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# RETRACTED: The efficacy and adverse effects of anlotinib in the treatment of high-grade glioma: A retrospective analysis

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**Introduction:** Anlotinib, a novel multi-kinase inhibitor, was found to improve progression-free survival (PFS) in brain metastases.

**Methods:** This paper retrospectively analyzed 26 newly diagnosed or recurrent high-grade gliomas from 2017 to 2022, and the patients received oral anlotinib during concurrent postoperative chemoradiotherapy or after recurrence. Efficacy was evaluated according to the Response Assessment in Neuro-Oncology (RANO) criteria, and the main study endpoints were PFS at 6 months and overall survival (OS) at 1 year.

**Results:** After the follow-up, until May 2022, 13 patients survived and 13 patients died, with a median follow-up time of 25.6 months. The disease control rate (DCR) was 96.2% (25/26), and the overall response rate (ORR) rate was 73.1% (19/26). The median PFS after oral anlotinib was 8.9 months (0.8–15.1), and the PFS at 6 months was 72.5%. The median OS after oral anlotinib was 12 months (1.6–24.4), and the OS at 12 months was 42.6%. Anlotinib-related toxicities were observed in 11 patients, mostly grades 1–2. In the multivariate analysis, patients with Karnofsky Performance Scale (KPS) above 80 had a higher median PFS of 9.9 months ( $p = 0.02$ ), and their sex, age, IDH mutation, MGMT methylation, and whether anlotinib was combined with chemoradiotherapy or maintenance treatment had no effect on PFS.

**Conclusion:** We found that anlotinib combined with chemoradiotherapy in treating high-grade central nervous system (CNS) tumors can prolong PFS and OS and that it was safe.

## KEYWORDS

anlotinib, high-grade glioma, retrospective analysis, PFS, OS

## Introduction

High-grade glioma is a highly malignant tumor of the central nervous system. There is a clear classification of gliomas; usually, low-grade gliomas mainly occur in young adults, and high-grade malignant gliomas mainly occur in the elderly. Research data in the United States show that about half of glioblastoma cases occur in the elderly, and almost all gliomas in the elderly are high-grade, that is, highly malignant, while the possibility of low-grade glioma is almost non-existent. Even after complete resection, most of the patients will relapse. Moreover, the efficacy of reoperation or radiotherapy after recurrence is not very good; overall survival (OS) of 2 years is only 20% (1–5). Electric field therapy brings us hope, but the expensive price and the requirement to wear the device for more than 20 hours a day discourage patients. Moreover, cerebral edema inevitably occurs during the treatment of high-grade glioma. Anlotinib is a novel multi-kinase inhibitor that not only can contribute to anti-tumor cell proliferation but can also inhibit tumor angiogenesis to reduce edema response. Anlotinib has been approved for the treatment of non-small cell lung cancer as well as soft tissue sarcoma in China. It was found that anlotinib improved the PFS of brain metastases, with a disease control rate (DCR) of 85.7%, and did not increase the incidence of neurotoxicity and cerebral hemorrhage (6–10). Chen et al. found that SNX20 is upregulated in low-grade glioma (LGG), and its high expression is associated with adverse clinical outcomes and adverse clinical features, including WHO grade, IDH mutation, 1p/19q co-deletion, and primary treatment outcomes (11). Chen et al. also established a nomogram based on SNX20 to predict 1-, 3-, and 5-year survival in LGG patients and found that DNA hypomethylation leads to overexpression in LGG (11). In their study, the study identified SNX20 as a novel potential prognostic biomarker and described the functional role of SNX20 in the progression of LGG, providing a new potential diagnostic and therapeutic biomarker for LGG in the future (11). We tried to include anlotinib in the treatment process of high-grade glioma and retrospectively analyzed its efficacy and adverse effects.

## Materials and methods

### Therapeutic methods

A retrospective analysis was made of 26 patients who were newly diagnosed or had recurrent high-grade glioma treated in the Department of Radiotherapy of Jinling Hospital from 2017 to 2022.

