



Treatment-Related Change Versus Tumor Recurrence in High-Grade Gliomas: A Diagnostic Conundrum—Use of Dynamic Susceptibility Contrast-Enhanced (DSC) Perfusion MRI

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OBJECTIVE. The purpose of this article is to address radiation necrosis, pseudoprogression, and pseudoresponse relative to high-grade gliomas and evaluate the role of conventional MRI and, in particular, dynamic susceptibility contrast-enhanced perfusion MRI in assessing such treatment-related changes from tumor recurrence.

CONCLUSION. Posttreatment imaging assessment of high-grade gliomas remains challenging. Familiarity with the expected MR imaging appearances of treatment-related change and tumor recurrence will help distinguish these entities allowing appropriate management.

Imaging plays a key role in assessment of response to various treatment regimens for high-grade gliomas. For years, a set of guidelines by Macdonald et al. [1], commonly referred to as the “Macdonald criteria,” were used to assess treatment response by tumors. Those authors proposed four response categories: complete response, disappearance of all enhancing tumor on consecutive CT or MRI examinations at least 1 month apart, off steroids, and neurologically stable or improved; partial response, $\geq 50\%$ reduction in size of enhancing tumor on consecutive CT or MRI examinations at least 1 month apart, steroids stable or reduced, and neurologically stable or improved; progressive disease, $\geq 25\%$ increase in size of enhancing tumor or any new tumor on CT or MRI, neurologically worse, and steroids stable or increased; and stable disease, all other situations.

With new treatment strategies for high-grade gliomas, including the current standard of care that includes a combination of radiation with temozolomide followed by adjuvant temozolomide, and the recently U.S. Food and Drug Administration (FDA)-approved antiangiogenic therapy, such as bevacizumab (Avastin, Genentech), it has become increasingly clear that such conventional imaging evaluation has its limitations [2–5]. In particular, posttreatment entities, such as radionecrosis and pseudoprogression that represent a favorable response but mimic tumor recurrence, have been recognized. Converse-

ly, antiangiogenic therapies can result in pseudoresponse, with a significant rapid improvement in the imaging appearance of the tumor without affecting the biologic activity of the tumor itself, thereby limiting imaging evaluation. This article focuses on the role of conventional MR imaging and perfusion MRI in the evaluation of such treatment-related effects.

Why Perfusion MRI Plays an Integral Role in Evaluation of High-Grade Gliomas and Their Treatment

The association between neoangiogenesis and tumor growth and grading has been well-established [6]. Glioblastoma is the most common and most aggressive malignant primary brain tumor, categorized as World Health Organization grade IV. It is therefore understandable that glioblastomas are associated with a high degree of vascular proliferation. Several different MRI approaches that might be used to assess tumor vasculature have been proposed [7]. Arterial spin labeling is a method that uses tagged blood spins to measure flow and has been applied to tumors [8]. However, arterial spin labeling suffers from low signal-to-noise ratio and has not found wide clinical acceptance.

Other techniques that are more robust and have gained widespread clinical acceptance include contrast-enhanced perfusion MRI techniques. Dynamic susceptibility contrast-enhanced (DSC) MRI can be used to make measurements of absolute cerebral blood flow

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(CBF) and volume (CBV) and relative CBV [9, 10]. The DSC analysis assumes that contrast material remains intravascular (i.e., the blood-brain barrier is intact). Although this is not generally true, techniques such as γ variate fitting and baseline subtraction can correct for contrast extravasation generally seen in gliomas [11]. Alternatively, dynamic contrast-enhanced MRI methods model contrast agent extravasation and yield estimates of additional parameters related to vascular permeability, such as the vascular transfer constant (K^{trans}). Such parameters are potentially useful because the vessels created by tumor angiogenesis are known to be hyperpermeable.

Historically, DSC analyses have been applied to T2* weighted images (usually echo planar imaging) acquired during the injection of a bolus of contrast material, whereas dynamic contrast-enhanced analyses have been applied to T1-weighted images during the washout of contrast material from the tumor. Both DSC and dynamic contrast-enhanced approaches have shown their utility in evaluation of glioma grades [12, 13]. Radiation-induced effects and chemotherapeutic agents, which will be discussed later, affect the vascular microenvironment of such tumors. The ability to document any such change in the tumoral bed blood volume can therefore help evaluate treatment response [14].

Why Optimization of Perfusion MRI Technique Is Essential to Evaluate Treatment Response

An inherent limitation of DSC MRI is underestimation of the blood volume in areas of significant blood-brain barrier breakdown. These errors can be reduced by a variety of methods, including the use of approximate correction algorithms, preloading with a small dose of contrast agent, or reducing the flip angle (35°) [9, 15–17]. The last method is the simplest, and we have found it to be largely effective with gradient-echo sequences.

