The role of advanced MR imaging in understanding brain tumour pathology

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The role of advanced MR imaging in understanding brain tumour pathology

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Abstract
Although MRI is the imaging modality of choice for brain tumours, the standard clinical sequences cannot tell us about certain features of brain tumours. Improvements in imaging technology now allow advanced sequences, once used exclusively for research, to be used clinically. Assessment of brain tumours with diffusion weighted MR (a marker of cellularity), diffusion tensor MR (shows integrity of surrounding white matter tracts), perfusion MR (marker of tumour vascularity and angiogenesis), MR spectroscopy (showing tumour metabolism) and functional MR (to identify eloquent cortex) provide information that is complementary to the structural information. These techniques can be used to improve identification of the tumour margin, tumour grading, reducing surgical risk and assessing the response to therapy. It is important for the neurosurgeon to understand what information can be obtained from these sequences, and that they ensure they are used to further develop the assessment and management of brain tumours.

Key words: Diffusion MRI, functional MRI, gliomas, magnetic resonance imaging, MR spectroscopy, perfusion MRI, response to therapy, tumour grading.

Introduction
The excellent soft tissue contrast provided by magnetic resonance imaging (MRI), and the range of sequences that can explore differences in the biophysical properties of the brain and tumours, has made MRI the imaging modality of choice for the assessment of brain tumours. Although MRI has improved our visualization of these tumours, there are a number of areas where it fails to provide us with sufficient information. In particular, there are four areas where further information would be very useful. The first is the inability of conventional imaging to show tumour infiltration. Infiltrating gliomas cells extend beyond the limits of both the enhanced T1-weighted and T2-weighted abnormalities.1–3 Our inability to detect these cells makes it impossible to deal with these regions during tumour resection and results in a margin to be indiscriminately added to radiotherapy treatment volumes to account for these infiltrating cells. As this margin includes normal brain, the total dose used has to be reduced to reduce the risk of radiation necrosis. As a consequence, gliomas recur within the treatment volume in the majority of patients.4,5 Better delineation of the tumour margin would certainly improve radiotherapy planning.

A second area where conventional MR is deficient relates to tumour grading. Although histology is the gold standard in characterizing brain tumours, even image-guided biopsies have an appreciable morbidity and mortality. The heterogeneity of these tumours also introduces problems with ‘sampling’ error under grading the tumour.6–8 For all high grade tumours MRI can correctly classify them with 65% sensitivity and 95% specificity.9 For low grade gliomas studies suggest that only half could be correctly classified using MRI10 and that one-third of non-enhancing tumours are in fact high grade gliomas.11

A third problem with conventional MR is that it is often insensitive to detecting subtle changes in tumours due to the effects of treatment. There is now evidence that the early detection of tumour recurrence at an asymptomatic stage is associated with improvements in patient survival.12 At present the methods of assessing response, all based on structural imaging, rely on changes in tumour size. This is particularly difficult for the newer cytostatic therapies where successful treatment may not be accompanied by much change in tumour size. The delays in determining that a treatment has failed may result in the patient being too ill to be considered for second-line therapies. Manual inspection, the standard method of neuroradiology reporting, is made
more difficult with the large amount of information presented to the radiologist in the form of multiple pulse sequences in different planes. In addition, the irregular tumour margin and differences in positioning can make interpretation even more difficult. Recent studies suggest that even in the hands of experts, volume changes up to 59% may not be appreciated. Simple one-dimensional (e.g. the RECIST criteria) or two-dimensional methods (such as the MacDonald Criteria) have been used for a more objective assessment of response, but again these can be insensitive to subtle changes because measurements are only made in the imaging axis and the irregular margin makes measurements difficult. In addition, changes in volume may only have a slight effect on tumour diameter; an increase in tumour volume of 145%, for example, is only associated with an increase in the tumour radius of 2.3 mm. For brain tumours changes in area do not correlate with changes in survival, but do correlate with the time to progression for enhancing tumours. Volumetric methods can overcome some of these problems, but are time consuming, subject to bias, and have poor inter-observer agreement. Automated volumetric methods have problems with defining the tumour margin. In addition, outcome may not relate to changes in tumour volume with treatment.

