Comparison between Dynamic Contrast-Enhanced MRI and Dynamic Susceptibility Contrast MRI in Glioma Grading

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ABSTRACT

Objective: To determine the usefulness of the dynamic contrast enhanced MRI (DCE-MRI) technique for differentiating between low grade glioma and high grade glioma and compare with dynamic susceptibility contrast (DSC) MRI.

Methods: Conventional MRI, DCE-MRI and DSC-MRI were performed preoperatively in 17 patients with gliomas. Permeability indices (K^{trans}, rK^{trans}, V_e and K_{ep}) from DCE-MRI and cerebral blood volume (CBV), rCBV from DSC-MRI were quantified. The differences in K^{trans}, rK^{trans}, V_e, K_{ep}, CBV and rCBV between low grade glioma and high grade glioma were analyzed and compared. Receiver operating characteristic (ROC) curve analyses were conducted.

Results: K^{trans}, rK^{trans}, V_e, CBV and rCBV were significantly different between low grade glioma and high grade glioma ($p = 0.001$, 0.014, 0.02, 0.025, and 0.034, respectively). The areas under the ROC curve for K^{trans}, rK^{trans}, V_e, rCBV and CBV were 0.986, 0.896, 0.829, 0.852, and 0.833, respectively. K^{trans} was the best parameter for differentiating low grade glioma from high grade glioma with cutoff value of 0.0091 min-1 (sensitivity 100%, specificity 80%, PPV 87.5%, NPV 100%, accuracy 94.1%).

Conclusion: DCE-MRI could be used to estimate neovascular permeability and for pre-operative grading of glioma. Among the perfusion parameters, K^{trans} was the best parameter for differentiating low grade glioma from high grade glioma . DCE-MRI may be promising for better diagnostic performance than DSC-MRI.

Keywords: Dynamic contrast-enhanced MRI; cerebral blood volume; Ktrans; glioma (Siriraj Med J 2017;69: 369-376)

INTRODUCTION

Glioma is the most common primary intracranial neoplasm, being graded according to World Health Organization (WHO) classification from grade 1 to 4. The grading of glioma is clinically important as it determines the appropriate therapy for the patients. Conventional MRI (cMRI) provides important anatomical and diagnostic information of brain tumors. Although gadolinium-based cMRI is routinely used to predict the grade of a glioma, it is sometimes unreliable with wide range of sensitivity from 55.1% to 83.3%.[1-5]

Neovascular proliferation and degree of permeability are important in evaluation of biological aggressiveness and malignant grade in the context of glioma. The noninvasive perfusion MRI using dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced (DCE) methods have been widely implicated in the assessment of glial neoplasm. In many previous studies, relative cerebral blood volume (rCBV) measurements from DSC-MRI showed reliable correlation with tumor grade and histopathologic findings of increased tumor vascularity[6-9]. However, intratumoral hemorrhage or calcification may cause

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susceptibility artifact due to T2* effect on DSC-MRI which may influence the measurement. Recently, T1-weighted DCE–MRI has been found to permit evaluation of tumor neovasculature and permeability change with higher-spatial resolution and less susceptibility effect compared with DSC-MRI. Based on the MRI signal and pharmacokinetic models, the data have permitted the creation of parameters such as volume transfer constant (K^{trans}) and volume of extravascular extracellular space (EES) per unit volume of tissue (V_e) which lead to the qualitative and quantitative evaluation of the angiogenetic characteristics of tumors, assessment of tumor grade, and determination of the site for biopsy. Presently, there is no standard guideline or pharmacokinetic model of DCE-MRI in brain tumor. Additionally, the value of DCE parameters from each institute cannot be compared.

The aim of this study was to evaluate the diagnostic accuracy of the differentiation between low grade glioma and high grade glioma with DCE-MRI compared to DSC-MRI in our institute.

