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# The correlation between MR diffusion-weighted imaging and pathological grades on glioma

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**Abstract. – OBJECTIVE: This work intends to quantitatively analyze on pathological grade of glioma using Magnetic Resonance (MR) diffusion weighted imaging (DWI) and exploring the relativity of pathological grade and Apparent Diffusion Coefficient (ADC) value of MR diffusion weighted imaging.**

**PATIENTS AND METHODS: 40 patients with glioma accepted the MR diffusion weighted imaging to measure the ADC value of tumor with 3.0T MR machine before the surgery. Tumor samples were sent for pathologic diagnosis and tumor cell density measurement after the operation. The acquired data were analyzed statistically.**

**RESULTS: The ADC values of low-grade (WHO I-II) glioma were higher than that of high-grade (WHO III-IV), but the cell density of low-grade glioma was apparently lower than that of high-grade glioma. The ADC values and density of tumor cells were negatively correlated with WHO malignant grades, while the density of cells of glioma was positively correlated with WHO malignant grades.**

**CONCLUSIONS: MR diffusion weighted imaging is an objective and effective examination method.**

*Key Words:*
Glioma, MR diffusion weighted imaging, Pathological grade.

## Introduction

Glioma is the most common primary intracranial tumor. The comprehensive treatment measure such as operation, radiotherapy, chemotherapy, immunotherapy and biotherapy should be chosen according to pathological types and malignant grades of tumor. Thus, imaging examination is important for choosing therapy strategy and judging prognosis to determine the malignant grades of glioma before treatment. The conventional imaging examination only describes the glioma morphologically. The diagnosis is mainly made by experience and subjective decision and it is inevitable to make mistakes.

In this research, we used the 3.0T MRI system to do the Diffusion Weighted Imaging (DWI) in order to measure the Apparent Diffusion Coefficient (ADC) value precisely. We combined it with the pathological grades and density measurement of tumor cell to study quantitative MR of the glioma comparatively. This work intends to explore the relativity of the ADC value with pathological grades and density of cells to exactly assess the pathological grades of glioma. This work can offer the basis for anticipating prognosis and making treatment plans.

## Patients and Methods

### Patient Information

There were 67 cases of craniotomy glioma resection from June 2010 to June 2012. We choose 40 cases according with our research condition. 22 patients are male and 18 are female, aged 23 to 68 years old with the average age 46.5. Postoperatively, all cases were proved to be glioma by pathological method. The pathological grades were as follows: the cases were divided into two groups according to WHO criteria of central nervous system neoplasms made in 2007. The group of low grade consisted of 19 cases: 12 cases of astrocytoma (WHO II), 5 cases of oligodendroglioma, 1 case of ganglioglioma and 1 case of transparent cells ependymoma. The group of high grade (WHO III-IV) was made up of 21 cases, 9 cases of anaplastic astrocytoma (WHO III), 8 cases of glioblastoma (WHO IV), and 4 cases of anaplastic oligodendrogliomas. To avoid the errors caused by the small tumor or non-solid tumor tissue when measuring the ADC value, it was necessary to remove 27 cases of patients, because the diameter of the tumors were less than 2 cm or the tumors were mainly cystic degeneration.

### MRI Scanning

We used the Seimens Trio superconducting MR machine of 3.0T. The related scanning se-



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quence and parameters were set as follows: fast spin echo T2WI TR/TE 3020/114 ms, slice thickness 7 mm, interval 1.4 mm, matrix 202×384, FOV 169×240 mm; spin echo T1WI: TR/TE 350/8.1 ms, slice thickness 7 mm, interval 1.4 mm, matrix 202×384, FOV 169×240 mm; Flair sequence: TR/TI/TE:9000/2100/95 ms, slice thickness 7 mm, interval 1.4 mm, matrix 202×384, FOV 169×240 mm; DWI of the same level scanning, using the single-shot spin-echo echo-planar imaging (SE-EPI) sequence, TR/TE 3000/91 ms, matrix 192×192, FOV 230×230 mm, b = 0, 500, 1000 s/mm$^2$. After obtained the DWI the built-in software of the machine will reconstruct the apparent diffusion coefficient (ADC) map. Finally, we did the enhanced scanning of the same level. The contrast agent was used by gadolinium-diethylenetriamine (Gd-DTPA), 0.2 ml/kg and injected it from a periphery vein.