The final problem with conventional techniques is the poor identification of the relationship of eloquent cortex or white matter tracts to the tumour. Slow growing tumours frequently distort these regions and may include functional tissue that is at risk during surgery. Structural imaging is not able to identify these regions with the degree of confidence required to reduce the risk during surgery.

Until recently, the assessment of brain tumours with MRI has focused on structural changes. Over the last few years newer sequences have been developed that allow us to study pathological and biological changes within tumours. These techniques, initially used as research tools are now being transferred to the clinical arena. In this review I will explore the potential use of five of the most commonly used methods, namely diffusion weighted imaging (DWI), diffusion tensor imaging (DTI), perfusion imaging, MR spectroscopy (MRS) and functional MRI (fMRI), and explain how these methods can provide clinicians with more information to improve the management of brain tumours.

**Diffusion weighted imaging (DWI)**

*Principles of diffusion weighted imaging*

DWI is dependent on the movement of protons in water. A proton that experiences the same magnetic field will spin at the same rate. If a pulsed gradient is applied, the proton will spin at different rates depending on the strength, duration and direction of the gradient. If a second pulse gradient is then applied, the protons will be refocused. Where protons have not moved this rephasing will be complete and the signal will be unchanged. Where protons have moved between the two pulses there will be a loss of signal that is dependent on the degree of diffusion weighting, referred to as the b-value, and the diffusion coefficient. As a result, where there is free water movement, for example, CSF or in areas of vasogenic oedema, there is a drop in signal, where there are regions of water trapping, for example within swollen cells in areas of cytotoxic oedema, there is an increase in signal.

Since the signal change with DWI is also dependent on the underlying T2-weighted signal, it is not possible to use signal changes alone to quantify diffusion processes. Instead the gradient of the signal intensity due to different b-values is plotted. This coefficient, a measure of all motional processes such as diffusion and flow, is called the apparent diffusion coefficient (ADC). The ADC measures water diffusion and, therefore, often mirrors changes in DWI signal. In areas of increased diffusion (e.g. vasogenic oedema) there is an increase in ADC. In areas of restricted water diffusion (e.g. cytotoxic oedema), ADC decreases.

**The role of diffusion weighted imaging in tumours**

One of the commonest uses of DWI for the assessment of tumours is differentiating between cystic lesions. One particular use is distinguishing between epidermoids (where the thick content of the cyst restricts the diffusion of water), and arachnoid cysts where diffusion is free. Similarly, the viscous content of abscesses can be differentiated from cystic tumours.

For gliomas the DWI changes are more complex. Experimental studies suggest that the main determinant of the ADC is the extracellular volume fraction. In tumours there are two processes that can affect the extracellular volume fraction. First, there is the vasogenic oedema produced due to defects in the blood–brain barrier. As this increases the volume of the extracellular volume fraction, it causes a decrease in the DWI signal and an increase in the ADC. An example is shown in Fig. 1. These changes occur even in areas of solid tumour. The second effect is due to the increased cellularity seen in tumours. Increased cell numbers will restrict diffusion, reduce the extracellular volume fraction and would increase DWI signal and reduce the ADC. Most studies have shown that tumours have higher ADC values compared with normal brain. The regions with the highest ADC values are within cysts or areas of necrosis. Some studies have shown that there is an inverse relationship between cellularity and ADC. Although other studies have failed to demonstrate this, there is good evidence that densely cellular tumours (e.g. lymphomas) have a lower ADC than other tumour types.
Diffusion tensor imaging (DTI)

