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Running title: Prognosis and vascular therapy in GBM

Postoperative clinical prognosis in 160 cases of glioblastoma and efficacy of vascular targeted therapy for recurrence

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Glioblastoma (GBM) is the most common primary malignant brain tumor. Concurrent chemoradiotherapy and adjuvant chemotherapy have become the standard treatment modalities after surgery. However, despite such aggressive treatment, the overall survival (OS) rate remains low, and the disease is highly prone to recurrence with an extremely poor prognosis after recurrence. Currently, there is no standard salvage treatment regimen. This study conducted a clinical prognostic analysis of 160 patients with GBM after surgery and evaluated the clinical efficacy of anti-angiogenic drugs (apatinib/bevacizumab) as salvage treatment after recurrence, providing a strong direction for future treatment. Among the 160 patients with GBM included in the study, univariate analysis showed that age, use of apatinib, adjuvant chemotherapy, and radiotherapy were significantly associated with OS, while gender, CD34 expression, Ki-67 expression, bevacizumab, and P53 expression were not significantly associated with OS. Multivariate analysis revealed that adjuvant chemotherapy, age, and radiotherapy were independent prognostic factors for OS in patients with GBM. The median overall survival of the entire cohort was 20.0 months, with 1-year, 3-year, and 5-year survival rates of 74.6%, 28.7%, and 12.4%, respectively. Analysis of the clinical efficacy of salvage chemotherapy in 65 patients with recurrent GBM showed that the combined anti-angiogenic drug group had a significant survival advantage compared to the chemotherapy-only group (33 months vs. 19 months). Among patients in the combined anti-angiogenic drug group, 36 patients achieved clinical control, with a disease control rate (DCR) of 73.47%, significantly higher than the 43.75% DCR in the control group. The chemotherapy combined with apatinib group had a significant survival advantage in OS ($p = 0.012$) and also benefited in DCR (66.67% vs. 43.75%); however, the chemotherapy combined with the bevacizumab group did not show a survival benefit in OS ($p = 0.078$).

Key words: glioblastoma; survival analysis; recurrent; apatinib; bevacizumab

GBM is the most common primary malignant brain tumor in adults, accounting for 15–20% of all intracranial tumors; its incidence increases with age [1], and it predominantly affects males around the age of 64 years (the male/female ratio is 1.6:1) [2]. GBM is mainly located in the cerebral hemispheres, most frequently in the frontal lobe [3] Despite availability of a standard treatment regimen of maximal safe resection followed by concurrent chemoradiotherapy with temozolomide, the prognosis of patients with GBM remains poor, with a median overall survival (OS) of 14.6 months and a 5-yearsurvival rate of less than 5% [4]. The limited efficacy of treatment is primarily due to the high diffusivity and invasiveness and complex genetic mutations of GBM [5], as well as the absence of a specific curative approach; salvage therapy after recurrence lacks standardized protocols and requires individual management based on each patient's specific condition.

GBM is characterized by excessive angiogenesis triggered by elevated levels of vascular endothelial growth factor (VEGF), which promotes tumor growth by facilitating formation of new blood vessels [6, 7]. However, this pronounced vascular phenotype is often accompanied by complex tumor–stromal interactions involving numerous types of immune cell, which may have negative effects on response to immunotherapy [8]. Moreover, the hypoxic microenvironment resulting from rapid tumor growth drives further formation of abundant new blood vessels [9]. In light of this, clinical strategies have been developed that involve use of multigenerational VEGF inhibitors to overcome resistance and enhance therapeutic efficacy.

Bevacizumab is a monoclonal antibody that disrupts VEGF signaling, thereby inhibiting angiogenesis and exerting antitumor effects [10]. On the basis of successful phase II trials, bevacizumab was approved by the U.S. Food and Drug Administration in 2009 for treatment of rGBM [11, 12]. Since then, it has become a second-line treatment option globally owing to its efficacy and favorable safety profile [13]. However, controversy remains regarding the survival benefit it confers. Apatinib mesylate, a novel small-molecule tyrosine kinase inhibitor targeting the VEGF pathway, has demonstrated tolerability and efficacy in patients with various cancers. Research regarding the therapeutic value of apatinib in GBM has been limited to date and requires further validation.

