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ORIGINAL ARTICLE

Pilot study on evaluation of any correlation between MR perfusion (K^{trans}) and diffusion (apparent diffusion coefficient) parameters in brain tumors at 3 Tesla

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Abstract

Purpose: To assess any correlation of volume transfer constant (K^{trans}) with apparent diffusion coefficient (ADC) in different brain tumor types at 3 T magnetic resonance (MR) imaging. **Materials and methods:** Thirteen patients with brain tumors (8 men, 5 women; mean age 54.6 ± 17.7 years) were enrolled in this retrospective study. All patients underwent dynamic contrast-enhanced T_1-weighted MR perfusion and diffusion-weighted imaging using a 3 T scanner. K^{trans} was estimated by specially designed software. For each tumor, regions of interest (ROIs) were manually selected on corresponding K^{trans} and ADC maps. Pearson correlation coefficients were obtained for maximum, mean and minimum values of K^{trans} and ADC of all ROIs. Based on clinicopathologic results, the final diagnoses of patients were glioblastoma multiforme (3), low-grade to anaplastic gliomas (4), meningiomas (3) and metastatic tumors (3). **Results**: K^{trans}(max) values were significantly inversely correlated with ADC(min) values ($r = -0.536$, $P < 0.001$) and ADC(mean) values ($r = -0.465$, $P < 0.001$). K^{trans}(mean) and K^{trans}(min) values were significantly inversely correlated with ADC(mean) ($r = -0.228$, $P = 0.038$) and ADC(max) values ($r = -0.355$, $P = 0.001$), respectively. **Conclusion**: We found that irrespective of brain tumor type, there is an inverse correlation between ADC and K^{trans}. Our findings highlight an intricate relationship between vascular permeability and the tumor microenvironment, probably modulating and/or interacting with changes such as increased cellularity, ischemic insult and varying extracellular matrix composition.

Keywords: *Dynamic contrast-enhanced MRI; diffusion-weighted imaging; brain tumor; apparent diffusion coefficient; permeability; blood–brain barrier.*

Introduction

The World Health Organization grading system of cerebral tumors is based on criteria such as cellular and nuclear pleomorphism, increased cellularity, microvascular proliferation, and/or necrosis. These features tend to appear in a predictable sequence[1]. Microvascular proliferation can be assessed by microvessel density in postoperative specimens and vascular endothelial growth factors (VEGF) by serum studies[2]. Recent evidence suggests that vascular permeability and the presence of VEGF/vascular permeability factor are important mediators of brain tumor growth in addition to angiogenesis[3].

Previous studies on perfusion and permeability magnetic resonance imaging (MRI), either by T1 dynamic contrast-enhanced (DCE MRI or T2* dynamic susceptibility contrast (DSC) MRI, had shown correlations between regional cerebral blood volume, microvascular permeability and tumor grading[4–7] as well as molecular markers such as VEGF[8,9]. In the last decade, many studies on the measurement of volume transfer constant (K^{trans}) in different types of brain tumors were published[10–14]. Despite variations in acquisition methods and

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Table 1 A summary of demographic data, clinical and histological diagnoses of 13 patients

Age (years)	Gender	Clinical diagnosis	Histologic diagnosis	Use of steroids prior to MRI
27	M	Duodenal stromal tumor, left frontal temporal tumor	Metastatic gastrointestinal stromal tumor	Nil
30	M	Right temporal parietal tumor	Anaplastic oligoastrocytoma, (grade III)	Nil
41	M	Left frontal tumor	Astrocytoma (grade II)	Nil
46	M	Left frontal tumor	Anaplastic oligoastrocytoma (grade III)	No steroids
48	M	Turcot syndrome, left frontal tumor	Oligoastrocytoma (grade II, progressing to grade III)	Nil
48	F	Right upper lobe lung mass, left temporal tumor	High-grade malignant tumor, consistent with rhabdoid tumor	Steroids for 1 day
51	M	Splenium of corpus callosum	Glioblastoma in background of gemistocytic astrocytoma	Nil
55	M	Left insula tumor	Glioblastoma	Nil
57	F	Known parasagittal meningioma	Nil	Nil
72	F	Solitary right inferior parietal tumor, known carcinoma of lung	Nil	Nil
74	F	Known frontal meningioma	Nil	Nil
77	M	Left temporal tumor	GBM	No record available
84	F	Left parietal tumor	Meningioma	Steroid for 1 day

pharmacokinetic modeling (either first-pass T2* DSC MRI or steady-state T1 DCE MRI), these studies have validated the consistencies in the quantitative measurement of K^{trans} and other kinetic parameters such as total extravascular extracellular space (EES) (v_e)[15].