MATERIALS AND METHODS

Patient selection

The approval for the study was obtained from ethical committee of the institute before enrolling the patients. The patients were enrolled during June 2013 to December 2014. Seventeen patients (8 males, 9 females; mean age 44.29 years old; age range 17-73 years old) who underwent tumor resection or biopsy with pathologically confirmed gliomas and classified into low grade glioma and high grade glioma according to the 2007 WHO classification were recruited (Table 1). No patient received any other treatment (radiotherapy, chemotherapy) before imaging or surgery. All patients underwent cMRI and DCE–MRI, but only 15 out of 17 patients underwent DSC-MRI within 1-34 days, preoperatively.

TABLE 1. Histopathologic diagnoses of gliomas.

Diagnosis	Number of patients
Low-grade gliomas (n=10, 58.8%)	
Ganglioglioma (WHO grade I)	1
Diffuse astrocytoma (WHO grade II)	5
Oligoastrocytoma (WHO grade II)	3
Oliogodendroglioma (WHO grade II)	1
High-grade gliomas (n=7, 41.2%)	
Anaplastic oligoastrocytoma (WHO grade III)	1
Anaplastic oligodendroglioma (WHO grade III)	1
Glioblastoma (WHO grade IV)	5

Magnetic resonance techniques

MRI examinations were performed on a 3-Tesla MR system (Ingenia, Philips Medical System, Best, the Netherlands) with a 16-element head matrix coil. Routine cMRI included the following: non-contrast enhancement axial and sagittal T1-weighted image, axial and coronal T2-weighted image, axial fluid-attenuated inversion recovery (FLAIR), susceptibility weighted imaging (SWI) and diffusion weighted imaging/apparent diffusion coefficient map (DWI/ADC). Contrast-enhanced T1-weighted image was achieved in three orthogonal planes.

Perfusion MRI

DCE-MRI was performed in the first gadolinium injection. Three datasets of precontrast images were acquired as baseline acquisitions by using T1 weighted turbo field echo (repetition time (TR)/echo time (TE), 3.7/1.82 ms; field of view (FOV), 220 mm x 178 mm; matrix, 168 x 136; slice thickness, 3 mm; turbo field echo factor 40) with flip angles of 5, 10 and 15 degrees. After the second baseline acquisition, a gadolinium-based (Gd) contrast agent, Gadobutrol (Gadovist; Bayer Schering Pharma) was injected through the antecubital vein as a bolus at 2 mL/s and a dose of 0.05 mmol/kg of body weight, immediately followed by 30 mL saline flush with the help of a power injector. The 36 slice of DCE acquisition series were performed after the third baseline acquisition by using T1-weighted turbo field echo (TR/TE, 3.7/1.82 ms; FOV, 220 mm x 178 mm; matrix, 168 x 136; slice thickness, 3 mm; turbo field echo

factor 40) with flip angle of 6 degrees. The last image set consisted of 30 or 70 dynamic time points for each slice with temporal spacing of approximately 5.1 seconds. The total scan time of 30 and 70 dynamic measurements from DCE-MRI technique were 2.33 and 5.57 minutes, respectively. DCE-MRI was performed with 30 dynamic acquisitions in 12 patients and 70 dynamic acquisitions in 5 patients. From the datas of 70 dynamic series, DCE parameters of 30 dynamic series could also be evaluated. Then, DSC-MRI was performed using 3D Principles of Echo Shifting with a Train of Observations (PRESTO) sequence acquired during the first pass of Gadobutrol in the same amount of DCE at a rate of 5 mL/sec followed by a 30 mL saline flush. Imaging parameters were: FOV, 220x179 mm; section thickness, 3.5 mm; matrix, 64x 128; in-plane voxel size, 1.72x1.72 mm; flip angle, 7 degrees. A total of 60 dynamic images were acquired at 1-second intervals. Three baseline acquisitions were acquired before contrast injection. The total scan time of DSC-MRI technique was 1.16 minutes. The DSC-MRIs were available in 15 cases.

Image analysis

DCE data processing

Image analysis of DCE was carried out by using commercially available software (Philips IntelliSpace Portal, Philips Healthcare, Best, the Netherlands). The modified Tofts and Kermode pharmacokinetic model was used to calculate the K^{trans}, V_e and K_{ep} values[10]. This pharmacokinetic model is based on the assumption that contrast agents exist in two interchanging compartments (plasma and EES).

