Diffusion-weighted imaging of the brain for glioblastoma: Implications for radiation oncology

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Magnetic resonance imaging (MRI) has become the foundation of diagnosis and monitoring in glioblastoma, and advanced techniques in data acquisition and analysis hold promise in improving clinical practice. Diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI) represent 2 advanced image acquisition sequences that have been under development for over 2 decades and are now assuming a role in routine management of oncologic patients. These approaches are being investigated across body systems and have already established value in the diagnosis and management of prostate cancer.[1-3] In a similar fashion in glioblastoma, the use of DWI and DTI has begun to expand outside of research settings and into patient care.

Rationale for diffusion imaging in neuro-oncology

This review focuses on diffusion imaging in glioma and, more specifically, on the ways DWI and DTI are becoming

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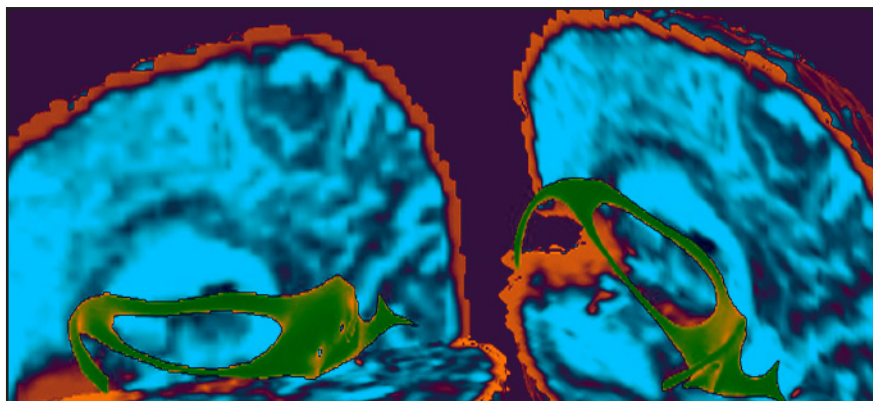
part of the management of patients with glioblastoma. These advances are based on the observation that tumor cell density is typically higher than normal tissue, and this increased cellularity leads to restricted extracellular water diffusion. DWI is sensitive to the degree of this water restriction and DTI offers a means of further quantifying the orientation of the restriction. The ability to use diffusion imaging as a noninvasive measure of cellularity has been demonstrated through extensive preclinical work. Recent studies have demonstrated that these methods might be used in patients to aid in the diagnosis and grading of tumors, estimate the extent of tumor infiltration, evaluate for residual or recurrent disease after an intervention, stratify a cohort based on the likelihood for an individual's response, modify

radiation contours to avoid low-risk areas and target areas with subclinical disease, improve neurosurgical approaches, look for early responses or progression, and differentiate between true progression and pseudoprogression. How to sort through these lofty goals and identify what holds the most promise will be part of the challenge in glioblastoma management. This review is aimed at helping the reader gain an understanding of the concepts of diffusion imaging and several of the emerging applications of the technique for radiation therapy utilization.