In the present study, we conducted a retrospective analysis of clinical data from 160 GBM patients to evaluate the impact of anti-angiogenic agents (apatinib/bevacizumab) on the prognosis of these patients, with the aim of gaining deeper insight into the efficacy of these agents in the management of rGBM.

Patients and methods

Study population. This was a retrospective, observational, non-interventional study. We retrospectively analyzed 160 patients with GBM who were hospitalized in our institution from January 2014 to January 2020. Patients could be included if they had 1) undergone maximal safe resection with pathological confirmation of GBM; 2) received standard-dose radiotherapy with concurrent temozolomide chemotherapy; and 3) had a Karnofsky performance status (KPS) score ≥ 70. Patients were excluded if they 1) had a history of secondary malignancies other than GBM; 2) did not complete adjuvant radiotherapy; 3) had insufficient follow-up data (defined as follow-up duration < 6 months); or 4) were excluded for ethical reasons.

Recurrence was defined per RANO criteria for high-grade gliomas [14]: an increase in the sum of perpendicular diameters by ≥ 25%, or an increase in two-dimensional area (product of perpendicular diameters) by ≥ 10 mm^2. all magnetic resonance imaging (MRI) was performed every 2 months. All scans were independently reviewed by two blinded senior neuroradiologists; disagreements were resolved by consensus or a third reviewer.

Baseline information for the 160 patients included in this study comprised gender, age, KPS score, date of initial diagnosis, date of surgery, pathological markers (CD34 [15], Ki-67 [16], p53, etc.), radiotherapy plan, chemotherapy regimen and cycles, time and location of recurrence, whether salvage surgery was performed, date of last discharge, current status, and whether any treatment was received after discharge.

Treatment methods. After evaluation by neurosurgeons, maximal safe resection was performed via standard open craniotomy. No intraoperative adjunctive technologies (e.g., neuronavigation, image-guided surgery) were used. Postoperatively, patients were required to have a KPS score of at least 70. For radiotherapy (linear accelerator), patients were immobilized using a thermoplastic mask. Target volumes were delineated based on fused computed tomography/MRI images and included gross tumor volume, clinical target volume (expanded by 1.5 cm from the gross tumor

volume), and planning target volume (expanded by 0.3 cm from the clinical target volume). A total dose of 60 Gy (2 Gy per fraction) was delivered to 95% of the planning target volume under supervision by radiation oncologists.

Regarding chemotherapy, all patients received concurrent temozolomide during radiotherapy at a dose of 75 mg/m²/day, followed by an adjuvant at 150 mg/m²/day (28-day cycles) after completion of radiotherapy. MRI scans were performed every 2 months to assess treatment response. For patients with confirmed recurrence, salvage therapy was initiated on the basis of individual circumstances, including cisplatin (intravenous, 75 mg/m² every 3 weeks), lomustine (oral, 100-140 mg/m² every 6 weeks), apatinib (oral, 500 mg/day, reduced to 250 mg/day if the higher dosage was not tolerated), or bevacizumab (intravenous, 10 mg/kg every 2 weeks). During treatment, blood cell counts, renal function, blood pressure, and skin condition were regularly monitored, and adverse reactions were managed symptomatically.

Assessment of treatment efficacy. During treatment, patients underwent cranial MRI scans every two chemotherapy cycles. Treatment response was jointly evaluated by radiologists and radiation oncologists according to the Response Assessment in Neuro-Oncology criteria [14] and categorized as complete response (CR), partial response (PR), progressive disease (PD), or stable disease (SD). Disease control rate (DCR) was calculated as follows:

$$DCR=(CR+PR+SD)/(CR+PR+SD+PD) \times 100\%.$$

DCR was assessed every 28 days (one cycle), with evaluation after 2 cycles. Progression-free survival (PFS) was defined as the time from treatment initiation to disease progression, death from any cause, or last follow-up (whichever occurred first). OS was defined as the time from treatment initiation to death from any cause or last follow-up. Patients who died from non-glioma causes were excluded.