Inclusion criteria: 1) Karnofsky Performance Scale (KPS)  $\geq 60$ ; 2) age  $\geq 18$  years old; 3) pathologically confirmed as World Health Organization Level IV glioblastoma (GBM); 4) recurrence after magnetic resonance imaging (MRI) review (including MR spectroscopy (MRS) and perfusion imaging) is assessed by surgeons, radiologists, and oncologists according to Response Assessment in Neuro-Oncology (RANO) criteria; 5) measurable lesions; 6) good bone marrow, liver, and kidney functions; 7) anlotinib combined with dose-intensive temozolomide (TMZ) in the treatment of relapse; 8) previous standard concurrent chemoradiotherapy (CCRT) and adjuvant chemotherapy (AC).

Exclusion criteria: 1) complications of other malignant tumors or serious diseases; 2) patients with hypertension whose blood pressure still cannot be reduced to the normal range after treatment with antihypertensive drugs, patients with grade I and above myocardial ischemia or myocardial infarction, and arrhythmias (including QT interval  $\geq 440$  ms), patients with grade II cardiac insufficiency, and patients with arteriovenous thrombosis, such as cerebrovascular accident (including transient ischemic attack), deep vein thrombosis, and pulmonary embolism within 6 months; 3) lack of follow-up data.

All the patients were younger than 75 years old and their KPS scores were above 60 points. Anlotinib was taken orally during postoperative concurrent chemoradiotherapy or after relapse. It was used as 12 mg once a day for 2 weeks and stopped for 1 week. Efficacy was evaluated according to the RANO criteria, and the cranial MR examination was conducted every 1–3 months. According to the MR results and clinical symptoms, the efficacy was divided into complete remission (CR), partial response (PR), stable disease (SD), and progressive disease (PD). The overall response rate (ORR) means CR and PR. The DCR means CR, PR, and SD. The primary study endpoints were PFS at 6 months and OS at 1 year (both were calculated at the start of anlotinib treatment).

### Statistical methods

Data analysis was performed with SPSS 21.0. Survival analysis was estimated by the Kaplan–Meier method with 95% credible intervals (CIs) and compared by the log-rank test. Statistical significance was defined as an alpha level of 0.05 ( $p < 0.05$ ).

## Results

There were 26 patients, 18 men and eight women, who had an age range of 27–74 years, with a median of 50 years. The KPS scores were from 60 to 90, with a median score of 80. A total of 11 patients had a functional area biopsy, and 14 patients had subtotal resection or local resection due to multiple lesions and lesion locations in the corpus callosum region or the functional area. A total of 24 cases had pathological patterns of grade III and IV gliomas. Two of them were initially diagnosed with diffuse astrocytoma of WHO grade II. One patient had multimorbidity areas in the cerebellar vermis, hemisphere, and lateral ventricle, with only one local excision biopsy. However, this patient's MR revealed that the tumor had a more advanced component. Magnetic resonance spectroscopy imaging showed the other patient had a higher-grade glioma at recurrence. However, this was not confirmed by pathological findings (Table 1).

At the time of anlotinib treatment, 22 patients had evaluable positive lesions (14 postoperative residual and eight recurrent).

Anlotinib was taken by 15 patients together with concurrent chemoradiotherapy. Of these, two patients did not take the medication again after the course of treatment due to economic reasons and severe fatigue. The remaining 11 patients took anlotinib because of disease progression after the completion of concurrent chemoradiotherapy. After the follow-up period until May 2022, 13 patients survived and 13 patients died, with a median follow-up time of 25.6 months.

TABLE 1 Patient information.

|   |            |
|---|------------|
| Sex   |            |
| Male  | 18 (69.2%) |
| Female  | 8 (30.8%)  |
| WHO   |            |
| II  | 2 (7.7%)   |
| III   | 4 (15.4%)  |
| IV  | 20 (76.9%) |
| Is there any residual post-surgery                  |            |
| Yes   | 16 (61.5%) |
| No  | 10 (38.5%) |
| Tumor location                                      |            |
| Single shot   | 20 (76.9%) |
| Pilosity  | 6 (23.1%)  |
| MGMT is methylated or not                           |            |
| Yes   | 9 (34.6%)  |
| No  | 11 (42.3%) |
| Unknown   | 6 (23.1%)  |
| 1p/19q  |            |
| Complete  | 13 (50%)   |
| Hiatus  | 5 (19.2%)  |
| Unknown   | 6 (23.1%)  |
| Complete 19q deletion of 1p                         | 2 (7.7%)   |
| IDH   |            |
| Wild  | 16 (61.5%) |
| Mutation  | 4 (15.4%)  |
| Unknown   | 6 (23.1%)  |
| TERT  |            |
| Sudden change                                       | 8 (30.8%)  |
| No mutation   | 3 (11.5%)  |
| Unknown   | 15 (57.7%) |
| Whether anlotinib is synchronized with radiotherapy |            |
| Yes   | 15 (57.7%) |
| No  | 11 (42.3%) |
| Maintenance therapy with anlotinib                  |            |
| Yes   | 23 (88.5%) |
| No  | 3 (11.5%)  |
| Best efficacy                                       |            |
| CR  | 3 (11.5%)  |
| PR  | 16 (61.5%) |
| SD  | 6 (23.1%)  |

