

Surrogate Markers for Glioma Diagnosis: Diffusion Weighted Magnetic Resonance Imaging and Magnetic Resonance Spectroscopy

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Background and Significance

Previous use of ADC: Treatment Efficacy

As indicated above, the ADC has been used to monitor cancer treatment efficacy, including both chemotherapy and radiation therapy. Diffusion weighting the MRI sensitizes the scan to mobility of H_2O . It is hypothesized that as effective cytotoxic cancer therapy progresses, cellular breakdown of the tumor occurs, thereby allowing H_2O to move more easily in and around the disease site. Since necrotic tissue, cancerous or otherwise, is thought to undergo cellular breakdown leading to increased water mobility, it has been suggested that DWMRI could also be useful in discriminating between Radiation Induced Necrosis (RIN) and recurrent disease.

Previous use of MRS: Differential Diagnosis

MRS, also known as Chemical Shift Imaging (CSI), has proven useful in discriminating between RIN and recurrent disease. It can determine metabolite levels, the ratios of which have the potential ability to differentiate RIN and recurrent disease. MRS obtains its signal from the shift in the MR signal due to the surrounding chemical environment[14]. Regarding the brain, three of the main metabolites of interest are: 1) Choline (Cho) a neurotransmitter that is increased in tumors. 2) N-Acetyl Aspartate (NAA) a neuronal metabolite that is decreased in tumors. 3) Creatin (Cr), a brain metabolite. Figure 4 shows a plot of the potential discriminating power of metabolite ratios from some previous work [7].

Apoptosis/Mitosis

The two primary mechanisms of clonogenic cell death following irradiation are mitotic death and apoptosis[22]. Mitotic death, which occurs when cells fail to divide because of damaged or lost chromosomal material or the failure of spindle formation during cytokinesis, is the most

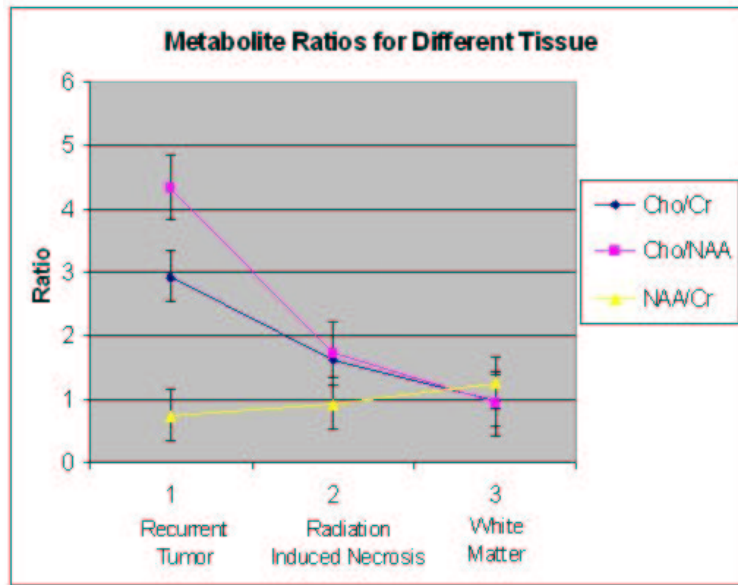


Figure 4: Metabolite ratios of recurrent disease, RIN and normal white matter.

common mechanism. One or more cell divisions may occur prior to cell death. Apoptosis prevalence depends strongly on the tumor type and occurs without cell division.

The expected ADC signal is significantly different for mitotic and apoptotic death. Cells undergoing mitotic death increase their size, for example when giant cells with multiple nuclei form. The ADC is expected to decrease during this process since the intercellular spacing and fluid are reduced. Then these cells become necrotic and their membranes are compromised, resulting in excess intercellular fluid and expected increases in water mobility and the ADC. The duration of this process depends on the cell cycle time since cells undergo one or more cell divisions before dying. This would be considered a delayed response to radiation as it would occur days after exposure. In apoptotic death, the cell detaches from its neighbors, chromatin condenses at the nuclear membrane, cytoplasmic condensation causes the cell to shrink, and water is lost. An increase in ADC is expected to occur[15]. Next, these cells become necrotic and are then phagocytized. During these processes, the ADC is expected to be larger than prior to irradiation. Apoptosis occurs within 4 to 24 hours following exposure. Finally, for either mechanism, the tissue in the irradiated volume must reorganize. The ADC in this region may be larger or smaller than in the pretreatment scan, depending on whether tumor or normal cells occupy this volume and their density within it.