Tumour progression or pseudoprogression?: A review of post-treatment radiological appearances of glioblastoma

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Introduction

Glioblastoma (previously called glioblastoma multiforme, GBM) is the most common malignant primary brain tumour in adults. Despite multimodality treatment comprising maximal safe resection, radiotherapy and concomitant (chemo-RT) and adjuvant chemotherapy, the best median survival is in the range of 14-18 months.[1,2] Efficacy of therapy may be evaluated by patient survival, though image-based criteria to evaluate disease response exist. Macdonald et al.[3] developed criteria for assessing the response of supratentorial GBM based on the area of contrast enhancement (CE) on computed tomography (CT), subsequently adapted for MRI, in conjunction with clinical assessment and steroid use.

By the Macdonald criteria, progressive disease is determined by a 25% or greater increase in the product of the perpendicular diameters of the largest area of contrast enhancement. Increasingly, transient treatment-related changes on imaging mimicking progressive disease are being recognised. An increase in the enhancing area on MRI can be induced by a variety of nontumoural processes such as post-surgical changes, radiation effects and ischaemia[4,5]. These “pseudoprogression” cases, which are generally not associated with clinical deterioration, stabilize or resolve without any change in treatment (figure 1).

Figure 1

Pseudoprogression has been observed in multiple studies and is estimated to occur in about 20% of patients following GBM treatment.[6–10] In a large study by Taal et al.[11] 50% of patients treated with chemoRT for GBM with worsening MRI features on early MRI actually showed stabilization or resolution of those MRI features without any change in treatment. Wrongly diagnosing pseudoprogression as true tumour progression on gadolinium-enhanced MRI could lead to an inappropriate change in therapy and errors in assessing the efficacy of novel treatments. This was addressed in the updated response assessment criteria developed by the Response Assessment in Neuro-Oncology Working Group (RANO) which

suggests that in the first 12 weeks after therapy, when pseudoprogression is more prevalent, progression can only be diagnosed if there is new enhancement outside the radiation field (image 1).[12] More advanced MRI techniques and molecular imaging are showing promise in differentiating responders to treatment from non-responders at an early stage and will allow more judicious treatment administration and early termination of ineffective treatment plans.

Table 1. RANO criteria for high-grade gliomas

The purpose of this review is to outline the current research into radiological assessment of GBMs, specifically the differentiation between pseudoprogression and true tumour progression.

It should be noted that pseudoprogression and radiation necrosis (late-delayed radiation effects) are not interchangeable terms.[14] Pseudoprogression typically occurs earlier (within 6 months of chemo-RT) and the histopathology is not completely understood.[15] For the purpose of this review studies that include patients with apparent progression on imaging occurring within six months of treatment have been categorised as pseudoprogression.

Literature search

A broad search was conducted between April 2014 to November 2014 on PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) using "ALL FIELDS" and entering "GLIOBLASTOMA" AND "PSEUDOPROGRESSION". Abstracts were hand searched and those that were not on topic excluded. Electronic copies of the relevant studies were accessed via secure access to the hospital library.

The exclusion criteria applied included laboratory only studies; non-human studies; non-english language studies; paediatric population; and newly diagnosed glioblastoma patients.

Overall, 69 publications met the criteria. These included five focusing on conventional MRI; 16 on diffusion weighted MRI (DWI); 13 on perfusion MRI; 13 on MR spectroscopy (MRS);

18 on positron emission tomography (PET); 12 on single photon emission computed tomography (SPECT); and eight on serial studies and multimodality imaging.

Imaging techniques

Conventional MRI

Tissue signal intensity appearances on T2-weighted MRI (T2W) and T1-weighted gadolinium-enhanced MRI (T1WGd) do not reliably distinguish pseudoprogression from tumour progression as both can show new enhancement on T1WGd next to the resection cavity and progressive enlargement with mass effect.[4,16] Some distinguishing features of tumour progression include corpus callosum involvement, subependymal spread, and multiple lesions.[17] A larger 3D volume has been used to predict a worse prognosis.[18]

In a more recent study the MRI scans of 321 patients were retrospectively analysed based on 11 MRI signs.[19] Only subependymal enhancement (figure 2) was predictive for true tumour progression (p = 0.001) with 93.3% specificity, though the sensitivity and negative predictive values were only 38.1% and 41.8% respectively. The poor predictive value of subependymal enhancement is reflected in the earlier retrospective study of Kumar et al.[4] which found that radiation necrosis showed a predilection for the periventricular white matter within the radiation portal. They found that a “Swiss cheese” enhancement pattern more frequently showed radiation necrosis on histopathology.

