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Original Article

Diagnostic value of 3D-ASL in radiation-induced injuries and recurrence after glioma surgery

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Abstract: Objective: The aim of this study was to investigate the clinical significance of three-dimensional arterial spin labeling (3D-ASL) in differential diagnosis of radiation-induced brain injuries and disease recurrence after glioma surgery. Methods: A total of 56 patients clinically diagnosed with gliomas, undergoing radiotherapy in Guizhou Provincial People's Hospital, from March 2015 to October 2017, were selected. Retrospective and relevant statistical analyses were conducted for follow up results and perfusion parameters. Receiver operating characteristic (ROC) curve was adopted to measure the relative cerebral blood flow (rCBF) value in distinguishing radiation-induced brain injuries and disease recurrence after glioma surgery. Results: Among 56 patients, 30 were diagnosed with recurrent gliomas while 26 had radiation-induced brain injuries. rCBF values of the glioma recurrence group were 2.64 ± 0.16, while values of the radiation-induced brain injury group were 1.23 ± 0.11. Differences between the two groups were statistically significant. ROC curves manifested that the sensitivity and specificity of rCBF in identifying radiation-induced brain injury were 85.7% and 73.7%, respectively. Those in identifying disease recurrence were 83.3% and 79.2%. Area under ROC curve was 0.808 and 0.799, respectively, displaying statistically significant differences (all $P < 0.05$). Conclusion: 3D-ASL has important clinical significance in the diagnosis and identification of recurrent gliomas and radiation-induced brain injuries.

Keywords: Three-dimensional arterial spin labeling, after glioma surgery, radiation-induced brain injury, recurrence

Introduction

Gliomas are the most common primary brain tumors in adults, with high incidence rates [1]. At the same time, they are characterized by invasive growth. Due to this characteristic, it is hard to completely remove them via surgery and they easily recur after surgery. Therefore, most patients resort to postoperative adjuvant radiotherapy or chemotherapy to prolong survival [2]. However, in addition to killing residual tumor cells, radiotherapy can also cause normal brain tissue damage and necrosis [3]. In recent years, with the popularization of 3.0T high-field magnetic resonance imaging (MRI) apparatus, three-dimensional arterial spin labeling (3D-ASL), a non-invasive and non-contrast agent-enhanced magnetic resonance perfusion imaging technique, has been widely employed in clinical and scientific research [4, 5]. It can quantitatively analyze changes of hemodynamic parameters, such as cerebral blood flow (CBF), to achieve the diagnosis of cerebrovascular diseases and brain tumors. The technique has unique advantages in treatment and prognosis. However, little is known about the application of 3D-ASL perfusion imaging regarding the study of radiation-induced brain injury and disease recurrence after glioma surgery. In this study, 3D-ASL perfusion parameters were analyzed to further explore the 3D-ASL technique in distinguishing radiation-induced brain injury from disease recurrence.

Materials and methods

Clinical data

In this study, complete data of 56 patients with gliomas, admitted to Guizhou Provincial People's Hospital, from March 2015 to October 2017, were retrospectively analyzed. Among them, 34 were males and 22 were females, aged 17-68 years old, with an average age of (38.82 ± 14.67) years old.

Table 1. Comparison of general data between the two groups

	Recurrence group	Injury group	Statistical magnitude	P
Gender			X^2 = 2.336	0.126
Male	21	13		
Female	9	13		
Age (years old)	36.95 ± 2.67	40.97 ± 2.88	t = -1.021	0.312
Radiotherapy method			X^2 = 0.678	0.410
Whole skull	14	15		
Part of the skull	16	11		
Tumor diameter (cm)			X^2 = 0.137	0.712
< 5	17	16		
≥ 5	13	10		
Preoperative edema			X^2 = 0.042	0.838
Yes	20	18		
No	10	8		
Radiation dose (Gy)			X^2 = 0.663	0.197
< 20	19	12		
≥ 20	11	14		

Inclusion criteria: 1) Patients histologically confirmed with gliomas after surgery; 2) Patients received radiotherapy at the radiation dose of 10-40 Gy after surgery, with 1-31 months of follow up; and 3) Patients had complete MRI, 3D-ASL perfusion imaging, and related data.

