Neurology Asia 2024; 29(3) : 629 – 636

The effectiveness and safety of bevacizumab in improving the efficacy of antiseizure medication in treating refractory epilepsy induced by stereotactic radiosurgery in meningiomas

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Abstract

Background: Refractory epilepsy (RE) increases rapidly after stereotactic radiosurgery (SRS), but the reports on RE treatment are rare, with various methods and efficacy. In recent years, bevacizumab (BEV) has been widely used as it is effective in eliminating intracranial oedema and reducing radioactive damage. The aim of this study was to evaluate the application of additional BEV to RE after SRS in the real world. *Methods:* Seizure freedom and seizure response were defined as 100% and ≥ 50% reduction in seizure frequency at baseline and 6-, 9- and 12-month follow-ups. The sustained seizure-free (SSF), sustained seizure response (SSR) was used to assess the effectiveness of BEV. The number of anti-seizure medications (ASM), seizure severity (NH3), and epilepsy quality of life rating scale (QOLIE-31) scores were compared before and 12 months after treatment. *Results:* Forty-one patients were included from January 2020 to December 2022. During the 1-year follow-up, 5 patients (12.2%) achieved SSF lasting 12 months, and 4.9% and 7.3% enjoyed SSF more than 6 months and 9 months, respectively. Twelve patients (29.3%) achieved SSR lasting for 12 months, and 19.5% and 24.4% of the study cohort achieved SSR more than 6 months and 9 months, respectively. Patients' ASM, NH3, and QOLIE-31 scores significantly improved 12 months after treatment, and the adverse reactions were controllable.
Conclusion: This study is the first to explore and report the additional use of BEV in the treatment of RE after SRS in meningiomas. BEV was effective and safe in the treatment of SRS-induced RE.

Keywords: Radiosurgery, refractory epilepsy, bevacizumab, meningiomas, seizure freedom

INTRODUCTION

Epilepsy could be induced by stereotactic radiosurgery (SRS) for intracranial lesions, such as cerebral arteriovenous-malformations[1-3], meningioma[4], nasopharyngeal carcinoma[5], and is increasingly common in clinical practice. According to the literature, the incidence of epilepsy after SRS for some intracranial diseases, such as cerebral arteriovenous malformations and meningioma, is 12.0-18.4%.[1-4] However, the management of epilepsy and even refractory epilepsy (RE) after SRS is still disappointing.

The failure of first-line and second-line treatment for epilepsy is defined as 'refractory epilepsy' (RE).[6] RE after SRS in meningioma was reported to account for 50% of all epilepsy after SRS.[4] In recent years, there have been better plans of staged SRS for intracranial malignancy[7-10], and the incidence of RE has been reduced. However, researchers still regard radioactive epilepsy as an uncontrolled type of seizure because its pathogenesis is different from traditional epilepsy, and the curative effect of the traditional method is poor.[4] There is an urgent need to explore and find an effective method for this type of epilepsy.

This study on patients with SRS-induced RE and their treatment aimed to assess the sustained clinical response to additional BEV in patients

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Date of Submission: 30 April 2024; Date of Acceptance: 1 June 2024.

https://doi.org/10.54029/2024rmw

with RE after SRS treated in the setting of real-world practice.

METHODS

Patients

The meningioma patients with RE after SRS were retrospectively studied from four gamma knife centre hospitals from January 2020 to December 2022. The diagnosis of RE after radiosurgery met the 2017 International Classification of Seizures by the International League Against Epilepsy (ILAE).[11] We included patients above 16 years. The inclusion criteria for RE are reasonable selection and correct use of at least two well-tolerated antiepileptic drugs, either monotherapy or combination therapy, with no seizures in patients The duration did not reach three times the longest interval between episodes before treatment; 2) received more than 2 anti-seizure medication (ASMs); 3) received additional BEV besides ASMs; and 4) followed-up more than 12-month. Exclusion criteria included: 1) history of alcoholism; 2) drug abuse; 3) history of psychological disorders. Data on patients' demographic characteristics, clinical history, type of seizures, previous/concomitant ASMs, and seizure frequency were collected. Adverse events (AEs) and drug withdrawal were collected from clinical records of patient's follow-up visits at 3-, 6-, and 12 months. The study was approved by the ethical committee of The Institutional Ethics Committee of Affiliated People's Hospital of Hangzhou Medical College (ZHRYRS 2023 No.066).

