Safety and Efficacy of Hypofractionated Stereotactic Radiotherapy with Anlotinib Targeted Therapy for Glioblastoma at First Recurrence: A Preliminary Report

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Abstract

Background

The optimal treatment for recurrent glioblastoma (rGBM) remains uncertain. Hypofractionated stereotactic radiotherapy (HSRT) and anti-vascular endothelial growth factor (VEGF) antibodies (e.g., bevacizumab) have been reported to have a promising survival benefit and acceptable toxicity in recent studies. Anlotinib is a new orally administered tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR) and c-kit. It has dual anti-angiogenic and anti-tumour growth effects. This preliminary study describes our initial experience with HSRT and anlotinib as a salvage treatment for rGBM.

Methods

Between December 2019 and June 2020, rGBM patients treated with HSRT using CyberKnife concurrently with anlotinib were retrospectively analysed. Anlotinib was prescribed at 12 mg daily during HSRT. Adjuvant anlotinib was administered at 12 mg d1-14 every 3 weeks. The primary endpoint was the objective response rate (ORR) determined by the treating investigators using the Response Assessment in Neuro-Oncology (RANO) criteria, and secondary endpoints included overall survival (OS), progression-free survival (PFS) after salvage treatment, and toxicity. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Results

We retrospectively reviewed five patients who received salvage HSRT and anlotinib for recurrent GBM.

The median planning target volume (PTV) was 26.94 cm3 (5.53–54.41 cm3). The prescribed dose was 25.0 Gy in 5 fractions. The median number of cycles of anlotinib was 9 (4–15) cycles. The median baseline Karnofsky Performance Status (KPS) was 80 (70–90). The follow-up ranged from 4 to 10 months. The ORR was 100%. Three (60%) patients had a best outcome of a partial response (PR), and 2 (40%) achieved a complete response (CR). No patients died or had progressive disease (PD) at the last follow-up. Two patients had grade 2 hand-foot syndrome, which was relieved after dermatologic treatments, and no other grade 3 or higher toxicities were recorded.Conclusions

Salvage HSRT combined with anlotinib showed a favourable outcome and acceptable toxicity for rGBM patients in this preliminary report. A prospective phase II study (NCT04197492) is ongoing to further investigate the value of HSRT combined with anlotinib in rGBM.

Introduction

Glioblastoma is the most frequently diagnosed malignant primary brain tumour in adults [1]. The development of surgery and adjuvant temozolomide-based chemoradiotherapy improved overall survival. However, the majority of patients still suffer from recurrence within 8 months after primary treatment, and

approximately 90% of recurrences occur within a 2cm margin of the original tumour resection cavity [2]. The management of recurrent glioblastoma is highly challenging due to resistance to available therapeutic approaches, and treatment outcomes remain uniformly poor.

For recurrent glioblastoma (rGBM), several options have been studied, including surgery, re-irradiation, tumour-treating fields, and systemic therapy. Many second-line targeted agents and chemotherapy regimens have been examined in trials with limited success. The anti-vascular endothelial growth factor (VEGF) antibody bevacizumab has been demonstrated to prolong the PFS of GBM; however, patients still progress after 3–6 months with an OS of 6–9 months after salvage treatments [3]. Anlotinib is a novel tyrosine kinase inhibitor that targets VEGFR1/2/3, PDGFR, FGFR1/2/3/4, c-Kit, and Ret. It has been reported to have a promising effect on tumour control in an rGBM case report [4]. However, as a salvage treatment, failure ultimately occurs. It is crucial to increase local treatment to reduce the risk of disease progression. The RTOG 1205 trial reported a prolonged PFS for bevacizumab with hypofractionated stereotactic radiotherapy (HSRT) compared with bevacizumab alone [5]. As the main pattern of failure remains local recurrence, it is crucial to optimize local control to improve survival.

Advances in stereotactic radiation can deliver high doses to tumours while limiting toxicity to normal structures.

CyberKnife is a noncoplanar radiosurgery system that allows highly conformal image-guided radiotherapy and shows a promising tumour control effect for central nervous system tumours.
A prior retrospective study at our centre showed the efficacy of hypofractionated stereotactic radiotherapy for rHGG patients with mild toxicity. This study aimed to report the preliminary outcome of HSRT combined with anlotinib. To our knowledge, this is the first cohort of rGBM patients treated with HSRT combined with anlotinib.

