

1 Tumour progression or
2 pseudoprogression?: A review of post-
3 treatment radiological appearances of
4 glioblastoma

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6 Introduction

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

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

23 Figure 1

24 Pseudoprogression has been observed in multiple studies and is estimated to occur in about
25 20% of patients following GBM treatment.⁶⁻¹⁰ In a large study by Taal et al.¹¹ 50% of patients
26 treated with chemoRT for GBM with worsening MRI features on early MRI actually showed
27 stabilization or resolution of those MRI features without any change in treatment. Wrongly
28 diagnosing pseudoprogression as true tumour progression on gadolinium-enhanced MRI
29 could lead to an inappropriate change in therapy and errors in assessing the efficacy of
30 novel treatments. This was addressed in the updated response assessment criteria
31 developed by the Response Assessment in Neuro-Oncology Working Group (RANO) which

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

37 **Table 1. RANO criteria for high-grade gliomas**

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

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

46 **Literature search**

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

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

54 Overall, 69 publications met the criteria. These included five focusing on conventional MRI;
55 16 on diffusion weighted MRI (DWI); 13 on perfusion MRI; 13 on MR spectroscopy (MRS);

56 18 on positron emission tomography (PET); 12 on single photon emission computed
57 tomography (SPECT); and eight on serial studies and multimodality imaging.

58 **Imaging techniques**

59 **Conventional MRI**

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

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

74 **Figure 2**

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

78 **Diffusion-weighted MRI**

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

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

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

95 This result was repeated in other prospective studies showing that the maximal ADC values
96 were significantly lower for the recurrence group than for the pseudoprogression groups
97 (maximal ADC 2.30 ± 0.73 for radiation group and 1.68 ± 0.37 for tumour progression)²⁵ and
98 that the minimum ADC value was significantly lower in the recurrent tumour group than in
99 the radiation-injuries group²⁶ based upon non-progression on follow-up and histology.

100 **Limitations**

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

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

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

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

118 **Susceptibility weighted imaging with DWI**

119 Susceptibility weighted imaging (SWI) is an alternative to T1WGd that may better identify
120 areas suitable for ADC measurements. SWI is a 3D gradient echo technique that provides
121 images that are sensitive to subtle variations in susceptibility caused by deoxyhaemoglobin.
122 SWI has been shown to be more sensitive than T1WGd for showing the heterogeneity of
123 tissue pathology in brain tumours.³⁰⁻³² Also, gadolinium-enhanced SWI (SWI-Gd) can
124 provide clinically useful information on altered tumour microvasculature and cellular density³³;
125 the degree of intratumoural necrosis³⁴; and the presence of abnormal enhancement around
126 the tumour post-contrast suggesting a breakdown in the blood-brain barrier.³⁵

127 Targeting areas for ADC analysis using SWI-Gd instead of T1WGd has shown promise.³⁶
128 ADC measurements taken from enhancing areas on SWI-Gd were significantly reduced in
129 10 out of 11 patients with tumour recurrence. ADC values also fell over time. Conversely,
130 ADC measures taken from enhancing areas on T1WGd were significantly reduced in only
131 three of 11 patients and actually increased in four of 11 patients.

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

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

138 **Diffusion-tensor imaging**

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

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

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

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

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

160 **Limitations**

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

165 **Perfusion MRI**

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

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

174 **Figure 3**

175 Pre-operative DSC-MRI images were obtained of 13 patients with new enhancing lesions on
176 MRI following treatment for GBM and in whom further resection was planned.⁴² The rCBV
177 values of the biopsied sites were compared with the histopathology by recording stereotactic
178 biopsy locations and co-registering these to the perfusion images. rCBV values higher than
179 0.71 indicated tumour progression with a sensitivity of 91.7% and a specificity of 100%.
180 However, co-registration is imperfect due to brain movement during biopsy and DSC-MRI
181 images are of low resolution. This has been supported by other studies that found a higher
182 rCBV in patients with recurrent tumour than in patients with radiation necrosis. However,
183 patients received only dendritic cell immune therapy and surgery⁴³ or external beam
184 radiotherapy⁴⁴. A study also found a negative correlation between rCBV and median
185 survival.⁴⁵