### Analysis of Data and Images

The obtained images were transmitted to Siemens 3.0T Trio MRI image analysis Workstation by fiber optics. The Workstation analyzed and measured the obtained images. Referring to T2WI, T1WI, Fair and weighted images of the same level (Figure 1), we chose all the levels of the tumor to measure the ADC value in the ADC map except bottom layer and top layer. This can avoid the errors. The region of interest (ROI) used the combination of quadrilateral, round, oval and random handmade graph to cover the solid part of the tumor and avoid the necrotic, liquefacient and cystic region. The ADC value of each level was the average ADC value of ROI of the same level. The ADC value of each patient was the average ADC value of all levels. Meanwhile, we measured the ADC value of the opposite normal brain tissue and cerebrospinal fluid of the same level.

### Pathological Grade and Cell Density Measurement

All the glioma specimens obtained from the operation were paraffin-embedded, sectioned and routine HE stained. Two senior pathologists used

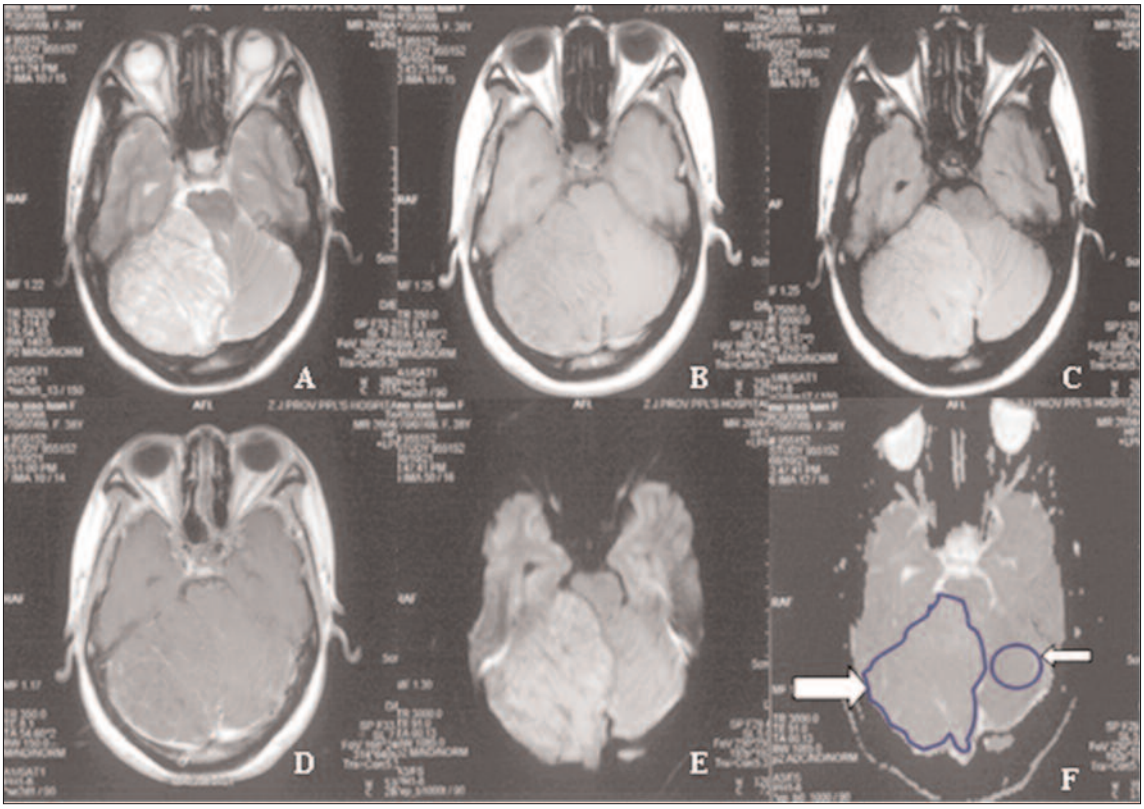


