Role of Advanced MRI in the Modern Management of Brain Tumours

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The problems with conventional MRI

Imaging plays a key role in the management of brain tumours. Surgery is now directed by imaging to ensure accurate craniotomy placement and biopsy targeting. Post-operative MRI is the only objective method of assessing residual tumour. Imaging has allowed radiotherapy treatment volumes to reduce in size to reduce the risk of radiation injury to the normal brain. Imaging is also used to define response to therapy and tumour progression. Although MRI is the imaging-modality of choice for the assessment of brain tumours, it is becoming clear that conventional MRI methods often don't provide sufficient information for management decisions. In particular, they are unable to deal with:

1. *Identifying non-enhancing tumour* – conventional MRI concentrates on the enhancing component of the tumour, yet it is well understood that much of the tumour does not enhance. Non-enhancing tumour extends at least as far as the T2-weighted abnormality. As the non-enhancing tumour cannot be identified it is not possible to identify the tumour margin which has implications in surgery, radiotherapy planning and assessing treatment response.
2. *Assessing response to therapy* – this traditionally has assessed changes to the contrast enhanced region. The MacDonald criteria of response and even the updated Response Assessment in Neurooncology (RANO) criteria measure the sum of the product of perpendicular diameters to assess response/progression. As brain tumours are typically very irregular there is poor interobserver agreement. Since many new agents are cytostatic rather than cytotoxic, changes in tumour size occur at a late stage. In addition, the antiangiogenic drugs (e.g. bevacizumab) rapidly block vessel leakiness reducing tumour enhancement. This so-called pseudoresponse means it is not possible to assess who has responded with conventional methods.
3. *The non-specificity of enhancement* – which cannot be used to identify high grade tumour. This is particularly important in low grade gliomas where it is known that 35% of low grade tumours enhance, whilst 16% of high grade tumours don't enhance. Enhancement is also seen as a response to therapy. Increased enhancement from the resection cavity is seen following local therapy with carmustine wafers. Enhancement commonly increases following chemoradiotherapy, before either regressing or stabilising. This pseudoprogression is a treatment effect that appears to confer a better prognosis. In addition, radiation injury will also enhance and can appear to progress making it very difficult to differentiate from tumour progression.

Advanced MRI methods

The development of advanced MR methods that allow pathological changes to be studied non-invasively is beginning to transfer from a research setting into clinical practice. The ability to study processes that are smaller than the size of the voxel makes these powerful tools to monitor tumours. Although there are a large number of methods available, there are three main methods being used in clinical studies (Figure 1).

Diffusion MRI

Diffusion MR (DWI) is dependent on the Brownian motion of water protons. By applying a diffusion gradient, water molecules that diffuse away between the initial pulse and a refocusing pulse result in a drop in signal (e.g. as seen in CSF). Where there is an excess of protons that can't move, for example within the swollen cells in cytotoxic oedema or in the pus of

