

# Bevacizumab-associated intracerebral hemorrhage in patients with malignant glioma

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Received December 9, 2024; Accepted March 11, 2025

DOI: 10.3892/mco.2025.2852

**Abstract.** Intracerebral hemorrhage (ICH) is a serious complication of the use of bevacizumab in patients with malignant glioma; however, the risk factors are unclear. Therefore, the present study retrospectively analyzed a cohort of patients treated with bevacizumab for malignant glioma to investigate the characteristics of those in the cohort who had ICH. Between January 2015 and December 2022, 64 patients with malignant glioma were treated with bevacizumab. Clinical and molecular biological information, treatment details, and information regarding the presence of ICH after bevacizumab administration were extracted from the hospital database. ICH was found to have occurred in seven patients (10.9%) after bevacizumab administration. The mean (standard deviation) age of these seven patients was 64 (11) years, and six of them (85.7%) underwent needle biopsy. Two patients (28.6%) had grade  $\geq 3$  hemorrhage. The median number of administrations of bevacizumab before the onset of ICH was seven (range: 1-32), and the duration from first administration to ICH was 4 months (range: 1-22). Furthermore, ICH was associated with a comparatively short overall survival time (log-rank,  $P=0.008$ ). Tumor invasion into the corpus callosum on contrast-enhanced magnetic resonance imaging before bevacizumab administration was associated with ICH according to univariate analysis ( $P=0.01$ ) and multivariate analysis ( $P=0.02$ ). In conclusion, bevacizumab-associated ICH was associated with poor prognosis in the present cohort of patients with malignant glioma. Furthermore, corpus callosum infiltration shown on magnetic resonance imaging before bevacizumab administration was suggested to be a risk factor for ICH; however, further studies on larger cohorts are required for confirmation.

## Introduction

Malignant glioma including glioblastoma has poor prognosis, despite recent advances in molecular diagnostics and in modern individual treatment (1). The current standard of care comprises surgical resection followed by adjuvant radiotherapy and chemotherapy (2). Glioblastoma is characterized by overexpression of vascular endothelial growth factor (VEGF), a crucial factor of tumor-associated angiogenesis, and these tumors are composed of highly disorganized vessels (3). A promising alternative therapeutic approach for glioblastoma is the inhibition of angiogenesis through VEGF, which may slow down tumor growth and enhance the effects of radiotherapy and chemotherapy (4). Bevacizumab is a recombinant humanized monoclonal antibody targeting VEGF, which suppresses tumor angiogenesis and growth (5). In the AVAglio study, bevacizumab combined with standard treatment for patients with newly-diagnosed glioblastoma was associated with a 4.4-month increase in median progression-free survival (6). In the RTOG 0825 trial, first-line use of bevacizumab did not improve overall survival in patients with newly diagnosed glioblastoma, however, progression-free survival was longer in the bevacizumab group than in the placebo group (10.7 months vs. 7.3 months) (7).

Bevacizumab has some specific adverse effects, however, including proteinuria, hypertension, severe bleeding, protracted wound healing, and gastrointestinal perforation (5). In the RTOG 0825 trial, some adverse events were more prevalent in the bevacizumab group than in the placebo group, including hypertension (4.2% vs. 0.9%), thromboembolic disease (7.7% vs. 4.7%), and wound dehiscence (1.5% vs. 0.9%) (7). Administration of bevacizumab in patients with glioblastoma has been associated with an increased risk of intracerebral hemorrhage (ICH) (8). However, risk factors for the occurrence of ICH as a result of bevacizumab treatment are unclear. In this study, we therefore analyzed patients treated with bevacizumab for malignant glioma and investigated the characteristics of the patients in the cohort that developed ICH.

## Materials and methods

**Patients.** We retrospectively identified 118 patients with malignant glioma (newly diagnosed or recurrent) that were treated at Wakayama Medical University Hospital between January 2015 and December 2022. Among them, 64 had been

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**Key words:** bevacizumab, malignant glioma, glioblastoma, intracerebral hemorrhage, corpus callosum infiltration

treated with bevacizumab, of which 61 were men (51.7%) and 57 were women (48.3%), with a median age of 66 years (range: 18-91 years). We extracted their clinical and molecular biological information, treatment details, and the presence of ICH after bevacizumab administration from the hospital database. We retrospectively analyzed potential risk factors involved in ICH. This study was carried out in accordance with the principles of the Declaration of Helsinki. Approval was obtained from the Wakayama Medical University Institutional Review Board (approval no. 98). As this is a retrospective chart review involving de-identified patient data, patient consent was not required for this study.

