

## Symposium

# Recent advances in imaging of brain tumors

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## Abstract

The recent advances in brain tumor imaging offer unique anatomical as well as pathophysiological information that provides new insights on brain tumors, directed at facilitating therapeutic decisions and providing information regarding prognosis. This information is presently utilized in clinical practice for initial diagnosis and noninvasive, preoperative grading of tumors, biopsy planning, surgery, and radiation portal planning, as well as, prognostication. The newer advances described in this review include magnetic resonance (MR) diffusion and diffusion tensor imaging with tractography, perfusion imaging, MR spectroscopy, and functional imaging, using the blood oxygenation level dependent (BOLD) technique.

Diffusion tensor MR imaging is the only noninvasive *in vivo* method for mapping white matter fiber tract trajectories in the human brain. In the current clinical practice, one of the most important indications of diffusion tensor imaging (DTI) is to study the relation of a tumor to the adjacent white matter tracts. Perfusion imaging with computed tomography (CT) and magnetic resonance imaging (MRI) is an exciting new radiological technique for noninvasive evaluation of cerebral hemodynamics, in certain definite clinical settings. Cerebral perfusion imaging describes the passage of blood through the brain's vascular network. Perfusion imaging, especially with MRI has become an integral component of the complete radiological assessment of brain tumors. MR Spectroscopy (MSR) is the only noninvasive technique capable of measuring chemicals within the body. MRS distinguishes various metabolites on the basis of their slightly different chemical shifts or resonance frequencies. Functional MRI refers to the demonstration of brain function with neuroanatomic localization on a real-time basis. In patient care, functional MR imaging is primarily used in the preoperative evaluation of the relationship of a brain tumor with an eloquent cortex.

The next decade will witness further sophistication of these techniques, with data available from larger studies. It is expected that imaging will continue to provide new and unique insights in neuro-oncology, which should hopefully contribute to the better management of patients with brain tumors.

**Key words:** Diffusion, perfusion, spectroscopy, functional imaging, brain tumors

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## Introduction

Over the past few decades, as novel therapies for patients with brain tumors are being developed, we are witnessing a shift in imaging from merely providing anatomical information toward providing information about tumor physiology. The recent advances in brain tumor imaging offer unique anatomical as well as pathophysiological information that provides new insights on brain tumors, directed at facilitating therapeutic decisions and providing information regarding the prognosis. This information is presently utilized in clinical practice for the initial diagnosis and noninvasive, preoperative grading of tumors, biopsy planning, surgery, and radiation portal planning as well as prognostication. In research environments, these tools

are utilized by investigators of studies on brain tumors in a variety of study designs with various aims.

The newer advances described in this review include MR diffusion and diffusion tensor imaging with tractography, perfusion imaging, MR spectroscopy, and functional imaging using the BOLD technique. The physics of each technique is only briefly described with greater emphasis on clinical applications, since the review is aimed primarily at neurosurgeons, neurophysicians, and oncologists and not at a radiology audience.

## Diffusion and diffusion tensor imaging

### Diffusion weighted (DW) imaging

Diffusion-weighted MR imaging is the simplest form of

diffusion imaging.<sup>[1]</sup> A diffusion weighted MR sequence is an integral component of the MRI brain protocol for tumors. It is a pulse sequence sensitized to the random motion of water molecules (which is termed 'Brownian motion'). Certain pathologies constrain the normal random motion of water molecules in the brain tissue and this is referred to as 'restricted diffusion'. Diffusion weighting enables one to distinguish between rapid diffusion of protons (unrestricted diffusion) and slow diffusion of protons (restricted diffusion). Lesions that have restricted diffusion appear hyperintense on diffusion images and hypointense on the accompanying apparent diffusion coefficient (ADC) maps. Using an ADC map it is possible to quantify the diffusion in brain tissues.