Principles of diffusion imaging

The effect of molecular diffusion on the magnetic resonance signal was noted in the classic paper on spin echoes by E.L. Hahn in 1950, which forms the
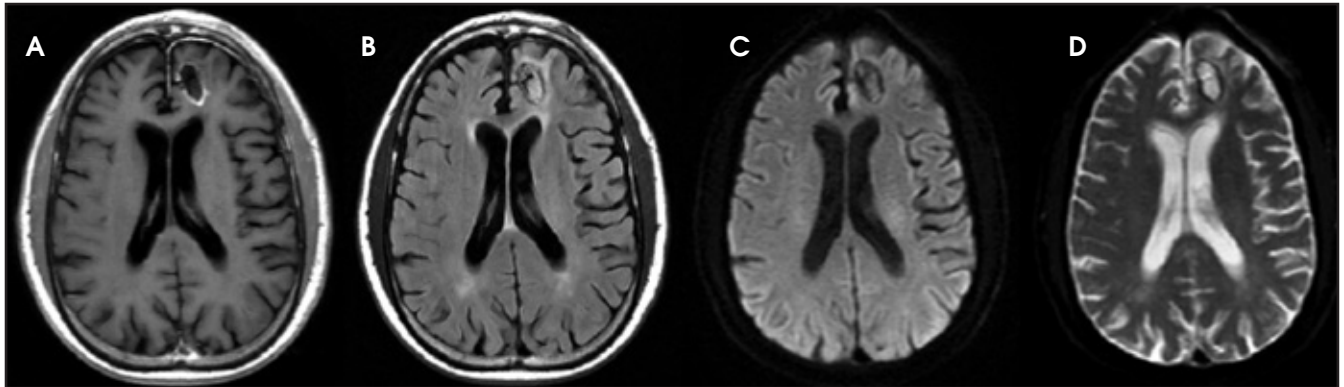
FIGURE 1. Axial MRI taken for a patient with a left frontal glioblastoma with four sequences, A) T1 post contrast, B) T2 FLAIR, C) DWI and D) ADC map. ADC was calculated using b0 and b1000 diffusion-weighted images. These studies demonstrate the qualitative differences between imaging sequences that can highlight enhancing gross tumor involvement seen in image A, surrounding edema in B, and diffusion restriction at the rim of the tumor cavity along with unrestricted diffusion in the cystic/necrotic tumor core seen in images C and D.

basis of DWI and DTI to this day.[4] Medical imaging is almost exclusively devoted to protons, which comprise about 2/3 of the atoms in the human body. Most of that is water, although the protons in the CH_2 groups in fat can also be imaged. Water molecules will diffuse according to the principle of Brownian motion (i.e., random walk) unless restricted by their environment. If water molecules diffuse in any volume where the external magnetic field is inhomogeneous (e.g., through application of transient external field gradients), this will affect resonant echoes of the protons being probed by MRI. Within the body, cell membranes provide a barrier to diffusion. Fluid in the extracellular space will diffuse less readily in a crowded environment, such as in cases of tumor infiltration or when cells swell from a shift of fluid intracellularly where restriction is high. Diffusion MRI pulse sequences allow detection of both the magnitude and direction of water diffusion.

Diffusion-weighted image acquisition

The concept of how diffusion of water molecules can affect their resonant signals is easy to grasp, but the physics and mathematics for this procedure are extremely technical in detail. Interested readers are referred to a very concise review by Le Bihan et al., or to Koh and Collins for an excellent overview of general clinical applications.[5,6]

For the purposes of this review, we must introduce some commonly used mathematical terms. In the idealized case of isotropic diffusion, and ignoring other flows such blood, the DWI signal would be expected to have a simple exponential relationship where b is an experimentally adjustable parameter that includes the timing and magnitude of the external magnetic field gradients used in the DWI pulse sequences, D is the diffusion coefficient, and A_0 is the signal in the absence of diffusion:

$$A = A_0 \exp(-bD)$$

For water in an isotropic medium, D = 2 x 10^{-3} mm^2/s at room temperature; note that the viscosity of water and, hence, self-diffusion is very temperature-dependent, with an increase of about 2% per degree C. Higher b values essentially mean that the image was acquired allowing longer times for diffusion to affect the signals detected. With b=0, one gets a standard T2-weighted image that depends on the other acquisition parameters.

By acquiring DWI images at even a few b-values, one can estimate the diffusion coefficient for the resonant protons. In fact, this is an empirical parameter since it likely includes other flow mechanisms besides simple Brownian motion. The result is called the ADC, the apparent diffusion coefficient. As the review by Koh and Collins notes, ADC's are often reported as indices of therapeutic response, but the actual numbers obtained for ADC can vary widely depending on the exact details under which the DWI images were taken, and standardization is lacking.[6]

Diffusion-tensor imaging

In the cerebrospinal fluid, diffusion is largely unrestricted and the motion of water molecules is isotropic. In white matter tracts, diffusion is restricted by axonal cell membranes and water diffuses anisotropically. By quantifying diffusion anisotropy along multiple directions within a tissue, the density and orientation of the cellular structure within a unit of measurement (i.e., a voxel) in an MRI image can be estimated.