Another key histologic feature in tumor grading is cellular density. Diffusion-weighted imaging (DWI) has been successful in assessing cellularity of brain tumors as apparent diffusion coefficient (ADC) is thought to be inversely correlated with tumor cellularity and hence glioma grade[16,17]. A recent study by Murakami et al.[18] found that combining ADC difference values with minimum values facilitated grading of astrocytic tumors despite background heterogeneity. The role of DWI in other tumor types has also been explored[19,20]. Generally speaking, ADC is not sensitive enough to differentiate between different tumor pathologies. Nonetheless, ADC has been proposed as an early biomarker for tumor response[21]. An increase in ADC was found to occur shortly after successful treatment, which correlated with breakdown of cellular membranes and reduction in cell density, both preceding changes in tumor size.

Although ADC is thought to be inversely correlated with tumor cellularity, a recent study on oligodendrogliomas showed no such relationship[22]. The complex nature of the tumor microenvironment is further exemplified by a recent study that found no relationship between v_e and ADC[23], although both parameters are postulated to be inversely related to cellularity.

As K^{trans} (index of endothelial permeability) and ADC (marker of tissue water diffusion restriction and cellularity) provide physiologic and functional information on the tumor microenvironment, we hypothesize that there exists an intricate relationship between them. In addition, we attempt to explore this relationship in a wide spectrum of brain tumors, which we found lacking in the current literature because previous studies tend to focus on a single type of brain pathology. In this pilot study, we attempt to evaluate the correlation between K^{trans} and ADC in different types of brain tumors at 3 T MRI and the possible underlying mechanisms.

Materials and methods

Patients

All patients were scanned either for preoperative assessment or clinical management, with informed consent obtained for use of their MR images. Local institutional review board approval was not required for such a retrospective study.

Thirteen patients with different types of brain tumor (8 male and 5 female patients; mean age 54.6 years SD $\pm$ 17.7 years) were enrolled in this retrospective study between August 2009 and March 2010. All patients underwent preoperative T1 DCE MR perfusion and DWI using a 3 T MRI scanner.

In 10 of the 13 patients, pathologic results were obtained either postoperatively or at biopsy and for the remaining 3 patients, clinical diagnoses were based on medical history and brain MRI. They were classified into 4 groups (Table 1): (1) glioblastoma multiforme (GBM) (3 cases); (2) astrocytoma/oligoastrocytoma/anaplastic oligoastrocytoma (4 cases); (3) meningioma (3 cases); (4) metastatic carcinoma (3 cases).

