Diffusion-weighted MR Imaging for the Differentiation of True Progression from Pseudoprogression Following Concomitant Radiotherapy with Temozolomide in Patients with Newly Diagnosed High-grade Gliomas

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Rationale and Objectives: The assessment of the therapeutic response of high-grade gliomas treated with concomitant chemoradiotherapy (CCRT) using temozolomide is difficult because of the frequent occurrence of early imaging changes that are indistinguishable from tumor progression, termed pseudoprogression. The purpose of this study was to determine whether diffusion-weighted imaging could be used to differentiate true progression and pseudoprogression.

Materials and Methods: Magnetic resonance images and diffusion-weighted images obtained within 2 months of CCRT completion in patients with high-grade gliomas were retrospectively reviewed. A total of 22 patients with increases in measurable enhancing regions were identified and classified into true progression and pseudoprogression groups on the basis of contrast-enhanced magnetic resonance images obtained 12 weeks after CCRT. Qualitative and quantitative analysis of diffusion-weighted images and apparent diffusion coefficient maps, respectively, was performed to discriminate true progression and pseudoprogression. Statistical analyses were performed using Fisher's exact test, unpaired *t* tests, and receiver-operating characteristic analysis.

Results: The true progression group showed a higher incidence of homogeneous or multifocal high signal intensity on diffusion-weighted images (seven of 10 patients [70%]), whereas rim high or no high signal intensity (10 of 12 [83%]) was observed in the pseudoprogression group ($P = .027$). True progression was defined by newly appearing or enlarged enhancing lesions with mean apparent diffusion coefficient values of 1200×10^{-6} mm^2/s inside the radiation field after CCRT; the sensitivity, specificity, and accuracy were 80% (eight of 10), 83.3% (10 of 12), and 81.2% (18 of 22), respectively.

Conclusions: The assessment of diffusion-weighted images for patients with increases of measurable enhancing regions 2 months after CCRT completion is useful for differentiating true progression from pseudoprogression.

Key Words: Progression; pseudoprogression; high-grade glioma; concomitant chemoradiotherapy; diffusion-weighted imaging.

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Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. The current standard care for newly diagnosed GBM includes postoperative concomitant chemoradiotherapy (CCRT) with temozolomide (TMZ) followed by maintenance TMZ, which significantly prolongs overall survival compared to radiation alone (1–3). Assessment of the response to treatment and disease progression, which includes variations in the contrast-enhancing tumor volume on radiologic imaging, neurologic function, and steroid dosage, is based on the criteria defined by Macdonald et al (4) in 1990. However, this traditional method of measuring the enhancing tumor may

not assess the true treatment response, particularly with pseudoprogression of high-grade gliomas after CCRT.

Pseudoprogression has been recognized and widely accepted to occur in the treatment of high-grade gliomas, as transient increases of the enhancing area usually <3 months after CCRT (5–9). This phenomenon was originally reported by Hoffman et al (10) in 1979 and more fully described by de Wit et al (8) in 2004 as the early tumor bed enhancement of high-grade gliomas treated with radiation therapy with or without carmustine. More recently, this was better defined in the era of the currently used TMZ regimen (7,11). Recent reports suggest that up to 30% of patients treated with this regimen may develop lesion changes that mimic early tumor progression on standard contrast-enhanced magnetic resonance (MR) imaging (5,9,11). This treatment-related change has implications for patient management and may result in premature discontinuation of effective adjuvant therapy. The absence of reliable and accepted imaging methods and biochemical markers to discriminate pseudoprogression from true progression further challenges its diagnosis.

The updated Response Assessment in Neuro-Oncology (RANO) criteria for high-grade gliomas were proposed by Wen et al (12) in 2009 to overcome the present limitations of the Macdonald criteria. The RANO criteria suggest that within the first 12 weeks of CCRT completion, when pseudoprogression is most prevalent, progression can be determined only if the new enhancement is outside of the radiation field or if there is pathologic confirmation of progression. In patients with new enhancement inside the radiation field within 12 weeks, pseudoprogression cannot be differentiated from true progression. Among those patients, lesions remaining stable or decreasing in enhancement size after 12 weeks without change in any therapy were defined as pseudoprogression, whereas those further increasing in enhancement size were defined as progression.

