

## PERFUSION MAGNETIC RESONANCE IMAGING PREDICTS PATIENT OUTCOME AS AN ADJUNCT TO HISTOPATHOLOGY: A SECOND REFERENCE STANDARD IN THE SURGICAL AND NONSURGICAL TREATMENT OF LOW-GRADE GLIOMAS

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**OBJECTIVE:** To determine whether relative cerebral blood volume (rCBV) can predict patient outcome, specifically tumor progression, in low-grade gliomas (LGGs) and thus provide a second reference standard in the surgical and postsurgical management of LGGs.

**METHODS:** Thirty-five patients with histologically diagnosed LGGs (21 low-grade astrocytomas and 14 low-grade oligodendrogliomas and low-grade mixed oligoastrocytomas) were studied with dynamic susceptibility contrast-enhanced perfusion magnetic resonance imaging. Wilcoxon tests were used to compare patients in different response categories (complete response, stable, progressive, death) with respect to baseline rCBV. Log-rank tests were used to evaluate the association of rCBV with survival and time to progression. Kaplan-Meier time-to-progression curves were generated. Tumor volumes and CBV measurements were obtained at the initial examination and again at follow-up to determine the association of rCBV with tumor volume progression.

**RESULTS:** Wilcoxon tests showed patients manifesting an adverse event (either death or progression) had significantly higher rCBV ( $P = 0.003$ ) than did patients without adverse events (complete response or stable disease). Log-rank tests showed that rCBV exhibited a significant negative association with disease-free survival ( $P = 0.0015$ ), such that low rCBV values were associated with longer time to progression. Kaplan-Meier curves demonstrated that lesions with rCBV less than 1.75 ( $n = 16$ ) had a median time to progression of  $4620 \pm 433$  days, and lesions with rCBV more than 1.75 ( $n = 19$ ) had a median time to progression of  $245 \pm 62$  days ( $P < 0.005$ ). Lesions with low baseline rCBV ( $<1.75$ ) demonstrated stable tumor volumes when followed up over time, and lesions with high baseline rCBV ( $>1.75$ ) demonstrated progressively increasing tumor volumes over time.

**CONCLUSION:** Dynamic susceptibility contrast-enhanced perfusion magnetic resonance imaging may be used to identify LGGs that are either high-grade gliomas, misdiagnosed because of sampling error at pathological examination or that have undergone angiogenesis in the progression toward malignant transformation. This suggests that rCBV measurements may be used as a second reference standard to determine the surgical management/risk-benefit equation and postsurgical adjuvant therapy for LGGs.

**KEY WORDS:** Brain, Low-grade gliomas, Perfusion magnetic resonance imaging, Survival

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The management of patients with low-grade gliomas (LGGs) remains controversial and is variable from one center to another (20). There are numerous approaches, which range from serial imaging/observation to early tissue diagnosis/gross total resection followed by radiation, and more recently, chemotherapy. As a consequence, there are very

little prospective data on outcomes for end points such as time to progression, malignant transformation, mortality, and morbidity in LGGs (2). This further compounds the difficulty, evident from the literature, in determining optimal treatment strategies. One of the few large prospective clinical trials of LGGs determined significant prognostic factors to

include the extent of surgical resection, histological features, tumor size, and age (29). Although the current approach to therapy for LGG is controversial, the Joint Section on Tumors of the American Association of Neurological Surgeons/Congress of Neurological Surgeons has provided practice guidelines, (4) with the only firm recommendation being that biopsy is the standard of practice whether observation or further treatment is recommended.

The current reference standard for determining glioma grade is histopathological assessment. However, the limitations of histopathology obtained are well known: 1) because only a few small samples of tissue are assessed, particularly from stereotactic biopsy, the most malignant portion of a tumor may not be sampled (sampling error); 2) it may be difficult to obtain a range of samples if the tumor is inaccessible to the surgeon (eloquent brain); 3) there are numerous classification/grading systems used between different institutions; 4) interpathologist and intrapathologist variability (7, 23); 5) the dynamic nature of central nervous system tumors, with at least 50% dedifferentiating into more malignant grades (9, 10, 29). As a result, therapy and clinical outcome based on histopathologic assessment of LGGs may not be best for determining surgical and postsurgical therapy to optimize overall survival.

The differentiation of an LGG from a higher-grade glioma is based primarily on increased cell nuclear pleomorphism and vascular hyperplasia (8, 19, 25). It has been shown that microvessel density and vascular endothelial growth factor expression are independent prognostic markers of survival in LGGs and that LGGs may represent a spectrum of tumors with differing propensities to undergo malignant transformation that is at least partly based on their inherent angiogenic potential (1). Relative cerebral blood volume (rCBV) measurements from dynamic susceptibility contrast perfusion magnetic resonance imaging (DSC MRI) have been shown to be closely correlated with histological measurements of microvascular density in gliomas (6). rCBV measurements can provide physiological information about neovascularity and angiogenesis of the entire brain and have been shown to correlate well with glioma grade in humans (12–16, 31, 34). DSC MRI may be performed on the entire brain, thus helping to overcome some of the limitations of histopathological examination.

The purpose of this study was to determine whether rCBV measurements can be used to predict patient outcome, specifically tumor progression in LGGs, and whether those predictions are more accurate than those obtained by histological assessment. We propose a new algorithm that includes rCBV as a second reference standard in the surgical management of LGGs.

## PATIENTS AND METHODS

### Patient Population

Approval for this study was obtained from the Institutional Board of Research Associates. The patients were not required

to provide informed consent because the studies represented part of their clinical evaluation, and a retrospective waiver of consent was obtained for review of the images and charts. Thirty-five consecutive patients with LGGs (World Health Organization Grade II) were drawn from our database and retrospectively reviewed. There were 23 male patients and 12 female patients (median age, 39 yr; range, 4–80 yr). Pathological specimens had been obtained by either stereotactic resection ( $n = 21$ ) or stereotactic-guided subtotal resection/biopsy ( $n = 14$ ) performed by one of two surgeons (JG, PJK). Histopathologic evaluation was performed by an experienced neuropathologist (DZ) and based on the World Health Organization Grade 4 tier classification of gliomas (11): Grade II, low-grade astrocytoma ( $n = 21$ ); Grade II, low-grade oligoastrocytoma ( $n = 1$ ); and Grade II, low-grade oligodendroglioma ( $n = 13$ ). These patients were assessed by their neurosurgeon/neuro-oncologist at 3-month intervals for an average of 4.2 years (range, 1–12.6 yr). At each follow-up, conventional MRI and DSC MRI were performed. Volume measurements of T1 enhancement (designated T1 volume) and T2 signal hyperintensity (designated T2 volume) and rCBV measurements were calculated (see below). Each patient was assigned to a different clinical response category on the basis of data obtained by reviewing the clinical charts and MRI findings. The four categories, based in part on the methodology described by Levin et al. (17), were complete response, stable disease, progressive disease, and death. A complete response was defined as an MRI scan with no visible tumor and no new neurological deficit. Stable disease was defined as no change in the patient's neurological examination, Karnofsky score, and a <25% change in either the T1 and/or T2 volume on MRI. Progressive disease was defined as a decline in the neurological status or Karnofsky score, or an increase in either the T1 and/or T2 volume by >25% on MRI. MRI perfusion data were not used to segregate patients into different clinical response groups.