Safety analysis. Adverse reactions, including hypertension, vomiting, diarrhea, leukopenia, thrombocytopenia, hepatic/renal dysfunction, and rash, were graded from 1 to 5 according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v. 5.0 standards and relevant clinical guidelines. Specific grading and management strategies are detailed in the Supplementary Table S1. We strictly followed NCI-CTCAE standards and institutional protocols for monitoring adverse drug reactions in patients receiving antiangiogenic agents, including detection (healthcare professionals continuously observed patients during medication),

recording (suspected adverse drug reactions were immediately documented with patient information, drug name/batch number, dose, time, manifestations, and severity), assessment (using World Health Organization causality assessment criteria or the Naranjo scale to exclude confounding factors), treatment (measures were taken according to NCI-CTCAE grading), and reporting (data were aggregated monthly and submitted via the national adverse drug reaction monitoring system).

Immunohistochemical assessment. Ki-67, CD34, MGMT promoter methylation, IDH, TERT, 1p/19q, and BRAF V600E results were obtained from postoperative pathology or molecular reports issued by the Department of Pathology, Second Hospital of Hebei Medical University. This was a retrospective, non-interventional study; no additional testing was performed for research purposes. All tests followed standard diagnostic protocols [17].

Data and statistical analysis. Survival curves were generated using the Kaplan–Meier method, and group differences were compared using the log-rank test. Variables with $P < 0.05$ in univariate analysis were entered into multivariate Cox regression models, with multicollinearity assessed by variance inflation factor (all values < 5). For missing CD34, p53, and Ki-67 data, available case analysis was applied (only patients with recorded values were analyzed); sensitivity analyses showed no significant baseline differences between patients with and without data (all $p > 0.05$). Statistical analyses were performed using SPSS v. 23.0 and Prism, with a significance level of $\alpha=0.05$.

Ethics approval and consent to participate. This study was conducted in accordance with institutional ethical standards and the Declaration of Helsinki and was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (Approval No. 2026-R075). This was a retrospective study, Written informed consent was obtained from all participants or their legal guardians, and all patient data were de-identified prior to analysis.

Results

Patients with GBM

Baseline characteristics of patients. The 160 patients with GBM included in this study comprised 97 males (60.6%) and 63 females (39.4%). The age range was 18-76 years, with a median age of 52 years. The median follow-up time was 18.7 months. Thirty-four patients did not receive adjuvant chemotherapy (Table 1).

Survival analysis (160 patients with GBM). mOS was 20.0 months (95% CI: 18.47–21.53). The 1-, 3-, and 5- year survival rates were 74.6%, 28.7%, and 12.4%, respectively (Figure 1A).

Univariate analysis of OS in GBM patients. To identify prognostic factors, we first performed univariate analysis, including the following variables: age (≥ 50 years vs. < 50 years), gender (male vs. female), CD34 expression (positive vs. negative), Ki-67 expression (< 20% vs. ≥ 20%), p53 expression (positive vs. negative), adjuvant chemotherapy (yes vs. no), use of apatinib (yes vs. no), and use of bevacizumab (yes vs. no).

As shown in Table 2 and Figure 1, age (p=0.027; Figure 1B), use of apatinib (p=0.014; Figure 1E), adjuvant chemotherapy (p=0.014; Figure 1C), and radiotherapy (p=0.003; Figure 1D) were significantly associated with OS. By contrast, gender (p=0.288), CD34 expression (p=0.206; Figure 1G), Ki-67 expression (p=0.126; Figure 1H), use of bevacizumab (p=0.187; Figure 1F), and p53 expression (p=0.663) showed no significant association with OS. Although the association for CD34 expression was not statistically significant (p=0.206), the survival curve suggested a potential survival advantage for CD34-positive patients. Furthermore, the survival analysis for Ki-67 expression indicated that patients with Ki-67 < 20% had better survival outcomes than those with Ki-67 ≥ 20%.

