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Differential diagnostic value of 3.0T MR 3D-ASL technique for recurrence and pseudo-progression of high-grade glioma

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Abstract. – OBJECTIVE: This study aimed to explore the value of 3.0T magnetic resonance three-dimensional arterial spin labeling imaging (3D-ASL) technology in the differential diagnosis of recurrence and pseudo-progression of high-grade gliomas.

PATIENTS AND METHODS: Fifty patients with high-grade glioma were selected as research objects. All 50 patients were examined by magnetic resonance imaging (MRI), and the lesions were found to be enlarged or abnormally enhanced. All the patients were examined using the 3.0T MR 3D-ASL technique. With targeted biopsy pathology as the gold standard, the diagnostic results of the 3.0T MR 3D-ASL technique were analyzed, and the cerebral blood flow (rCBFmax) ratio was compared between patients with recurrent glioma and patients with pseudo-progression [maximum blood flow value/contralateral mirror area (CBFmax/contralateral mirror area), CBFmax/contralateral white matter, CBFmax/contralateral gray matter].

RESULTS: Among 50 glioma patients, 31 (62.00%) were diagnosed with recurrence through pathological examination, and 19 (38.00%) were diagnosed with pseudo-progression. 30 patients with recurrence (60.00%) and 20 patients with pseudo-progression (40.00%) were diagnosed using 3.0T magnetic resonance 3D-ASL technology. The diagnostic accuracy of 3.0T magnetic resonance 3D-ASL technology was 96.77% (30/31) ($p > 0.05$). Using pathological results as the "gold standard", the relevant parameters of 3.0T magnetic resonance 3D-ASL technology under different pathological results were analyzed. The results showed that the CBFmax/contralateral mirror area, CBFmax/contralateral white matter, and CBFmax/contralateral gray matter ratios of advanced glioma recurrence patients were significantly higher than those of pseudo-progression ($p < 0.05$).

CONCLUSIONS: The application of 3.0T MR 3D-ASL in high-grade glioma can effectively distinguish recurrence and pseudo-progression, with significant diagnostic value.

Key Words:
High-grade glioma, Recurrence, Pseudo progression, 3.0T MR 3D-ASL, Differential, Diagnostic value.

Introduction

Glioma is the most common primary brain tumor in clinical practice, and pseudo-progression is the reactive change of normal brain tissue in the lesion area against high-level glioma after comprehensive treatment. Microscopic pathological changes mainly include tissue destruction and inflammatory reactions, and new enhancement and edema can be seen in the surgical area or surrounding areas by imaging. The incidence of pseudo-progression in high-grade gliomas is 15-30%. Due to the use of temozolomide in clinical practice, this reactivity change has a higher incidence and more pronounced degree of response compared to simple radiation-induced brain necrosis, making it difficult to differentiate from tumor recurrence[1,2]. For patients with high-grade glioma, surgical resection therapy is the preferred clinical option, and postoperative combined radiotherapy and chemotherapy are required to improve patients' prognosis and quality of life. However, in the process of postoperative radiotherapy and chemotherapy, the postoperative recurrence rate is high in patients, and some patients have the illusion of abnormal enhancement or scope

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expansion in the surgical area due to factors such as radiotherapy and chemotherapy[3]. Clinical diagnosis and differentiation are difficult due to the similarity in clinical manifestations between postoperative recurrence and pseudo-progression of high-grade glioma, and there is less specificity in clinical symptoms in the early stages of onset. Although surgical pathology is taken as the "gold standard" in the differential diagnosis of the recurrence and pseudo-progression of high-grade glioma, there are still some limitations in clinical application because of the invasive examination of this method[4]. 3.0T MR 3D-ASL is a perfusion imaging examination with endogenous water molecules as the tracer, which can distinguish inflammatory tissues from tumor tissues by observing the local blood perfusion of the corresponding brain tissues of patients and then effectively distinguishing the recurrence from pseudo progression[5]. This study mainly explored the value of 3.0T magnetic resonance three-dimensional arterial spin labeling imaging (3D-ASL) technology in the differential diagnosis of recurrence and pseudo-progression of high-grade glioma.