Treatment-Related Effects

Radiation Necrosis

Radiation therapy in patients with malignant gliomas usually consists of fractionated focal irradiation at a dose of 1.8–2.0 Gy per fraction, administered once daily for 5 days a week for 6 or 7 weeks, until a dose of 60 Gy is reached [2]. Radiation necrosis is a severe local tissue reaction to radiotherapy. It generally occurs 3–12 months after radiotherapy but can occur up to years and even decades later [18]. Its occurrence is related to the ir-

radiated brain volume and delivered dose of radiation, with a steep increase in occurrence when doses exceed 65 Gy in fractions of 1.8–2.0 Gy [19]. In adults, the reported incidence of radiation necrosis after radiotherapy for brain tumors ranges from 3% to 24% [20].

Pathology

The postulated mechanisms that may contribute to radiation-induced neurotoxicity include vascular injury, glial and white matter damage, effects on the fibrinolytic enzyme system, and immune mechanisms. Of these, although controversial, it is thought that the vascular injury is pivotal in the development of radiation-induced neurotoxic effects in the brain and precedes development of parenchymal changes in the brain. The endothelium is particularly susceptible to radiation damage, resulting in greater disruption of the blood-brain barrier. More chronic and permanent forms of endothelial damage account for the more classic changes, including thrombosis, hemorrhage, fibrinous exudates, telangiectasias, vascular fibrosis or hyalinization with luminal stenosis, and fibrinoid vascular necrosis [21].

Imaging

Conventional Imaging

Radiation necrosis most often occurs at the site of maximum radiation dose, usually in and around the tumor bed. The MRI features of radiation necrosis described by Kumar et al. [22] are a soap bubble- or Swiss cheese-like interior of the enhancing lesion, which occurs secondary to increased blood-brain barrier disruption and greater vulnerability to ischemic effects. This soap bubble pattern results from diffuse necrosis affecting the white matter and adjacent cortex and is seen as a diffusely enhancing lesion, with intermixed foci of necrosis. Compared with lesions showing the soap bubble pattern, Swiss cheese lesions are larger, more variable in size, and more diffuse. Also noted is an increase in the amount of vasogenic edema surrounding the enhancing lesion, likely reflecting greater breakdown of the blood-brain barrier. In contrast, corpus callosum involvement in conjunction with multiple enhancing lesions, with or without extension across the midline and subependymal spread, favors glioma progression [23]. However, the imaging appearance on the follow-up scan does not always show the appearance of radiation necrosis or tumor recurrence. At such times, advanced imaging studies can be used to dis-

tinguish these two entities. Bisdas et al. [24] recently showed that a K^{trans} cutoff value of greater than 0.19 resulted in 100% sensitivity and 83% specificity for diagnosing recurrent gliomas.

Pseudoprogression

In 2005, results from a randomized phase 3 trial indicated that the addition of temozolomide chemotherapy to radiation therapy for the treatment of newly diagnosed glioblastoma prolonged mean survival from 12.1 to 14.6 months [2]. An interesting phenomenon documented during the imaging surveillance of a few patients treated similarly was an increase in the contrast-enhancing lesion size followed by subsequent improvement or stabilization [18, 25]. This initial occurrence of increasing size of enhancement, which mimics tumor progression, is termed “pseudoprogression.” It is most often seen after concomitant radiotherapy-temozolomide but can also be seen after radiotherapy alone or in cases in which chemotherapy-infused wafers are placed in the surgical cavity [20]. It is seen in approximately 20% of patients treated with concomitant radiotherapy-temozolomide and is often seen in the 2- to 6-month period after chemoradiotherapy, with a median of approximately 3 months.

Pathology—Pseudoprogression is most likely induced by a pronounced local tissue reaction with an inflammatory component, edema, and abnormal vessel permeability [26]. Pathologically, pseudoprogression is found to correspond to gliosis and exaggerated reactive radiation-induced changes [27].

Clinical relevance—Preliminary studies have shown that the development of pseudoprogression seems to result in a better outcome and overall survival [28]. Pseudoprogression is therefore a favorable treatment response and not a treatment failure. Recognition of this entity therefore becomes important so that the patient continues with the ongoing treatment and does not enter a new treatment trial. Switching treatment trials in cases in which this entity is not recognized can pose two problems. The first and more important is that the patient may be switched from a trial that is working well to one that potentially might not, and the second is that, because pseudoprogression improves spontaneously, changing therapy can lead to an erroneous interpretation of efficacy of the new trial [4]. Furthermore, some patients, faced with the onerous news of “misdiagnosed” early treatment failure, might mistakenly elect to abandon further treatment [29].