A diffusion tensor is the mathematical description of the three-dimensional orientation of an ellipse, which in DTI represents the principal direction of water motion. While DWI acquires data in only 3 directional planes, DTI requires that at least 6 directions be imaged in order to calculate a diffusion tensor. The greater the number of diffusion directions acquired, the more accurately the calculated diffusion tensor represents the true direction of water movement.

Table 1. Differences in signal intensity vary based on a number of factors, and a general guide for relative signal intensities is provided. Bright (hyperintense) and dark (hypointense) notations are qualitative descriptors relative to other tissue components in the image.

	FLAIR	DWI	ADC
White matter	Iso/Hypo	Dark	Bright
Gray matter	Iso/Hyper	Bright	Dark
CSF	Dark	Dark	Bright
Dense tumor	Variable	Bright	Dark
Tumor necrosis	Variable	Variable	Variable
Cystic	Often dark for simple cysts and bright for proteinacious or tumor cysts	Variable	Bright
Abscess (centrally)	Bright	Bright	Dark
Edema	Bright	Bright	Bright
Acute infarct	Variable	Bright	Dark

Common parameters derived from DTI include the fractional anisotropy (FA) and mean diffusivity (MD). Occasionally, the components of fractional anisotropy are analyzed independently, such as axial and radial diffusivity or the isotropic and anisotropic components of FA. MD is used interchangeably with ADC, since the ADC is an average of the measured diffusion directions. While ADC and MD represent the magnitude of diffusion, FA describes the degree of anisotropy of diffusion. For example, in the body of the corpus callosum, diffusion is anisotropically oriented along the axis of fiber tracts as they cross from one hemisphere to another. The magnitude of FA will decrease as the anisotropy decreases, such as in areas of crossing fibers with different orientations or where there is more gray matter. FA, which varies between 0 and 1, will be near-0 in cerebrospinal fluid (CSF) and near-1 in white matter. An example demonstrating qualitative differences of MRI sequences in glioblastoma is shown in Figure 1.

Because DTI quantifies the degree of anisotropy across voxels in the brain based on the orientation of fiber tracts, a voxel-wise analysis may be performed to generate white matter fiber tracts. DTI tractography has developed into a large field of study with broad research and potential clinical applications.

Standard clinical applications

Clinicians are most familiar with diffusion imaging in the setting of neurovascular injury. DWI began being applied in the setting of stroke evaluation approximately 2 decades ago and is now routinely used in clinical practice to determine the presence and chronicity of stroke evolution.[7,8] In the setting of acute ischemia, it is hypothesized that extracellular fluid moves into the intracellular compartment where diffusion is relatively restricted. This displays a pattern of restriction, where areas of acute ischemia appear hyperintense (i.e., high value) on DWI and hypointense (i.e., low value) on ADC images. As ischemia resolves over the course of several weeks, ADC increases above normal and serves to highlight areas of more chronic injury. The sensitivity of DWI and ADC to distinguish between acute and chronic injury has led to their application as the standard imaging sequences in evaluating stroke. Other clinical uses of diffusion imaging include evaluating infection (e.g., abscesses), inflammation, demyelination (e.g., multiple sclerosis), edema, cysts and trauma. Signal intensities for benign and pathologic imaging findings vary across MRI sequences and a general overview of common descriptors is provided in Table 1.

Experimental applications in glioblastoma
Improved diagnosis and histologic subclassification

MRI provides a noninvasive means of identifying intracranial pathologies, and diffusion imaging has a natural role in separating certain benign (e.g., cystic or infectious) lesions from malignancies. There has been considerable interest in diagnostic radiology to apply diffusion imaging techniques in the setting of suspected neoplasia within the central nervous system. Innumerable studies in the literature aim to correlate diffusion parameters across disease sites with various pathologic findings and patient outcomes. These studies hypothesize that tumors with high cellular density will restrict extracellular diffusion and correlate with diffusion parameters.