Figure 2

Conventional MRI is, therefore, inadequate for differentiating tumour progression from pseudoprogression except in the situation in which new enhancement occurs outside the radiation field.[20]

Diffusion-weighted MRI

The signal created in DWI depends upon the self-diffusion of tissue water. The presence of cell walls and other tissue structures restricts water diffusion leading to increases in the DWI signal. However, the DWI signal is a complex function of many parameters and high signal can also be caused by elevated T2 values (the T2 shine-through artefact). If is therefore usual to calculate an apparent diffusion coefficient (ADC) map from the DWI signal. Low ADC values unambiguously identify restricted diffusion of water molecules caused by increased cellularity or changes in the cytoarchitecture of cells in tumours.

GBMs are highly cellular structures causing restricted diffusion of water. Diffusion signal characteristics are already being used to diagnose and grade cerebral gliomas.[21–23]

Hein et al.[24] investigated the use of DWI in differentiating pseudoprogression from tumour progression. ADC maps were obtained starting one month after the treatment of GBM in patients with newly enhancing lesions. MRI Recurrence was established by clinical course or histological examination in combination with imaging studies. The mean ADC value of newly enhancing lesions was significantly lower in the tumour progression group than in the pseudoprogression group ($p < 0.006$). ADC ratios (ADC of enhancing lesion to ADC of normal contralateral white matter) were also lower ($p < 0.001$).

This result was repeated in other prospective studies showing that the maximal ADC values were significantly lower for the recurrence group than for the pseudoprogression groups (maximal ADC 2.30 ± 0.73 for radiation group and 1.68 ± 0.37 for tumour progression)[25] and that the minimum ADC value was significantly lower in the recurrent tumour group than in the radiation-injuries group[26] based upon non-progression on follow-up and histology.

Limitations

There are several limitations of DWI in post-treatment GBM due to spatial and temporal sampling errors.

Like any quantitative measurement of a dynamically evolving pathological process like a GBM, ADC measurements will change over time so that obtaining a “characteristic” value at a single time point is not possible.

Spatially there are three issues. Firstly, the ADC value measured will differ depending on the relative amounts of tumour, peritumoural oedema, and necrosis included in the sample. The area sampled is usually determined by regions of enhancement on T1WGd – which has a poor specificity for differentiating between different pathological features – and ADC has been shown to be poor in differentiating tumour from peritumoural oedema.[21,27] Secondly, a potential pitfall is inter-observer variance in drawing the region of interest (ROI) and, therefore, measuring inconsistent ADC values.[28] Finally, the diffusion anisotropy of different areas of normal brain varies considerably and care must be taken to compare the fractional anisotropy (FA) values of the ROI to an area as similar as possible in the contralateral hemisphere.[29]

It should be noted that these limitations are not unique to DWI but are shared with most of the techniques described below.

Susceptibility weighted imaging with DWI

Susceptibility weighted imaging (SWI) is an alternative to T1WGd that may better identify areas suitable for ADC measurements. SWI is a 3D gradient echo technique that provides images that are sensitive to subtle variations in susceptibility caused by deoxyhaemoglobin. SWI has been shown to be more sensitive than T1WGd for showing the heterogeneity of tissue pathology in brain tumours.[30–32] Also, gadolinium-enhanced SWI (SWI-Gd) can provide clinically useful information on altered tumour microvascularity and cellular density[33]; the degree of intratumoural necrosis[34]; and the presence of abnormal enhancement around the tumour post-contrast suggesting a breakdown in the blood-brain barrier.[35]

Targeting areas for ADC analysis using SWI-Gd instead of T1WGd has shown promise.[36] ADC measurements taken from enhancing areas on SWI-Gd were significantly reduced in 10 out of 11 patients with tumour recurrence. ADC values also fell over time. Conversely, ADC measures taken from enhancing areas on T1WGd were significantly reduced in only three of 11 patients and actually increased in four of 11 patients.