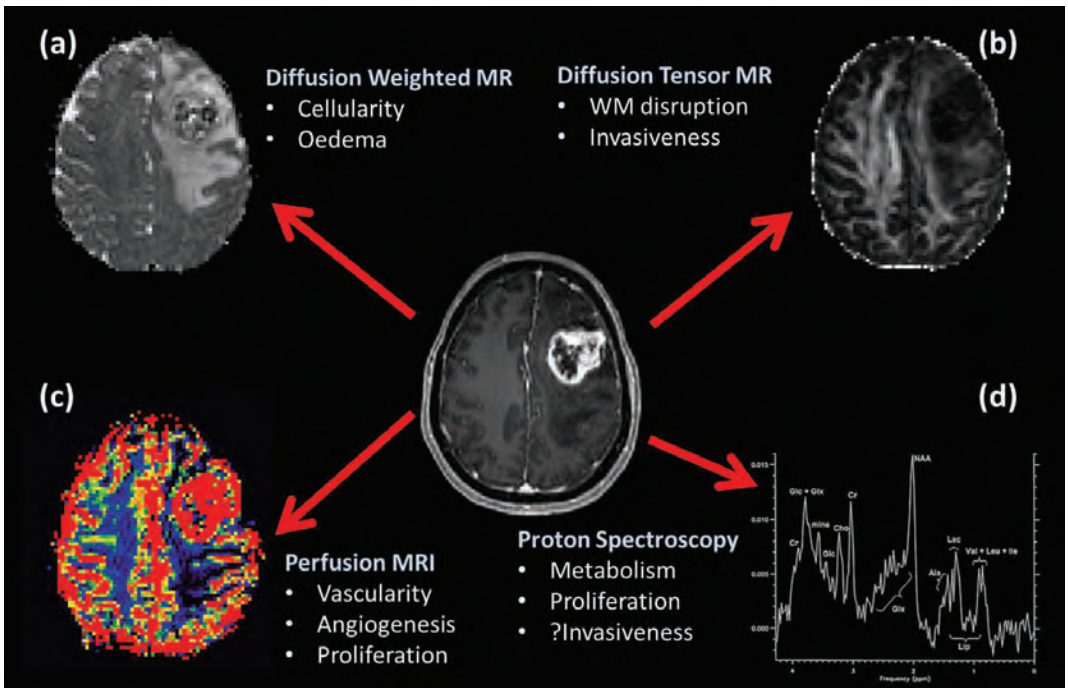

Figure 1: The commonly used advanced MR methods. The glioblastoma imaged in the centre is shown with the other modalities. (a) Diffusion weighted MRI ADC map – there is a decrease in ADC the centre of the tumour due to the increased cell numbers and presence of necrosis with an increase in the ADC in the surrounding brain due to vasogenic oedema. (b) Diffusion Tensor MR fractional anisotropy map – there is a loss of the anisotropic diffusion in the centre of the tumour and the peripheral white matter tracts. This is due to oedema and tumour invasion. (c) Perfusion MRI rCBV map – there is increased rCBV in the tumour due to increased vascularity, angiogenesis and proliferation. (d) A proton spectra from normal brain showing the relative peaks.

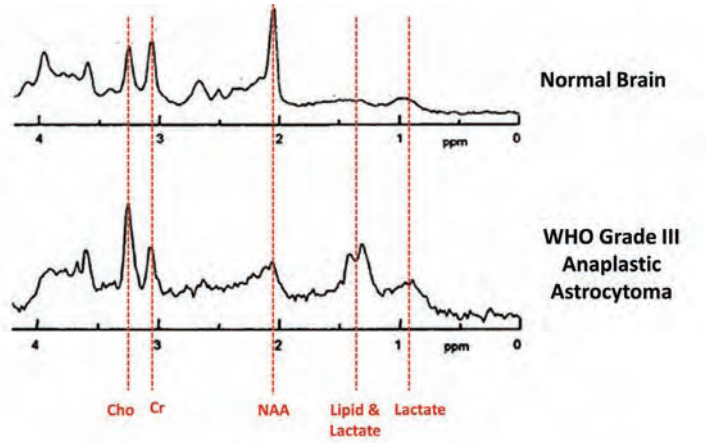

Figure 2: An example of spectra from normal brain and a high grade glioma. The choline (Cho) peak is increased and is now larger than the NAA peak in the anaplastic astrocytoma. The creatine (Cr) peak is largely unchanged. In the anaplastic astrocytoma you can now detect both lipids (correlates well with cell proliferation) and lactate (due to tumour hypoxia).

abscesses, there is an increase in signal (it appears bright). The magnitude of the diffusion weighting is measured by the b-value. The intensity of diffusion weighted MR is also dependent on the T2-weighted signal; regions that appear bright on T2-weighted images can appear bright on diffusion-weighted sequences (so called T2-shine through) and therefore cannot be quantified. Instead, the apparent diffusion coefficient (ADC) is calculated. This effectively gives a measure of how far the water molecules can move. Areas of high movement (e.g. CSF or vasogenic oedema) have the highest ADC.

Experimental evidence suggests that that the main determinant of the diffusion coefficient is the extracellular volume fraction. In tumours this is altered by both vasogenic oedema (which increases ADC) and tumour cellularity (which decreases the distance water molecules can diffuse and hence decreases the ADC). This means that the ADC is increased in tumours compared to normal brain, but as the grade increases the ADC decreases. Attempts at using this to predict tumour grade have been mixed with some studies suggesting good predictive value [1] while others showing no correlation with grade.

Although ADC measures cannot be reliably used to compare different tumours, it can be used to monitor individual tumours. Animal studies have suggested that there is a rapid increase in ADC following treatment that correlates to a decrease in cellularity. A similar finding has been shown in brain tumour patients [2]. By calculating the changes in ADC for each voxel in the tumour it is possible to create a functional diffusion map that can predict response to therapy after only three weeks of treatment [3]. Monitoring diffusion changes with treatment is particularly useful in assessing the non-enhancing tumour component. The development of a reduced ADC predicts sites of tumour progression and failure of therapy.

DWI assumes water diffuses in all directions (isotropic diffusion). In the brain, however, water molecules preferentially diffuse along white matter tracts (anisotropic diffusion). By measuring the diffusion in different directions it is possible to understand the integrity of white matter tracts. This technique of diffusion tensor imaging (DTI) has been shown in a number of disorders to be more sensitive at detecting white matter disruption compared to normal appearing white matter. Studies in brain tumours have shown that DTI can identify abnormalities not seen on conventional imaging [4]. These abnormalities predict the site of tumour progression [5] and image-guided biopsies have shown that it can identify occult tumour [6].

