Abstract. The present study aimed to investigate the value of diffusion-weighted imaging (DWI) combined with dynamic susceptibility contrast-enhanced (DSC) magnetic resonance imaging (MRI) scans in astrocytoma grading, and correlated MRI scan parameters of values of apparent diffusion coefficient (ADC) and relative cerebral blood volume (rCBV) with the immunohistochemical (IHC) indices of glial fibrillary acidic protein (GFAP), topoisomerase IIα (Topo IIα) and O 6-methylguanine-DNA methyltransferase (MGMT). A total of 123 patients with pathologically confirmed astrocytomas of differing grades underwent DWI and DSC scans. The values of the ADC and relative cerebral blood volume rCBV were compared with the grade II-IV astrocytomas. Receiver operating characteristic curves were used to compare astrocytoma grading efficiency of ADC, rCBV and the combination of the two values. The parameters of ADC and rCBV with GFAP, Topo IIα and MGMT indices were then correlated. The differences in ADC values were significant between the grades II, III and IV astrocytomas, and the rCBV values for grades II, III and IV were also significant. The combination of DWI and DSC demonstrated the highest values for area under curve in identifying grades II and III, and identifying grades III and IV, respectively. GFAP displayed a positive correlation with ADC and a negative correlation with rCBV. Topo IIα exhibited a negative correlation with ADC, and a positive correlation with rCBV. No correlation was observed between MGMT and ADC or rCBV. The combined application of DWI and DSC may increase astrocytoma grading accuracy. Values of ADC and rCBV exhibit certain correlations with IHC indices, and may predict degree of malignancy of astrocytoma.

Introduction

Astrocytoma is the most common type of adult primary brain tumor (1,2), and accurate grading of this tumor is critical to prepare appropriate treatment and to evaluate the prognosis of the patient. Classical histological classification and malignancy grading are based on the criteria of the 2007 World Health Organization (WHO) classification of tumors of the central nervous system (3), and astrocytoma are classified into I-IV grades; grade I-II, benign; Grade III-IV, malignant. However, for patients treated without surgery, it is not possible to obtain a pathological grade. Additionally, grades of pathological diagnosis made from surgical resection samples may be underestimated due to tumoral heterogeneity.

Functional magnetic resonance imaging (MRI) scanning technologies, such as diffusion-weighted imaging (DWI), may provide data on tumor cell density and proliferation and serve as an important supplement to conventional MRI scans such as T1-weighted image (T1WI), T2-weighted image (T2WI), T2-fluid attenuated inversion recovery (FLAIR) scans (4-8). DWI may quantify the diffusion rate of extracellular water molecules, and the limited diffusion of water molecules in high-grade astrocytoma results in a low apparent diffusion coefficient (ADC) value. In addition, the astrocytoma grade is associated with the vasculature of the tumor, and may be reflected by relative cerebral blood volume (rCBV), thus guiding astrocytoma grading (8,9).

However, functional MRI scanning technology with DWI or DSC cannot incorporate all features of astrocytomas comprehensively. A previous study demonstrated that the accuracy of DWI or dynamic susceptibility contrast-enhanced (DSC) measurements in differentiating between grades of astrocytoma exhibited unsatisfactory consequences (4). For example, DWI has been revealed to increase diagnostic accuracy of astrocytoma grade, but a singular DWI-MRI scan cannot provide sufficient quantitative data concerning tumor structure (10). Additionally, previous studies have not investigated the associations between DWI- and DSC-MRI scans and immunohistochemical (IHC) indices.

In the present study, the efficacy of the combination of DWI- and DSC-MRI scans in astrocytoma grading, and the associations between these MRI scans and the
histologic indices of glial fibrillary acidic protein (GFAP), topoisomerase IIα (Topo IIα) and O 6-methylguanine-DNA methyltransferase (MGMT) were investigated. Histologic measurement of GFAP, Topo IIα and MGMT is widely used in evaluating the levels of tumor infiltration and proliferation, and has been demonstrated to correlate with tumor grade and prognosis (11-13). The main aim of the present study was to identify the accuracy of combined diagnostic techniques in differentiating between grades II-IV astrocytoma, and to predict astrocytoma malignancy through comparing histologic measurement of levels of GFAP, Topo IIα and MGMT.

Materials and methods

Ethical considerations. The present study was approved by Shanxi Medical University review board. All manuscripts comply with the guidelines of the February 2006 consensus statement of the International Committee of Medical Journal Editors, and all patients provided written informed consent.

