS-12), 36-month PFS (PFS-36), median PFS (M-PFS), 12-month OS (OS-12), 36-month OS (OS-36), and median OS (M-OS). However, there was no statistical difference between the BV group and the non-BV group in terms of 6-month PFS (PFS-6), 60-month PFS (PFS-60), and 60-month OS (OS-60). The log-rank test indicated significant differences in PFS and OS between the BV group and the non-BV group.

Conclusion: The role of BV in patients with HGMs is to relieve the symptoms of peritumoral brain edema (PTBE) and prolong PFS and OS. However, whether increasing the dose of BV after surgery can improve the long-term PFS and OS of patients with HGMs needs further research.

1. Introduction

Meningiomas are the most frequent intracranial tumors arising from the meninges of the brain and spinal cord, with a reported incidence that increases with age (median age of 65 years and an incidence of 7.86 per 100,000 population), and an overall 1% lifetime risk [1, 2]. According to the World Health Organization (WHO) Grading System, 80% of meningiomas are grade I, 15–20% are grade II and III, with the latter also called High-grade Meningiomas (HGMs) [1, 2].

The occurrence of peritumoral brain edema (PTBE) is not rare in intracranial meningiomas. PTBE may raise morbidity and mortality by increasing brain shift and intracranial pressure, making the surgical removal challenging, and it also is a predisposing factor to perioperative epilepsy [3, 4]. Moreover, PTBE has associated with a higher risk of postoperative intracranial hematoma [5] as well as neurological deficits. The pathogenesis of PTBE in meningiomas is still unclear and implicates to varying degrees with vascular endothelial growth factor A (VEGF-A) [6, 7], aquaporin 4 [8], and matrix metalloproteinase 9 (MMP-9) [9, 10]. Mannitol, diuretics, and steroids are used to relieve brain edema. However, these drugs have limited curative effects on refractory PTBE and have many side effects. VEGF-A promotes angiogenesis and vascular permeability [11]. Therefore, it is considered to play an important role in PTBE. Recently, clinical trials [12, 13] have shown that Bevacizumab (BV), a monoclonal antibody against VEGF-A, provides an effective treatment for brain edema.

In our study, BV was used in patients whose PTBE was proved by preoperative magnetic resonance imaging (MRI), and the clinical symptoms were not relieved after mannitol or glucocorticoid treatment for

more than 3 days. In this study, we retrospectively analyzed the clinical data of patients with HGMs with refractory PTBE treated with BV. We found that BV can alleviate PTBE, reduce the recurrence of HGMs, and prolong progression-free survival (PFS) and overall survival (OS).

2. Methods

2.1 Patients

The inclusion criteria included meningioma was confirmed by postoperative pathology with definite pathological type, patients sign informed consent. The exclusion criteria were patients without a history of anti-tumor treatment, patients without malignant tumors, and patients whose postoperative pathology is WHO grade I. From January 2014 to January 2021, a total of 657 meningioma patients underwent surgical treatment in our hospital, of which 86 were at WHO grade II and 53 were at WHO grade III. A total of 157 patients were treated with BV, of which 38 were at WHO grade II and 26 were at WHO grade III. All patients had signed informed consent before inclusion in the study. This study was approved by the hospital academic and ethics committee.

2.2 The demographic characteristics

139 patients met the inclusion and exclusion criteria and were included in the study. 64 patients received BV, and 75 did not receive BV. The mean age of the BV group was 57.1 ± 10.2 years, and that of the non-BV group was 53.7 ± 10.1 years. PFS ranged from 4 to 84 months, and OS ranged from 7 to 84 months. 61 patients relapsed after the first operation, 33 of them underwent reoperation, 26 underwent gamma knife stereotactic radiosurgery (GSRS), and 13 refused treatments. 11 patients received both surgical treatment and GSRS after recurrence.

2.3 Treatment doses

Previous studies reported the dosage and schedule of BV, which was usually administered every 2 weeks. Some studies reported a dose of 5 mg/kg, others reported a dose of 10 mg/kg [13, 14]. Even a study has reported that the dose of BV is 15 mg/kg [15]. The purpose of BV is to alleviate the symptoms of PTBE. The dose of BV in our study was 10 mg/kg. Pre and postoperative medications were administered once, with an interval of 2 weeks.