### Conventional MRI and Tumor Volume Measurements

Imaging was performed on 1.5-Tesla systems (Siemens Vision or Symphony; Siemens AG, Erlangen, Germany). A localizing sagittal T1-weighted image was obtained followed by nonenhanced axial T1-weighted spin echo (repetition time/echo time [TR/TE], 600/14 ms), axial fluid-attenuated inversion recovery (9000/110/inversion time [TI] 2500), and T2-weighted (3400/119) images. Postcontrast axial T1-weighted imaging was performed after the acquisition of the DSC MRI data. Regions of interest (ROI) were drawn around the enhancing region of the tumor and around the hyperintense region on T2-weighted or fluid-attenuated inversion recovery images to generate tumor volumes using Medical Image Display and Analysis System software (35). Each ROI was independently checked for accuracy by the other observer and any changes were made by joint agreement. The observers were experienced senior board certified neuroradiologists (ML, SO).

## Dynamic Susceptibility-weighted, Contrast-enhanced MRI

DSC MRI scans were acquired with a gradient echo echo-planar imaging sequence during the first pass of a standard dose (0.1 mmol/kg) bolus of gadopentetate dimeglumine (Magnevist; Berlex Laboratories, Wayne, NY). Seven to 10 slices were positioned to cover the tumor based on T2-weighted and fluid-attenuated inversion recovery images. Imaging parameters were: TR/TE, 1000/54; field of view, 230 × 230 mm; section thickness, 5 mm; matrix, 128 × 128; in-plane voxel size, 1.8 × 1.8 mm; interslice gap, 0 to 30%; flip angle, 30°; signal bandwidth, 1470 Hz/pixel. Contrast was injected at a rate of 5 ml/s followed by a 20-ml bolus of saline at 5 ml/s. The injection rate was 5 ml/s in all patients, except for the three patients in the 0 to 9-year age group, where the injection rate was reduced to 3 ml/s. A total of 60 images were acquired at 1-second intervals with the injection occurring at the fifth image, so that the bolus would typically arrive at the 15th to 20th image.

## rCBV Measurements

The procedure used to calculate rCBV from the DSC MRI data is based on standard algorithms that have been described previously (12, 26, 27). Data processing was performed on a Unix workstation with programs developed in-house using C and IDL programming languages. Color overlay maps of rCBV were calculated. To improve signal to noise, however, the rCBV measurements used in this study were calculated from ROIs, placed in regions of highest perfusion seen on the rCBV color overlay maps. Four separate ROI measurements were made, and the maximum value was recorded. It has been demonstrated that this method for the measurement of maximal abnormality provides the highest intraobserver and interobserver reproducibility in rCBV measurements (36). To minimize confounding factors in rCBV analysis, the size of the ROIs was kept constant (radius, 3.6 mm). rCBV measurements were obtained by a board certified neuroradiologist with more than 5 years of experience in perfusion data acquisition at our institution (ML).

## Statistical Methods

Means, standard deviations, and medians of rCBV measurements for patients in each clinical response category (complete response, stable, progressive, death) were obtained. Wilcoxon tests were used to compare patients in different clinical response categories with respect to baseline rCBV. Log-rank tests were used to evaluate the association of rCBV with time to progression, defined as the time from the initial surgical diagnosis to the time of decline in the neurological status, Karnofsky score, or an increase in tumor size by >25% on MRI. It is noted that patients who died of disease provided uncensored times to progression, whereas data for those patients with complete response and stable disease at the time of most recent follow-up were right censored. Patients were divided into two groups, low and high rCBV, using a threshold

value of 1.75. This threshold has been found to give the optimal sensitivity and specificity for differentiating LGGs from high-grade gliomas (HGGs) in a logistic regression analysis of 120 high-grade and 40 low-grade gliomas (14). Kaplan-Meier survival curves and the log-rank test were used to characterize and compare the high and low rCBV groups in terms of time to progression. Binary logistic regression was used to determine whether age, sex, resection versus biopsy, presence or absence of enhancement, tumor volume, or CBV were associated with an adverse event (progression or death).

Least squares regression was conducted to examine the association of rCBV with changes in T1 and T2 volumes after adjusting for the potential confounding effects of age and sex. The regression analyses used the change in T1 or T2 volume as the dependent variable and considered baseline rCBV and the change in rCBV as linear numeric predictors in separate analyses. In each case, the model included age and sex as fixed classification factors. The analyses were conducted both with and without inclusion of terms representing the interaction of rCBV with age and sex as well as with and without deletion of the data from those with an inordinately high increase in both T1 and T2 volume. All statistical computations were carried out using SAS System for Windows software, version 9.0 (SAS Institute, Inc., Cary, NC), and results were declared statistically significant at the two-sided 5% comparison-wise significance level (i.e.,  $P < 0.05$ ).

## RESULTS

The patient demographics, histological results, baseline rCBV, clinical response, and a summary of the treatment protocols are shown in *Table 1*. The mean, standard deviation, and median of rCBV for patients in each clinical response category are shown in *Table 2*. There were 16 LGGs with low baseline rCBV (<1.75) and 19 LGGs with a high baseline rCBV (>1.75).

### Clinical Response

Wilcoxon tests used to compare patients in different clinical response categories (complete response, stable, progressive, death) indicate that patients with stable disease could not be distinguished from those manifesting complete response ( $P = 0.617$ ), and patients who died of disease could not be discriminated from those exhibiting progression ( $P = 0.738$ ). However, patients manifesting an adverse event (either death or progression) had significantly higher rCBV ( $P = 0.003$ ) than did patients without adverse events.

