Editorial

Facing pseudoprogression after radiotherapy in low grade gliomas

Fernando Carceller[1,2], Henry Mandeville[3], Andrew D. Mackinnon[4], Frank Saran[3]

[1]Children and Young People's Unit, Paediatric & Adolescent Drug Development Team, The Royal Marsden NHS Foundation Trust, London, UK; [2]Division of Clinical Studies and Cancer Therapeutics, The Institute of Cancer Research, London, UK; [3]Radiation Oncology Unit, The Royal Marsden NHS Foundation Trust, London, UK; [4]Department of Neuroradiology, St George's University Hospitals NHS Foundation Trust, London, UK

Correspondence to: Fernando Carceller. Children and Young People's Unit, The Royal Marsden NHS Foundation Trust, Downs Road, Sutton, Surrey, SM2 5PT, UK. Email: Fernando.Carceller@icr.ac.uk.

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Pseudoprogression has been defined as a transient increase in the contrast enhancement within the treated tumour after radiotherapy, which eventually subsides without any change in the anti-cancer therapy (1,2). This constitutes most likely a subacute post-treatment effect of radiotherapy characterised by a local inflammatory reaction on tumour cells and/or vascular injury resulting in increased permeability (1,2). The concept of pseudoprogression was initially developed in adults with high-grade gliomas treated with radiotherapy +/– alkylating agents (3); and it has subsequently been extended to other brain tumours, including low-grade gliomas (LGG). Pseudoprogression has been reported to occur more frequently when temozolomide is combined with radiotherapy (4,5), although the magnitude of this effect yet remains to be established (3). Pseudoprogression can produce a clinical impact both at an individual and at a population level. Firstly, increased contrast enhancement in adults with LGG is highly suggestive of malignant transformation (6), so undiagnosed pseudoprogression may cause major distress for the patients and their families, and can even result in initiation of a new anti-cancer therapy inappropriately. Secondly, because failure to exclude patients with pseudoprogression at the time of enrolment in clinical trials may lead to falsely elevated response rates (1). And finally, because failure to identify pseudoprogression whilst on trial, limits the validity of progression-free survival as a primary endpoint (1). Hence, a better understanding and diagnosis of pseudoprogression is crucial to ensure adequate clinical management and to minimise hindrance to clinical trials.

Pseudoprogression has been extensively studied in adults with high-grade gliomas, where it occurs approximately in 20% of cases, with reported rates ranging from 6% to 31% (3). It has been suggested that pseudoprogression occurs more frequently in the context of methylated *MGMT* promoter (7), although not all studies have found this association (8). In children and adolescents, a retrospective series of 47 cases with non-brainstem high-grade gliomas found a rate of pseudoprogression of 8.5% (9). Likewise, few studies have evaluated the topic of pseudoprogression in LGG patients: Bakardjiev *et al.* analysed prospectively 28 children and young adults with LGG treated with stereotactic radiotherapy (10); Naftel *et al.* evaluated retrospectively 24 children and adolescents with LGG, mainly pilocytic astrocytomas (11); Lin *et al.* assessed retrospectively 88 adults with oligodendroglial tumours, including WHO grades II and III (12); and more recently, van West *et al.* have expanded the body of knowledge in this field with a retrospective evaluation of 63 adults with LGG WHO grade II treated with external beam radiotherapy (13). Heterogeneity in the age groups and tumour histologies between these studies precludes meaningful comparisons, but the reported rates of pseudoprogression in LGG ranged between 19% and 54% (10-13).

The age group and the tumour histology need to be taken into consideration when assessing pseudoprogression.

Increased contrast enhancement in adults with LGG is frequently suggestive of disease progression (6), whereas contrast enhancement in paediatric LGG is variable and does not accurately reflect tumour response (14,15). As regards the histology, areas of patchy enhancement can be seen in up to 10% of non-transformed LGG, mainly in oligodendroglioma subtypes (6).

Furthermore, although the terms pseudoprogression and radiation necrosis are sometimes used interchangeably in the literature, traditionally they have been distinguished radiologically by the fact that radiation necrosis represents radiation injury to the adjunct peritumoural white matter and/or to the white matter in the radiation field, rather than to the actual tumour cells (16). While it is likely that the pathophysiology of both entities is different, it has been argued that both pseudoprogression and radiation necrosis may be part of the same spectrum of radiation-related radiographic changes (3). van West *et al.* were aligned with this view and therefore included certain cases, particularly those with radiation injury lesions located in the peritumoural white matter, or remote from the tumour but within the radiation field (13), that might have been regarded as radiation necrosis by other research groups. The distinction between these two entities, or whether radiation necrosis should be considered a subset of pseudoprogression, is still a matter of debate.