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Conventional imaging—Pseudoprogression represents an exaggerated response to effective therapy [30]. Therefore, on imaging based solely on the Macdonald criteria, it can be misinterpreted as tumor progression. It is therefore essential to understand the concept of pseudoprogression. Pseudoprogression likely results from treatment-related cellular hypoxia, which results in expression of hypoxia-regulated molecules from tumor and surrounding cells, with subsequent increased vascular permeability or increased tumor enhancement [31]. It is also likely that the greater disruption of the blood-brain barrier must contribute to the increased enhancement. If this increased enhancement stabilizes or decreases on follow-up studies, it can be assumed to be pseudoprogression. If it worsens, it represents tumor progression.

Dynamic susceptibility contrast-enhanced perfusion MRI in evaluation of radiation necrosis or pseudoprogression—Sugahara et al. [32] prospectively evaluated 20 patients (heterogeneous patient population. astrocytomas grade II–IV, gangliogliomas, germinoma, primitive neuroectodermal tumor) in whom new enhancing lesions developed within irradiated regions with perfusion-sensitive contrast-enhanced MRI to distinguish tumor recurrence from treatment-related changes. They reported that an enhancing lesion with a normalized relative CBV ratio higher than 2.6 is suggestive of tumor recurrence, and a relative CBV value lower than 0.6 suggests non-neoplastic contrast-enhancing tissue. When the normalized relative CBV ratio is between 0.6 and 2.6, ^{201}Tl -SPECT may be useful in making the differentiation [32].

Barajas et al. [17] retrospectively evaluated 57 patients (glioblastoma) with progressive contrast enhancement within the lesion with DSC perfusion MRI to distinguish recurrent glioblastoma from radiation necrosis. They reported that the mean, maximum and minimum relative peak height and relative CBV were significantly higher ($p < 0.01$) in patients with recurrent glioblastoma than in patients with radiation necrosis. The mean, maximum, and minimum relative percentage of signal intensity recovery values were significantly lower ($p < 0.05$) in patients with recurrent glioblastoma than those with radiation necrosis. Of these measurements, a relative peak height value of 1.38 was most reliable in distinguishing tumor recurrence from radiation necrosis. Although relative CBV in cases of tumor recurrence showed a significantly higher mean relative CBV of 2.38 ± 0.87 than

in cases of radiation necrosis, which showed mean relative CBV of 1.57 ± 0.67 , there was still some degree of overlap between these two entities. The authors speculated that the overlap resulted from tumor heterogeneity and inherent shortcomings from a disrupted blood-brain barrier [17].

Hu et al. [33] prospectively evaluated 42 tissue specimens from 13 patients (high-grade gliomas [III and IV]) using threshold relative CBV values to distinguish recurrent tumor from posttreatment radiation effect. They reported that the treatment-related nontumoral group showed relative CBV values from 0.21 to 0.71, whereas the recurrent tumor group reported relative CBV values from 0.55 to 4.64. A threshold value of 0.71 optimized differentiation between the two groups with sensitivity of 91.7% and specificity of 100%.

Gasparetto et al. [34] retrospectively evaluated 30 patients (high-grade gliomas [III and IV]) with recurrent enhancing masses appearing after treatment with surgery and radiation, with or without chemotherapy, using relative CBV maps. They showed that a relative CBV threshold of 1.8 relative to normal-appearing white matter was most efficient in distinguishing masses with more than 20% malignant histologic features from those with 20% or fewer malignant histologic features [34].

Mangla et al. [35] retrospectively evaluated perfusion parameter changes in patients with glioblastoma before and 1 month after combined radiation and temozolomide therapy. They showed that a greater than 5% increase in relative CBV after treatment was a poor predictor of poor survival (median survival,