Multivariate analysis. Variables identified as statistically significant ($p < 0.05$) in the univariate analysis were entered into a multivariate Cox proportional-hazards regression model to determine independent prognostic factors. The multivariate analysis included age, adjuvant chemotherapy, use of apatinib, and use of radiotherapy. The multivariate model was statistically significant (p=0.006). The results indicated that adjuvant chemotherapy (p=0.034), age (p=0.030), and radiotherapy (p=0.035) were independent prognostic factors for GBM patients. However, use of apatinib (p=0.078) was not significantly associated with prolonged OS. Details are provided in Table 2.

Salvage therapy for rGBM patients

Baseline information. Among the 160 GBM cases collected, 65 patients with recurrent disease who received salvage therapy were further analyzed. Inclusion criteria were: 1) completion of standard postoperative radiotherapy and chemotherapy, including adjuvant temozolomide; 2) recurrence confirmed by imaging and assessment by radiation oncology specialists; 3) receipt of salvage chemotherapy without subsequent surgery or radiotherapy; and 4) regular MRI evaluation

with respect to treatment response.

Of the 65 patients receiving salvage chemotherapy, 26 received apatinib-based chemotherapy, and 28 received bevacizumab-based chemotherapy (five of whom received both apatinib and bevacizumab during salvage treatment). These 65 patients were divided into two main groups according to the use of anti-angiogenic agents during salvage therapy: a combination anti-angiogenic therapy group (n = 49) and a chemotherapy-only group (n=16). The combination anti-angiogenic therapy group was further divided into three subgroups based on the specific salvage regimen: chemotherapy plus apatinib (n=20), chemotherapy plus bevacizumab (n=23), and chemotherapy plus apatinib plus bevacizumab (n=6) (Table 3). There was no difference in the baseline values between the two groups (Supplementary Table S2).

The median duration of apatinib treatment was 3 months (range: 1-7 months). Dose reduction due to adverse reactions was required in 7.69% of patients receiving apatinib.

Survival analysis (65 patients with rGBM). Compared to chemotherapy alone, combination anti-angiogenic therapy showed a significant survival advantage (p=0.011; Figure 2A), with a median overall survival (mOS) of 33 months in the combination anti-angiogenic therapy group versus 19 months in the chemotherapy-only group. Chemotherapy plus apatinib demonstrated a significant survival benefit in terms of OS (p=0.012; Figure 2B), whereas chemotherapy plus bevacizumab did not (p=0.078; Figure 2C).

Clinical efficacy. Of the 49 patients in the combination anti-angiogenic therapy group, one achieved PR and 35 achieved SD. Thirteen patients experienced PD. Thus, disease control was achieved in 36 patients, yielding a DCR of 73.47%. The DCR in the control (chemotherapy-only) group was 43.75%, whereas that in the combination anti-angiogenic therapy group was significantly higher (p=0.028; Table 3).

Management of toxicities. In the combination anti-angiogenic therapy group, 24 patients experienced grade I/II adverse events, including nine cases of myelosuppression, six of rash, six of mild gastrointestinal reactions (e.g., nausea and vomiting), and three of elevated blood pressure. Two patients experienced grade III/IV adverse events, including one case of cerebellar hemorrhage. This patient developed significant limb weakness after two treatment cycles, and follow-up MRI revealed new hemorrhage within the lesion. After exclusion of other confounding factors, this was diagnosed as a grade III adverse event. Apatinib was subsequently discontinued and the treatment

regimen was modified, with supportive care initiated. The other case involved a severe gastrointestinal reaction.

In the chemotherapy-alone group, ten patients experienced grade I/II adverse events, including four cases of myelosuppression and six of gastrointestinal reactions. One grade III/IV adverse event (severe myelosuppression) was observed. All adverse events were alleviated with symptomatic treatment, and no fatalities occurred. Statistical analysis showed no significant difference in adverse events between the two groups (p=0.888).

Apatinib-related adverse effects included elevated blood pressure, vomiting, diarrhea, leukopenia, rash, and hepatic/renal dysfunction. Among the 26 patients treated with apatinib, six developed elevated blood pressure; in five of these cases, this was controlled with oral antihypertensive medication, with only one patient developing malignant hypertension requiring drug discontinuation. Two cases of myelosuppression were relieved with medication. Rash occurred in five patients and gastrointestinal adverse reactions in three; these symptoms were alleviated by dose reduction. In one patient, treatment was discontinued owing to minor intracranial hemorrhage. No significant side-effects were observed in the remaining patients.

