Contribution of susceptibility- and diffusion-weighted magnetic resonance imaging for grading gliomas

JIANXING XU[1], HAI XU[2], WEI ZHANG[2] and JIANGANG ZHENG[1]

[1]Department of Radiology, Affiliated Wujin Hospital of Jiangsu University, Changzhou, Jiangsu 213002; [2]Department of Radiology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 213002, P.R. China

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Abstract. The aim of the present study was to assess the value of susceptibility-weighted imaging (SWI) and diffusion-weighted imaging (DWI) in the grading of gliomas and to evaluate the correlation between these quantitative parameters derived from SWI and DWI. A total of 49 patients with glioma were assessed by DWI and SWI. The evaluation included the ratio of apparent diffuse coefficient values between the solid portion of tumors and contralateral normal white matter (rADC) and the degree of intratumoral susceptibility signal intensity (ITSS) within tumors. Receiver operating characteristic curve (ROC) analyses were performed and the area under the ROC curve was calculated to compare the diagnostic performance, determine optimum thresholds for tumor grading, and calculate the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for identifying high-grade gliomas. The correlation between DWI- and SWI-derived parameters was also evaluated. The rADC and the degrees of ITSS within tumors were significantly higher in high-grade gliomas than those in low-grade gliomas. ROC curve analysis indicated that the rADC was a better index for grading gliomas than the ITSS degree. Statistical analysis demonstrated a threshold value of 1.497 for rADC to provide a sensitivity, specificity, PPV and NPV of 86.2, 85.0, 89.3 and 81.0%, respectively, for determining high-grade gliomas. A degree of ITSS of 1.5 was defined as the threshold to identify high-grade gliomas and sensitivity, specificity, PPV and NPV of 82.8, 75.0, 82.8 and 75.0% were obtained, respectively. Furthermore, a moderate inverse correlation between rADC and the ITSS degree was revealed. Combination of SWI with DWI may provide valuable information for glioma grading.

Correspondence to: Dr Jiangang Zheng, Department of Radiology, Affiliated Wujin Hospital of Jiangsu University, 2 Yongning North Road, Tianning, Changzhou, Jiangsu 213002, P.R. China
E-mail: zhengjgwj@126.com

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Introduction

Cerebral glioma is the most important and common type of primary brain tumor (1). Sufficient grading of gliomas is important, as the clinical treatment and prognosis differ between distinct grades of tumor. However, conventional magnetic resonance imaging (MRI) may not accurately predict the glioma grade in all instances. Several advanced MRI methods have therefore been introduced for grading of gliomas (2,3). Diffusion-weighted imaging (DWI) is applied routinely for grading gliomas, as it provides the valuable information of cellularity and extracellular spaces within tumors (4). The apparent diffusion coefficient (ADC) derived from DWI is negatively correlated with cell density and certain proliferation indices (4-6). Furthermore, the ADC is significantly different between low-grade gliomas (LGGs) and high-grade gliomas (HGGs) (6,7).

However, discrepancies in the DWI results exist among available studies (8,9), as the pathological criterion for grading gliomas includes not only cellularity, but also vascular and cellular proliferation (10). Therefore, susceptibility-weighted imaging (SWI) has been added to routine neuroimaging to increase the sensitivity vs. susceptibility effects of microvenous structures and blood products (11). Intratumoral susceptibility signal intensity (ITSS) is defined as low signal intensity seen within the tumor on magnitude images of SWI and is useful for assessing the World Health Organization (WHO) tumor grade (12). Various studies have demonstrated the usefulness of this technique at 3T or 7T for grading gliomas (13-15).

Combination of different imaging modalities has the potential to increase the diagnostic accuracy by providing complementary information (2,16) and comparative analysis of these techniques is also required. However, only few studies have combined the diagnostic performance of SWI with other methods for glioma grading (12,17). To the best of our knowledge, the combination of SWI with DWI has not been fully addressed, yet. Furthermore, the present study hypothesized that there may be a correlation between the parameters derived from DWI and SWI, as the cell density and proliferation are expected to be associated with microvenous structures and remnants of blood in tumors. The present study aimed to evaluate the contribution of DWI and SWI in the grading of gliomas and assess the association between DWI- and SWI-derived parameters.