### Applications of DW imaging

The prototype pathology that markedly displays restricted diffusion is the hyperacute arterial infarct where the bright signal on DW images or low ADC values are attributed to cytotoxic edema. In brain tumors, diffusion imaging is helpful in the preoperative, noninvasive, radiological grading of gliomas.<sup>[2]</sup> Restricted diffusion or low ADC in the peripheral, solid component of a glioma is known to correspond to higher grades, which include anaplastic astrocytoma and glioblastoma multiforme (GBM), whereas, low-grade fibrillary astrocytomas display increased diffusivity. The low ADC of the solid peripheral components of high-grade astrocytomas is attributed to hypercellularity and high nuclear to cytoplasmic ratios. Other brain tumors that characteristically display restricted diffusion for the same reason are lymphoma,<sup>[3]</sup> medulloblastoma, and meningioma.<sup>[4]</sup> The depiction of restricted diffusion in a posterior fossa space occupying lesion (SOL) in a child, favors the diagnosis of medulloblastoma<sup>[5]</sup> rather than ependymoma. Finally epidermoid cysts almost always display restricted diffusion.

In the setting of a ring enhancing lesion with perilesional edema and mass effect on CT or conventional MRI, it is often not possible to distinguish an abscess from a high-grade necrotic glioma. The presence of a markedly restricted diffusion in the center of a ring enhancing lesion corresponds to pus, and establishes the diagnosis of a cerebral abscess.<sup>[6]</sup> The necrotic fluid in the center of a ring enhancing high-grade astrocytoma almost never displays restricted diffusion. Thus diffusion-weighted images and ADC maps have a reliable role in the diagnosis and grading of brain tumors.

### Diffusion Tensor Imaging

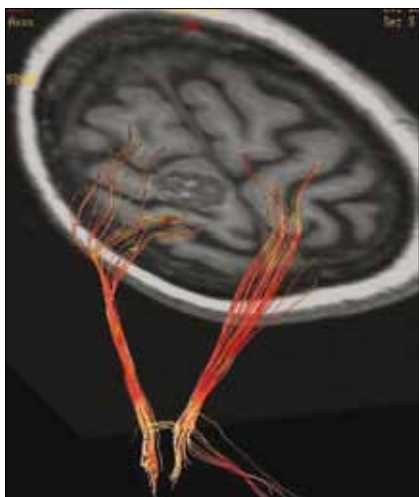
A more sophisticated extension of diffusion imaging is diffusion tensor imaging. Diffusion tensor MR imaging is the only noninvasive *in vivo* method for mapping white matter fiber tract trajectories in the human brain.<sup>[7]</sup> Diffusion tensor imaging is based on the

concepts of isotropic and anisotropic diffusion. The movement of water molecules occurs in all three directions. When water molecules diffuse equally in all three directions, this is termed as *isotropic diffusion*. This is typical in the ventricles, but is also true in the gray matter. In the white matter, free water molecules move *anisotropically*, that is, water diffusion is not equal in all three directions. This is because, in the white matter tracts, the myelin sheath surrounding the white matter causes the water molecules to move more along the long axis of a fiber bundle and less perpendicularly. Maximum diffusivity coincides with the white matter fiber tract orientation.

Information from DTI is presented in two formats, which are FA (fractional anisotropy) maps and tractography. FA maps are cross-sectional images that may be in a gray scale format or may be color coded for directional information. FA stands for fractional anisotropy. Structures that have anisotropy, that is, white matter, appear bright on the gray scale FA maps and the degree of brightness is proportional to the anisotropy. When a white matter tract is destroyed by say a tumor, there is loss of anisotropy and therefore a reduction in the FA values, which is manifested on the gray scale FA maps, as loss of brightness. FA values can also be quantified numerically. The color FA maps show the direction of white matter tracts; conventionally, commissural tracts like the corpus callosum are depicted in red, association fibers such as the superior longitudinal fasciculus are displayed in green and the superoinferiorly running projection fibers are seen in blue. Again the intensity of the color hues is proportional to the extent of anisotropy. In addition to assessment of the diffusion in a single voxel, DTI has been used to map the white matter fiber tracts. These 3-D reconstructions are called tractography. The principle direction of diffusion in a voxel is called the Eigenvector. Tractography is done by connecting a given voxel to the appropriate adjacent voxel, in accordance with the direction that the voxel's principle eigenvector is oriented.

