Original Article

Direct measurement of the signal intensity of diffusion-weighted magnetic resonance imaging for preoperative grading and treatment guidance for brain gliomas

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Abstract

Background: Magnetic resonance diffusion-weighted imaging (DWI) has been widely used clinically in imaging diagnosis of intracranial disorders. The purpose of current study was to present a quantitative method of direct measuring the DWI signal intensity of brain gliomas on the monitors of hospital picture archiving and communicating system (PACS) for grading gliomas.

Methods: This study recruited 135 patients with treatment-naive brain gliomas. Direct measurement of the signal intensity of selected tumoral regions of interest (ROIs) by DWI on the monitors of the hospital PACS was performed for all patients. From the measurements, we obtained three values, defined as DWIT (tumor), DWIN (the homologous normal-appearing area of the tumor ROI in the contralateral hemisphere), and DWIWM (normal-appearing white matter) in the contralateral frontal lobe. Two ratios, DWIT/WM and DWIT/N, were obtained for each tumoral ROI. The same method was used for apparent diffusion coefficient (ADC) ratios of the tumoral ROI. Fractional polynomial regression and the Mann–Whitney U test were applied to determine the correlation between tumor grading, MIB-1 labeling index, and DWI and ADC ratios. Logistic regression models and receiver operating characteristic curve analysis were used to establish diagnostic models. Measurements of intraobserver and interobserver agreement were also made at 1-month interval.

Results: The DWI ratios correlated positively with tumor grade and MIB-1 value (p < 0.01). Cut-off ratios of 1.62 for DWIT/WM and 1.47 for DWIT/N generated the optimal combination of sensitivity (0.82, 0.80), specificity (0.79, 0.86), and sound discriminating power, with an area under the curve of 0.87 and 0.84, respectively, to differentiate low-grade from high-grade gliomas. ADC ratios showed relatively worse sensitivity, specificity, and discriminating power than DWI ratios. Almost all intraobserver and interobserver measurements were within 95% agreement.

Conclusion: The proposed method — direct measuring of tumor signal intensity of DWI on PACS monitors — is feasible for grading gliomas in clinical neuro-oncology imaging services and has a high level of reliability and reproducibility.

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Keywords: brain neoplasm; diffusion-weighted imaging; glioma; grading

1. Introduction

The most common primary brain neoplasms are of glial origin. Magnetic resonance (MR) imaging has been the most frequently used imaging modality to evaluate intracranial
tumors due to its ability to provide good tissue characterization and abundant anatomical information. In addition to conventional morphological imaging, MR diffusion-weighted imaging (DWI) is at present applied almost routinely for imaging intracranial gliomas to obtain the valuable information regarding alterations in cellularity and extracellular spaces that is provided by the imaging. The apparent diffusion coefficients (ADCs) quantitatively derived from DWI were further found to be inversely correlated with cell density and certain proliferation indices. Hence, researchers had previously hoped that the noninvasive DWI could also be applied as an effective preoperative tumor grading method. However, some issues remain unanswered regarding the use of DWI in glioma grading. Reports from early preliminary studies either comprised small series and a limited number of patients or involved mixed tumor types such as metastases or meningiomas. Furthermore, the literature reported inconsistent cut-off values for ADC in distinguishing between low- and high-grade gliomas. Therefore, evaluating the DWI characteristics of gliomas in a larger patient cohort is a clinically demanding task. Considering possible variations of the technical factors, such as the b value for diffusion weighting or eddy-current-related geometric distortions/corrections that might affect the quantification of ADC, DWI which is less sensitive to scan settings would be preferential over ADC. In a recent study by El Kady et al, ADC values measured on a routine picture archiving and communicating system (PACS) workstation proved to be as accurate as the values obtained using a dedicated specialized workstation. Thus, the purpose of this study was to provide a comprehensive investigation into the usefulness of DWI and ADC signal intensities directly measured on the hospital PACS monitors for tumor grading, including only those gliomas with an astrocytic origin.

2. Methods

Our institute provided a pathologic diagnosis for 214 consecutive glial tumors in patients between January 2005 and
June 2008. All tumors were classified according to the World Health Organization classification (2007) into low-grade (grades I and II) and high-grade (grades III and IV) gliomas. This study excluded 21 patients without preoperative MR imaging, 22 patients without DWI, 10 patients who had had previous radiation and/or chemotherapy before inhouse MRI examination, 24 patients with tumors composed mainly of cysts and without measurable soft tissue components, and two patients with evident tumor bleeding on conventional MR imaging. The analysis ultimately comprised 135 patients, of whom 57 were male and 78 were female, aged 1–80 (mean 49) years old. Of the total of 135 patients, 41 patients (30%) had low-grade gliomas [grade I = 8 (6%); grade II = 33 (24%)], and 94 patients (70%) had high-grade gliomas [grade III = 43 (32%); grade IV = 51 (38%)].