Severe adverse events potentially associated with bevacizumab include hypertension, arterial and venous thrombosis, cerebral hemorrhage (including tumor hemorrhage), proteinuria, delayed wound healing, and gastrointestinal perforation. However, among the 29 bevacizumab-treated patients in our study, no arterial/venous thrombosis, proteinuria, or gastrointestinal perforation was observed. The main side-effects were hypertension, leukopenia, and neutropenia, similar to those in the chemotherapy-only group.

Discussion

GBM is the most common primary malignant central nervous system tumor and is characterized by its highly aggressive nature. Concurrent and adjuvant temorolomide with radiotherapy became the standard regimen for patients with newly diagnosed GBM in 2005. Regular and active adjuvant chemotherapy post-surgery significantly prolongs overall patient survival. However, even with strict adherence to this protocol, recurrence is almost inevitable, resulting in a median PFS of approximately 6.9 months. Currently, there is no standard salvage treatment for patients with rGBM. In addition to repeat surgery or re-irradiation, the primary systemic therapeutic options are

chemotherapy, targeted therapy, and immunotherapy. However, existing regimens, whether used alone or in combination, have not demonstrated a substantial improvement in patient survival rates. Notably, cytarabine combined with immune checkpoint blockade has shown anti-tumor activity in preclinical glioma models, providing a rationale for exploring similar strategies in rGBM [18]. In recent years, multiple preclinical studies and clinical trials have suggested that immunotherapy and targeted therapy could extend patient survival, with antiangiogenic agents (which inhibit the VEGF signaling pathway), in particular, showing potential efficacy. Examples include bevacizumab and ramucirumab, which are widely used in various cancers, as well as tyrosine kinase inhibitors such as sunitinib, sorafenib, and apatinib [19]. The updated Chinese clinical practice guidelines for adult diffuse gliomas emphasize molecular diagnostics and targeted therapy [20].

The factors influencing the prognosis and survival of GBM patients are complex. In this study, univariate and multivariate analyses were performed with variables including age, sex, chemotherapy, radiotherapy, CD34 expression, Ki-67 expression, use of bevacizumab, and use of apatinib. Age and chemotherapy emerged as independent risk factors affecting patient prognosis. Apatinib did not show independent prognostic significance in the multivariate model. This finding could be attributable to interactions between apatinib and other concurrent therapies, or it may have been due to the limited sample size in the subgroup analyses.

Age is a significant prognostic factor in GBM, which is associated with the biological mechanisms of cellular senescence. In the present study, the median survival of patients under 50 years older was 23 months, compared to 20 months for patients more than 50 years old. Elderly patients (≥70 years) are often excluded from standard clinical trials and receive less intensive treatment, and their optimal therapeutic regimen thus remains undefined. Differences in survival rates among elderly patients may also be influenced by factors such as KPS score, tumor biology, and central nervous system functional status.

Ki-67 is a commonly used biomarker that reflects proliferative activity of tumor cells, with high expression typically indicating rapid tumor progression and poor prognosis. Previous studies [21] have shown that GBM patients with low Ki-67 expression have significantly better OS (26.8 months) compared to those with high expression (15.8 months), and Ki-67 has been identified as an independent prognostic factor after gross total resection. Among the 141 patients in this study, the median survival of those with Ki-67 ≥ 20% (20.0 months) was significantly lower than that of those

with Ki-67 < 20% (40.0 months).

VEGF is a potent pro-angiogenic cytokine. Under hypoxic conditions, cells activate hypoxia-inducible factors to release VEGF, which in turn binds to its receptors to activate the tyrosine kinase signaling pathway, thereby driving angiogenesis. In GBM, VEGF has crucial roles in maintenance of tumor stem cell activity, optimization of the tumor microenvironment, and promotion of neovascularization. As angiogenesis is a key mechanism for tumor blood supply and growth [22], its inhibition by blockade of the VEGF signaling pathway represents an important therapeutic strategy.

