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Original paper

Differentiation of glioma malignancy grade using diffusion MRI

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ABSTRACT

Modern diffusion MR protocols allow one to acquire the multi-shell diffusion data with high diffusion weightings in a clinically feasible time. In the present work we assessed three diffusion approaches based on diffusion and kurtosis tensor imaging (DTI, DKI), and neurite orientation dispersion and density imaging (NODDI) as possible biomarkers for human brain glioma grade differentiation based on the one diffusion protocol. We used three diffusion weightings (so called *b*-values) equal to 0, 1000, and 2500 s/mm^2 with 60 non-coplanar diffusion directions in the case of non-zero *b*-values. The patient groups of the glioma grades II, III, and IV consist of 8 subjects per group. We found that DKI, and NODDI scalar metrics can be effectively used as glioma grade biomarkers with a significant difference ($p < 0.05$) for grading between low- and high-grade gliomas, in particular, for glioma II versus glioma III grades, and glioma III versus glioma IV grades. The use of mean/axial kurtosis and intra-axonal fraction/orientation dispersion index metrics allowed us to obtain the most feasible and reliable differentiation criteria. For example, in the case of glioma grades II, III, and IV the mean kurtosis is equal to 0.31, 0.51, and 0.90, and the orientation dispersion index is equal to 0.14, 0.30, and 0.59, respectively. The limitations and perspectives of the biophysical diffusion models based on intra-/extra-axonal compartmentalisation for glioma differentiation are discussed.

1. Introduction

Diffusion MRI is one of the most powerful imaging modalities that allows one to probe and visualise the human brain organisation *in vivo* at the micrometer scale. Diffusion weighted imaging allows one to probe and observe anisotropic features of axon bundles in the white matter or intricate tissue compartmentalisation in the grey matter through associated attenuation of the diffusion signal depending on the magnitude and direction of applied diffusion gradients [1]. In turn, an interpretation of measured diffusion signal attenuation in a macroscopic voxel in terms of a characteristic diffusion length is a theoretically and computationally very challenging problem [2]. Many diffusion approaches have been suggested in order to explain the signal attenuation depending on diffusion weightings (so called *b*-values) and diffusion encoding gradient schemes. The widely used phenomenological approach is based on a simple data fit of signal decay using the Gaussian diffusion assumption, i.e. the normalised signal attenuation *S* reads: $\log(S) = -b \cdot D_{ADC}$; also known as diffusion tensor imaging (DTI), where D_{ADC} is the apparent diffusion coefficient [3]. Later, the DTI model was extended in order to take into account the higher-order terms of the diffusion propagator by use of a cumulant expansion of signal attenuation: $\log(S) = -b \cdot D_{ADC} + 1/6\ (b \cdot D_{ADC})^2 \cdot K_{AKC}$, where K_{AKC} is the apparent kurtosis coefficient. This approach is known as diffusion kurtosis imaging (DKI) [4]. Purely mathematical fitting of the signal attenuation limits the tensor based approaches due to omitting an explanation of the underlying microstructure. It motivated additional attempts to describe the diffusion processes in terms of different compartments and to provide an adequate interpretation of diffusion signal attenuation. The diffusion MRI community developed a few biophysical models, for example, the composite hindered and restricted model of diffusion (CHARMED) [5], AxCaliber [6], ActiveAx [7], white matter tract integrity (WMTI) with intra- and extra-axonal spaces [8], neurite orientation dispersion and density imaging (NODDI) [9,10], and some others.

The resulting scalar metrics of developed diffusion approaches, in particular, DTI and DKI, are extensively used in clinical studies as sensitive biomarkers of many diseases [11,12]. The role of diffusion imaging in oncology diagnostics is constantly growing, especially, in neurooncology research and glioma grade differentiation [13–15]. Gliomas are the most common type of brain tumours and include around half of the primary brain tumour diagnoses. The World Health Organisation (WHO) divides the glioma grades

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into four groups [16]. Accurate and robust glioma differentiation is a critical procedure for the selection of treatment strategies, evaluation of radiochemotherapy, and prognosis of survival rates. The "gold standard" in the glioma grading is still based on histological and immunohistochemical features of the tumour such as atypia, cellular proliferating index, miotic activity, and the presence of necrosis. The grading examination often requires invasive manipulations such as biopsy or surgical resection with associated risks. In contrast, diffusion MRI offers a non-invasive neuroimaging technique with an ability to perform the glioma malignancy differentiation using the diffusion scalar metrics provided by the chosen diffusion tools [13,15,17–22]. However, the results reported in few published studies remain controversial [15,23] due to an absence of biophysical interpretation of the diffusion signal attenuation. As a result, conventional diffusion metrics such as fractional anisotropy or mean/apparent diffusivity cannot be used as reliable biomarkers even in the case of low- and high-grade glioma differentiation.

Due to a very general mathematical description of the cumulant expansion the DTI and DKI metrics are not structurally unique. Depending on the diffusion weightings one can perform multiple fitting parametrisations of the signal curve [24] and obtain the scalar diffusion metrics which are applicable to many types of tissue including the tumour. However, neither DTI nor DKI explain the structural changes ongoing during the tumour growth and transformation. Thus, a more accurate biophysical model of tumour in the brain still remains highly desirable [25,26]. It is known that besides the WHO grades, tumours can be characterised by other parameters. A range of tissue features associated with tumour, such as different cell sizes, proliferation index, increased vascularisation of the tumour region, peritumoural edema, intra- and extra-cellular water fractions, remaining white matter anisotropy of axon bundles stay out of reach for tumour modelling. At the same time some of these parameters have been modelling in the literature [6,9]. With this idea in mind we assessed the applicability and accuracy of NODDI model [9] as a possible source of biomarkers for the glioma differentiation complementary to DTI and DKI. We used the NODDI metrics with orientation distribution index, tract density and isotropic diffusion fraction [9]. Few previous results of NODDI application [12,27] to the tumour tissue are under debate and need more detailed and accurate investigation. For example, Wen and colleagues [12] found that the neurite density is an unreliable parameter of tumour modelling due to specific degradation in white matter. In turn, recent theoretical and experimental investigation of the NODDI application in gliomas [27] also demonstrated a quantitative bias and possible incorrect interpretation of the estimated NODDI metrics.