Patient selection. A total of 123 patients, 62 male and 61 female, with an age range between 25 and 77 years, and a mean age of 51.3±11.2 years, with histologically confirmed astrocytoma subsequent to surgical resection in The First Hospital of Shanxi Medical University between April 2010 and December 2015 were included. All patients underwent DWI, DSC and conventional MRI scans within 2 weeks prior to surgical resection. Pathological specimens were classified according to the WHO 2007 central nervous system tumor classification guidelines (3). Astrocytoma were grouped into low-grade astrocytoma, WHO grade II, 23 patients; anaplastic astrocytomas, WHO grade III, 44 patients; and glioblastoma multiforme, WHO grade IV, 56 patients.

MRI acquisition. MRI scans were performed using the General Electric (GE) SIGNA HDx 3.0 Tesla MR scanner with an 8-channel phased-array coil with a head and neck combination. All patients underwent conventional TIW1, T2WI, T2-FLAIR and DWI axial scanning, followed by DSC-MR perfusion scanning. DSC-MR perfusion images were captured by elbow vein bolus injection of gadopentetate dimeglumine (Magnevist®, Bayer Schering Pharma AG, Berlin, Germany) at a flow rate of 4.5 ml/s and a dose of 0.1 mmol/kg. Finally, conventional TIW1 enhancement scanning was performed.

The scan protocol of each conventional MRI scan included: T1WI, with a repetition time (TR)/echo time (TE) of 1677/24 ms; T2WI, with a TR/TE of 6800/105 ms; T2-FLAIR, with a TR/TE of 8002/132 ms, a thickness of 6 mm, spacing of 1.2 mm between two adjacent images, a field of view (FOV) of 240x240 mm, matrix 320x256 mm, and number of excitations (NEX)=1. DWI scans used a spin echo/echo planar imaging sequence, a TR/TE of 5.000/74 ms, a thickness of 6 mm, spacing of 1.2 mm, FOV 240x240 mm, matrix 160x160 mm, and NEX=2; the diffusion coefficient of sensitivity was selected as 0.1000 s/mm². The parameters of the DSC MRI perfusion scans were as follows: TR/TE of 1500/14.5 ms, FOV of 240x255 mm, a matrix of 128x128 mm, a flip angle of 90° and a NEX=1. The elbow intravenous bolus injections of gadopentetate dimeglumine were administered with a flow rate of 4.5 ml/s, followed by injection of normal saline at the same flow rate.

Results

Comparisons of ADC and rCBV values among grade II-IV astrocytoma. The DWI parameter value, ADC, and DSC parameter value, rCBV, of the tumoral parenchyma are illustrated in Table I. The ADC values in the grade II astrocytoma were significantly higher compared with the grade III astrocytoma (P=0.003). The rCBV values in the grade II astrocytoma were significantly lower compared with the grade III astrocytoma.
The ADC values in the grade III astrocytoma were significantly higher compared with the grade III astrocytoma (P=0.012). The rCBV values in the grade III astrocytoma were significantly lower compared with the grade IV astrocytoma (P=0.035).

The maps of the aforementioned conventional MRI scans of grade II astrocytoma are demonstrated in Fig. 1A-C. Grade II astrocytoma exhibited low signal on DWI sequence, and high ADC values, as illustrated in Fig. 1D and E. The parenchyma of grades II astrocytoma on the rCBV maps exhibited low signals, as illustrated in Fig. 1F-J demonstrate the HE staining map, IHC, GFAP map, IHC, Topo IIα map and IHC. MGMT map of grades II astrocytoma respectively. The conventional MRI scans of grade III astrocytoma are demonstrated in Fig. 2A-C. Grade III astrocytoma demonstrated high signal on DWI sequence, and the ADC values of the tumor parenchyma were lower, as illustrated in Fig. 2D and E. The parenchyma of grades III astrocytoma on the rCBV maps exhibited high signals, as illustrated in Fig. 2F-J demonstrate the HE staining map, IHC, GFAP map, IHC, Topo IIα map and IHC. MGMT map of grades III astrocytoma respectively. The grade IV astrocytoma on the rCBV map

Figure 1. Right frontal lobe low-grade astrocytoma (Grade II) in a 25-year old male. (A) The right frontal lobe lesion exhibited irregular long T1 and (B) T2 signals. (C) Axial contrast-enhanced T1 weighted image revealed no significant enhancement. (D) Lesions displayed iso-low signal on the diffusion-weighted imaging map. (E) The apparent diffusion coefficient map displayed high signal (arrow). (F) The relative cerebral blood volume value was low in the tumor parenchyma (arrow). (G) Well-differentiated tumor cells with slight nuclear atypia were exhibited on a hematoxylin and eosin staining map. (H) High expression of glial fibrillary acidic protein in the cytoplasm. (I) A limited level of expression of topoisomerase IIα in the nucleus. (J) The O 6-methylguanine-DNA methyltransferase proteins demonstrated moderate expression levels in the cytoplasm and nucleus.