Methods

Eligibility Criteria and Endpoints

The local ethics committee approved this retrospective study.
Between December 2019 and June 2020, five rGBM patients received salvage HSRT with anlotinib at Huashan Hospital, Fudan University.
All patients received surgery followed by standard chemoradiotherapy before recurrence.
Recurrence was confirmed by the Response Assessment in Neuro-Oncology (RANO) criteria. Patients who were able to lie flat to receive radiotherapy and had Karnofsky Performance Status (KPS) scores higher than 60 were considered eligible for the regimen at our institution. All patients were treated at first recurrence within the radiation field and refused to receive intravenous bevacizumab.

The outcome endpoint was the objective response rate (ORR). Other endpoints included overall survival after HSRT, progression-free survival after salvage treatment, the best tumour response defined by the RANO criteria, and toxicity defined by the CTCAE 5.0.

Baseline Evaluation and Treatment Delivery

Patients were immobilized with a custom thermoplastic mask and underwent localised 1.25-mm thin-slice computed tomography (CT, GE Light speed Ultra 16 Slice, USA) and 2-mm thin-slice magnetic resonance imaging (MRI) including T1 post-contrast and T2 FLAIR images.
CT and MRI scans were then fused using the planning system for contouring. HSRT was delivered by a CyberKnife Radiosurgery System (Accuray, Sunnyvale, CA, USA).

Radiation oncologists, neurosurgeons, and radiation physicists participated in tumour delineation and planning. The prescribed dose was 25.0 Gy in 5 fractions. Gross tumour volume (GTV) was defined as the gadolinium-enhanced tumour on the T1-weighted series. The clinical tumour volume (CTV) was considered equal to the GTV. The planning target volume (PTV) was a uniform 1-mm expansion of the CTV. Multiplan software was used for inverse planning. The prescribed isodose line to the PTV was determined according to the target volume, site, previous irradiation volume, and interval between treatments. Anlotinib (Tai-Tianqing Pharmaceutical Co., Ltd, Jiangsu, China) was prescribed at a dose of 12 mg daily for 14 consecutive days every 3 weeks from the first day of HSRT.

Assessment and Toxicity

All patients underwent clinical and radiological follow-up every two months after HSRT. If there was any significant deterioration in the patient's performance, MRI was performed immediately. The radiological examination included MRI and other necessary examinations, such as MRI-based spectroscopy, perfusion MRI, and methionine positron emission tomography. The KPS after treatment, adverse event occurrence, and associated clinical outcomes were recorded. Toxicity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) 5.0.

Statistics

The outcome measures considered were the objective response rate (ORR) based on the proportion of patients with a best overall response of a confirmed complete response (CR) or partial response (PR). Other measures included overall survival after HSRT, defined as survival from the time of the completion of HSRT to death due to any cause, progression-free survival after salvage treatment, and treatment-related toxicities.

The CTCAE 5.0 was used to assess toxicity. The number of events, number of subjects, and incidence rate are used to describe the measurement. The maximum, minimum, and median values are used to describe the measurements of patient characteristics.

Results

Patient Characteristics

Five glioblastoma patients with clinical and radiographic evidence of recurrence were treated with HSRT between December 2019 and June 2020. All patients were initially treated with maximum safe resection and adjuvant radiation treatment with a median dose of 60 Gy in 30 fractions with concurrent and maintenance temozolomide. All patients had information on methyl-guanine-methyltransferase (MGMT), isocitrate dehydrogenase 1 (IDH1), 1p/19q co-deletion, and telomerase reverse transcriptase (TERT) after initial resection. Five patients were TERT- and MGMT-positive, 1 patient had a 1p/19q co-deletion and no patient was IDH1-positive. Three patients were male and 2 were female. The median age was 51 years (range 43–60 years). The KPS score at the time of salvage treatment ranged from 70 to 90. The median time from initial diagnosis to salvage HSRT was 10.4 months, with a range of 6.7 to 14.8 months. The median PTV was 26.9 cm^3 (5.5–54.4 cm^3). The treatment was delivered daily, and the dose was 25 Gy in 5 fractions with a median isodose line of 68% (65–70%). Patient characteristics are listed in Table 1.

