

MR Biomarkers in Brain Tumor

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Introduction

Advanced MR imaging offer insights related to biophysical, physiologic, and metabolic status of tissue, that compliments the exquisite anatomical detail of routine MRI. Harnessing these features for prediction of treatment response of individual brain tumor patients has compelling potential to improve their clinical management. Based on tumor biology and mechanism of therapeutic action, response biomarkers sensitive to tissue perfusion and BBB integrity are rational choices to assess chemo-agent access, tissue viability and therapeutic effect of conventional and vascular-active agents. Given that water mobility is affected by density of cellular constituents that impede water mobility, alteration of cellular properties secondary to cytotoxic treatment has also prompted interest in diffusion MRI as a therapy response biomarker. Proton MRS has demonstrated potential identify tumor beyond margins defined on conventional imaging thereby guide biopsy toward greater yield as well as aid therapy planning. Whether used individually or in combination, advanced imaging indices can reveal a more complete description of the tumor prior to treatment, during treatment for mid-course response assessment, as well as for post-therapy management. This lecture will summarize biophysical principles and role of MR biomarkers in brain tumor management.

MRS

Proton MRS is particularly valuable in application prior to, and well after therapeutic intervention [1, 2]. Elevated choline and lactate/lipid signal in untreated brain tumor can aid tumor grading, can direct the surgeon toward highest grade tumor for biopsy/resection and is being used for margin definition in radiotherapy treatment planning [3, 4]. MRS is also recognized to be beneficial for long-term treatment follow up since newly enhancing lesions long after radiotherapy presents a significant clinical dilemma between diagnoses of recurrent tumor versus radiation-induced necrosis. Proton MRSI studies have demonstrated elevated Cho/NAA and Cho/Cr in recurrent tumor relative to radiation injury, thereby offering MRS as a non invasive alternative biopsy, although situations of mixed tumor and necrosis are still problematic [5-7].

Perfusion / Permeability

Brain tumor blood volume, flow, and vascular permeability can be assessed using heavily T1-weighted (dynamic contrast-enhanced, DCE) or T2*-weighted (dynamic susceptibility contrast, DSC) sequences to document agent distribution kinetics. One of several well-established mathematical models is then applied to derive maps that infer relevant physiologic properties such as vessel permeability-surface area product, and blood volume. Use of perfusion-sensitive approaches in brain tumor management is motivated by the linkage between tumor vascularity and tumor grade, access of systemic chemotherapy agents to the tumor, as well as monitoring impact of antiangiogenic and vascular disruptive agents [8]. In terms of treatment response assessment, the majority studies of humans have employed DSC due to its relative technical ease. Pretreatment perfusion MRI has been shown to be predictive of treatment response and overall survival in both low-grade [9] and high-grade glioma [10] where increased CBV/CBF features are associated with patients having poor outcome. These observations are consistent with a correlation between tumor grade and increased perfusion and/or vascular permeability [11]. Perfusion/permeability changes during conventional and antiangiogenic treatment of patients were also informative of response [8, 10, 12]. DSC perfusion also aids distinction between recurrent glioma and radiation necrosis [7, 13-15].

Diffusion

Preclinical studies have demonstrated a consistent pattern of increased diffusion following effective treatment where increased water mobility is attributable to therapy-induced necrosis. In translation to human brain tumor patients, an increase in ADC is generally associated with a positive response although studies are few and ADC change patterns are more variable and clearly affected by tumor heterogeneity [16-18]. A potentially remedy to heterogeneity is to analyze ADC changes on voxel-by-voxel basis using co-registered pre- and post-Tx ADC maps. By this voxel-based analysis it has been shown that tumors exhibiting ADC change at 3 weeks into treatment were predictive of delayed radiographic response, disease time to progression and overall survival in patients with malignant glioma [14, 19].

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