Progression or Pseudoprogression? A Review of Post-Treatment MRI Appearances of Glioblastoma

Poster No.: C-1770
Congress: ECR 2015
Type: Educational Exhibit
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Keywords: Neoplasia, Cancer, Comparative studies, MR, Oncology, Neuroradiology brain
DOI: 10.1594/ecr2015/C-1770

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Learning objectives

1. To outline the phenomenon of pseudoprogression and the problems it introduces in the treatment of glioblastoma.

2. To know the features on different MRI techniques that differentiate progression from pseudoprogression, specifically:
   - Conventional contrast-enhanced MRI
   - Diffusion-weighted MRI
   - Diffusion tensor imaging
   - Perfusion MRI
   - MR spectroscopy

3. To review the current literature on the strengths and weaknesses of each technique in differentiating progression from pseudoprogression.
Background

Glioblastoma (GBM) is a common brain tumour in adults which has a poor median survival despite multimodality treatment. On MRI follow-up there is a recognised subset of treated patients with imaging features that indicate "progressive disease" but who subsequently show stabilisation or resolution despite no change in treatment. In these cases of "pseudoprogression" it is believed that non-tumoural causes lead to increased contrast enhancement and conventional MRI is inadequate in distinguishing this from true tumour progression.

Incorrect diagnosis of this pseudoprogression group as tumour progression could lead to an inappropriate change of effective therapy. The purpose of this e-poster to outline the MRI features of different MRI techniques that current research has identified as valuable in differentiating between the two conditions.
Findings and procedure details

Introduction

Glioblastoma (GBM) is the most common malignant primary brain tumour in adults and, despite multimodality treatment, the best median survival is still poor.

The previously used Macdonald criteria characterised progressive disease by there being a >25% increase in the area of enhancement (Macdonald et al, 1990). However, a subset of patients fulfil this criteria despite the enhancement stabilising or resolving with no change in treatment. This 'pseudoprogession' occurs in about 20% of patients (Brandes et al, 2008; Chaskis et al, 2009).

More advanced MRI techniques are showing promise in differentiating progression from pseudoproggression at an early stage and allowing more judicious treatment administration and early termination of ineffective treatment plans. The MRI techniques to be covered include:

- Conventional gadolinium-enhanced MRI
- Diffusion-weighted imaging
- Diffusion-tensor imaging
- Perfusion MRI
- MR spectroscopy

Conventional gadolinium-enhanced MRI

T2-weighted (T2W) and T1-weighted gadolinium-enhanced MRI (T1WGd) do not reliably distinguish pseudoproggression from tumour progression. Both can show the same features of mass effect and new enhancement (Kumar et al, 2000; Tassel et al, 1995). Some distinguishing features of pseudoproggression as shown by Mullins et al (2005), Valery et al (2001) and Kumar et al (2000) include:

- Corpus callosum involvement
- Subependymal spread (Fig. 1 on page 10)
- Multiple lesions
- Swiss cheese enhancement pattern

However, none of these features are sensitive or specific enough to reliably diagnose pseudoproggression.
Diffusion-weighted MRI (DWI)

DWI signal depends upon the self-diffusion of tissue water. The presence of cell walls and other tissue structures restricts water diffusion and leads to an increase in the DWI signal. However, the DWI signal is a complex function and is affected by more than just the self-diffusion of tissue water. It is, therefore, evaluated along with the ADC map, which is calculated from DWI. This is because a low ADC signal unambiguously identifies restricted diffusion that is caused by increased cellularity and architectural change in the cells.

GBMs are highly cellular structures leading to restricted diffusion of water and, therefore, a high DWI and low ADC signal. A low ADC value has been shown to be valuable in diagnosing pseudoprogression across several studies (Hein et al, 2004; Asao et al, 2005; Zeng et al, 2007; Wang et al, 2012).

Limitations:

- ADC measurements change over time with the evolving pathological process and so a "characteristic" value at a single time point is not possible.
- ADC value measured differs depending on amount of tumour, peritumoural oedema and necrosis included in the sample which are not well differentiated on T1WGd imaging.
- There is considerable inter-observer variance in drawing the region of interest.
- ADC values of different areas of normal brain differ considerably, which will influence pathological ADC measurement to varying degrees.