Compliance and Toxicities

All patients received the planned radiation dose without interruption. The median number of cycles of anlotinib administered were 9 and ranged from 4 to 15 cycles. No acute clinical morbidity was observed. Grade 2 hand-foot syndrome was observed in two patients during cycles 8 and 10. Anlotinib was discontinued for one week in these two patients. The symptoms were relieved after dermatologic treatment, and the regimen was continued. Details are shown in Table 2. No operations or hospitalization was required related to acute or delayed toxicity of HSRT and anlotinib.

Treatment Outcomes

By the end of the study, no patient died of tumour progression. All patients were assessed by the RANO criteria. Three (60%) patients had a best outcome of PR, and 2 (40%) achieved CR; the ORR was 100% (Fig. 1A). The median follow-up from the time of HSRT was 6 months, ranging from 4 to 10 months (Fig. 1B). No patient had progressive disease (PD) or pseudoprogression defined as an increase in the size of the recurrent tumour until the last follow-up.

All patients discontinued steroids after salvage treatment according to the achievement of neurological improvements.

Discussion

Recurrent glioblastoma has been reported to have a poor prognosis. Due to its therapeutic resistance and aggressiveness, its clinical management is challenging. GBM is a vascularized tumour that produces VEGF. Anti-VEGF treatments have been widely used in recurrent GBM. The mechanism of anti-VEGF treatments may have two aspects. First, inhibiting VEGF and its receptor reduces tumour angiogenesis to produce a hypoxic environment and inhibits tumour growth [6]. Second, the tumour vessel diameter was normalised, and the basement membrane was thin. A reduced volume of tumour microvessels has been reported to be related to longer survival [7].

Bevacizumab is approved for treating recurrent glioblastoma by the US Food and Drug Administration and has become a recommended treatment in the National Comprehensive Cancer Network (NCCN) guidelines, with several phase II and III randomized trials indicating a prolonged PFS compared with chemotherapy alone [8–10]. A phase III RCT reported a prolonged median PFS (4.2 vs. 1.5 months) in the bevacizumab and Lomustine groups compared with the Lomustine alone group. However, this trial did not find a difference in OS between the two groups. The grade 3 to 5 toxicity rate in the experimental group was 63.6% [10]. Friedman et al reported a phase II randomized controlled trial (RCT) in which a higher 6-month PFS rate (50.3% vs. 42.6%) and better ORR (37.8% vs. 28.2%) were observed in the bevacizumab with irinotecan group than in the bevacizumab alone group [9]. Other anti-angiogenic drugs, including sorafenib, pazopanib, sunitinib, etc., were reported in phase I and II trials treating rGBM. The ORR reported for anti-VEGF treatments for rGBM ranged from 6–30% (Table 3), and the 6-month PFS ranged from 3–63%. The treatment-related toxicity was mild for these anti-VEGF treatments. However, the efficacy seems to be unsatisfactory.

Anlotinib is an oral novel multi-target tyrosine kinase inhibitor targeting the VEGF1/2/3 receptor, fibroblast growth factor receptor and platelet-derived growth factor receptor. It inhibits more targets than bevacizumab, sunitinib, sorafenib, etc. and has been reported to reduce both tumour proliferation and angiogenesis [3]. Lv et al published the first case report of the administration of 12 mg anlotinib to an rGBM patient. The patient achieved a PR after 26 days, but the tumour progressed in two months [4]. Wang et al reported a recurrent GBM patient with an FGFR-TACC3 fusion who was administered anlotinib 12 mg and temozolomide 100 mg/m^2. The patient achieved a PR after 2 months and maintained stable disease for more than 17 months [11].