The scanning in this study was all performed with 1.5-T clinical MR scanners (GE Medical Systems, Milwaukee, WI, USA) and conventional circularly polarized head coils. Either gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) or gadodiamide (Omniscan; GE Medical Systems, Milwaukee, WI, USA) was administrated intravenously in standard doses. In addition, conventional MR imaging and transaxial DWI were routinely included in the protocol using spin-echo echo-planar imaging sequences with the following characteristics: repetition time ms/echo time ms, 8000/70; number of signals acquired, 1; section thickness, 5 mm; section gap, 2.5 mm; matrix size, 128 × 128 pixels; field of view, 20 × 20 cm², with diffusion gradient encoding in three orthogonal directions (b = 1,000 s/mm²), followed by automatic generation of isotropic DW images. The total acquisition time for DWI was 40 seconds. The time intervals between MR images and biopsies or surgical tumor extirpation were less than 1 month.

This study measured the signal intensity of selected regions of interest (ROIs) on DWI directly on the monitors of the hospital PACS. Three standardized ROI measuring 25 ± 5 mm² were placed on the enhancing solid portion of the tumor that presented the highest signals on DWI, the normal-appearing white matter of the contralateral frontal lobe, and the normal-appearing homologous area of the ROI of the tumor in the contralateral hemisphere. Throughout the measurement, we used “copy” and “paste” of the ROI to standardize the ROI sizes and to avoid sampling errors.

The signal intensities obtained were accordingly defined as the DWI value of the tumor (DWIT), the DWI value of white matter (DWIWM), and the DWI value of homologous normal brain tissue (DWIN). Fig. 1 shows the two ratios obtained for each tumoral ROI namely DWIT/WM and DWIT/N. The ADC ratios (ADCT/WM and ADCT/N) were obtained in a similar manner. When geometric distortions occurred on echo-planar images and/or the tumoral homologous area contained artifacts, ROIs were repositioned at areas without evidence of tumor involvement according to anatomical references. The mean of three measurements for each ROI was used for statistical analysis.

Intraobserver variation was assessed by repeated measurements in 91 of the 135 cases at 1-month interval by the same author. Another neuroradiologist repeated the measurements for 20 of the 135 cases, with blinding procedures in place, using the same PACS system and same measuring method, in order to evaluate interobserver agreement.

Fig. 2. Bland–Altman plots illustrate examples of intraobserver (A) and interobserver (B) variation for measurement of the ratio of diffusion-weighted imaging results for the tumor and the white matter (DWIT/WM). SD = standard deviation.
The cut-off value of the MIB-1 labeling index (LI) for grading gliomas was set at 11%. Gliomas with an MIB-1 LI of over 11% (high grade) were associated with a shorter survival time than those an MIB-1 LI value of 11% or less (low grade). Fractional polynomial regression was used to define the relationship between the DWI value ratio and MIB-1 LI. In order to compare the value of the DWI ratio and the tumor grade, and the variances between groups, the Mann–Whitney U test and independent t test were applied, a significant difference being accepted if \( p < 0.05 \). Logistic regression models and receiver operating characteristic (ROC) curve analysis were used to establish diagnostic models. All analyses were conducted using STATA 10.0 for Windows software (StataCorp. LP, College Station, TX, USA). Bland–Altman plots (Fig. 2) were used to assess intra- and interobserver variation.

3. Results

The DWI ratios were positively correlated with MIB-1 LI values and tumor grades (Fig. 3A). The mean DWI ratios of low-grade gliomas were significantly lower than those of high-grade gliomas ( \( p < 0.001 \); Fig. 3B and C). The trend applied to both ratios derived from DWI – DWI\(_{T/WM}\) and DWI\(_{T/N}\) – while the trends were reversed for ADC ratios. Using the logistic regression models, cut-off ratios of 1.62 for DWI\(_{T/WM}\) and 1.47 for DWI\(_{T/N}\) generated the optimal combination of sensitivity (0.82, 0.80) and specificity (0.79, 0.86), and good discriminating power, the area under curve being 0.87 and 0.84, respectively, to differentiate low-grade from high-grade gliomas (Fig. 3D). The sensitivity, specificity, and discriminating power of ADC\(_{T/WM}\) and ADC\(_{T/N}\) were relatively worse than those of DWI (Table 1). No significant difference was present in DWI ratios between grade I and grade II tumors ( \( p = 0.63 \) for DWI\(_{T/WM}\), \( p = 0.3 \) for DWI\(_{T/N}\)), or between grade III and grade IV tumors ( \( p = 0.69 \) for DWI\(_{T/WM}\), \( p = 0.12 \) for DWI\(_{T/N}\)). The results of the tumor grading and DWI and ADC ratios are shown in Table 1.