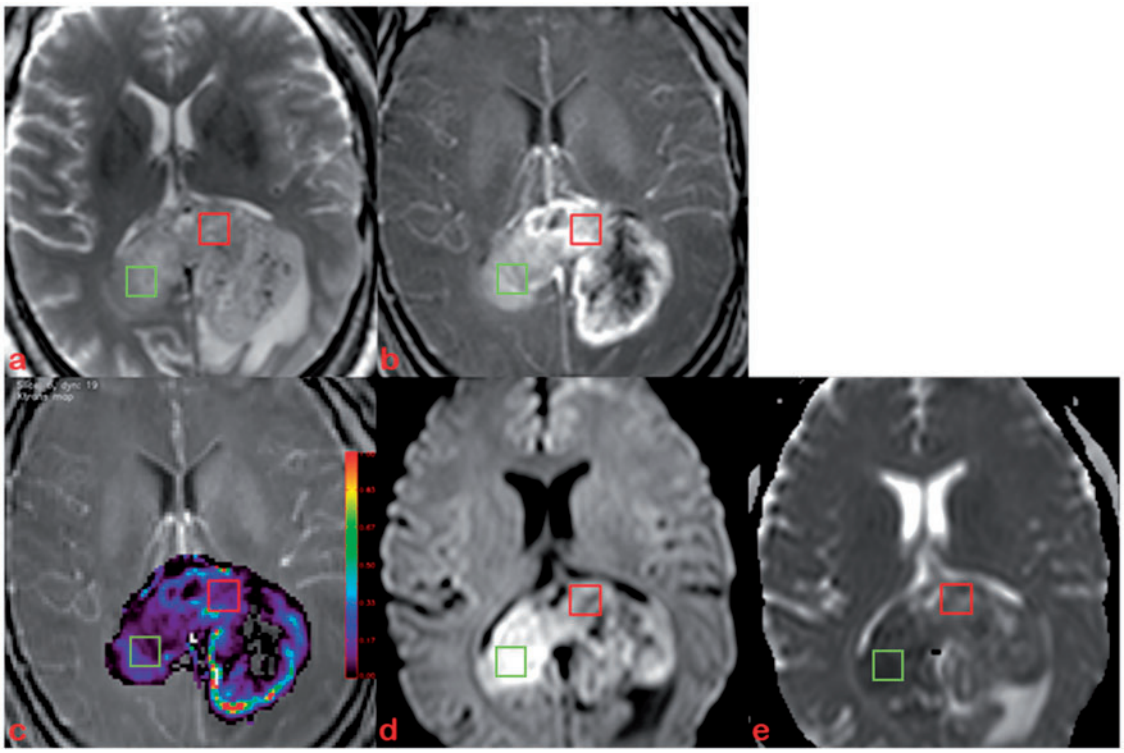

Figure 1 **Axial T_2-weighted image (a), post-contrast T_1-weighted image (b) of a 51-year-old man with GBM in splenium of corpus callosum. Five to 7 ROIs (40–60 mm^2, 2 examples shown) were manually selected on the corresponding slices of K^{trans} (c), DWI (d) and ADC map (e) using Image J.**

Imaging protocol

All MRI studies were performed with a 3 T MRI scanner (Philips Healthcare, Netherlands). Conventional MRI, DCE images and DWI were acquired during the same procedure. Conventional MRI consisted of a T_1-weighted sequence (inversion recovery turbo spin-echo, repetition time (TR)/time for inversion (TI) 2000/800 ms, echo time (TE) 20 ms, field of view (FOV) 230 × 230 × 137 mm, slice thickness 5 mm, gap 0.5 mm); T_2-weighted sequence (spin-echo, TR/TE 3937/80 ms, FOV 230 × 230 × 137 mm, slice thickness 5 mm, gap 0.5 mm); susceptibility weighted imaging (three-dimensional (3D) T_1-weighted fast-field echo (FFE), TR/TE 17/24 ms, flip angle 15°, voxel size 0.9 × 0.9 × 2 mm^3); fluid attenuated inversion recovery (TR/TI 11000/2800 ms, TE 125 ms, slice thickness 5 mm, gap 0.5 mm, coronal plane).

DWIs were acquired in the transverse plane by using a spin-echo single-shot echoplanar imaging sequence (TR/TE 3491/44 ms, FOV 230 × 230 × 137 mm, thickness 5 mm, flip angle 90°, b-values of 0 and 1200 s/mm^2).

Pre-contrast 3D FFE images were acquired prior to contrast injection (TR/TE 13/1.36 ms, FOV 230 × 193 × 70 mm, voxel size 1.4 × 1.4 × 6 mm^3, flip angle 5°). This was followed by a DCE series using the same sequence except for a flip angle of 15°. After 10 dynamic scans, a bolus of 0.1 mmol/kg gadoteric acid (Dotarem; Guerbet, France) was injected intravenously at 3 ml/s, followed by saline flush of an equal amount. Conventional contrast-enhanced T_1-weighted sequence (spin-echo, TR/TE 450/10 ms, FOV 230 × 230 × 137 mm; slice thickness 5 mm, gap 0.5 mm) was also obtained afterwards.