Patients and Methods

Patients Information

Fifty patients with high-grade glioma underwent surgery and four cycles of postoperative and concurrent chemoradiotherapy at our hospital between April 2019 and April 2022 were selected. Among them, there were 35 males and 15 females, aged 19-67 years old, with a mean age of (43.29 ± 5.71) years old, and weighed 45-70 kg, with a mean weight of (60.12 ± 3.05) kg. Disease grading: 34 cases at level III, 16 cases at level IV. This study was in line with the ethics committee's approval, and the patients signed consent forms. Inclusion criteria: (1) Patients with complete results of stereotactic pathological examination referred to advanced diagnostic criteria for gliomas; (2) Patients who had surgical treatment and underwent routine postoperative radiotherapy and chemotherapy; (3) Patients had no contraindications for 3.0T magnetic resonance 3D-ASL technology examination and can tolerate; (4) Patients with enlarged or abnormally enhanced lesions detected by MRI examination. Exclusion criteria: 1. Patients with contraindications to MRI; 2. Patients who could not be evaluated because of severe MRI image artifacts; 3. Patients with incomplete clinical data; 4. Patients with psychiatric disorders or cognitive impairment. This study has been approved by the ethics committee of our hospital (2023LWB305) and was performed normally.

Methods

Pathological examination

All enrolled cases have a complete pathological examination result. The nature of the lesion was determined through histopathology in each group of cases. Tumor recurrence: any number of tumor cells were found (only containing tumor tissue or tumor tissue mixed with necrotic components). Pseudo progression: inflammatory or necrotic tissue with no tumor cells. All patients were given the technical examination through 3.0T MR 3D-ASL (Siemens Healthineers, Erlangen, Bavaria, Germany), and specific methods are as follows. Examination process: the patients were examined with Siemens 3.0T MRI scanning instrument and 8-channel cranial-controlled front circle and were instructed to select the supine position, mainly with magnetic resonance imaging (MRI) plain scan, enhanced scan and 3D-ASL technique. Scanning parameters: axis T1WI TE 10 ms, visual field 24 cm × 24 cm, layer spacing 0.3 mm, layer thickness 5 mm, excitation number 1; Axial spin-echo T2WI, axial T2WI fat inhibition sequence TE 131 ms, TR4000 ms, visual field 24 cm × 24 cm, layer spacing 0.3 mm, layer thickness 5 mm, matrix 350282, excitation number 1. The continuous automatic spin labeling (pCASL) technique was used in 3D-ASL to complete 1,000 consecutive labeling within 1.5 seconds to obtain imaging images.

Image processing and analysis

The scanned images were uploaded to Siemens 3.0T software for processing and measurement. Meanwhile, the 3D-ASL module of Functool software was used to process the ASL data, and the maximum level of the solid part of the tumor was selected as the analysis level in combination with the enhanced scanning images. The abnormally enhancing parenchymal portion, the area surrounding the enhancing lesion, and cerebral blood flow (CBF) and rCBF values of the contralateral normal mirror area in the location of the operative area of the patients, were measured three times and recorded. The mean was calculated, and CBF and rCBF values were normalized. At the same time, the images were analyzed and judged by two experienced imaging diagnostic physicians,