As DTI can identify the directionality of water diffusion, it can be used to visualise white matter tracts. These provide valuable information for surgical planning to help avoid deficits. A randomised controlled trial of DTI-based navigation vs. standard surgery showed a significantly reduced risk of motor deterioration and even an improvement in survival in patients who had DTI-based neuronavigation [7].

Perfusion MRI

Imaging perfusion with MRI can be done using two main methods. The first tracks the passage of a 'tracer' through the vasculature – either a contrast agent as in dynamic susceptibility imaging (DSCI), or labelled water molecules in arterial spin labelling (ASL). Alternatively, the transfer of contrast agent into the tissue studied in dynamic contrast enhanced MR (DCE). Most clinical studies use the DSCI method. The relative cerebral blood volume (rCBV), calculated from the area under the signal drop curve, correlates with vessel density, expression of vascular endothelial growth factor (VEGF) and the proliferation index of the tissue [8]. As these processes are diagnostic features of high grade gliomas, attempts have been made to use this for tumour grading. Various studies suggest high grade gliomas have higher rCBV values, but there is significant overlap that it is difficult to use them in diagnosis. Targeting biopsies on the areas of highest rCBV can overcome the problems of sampling error in these heterogeneous tumours by focusing on the highest grade part. In low grade gliomas, however, an rCBV > 1.75 predicts a more rapid transformation into a higher grade tumour and is a better predictor of prognosis than histopathology [9]. Longitudinal assessment suggests an increase in rCBV can be seen up twelve months before obvious tumour transformation [10].

One major use of perfusion imaging is in differentiating tumour from treatment effects. Unlike active tumour, radiation necrosis has reduced perfusion. An rCBV of >2.6 predicts progressive tumour and an rCBV of <0.6 identified radiation necrosis in all cases [11]. True tumour progression (high rCBV) and pseudoprogression (lower rCBV) can be differentiated with high sensitivity and specificity.

Perfusion imaging has had a more limited role in monitoring tumour response. This is largely due to the effects of steroids on rCBV. Changes in rCBV in glioblastomas can be detected within the first three weeks of radiotherapy, and this predicts the overall response and survival. Using a similar method to the functional diffusion map, it is possible to derive a parametric response map using changes in rCBV that highly correlate with survival following three weeks of radiotherapy. One of the main hopes of using perfusion to monitor response was with the antiangiogenic drugs. It appears, however, that although DCE can predict the degree of enhancing volume decrease, it could not predict the time to progression or overall survival.

MR spectroscopy

Spectroscopy is able to study the chemical composition of the brain. Although a number of nuclei are suitable for MR spectroscopy, the abundance and higher gyromagnetic ratio of protons (1H) mean it is feasible to study at 1.5T. Protons in different molecules will experience different magnetic environments due to 'chemical shielding'. By imaging small regions without imaging gradients it is possible to obtain a spectra consisting of a number of peaks whose heights are related to the extracellular concentration and whose location are determined by their resonant frequency. A number of typical substances can be reliably identified (Figure 2), including:

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1. N-acetyl aspartate (NAA): a marker of neuronal integrity. In tumours there is a reduction in NAA – the higher the grade the more the NAA is reduced [12].
2. Choline (Cho): choline compounds are involved in membrane synthesis and degradation and are increased in higher grade tumours [12]. The Cho/NAA ratio correlates well with cellular proliferation and can be increased in normal appearing peritumoural brain.
3. Creatine: this is involved in ATP synthesis and energy metabolism. As it is relatively stable, other metabolites are often expressed as a ratio to creatine.
4. Lactate and lipids: these peaks are in the same region of the spectra and need editing to separate. Lactate is a sign of hypoxia and lipids are a sign of cell turnover and proliferation. They are not found in normal brain but are found in higher grade tumours.
5. Glutamate/Glutamine: the peaks for these are difficult to separate. Increased glutamate occurs in the glioma periphery to cause excitotoxic neuronal loss to provide space for tumour invasion.

As the tumour grade increases there is an increase in the Cho/Cr ratio, a reduction in NAA and an increase in lipid/lactate peaks [12]. Comparative studies with perfusion MR suggest MRS is inferior in tumour grading, but combining data improves diagnostic accuracy.

Conclusion

It is clear that conventional MR techniques may no longer provide enough information for modern neuro-oncological practice. The newer advanced MR techniques are available on standard clinical MR machines and provide useful information on pathological processes within tumour that can overcome some of these. Research is now needed to demonstrate how these tools influence patient management. ■

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