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

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

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

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

201 **Limitations**

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

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

213 **Contrast Leak**

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

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

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

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

234 **MR spectroscopy**

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

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

250 Figure 4

251 Figure 5

252 Multivoxel spectroscopic imaging – 2D or 3D chemical shift imaging (CSI-MRS) – is now
253 commonplace and enables coverage of a larger volume as well as investigation of multiple
254 regions of the lesion and surrounding tissue, although voxels are still large. Using 2D CSI-
255 MRS an elevated Cho/NAA ratio⁶² and NAA/Cr ratio⁶³ have been found to correlate with
256 recurrent tumour (figure 4 and 5)⁶⁴. There is also the potential of applying cutoff values to
257 assist in diagnosis as in a retrospective study of 29 patients (24 of whom had GBM) 2D CSI-
258 MRS which was used to assess areas of new enhancement at the site of previously treated
259 brain neoplasm.⁵⁶ A cut-off value of 1.8 for both Cho/Cr and Cho/NAA ratios correctly
260 categorised 27 out of 28 patients as either recurrent/residual tumour or radiation injury. A
261 similar study found that a Cho/Cr value greater than 1.79 gives a sevenfold increased
262 likelihood of being pure tumour than pure necrosis.⁶⁵ Using 3D-MRS gives slightly different
263 cut-off values of 1.71 for both Cho/Cr and Cho/NAA ratios with a sensitivity of 94.1%, a
264 specificity of 100%, and a diagnostic accuracy of 96.2%.⁶⁶ Several studies support these
265 findings but only included patients who had not received chemotherapy.^{67–69}

266 **Limitations**

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

271 **Positron emission tomography imaging**

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

276 18F-labelled fluorodeoxyglucose (18F FDG-PET) is the most commonly used. Early studies
277 into the use of 18F FDG-PET for differentiating between tumour progression and
278 pseudoprogession were promising but suffered from very small samples, limited correlation
279 with pathology, and only investigating patients who had been treated with radiation with or
280 without surgery and with no concomitant chemotherapy.⁷⁰⁻⁷²

281 Although a pilot study⁷³ and an early study⁷⁴ supported the use of 18F FDG-PET subsequent
282 studies have shown that the sensitivity and specificity rates are too low to be clinically useful.
283 A retrospective study of 31 patients correlated PET appearance with histological diagnosis.
284 Histologically, 22 patients had tumour recurrence, eight radiation necrosis and one gliosis.
285 16 patients with recurrence and seven patients with radiation necrosis had hypermetabolic
286 PET scan. This study misidentified a large number of lesions as tumour progression (nine
287 out of 30, 29%) due to radiation necrosis being of unexpectedly high FDG uptake.⁷⁵

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

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

302 **Amino Acid Biomarkers**

303 Novel radiolabelled amino acid biomarkers are currently being investigated as a means of
304 improving tumour identification by PET. These include 11C-methionine (C-Met), O-(2-
305 [18F]fluoroethyl)-L-tyrosine (18F-FET) and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine
306 (18F-FDOPA). These show a lower uptake in normal brain tissue in comparison to 18F-
307 FDG-PET.

308 Most research has been conducted using 11C-Met-PET (figure 6)⁷⁹. This biomarker has
309 been found to show increased uptake in a range of cerebral malignancies when compared to
310 benign lesions (including radiation necrosis) with a sensitivity of 92% and a specificity of
311 100%.⁸⁰ It has also been shown to be more sensitive than 18F-FDG-PET.⁸¹ However,
312 studies into whether 11C-Met-PET is useful for differentiating between tumour progression
313 and pseudoprogression have been contradictory or suffered from a small patient sample.⁸² A
314 study of 26 patients with glioma found that although the standardised uptake values for
315 recurrent tumour was higher than for necrosis, the sensitivity and specificity were only
316 75%.⁸³ However, metastatic brain tumours and gliomas were included in the study and
317 patients had been treated with radiotherapy but not concomitant chemotherapy or surgery. A
318 more recent and larger study found 11C-Met-PET to be superior to 18F-FDG-PET in
319 diagnosing tumour progression versus pseudoprogression with a sensitivity of 95% and a
320 specificity of 89% but, it was found to be inferior to DWI.⁸⁴ A further study found no

321 significant difference with 11C-MET-PET between recurrent tumour and
322 pseudoprogression.⁸⁵

323 **Figure 6**

324 A limiting factor is the short half-life of 11C-methionine requiring on-site cyclotron facilities
325 and, therefore, limiting clinical use. 18F labelled aromatic amino acid analogues, including
326 18F-FET and 18F-FDOPA, have now been developed which have a longer half-life.

327 A study showed 18F-FET-PET had a sensitivity of 100% and specificity of 93% in diagnosing
328 tumour progression in patients with subsequent clinical or histological confirmation.⁸⁶
329 Interestingly, these values were higher than for T2W, T1W and T1WGd MRI (sensitivity of
330 50% and specificity of 94%). A subsequent prospective study with 18F-FET-PET and
331 subsequent biopsy results available found a positive-predictive value of 84%.⁸⁷

332 18F-FDOPA is believed to rely on active transport mechanisms rather than, as in
333 gadolinium-enhanced MRI, depending on BBB breakdown. In preliminary studies 18F-
334 FDOPA-PET has been shown have a greater contrast between tumour tissue and normal
335 tissue than with 18F-FDG-PET and also showed a sensitivity of 97% and specificity of 86%
336 for true progression.⁸⁸ The same group also investigated 18-F-FDOPA-PET/MRI fusion to
337 improve resolution and localisation and proposed that FDOPA-PET may detect recurrence
338 earlier than MRI and also better differentiate non-enhancing tumour from other causes of
339 T2W signal change such as oedema.⁸⁹