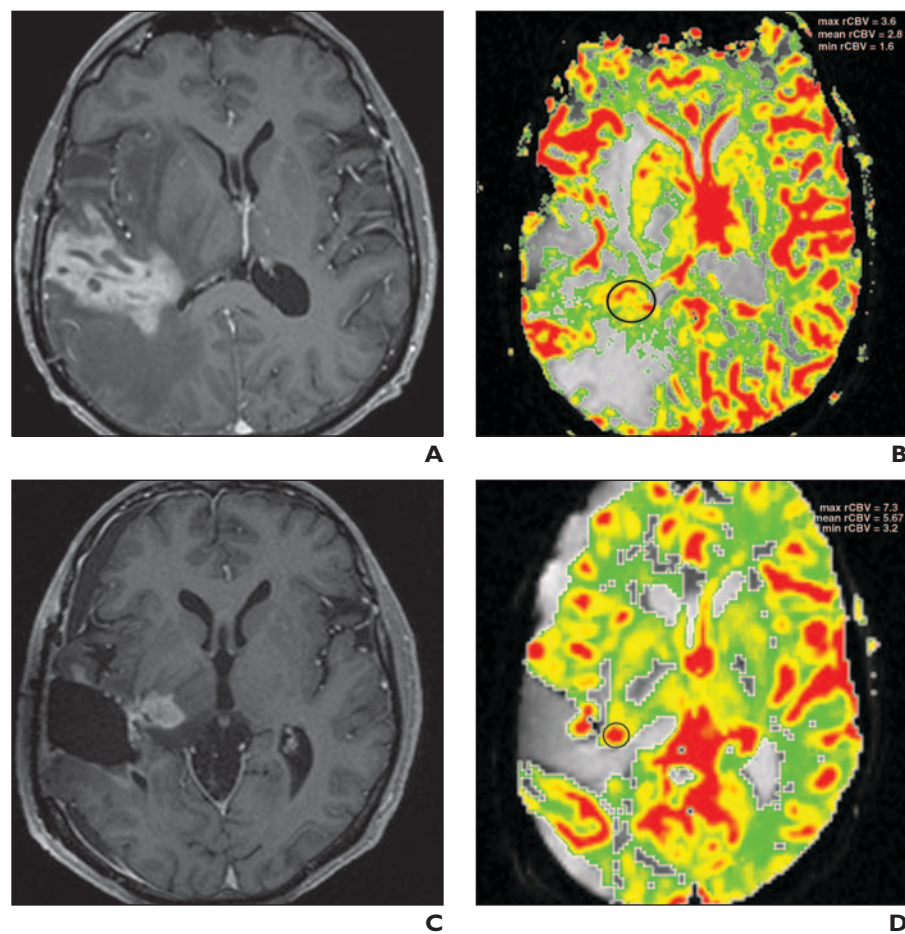


Fig. 1—63-year-old man with glioblastoma. **A**, Contrast-enhanced axial T1-weighted image shows enhancing lesion in right temporoparietal lobe. **B**, Dynamic susceptibility contrast-enhanced (DSC) perfusion MR image shows mean relative cerebral blood volume (rCBV) of 2.8 from tumor (circle). **C**, Follow-up study obtained 6 months after surgical resection and treatment with radiation therapy and temozolomide shows enhancing nodule along medial aspect of resected lesion. **D**, DSC perfusion MR image shows mean relative CBV (rCBV) of 5.67 from enhancing lesion (circle). Diagnosis: Recurrent glioblastoma.

