Original Article
3D-ASL combined with 3.0T MRI is helpful for preoperative grade and postoperative relapse prediction in glioma

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Abstract: Objective: To explore the diagnostic value of three-dimensional arterial spin labeling perfusion imaging (3D-ASL) combined with 3.0T magnetic resonance (MR) in preoperative grading and relapse prediction of glioma. Methods: Totally 136 patients with glioma admitted to our hospital were selected as study objects, of which 45 patients with high-grade glioma were taken as high-grade group and 23 patients with low-grade glioma were taken as low-grade group (all confirmed for the first time). In addition, there were 30 cases of high-grade glioma patients with postoperative radiation brain injury (RBI, RBI group), and 38 cases of high-grade glioma patients with relapse (relapse group). The cerebral blood flow (CBF) in the lesion area of the patients was detected by plain or enhanced 3.0T MR and 3D-ASL. The diagnostic value of 3D-ASL combined with 3.0T MR for glioma was analyzed by receiver operating characteristic curve (ROC). Results: The mean blood flow (mCBF) and relative blood flow (rCBF) in high-grade group were significantly higher than those in low-grade group. In addition, the area under the curve (AUC) of mCBF for glioma grade was 0.964, while the AUC of rCBF for glioma classification was 0.910. The average maximum relative CBF ($rCBF_{max}$) of each lesion in relapse group was remarkably higher than that in RBI group. Compared with conventional 3.0T MR plain scan + enhanced scan, the accuracy of 3D-ASL combined with conventional 3.0T MR plain scan + enhanced scan in predicting postoperative relapse and RBI was notably increased. Conclusion: 3D-ASL combined with 3.0T MR is helpful for preoperative grade and postoperative relapse prediction in glioma.

Keywords: Three-dimensional arterial spin labeling perfusion imaging, 3.0T magnetic resonance, glioma, diagnosis, preoperative grade

Introduction

Glioma is a tumor of the nervous system with high mortality and poor prognosis [1, 2]. Due to its malignant expansion and characteristics of persistent invasion and rapid growth, it is almost impossible to perform radical resection to achieve the purpose of recovery [3]. According to the World Health Organization (WHO) classification of tumors in the central nervous system, glioma can be divided into low-grade glioma (I, II) and high-grade (III, IV) glioma [4]. It is understood that high-grade glioma is not only aggressive and fatal, but also has a relapse rate of more than 85% [5, 6]. At present, the main challenges of glioma are the late stage of preoperative diagnosis and the high risk of relapse after treatment [7]. Therefore, it is still of great significance to explore tools for diagnosis and relapse predic-

tion of glioma to reduce the mortality and the relapse rate of glioma.

Magnetic resonance (MR) is a conventional imaging tool, and 3.0T is the static magnetic field strength value. Compared with 1.5T, it has greater advantages in spatial resolution and acquisition time, mainly due to the enhancement of signal-to-noise ratio [8, 9]. According to research, it has been applied in the diagnosis of neurological diseases such as cerebral arteriovenous malformation, refractory temporal lobe epilepsy, stoke, and has great application value for grasping the pathological conditions and disease classification of patients [10-12]. 3.0T MR has also been applied to the grading diagnosis of glioma, with an accuracy of 81.3%, which still needs to be improved [13]. Three-dimensional arterial spin labeling perfusion imaging (3D-ASL) is also an MR technology,

which is non-invasive and requires no contrast agent. It can be used to measure cerebral blood flow (CBF) in lesion area [14, 15]. CBF is an important index of brain function, which has the potential to evaluate radiation efficacy and can even be used to evaluate tumor grade [16, 17]. It has been reported that, based on relative cerebral blood flow (rCBF), the sensitivity and specificity of 3D-ASL were 83.2% and 77.7%, respectively [18]. Moreover, its area under the curve (AUC) was higher than that of dynamic susceptibility contrast perfusion weighted imaging (DSC-PWI)-rCBF, suggesting that the perfusion parameters of 3D-ASL have higher value in the screening of glioma classification. We speculated that the combination of 3D-ASL and 3.0T MR for diagnosis and relapse prediction of glioma patients may have greater efficacy. However, there is little research on the application of 3D-ASL combined with 3.0T MR in the diagnosis and relapse prediction of glioma. We therefore, conduct relevant research and to provide reference for the diagnosis and relapse of glioma.