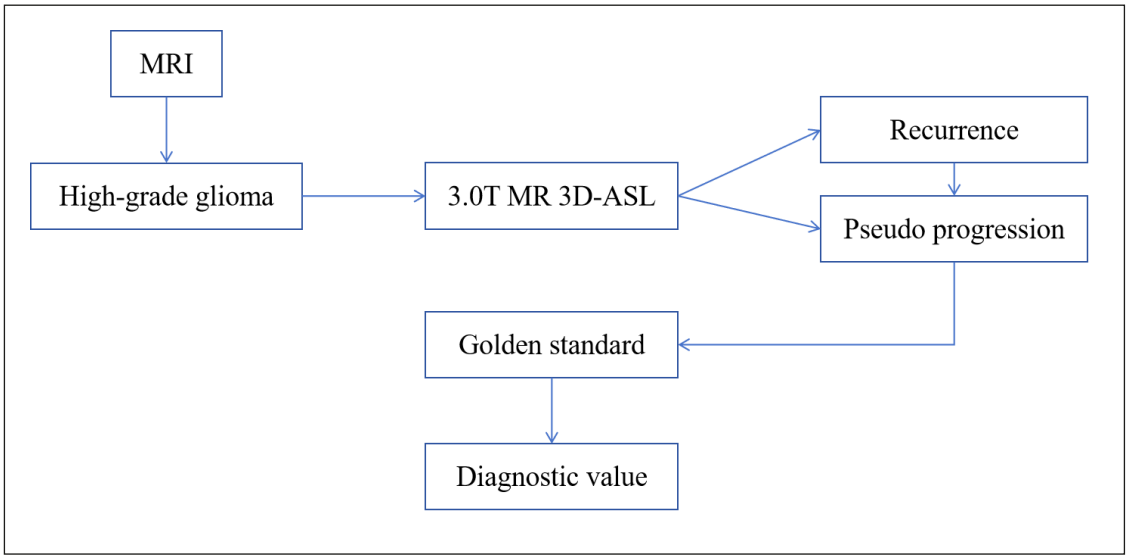

Figure 1. The flow diagram of this study.

the relative mean rCBFmax) of enhanced center and enhanced marginal area = mean CBF and rCBF values of enhanced center and enhanced marginal areas/mean CBF and rCBF values in the contralateral mirror area. Figure 1 shows the flow diagram of this study.

Observation Indicators

Diagnostic accuracy: using pathological examination results as the gold standard, analyze the diagnostic results of 3.0T magnetic resonance 3D-ASL technology and calculate and record the diagnostic accuracy of 3.0T magnetic resonance 3D-ASL technology. 3.0T magnetic resonance 3D-ASL technical parameters under different results of pathological examination. The ratio of rCBFmax in patients with recurrent glioma and pseudo-progression after chemotherapy was recorded and compared [maximum blood flow value/contralateral mirror area (CBFmax/contralateral mirror area), CBFmax/contralateral white matter in patients with glioma].

Statistical Analysis

SPSS 26.0 software (IBM Corp., Armonk, NY, USA) was used to process the data. Counting data was calculated using the χ^2 test and represented by n (%). The measurement data was calculated using *t*-test and represented by (±s). The receiver operating characteristic (ROC) curve was plotted, and the differential efficacy of 3.0T magnetic resonance 3D-ASL technology in recurrent patients and pseudo-progression patients was analyzed. The difference between $p < 0.05$ was statistically significant.

Results

The Differential Value of 3.0T Magnetic Resonance 3D-ASL Technology in Recurrent Patients and Pseudo-Progression Patients

Among 50 glioma patients, 31 (62.00%) were diagnosed with recurrence through pathological examination, and 19 (38.00%) were diagnosed with pseudo-progression. 30 patients with recurrence (60.00%) and 20 patients with pseudo-progression (40.00%) were diagnosed using 3.0T magnetic resonance 3D-ASL technology. The diagnostic accuracy of 3.0T magnetic resonance 3D-ASL technology was 96.77% (30/31) ($p > 0.05$), as shown in Table I and Figure 2.