In the same study, ADC measurements of enhancing areas on SWI-Gd were increased in four out of six patients with pseudoprogression and increased further over time. The findings are promising but more data is required to assess the validity of using SWI-Gd and DWI.

Although identification of enhancing regions by SWI-Gd has only been applied to DWI measurements it could in principle be combined with any of the MRI methods described below and may thus improve their performance.

Diffusion-tensor imaging

Diffusion-tensor imaging (DTI) is an extension of DWI that samples water motion in at least six non-collinear directions to provide additional information about the direction of water motion. This data can then be used to compute maps of fractional anisotropy (FA) showing the preferential direction of water diffusion along white matter tracks as well as computing

the ADC map. Confusingly, ADC is usually called mean diffusivity (MD) in the DTI literature but the two are essentially identical. Since the direction of diffusion is largely determined by the presence of white matter tracts DTI provides a sensitive means of detecting alterations in the integrity of white matter structures and hence a means of detecting infiltrating tumour.

In a prospective study the mean ADC ratio in new enhancing areas on T1WGd was significantly lower and the mean FA ratio significantly higher in patients with tumour recurrence compared to those with pseudoprogression.[37] Neither the mean ADC ratio nor the FA ratio in the areas of oedema showed any significant difference. They suggested that an ADC ratio of less than 1.65 or an FA ratio greater than 0.36 in the enhancing lesion suggested tumour recurrence. However, with this cutoff three patients with recurrent tumour and two with radiation injury were misclassified.

A later study supported these findings.[38] An ADC ratio cut-off value of 1.27 could differentiate recurrence from treatment-induced necrosis with 65% sensitivity and 100% specificity. However, DTI was found to be inferior to both dynamic susceptibility contrast MRI and brain SPECT in differentiating tumour recurrence from necrosis.

ADC ratios may also be useful in assessing perilesional oedema as it has been shown to differentiate recurrent tumour from pseudoprogression.[39]

Limitations

The low sensitivity of DTI means that it is not an ideal method for assessing recurrence post-treatment. One area it may be useful in is in predicting the pattern of glioma recurrence.[40] Also, the cutoff values proposed by authors have differed which may be due to different MRI sequence protocols and equipment.

Perfusion MRI

The most common perfusion MRI technique to assess glioma is T2* echo-planar dynamic susceptibility contrast imaging (DSC-MRI). DSC-MRI provides estimates of absolute cerebral

blood flow (CBF), cerebral blood volume (CBV), and relative CBV (rCBV). Radiation necrosis is typically a diffuse process with fibrinoid necrosis of small vessels, endothelial thickening and hyalinization, and vascular thrombosis leading to reduction of perfusion to the brain. By contrast, active glioma growth is tightly coupled with angiogenesis leading to increased perfusion. DSC-MRI could therefore provide a valuable means of differentiating the two based on the vascularity of the imaged areas (figure 3)[41].

Figure 3

Pre-operative DSC-MRI images were obtained of 13 patients with new enhancing lesions on MRI following treatment for GBM and in whom further resection was planned.[42] The rCBV values of the biopsied sites were compared with the histopathology by recording stereotactic biopsy locations and co-registering these to the perfusion images. rCBV values higher than 0.71 indicated tumour progression with a sensitivity of 91.7% and a specificity of 100%. However, co-registration is imperfect due to brain movement during biopsy and DSC-MRI images are of low resolution. This has been supported by other studies that found a higher rCBV in patients with recurrent tumour than in patients with radiation necrosis. However, patients received only dendritic cell immune therapy and surgery[43] or external beam radiotherapy[44]. A study also found a negative correlation between rCBV and median survival.[45]

The percentage change in rCBV one month following treatment was found to be the variable that had the most significant correlation with median survival.[46] Those with an increase in rCBV had a significantly lower median survival than those with a decrease in rCBV.

