Clinical Case Report

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Conventionally fractionated stereotactic radiotherapy (CFRT) in combination with dose-dense temozolomide (TMZ) in relapsed malignant glioma

A case report

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Abstract

Rationale: At present, there is no uniform consensus on the treatment of recurrent glioblastoma, especially the re-irradiation dose and temozolomide (TMZ) dose. The literature on the treatment of recurrent glioblastoma (GBM) by conventionally fractionated stereotactic radiotherapy (CFRT) is even rarer.

Patient concerns: A 44-year-old woman was admitted to our hospital for residual tumor after reoperation.

Diagnoses: Postoperative pathological diagnosis was GBM, WHO grade IV. The brain magnetic resonance imaging re-examination showed abnormal enhancement around the local operative region after resection of the left frontal lobe tumor, and there was presence of residual tumor.

Interventions: The patient was treated with reoperation followed by re-irradiation plus dose-dense TMZ to achieve complete remission.

Outcomes: Complete remission was observed at the end of radiotherapy and at the 1 month follow-up after radiotherapy.

Lessons: This study suggests that CFRT plus dose-dense TMZ might be a feasible option for the treatment in relapsed malignant glioma patients with good general condition.

Abbreviations: CFRT = conventionally fractionated stereotactic radiotherapy, GBM = glioblastoma, OS = overall survival, PFS = progression-free survival, TMZ = temozolomide.

Keywords: case report, malignant glioma, temozolomide

1. Introduction

In the past 30 years, the incidence of primary malignant brain tumors has been increasing year by year, with an annual growth rate of about 1% to 2%, especially among the elderly.[1] Glioma is the most common primary tumor in the central nervous system. Among adults, glioma accounts for 30% to 40% of all brain tumors and about 80% of brain malignancies. It has the characteristics of high incidence, high recurrence rate, high mortality rate, and low cure rate.[2] Because of the invasive nature of high-grade glioma, progression-free survival (PFS) is only 6.9 months even after chemoradiation and adjuvant chemotherapy of temozolomide (TMZ), suggesting that the vast majority of patients with high-grade glioma first would relapse after treatment.[3] Recurrence of gliomas is progression of clinical symptoms in the process of treatment or tumor increase obvious on imaging or new tumor lesions emerged. Local recurrence is the most frequent form of primary recurrence.[3]

Due to the lack of the corresponding randomized controlled study, the initial radiation dose, the interval between the initial radiation therapy and re-irradiation, the location and volume of the tumor, and other factors should be taken into account when the recurrent glioma occur. In this case report, we reported a 44-year-old female patient who underwent postoperative radiotherapy and chemotherapy 4 years ago. She was diagnosed with recurrence via magnetic resonance imaging (MRI) on May 18, 2018.

2. Case history

A 44-year-old woman was admitted to the neurosurgery department of our hospital on December 8, 2014, due to epilepsy, accompanied by headache and decreased muscle strength of both lower limbs for 1 month. Enhanced cranial MRI showed a solid lesion in the left frontal lobe. Intracranial tumor resection was performed on December 17, 2014. The pathological diagnosis was grade II astrocytoma. The prescription dose of head postoperative