**Statistical analyses.** Statistical analysis was performed using the SAS package and JMP Pro version 16 (SAS Institute, Cary, NC, USA). The overall survival was measured from date of diagnosis until death and the overall survival curves were obtained by the Kaplan-Meier method and compared with log-rank test. Categorized data were compared between subgroups using the Fisher's exact test. Continuous variables were compared using unpaired Student's t-tests. Multivariate analyses were performed using logistic regression analysis.  $P < 0.05$  was considered to indicate a statistically significant difference. All incidences of ICH were graded according to the common terminology criteria for adverse events version 5.0 (9).

## Results

**Patient characteristics.** Within the study cohort were 64 patients that had been treated with bevacizumab; their demographic and clinical characteristics are summarized in Table I. There were 38 men (59.4%) and 26 women (40.6%) with a mean (standard deviation) age of 69 (14.6) years. Based on integrated diagnosis by 2021 WHO Classification, 54 patients (84.4%) had glioblastoma, IDH-wildtype, four patients (6.3%) had astrocytoma, IDH-mutant, and two patients (3.1%) had oligodendroglioma, IDH-mutant, and 1p/19q-codeleted. Of the 64 patients, seven (10.9%) developed ICH while on bevacizumab.

**Univariate and multivariate analyses for the determination the factor of ICH.** The clinical and molecular characteristics of patients who developed ICH after bevacizumab administration are summarized in Table II. ICH occurred in four men and three women, with a mean age (standard deviation) of 64.4 (11.6) years. Regarding the extent of resection, six patients had a needle biopsy and one patient had a subtotal resection. Based on the 2021 WHO Classification, six patients had glioblastoma, IDH-wildtype, and the other patient had oligodendroglioma, IDH-mutant, and 1p/19q-codeleted. Five patients received radiation treatment and seven patients received temozolomide. Two patients (28.6%) had grade  $\geq 3$  hemorrhage (Table II). At the time of ICH, computed tomography showed peritumoral hemorrhage rather than intra-tumor hemorrhage (Fig. 1). The median number of administrations of bevacizumab before the onset of ICH was seven times (range: 1-32), and the median duration from first administration to ICH was 4 months (range: 1-22). One patient (14.2%) was taking anti-thrombotic medication. ICH itself was associated with shorter overall

Table I. Patient demographic and clinical characteristics (n=64).

Characteristic	Value
Mean age at diagnosis, years (SD)	69 (14.6)
Sex, n (%)	
Female	26 (40.6)
Male	38 (59.4)
Main anatomical location, n (%)	
Frontal lobe	20 (31.3)
Temporal lobe	11 (17.2)
Parietal lobe	12 (18.8)
Occipital lobe	3 (4.7)
Basal ganglia	10 (15.6)
Insula	1 (1.6)
Corpus callosum	4 (6.3)
Cerebellum	3 (4.7)
Laterality, n (%)	
Left	23 (35.9)
Right	38 (59.4)
Midline	3 (4.7)
Corpus callosum infiltration, n (%)	17 (26.6)
Diabetes mellitus, n (%)	8 (12.5)
Hypertension, n (%)	30 (46.9)
Use of antithrombotic drugs, n (%)	8 (12.5)
Proteinuria, n (%)	33 (51.6)
Extent of resection, n (%)	
Gross total resection	6 (9.4)
Partial resection	21 (32.8)
Biopsy	37 (57.8)
CNS WHO grade, n (%)	
3	6 (9.4)
4	58 (90.6)
Molecular diagnosis, n (%)	
Astrocytoma, IDH-mutant	4 (6.3)
Oligodendroglioma, IDH-mutant, and 1p/19q-codeleted	2 (3.1)
Glioblastoma, IDH-wildtype	54 (84.4)
Diffuse midline glioma, H3K27-altered	2 (3.1)
Diffuse glioma. NOS	2 (3.1)
Molecular alterations, n (%)	
IDH mutation	6 (9.4)
TERT promoter mutation	39 (60.9)
H3K27M	2 (3.1)
MGMT promoter methylation	20 (31.3)
Radiation therapy, n (%)	42 (65.6)
Chemotherapy, n (%)	
Temozolomide	60 (93.8)
Bevacizumab	64 (100.0)
Hemorrhage, n (%)	7 (10.9)