Observation indicators

The primary outcome was sustained seizure freedom (SSF), defined as a 100% reduction in baseline seizure frequency that continued without interruption from the first time it was achieved through the 12-month follow-up. The secondary outcome was sustained seizure response (SSR), defined as a ≥50% reduction in baseline seizure frequency that continued without interruption from the first time it was achieved through 12 months.[12] The time of achievement of SSF and SSR was established using data at visits at 3, 6, and 12 months. At the same time, the number of ASMs used for epilepsy control, the patients' severity of seizures, and the patient's quality of life were compared before and after BEV treatment. The NH3 was used to assess the severity of seizures in patients with epilepsy and evaluate the efficacy of clinical treatment, with a total score of 27 points; the higher the score, the more severe the seizure.[13] The patient's quality of life was accessed by epilepsy quality of life rating scale (QOLIE-31).[14] Patients' discontinuation of BEV, as well as adverse events (AEs), were also recorded and analysed.

Treatment prescription

In the study cohort, the dose of BEV was 7.5mg/kg iv gtt, repeated once every 21 days for 8 cycles. ASMs are treated according to the previous treatment plan, but patients with poor liver and kidney function are given a slow reduction of ASM under the premise of significant improvement in epilepsy control.

Statistical analysis

The mean ±SD value is presented for continuous variables. Median (inter-quartile range) value or number (percentage) of subjects are presented for categorical variables. Continuous variables are compared using the t-test, and categorical variables are compared using the Mann-Witney U test. Results were considered significant for p values <0.05 (two-sided). Data analysis was performed using SPSS version 19.0 (IBM Corp. Armonk, New York) or Graph Pad Prism 8.0 (La Jolla, California, United States).

RESULTS

Demographic characteristics of the patients

Of all 49 patients that suffered from RE after SRS, 8 patients were excluded because follow-up time was less than one year at the time of the current analysis. The 41 patients were included in further analysis, and their baseline characteristics are summarised in Table 1.

Clinical outcomes of sustained seizure freedom and sustained seizure response

During the 1-year study period, SSF was achieved by 5 (12.2%) patients, SSR was achieved by 12 (29.3%), The Kaplan Meier cumulative event plot is shown in Figure 1.

Regarding specific data, among all patients who reached SSF, 4.9%, 7.3%, and 12.2% maintained a continuous SSF for ≥ 6, ≥ 9, and 12 months. Among the patients with total SSR, 19.5%, 24.4%, and 29.3% maintained a sustained SSR ≥ 6, ≥ 9, and 12 months (Figure 2). The overall rate of SSF was 12.2 % when BEV was added

Table 1: Demographic characteristics of the study participants (N = 41)

Characteristic	Patient n=41 (*range* or %)
Age, years	51 (*29-75*)
Sex	
Male	20 (48.8)
Female	21 (51.2)
Age at epilepsy onset, years,	48 (*26-73*)
Duration of epilepsy, years,	2 (*0.5-6.5*)
Type of seizures,	
Focal onset	28 (68.3)
Focal to bilateral tonic–clonic	7 (17.1)
Focal onset and focal to bilateral tonic–clonic	6 (14.6)
Aetiology	
WHO grade 1 meningioma	41 (100)
Number of previous ASMs	5 (*4-8*)
Concomitant use of Mannitol and steroid hormones at baseline	41
Baseline monthly seizure frequency [a]	10 (*7-30*)

Note: Data are median (interquartile range) for continuous variables, and n (%) for categorical variables.
ASM=anti-seizure medication; WHO=World Health Organization.
[a] Based on the number of seizures during the 90 days before starting adjunctive bevacizumab.

to treatment, compared to the failure to achieve seizure freedom before treatment (p=.021); The overall incidence of SSR was 29.3%, compared to the failure to achieve seizure responders before treatment (p<0.001).

