

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

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Abstract

A series of surrogate markers are proposed that will investigate the ability to predict efficacy of radiation therapy for primary or metastatic gliomas. The Apparent Diffusion Coefficient (ADC), obtained from Diffusion Weighted Magnetic Resonance Imaging (DWMRI), along with Magnetic Resonance Spectroscopy (MRS) are both probed for their predictive ability.

Introduction

The goal of a surrogate marker that can predict efficacy of radiation therapy remains elusive. Such a marker could, in principal, allow for informed clinical decisions on therapeutic patient care, thereby increasing the quality of life for the patient under treatment. A number of promising potential candidates will be examined, primarily consisting of the Apparent Diffusion Coefficient (ADC), determined from Diffusion Weighted Magnetic Resonance Imaging (DWMRI), and Magnetic Resonance Spectroscopy (MRS). Due in part to lack of motion artifacts, the brain lends itself to these types of imaging modalities.

The ADC has been shown to have potential to predict whether or not tumors are responding to cytotoxic therapies[1,2]. In addition, the ADC has also been utilized in an attempt to differentiate radiation necrosis from recurrent disease in gliomas both by itself[3], and in conjunction with MRS[4]. Each of these complimentary imaging modalities will be investigated for monitoring efficacy, as well as differential diagnosis (necrosis vs. recurrent disease).

Specific Aims

Lesion Volume/Location

An important criteria when considering diagnosis and/or therapy for gliomas are the size and location of the lesion. The lesion size is known to be inversely correlated with survival, with tumors (GBM) larger than 5cm having a poorer prognosis ($p=0.04$)[5].

While lesion location has yielded less predictive information, there has been recent speculation that tumors situated adjacent to the lateral ventricles have a poorer prognosis[6]. Regardless of whether or not these prognostic suspicions are true, the location does have an important role in determining how easily the lesion can be probed, e.g., with MRS[7]. In addition to affecting MRS, lesion location can also influence the accuracy with which ADCs can be calculated. e.g., in the cerebrum, the sulci density can impact the value of the ADC derived from DWMRI scans[8].

In view of these facts, in this study we propose to undertake we will record as accurately as possible, the size and location of the lesions being treated with radiotherapy in our department. This information is of ultimate importance, as it will allow for differences to be quantified. The question of whether or not the lesion is resected is also central to this study (see below).

MRS Spectra and DWMRI Scans

For the patients enrolled, DWMRI scans as well as MRS scans will be obtained. After the initial clinical scans have taken place, and it is determined that the patient is eligible to enroll (see criteria below), the patient will undergo three multivoxel MRS scans, one coincident with the lesion, one inferior and one superior. The slice thickness will be one cm and the voxel size will be 2x2cm. Figure 1 shows a sample of the 7x7 multivoxel MRS grid superimposed on an MRI scan.

Quantify Tumor Response

Of paramount importance when attempting to evaluate surrogate markers is the ability to quantify how the tumor reacts, if at all, to radiation therapy. For this study, the primary endpoint is objective tumor response. For solid tumors not in the brain, the Response Evaluation Criteria In Solid Tumors (RECIST) is often used to quantify tumor response[9]. However, the brain has different criteria due in part, to the ethical problems involved with obtaining 'margins' from grossly intact white matter[10], as well as the blood brain barrier. For this reason, we will adhere to the criteria developed in an earlier study[11].

Unresected

If the tumor, for whatever reason, is not resected/debulked, then the dimensions are more straightforward to obtain. As indicated in this previous work, the *size* of the tumor is considered as the largest cross-sectional area on a contrast enhanced T1 weighted MRI scan[11]. Once the

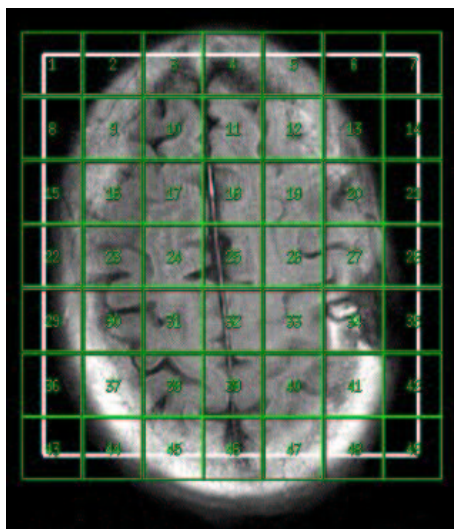


Figure 1: MRS Grid.