Comparison of r CBFmax Ratio Between Patients with Recurrence and Patients with Pseudo-Progression

Details are shown in Table II, Figure 3, and Figure 4. Using pathological results as the "gold standard", the relevant parameters of 3.0T magnetic resonance 3D-ASL technology under different pathological results were analyzed. The results showed that the CBFmax/contralateral mirror area, CBFmax/contralateral white matter, and CBFmax/contralateral gray matter ratios of advanced glioma recurrence patients were signifi-

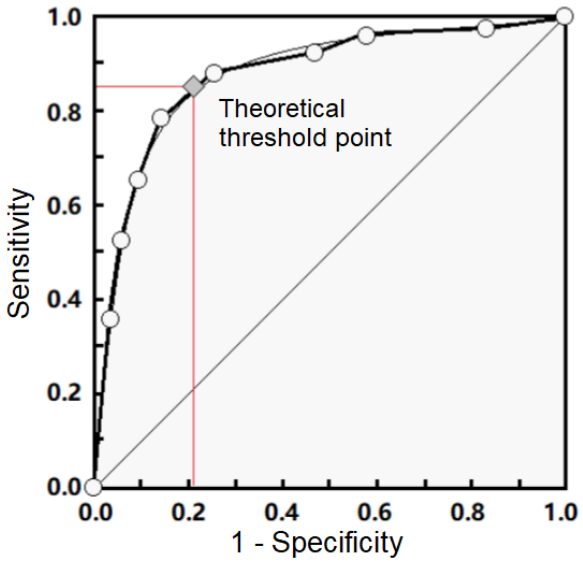

Figure 2. Differential ROC curve of 3.0T magnetic resonance 3D-ASL technology in patients with recurrent and pseudo-progression.

cantly higher than those of pseudo-progression ($p < 0.05$).

Discussion

Our results show that the diagnostic accuracy of 3.0T magnetic resonance 3D-ASL technology was 96.77%, and that the CBFmax/contralateral mirror area, CBFmax/contralateral white matter, and CBFmax/contralateral gray matter ratio of advanced glioblastoma recurrence patients were significantly higher than those of pseudo-progression ($p < 0.05$). The pseudo-progression of high-grade glioma after surgery mainly refers to the reactivity change of normal brain tissues in the local area after comprehensive treatment and is mainly manifested as an inflammatory reaction and necrotic tissue[5].

During the course of postoperative chemoradiation, the incidence of reactivity change in normal brain tissue in the affected area is increased by drug therapy, and the response degree will be more obvious, leading to clinical symptoms similar to postoperative recurrence. Both recurrence and pseudo-progression can be found under routine MRI examination as enlarged lesion extent or abnormal enhancement in the lesion area, resulting in difficult clinical differentiation. The pathological basis of the recurrence of glioma is different from that of pseudo-progression, so in clinical treatment, the treatment principles and plans are completely different. If there is a misjudgment, the timely treatment of recurrent patients will be delayed, and the survival rate and quality of life will be reduced.

Although surgical pathological diagnosis has been taken as the "gold standard" to distinguish between recurrence and pseudo-progression, this method belongs to invasive examination, which

Table I. Genotypes distribution and association with different risk factors.

Examination method	Number of patients	Recurrence of high-grade glioma	Pseudo-progression
Pathology	50	31 (62.00)	19 (38.00)
3.0-T MR 3D-ASL technique	50	30 (60.00)	20 (40.00)
χ^2	--	0.04	
p	--	> 0.05	

"*p*" in bold indicates a statistically significant difference.

Table II. Comparison of r CBFmax ratio of patients with the recurrence of glioma and those with pseudo-progression ($\bar{x}\pm s$).

Type of patients	Number of patients	CBFmax/contralateral side mirror area	CBFmax/contralateral white matter	CBFmax/contralateral gray matter
Recurrence	31	2.75 ± 0.48	3.42 ± 0.71	2.09 ± 0.36
Pseudoprogression	19	0.93 ± 0.21	1.18 ± 0.30	0.81 ± 0.19
t	--	15.93	5.35	14.57
p	--	< 0.05	< 0.05	< 0.05

CBF: cerebral blood flow.