Bland–Altman plots (see Fig. 2) were used to assess intra- and interobserver variation. For all factors, all measurements were within 95% agreement, except for one outlier for the interobserver measurements and three for the intraobserver measurements.

4. Discussion

Pathological alteration of water diffusion in the brain tissues can be illustrated by DWI or ADC mapping. The brightness of each DWI pixel is proportional to the recorded MR signal intensity, and the brightness of each pixel of the ADC map is proportional to its calculated ADC value. A definite quantitative diffusion measurement can only be obtained from an ADC map on a workstation equipped with software capable of post-processing. The process is still complex and not commonly accessible for most clinical imaging practitioners. Accordingly, visual and empirical assessment and qualitative descriptions of DWI are commonly employed in current practice. In addition, the ADC darkness is less visually sensitive than the DWI brightness on PACS. Furthermore, we used ROIs instead of average signal intensity values for DWI of whole tumor, since the mean value may downstage the tumor because of its low-grade area, as gliomas are commonly heterogeneous in terms of tissue content. This study provided a useful method that is both quantitative and user-friendly for preoperatively grading gliomas, with a direct measurement of signal intensity of DWI on PACS.

A large number of studies have focussed on correlating tumor grading and ADC values. Most of these studies examined various histologic tumor types, including gliomas and nongliarial tumors. Murakami et al showed that the minimum
ADC corresponded to the highest-grade glioma foci within heterogeneous tumors and helped to distinguish grade I and grade IV tumor foci from those of other grades. The current study recruited patients with only glial tumors and provided a larger cohort of patients with higher recruitment homogeneity.

The results revealed that high-grade gliomas had higher DWI value ratios than low-grade gliomas, which was consistent with previous studies showing a lower diffusion coefficient (more restricted diffusion) for high-grade gliomas. The authors hypothesized that higher grade brain tumors contained greater cellularity and fewer extracellular spaces, for instance, high-grade gliomas and lymphomas. In the tissue microenvironment, water diffusion was more constrained, and tissues consequently displayed greater signal intensity on DWI and low signal intensity on an ADC map. The hypothesis was also supported by the reverse correlation between the ADC value and the proliferation index (Ki-67 or MIB-1 LI), as has previously been reported. However, a large overlap of ADC values was present between high-grade and low-grade tumors, irrespective of whether the mean ADC, minimum ADC, or normalized ADC value was used. A similar overlap of values for the DWI ratio existed between low-grade and high-grade tumors in this study.

This finding is particularly useful for preoperative evaluations of pilocytic astrocytoma, which is a grade I glioma, albeit usually showing heterogeneous and marked enhancement on conventional MR images after intravenous contrast medium administration, and once being called a “crazy” tumor that mimicked high-grade gliomas. In these cases, DWI was proven to be more useful than gadolinium-enhanced structural imaging. Currently, the cut-off value of 1.6 for DWI_{T/WM} and 1.5 for DWI_{T/N} has become a significant imaging parameter in our pediatric neuro-oncological practice (Fig. 4).

The results also showed a substantial positive correlation between MIB-1 LI and DWI ratio, which was consistent with the results of previous studies showing a significant increase in Ki-67 LI with a rising malignancy grade of astrocytomas and a significantly poorer prognosis in patients with tumors with higher Ki-67 and MIB-1 LI values. Higano et al observed

![Fig. 4](image.png) The usefulness of values of the diffusion-weighted imaging (DWI) ratio for preoperative tentative diagnosis. Conventional magnetic resonance (MR) images show a biopsy-proved pilocytic astrocytoma. The tumor shows as hyperintense on a T2-weighted (T2W) image (A), and has good enhancement on an axial postcontrast enhanced T1-weighted (T1W) image (B), mimicking a high-grade glioma. Using our proposed method to measure the DWI values from DWI scans (C, D), we obtain the DWI value of the tumor (circle; T in Fig. 4C), the DWI value of homologous normal brain tissue (circle; N in Fig. 4C), and the DWI value of white matter (circle; WM in Fig. 4D). As a result, the ratio of DWI for tumor to white matter (DWI_{T/WM}) is 1.1 and the ratio for DWI for tumor to normal tissue (DWI_{T/N}) is 0.8 in the current case, indicating a low-grade glioma based on our cut-off values for DWI_{T/WM} (1.62) and DWI_{T/N} (1.47). The surgical result confirmed our tentative preoperative diagnosis of a low-grade glioma.
an inverse correlation between ADC and Ki-67 LI values. Since gliomas are commonly heterogeneous in terms of tissue content, a proper target selection for biopsy is crucial in order to obtain the most representative tumor portion and avoid underestimating the tumor grade. According to the current analysis, for a suspected high-grade tumor with a heterogeneous tissue content, the tumor portion with the highest DWI ratio indicates the most representative area for tumor grading. The quantitative measurement can not only improve the visualization of a lesion, but also may translate the MR parameters into the pathophysiologic changes of gliomas. This informative imaging tool has been applied in our current routine neuro-oncology practice to guide tissue biopsy or tumor extirpation.