Figure 2. Right frontal lobe anaplastic astrocytoma (Grade III) in a 43-year-old female patient. (A) The right frontal lobe lesion exhibited a phymatoid isointense signal on T1 and (B) T2 WI. (C) Axial contrast-enhanced T1 WI revealed mild to moderate enhancement. (D) Lesions exhibited a hyper-intense signal on diffusion-weighted imaging map. (E) The apparent diffusion coefficient map displayed low signal in the tumor parenchyma (arrow). (F) The relative cerebral blood volume value was high in the tumor parenchyma (arrow). (G) hematoxylin and eosin staining map revealed moderately differentiated tumor cells with nuclear atypia. (H) Moderate glial fibrillary acidic protein expression level in the cytoplasm. (I) Moderate expression level of topoisomerase IIα in the nucleus. (J) The O 6-methylguanine-DNA methyltransferase proteins demonstrated a low to moderate expression level in the cytoplasm and nucleus. WI, weighted image.
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Figure 3. Right occipital lobe glioblastoma multiforme (Grade IV) in a 59-year-old male. (A) The cystic wall of the right occipital lobe lesion demonstrated a iso-intense signal on T1 and (B) T2WI, and the cystic fluid was hypo-intense on T1WI and hyper-intense on T2WI. (C) Axial contrast-enhanced T1W image exhibited marked enhancement of the cystic wall. (D) The cystic wall demonstrated a hyper-intense signal on diffusion-weighted imaging map. (E) The apparent diffusion coefficient value was low in the cystic wall (arrow). (F) The relative cerebral blood volume value was highest in the cystic wall (arrow). (G) Poorly differentiated tumor cells with remarkable nuclear atypia with nucleolar enlargement and increased karyokinesis were displayed on a hematoxylin and eosin staining map. (H) Low glial fibrillary acidic protein expression level in the cytoplasm. (I) High expression level of topoisomerase IIα in the nucleus. (J) The O 6-methylguanine-DNA methyltransferase proteins displayed low expression levels in the nucleus. WI, weighted image.

Figure 4. (A) ROC analysis of DWI, DSC and combined parameters in differentiating grade II and III astrocytomas; (B) ROC analysis of DWI, DSC and combined parameters in differentiating grade III and IV astrocytomas. ROC, receiver operating characteristic; DWI, diffusion-weighted imaging; DSC, dynamic susceptibility contrast-enhanced imaging; rCBV, relative cerebral blood volume; ADC, apparent diffusion coefficient.

Table I. Comparison of DWI and DSC parameters among grade II-IV astrocytoma.

| Parameters | Grade II (n=23) | Grade III (n=44) | P-value | Grade III (n=44) | Grade IV (n=56) | P-value |
|------------|----------------|-----------------|---------|-----------------|-----------------|---------|
| ADC        | 1.299±0.294    | 0.929±0.170     | 0.003   | 0.929±0.170     | 0.790±0.176     | 0.041   |
| rCBV       | 2.552±0.705    | 5.195±1.883     | 0.012   | 5.195±1.883     | 7.070±1.721     | 0.035   |

ADC, apparent diffusion coefficient; rCBV, relative cerebral blood volume; the units for ADC was mm²/s. *Statistically significantly difference between 2 groups.

demonstrated the highest signal, as illustrated in Fig. 3F-J demonstrate the HE staining map, IHC. GFAP map, IHC. Topo IIα map and IHC. MGMT map of grades IV astrocytoma respectively.

ROC analysis of DWI, DSC and combined parameters in identifying grade II-III and III-IV astrocytoma. ROC analysis of value of ADC, value of rCBV, and the combined value of ADC and rCBV in differentiating between grades II and III
Astrocytoma was illustrated in Fig. 4A and Table II. The combined diagnostics method had the highest area under the curve (AUC), 0.958, in distinguishing between grades II and III astrocytoma, followed by rCBV, 0.913, and ADC, 0.885. ROC analysis of ADC, rCBV and the combined diagnostics method in differentiating between grades III and IV astrocytoma is demonstrated in Fig. 4B and Table II. The combined parameter had the highest AUC, 0.904, in distinguishing between grades III and IV astrocytoma, followed by rCBV, 0.889, and ADC, 0.712.