Principles of diffusion tensor imaging

For DWI it is assumed that water diffuses in all directions, i.e. diffusion is isotropic. This is not the case in the brain where water diffuses preferentially along white matter tracts. This directional diffusion, called anisotropic diffusion, is due to the presence of both intracellular barriers (e.g. neurofilaments and organelles) and extracellular barriers (e.g. myelin sheaths and glial cells). In this situation a water molecule could be described as diffusing in a volume that is described by an ellipse. Mathematically, ellipses can be described by a tensor. These tensors can be described by three eigen values that describe the magnitude of the axes of the ellipsoid direction, and three eigen vectors that describe their direction. To quantify the tensor the eigen values are used to calculate ‘rotationally invariant’ indices. A number of these measures exist; the most commonly used in the literature include the mean diffusivity ($D$ – the mean of the eigen values) as a measure of isotropic diffusion and the fractional anisotropy (FA) as an anisotropic measure. An example of this is in a normal volunteer is shown in Fig. 2. The eigenvectors can be used to provide directional information. The direction of the largest eigen value, referred to as the principle axis of diffusion, can be colour-coded to provide directionally encoded colour maps, so that fibres passing in the $x$ direction are coloured red, those in the $y$ direction coloured green and those in the $z$ direction coloured blue.38 In addition, by following these eigen vectors on a voxel-by-voxel basis it is possible to display the direction of the white matter tracts using tractography.

Diffusion tensor imaging in tumours

In tumours there is a reduction in diffusion anisotropy, caused by the disruption of normal brain architecture with loss of tissue organization, destruction of axonal processes, widening extracellular space and changes in cell size. The reduction in fractional anisotropy correlates with cell density39,40 and the proliferation index of the glioma.39 One of the main roles of DTI is to study the effects the tumour has on surrounding white matter tracts.41 Where a tumour has displaced a white matter tract it has a different colour hue on the directionally encoded colour maps with normal FA values compared with contralateral side. Where the tumour is infiltrated the FA is reduced compared with the contralateral side and the colour hues are abnormal. Where tumour has completely disrupted a tract then it is not identifiable on either FA or directionally encoded colour maps. An example is shown in Fig. 3.

Perfusion MR imaging

There are three main methods to study brain perfusion.

Dynamic susceptibility contrast imaging (DSCI)

This is the most widespread method of perfusion imaging and is likely to be a standard sequence on most MR machines. It relies on the T2* signal drop caused by the passage of a gadolinium-containing contrast agent through the tissues. The drop in signal is proportional to the concentration of the contrast agent and the tissue vascularity. An example of the
FIG. 2. The diffusion tensor can be measured by using the magnitude of 3 eigenvalues. These can be used in equations to produce maps of mean diffusivity and fractional anisotropy. These examples are from a normal volunteer.

\[
D = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}
\]

\[
FA = \sqrt[3]{\frac{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}
\]

FIG. 3. Differentiating white matter infiltration from compression. In the upper row there is a reduction in the FA within the white matter tract adjacent to the tumour (arrowed) due to tumour infiltration. In the low row the FA appears normal but the colour map shows a different colour compared to the contralateral side. This is a feature of white matter compression.
signal drop in different regions is shown in Fig. 4. Simple, semi-quantitative measures such as the peak height of the T2* relaxivity curve (the reciprocal of signal drop) or the time to peak are frequently used to provide a rough measure of perfusion, but cannot be generalized to other MR machines or sequences. The time-to-peak in particular is especially insensitive in brain tumours since, unlike in infarcts, there rarely is much of a delay in blood flow within tumours. More quantitative measures involve the calculation of the relative cerebral blood volume (rCBV)—defined as the volume of blood in the voxel/mass of tissue within the voxel. This can be calculated by the area under the relaxivity curve (Fig. 5). An example of an rCBV map is shown in Fig. 6 in a patient with a glioblastoma. From this the relative cerebral blood flow (rCBF) and mean transit time (MTT) can be calculated.