The measurements of K^{trans}, V_e and K_{ep} were obtained by simultaneous observation on axial post-contrast T1-weighted image and the corresponding parametric maps. Post-contrast T1-weighted image for enhancing tumors and T2-weighted image or FLAIR for non-enhancing tumors were used as a guide for tumor location. In some case, the parametric maps showed no color abnormality as compared with the normal background. The regions of interest (ROIs) were positioned on axial post-contrast T1-weighted mapping after careful inspection of T2-weighted image and FLAIR which showed the location of the tumor and automatically transferred on to the parametric maps. (Fig 1 and 2). Automatic search for arterial input function was done.

DSC data processing

Data processing was performed on commercial software (Philips Extended MR WorkSpace 2.6.3.5, Philips Healthcare, Best, the Netherlands). The measurements of CBV were obtained by observation on color maps.

ROI selection

An experienced neuroradiologist (S.P.) and neuroimaging fellow (C.S.) placed three to five separated ROIs for lesion in the most obvious enhancing portion or the maximal perfusion abnormality and the contralateral normal appearing white matter (NAWM) on DSC and DCE maps to obtain the K^{trans}, V_e, K_{ep} and CBV values. Then the mean values of each parameter were calculated. Cystic, necrotic, hemorrhagic regions, and normal vessels within the ROI were avoided during ROI selection (Fig1 and 2). The ratios of CBV (rCBV) and ratio of K^{trans} (rK^{trans}) from the lesion compared with contralateral NAWM were calculated.

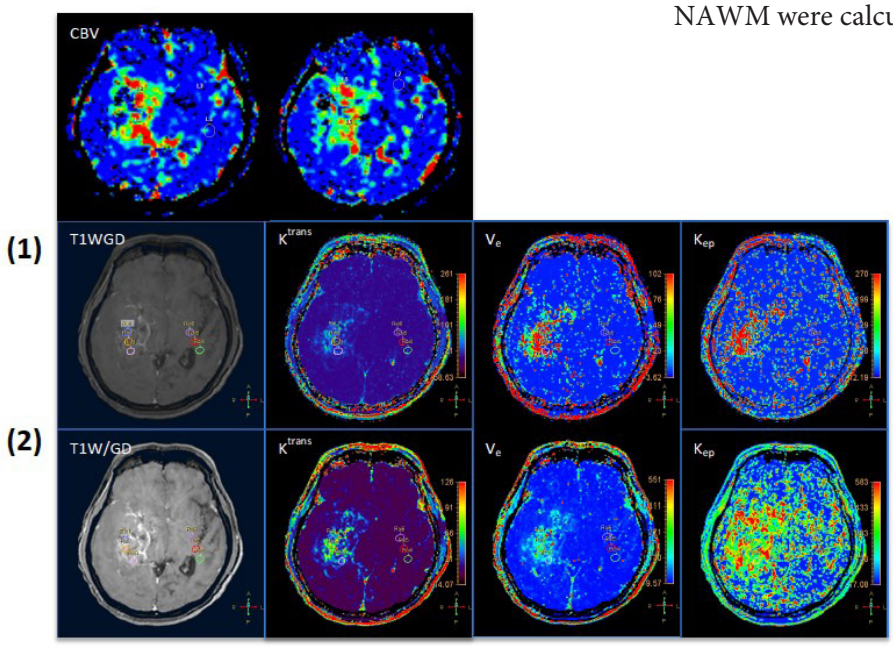

Fig 1. A 43-year-old male with pathologically proven glioblastoma with oligodendroglial component WHO 2007 grade IV. Images demonstrate ROIs in enhancing areas of tumor and contralateral NAWM. a. CBV map from DSC-MRI and parameter maps from DCE-MRI with (1) 30 and (2) 70 dynamic acquisitions