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radiation was: PGTVtb64.4Gy/28fractions; PTVtb50.4Gy/28fractions; TMZ was concurrently administrated with postoperative radiotherapy. The dose of TMZ was 75 mg/m^2 daily concurrent with radiotherapy, then 150 mg/m^2 postirradiation on a 5-day schedule every 4 weeks. The patient was followed up regularly after radiotherapy. The brain MRI on March 9, 2018, showed irregular ring enhancement in the left frontal lobe, with a range of about $2.9 \times 3.4 \times 3.5$ cm (Fig. 1 A–C). The patient underwent intracranial tumor resection on March 23, 2018, and postoperative pathology was glioblastoma (GBM), WHO grade IV. Immunohistochemistry results: vimentin (+++), glial fibrillary acidic protein (+++), isocitrate dehydrogenase (+++), Olig2 (+++), P53 (+80%), S-100 (+++), neuron-specific enolase (−), Syno (+), NeuN (−), NF (−), ChrA (−), epithelial membrane antigen (−), Ki-67 (+30%). She rejected gene mutation detection of the status of 1p/19q. The brain MRI re-examination on May 11, 2018 showed abnormal enhancement around the local operative area after resection of the left frontal lobe tumor, and there was residual tumor present (Fig. 2 A–C). After the reoperation of recurrence, the patient received conventionally fractionated stereotactic radiotherapy (CFRT) plus TMZ concurrent chemotherapy. The TMZ dose applied was 150 mg/m^2 day 1 to day 7, every 2 weeks, concurrent with radiotherapy, then 150 mg/m^2 postirradiation on a 7-day schedule every 2 weeks. Epilepsy did not appear again so far. Evaluation of cranial enhanced MRI (Fig. 3 A–C) after chemoradiotherapy showed complete remission of remaining intracranial lesions at the end of radiotherapy and 1 month after radiotherapy. Informed consent of the patient has been obtained.

3. Discussion

At present, there has been no uniform treatment plan for recurrent malignant glioma. At present, comprehensive treatment methods such as reoperation, radiotherapy, and chemotherapy are mainly adopted. Whether reoperation can benefit patients with recurrent high-grade glioma is still lacking of evidence.

A prospective study confirmed that the median overall survival (OS) (26 months) of patients with recurrent glioma undergoing