### Applications of DTI

Diffusion tensor imaging has widespread applications in Neurology and Neurosurgical cases. In the current clinical practice, one of the most important indications of DTI is to study the relation of a tumor to the adjacent white matter tracts<sup>[8]</sup> [Figure 1]. White matter involvement by a tumor can be arranged into various categories with DTI, such as, displaced, invaded, edematous, and destroyed white matter tracts. This in turn helps guide the surgical approach and extent of resection.<sup>[9]</sup> DTI demonstration of the corticospinal tracts is a useful adjunct to intraoperative fiber stimulation.<sup>[10-12]</sup> Preoperative tractography



**Figure 1: Right frontal lobe cavernoma. DTI shows splaying of the cortico-spinal tract fibers around the lesion. Courtesy Dr Santosh Gupta. P D Hinduja Hospital**

showing tumor involvement of the corticospinal tract has been correlated to motor deficits, even when the motor cortex is uninvolved.<sup>[13]</sup> Conversely, normalization at postoperative tractography was predictive of improvement in function, suggesting a role for intraoperative tractography.<sup>[14,15]</sup> Thus, diffusion tensor imaging, by improving the recognition and characterization of white matter tracts, offers a glimpse into the brain microstructure at a scale that is not easily accessible with other modalities.

### Perfusion Imaging

Perfusion imaging with CT and MRI is an exciting new radiological technique for noninvasive evaluation of cerebral hemodynamics in certain definite clinical settings. Cerebral perfusion imaging describes the passage of blood through the brain's vascular network. In a CT / MRI perfusion study, an intravenous injection of a contrast agent is followed by serial imaging to track its first pass circulation through the brain tissue capillary bed. Usually a double dose of contrast is employed, which is administered intravenously at a very rapid rate of 3 - 4 ml/second using a pressure injector. Approximately 700 images are obtained in 1 minute 20 seconds on an average; this raw data is post-processed to obtain color-coded maps of the four perfusion parameters, which are cerebral blood volume (CBV), cerebral blood flow (CBF), mean transit time (MTT), and time to peak (TTP). Arterial spin labeling is a new perfusion technique that does not require exogenous contrast, instead it exploits the spins of endogenous water protons that perfuse the imaging plane.