SD, standard deviation; CNS, central nervous system; IDH, isocitrate dehydrogenase; H3K27, histone 3 lysine 27; NOS, not otherwise specified; TERT, telomerase reverse transcriptase; H3K27M, substitution of lysine 27 to methionine in histone H3; MGMT, O-6-methylguanine-DNA methyltransferase.

Table II. Summary of patients in our cohort with intracerebral hemorrhage after bevacizumab administration (n=7).

No.	Sex	Age, years	Administration times of BEV	Duration from first administration to hemorrhage, months	Hemorrhagic grade on CTCAE version 5.0	Outcome after ICH
1	Female	59	32	22	2	BSC
2	Male	79	8	4	4	Death
3	Male	66	1	5	2	BEV rechallenge
4	Female	58	8	3	4	Death
5	Male	68	2	1	1	BSC
6	Male	45	7	7	1	Reoperation
7	Female	76	4	2	2	BSC

CTCAE, Common Terminology Criteria for Adverse Events; ICH, intracerebral hemorrhage; BSC, best supportive care; BEV, bevacizumab.

survival (Fig. 2, log-rank,  $P=0.008$ ). Tumor invasion into the corpus callosum on contrast-enhanced magnetic resonance imaging before administration of bevacizumab was associated with ICH in both univariate analysis (Table III, odds ratio, 9.38; 95% confidence interval, 1.61-54.4;  $P=0.01$ ) and multivariate analysis (Table IV, odds ratio, 9.76; 95% confidence interval, 1.44-65.8;  $P=0.02$ ).

## Discussion

Bevacizumab has a specific toxicity profile related to its anti-angiogenic effect, and some bevacizumab-associated adverse events can be life-threatening (8). We investigated the overall incidence and risk of ICH among patients with high-grade glioma that underwent bevacizumab therapy. We found ICH to be associated with shorter overall survival. Also, tumor invasion into the corpus callosum before administration of bevacizumab was associated with an increased risk of developing ICH.

Among brain tumors, gliomas and metastasis tend to bleed most frequently (10). ICH occurs in 3.7-7.2% of gliomas, mainly in glioblastoma and oligodendroglioma (10). The most important etiopathogenesis of ICH in glioblastoma is considered to be the abnormalities of tumor vascularization (10). Glioblastomas are highly angiogenic and infiltrative tumors. Tumor cells invade along blood vessels to increase tumor growth, and glioblastomas displace the endfeet of astrocytes and affect pericyte stability, leading to perivascular niches and cell evasion (11). Microvascular proliferation with hyperplasia of endothelial cells following obliteration and the presence of numerous thin-walled, poorly formed, or dilated vessels may induce hemorrhages (10,11).

In the AVAglio study, the incidence of ICH was 2.5% in the placebo group and 4.3% in the bevacizumab group, suggesting that bevacizumab may contribute to development of ICH (6). A post-marketing surveillance study of bevacizumab for patients with newly diagnosed or recurrent malignant glioma in Japan reported an ICH incidence of 5.4% (12). In the current study, the hemorrhage rates were higher than in these reports. The AVAglio study reported that just 13% of patients in the bevacizumab-treated group underwent a biopsy (6), as compared