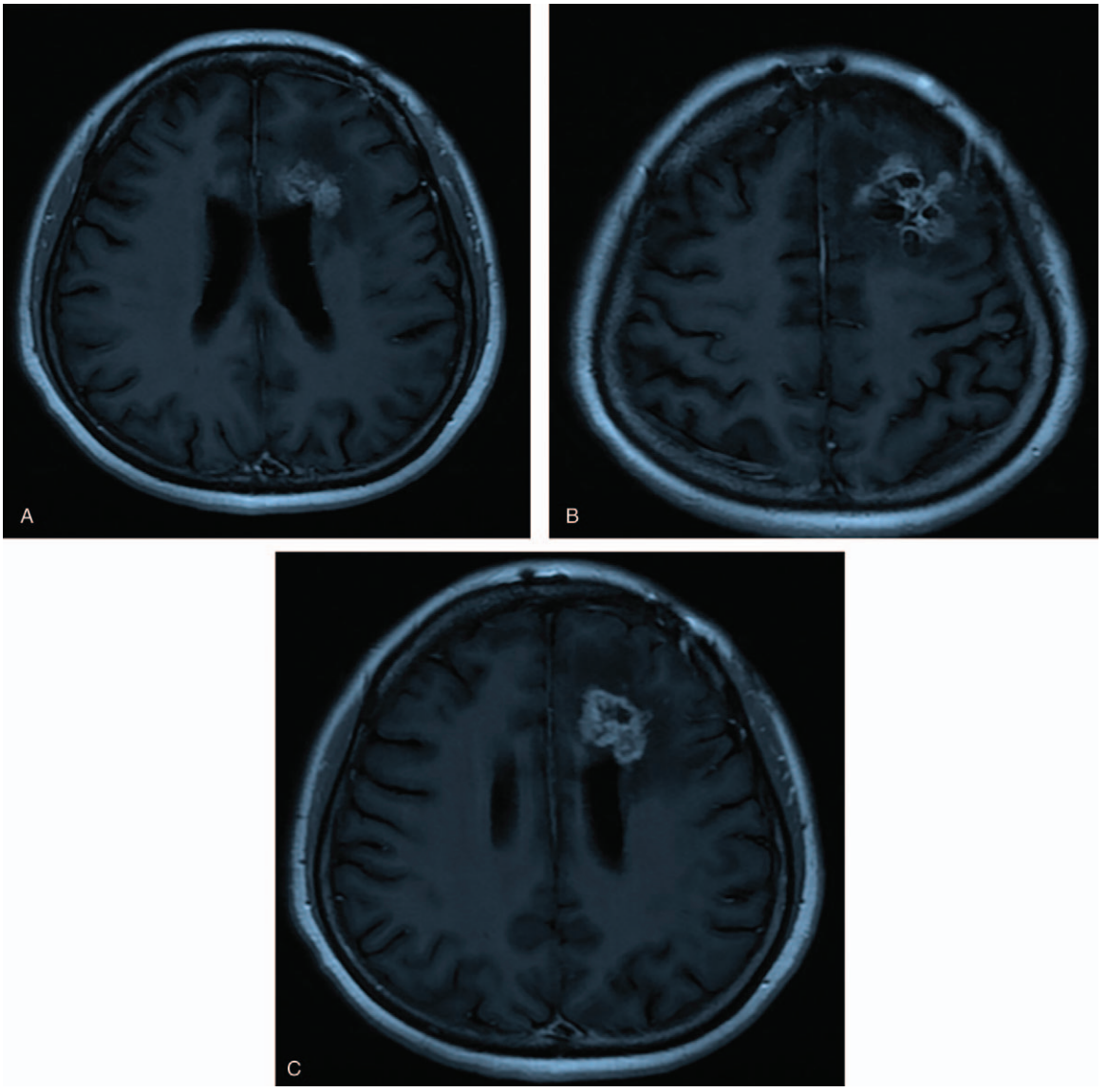

Figure 1. (A–C) Magnetic resonance imaging (MRI) of the patient with diagnosis of recurrence.