Correlations between MRI parameters and IHC indices. A positive correlation was exhibited between levels of GFAP and ADC ($r=0.574$, $P<0.001$), whilst a negative correlation was exhibited between levels of GFAP and ADC ($r=-0.574$, $P<0.001$), whilst a negative correlation was exhibited between levels of GFAP and ADC ($r=-0.574$, $P<0.001$).
demonstrated between levels of GFAP and rCBV ($r=-0.610$, $P<0.001$; Fig. 5A). A negative correlation was demonstrated between levels of Topo IIα and ADC ($r=-0.435$, $P<0.001$; Fig. 5B), and a positive correlation was exhibited between levels of Topo IIα and rCBV ($r=0.571$, $P<0.001$; Fig. 5C). No correlation was observed between levels of MGMT and ADC ($r=-0.082$, $P=0.364$ or rCBV of the astrocytoma ($r=0.024$, $P=0.790$). These correlations between the MRI parameters and the IHC indices are summarized in Table III.

**Table III. Correlation between the values of DWI/DSC and IHC parameters.**

| MRI and IHC parameters | r-value | P-value |
|------------------------|---------|---------|
| GFAP                   |         |         |
| ADC-GFAP               | 0.574   | <0.001  |
| rCBV-GFAP              | -0.610  | <0.001  |
| Topo IIα               |         |         |
| ADC-Topo IIα           | -0.435  | <0.001  |
| rCBV-Topo IIα          | 0.571   | <0.001  |
| MGMT                   |         |         |
| ADC-MGMT               | -0.082  | 0.364   |
| rCBV-MGMT              | 0.024   | 0.790   |

$P=<$DWI/DSC vs. IHC marker. IHC, immunohistochemistry; MRI, magnetic resonance imaging; GFAP, glial fibrillary acidic protein; Topo IIα, topoisomerase IIα; MGMT, O 6-methylguanine-DNA methyltransferase; ADC, apparent diffusion coefficient; rCBV, relative cerebral blood flow.

**Table II. Receiver operating characteristic analysis of diffusion-weighted imaging, dynamic susceptibility contrast-enhanced imaging and combined values in differentiating grade II-IV astrocytoma.**

| Parameters          | Grade II vs. III | Grade III vs. IV | Grade III vs. IV |
|---------------------|------------------|------------------|------------------|
| ADC                 | 0.885            | 0.712            | 0.721            |
| rCBV                | 0.913            | 0.889            | 0.904            |
| Combined value      | 0.958            | 0.983            | 0.994            |

Discussion

In the present study, the DWI and DSC parameters of different grade astrocytoma were compared and the potential of combing DWI and DSC data in astrocytoma grading was evaluated. In addition, the correlation between DWI and DSC parameters and IHC indices were examined. The results demonstrate that the ADC and rCBV data exhibited significant differences between the grades II-IV astrocytoma. Concurrently, the combined diagnostic method exhibited the highest accuracy in differentiating between grades II-IV astrocytoma. ADC and rCBV measurements demonstrated correlations with levels of GFAP and Topo IIα. No association between MRI parameters and levels of MGMT was observed.

Cells and subcellular structures limit the diffusion of water molecules (14), and ADC values can quantify this limited degree of diffusion. Thus, DWI can non-invasively assess tumor cell density (15-17). In the present study, there was a significant difference in ADC values of tumor parenchyma between grades II and III ($P<0.05$); this result is consistent with the findings of Lee et al (15), Kono et al (16) and Calli et al (18). These previous studies revealed that the ADC values of high-grade astrocytoma decreased significantly, and the DWI signal increased. Previous studies on DWI of gliomas examined the differences in ADC value between high-grade and low-grade gliomas, yet the present study explored the values of DWI in differentiating between grades II, III,
and IV astrocytoma. In the present study, the ADC value for grade IV astrocytoma was 0.790±0.176×10⁻³ mm²/s, which was lower compared with the value revealed by Stadnik et al., 1.14×10⁻³ mm²/s (19). This difference may be associated with the selection of ROI in the tumor parenchyma.

Invasiveness and tumor growth are closely associated with neovascularization (20). Therefore, utilizing a rCBV map of MR perfusion images for the description of the characteristics of astrocytoma exhibits potential that an rCBV map may be able to evaluate the degree of angiogenesis. One study suggested that DSC-MR perfusion-weighted imaging serves a major role in the identification of high- and low-grade gliomas, and the rCBV values are significantly different (6). The aforementioned study is consistent with the results reported in the present study, in which grades II and IV were compared with grade III astrocytoma, and a statistically significant difference in rCBV values was revealed. The results of the present study are different from those reported in the study by Hakyemez et al (2), in which no significant difference as observed between grades III and IV; this may be due to the correction of the rCBV value with the contralateral NAWM in the present study.

