Pan Birmingham NHS
Cancer Network

Guideline for the Management of Pseudoprogression in High Grade Gliomas

Version History

Version	Date Issued	Brief Summary of Change / Process
0.1	10.09.09	First draft discussed at meeting on 10 September 2009.
0.2	06.10.09	Updated by Dr Paul Sanghera.
0.3	30.12.09	Reformatted by Lara Barnish following presentation at the guidelines subgroup of the Governance Committee November 2009.
0.4	09.11.11	Updated by Professor Cruickshank to clarify patient groups.
0.5	07.02.12	Updated by Professor Cruickshank following circulation to West Midlands Brain and CNS Supra Network Group
0.6	11.04.12	Reviewed and updated by Professor Garth Cruickshank and Karen Metcalf. Prepared for discussion by Guidelines Sub Group
1.0	19.04.12	Reviewed and endorsed by Guidelines Sub Group

Date Approved by Network Governance	**April 2012**

Date for Review	**April 2015**

1. Scope of the guideline

This guidance has been produced to support the management of patients with high grade gliomas who appear to be progressing on treatment, but may in fact be presenting with pseudoprogression (psPD) (apparent growth of their tumours).

2. Background

2.1 This guideline is with reference to the interpretation of imaging and clinical performance to determine whether psPD is present, and hence support clinical decisions to continue or alter treatment.

2.2 psPD has been previously recognised to follow radiotherapy alone for high grade gliomas[1] but is now widely believed to occur more frequently, and earlier in the treatment pathway in patients taking Temozolomide.

There is evidence that psPD may represent a marker of treatment efficacy and is related to an improved prognosis[2]. This is supported by correlation with the degree of MGMT promoter methylation[3]*. Data defining the incidence of psPD following radiotherapy/Temolozolomide (RT/TMZ) is widely variable [12 – 64% of patients with early progression] and may reflect different defining criteria used within studies (see table 1 in appendix 1)[3-11].

* MGMT (methyl guanine methyl transferase) is a DNA repair enzyme which demethylates methylated DNA caused by Temozolomide. Absence of MGMT due to silencing of its gene promoter from methylation itself is associated with a markedly increased survival due to persisting effect of Temozolomide on DNA.

At present there is no reliable way to distinguish psPD from true disease progression and the most reliable method is clinical follow up with serial imaging.

2.3 Temozolomide is given concurrently with radiotherapy throughout the radiation period. It is stopped for four weeks post-completion of radiotherapy. It is restarted (adjuvant phase) at four weeks post-radiotherapy and it is normally given for the first five days of a thirty day cycle, for six cycles (NICE Technology Appraisal 121).

2.4 Patients may present with psPD in the following clinical scenarios:

a. During post radiotherapy early adjuvant phase of primary Temozolomide therapy in Glioblastoma Multiforme (GBM) (WHO grade 4). See section 3.1 for treatment of these patients.
b. During post radiotherapy treatment with chemotherapy in High Grade Glioma (HGG) (WHO grade 3) including Anaplastic Astrocytoma and Anaplastic Oligoastrocytoma. See section 3.2 for the treatment of these patients.

c. Early phase of treatment of recurrent disease with chemotherapy or biological agents. See section 3.2 for treatment of these patients.

2.5 Presentation of psPD following radiotherapy with Temozolomide for GBM (see 2.5a above) which is the most common presentation.

2.6 Patients present with radiological features of increased enhancement and of increase in tumour size following radiotherapy with concurrent Temozolomide (RT/TMZ). In addition, there may be associated clinical deterioration. Imaging and clinical status subsequently improve or stabilise without changes to the current treatment regimen.

2.7 Why is recognising early psPD following chemoradiation for GBM important?

a. Second line options for GBM are limited and patients should be allowed to get maximum benefit from adjuvant Temozolomide
b. It is important to distinguish as many patients as possible with true disease progression to avoid unnecessary treatment
c. Survival benefits from agents under phase II evaluation will be over-estimated if including patients with psPD

2.8 The clinical importance of psPD

Evidence confirms that in psPD based on imaging and clinical performance, a significant number of patients will "settle down" if treatment continues unchanged. The problem is that a significant complementary proportion of patients will progress and deteriorate. Under these circumstances a protocol is needed to help decide at what point we should interfere with patients' treatment and consider them at risk of recurrent or progressive deterioration.