Materials and methods

Subjects. The local institutional review board of the Affiliated Wujin Hospital of Jiangsu University (Jiangsu, China) approved the present study. Due to the retrospective nature of the study, informed consent was waived. The study included all glioma patients who underwent surgery (subtotal or total resection of the tumor) and were confirmed by an experienced neuropathologist according to the WHO classification system at the Affiliated Wujin Hospital of Jiangsu University (Jiangsu, China) between February 2015 and August 2016 (18). The exclusion criteria were as follows: i) Contraindication regarding the application of gadopentetate dimeglumine (renal dysfunction or allergy), ii) radiotherapy or chemotherapy prior to surgery, iii) contraindication for high-field strength MRI (known metallic implants and/or claustrophobia) and iv) poor visualization of the tumor on MRI. None of the patients had any history of surgery for brain tumors. The parameters derived from DWI and SWI were retrospectively evaluated.

Image acquisition. All examinations were performed on a Siemens Trio Tim 3 T Excite HDMR scanner (Siemens AG, Munich, Germany) using an eight-channel head coil. All patients underwent T1-weighted imaging (T1WI), T2WI, fluid-attenuated inversion recovery, DWI, SWI and contrast-enhanced T1WI. DWI was performed using a single-shot echo-planar imaging sequence with the following parameters: Repetition time (TR)/echo time (TE), 6,000/60 msec; number of excitations (NEX), 2; flip angle (FA), 90˚; slice thickness, 5 mm; slice gap, 1 mm; field of view (FOV), 220x220 mm; matrix size, 128x128; total acquisition time, 1 min 59 sec. ADC maps were generated from DWI in the b-value range of 1,000 and 0 s/mm^2. Imaging parameters for SWI were as follows: TR/TE, 27/20 msec; NEX, 2; FA, 10˚; slice thickness, 1.5 mm; slice gap, 0 mm; FOV, 172x230 mm; matrix, 182x256; total acquisition time, 2 min 59 sec.

Data analysis. All images were reviewed independently by two radiologists with 16 years and 18 years of clinical experience in MRI, who were blinded to the histopathological results. First, the ADC maps were generated by using the DWI post processing software of the MR system. The ADC values represent averaged ADC values of three regions of interest (ROIs). ROIs were carefully positioned to avoid cystic, necrotic and hemorrhagic regions. The ratio between the ADC of the solid portion of the tumor and that of the contralateral normal white matter (rADC) was calculated in order to standardize variations in each examination.

Furthermore, the corrected-phase images and magnitude images were obtained by using the SWI post-processing software of the MR system. The susceptibility effects were foci of hypointensity in the tumor on the magnitude images and calcium was excluded by generating phase images of SWI and computed tomography images. Intratumoral susceptibility signal intensity (ITSS) was defined as low signal intensity seen within the tumor on magnitude images of SWI. For assessment of the dominant hypointense structure, the degrees of ITSS were divided into 4 grades: 0, no hypointense focus in the tumor; 1, hypointense foci indicating bleeding (dot-like or conglomerated dot shape) in the tumor; 2, hypointense foci indicating bleeding and vascular structure (linear or tortuous shape) less than half of the tumor on any image; 3, hypointense foci almost equally present in the tumor in any image (14,15,19).

Statistical analysis. Data are presented as the mean ± standard deviation. Statistical analysis was performed using SPSS version 19.0 (IBM, Corp., Armonk, NY, USA). P<0.01 was considered to indicate a statistically significant difference. The rADC was compared between two groups using an independent-samples t-test. The degree of the ITSS on SWI was compared between two groups using the Mann-Whitney U-test. The receiver operating characteristic (ROC) curve was analyzed to compare the diagnostic performances and the area under ROC curve (AUC) was calculated. Using an optimal cut-off value determined by the ROC analysis, the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for grading of gliomas were calculated. Spearman's correlation coefficient was also calculated to examine the correlation between DWI- and SWI-derived parameters.

Results

Patient characteristics. A total of 51 patients with gliomas were retrospectively analyzed. Two patients were excluded, as their maps were not suitable for diagnosis due to severe movement. The remaining 49 patients (26 females and 23 males; median age, 45 years; age range, 13-71 years) with histologically confirmed gliomas at our hospital were finally enrolled. Regarding the histological type, 2 gliomas were grade 1, 18 were grade 2, 15 were grade 3 and 14 were grade 4. Gliomas of WHO grades 1 and 2 were grouped as low-grade gliomas and those of WHO grades 3 and 4 were grouped as high-grade gliomas for the purpose of analysis.