(Continued)

TABLE 1 Continued

|      |          |
|------|----------|
| PD   | 1 (3.9%) |
| Dead |          |
| Yes  | 13 (50%) |
| No   | 13 (50%) |

Among the patients with SD, four patients were evaluated because there were no positive lesions, and the best efficacy can only be SD according to the RANO criteria. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; RANO, Response Assessment in Neuro-Oncology.

The DCR after oral anlotinib was 96.2% (25/26), and the ORR rate was 73.1% (19/26). The median OS (calculated from the surgical diagnosis) was 25.6 months (2.7–101.6 months). The median PFS was 8.9 months (0.8–15.1 months), and the PFS rate at 6 months was 72.5% (Figure 1A). The median OS was 12 months (1.6–24.4 months), and the OS rate at 12 months was 42.6% (Figure 1B).

Anlotinib-related toxicity was observed in 11 patients: two with grade 1 gingival bleeding, four with hypertension (1 in grade 3), two with grade 2 oral ulcers, two with grade 2 skin toxicity, and three with grade 1 fatigue. None of the remaining 15 patients showed related toxicity. One of the bleeding patients died of concurrent immune-related toxicity (Table 2).

A total of 11 patients had residual or recurrent disease after surgery. Anlotinib was used during concurrent chemoradiotherapy and as a maintenance treatment. As of the follow-up date, three patients had achieved CR, seven patients had PR, and one patient had SD. The DCR was 100%. The median PFS was 6.7 months (0.8–15.1 months), and the PFS at 6 months was 6.5% (Figure 1C). The median OS was 10.2 months (1.6–16.4 months), and the OS at 12 months was 21.9% (Figure 1D).