In previous studies, the homologous tissue in the contralateral hemisphere of a tumor was selected as a reference for normalization. However, the normal gray matter was brighter than the normal white matter on DWI, and the tumor might involve gray and/or white matter. Furthermore, the homologous tissue might be difficult to define if the tumor originated from midline structures, such as the brainstem or corpus callosum, or the tumor crossed the midline and involved both hemispheres. Therefore, this study proposed incorporating the normal-appearing white matter of frontal lobe and the normal-appearing homologous area of the ROI of the tumor in the contralateral hemisphere for normalization. The frontal lobe white matter was selected as a reference point because it could easily be identified on DWI due to good tissue contrast.

The signal intensity on DWI contains mixed contributions from changes in T2 effect, spin density, and ADC. Occasionally, a high signal intensity on DWI may reflect a strong T2 effect (called T2 “shine-through”) rather than reduced diffusion, especially when the value of b is small. Thus, previous studies used the ADC value to represent the diffusibility of brain tumors. The rate of tissue diffusion in a brain tumor was not only affected by tumoral cellularity, but was also influenced by a large number of other determinants, including the degree of neuroarchitectural destruction, the nucleus to cytoplasm ratio, the presence of tumoral necrosis, the cellular features of the tumor, the presence of peritumoral vasogenic edema, and the pore sizes of the extracellular space. The combination of all these factors determines the final brightness on DWI and the ADC value, and this might be responsible for the overlapping of ADC values between individual tumor grades, and between the tumor and any peritumoral edema.

We also found that gliomas that contain gemistocytic components presenting high signals on DWI, although they are classified as grade II. The biological behavior and prognosis of gemistocytic tumors may be clinically inconclusive and puzzling. It is feasible to hypothesize that gemistocytes contain more intra- than extracellular water due to their voluminous, homogenous, and slightly eosinophilic cytoplasm, with few branching processes and an eccentric nucleus, and present higher signals on DWI than other grade II gliomas.

Furthermore, the pathological criteria for high-grade gliomas include not only cellularity or nucleus to cytoplasm ratio, but also vascular and cellular proliferation and necrosis, while vascular proliferation and necrosis differentiate between grade III and grade IV gliomas. A study reported that decreased brightness on DWI served as an imaging indication to differentiate necrotic grade IV gliomas from abscesses. Interestingly, the results of this study revealed that the DWI ratios for grade IV tumors tend to be lower instead of higher than the ratios found for grade III tumors. Although this study excluded tumors composed mainly of cyst without measurable solid portions in the first instance, and ROI placement was, with reference to conventional MR images, conducted carefully to avoid including cystic portions of tumors, the microscopic necrosis beyond the resolution of morphological MR images may be illustrated by brighter signals for grade III tumors than grade IV tumors on DWI.

Limitations of DWI in tissue characterization also refer to the post-intervention changes in brain tumors. The effects of previous irradiation and/or chemotherapy on DWI signal intensities are complex and beyond the scope of this study. However, this paper excluded cases where there had been previous treatment by irradiation and/or chemotherapy, in order to avoid potential confounding factors for tissue diffusion. The exclusion criteria also included tumor bleeding as hemoglobin and its degradation products could interfere with DWI signal intensity. One of the limitations of the current analysis was the relatively small case number of grade I gliomas. Multiple grade I glial tumors (pilocytic astrocytomas) were excluded due to their vast cystic components.

There are some other limitations of the current study. First, the placement of the ROI on the tumor portion with the brightest signals was based on subjective visualization by the observers. However, the current study results showed good agreement (95%) among observers. This simple and highly reproducible method can be reliably applied to daily clinical imaging practice. Second, partial volume effects might affect the signal ratios, but integration and correlation of multiple pulse sequences in MR imaging were employed to minimize partial volume effects. Finally, since this is a retrospective study, a point to point correlation between pathologic findings and DWI signal measurement is infeasible. A future prospective study with a point to point basis for targeting tumor tissues in surgical biopsy may further validate the power of this preoperative glioma grading method.

In conclusion, the current study identified the DWI characteristics of gliomas by directly measuring tumor signal intensity from DWI on PACS monitors in a large cohort of cases. The proposed method of measuring signal ratios presented high reliability and reproducibility in grading gliomas. The method can be feasibly used by clinical neuro-oncology imaging services and is applicable to guiding therapeutic strategy, especially stereotactic biopsy.

References