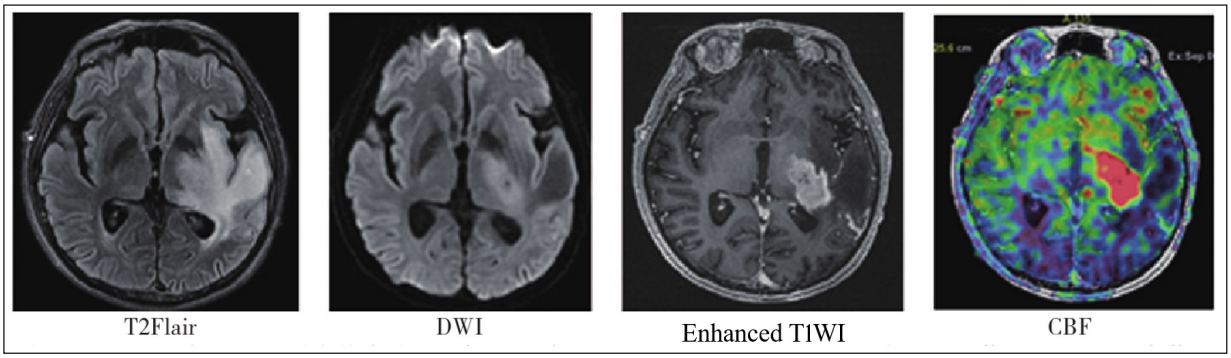

Figure 3. Imaging examination results of typical glioma cases. The patient, male, 52 years old, was confirmed by pathological results to have a recurrence of left temporal lobe glioma after comprehensive treatment. The brain tissue in the left temporal lobe and thalamus area swelled and showed long T2 signals, with slightly higher DWI signals; T1WI enhanced scan showed significant irregular large enhancement. In the 3.0T magnetic resonance 3D-ASL technique, CBF showed significant high perfusion.

will cause secondary injury to the body if the patient is pseudo-progression. In recent years, with the continuous development of functional imaging techniques, MRI perfusion imaging has been widely used in clinical disease diagnosis. The ASL technique is a type of MRI perfusion imaging that mainly uses water molecules in endogenous arterial blood as a tracer[6,7]. ASL technique can avoid allergy or damage to liver and kidney functions caused by the contrast agent, with high safety. Under this technique, the blood perfusion information of the patients can be clearly reflected so that the diagnostic physician can accurately grasp the patients' blood perfusion situation. The combination with the 3.0T MR 3D-ASL technique can make the ASL technique more reliable, obtaining more real information. A 3D volumetric acquisition can improve the signal-to-noise of ASL perfusion imaging and provide wide coverage of the whole brain, which is beneficial for