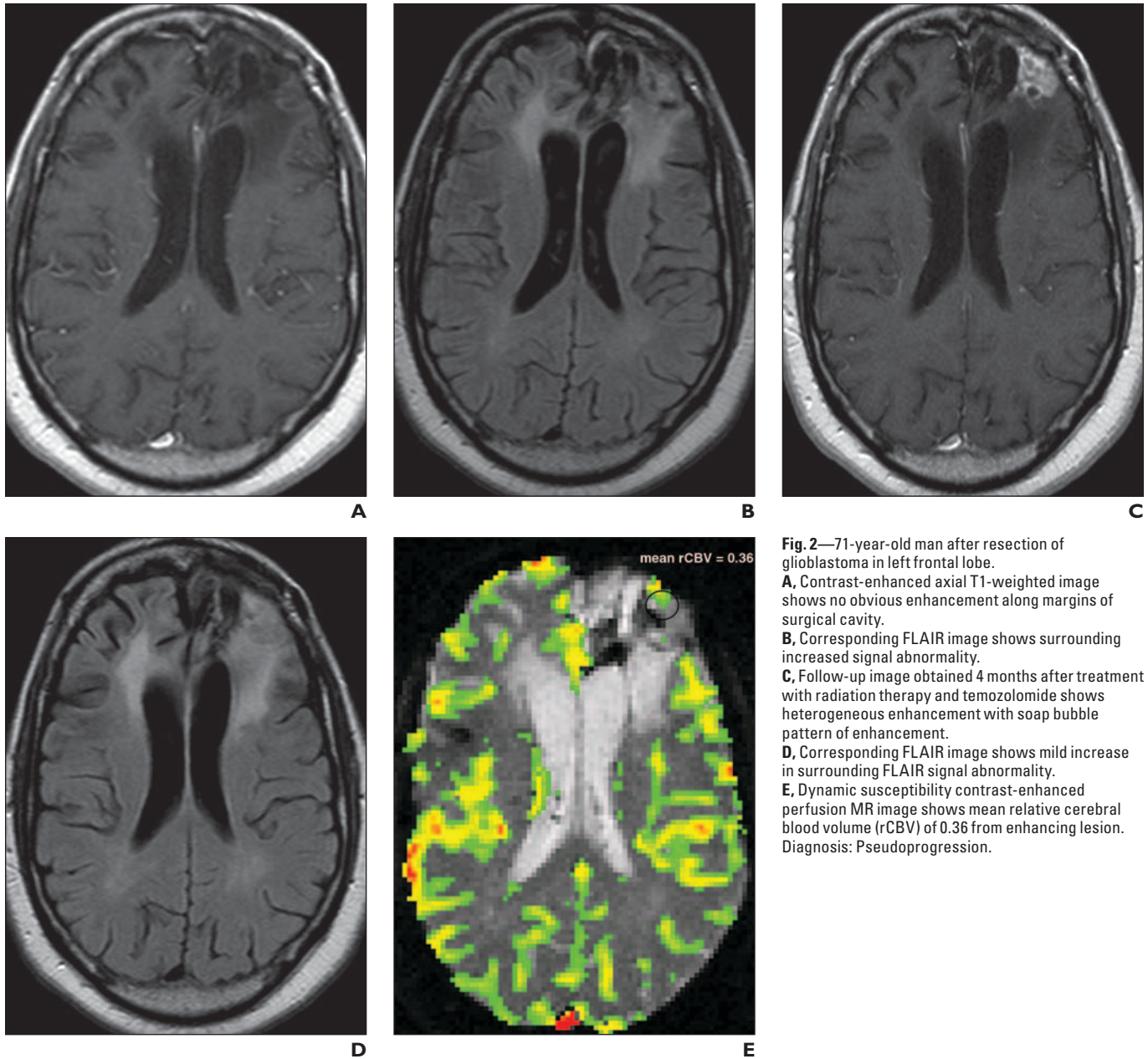


Fig. 2—71-year-old man after resection of glioblastoma in left frontal lobe. **A**, Contrast-enhanced axial T1-weighted image shows no obvious enhancement along margins of surgical cavity. **B**, Corresponding FLAIR image shows surrounding increased signal abnormality. **C**, Follow-up image obtained 4 months after treatment with radiation therapy and temozolomide shows heterogeneous enhancement with soap bubble pattern of enhancement. **D**, Corresponding FLAIR image shows mild increase in surrounding FLAIR signal abnormality. **E**, Dynamic susceptibility contrast-enhanced perfusion MR image shows mean relative cerebral blood volume (rCBV) of 0.36 from enhancing lesion. Diagnosis: Pseudoprogression.

235 days versus 529 days with decreased relative CBV). They also showed that patients with pseudoprogression had a mean decrease in relative CBV of 41%, whereas those with true disease progression showed a mean increase in relative CBV of 12% [35].

Kim et al. [36] analyzed the characteristics of perfusion MRI, ^{18}F FDG PET, and ^{11}C -methionine PET to help distinguish radiation necrosis from tumor recurrence. Ten patients with high-grade gliomas treated with radiotherapy with or without chemotherapy were included in the study. The authors concluded that a quantitative relative CBV value from perfusion MRI

was superior to the PET modalities in terms of distinguishing tumor recurrence from radiation necrosis. A relative CBV of 5.72 ± 1.77 was seen in patients with tumor recurrence versus a relative CBV 2.53 ± 0.81 in the pseudoprogression or radiation necrosis group, a statistically significant difference [36].

Although these studies show that an increase in the relative CBV value favors tumor recurrence and a decrease shows pseudoprogression (Figs. 1 and 2), there is still some degree of overlap between these two disease entities. Recent advances have tried to address this by introducing the concept of parametric response

map (PRM), which is a voxel-based imaging method of analysis applied to perfusion maps to quantify early hemodynamic alterations after treatment. PRM_{CBV} is a measure of the difference between serial relative CBV maps for each voxel within the gross target volume. Using a threshold value of change in relative CBV of 1.2 between the two studies, Tsien et al. [27] prospectively evaluated 27 patients treated with concurrent radiotherapy-temozolomide and showed that the PRM_{CBV} can be considered a potential biomarker to distinguish tumor recurrence from pseudoprogression. The authors also mention that standard individual

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measurements of relative CBV after treatment were not useful in distinguishing treatment-related change from tumor recurrence.

Gahramanov et al. [37] recently concluded that DSC MRI using a blood pool agent, such as ferumoxytol, provides a better monitor of tumor relative CBV than DSC MRI with

gadoteridol. Lesions showing enhancement on T1-weighted MRI with low-ferumoxytol relative CBV (0.7 ± 0.2) likely exhibit pseudo-progression, whereas high relative CBV (10.3 ± 3.4) favors tumor recurrence. Ferumoxytol is minimally extravasated even with blood-brain barrier disruption and should

therefore provide more accurate estimates of relative CBV than gadoteridol.

Association with MGMT (oxygen-6-methylguanine-DNA methyltransferase) promoter methylation status and pseudoprogression—Methylation of oxygen-6-methylguanine-DNA methyltransferase (MGMT) promoter