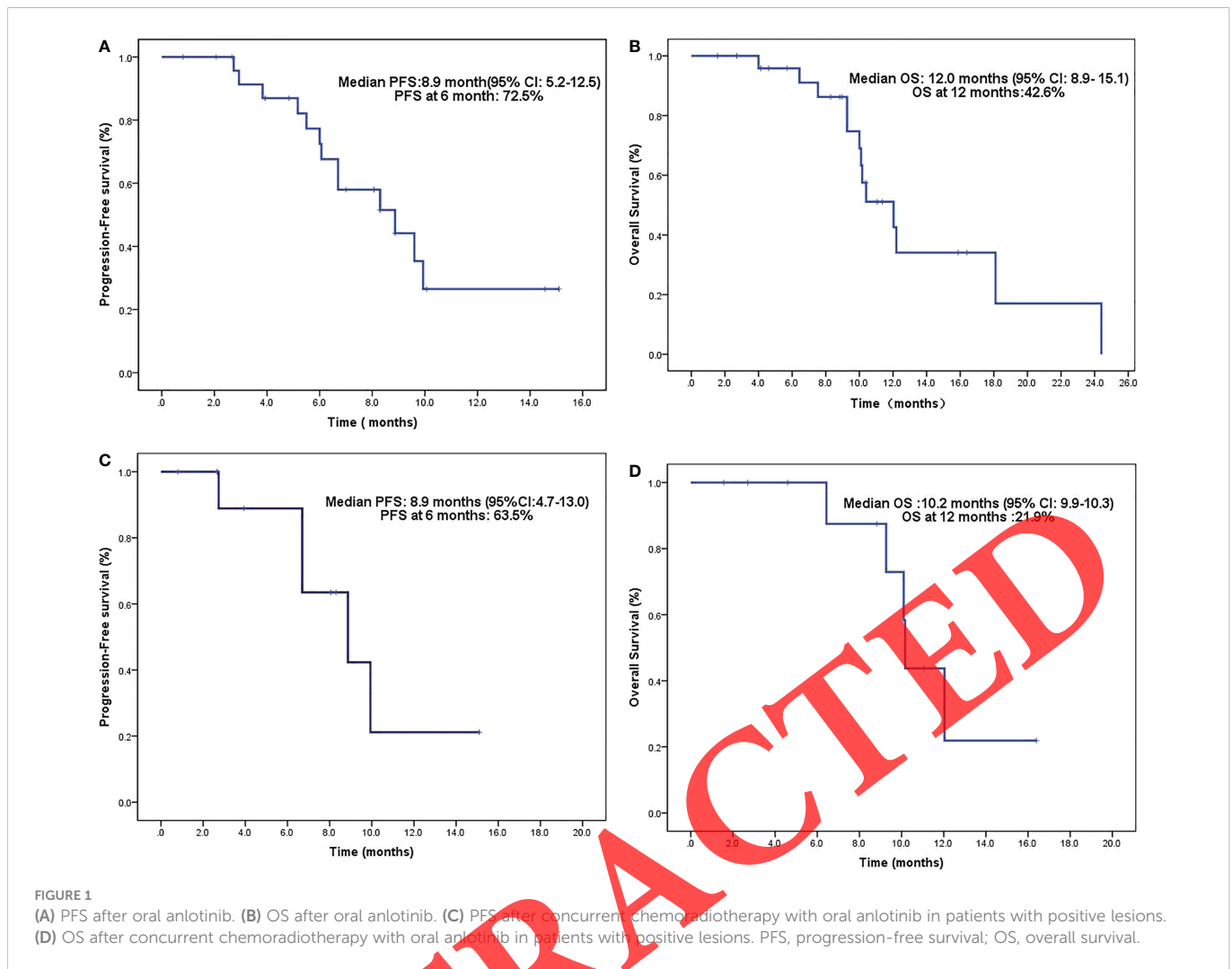
In the multivariate analysis of the PFS, patients with higher KPS scores (above 80) had a median PFS of 9.9 months ( $p = 0.02$ ). The gender, age, IDH mutation, MGMT methylation, whether anlotinib was combined with chemoradiotherapy, and whether there was maintenance treatment had no effect on the PFS.

## Safety

Adverse reactions related to anlotinib were hypertension (15.4%), oral ulcers (7.7%), hand-foot syndrome (7.7%), bleeding (7.7%), and fatigue (11.5%). Adverse reactions related to temozolomide were leukocyte decline (15.4%), anemia (3.8%), and liver function impairment (7.7%). Except for one patient presenting with grade 3 hypertension (who had a previous history of hypertension), all the treatment-related adverse effects were at grade 1–2 (Table 3).

## Discussion

The annual incidence of glioma in China is 5–8/100,000, and the 5-year mortality rate is next only to pancreatic cancer and lung cancer (12). The 5-year OS of glioblastoma is even less than 5% (13). TMZ combined with radiotherapy is the standard treatment after high-grade glioma surgery, but it still cannot prevent a recurrence. In particular,



most patients with glioblastoma relapse within 8 months of initial treatment (14). Some scholars are working in III phase trials to improve the dose and frequency of adjuvant temozolomide chemotherapy in newly diagnosed GBM patients (temozolomide was taken orally every 28 days for 21 days at a dose of 75–100 mg/m<sup>2</sup> per

day, compared with standard treatment (temozolomide was taken orally every 28 days for 5 days at a dose of 75 mg/m<sup>2</sup> per day) but have no survival benefit (15). However, in the relapsed and progressive GBM, the 7/14 (temozolomide was given orally at 75 mg/m<sup>2</sup>, once a week, with 1 week off, for 7 days) regimen was superior to the standard regimen in both PFS and OS, with no significant increase in adverse events (16).