Image processing

K^{trans} was estimated by specially designed software[24] based on the two-compartment model (generalized kinetic model), which has been described thoroughly in a previous review by Tofts et al.[25]. K^{trans}, one of the principle parameters, is equal to the product of the capillary wall permeability and capillary wall surface area per unit volume. K^{trans} maps were automatically generated by this software, after input of preliminarily acquired T_1-weighted maps of flip angle 5° and 15°. In this procedure, the anterior cerebral artery (ACA) was selected as arterial input function (AIF). K^{trans} and ADC maps were then quantitatively analyzed using Image J software. For each tumor, 5 to 7 ROIs of 40–60 mm^2 were manually selected on the corresponding slices of K^{trans} and ADC maps (Fig. 1) by an experienced radiologist (JPC), supervised by a neuroradiologist (HKM). Both had more than 10 years experience in reading brain images. ROI selection was based on enhanced T_1-weighted images avoiding

necrotic and cystic components. For low-grade gliomas, T_1-weighted and T_2-weighted images were also used in addition to enhanced T_1-weighted images for ROI placement. The maximum, mean and minimum values of K^{trans} and ADC in each ROI were calculated by Image J. There were 83 ROIs in total: group 1 (20), group 2 (24), group 3 (20) and group 4 (19).

Statistical analysis

The mean ± SD of maximum, mean and minimum values of K^{trans} and ADC in all ROIs were computed. Correlation between these values of K^{trans} and ADC were analyzed by Pearson correlation.

Results

Correlation of K^{trans} and ADC values

The mean ± SD of maximum, mean and minimum values of K^{trans} and ADC for 83 ROIs are summarized in Table 2.

K^{trans}(max) values were significantly inversely correlated with ADC(min) values ($r = -0.536$, $P < 0.001$) and ADC(mean) values ($r = -0.465$, $P < 0.001$); K^{trans}(mean) values were also inversely correlated with ADC(mean) ($r = -0.228$, $P = 0.038$) and ADC(max) ($r = -0.421$, $P < 0.001$) values; K^{trans}(min) values were significantly inversely correlated with ADC(max) values ($r = -0.355$, $P = 0.001$) and significantly directly correlated with ADC(min) values ($r = 0.222$, $P = 0.043$) (Table 3).

Table 2 The mean ± SD of maximum, mean and minimum values of K^{trans} and ADC in 83 ROIs

	Mean ± SD
K^{trans} (mean)	0.34 ± 0.27
K^{trans} (min)	0.21 ± 0.20
K^{trans} (max)	0.91 ± 1.01
ADC (mean)	0.90 ± 0.30
ADC (min)	0.73 ± 0.26
ADC (max)	1.16 ± 0.41

K^{trans} measurements are expressed/min; ADC measurements are expressed in $\times 10^{-3}$ mm^2/s.

Discussion

Our results demonstrated that irrespective of tumor type, K^{trans}(max) values were significantly inversely correlated with ADC(min) values ($r = -0.536$, $P < 0.001$), and K^{trans}(mean) values were significantly inversely correlated with ADC(mean) ($r = -0.228$, $P = 0.038$).

To our knowledge, this relationship has not been reported in a single study based on a spectrum of brain tumor types. The findings supported our hypothesis that there was an intricate relationship between capillary membrane permeability and water diffusion property in the tumor microenvironment although the exact mechanism is not understood. A similar observation had been reported by Langer et al.[26] in prostate cancer although the inverse correlation between K^{trans} and ADC was weak in their study (Pearson correlation coefficient = –0.213).

We propose several possibilities for this phenomenon in our study. First, this significant inverse correlation between K^{trans}(max) and ADC(min) or K^{trans}(mean) and ADC(mean), irrespective of tumor type, might be explained by tumor cellularity. Yankeelov et al.[27] found that lower ADC values correspond to increased K^{trans} in pre-treatment breast cancer, and the authors reasonably expected that areas of rapid proliferation and increased cell density present a decreased ADC. Moreover, high-grade tumors with florid microvascular proliferation tend to have an increase in immature tumoral vessels, which might also explain the inverse correlation between K^{trans} and ADC[28].

