Pseudoprogression and Pseudoresponse: Challenges in Brain Tumor Imaging

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Assessment via MRI is an integral part of the management of primary brain tumors. However, reliance on imaging to determine treatment response is not without its pitfalls. Necrosis is a known late effect of radiation treatment of the brain that can mimic tumor recurrence. It is now appreciated that pseudoprogression, a similar effect, can occur after combined chemoradiotherapy and can occur more quickly and dramatically than after radiation alone. Although several adjunct imaging modalities are under investigation, none is yet widely accepted as being able to distinguish between true progression and pseudoprogression. Conversely, at disease progression, antiangiogenic therapies are frequently used and can have a rapid positive effect on imaging. These changes, increasingly known as “pseudoresponses,” can occur immediately after initiating treatment, making accurate assessment of true tumor response difficult. This article reviews the challenges of brain tumor imaging and its use in assessment of treatment response.

Introduction

Glioblastoma (GBM), the most common primary brain tumor in adults, carries a dismal prognosis. The current standard of care for GBM includes the combination of radiation with temozolomide treatment, followed by adjuvant temozolomide, which was shown to be significantly, though modestly, better than radiation therapy alone [1]. The median progression-free survival (PFS) after radiation with temozolomide and adjuvant temozolomide is only 7 months, and some tumors show inexorable growth despite treatment with chemoradiotherapy. Treatment response is typically evaluated via imaging, usually with gadolinium-enhanced MRI. New or increased enhancement is interpreted as tumor growth, also called progression of disease. A set of guidelines commonly referred to as the “Macdonald criteria” [2] has been used to guide the assessment of response to treatment for a number of years.

However, there are a number of caveats to this paradigm. First and foremost, gadolinium enhancement demonstrates impairment of the blood–brain barrier (BBB) rather than directly demonstrating tumor. Therefore, any intervention that affects the BBB will potentially change the degree of enhancement on MRI. For example, many patients with GBM take corticosteroids such as dexamethasone to reduce symptoms resulting from peritumoral edema. Steroids reduce peritumoral edema by improving the integrity of the BBB. As a result, it has been well established over the years that steroids can improve the magnetic resonance (MR) appearance of tumors both by reducing the T2 abnormality representing edema and by reducing enhancement. Postictal changes on MRI can also transiently increase enhancement [3], as can postsurgical changes [4]. In particular, regions that demonstrate restricted diffusion on an immediately postoperative MRI will commonly enhance subacutely for up to 2 to 3 months after surgery. All of these possibilities must be considered in the evaluation of a gadolinium-enhanced MR image.

A second caveat is the presence of a nonenhancing abnormality on MRI. Regions of increased signal on T2-weighted imaging surrounding enhancing disease are common and can represent peritumoral edema, radiation treatment effects, nonenhancing tumor, or a combination of these findings. Increasing areas of a T2 abnormality, particularly in the setting of worsening clinical function, may represent tumor progression despite stable or reduced enhancement.

A third caveat is that, over the years, it has been appreciated that late effects of radiation therapy can occur, especially after high-dose focal radiotherapy techniques...
such as radiosurgery and brachytherapy. One late effect is radiation necrosis, which can manifest months to years after treatment. Changes noted on imaging may be transient (improving or disappearing after weeks to months) or persistent. With the addition of concurrent chemotherapy to radiation, it is now appreciated that similar treatment effects can manifest more quickly—as early as the immediate postradiation period. Several articles have been published in the past few years describing this phenomenon, called pseudoprogression, in patients who have received chemoradiotherapy. Several novel imaging modalities are being evaluated to try to differentiate between patients with pseudoprogression and patients with true early progression of disease, but none has yet been widely accepted as standard practice.