2.4 Follow-up Data

OS is defined from the date of the first operation to the date of the last follow-up or death. PFS is from the date of the first surgery to the date of recurrence or the last follow-up. The patient's physical status was evaluated according to the Karnofsky performance scale (KPS) 2 weeks post-operation. All patients with meningioma underwent craniotomy for tumor resection. The extent of surgical resection was evaluated according to the Simpson grading-scale [16]. Gross total resection (GTR) was defined as Simpson grades I and II, and sub-total resection (STR) is Simpson grades III, IV, and V. Recurrence was defined as tumor

intracranial progression in the original and regional locations. MRI was reviewed once a year post-operation. Figure 1 showed imaging and pathological results of HGMs. (Fig. 1)

2.5 Statistical analyses

Continuous variables were compared using an independent-samples T-test. The Chi-square test was used to compare categorical variables. The Kaplan-Meier method (Log-rank test) was used to analyze PFS and OS between different groups (BV/non-BV, Grade 2/ Grade 3, GTR/STR). $P < 0.05$ was considered significant. Statistical analyses were performed with SPSS software (Version 26.0, IBM, USA).

3. Results

Table 1 summarizes the clinical characteristics of all patients. (Table 1)

We compared whether there were significant differences in PFS and OS between different groups. The Kaplan-Meier method was used to analyze PFS and OS between different groups. Both the Chi-square and the log-rank test showed significant differences in PFS and OS between different pathological grades. In addition, the Chi-square and the log-rank test indicated GTR and STR also have significant differences in PFS and OS. The log-rank test showed significant differences in PFS and OS between different groups based on median progression-free survival (M-PFS) and median overall survival (M-OS). (Table 2) In addition, the log-rank test indicated significant differences in PFS, and OS between different groups based on 60-month progression-free survival (PFS-60) and 60-month overall survival (OS-60). (Fig. 2)

The independent sample T-test showed no significant difference in age between the BV group and the non-BV group ($P > 0.05$). The M-PFS was 41.8 ± 21.7 months in the BV group and 24.6 ± 13.8 months in the non-BV group ($P = 0.000$). The M-OS was 49.3 ± 22.3 months in the BV group and 30.9 ± 18.2 months in the non-BV group ($P = 0.019$). The Chi-square test showed no significant difference in gender, pathological grade, Simpson grade, 6-month progression-free survival (PFS-6), PFS-60, OS-60, and postoperative KPS score between the BV group and the non-BV group ($P > 0.05$). The Chi-square test showed that there were significant differences in preoperative KPS score, 12-month progression-free survival (PFS-12), 36-month progression-free survival (PFS-36), M-PFS, 12-month overall survival (OS-12), 36-month overall survival (OS-36), and M-OS between the BV group and the non-BV group ($P < 0.05$). The Kaplan-Meier method was used to analyze PFS, and OS between the BV group and the non-BV group based on different period. (Table 3) The log-rank test showed that there were significant differences in PFS-12, PFS-36, M-PFS, and PFS-60 between the BV group and the non-BV group. There is no significant difference in PFS-6 between the BV group and the non-BV group. (Fig. 3) In addition, the log-rank test indicated significant differences in OS between the BV group and the non-BV group for all time. (Fig. 4)

The Chi-square test indicated a significant difference in the preoperative KPS between the BV group and the non-BV group. 15 cases (23.4%) in the BV group had pro-operation KPS greater than 80, while 53 (70.7%) were in the non-BV group ($P = 0.000$). There was no statistical difference in postoperative KPS

between the BV group and the non-BV group (P = 0.345). By the end of the follow-up, 61 patients recurred. 33 patients underwent reoperation, 26 patients received GSRS, and 13 patients refuse treatment. The PFS and OS of reoperation were higher than GSRS (P = 0.046). 11 patients received reoperation and GSRS after recurrence. The PFS and OS were higher than reoperation alone (P = 0.039).