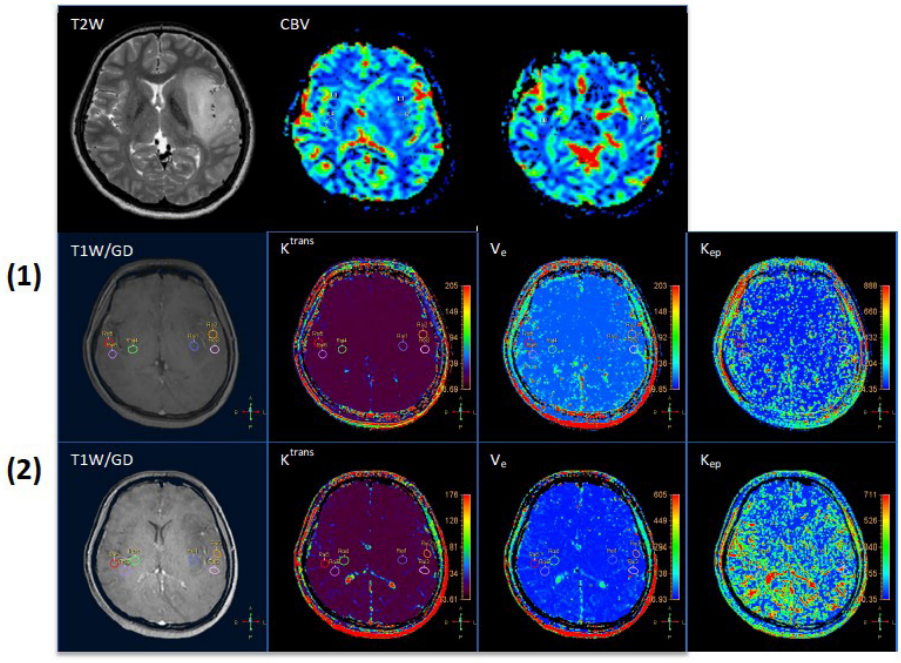

Fig 2. A 19-year-old female with diagnosed diffuse astrocytoma, WHO 2007 grade II. Images demonstrate ROIs in non-enhancing tumor and contralateral NAWM. T2-weighted image or FLAIR were used as a guide for tumor. CBV map from DSC-MRI and parameter maps from DCE-MRI with (1) 30 and (2) 70 dynamic acquisitions

Statistical analysis

All statistical analyses were performed by using SPSS software (version 18.0.0, SPSS Inc., Chicago, IL, USA) The Wilcoxon signed ranks test was used to compare the lesions with contralateral NAWM. The median of the K^{trans}, rK^{trans}, V_e, K_{ep}, CBV and rCBV were compared in each low grade glioma and high grade glioma. The Mann-Whitney U test was used to compare the low grade glioma and high grade glioma with respect to K^{trans}, rK^{trans}, V_e, K_{ep}, CBV and rCBV values. A value of $p < 0.05$ was regarded as statistically significant. The ROC curve was performed to identify cutoff point and the diagnostic performance of each parameter for distinguishing low grade glioma from high grade glioma was calculated.

RESULTS

For the K^{trans} of both groups of tumors, V_e and CBV of high grade glioma were significantly higher than NAWM. Whereas the K_{ep} in both groups of tumor, V_e and CBV of low grade glioma were not significantly different from NAWM.

In low grade glioma, the K^{trans}, rK^{trans} and V_e value from 30 dynamic acquisitions DCE; CBV and rCBV from DSC were significantly lower than those of high grade glioma ($p = 0.001$, 0.014, 0.02, 0.025, and 0.034, respectively). There was no significant difference of K_{ep} between low grade glioma and high grade glioma ($p = 0.89$) (Tables 2, 3 and 4).

The ROC curve analysis of K^{trans}, rK^{trans}, V_e, CBV and rCBV values for differentiation between low grade glioma and high grade glioma were statistically significant. (Fig 3)

Diagnostic performance, including sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) of imaging parameters with high predictive value ($p < 0.05$) in differentiation of low grade glioma and high grade glioma using ROC analysis were demonstrated in Table 5.

When compared between 30 and 70 dynamic DCE, there was tendency of higher values of all parameters from 70 dynamic scans than that of 30 dynamic scans (Table 3).