These limitations are not unique to DWI but are shared with most of the techniques described below.

Susceptibility-weighted MRI (SWI)

Rather than being used as a stand-alone technique, conventional SWI and gadolinium-enhanced SWI (SWI-Gd) have been shown to be valuable in identifying areas suitable for ADC measurements. Using T1WGd to identify areas for ADC measurement showed an increase in three out of 11 patients who later were shown to have tumour recurrence. Using SWI-Gd instead for choosing the region-of-interest on the ADC map showed an increased ADC in 10 out of 11 patients and, therefore, gave a higher sensitivity and specificity (Sayyari et al, 2010).
Diffusion-tensor imaging (DTI)

DTI is an extension of DWI that computes the fractional anisotropy (FA) map showing the preferential direction of water diffusion along white matter tracks as well as computing the ADC map.

As shown with DWI, the mean ADC signal in DTI has been shown to be significantly lower in patients with tumour recurrence than in those with pseudoprogression (Xu et al, 2010). Also, the mean FA ratio was significantly higher in those same patients. Potentially a cut-off value can be applied to more easily differentiate the two conditions (Alexiou et al, 2014). An ADC ratio cut-off value of 1.27 differentiated treatment-induced necrosis from recurrence with 65% sensitivity and 100% specificity.

Limitations:

- Not as sensitive as perfusion MRI or brain SPECT
- Not as readily available

Perfusion MRI

T2* echo-planar dynamic susceptibility contrast imaging (DSC-MRI) is the most common perfusion MRI technique and provides estimates of absolute cerebral blood flow (CBF), cerebral blood volume (CBV), and relative CBV (rCBV). Active tumour growth incites angiogenesis leading to increased perfusion. Conversely, radiation necrosis and other non-tumoural post-treatment pathology results in fibrinoid necrosis of small vessels, endothelial thickening, and vascular thrombosis leading to reduction of perfusion.

The perfusion characteristics have been shown to be useful in differentiating tumour progression from pseudoprogression. rCBV values higher than 0.71 indicated tumour progression with a sensitivity of 91.7% and a specificity of 100% (Hu et al, 2009).

Further supporting this, the percentage change in rCBV one month following treatment was the one variable that had the most significant inverse correlation with median survival (Mangla et al, 2010).

Limitations:

- Low spatial resolution.
- Degraded by susceptibility artefacts meaning that imaging of the posterior fossa is less reliable.
• rCBV in normal cortex is higher than in normal white matter. The proportion of each in the sample area may influence rCBV values independently of underlying pathology.
• Contrast leak, due to disruption of the blood brain barrier, leads to incorrect estimation of the lesion size.

**Contrast leak:**

Gadolinium has a small molecular size meaning it crosses defects in the blood brain barrier easily leading to changes in the T1 measurement and inaccurate measurements of CBV and CBF. There have been several methods to overcome this:

1. **Software leak correction** (Haris et al, 2008)
2. **Alternative contrast agent** - ferumoxytol, an iron oxide nanoparticle, has a larger molecular size and does not readily cross the blood brain barrier. Its use is still research-based but Gahramanov et al (2013) found that rCBV measurements using ferumoxytol instead of leak-corrected gadolinium correlated better with median survival.

**MR spectroscopy (MRS)**

MRS can identify choline (Cho), creatine (Cr), N-acetylaspartate (NAA), lactate and lipids. It is normally the ratios, rather than the absolute values, that are expressed. Different pathologies demonstrate different ratios and metabolite levels as shown in Table 1 on page 10.
Table 1: Table showing the metabolites typically found in different pathological processes.

References: Norfolk and Norwich Hospital - Norwich/UK

An elevated Cho/NAA (Smith et al, 2010) and NAA/Cr ratio (Elias et al, 2011) have been found to correlate with recurrent tumour. Potentially, cut-off values may be applied to aid in diagnosis although the exact value is slightly different between studies (Weybright et al, 2005; Rock et al, 2011; Zeng et al, 2007).

Limitations:

- Low spatial resolution.
- High susceptibility to artefact, making imaging of the posterior fossa difficult.
- Difficulty in developing universal cut-offs due to different MRI strengths, imaging protocols and algorithms used in different centres.