4. Discussion

The most important prognostic factor regarding tumor recurrence is the pathological grade. In WHO grade I tumors, the chance of recurrence is 7–25%, in grade II 29–59%, whereas, in grade III, it is 60–94% [17]. In our study, the 5-year recurrence of grade 2 and 3 meningiomas were 36.0%(n = 31) and 56.6% (n = 30), respectively (P = 0.014). The 5-year OS of grade 2 and 3 meningiomas were 82.6% (n = 71) and 67.9% (n = 36), respectively (P = 0.038). GTR has been widely recognized as a favorable factor that was strongly associated with better survival [18, 19]. A retrospective study of 132 atypical meningioma cases revealed that GTR was associated with better PFS, but not OS [20]. In a series of 44 patients, Zaher reported that patients with GTR had longer OS than patients with STR (75 vs 46 months) [21]. Our data are consistent with previous reports showing that patients who underwent GTR had favorable outcomes. In our study, the 5-year recurrence of GTR and STR were 35.9%(n = 33) and 59.6% (n = 28), respectively (P = 0.007). The 5-year OS of GTR and STR were 84.8% (n = 78) and 61.7% (n = 29), respectively (P = 0.003). There were significant differences in the 5-year recurrence and OS between GTR and STR.

Complete surgical resection is considered the gold standard for treatment. However, this approach is often not sufficient in WHO grade II and III meningiomas. The importance of deregulated cell signaling pathways as drivers of neoplastic transformation is increasingly getting attention. Several studies have suggested a critical role of VEGF in meningioma pathogenesis, as its expression correlates with tumor grade, peritumoral edema, and necrosis [22, 23]. For this reason, in the last few years, antiangiogenetic factors have been used, not only for malignant glial brain tumors but also for meningiomas not responsive to standard treatments [24]. Bevacizumab is a monoclonal antibody against VEGF. Few studies described its use in grade II and III meningiomas [25]. In our study, the purpose of BV is to alleviate the symptoms of PTBE. The Chi-square test showed that there were significant differences in PFS-12, PFS-36, M-PFS, OS-12, OS-36, and M-OS between the BV group and the non-BV group. The log-rank test indicated significant differences in PFS and OS between the BV group and the non-BV group. Thus, we believe that BV can reduce the recurrence and improve PFS and OS in patients with HGMs.

KPS in the BV group was significantly improved after treatment. Surgery can alleviate the symptoms of PTBE to a certain extent. Considering the obvious changes of KPS in the BV group pre- and post-treatment, we believe that BV can alleviate PTBE and improve the quality of life of patients. There are some treatments such as reoperation, GSRS, and medicine therapy that can be chosen after recurrence. These patients who received both reoperation and GSRS after recurrence have a better outcome than others. Therefore, GSRS is a recommended treatment option. The OS of patients who refused treatment was short. We recommend that patients with HGMs receive active treatment after recurrence.

The adverse reactions of BV include hypertension, various bleeding, venous thrombus exfoliation, and albuminuria. In previous reports, the incidence of all kinds of bleeding was 30%, including intracranial hemorrhage, epistaxis, gingival bleeding, conjunctival bleeding, injection-site bleeding, and hematuria [26]. Besse reported in 2010 that the incidence of brain hemorrhage in patients with brain metastases after applicated BV was 0.8%-3.3%, while the incidence of non- applicated was 1.0% [27]. Khasraw reported in 2012 that the incidence of brain hemorrhage in patients with glioma or brain metastases after BV treatment was 3.7%, while the incidence of non-BV was 3.6% [28]. Due to the low dose of BV in this study, only 8 patients developed hypertension.

5. Conclusion

Patients who received BV showed significant improvement in preoperative symptoms, which may be helpful to the success of the operation. Interestingly, PFS-12, PFS-36, M-PFS, OS-12, OS-36, and M-OS of the BV group were significantly higher than the non-BV group. Therefore, we believe that the role of BV in patients with HGMs is to relieve the symptoms of PTBE and prolong PFS and OS. However, there was no significant difference in PFS-6, PFS-60, and OS-60 between the BV group and the non-BV group. Whether increasing the dose of BV after surgery can improve the long-term PFS and OS of patients with HGMs needs further research.

Declarations

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Conflicts of interest

The authors have no relevant financial or non-financial interests to disclose.

Availability of data and material

The authors declare that relevant raw data can be provided.

Code availability

Not applicable

Authors' contributions

Xuexue Bai and Yiyao Cao participated in the design of this study and collected important background information. Xiangyu Wang completed related literature retrieval, data acquisition and data analysis. Xuexue Bai drafted the manuscript, Yiyao Cao completed the revision of the manuscript. All the authors read and approved the final manuscript. Yiyao Cao are responsible for the final manuscript. The authors declare that there are no conflicts of interest.