**Figure 1.** Female, 39 years old, right cerebelluar cerebral ganglioglioma. ***A,*** T2WI. ***B,*** T1WI. ***C,*** Flair. ***D,*** Gd-DTPA. ***E,*** DWI. ***F,*** ADC map. In the ADC map, the big arrow is the manual traced Irregular ROI, to cover the area of the tumor. The ADC value of the ROI is 1.203 ± 0.128 ($10^{-3}$ mm$^2$/s). The small arrow is oval ROI of the normal brain tissue. The ADC value is 0.773 ± 0.064 ($10^{-3}$ mm$^2$/s).

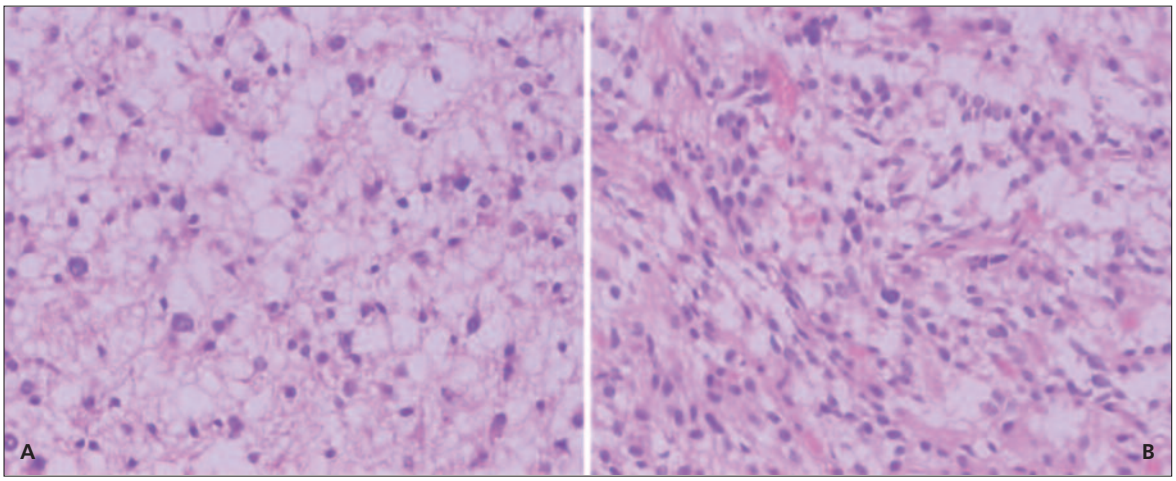


**Figure 2.** ***A,*** Astrocytoma (WHO II), cell density: 176. ***B,*** Glioblastoma (WHO-IV), cell density: 419.

the same Olympus-BX50 Optical Microscope to make definite diagnosis and grade diagnosis of glioma according to the grading criteria of the tumor about Central Nervous System made by WHO in 2007. Meanwhile, we used the Mias software Verb 4.0, a data and picture processing software, to measure the density of the tumor cell. We chose three pathological section of each patient and three typical fields of each section were chosen under the × 200 magnification microscopy. The computer measured the density of each field. Then we can get the average cell density of each glioma by 9 fields. (unit of density: the number of cells/× 200 magnification field) (Figure 2).