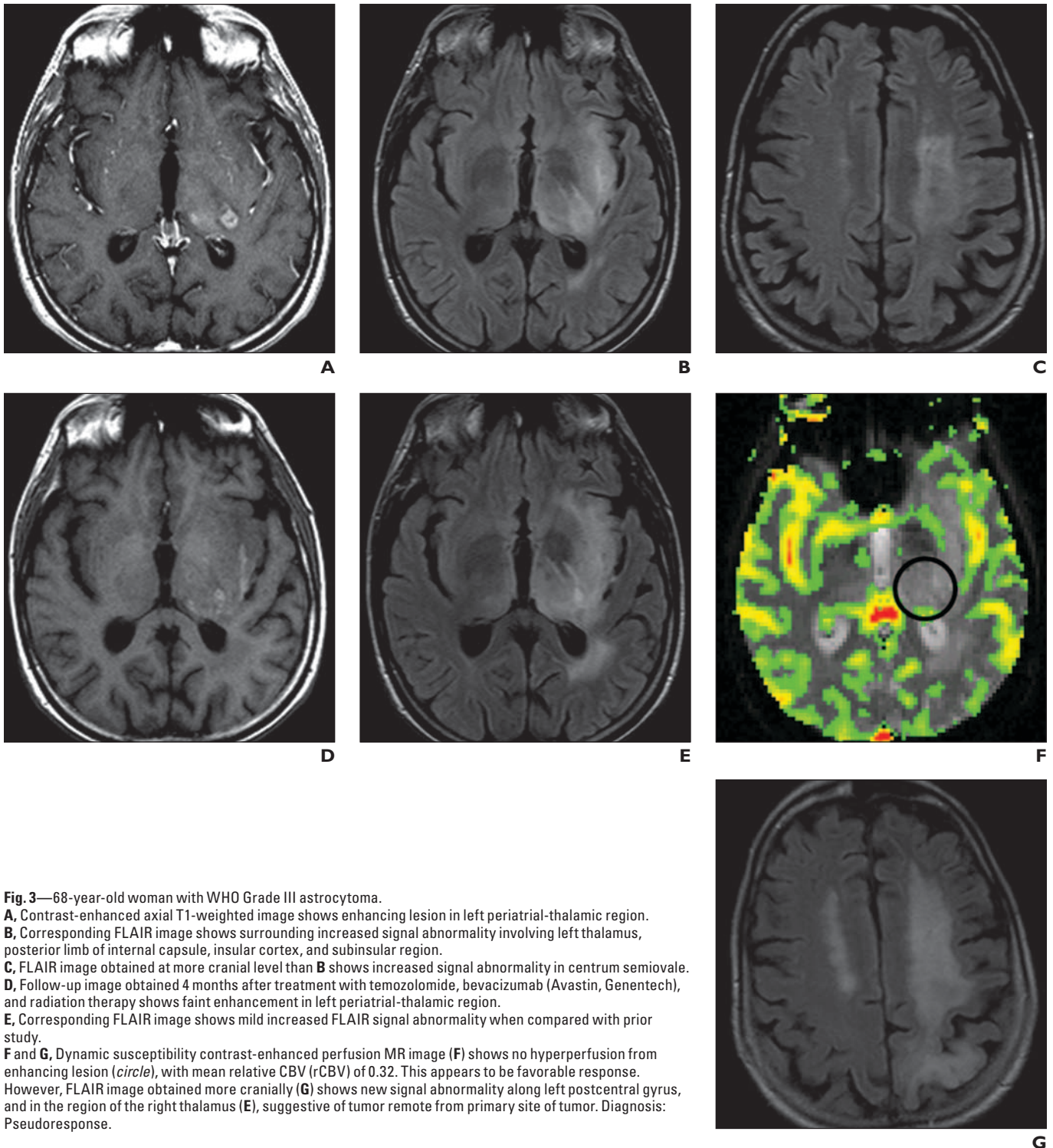


Fig. 3—68-year-old woman with WHO Grade III astrocytoma. **A**, Contrast-enhanced axial T1-weighted image shows enhancing lesion in left peritrial-thalamic region. **B**, Corresponding FLAIR image shows surrounding increased signal abnormality involving left thalamus, posterior limb of internal capsule, insular cortex, and subinsular region. **C**, FLAIR image obtained at more cranial level than **B** shows increased signal abnormality in centrum semiovale. **D**, Follow-up image obtained 4 months after treatment with temozolomide, bevacizumab (Avastin, Genentech), and radiation therapy shows faint enhancement in left peritrial-thalamic region. **E**, Corresponding FLAIR image shows mild increased FLAIR signal abnormality when compared with prior study. **F** and **G**, Dynamic susceptibility contrast-enhanced perfusion MR image (**F**) shows no hyperperfusion from enhancing lesion (*circle*), with mean relative CBV of 0.32. This appears to be favorable response. However, FLAIR image obtained more cranially (**G**) shows new signal abnormality along left postcentral gyrus, and in the region of the right thalamus (**E**), suggestive of tumor remote from primary site of tumor. Diagnosis: Pseudoprogression.