In any case, the diagnosis of pseudoprogression is retrospective, unless histological confirmation can be attained. Currently there are no standardised imaging techniques, or consensual diagnostic criteria of pseudoprogression, that can reliably differentiate it from tumour recurrence (3). This entails important limitations, such as variable definitions of pseudoprogression and patient selection bias. Most studies in patients with high-grade gliomas defined pseudoprogression as a transient increase in the post-contrast enhancement of tumour lesions (1-3). Nonetheless, contrast enhancement by brain tumours post-treatment is variable, non-specific and not necessarily representative of tumour burden, particularly in children (1,17). This raises the question of whether a consensual definition of pseudoprogression should also include changes in diffusion-weighted imaging (DWI), fluid attenuated inversion recovery (FLAIR) and T2-weighted sequences.

Other aspects of a potential definition of pseudoprogression where consensus is needed include: the timing for the development of pseudoprogression, its duration, the relevance of concurrent symptoms, the use of concomitant medications and the indication for pursuing histological confirmation.

As regards the timing of pseudoprogression, van West *et al.* reported the occurrence of pseudoprogression at a median of 12 months (range, 3–78 months) from the end of radiotherapy (13). In contrast, Lin *et al.* only included cases detected within 6 months from the end of radiotherapy, reasonably arguing that areas of contrast enhancement occurring >6 months after the end of radiotherapy are more likely to be related to ischemic injury, rather than increased inflammatory reaction. Given the heterogeneity of the population presenting pseudoprogression, it can be hypothesized that pseudoprogression might be originated by means of different pathophysiological mechanisms converging in common clinico-radiological manifestations (9,16). However, post-radiotherapy effects can occur even years later, which may indicate variable pathogenesis, and need to be considered in the differential diagnosis along with true progression (16). Therefore, a pragmatic definition of pseudoprogression should reflect these broad timelines.

The duration of the episodes of pseudoprogression should also be carefully assessed, because where the radiological findings raise the suspicion of progressive disease ultimately they must resolve, improve or stabilize. However, there is no consensus to define this improvement/stabilisation (3). van West *et al.* established an arbitrary cut-off of 1 year for stable radiological appearances to qualify for pseudoprogression (13). Interestingly, overall they found a median duration of pseudoprogression (including resolution and stabilization) of 6 months (range, 2–26 months). In children, a much longer duration has been reported, with radiographic changes associated with pseudoprogression lasting a median of 2.1 years (range, 6.5 months–5.1 years) (11). Median radiotherapy doses were comparable between both studies: 50.4 Gy (range, 50.4–60 Gy) in adults and 52.2 Gy (range, 50.4–54 Gy) in children (11,13). Future definitions of pseudoprogression should agree upon a specific duration for stable radiological appearances.

The relevance of symptoms associated with pseudoprogression is unclear. In patients with high-grade gliomas, pseudoprogression can be associated with concurrent symptoms in 21–34% cases (7,9). In adults with LGG, symptomatic presentation of pseudoprogression is exceptional (12,13), whereas 66–69% of paediatric LGG with pseudoprogression were symptomatic (10,11). Obviously, the site and extent of the observed radiological changes are important factors for the development

of symptoms, and these need to be considered when determining the optimal management strategy for individual patients with radiological findings suggestive of pseudoprogression.

The role of concomitant medications is another controversial area when defining pseudoprogression. In their series van West *et al.* excluded patients treated with dexamethasone (13), whereas Lin *et al.* justified excluding cases with late pseudoprogression because of the frequent use of bevacizumab at that stage (12). Both steroids and bevacizumab constitute confounding factors by virtue of improving the clinico-radiological findings, potentially both in cases of pseudoprogression or true progression. However, up to 50% of cases with LGG may require steroids before, during or after radiotherapy due to symptoms associated with pseudoprogression, true progression or unexpected side-effects (18). Hence, the inclusion of patients with steroids needs to be considered in future studies on pseudoprogression, as long as its methodology can ensure that those with true progression are excluded appropriately.

