Letter to the Editor: "Tumour progression or pseudoprogression? A review of post-treatment radiological appearances of glioblastoma" [Clin Radiol 2015; 70:1299–1312]

To the Editor,

We have read with interest the review by Abdulla et al. about the role of imaging in the management of progressive glioblastoma[1]. The authors have highlighted that pseudoprogression and radiation necrosis (late-delayed radiation effects[2]) are not interchangeable terms. Although some researchers have interchangeably used the terms radiation necrosis and pseudoprogression,[3] this practice should be avoided as there are differences in the clinical and radiological course of the two entities[2] and, as alluded to by Abdulla et al., the histopathological and molecular phenotype of pseudoprogression has yet to be properly characterised.[4] Some authors also suggest that pseudoprogression is significantly correlated with O6 methylguanine-DNA methyltransferase (MGMT) promoter methylation.[5]

Distinguishing radiation necrosis (late-delayed radiation effects[2]) and disease progression has been an important clinical challenge for decades which has lead to substantial imaging research to avoid recurrent disease being a false positive diagnosis. Since 2005 adjuvant and concomitant temozolomide has become the standard of care for the treatment of glioblastoma[6] and has lead to a large increase in the incidence of the phenomenon of pseudoprogression[7] which describes false positive progressive disease, typically within 6 months of chemoradiotherapy.[8] Pseudoprogression is an early-delayed treatment effect in contrast to the late-delayed radiation effect,[2] and gives the neuro-oncologist a distinct set of management issues as the patient is receiving adjuvant temozolomide but appears to not be responding to treatment. Because this occurs in 20-30% of cases, this has motivated additional imaging research.[9] The authors have described some of these recent imaging studies which have been performed using perfusion, permeability and diffusion techniques. These do show promise in being able to differentiate pseudoprogression from progression. However, most of the data from the imaging studies used in Abdulla et als' article was either (1) obtained in the era before adjuvant and concomitant temozolomide became the standard of care when early-delayed treatment effects were rare (the term 'pseudoprogression' had yet to be coined), associated with entirely different treatments and arguably had a different

histopathological and molecular phenotype; (2) related to late-delayed radiation effects; (3) or was a combination of both. For example, this includes most of the data from the cited diffusion imaging and magnetic resonance spectroscopy studies, all the data from the single-photon emission computed tomography imaging studies, and it is noteworthy that many of the [^{18}F]fluorodeoxyglucose positron emission tomography studies are from the era when brain tumours were not followed up with MRI. In Abdulla et als' review article, despite recognising the dangers, the authors have themselves admixed data due to radiation necrosis (late-delayed radiation effects), data from early-delayed treatment from before the temozolomide era and data from the era when temozolomide use became standard practice (when the term 'pseudoprogrogression' was adopted).

The review article is therefore misleading to those not familiar with the evidence in this evolving subject.

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