3. Guidelines statements

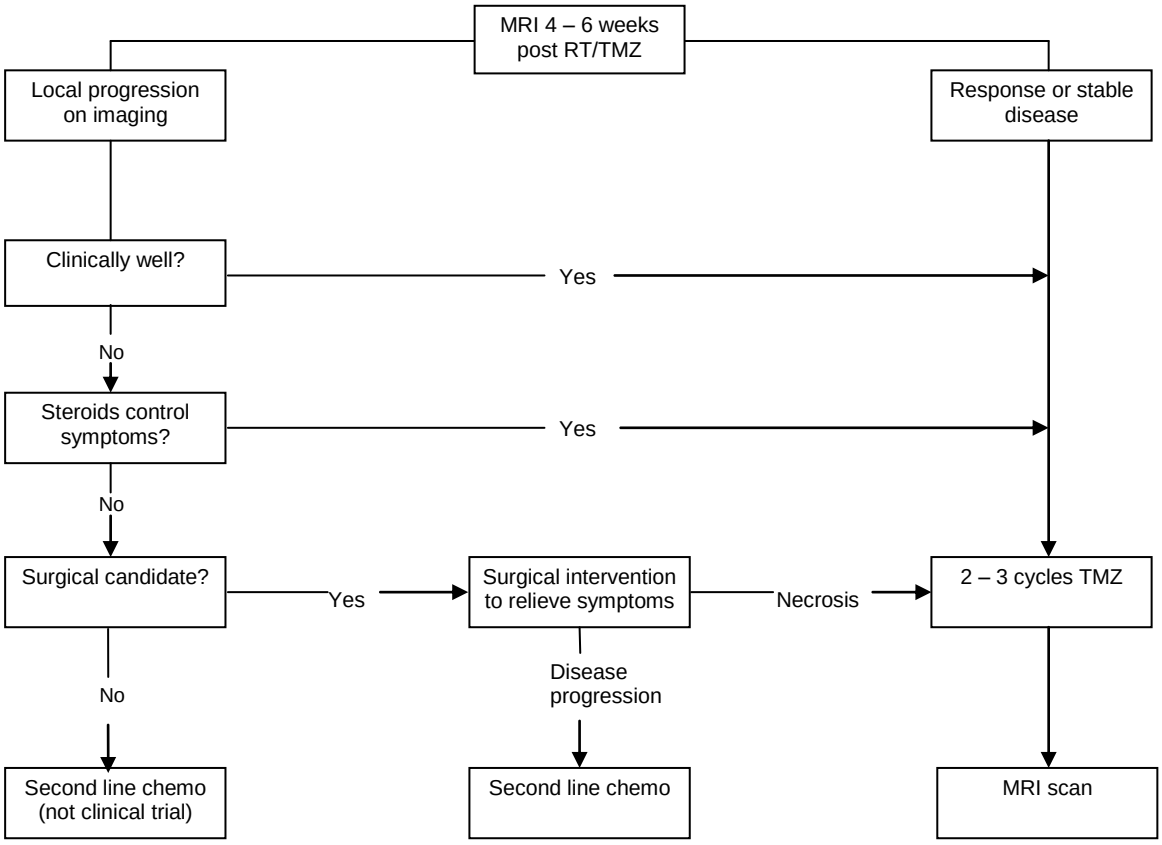
Radiological studies are required to assess psPD:

- Radiological features are based on comparison of T1 weighted MRI scans with gadolinium contrast.
- Scans from either the post-operative period or planning radiotherapy are compared with MRI scans from between the fourth and sixth week post-completion of radiotherapy.

<u>Clinical scenario 2.5a</u>

3.1 This section refers to patients presenting during post radiotherapy early adjuvant phase of primary Temozolomide therapy in GBM i.e. clinical scenario 2.5a.

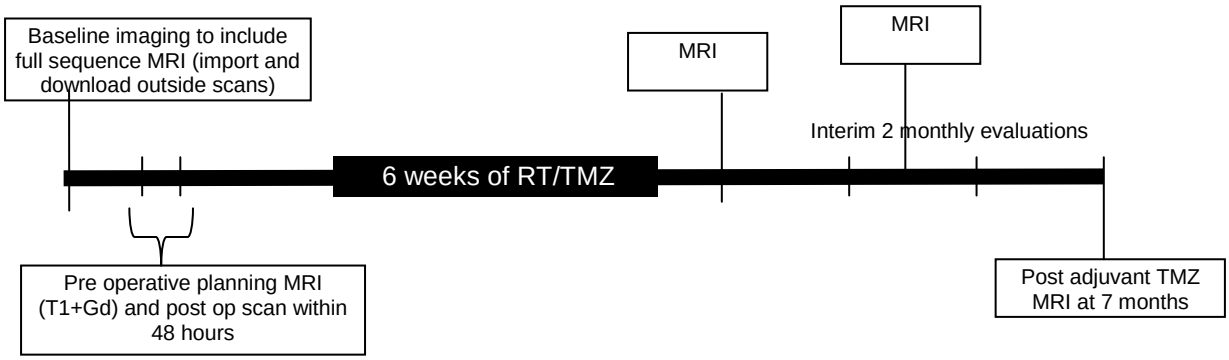
Figure 1 - management of early imaging changes post chemo radiotherapy for GBM