Materials and methods

General data

Totally 136 patients with glioma admitted to our hospital from April 2015 to April 2020 were selected. Among them, 45 patients diagnosed with high-grade glioma for the first time were enrolled in high-grade group, and 23 patients diagnosed with low-grade glioma for the first time were enrolled in low-grade group. In addition, there were 30 patients with postoperative radiation brain injury (RBI) who were not diagnosed with high-grade glioma for the first time; all of them were enrolled in the RBI group. Thirty-eight patients who were confirmed to have relapse after secondary operation or follow-up were taken as relapse group. Among them, the low-grade group included 15 males and 8 females, aged 15-78 years old, with a mean age of (43.29±10.84) years old, with 12 WHO grade I and 11 WHO grade II. The high-grade group included 32 males and 13 females, aged 14-75 years old, with a mean age of (42.76±11.05) years old, with 15 cases of WHO III grade and 30 cases of IV grade. In addition, the RBI group included 20 males and 10 females, aged 18-70 years old, with a mean age of (44.58±10.87) years old, with 9 WHO III grade and 21 IV grade. And the relapse group

included 24 males and 14 females, aged 16-71 years, with a mean age of (45.03±11.28) years old, with 9 WHO III grade and 29 IV grade. The study was approved by the ethics committee of our hospital. The subjects and their guardians were informed and signed a fully informed consent form.

Inclusion and exclusion criteria

Inclusion criteria: Patients whose glioma was confirmed by surgery or pathology [19], patients whose pathological grading conformed to WHO standard [20], patients were followed up after operation for at least half a year, patients could receive MR or 3D-ASL examination.

Exclusion criteria: Patients were complicated with other malignant tumors, other brain diseases, or infectious diseases, patients whose pathological data or follow-up data were incomplete.

Detection methods

MR examination was performed by a 3.0T superconducting MR scanner (Huanxi Medical Devices Co., Ltd., Shanghai, China, 18679), including plain scan and enhanced scan. Conventional axial T1W1, T2W1 and FLAIR sequences were used for scanning, with a layer thickness of 5 mm and a layer spacing of 1 mm. The scanning plane was parallel to the anterior-posterior joint line of the corpus callosum, and the field of vision = 220 mm × 220 mm.

3D-ASL examination was performed by fast spin echo imaging sequence. Parameters: repetition time 4630 ms, echo time 10 ms, layer thickness 4 mm, layer number 36, matrix 96 × 96, field of view = 240 mm × 240 mm. The time interval between acquisition and marking was 1.5 ms and 2.0 ms, respectively. The delayed scanning time after marking was 1.5 ms, 2.0 ms and 2.5 ms, respectively. The excitation number was 3, and the scanning time was 4 min 24 s.

Outcome measures

For low-grade group and high-grade group, CBF in lesion area was measured three times by two researchers to calculate mean blood flow (mCBF), and relative blood flow (rCBF) was calculated for contralateral mirror image area (M). rCBF = M-CBF/contralateral normal tissue CBF.

Table 1. General data of patients in the low-grade group and the high-grade group [n (%), mean ± SD]

Factors	n	Low-grade group (n = 23)	High-grade group (n = 45)	χ^2/t	P
Gender				0.248	0.619
Male	47	15 (65.22)	32 (71.11)		
Female	21	8 (34.78)	13 (28.89)		
Mean age (year)	68	43.29±10.84	42.76±11.05	0.188	0.851
WHO grade				68.000	< 0.001
Grade I	12	12 (52.17)	-		
Grade II	11	11 (47.83)	-		
Grade III	15	-	15 (33.33)		
Grade IV	30	-	30 (66.67)		

Table 2. General data of patients in the RBI group and the relapse group [n (%), mean ± SD]

Factor	n	RBI group (n = 30)	Relapse group (n = 38)	χ^2/t	P
Gender				0.090	0.764
Male	117	20 (62.63)	24 (68.75)		
Female	62	10 (37.37)	14 (31.25)		
Mean age (year)	179	44.58±10.87	45.03±11.28	0.166	0.869
WHO grade				0.344	0.558
Grade I	-	-	-		
Grade II	-	-	-		
Grade III	18	9 (30.00)	9 (23.68)		
Grade IV	50	21 (70.00)	29 (76.32)		

For relapse group and RBI group, measurement was carried out in combination with MR scanning. The maximum blood flow irrigation area of lesion parenchyma, contralateral gray matter (G), contralateral white matter (W) and M were measured at the maximum level of lesion for 3 times and averaged. In order to eliminate individual differences, we standardized the lesion maximum CBF (CBF_{max}), and the obtained value was the lesion average maximum relative CBF ($rCBF_{max}$), i.e. $G\text{-}rCBF_{max} = G\text{-}mCBF/CBF_{max}$, $W\text{-}rCBF_{max} = W\text{-}mCBF/CBF_{max}$, $M\text{-}rCBF_{max} = M\text{-}mCBF/CBF_{max}$.