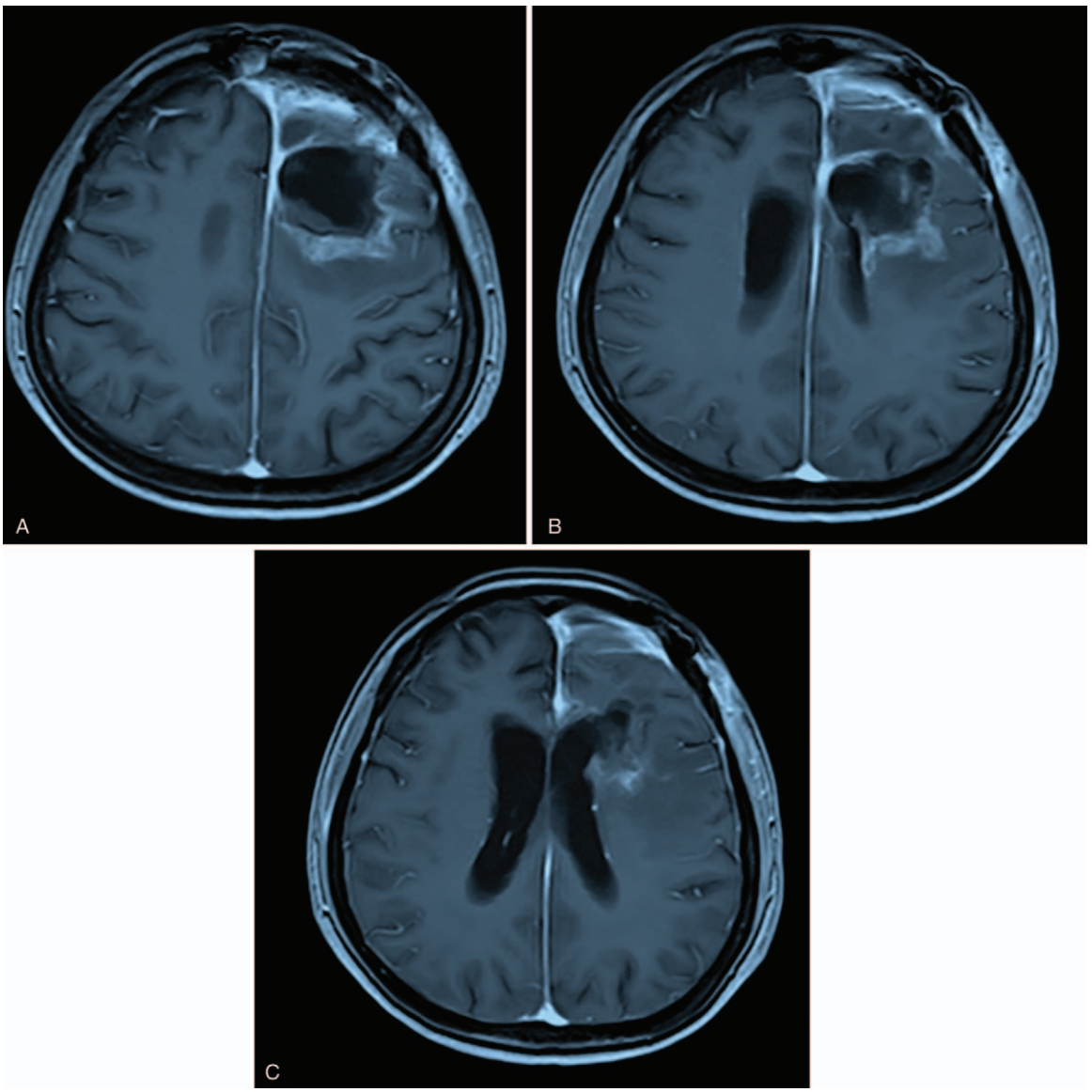

Figure 2. (A–C) Residual tumor present after the reoperation.

surgical resection was significantly longer than that of patients in the nonsurgical group (16 months), with a 2-year survival rate of 58.3%, 3-year survival rate of 31.1% in the surgical group, and a 2-year survival rate of 29% and 12.4% in the nonsurgical group, respectively.[4] However, some studies indicated that reoperation combined with postoperative chemotherapy was significantly different from chemotherapy alone in terms of the extension of survival. Reoperation is only applicable to patients with good general condition, with tumor located in nonfunctional area, long recurrence interval from the first operation, and moderate tumor volume. For the poor general condition, the tumor location in an important functional area, the shorter recurrence interval, the reoperation could not achieve the expected effect in the patients with large tumor volume. The recurrent tumor of this patient was located in the original tumor bed area, which was a nonfunctional area, and the clinical condition of the patient was generally good, so the surgery was performed again.

Because of radioactive toxicity, particularly radioactive brain necrosis, re-irradiation of recurrent glioma is a challenge for clinicians. How to select the appropriate patient for the re-irradiation is a key point. To screen patients who can benefit from re-irradiation, Combs ET AL[5] established a scoring system in 2013, which is based on age, Karnofsky (KPS) score, tumor volume, pathological grade, and time interval between initial radiotherapy and re-irradiation (Table 1).[5] According to this scoring system, this patient, with residual tumor, scored 2 points, and could benefit from re-radiotherapy. So after the secondary resection, the patient went through re-irradiation.

At present, there has been lack of prospective research on recurrence of high-grade glioma by re-irradiation. As far as we know, there is only 1 prospective cohort clinical trial studying stereotactic radiosurgery for recurrent glioma.[6] Patients with recurrent glioma (grade III) had a total survival median of 37.5 months, and patients with GBM had a total survival median of 23 months. The median PFS after stereotactic radiosurgery was 8.6 months in grade III glioma patients and 4.6 months in GBM patients. In the treatment of related complications, 22 out of