The kinds of ASM used for epilepsy control before and after BEV treatment

Taking 12 months as the observation end, the kinds of ASMs needed for epilepsy control also significantly decreased from a median of 5 to 4. Indicating that with the help of BEV, epilepsy is easier to control than before, as shown in Figure 4.

NH3 and RRLIE-31 score changes before and after BEV treatment

The RE patients received 12-month treatment. Seizure severity (NH3) and epilepsy quality of life rating scale (qqlie-31) scores were compared before and after BEV treatment. The NH3 score

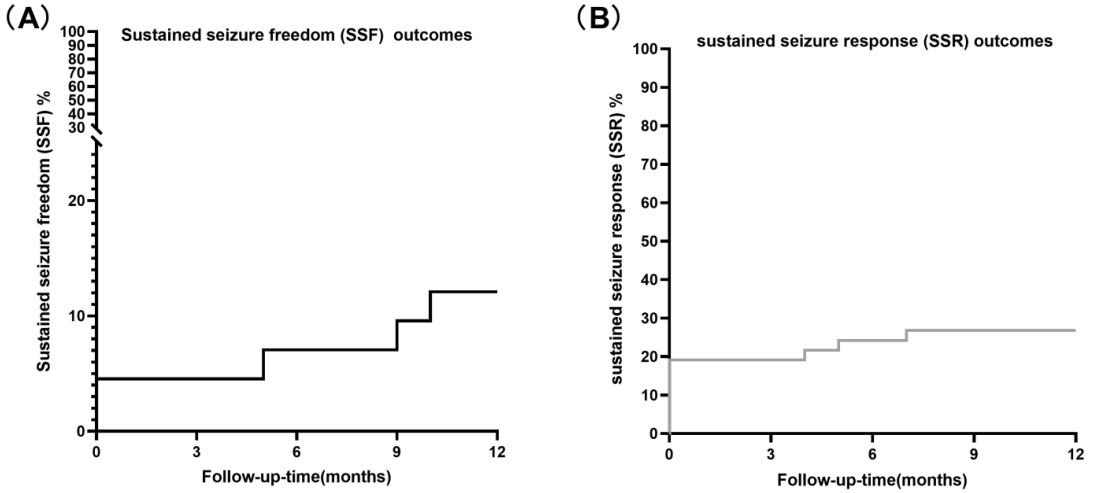

Figure 1. Kaplan–Meier cumulative event plots - (1A) Sustained seizure freedom (SSF) and (1B) Sustained seizure response (SSR).

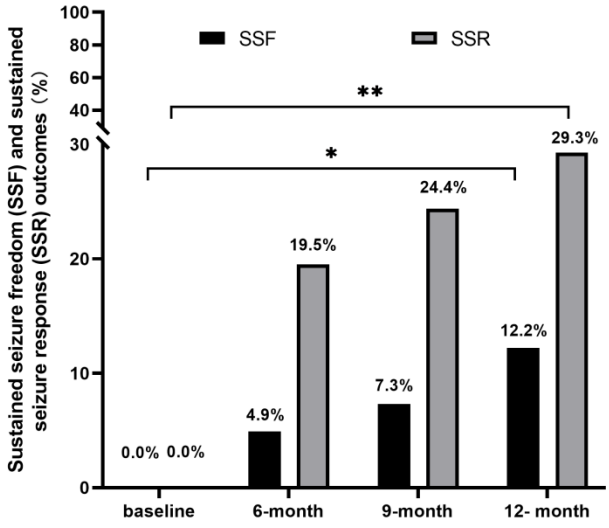

Figure 2. SSF and SSR results show the proportion of patients in the study cohort with no seizures and seizure response at baseline, 6 months, 9 months and 12 months, respectively.

