Value of Diffusion Tensor Imaging in Differentiating High-Grade from Low-Grade Gliomas

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Objective: *To determine the usefulness of diffusion tensor imaging (DTI) in differentiating high-grade glioma (HGG) from low-grade glioma (LGG).*
Material and Method: *Patients with cerebral gliomas underwent conventional MRI and DTI before surgery. All proven pathologies were classified into two groups, i.e. LGG and HGG. The authors measured fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values in region of interest (ROI) including solid tumoral region, necrotic region, peritumoral edema, contralateral normal appearing white matter (NAWM) and normal corpus callosum as well as calculated ADC ratios. Pairwise comparisons were performed by using the t-test. The ROC curves of imaging parameters were employed to determine the best parameter for differentiating the two entities.*
Results: *Forty-three patients with cerebral gliomas, 17 with LGG and 26 with HGG, no statistical significant difference between LGG and HGG using mean FA values in each ROI. The ADC and minimal ADC values of solid tumoral region and peritumoral edema, the ADC and minimal ADC ratios of solid tumoral region are statistical significant to differentiate HGG from LGG, $p<0.05$. The ratio ADC solid tumoral region to normal corpus callosum had highest predictive accuracy to differentiate the two entities with AUC of 0.74.*
Conclusion: *The ADC value, minimal ADC value, and ADC ratios of solid tumoral region appeared to be useful for differentiating HGG from LGG.*

Keywords: *Brain tumor, Glioma, DTI*

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Gliomas are the most common primary brain tumors of the central nervous system[1-3]. The prognosis for patients depends on histopathologic grading and remains poor for high-grade gliomas (HGG)[4]. Accurate preoperative diagnosis of tumor grade is important for appropriate treatment[3,5]. The characteristic heterogeneity and infiltrative tumor might be difficult to accurately grade tumor[5]. Despite optimization of sequences and protocols, preoperative grading of gliomas with conventional MRI (cMRI) is sometimes unreliable[6]. Diffusion tensor imaging (DTI) gives information about direction of molecular water movement within tissues and reflects microstructural organization of brain tissue[3]. The histological diagnosis of HGG is based on the presence of nuclear heteromorphism, nuclear mitosis, endothelial proliferation, and necrosis, which may affect the fractional anisotropy (FA) and mean diffusivity (MD) values[7]. The purpose of the present study was to determine the usefulness of DTI in differentiating HGG from low-grade glioma (LGG).

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Material and Method

Patient population

The present study was approved by the Ethics committee of the faculty of Medicine Siriraj Hospital. The prospectively study was done between June 2009 and March 2011 on patients with suspected cerebral gliomas undergoing cMRI and DTI before surgery at Siriraj Hospital. All patients underwent tumor

resection or biopsy and had pathologically proven cerebral gliomas, who were classified into two groups, LGG (WHO grade I and II) and HGG (WHO grade III and IV).

Image acquisition

All images were obtained with a 3.0-T whole-body scanner (Achieva, Philips Medical System, Best, the Netherlands) with an eight-channel head coil utilizing sense parallel imaging technique. DTI was acquired by using single shot spin-echo echo-planar imaging (TR = 11,000; TE = 54; bandwidth = 23.8 Hz; matrix, 112x112; FOV, 224 mm; EPI factor 59; slice thickness, 2.3 mm, no gap; NEX, 1; b factor = 0 and 1,000 mm^2/s; directions of gradient sampling, 16). The associated with brain mapping MRI protocols were obtained that included axial T2-wi, FLAIR and postgadolinium axial T1-wi. The routine cMRI were also obtained including pregadolinium sagittal T1-wi, axial and coronal T2-wi, axial FLAIR, axial DWI/ADC map, axial SWI, postgadolinium axial, sagittal and coronal T1-wi.

Image analysis

Post processing analysis was performed on commercial software (Fiber Tract, View Forum, Philips, Best, the Netherlands). The authors measured FA and apparent diffusion coefficient (ADC) values by manually placing region of interest (ROI) within enhancing region of tumor that represent high grade portion or solid non-enhancing region if tumors did not enhance identified by neuroradiologist's opinion. The measured FA and ADC values within necrotic region, peritumoral edema, contralateral normal appearing white matter (NAWM) and normal corpus callosum were also obtained (Fig. 1) Each reviewer placed five ROIs in solid tumoral region, necrotic region and peritumoral edema to obtain the minimum and maximum FA and ADC values (less ROIs for smaller lesions). The average FA and ADC in each area were calculated. The five ROIs were placed in NAWM as well as a single ROI in genu or splenium of corpus callosum and then average FA and ADC values were calculated. The NAWM and corpus callosum were selected as internal normal control and FA and ADC ratios of each lesional region were established.