DISCUSSION

Our study demonstrated significant higher CBV in high grade glioma than in NAWM. However, CBV of low grade glioma was not significantly different from NAWM. Previous studies also showed the same findings.[4,9]

CBV and rCBV values of high grade glioma were also significantly higher than that of low grade glioma with the cutoff values of 0.928 ml/100gm for CBV (sensitivity 100%, specificity 66.7% and accuracy 80.0%) and 2.306 for rCBV (sensitivity 83.3%, specificity 77.8% and accuracy 90.0%). The cutoff rCBV value with sensitivity and specificity from our study were approximate to the result from Direksunthorn et al's study.[8]

The permeability of vascular structure is able to be measured with DCE–MRI. According to the modified Tofts and Kermode pharmacokinetic model, K^{trans} and V_e values were approximately zero in normal tissue with an intact blood–brain barrier because of no extravascular leakiness of contrast medium. In the other hand, if blood-brain barrier was destroyed, the contrast medium leakage into the extravascular or interstitial space. Therefore, K^{trans}

TABLE 2. The median (range) for DCE parameters of 30 acquisitions from the tumor ROIs and the contralateral NAWM ROIs.

DCE 30 Dynamic scans	LGG (n=10) Lesions	NAWM	P value LGG vs. NAWM*	HGG (n=7) Lesions	NAWM	p value HGG vs. NAWM*	p value LGG vs. HGG#
K^{trans} (10^{-3}/min)	0.53 (0.04-21.61)	0.19 (0-0.38)	0.014†	42.22 (12.54-280.36)	0.23 (0-1.04)	0.018†	0.001†
rK^{trans}	2.49 (0.62-207.82)			94.63 (40.52-4833.72)			0.014†
V_e (10^{-3})	0 (0-71.66)	0 (0-0)	0.068	114.88 (0-3456.28)	0 (0-0.74)	0.028†	0.02†
K_{ep} (10^{-3}/min)	0 (0-183.72)	0 (0-183.72)	0.109	54.36 (0-223.52)	0 (0-62.78)	0.075	0.089

Abbreviations: LGG = low-grade glioma, HGG = high-grade glioma, NAWM = contralateral normal appearing white matter, K^{trans} = volume transfer constant between EES and plasma (10^{-3}/min), rK^{trans} = relative volume transfer constant between EES and plasma, V_e (10^{-3}) = volume of extravascular extracellular space per unit volume of tissue (10^{-3}), K_{ep} (10^{-3}/min) = rate transfer coefficient between EES and plasma (10^{-3}/min)
*p value from *Wilcoxon signed ranks test*
p value from *Mann-Whitney U test*
† significantly different between lesions and contralateral NAWM and between LGG and HGG, $p < 0.05$.

TABLE 3. The median (range) for DCE parameters of 30 and 70 acquisitions from the tumor ROIs and the contralateral NAWM ROIs in cases which underwent DCE with 70 dynamic acquisitions.

DCE	LGG (n=3) Lesions 30D	Lesions 70D	NAWM 30D	NAWM 70D	HGG (n=2) Lesions 30D	Lesions 70D	NAWM 30D	NAWM 70D
K^{trans} (10^{-3}/min)	5.38 (0.68-5.7)	15.28 (3.35-16.40)	0.18 (0-0.38)	1.03 (0.02-1.91)	31.94 (21.66-42.22)	63.75 (51.84-75.66)	0.73 (0.41-1.04)	3.21 (2.42-4.00)
V_e (10^{-3})	20.30 (1.73-71.6)	46.49 (5.73-72.06)	0 (0)	2.49 (0-4.42)	146.86 (32.49-261.23)	751.83 (171.00-1332.67)	0.37 (0-0.74)	5.39 (3.37-7.42)
K_{ep} (10^{-3}/min)	168.06 (49.35-183.72)	385.75 (229.44-568.17)	0 (0)	265.00 (42.36-335.24)	95.40 (24.54-166.25)	163.72 (15.64-311.79)	31.39 (0-62.78)	471.23 (405.57- 536.90)