The present study focused on examining whether the combined methods of ADC and rCBV measurements may improve efficiency in astrocytoma grading. This is the first study in which the combination of DWI and DSC MRI scanning may be used as a classifying instrument in the grading of astrocytoma. The combined diagnostic method increased the diagnostic power and had the highest AUC, 0.943, and highest sensitivity, 87.5%, compared with ADC and rCBV measurements alone, and a higher specificity, 100%, compared with ADC measurements in astrocytoma grading. Through the joint application of an arterial spin labeling technique and ADC values to glioma grading, Kim et al (21) also concluded that the use of multiple techniques improves the diagnostic accuracy of gliomas, serving as an effective supplement to conventional MRI techniques. Hilario et al (22) demonstrated that the combination of minimum ADC and maximum rCBV measurements improves the diagnostic accuracy of glioma grading. However, these previous studies focus on gliomas as the type of cancer studied, which covers several types of brain tumor. There have been fewer reports investigating astrocytoma grading which apply DWI and DSC imaging. In the present study, the range was narrowed to astrocytoma from gliomas, which may provide increased precision for preoperative astrocytoma grading systems, and generate data pertinent for decisions concerning treatments.

GFAP is an intermediate filament cytoskeleton protein which is expressed specifically by the gliocyte (11). Ilhan-Mutlu et al (23) reported that a decreased GFAP expression was associated with an increasing malignancy grade in gliomas. In the present study, a significant negative correlation between GFAP and rCBV (r=-0.610, P<0.001), and a positive correlation between GFAP and ADC (r=0.574, P<0.001) was revealed. The decreased GFAP expression level correlated with the aggressiveness and malignancy of astrocytoma, whilst rCBV and ADC levels reflected the vasculature and cell density, which were associated with the malignancy of tumors, which many be potential explanations for the above correlation.

It was suggested that Topo IIα was associated with cellular proliferation (24). In the present study, it was demonstrated that Topo IIα was negatively correlated with ADC (r=-0.435, P<0.001), and positively correlated with rCBV (r=0.571, P<0.001). ADC reflects the cell density of tumor, which may explain the correlation between Topo IIα and ADC. Therefore, ADC may reveal the Topo IIα expression levels, to predict the malignancy of astrocytoma. In addition, it was revealed that rCBV also reflected the levels of Topo IIα expression (25). Further studies are required to examine the internal association between rCBV and Topo IIα expression.

MGMT promoter methylation reflects the sensitivity of chemotherapeutic drugs (temozolomide) to astrocytoma patients. The existence of an association between expression levels of MGMT protein and MGMT promoter methylation remains unknown (26). In the present study, no correlation was observed between values of ADC and rCBV and MGMT protein expression. As aforementioned, this association requires additional study.

The present study included certain limitations. Firstly, cystic-solid tumors may possess thin cystic wall tissues, and the selected ROIs of ADC or rCBV may contain a portion of normal brain parenchyma outside the cystic wall of the tumor (27). This may lead to inaccurate assessment of ADC and rCBV values to tumor cell proliferation and vascular proliferation. Secondly, pathological misdiagnosis may occur due to sampling errors caused by tumor heterogeneity, particularly for malignant astrocytoma: For example, the tumor samples may contain grades II and III astrocytoma cells. In addition, manually drawing ROIs is a tedious procedure and may incur personal error. Finally, the investigation did not involve analysis of prognoses, which should be explored in future studies.

In conclusion, the present study demonstrated that the combination of DWI and DSC measurements may improve the accuracy of astrocytoma grading. The DWI and DSC measurements which exhibit correlations with IHC indices of GFAP and Topo IIα may be useful biomarkers in predicting the levels of malignancy in astrocytoma.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

HZ proposed the notion of the present study and interpreted the patient data. JQ performed the majority of the experiments.
and was a major contributor in writing the manuscript. XWa analyzed the data and designed the figures. YT and XWu collected and managed the samples. All authors read and approved the final manuscript for publication.

Ethics approval and consent to participate

The present study was approved by Shanxi Medical University review board. All manuscripts comply with the guidelines of the February 2006 consensus statement of the International Committee of Medical Journal Editors, and all patients provided written informed consent prior to their inclusion within the study.

Consent for publication

All patients provided written informed consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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