ORIGINAL ARTICLE

Pseudoprogression Following Chemoradiotherapy for Glioblastoma Multiforme

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ABSTRACT: ***Purpose:*** Pseudoprogression (psPD) is now recognised following radiotherapy with concurrent temozolomide (RT/TMZ) for glioblastoma multiforme (GBM). The aim of this study was to determine the incidence of psPD following RT/TMZ and the effect of psPD on prognosis. ***Materials/Methods:*** All patients receiving RT/TMZ for newly diagnosed GBM were identified from a prospective database. Clinical and radiographic data were retrospectively reviewed. Early progression was defined as radiological progression (RECIST criteria) during or within eight weeks of completing RT/TMZ. Pseudoprogression was defined as early progression with subsequent disease stabilization, without salvage therapy, for at least six months from completion of RT/TMZ. The primary outcome was overall survival (Kaplan-Meier) and log rank analysis was used to compare groups. ***Results:*** Out of 111 patients analyzed, 104 were evaluable for radiological response. Median age was 58 years and median follow-up 55 weeks. Early progression was confirmed in 26% and within this group 32% had psPD. Median survival for the whole cohort was 56.7 weeks [95% CI (51.0, 71.3)]. Median survival for patients with psPD was significantly higher than for patients with true early progression (124.9 weeks versus 36.0 weeks, p=0.0286). ***Conclusions:*** Approximately one third of patients with early progression were found to have psPD which was associated with a favourable prognosis. Maintenance TMZ should not be abandoned on the basis of seemingly discouraging imaging features identified within the first three months after RT/TMZ.

RÉSUMÉ: Pseudoprogression après la chimioradiothérapie dans le traitement du glioblastome multiforme. ***Objectif :*** La pseudoprogression (psPD), qui survient après le traitement par radiothérapie associée à l'administration de témozolomide (RT/TMZ) pour traiter le glioblastome multiforme (GBM), est maintenant bien connue. Le but de cette étude était de déterminer l'incidence de la psPD après le traitement par la RT/TMZ et ses conséquences sur le pronostic. ***Matériel et méthodes :*** Tous les patients traités par RT/TMZ pour un GBM nouvellement diagnostiqué ont été identifiés dans une banque de données prospective. Les données cliniques et radiologiques ont été révisées rétrospectivement. Une progression précoce était définie comme une progression radiologique (critères RECIST) pendant ou au cours des 8 semaines suivant la fin du traitement par RT/TMZ. La pseudoprogression était définie comme la progression précoce suivie d'une stabilisation de la maladie, sans traitement de rattrapage pendant au moins 6 mois après la fin du traitement par RT/TMZ. L'issue primaire était la survie (Kaplan-Meier) et les groupes ont été comparés au moyen du test du log-rank. ***Résultats :*** Nous avons pu évaluer la réponse radiologique chez 104 des 111 patients étudiés. L'âge médian était de 58 ans et le suivi médian de 55 semaines. Une progression précoce a été confirmée chez 26% des patients et de ce groupe, 32% avaient eu une psPD. La survie médiane de la cohorte entière était de 56,7 semaines (IC à 95% de 51,0 à 71,3). La survie médiane chez les patients qui avaient présenté une psPD était significativement plus élevée que celle des patients qui avaient eu une véritable progression précoce (124,9 semaines versus 36,0 semaines, p = 0,0286). ***Conclusions :*** Environ un tiers des patients qui ont présenté une progression précoce avaient présenté une psPD associée à un pronostic favorable. Le traitement d'entretien par la TMZ ne devrait pas être abandonné à cause d'une imagerie dont l'aspect semble décourageant dans les trois premiers mois après la RT/TMZ.