One of the main problems with DSCI is that it is not possible to produce absolute values as there is a

![Fig. 4](image1.png)

Fig. 4. An example of the dynamic susceptibility contrast effect. The graph shows the change in signal intensity taken from regions of interest in the tumour (red), normal white matter (green) and normal grey matter from the contralateral thalamus (blue). There is a reduction in the signal intensity after the bolus is given (arrow). For the tumour this drop in signal intensity is greater than that of either of the normal tissues and this drop last for longer. The drop in signal intensity is greater for grey matter than white matter, and is mirrored by the increased blood flow to grey matter.

![Fig. 5](image2.png)

Fig. 5. A graph showing the changes of T2*-relaxivity (reciprocal of signal change) after a bolus of contrast passes through the tissues. Semi-quantitative markers of this perfusion include the time to peak and the peak height. Calculating the area under the curve provides a more robust marker, relative cerebral blood volume (rCBV). The difficult in determining rCBV is that due to leakage of contrast into the extravascular space the curve does not return to baseline levels. Various computational methods have to account for this.
non-linear relationship between the signal change and gadolinium contrast. As a result, all values are usually reported relative to the contralateral white matter. One assumption made is that all the contrast remains within the vessel. This is not the case; in Fig. 5 it can be seen that the baseline relaxivity does not return to normal. Various computational methods are employed to account for this.

**Dynamic contrast enhancement (DCE)**

This method uses a rapid T1 sequence to measure changes in signal intensity as a bolus of gadolinium diffuses across the damaged blood-brain barrier into the extracellular, extravascular space (EES). By applying a multicompartmental model\(^\text{42}\) it is possible to calculate two parameters, the capillary transfer coefficient \((K_{\text{trans}})\) and the volume of the EES \((v_e)\)\(^\text{43}\). \(K_{\text{trans}}\) has several physiological interpretations depending on the balance between permeability and blood flow\(^\text{43}\). In situations of high capillary permeability, flux across the capillary is flow limited, so \(K_{\text{trans}}\) reflects the blood plasma flow per unit volume of tissue. In low permeability situations flux is permeability limited, so \(K_{\text{trans}}\) reflects the permeability surface area product. In most tumours the permeability is probably sufficiently high that \(K_{\text{trans}}\) reflects mainly capillary flow, but also some permeability. This technique may be a useful method of studying the microcirculation of tumours.

**Arterial spin labelling (ASL)**

This is a newer technique that uses an endogenous contrast mechanism, whereby the blood flowing into the brain is magnetically labelled (arterial spin labelling). This technique is still largely research-based and provides truly quantitative values of cerebral blood flow. It has the advantage that it is repeatable over a short time frame and it is possible to label individual vessels to show their involvement blood flow to the region.

As the development of a blood supply is crucial for tumour growth, there is much interest in finding methods that can image tumour vascularity. Evidence suggests that the rCBV of tumours correlates with tumour vascularity as assessed by non-quantitative scales of histological vascularity,\(^\text{44,45}\) measures of microvascular density\(^\text{46}\) and angiographic vascularity.\(^\text{45}\)

**MR spectroscopy**

**Principles of MR spectroscopy**

MR spectroscopy is based on the principle of chemical shift. If we take two protons as an example, one bound to an oxygen molecule with another proton in water and one bound with many others to a carbon molecule in fat, these protons will be in different magnetic environments. These differences are due to different degrees of ‘chemical shielding’ on the protons, so the water protons will spin slower than those in fat. Rather than referring to the frequencies in absolute terms, the frequency differences are used and expressed as a ppm scale where the resonant frequency is related to a reference frequency.

In theory, MR spectroscopy can be performed on any nucleus that exhibits nuclear spin. Studies have reported spectroscopic imaging using deuterium \((^2\text{D})\), \(^{13}\text{C}\), \(^{15}\text{N}\), \(^{17}\text{O}\), \(^{23}\text{Na}\) and \(^{19}\text{F}\) using either
endogenous nuclei or exogenous compounds. As these substances are present in very small quantities, detection is very difficult on conventional clinical scanners. Proton spectroscopy (1H) and phosphorous spectroscopy (31P), however, are feasible on most clinical 1.5 T MR machines. Phosphorous spectroscopy is largely limited to research applications looking at tissue energy production. The low signal-to-noise ratio means that at present the resolution only allows assessment of large lesions or global disorders. Proton spectroscopy acquisition sequences require water suppression since the concentration of water protons is over 10,000 times more than other substances. Signals are localized either using single voxel techniques, where a single volume of tissue is excited, or more recently multiple voxel techniques (also referred to as chemical shift imaging).