On the basis of log-rank tests, neither age ( $P = 0.333$ ) nor gender ( $P = 0.172$ ) was significantly associated with time to progression. However, rCBV exhibited a significant negative association with disease-free survival ( $P = 0.001$ ), such that low rCBV values were associated with longer times to progression. The Kaplan-Meier survival plots for time to progression (*Fig. 1*) indicate that lesions with rCBV < 1.75 ( $n = 16$ )

**TABLE 1. Patient demographics, histological results, baseline relative cerebral blood volume, clinical outcome, and treatment protocols<sup>a</sup>**

Patient no.	Age (yr)/sex	Histological results	Baseline rCBV	Clinical outcome	Surgery	Radiation <sup>b</sup>
1	34/M	LGO	1.33	S	Resection	None
2	41/F	LGO	1.42	S	Biopsy	None
3	26/M	LGO	1.24	S	Resection	None
4	57/M	LGA	1.42	S	Resection	Yes
5	4/F	LGA	1.15	S	Resection	Yes
6	28/F	LGA	1.26	S	Resection	None
7	27/M	LGA	1.24	CR	Biopsy	Yes
8	40/F	LGA	1.39	CR	Resection	Yes
9	52/M	LGA	1.74	S	Biopsy	None
10	26/M	LGA	0.56	S	Resection	Yes
11	50/F	LGO	1.02	S	Resection	Yes
12	28/M	LGO	1.53	CR	Biopsy	Yes
13	41/M	LGA	0.37	P	Resection	Yes
14	68/M	LGA	0.56	P	Resection	Yes
15	42/F	LGO	1.48	CR	Resection	Yes
16	47/M	LGA	1.44	D	Resection	Yes
17	44/M	LGA	4.51	D	Biopsy	Yes
18	40/M	LGA	5.89	P	Resection	Yes
19	80/M	LGO	3.21	P	Biopsy	None
20	44/F	LGA	2.08	P	Resection	None
21	14/M	LGA	2.37	P	Resection	Yes
22	11/M	LGA	5.16	S	Resection	Yes
23	49/M	LGOA	5.81	P	Biopsy	Yes
24	39/M	LGA	3.37	P	Resection	Yes
25	33/M	LGO	2.00	S	Biopsy	Yes
26	65/M	LGA	3.09	P	Biopsy	Yes
27	34/M	LGO	3.68	P	Resection	None
28	9/F	LGA	2.73	P	Biopsy	None
29	53/M	LGA	4.29	D	Resection	Yes
30	27/M	LGO	2.61	P	Biopsy	Yes
31	4/F	LGO	1.88	S	Resection	None
32	33/M	LGO	2.74	S	Resection	None
33	52/F	LGO	1.75	S	Biopsy	None
34	69/F	LGA	5.96	P	Biopsy	None
35	54/F	LGA	2.12	S	Biopsy	None

<sup>a</sup> rCBV, relative cerebral blood volume; M, male; LGO, low-grade oligodendroglioma; S, stable; F, female; LGA, low-grade astrocytoma; CR, complete response; P, progressive; D, death; LGOA, low-grade oligoastrocytoma.

<sup>b</sup> Average dose of conformal fractionated external photon beam radiation was 58.3 Gy (range, 54.0–63.0 Gy).

had a median time to progression of  $4620 \pm 433$  days, and lesions with rCBV  $> 1.75$  ( $n = 19$ ) had a median time to progression of  $245 \pm 62$  days ( $P < 0.005$ ).

Binary logistic regression indicated that neither patient age ( $P = 0.141$ ) nor sex ( $P = 0.267$ ) were significant predictors of an adverse event (progression or death), whereas rCBV was a significant predictor of adverse outcomes both with and without adjustment for age and sex ( $P = 0.027$  and  $0.012$ , respectively). As a predictor of adverse events, rCBV was estimated to have an odds ratio of 2.38 (95% confidence interval, 1.21–4.68), with 81.3% (13/16) of all adverse events experienced by patients having rCBV  $> 1.75$ . Using the Cox proportional

hazards model, rCBV was estimated to have a hazards ratio of 1.49 (95% confidence interval, 1.14–1.94). This was significantly associated with time to progression both with and without adjustment for age and gender ( $P = 0.011$ ,  $0.0029$ , respectively).

### MRI Volume Measurements

Forty-six percent of the LGGs enhanced on T1-weighted imaging ( $n = 16$ ), and the remainder did not enhance after contrast administration on the initial MRI. Eight of these non-enhancing lesions developed contrast enhancement on

DISCUSSION

The management of LGGs remains a diagnostic and therapeutic challenge. Although stereotactic biopsy or a limited resection is the current reference standard for confirming the diagnosis for patients with an imaging diagnosis of LGG, there are inherent limitations with the technique and interpretation. In particular, because only a few small samples of tissue

TABLE 2. Mean, standard deviation, and median of relative cerebral blood volume for patients with pathologically proven low-grade gliomas in each clinical response category<sup>a</sup>

Clinical response	Mean rCBV	SD	Median rCBV
Complete response	1.41	0.13	1.43
Stable	1.77	1.07	1.42
No adverse event: CR + S (n = 19)	1.70	0.96	1.42
Progressive	3.21	1.81	3.09
Death	3.41	1.71	4.29
Adverse event: D + P (n = 16)	3.25	1.74	3.15

<sup>a</sup> rCBV, relative cerebral blood volume; SD, standard deviation; CR, complete response; S, stable; P, progressive; D, death.