Determination of the O-6-methylguanin-DNA methyltransferase (MGMT) status of patients may be necessary for accurate interpretation of the significant difference between pseudoprogression and true progression. GBMs that show methylation of the MGMT gene promoter have been associated with an improved response to chemotherapeutics.[47] The significance was greater in patients with unmethylated MGMT than in those with

hypermethylated MGMT (p = 0.003)[31] and not significant at all in patients with methylated MGMT (p = 0.258).[48]

An alternative technique, dynamic contrast enhanced (DCE) T1-weighted perfusion MRI has not been as commonly investigated as DSC-MRI. Analysis of the mean area under the curve (AUC) of signal-intensity over time histograms (calculated as the initial AUC (at 0-30 seconds) divided by the final AUC (at 320-250 seconds)) using DCE-MRI showed a significant difference between pseudoprogression and true progression (p = <0.001).[49]

Limitations

The imaging resolution of perfusion MRI studies is low making small areas of enhancement more difficult to assess. Analysis alongside high-resolution T1-weighted (T1W) or T2W imaging may help to alleviate this although partial volume effects are likely to remain. DSC-MRI is also degraded by susceptibility artefacts making imaging of the posterior fossa less reliable.

Spatially, care needs to be taken when using DSC-MRI to analyse tumours. Many lesions post-treatment are often intermingled tumour and necrotic tissue. rCBV may incorrectly estimate the lesion size due to contrast leak into necrotic tissue, a phenomenon which is discussed later. Also, the rCBV in the normal cortex is higher than in white matter.[50] Different proportions of grey and white matter influence rCBV values independently of underlying pathology.

Contrast Leak

Because of the small molecular size of gadolinium (Gd), it rapidly crosses defects in the blood brain barrier (BBB). The BBB is frequently disrupted after chemoradiotherapy, as well as by the angiogenesis incited by tumours. Thus, gadolinium is rapidly cleared from the circulation. This leads to a contrast leak causing a reduction in T1. However, DSC-MRI calculations of CBV and CBF are only accurate if T1 remains unchanged. Several methods

have been proposed to overcome this problem.[51] For example, a software leak correction to values has been found to result in more accurate grading of gliomas.[52] Alternatively, a contrast agent with a larger molecular size that does not readily cross a disrupted BBB can be used. Several groups have investigated ferumoxytol, an iron oxide nanoparticle with a modified carbohydrate coating that has a longer half-life and remains in the intravascular space longer than Gd. A pilot study found lesions that enhance on T1WGd and have low rCBV on ferumoxytol-DSC-MRI are more likely to represent pseudoprogression.[53] Gahramanov et al.[54] found that ferumoxytol-based measurements of rCBV measurements that correlate better with median survival than leak corrected Gd-based measurements.

Ferumoxytol also allows the use of steady-state imaging methods which can produce high resolution and distortion free maps of CBV.[55]

In conclusion, perfusion MRI has the potential to be a very useful adjunct in assessing post-treatment gliomas. However, optimum cutoff rCBV values reported in the literature vary widely and require further study.[14] Similarly, the use of software leak correction and alternative intravascular contrast agents needs to be investigated further.

MR spectroscopy

MRS can identify various metabolic compounds in the imaged tissue including choline (Cho), creatin (cr), N-acetylaspartate (NAA) lactate, and lipids. Although absolute quantification of metabolite concentrations is possible, it is normal to express measurements at the ratio of the metabolite signal to that of creatine, since the latter is largely unchanged with disease. Tumours demonstrate high Cho/Cr ratios due to an increased number of cells and increased synthesis of cell membranes, and low NAA/Cr ratios due to neuronal loss or damage. Necrotic tissue shows elevated lactate, a marker for anaerobic glycolysis, and elevated lipids in keeping with cell membrane degradation. MRS can be potentially used to distinguish tumour progression from radiation injury since the former will demonstrate higher Cho/Cr ratios and lower NAA/Cr ratios.[56]

Single-voxel MRS used in early studies found significant differences in the Cho/Cr and NAA/Cr ratios between neoplastic, non-neoplastic lesions and contralateral normal brain.[57] However, single-voxel MRS proved problematic as lesions are often heterogeneous and sampling results in partial voluming and cross-contamination of metabolic ratios.[58] Some studies suffered from a small sample size and being non-blinded.[59–61]