An important topic in this area is the diagnosis and grading of primary glial tumors through imaging. A reliable noninvasive diagnostic method for suspected glioma may be useful in cases where a brain biopsy either cannot be safely obtained or if a biopsy is attempted and is nondiagnostic. Perhaps a more frequently encountered scenario is when a biopsy is positive for a low-grade glioma, but the presence of new clinical symptoms or the appearance of the disease by standard radiographic techniques suggests a more aggressive histology. In these cases, biopsy results indicating low-grade histology may be due to random sampling, such as in a lesion with mixed features. Furthermore, it may be possible to follow patients with a low-

grade glioma to noninvasively monitor for conversion to a higher grade.

Preclinical work in rodent models has motivated the application of diffusion imaging to estimate tumor cellularity in humans. These studies have been discussed elsewhere and demonstrate a high sensitivity of diffusion parameters to changes in the cellular density of a tumor.[9-11] However, there are many added limitations when applying DWI in humans (e.g., patient heterogeneity, lower field magnets, head motion, restricted scan time and data acquisition, etc.). To test the ability of diffusion imaging to quantify the cellular density in humans, Sugahara and coworkers acquired DWI data from 20 patients with pathologically confirmed glial cell tumors.[12] The minimum ADC value was correlated with the density of cellular nuclei across a standard pathologic slide, and the authors found a strong relationship (r = -0.77) between the 2 variables. In a similar study of 10 patients, including WHO grade II and IV tumors, the authors also found a relationship between ADC and cell density of the same magnitude (r = -0.77).[13] In one of the largest series to examine this question, a Chinese group retrospectively evaluated over 100 glial tumors and correlated the minimum ADC value with glioma grade.[14] In their study, minimum ADC was significantly correlated with grades 2, 3 and 4 glioma (r = -0.524) and a weaker, but statistically significant, relationship was found between the minimum ADC and the Ki-67 mitotic labeling index (r = -0.312). These data along with other studies help to confirm preclinical findings that highly cellular tumors are associated with low ADC values, which supports this modality as a noninvasive measure of tumor grade.[15,16]

The tendency of glioblastoma to infiltrate along white matter tracts often leads to extensive disease and may underlie multifocal presentations or recurrences after treatment. Currently, edema (i.e., radiographically T2/FLAIR positive) is the best marker for the subclinical spread of tumor, but is a qualitative measure and is not specific to changes due to tumor infiltration. Diffusion imaging, particularly DTI, may offer an improved means of evaluating the presence of subclinical disease that is not only qualitative, but may also quantify spatial and temporal changes to assist in radiation treatment planning.

Because white matter is arranged in a highly organized pattern, diffusion is similarly restricted along the axis of fiber tracts, but as glioma cells infiltrate these tracts, they disrupt this order along with anisotropic diffusion (i.e., fractional anisotropy [FA]). Therefore, DTI measures should be sensitive to infiltrating the tumor and be particularly useful in identifying glioblastoma. This idea has been illustrated in a comparison between high-grade glioma and other brain tumors.[17] However, while some studies of FA have been promising, [18-20] others have questioned the utility of FA over other radiographic measures, including other diffusion parameters.[21-23] Many of these studies suffer from small sample sizes and a heterogeneous population of patients making negative studies difficult to interpret.

The most definitive test for FA in estimating the presence of a tumor is through pre-biopsy measurements. In one of the few studies to address this, 19 patients were scanned with DTI prior to stereotactic biopsy of brain tissue.[24] Here, FA was found to significantly correlate with cell density (r=0.73) and the Ki-67 labeling index (r = 0.8). Similarly, a Japanese group utilized DTI to calculate the FA and MD values within pathology-confirmed gliomas of grades I – IV.[20] In 41 patients, the authors found a clear separation in FA values between high grade (III – IV) and low grade (I – II) glioma. MD served less well as a marker for tumor grade, but results were still in-line with previous reports showing increased values for grade I relative to higher grade tumors. These studies represent a small sample of the promising work being done to apply DTI in clinical settings, but there are limitations in image quality, lengthened acquisition time and labor-intensive data analysis to overcome before the methods are more widely adopted.