Statistical analysis

SPSS20.0 (Beijing, China) was used for statistical analysis, and Graphpad Prism6 (Graphpad Software, San Diego, USA) was used to generate pictures. The counting data were expressed by the number of cases/percentage [n (%)], the measurement data were expressed by mean ±

SD, and the data difference was analyzed by chi-square test, independent sample t test, etc. Receiver operating characteristic curve (ROC) was used to evaluate the diagnostic value of mCBF and rCBF in differentiating preoperative grade of glioma. *P* < 0.05 was considered to be statistically different.

Results

General data of patients with glioma

We compared the general data of glioma patients in the low-grade and high-grade groups and those in the RBI and recurrent groups, respectively. The results showed that there was no significant difference in gender, mean age (*P* > 0.05), and significant difference in WHO grade (*P* < 0.05) between the low-grade group and the high-grade group of glioma patients. On the other hand, there was no significant difference between the RBI and relapse groups in terms of gender, mean age, and WHO grade (*P* > 0.05). See **Tables 1**, **2** for details.

mCBF and rCBF of high-grade group are remarkably higher than those of low-grade group

In our study, mCBF and rCBF of the low-grade group were (30.25±12.14) ml/(min·100 g), (72.10±44.87) ml/(min·100 g), respectively, while those of the high-grade group were (81.74±31.59) ml/(min·100 g), (161.67±63.89) ml/(min·100 g), respectively. The two of the high-grade group were remarkably higher than those of the low-grade group. As shown in **Figure 1**.

mCBF and rCBF have higher sensitivity and specificity in differentiating preoperative grade of glioma

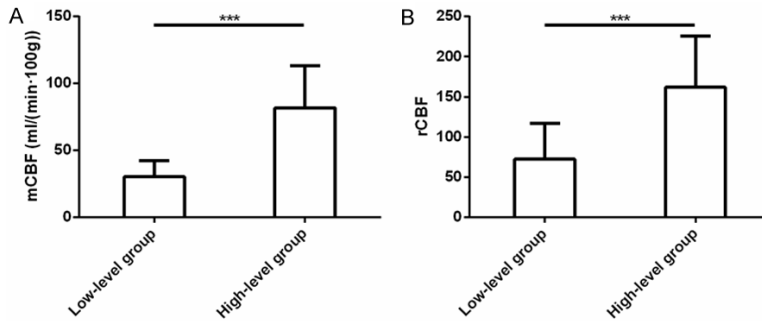In order to explore the diagnostic value of mCBF and rCBF in differentiating preoperative grade

Figure 1. mCBF and rCBF levels in different grades of glioma. A. mCBF in high-grade group was significantly higher than that in low-grade group. B. rCBF in high-grade group was significantly higher than that in low-grade group. Notes: *** represents comparison between the two groups, $P < 0.001$.
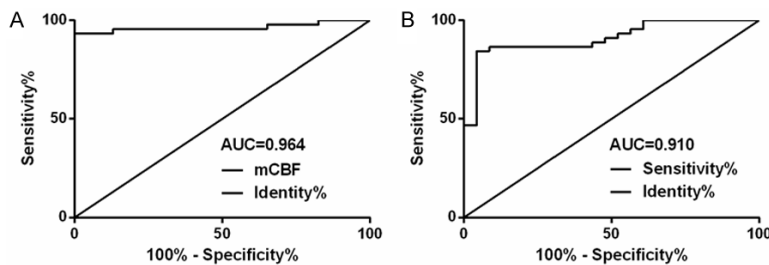

Figure 2. ROC curve of mCBF and rCBF in differentiating preoperative grade of glioma. A. The AUC of mCBF in differentiating preoperative grade of glioma was 0.964. B. The AUC of rCBF in differentiating preoperative grade of glioma was 0.910.

of glioma, ROC curves were drawn to distinguish low grade from high grade of glioma. The results showed that the area under the curve (AUC) of mCBF in differentiating preoperative grade of glioma was 0.964, with sensitivity of 93.33%, specificity of 100.00%, and the optimal cut-off value of 45.96 ml/(min·100 g). The AUC of rCBF in differentiating preoperative grade of glioma was 0.910, with sensitivity of 84.44%, specificity of 95.65%, and the optimal cut-off value of 128.50. As shown in **Figure 2** and **Table 3**.

rCBF in relapse group is significantly higher than that in RBI group

In order to understand the difference of rCBF between relapse group and RBI group, we compared $G\text{-rCBF}_{max}$, $W\text{-rCBF}_{max}$, and $M\text{-rCBF}_{max}$ of two groups. The results showed that $G\text{-rCBF}_{max}$, $W\text{-rCBF}_{max}$, $M\text{-rCBF}_{max}$ in relapse group were notably higher than those in RBI group. As shown in **Figure 3**.