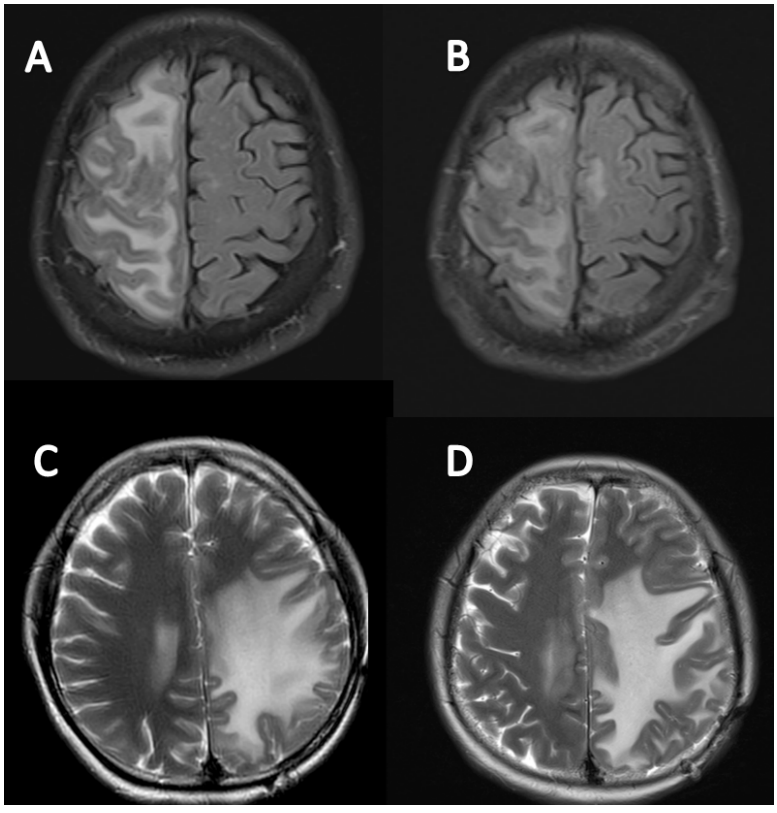

Figure 3. **Case 1:** RE appeared after SRS surgery for meningioma, and after receiving BEV adjuvant treatment, the therapeutic effect (SSF) was achieved. Figure 3A: Magnetic resonance FLAIR imaging showed large areas of oedema and radiation damage during the RE period after SRS. Figure 3B: Magnetic resonance FLAIR shows that after 6 cycles of BEV-assisted ASM treatment, oedema is reduced, and the range of radiation damage is reduced. **Case 2:** After SRS surgery for meningioma, RE appeared, and after receiving BEV adjuvant treatment, the treatment effect (SSR) was achieved. Figure 3C: Magnetic resonance T2 imaging showed extensive oedema during the RE period after SRS. Figure 3D: After 8 cycles of BEV supplementation therapy, oedema regressed and reached SSR

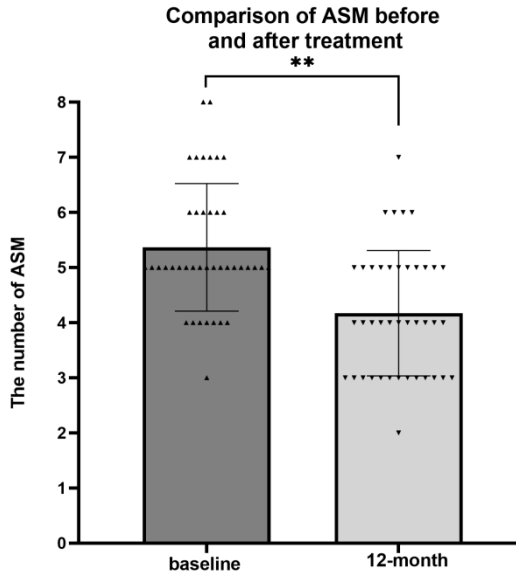

Figure 4. Achieved a significant reduction in the number of favourable ASM During the follow-up period (**p < 0.01, Wilcoxon test).

decreased from 19.13 ± 5.13 before treatment to 9.21 ± 4.27 after treatment, and the QOLIE-31 score increased from 39.92 ± 5.35 before treatment to 66.89 ± 11.37 after treatment. Both scores improved significantly, as shown in Figure 5 below.

