

## Brain Tumors: Physics Perspective Thomas L. Chenevert

### Introduction

Advanced MRI/S techniques offer insight to fundamental biophysical, physiologic, metabolic and cellular tissue qualities. Harnessing these features for detection, grading, and prediction of treatment response in brain tumor patients holds great promise to improve clinical management, particularly if these methods provide quantitative tissue metrics. Functional properties related to perfusion, vascular integrity and metabolism are common targets for advanced techniques as they reflect basic tumor biology that is also sensitive to therapeutic alteration. Given that water mobility is affected by cellular impediments, change in cellular integrity due to cytotoxic treatment has prompted interest in specialized diffusion techniques for response assessment. 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 reveal a more complete description of the tumor for characterization or early response assessment, as well as for long-term post-therapy management. This lecture will focus on recent enhancements to these techniques in application to brain tumor.

### MRS

Proton MRS has seen recent advances in acquisition efficiency by interleaved rapid spatial and spectral encoding, such as in Echo Planar Spectroscopic Imaging (EPSI) (1-3), as well as use of parallel imaging in MRSI (4). Good quality, sub-minute 2D MRSI can be acquired, and high-speed 3D EPSI can provide whole-brain coverage at ~7mm isotropic resolution in ~15minutes (5). Such efficiency facilitates incorporation of MRSI for quantitative multi-modality MR brain examination. Extremely high sensitivity gains (~ $10^4$ -fold) in non-proton MRS have been realized via dynamic nuclear polarization (DNP) (6-9). Hyperpolarized C13 technology allows real-time inspection of enzymatic reaction rates, such as conversion of pyruvate to lactate in glioma. Elevated lactate production in human glioma has been noted in several studies, thus may be useful for prognosis and treatment response assessment (8, 10, 11). While hyperpolarized C13 study of humans is technically feasible, to date this technology has been largely confined to preclinical studies. As with lactate, sodium is high in necrotic areas and can be directly observed via sodium MRI (12-14). Sodium imaging requires specialized hardware/sequences, though is certainly feasible as demonstrated in several human brain tumor studies. Proton MRS/I remains the mainstay, and is valuable in application prior to, and well after therapeutic intervention.

### Perfusion / Permeability

Brain tumor blood volume, flow, and vascular permeability can be assessed using well-established techniques that capture contrast agent kinetics via heavily T1-weighted (dynamic contrast-enhanced, DCE) or T2\*-weighted (dynamic susceptibility contrast, DSC) sequences (15-18). One of several kinetic models is then applied to derive quantitative maps of the targeted physiologic property. Use of perfusion-sensitive approaches in brain tumor management is motivated by the linkage between tumor vascularity and tumor grade, as well as access of systemic chemotherapy agents to the tumor. 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 (18) and high-grade glioma (19) 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 (15). Perfusion changes during conventional and antiangiogenic treatment of patients were also informative of response (19, 20). Standardization of data acquisition and processing remains a challenge to quantitation of perfusion metrics across platforms as needed for multicenter trials.

### Diffusion

The traditional diffusion metric, ADC, is a mature technology in application for grading glioma and treatment response. Many preclinical and several clinical studies indicate a pattern of increased diffusion following effective cytotoxic treatment where increased water mobility is attributable to therapy-induced necrosis (21, 22). More recently, advanced techniques such as diffusion kurtosis imaging are being used to reveal higher-order complexity imposed by cytoarchitecture (23-26). Simple thermally-driven molecular diffusion free of impediments exhibits "Gaussian" diffusion, whereas the degree of non Gaussian

behaviour observed in tissue is an indicator of tissue microstructure that is quantifiable by a dimensionless kurtosis coefficient. Diffusion kurtosis imaging (DKI) is an extension of diffusion tensor imaging (DTI) used to quantify the degree of directional non uniformity. Relative to normal grey matter, higher kurtosis values are observed in white matter, and glioma indicating greater intravoxel diffusional heterogeneity in these tissues. Studies suggest microstructure, quantified by DKI may offer greater distinction between glioma grades (25, 26).

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