Several reports have suggested that re-irradiation has reasonable efficacy with acceptable safety profiles in selected patients with recurrent GBM. However, for rGBM, salvage treatment failure ultimately occurs. It is crucial to increase local treatment to reduce recurrence risk. In a meta-analysis, a highly conformal technique with a hypofractionated regimen (e.g. 25 Gy in 5 fractions or 35 Gy in 10 fractions) is recommended, taking into account the volume and location of the recurrent tumour. The RTOG 1205 trial reported a prolonged PFS with anti-VEGF treatment with HSRT compared with bevacizumab alone [5]. Philip et al theorized that additional anti-VEGF treatment sensitised the tumour endothelia to radiotherapy and induced apoptosis [12].

New-generation automated noncoplanar HSRT delivery systems can deliver high-dose treatment by limiting the dose to normal structures and can provide a higher local treatment intensity for recurrent tumours.
In this study, the ORR rate of salvage treatment was 100% in 2 CR and 3 PR patients. The ORR was higher than other results of anti-VEGF treatments [13–25], which ranged from 6–30% (Table 3). There may be several possible reasons. Patient selection may be a reason for good outcomes. All patients had a KPS of 70 or higher, and HSRT was performed after the first recurrence. Moreover, the administration of HSRT increased local treatment intensity. The preliminary result of RTOG 1205 also reported an increased PFS in the intensified treatment groups. Additionally, patients with a smaller tumour volume may have a better

response. The two CR patients (Fig. 2A, Fig. 2B) in this study had a relatively smaller PTV (7.08 and 5.53 cm3) than the 3 PR patients (26.94, 44.33, and 54.41 cm3).

No treatment failure was observed until the last follow-up. Salvage HSRT was administered with a full dose of 25 Gy/5 fx for all five patients without and interruption. No radionecrosis occurred during the follow-up. Grade 2 hand-food syndrome was found in 2 patients (40%), and rash and hypertension were observed in 1 patient (20%). These adverse effects were considered related to anlotinib. In a phase II randomized trial of non-small-cell lung cancer patients, 28.33% of the subjects had grade 2 hand-foot syndrome, and grade 2 hypertension was observed in 55% of patients [26]. These toxicities were also observed in our study.

The study had some limitations due to its retrospective nature: inherent patient selection bias was created when the physicians chose eligible patients to receive the regimen. The treatment option was provided for patients with high KPS scores who were not willing to receive standard intravenous bevacizumab treatment. Thus, the cohort was enriched with patients with a better prognosis. Another limitation was that recurrence before salvage treatment was diagnosed by radiological parameters according to the RANO criteria, which is a common practice [27]. However, the lack of biopsy samples limited the information on tumour genomic characterizations. It is crucial to consider whether the previously detected mutation still presents as the dominant clone at the time of recurrence [28]. Further investigation is warranted to explain the potential treatment mechanisms and select good responders to the regimen. Additionally, although no patient died or had progressive disease at the last follow-up, a longer follow-up duration is needed to further evaluate the OS and PFS of patients.

Despite the limitations, this study provides initial evidence of a promising outcome using salvage HSRT with anlotinib in a real-world scenario. Responses were observed in all rGBM patients included in the study. Further investigation is needed to identify patients who can benefit from this regimen. A prospective phase II study HSCK-002 (ClinicalTrials.gov identifier: NCT04197492) is ongoing to further investigate the value of HSRT with anlotinib.

Conclusions

Salvage radiosurgery with anlotinib appeared to achieve a clinical benefit with acceptable toxicity for rGBM patients in this preliminary report. A prospective phase II study (NCT04197492) is ongoing to further investigate the value of HSRT with anlotinib in rHGG.

Abbreviations

Recurrent Glioblastoma (rGBM); Hypofractionated Stereotactic Radiotherapy (HSRT); Vascular Endothelial Growth Factor (VEGF); Vascular Edothelial Growth Factor Receptor (VEGFR); Platelet-derived Growth Factor Receptor (PDGFR); Fibroblast Growth Factor Receptor (FGFR); Objective Response Rate (ORR); Response Assessment in Neuro-Oncology (RANO); Overall Survival (OS); Progression-free Survival

(PFS); Planning Target Volume (PTV); Karnofsky Performance Status (KPS); Partial Response (PR); Complete Response (CR); Progressive Disease (PD); Response Assessment in Neuro-Oncology (RANO); Computed Tomography (CT); Magnetic Resonance Imaging (MRI); Gross Tumour Volume (GTV); Clinical Tumour Volume (CTV); Common Terminology Criteria for Adverse Events (CTCAE); Methyl-guanine-methyltransferase (MGMT); Isocitrate Dehydrogenase 1 (IDH1); Telomerase Reverse Transcriptase (TERT); Progressive Disease (PD); Randomized Controlled Trial (RCT).