According to small sample size of DCE 70 dynamic acquisitions, the statistical significant was not calculated.
Abbreviations: LGG = low-grade glioma, HGG = high-grade glioma, NAWM = contralateral normal appearing white matter, K^{trans} = volume transfer constant between EES and plasma (10-3/min), rK^{trans} = relative volume transfer constant between EES and plasma, V_e (10-3) = volume of extravascular extracellular space per unit volume of tissue (10-3), K_{ep} (10-3/min) = rate transfer coefficient between EES and plasma (10-3/min)

TABLE 4. The median (range) for CBV and rCBV of DSC-MRI from the tumor ROIs and the contralateral NAWM.

DSC parameters	LGG (n=9) Lesions	NAWM	p value LGG vs. NAWM*	HGG (n=6) Lesions	NAWM	p value HGG vs. NAWM*	P value LGG vs. HGG#
CBV (mL/100gm)	0.59 (0.25-3.70)	0.43 (0.22-0.68)	0.214	2.75 (1.01-6.16)	0.49 (0.30-2.46)	0.028†	0.025†
rCBV	1.18 (0.65-8.53)			3.96 (1.72-9.14)			0.034†

Abbreviations: LGG = low-grade glioma, HGG = high-grade glioma, NAWM = contralateral normal appearing white matter, CBV= cerebral blood volume (ml/100 gm), rCBV = relative cerebral blood volume
* *p* value from *Wilcoxon signed ranks test*
# *p* value from *Mann-Whitney U test*
† significantly different between lesions and contralateral NAWM and between LGG and HGG, $p < 0.05$.

TABLE 5. Threshold values and diagnostic performance for each parameters for differentiation between LGG and HGG.

Parameters	Cut off value	Sensitivity %	Specificity %	Accuracy %	PPV %	NPV %	AUC	P value
K^{trans} ($x10^{-3}$)	9.119	100	90	94.1	87.5	100	0.986	0.001
rK^{trans}	27.719	100	87.5	92.9	85.7	100	0.896	0.014
V_e ($x10^{-3}$)	26.395	71.4	80	76.5	71.4	80.0	0.829	0.02
CBV (mL/100 gm)	0.928	100	66.7	80.0	66.7	100	0.852	0.025
rCBV	2.306	83.3	77.8	90.0	71.4	87.5	0.833	0.034

Abbreviations: LGG = low-grade glioma, HGG = high-grade glioma

and V_e values were increased. In our study, K^{trans} and V_e values were significantly different between tumors and NAWM, particularly in high grade glioma which might be from more destroyed blood–brain barrier.

Our results also showed that the K^{trans}, rK^{trans} and V_e from DCE-MRI 30 dynamic acquisitions were able to distinguish low grade glioma from high grade glioma. This finding was in agreement with a prior study that showed a good correlation between K^{trans} or V_e and the grades of gliomas.[11]

It was known that K^{trans} depended on blood flow, blood volume, the product of the capillary wall permeability and the surface area, whereas V_e was the ratio of quantity of contrast agent leaked into the EES to that returned to the plasma space.[11,12]

Among three DCE-MRI parameters, K^{trans} had the best discrimination between the low grade glioma and high grade glioma with the best sensitivity (100%), specificity (90%), PPV (87.5%), NPV (100%) and accuracy (94.1%) with the largest area under the ROC curves (0.986) and lowest p-value (0.014). A number of studies on glioma grading by using pharmacokinetic parameters from DCE MR imaging (in particular, K^{trans}, V_e, K_{ep} and V_p) have been published.[6,11,13-17] The results of these and previous investigations suggested that K^{trans} was a better predictive parameter for grading glioma.[11,16]

In this study, the best cutoff value of K^{trans} = 0.0091/min, and V_e = 0.0264 for differentiating between low grade glioma and high grade glioma were lower than obtained from previous studies.[11,16,18] Jia et al., showed that the cutoff value of K^{trans} = 0.035/min (sensitivity 88.9%, specificity 82.4% and AUC 0.901) and the cutoff

value of V_e = 0.130 (sensitivity 81.5%, specificity 94.1% and AUC 0.883) gave the best discrimination.[11] The discrepancy of the DCE parameters from each study may be associated with the difference in pulse sequence, arterial input function selection, the pharmacokinetic models and dynamic scan time.[19]

