Diffusion-based Heterogeneity Models in Magnetic Resonance Imaging for Characterization of Brain Tumors - An Introductory Study

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Introduction

Brain and other nervous system tumors account for approximately 1.4 percent of new primary cancer cases in the United States. Even more common within the brain are metastases from other primary sites, which have been estimated to affect 20 to 40% of all adult cancer patients - 150,000 to 170,000 persons annually[1]. Although brain tumors occur less frequently than tumors of more common primary sites, they are often refractory to treatment, are more difficult to manage surgically, and confer extremely high morbidity and mortality.

Clinical management of brain tumor patients has increasingly relied on neuroimaging, in particular magnetic resonance (MR) imaging, to provide information central to patient care. While conventional T1-weighted and T2-weighted images remain central to radiologic evaluation, additional MR modalities are being increasingly used for diagnosis and disease management.

One such method, diffusion MR imaging, provides information regarding the diffusion characteristics of water within tissues. Diffusion-based imaging includes a variety of modalities, including more basic diffusion-weighted imaging (DWI), which generally describes mean water diffusion within an imaging voxel. Apparent diffusion coefficient (ADC) maps, discussed later, also provide a modified method of quantifying mean diffusion. Other higher-order diffusion models can provide more specific information - for example, regarding directionality of diffusion (as in diffusion tensor imaging, or DTI) or even heterogeneity of water diffusion behavior, discussed here.

Recently developed diffusion-based protocols have been proposed for assessing the heterogeneity of water diffusion in neural tissues, including brain tumors. A conceptual representation of water diffusion heterogeneity is shown in Figure 1. In this introductory study, a small set of patients were scanned using conventional diffusion-weighted MR sequences and fitted with two recently developed diffusion heterogeneity models - α heterogeneity[2] and diffusion kurtosis imaging (DKI)[3] models - with the goal of assessing applicability toward tumor grading and localization.

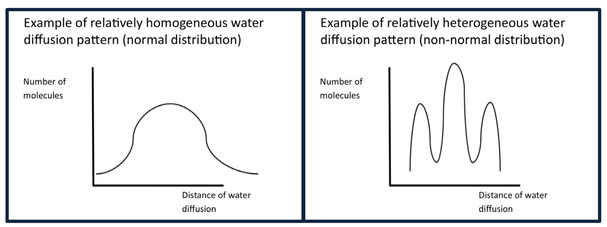

Figure 1: Two histograms for conceptual representation of water diffusion behavior. At left, generally homogeneous, or "Gaussian" diffusion. At right, generally heterogeneous, or "non-Gaussian" diffusion.

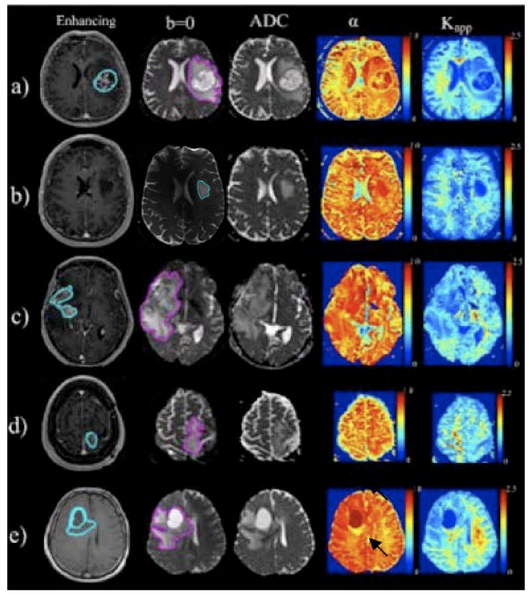

Figure 2: Columns from left to right: T1-weighted contrast-enhanced MR, T2-weighted MR, ADC maps, α-heterogeneity maps (orange), and DKI maps (blue) for patients (a – e).

Methods

In this introductory study, five patients were scanned with full institutional review board approval at a major medical center. All were undergoing clinical contrast-enhanced stereotactic MRI for previously diagnosed tumor evaluation. Each tumor was pathologically identified and graded at time of surgery, using World Health Organization (WHO) classification system. One patient had metastatic disease (a), one had a low-grade glioma (WHO grade II, b), and three had high-grade gliomas (WHO grade III or IV, c - e).