The proton spectra produced show different peaks at particular resonant frequencies. An example of such a spectrum is shown in Fig. 7. Although up to 30 compounds can be detected in the proton spectra of the normal brain at 1.5 T, the most commonly seen peaks are:

- **N-acetyl aspartate (NAA):** this provides the largest peak of the spectra at 2.02 ppm. Immunocytochemistry has shown that NAA is predominantly localized to neurons. As it is reduced in disorders that result in axonal loss it has been labelled as a ‘neuronal marker’ and used to provide a measure of ‘neuronal density’ and as a surrogate marker of neuronal integrity.
- **Choline (Cho):** this signal found at 3.24 ppm, is actually made up from glycerophosphocholine (GPC), phosphocholine (PC) and a small amount of free choline. These choline compounds are involved in membrane synthesis and degradation. Increased choline occurs with disorders causing increased membrane turnover.
- **Creatine (Cr and PCr):** this signal at 3.02 ppm is made up from both creatine and phosphocreatine. Both these compounds are involved in ATP generation and energy metabolism. As the amount of creatine and phosphocreatine appears to be relatively constant in the normal brain, it is used as a reference signal. The concentrations of other metabolites are often expressed as the ratio of the peak areas compared with the creatine peak.
- **Lactate:** the peak of lactate at 1.33 ppm is usually below the level of detection in the normal brain. Increased lactate production occurs in disorders of energy metabolism and an increase in non-oxidative glycolysis.
- **Glutamate and glutamine (Glx):** are difficult to separate at 1.5 T and often appear as a composite peak at 2.1 – 2.4 ppm and at 3.6 – 3.8 ppm. Elevated glutamate levels lead to excitotoxic cell damage. Increased glutamine synthesis occurs as a result of increased blood ammonia levels.
- **Mobile lipids** are found using short TE’s unless they are grossly elevated. The produce a double peak at 0.9 ppm (methyl lipid) and 1.3 ppm (as methylene lipid). The latter peak can be difficult to differentiate from lactate and can only be demonstrated by either inverting the lactate peak by using long TE MRS or lactate editing. Mobile lipids are not seen in normal brain but are increased when membranes breakdown and lipid droplets are formed in necrotic/perinecrotic areas.

**Proton MR spectroscopy in brain tumours**

The spectra seen in brain tumours differ greatly from normal brain. The typical spectrum of a glioma shows:

- **NAA:** There is a marked reduction in the NAA peak due to the lack of viable neurons within a tumour. Gliomas demonstrate a reduction in the NAA/Cr ratio.
- **Choline:** The choline peak is increased as a result of increased membrane turnover. Most studies expresses this increase in total choline as an increase in the Cho/Cr and Cho/NAA ratios.
- **Creatine:** The creatine peak has been assumed to be constant yet in tumours methods that use absolute quantification have shown that the total creatine level are lower than the normal brain.
- **Lactate:** Within tumours there is disruption of the normal glucose metabolism and a significant degree of hypoxia, as a result there are elevated lactate levels within tumours.
- **Mobile lipids:** As mentioned above, these are seen when lipid droplets form in the perinecrotic/necrotic areas. Lipid is therefore commonly seen in malignant tumours and is associated with the degree of malignancy and presence of necrosis.
Studies comparing MRS with tumour pathology suggest that the choline peak correlates with the cell density, and the lipid peak appears to provide the best marker of proliferation. More recent studies have shown that using the Cho/NAA ratio correlated with cell density, cell proliferation index and the ratio of proliferating cells to dying cells.