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and the 1964 Helsinki declaration and its later amendments. This retrospective study was approved by the Huashan ethics committee. All participants provided written informed consent and studies were approved by the local ethics committee.

Consent for publication

Not applicable.

Availability of data and material

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Competing interests

All the authors have nothing to disclose.

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Author's contributions

Yun Guan, Jing Li, and Xiu Gong contributed equally to the work.

Conception design and interpretation of data: Enmin Wang, Xin Wang, Ying Liu and Yun Guan.

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Tables

Table 1 Patient characteristics and treatment outcomes

Case	Age Sex	Interval between Initial Diagnosis to HSRT (months)	Upfront RT Dose/fx	Upfront Chemotherapy (cycles)	MGMT	IDH1	1p/19q
1	60 Male	12.6	60Gy/30	TMZ (12)	+	-	-
2	46 Female	10.4	60Gy/30	TMZ (6)	+	-	-
3	55 Female	14.8	60Gy/30	TMZ (12)	+	-	+
4	51 Male	9.6	60Gy/30	TMZ (4)	+	-	-
5	43 Male	6.7	60Gy/30	TMZ (4)	+	-	-

Case	TERT	Recurrent Lesion	Recurrent PTV (cm^3)	KPS at HSRS	Dose (iso-dose line)	Cycles of Anlotinib	F/U Interval from HSRS (months)
1	+	Left Frontal Lobe	7.08	80	68	15	10
2	+	Left Frontal Lobe	26.94	80	65	14	10
3	+	Left Occipital Lobe	54.41	70	70	9	6
4	+	Right Frontal Lobe	5.53	90	70	4	4
5	+	Left and Right Frontal Lobe	44.33	90	68	8	6

Table 2. Best Treatment outcomes and Adverse Events Occurred in rGBM Patients

Outcomes/AE	Total No. of Patients	No. of Patients		
		Grade 1	Grade 2	Grade 3
ORR	5 (100%)		N/A	
CR	2			
PR	3			
Haematologic				
Thrombocytopenia	1	0	1	0
Nonhaematologic				
Hand foot syndrome	2	0	2	0
Rash	1	0	1	0
Hypertension	1	0	1	0

Table 3 Anti-angiogenic treatment for recurrent glioglastoma reported.

Author, year	Treatment	Phase (Sample Size)	Outcome (ORR rate%)	Median PFS (months)	Median OS (months)	6-momth PFS
Reardon, 2018 [13]	Trebananib	II (11)	2CR (18)	0.7	11.4	N/A
Reardon, 2005 [14]	Imatinib	II (33)	3PR (9)	3.3	N/A	27.0%
Iwamoto, 2010 [15]	Pazopanib	II (35)	8PR (22)	3.0	8.1	3.0%
Pan, 2012 [16]	Sunitinib	II (16)	0	N/A	12.6	16.7%
Hutterer, 2014 [17]	Sunitinib	II (40)	0	2.0	9.2	12.5%
Hassler, 2014 [18]	Imatinib	II (24)	2PR (8)	3.0	6.2	N/A
Batchelor, 2010 [19]	Cediranib	II (131)	1CR, 17PR (14)	3.0	8.0	16.0%
Gerstner, 2015 [20]	Cediranib	I (45)	2CR, 2PR (9)	1.9	6.5	4.4%
Chheda, 2015 [21]	Vandetanib	I (19)	2PR (11)	1.9	7.2	63%
McNeill, 2014 [22]	Vandetanib	II (32)	2PR (6)	1.7	5.6	N/A
Duerinck, 2016 [23]	Axitinib	II (22)	2CR, 4PR (27)	N/A	6.7	34%
Lee, 2012 [24]	Sorafenib	I/II (18)	2PR (11)	1.8	N/A	N/A
Groot, 2020 [25]	Aflibercept	II (27)	8PR (30)	N/A	N/A	N/A

Abbreviations: TTF = Tumor Treatment Field; HSRT = Hypofractionated stereotactic radiotherapy; BVZ = Bevacizumab; TMZ = Temozolomide; GBM = Glioblastoma Multiforme.