Ethics approval

All persons gave their informed consent prior to their inclusion in the study. This study was approved by the hospital ethics and academic committee.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Authors are responsible for correctness of the statements provided in the manuscript. All authors agree to submit and publish the manuscript.

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Tables

Table 1
The clinical characteristics of all patients

Parameter	BV(N = 64)	Non-BV(N = 75)	P-Value
Age(median), years	57.1 ± 10.2	53.7 ± 10.1	= .698
Sex (N, %)			= .475
Male	26(40.6%)	29(38.7%)	
Female	38(59.4%)	46(61.3%)	
Simpson grade (N, %)			= .547
Grade 1	24(37.5%)	33(44.0%)	
Grade 2	16(25.0%)	17(22.7%)	
Grade 3	15(23.4%)	14(18.7%)	
Grade 4	9(14.1%)	11(14.6%)	
Pathological grade (N, %)			= .422
Grade 2	38(59.4%)	48(64.0%)	
Grade 3	26(40.6%)	27(36.0%)	
Pre-KPS			= .000
<80	49(76.6%)	22(29.3%)	
≥80	15(23.4%)	53(70.7%)	
Post-KPS			= .345
<80	11(17.2%)	10(13.3%)	
≥80	53(82.8%)	65(86.7%)	
PFS (N, %)			
PFS-6 Months	61(95.3%)	69(92.0%)	= .332
PFS-12 Months	59(92.2%)	60(80.0%)	= .034
PFS-36 Months	54(84.4%)	49(65.3%)	= .008
M-PFS Months	45(70.3%)	41(54.7%)	= .042
PFS-60 Months	40(62.5%)	38(50.1%)	= .109
OS (N, %)			
OS-12Months	63(98.4%)	67(89.3%)	= .029

Parameter	BV(N = 64)	Non-BV(N = 75)	P-Value
OS-36 Months	59(92.2%)	60(80.0%)	= .034
M-OS Months	57(89.1%)	57(76.0%)	= .036
OS-60 Months	51(79.7%)	56(74.7%)	= .310

Note: BV= Bevacizumab, KPS=Karnofsky performance scale, Progression-free survival=PFS, PFS-6=6-month PFS, PFS-12=12-month PFS, PFS-36=36-month PFS, M-PFS=Median PFS, PFS-60=60-month PFS, OS=Overall survival, OS-12=12-month OS, OS-36=36-month OS, M-OS=Median OS, OS-60=60-month OS

Table 2
Log Rank test of PFS and OS between different groups based on M-PFS and M-OS.

Parameter	Mean value (months)	95%CI	P-Value
PFS:			
Treatment			= .001
BV	63.2 ± 3.8	55.7–70.7	
Non-BV	34.3 ± 2.2	30.0-38.6	
Pathological grade			= .016
Grade 2	57.5 ± 3.7	50.3–64.8	
Grade 3	46.3 ± 4.9	36.7–55.9	
Simpson grade			= .001
GTR	59.0 ± 3.6	51.9–66.0	
STR	41.2 ± 4.8	31.7–50.6	
OS:			
Treatment			= .006
BV	76.9 ± 2.5	71.9–81.8	
Non-BV	52.4 ± 2.9	46.6–58.1	
Pathological grade			= .005
Grade 2	75.6 ± 2.6	70.5–80.7	
Grade 3	61.3 ± 4.5	52.5–70.0	
Simpson grade			= .000
GTR	78.6 ± 2.1	74.5–82.7	
STR	53.3 ± 4.7	44.1–62.5	

Note: BV= Bevacizumab, Progression-free survival=PFS, OS=Overall survival, GTR= Gross total resection, STR=Sub-total resection, M-PFS=Median PFS, M-OS=Median OS

Table 3
Log Rank test of PFS and OS between BV group and non-BV group based on different period