**Functional MR Imaging (fMRI)**

When an area of the brain is active there is a corresponding increase in blood flow. This coupling of blood flow and brain metabolism was first described in 1890 by Sherrington and is the principle behind fMRI. The increased blood flow is not matched by an increase in oxygen extraction, so the concentration of deoxyhaemaglobin is reduced. Since deoxyhaemaglobin is paramagnetic there is a change in the T2* signal. This change, referred to as blood-oxygen level dependent contrast (BOLD), is detected by the MR sequence.

To produce reproducible results, activation paradigms are devised to allow specific functions to be assessed. It is possible to assess any brain activation, but in practice only assessment of motor function and language are considered clinically. Motor activation is stimulated by movement of the relevant part of the body, interspersed with rest. Studies comparing motor fMRI to direct cortical stimulation in awake patients have found excellent correlation. Language activation is more problematic as this is a more complicated series of processes that involve many brain regions. The accuracy of fMRI in mapping language tasks is poorer than motor studies and usually will require the assessment of multiple language tasks. For bilingual patients there is evidence that there are different areas responsible for each language function, and this needs to be accounted when language is being assessed.

**Problems with fMRI for presurgical planning**

There are a number of problems with fMRI for presurgical planning. The first is that it shows areas that are activated but not necessarily essential to avoid causing a neurological deficit. The second is that the BOLD signal is lost adjacent to gliomas. This is probably due to the loss of autoregulation in these vessels and can also be seen following previous surgery. Care also must be taken with lesions that appear to be adjacent to areas of activation. Lesions closer than 5 mm to the motor cortex, for example, are associated with much higher incidence of neurological deficit. This probably reflects injury to cortical vessels that supply either side of a gyrus. A further problem is that fMRI provides no information regarding the relationship of white matter tracts to the tumour. Studies have shown that it is feasible to combine fMRI with DTI to accurately identify both areas of cortical activation and white matter tracts, although intraoperative MR studies have suggested marked shifts in white matter tracts intraoperatively making accurate detection of these tracts a problem. The final problem relates to the poor intrasubject repeatability of fMRI. For language paradigms this repeatability is, at best, 40%. Motor activation has better repeatability with the centre of the activated area varying by about 4 mm, but the size of the regions activated by a finger tapping task varies by about 50%, even when repeated after only 30 min. More work is needed to improve paradigm design to improve the repeatability of tasks.

**Using these techniques to improve the management of gliomas**

It is clear from the previous sections that these new techniques are sensitive to some of the pathological processes that occur in gliomas. These new sequences can provide information on tumour cellularity (DWI), the effect of tumours on white matter tracts (DTI), tumour vascularity (perfusion MR) and tumour metabolism (MRS). Their main use maybe to overcome some of the problems that conventional imaging cannot tackle.

**Identifying occult tumour infiltration**

It has been known for many years that gliomas preferentially grow along white matter tracts. As DTI is sensitive to subtle disruption of white matter tracts, attempts have been made to differentiate them from non-invasive tumours (e.g. meningiomas and metastases). The results appear mixed with some studies showing a larger reduction of FA in the peritumoural region than for gliomas, while other studies only showing significant increases in mean diffusivity. These results probably reflect the recent concerns that FA may not be a particularly sensitive measure of anisotropic diffusion and is insensitive to detecting occult white matter infiltration. Using other methods of analysing the diffusion tensor, differences can be identified.

Attempts have been made to correlate DTI abnormalities with histology. In one study the FA and mean diffusivity values inversely correlated with the total number of tumour cells and the ratio of tumour to normal cells. In another study that used an analysis method that split the diffusion tensor into pure isotropic and anisotropic components, DTI could correctly identify tumour infiltration with an overall sensitivity of 98% and specificity of 81%. Using this method it is possible to define a region that corresponds to the tumour margin. A retrospective study suggests that the arrangement of this region can predict the pattern of glioma recurrence. This study needs repeating prospectively in a larger, more homogeneous cohort of patients, but might allow a degree of individualizing treatment on the
basis of potential recurrence pattern. Attempts are being made to plan radiotherapy on the basis of this data.88

