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Pictorial Review

Tumour progression or pseudoprogression? A review of post-treatment radiological appearances of glioblastoma

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Glioblastoma (GBM) is a common brain tumour in adults, which, despite multimodality treatment, has a poor median survival. Efficacy of therapy is assessed by clinical examination and magnetic resonance imaging (MRI) features. There is now a recognised subset of treated patients with imaging features that indicate "progressive disease" according to Macdonald's criteria, but subsequently, show stabilisation or resolution without a change in treatment. In these cases of "pseudoprogression", it is believed that non-tumoural causes lead to increased contrast enhancement and conventional MRI is inadequate in distinguishing this from true tumour progression. Incorrect diagnosis is important, as failure to identify pseudoprogression could lead to an inappropriate change of effective therapy. The purpose of this review is to outline the current research into radiological assessment with MRI and molecular imaging of post-treatment GBMs, specifically the differentiation between pseudoprogression and tumour progression.

Introduction

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

Using the Macdonald criteria, progressive disease is determined by a 25% or greater increase in the product of the perpendicular diameters of the largest area of contrast enhancement. Increasingly, transient treatment-related changes on imaging mimicking progressive disease are being recognised. An increase in the enhancing area on MRI can be induced by a variety of non-tumoural processes, such as post-surgical changes, radiation effects, and ischaemia.[4,5] These "pseudoprogression" cases, which are generally not associated with clinical deterioration, stabilise or resolve without any change in treatment (Fig 1).

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Pseudoprogression has been observed in multiple studies and is estimated to occur in approximately 20% of patients following GBM treatment.[6–10] In a large study by Taal *et al.*[11] 50% of patients treated with chemo-radiotherapy (CRT) for GBM with worsening features on early MRI actually showed stabilisation or resolution of those MRI features without any change in treatment. Wrongly diagnosing pseudoprogression as true tumour progression on gadolinium-enhanced MRI could lead to an inappropriate change in therapy and errors in assessing the efficacy of novel treatments. This was addressed in the updated response assessment criteria developed by the Response Assessment in Neuro-Oncology Working Group (RANO), which suggests that in the first 12 weeks after therapy, when pseudoprogression is more prevalent, progression can only be diagnosed if there is new enhancement outside the radiation field (Table 1).[12] More advanced MRI techniques and molecular imaging are showing promise in differentiating responders to treatment from non-responders at an early stage and will allow more judicious treatment administration and early termination of ineffective treatment plans.

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

It should be noted that pseudoprogression and radiation necrosis (late-delayed radiation effects) are not interchangeable terms.[13] Pseudoprogression typically occurs earlier (within 6 months of CRT) and the histopathology is not completely understood.[14] For the purpose of this review, studies that include patients with apparent progression on imaging occurring within 6 months of treatment have been categorised as pseudoprogression.

Literature search

A broad search was conducted between April 2014 to November 2014 on PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) using “ALL FIELDS” and

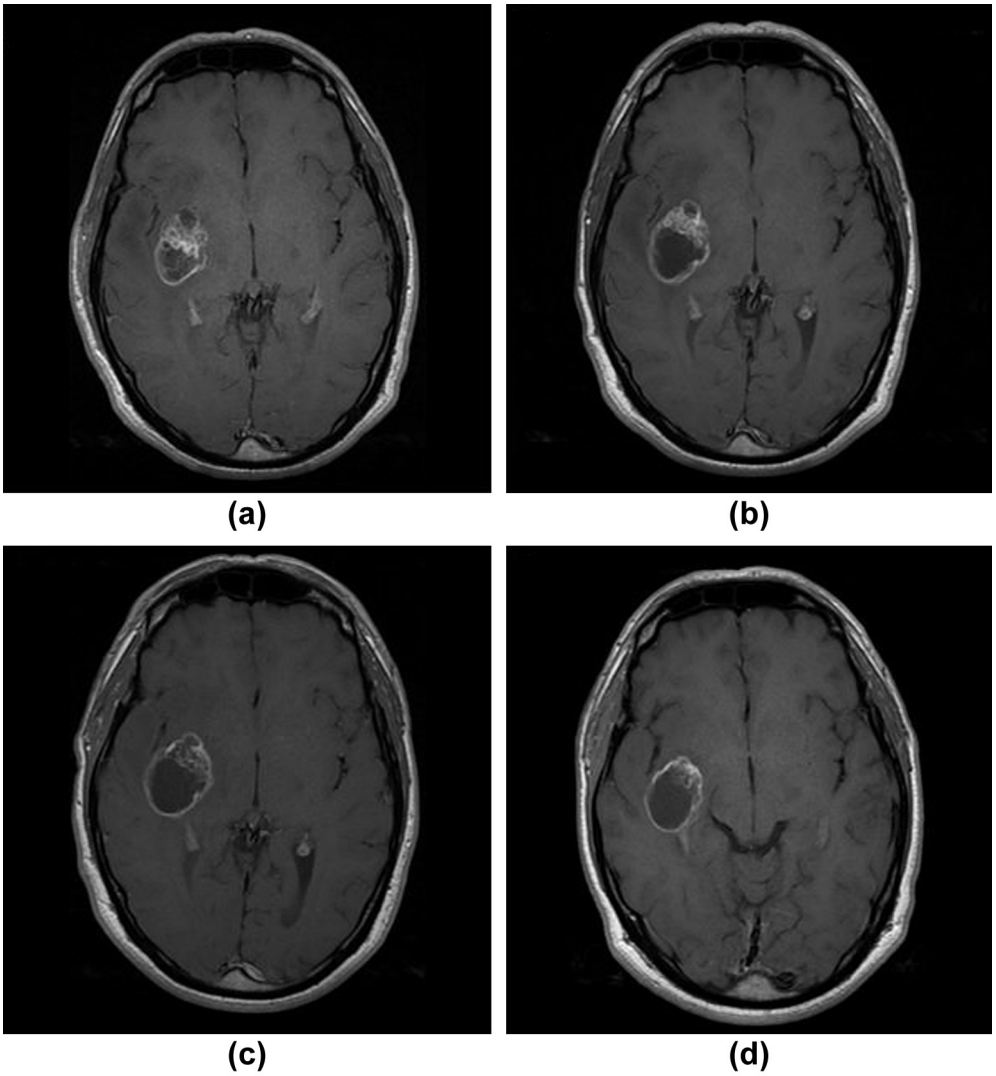

Figure 1 A patient with GBM. (a) Post-surgical MRI image showing progression on MRI at (b) 1 months and (c) 4 months post-radiotherapy; however, there was subsequent stabilisation at (d) 7 months post-radiotherapy indicating pseudoprogression.