size has been determined, the tumor will be monitored longitudinally during which time it will be categorized according to its' response (if any) to radiation therapy. These criteria are listed in Table 1:

Resected/Debulked

It is expected that the majority of patients enrolled in this study will be candidates for resection. This substantially complicates the determination of lesion size. e.g., if the tumor is successfully removed, in principal there should be no enhancing lesion left to quantify/monitor. Figure 2 shows such a situation. If, as in this figure, the lesion (frontal lobe, patient right, hypo-intense) has been successfully resected, the surrounding intact white matter will be longitudinally monitored for recurrence. It is also possible that an area around the initial enhancing lesion remains after resection. This is shown in Figure 3. As can be seen here, there remains a small enhancing lesion (frontal lobe, posterior to hypo-intense cavity) that can and will be longitudinally monitored.

Pseudoprogession

A confounding factor in regards to objectively quantifying tumor response is the so called phenomena of *pseudoprogession*[12]. Pseudoprogession can be characterized as an exaggerated response to effective therapy. i.e. although the lesion may appear to grow on a 'normal' T1-weighted contrast enhanced MRI, the growth is actually false, and the patient is in fact responding to therapy. This has the potential to, e.g., increase the number of patients categorized as PD and/or SD, while decreasing the number of patients categorized as CR and/or PR(see Table 1). We will attempt to remain aware of the possibility of this occurring, and act accordingly.

Table 1: Response Criteria for Registered Lesions

Complete Response (CR)	Disappearance of all enhancing lesion on consecutive MRI scans at least one month apart, off steroids and neurologically stable or improved.
Partial Response (PR)	$\geq 50\%$ reduction in size of enhancing lesion on consecutive MRI scans at least one month apart, steroids stable or reduced and neurologically stable or improved.
Progressive Disease (PD)	$\geq 25\%$ increase in size of enhancing lesion on consecutive MRI scans, or neurologically worse and steroids stable or increased.
Stable Disease (SD)	All other situations.

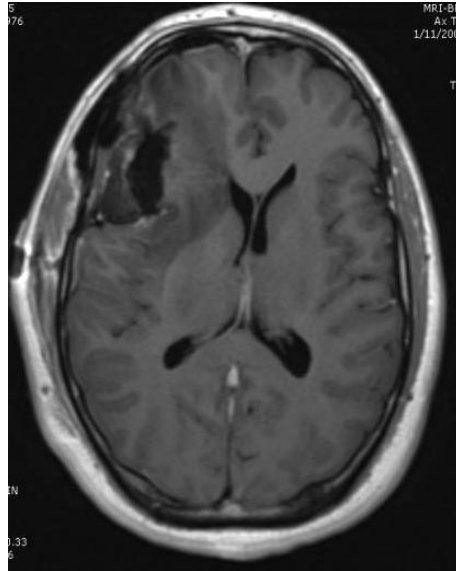


Figure 2: Glioma successfully resected.

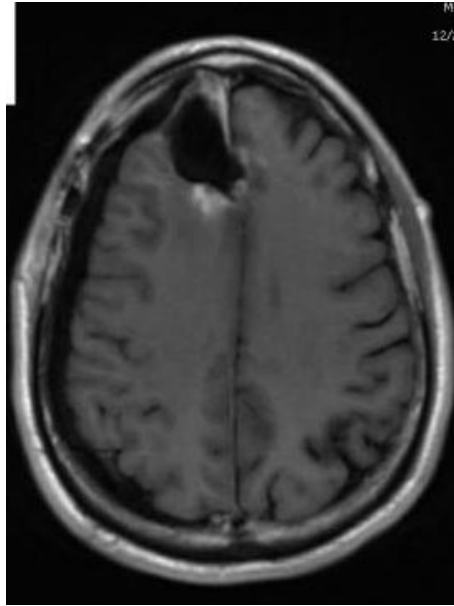


Figure 3: Glioma resected with small enhancing lesion remaining.

Radiation Necrosis vs. Recurrent Disease

In addition to quantifying tumor response to radiation therapy, an important diagnostic consideration regarding gliomas is the ability to differentiate radiation necrosis from recurrent disease. In a typical T1 weighted MRI scan, both radiation necrosis (a side effect from radiation) and recurrent disease can appear as 'enhancing lesions' (hyperintense region)[13]. In view of this fact, we will monitor all areas of the brain that receive enough radiation to have a *reasonable*(between 5% and 24%[13]) chance to suffer from radiation necrosis.