Exclusion criteria: 1) Females in the lactation or gestation period; 2) Patients suffering from chronic diseases of the heart, liver, kidneys, etc.; 3) Patients tolerant to radiotherapy; and 4) Patients having dizziness, headaches, nausea, hemiplegia, epilepsy, disturbance of cognition and consciousness, or other various non-specific symptoms.

This study was approved by the Ethics Committee of the Guizhou Provincial People's Hospital. All patients voluntarily participating in this study signed informed consent.

Parameter detection

Routine MRI scanning parameters: sagittal T_2-weighted image (T_2WI) (fast recovery fast spin echo sequence): repetition time (TR): 3,260.0 ms, echo time (TE): 93.0 ms, layer thickness: 4.8 mm, interval between layers: 0.9 mm, matrix: 384.0 * 384.0, field of view (FOV): 24.0 * 24.0, and number of excitations: 2; T_1-weighted-fluid-attenuated inversion recovery (T_1-FLAIR) sequence (axial T_1WI): TR: 1,750.0 ms, TE: 25.0 ms, and time for inversion (TI): 780.0 ms; fast spin echosequence (axial T_2WI): TR: 4,257.0 ms, and TE: 103.8 ms; axial T_2-FLAIR: TR: 8,400.0 ms, TE: 148.5 ms, TI: 2,100.0 ms, layer thickness: 4.8 mm, interval between layers: 0.9 mm, matrix: 512.0 * 256.0, FOV: 24.0 * 24.0, and number of excitations: 1.

3D-ASL scanning parameters: TR: 4,630.0 ms, TE: 10.5 ms, TI: 1,525.0 ms, matrix: 512.0 * 8.0, layer thickness: 4.0 mm, FOV: 24.0 * 24.0 cm, scanning time: 5 minutes, the number of scanned layers: 40, and number of excitations: 3.

To ensure image quality, the mean-field process was adopted before scanning. The whole brain was selected as the scanning range. Enhanced T_1WI scanning parameters: axial T_1WI: TR: 7.9 ms, TE: 2.9 ms, TI: 450.0 ms, layer thickness: 1.0 mm, and matrix; FOV and number of excitations were the same as the MRI.

Image processing and analysis

Collected raw data were uploaded to a workstation (GEADW 4.6). Post-processing was performed using FuncTool software to obtain CBF, fuse the ASL reconstructed images with conventional MRI images, and measure CBF values at lesion sites and contralateral mirror image sites, respectively. Measurements were repeated three times at each site, taking the average. The region of interest was placed away from large blood vessels, obvious artifact areas, and hemorrhage and cyst sites using the hotspot method. Relative CBF (rCBF) was calculated via the formula (rCBF = $CBF_{real\ image}/CBF_{mirror\ image}$). 0.9 ≤ rCBF ≤ 1.1 indicated normal perfusion, rCBF > 1.1 indicated high perfusion, and rCBF < 0.9 indicated hypoperfusion. 3D-ASL CBF perfusion in two types of patients was analyzed, based on which values of 3D-ASL, in distinguishing radiation-induced injury from disease recurrence after glioma surgery, were observed and summarized in combination with conventional MRI images.

Table 2. Comparison of rCBF in patients after glioma surgery between the injury group and recurrence group

Group	rCBF	Z	P
Injury group (n = 26)	1.23 ± 0.11	-5.373	< 0.01
Recurrence group (n = 30)	2.64 ± 0.16		

Note: rCBF, relative cerebral blood flow.

Statistical analysis

SPSS 20.0 analysis software was utilized. Measurement data are expressed as mean ± standard deviation ($\overline{x}$ ± sd). Data in line with the normal distribution were detected using t-tests, while those not conforming to normal distribution were examined via Mann-Whitney U-tests. X^2 tests were conducted for count data. ROC curve was applied to obtain area under the curve, cut-off values, and diagnostic sensitivity and specificity. Inspection level α = 0.05. P < 0.05 indicated that differences were statistically significant.