Parameter	Mean value (months)	95%CI	P-Value
PFS-6			= .431
BV	80.3 ± 2.1	76.2–84.4	
Non-BV	49.1 ± 1.5	46.2–52.1	
PFS-12			= .036
BV	77.9 ± 2.6	72.9–83.0	
Non-BV	43.5 ± 2.2	39.2–47.8	
PFS-36			= .002
BV	72.4 ± 3.4	65.8–79.0	
Non-BV	37.8 ± 2.4	33.2–42.5	
Median-PFS			= .001
BV	63.2 ± 3.8	55.7–70.7	
Non-BV	34.3 ± 2.2	30.0-38.6	
PFS-60			= .000
BV	59.3 ± 3.7	52.0-66.5	
Non-BV	33.3 ± 2.1	29.2–37.4	
OS-12			= .025
BV	82.8 ± 1.1	80.6–85.1	
Non-BV	60.5 ± 2.2	56.3–64.8	
OS-36			= .018
BV	78.5 ± 2.3	73.9–83.1	
Non-BV	55.1 ± 2.7	49.7–60.4	
Median-OS			= .006
BV	76.9 ± 2.5	71.9–81.8	
Non-BV	52.4 ± 2.9	46.6–58.1	
OS-60			= .032

Parameter	Mean value (months)	95%CI	P-Value
BV	72.2 ± 2.8	66.6–77.8	
Non-BV	51.7 ± 2.9	45.9–57.4	

Note: BV= Bevacizumab, KPS=Karnofsky performance scale, Progression-free survival=PFS, PFS-6=6-month PFS, PFS-12=12-month PFS, PFS-36=36-month PFS, M-PFS=Median PFS, PFS-60=60-month PFS, OS=Overall survival, OS-12=12-month OS, OS-36=36-month OS, M-OS=Median OS, OS-60=60-month OS