The rADC and degrees of ITSS in the LGGs and HGGs are presented in Tables I and II. The rADC in HGGs was lower than that in LGGs (t=5.977, P<0.01; Fig. 1). ITSS was identified in 27 out of 29 HGGs (93%) and in 8 out of 20 LGGs (40%). The degree of ITSS within the tumor in HGGs was significantly higher than that in LGGs (Z=4.05, P<0.01; Fig. 2). Typical ROC curves for the rADC and degree of ITSS are presented in Fig. 3. ROC curve analysis indicated that the rADC was a better index for grading of gliomas compared with the ITSS degree. A threshold value of 1.497 for rADC provided an AUC of 0.903 and the cut-off value of 1.5 for the ITSS degree resulted in an AUC of 0.826. As presented in Table III, statistical analysis demonstrated that the value of 1.497 for rADC provided a sensitivity, specificity, PPV and NPV of 86.2, 85.0, 89.3 and 81.0% for determining HGGs, respectively. For the ITSS degree, the value of 1.5 was defined as a threshold to identify HGGs and a sensitivity, specificity, PPV and NPV of 82.8, 75.0, 82.8 and 75.0% were obtained, respectively.

The present study also evaluated the correlation between the rADC and the ITSS degree. The ITSS degree exhibited a moderate inverse correlation with the rADC (r=-0.498, P<0.01). Furthermore, as presented in Table IV, the rADC values were >1.497 in three cases of HGG, but the respective degrees of ITSS were 1, 2 and 3. In addition, the rADC

Table I. Comparison of ADC values and the rADC in LGGs and HGGs.

Parameter	LGG	HGG	P-value
ADC (Solid portion of tumors)	1.35±0.23	0.98±0.23	<0.01
ADC (Contralateral normal white matter)	0.74±0.07	0.78±0.07	0.109
rADC	1.82±0.33	1.23±0.31	<0.01

Values are expressed as the mean ± standard deviation. LGG, low-grade gliomas; HGG, high-grade gliomas; rADC, ratio of apparent diffuse coefficient between the solid portion of tumors and contralateral normal white matter.

Table II. Comparison of the degree of ITSS in LGGs and HGGs (n).

	Grade				
Group	0	1	2	3	P-value
LGG	12	3	2	3	<0.01
HGG	2	3	7	17	<0.01

Median of the degree of ITSS: LGG, 0; HGG, 3. LGG, low-grade gliomas; HGG, high-grade gliomas; ITSS, intratumoral susceptibility signal intensity.

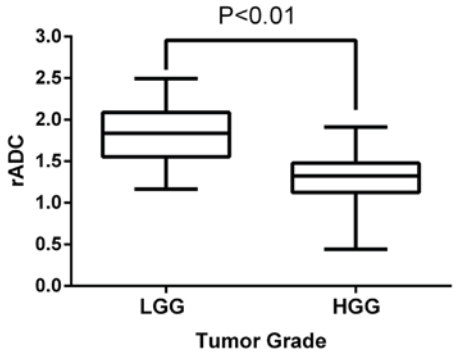

Figure 1. Box plot comparing rADC measurements according to glioma grades. LGG refers to gliomas of WHO grades 1 and 2; HGG refers to gliomas of WHO grades 3 and 4. WHO, World Health Organization; LGG, low-grade gliomas; HGG, high-grade gliomas; rADC, ratio of apparent diffuse coefficient values between the solid portion of tumors and contralateral normal white matter. The horizontal line through the center of the box represents median. Data are presented as the mean ± standard deviation.

values were <1.497 in three cases of LGG, while the respective degrees of ITSS were 0, 0 and 1.

Discussion

The present study evaluated the value of SWI and DWI for grading of gliomas and the correlation between the rADC and the degree of ITSS. The results regarding DWI were consistent with those of previous studies. Reportedly, ADC values have been correlated with the degree of tumor cellularity (5,20). Murakami *et al* (21) demonstrated that the minimum ADC corresponds to the highest-grade glioma foci within heterogeneous tumors. In the present study, the rADC was calculated

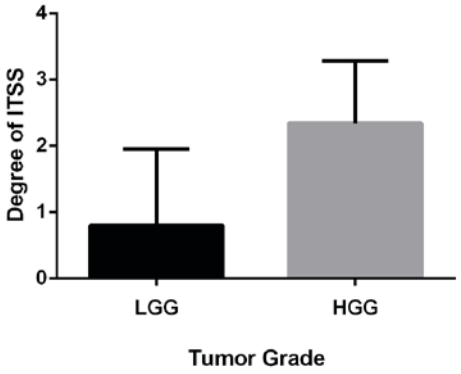

Figure 2. Column bar graph comparing the degrees of ITSS measurements according to glioma grades (error bars 95% CI). LGG refers to gliomas of WHO grades 1 and 2; HGG refers to gliomas of WHO grades 3 and 4. WHO, World Health Organization; LGG, low-grade gliomas; HGG, high-grade gliomas; ITSS, intratumoral susceptibility signal intensity. Data are presented as the mean ± standard deviation.