Predicting and evaluating treatment response for glioblastoma

DWI has been proposed as a potential marker of early treatment response and may be used to predict who will benefit from a particular therapy before initiation of radiation treatment. The rationale is that necrotic tumors and/or those low in vascularity may be more resistant to either systemic agents (e.g., due to decreased delivery) or radiation (e.g., due to poor tumor oxygenation). Additionally, if a tumor is sensitive to treatment, its cellularity is expected to decrease either during or soon after a course of therapy. The role of diffusion imaging in respect to this topic has been investigated and reviewed largely by a group at the University of Michigan, who has performed a number of seminal studies on the topic.[25] They have reported results from a cohort of 60 patients with WHO grade III or IV glioma.[26] In this prospective study, DWI data were acquired at 3 time points during the course of treatment. Rather than taking an intra-lesion measure of ADC, a voxel-wise analysis was performed on each brain, and changes in this map across time were correlated with survival outcomes. Intriguingly, the authors found that increases in diffusion at 3 weeks into a course of radiotherapy were associated with improved rates of survival at 1 year. Other work has supported this use of diffusion imaging in guiding conventional radiotherapy and stereotactic radiosurgery with promising results.[27-32]

Bevacizumab is one systemic agent that has been used to treat glioblastoma,

although despite promising phase II data it was not shown to improve overall survival in a randomized controlled trial.[33] However, there is interest in identifying a subgroup of glioblastoma patients for whom bevacizumab may be appropriate, particularly because the drug improved progression-free survival when added to standard management. Ideally, a pretreatment marker would be used to predict response to the intervention, and this could be used to stratify patients in future trials. A group at the University of California, Los Angeles has proposed a method for filtering the ADC histogram taken from non-necrotic portions of tumor. These values likely correlate with more densely cellular regions of tumor, and the authors found that they were a reliable biomarker to predict a response to bevacizumab.[34] Moreover, the authors found that their quantification of the ADC distribution was a superior predictor of progression-free survival relative to the Macdonald criteria, a standardized post-treatment radiographic assessment.[35] Others have begun to validate the ability of ADC to serve as a biomarker of response and have published encouraging results.[36, 37]

ADC may also serve as a useful biomarker for early responsiveness to the current standard of care. The success of temozolomide (TMZ) and radiation therapy in a large randomized trial has established it as the first-line chemotherapeutic agent in this disease.[38,39] Furthermore, important work in understanding the biochemical mechanism of its effectiveness has led to a valuable epigenetic marker for predicting treatment response.[40] These advances have changed management of glioblastoma and revealed further subgroups of patients who may experience relatively dramatic improvements in survival. How to identify these patients early in their course of therapy has become an important question, particularly with the hope that novel interventions will provide options for alternative treatment courses for poor-responders. To test the ability of diffusion imaging to predict response to TMZ, Khayal and coworkers evaluated MRI data before, during and immediately after a course of concurrent RT-TMZ for glioblastoma.[41] The authors acquired DWI and DTI data between 3-5 weeks into a course of radiotherapy with daily TMZ. They quantified several diffusion parameters at this time point and compared these to a post-treatment scan. Here, an increase in ADC after chemoradiation relative to during treatment was correlated with a lower risk of 6-month progression. Many studies are underway to further characterize the ability of various diffusion measures to predict and evaluate treatment responses. Published literature has begun to establish this role, but should be interpreted with caution as these methods are experimental, often involve a small number of patients, and are subject to publication bias. Another significant problem raised on Koh and Collins review was the lack of standardization in the DWI acquisition parameters, which can affect results.[6] With the work of the Michigan group as a foundation, clinical trials may soon test the utility of DWI to assess a patient's disease during treatment. A convincing study will ensure standardized data acquisition and analysis techniques with quality assurance measures to remove poor-quality MRI scans. The implication is that DWI may provide an early marker of treatment response to guide modifications in radiation target delineation and dose prescription as well as chemotherapeutic modifications.

Monitoring for recurrence

In addition to predicting or tracking response to treatment, there is an interest in utilizing DWI to estimate the probability of recurrent disease after radiation therapy. Noninvasively assessing the existence of recurrent disease has long been a challenge due to post-surgical and radiation changes along with pseudoprogression or pseudoresponse.[42,43] This is a commonly encountered problem, with up to 50% of patients treated with standard management found to have pseudoprogression, with each case causing a clinical dilemma in determining further management.[44] Standard radiographic methods have been proposed, such as the Macdonald, RECIST and RANO criteria, but additional measures are clearly needed.[35,45-47] As described above, diffusion imaging is a sensitive measure of tissue cellularity, but its susceptibility to post-treatment artifacts has not been clearly defined.