### Statistical Analysis

Statistic significance analysis were performed separately on the ADC value of high-grade and low-grade group of glioma compared with their ADC value of opposite normal white matter by using *t* test. The cell density of high-grade and low-grade group of glioma were also performed the same statistic significance analysis. $p < 0.05$ was used as a significant criterion. Pearson correlation analysis was performed between the ADC value and the cell density of each case. Spearman correlation analysis was performed between the ADC value and pathological grades of each case. Spearman correlation analysis was also performed between the cell density and pathological grades of each case. Relative coefficient were calculated and the results showed that there were statistical significance ($p < 0.05$). All the statistical analysis was performed by SPSS 13.0 software (SPSS Inc., Chicago, IL, USA).

## Results

DWI examination on solid part of glioma in 19 WHO I-II grade showed 11 hypointensity cases and 8 isointensity cases. ADC map showed all the cases had significant high ADC value. DWI examination on solid part of glioma in 21 WHO I-IV grade showed 14 hypointensity and 7 appeared isointensity. On the ADC map, 19 cases showed slightly high value and 2 cases appeared significant low value.

The results of *t*-test showed that the ADC values of low-grade group glioma were significantly higher than that of high-grade group glioma and normal brain tissue. And, the ADC values of high-grade group were significantly higher than that of normal brain tissue. The ADC values of three groups were significantly different with each other (Table I). Cell density of high-grade group of glioma was significantly higher than that of low-grade group of glioma. Cell density of the three groups was significantly different with each other (Table II).

**Table I.** The adc value of high-grade group, low-grade group of glioma and normal brain tissue ($10^{-3}$ $mm^2/s$).

| Pathology classification groups | Cases | ADC value |
|---|---|---|
| Low-grade group | 19 | 1.599 ± 0.237 |
| High-grade group | 21 | 1.151 ± 0.336 |
| Normal white matter | 40 | 0.738 ± 0.025 |

**t*-test in the ADC value of high-grade and low-grade groups of gliomas $p < 0.01$; ***t*-test in the ADC value of high-grade and normal brain tissue, $p < 0.01$.

**Table II.** Cell density of different pathological grade of glioma (the number of cells/× 200 magnification fields).

| Pathology classification groups | Cases | Cell density of tumor |
|---|---|---|
| Low-grade group | 19 | 242.32 ± 117.23 |
| High-grade group | 21 | 421.71 ± 149.56 |

*$t$-test in the cell density of high-grade, low-grade group of glioma, $p < 0.01$.

The scatter diagram of Pearson correlation analysis showed that there was a significant negative correlation between the ADC value and cell density of glioma (Figure 3).

The scatter diagram of Spearman correlation analysis showed that there was a negative correlation trend between the ADC value and pathological grades of glioma (Figure 4).

The scatter diagram of Spearman rank correlation analysis showed that there was a positive correlation between cell density and pathological grades of glioma (Figure 5).

The $t$-test in the rADC (relative ADC) value of high-grade group and low-grade group showed that the rADC value of high-grade group was lower than that of low-grade group and there was significant difference between the two groups (Table III).

## Discussion

Glioma is the most common primary tumor of central nervous system, accounted for 40% in intracranial tumor[1]. According to the WHO criteria, the biological effect and pathological malignancy are divided into I-IV. I-II grade are low-grade glioma, I-IV grade are high-grade glioma[2]. It was reported that the therapeutic result and prognosis of glioma largely depend on pathological malignancy of tumor[3]. The gliomas of low-grade and high-grade are significantly different in treatment strategy and prognosis[4-7]. Thus, accurate assessment of pathological malignancy on glioma before operation is important for therapeutic scheme determination. Currently, MRI is the most common and most effective non-invasive method for examination and evaluation of tumor before operation in clinical practice. But the qualitative and quantitative diagnosis (malignancy grades) of glioma by regular MRI mostly depend on position, size and the shape of tumor showed on MR map and the signal intensity of