However, there were some disagreements in the ability of V_e values for differentiation between low grade glioma and high grade glioma. Lüdemann et al found that there were no significant differences of V_e between low grade glioma and high grade glioma.[20] Our results showed that V_e of low grade glioma was significantly lower than that of high grade glioma (Table 2). This indicated that the leakage volume was greater in high grade glioma than in low grade glioma. V_e value is influenced by several factors, such as the volume of the EES and the permeability of the vessels. For example, the volume of the EES increases in areas of necrosis or cyst formation and decreases in areas of higher cellularity. The volume of EES in high grade glioma is larger, probably due to necrosis, which may be why V_e in high grade glioma is increased. Although we avoided visualized cystic or necrotic portion on ROIs, there were micronecrosis and partial volume effect which might include more than one tissue types such as micronecrosis in a voxel.[19] The different method in placing ROI from the parameter maps of DCE-MRI may have influenced the V_e value due to the tumor inhomogeneity including area of higher cellularity, necrosis or micronecrosis.

The ability of K_{ep} for tumor grading is still inconclusive. Awasthi et al found significant higher K_{ep} in high grade glioma than low grade glioma and positive correlation between K_{ep} and matrix metalloproteinase 9 which was overexpressed in malignant glioma cells and facilitated the invasiveness of tumor cells and tumor angiogenesis.[13] Zhang et al found K_{ep} in tumor tissue was significantly lower than that in normal brain tissue, but almost constant with the tumor grades.[16] In our study, K_{ep} tended to be higher in high grade glioma in 30 dynamic scans, but we did not find any significant differences between the tumor and contralateral NAWM and between tumor grades. We also demonstrated the tendency of higher values of DCE-MRI parameters from 70 dynamic scans than that of 30 dynamic scans. These results could be due to too short scan time in 30 dynamic acquisitions (2.33 minutes) which might not allow the contrast agent into the equilibrium stage, so that K_{ep} values might not be well-evaluated. In 70 dynamic acquisitions (5.57 minutes), we observed more obvious enhancement on T1 mapping and more prominent abnormal permeability on DCE parametric maps. (Fig 1)

There were some limitations in this study. First, the sample size was slightly small for an effective statistical comparison, including accuracy of significant threshold value to distinguish the groups. Second, because of tumor inhomogeneity, the perfusion values from some parts of tumor might not reflect the entire-tumor characteristics and might have partial volume effect. Therefore, histogram analyses of pharmacokinetic parameters from parts of entire-tumor volumes may be useful. Lastly, short DCE scan time might not allow the contrast agent into the equilibrium stage. Longer DCE series might be better in representing the permeability.

CONCLUSION

DCE–MRI can be used to estimate neovascular permeability and for pre-operative grading of glioma. High grade glioma had significantly higher values of K^{trans}, and V_e than low grade glioma. The cutoff values of K^{trans} = 0.0091/min and V_e = 0.0264 were effective for differentiating between low grade glioma and high grade glioma. Among the perfusion parameters, K^{trans} is the best predictor due to highest sensitivity, specificity, accuracy, largest AUC. DCE-MRI had better diagnostic performance than DSC-MRI.

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REFERENCES

1. Dean BL, Drayer BP, Bird CR, Flom RA, Hodak JA, Coons SW, et al. Gliomas: classification with MR imaging. Radiology. 1990;174(2):411-5.
2. Watanabe M, Tanaka R, Takeda N. Magnetic resonance imaging and histopathology of cerebral gliomas. Neuroradiology. 1992;34(6):463-9.
3. Kondziolka D, Lunsford LD, Martinez AJ. Unreliability of contemporary neurodiagnostic imaging in evaluating suspected adult supratentorial (low-grade) astrocytoma. J Neurosurg. 1993;79(4):533-6.
4. Knopp EA, Cha S, Johnson G, Mazumdar A, Golfinos JG, Zagzag D, et al. Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging. Radiology. 1999;211(3):791-8.
5. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, et al. Glioma grading: sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. AJNR Am J Neuroradiol. 2003;24(10):1989-98.
6. Law M, Yang S, Babb JS, Knopp EA, Golfinos JG, Zagzag D, et al. Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR

imaging with glioma grade. AJNR American journal of neuroradiology. 2004;25(5):746-55.
7. Law M, Young R, Babb J, Pollack E, Johnson G. Histogram analysis versus region of interest analysis of dynamic susceptibility contrast perfusion MR imaging data in the grading of cerebral gliomas. AJNR Am J Neuroradiol. 2007;28(4):761-6.
8. Direksunthorn T, Chawalparit O, Sangruchi T, Witthiwej T, Tritrakarn SO, Piyapittayanan S, et al. Diagnostic performance of perfusion MRI in differentiating low-grade and high-grade gliomas: advanced MRI in glioma, A Siriraj project. J Med Assoc Thai. 2013;96(9):1183-90.
9. Aronen HJ, Gazit IE, Louis DN, Buchbinder BR, Pardo FS, Weisskoff RM, et al. Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings. Radiology. 1994;191(1):41-51.
10. Chikui T, Obara M, Simonetti AW, Ohga M, Koga S, Kawano S, et al. The principal of dynamic contrast enhanced MRI, the method of pharmacokinetic analysis, and its application in the head and neck region. Int J Dent. 2012;2012:480659.
11. Jia Z, Geng D, Xie T, Zhang J, Liu Y. Quantitative analysis of neovascular permeability in glioma by dynamic contrast-enhanced MR imaging. J Clin Neurosci. 2012;19(6):820-3.
12. Peng SL, Chen CF, Liu HL, Lui CC, Huang YJ, Lee TH, et al. Analysis of parametric histogram from dynamic contrast-enhanced MRI: application in evaluating brain tumor response to radiotherapy. NMR Biomed. 2013;26(4):443-50.
13. Awasthi R, Rathore RK, Soni P, Sahoo P, Awasthi A, Husain N, et al. Discriminant analysis to classify glioma grading using dynamic contrast-enhanced MRI and immunohistochemical markers. Neuroradiology. 2012;54(3):205-13.
14. Choi HS, Kim AH, Ahn SS, Shin NY, Kim J, Lee SK. Glioma grading capability: comparisons among parameters from dynamic contrast-enhanced MRI and ADC value on DWI. Korean journal of radiology. 2013;14(3):487-92.
15. Jackson A, O'Connor JP, Parker GJ, Jayson GC. Imaging tumor vascular heterogeneity and angiogenesis using dynamic contrast-enhanced magnetic resonance imaging. Clin Cancer Res. 2007;13(12):3449-59.
16. Zhang N, Zhang L, Qiu B, Meng L, Wang X, Hou BL. Correlation of volume transfer coefficient Ktrans with histopathologic grades of gliomas. J Magn Reson Imaging. 2012;36(2):355-63.
17. Provenzale JM, Wang GR, Brenner T, Petrella JR, Sorensen AG. Comparison of permeability in high-grade and low-grade brain tumors using dynamic susceptibility contrast MR imaging. AJR Am J Roentgenol. 2002;178(3):711-6.
18. Jung SC, Yeom JA, Kim JH, Ryoo I, Kim SC, Shin H, et al. Glioma: Application of histogram analysis of pharmacokinetic parameters from T1-weighted dynamic contrast-enhanced MR imaging to tumor grading. AJNR Am J Neuroradiol. 2014;35(6):1103-10.
19. Jackson A. Analysis of dynamic contrast enhanced MRI. Br J Radiol. 2004;77 Spec No 2:S154-66.
20. Ludemann L, Grieger W, Wurm R, Wust P, Zimmer C. Quantitative measurement of leakage volume and permeability in gliomas, meningiomas and brain metastases with dynamic contrast-enhanced MRI. Magn Reson Imaging. 2005;23(8):833-41.