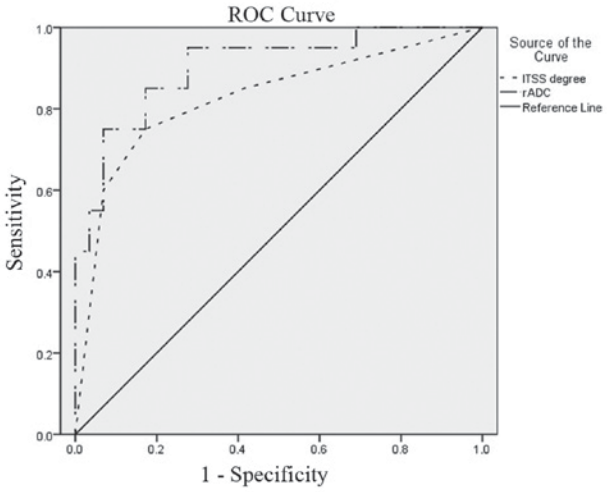

Figure 3. ROC curves for rADC and degrees of ITSS. The curve for rADC demonstrates superior sensitivity and specificity compared with degrees of ITSS for glioma grading. ROC, receiver operating characteristic; ITSS, intratumoral susceptibility signal intensity; rADC, ratio of apparent diffuse coefficient values between the solid portion of tumors and contralateral normal white matter.

in order to standardize variations, which were lower in HGGs than that in LGGs.

However, in another study, in which the regional heterogeneity of gliomas is taken into account, this inverse correlation between ADC and cell density was not confirmed (22). HGGs

Table III. Results of ROC curve analysis

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
rADC (1.497)	86.2	85.0	89.3	81.0
ITSS degree (1.5)	82.8	75.0	82.8	75.0

ROC, receiver operating characteristic curve; rADC, ratio of apparent diffuse coefficient between the solid portion of tumors and contralateral normal white matter; ITSS, intratumoral susceptibility signal intensity.

Table IV. Comparison of results between the rADC value and the ITSS degree (r=-0.498, P<0.01).

Parameter	rADC	ITSS degree		
HGG	>1.497	1	2	3
LGG	<1.497	0	0	1

rADC, ratio of apparent diffuse coefficient between the solid portion of tumors and contralateral normal white matter; ITSS, intratumoral susceptibility signal intensity; HGG, high-grade gliomas; LGG, low-grade gliomas.

and LGGs have a large overlap of ADC values, regardless of whether the mean, minimum or normalized ADC value is used (7,20). The present results also indicated a certain overlap in the rADC and accordingly, the differentiation between HGGs and LGGs should not be based solely on the rADC. The rate of tissue diffusion in tumors is not only affected by tumor cellularity and cell density, but also influenced by other determinants, including the nucleus-to-cytoplasm ratio, the presence of peritumoral vasogenic edema or tumor necrosis, the degree of neuroarchitectural destruction and the pore sizes of the extracellular space (23). The final ADC value is determined by combination of all of these factors, which may account for the overlapping of ADC values.

Therefore, another contributing factor in the malignancy of tumors is their ability to synthesize vascular networks for further growth and proliferation (24). SWI is a useful tool for evaluating intratumoral structures, including microvasculature (13). However, probably due to angiogenesis and increased blood supply to the tumor, HGG contains a relatively large amount of deoxyhemoglobin, which generates susceptibility effects and causes signal-intensity loss. Pinker *et al* (15) reported that the ITSS is correlated with the tumor grade as determined by positron-emission tomography and histopathology. Park *et al* (19) reported that glioblastoma multiforme have the highest degree of ITSS, suggesting that ITSS may be useful in the correct diagnosis of HGGs. The present results also indicated that the degree of ITSS within the tumor was significantly higher in HGGs than that in LGGs patients.