Statistical analysis

A t-test was used to test the difference between HGG and LGG in terms of ADC, minimal ADC, ADC ratio, minimal ADC ratio, and FA values in each ROI. Predetermined p-value <0.05 was determined significant. The ROC curves of the significant parameters were performed to identify cutoff point and diagnostic performance of the values was calculated. All data analysis was performed by using SPSS 13.0.

Results

The patient characteristic and tumor group were described as shown in Table 1. Forty-three patients

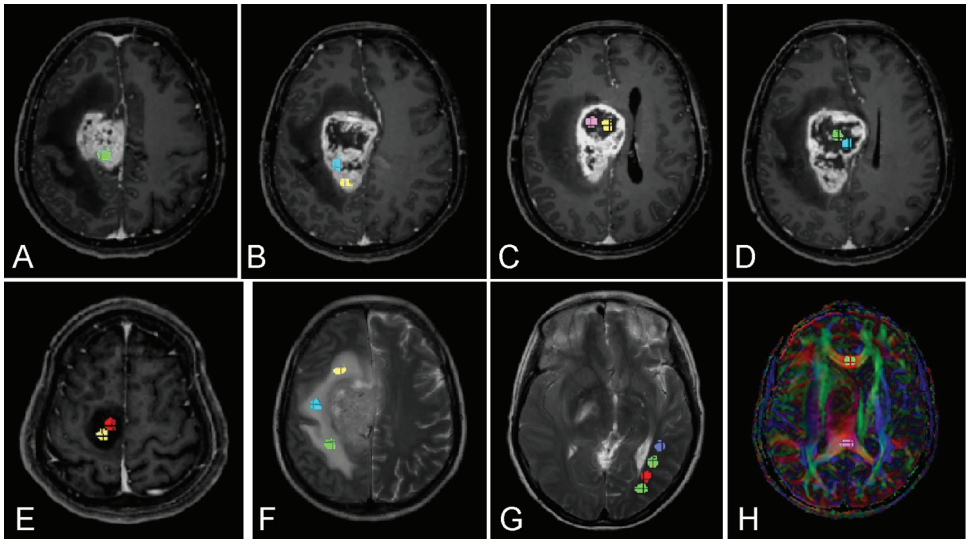

Fig. 1 Images demonstrate region of interest in different areas of tumor and normal reference (A, B = enhancing area, C, D = necrotic area, E = non-enhancing area, F = peritumoral high T2 area, G = NAWM, and H = normal corpus callosum).

with cerebral gliomas, 17 with LGG and 26 with HGG were selected. There was no statistical significant difference between LGG and HGG using mean FA values in solid tumoral region, necrotic region, and peritumoral edema. The information for ROI analysis in low-grade and high-grade gliomas was described as shown in Table 2. The mean ADC value in solid tumoral region, necrotic region, and peritumoral edema in both two groups of tumor was higher than NAWM or corpus callosum and the value was highest in necrotic region. The ADC and minimal ADC values of solid tumoral region and peritumoral edema, ratio of ADC, and minimal ADC of solid tumoral region relation to NAWM or corpus callosum were statistically significant to differentiate HGG from LGG, $p<0.05$ (Table 3). Each parameter with significant difference was evaluated for its discriminative ability using ROC analysis as shown in Table 4. The highest prediction accuracy parameter for differentiate HGG from LGG was ratio ADC solid tumoral region to corpus callosum (AUC = 0.74), followed by ADC solid tumoral region (AUC = 0.71), ratio minimal ADC solid tumoral region to corpus callosum (AUC = 0.75), and minimal ADC solid tumoral region (AUC = 0.74). The ratio ADC value had higher sensitivity than absolute ADC value in differentiating the two groups of tumor.

Discussion

The present study demonstrated that in the solid tumoral region, necrotic region and peritumoral edema FA values were not significantly different between LGG and HGG. However, the FA values in these regions of both HGG and LGG were lower than those of contralateral NAWM or corpus callosum that were consistent with prior studies[8-12]. The FA value is an indicator of white matter integrity and decreased FA was putative destruction of white matter tract[4,13]. However, studying the relationship between FA values of LGG and HGG is still controversial[8-10]. Inoue T et al[3] found that the FA values in solid portion of HGG were significantly higher than those of LGG. High anisotropy implies that the tissue is symmetric histologically organization. It may influence the anisotropy and increase the FA value. However, they limited the ROIs in solid portion and to avoid the necrosis because the necrotic core in HGG showed low FA values[3]. Conversely, some studies have found no significant difference in FA values between LGG and HGG[10,14,15]. Beppu T et al[16] hypothesized that the FA value of astrocytic tumor tissue is determined by a balance between factors decreasing the degree of the directionality of water diffusion, such as fiber destruction or displacement, and factors increasing it, such as high cell density and/or vascularity that influenced blood water movement[16]. In the present study found that FA value in corpus callosum is higher than NAWM, which corresponded with a previous study[11,16]. Therefore, the location of tumors may affect the FA values. Up to now, the FA value of cerebral gliomas remains unclear. It suggests that