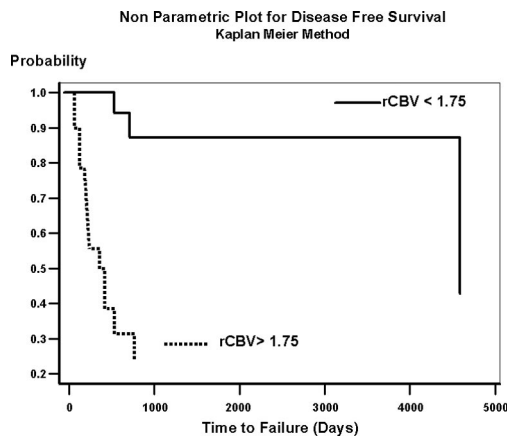


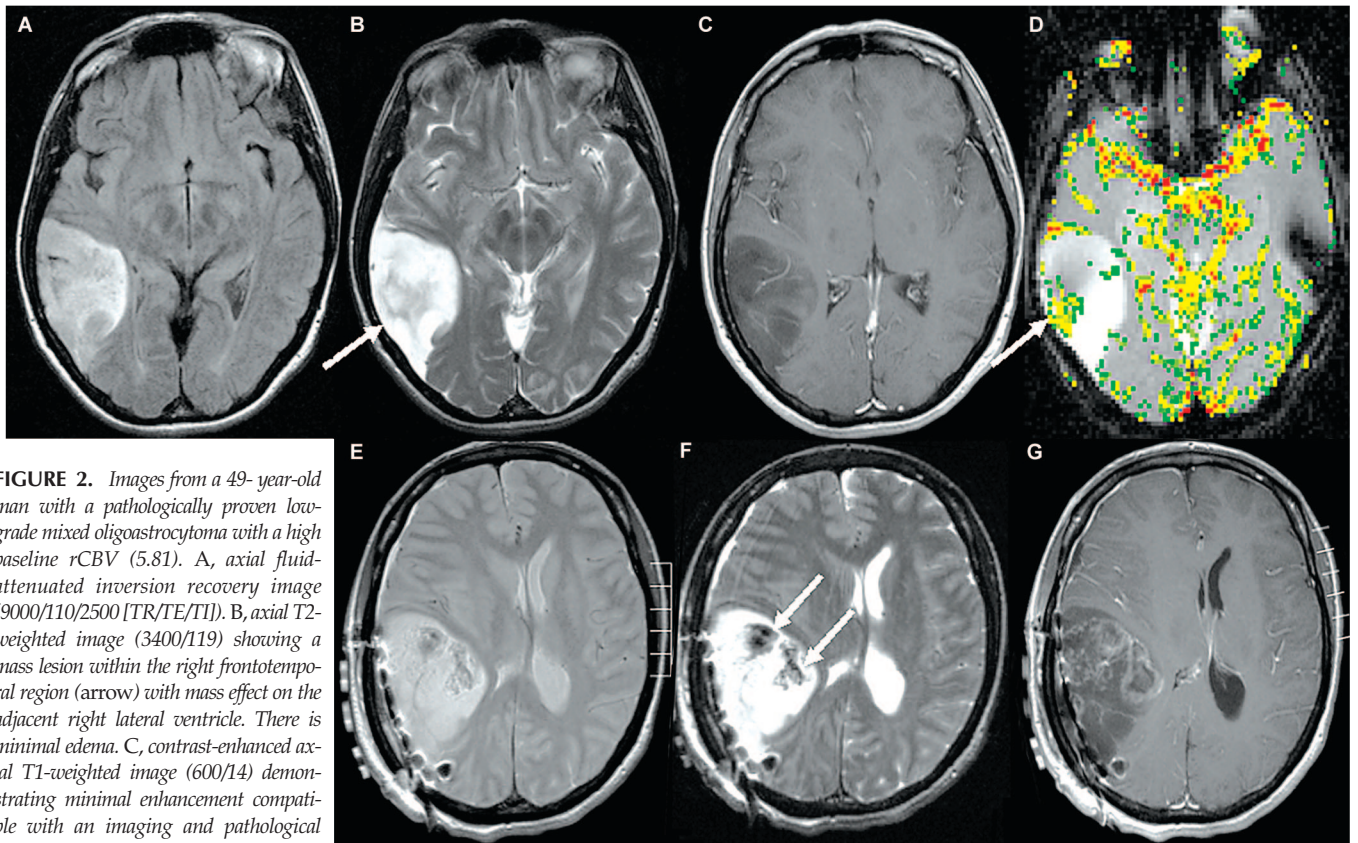
FIGURE 1. Kaplan-Meier survival curves for demonstrating the probability of time to progression at the most recent clinical follow-up. LGGs with rCBV < 1.75 had a median time to progression of 4620 ± 433 days (black solid curve which is far right shifted). LGGs with rCBV > 1.75 had a median time to progression of 245 ± 62 days (black dashed curve which is far left shifted; P < 0.005). The data suggest that baseline rCBV may be a stronger predictor of patient outcome than the initial histopathologic diagnosis, because if these were all true LGGs, the median time to progression would be much longer than 245 days (8 mo).

follow-up MRI. Least squares regression demonstrated no significant association between baseline rCBV and changes in T1 or T2 volume (P > 0.14). However, lesions with low baseline rCBV (<1.75) demonstrated stable tumor volumes when followed over time. Lesions with higher baseline rCBV (>1.75) demonstrated progressively increasing tumor volumes over time (Figs. 2 and 3). LGGs with low baseline rCBV demonstrated an rCBV of 1.20 ± 0.39 (mean ± standard deviation) initially and 1.52 ± 0.81 at follow-up (P = 0.36). LGGs with high baseline rCBV demonstrated rCBV of 3.42 ± 1.44 initially and 5.06 ± 2.95 at follow-up (P < 0.05). There was also no association between resection versus biopsy, nor the presence/absence of contrast enhancement or tumor volume, with time to progression, with P values of 0.312, 0.285, and 0.138, respectively.

are assessed, the most malignant portion of a tumor may not be sampled (sampling error). This problem can be exacerbated when the tumor is inaccessible to the surgeon. Jackson et al. (10) compared diagnoses based on initial biopsy and subsequent resection in 81 glioma patients and found discrepant results in 49% of cases. Furthermore, after biopsy, it is not uncommon to have significant intraobserver and interobserver variability (7, 23). The decision to resect surgically, to administer radiotherapy, to administer chemotherapy, or to observe the patient is confounded by this uncertainty in the histopathologic diagnosis. In this study, we have demonstrated that rCBV measurements may be a better predictor of tumor progression than initial histopathologic interpretation and can be used as a useful adjunct. This may be caused by sampling error or interpathologist and intrapathologist variability, but it is also possible that rCBV measurements are revealing changes in microvascular density that precede malignant transformation (1).

Neurosurgical intervention is indicated in LGGs to establish a diagnosis, to resect a seizure focus, to alleviate symptoms from mass effect, hydrocephalus, or hemorrhage, and to decrease the volume of neoplastic cells, which could undergo malignant degeneration. The most common cause of death in patients with LGG is dedifferentiation into a higher-grade glioma, and hence the goal for the neurosurgeon whenever possible is to achieve maximal surgical resection (21). Based on the results of five prospective clinical trials of 1600 patients with LGGs, the important prognostic factors for predicting outcome in LGGs are the extent of surgical resection, age, histological results, and size of the lesion (29, 30, 32, 33). Of these, the extent of surgical resection is the only independent factor that can be altered by the neurosurgeon. Surgical decision-making is a risk and benefit analysis, which becomes even more pertinent in neurosurgery, where the risks are greater and the benefits sometimes uncertain. Hence an objective, reproducible technique such as perfusion MRI, which can alter the risk-benefit equation, becomes very important.