Figure 4

Figure 5

Multivoxel spectroscopic imaging – 2D or 3D chemical shift imaging (CSI-MRS) – is now commonplace and enables coverage of a larger volume as well as investigation of multiple regions of the lesion and surrounding tissue, although voxels are still large. Using 2D CSI-MRS an elevated Cho/NAA ratio[62] and NAA/Cr ratio[63] have been found to correlate with recurrent tumour (figure 4 and 5)[64]. There is also the potential of applying cutoff values to assist in diagnosis as in a retrospective study of 29 patients (24 of whom had GBM) 2D CSI-MRS which was used to assess areas of new enhancement at the site of previously treated brain neoplasm.[56] A cut-off value of 1.8 for both Cho/Cr and Cho/NAA ratios correctly categorised 27 out of 28 patients as either recurrent/residual tumour or radiation injury. A similar study found that a Cho/Cr value greater than 1.79 gives a sevenfold increased likelihood of being pure tumour than pure necrosis.[65] Using 3D-MRS gives slightly different cut-off values of 1.71 for both Cho/Cr and Cho/NAA ratios with a sensitivity of 94.1%, a specificity of 100%, and a diagnostic accuracy of 96.2%.[66] Several studies support these findings but only included patients who had not received chemotherapy.[67–69]

Limitations

Potential pitfalls for the application of MRS are the susceptibility to artefact, especially for imaging the posterior fossa;[56] low spatial resolution; the decreased specificity for heterogeneous tissue; and the difficulty in applying ratios universally due to the different MRI strengths, imaging protocols and algorithms used in different centres.

Positron emission tomography imaging

Theoretically, PET imaging should be useful in diagnosing tumour progression as these are metabolically active lesions with greater utilisation of glucose and, therefore, exhibiting greater uptake. However the application of PET in differentiating between tumour progression and pseudoprogression has not been straightforward.

18F-labelled fluorodeoxyglucose (18F FDG-PET) is the most commonly used. Early studies into the use of 18F FDG-PET for differentiating between tumour progression and pseudoprogression were promising but suffered from very small samples, limited correlation with pathology, and only investigating patients who had been treated with radiation with or without surgery and with no concomitant chemotherapy.[70–72]

Although a pilot study[73] and an early study[74] supported the use of 18F FDG-PET subsequent studies have shown that the sensitivity and specificity rates are too low to be clinically useful. A retrospective study of 31 patients correlated PET appearance with histological diagnosis. Histologically, 22 patients had tumour recurrence, eight radiation necrosis and one gliosis. 16 patients with recurrence and seven patients with radiation necrosis had hypermetabolic PET scan. This study misidentified a large number of lesions as tumour progression (nine out of 30, 29%) due to radiation necrosis being of unexpectedly high FDG uptake.[75]

There are also issues particular to imaging of the brain that makes FDG-PET problematic in assessing post-treatment gliomas. Firstly, subclinical seizure activity may increase uptake temporarily and mimic a hypermetabolic lesion.[76] Secondly, tracer uptake is compared to the contralateral hemisphere, which is used as a control, but in whole brain irradiation the contralateral brain may demonstrate post-radiation changes in uptake. Thirdly, the brain, especially grey matter, has high background glucose metabolism making subtle focal increases in uptake difficult to see.

Glucose loading has been used to better distinguish between tumour and brain tissue but this method is complicated by the need for constant glucose monitoring.[77] Alternatively, delayed FDG-PET scanning, in which scanning takes place 180-480 mins after isotope injection, resulted in better delineation of the high uptake of cerebral tumours relative to grey matter, whole brain, or white matter.[78] In this study, however, a range of pre- and post-treatment gliomas of different grades were included. Also, the ability to differentiate between tumour progression and pseudoprogression was not addressed.

Amino Acid Biomarkers

Novel radiolabelled amino acid biomarkers are currently being investigated as a means of improving tumour identification by PET. These include 11C-methionine (C-Met), *O*-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-FDOPA). These show a lower uptake in normal brain tissue in comparison to 18F-FDG-PET.