Figures

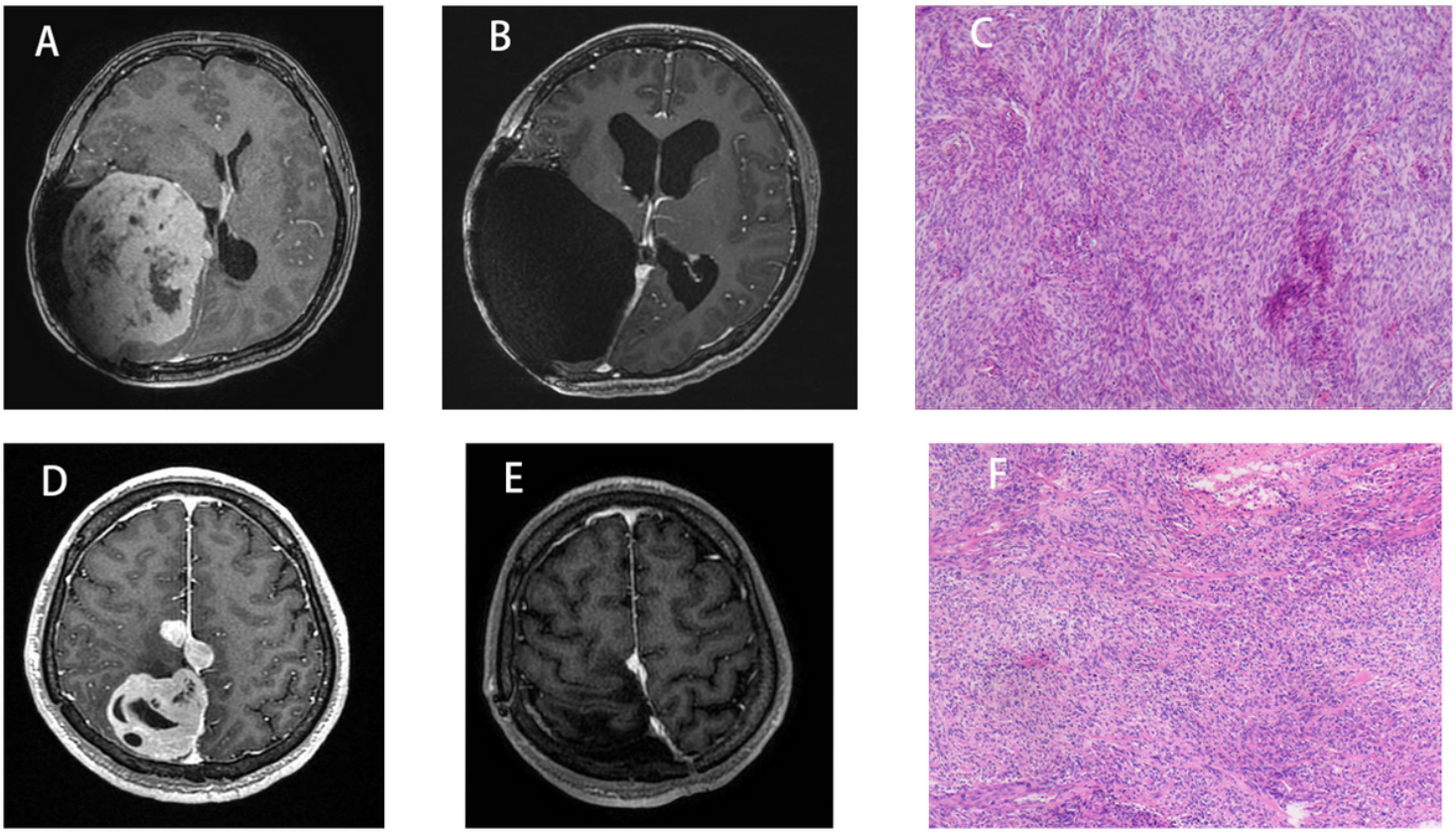

Figure 1

Imaging and pathological results of High-grade meningioma. A: Preoperative imaging examination of grade 2 meningioma. B: Postoperative imaging examination of grade 2 meningioma. C: Postoperative pathological results of grade 2 meningioma. D: Preoperative imaging examination of grade 3 meningioma. E: Postoperative imaging examination of grade 3 meningioma. F: Postoperative pathological results of grade 3 meningioma.