3.1.1 Assessment Timing: To support this management pathway, regular imaging is recommended during the first six months post radiotherapy\Temozolomide. Baseline imaging following any intervention is necessary to interpret subsequent scans. This is particularly important following resection of tumour and prior to radiotherapy planning, although it is acknowledged that surgical enhancement can cause problems with scan interpretation. Post surgical imaging performed within seventy two hours may minimise interpretation difficulties due to enhancement related to surgery. [Post therapy imaging is also important to enable eligibility for clinical trials (NCRI Directive, IOG 2008)]. Dependent upon clinical performance, regular imaging is then done at six to eight week intervals after radiotherapy completed. This allows sequential radiotherapy assessment of tumour and patient performance can be assessed in clinic. The use of standardised imaging protocols can help to minimise the problems associated with comparing scans between different institutions.

3.1.2 Figure 2, on the next page, outlines the early imaging protocol for high grade gliomas.

Figure 2 - early imaging protocol for high grade gliomas



3.1.3 A comprehensive MRI protocol on a 1.5T MRI scanner that would allow good characterisation of the abnormality includes:

- Axial T1
- Axial T2
- Coronal FLAIR
- Post-gadolinium axial, coronal and sagital T1.

3.1.4 During post radiotherapy\ Temozolomide treatment for GBM or other HGG, the following criteria are proposed for consideration of psPD:

- Neurological examination status is better, but brain MRI scan indicates disease progression
  OR
- Neurological examination status is worse, but brain MRI scan does not indicate progression

3.1.5 If one of the above scenarios is present, it is recommended that the patient continues treatment until the next MRI evaluation in six to eight weeks.

3.1.6 If the next scan shows further progression and\or the patient demonstrates worsening clinical status then this would indicate clinical progression and a formal diagnosis of recurrence\progression can be made. Complementary imaging (e.g. spectroscopy) may prove helpful during this period although data remains uncertain.

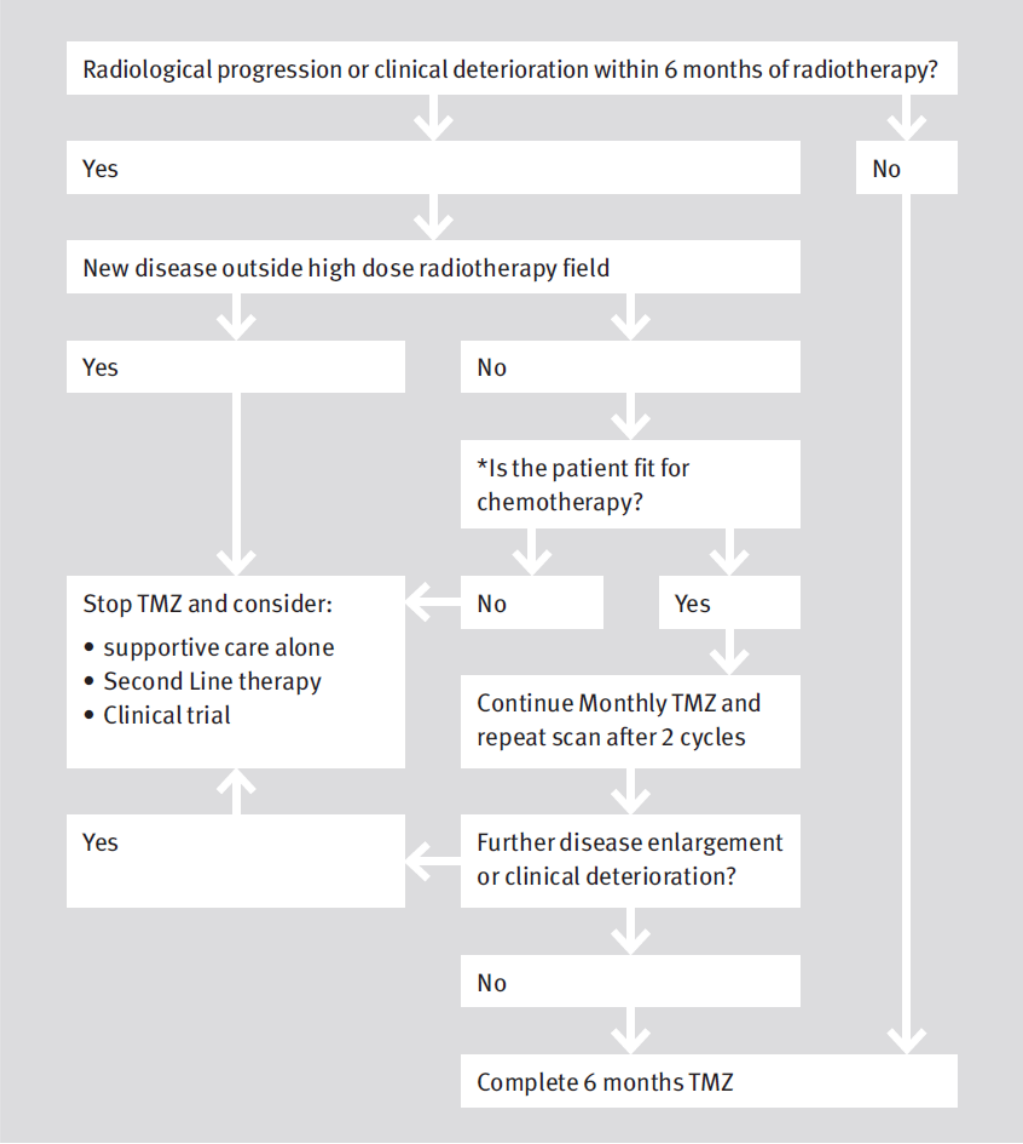
3.1.7 If the next scan however shows further progression and the patient demonstrates stable or improving clinical status then continue Temozolomide for a further cycle and re-image, or 3.1.8.