Most research has been conducted using 11C-Met-PET (figure 6)[79]. This biomarker has been found to show increased uptake in a range of cerebral malignancies when compared to benign lesions (including radiation necrosis) with a sensitivity of 92% and a specificity of 100%.[80] It has also been shown to be more sensitive than 18F-FDG-PET.[81] However, studies into whether 11C-Met-PET is useful for differentiating between tumour progression and pseudoprogression have been contradictory or suffered from a small patient sample.[82] A study of 26 patients with glioma found that although the standardised uptake values for recurrent tumour was higher than for necrosis, the sensitivity and specificity were only 75%.[83] However, metastatic brain tumours and gliomas were included in the study and patients had been treated with radiotherapy but not concomitant chemotherapy or surgery. A more recent and larger study found 11C-Met-PET to be superior to 18F-FDG-PET in diagnosing tumour progression versus pseudoprogression with a sensitivity of 95% and a specificity of 89% but, it was found to be inferior to DWI.[84] A further study found no

significant difference with 11C-MET-PET between recurrent tumour and pseudoprogression.[85]

Figure 6

A limiting factor is the short half-life of 11C-methionine requiring on-site cyclotron facilities and, therefore, limiting clinical use. 18F labelled aromatic amino acid analogues, including 18F-FET and 18F-FDOPA, have now been developed which have a longer half-life.

A study showed 18F-FET-PET had a sensitivity of 100% and specificity of 93% in diagnosing tumour progression in patients with subsequent clinical or histological confirmation.[86] Interestingly, these values were higher than for T2W, T1W and T1WGd MRI (sensitivity of 50% and specificity of 94%). A subsequent prospective study with 18F-FET-PET and subsequent biopsy results available found a positive-predictive value of 84%.[87]

18F-FDOPA is believed to rely on active transport mechanisms rather than, as in gadolinium-enhanced MRI, depending on BBB breakdown. In preliminary studies 18F-FDOPA-PET has been shown have a greater contrast between tumour tissue and normal tissue than with 18F-FDG-PET and also showed a sensitivity of 97% and specificity of 86% for true progression.[88] The same group also investigated 18-F-FDOPA-PET/MRI fusion to improve resolution and localisation and proposed that FDOPA-PET may detect recurrence earlier than MRI and also better differentiate non-enhancing tumour from other causes of T2W signal change such as oedema.[89]

Limitations

In the studies on FDG-PET usage in post-treatment gliomas patients have been scanned at different intervals making correlation difficult. Although amino acid tracers are promising the degree of amino acid uptake in radiation necrosis is not well known and more research is needed to justify their use clinically.

Single positron emission computed tomography

SPECT is a 3D nuclear medicine technique. Thallium-201 (^{201}Tl) has been shown to be useful in differentiating pseudoprogression from true progression with a sensitivity from 84% to 100% and a specificity from 50% to 100%.[90–93] Yamamoto et al found a potential for cutoffs to be applied.[93] The addition of 99mTechnetium-hexamethyl-propyleneamine oxime (^{99m}Tc-HMPOA) has been proposed as differentiating between pseudoprogression and true progression in intermediate cases.[94] However, ^{201}Tl has a low spatial resolution and a relatively high radiation dose. This also results in an insensitivity to small or thinly rim-enhancing lesions.[95]

^{99m}Technetium (^{99m}Tc) based radiotracers have a better photon flux resulting in greater spatial resolution and lower radiation doses. ^{99m}Tc-sestamibi is the most commonly used technetium-based tracer and has a sensitivity of 95% and a specificity of 60% in differentiating pseudoprogression from tumour progression in patients who had only received radiotherapy.[96] However, unlike ^{201}Tl, ^{99m}Tc shows uptake in normal tissues such as the choroid plexus.

Other ^{99m}Technetium-based tracers have also been studied. ^{99m}Tc-tetrofosmin does not cross the BBB meaning there is no uptake in normal brain tissues and it shows greater uptake in tumour relative to the background than ^{201}Tl.[97] Similarly, ^{99m}Tc-glucoheptonate provided more information on recurrent tumour including the tumour margins, extent and intratumoural necrosis.[98]

Limitations

^{201}Tl studies have a low spatial resolution and a relatively high radiation dose. Despite having a greater photon flux ^{99m}Tc-sestamibi radiotracer shows uptake in normal tissues of the choroid plexus and pituitary gland, which limits the sensitivity. It also has poor sensitivity for posterior fossa tumours. Although ^{99m}Tc-tetrofosmin does not cross the BBB and ^{99m}Tc-

glucoheptonate provides more information on the extent and intratumoural necrosis of recurrent tumour, the availability is limited and more studies are required to establish the sensitivity and specificity.[97,98]

Sequential imaging and combination of techniques

So far each technique has been assessed individually with imaging mainly at one point in time. In practice techniques are often combined and changes assessed over time to give a greater overview of pathology.