Figures

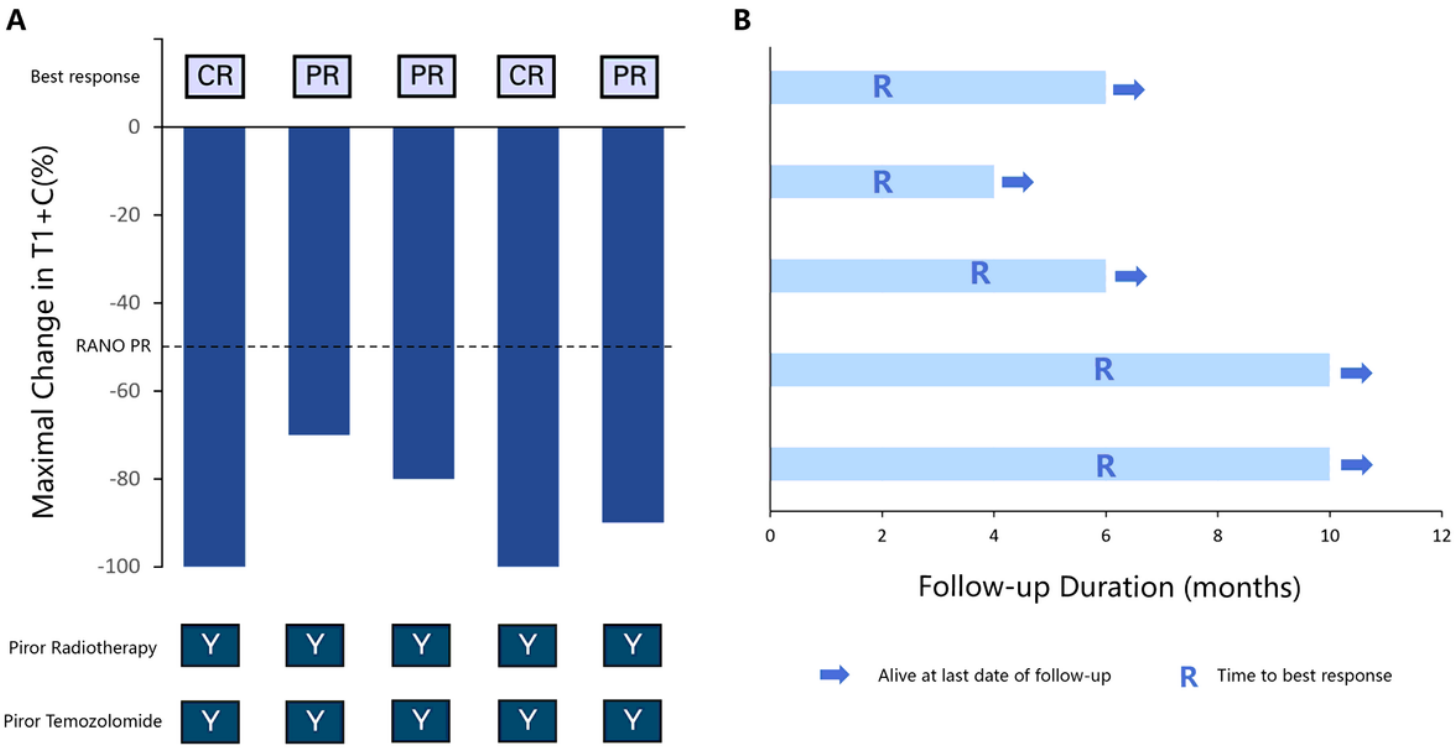

Figure 1

A. Maximal change in the product of the perpendicular diameter in MRI T1 contrast before and after HSRT with anlotinib in each patient. CR, complete response. PR, partial response. RANO, Response Assessment in Neuro-Oncology. Y, yes. B. Follow-up duration and time to the best response in each patient.