Results

General data

A total of 56 patients with gliomas, undergoing radiotherapy, were selected. Median follow up time was 632 days. Pathological sections confirmed that 30 cases suffered from recurrent gliomas while 26 cases endured radiation-induced injuries. Data of patients were compared between the recurrence group and injury group. Results demonstrated that there were no statistically significant differences in gender, age, radiotherapy method, tumor diameter, preoperative edema, and radiation dose between the two groups (all P > 0.05). These data were comparable (**Table 1**).

Comparison of rCBF in patients after glioma surgery between the injury group and recurrence group

According to the rCBF calculation formula, rCBF values of patients in the postoperative injury group were 1.23 ± 0.11, while values in the recurrence group were 2.64 ± 0.16. Comparisons, using Mann-Whitney U-tests, manifested that rCBF values in the recurrence group were higher than radiation-induced brain injury group, displaying statistically significant differences (P < 0.01). See **Table 2**.

MRI and 3D-ASL results of radiation-induced brain injury and disease recurrence after glioma surgery

Increased CBF perfusion was manifested in 30 cases with recurrent gliomas and 26 patients with radiation-induced brain injuries (**Figure 1**).

ROC curve analysis of values of rCBF in the diagnosis of recurrent gliomas and radiation-induced brain injuries

The status of patients, with recurrent gliomas and radiation-induced injuries after glioma surgery, was considered as an outcome indicator. Patient conditions were analyzed according to rCBF values. Critical value of rCBF in the injury group was 1.445, with sensitivity and specificity of 85.7% and 73.7%, respectively. In the recurrence group, critical value of rCBF was 3.110, with sensitivity and specificity of 83.3% and 79.2%, respectively. Areas under the ROC curve in the injury group and the recurrence group were 0.808 and 0.799, respectively, and all differences were statistically significant (all P < 0.05). See **Figure 2** and **Table 3**.

Discussion

The incidence rates of gliomas are high. Most of them have invasive growth without obvious borders. They are difficult to remove, completely, by routine surgery and local recurrence is one of the crucial reasons leading to surgical failure [6-8]. At present, adjuvant radiotherapy for postoperative glioma patients can control the recurrence rate of the disease, to some extent, in clinical practice [9]. However, complications, such as radiation-induced brain injury, often occur after radiotherapy. There are no differences in the clinical manifestations between radiation-induced brain injuries and disease recurrence, thus, it is difficult to distinguish them by routine examination [10].

3D-ASL is a technique that can quantitatively evaluate CBF perfusion in the brain. At the same time, this technique has advantages such as adequate background suppression, efficient data collection, high signal-to-noise ratio, and accurate quantitative analysis. 3D-ASL does not require intravenous injection of contrast agents and there is no ionizing radiation generated during the inspection process, greatly protecting patient health [11]. At pres-