Table 1. Group of gliomas (n = 43)

	Low-grade gliomas (n = 17)	High-grade gliomas (n = 26)
Tumor type	Diffuse astrocytoma (n = 7) Oligodendroglioma (n = 7) Pilocytic astrocytoma (n = 1) Astrocytoma (n = 1) Chordoid glioma (n = 1)	Glioblastoma (n = 18) Anaplastic astrocytoma (n = 7) Glioblastoma with oligodendroglia component (n = 1)
Age (year*)	41.0±15.8 (12-66)	43.4±13.6 (26-74)
Gender		
Male	9	12
Female	8	14

* Mean value ± standard deviation. Numbers in parentheses are range.

Table 2. Information for ROI analysis in low grade and high grade gliomas (n = 43)

	Enhancing/non-enhancing regions	Necrotic region	Peritumoral edema	NAWM	Corpus callosum
Low grade (n = 17)	17	2	13	17	17
High grade (n = 26)	26	17	25	26	26

Data represent number of patients in each region. Numbers in parentheses indicate number of patients.

Table 3. Comparison of DTI parameters between low-grade and high-grade gliomas

Parameter	Low-grade	High-grade	p-value*
STR			
FA	0.139±0.053	0.152±0.058	0.459
ADC (x10-3 mm^2/sec)	1.504±0.471	1.180±0.209	0.015+
NR			
FA	0.114±0.045	0.118±0.043	0.896
ADC (x10-3 mm^2/sec)	2.573±0.312	2.108±0.681	0.364
PTE			
FA	0.218±0.05	0.196±0.059	0.286
ADC (x10-3 mm^2/sec)	81.244±0.170	1.398±0.203	0.025+
NAWM			
FA	0.453±0.067	0.448±0.065	0.841
ADC (x10-3 mm^2/sec)	0.764±0.037	0.756±0.034	0.439
CC			
FA	0.783±0.059	0.746±0.052	0.041+
ADC (x10-3 mm^2/sec)	0.771±0.094	0.789±0.073	0.469
Minimal ADC value (x10-3 mm^2/sec)			
STR	1.340±0.397	1.037±0.196	0.008+
NR	2.064±0.958	1.806±0.746	0.656
PTE	1.104±0.140	1.251±0.208	0.029+
ADC ratios			
STR: NAWM	1.968±0.613	1.567±0.305	0.021+
STR: CC	1.979±0.650	1.512±0.348	0.013+
Minimal ADC ratios			
STR: NAWM	1.751±0.507	1.378±0.289	0.012+
STR: CC	1.762±0.567	1.335±0.344	0.010+

Data are mean values ± standard deviation.
STR = solid tumoral region; NR = necrotic region; PTE = peritumoral edema; NAWM = normal appearing white matter; CC = corpus callosum
* p-value from t-test
+ Significantly different between low-grade and high-grade gliomas, $p<0.05$

Table 4. Sensitivity, specificity, accuracy, PPV and NPV of imaging parameters with high predictive value ($p<0.05$, t-test) in differentiation of low-grade and high-grade gliomas using receiver operating characteristic curve analysis

Parameters	Cut off value	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %	AUC
ADC STR	1.326	88.46	58.82	76.74	76.67	76.92	0.71
Minimal ADC STR	1.167	80.77	58.82	72.09	75.00	66.67	0.74
Ratio ADC STR: CC	1.832	96.15	58.82	81.40	78.13	90.91	0.74
Ratio minimal ADC STR: CC	1.582	84.62	58.82	74.42	75.86	71.43	0.75

STR = solid tumoral region; CC = corpus callosum; AUC = area under curve

complex mechanism of diffusion anisotropy in gliomas is possible.

In contrast to FA value, in the present study, the ADC value, minimal ADC value and ADC ratios in solid tumoral region, and peritumoral edema were significant difference between LGG and HGG. The authors also found the values in solid tumoral region were useful in differentiating HGG from those of LGG more than in peritumoral edema. Furthermore, the ADC ratios have more accuracy than absolute ADC value. The ADC value of LGG was higher than those of HGG, which correlated with tumor cellularity. Multiple previous studies have similar results[5-7,17-22]. Another observation from the present study is that

slightly higher sensitivity and accuracy of ADC ratio in solid tumoral region relative to corpus callosum as compared with ADC ratio relative to NAWM. However, the cutoff value from ROC in all parameters to differentiate HGG from LGG have low specificity (58.82%), Table 4. It may be due to overlap ADC value in the present study. However, to avoid missing high-grade lesion, high sensitivity is needed and higher threshold is appropriate.