Lastly, while surgery to obtain histology can discriminate pseudoprogression from true progression, conducting a biopsy is not always feasible, nor ethically justifiable, due to the potential risks of the procedure. In selected patients with significant symptoms, surgery may be indicated as treatment for this. There are some high-grade glioma studies on pseudoprogression reporting surgical resection confirming radionecrosis (4,19), whereas others define pseudoprogression based solely on imaging findings and clinical course (5,9). Although histology, when available provides valuable information in specific cases (12), a definition of pseudoprogression based on clinico-radiological findings is more pragmatic, as illustrated by the fact that none of the case series on LGG mandated histological confirmation (10-13).

Overall, the challenges to define pseudoprogression illustrate the limited understanding of the pathophysiology and the implications of pseudoprogression. Notwithstanding, van West *et al.* reported some valuable observations:

Firstly, the study addresses the controversy regarding the prognostic value of pseudoprogression. Patients with pseudoprogression had a superior overall survival than those without pseudoprogression (13). Nonetheless, pseudoprogression is a time-dependent variable, because patients need to live long enough to meet the definition of pseudoprogression. Hence, interestingly, when patients who progressed or died before an arbitrary landmark (i.e., the 95th percentile of the time to development of pseudoprogression) were excluded from the survival analysis, there were no differences in the overall survival of patients with or without pseudoprogression. In patients with high-grade gliomas pseudoprogression has been advocated as a marker of improved survival (7), but a number of studies have failed to find significant differences in survival when patients with early progression were excluded (9,19,20).

Secondly, the lesions at the time pseudoprogression were significantly smaller than at the time of true progression (13): only one episode of pseudoprogression (7%) presented an enhancing lesion with a cross-sectional diameter ≥10 mm.

And lastly, seven episodes of pseudoprogression (47%) were located subependymally in the ventricular wall (13). The authors hypothesised that a relatively poor blood supply in the periventricular area may make this region more prone to radiation-induced ischaemic processes. Although, as previously discussed, some of these lesions would have been regarded as radiation necrosis by some research groups.

As regards the management of pseudoprogression, the authors propose that LGG patients who have received radiotherapy and develop asymptomatic small (bidirectional diameter <10 mm) enhancing lesions within the radiotherapy field, particularly if these lesions are located subependymally, should continue with the same therapeutic strategy (13). We agree with this approach, but its application is limited to specific cases. Hence we stress the importance of RANO criteria as the most reliable strategy to address suspected cases of pseudoprogression, both for high-grade and LGG (1,6); since most cases of pseudoprogression will not meet the definition of disease progression (13,20).

However, RANO criteria are not able to tease out all patients with pseudoprogression and there might be some of them who fulfill the criteria for disease progression. Yet once they start a new therapy it becomes virtually impossible to re-label these cases as pseudoprogression. Therefore, complementary diagnostic tools are still needed at the time of suspected disease progression. To this effect, functional imaging techniques such as magnetic resonance spectroscopy, perfusion magnetic resonance imaging (MRI), DWI and amino-acid positron emission tomography (PET), have a promising role to aid in the distinction between true progression and pseudoprogression (1,2,6). In this regard, van West *et al.* incorporated perfusion MRI in approximately half of the cohort. The sample was limited as to draw meaningful conclusions, but the relative cerebral blood volume (rCBV) was increased in 68% of the cases with true progression, as opposed to 20% of the cases with

pseudoprogression (13). This observation is in line with previous reports correlating higher rCBV with higher histological grade in gliomas and in case of malignant transformation of LGG (21,22).

Future directions in the field of pseudoprogression should also assess its role in the setting of novel therapies. Thus far little is known about pseudoprogression following proton-beam therapy or immunotherapy (23,24). With the advent of these innovative treatments, a better knowledge of the rate and implications of pseudoprogression is required to ensure optimal development of these treatments.

In summary, at present pseudoprogression raises more questions than answers, but it has major implications in the treatment of patients with LGG. Future drug development makes it necessary to develop a more systematic approach to the diagnosis and management of pseudoprogression. Advances in this direction will require a consensual definition of pseudoprogression, as well as formal guidelines or recommendations to deal with cases of pseudoprogression homogeneously. This endeavour is well illustrated by van West *et al.* who have taken another step forward in this direction.

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Footnote

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