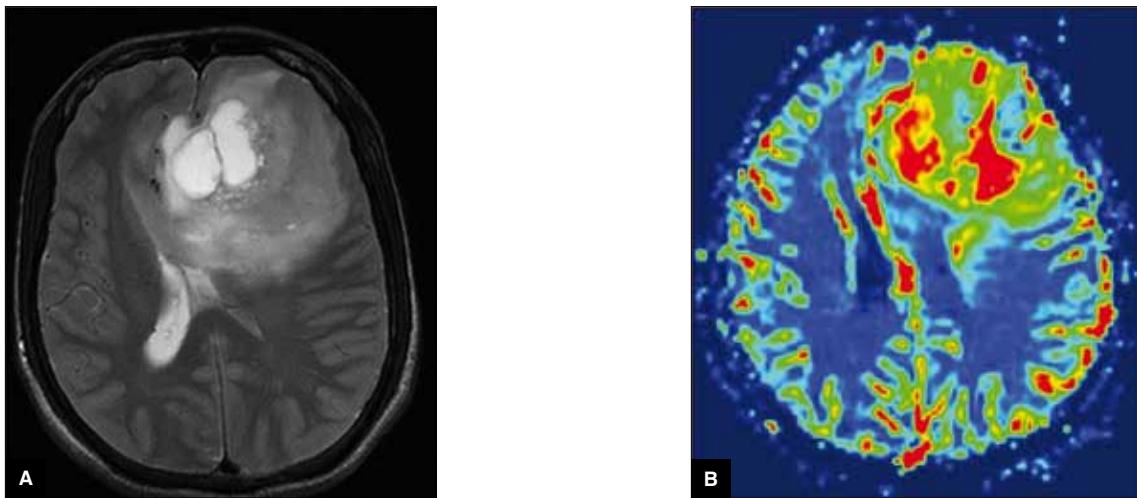
### Applications of perfusion imaging

The two important clinical settings in which perfusion

imaging is used in modern clinical practice are: in the evaluation of brain tumors and for the depiction of the penumbra in hyperacute ischemic strokes, to direct thrombolytic therapy. Over the last decade, advanced MR techniques that produce image contrast, reflecting attributes of tissue physiology and microstructure, have begun to be widely applied in clinical brain tumor imaging at major academic centers.<sup>[16]</sup> Perfusion imaging, especially with MRI has become an integral component of the complete radiological assessment of brain tumors. Like all cancers, brain tumors are associated with a high cell turnover, which leads to cellular hypoglycemia and hypoxia. This, in turn, induces the production of the vasoactive endothelial growth factor (VEGF)<sup>[17,18]</sup> which leads to neoangiogenesis. Neoangiogenesis refers to the formation of new dense beds of characteristically tortuous and structurally abnormal "corkscrew" neocapillaries, which produce extremely high blood volume in the local tissue.<sup>[17]</sup> Thus, increased capillary density in the tumor environment is the cause of markedly elevated cerebral blood volume (CBV) and cerebral blood flow (CBF) in the tumor, as compared to the contralateral normal brain parenchyma. The new vessels are more tortuous than the native cerebral vessels, leading to increased mean transit times (MTT). Hence perfusion imaging is often useful to establish the diagnosis of tumor and to distinguish tumor from tumor mimics, such as, infective granulomas and tumefactive demyelination, which are hyperperfused with low values of CBV, CBF, and MTT.

Furthermore, numerous studies<sup>[19-21]</sup> have shown that perfusion imaging can noninvasively grade tumor histology preoperatively. Low-grade astrocytomas are hypoperfused as compared to grade III and IV lesions [Figure 2]. Upto one-third of the high-grade tumors do not enhance on post contrast T1 weighted images, which may lead to a false radiological impression of low grade; unless a perfusion study is performed, which demonstrates hyperperfusion due to neoangiogenesis, which is associated with higher grade.

Some authors<sup>[22]</sup> have suggested that MR perfusion along with spectroscopy may aid in differentiating a high-grade primary tumor from solitary cerebral metastasis. Primary high-grade tumors are infiltrative by nature, hence the peritumoral edema shows elevated CBV values. In contrast, metastases are well encapsulated and noninfiltrative by nature and hence the perilesional edema being purely vasogenic shows low CBV values. MR perfusion may also be used as a guide to direct stereotactic biopsies from the most aggressive component of a heterogeneous tumor. Upto one-third of high-grade tumors are under-reported at



**Figure 2: T2 weighted image (A) shows a large complex glioma in the left frontal lobe and anterior corpus callosum. Relative cerebral blood volume (rCBV) map (B) shows the tumor is markedly hyperperfused indicating the high grade of the tumor**

stereotactic biopsy and this may be because the biopsy has not been acquired from the most aggressive portion of the lesion.

MR perfusion can help distinguish gliomas from nonglial lesions like lymphoma and metastases or extra-axial tumors like meningioma. This is because extra-axial tumors and nonglial lesions lack a blood brain barrier (BBB), hence, a very large fraction of the bolus leaks into the extravascular space during the first pass.<sup>[23-25]</sup> On the other hand, gliomas have a BBB that is impaired but not absent and this reflects in the perfusion data. The difference between these perfusion patterns can contribute significantly to the discrimination of tumor types in cases of peripherally located enhancing tumors when the differential diagnosis includes meningioma and peripheral GBM, and in periventricular enhancing lesions when the differential diagnosis includes choroid plexus papillocarcinoma and GBM.<sup>[17]</sup> It has been reported that MR perfusion is more accurate in determining the true anatomical extent of a lesion as compared to conventional imaging. This is because the perilesional edema often contains microscopic tumors, which manifest on perfusion studies as areas of increased CBV. Hence perfusion maps may show true tumor margins beyond what is visible on conventional MR imaging. The demonstration of the true anatomical extent of a tumor aids in proper surgical and radiation therapy planning.