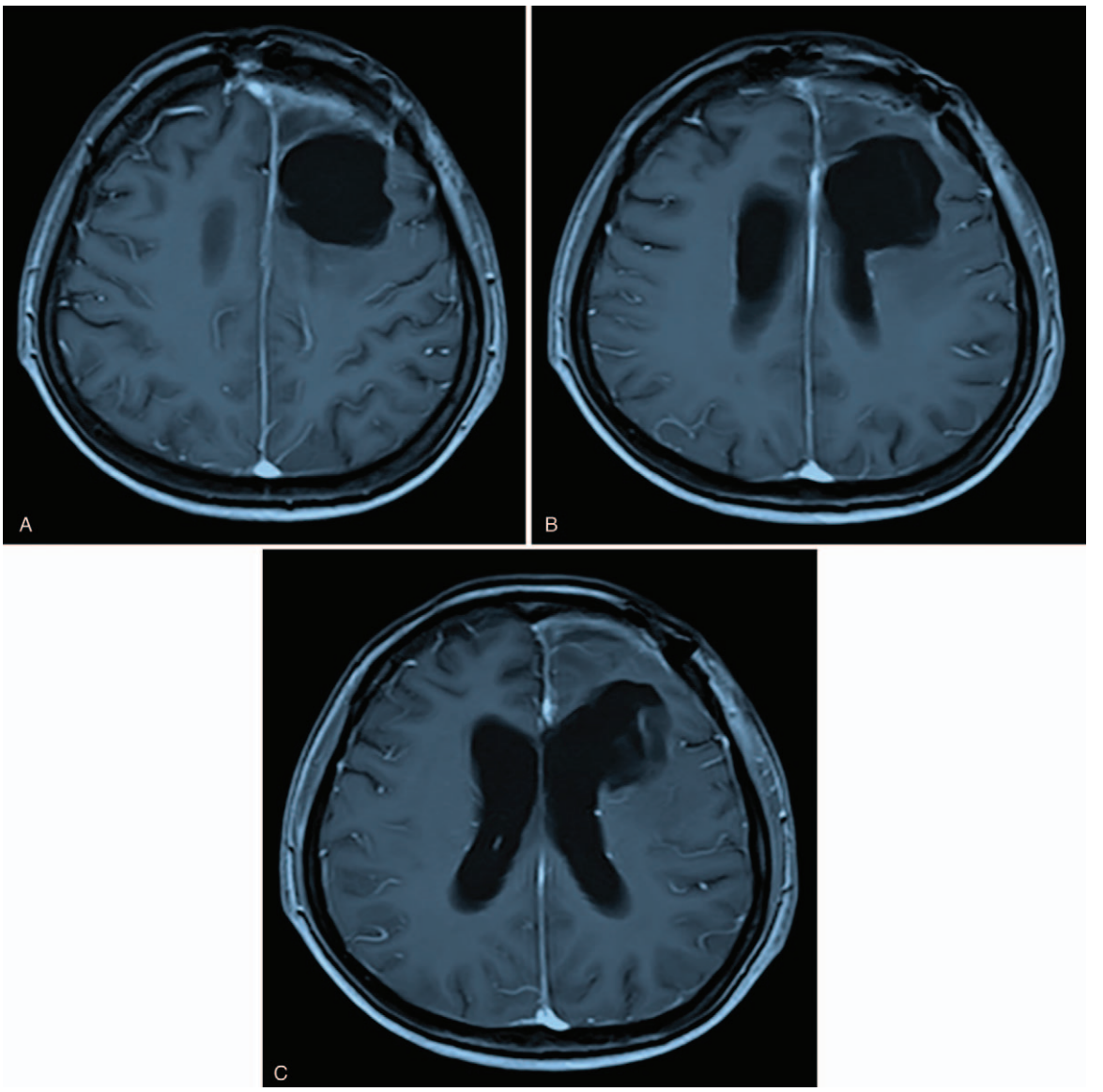

Figure 3. (A–C) Magnetic resonance imaging (MRI) of the patient 1 month after radiotherapy.

114 patients (24.4%) developed radio-necrosis. Compared with this historic control group, stereotactic radiosurgery as a life-saving treatment for recurrent GBM (23 vs 12 months) significantly prolonged OS ($P < .0001$), but surgery failed to improve OS for patients with recurrent grade III glioma (37.5 vs 26 months; $P < .789$). Other clinical studies were mostly retrospective.[7–10] Median margin dose ranged from 12 Gy[10] to 18 Gy,[7,11] with a very wide range in the median target volume, which ranged from 4 mL[7] to 21.6 mL.[10] Only GBM trials have reported OS and PFS. The OS ranged from 7.5 m[7] to 10 m.[12] The PFS ranged from 4.6 m[6] to 7 m.[12] The most frequent side effect was radio-necrosis, with a maximum incidence of 31.3% reported by Hsieh et al.[10] Considering the poor prognosis of recurrent GBM, severe side effects with a risk of <3% were arbitrarily defined as acceptable toxicity.[13] Therefore, the above data indicate that stereotactic radiosurgery is feasible for patients with small volumes (<12.5 mL), and the average prescription dose should remain ranging from 12 to 15 Gy, because higher doses can lead to severe side effects.