To compare the ability of ADC values to distinguish progression versus treatment-induced changes, one study analyzed data from 18 patients in whom 7 had histologic confirmation of tumor recurrence.[48] ADC values were significantly lower on tissue identified as recurrent disease relative to areas of non-recurrence. These data are consistent with other work that has relied on long-term radiographic follow-up to distinguish progression versus pseudoprogression, but additional studies that utilize post-treatment biopsy or resection tissue are needed.[49-51]

Other work is underway to develop a multimodality approach, as opposed to a single measure, to describe post-treatment changes. In a recent example, Cha et al., analyzed patients who received standard therapy with surgery plus adjuvant chemoradiotherapy and were found to have possible radiographic progression.[52] Both ADC and regional cerebral blood flow (rCBV) histograms were generated from enhancing areas that were questionable for progression versus pseudoprogression. The authors found that the combined analysis was superior to either analysis alone, and that the multiparametric measure was predictive of progression-free and overall survival. They hypothesize that ADC and rCBV are particularly well-suited in evaluating tumor recurrence because they each supplement for some of the deficiencies of the other.
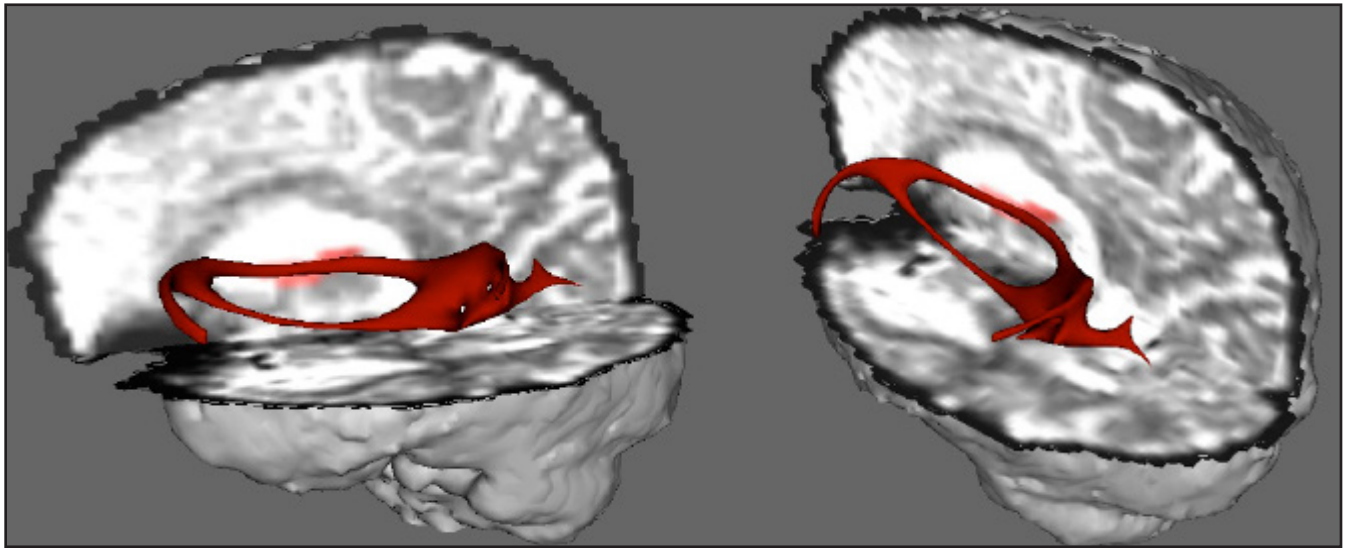
FIGURE 2. DTI may be useful for neurosurgical planning, as in this example where an intracranial mass in the left hemisphere has produced mass effect. DTI fiber tractography was performed between language areas to map the arcuate fasciculus, which appears to be displaced and abnormally divergent into superior and inferior tracts.