Perfusion imaging is excellent in the differentiation of tumor recurrence from radiation necrosis, which can be confusing on conventional MR imaging. On conventional imaging, both recurrent high-grade tumor and radiation necrosis appear as space occupative lesions

with post contrast enhancement, perilesional edema, mass effect, and intralesional hemorrhage. Furthermore, for reasons not well understood, radiation necrosis most commonly occurs in the tumor bed, even in cases of whole brain irradiation. However, radiation therapy leads to endarteritis and therefore the lesions of radiation necrosis are hypoperfused, whereas, recurrent tumor being most often high-grade, is hyperperfused.

Finally, it is expected, that in the future, perfusion imaging may be a surrogate marker to study response in clinical trials of newer antiangiogenic pharmaceuticals.

### MR Spectroscopy

MRS is the only noninvasive technique capable of measuring chemicals within the body. MRS distinguishes various metabolites on the basis of their slightly different chemical shifts or resonance frequencies. Biologically, relevant nuclei that are amenable to MR analysis are those with an odd number of protons and neutrons, such as,  $^1\text{H}$ ,  $^{31}\text{P}$ ,  $^{13}\text{C}$ ,  $^{19}\text{F}$  and  $^{23}\text{Na}$ . Of these, the one we commonly use is hydrogen or proton spectroscopy. The metabolic information received is displayed as a graph. On the x-axis are plotted the resonance frequencies, which allow us to identify each unique metabolite. These frequencies are plotted in an unit called parts per million (ppm). Using the y-axis, it is possible to quantify the metabolite by either measuring the peak value referred to as the amplitude, or the area under the curve, called the integral value. Various ratios are often calculated. Single or multiple voxels of the brain can be interrogated with this technique. Multivoxel spectroscopy is also called chemical shift imaging or CSI. With CSI it is possible to create visually appealing color

maps or metabolite maps, for spatial demonstration of the metabolite peaks and ratios. These color maps are overlapped or fused with conventional MR techniques to improve anatomical localization.

### Applications of MR Spectroscopy

Clinically relevant metabolites that feature on the brain spectral graph are branch-chained amino acids (appear at 0.9 to 1.0 ppm on the x-axis), lipid (0.9 to 1.5 ppm), lactate (1.3 ppm), alanine (1.5 ppm), N-acetyl aspartate (2.0 ppm), choline (3.2 ppm), creatine (3.0 and 3.9 ppm), and myoinositol (3.6 ppm). MR spectroscopy is useful in establishing the diagnosis of tumor by demonstration of elevated choline, a metabolite that is found in the normal brain and raised in tumors due to high cell turnover. The characteristic spectral graph of a glioma depicts depressed N-acetyl aspartate (NAA), a neuronal marker, elevated choline, and lipid and / or lactate peaks [Figure 3]. It is thus possible to separate tumors from tumor mimics like granuloma and radiation necrosis, which are not associated with markedly elevated choline. It is also useful in the differential diagnosis of brain SOLs, for example, elevated alanine is a marker for meningioma. Along with MR perfusion, spectroscopic analysis of the peritumoral edema may help to differentiate high-grade glioma from solitary cerebral metastases,<sup>[22]</sup> when there is a doubt on conventional MRI. The demonstration of elevated choline in peritumoral edema suggests a diagnosis of primary glioma rather than metastases. This may be ascribed to the infiltrative nature of primary high-grade cerebral gliomas. Certain authors have advocated the use of MR spectroscopy for biopsy guidance from the most metabolically active area of the tumor, that is, the area with highest choline.<sup>[26,27]</sup> However the benefit of using

spectroscopy in this setting has not been unequivocally established. The disadvantages of MR spectroscopy are that it suffers from poor spatial resolution and may sometimes be nonspecific.