The results of this study suggest that DSC MRI, in particular rCBV measurements, may be a useful tool in the management of LGGs. Currently, surgical options for LGG are determined in part by whether patients are considered to be high risk: age



**FIGURE 2.** Images from a 49-year-old man with a pathologically proven low-grade mixed oligoastrocytoma with a high baseline rCBV (5.81). A, axial fluid-attenuated inversion recovery image (9000/110/2500 [TR/TE/TI]). B, axial T2-weighted image (3400/119) showing a mass lesion within the right frontotemporal region (arrow) with mass effect on the adjacent right lateral ventricle. There is minimal edema. C, contrast-enhanced axial T1-weighted image (600/14) demonstrating minimal enhancement compatible with an imaging and pathological diagnosis of LGG. D, gradient-echo (TR/TE, 1000/54) axial DSC MRI image with rCBV color overlay map showing a lesion with high initial perfusion with an rCBV of 5.81 (arrow), more in keeping with an HGG than an LGG. E, MRI at 71 days (18 wk) follow-up. Axial proton density image (4790/14). F, axial T2-weighted image (8730/94) showing an increase in tumor volume and volume of T2 signal abnormality by 66.97 cm<sup>3</sup>. There is now increasing mass effect on the right lateral ventricle. There are also blood products within the lesion from blood-brain barrier compromise (arrows). G, contrast-enhanced axial T1-weighted image (600/14) demonstrating new contrast enhancement with an increase in enhancing tumor volume by 30.23 cm<sup>3</sup>. Final histopathologic diagnosis after stereotactic resection was an anaplastic oligoastrocytoma.

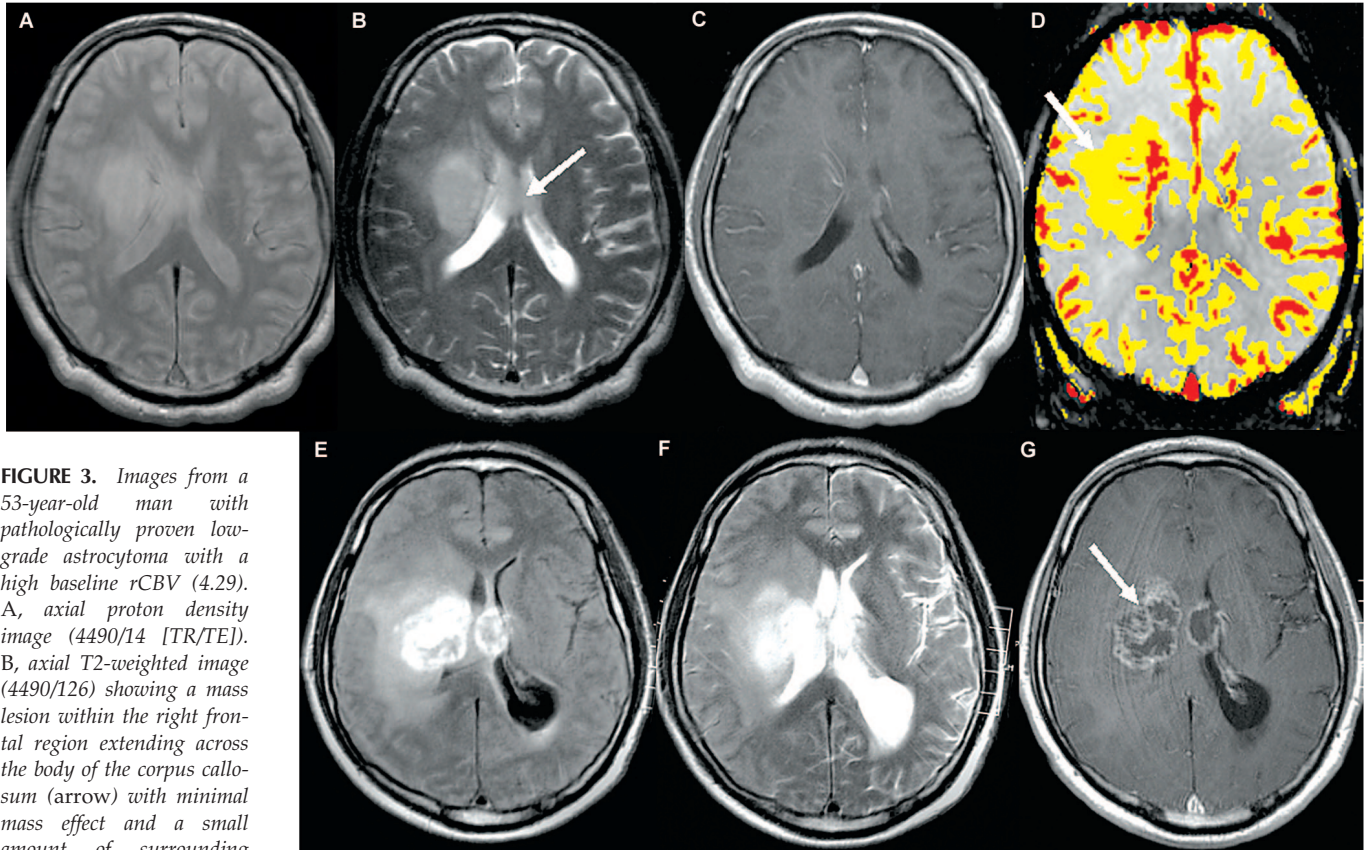
> 40 years; lesions > 3 to 5 cm with contrast enhancement, mass effect, papilledema, and neurological deficits other than seizures (2).

We propose a new algorithm that incorporates rCBV measurements for the management of patients with an imaging diagnosis of LGG (Fig. 4). Lesions not involving eloquent regions of the brain all undergo gross total resection (left side of the algorithm), because it has been shown that maximal resection improves survival in patients with LGG (2, 21, 29, 30, 32, 33). If a pathological diagnosis of a HGG is made, or if the rCBV is high (>1.75 LGG or HGG), the patient should be considered for adjuvant chemotherapy and/or radiation therapy. If a pathological diagnosis of LGG is made and rCBV is low (<1.75), the patient should be followed up serially. If there is risk of neurological deficit from resection at, or close to, an eloquent region (speech, precentral gyrus or brainstem), then the patient should be considered for a subtotal resection or stereotactic biopsy. Because of the possibility of sampling error, the perfusion again should be considered so that lesions with high perfusion (rCBV > 1.75) should be considered for adjuvant therapy and lesions with low perfusion (rCBV < 1.75) can be observed serially. As a caveat,

even though a lesion may be involving an eloquent region, if there is elevated perfusion (CBV > 1.75), then consider increasing the risk-benefit equation to resect more maximally (Fig. 5). Low perfusion (CBV < 1.75) would allow the surgeon to consider more conservative surgical options. In a lesion within an eloquent region (such as the brainstem) with low perfusion, nonsurgical therapy with serial observation becomes an option.