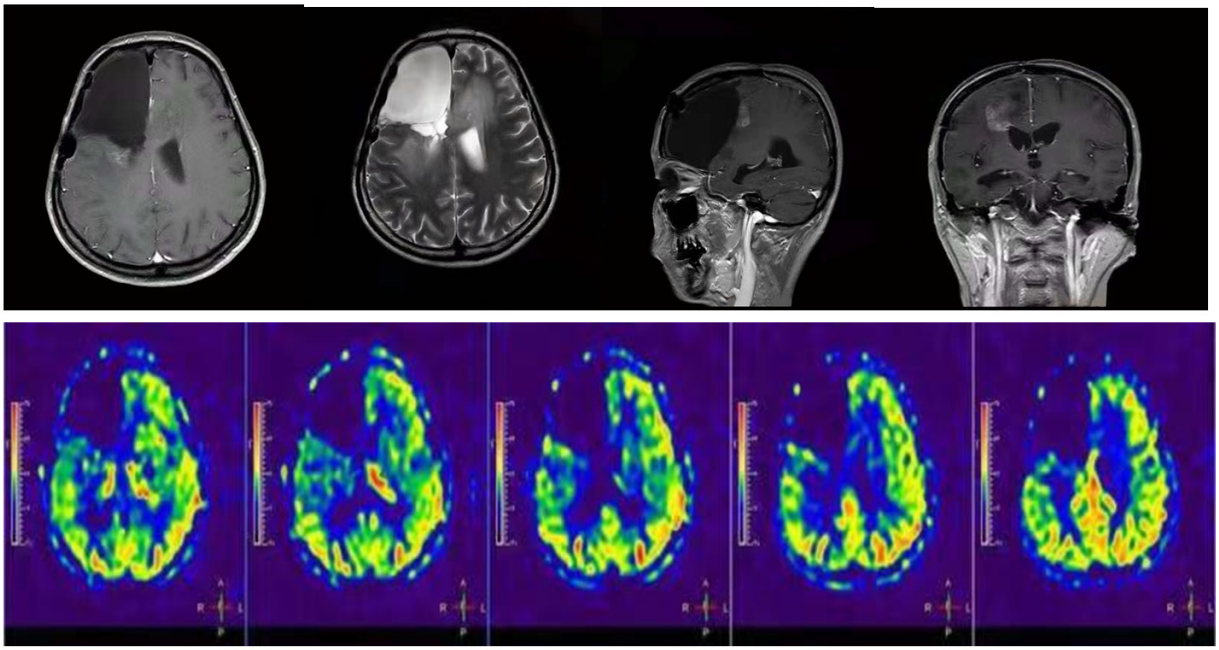

Figure 4. Imaging examination results of pseudo-recurrence cases after glioma surgery. The patient, male, 36 years old, was confirmed by pathological results to have a right frontal lobe glioma and underwent surgical resection. Within three months after using temozolomide chemotherapy, there was pseudo-progression. Irregular short T2 signals appeared in the white matter of the right frontal lobe at the surgical margin, and the enhanced scan showed significant uneven enhancement. CBF showed significant hypoperfusion in the 3.0T magnetic resonance 3D-ASL technique.

differentiating inflammatory or necrotic tissues from recurrent tumors[8]. At the same time, as a novel volumetric perfusion imaging technique, the 3.0T MR 3D-ASL technique enables whole brain 3D volumetric imaging through spiral data acquisition with high efficiency, a wide imaging scope, and spiral filling of K space. Through FSE sequence frame scanning, it can effectively make up for the magnetic sensitive artifacts of pure ASL technique, and then obtain clearer perfusion images, and improve the accuracy of differentiation between recurrence and pseudo-progression.

It breaks through various limitations of CASL and PASL in the following aspects: (1) Pseudo-continuous labeling. Based on a high fidelity and stability RF platform, pseudo-continuous labeling can be achieved, overcoming the shortcomings of low signal-to-noise ratio and perfusion bias caused by magnetization transfer effect in PASL sequences, enabling the implementation of three-dimensional whole brain volume perfusion imaging. (2) SpiralK space acquisition. Based on a high-fidelity RF platform, efficient SpiralK spatial acquisition technology is implemented, with a filling efficiency that is about 20.0% higher than EPI acquisition. It can improve the signal-to-noise ratio of the image using center oversampling in K-space. (3) FSE reading method. This reading method is not sensitive to the uneven characteristics of the magnetic field and can overcome the EPI magnetic sensitive artifacts used with PASL technology. It can better evaluate the signal-to-noise ratio of MR perfusion imaging and CASL and PASL technology, and the signal-to-noise ratio of pCASL technology is low.