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Glioblastoma Multiforme (GBM) is a rapidly dividing tumour associated with a poor prognosis.[1,2] The current standard of care for newly diagnosed GBM is surgical resection followed by radiotherapy with concurrent temozolomide (RT/TMZ) and then maintenance temozolomide for at least six months.[3]

Contrast-based imaging studies, computerized tomography (CT) or magnetic resonance (MR), may reveal increased contrast-enhancement and peritumoural edema following radiotherapy, with or without the use of concurrent temozolomide. Although in some cases these changes reflect tumour growth due to the treatment resistant nature of GBM , we

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and others have observed that in a significant proportion of these patients the changes detected will remain stable or diminish over time. The term 'pseudoprogression' has been recently used to describe this situation since it is believed that the adverse changes represent certain treatment-related effects rather than true disease progression.[4]

Although recognized following radiotherapy alone,[5] pseudoprogression (psPD) is widely believed to be more frequent following RT/TMZ. Data defining the precise incidence of psPD following RT/TMZ is emerging but vary widely (see Table 1).[6-11] A lack of defined criteria for psPD may explain this variation. In this study we determine the incidence of psPD following RT/TMZ using the Response Evaluation Criteria in Solid Tumours (RECIST) criteria,[12] easily applicable in the clinic and shown to be comparable to more complex radiological assessment for GBM.[13] Using these strict radiological criteria, we also explored the effect of psPD on prognosis.

Methods

All patients receiving RT/TMZ for newly diagnosed GBM between July 2003 and October 2008 were identified from a prospective database. Patients with pathological WHO grade 3 tumours (anaplastic) were only included if the initial radiological features were more consistent with GBM as prognosis has been reported similar to grade 4 tumours.[14] Patients with recurrent disease were excluded. Temozolomide was administered at a dose of 75 mg per m^2 concurrent with daily radiotherapy and followed by 150 mg-200 mg per m^2 for 5 days every 28 days.

Local Research Ethics Board approval was obtained for a retrospective chart review and data collected included age, performance status, extent of surgery, pathology, radiation dose, number of adjuvant temozolomide cycles, and date of death. For patients remaining alive, community physicians were contacted and, where relevant, other institutions, to ensure all follow-up imaging and salvage therapy information was made available. A review of imaging was performed by two neuro-radiologists (RA, SS) and two radiation-oncologists (PS, AS). RECIST criteria were retrospectively applied. Contrast enhanced MR or CT scans were used to define response.

Patients were first categorized as early progression (ePD), defined as progression during radiation or within eight weeks of completing RT/TMZ, or no early progression (nPD). Patients with ePD were further subdivided between psPD and true early progression (tPD). Patients were allocated to the psPD group if

Table 1: Incidence of pseudo-progression reported in the literature

Study	Number of Patients	Response Criteria	Criteria for ePD	Number with ePD	Number with tPD	psPD (% of ePD)
Brandes et al, JCO 2008	103	Enhancement increase for ePD then Macdonald	4 weeks	50	18	32/50 (64%)
Taal et al, Cancer 2008	85	Macdonald	4 weeks	36	18	†15/31 (48%)
Clarke et al, abstract 2008	80	Increased contrast enhancement	Not Specified	33	17	*8/25 (32%)
Gerstner et al, JNO 2009	#45	Macdonald	17-28 days	24	11	13/24 (54%)
Jefferies et al, abstract 2007	15	Not specified	6 months	9	6	3/9 (33%)
Chaskis et al, Surg Neurol 2009	54	Increased contrast enhancement	6 months	25	22	3/25 (12%)
Present Study	104	RECIST	8 weeks	27	15	*7/22 (32%)

GBM, Glioblastoma Multiforme; ePD, Early Progression; tPD, true 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

Table 2: Demographics of population

Age		
	Median	58years
	<50 years	23
	50-59years	43
	60-69years	32
	70years and above	13
Sex		
	Male	65
	Female	46
Surgery		
	Biopsy	31
	Debulking	68
	Gross total	12
ECOG PS		
	0 to 2	101
	3	10
Adjuvant TMZ cycles		
	Median	3
	Range	0-13
Radiation Dose		
	≥BED $60Gy_{10}$	98
	≤BED $60Gy_{10}$	13

ECOG PS = Eastern Cooperative Oncology Group Performance status, TMZ = temozolomide, BED = Biological equivalent dose calculated using