As the MR spectra of tumours differ from normal brain, studies have attempted to use this to determine tumour margins. The region of oedema surrounding a tumour has a similar spectroscopic pattern as the centre of the tumour with increased choline peaks and reduced NAA as compared with normal brain.89 Some of these areas of oedema identified on T2-weighted imaging have Cho/NAA ratios greater than 2, which is within the range seen with tumours.90 In an image-guided biopsy study the Cho/NAA and normalized choline ratios correlated with the degree of tumour infiltration.92 Although spectroscopy was better than conventional MRI at defining the tumour margin, they were unable to differentiate between normal brain and mild tumour infiltration. Using these techniques it appears that MRS-derived radiotherapy volumes extended beyond the T2-signal abnormality in 60% of cases, and that these areas of abnormality can predict the development of contrast enhancement.

Combining DTI and MRS shows that where the anisotropy is loss due to white matter infiltration, there is a corresponding finding of reduced NAA and increased Cho ratios—a metabolic profile of tumour that correlates with the disruption of white matter tracts.91 Combining these two techniques could differentiate between white matter disruption due to tumour and disruption due to oedema alone.

Tumour grading

As a tumour grade increases various pathological processes occur within the tumour. There is a marked increase in cellularity that is accompanied by an increase in vascularity and the development of necrosis. These tumours will demonstrate higher metabolic rates, with increased cellular proliferation. As these new techniques are able to non-invasively study these processes, attempts have been made use them to grade tumours.

Attempts have been made to use diffusion imaging, as a measure of cellularity, to grade gliomas. Studies have shown that the ADC in high grade gliomas is significantly lower than the less cellular low grade gliomas.31,57 In both tumour grades the values for individual patients overlapped precluding using this technique for accurate preoperative diagnosis. More recent studies suggest that an ADC value threshold of 1.0 x 10^{-3} mm^2/s showed that this was a strong prognostic marker with 14% of those with ADC values below this alive at 2 years compared with 84% of those with values above this threshold.92

In gliomas, microvascular proliferation is one of the histological characteristics that can define a tumour as a glioblastoma.93 Many studies have attempted to use rCBV to provide a method to non-invasively grading gliomas.44–46,94,94–98 Attempts to find a threshold that can differentiate between high and low grade gliomas have been hampered by the use of different acquisition techniques and methods of reporting the rCBV. The use of a spin echo (SE) T2* technique tends to give a lower ratio than using a gradient echo (GE) technique.97,99 Studies using SE sequences suggest that a threshold of 1.5 can differentiate between high and low grade gliomas.44,100 Published thresholds for GE sequences depend on whether the aim is to increase specificity96 (using a ratio of 3.57) or increase sensitivity54 (where a ratio of 1.75 was suggested). A ratio of 2.93 appears to maximize both specificity and sensitivity.96

For low grade gliomas, rCBV measurements appear to provide prognostic information. An rCBV of 1.75 is a better predictor than histology alone for predicting outcome and time to progression for low grade tumours.101,102

There are a number of problems using perfusion parameters to grade gliomas. The first is that oligodendrogliomas have higher rCBV values than astrocytic tumours.100,103 As a result, a low grade oligodendrogliomas could be falsely graded as a higher grade tumour. In fact further studies suggest that a higher rCBV is predictive of chromosome 1p deletions suggesting that this is associated with increased neovascularization.104,105 Secondly, all studies show marked overlap of rCBV with different tumour grades45,95–97,106 making grading in an individual patient inaccurate. In particular, it was difficult to differentiate WHO Grade II vs. WHO Grade III and WHO Grade III vs. WHO Grade IV gliomas using these techniques.