This principle has been applied in several other investigations aimed at developing multimodality measures (see below).

Overcoming limitations and future directions
Special challenges in data acquisition

A major limitation of single measures of ADC (e.g., minimum, maximum or mean) is the information lost in data reduction. This may greatly reduce the sensitivity of ADC measures of glioma, which are often heterogeneous lesions with areas of dense tumor, necrosis, cystic fluid, and hemorrhage all potentially within a single focus of disease. Many of the studies mentioned in this review are limited in this regard and others have described more sophisticated approaches to data analysis.

One method to address this obstacle is to perform voxel-wise ADC analyses as proposed by Moffat and colleagues,[30] or to perform ADC histogram analyses as described in several of the studies reviewed here.[34,52] This may be a particularly important consideration when analyzing tumor responses to therapy because there may be a nonuniform re-

sponse to treatment that may not be captured by taking, for example, the mean ADC value across the full volume of a lesion, or even the non-necrotic portion of a tumor.

Another limitation is the variability in DWI sequences from one center to another, between scanners in the same center or in a single scanner across time. Also, the reliability of ADC depends on how the data are acquired. For example, diffusion neuroimaging in most practices is carried out by acquiring a b0 (i.e., T2-weighted) image and a b1000 image. ADC is calculated from these 2 points, which places the accuracy of the measure upon the quality of only 2 images. Furthermore, higher b-values are impaired by an inherently low signal-to-noise ratio. Added to the natural susceptibility of echo-planar imaging to artifacts and the particular sensitivity of diffusion-weighted imaging to head motion, these factors make high-quality data acquisition a challenge.[53,54] One way to improve data quality is through scan averaging, where multiple diffusion sequences are acquired and merged post-hoc. This can improve the accuracy of ADC while maintaining image resolution, particu-

larly when data are acquired at higher field strengths. Another approach to improving accuracy is through acquiring additional b-values, which is more often performed in diffusion imaging of other body systems. The difficulties in obtaining high-quality diffusion data make it difficult to interpret negative studies, particularly when performed on a small cohort. Furthermore, in the clinical setting there are practical limitations to scan time, and these added MRI sequences must be well-justified both from the perspective of scan time for patients and health care costs.

Other challenges relate to data analysis, which can be time- and labor-intensive, and require proper equipment and expertise. While many commercial and public software packages are available, developing more standard protocols for data processing and quality assurance must precede adopting these techniques to general clinical practice.

Determining radiation treatment volumes

Over the past several decades, radiation treatment volumes for glioma have decreased from whole-brain irradiation with two-dimensional planning

to three-dimensional conformal partial brain radiotherapy often utilizing intensity-modulated radiation.[33,55,56] It has also been well-established that the majority of tumor recurrence occurs within the high-dose treatment volume, and that boosting presumed high-risk areas does not necessarily improve local control.[57-59] These findings bring into question the current standard in treatment volume delineation. While lower overall doses may negatively impact survival, it may be possible to continue the trend toward smaller treatment volumes by using diffusion imaging to tailor the high-dose region to areas at highest risk for subclinical spread.[60] Rather than using a somewhat arbitrary, but still standard 2 cm margin upon T2/FLAIR hyperintensity, a more sophisticated method of estimating subclinical spread of disease is needed. It may be that dose escalation studies have failed to improve outcomes because of overtreatment of low-risk areas of viable brain without sufficient dose intensification to the highest risk regions.

Many groups deviate from the traditional treatment volumes used in RTOG studies, but evidence-based alternatives to target delineation is lacking. Investigations by Price and colleagues have begun to address this.[17,19,61] In one study, the authors performed a prospective analysis of 20 patients who underwent standard and diffusion-tensor MRI followed by stereotactic or image-guided biopsies.[61] Histopathologic findings were correlated with the voxels corresponding to the sampled area and DTI data were analyzed. The authors found that the degree of isotropic and anisotropic diffusion was closely correlated with the presence of gross and infiltrative tumor. In fact, they describe their method as being 98% sensitive and 81% specific for disease.