However, a word of caution should be made prior to this generalization. Theoretical Monte Carlo simulations suggest that changes in tissue water diffusion following tissue damage are predominately attributable to alterations in the volume and tortuosity of the extracellular space. Although these properties of the extracellular space are primarily a function of cell density, ADC values cannot predict tumor cellularity[29].

Second, rapidly growing tumors are capable of outstripping their vascular supply, leading to cellular ischemia. DWI has been shown to be efficacious in demonstrating areas of acute infarction in the setting of brain tumors[30]. In a recent study of blood–brain barrier leakage in rats[31] following temporary focal cerebral

Table 3 The correlation between K^{trans} and ADC in all ROIs (n = 83)

		ADC(mean)	ADC(min)	ADC(max)
Ktrans(mean)	Pearson correlation	–0.228*	–0.004	–0.421**
	(*P* value)	(0.038)	(0.968)	(<0.001)
Ktrans(min)	Pearson correlation	–0.033	0.222*	–0.355**
	(*P* value)	(0.770)	(0.043)	(0.001)
Ktrans(max)	Pearson correlation	–0.465**	–0.536**	–0.097
	(*P* value)	(<0.001)	(<0.001)	(0.383)

*Correlation is significant at a 0.05 significance level (2-tailed).
**Correlation is significant at a 0.01 significance level (2-tailed).

ischemia, ADC values were significantly inversely correlated and ischemic lesion volumes significantly directly correlated with K^{trans} values. The results further showed that after ischemia reperfusion in rats, the magnitude of blood–brain barrier leakage diminished over time and correlated with the severity and extent of ischemic injury. Hence, besides increased cellularity, ischemic episodes in tumors might be partly responsible for our findings.

Third, extracellular matrix composition might be an additional factor. Jenkinson et al.[22] found no linear correlation between mean ADC and mean cell density in oligodendroglial tumors and suggested that the composition of the extracellular matrix might influence ADC more than cellularity. Hyaluronan, one of the main hydrophilic components of the extracellular matrix in gliomas, contributing to ADC differences between high- and low-grade glial tumors has been proposed[32].

Moreover, interstitial edema might affect the extracellular composition in tumors with a leaky blood–brain barrier. The study of therapeutic response in breast carcinoma by Yankeelov et al.[27] reported a negative correlation between v_e and ADC values, with ADC increasing and v_e decreasing following treatment. They hypothesized that these findings may reflect a decrease in interstitial fluid pressure following treatment, aiding the elimination of cell debris and causing an increase in ADC but an overall decrease in v_e. In the study by Mills et al.[23], the authors hypothesized that both ADC and v_e reflect the size of the EES in patients with GBM but found no direct correlation between the 2 parameters. Their findings revealed the complex nature of the tumor environment and supported our views that ADC may be influenced by multiple parameters, some of which are proposed in the current study.

The limitations of our study were as follows: first, the relatively small sample size (83 ROI records from 13 patients). Hence, our findings should be further evaluated and confirmed by a large-scale study. Second, the choice of ACA for AIF was empirical. It was based on a subgroup analysis of our dataset (8 patients) using either anterior cerebral, right middle cerebral or left middle cerebral arteries as AIF, which revealed that ACA as input resulted in the best shape of the AIF curve. Although ACA as AIF input also led to higher absolute K^{trans} values compared with the other 2, our observations based on statistical trends were unlikely to be affected. Furthermore, the cranio-caudal coverage was limited (only 7 cm) in the DCE study and could not include the proximal middle cerebral arteries in some patients. Conversely, the anterior cerebral arteries could be consistently located for all patients. Third, any use of steroids could affect ADC and K^{trans} results. In our study, 10 of 13 patients did not receive any steroids prior to MRI scanning and 2 were on steroids for just 1 day (Table 1). The effect of steroids in our group of patients was therefore minimal.

Conclusion

We found that irrespective of brain tumor type, there is an inverse relationship between ADC and K^{trans}. Our finding highlights an intricate relationship between vascular permeability and the tumor microenvironment, probably modulating and/or interacting with changes such as increased cellularity, ischemic insult and varying extracellular matrix composition.

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