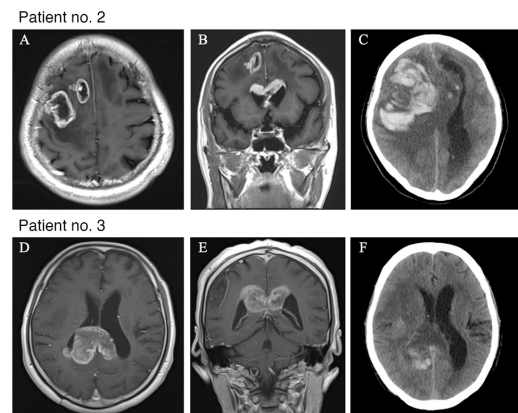


Figure 1. Representative cases of intracerebral hemorrhage after bevacizumab administration. Contrast-enhanced T1-weighted images before bevacizumab administration. Axial images from (A) patient no. 2 and (D) patient no. 3, and coronal images from (B) patient no. 2 and (E) patient no. 3 show the tumor infiltrates the corpus callosum. Computed tomography images from (C) patient no. 2 and (F) patient no. 3 show intracerebral hemorrhages.

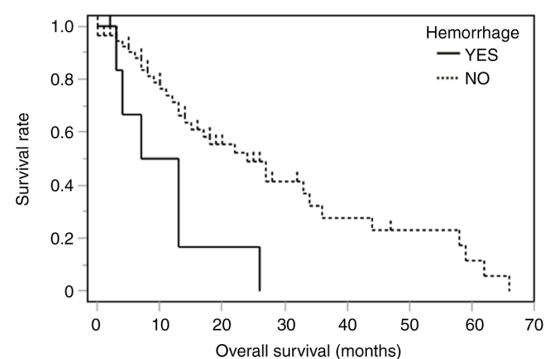


Figure 2. Kaplan-Meier survival curve estimates of overall survival in patients treated with bevacizumab. The group that developed hemorrhage after bevacizumab administration had significantly shorter overall survival time (log-rank,  $P=0.008$ ).

with 58% in this study. We suggest the high hemorrhagic rate may be related to the patient population in this study, which includes a large portion of patients who underwent biopsy

Table III. Univariate analysis of risk factors for intracerebral hemorrhage (n=64).

Characteristic	Hemorrhage		P-value
	Yes N=7	No N=57	
Mean age, years (SD)	64.4 (11.6)	68.1 (15.0)	0.36
Female, n (%)	3 (42.9)	23 (40.3)	0.89
Laterality, n (%)			0.36
Left	3 (42.9)	20 (35.1)	
Right	3 (42.9)	35 (61.4)	
Midline	1 (14.3)	2 (3.5)	
Corpus callosum infiltration, n (%)	5 (71.4)	12 (21.1)	0.01 <sup>a</sup>
Diabetes mellitus, n (%)	1 (14.3)	7 (12.3)	0.88
Hypertension, n (%)	3 (42.9)	26 (45.6)	0.89
Use of antithrombotic drugs, n (%)	1 (14.3)	7 (12.3)	0.87
Proteinuria, n (%)	4 (57.1)	29 (50.9)	0.75
Extent of resection, n (%)			0.27
Gross total resection	0 (0)	6 (10.5)	
Partial resection	1 (14.2)	20 (35.1)	
Biopsy	6 (85.7)	31 (54.4)	
CNS WHO grading, n (%)			0.51
3	1 (14.3)	5 (8.8)	
4	6 (85.7)	52 (91.2)	
Molecular diagnosis, n (%)			0.49
Astrocytoma, IDH-mutant	0 (0)	4 (7.0)	
Oligodendroglioma, IDH-mutant, and 1p/19q-co-deleted	1 (14.3)	1 (1.8)	
Glioblastoma, IDH-wildtype	6 (85.7)	48 (84.2)	
Diffuse midline glioma, H3K27-altered	0 (0)	2 (3.5)	
Diffuse glioma. NOS	0 (0)	2 (3.5)	
IDH1/2 mutation, n (%)	1 (14.3)	5 (8.8)	0.51
TERT promoter mutation, n (%)	5 (71.4)	34 (59.7)	0.69
H3K27M, n (%)	0 (0)	2 (3.5)	0.61
MGMT promoter methylation, n (%)	2 (28.6)	18 (31.6)	0.87
Radiation therapy, n (%)	5 (71.4)	37 (64.9)	0.73
Temozolomide, n (%)	7 (100)	53 (93.0)	0.47

<sup>a</sup>P<0.05. SD, standard deviation; CNS, central nervous system; IDH, isocitrate dehydrogenase; H3K27, histone 3 lysine 27; TERT, telomerase reverse transcriptase; H3K27M, substitution of lysine 27 to methionine in histone H3; MGMT, O-6-methylguanine-DNA methyltransferase.