Discontinuation of BEV and BEV treatment AEs

BEV was discontinued in 9(18.4%) patients; the reasons were insufficient efficacy (n = 4/9,44.4%), AEs (n = 1/9, 11.1%), and a combination of both (n = 3/9, 33.3%); in one case, BEV was discontinued due to the patient's request, and one patient died from a cause unrelated to treatment. This study investigated adverse event (AEs) risk signals using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) database. Grade I AEs patients who are fatal or life-threatening and require immediate withdrawal of medication and emergency treatment; For patients with grade II AEs who have obvious symptoms, pathological and physiological changes in various organs or abnormal tests, and are forced to withdraw the medication and receive special treatment for more than one month, directly affecting the patient's recovery; Grade III AEs patients who persist for more than 7 days are intolerable and are forced to stop or reduce their medication. After general symptomatic treatment, they improve and have no direct impact on the patient's health. Grade IV AE patients can tolerate it without stopping or reducing their medication. With general symptomatic treatment or no treatment, they can recover quickly and have no direct impact on the patient's recovery .18.4% of patients reported AEs, including grade IV (79.6%), grade III (18.4%), and grade II (2.0%), with no occurrence of grade I AEs. The most common AEs are nosebleeds (8.2%), fatigue (6.1%), and hypertension (6.1%) (Table 2).

DISCUSSION

This study confirmed that BEV also has an obvious curative effect on RE after SRS. As far as we know, this is the first long-term observation report of BEV in treating RE. About 18.4% of patients discontinued BEV. According to the characteristics of patients and the study inclusion criteria, the lack of efficacy was the main reason for discontinuation. One-fifth of the population

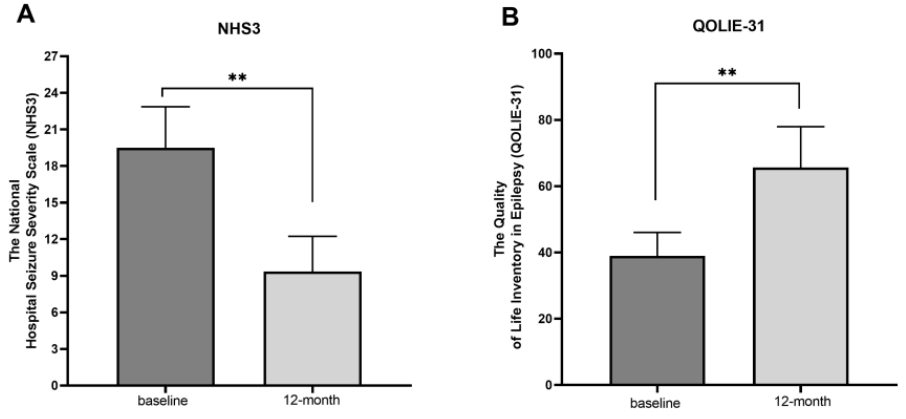

Figure 5. The improvement of RE score in NHS3(FIGURE 5A) and QOLIE-31 (FIGURE 5B) epilepsy patients with BEV adjuvant therapy (**p < 0.01, T-test).

Table 2: Adverse events with bevacizumab treatment

Most frequently reported adverse events [reported by ≥1 of patients]	*N (%)*	**grade IV**	**grade III**	**grade II**	**Frequency**
epistaxis, n (%)	4 (8.2)	1	2	1	7
fatigue, n (%)	3 (6.1)	2	1	0	5
hypertension, n (%)	3 (6.1)	2	1	0	8
diarrhoea, n (%)	2 (4.1)	2	0	0	5
Myelosuppression, n (%)	2 (4.1)	2	0	0	2
Somnolence, n (%)	2 (4.1)	2	0	0	8
proteinuria, n (%)	2 (4.1)	0	2	0	4
Liver function damage, n (%)	2 (4.1)	2	0	0	3
Sleep disturbances, n (%)	2 (4.1)	2	0	0	6
Nausea/vomiting, n (%)	1 (2.0)	1	1	0	4
skin disorders, n (%)	1 (2.0)	0	1	0	2
abdominal pain, n (%)	1 (2.0)	1	0	0	4
diplopia/blurred vision, n (%)	1 (2.0)	1	0	0	1

reported AEs, and the severity of AEs was generally mild or moderate, such as epistaxis, fatigue, and hypertension. These findings suggest that additional BEV adjuvant therapy is safe.