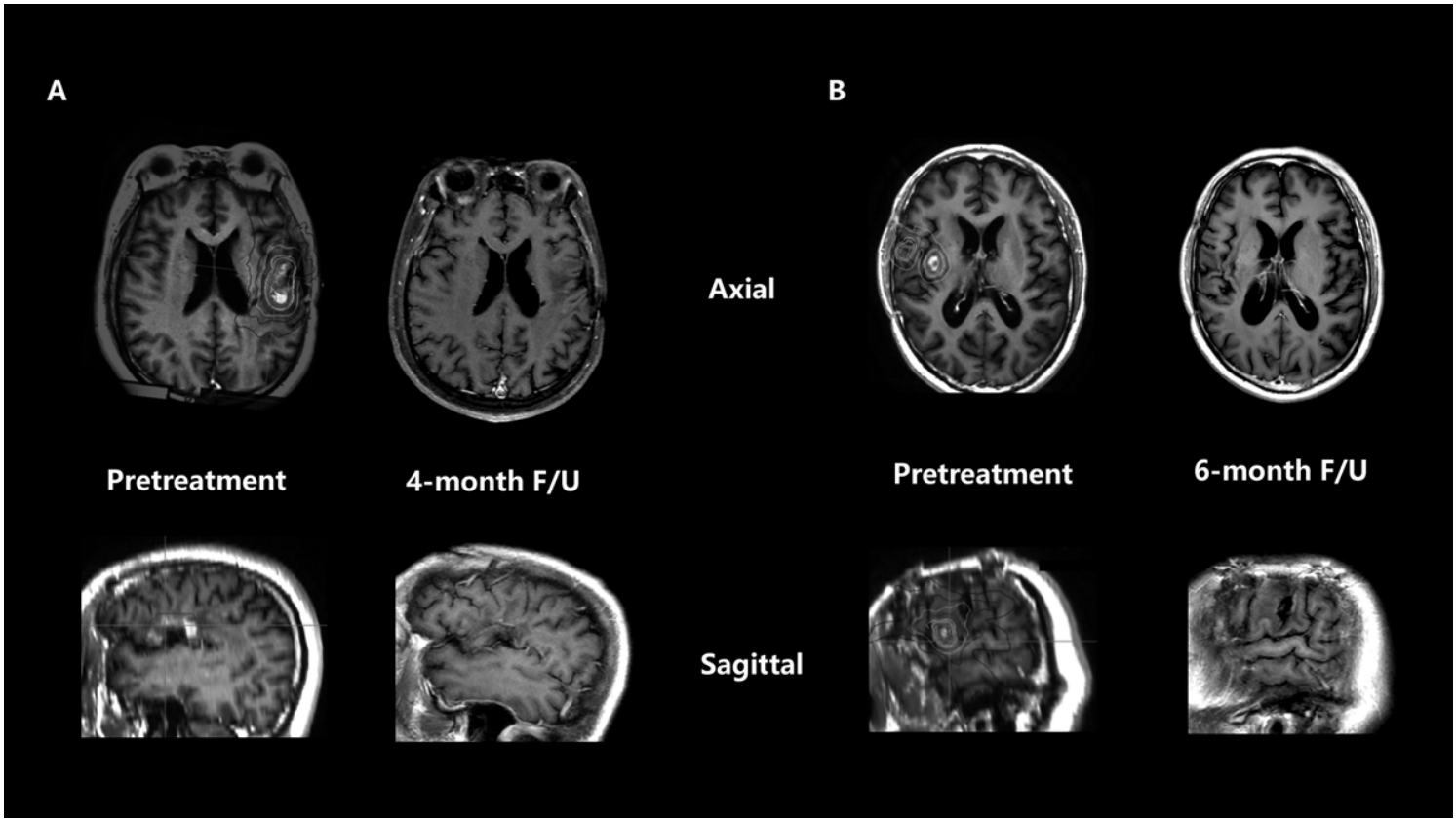

Figure 2

Contrast-enhanced MRI T1 of responses to HSRT and anlotinib, including patient case 1 (A) and patient case 4 (B), who achieved a complete response.