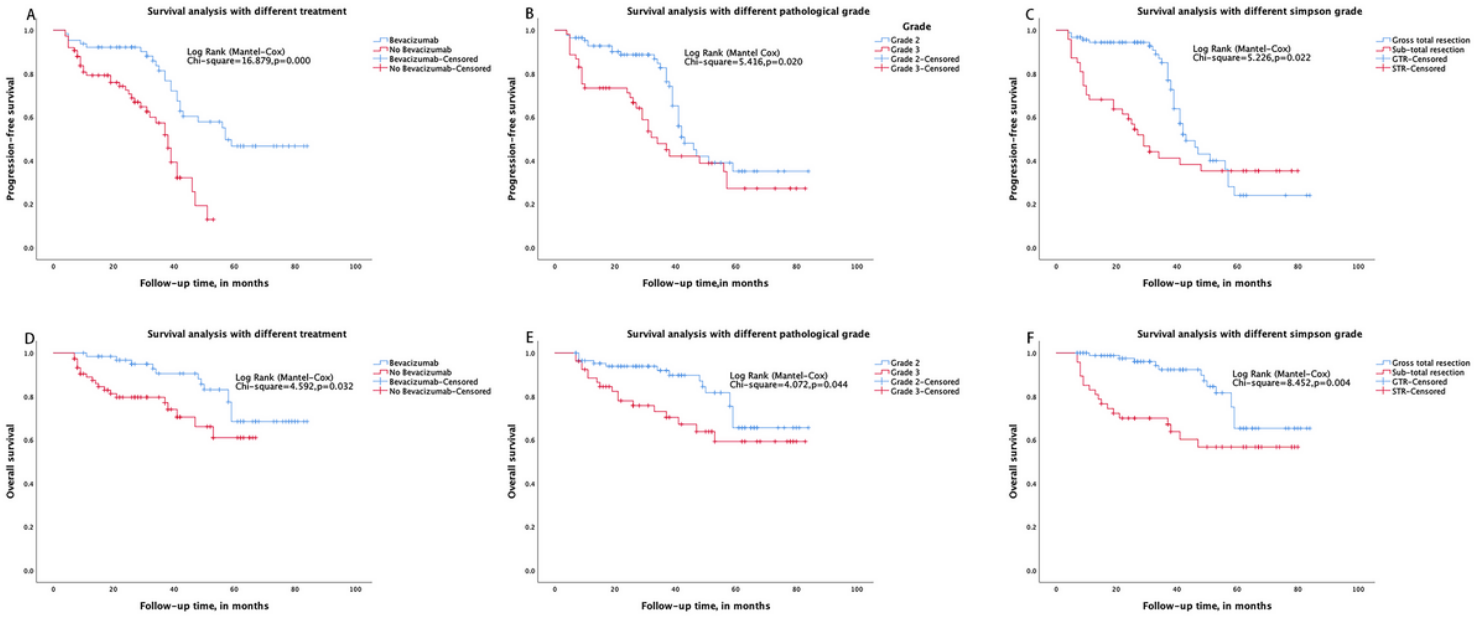

Figure 2

Progression-free Survival curves and Overall Survival curves for High-grade Meningioma patient. A: Kaplan-Meier curves of progression-free survival according to the treatment group. B: Kaplan-Meier curves of progression-free survival according to the pathological grade. C: Kaplan-Meier curves of progression-free survival according to the Simpson grade. D: Kaplan-Meier curves of overall survival according to the treatment group. E: Kaplan-Meier curves of overall survival according to the pathological grade. F: Kaplan-Meier curves of overall survival according to the Simpson grade.

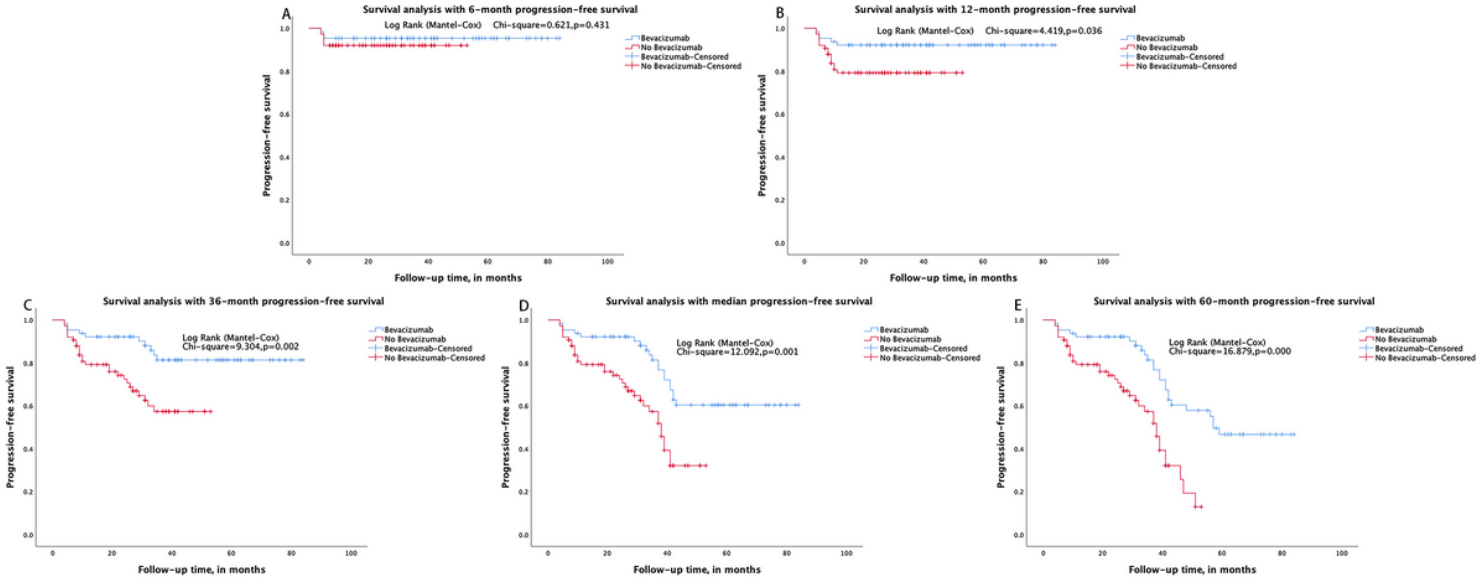

Figure 3

Progression-free Survival curves for the Bevacizumab group and the non-Bevacizumab group. A: Kaplan-Meier curves according to the treatment group based on 6-month progression-free survival. B: Kaplan-Meier curves according to the treatment group based on 12-month progression-free survival. C: Kaplan-

Meier curves according to the treatment group based on 36-month progression-free survival. D: Kaplan-Meier curves according to the treatment group based on the median progression-free survival. E: Kaplan-Meier curves according to the treatment group based on 60-month progression-free survival.