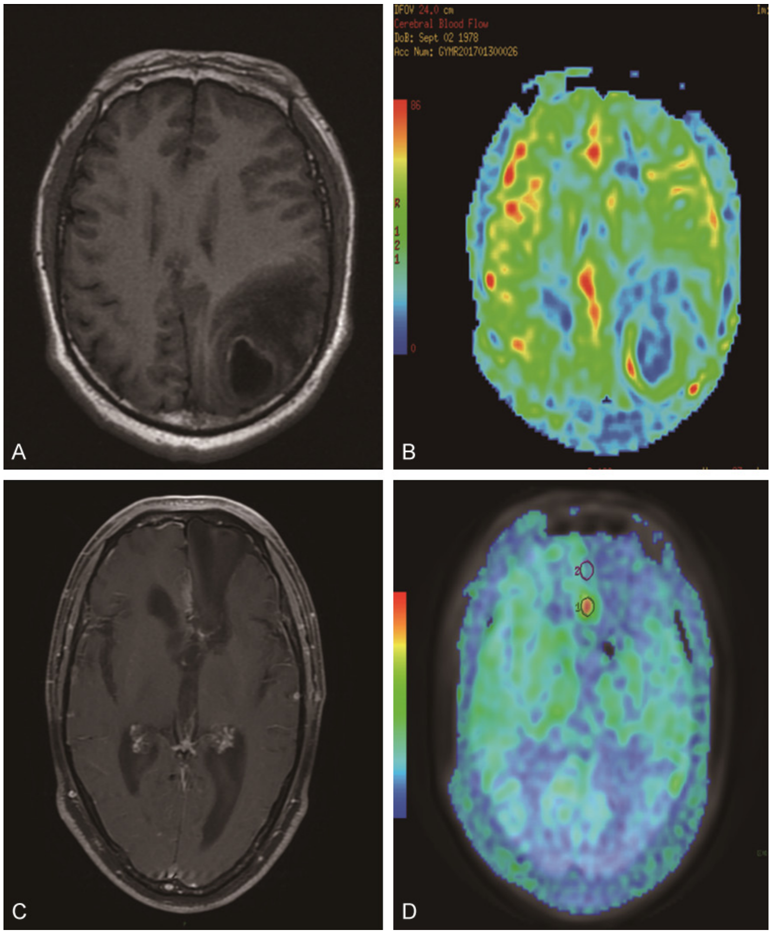

Figure 1. MRI and 3D-ASL results of disease recurrence and radiation-induced injury after glioma injury. A: A male patient aged 44 years old was diagnosed with recurrent gliomas confirmed by the follow-up and enhanced T_2WI indicates obvious linear intensification in lesions. B: 3D-ASL CBF false-color images display the hyper-perfusion zone corresponds to the enhancement zone (rCBF = 1.25). C: A female patient aged 39 years old is confirmed to be radioactively damaged by the follow up and enhanced T_1WI indicates annular anomalous intensification in the enhanced rear edge. D: 3D-ASL CBF false-color images manifest weak intensification around the lesion sites after enhancement, and that the intensification range was small. Marker 1 shows the site of radiation-induced injury, and Marker 2 is the control point. MRI, magnetic resonance imaging; 3D-ASL, three-dimensional arterial spin labeling; T_2WI, T_2-weighted image; rCBF, relative cerebral blood flow; T_1WI, T_1-weighted image; CBF, cerebral blood flow.

ent, there are still some limitations in application of the parameter ratio between the lesion side and normal side in distinguishing radiation-induced brain injuries from disease recurrence. If tumor lesions grow beyond the midline of the brain, reliability of the ratio of perfusion parameters will be significantly reduced. At the same time, if lesions are close to the skull base, the perfusion image displaying effects will be affected by the bones and artifacts will appear, thus, influencing observation and measurement results.

As the only parameter of 3D-ASL, CBF can reflect the amount of blood delivery and comprehensively embody single blood flow and number of blood vessels in tissues [12]. Current studies have indicated that CBF can effectively assess tissue perfusion [9, 13]. Tian et al. employed 3D-ASL to evaluate the classification and identification value of brain gliomas. Analysis of clinical and pathological data of 25 patients and comparison of rCBF values between brain white matter and gray matter manifested that the 3D-ASL technique is of great application value in identifying brain gliomas [14]. Lehmann et al. selected patients with different brain tumors and studied them using 3D-ASL and differential scanning calorimetry (DSC) techniques [15]. Their results revealed that 3D-ASL can effectively evaluate the perfusion of tumor blood flow and is in good consistency with rCBF of DSC (r = 0.97). In this present study, 3D-ASL was applied to discriminate radiation-induced injuries from disease recurrence in glioma patients after surgery. Comparison of perfusion parameters illustrated that rCBF values of patients with recurrent gliomas were significantly higher than that of patients with radiation-induced injuries, consistent with pathophysiological results of recurrent glioma. The underlying reason might be that tumor tissues have abundant blood vessels that provide nutritional support for the continuous growth and metabolism of tumor tissues [16]. After radiotherapy, a series of pathological changes occur in brain tissue of patients with radiation-induced brain injuries. Small blood vessels and endothelial cells are damaged, resulting in local tissue necrosis. Besides, the degree of blood vessel distribution is remarkably reduced, resulting in low per-