Data-driven methods for defining radiation treatment volumes are unlikely to improve local control, but will likely reduce exposure of viable brain to high doses of radiation. With modest, but important improvements in survival

with modern care, brain re-irradiation is becoming more common for treatment glioblastoma and is being tested in an RTOG trial (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1205). By sparing as much normal tissue as possible in a patient's initial course of radiotherapy, additional radiation in the recurrent setting might fall within an acceptable therapeutic window.

Neurosurgical planning

Somewhat more experimental is the application of DTI tractography for neurosurgical planning purposes. Functional neuroimaging is used in some centers to better identify eloquent brain regions, such as language, motor or sensory cortices in an effort to preserve function after tumor resection.[62-65] DTI may improve delineation of important white matter fiber tracts that may be displaced or deformed due to tumor mass effects. Figure 2 illustrates a patient with a large tumor in the left temporal lobe that was planned for surgical resection. DTI and fiber tractography were performed between the left inferior frontal gyrus representing Broca's area and the left superior temporal gyrus representing Wernicke's area. Robust fibers were identified representing the arcuate fasciculus and mass effect from the tumor not only displaced the fibers medially, but also appeared to separate the arcuate into a superior and inferior tract with no coherent fiber orientation between the two. In conjunction with other presurgical and intraoperative assessments, these images can guide the resection approach and extent. Early work in this area has demonstrated the feasibility of the method with neurosurgical and even radiosurgical planning, but future studies are needed to determine its role in improving resection and treatment outcomes.[66,67]

Multifactorial modeling

The evidence presented in this review demonstrates a significant role for

diffusion MRI techniques for the non-invasive clinical management of brain tumor patients. Along with improvements in diffusion MRI acquisition and analysis, there have been concurrent gains in other noninvasive strategies of tumor assessment. Namely, PET, MR spectroscopy and cerebral blood flow measures have become available in clinical practice and may be used in combination with diffusion imaging to help guide treatment decisions.

Numerous studies have begun to investigate the ability of multimodality imaging to better characterize tumors. As mentioned above, a recent study described a method for combined rCBV and ADC to distinguish between progression and pseudoprogression.[52] The same group has applied the method to evaluating brain metastases.[68] Others have employed combinations of imaging modalities to improve diagnostic capabilities,[69,70] perform noninvasive histologic assessment,[71,72] distinguish between disease and radiation injury,[73] and to correlate pre-treatment imaging with survival.[74]

A goal of research in this area is to formulate a standard multiparametric model to assess for the presence of subclinical disease. This would aid in nearly every stage of management for brain tumor patients, from diagnosis to tailoring treatment regimens. As these multiple noninvasive techniques continue to be refined, it will become more important for clinicians to understand their potential roles and limitations.

Summary

At present, diffusion imaging is not a primary modality in the diagnosis and characterization of glioblastoma, but practical applications are being developed. Results from prospective studies to validate findings from retrospective series have indicated how diffusion parameters may be correlated with tumor cellularity, invasiveness and prediction of treatment response. Early work has

demonstrated the feasibility of altering radiation target volumes based on findings from diffusion imaging, but there have been no trials to date implementing this in treatment planning.

MRI continues to develop fascinating imaging views due to the ability to manipulate the nuclear spin resonance via precisely determined rf pulse sequences, and also the addition of pulsed magnetic field gradients of sufficient size to dwarf any inhomogeneities in the static field created by the main superconducting coils. Taking advantage of differences in the nuclear spin relaxation times of protons in different tissues, rf pulse sequences can contrast out some tissues (or make them the main detected signal), at the discretion of the MRI experimentalist. DWI and DTI open new windows for the clinician due to its potential to directly observe small regions of high cellularity, which may indicate otherwise unobservable areas of malignancy both before and after standard treatment.

The most promising role of diffusion imaging may be in multiparametric analyses where advances in several modalities may be considered together. The next step in applying these techniques to clinical practice will be formalizing a standard means of data acquisition, analysis and interpretation. Functional diffusion maps and multimodal ADC histogram models appear to be the most promising approaches at this time and will require further validation. Finally, clinical trials involving larger numbers of patients with strictly defined imaging protocols are needed to move the promising experimental results into generalized clinical disease management for glioma.

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