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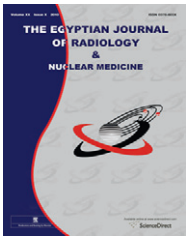

Functional diffusion map of malignant brain tumors: A surrogate imaging biomarker for early prediction of therapeutic response and patient survival

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KEYWORDS

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Abstract *Purpose:* To evaluate the ability of functional diffusion mapping "fDM" to early predict treatment response and survival in patients with primary malignant brain tumors.
Patients and methods: Forty-six brain tumor patients were examined by diffusion MRI before and 3 weeks after initiation of chemo- and/or radiotherapy. Images were co-registered to pretherapy scans, and tumor volumes with significant changes in apparent diffusion coefficient values were spatially displayed as functional diffusion maps. The predictive values of percentage of change in whole-tumor volume, mean ADC and fDM parameters for treatment response were evaluated by

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their correlation with the standard clinico-radiologic response criteria and overall survival of the two response groups was determined.

Results: Of the analyzed 46 brain tumors, 21 tumors were responding and 25 were stable/non-responding. At 3 weeks after initiation of therapy, the percentage of tumor volume with significant increase in diffusion (VR; red voxels) was the strongest predictor of treatment response than the changes in whole-tumor volume and mean ADC values determined at the same time point as compared to their pretherapy values. VR threshold of 14.5% at 3 weeks had sensitivity, specificity, positive and negative predictive values of 100% for all for differentiating responding from stable/non-responding tumors. Overall survival in stable/non-responding group was shorter than in the responding group (8.7 versus 35.6 months; $^{**}P < 0.001$).

Conclusion: The use of fDM provided an early and direct surrogate marker for predicting treatment response and patient survival in patients with malignant brain tumor.

1. Introduction

Although most brain tumors, especially the malignant variety, remain difficult to cure, there are promising novel therapies and drug delivery systems that are under active investigation (1). One of the greatest challenges in developing effective therapy for brain tumors is the lack of specific markers to directly and accurately assess anti-tumor effect early and non-invasively (2). Further challenge lies in the fact that early treatment response can be transient and may not necessarily translate into long-term response or a favorable clinical outcome (3). In addition, due to the short life span of these patients there may be a small window of opportunity to assess therapeutic efficacy so that an early biomarker of tumor response might prevent continued treatment of the patient with a high-cost and/or high-risk regimen with no demonstrated individual benefit and rapidly switch the patient to another therapy that may increase treatment response and patient survival before there is widespread damage to the normal brain (4,5).

Conventional imaging techniques such as contrast enhanced magnetic resonance imaging and contrast enhanced computed tomography are currently used to assess and monitor radiation and chemotherapy response for brain tumors. These imaging modalities relied upon identifying morphological changes in tumor size weeks to months after the conclusion of a therapeutic protocol to define response or progression (6). These changes in gross tumor size significantly lag behind the biological and molecular changes that occur early in responders (7,8). Due to tumor heterogeneity, it is unlikely that all cancers of a particular type will respond to a specific therapy, besides that, with the development anti-angiogenesis agents, certain tumors would not reduce in size emphasizing the need for a reliable and early predictor marker of treatment outcome that can be used to guide therapy and to improve survival in patients in malignant brain tumors (8,9).

The ability of diffusion magnetic resonance imaging (DW-MRI) to predict tumor response has been reported (5). Particular advantages of DW-MRI are that it is non-invasive and does not require intravenous contrast media. It measures the random (Brownian) motion of water. Increased diffusion of water molecules (measured as an increase in the apparent diffusion coefficient [ADC]) occurs shortly after a successful treatment, and correlates with the breakdown of cellular membranes and reduction in cell density that both precede changes in tumor size (10–12). The change in cellularity may lead to heterogeneous changes in the underlying tissue morphology (e.g. ratio of intra- to extra-cellular water) resulting in spatially varying changes in tumor apparent diffusion coefficient (ADC) values (13,14).

Quantification of diffusion changes has evolved from the mean change in ADC to a voxel-by-voxel approach termed the functional diffusion map (fDM) (15–20). Functional diffusion mapping (fDM), was recently proposed as an MRI imaging biomarker for quantifying early brain tumor response to therapy. This approach quantifies local apparent diffusion coefficient (ADC) changes in tumors using a voxel-based analysis implemented by rigid registration of the patient's data between interval exams (18–23).

The purpose of the current study was to evaluate the ability of functional diffusion mapping (fDM) as a validated imaging biomarker for early and direct prediction of therapeutic response and survival in patients with primary malignant brain tumors.

2. Patients and methods

2.1. Patient population

Between October 2005 and October 2009, 46 consecutive patients with pathologically proven primary malignant brain tumors who were scheduled to receive radiation therapy, chemotherapy or combination therapy were included on our prospective study. These patients were serially imaged using diffusion-weighted magnetic resonance imaging (DW-MRI) 1 week before and 3 weeks after initiation of therapy.

2.2. Protocol of diffusion-weighted MR imaging

Magnetic resonance imaging was performed on 1.5-T units (General Electric Medical Systems, Milwaukee, WI) using a standard head coil. Each patient underwent baseline MR imaging 1 week before initiation of therapy consisting of precontrast *T*2-weighted, fluid-attenuated inversion-recovery, and gadolinium-enhanced *T*1-weighted images. Acquisition sequence (TR = 10,000 and TE = 100) was set to acquire 14.6-mm axial sections through the brain using a 22-cm field of view (FOV) and 128 matrix. Once the tumor had been fully visualized, diffusion-weighted imaging was performed in the transverse plane by using a single-shot, spin-echo, echo-planar acquisition sequence with diffusion gradient encoding in three orthogonal directions at a low ($b = 0$), and a high ($b = 1000$ s/mm^2)