340 **Limitations**

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

345 **Single positron emission computed tomography**

346 SPECT is a 3D nuclear medicine technique. Thallium-201 (^{201}Tl) has been shown to be
347 useful in differentiating pseudoprogression from true progression with a sensitivity from 84%
348 to 100% and a specificity from 50% to 100%.⁹⁰⁻⁹³ Yamamoto et al found a potential for
349 cutoffs to be applied.⁹³ The addition of $^{99\text{m}}\text{Tc}$ -hexamethyl-propyleneamine oxime
350 ($^{99\text{m}}\text{Tc}$ -HMPOA) has been proposed as differentiating between pseudoprogression and true
351 progression in intermediate cases.⁹⁴ However, ^{201}Tl has a low spatial resolution and a
352 relatively high radiation dose. This also results in an insensitivity to small or thinly rim-
353 enhancing lesions.⁹⁵

354 $^{99\text{m}}\text{Tc}$ -Technetium ($^{99\text{m}}\text{Tc}$) based radiotracers have a better photon flux resulting in greater
355 spatial resolution and lower radiation doses. $^{99\text{m}}\text{Tc}$ -sestamibi is the most commonly used
356 technetium-based tracer and has a sensitivity of 95% and a specificity of 60% in
357 differentiating pseudoprogression from tumour progression in patients who had only received
358 radiotherapy.⁹⁶ However, unlike ^{201}Tl , $^{99\text{m}}\text{Tc}$ shows uptake in normal tissues such as the
359 choroid plexus.

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

365 **Limitations**

366 ^{201}Tl studies have a low spatial resolution and a relatively high radiation dose. Despite
367 having a greater photon flux $^{99\text{m}}\text{Tc}$ -sestamibi radiotracer shows uptake in normal tissues of
368 the choroid plexus and pituitary gland, which limits the sensitivity. It also has poor sensitivity
369 for posterior fossa tumours. Although $^{99\text{m}}\text{Tc}$ -tetrofosmin does not cross the BBB and $^{99\text{m}}\text{Tc}$ -

370 glucoheptonate provides more information on the extent and intratumoural necrosis of
371 recurrent tumour, the availability is limited and more studies are required to establish the
372 sensitivity and specificity.^{97,98}

373 **Sequential imaging and combination of techniques**

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

377 Combining MRS with DWI⁹⁹, perfusion MRI¹⁰⁰ or both¹⁰¹ has been shown to improve the
378 sensitivity and specificity of differentiating true progression from tumour progression.
379 Similarly, combining 18F-FET-PET and MRS with conventional MRI increased the accuracy
380 of detecting brain tumours from 68% to 97%.¹⁰²

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

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

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

391 Limitations to imaging with multiple techniques over time are high cost, lengthy scan times
392 and patients having to attend several appointments. Also, centres may not have access to
393 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

395

396 Discussion

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

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

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704

705 **Figure Legends**

706 Figure 1.

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

710 Figure 2.

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

715 Figure 3.

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

722 Figure 4.

723 Radiation injury in a 46-year-old man who underwent surgery, radiotherapy, and
724 chemotherapy for a left insular lobe glioblastoma multiforme (*N*-acetylaspartate, NAA;
725 choline-containing compounds, Cho; creatine, Cr). **(A)** The first contrast-enhanced axial T1-
726 weighted image which volume of interest for MR spectroscopy is placed on. **(B)** 3D proton
727 MR spectroscopy of contrast-enhancing region which shows pathologic spectra (Cho/NAA,
728 1.35; Cho/Cr, 1.63; NAA/Cr, 1.21). **(C)** The contrast-enhanced T1-weighted image at 15-

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

731 Figure 5.

732 Tumor recurrence in a 32-year-old woman who underwent surgery and radiotherapy for a
733 right temporal lobe anaplastic astrocytoma (*N*-acetylaspartate, NAA; choline-containing
734 compounds, Cho; creatine, Cr). **(A)** The contrast-enhanced axial T1-weighted image which
735 volume of interest for MR spectroscopy is placed on. **(B)** 3D proton MR spectroscopy of
736 contrast-enhancing region in right hippocampus which shows pathologic spectra (Cho/NAA,
737 2.91; Cho/Cr, 2.63; NAA/Cr, 0.90). **(C)** Photomicrograph (hematoxylin-eosin stain; original
738 magnification, 400×) which shows a hypercellular astrocytic neoplasm. With kind permission
739 from Springer Science and Business Media.

740 Figure 6.

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