Table IV. Multivariate analysis of risk factors for intracerebral hemorrhage (n=64).

Characteristics	Odds Ratio	95% CI	P-value
Laterality			
Left	1.67	(0.25-11.1)	0.59
Corpus callosum infiltration	9.76	(1.44-65.8)	0.02 <sup>a</sup>
Extent of resection			
Biopsy	5.67	(0.53-61.1)	0.15

<sup>a</sup>P<0.05. CI, confidence interval.

rather than tumor removal due to old age, poor preoperative performance status, and dissemination.

The pathophysiology underlying ICH in high-grade glioma with bevacizumab still requires elucidation. VEGF is thought

to be important for endothelial cells to maintain the architecture and integrity of the microvasculature (5). In metastatic brain tumors, overexpression of VEGF and metalloproteinase, which degrade the extracellular matrix, may play a role in causing hemorrhages through rapid growth and breakdown of vessels around the tumor (13). Bevacizumab may cause hemorrhage by reducing the regenerative capacity of endothelial cells (14). However, dysfunction of endothelial cells alone cannot explain the ICH in patients that have received bevacizumab (13,14).

In our cohort, tumor invasion into the corpus callosum before administration of bevacizumab was associated with an increased risk of ICH. Gliomas invading the corpus callosum reportedly account for approximately 14% of gliomas (15,16). Tumor invasion into the corpus callosum has been said to be a more aggressive subtype of an already aggressive and incurable disease (16). In a recent retrospective cohort study, it was significantly associated with glioma WHO grade and PDGFRA mutation (17). Endocan, an endothelial-secreted proteoglycan reportedly activates PDGFRA and promotes a hypervascular phenotype of glioblastoma (18). The aggressive biological behavior and hypervascularization of the tumor might affect ICH after bevacizumab administration.

In relation to tumor-related ICH, a number of reports have discussed feeding arteries (11,19), but there has been little mention of the draining veins. Brain arteriovenous malformations with deep venous drainage have shown higher rates of hemorrhage, suggesting arteriovenous malformation pressurization due to draining veins (20). Inhibition of VEGF signaling suppresses the endothelial cell activation, predisposing to thromboembolic events (14). Even in malignant gliomas, the lesions invading the corpus callosum are associated with deep venous drainage, and we suggest that thrombosis of deep cerebral veins due to the use of bevacizumab may contribute to ICH.

This study has several limitations. Unlike a randomized study, there is a possibility of selection bias in the decision-making on treatment strategy. Second, the limited number of patients could be responsible for the absence of statistical power to detect differences between groups. The sample size of this study is insufficient to establish an association between invasion of corpus callosum and ICH after bevacizumab administration. Perhaps due to the small sample size, no risk factors other than corpus callosum invasion could be observed in this study. Further investigation in a larger population is required to examine other factors, such as antithrombotic medications, angiographical features, and microbleeds in the magnetic resonance imaging, which would contribute to a better understanding of bevacizumab-associated ICH in patients with malignant glioma.

In conclusion, in our cohort of patients with malignant glioma treated with bevacizumab, ICH was associated with shorter overall survival. It was suggested that invasion of the corpus callosum shown on magnetic resonance imaging might be a predictor of development of ICH in some patients that receive bevacizumab. Further studies in larger cohorts are required to confirm these results. Meticulous management, such as frequent follow-up and treatment of hypertension, may be necessary in patients at high risk for ICH after administration of bevacizumab.

## Acknowledgements

The authors would like to thank Mr. Benjamin Phillis (Clinical Study Support Center at Wakayama Medical University) for proofreading and editing the manuscript.

## Funding

No funding was received.

## Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

## Authors' contributions

All authors (YH, TS, JF and NN) contributed to the study conception and design. YH and TS wrote the final manuscript and acquired all data. YH and TS confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Approval was obtained from the Wakayama Medical University Institutional Review Board (approval no. 98). This was a retrospective chart review involving de-identified patient data, so patient consent was not required for this study.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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