The transient increased contrast enhancement noted in pseudoprogression may result from a transient radiation effect of the vasculature, leading to vasodilatation, edema, and increased capillary permeability (6,8). In addition, TMZ is known to have a radiosensitizing effect on adjacent normal tissue (5,6,13). Histologically, most specimens of pseudoprogression demonstrate inflammatory cells, necrosis, and absence of or sparse tumor cells (5,7,9,11). Therefore, we hypothesized that this treatment-related change mainly degrades cellular integrity, leading to pathologic changes, such as necrosis, which are thought to cause increases in apparent diffusion coefficient (ADC) values. To the best of our knowledge, there has been no report concerning the use of diffusion-weighted MR imaging (DWI) to differentiate pseudoprogression from true progression. The aim of the present study was to determine whether DWI could be used to differentiate pseudoprogression from true progression in high-grade gliomas treated with CCRT with TMZ, when enlarged or newly appearing enhancing lesions are observed within the radiation field on the first follow-up MR image obtained within 2 months after treatment completion.

MATERIALS AND METHODS

Patients

Fifty-two patients with newly diagnosed GBM or anaplastic astrocytoma who had undergone surgical resection or stereotactic biopsy at our institution between February 2009 and May 2011 were selected from our radiology report database. Inclusion criteria were as follows: patients (1) had histopathologic diagnoses of GBM or anaplastic astrocytoma on the basis of World Health Organization criteria without oligodendroglial components, (2) underwent CCRT with TMZ and six cycles of adjuvant TMZ after surgery or biopsy, (3) underwent baseline MR imaging with contrast enhancement within 24 to 48 hours after surgery, (4) underwent first follow-up 3-T MR imaging performed with DWI at b = 0 and 1000 s/mm^2 <2 months (mean, 24 days; range, 11–60 days) after the end of CCRT, (5) had newly appearing or enlarged enhancing lesions inside the radiation field that were defined as bidimensionally contrast-enhancing lesions with two perpendicular diameters of ≥10 mm on first follow-up MR images (13), and (6) had undergone second follow-up MR imaging with contrast enhancement after three cycles of adjuvant TMZ for confirmation of true progression or pseudoprogression, which was performed 3 months (mean, 96 days; range, 80–102 days) after CCRT. We excluded 28 patients for the following reasons: (1) inadequate MR imaging, (2) no newly appearing or enlarged enhancing lesion on follow-up MR images, and (3) definite disease progression according to the RANO criteria (newly appearing enhancing lesion outside of the radiation field or pathologic confirmation of disease progression [12]). Additionally, we excluded two patients because of loss to follow-up or switching to bevacizumab during adjuvant TMZ because of a clinical decision on the basis of Karnofsky performance status. As a result, a total of 22 patients, consisting of 19 patients with GBM and three patients with anaplastic astrocytoma (14 men, eight women; mean age, 48.5 years; range, 18–69 years), were included and confirmed to have true progression (n = 10) and pseudoprogression (n = 12) after the end of adjuvant TMZ therapy according to the RANO criteria (Fig 1). This retrospective study was approved by the institutional review board, and the requirement for informed consent was waived.

Promoter Methylation Status of O6–Methylguanine–Deoxyribonucleic Acid–Methyltransferase

The promoter methylation status of O6–methylguanine–deoxyribonucleic acid–methyltransferase (MGMT), a deoxyribonucleic acid repair enzyme that removes alkyl groups from guanine residue, was investigated with surgical specimens using the methylation-specific polymerase chain reaction technique. The promoter methylation status of MGMT has been found to be associated with the sensitivity of GBM to alkylating agents in the context of treatment (14).