gene promoter is associated with a favorable prognosis in adult patients with glioblastoma treated with temozolomide [38, 39]. Kong et al. [40] prospectively assessed the maximum relative CBV in glioblastoma patients treated with concurrent radiotherapy-chemotherapy to distinguish treatment-related change from tumor recurrence and assess its relationship to the patient's *MGMT* status. They found that the mean relative CBV values for patients with stable disease was 1.29 (95% CI, 0.73–1.84); for tumor progression, 2.85 (95% CI, 1.99–3.70); and for pseudoprogression, 1.49 (95% CI, 1.04–1.93) [40]. In patients with glioblastoma with an unmethylated *MGMT* promoter, there was a significant difference of mean relative CBV between pseudoprogression and real progression (0.87 vs 3.25, $p = 0.009$), whereas in the methylated *MGMT* promoter group, no definite difference was observed between the two groups (1.56 vs 2.34, $p = 0.258$). On the basis of this work and the work by Brandes et al. [39], the authors propose that in patients with methylated *MGMT* status, and a mild increase in the mean rCBV, pseudoprogression should be considered first, and therefore there should be no change in the treatment regimen [40]. In contrast to this, in patients with unmethylated *MGMT*, the relative CBV measurement should be used to distinguish pseudoprogression from tumor recurrence. They propose that relative CBV greater than 1.47 in unmethylated *MGMT* status patients should be considered as worrisome for tumor progression and managed accordingly [40].

Pseudoresponse

The prognosis for patients with recurrent glioblastoma is poor, with a median overall survival of 3–6 months [41]. In the trial reported by Yung et al. [41], the response rate was 8% with a 6-month progression-free survival of 21% and a median progression-free survival of 12.4 weeks. In contrast, in 35 recurrent glioblastoma patients treated with bevacizumab and irinotecan, Vredenburgh et al. [42] showed the 6-month progression-free survival to be 46%, with a median progression-free survival of 24 weeks. The authors also documented that early MRI response to treatment as reflected by improvement in enhancement, secondary to antiangiogenic response to bevacizumab suggestive of pseudoresponse was predictive of long-term progression-free survival.

In 2009, on the basis of two historically controlled single-arm or noncomparative phase 2 trials, the FDA granted accelerated

approval of bevacizumab monotherapy for patients with glioblastoma with progressive disease after prior therapy [5, 43]. Bevacizumab, an anti-VEGF (vascular endothelial growth factor) antibody is an antiangiogenic agent and produces a rapid decrease in the degree of enhancement, sometimes within hours of beginning therapy. However, within the lesion bed, there is no true tumor reduction. Such an imaging appearance, which mimics a favorable treatment response, is therefore termed “pseudoresponse.”

Pathology and clinical relevance—Pseudoresponse results from a “normalization” of the blood-brain barrier by antiangiogenic agents. This response by the tumor bed is manifested on imaging as a reduction in the degree of enhancement, a reduction in the surrounding FLAIR signal abnormality, vasogenic edema, and mass effect. This radiologic response should be interpreted with caution because studies have shown that antiangiogenic agents produce a high imaging-based response rate but only a modest effect on overall survival [44]. It should also be noted that reversibility of this vascular normalization, with rebound enhancement and edema, was noted in patients requiring a “drug holiday” because of toxicity with a response after restarting the treatment [28]. Corticosteroids, which act to reestablish the blood-brain barrier, also have a profound impact on the area of enhancement, and diminution in the area of enhancement may be due to corticosteroids alone. Therefore, to determine a radiographic response to therapy, patients should be on the same or a lower dose of corticosteroids than the dose at the time of the pretreatment imaging study [45].

Conventional imaging—Pope et al. [46] showed that contrast-enhancing tumors in patients with recurrent gliomas shrank as early as 2 weeks after treatment with bevacizumab and carboplatin. Treatment seemed more effective for heterogeneously enhancing tumors compared with solid tumors. Norden et al. [47] showed that combination therapy with bevacizumab and chemotherapy provided long-term disease control in only a small subset of patients. However, the 6-month progression-free survival was much improved. Such a response also results in reduced symptoms (reduced mass effect), reduced steroid dependence (reduced vasogenic edema), and improved quality of life. However, an interesting finding in this study was that of a larger than expected number of patients showing diffuse infiltrating disease or distant disease at the

time of tumor progression after showing an initial beneficial response (Fig. 3). This was seen as diffuse hyperintensity on T2-weighted or fluid-attenuated inversion recovery (FLAIR) MRI sequences rather than abnormal enhancement. It was therefore hypothesized that bevacizumab treatment controls local tumor growth but promotes distant and diffuse recurrences [47]. A plausible mechanism proposed is that VEGF-induced angiogenesis blockade facilitates cooption of the normal vasculature and tumor invasion [48, 49]. Desjardins et al. [50] also showed similar findings wherein there was overall improvement in the 6-month progression-free survival (55%) and 6-month overall survival (79%), with no significant change in the overall outcome in recurrent high-grade glioma patients treated with bevacizumab and irinotecan.