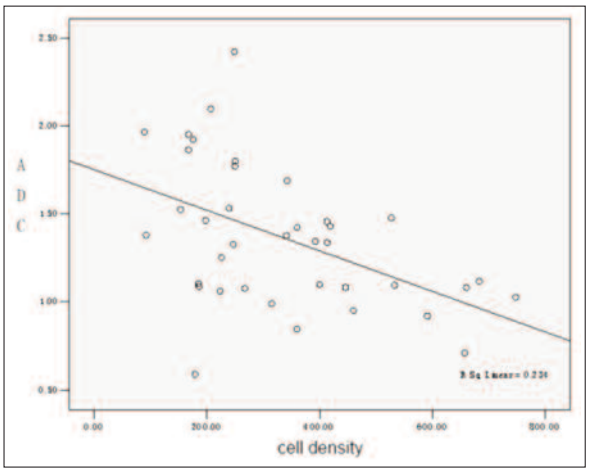


**Figure 3.** The scatter diagram of Pearson correlation Analysis showed that there was a significant negative correlation between the ADC value and cell density of glioma. Correlation Coefficient: r = -0.483, $p < 0.01$.

MR imaging. The results were influenced by the experience of diagnostician. The regular method could not avoid subjectivity and the quality of images also influenced the conclusion of the diagnostician, which likely leading to misjudgment. In this research, we analyzed MR diffusion weighted imaging of glioma and measured the ADC value of glioma. This can avoid the errors caused by experience and subjective factors to large extent, meanwhile, improving the accuracy and objectivity of glioma pathological-graded diagnosis.

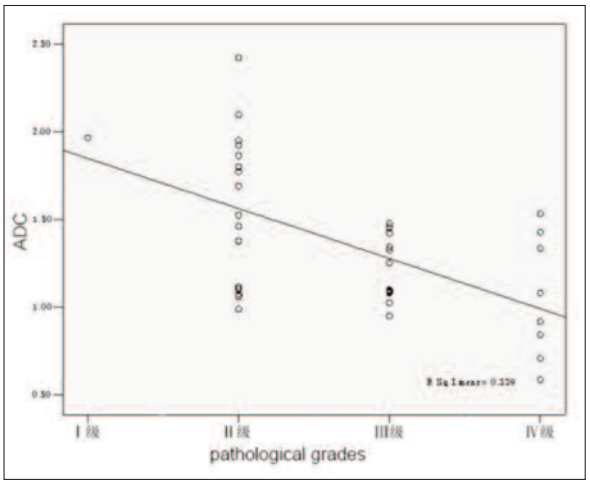


**Figure 4.** The scatter diagram of Spearman correlation analysis showed that there was a negative correlation trend between the ADC value and pathological grades of glioma, Correlation Coefficient: r = -0.560, $p < 0.01$.

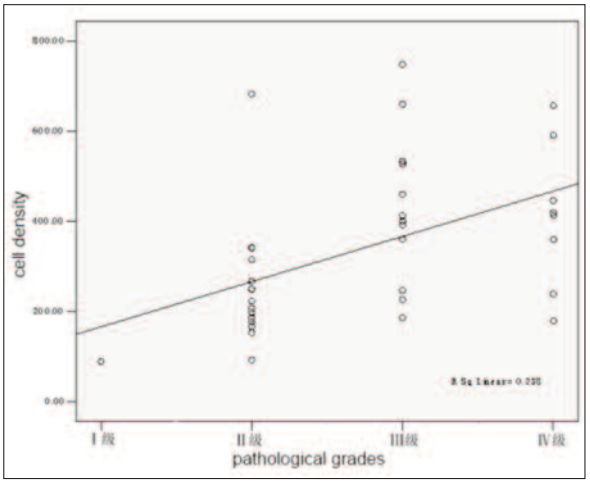


**Figure 5.** The scatter diagram of Spearman rank correlation analysis showed that there was a positive correlation between cell density and pathological grades of glioma. Correlation Coefficient: r=0.551, $p < 0.01$.