### Functional MRI (F MRI)

Functional MRI refers to the demonstration of brain function with neuroanatomic localization on a real-time basis. The vast majority of these studies are performed using blood oxygen level-dependent contrast or BOLD, which requires the detection of very small signal intensity changes - 0-3% at 1.5 Tesla and up to 6% at 3 Tesla for voxel volumes as small as 3 x 3 x 5 mm.<sup>[28]</sup> The principle of the BOLD technique of F MRI is that performing a predefined cognitive task leads to regionally increased neuronal activity and localized hemodynamic changes that produce a signal response.

### Applications of Functional MRI

In patient care, functional MR imaging is primarily used for the preoperative evaluation of the relationship of a brain tumor with an eloquent cortex.<sup>[29]</sup> The correlating function on conventional anatomical images is inaccurate due to significant variability and displacement of functional areas, as a result of the mass effect from a lesion.<sup>[30]</sup> Although functional MR imaging cannot yet replace intraoperative electrocortical stimulation in patients undergoing neurosurgery, it may be useful for guiding surgical planning and mapping, thereby, reducing the extent and duration of craniotomy.<sup>[31]</sup>

In addition, hemispheric dominance for language processing needs to be established preoperatively in both brain tumor patients and patients with temporal

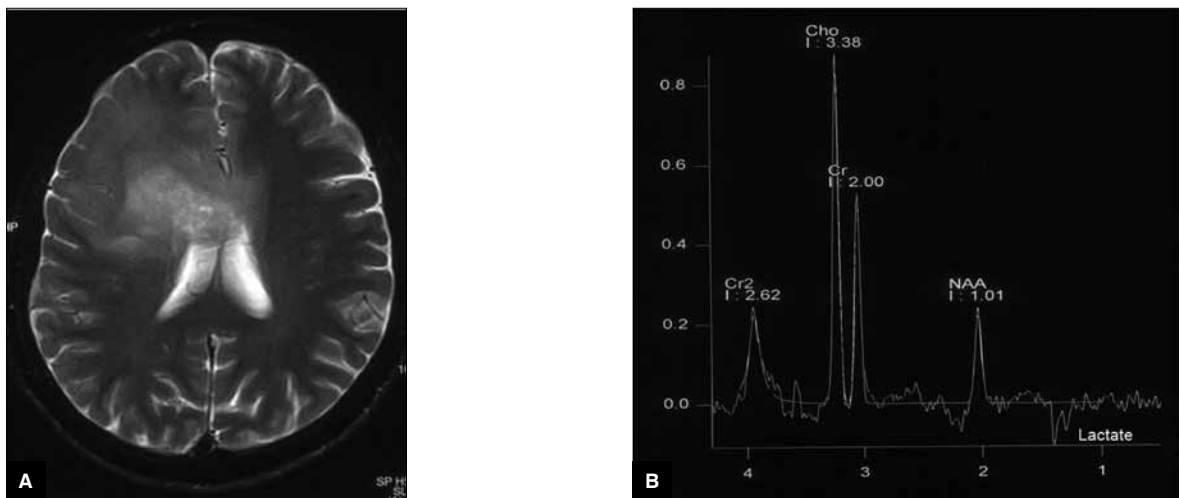


Figure 3: T2 weighted image (A) shows a right cerebral glioma involving the cortex and white matter of the frontal lobe and the anterior corpus callosum . The spectral graph of MR Spectroscopy (B) shows the characteristic features of a tumor with low NAA, elevated choline, and a lactate complex

lobe epilepsy. A preoperative functional MR imaging study of language processing provides information on the feasibility of surgery and allows adequate assessment of the risk of postoperative neurological deficits. A current limitation of functional MRI is that it is unable to distinguish between critical areas, whose resection would lead to permanent disability, from accessory or modulatory brain regions that may be resected without significant postoperative disability.

## Conclusions

The past few decades have witnessed the dramatic development of a variety of new imaging techniques for the complete anatomical, biochemical, and pathophysiological assessment of a brain tumor. These techniques have important implications in planning therapy and in prognostication. The next decade will witness further sophistication of these techniques and with data available from larger studies, it is expected that imaging will continue to provide new and unique insights in Neuro-oncology which should hopefully contribute to the better management of patients with brain tumors.

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