This study provides a therapeutic method for the long-term response of RE after SRS. The effectiveness of using additional BEV for RE control from the clinical perspective is still overlooked, and there is a lack of research.

In a real-world cohort of patients with uncontrolled RE after SRS, approximately 12.2% and 29.3% of the population treated with adjunctive BEV reached SSF and SSR, and most cases achieved sustained seizure frequency reduction in the first course of treatment. Seizure freedom is recognised as the goal of epilepsy treatment by patients and caregivers.[15] Quality of life in patients with refractory epilepsy was influenced by seizure frequency. The International League Against Epilepsy emphasises seizure freedom as a major study endpoint. Despite its importance, many trials fail to report the outcome of seizure freedom, and great heterogeneity exists in its definition. Importantly, the maintenance of seizure freedom is a clinical priority, and it remains uncertain whether short-term seizure freedom observed in pivotal trials is a predictor of long-term seizure freedom.[15] The responder rate was regarded as a regulatory outcome, but there is no requirement for continuous seizure reduction over time. In this regard, sustained efficacy outcomes that exclude patients presenting a transient seizure frequency reduction and those interrupting treatment are more rigorous and informative measures of response. Although RE after SRS has its particularity, this study still counts and observes the treatment effect of epilepsy according to the standards of the International Anti-Epilepsy League, including SSF and SSR in the traditional and complete sense.

BEV is not ASM but an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, which can inhibit endothelial cell proliferation and neovascularisation. Animal models have confirmed that VEGF is highly expressed in the necrotic and hypoxic areas of radiation-induced brain injury.[16,17] In recent years, BEV has become a feasible and favourable salvage treatment for patients with radiation-induced brain injury after radiosurgery.[18] For example, Gondo reported intravitreal BEV for delayed radiation maculopathy and papillopathy after irradiation for maxillary sinus cancer.[19] Dutta reported that BEV for radiation-induced optical neuritis among aggressive residual/recurrent suprasellar tumours has more than a mere antimicrobial effect.[20] Studies have shown that BEV has an immunochemical basis for treating and reversing radiation damage.[21] A series of clinical reports have a clear effect on radioactive damage and radioactive necrosis[22-26], and even low doses have satisfactory effects.[27,28] In terms of oedema, animal model studies have confirmed that bevacizumab reduces cerebral oedema[29], and it has been clinically reported that bevacizumab can be very effective in reducing radioactive oedema after SRS.[7-10]

This study is a single-centre retrospective study with a small number of cases, and therefore, there was no classification of epilepsy subtypes. At the same time, no randomised control group was

established for comparison. Additionally, due to the difficulty in early treatment of RE, patients taking a variety of ASMs had a certain impact on liver and kidney function. After using BEV to control epilepsy in some patients, some drugs with high liver and kidney toxicity were reduced. The standardised questionnaire for AEs was not perfect enough. Therefore, there are potential biases and limitations in the research design and methods of this study, and caution should be exercised when generalising the research results to all RE populations. Despite these limitations, this study is the first to report an effective adjuvant therapy for RE after SRS, laying a partial foundation for future research and targeted interventions.

In conclusion, this is the first study to report the potential resolution strategy of RE after SRS. Additional BEV besides ASMs associated with the reduction of the persistent seizure frequency in a group of RE patients after SRS. With the help of BEV, the incidence of SRS-induced RE would decrease greatly, patients could take fewer kinds of ASMs, and the patients' NH3 and QQLIE-31 scores would improve greatly. We hope the findings of this study can help practitioners provide effective treatment for RE patients after SRS.

DISCLOSURE

Data availability: The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Financial support: The work was supported by the Zhejiang Provincial Department of Education Research Support Project (Y202249332) and the Zhejiang Provincial Medical and Health Research Support Project (2023KY475).

Conflict of interest: None

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