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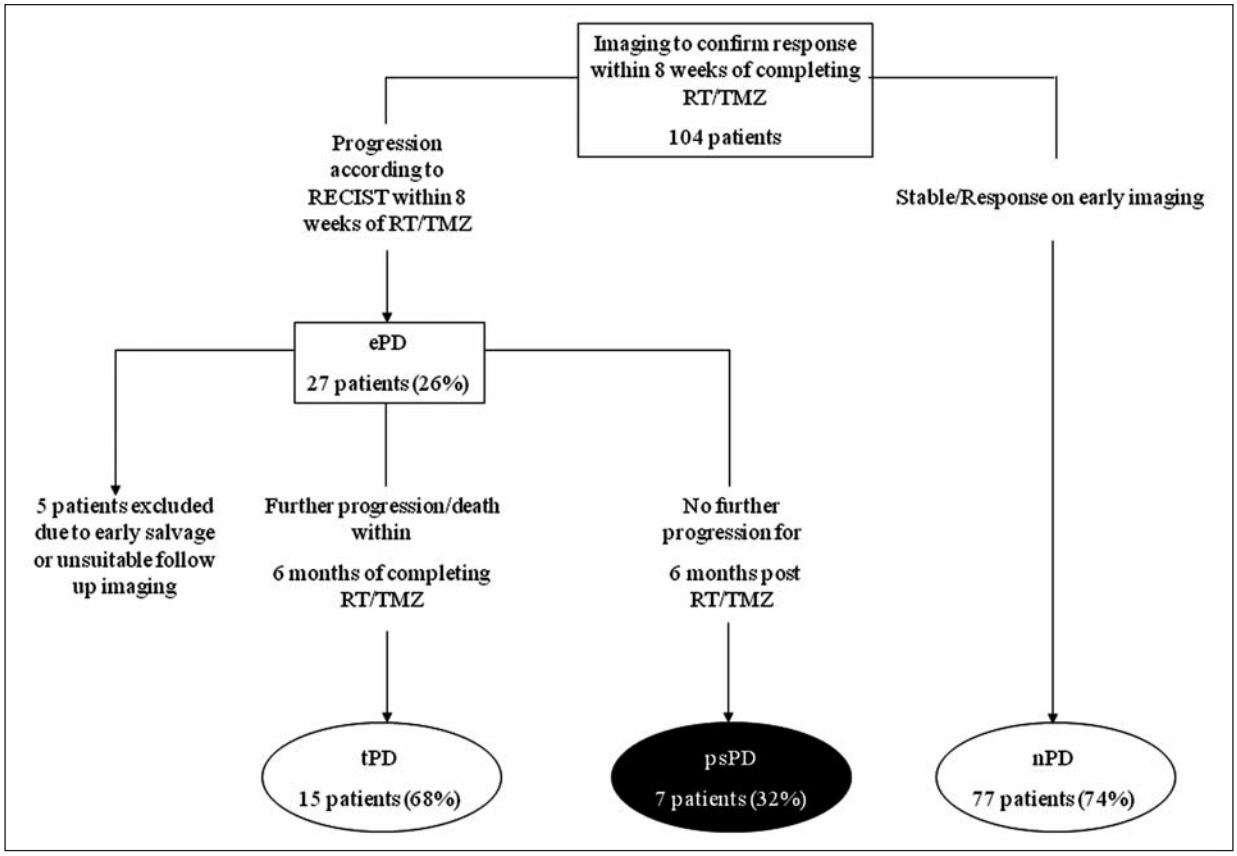

Figure 1: *Distribution of Patients by Response Category. Non-evaluable patients either received salvage therapy after initial progression or failed to have further imaging within the initial six month period. ePD, early radiological progression; nPD, no early progression; psPD, pseudoprogression; tPD, true early progression.*