This technology can break through 3D ASL technology and be more widely used in clinical practice. Among 50 glioma patients, 31 (62.00%) were diagnosed with recurrence through pathological examination, and 19 (38.00%) were diagnosed with pseudo-progression. 30 patients with recurrence (60.00%) and 20 patients with pseudo-progression (40.00%) were diagnosed using 3.0T magnetic resonance 3D-ASL technology. The diagnostic accuracy of 3.0T magnetic resonance 3D-ASL technology was 96.77% (30/31) ($p > 0.05$). Thus, it was concluded that the 3.0T MR 3D-ASL technique has a high diagnostic concordance rate in the differential diagnosis of the recurrence and pseudo-progression of high-grade glioma. Using ASL technology for perfusion imaging is safer and can more accurately reflect tissue blood flow perfusion information. Unlike previous ASL technologies, 3.0T magnetic resonance 3D-ASL technology images ensure more uniform and stable perfusion contrast, greatly improving the reliability of ASL perfusion imaging. At the same time, three-dimensional volume acquisition can improve the signal-to-noise ratio of ASL perfusion imaging, achieve large-scale whole-brain coverage, and achieve whole-brain perfusion imaging within 4.5 minutes, ensuring the detection of perfusion abnormalities.

There are relatively more parameters in MR perfusion imaging, and CBF is the most valuable parameter for tumor evaluation, which is the only common parameter for 3D ASL and DSC[9,10]. CBF can effectively evaluate the microcirculation blood flow perfusion of tissues, and there are also clinical reports on the correlation between ASL and cerebral blood flow using DSC[11]. In a previous study[12], 11 patients with brain tumors were studied, and the correlation analysis between ASL and rCBF values was completed. The results showed a positive correlation between the two methods. There are also researchers who believe that the pASL technology and DSC technology are consistent in evaluating tumor blood flow perfusion, and there is a significant correlation between the rCBF values of the two technologies, which can accurately reflect the blood flow perfusion information of gliomas, thus achieving the distinction and differentiation between high-grade glioblastoma recurrence and falsehood[13-15].

In this study, pathological results were used as the "gold standard" to analyze the parameters related to the 3.0T magnetic resonance 3D-ASL technique under different pathological results. From the results of this study, it can be seen that new blood vessels will form in the lesion area of recurrent patients, and vascular endothelial growth factor is in a high expression state; the pseudo-progression is mostly blood vessels, blood-brain barrier damage or tissue hypoxia. Therefore, the recurrence mainly showed blood flow hyperperfusion, and the pseudo-progression mainly presented ischemic hypoperfusion. 3.0T MR 3D-ASL technique mainly uses an endogenous tracer to reflect the blood perfusion information of patients more truly and accurately through the free diffusion of water molecules in arterial blood. Blood perfusion has become an important basis for this examination method to identify postoperative recurrence and pseudo-progression of patients. However, this study has some limitations. On one hand, due to the limited number of cases included in the study, further validation with a large sample size is needed in the future. On the other hand, there are certain biases in data processing and patient imaging examinations, which can easily

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lead to bias in the results of this study. Further research and exploration are needed.

To summarize, the study has the potential to improve the accuracy of diagnosing high-grade glioma by utilizing the 3.0T MR 3D-ASL technique. This advancement could help progress brain tumor imaging technology, tackle clinical challenges related to recurrence and pseudo-progression, and provide a deeper understanding of the biological aspects of high-grade gliomas.

Conclusions

The application of the 3.0T MR 3D-ASL technique in the differential diagnosis of the recurrence and pseudo-progression of high-grade glioma can accurately identify the recurrence and pseudo-progression through more realistic flow perfusion information and, then provide an accurate reference for the development of the targeted clinical intervention.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki of 1975 (as revised in 2013), and the protocol was reviewed and approved by the Institutional Review Board (or Ethics Committee) of Zhangzhou Municipal Hospital of Fujian Province, Zhangzhou Affiliated Hospital of Fujian Medical University (No. 2023LWB305).

Informed Consent

Written informed consent was provided by all the patients for permission to receive therapy and to publish this research paper.

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None.

Authors' Contributions

YC, SZ and AZ are responsible for the conception or design of the work. YC, LH, YX, YL and AZ contribute the acquisition, analysis, or interpretation of data for the work. SZ and LH provide the samples. YX and YL help in the follow-up of the patients. AZ and SC help in reviewing the histopathology slides. All authors finally approved the manuscript version to be published. AZ is the guarantor of the article.

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Data Availability

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

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