Combining MRS with DWI[99], perfusion MRI[100] or both[101] has been shown to improve the sensitivity and specificity of differentiating true progression from tumour progression. Similarly, combining 18F-FET-PET and MRS with conventional MRI increased the accuracy of detecting brain tumours from 68% to 97%.[102]

Performing DSC-MRI before treatment and one month after treatment showed that in pseudoprogression there was a 41% mean decrease in rCBV whereas tumour progression showed a 12% increase in rCBV.[46] This was supported by a later study.[103]

ADC measurement decreased at follow-up with tumour progression but increased in those with pseudoprogression when performing DTI at two time-points after treatment.[36]

A recent study that performed DWI and perfusion MRI at two time points after treatment found the analysis that gave the most accurate differentiation between pseudoprogression and tumour progression was the mode of the rCBV on a multiparametric subtracted histogram. This was created by combining the ADC and rCBV histograms then subtracting the histogram of the initial MRI from the follow-up MRI.[104]

Limitations to imaging with multiple techniques over time are high cost, lengthy scan times and patients having to attend several appointments. Also, centres may not have access to certain imaging methods leading to patients having to travel for further scans.

Summary

Imaging Method	Supporting Studies	Pattern associated with progression	Strengths	Weaknesses
Conventional MRI and T1WGd	[4,16–19]	Subependymal spread Corpus callosum involvement	Readily available	Large overlap of features meaning inadequate differentiation of tumour recurrence from pseudoprogression
Diffusion weighted MRI	[24–26,36,66]	ADC ratio and mean ADC lower	Readily available Assesses pathology at microscopic level	Confounded by temporal and spatial variation Improved by using SWI to select appropriate enhancing area to sample [36]
Diffusion Tensor Imaging	[37–40]	Mean ADC lower and mean FA ratio higher	Potentially could apply cut-off values	Inferior to DSC-MRI and brain SPECT Low sensitivity
Perfusion MRI (DSC-MRI)	[31,42–46,48,51–55]	Higher rCBV	High rates of sensitivity and specificity	Low resolution Prone to susceptibility artefacts

				Contrast leak – may be overcome by alternative contrast agent [53,54]
Perfusion MRI (DCE-MRI)	[49]	Increase in area under curve histogram analysis	Less susceptible to artefacts than DSC-MRI Potentially could apply cut-off values	Not commonly used technique Requires more research
MR Spectroscopy	[56–63,66–69]	Higher Cho/Cr ratios and lower NAA/Cr ratios	Potentially could apply cut-off values High sensitivity and specificity	Susceptible to artefact Low spatial resolution Difficulty in imaging mixed tumour/necrotic tissue
FDG-PET imaging	[70–75,77,78]	Considerable overlap	Readily available	High background signal – could be improved by delayed imaging Unacceptably low sensitivity and specificity
C-Met-PET	[80,82–85]	Higher SUV	Lower background activity than FDG-PET	Short half-life limits availability
FET-PET and FDOPA-PET	[86–89]	Higher SUV	Could give higher sensitivity and	Still in early research stages

			specificity than conventional MRI Greater contrast between tumour and normal brain tissue	
SPECT	[90–94,96–98]	Higher SUV	^{99m}Tc-glucoheptonate and ^{99m}Tc-tetrofosmin show high sensitivity and specificity	^{99m}Tc-sestamibi crosses the BBB and is poor for posterior fossa tumours Limited availability of ^{99m}Tc-glucoheptonate and ^{99m}Tc-tetrofosmin

Discussion

Currently the criteria for assessing tumour progression after GBM treatment is based upon an increase in the 2D area of contrast enhancement. However, up to 20% of patients may show transient sub-acute reactions usually within 6 months of treatment that mimic progression.[6–10,15] Distinguishing tumour progression from pseudoprogression is important in the ongoing management of patients after treatment of GBMs and in accurately investigating treatment response in clinical trials. Both have overlapping features on radiology that make differentiation difficult. In this review the current literature on the use of different imaging modalities and their limitations has been outlined. Conventional T2W, T1W and T1WGd MRI has been shown to be inadequate in correctly differentiating true progression from pseudoprogression but more advanced MRI sequences, as well as molecular imaging, are proving promising.