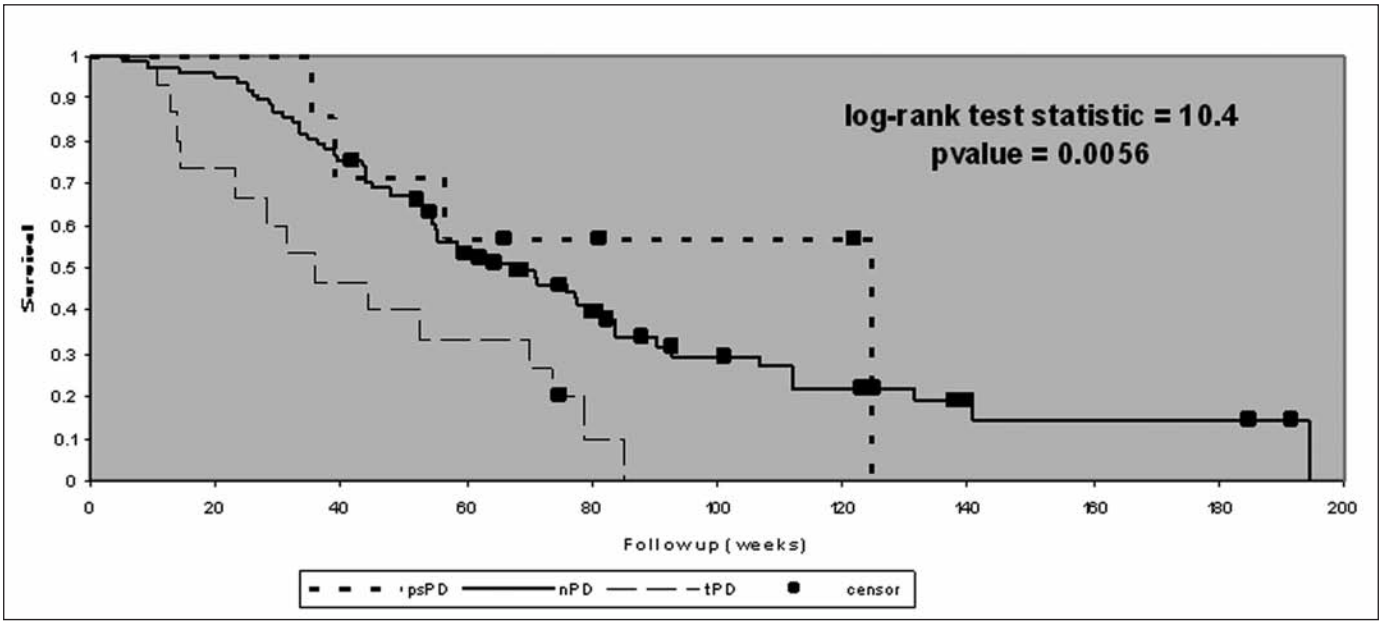

Figure 2: *Survival by Progression Type. psPD, pseudoprogression; nPD, no early progression; tPD, true early progression.*

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there was no further radiological progression, without using salvage therapy (any anti-cancer therapy, other than the monthly adjuvant temozolomide schedule), during the initial six months following RT/TMZ. Stability of dexamethasone dose was confirmed in patients within the psPD group. Patients were allocated to the tPD group if there was radiological progression or death during the same initial six-month period. Patients having ePD receiving salvage therapy (without further radiological PD), or patients that had no further imaging following ePD and surviving the initial six months, were excluded from the sub-categorization of tPD or psPD. Patients without any contrast enhanced imaging to confirm response prior to death were excluded from any of the above response categorization. Details of early clinical deterioration and steroid use were recorded in patients meeting psPD criteria.

Statistics

The primary endpoint was overall survival calculated from the date of surgical resection. Patients were censored from the date last seen by a physician. Kaplan-Meier product-limit analysis was conducted and 95% confidence intervals calculated. Log-rank test was used to detect statistically significant differences in survival distributions among progression types and the following prognostic variables: radical radiation dose (biological equivalent dose ≥ $60Gy_{10}$ using linear quadratic model / 2Gy equivalence of 50Gy) versus low dose radiation (biological equivalent dose ≤ $60Gy_{10}$ / 2Gy equiavalence of 50Gy), ECOG performance status 0-2 versus ECOG performance status 3, age below 60 years versus above, gender and extent of surgery (biopsy versus open surgery). Radiation dose was considered by intention to treat. Significance levels were as set at 5% and all statistical tests were performed using proc lifetest in SAS® version 9.1.3.