How to prolong the PFS after high-grade glioma surgery is our focus. Studies have shown that the antiangiogenic agent bevacizumab can improve the efficacy of temozolomide by blocking the vascular growth factor VEGF-A (17). Unfortunately, bevacizumab combined with temozolomide had no survival benefit in two randomized clinical trials (AVAglio and RTOG0825). However, interestingly, the subanalysis of the AVAglio study showed that antiangiogenic therapy can improve clinical symptoms by reducing cerebral edema and, thus, improve the quality of survival (18, 19). Recently, bevacizumab combined with a dose-dense TMZ (ddTMZ) regimen was expected to produce efficacy in progressive or recurrent GBM (20, 21).

Tumor cells absorb vascular endothelial cells, circulating endothelial cells, and progenitors from new blood vessels to support their own growth and metastasis. VEGF, PDGF-BB, and FGF-2 are the three major proangiogenic factors that promote angiogenesis. Anlotinib is a potent multi-tyrosine kinase inhibitor (MTKI) that suppresses VEGF/PDGF-BB/FGF-2-induced cell migration and the

**TABLE 2** Adverse reactions.

| Anlotinib-related adverse effects |              |
|-----------------------------------|--------------|
| Hypertension                      | 4/26 (15.4%) |
| Dental ulcer                      | 2/26 (7.7%)  |
| Hand-foot syndrome                | 2/26 (7.7%)  |
| Hemorrhage                        | 2/26 (7.7%)  |
| Fatigue                           | 3/26 (11.5%) |
| TMZ adverse effect                |              |
| White blood cell decline          | 4/26 (15.4%) |
| Anemia                            | 1/26 (3.8%)  |
| Liver function injury             | 2/26 (7.7%)  |

One patient had grade 3 hypertension and the rest had grade 1–2 adverse effects. TMZ, temozolomide.

TABLE 3 Multivariate analysis.

| Characteristics                         | Numbers of patients | Median PFS<br>Months 95% CI | p-Value | HR (95% CI)  |
|---|---------------------|-----------------------------|---------|--------------|
| <b>Gender</b>                           |                     |                             |         |              |
| Male                                    | 18                  | 6.7 (5.9–7.5)               | 0.054   | 0.963–61.425 |
| Female                                  | 8                   | 9.9 (8.3–11.5)              |         |              |
| <b>Age</b>                              |                     |                             |         |              |
| ≥40                                     | 18                  | 8.3 (5.9–10.7)              | 0.315   | 0.091–2.166  |
| <40                                     | 8                   | 9.6 (4.7–14.4)              |         |              |
| <b>KPS</b>                              |                     |                             |         |              |
| ≥80                                     | 18                  | 9.9 (9.1–10.7)              | 0.022   | 0.046–0.790  |
| <80                                     | 8                   | 6.1 (5.9–6.2)               |         |              |
| <b>Anlotinib plus radiochemotherapy</b> |                     |                             |         |              |
| Yes                                     | 15                  | 9.6 (6.3–12.9)              | 0.502   | 0.139–2.624  |
| No                                      | 11                  | 6.0 (2.7–9.2)               |         |              |
| <b>Anlotinib maintenance treatment</b>  |                     |                             |         |              |
| Yes                                     | 23                  | 8.3 (5.33–11.3)             | 0.527   | 0.078–3.688  |
| No                                      | 3                   | –                           |         |              |
| <b>MGMT</b>                             |                     |                             |         |              |
| Methylation                             | 9                   |                             | 0.186   |              |
| Wild type                               | 11                  | 6.7 (3.2–10.1)              |         |              |
| Na                                      | 6                   | 6.7 (5.2–8.2)               |         |              |
| <b>IDH 1/2</b>                          |                     |                             |         |              |
| Mutation                                | 4                   | 8.9 (3.3–14.4)              | 0.440   |              |
| Wild type                               | 16                  | 8.3 (5.1–11.5)              |         |              |
| Na                                      | 6                   | 6.7 (5.2–8.2)               |         |              |

Na, unknown; PFS, progression-free survival; KPS, Karnofsky Performance Scale.

formation of capillary-like tubes in endothelial cells. Its antiangiogenic effect is better than that of sunitinib, sorafenib, and nintedanib, which are the three major clinical antiangiogenic drugs (22). TMZ enhances the anti-glioblastoma effects of anlotinib through the same signaling pathway, indicating that anlotinib can serve as a therapeutic option for glioblastoma (23).