This biophysical model uses a set of zero-radius cylinders as an approximation of intra-axonal space. The cylinders are chosen to be impermeable, i.e. the possible water exchange between intra- and extra-axonal spaces is neglected. For NODDI the water diffusion in the intra- and extra-axonal spaces are assumed to be the Gaussian. Thus, the signal attenuation reads as:

$$S = (1 - f_{\mathbf{iso}}) \cdot (f_{\mathbf{a}} \cdot S_{\mathbf{a}} + (1 - f_{\mathbf{a}}) \cdot S_{\mathbf{e}}) + f_{\mathbf{iso}} \cdot S_{\mathbf{iso}}, \quad (1)$$

where $f_{\mathbf{iso,a}}$ are the water fractions of isotropic and intra-axonal spaces, respectively, and $S_{\mathbf{a,e,iso}}$ are the signals from intra-, extra-axonal, and isotropic compartments, respectively. In the NODDI model the axon bundle of zero-radius cylinders is described by the orientation distribution Watson function [9]. In order to obtain a reliable signal fitting, the two diffusivities mimicking the isotropic compartment and intrinsic intra-axonal diffusivity are fixed to $d_{\mathrm{iso}} = 3.0\ \mu m^2/s$ and $d_{||} = 1.7\ \mu m^2/s$, respectively.

The goal of the present work is to address the problems related to the biophysical/phenomenological modelling of the tumour, a statistical assessment of the diffusion scalar metrics for glioma differentiation and to assess the novel perspective biomarkers using standard clinical setup. We considered an application of DTI, DKI, and NODDI metrics for glioma differentiation in the case of patients with glioma grades II, III, and IV. We performed a comparative analysis of the diffusion metrics and their statistical usability for the glioma grade problem. We assume that these results will stimulate one to take the complex tissue characteristics of glioma into account and thereby to improve biophysical description of heterogeneous glioma media. The limitations and perspectives of the NODDI model for tumour studies are discussed as well.

2. Material and methods

The study was approved by the Burdenko Neurosurgery institutional ethics committee. Written informed consent was obtained from all patients. The 24 patients with supratentorial gliomas were enrolled in this study. All patients have undergone MRI screening at the Burdenko Neurosurgery Institute where they were treated. All gliomas were newly diagnosed, without any radiation, surgery or chemotherapy. The patients with other oncological history were excluded from the study. All patients underwent tumour removal or stereotactic biopsy 1–2 weeks after undergoing MRI examination. The diagnosis of glioma and WHO grade were confirmed by histology and immunohistochemical examination in all cases. According to the generally accepted approach [16], high grade glioma (HGG) includes the glioma grade III (glioma-III) and glioma grade IV (glioma-IV) and low grade glioma (LGG) includes glioma grade I and glioma grade II (glioma-II). In our study we included into the LGG group the patients with glioma-II only.

The study included 16 patients with HGG (8 patients with glioma-IV and 8 patients with glioma-III) and 8 patients with LGG (8 patients with glioma-II). The group of patients with glioma-IV consisted of the subjects with glioblastoma. The group of patients with glioma-III consisted of 8 subjects with anaplastic astrocytoma. The group of patients with glioma-II consisted of 8 subjects with diffuse fibrillary astrocytoma. All patients in the groups were chosen from a larger, previously acquired study (84 subjects in total). We used only patients with equal glioma morphology for each grade in order to avoid a possible estimation bias. The study included 16 males and 8 female patients in the age range from 18 to 59 years.

All patients underwent MRI examination with a 3 T GE scanner using a diffusion weighted spin-echo echo-planar imaging sequence with three b-values (0, 1000, and 2500 s/mm^2) and 60 non-coplanar diffusion gradient directions for each non-zero b-value. Other diffusion protocol parameters were: repetition time (TR) = 10000 ms; echo time (TE) = 103.4 ms; field of view (FoV) = 240 × 240 mm^2; matrix-size 80 × 80; slice thickness 3 mm; total number of slices 32; number of excitation (NEX) = 1; total acquisition time was 22 min. Additionally, we acquired anatomical reference images: T_2-weighted images (TR = 4300 ms; TE = 85 ms; turbo factor = 21; FoV = 240 × 240 mm^2; matrix-size = 512 × 512; slice thickness = 3 mm; NEX = 2); T_2-FLAIR-weighted images (TR = 9500 ms; TE = 120 ms; inversion time (TI) = 2250 ms; FoV = 240 × 240 mm^2; matrix = 352 × 325; slice thickness = 5 mm; NEX = 1) before the gadolinium (Gd) contrast agent administration and T_1-weighted images (TR = 875 ms; TE = 85 ms; FoV = 240 × 240 mm^2; matrix-size = 384 × 384, slice thickness = 3 mm, NEX = 2) before and after Gd contrast agent administration (0.1 mmol/kg).

Prior to estimation of the diffusion scalar metrics, the original raw diffusion datasets were corrected for the eddy-current distortions and motion artefacts using affine transformations with the mutual information as a quality criterion. The coregistration procedure was implemented in the ElastiX software [28] and later

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