Bevacizumab is among the most extensively studied drugs with respect to treatment of rGBM. In early clinical trials, bevacizumab combined with irinotecan achieved an objective response rate of 42% and increased the 6-month PFS rate to 46%; the corresponding response rates for radiotherapy alone and salvage chemotherapy were only 9-21% and 4-9%, respectively [23, 24]. In 2009, the FDA granted accelerated approval for bevacizumab in rGBM based on two phase II studies. By contrast, the European Medicines Agency did not approve it, citing a lack of control groups, limitations regarding response assessment criteria, and difficulties in interpreting OS and PFS data in the relevant studies [25]. Large-scale clinical studies and meta-analyses in recent years have indicated that although bevacizumab significantly prolongs PFS in rGBM patients, it does not significantly improve OS. However, the drug has a clear benefit in terms of reducing intracranial pressure, alleviating peritumoral edema, and improving patients' neurological function and quality of life. Moreover, bevacizumab extended the median OS of rGBM patients to 23.7 months in a retrospective analysis of 202 patients [26]. Therefore, bevacizumab is currently regarded as an important palliative treatment option for rGBM.

Apatinib is a highly selective oral VEGFR-2 tyrosine kinase inhibitor that exerts antitumor effects by blocking angiogenesis-related signaling pathways. It has been approved in China for treatment of advanced gastric cancer [27] and has demonstrated survival benefits in various solid tumors, including liver cancer, ovarian cancer, and nonsmall-cell lung cancer [28-30] Furthermore, studies have shown that apatinib can reverse multidrug resistance and enhance the efficacy of conventional chemotherapeutic agents including temozolomide [31, 32] .A clinical trial evaluating the salvage therapeutic effect of apatinib combined with temozolomide in patients with rGBM reported an objective response rate of 26.3%, a DCR of 84.2%, and median PFS and mOS of 4.9 months and

8.2 months, respectively, suggesting that this combination regimen provides clinical benefit [33]. Another retrospective analysis of 108 patients with recurrent malignant glioma showed that apatinib combined with temozolomide significantly improved objective response rate (p=0.033) and DCR (p=0.036) compared with temozolomide alone, as well as prolonging median PFS (11.7 months vs. 8.5 months) and mOS (7.4 months vs. 4.9 months) [34]. In addition, a meta-analysis of ten studies involving 357 patients with recurrent high-grade glioma also found that apatinib combined with temozolomide could improve treatment efficacy and prognosis [35]. Thus, current evidence suggests that apatinib demonstrates disease control capability and survival benefits in the treatment of recurrent high-grade glioma.

In the present study, anti-angiogenic agents combined with chemotherapy significantly improved patient survival compared with chemotherapy alone, with a median OS of 33 months in the combination group versus 19 months in the chemotherapy-only group. The DCR was also higher in the combination group, and the two groups had similar incidence of adverse reactions. As some patients received both apatinib and bevacizumab during salvage therapy, we further performed a stratified analysis of the combination treatment group. Chemotherapy combined with apatinib showed a more favorable trend in terms of survival benefit compared to chemotherapy combined with bevacizumab. However, owing to the high heterogeneity of the salvage treatment regimens, it was difficult to conduct a sufficient stratified comparison between the two antiangiogenic agents (apatinib vs. bevacizumab). Future large-scale prospective studies are therefore needed to clarify the efficacy of apatinib in rGBM.

This retrospective study has limitations. This retrospective study has several limitations. First, data were missing for CD34 (18.7%), p53 (27.5%), and Ki-67 (11.9%) due to non-routine clinical ordering or limited specimens. Although available case analysis was used, the high missing proportion—especially for p53-may introduce bias. Second, PFS data were missing for some patients due to variable treatment adherence. Third, molecular subgroup sample sizes were too small for robust analysis (IDH mutant: 3; MGMT methylated: 15; TERT mutant: 28; 1p/19q codeletion: 0; BRAF V600E mutant: 2), consistent with common real-world challenges [36]. Larger studies are needed to validate our findings. Nonetheless, we performed sensitivity analyses (intention-to-treat and per-protocol) and excluded crossover patients to minimize bias.