It is clear from the literature that conventional radiological findings, such as the absence of contrast enhancement, are not only poor predictors of tumor grade but may or may not be prognostic factors for either survival or progression-free survival (2, 16, 19, 20, 22, 24, 37). In this study, 46% of the lesions did not enhance after contrast administration. There was no association between presence of contrast enhancement and time to progression. Despite this, most institutional algorithms for the management of LGGs are based on imaging findings such as lesion size, presence/degree of contrast enhancement, and mass effect (2).

For the neurosurgeon and neuro-oncologist, all preoperative information on the aggressiveness of a glioma affects decision-making before, during, and after surgery. This is



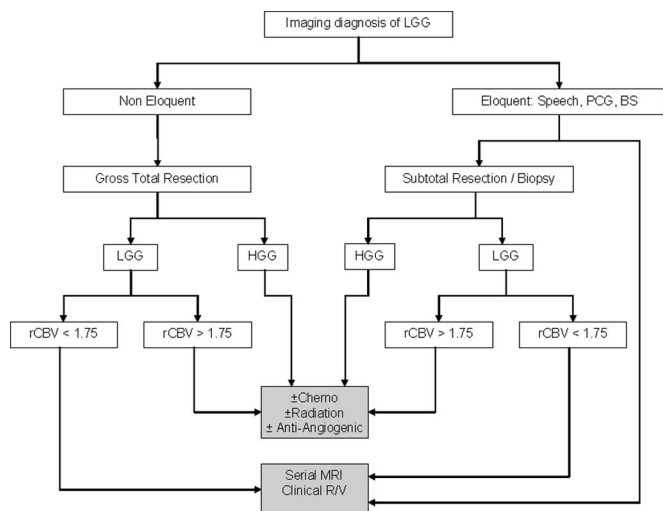
**FIGURE 3.** Images from a 53-year-old man with pathologically proven low-grade astrocytoma with a high baseline rCBV (4.29). A, axial proton density image (4490/14 [TR/TE]). B, axial T2-weighted image (4490/126) showing a mass lesion within the right frontal region extending across the body of the corpus callosum (arrow) with minimal mass effect and a small amount of surrounding edema. C, contrast-enhanced axial T1-weighted image (600/14) demonstrating minimal enhancement compatible with an imaging and pathological diagnosis of LGG. D, gradient-echo (TR/TE, 1000/54) axial DSC MRI image with rCBV color overlay map showing a lesion with high initial perfusion with an rCBV of 4.29 (arrow), more in keeping with an HGG than an LGG. (E) MRI at 43 days (11 wk) follow-up. Axial fluid-attenuated inversion recovery image (9000/110/2500 [TR/TE/TI]). F, axial T2-weighted image (8730/94) showing an increase in tumor volume and volume of T2 signal abnormality by 38.97 cm<sup>3</sup>. There is now increasing edema, mass effect with evidence of hydrocephalus, likely from obstruction at the foramen of Monroe. G, contrast-enhanced axial T1-weighted image (600/14) demonstrating new contrast enhancement with an increase in enhancing tumor volume by 45.23 cm<sup>3</sup>. There is also evidence of necrosis within the lesion (arrow). Final histopathological diagnosis after stereotactic resection was an anaplastic astrocytoma.

especially true given the known discordance between histopathologic grade and contrast enhancement. In the light of this study, knowledge of a lesion's rCBV may help determine whether to biopsy or to resect; the aggressiveness of resection; the planned size, shape, and extent of craniotomy; the use of postoperative adjuvant therapy (especially antiangiogenic therapies); and the frequency of follow-up examinations.

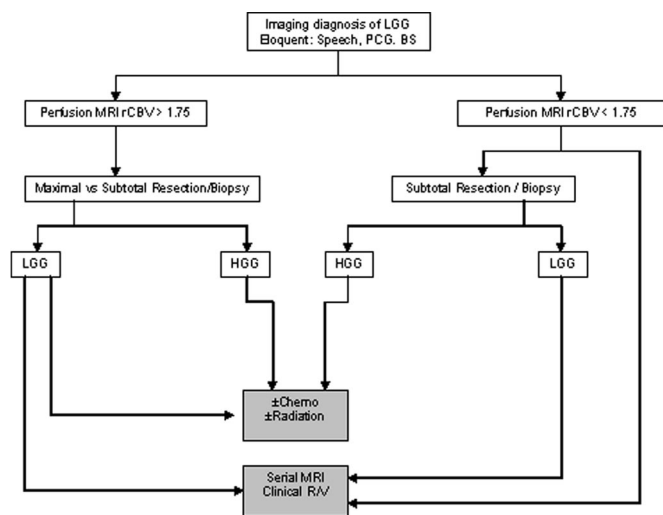
A potential limitation in our study is the potentially confounding effect of the patients' different treatment protocols on the time to progression. The initial treatment protocol at our institution for LGGs includes either stereotactic resection or biopsy ± radiation. Of the 16 patients with LGGs with low rCBV (n = 16), 5 did not receive adjuvant after surgery, 3 received radiation to the surgical bed, and 8 received a combination of radiotherapy and chemotherapy, which consisted of either temozolomide (Temodar; Schering AG, Berlin, Germany), carboplatin (Paraplatin; Bristol-Myers Squibb, Princeton, NJ), PCV- procarbazine/CCNU [chloroethyl-cyclohexyl-nitrosourea]/vincristine (Mutulane; Sigma-Tau Pharmaceuticals, Gaithersburg, MD), or a combina-

tion thereof. Of the 19 patients with LGGs with high rCBV, 7 did not receive adjuvant radiation after surgery, 1 received radiotherapy to the surgical bed, 2 received chemotherapy only, which consisted of either temozolomide or PCV, and 9 received a combination of radiotherapy and chemotherapy, which consisted of temozolomide, PCV, or a combination of temozolomide and high-dose carboplatin again, only after the tumor was shown to be progressive. It should be noted that at the time of surgery and diagnosis, chemotherapeutic agents were not routinely administered and therefore should not be a confounding factor. Furthermore, in both groups, most patients received either no adjuvant therapy or both surgery and radiotherapy in approximately the same proportions; because the histopathologic grade was the same, it is unlikely that this will have had a major effect on our overall results.