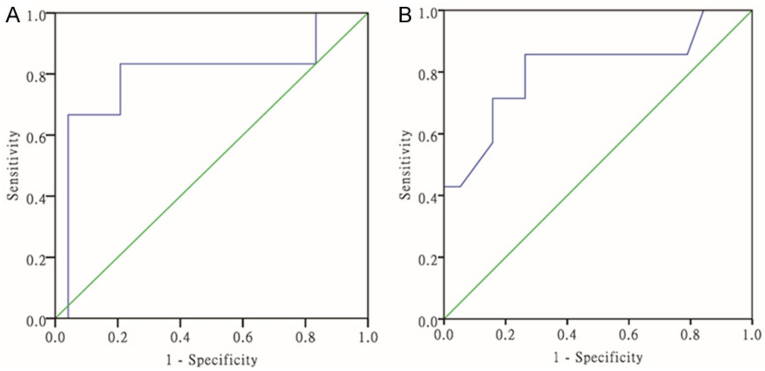

Figure 2. ROC Curve. A: ROC curve for rCBF in patients with recurrent gliomas; B: The ROC curve for rCBF in glioma patients with radiation-induced brain injury. ROC, receiver operating characteristic; rCBF, relative cerebral blood flow.

Table 3. Values of rCBF in the diagnosis of recurrent gliomas and radiation-induced brain injury

Group	AUC	AUC 95% CI	Cutoff value	Sensitivity (%)	Specificity (%)
Injury group	0.808	0.591-1.000	1.445	85.7	73.7
Recurrence group	0.799	0.553-1.000	3.110	83.3	79.2

Note: rCBF, relative cerebral blood flow.

fusion of blood flow [17]. Vascular regrowth in patients with recurrent gliomas leads to high perfusion. Therefore, it is believed that rCBF can play a certain role in distinguishing radiation-induced injuries from disease recurrence.

Late-stage radiation-induced brain injuries can give rise to severe brain necrosis, with the highest incidence rates of radiation-induced brain necrosis within one year after receiving radiotherapy [18]. This can lead to irreversible brain damage. The condition develops over time and even threatens life in severe cases [19, 20]. Conventional imaging findings of radiation-induced brain injuries are similar to recurrent tumors after radiotherapy. Clinically selected treatment options for them, however, are quite different. Therefore, it has become the focus of researchers to find an index that can effectively distinguish radiation-induced brain injuries from disease recurrence. This study explored the value of rCBF in distinguishing radiation-induced brain injuries from disease recurrence, via the ROC curve. The results evidenced that rCBF cut-off value of patients in the radiation-induced brain injury group was 1.445, with sensitivity and specificity of 85.7% and 73.7%, respectively. Area under the curve was 0.808, suggesting that the value of blood perfusion in identifying patients with radiation-induced brain injuries was higher. The rCBF cut-off value of patients in the recurrence group was 3.110, with sensitivity and specificity of 83.3% and 79.2%, respectively. Area under the curve was 0.799, suggesting that rCBF had higher identification value for disease recurrence. Therefore, it is believed that rCBF values of the 3D-ASL technique can effectively distinguish radiation-induced brain injuries from disease recurrence after glioma surgery.

In summary, the 3D-ASL technique has high reference value in distinguishing radiation-induced brain injuries and recurrent gliomas after glioma surgery. However, there were still limitations to this present study, such as the small sample size. Thus, this study cannot illustrate the overall condition. At the same time, indexes detected by 3D-ASL are relatively single and should be further confirmed based on clinical and pathological results.

Disclosure of conflict of interest

None.

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