Some scholars have shared the experience of hypofractionated stereotactic radiotherapy. But the patients included in these studies included patients with recurrent glioma of grade II[14,15] and III.[6,14–19] Fraction sizes of radiotherapy regimens were

Table 1

Scoring of prognostic factors in the Heidelberg prognostic score for re-irradiation of recurrent[5]glioma.

Prognostic factors	Subgroups	Value for prognostic score
Histology	WHO grade IV	2
	WHO grade III	1
	WHO grade II	0
Age	<50 y	0
	≥50 y	1
Time between primary radiotherapy and re-irradiation	≤12 mos	1
	12 mos	0

WHO = World Health Organization.

different, which ranged from 3 to 7 Gy, and fractions ranged from 5 to 10. Equivalent dose in 2Gy/f ranged between 37.5 and 78.5 Gy. The median OS[15,17] was 7.9 to 11 months, whereas PFS has barely been reported. The most frequently reported side effects were radio-necrosis, with the highest incidence reported in 12.5% of studies.[18]

There were 2 studies reported about CFRT as salvage treatment in recurrent GBM.[20,21] The dose fractionated model of re-irradiation consists of CFRT with a dose of 36 in 2 Gy fractions. Severe side effects were as low as 1.7%, although the maximum average volume was 49.3 mL. The median survival was 8 months after re-irradiation in patients with GBM and 16 months in patients with grade III tumors. Only progression time and histology had a significant effect on survival after re-irradiation. GBM progression-free survival after FSRT was 5 months, grade III tumors were 8 months, and low-grade gliomas were 12 months. A study reported by Lee et al[21] in 2016 confirmed that patients with a KPS score ≥70 and a re-irradiation dose ≥45 Gy, and that patients with a longer interval between initial and re-irradiation were associated with better OS. To reduce the severe side effects caused by radiation therapy, we treated the patient with CFRT for re-irradiation.

Temozolomide is an effective chemotherapy regimen for recurrent glioma, which can be used together with radiotherapy, but there is no consensus on optional treatment for recurrent glioma. An open-label phase II trial evaluated the efficacy and safety of TMZ in combination with conformal 3D-radiotherapy.[22] The enrolled patients were recurrent GBM confirmed by enhanced MRI. The enrolled patients first received TMZ systemic chemotherapy, for 4 to 5 cycles. For patients who had not used TMZ before, the dose was 200 mg/m^2/d. For patients who had used TMZ chemotherapy before, the dose was 150 mg/m^2/d. The PFS was 10.1 months, and the OS was 11.4 months with mild grade 1, 2 hematological toxicities. Therefore, we improved the TMZ synchronous chemotherapy, and we used TMZ 150 mg/m^2/d, day 1 to day 7, twice a week. No obvious hematological toxicity was observed during chemoradiotherapy.

4. Conclusions

The rarity of this case is that CFST in combination with TMZ in the treatment of recurrent glioma to achieve complete remission. Although the patient has achieved complete remission at present, the patient is still undergoing TMZ sequential chemotherapy (150 mg/m^2/d, day 1 to day 7, twice a week), due to the high recurrence rate, which still requires close follow-up.

Author contributions

Data curation: Shuai Qie, Xi Zhang.
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Funding acquisition: Shuai Qie.
Resources: Yanhong Li, Lanhui Yuan.
Software: Hongyun Shi, Lanhui Yuan.
Validation: Xi Zhang.
Writing – original draft: Shuai Qie.
Writing – review & editing: Shuai Qie.

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