Results

A total 111 patients receiving RT/TMZ for newly diagnosed GBM were identified and demographic data is given in Table 2. The median follow-up was 55 weeks and 85 patients have died to date. Glioblastoma multiforme was confirmed histopathologically in 104 patients. A further seven patients had anaplastic tumours but with radiological features more consistent with GBM.

Seven patients were excluded from any response categorization due to insufficient imaging data to confirm

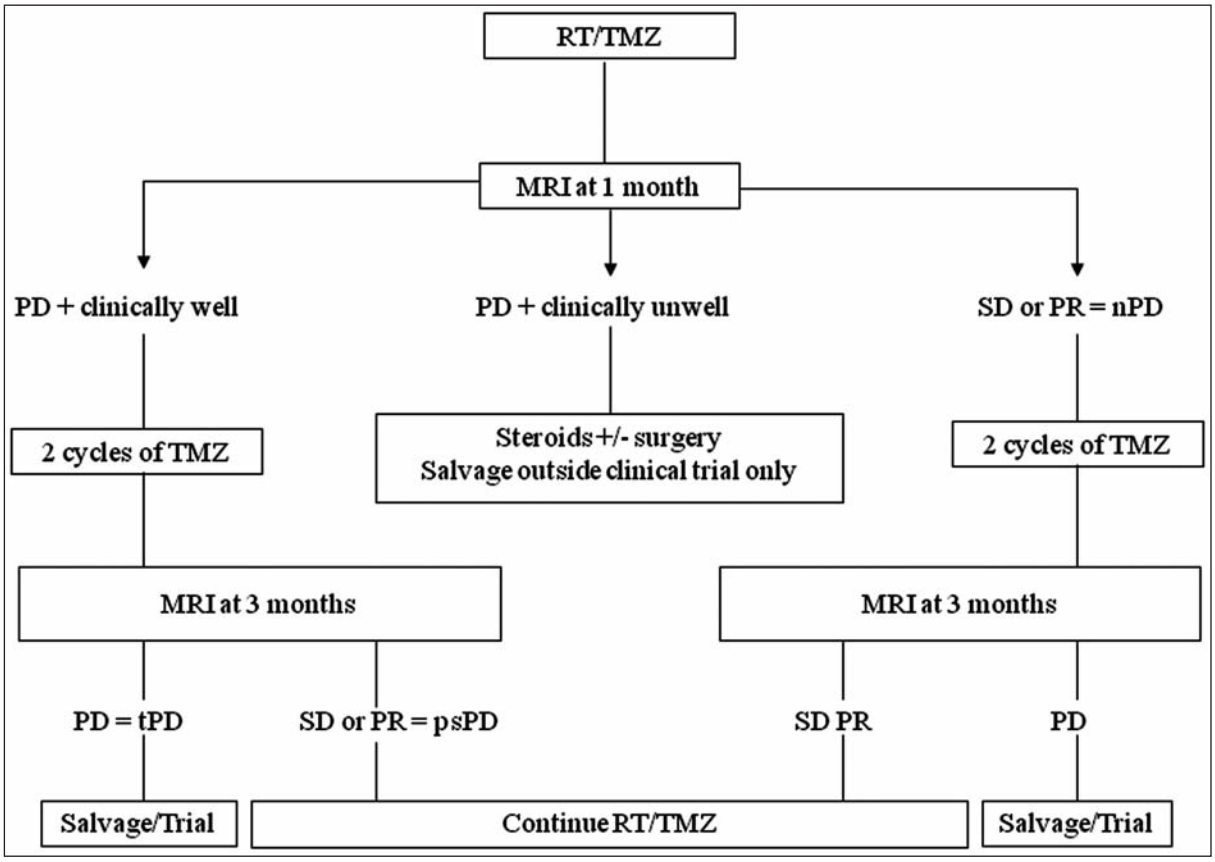

Figure 3: *Schema for the Management of the different Response Categories post Concurrent Chemotherapy and Temozolomide. RT/TMZ, radiotherapy with concurrent temozolomide; MRI, magnetic resonance imaging; TMZ, temozolomide, PD, radiological progression; SD, stable disease; PR, partial response; psPD, pseudoprogression; tPD, true early progression.*

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Table 3: Survival data by subgroup analysis

