

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

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Lars Ewell, Amarjeet Bhullar, Ray Carmody,
Russell Hamilton, Joshua Kim and Baldassarre Stea

Research Design and Methods

Imaging Protocol

Since the majority of gliomas recur within 2cm of the primary[21], we plan on initiating an imaging protocol whereby we will monitor the disease site longitudinally, using both DWMRI and MRS. Multi-voxel MRS with a 7x7 grid size and 2x2x1cm voxels will allow for both the disease itself to be monitored, along with contra-lateral brain for comparison. Three slices of MRS data will be acquired: One slice centered on the lesion, and a superior and inferior slice. Some of the characteristics of the scans are displayed in Table 5. In Table 6, some details of

Table 5: Imaging Sequence for Enrolled Patients

Time From End of Radiotherapy (days)	Scans Performed	Comments
-5	CT, MRI, DWMRI, MRS	Baseline scans. Used to plan radiotherapy. CT and MRI registered using Brainscan.
30	MRI, DWMRI, MRS	First scan for comparison. Look for reduction of edema from surgery.
90	MRI, DWMRI, MRS	Second scan for comparison. Potential radiation necrosis and pseudoprogression.
180	MRI, DWMRI, MRS	Second scan for comparison. Potential radiation necrosis and pseudoprogression.
360	MRI, DWMRI, MRS	Second scan for comparison. Potential radiation necrosis and pseudoprogression.

the actual scans to be performed are displayed.

Table 6: Scan Details

Scan Type	Scan Details	Time Echo (TE, ms)	Repetition Time (TR, ms)	Actual Patient Scan Time (min)
DWMRI	T2 Weighted, RFSE Diffusion Weighted, $b=0, 500$ and $1,000s/mm^2$	76	10,000	10
DWMRI	T2 Weighted, Echo Planar Diffusion Weighted, $b=0, 500$ and $1,000s/mm^2$	76	10,000	10
MRS	PRESS, 2D multivoxel 49 Voxels per slice 1cm slice thickness, 3 slices	144	1,500	30

Sulci Density

Once the data are acquired, we will compute sulci density maps for all patients enrolled. In a previous study[8], the importance of this density in calculating ADC values was emphasized. In Figure 13, a sulci density map of four different patients is displayed. Similar to the ADC values,

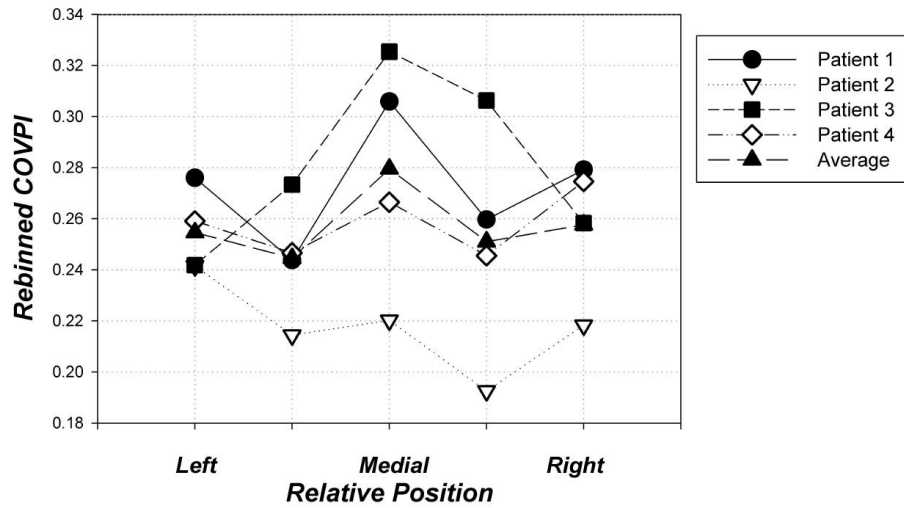


Figure 13: Sulci density map of four patients plotted in the sagittal direction (see reference 8 for details on map calculation).

the sulci density maps will be longitudinally monitored for change. By using two different type of isotropic diffusion weighting, as well as sulci density maps, we believe that we will achieve an unprecedented level of accuracy with which to monitor disease sites.

MRS-DWMRI Differences

We expect that DWMRI, particularly using the Radial Fast Spin Echo (RFSE) technique,

will have fine resolution (pixel size of 1mm^2 and slice thickness of 3mm). On the other hand the voxel size of the MRS, as indicated in Figure 1, we expect to be on the order of 4cm^3 . This disparity in voxel size has implications about how best to use both of these different imaging modalities. A likely scenario is that tissue within the larger MRS voxel will consist of normal tissue and/or recurrent disease and/or necrotic tumor and/or normal tissue suffering from RIN. How best to differentiate these four different tissue types is one of the main objectives of this study.

Radiation Necrosis/Recurrent Disease

With an α/β ratio of ≈ 2 , normal brain is thought to be a *late* responding tissue regarding therapeutic radiation[22]. For this reason, we do not expect to see evidence of any RIN for months to years after the patients have received therapeutic radiation to the disease site. On the other hand, the tumor is thought to have an α/β ratio of ≈ 10 , and is therefore thought of as an *early* responding tissue regarding therapeutic radiation. For this reason, we expect that we may begin to see reactions of the lesions to radiation in weeks to months after the end of radiation therapy.

Histology Correlation

In the normal course of patient care, histological examinations are common. We realize that the current 'gold standard' for definitive diagnosis of gliomas is a pathologic examination of tissue samples obtained from biopsy. However, in this imaging study, we do not plan on compelling any additional histology, from that which would otherwise be ordered in the absence of this study for the patients that choose to enroll. With this in mind, we will analyze histological data as they become available, and look for statistically significant ($p < 0.05$) correlations between recurrent disease, RIN, ADC value change and/or metabolite ratio change.

Receiver Operating Characteristics

Our ultimate goal in this study is to help facilitate non-invasive definitive diagnosis of gliomas. To this end, we will implement Receiver Operating Characteristics (ROC) to obtain sensitivity and specificity[23] values for MRS and DWMRI as they relate to this diagnosis.

Problems

In a technically demanding study such as this, we expect to encounter a number of problems. One such problem involves the composition of tissue in the Volume Of Interest (VOI). It is likely that many of the regions being probed will include not only pure recurrent disease or pure RIN, but some mixture of the two. This scenario will complicate the ability to draw firm conclusions from any correlations that may be apparent. We will likely have to separate

regions into pure disease, pure necrosis and a mixture of the two with the last category most likely containing most of the data points.

An additional problem has to do with VOI placement. We expect that it will be relatively rare that the center of the resection cavity will occur in the middle of a parallelepiped of brain tissue such that the entire VOI will be unobstructed. More likely is the situation that an anatomical feature, such as the skull or the posterior fossa will encroach upon the 588 (49x4x3) cc VOI such that a portion of it will be either obstructed, or have a large susceptibility gradient. We believe that the robustness of the RFSE technique against susceptibility gradients will minimize this problem with respect to the DWMRI scans. The MRS data may be truncated.