Most other anti-angiogenic agents (e.g., VEGFR-TKIs, PKC inhibitors) have shown insufficient

efficacy in GBM trials [37, 38] and resistance is common. Recent evidence indicates that VEGF blockade alone may be insufficient for effective vascular pruning, requiring combination with other targets [39]. Emerging reviews have detailed the multifaceted resistance mechanisms to anti-angiogenic therapy in GBM, including activation of redundant pro-angiogenic pathways, vasculogenic mimicry, and hypoxia-induced invasion [40, 41]. Furthermore, hypoxia induces GSC-to-endothelial transdifferentiation via the ROR1-WNT5A axis, promoting vascularization and anti-angiogenic resistance [42]. Contemporary reviews advocate for multi-targeted and combination strategies to overcome these adaptive resistance mechanisms [41, 43]. Therefore, elucidating resistance mechanisms and developing novel agents targeting alternative pathways remain key priorities for improving long-term efficacy [44].

In conclusion, our univariate analysis showed that age, adjuvant chemotherapy, and use of apatinib were associated with prognosis of GBM patients, with CD34 and Ki-67 expression levels also demonstrating reference value. Multivariate analysis further confirmed that age and chemotherapy were independent prognostic factors for GBM patients. In patients with rGBM, we found that apatinib could prolong OS and improve short-term efficacy with good tolerability. Currently, there is no standard treatment regimen for rGBM, and patient prognosis remains poor. Therefore, active exploration of effective treatment strategies to prolong survival and improve quality of life is of great importance. Finally, well-designed prospective studies with larger cohorts and standardized molecular profiling are warranted to confirm our findings, as well as to further elucidate resistance mechanisms and develop rational combination therapies with other targeted agents.

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Supplementary data are available in the online version of the paper.

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Figure Legends

Figure 1. Kaplan-Meier survival analysis of overall survival (OS). Kaplan-Meier curves illustrate the associations between clinicopathological factors and OS. Age (B), adjuvant chemotherapy (C), radiotherapy (D), and use of apatinib (E) were significantly associated with OS. In contrast, gender (A), use of bevacizumab (F), CD34 expression (G), Ki-67 expression (H), and p53 expression (I) showed no statistically significant associations with OS.

Figure 2. Kaplan-Meier curves of overall survival (OS) according to anti-angiogenic treatment strategies. Kaplan-Meier survival curves comparing OS between chemotherapy alone and combination anti-angiogenic therapy (A), chemotherapy plus apatinib (B), and chemotherapy plus bevacizumab (C).

531 **Table 1.** Clinical information of 160 patients with glioblastoma.

clinical features	Number (%)
Age, yr	
< 50	70 (43.7%)
≥ 50	90 (56.3%)
Gender, n (%)	
Male	97 (60.6%)
Female	63 (39.4%)
Adjuvant chemotherapy	
Yes	126 (78.7%)
No	34 (21.3%)
CD34	
Positive	76 (47.5%)
Negative	54 (33.8%)
NA	30 (18.7%)
P53	
Positive	81 (50.6%)
Negative	35 (21.9%)
NA	44 (27.5%)
Ki67	
< 20%	18 (11.2%)
≥ 20%	123 (76.9%)
NA	19 (11.9%)
apatinib use	
Yes	30 (18.8%)
No	130 (81.2%)
BEV use	
Yes	36 (22.5%)
No	124 (77.5%)

532 Abbreviations: NA-not available

533

534 **Table 2.** Results of univariate and multivariate analysis of glioblastoma patients and overall
535 survival.