DWI is one of the many MRI imaging sequence and currently is the only method that can reflect the microscopic diffusion of free water molecules in all living organisms. Recently, DWI was successfully used in the diagnosis and differential diagnosis on brain abscess, cerebral infarction, arachnoid cyst and so on[5-9]. However, there are few reports on the ADC value of intracranial tumor and the results are different[10-12]. This work intended to evaluate the accuracy of quantitative DWI method on quantitative and qualitative diagnosis of glioma.

The water diffusion in living tissue is complex, the amount and direction of it depends on cell density of the tissue, tissue space, viscosity of medium, the water active transport by cells, capillary blood flow and even the permeability and space size of biomembrane[13,14]. The protons of DWI imaging mainly come from free water. The protons in large molecular and cell membrane are relative unease to move and T2 is short and hardly participated in diffusion weighted imaging. Thus, the free water of intercellular substance is the very important factor of diffusion weighted imaging. In the case of brain glioma, the molecular of free water diffused differently in different tissue. As a result, the difference of free water diffusion in tumor and normal tissue can be manifested by diffusion weighted imaging. And the difference of free water diffusion in tissue space of different pathological grades tumor can also be manifested by diffusion weighted imaging. These differences can be obtained by measuring the ADC value. Generally, in tumor tissue, the ADC value changes as tumor cell density. As the increase of tumor cells, volume and nucleocytoplasmic ratio, the activity space of free water will decrease and then influence the water diffusion. This will lead to the decrease of ADC value[15]. Vice versa, the ADC value will increase. The results of the research show that the ADC value and tissue cell density of glioma are negatively correlated. The other considerable factor is that diffusion of free water, which is vertical to the nerve fiber, is restricted by nerve fibers in normal brain. The diffusion of free water that is parallel to the fiber is not influenced. The tissue structure of glioma is the chaos and intensive accumulation of tumor cells. Unlike the normal brain tissue, it does not contain orderly performed nerve fibers. This will restrict the directionality of water diffusion enhancing the ability of water diffusion. The results showed that the diffusion value of free water in most glioma tissue was higher than that of normal brain. This explains why the ADC value of most glioma tissue increased.

**Table III.** The average rADC value of high-grade group and low-grade group glioma.

| Pathological classification | Cases | The average rADC value |
|---|---|---|
| Low-grade group | 19 | 2.41 ± 0.73 |
| High-grade group | 21 | 1.59 ± 0.14 |

*$t$-test in the average rADC value between two groups, $p < 0.01$.

Previous studies demonstrated that the cell density and cell composition of glioma are important factors that determine the pathological grades of glioma[16,17]. The higher cell density, the stronger the ability of invasion and metastasis on tumor cells[18]. Thus, the pathological grades are higher. This conclusion was confirmed by this research and the results showed that the cell density and pathological grades of glioma were positively correlated. The research results of Filippi et al[19], Kono et al[20] are similar to ours. The ADC value and pathological grades of glioma were negatively correlated, but their research did not explain why the ADC value differed in different pathological grades of glioma. Our research found that it is the cell density is one of the main reasons for making this difference.

## Conclusions

Our research provides one quantitatively measuring pathological injury method for the imaging diagnosis of glioma. That is to say, the definite pathological indexes of glioma can be measured by the ADC value with MRI diffusion weighted imaging. This enables the clinician diagnose the malignancy and cell proliferation of glioma by quantifying the ADC value before obtaining the pathological examination results of glioma. This method will help to making therapeutic scheme and could evaluate the therapeutic result according to the change of ADC value. By this way, adjustment of the therapeutic scheme will be will guided. And also, the development of tumor can be estimated by observing the change of ADC value in the late tumor treatment phase in order to observe prognosis and recurrence.

### Conflict of Interest

The Authors declare that there are no conflicts of interest.

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