Comparison of dynamic contrast-enhanced MRI with WHO tumor grading for gliomas

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Abstract Assessment of vascular proliferation as an important grading criterion has been employed in both the histologic and the radiologic characterization of gliomas with encouraging results. Perfusion in gliomas can be measured by dynamic contrast-enhanced magnetic resonance imaging (dMRI). The goal of this study was to develop a model for simultaneously quantifying the fractional volumes of different tissue compartments of gliomas by dMRI. A modified method for evaluating dynamic contrast-enhanced MR images is presented which simultaneously determines the fractional vascular, interstitial, and cellular volumes of gliomas. This method differs from techniques used in other studies in that it is based on a three-compartment model: a single blood compartment and two interstitial ones. The fractional volume maps are compared with the WHO glioma grading. The results show the method to be feasible. Using cerebral blood volume (CBV), dMRI grading showed a correspondence with WHO grading in 83% of the cases (20/24 gliomas WHO grades II–IV). The use of interstitial volume maps can also be helpful, for instance, in differentiating gliomas from other brain tumors. As a supplement to conventional MRI, dynamic MR techniques thus provide a useful tool for improving in vivo glioma characterization.

Key words Cerebral blood volume (CBV) · Dynamic MRI · Glioma · Grading · Volume measurement

Introduction

Gliomas are the most common primary neoplasms of the central nervous system. Because therapeutic approaches to these tumors differ considerably according to tumor grade, the development of techniques capable of accurately determining tumor grade in vivo is important for the selection of appropriate treatment strategies. Gliomas are typically heterogeneous, and histologic samples obtained by biopsy may be subject to sampling error [1, 2]. If a biopsy site is chosen poorly or is too small, a lower tumor grade may be incorrectly assigned, resulting in the selection of suboptimal treatment strategies.

Studies of human neoplasms have demonstrated that increased malignancy is associated with increased vascularity [3, 4, 5]. Gliomas, especially when of a high grade, are highly vascular. Assessment of the microvascular structures of these tumors, including the proliferation of the endothelial cells that line tumor capillaries, is a component of most histologic grading systems. The assessment of vascular proliferation as a primary grading criterion has been employed with encouraging results [3, 6]. Koles et al. [7] even proposed a grading system based on tumor angiogenesis alone.

Much research has been done in recent years to gain more specific morphological information on tumor vascularization by dMRI after gadopentetate dimeglumine.
(Gd-DTPA) bolus administration. Dynamic MRI yields functional information about relative cerebral blood volume (rCBV) and perfusion/relative cerebral blood flow (rCBF) [8], interstitial and cell volume [9, 10], vascular permeability [11], and blood–brain barrier (BBB) integrity. Most of these studies, however, have used techniques developed to determine only a subset of the parameters, while neglecting other parameters and competing effects.

In this study a modified technique for evaluating dynamic contrast-enhanced MR images was used, which allows one to simultaneously quantify the fractional volume of the tissue compartments (blood/vascular, interstitial, cellular volume) and the transport parameters (perfusion and permeability). A grading system based on the fractional vascular volume distribution determined in a voxelwise manner by this technique is compared with the WHO grading of these tumors.

**Fig. 1** Two original measured curves are shown here, the arterial and the tumor signal vs. time curve. The bolus signal is reduced due to $T_2^*$ saturation effects. The tumor signal can be separated into three components: the blood signal, the signal of the fast extravasated CM (single curve), and the signal of the slowly extravasated CM (difference between fast extravasated CM signal and total interstitial signal).

$$J_i = PS (C_r - C_i)$$  \hspace{1cm} (1)

where $J_i$ is the net flow of solute (mol/s) and $P$ is the diffusive permeability (cm/s). The value of $C_j$ can be calculated by the following equation:

$$C_j = \frac{C_b}{1 - Hct}$$  \hspace{1cm} (2)

where $C_j$ represents the blood concentration of CM and $Hct$ the fractional hematocrit. Switching from a single voxel to a voxel containing a large number of vessels, the constants in Eq. 1 describe the total flux and capillary surface inside the voxel. Imbalances in flow exchange with other voxels are very small and can be neglected.

The surface of a vessel can be expressed by the blood volume $V_b$: $S = 2V_b/\pi$. The conversion is performed with a mean radius $r$. Therefore equation 1 can be rewritten as:

$$J_i = \frac{2PV_b}{r} (C_r - C_i)$$ \hspace{1cm} (3)

The change in the interstitial concentration $dC/\,dt$ is proportional to the flow $J_i$, and inversely proportional to the interstitial volume $V_i$:

$$\frac{dC}{dt} = \frac{J_i}{V_i} = \frac{2PV_b}{r V_t} (C_r - C_i)$$  \hspace{1cm} (4)

This would yield a monoexponential signal enhancement in the first phase. However, the signal enhancement vs. time actually observed (see Fig. 1) does not match this expectation. The measured curves can be adequately fitted by a biexponential function, indicating two distinct interstitial compartments with different time constants for filling (permeabilities). The fast extravasation component can be identified to describe the filling of viable tissue. The capillary permeability [15] and tissue diffusion constants [16] directly measured with a comparable tracer, sodium fluorescein, in viable tissue result in the same time constants for tracer extravasation. The slow extravasation component describes an additional transport process into another compartment, e.g., necrotic tissue.

Such distinct permeabilities or patterns of signal enhancement have been described earlier [17, 18], translated into a pharmacokinetic model [19], and applied to pharmacokinetic MRI [20, 21]. In such a model, two interstitial compartments are assumed, namely a fast-enriching compartment, $V_{fr}$ and a slowly enriching one, $V_{fs}$, with passive bidirectional exchange of CM between the blood and the interstitial compartments (Fig. 2). Transport between the interstitial compartments is excluded. Thus two rate equations with different permeability factors are used:

$$\frac{dC_{fr}}{dt} = \frac{-2PV_{fr}}{r V_f} (C_r - C_{fr})$$  \hspace{1cm} (5)

and

$$\frac{dC_{fs}}{dt} = \frac{2PV_{fs}}{r V_f} (C_r - C_{fs})$$  \hspace{1cm} (6)

Here a general description of the model is used. Every voxel under consideration contains the three compartments $V_b$, $V_{fr}$, and $V_{fs}$. The CM concentration in blood plasma, $C_b(t)$, is assumed not to be affected by the flow exchange inside a single voxel. Thus global (whole body) parameters for blood clearance (see Eq. 10) are separated from the local (voxel) one for extravasation. Therefore,