		95% Confidence Interval		
	Median Survival (weeks)	**Lower Bound**	**Upper Bound**	***Log-rank test p-value***
Overall	56.7	51.0	71.3	-
Pseudo-progression	124.9	38.9	124.9	*0.0056*
True early progression	36.0	23.0	70.1	
No early Progression	67.3	54.6	81.4	
BED > 60Gy$_{10}$	60.3	53.7	77.4	*0.0088*
BED < 60Gy$_{10}$	32.3	26.6	42.1	
ECOG PS 0-2	59.7	52.7	77.4	*0.0014*
ECOG PS 3	21.9	10.6	39.6	
Biopsy	38.9	30.7	52.6	*0.0001*
Debulking	71.3	53.7	85.1	
Resection	67.3	59.1	na	
Age < 60	67.3	53.7	79.0	*0.1981*
Age ≥ 60	43.9	33.4	63.6	
Female	56.7	42.1	90.6	*0.1918*
Male	*55.6*	*45.0*	*70.1*	

BED, Biological equivalent dose; ECOG PS, Eastern Cooperative Oncology Group performance status score

response. Four of these patients died within eight weeks of RT-TMZ. One developed bowel obstruction, another a subdural haemorrhage following a fall while anticoagulated and two others were frail and clincally deteriorated soon after treatment. Two patients died within six months of RT-TMX, one due to pneumonia and the other within the community without disease response assessment. One patient survived beyond six months (42 weeks) but did not want further follow-up and died without any response assessment within the community.

Distribution by response type is given in Figure 1. Following the radiology review ePD was confirmed in 27/104 (26%) patients and nPD in 77/104 (74%) patients. Within the ePD category one patient survived the intial six months post RT/TMZ (follow-up 40 weeks) but did not want further follow-up and there were no further scans to confirm disease response. In a further four patients the use of early salvage therapy (prior to further PD) makes it difficult to discriminate between tPD and psPD. One patient (surviving 59 weeks) underwent early salvage surgery but only radiation effect and low grade tumour was identified. Survival of the other three patients was 51, 51 and 148 weeks. The above five patients were excluded from allocation to type of early progression.

Out of the 22 evaluable patients with early progression, 15 patients (68%) had rPD and 7 (32%) psPD. Associated clinical deterioration occurred in 4 of the 7 psPD cases, improving over time in all cases. There was no fluctuation in steroid dose to account for temporary deterioration in any of the psPD cases.

The median overall survival for all 111 patients was 56.7 weeks [95% CI (51.0, 71.3)]. Survival data is presented in detail in Table 3. Performance status (p=0.0014), biopsy versus open surgery (p=0.0001) and radiation dose (p=0.0088) predicted outcome. Survival curves for the three progression categories are given in Figure 2. The median survival of the psPD group was 124.9 weeks [95% CI (38.9, 124.9)]. Overall there was a significant difference in survival when comparing the three groups (p=0.0056). When comparing psPD to the other two response groups, the difference from tPD is significant (p=0.0286) as opposed to nPD (p=0.5156).

Discussion

Using strict validated criteria we found the incidence of psPD to be 32%. This is lower than that reported by some investigators (Table 1).[6-11] The differences in incidence of psPD between studies may partly be due to patient selection, response criteria used and the time periods within which ePD and subsequent psPD were defined.

Brandes et al reported the highest rate of psPD in their series[6]; however they included scans in which they detected any degree of tumour enlargement following completion of chemoradiation. Furthermore, they reported on patients for whom O^6-methylguanine-DNA methyltransferase (MGMT) promotor

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methylation status was available and only one patient within this group underwent biopsy alone. In contrast, the consecutive cohort of patients presented here is relatively unselected and heterogenous. This is also an acknowledged limitation of our study. Our results are within the 95% confidence intervals presented by Taal et al who used the Macdonald criteria to define tumour progression.[7]