However, the present results were inconsistent with those of a previous study, which reported that ITSS was seen in all glioblastomas but never in any LGGs (19). This discrepancy may be due to the lack of established objective methods for evaluation of images. The intratumoral susceptibility effect on SWI may be easily changed by small variations in imaging parameters or post-processing methods (25). In addition, the distribution of the microvenous structures in HGG is often irregular, including uneven thickness, circuity disorder, formation of clusters and easy occurrence of thrombosis and hemorrhage, which makes it difficult to grade tumors within vascular structures, hemorrhage and tumor vascular thrombosis.

In the present study, the results revealed a moderate inverse correlation between rADC and the degree of ITSS. DWI is generally applied to obtain information on cellularity, and SWI to determine the sensitivity to susceptibility effects of microvenous structures. It is therefore not surprising that increased tumor cellularity is associated with increased tumor vascularity. However, these parameters are not direct measures of the same phenomenon. The direct correspondence between the rADC and the degree of ITSS was variable. In the present study, the rADC values were >1.497 in three cases of HGG, but the respective degrees of ITSS were 1, 2 and 3. In addition, the rADC values were <1.497 in three cases of LGG, while the respective degrees of ITSS were 0, 0 and 1.

This observation demonstrated that the information provided by the rACD values alone is not always conclusive and that further parameters should be considered. Future studies pursuing a point-to-point approach for targeting tumor tissues for surgical biopsy may validate the power of this pre-operative glioma grading method.

In the present study, although the results indicated that rADC was a better index for grading gliomas compared with the degree of ITSS, it must be emphasized that SWI may be used as a valid contributing parameter, for example when DWI fails or when conventional MR parameters are inconclusive. In the present study, SWI was used to assess the extent of hemorrhage in the tumor, which may potentially affect ADC values. Hence, the use these parameters increases the confidence in grading gliomas. Furthermore, conventional MRI with gadolinium-based contrast agents is an established and useful tool in the characterization of cerebral tumors (26). Contrast enhancement on T1WI signifies blood-brain barrier breakdown and its pattern and extent have been suggestive of malignant potential (27). Radiological grading of tumors with conventional MRI is not always accurate and errors may occur (28). DWI and SWI parameters are quantitative physiological metrics for tumor microenvironments and will complement glioma grading. DWI and SWI without contrast material may also reduce the risk associated with injection of contrast agents.

In addition, histopathology for grading of gliomas may also be inaccurate when biopsy samples are not taken from the tumor region with the highest degree of malignancy or when the tumor is not completely resected (10). The limitation

of histopathology includes tissue heterogeneity and inherent sampling errors, often resulting in an underestimation of the histological grade (2). Hence, an imaging-based method for determining the glioma grade is appealing due to its non-invasiveness and the possibility to cover larger areas of heterogeneous tumors, which may enhance the reliability of the histopathological grading. The lowest ADC value indicates that the region with the greatest cellularity and the information regarding venous vasculature and hemorrhage provided by SWI may be helpful in selecting biopsy targets.

The present study has several limitations. First, the sample size was relatively small and patient age was not appropriately controlled. Furthermore, a retrospective approach was used to select the cases examined and selection bias may have prevailed. In addition, the placement of the ROI and the quantitative scoring were performed in a subjective manner and the results may have been different if other individuals had performed the assessment. Finally, no other advanced MR techniques, including spectroscopy, perfusion or diffusion tensor imaging, were performed in the present study.

In conclusion, depending on pathological angiogenesis, malignant tumors usually have a high tumor cellularity, rapid growth of vascular structure and multiple microbleeds. Information on tumor cell proliferation, cell density, capillary formation and tumor hemorrhage will facilitate the pre-operative grading of gliomas. Therefore, DWI and SWI may have a complementary diagnostic role for grading of gliomas.

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Availability of data and materials

The analyzed data sets generated during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JX and HX carried out the data analysis and drafted the manuscript; JX and WZ significantly contributed to the acquisition of data; JZ and JX revised the manuscript; WZ carried out the quality control of the data; JZ and JX significantly contributed to the study design and reviewed the manuscript; HX and WZ contributed to the conception and design of the study, supervised the research program and edited the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The local institutional review board of the Affiliated Wujin Hospital of Jiangsu University (Jiangsu, China) approved the present study. Due to the retrospective nature of the study, informed consent was waived.

Consent for publication

Not applicable.

Competing interests

All authors have no conflict of interest to declare.

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