From our retrospective analysis, there were three cases of a temozolomide Stupp regimen combined with anlotinib (12 mg once a day) concurrent radiotherapy after complete resection of GBM. The PFS was measured (4.8, 8.9, and 10.1 months), and no recurrence was found during the follow-up procedure. Similar to the results of this second phase of the study (24), ten newly diagnosed glioblastoma patients were treated with 60 Gy/30 F radiotherapy, combined with anlotinib (8 mg once a day) and a temozolomide Stupp regimen chemotherapy. Subsequently, chemotherapy continued for 6 cycles, and anlotinib was the maintenance treatment. One patient experienced grade 3 weight loss at week 56 and a grade 3 radiotherapy-induced cognitive decline at week 60. The main adverse effects were fatigue and hypertension. There were no other serious toxic side effects. During the follow-up process, no disease recurrence was found.

In a retrospective study by Yang on anlotinib with or without temozolomide for recurrent high-grade gliomas (25), the median PFS was 4.5 months, the PFS at 6 months was 40.2%, the median OS was 7.7 months, and the OS at 12 months was 27.9%. Of the patients, 41.9% achieved PR and 35.5% had SD, and none of them reached CR. In our study, 11 patients with high-grade glioma had residual lesions after surgery. They had a temozolomide Stupp regimen combined with anlotinib 12 mg once a day, and the residual lesion was treated with synchronous high-dose radiotherapy [gross tumor volume (GTV) 60–70 Gy], with median PFS and OS of 6.7 and 10.2 months, respectively. Therefore, it shows that chemoradiotherapy combined with anlotinib may achieve better efficacy in treating high-grade gliomas with residual lesions.

Eight patients who had a postoperative recurrence of high-grade gliomas had anlotinib maintenance therapy until progression (one with concurrent chemoradiotherapy, one with concurrent immunization, and six with concurrent temozolomide therapy). The median PFS was 6 months (3.8–8.1), the PFS at 6 months was 42.9%, the median OS was 10 months (9.17–11.1), and the OS at 12 months was 35%. In She's retrospective study on anlotinib dose-

density regimen combined with temozolomide for recurrent glioblastoma (26), the PFS at 6 months was 55% and the OS at 12 months was 47.7%. In other studies using antiangiogenic agents for the treatment of recurrent glioblastoma (27–31), the median PFS was 0.7–1.9 months, the PFS at 6 months was 4.4%–63%, and the median OS was 6.5–12.6 months. Pan's prospective phase 2 clinical study of sunitinib had the longest median OS of 12.6 months, but its 6-month PFS was only 16.7%. The best efficacy was only SD. Our median PFS was improved in comparison. Thus, it was observed that the dose-density regimen combined with anlotinib improved the PFS and the OS in recurrent glioblastoma. In the future, we consider using a dose-density regimen of temozolomide combined with anlotinib after synchronous therapy.

Shanghai Huashan Hospital used hypofractionated stereotactic radiotherapy [tumor absorbed dose (Dt25 Gy/5 F)] with anlotinib targeted therapy for glioblastoma at the first recurrence. Two of five patients achieved CR (32). We were also surprised to observe that three patients with postoperative residual lesions achieved CR. The first one received hyperfraction as Dt61.8 Gy/38 F, the second one received conventional fraction as Dt69 Gy/30 F, and the third one received hypofraction Dt60 Gy/20 F. There was no recurrence during the follow-up, and the longest PFS was 8.3 months. There was also no significant cerebral edema after high doses of radiation. It may indicate that for WHO IV grade tumors with residual lesions, concurrent chemoradiotherapy with anlotinib therapy is as effective as surgery when an effective biological dose is sufficient.

## Conclusions

In our study, the number of cases is small, and the timing of combined anlotinib treatment is not completely consistent. Therefore, the statistics have a certain deviation. However, we also found that anlotinib combined with chemoradiotherapy in treating high-grade central nervous system (CNS) tumors can prolong PFS and OS and that it was safe.

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## Data availability statement

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

## Author contributions

FS contributed to the conception and design of the study. JL acquired the data. FL performed the data analysis, wrote the first draft of the manuscript, and revised the manuscript critically. All authors contributed to the manuscript revision, and NS read and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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