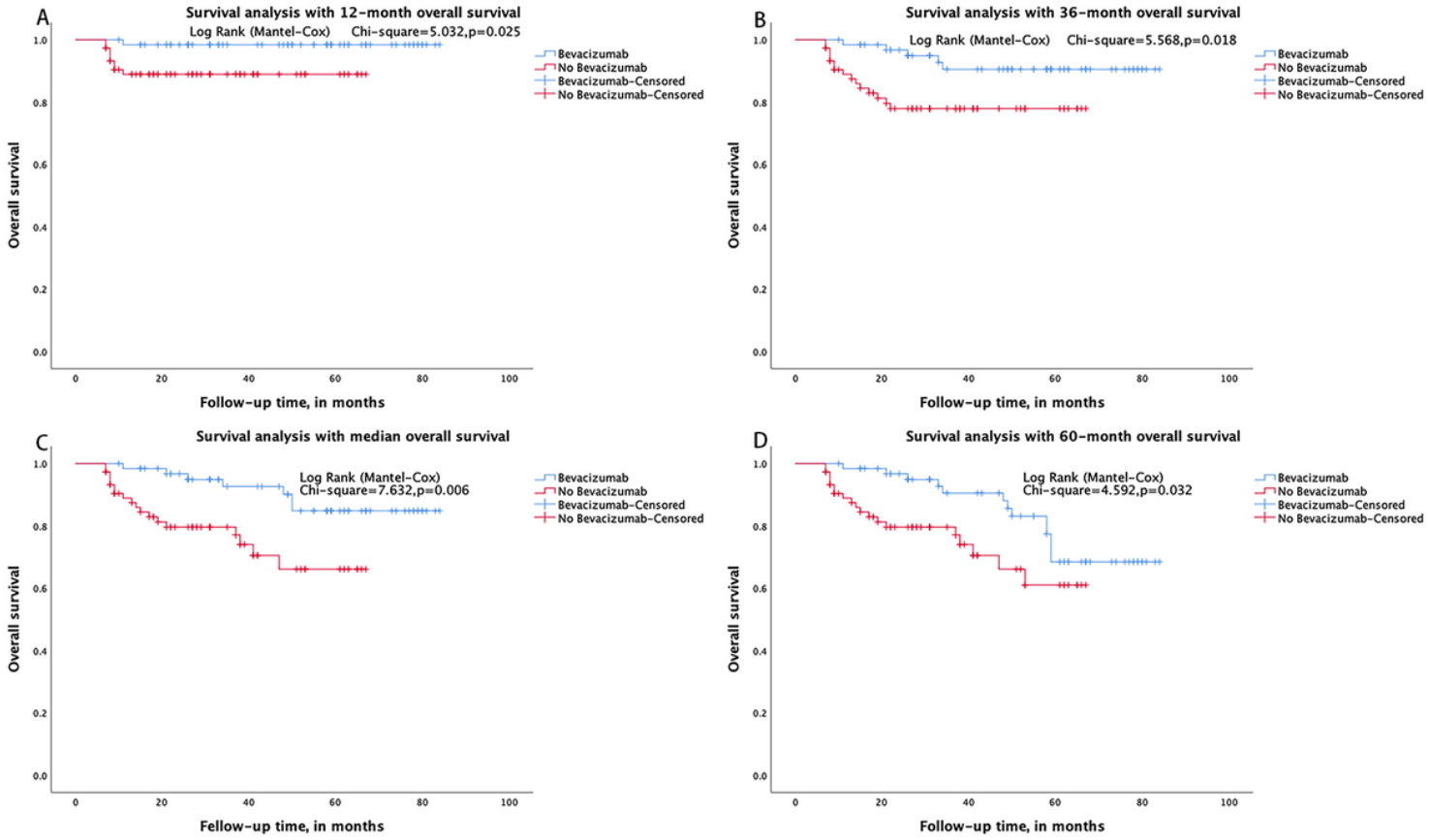

Figure 4

Overall Survival curves for the Bevacizumab group and the non-Bevacizumab group. A: Kaplan-Meier curves according to the treatment group based on 12-month overall survival. B: Kaplan-Meier curves according to the treatment group based on 36-month overall survival. C: Kaplan-Meier curves according to the treatment group based on the median overall survival. D: Kaplan-Meier curves according to the treatment group based on 60-month overall survival.