There are also no clear data demonstrating that any particular treatment regimen produces radically better outcomes than the other, (29) so that differences in the treatment protocol should not result in significant differences in patient out-



**FIGURE 4.** New algorithm in the management of low-grade gliomas. The overarching goal is for gross total resection (GTR) whenever feasible without undue neurological impairment.



**FIGURE 5.** Algorithm for lesions that may involve an eloquent region (speech, precentral gyrus, brainstem). A perfusion MRI (rCBV measurements) may be useful in changing the surgeon's risk-benefit equation.

come for LGGs. It is well known that some lesions respond to some therapies, whereas other lesions respond to differing therapies, and still other lesions respond to no therapy at all, even though they are classified as the same grade tumor (28). The only exception that has been recognized over the last decade has been the subgroup of oligodendroglioma with allelic loss on chromosomes 1p and 19q, which have a significantly better prognosis and a particular sensitivity to chemotherapy (5). In our study, only two patients had 1p19q deletions; therefore, this is unlikely to affect the overall time-to-progression statistics. Another potential limitation in our study is the effect of surgical resection versus biopsy on time to progression. It is important to note from our data that the

time to progression of patients who had a diagnosis made from stereotactic biopsy or subtotal resection (2063 d, n = 14) was very similar to that for patients who had a diagnosis made from gross total resection (2366 d, n = 21). The literature is also divided as to the survival benefit of gross total resection versus biopsy/subtotal resection (2, 3, 18, 21), although is generally thought that reducing the volume of tumoral tissue does improve survival.

The current reference standard for predicting glioma biological behavior has limitations. Partly because of this, the optimum assessment and treatment of LGGs remain unclear. However, patients with misclassified gliomas will not receive optimum treatment, compromising survival. Our study strongly suggests that cerebral blood volume measurements correlate more accurately with time to progression than initial histopathologic grading and rCBV may be a useful in vivo, second reference standard in the management of LGGs.

## REFERENCES

- Abdulrauf SI, Edvardsen K, Ho KL, Yang XY, Rock JP, Rosenblum ML: Vascular endothelial growth factor expression and vascular density as prognostic markers of survival in patients with low-grade astrocytoma. *J Neurosurg* 88:513-520, 1998.
- Bampoe J, Bernstein M: The role of surgery in low grade gliomas. *J Neurooncol* 42:259-269, 1999.
- Bauman G, Lote K, Larson D, Stalpers L, Leighton C, Fisher B, Wara W, MacDonald D, Stitt L, Cairncross JG: Pretreatment factors predict overall survival for patients with low-grade glioma: A recursive partitioning analysis. *Int J Radiat Oncol Biol Phys* 45:923-929, 1999.
- Brown PD, Wald JT, McDermott MW, Baumann GS, Cloughesy TF: Oncodiagnosis Panel: 2002: Adult central nervous system neoplasms. *Radiographics* 23:1591-1611, 2003.
- Cairncross J, Ueki K, Zlatescu M, Lisle D, Finkelstein D, Hammond R, Silver J, Stark P, Macdonald D, Ino Y, Ramsay D, Louis D: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. *J Natl Cancer Inst* 90:1473-1479, 1998.
- Cha S, Johnson G, Wadghiri YZ, Jin O, Babb J, Zagzag D, Turnbull DH: Dynamic, contrast-enhanced perfusion MRI in mouse gliomas: Correlation with histopathology. *Magn Reson Med* 49:848-855, 2003.
- Coons SW, Johnson PC, Scheithauer BW, Yates AJ, Pearl DK: Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. *Cancer* 79:1381-1393, 1997.
- Daumas-Duport C, Scheithauer B, O'Fallon J, Kelly P: Grading of astrocytomas: A simple and reproducible method. *Cancer* 62:2152-2165, 1988.
- Gilles FH, Brown WD, Leviton A, Tavaré CJ, Adelman L, Rorke LB, Davis RL, Hedley-Whyte TE: Limitations of the World Health Organization classification of childhood supratentorial astrocytic tumors. Children Brain Tumor Consortium. *Cancer* 88:1477-1483, 2000.
- Jackson RJ, Fuller GN, Abi-Said D, Lang FF, Gokaslan ZL, Shi WM, Wildrick DM, Sawaya R: Limitations of stereotactic biopsy in the initial management of gliomas. *Neuro-oncol* 3:193-200, 2001.
- Kleihues P, Cavaneé P: *WHO Classification of Tumors: Pathology and Genetic of Tumours of the Nervous System*. Lyon, IARC Press, 2000, pp 9-54.
- Knopp EA, Cha S, Johnson G, Mazumdar A, Golfinos JG, Zagzag D, Miller DC, Kelly PJ, Kricheff II: Glial neoplasms: Dynamic contrast-enhanced T2\*-weighted MR imaging. *Radiology* 211:791-798, 1999.
- Law M, Yang S, Babb JS, Knopp EA, Golfinos JG, Zagzag D, Johnson G: Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade. *AJNR Am J Neuroradiol* 25:746-755, 2004.