3.1.8 Where interpretation of scans and clinical performance suggests clear disease progression, or where there is significant doubt over the existence of psPD, consideration should be given to the dose intense Temozolomide schedule[7].

Clinical scenarios 2.5b and 2.5c

3.2 This section refers to patients presenting during post radiotherapy treatment with chemotherapy in High Grade Glioma (HGG) including Anaplastic Astrocytoma and Anaplastic Oligoastrocytoma (i.e. clinical scenario 2.5b) and early phase of treatment of recurrent disease with chemotherapy or biological agents (i.e. clinical scenario 2.5c):

The decision pathway is based on clinical presentation, which can occur at any time after primary treatment.



4. Monitoring of the Guideline

Adherence to the Network guidelines may from time to time be formally monitored.

5. Authors

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Approval Signatures

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Appendix 1

Table 1: Pseudoprogression Data

Study	Number of Patients	Response Criteria	Time from completion of Radiotherapy	Number with ePD	psPD (% of ePD)	Overall rate of psPD
Brandes *et al*, 2008 [3]	103	Enlargement for ePD then Macdonald	4 weeks	50/103 (52%)	32/50 (64%)	32/103 (31%)
Taal *et al*, 2008 [4]	†68	Macdonald	4 weeks	31/68 (46%)	15/31 (48%)	15/68 (22%)
Clarke *et al*, 2008 [5]	85	Increased Contrast Enhancement	2 – 4 weeks	35/85 (41%)	*10/27 (37%)	*10/77 (13%)
Gerstner *et al*, 2009 [6]	#45	Macdonald	17 – 28 days	24/45 (53%)	13/24 (54%)	13/45 (29%)
Chaskis *et al*, 2009 [7]	54	Increased Contrast Enhancement	6 months	25/54 (46%)	3/25 (12%)	3/54 (6%)
Jefferies *et al*, 2007 [8]	15	Not specified	6 months	9/15 (60%)	3/9 (33%)	3/15 (20%)
Fabi *et al*, 2009 [9]	12	Macdonald	2 months	4/12 (33%)	2/4 (50%)	2/12 (17%)
Roldan *et al*, 2009 [10]	43	Macdonald	4 – 6 weeks	25/43 (58%)	*10/20 (50%)	*10/38 (26%)
Sanghera *et al*, 2010 [11]	104	RECIST	8 weeks	27/104 (26%)	*7/22 (32%)	*7/99 (7%)

Abbreviations:

GBM	Glioblastoma Multiforme
ePD	Early Progression
rPD	Real Early Progression
psPD	Pseudoprogression
RECIST	Response Evaluation Criteria in Solid Tumours.

* Excluding patients in which psPD versus rPD unknown.
† Excluding patients with anaplastic disease.
# Excluding patients treated with radiotherapy alone.