A few studies have used T1 dynamic contrast enhancement techniques to grade gliomas. The tumour grade strongly correlates with permeability and weakly correlates with fractional blood volume.107,108 Although there were significant differences between the tumour grades, there was still marked overlap in values of permeability for individual patients making exact grading difficult. A later study in a larger cohort found that the permeability values correlated well with the MIB-1 index.109 The fractional vascular volume has been shown to differ significantly between WHO Grades II and III, and Grades III and IV.110 Studies that have compared perfusion techniques have shown that Ktrans is less sensitive and specific at tumour grading compared with rCBV.94

Attempts to grade tumours using MR spectroscopy suggest that with increasing grade there is an increase in the Cho/Cr ratio,50,51,53,54,58,89 a reduction in NAA51,53,54,58,90,96 and increase in lactate/lipid peak.50,51,53,58 An example of spectra from gliomas of different grades is shown in Fig. 8. Murphy et al. found that the MRS findings agreed with pathological diagnosis in 74% of cases.53 They found that in 17% there was a difference in grade and in 9% there was a difference in cell of origin. Overall, it was contributory in a total of
80% of cases. Computerized automated pattern recognition algorithms have now been developed that can differentiate different tumour groups based on MRS and these have been tested in a multicentre setting. Using a normalized Cho/Cr ratio of over 1.08 had a 97.5% sensitivity, a 77% positive predictive value and a 62.5% negative predictive value for differentiating between high and low grade gliomas. The use of such ratios for diagnosis in individual patients, however, are complicated by large variation in published values with marked overlap of values between different tumour types.

MR spectroscopy is less accurate than perfusion MR measures, but combination of both techniques improves diagnosis. A similar finding has been reported with combining MRS with diffusion weighted MRI.

Assessing response to therapy
One of the first changes that occur with successful treatment is tumour cell death. Since it appears that changes in tumour cellularity and tumour components (especially the presence of necrosis) cause changes in the ADC measurements, this might be a useful tool to assess the response to therapy. In a brain tumour model in rats, changes in ADC match changes in tumour volume and cellularity. These changes also occur before any change in size on T2-weighted imaging could be observed. These techniques have been used to assess the response to convection-enhanced delivery of taxol in three patients with recurrent glioblastomas. Again, ADC changes preceded any changes in gadolinium-enhanced T1 or T2-weighted imaging. By plotting the differences in ADC in patients undergoing treatment for high grade gliomas it is possible to create a functional diffusion map that can predict response to therapy after only 3 weeks. These techniques also show that there is marked regional heterogeneity in response to treatment.

Perfusion imaging has been largely used in the cancer literature to study the effect of anti-angiogenic or antivascular drugs. It is now commonly used for assessing early effects from antivascular drugs in Phase I or II studies. It is likely that this will be the standard method of assessing response to therapy for these drugs once they are used in routine clinical practice.
practice. Studies have also used perfusion imaging to study the response to radiotherapy. A reduction of rCBV during radiotherapy is a predictor for a better prognosis.\textsuperscript{119} These changes can even be detected after only one week of radiotherapy. Dose-related reduction in perfusion can also be detected in irradiated normal brain surrounding gliomas.\textsuperscript{120,121}

This potentially may be a marker for normal brain radiation injury.

MR spectroscopy has also been used to predict the response to therapy. In a cohort of patients with high-grade gliomas receiving radical radiotherapy (i.e. 60 Gy in 30 fractions), the lactate/NAA ratio was the strongest predictor of response to radiotherapy and overall survival.\textsuperscript{2,22} For patients with a ratio above 2, the 1-year survival was 30% and no patient survived more than 2 years. For patients with a ratio below 2, the 1-year survival rate was 80%. In another study looking to predict the response to tamoxifen chemotherapy as part of a Phase II study, patients that responded had a pretreatment increase in creatine and NAA/Cr, but a lower lactate/creatinine and lipid/creatinine ratios.

Conclusions

Improvements in MR technology mean that these techniques can be performed on 1.5 T clinical machines with acceptable imaging times. In addition to the structural information from conventional MR sequences, advanced MRI provides important information on tumour pathology and biology. It is likely that these techniques will become an essential tool in the assessment of brain tumours.

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