14. Law M, Yang S, Wang H, Babb JS, Johnson G, Cha S, Knopp EA, Zagzag D: Glioma grading: Sensitivity, specificity, and predictive values of perfusion MR imaging and proton MR spectroscopic imaging compared with conventional MR imaging. *AJNR Am J Neuroradiol* 24:1989–1998, 2003.
15. Lev MH, Rosen BR: Clinical applications of intracranial perfusion MR imaging. *Neuroimaging Clin N Am* 9:309–331, 1999.
16. Lev MH, Ozsunar Y, Henson JW, Rasheed AA, Barest GD, Harsh GR, Fitzek MM, Chiocca EA, Rabinov JD, Csavoy AN, Rosen BR, Hochberg FH, Schaefer PW, Gonzalez RG: Glial tumor grading and outcome prediction using dynamic spin-echo MR susceptibility mapping compared with conventional contrast-enhanced MR: Confounding effect of elevated rCBV of oligodendrogliomas [corrected]. *AJNR Am J Neuroradiol* 25:214–221, 2004.
17. Levin VA, Hess KR, Choucair A, Flynn PJ, Jaekle KA, Kyritsis AP, Yung WK, Prados MD, Bruner JM, Ictech S, Gleason MJ, Kim H-W: Phase III randomized study of postradiotherapy chemotherapy with combination alpha-difluoromethylornithine-PCV versus PCV for anaplastic gliomas. *Clin Cancer Res* 9:981–990, 2003.
18. Lote K, Egeland T, Hager B, Stenwig B, Skullerud K, Berg-Johnsen J, Storm-Mathisen I, Hirschberg H: Survival, prognostic factors, and therapeutic efficacy in low-grade glioma: A retrospective study in 379 patients. *J Clin Oncol* 15:3129–3140, 1997.
19. McCormack BM, Miller DC, Budzilovich GN, Voorhees GJ, Ransohoff J: Treatment and survival of low-grade astrocytoma in adults—1977–1988. *Neurosurgery* 31:636–642, 1992.
20. Piepmeier JM: Observations on the current treatment of low-grade astrocytic tumors of the cerebral hemispheres. *J Neurosurg* 67:177–181, 1987.
21. Piepmeier JM, Baehring JM: Surgical resection for patients with benign primary brain tumors and low grade gliomas. *J Neurooncol* 69:55–65, 2004.
22. Piepmeier JM, Christopher S: Low-grade gliomas: Introduction and overview. *J Neurooncol* 34:1–3, 1997.
23. Prayson RA, Agamanolis DP, Cohen ML, Estes ML, Kleinschmidt-DeMasters BK, Abdul-Karim F, McClure SP, Sebek BA, Vinay R: Interobserver reproducibility among neuropathologists and surgical pathologists in fibrillary astrocytoma grading. *J Neurol Sci* 175:33–39, 2000.
24. Rajan B, Pickuth D, Ashley S, Traish D, Monro P, Elyan S, Brada M: The management of histologically unverified presumed cerebral gliomas with radiotherapy. *Int J Radiat Oncol Biol Phys* 28:405–413, 1994.
25. Ringertz J: Grading of gliomas. *Acta Pathol Microbiol Scand* 27:51–64, 1950.
26. Rosen BR, Belliveau JW, Buchbinder BR, McKinstry RC, Porkka LM, Kennedy DN, Neuder MS, Fisel CR, Aronen HJ, Kwong KK, Weisskoff RM, Cohen MS, Brady TJ: Contrast agents and cerebral hemodynamics. *Magn Reson Med* 19:285–292, 1991.
27. Rosen BR, Belliveau JW, Vevea JM, Brady TJ: Perfusion imaging with NMR contrast agents. *Magn Res Med* 14:249–265, 1990.
28. Schmainda KM, Rand SD, Joseph AM, Lund R, Ward BD, Pathak AP, Ulmer JL, Baddrudoja MA, Krouwer HG: Characterization of a first-pass gradient-echo spin-echo method to predict brain tumor grade and angiogenesis. *AJNR Am J Neuroradiol* 25:1524–1532, 2004.
29. Shaw EG, Wisoff JH: Prospective clinical trials of intracranial low-grade glioma in adults and children. *Neuro-oncol* 5:153–160, 2003.
30. Shaw EG, Tatter SB, Lesser GJ, Ellis TL, Stanton CA, Stieber VW: Current controversies in the radiotherapeutic management of adult low-grade glioma. *Semin Oncol* 31:653–658, 2004.
31. Shin JH, Lee HK, Kwun BD, Kim J-S, Kang W, Choi CG, Suh DC: Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: Preliminary results. *AJR Am J Roentgenol* 179: 783–789, 2002.
32. Stupp R, Baumert BG: Promises and controversies in the management of low-grade glioma. *Ann Oncol* 14:1695–1696, 2003.
33. Stupp R, Janzer RC, Hegi ME, Villemure JG, Mirimanoff RO: Prognostic factors for low-grade gliomas. *Semin Oncol* 30:23–28, 2003.
34. Sugahara T, Korogi Y, Kochi M, Ikushima I, Hirai T, Okuda T, Shigematsu Y, Liang L, Ge Y, Ushio Y, Takahashi M: Correlation of MR imaging-determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas. *AJR Am J Roentgenol* 171:1479–1486, 1998.
35. Tsui WH, Rusinek H, Van Gelder P, Lebedev S: Analyzing multi-modality tomographic images and associated regions of interest with MIDAS. *SPIE Medical Imaging: Image Processing* 4322:1725–1734, 2001.
36. Wetzel SG, Cha S, Johnson G, Lee P, Law M, Kasow DL, Pierce SD, Xue X: Relative cerebral blood volume measurements in intracranial mass lesions: Interobserver and intraobserver reproducibility study. *Radiology* 224:797–803, 2002.
37. Wu W-C, Chen C-Y, Chung H-W, Juan C-J, Hsueh C-J, Gao H-W: Discrepant MR spectroscopic and perfusion imaging results in a case of malignant transformation of cerebral glioma. *AJNR Am J Neuroradiol* 23:1775–1778, 2002.

COMMENTS

The authors have shown that dynamic susceptibility contrast-enhanced perfusion magnetic resonance imaging (DSC MRI) can be used to identify those tumors thought to be low-grade gliomas that have been misdiagnosed due to either a sampling error of the pathology or because the tumor has increased propensity to progress to malignant transformation. This is potentially a very useful study, as the present means of diagnosing low-grade glioma are fraught with error. Sampling error, inadequate biopsy material, and inter- and intrapathologist variation can lead to a higher-grade tumor being misdiagnosed as low grade. This has considerable implications, as some studies of the management of low-grade glioma have shown a survival advantage with macroscopic resection of the tumor (1). There has been no definite improvement in outcome shown with either radiotherapy or chemotherapy for the low-grade diffuse fibrillary astrocytoma. Of course, those tumors that have an oligodendroglial component with a 1P or 19Q deletion have been shown to be much more responsive to chemotherapy.

While this is a useful study, the data needs to be interpreted with care, as the follow up is short (an average of 4.2 years, with a minimum of one year), the number of patients is relatively small, and numerous different treatment protocols were used. This is understandable, as the concepts of the treatment of low-grade glioma have changed over the past 10 years.

It is of particular interest that there was no association found between the presence or absence of contrast-enhancement and the time to progression, as I am usually fairly cautious of the diagnosis of low-grade glioma if there is enhancement on the MRI. Nevertheless, as predictor of tumor progression, DSC MRI seems to be a useful tool, and, in this study, it was possible to differentiate those tumors that had a medium progression time of greater than 12 years with those progressing in less than 1 year. Clearly, the latter were either never low-grade gliomas or, alternatively, were on the brink of malignant transformation.

The results of this study are of considerable practical value, and it is certainly worthwhile considering the addition of DSC MRI in the algorithm for the management of patients suspected to have low-grade glioma on imaging.

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1. Walker DG, Kaye AH: Low grade glial neoplasms. *J Clin Neurosci* 10:1–13, 2003.

Additional Comments Available Online