Dynamic susceptibility contrast-enhanced perfusion MRI in evaluation of pseudoresponse—Using perfusion imaging, as shown by Sorensen et al. [51] and Emblem et al. [52], the pseudoresponse produced can be quantified and correlated to progression-free survival and overall survival. Sorensen et al. postulated that the extent of vascular normalization by anti-VEGF therapy should be able to predict the clinical outcome in glioblastoma patients treated with anti-VEGF therapy. To this end, the authors combined three distinct but related parameters, all associated with “normalization” of the brain tumor vasculature— K^{trans} , microvessel volume, and circulating collagen—into a single measure termed “vascular normalization index.” They correlated this particular index to overall survival and progression-free survival in recurrent glioblastoma patients treated with cediranib (a pan-VEGF receptor tyrosine kinase inhibitor). They showed that a greater reduction in K^{trans} was seen in patients with increased progression-free survival and overall survival; a greater decrease in the relative CBV of the tumor microvessels was associated with an increased overall survival; a greater decrease in the CBV of tumor microvessels after one dose of cediranib was seen in the glioblastoma patients with increased overall survival; and a greater increase in collagen IV levels in plasma was detected in patients with extended progression-free survival. Using these indexes collectively and calculating the vascular normalization index, the authors concluded that the vascular normalization index correlated with progression-free survival ($\rho = 0.54$, $p = 0.004$) and overall survival ($\rho = 0.6$, $p = 0.001$), progression-free survival (Spearman

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$\rho = 0.60$, $p = 0.001$), and overall survival ($\rho = 0.54$, $p = 0.004$). Recently, Emblem et al. [52] hypothesized that a double-echo DSC MRI acquisition combined with contrast agent leakage correction can help obtain a much easier vascular normalization index parameter. Using this technique, the authors found that in 30 patients with recurrent glioblastomas treated with cediranib, the vascular normalization index parameter correlated with progression-free survival and overall survival. A higher (positive) vascular normalization index value indicated improved progression-free survival ($\rho = 0.50$, $p = 0.005$) and overall survival ($\rho = 0.55$, $p = 0.002$) [52].

We recently studied 26 recurrent glioma patients treated with bevacizumab and irinotecan. First-pass dynamic T2* weighted data were analyzed using both conventional dynamic contrast-enhanced analysis and the adiabatic tissue homogeneity model that, in addition to estimates of plasma volume and K^{trans} , yields estimates of the permeability surface area product. Although all parameters fell with treatment, only the fall in plasma volume with treatment was significant ($p < 0.001$). In another study of 28 patients with similar treatment, we found that progression-free survival at 6 months after Avastin was three of 14 (21.4%) with posttreatment relative CBV > 1.75 and nine of 14 (64.3%) with relative CBV < 1.75 ($p = 0.05$, Fisher exact test). These two findings suggest that measures of vascular volume may be a more reliable means of identifying pseudoresponse than measures of permeability, possibly due to the inherent nonspecificity of the latter.

Conclusion

The Macdonald criteria should no longer be used in evaluation of radiotherapy or chemotherapy managed high-grade gliomas. Pseudoprogression and pseudoresponse are entities that should always be considered in an appropriate clinical setting.

Pseudoprogression is common and represents approximately one third of all high-grade gliomas treated with concurrent radiotherapy-temozolomide. Enlargement of enhancing lesions with associated worsening edema after treatment (median interval of 3 months) is not always tumor recurrence. Follow-up studies should be obtained to document further evaluation of these lesions; a decrease in the extent of enhancing lesion should be suggestive of pseudoprogression. This occurrence improves the overall survival of these patients. It is more often seen in patients with methylated *MGMT*

promoter gene status. Most pseudoprogression patients are asymptomatic, whereas most tumor recurrent patients are symptomatic. Presence of the Swiss cheese or soap bubble pattern of enhancement with low relative CBV values should favor the diagnosis of pseudoprogression.

Pseudoresponse is often seen in recurrent glioma patients treated with antiangiogenic therapy, such as bevacizumab (Avastin) and cediranib. Local response to tumor growth is controlled, but diffuse infiltration and distant metastases are common after this treatment. Pseudoresponse significantly improves 6-month progression-free survival, but it is debatable whether it changes the overall survival. Use of indices, such as the vascularization normalization index, can help predict those patients who will respond better to treatment.

The treatment of high-grade glioma is a complex interplay between viable tumor cells, blood-brain barrier integrity, hypoxia, multiple VEGFs, tumoral neoangiogenesis, and vascular cooption. Our understanding of treatment-associated reactions, including the possibility of recurrence, continues to grow. However, we still cannot always determine with certainty, especially prospectively, whether the imaging appearance is suggestive of tumor recurrence or treatment-related change. Perfusion MRI, as described, does shed some additional light on this subject in terms of evaluation and predicting survival and should be a part of the imaging standard of care for these patients. However, there is still a lot of work that needs to be done to reliably distinguish tumor recurrence from treatment-induced change.

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