3D-ASL combined with 3.0T MR has high accuracy in predicting postoperative relapse and RBI of high-grade glioma

In order to explore the value of diagnostic methods in predicting postoperative relapse of high-grade glioma, we evaluated the diagnostic performance of 3.0T MR plain scan + enhanced scan and 3D-ASL combined with 3.0 T MR plain scan + enhanced scan in this respect. The results showed that the prediction coincidence rate of the former one for RBI was 40.00%, the prediction coincidence rate for relapse was 89.47%, and the total coincidence rate was 67.65%. As for the latter one, its predictive coincidence rate for RBI was 96.67%, the predictive coincidence rate for relapse was 95.59%, and the total coincidence rate was 95.59%. The coincidence rate of 3D-ASL combined with 3.0T MR for predicting postoperative RBI and RBI with relapse was evidently higher than 3.0T MR. As shown in **Table 4**.

Discussion

Glioma is a kind of primary brain tumor and is common in adults. Accurate classification of glioma is helpful for optimization of treatment strategies and for prognosis evaluation [21]. Although more and more prognostic factors of glioma, including surgical resection scope and treatment mode, have been identified, the clinical outcomes of glioma are still diversified [22]. Therefore, it is of positive significance to improve the clinical outcomes of patients with glioma to further explore the prediction and evaluation methods such as classification and relapse of glioma and their prediction values.

As a relatively mature imaging tool, 3.0T MR has been applied in guiding tumor classification, histological biopsy and other medical areas, but its sensitivity and specificity for dif-

Table 3. ROC parameters of mCBF and rCBF in differentiating preoperative grade of glioma

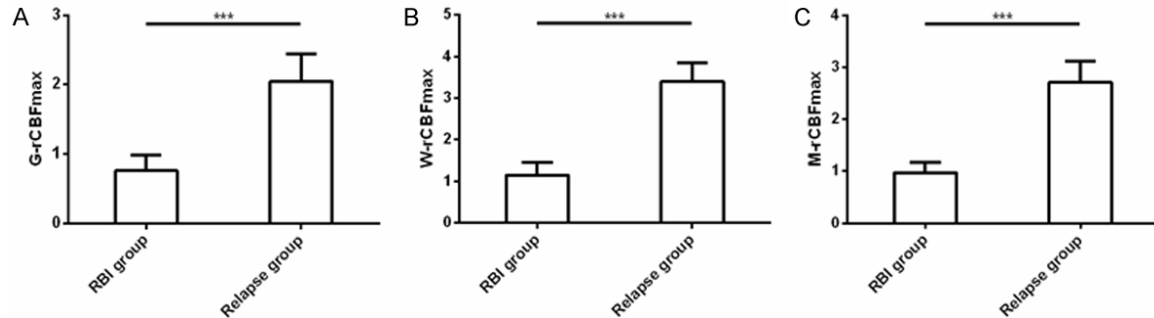| Parameters	AUC	95% CI	Standard error	Cut-off value	Sensitivity (%)	Specificity (%)
mCBF	0.964	0.918-1.010	0.024	45.96 ml/(min·100 g)	93.33	100.00
rCBF	0.910	0.840-0.981	0.036	128.50	84.44	95.65

Figure 3. Comparison of rCBF between relapse group and RBI group. A. G-rCBF$_{max}$ in relapse group was significantly higher than that in RBI group. B. W-rCBF$_{max}$ in relapse group was significantly higher than that in RBI group. C. M-rCBF$_{max}$ in relapse group was significantly higher than that in RBI group. Notes: *** represents comparison between the two groups, $P < 0.001$.