Factor	Median Survival time	Univariate analysis		Multivariate analysis	
		HR (95%CI)	p-value	HR (95%CI)	p-value
Age , yr			0.027	1.630 (1.049-2.532)	0.030
< 50	23.00 m	0.629 (0.414-0.955)			
≥ 50	20.00 m	1.591 (1.047-2.416)			
Gender n (%)			0.288		
Male	20.00 m	1.258 (0.824-1.922)			
Female	21.00 m	0.795 (0.520-1.214)			
Adjuvant chemotherapy			0.014	1.808 (1.046-3.113)	0.034
Yes	21.00 m	0.535 (0.282-1.016)			
No	11.00 m	1.868 (0.985-3.546)			
Radiotherapy			0.003	2.362 (1.061-5.257)	0.035
Yes	21.00 m	0.332 (0.094-1.181)			
No	8.00 m	3.010 (0.847-10.70)			
CD34			0.206		
Positive	22.00 m	0.746 (0.463-1.201)			
Negative	21.00 m	1.341 (0.833-2.159)			
P53			0.663		
Positive	21.00 m	0.880 (0.477-1.622)			
Negative	20.00 m	1.137 (0.617-2.157)			
Ki67			0.126		
< 20%	40.00 m	0.560 (0.299-1.045)			
≥ 20%	20.00 m	1.787 (0.957-3.338)			
apatinib use			0.014	1.688 (0.943-3.022)	0.078
Yes	33.00 m	0.518 (0.326-0.822)			
No	20.00 m	1.932 (1.216-3.071)			

BEV use			0.187
Yes	22.00 m	0.713 (0.444-1.144)	
No	20.00 m	1.403 (0.874-2.253)	

536 Abbreviations: m-months

537

538 **Table 3.** Clinical efficacy results.

Group	Number	CR	PR	SD	PD	DCR
Chemotherapy+anti-angiogenic therapy group	49	0	1	35	13	73.47%
Chemotherapy+apatinib group	21	0	0	14	7	66.67%
Chemotherapy+BEV group	23	0	0	18	5	78.26%
Chemotherapy+BEVsequential Apatinib group	5	0	1	3	1	80.00%
Chemotherapy alone group	16	0	1	6	9	43.75%
$\mathbf{X^2}$						4.758
p-value						**0.029**

539

Fig. 1 [Download full resolution image]

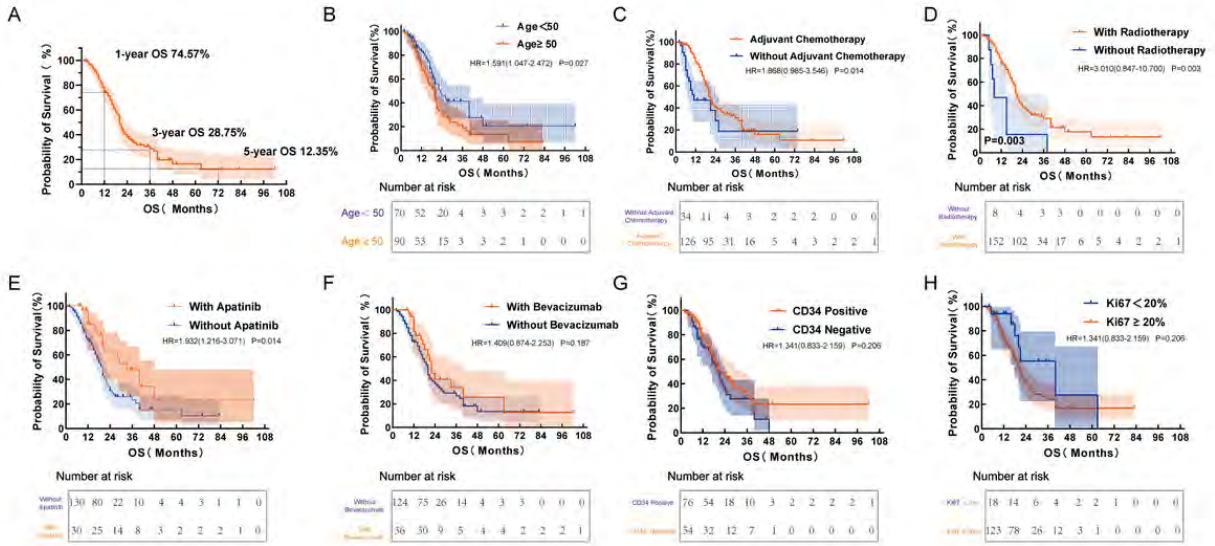

Fig. 2 Download full resolution image