No single technique is able to reliably differentiate between pseudoprogression and tumour progression and in practice a combination of different modalities and comparison of images over time may prove more useful. Anatomical imaging (conventional MRI), imaging of histological properties of tissue (DWI, SWI, DTI and MRS) and imaging of functional properties of tissue (perfusion MRI and PET) may be combined to provide a more complete assessment of post-treatment gliomas. The comparison of follow-up images over time also provides valuable information. Further investigation is required into the individual techniques and into combinations of techniques to provide a more robust framework for clinicians and radiologists in the evaluation of post-treatment gliomas.

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Figure Legends

Figure 1.

A patient with GBM with a a) post-surgical MRI showing progression on MRI at b) 1 months and c) 4 months post-radiotherapy. However, there was subsequent stabilisation at c) 7 months post-radiotherapy indicating pseudoprogression.

Figure 2.

The images are of a patient with recurrent GBM, as proven by clinical deterioration, at two time-points after treatment. Images show early subependymal enhancement 1 month after treatment on the T1WGd 1A) coronal and 1B) axial images with further subependymal enhancement at 4 months after treatment on the T1WGd 2A) coronal and 2B) axial images.

Figure 3.

Glioblastoma multiforme in a 65-year-old woman. Axial T2-weighted **(a)** and T1-weighted post contrast **(b)** images demonstrate a right temporal lesion with surrounding edema and ring-shaped enhancement. On the DW-image the lesion presents low signal intensity**(c)** resulting in higher intratumoral ADC **(d)**, lower intratumoral FA **(e)**, and high peritumoral rCBV **(f)**, reflecting tumor infiltration in the surrounding parenchyma. Reproduced from Cancer Imaging, Biomed Central Ltd.

Figure 4.

Radiation injury in a 46-year-old man who underwent surgery, radiotherapy, and chemotherapy for a left insular lobe glioblastoma multiforme (*N*-acetylaspartate, NAA; choline-containing compounds, Cho; creatine, Cr). (**A**) The first contrast-enhanced axial T1-weighted image which volume of interest for MR spectroscopy is placed on. (**B**) 3D proton MR spectroscopy of contrast-enhancing region which shows pathologic spectra (Cho/NAA, 1.35; Cho/Cr, 1.63; NAA/Cr, 1.21). (**C**) The contrast-enhanced T1-weighted image at 15-

month follow-up after 3D proton MR spectroscopy which reveals marked regression of enhancement area. With kind permission from Springer Science and Business Media.

Figure 5.

Tumor recurrence in a 32-year-old woman who underwent surgery and radiotherapy for a right temporal lobe anaplastic astrocytoma (*N*-acetylaspartate, NAA; choline-containing compounds, Cho; creatine, Cr). (**A**) The contrast-enhanced axial T1-weighted image which volume of interest for MR spectroscopy is placed on. (**B**) 3D proton MR spectroscopy of contrast-enhancing region in right hippocampus which shows pathologic spectra (Cho/NAA, 2.91; Cho/Cr, 2.63; NAA/Cr, 0.90). (**C**) Photomicrograph (hematoxylin-eosin stain; original magnification, 400×) which shows a hypercellular astrocytic neoplasm. With kind permission from Springer Science and Business Media.

Figure 6.

An example of a target planned for a hypofractionated stereotactic radiotherapy using intensity modulated radiation therapy. (A) Contrast-enhanced T1-weighted magnetic resonance imaging. (B) ^{11}C-methionine positron emission tomography (MET-PET). Gross tumor volume was defined as the region with high MET uptake (yellow line). The threshold for increased MET uptake was set to ≥1.3 in the contiguous tumor region. Reproduced from Radiation Oncology, Biomed Central Ltd.