Table 4. The diagnostic value of 3D-ASL combined with 3.0T MR for postoperative relapse of high-grade glioma

Diagnostic method	RBI		Relapse		Total coincidence rate (%)
	n	Coincidence rate	n	Coincidence rate	
3.0T MR plain scan + enhanced scan	30	12 (40.00)	38	34 (89.47)	46 (67.65)
3D-ASL+3.0T MR plain scan + enhanced scan	30	29 (96.67)	38	36 (94.74)	65 (95.59)
t/χ^2 value		22.259		0.724	17.692
P value		< 0.001		0.395	< 0.001

ferentiating glioma classification cannot be balanced [13, 23, 24]. 3D-ASL is an upgraded MR perfusion technique, which can also be used to evaluate the formation of brain tumor vessels. Arterial blood near the brain is used as endogenous contrast agent without exogenous contrast agent, which is ideal for long-term survival and follow-up of glioma patients [25, 26]. Although DSC-PWI is also a perfusion weighted imaging technology, its operation process requires rapid intravenous injection of exogenous paramagnetic contrast media to obtain local brain information. While 3D-ASL uses endogenous contrast media, which can accurately reflect the microcirculation of glioma, so that the grade of glioma can be evaluated more comprehensively and safely [18]. In addition, it can also be used for qualitative diagnosis of glioma grading, but as a screening tool alone, tumor grading may be overestimated or underestimated [27], therefore, its combination with

3.0T MR may be a better choice. In this study, we first explored the levels of mCBF and rCBF detected by 3.0T MR combined with 3D-ASL in different brain glioma grades, and their diagnostic value in differentiating brain glioma grades. The results showed that the high-grade group had higher levels of mCBF and rCBF than the low-grade group, suggesting that these two indicators may be helpful to indicate the classification of glioma. Previous studies have reported that CBF index detected by 3.0T MR combined with 3D-ASL is also an independent risk factor affecting the overall survival of patients with different glioma grades, and has a significant positive correlation with vascular endothelial growth factor in patients with low-grade or high-grade glioma [28]. Further analysis of the diagnostic value of these two indicators showed that the AUC of mCBF for distinguishing glioma classification was as high as 0.964, the optimal cut-off value was 45.96 ml/

(min·100 g), and the sensitivity and specificity were not less than 90.00%. The AUC of rCBF for distinguishing glioma grade was 0.910, the optimal cut-off value was 128.50, and the sensitivity and specificity were not lower than 80.00%. The results above indicated that both mCBF and rCBF detected under 3.0T MR combined with 3D-ASL have higher value in distinguishing glioma grade, and the diagnostic value of mCBF may be greater.

Then, we also analyzed the level of $rCBF_{max}$ of each lesion detected by 3.0T MR combined with 3D-ASL in the relapse group and the RBI group and its predictive value for glioma relapse. RBI is a common complication of high-grade glioma patients after conventional radiotherapy, and relapse is also a common prognosis result. Prognostic prediction of RBI or relapse for high-grade glioma patients is important to improve patient management [29, 30]. Our data showed that compared with the RBI group, $G\text{-}rCBF_{max}$, $W\text{-}rCBF_{max}$ and $M\text{-}rCBF_{max}$ in the relapse group were significantly increased, which indicates that the above three indicators may have certain potential for predicting glioma relapse. Finally, we compared the coincidence rates of different diagnostic methods for predicting the relapse of high-grade glioma and RBI. The results showed that the coincidence rates of 3D-ASL combined with conventional 3.0T MR plain scan + enhanced scan prediction of postoperative RBI and RBI with relapse were significantly higher than conventional 3.0T MR plain scan + enhanced scan, suggesting that 3D-ASL combined with 3.0T MR has higher application value for predicting the relapse and RBI of high-grade glioma, and is reliable and more accurate. In the study of Ye et al. [31], it is pointed out that 3D-ASL is an accurate predictor of recurrent and RBI for glioma patients, and is superior to dynamic sensitivity contrast-weighted perfusion MR scanning, which has a certain similarity with our research results.

Although our study confirmed that the combination of 3.0T MR and 3D-ASL can be applied to preoperative grading diagnosis, postoperative relapse and RBI prediction of glioma, there is still room for improvement. First, we can increase the ROC curve for $G\text{-}rCBF_{max}$, $W\text{-}rCBF_{max}$, $M\text{-}rCBF_{max}$ and other indicators to distinguish high-grade glioma relapse from RBI, and fur-

ther quantify the diagnostic value of the above indicators. Secondly, we can increase the correlation between CBF and pathological parameters of glioma patients, which may be helpful to expand its predictive potential for pathological parameters of glioma patients. In the future, we will gradually make the research more complete based on the above improvement space.

To sum up, 3D-ASL combined with 3.0T MRI is helpful for preoperative grading and prediction of postoperative relapse and RBI in glioma, which has certain clinical application value and is worthy of clinical promotion.

Disclosure of conflict of interest

None.

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