Pseudoprogression poses particular challenges for the clinical management of patients, the design of clinical trials of recurrent tumors, and the assessment of efficacy in these clinical trials. If initial treatment with temozolomide does not control disease, treatment should be switched without delay. One common scenario is to allow enrollment of that patient in a clinical trial, because there are few alternatives with proven efficacy for this treatment-resistant tumor. If, however, the clinical and/or imaging changes being noted are instead due to pseudoprogression, changing therapy poses two problems. First, it sacrifices a treatment that is working well. Second, because pseudoprogression improves spontaneously, changing therapy can lead to a false attribution of efficacy to the experimental treatment in question.

Conversely, at the time of recurrence patients are increasingly being treated with antiangiogenic therapies including bevacizumab, sunitinib, sorafenib, AZD2171, and aflibercept. Increasing experience with these agents has shown that there can be rapid and dramatic improvements in MRI, particularly with regard to gadolinium enhancement. These imaging changes reflect effects of the medications on the BBB rather than a true tumor response, an effect that is increasingly being known as “pseudoresponse.”

This review discusses pseudoprogression and pseudoresponse and the challenges they present for the neurooncologist. Although these issues are present to varying degrees for any treated brain tumor, be it primary or metastatic, most of the published research focuses on GBM, which is the focus of this review.

Pseudoprogression

Incidence

Several recent papers have attempted to quantify the incidence of pseudoprogression in patients with GBM who have received combined radiation and temozolomide treatment. Chamberlain et al. [5•] reported on 51 newly diagnosed patients with GBM who were treated with conventional external-beam radiation (59.4–61.2 Gy in daily 180 cGy fractions) with concurrent daily temozolomide. MRI was performed 2 to 3 weeks after finishing chemoradiotherapy and, if stable, patients were then treated with adjuvant temozolomide 5 days out of a 28-day cycle for up to six cycles. Follow-up MRI was performed every 2 months. Of the 51 patients, 26 showed clinical and radiographic worsening within 6 months of completion of radiation treatment and were considered to have progression of disease. Fifteen of these 26 patients underwent reoperation, and pathology from seven of the 15 showed only necrosis without evidence of recurrent or progressive tumor. Therefore, treatment effect (necrosis) was found in 47% (7 of 15) of those who underwent reoperation, 27% (7 of 26) of the patients whose MRI scans worsened within 6 months of completion of chemoradiotherapy, and 14% (7 of 51) of the entire treatment group.

Taal et al. [6] reported on 85 newly diagnosed patients with malignant glioma (68 GBM, 17 anaplastic gliomas) treated with the same regimen described by Chamberlain et al. [5•]. The initial postradiation MRI, performed 4 weeks after radiation was finished, showed worsening features in 36 patients (42%). The worsening occurred in 31 of the 68 GBM patients (45%) and five of the 17 patients with anaplastic glioma (29%). All but three patients continued with adjuvant temozolomide; the three who did not had significant neurologic deterioration and died within 4 months of the initiation of radiation treatment. Patients whose initial postradiation MRI looked worse were considered to have true early progression if their condition worsened again within the following 6 months. If they remained clinically and radiographically stable or improved over the ensuing 6 months with no other treatment than adjuvant temozolomide, they were considered to have pseudoprogression.

Fifteen of the 31 GBM patients (48%) and three of the five anaplastic glioma patients (60%) whose initial MRI looked worse were determined to have pseudoprogression. Only one of these patients underwent reresection, and pathology did show necrosis alone. The presence of neurologic deterioration was noted in six of the 18 patients (33%) with pseudoprogression and in 12 of the 18 patients (67%) with true early progression. As one would expect, survival in the group with true early progression was significantly worse than in the pseudoprogression group or the patients whose postradiation MRI was stable or improved.

Brandes et al. [7] reported on the incidence of pseudoprogression in patients enrolled in a clinical trial evaluating radiotherapy plus daily temozolomide followed by adjuvant temozolomide, similar to the regimen described above. However, instead of six cycles of adjuvant treatment, patients continued adjuvant temozolomide for at least 12 cycles or until progression occurred. The methylation status of the O6-methylguanine-DNA