Summary
<table>
<thead>
<tr>
<th>Imaging sequence</th>
<th>Features associated with pseudoprogression</th>
<th>Strengths</th>
<th>Weaknesses</th>
</tr>
</thead>
</table>
| Conventional MRI and T1W Gd | • Subependymal enhancement  
• Involvement of corpus callosum  
• Multiple lesions  
• Swiss cheese enhancement pattern | • Readily available | • Not sensitive or specific enough to enable accurate differentiation |
| Diffusion-weighted MRI | • Lower ADC and mean ADC ratio  
• Assess microscopic pathology  
• Enhancement on Gd-SWI (instead of T1W Gd) may select better areas for ADC measurement | • Readily available  
• High rates of sensitivity and specificity | • Different pathologies included in sample  
• Considerable inter-observer variance  
• ADC of different normal brain regions differs independently of underlying pathology |
| Diffusion-tensor imaging | • Lower mean ADC  
• Higher mean FA ratio | • Could apply cut-off values | • Inferior to perfusion MRI  
• Low sensitivity |
| Perfusion MRI          | • Lower rCBV                                                                                              | • High rates of sensitivity and specificity                                | • Low resolution  
• Susceptibility artefacts are prominent  
• Contrast leak – may be overcome by software correction or alternative contrast agent |
| MR spectroscopy        | • Lower Cho-Cr ratio  
• Higher NAA/Cr ratio | • Could apply cut-off values  
• High sensitivity and specificity | • Susceptible to artefact  
• Low spatial resolution |

**Table 2:** Table showing the features typical of pseudoprogression on different MRI techniques and the strengths and weaknesses of each technique.

**References:** Norfolk and Norwich Hospital - Norwich/UK
### Table 1: Table showing the metabolites typically found in different pathological processes.

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumour</strong></td>
<td>• High Cho/Cr ratio due to increased number of cells and increased synthesis of cell membranes.</td>
</tr>
<tr>
<td></td>
<td>• Low NAA/Cr ratio due to neuronal loss or damage.</td>
</tr>
<tr>
<td><strong>Necrotic tissue</strong></td>
<td>• Elevated lactate, which is a marker for anaerobic glycolysis</td>
</tr>
<tr>
<td></td>
<td>• Elevated lipds due to cell membrane degeneration</td>
</tr>
</tbody>
</table>
**Fig. 1:** The images are of one patient with recurrent GBM, as proven by clinical deterioration, at two time-points after treatment. One month post-surgery T1WGd 1b) coronal and 1c) axial images show early subependymal enhancement that increased in the T1WGd 2b) coronal and 2c) axial images taken 4 months after treatment. Key: 1) One month post-surgery with a) coronal T1W, b) coronal T1WGd, c) axial T1WGd images 2) Four months post-surgery with a) coronal T1W, b) coronal T1WGd, c) axial T1WGd images

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• Higher mean FA ratio                                                                                                    | • Could apply cut-off values                                             | • Inferior to perfusion MRI  
• Low sensitivity                                                                                   |
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| MR spectroscopy                  | • Lower Cho-Cr ratio  
• Higher NAA/Cr ratio                                                                                                         | • Could apply cut-off values                                             | • Susceptible to artefact  
• Low spatial resolution                                                                           |

**Table 2**: Table showing the features typical of pseudoproggression on different MRI techniques and the strengths and weaknesses of each technique.

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Conclusion

Pseudoprogression - the appearance on imaging of progressive tumour after treatment that then resolves or stabilises - introduces challenges in follow-up imaging of glioblastoma patients. Incorrectly diagnosing pseudoprogression as tumour progression may result in the inappropriate change in effective treatment.

Conventional MRI and T1WGd do not reliably differentiate between pseudoprogression and tumour progression. Newer techniques - such as diffusion-weighted imaging, diffusion-tensor imaging, perfusion MRI and MR spectroscopy - are being shown to be useful in post-treatment diagnosis of glioblastoma patients.

No one imaging technique is sensitive or specific enough to enable absolutely confident differentiation between tumour progression and pseudoprogression. However, in normal practice we rely upon imaging over time and a combination of different techniques. Similarly, combining techniques and making comparisons over time may result in better accuracy of diagnosis.
References