Research sequences were added to existing clinical scans. Echo planar imaging (EPI) sequences were implemented on a General Electric 3T scanner using 40mT/m gradients. DWI images were acquired using three gradient directions along the X, Y and Z axes and using six b-values (0, 500, 1000, 1500, 2000, and 2,500 s/mm^2). Imaging parameters used were TR/TE = 4000/104 ms, NEX = 6, slice thickness 5mm, FOV 240x240 mm^2, and matrix 128x128.

Two discrete regions were identified for further analysis in each patient. Tumor area was defined using standard contrast-enhanced T1-weighted MR. Peri-tumoral area was identified by abnormal T2-weighted signal around the tumor, signifying surrounding edema. Finally, diffusion heterogeneity maps were constructed using parameters α and K_{app}, as shown in Figure 2.

Results

Table 1 shows values for ADC and diffusion heterogeneity parameters α and K_{app} in the patients described.

In the high-grade gliomas (c – e), tumor areas showed generally more heterogeneity than in surrounding brain (lower α and higher $K_{app)}$, indicating more erratic diffusion behavior in the tumor than healthy brain. However, these results were not statistically significant when margin of error was taken into account. ADC was generally lower in high-grade primary tumor regions than corresponding peri-tumor regions, indicating reduced mean diffusion.

When compared to the low-grade glioma (b), tumor areas in high-grade gliomas did appear to behave differently; high-grade tumors displayed more heterogeneous diffusion parameters (lower α and higher K_{app}) when compared with the low-grade case.

The metastatic case (a) behaved differently, with less diffusion heterogeneity in the tumoral area than in surrounding brain. The metastasis had tumoral α values similar to that of high-grade gliomas, but K_{app} values corresponding to the low-grade case. ADC in the metastasis was much higher than surrounding brain, possibly due to altered cellularity.

In addition, we found that there exists a mismatch among the regions of heterogeneity by α and K_{app} maps and enhancing regions, suggesting a potential alternative for assessment of tumor margins.

Type	Metastasis		Low-grade glioma		High-grade glioma					
Case	A		B		C		D		E	
ROI	Tumor	Peri	Tumor	Peri	Tumor	Peri	Tumor	Peri	Tumor	Peri
ADC	2.90± 0.50	1.80± 0.40	1.90± 0.17		1.70± 0.70	2.00± 0.20	1.50± 0.15	1.7± 0.46	1.20± 0.34	1.70± 0.35
α	0.78± 0.12	0.77± 0.05	0.87± 0.04	-	0.76± 0.08	0.80± 0.03	0.76± 0.04	0.77± 0.04	0.73± 0.08	0.79± 0.04
K_{app}	0.36± 0.15	0.58± 0.14	0.36± 0.07	-	0.55± 0.14	0.46± 0.07	0.60± 0.06	0.55± 0.07	0.84± 0.24	0.55± 0.17

Table 1: Results showing ADC, α, and K_{app} *values for tumor and surrounding brain in 5 different patients. Patient B had no clear area of surrounding edema on imaging, so this region of interest was excluded.*

Conclusions

Despite limitations regarding study size, the exercise described shows potential utility of higher-order diffusion heterogeneity parameters α and K_{app} to gain further insight into tumor pathology. Specifically, these techniques may be promising diagnostically in determining tumor type and grade, especially in differentiating high-grade gliomas from lower-grade gliomas. This may become increasingly valuable as treatment options improve in coming decades. With respect to tumor margins, these modalities may prove a useful alternative to conventional methods of defining boundaries. Especially in biopsy-heavy centers, this has the potential to improve diagnostic yield of brain biopsies.

Application of these models to distinguish tumor recurrence from post-treatment change is ongoing. This exercise is consistent with other recent works in demonstrating the utility of parameters α and K_{app} in understanding brain anatomy and pathology[4].

Larger patient sets with distinct tumor histologies (e.g., low-grade glioma, high-grade glioma, meningioma, medulloblastoma, and metastatic disease from specific primary sites) could be examined in more detail. Pathologic correlation with tumor tissue morphology should be further explored. These parameters could be explored for evaluation and grading of other solid organ tumors, such as liver, colon, breast, or prostate cancer.

Sources

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