The present study has several limitations. First, discrepancy may have occurred between ROIs and histologic sample in heterogeneous tumor. Second, if enhancing or solid tumoral region is small, partial volume averaging of placing ROIs may occurred. Third, registration error with standard anatomic image data may have caused some inaccuracy due to spatial distortions inherent in echo-planar imaging sequence.

Conclusion

The present results demonstrated that there was significant difference in ADC value, minimal ADC value, and ADC ratios of solid tumoral region between HGG and LGG. In addition, both ADC and minimal ADC ratios gave higher prediction accuracy than absolute ADC value. Conversely, the FA value could not differentiate the two entities in the present study. The authors suggested that combination of DTI metrics and cMRI or other advanced MR imaging facilitated the accurately grading of cerebral gliomas.

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Potential conflicts of interest

None.

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คุณค่าของการตรวจภาพเอ็มอาร์ไอก้าวหน้าชนิดดิฟฟิวชั่นเท็นเซอร์ ในการแยกระหว่างเนื้องอกสมองไกลโอมาชนิดเนื้อร้ายและชนิดไม่ใช่เนื้อร้าย

ศิริวรรณ ปิยพิทยานันต์, อรสา ชวาลภาฤทธิ์, สิริอร ตริตระการ, ธีรพล วิทธิเวช, ตุ้มทิพย์ แสงรุจิ, ศรัณย์ นันทอารี, สิทธิ์ สาธรสุเมธี, ปฤณัต อิทธิเมธินทร์, จุฬาลักษณ์ โกมลตรี

วัตถุประสงค์: *เพื่อศึกษาประโยชน์และความสามารถของการตรวจภาพเอ็มอาร์ไอก้าวหน้าชนิดดิฟฟิวชั่นเท็นเซอร์ ในการแยกเนื้องอกสมองไกลโอมาชนิดเนื้อร้ายและชนิดไม่ใช่เนื้อร้าย*

วัสดุและวิธีการ: *ผู้ป่วยเนื้องอกสมองไกลโอมาได้รับการตรวจภาพเอ็มอาร์ไอก้าวหน้าชนิดดิฟฟิวชั่นเท็นเซอร์ก่อนได้รับการผ่าตัดยืนยันด้วยผลการตรวจชิ้นเนื้อทุกราย แบ่งออกเป็น 2 กลุ่ม ได้แก่ ชนิดไม่ใช่เนื้อร้ายและชนิดเนื้อร้าย ใช้ค่าวัดเอฟเอและเอดีซีในบริเวณที่สนใจ ซึ่งได้แก่ บริเวณก้อนเนื้องอก, บริเวณเนื้องอกส่วนเนื้อตาย, บริเวณสมองบวมรอบก้อน, บริเวณเนื้อสมองขาวปกติฝั่งตรงข้ามและเนื้อสมองปกติคอร์ปัสคอลโลซั่ม และคำนวณค่าเปรียบเทียบเอดีซี สถิติที่ใช้ได้แก่ t-test และ ROC curve เพื่อนำมาหาค่าวัดที่ดีที่สุดในการแยกเนื้องอกสมองสองกลุ่มนี้*

ผลการศึกษา: *มีผู้ป่วยเนื้องอกสมองไกลโอมา 43 ราย, ชนิดไม่ใช่เนื้อร้าย 17 ราย และชนิดเนื้อร้าย 26 ราย พบว่าไม่มีความแตกต่างอย่างมีนัยสำคัญของค่าเฉลี่ยเอฟเอในบริเวณที่สนใจต่าง ๆ ระหว่างไกลโอมาชนิดไม่ใช่เนื้อร้ายและชนิดเนื้อร้าย ค่าเอดีซีและค่าเอดีซีที่น้อยที่สุดของบริเวณก้อนเนื้องอกและบริเวณสมองบวมรอบก้อน, ค่าเปรียบเทียบเอดีซี และค่าเปรียบเทียบเอดีซีที่น้อยที่สุดของบริเวณก้อนเนื้องอก มีความแตกต่างอย่างมีนัยสำคัญในการแยกไกลโอมาชนิดเนื้อร้ายจากชนิดไม่ใช่เนื้อร้าย ($p<0.05$) และพบว่าค่าเปรียบเทียบของบริเวณก้อนเนื้องอกกับเนื้อสมองปกติคอร์ปัสคอลโลซั่มจะมีความแม่นยำมากที่สุดในการแยกเนื้องอกสมองสองกลุ่มนี้ (AUC = 0.74)*

สรุป: *ค่าเอดีซี, ค่าเอดีซีที่น้อยที่สุด และค่าเปรียบเทียบเอดีซีของบริเวณก้อนเนื้องอกมีประโยชน์ในการแยกก้อนเนื้องอกสมองชนิดเนื้อร้ายออกจากชนิดไม่ใช่เนื้อร้าย*