Detection of psPD is highly relevant to neuro-oncology practice. It should be considered as one possible explanation for worsening imaging studies and clinical deterioration following the completion of chemoradiation. Suspicion of psPD may influence the clinician's recommendation to continue with standard adjuvant chemotherapy rather than embarking upon second line therapy for recurrence. Imaging changes consistent with psPD commonly persist up to three months after completion of chemoradiation and are occasionally persistent for longer periods. A proposed algorithm for clinical management following completion of chemoradiation is shown in Figure 3. Temozolomide is one of the most active currently approved agents for GBM and is given as maintenance therapy for at least six months in appropriate patients. We suggest that maintenance TMZ not be abandoned on the basis of imaging features in the first three months following completion of chemoradiation. This recommendation is consistent with and lends evidence-based support to the Canadian Recommendations for practice.[15]

Using our study criteria the absolute number of patients with psPD is too small to confirm any prognostic effect. Furthermore it is difficult to draw firm conclusions on the prognostic effect in view of psPD being defined retrospectively on the basis of patients with prolonged disease stability following initial progression. This is a limitation of all such studies However, consistent with others studies[6,7] patients identified with psPD appeared to have a prolonged survival. Brandes et al found that both psPD and prolonged survival were associated with detection of epigenetic silencing of the MGMT promoter.[6] We were unable to obtain MGMT results from sufficient numbers of patients in our series to analyze this finding. Intriguingly, the Brandes et al data also suggest that patients with enlargement of the contrast-enhancing areas of their tumours who do not harbour MGMT methylation almost always are found to have true disease progression. If these findings are confirmed, MGMT methylation status may prove to be an important clinical factor in the evaluation of imaging-based changes early in the post-radiotherapy phase of GBM treatment.

The evaluation of response is a controversial topic in neuro-oncology.[16] Traditional response criteria, such as the Macdonald and the RECIST methods, are based upon the measurement of contrast-enhancing disease.[12,17] Such criteria have been very useful as a method to evaluate the efficacy of some therapies, especially alkylating agents; however, the utility of these methods has fallen into question in the era of targeted therapies.[18] For example, reductions in contrast-enhancing disease may not be expected for some biological agents, some therapies such as intracavitary radio-conjugated antibodies may increase enhancement seen on imaging, and some treatments, such as VEGF-targeted therapy, may cause dramatic reduction in contrast-enhancement without a clear survival advantage.[19-21] These problems were anticipated and have received appropriate attention; however, the treatment-related effects of the combination of RT/TMZ were not expected. In the pivotal EORTC-NCIC-CTG trial up to 20% of patients did not receive maintenance TMZ therapy,[3] usually because of deterioration in post-treatment imaging. The occurrence of psPD following standard therapy for GBM raises important issues related to the determination of disease progression, the optimal timing and method to judge treatment efficacy, when to recommend second-line or experimental therapy, and how to evaluate new agents administered on the 'backbone' of RT/TMZ.

New agents for malignant glioma are typically tested in phase II trials at the time of first recurrence following upfront therapy. The recognition of psPD as a significant occurrence following standard RT/TMZ must be considered in the design of future trials. If patients harbour treatment-related imaging changes destined to resolve are assumed to have progressive disease, then their entry into a phase II trial may lead to an overestimation of efficacy, particularly if traditional response criteria are used. In the Canadian Brain Tumour Consortium study of daily TMZ, the investigators anticipated pseudoprogression and restricted entry into this phase II trial of recurrent GBM only to patients with disease progression more than three months from the end of chemoradiation.[22] New studies evaluating agents in the upfront setting (standard RT/TMZ plus agent 'x') must carefully consider the issue of pseudoprogression and the appropriateness of imaging-based endpoints in the immediate post-radiotherapy period.

The biology of pseudoprogression is not clear. While Chamberlain et al have demonstrated that some patients develop early radionecrosis following RT/TMZ[23], the issue of psPD is different. Pseudoprogression likely involves early changes to the vascular endothelium and the blood-brain-barrier[4]; however, the precise mechanism remains complex and poorly understood. Future studies are likely to take advantage of developments in MRI-based vascular permeability, and flow imaging in order to elucidate the nature and timing of these changes. Perhaps an imaging tool can be developed to assist the clinician with determination of the difference between a patient with a robust treatment response (conferring a survival advantage) versus a patient with disease resistance. Until then, we must be cautious with the interpretation of imaging following the treatment of GBM.

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