# Low-Grade Gliomas: Six-month Tumor Growth Predicts Patient Outcome Better than Admission Tumor Volume, Relative Cerebral Blood Volume, and Apparent Diffusion Coefficient[1]

Gisele Brasil Caseiras, MD
Olga Ciccarelli, PhD
Daniel R. Altmann, PhD
Christopher E. Benton, BSc
Daniel J. Tozer, PhD
Paul S. Tofts, PhD
Tarek A. Yousry, Dr med Habil
Jeremy Rees, PhD
Adam D. Waldman, PhD
Hans Rolf Jäger, MD

**Purpose:** To prospectively compare tumor volume, relative cerebral blood volume (rCBV), and apparent diffusion coefficient (ADC) and short-term changes of these parameters as predictors of time to malignant transformation and time to death in patients with low-grade gliomas (LGGs).

**Materials and Methods:** Patients gave written informed consent for this institutional ethics committee–approved study. Patients with histologically proved LGGs underwent conventional, perfusion-weighted, and diffusion-weighted magnetic resonance (MR) imaging at study entry and at 6 months. At both time points, tumor volume, maximum rCBV, and ADC histogram measures were calculated. Patient follow-up consisted of MR imaging every 6 months and clinical examinations. To investigate the association between MR imaging variables and time to progression and time to death, a Cox regression curve was applied at study entry and at 6 months. The models were corrected for age, sex, and histologic findings.

**Results:** Thirty-four patients (22 men, 12 women; mean age, 42 years) with histologically proved LGGs (eight oligodendrogliomas, 20 astrocytomas, and six oligoastrocytomas) were followed up clinically and radiologically for a median of 2.6 years (range, 0.4–5.5 years). Tumor growth over the course of 6 months was the best predictor of time to transformation, independent of rCBV, diffusion histogram parameters, age, sex, and histologic findings. When only single-time-point measurements were compared, tumor volume helped predict outcome best and was the only independent predictor of time to death ($P < .02$).

**Conclusion:** Six-month tumor growth helps predict outcome in patients with LGG better than parameters derived from perfusion- or diffusion-weighed MR imaging. Tumor growth can readily be calculated from volume measurements on images acquired with standard MR imaging protocols and may well prove most useful among various MR imaging findings in clinical practice.



[1] From the University College London Institute of Neurology, London, England (G.B.C., O.C., D.R.A., C.B., D.J.T., T.A.Y., J.R., A.D.W., H.R.J.); Lysholm Department of Neuroradiology, The National Hospital for Neurology and Neurosurgery, 8-11 Queen Square, London WC1N 3BG, England (G.B.C., T.A.Y., H.R.J.); London School of Hygiene and Tropical Medicine, London, England (D.R.A.); Brighton and Sussex Medical School, Brighton, England (P.S.T.); Department of Neurology, The National Hospital for Neurology and Neurosurgery, London, England (J.R.); and Imperial College, London, England (A.D.W.). Received October 9, 2008; revision requested November 13; revision received February 3, 2009; accepted April 1; final version accepted June 1. Supported by the Samantha Dickson Brain Tumour Trust and the Department of Health's NIHR Biomedical Research Centres funding scheme. G.B.C. supported in part by the Brain Research Trust. D.J.T. supported by the Multiple Sclerosis Society of Great Britain and Northern Ireland. **Address correspondence to** H.R.J. (e-mail: *r.jager@ion.ucl.ac.uk*).

Low-grade gliomas (LGGs) in adults are diffusively infiltrating tumors (World Health Organization [WHO] grade II) that may transform into high-grade gliomas (WHO grade III and IV) at some point, which is a transformation that is highly variable and difficult to predict in an individual patient.

Management of LGG remains controversial, and potential benefits of early aggressive treatment must be weighed against therapy-related morbidity. One large population-based study (1) failed to demonstrate a significant benefit of gross total tumor resection, whereas another study (2) showed an 8-year survival rate of 91% with at least 90% extent of resection. A randomized multicenter trial (3) showed that early radiation therapy in adult LGG increased the median transformation-free survival but not the overall survival.

In view of the morbidity associated with surgery and radiation therapy, some centers, including ours, adopt a "watch and wait" policy for neurologically intact patients, especially with tumors in eloquent locations. Aggressive therapy is initiated only at the time of malignant transformation.

Magnetic resonance (MR) imaging plays an important role in the diagnosis of malignant transformation in gliomas. It is used to assess contrast enhancement (4,5) and size of glial tumors. Tumor size and growth rate of LGG were shown to be associated with clinical outcome (6–8). Perfusion- and diffusion-weighted MR imaging have been used to characterize brain tumors (9). Measurements of relative cerebral blood volume (rCBV) obtained with dynamic susceptibility-weighted contrast material–enhanced perfusion MR imaging improved the specificity and sensitivity for differentiating between high-grade gliomas and LGGs (10) and helped predict the clinical response of LGG to treatment (11).

Measurements of apparent diffusion coefficient (ADC) have yielded conflicting results for glioma grading (9) but have proved to be a useful predictor of patient survival in high-grade astrocytomas (12,13).

The relative accuracy of these MR imaging parameters in predicting LGG behavior and patient outcome is unclear. Thus, the purpose of our study was to prospectively compare tumor volume, rCBV, and ADC and short-term changes of these parameters as predictors of time to malignant transformation and time to death in patients with LGG.

### Advance in Knowledge

- In conservatively treated, low-grade gliomas (LGGs), tumor growth over 6 months proved to be a more powerful predictor of time to malignant transformation than either relative cerebral blood volume measurements or baseline tumor volumes; measurements of apparent diffusion coefficient had no predictive value for patient outcome in LGG.

## Materials and Methods

The study was approved by the local research ethics committee, and all patients provided written informed consent prior to inclusion.

### Subjects

All patients were recruited sequentially from the neuro-oncology clinic of The National Hospital for Neurology and Neurosurgery between August 2000 and September 2006. The inclusion criteria were as follows: *(a)* histologically confirmed WHO grade II gliomas, *(b)* no previous treatment except biopsy and anticonvulsive medication therapy, and *(c)* age of 18 years or older. Exclusion criteria were as follows: *(a)* baseline enhancement in astrocytomas and *(b)* previous tumor resection or radiation therapy. Patients underwent conventional, perfusion-weighted, and diffusion-weighted imaging at study entry and 6 months later. They underwent clinical assessment and MR imaging every 6 months thereafter until malignant transformation was diagnosed.

### Implication for Patient Care

- Assessment of short-term tumor growth with MR imaging can help stratify the risk of malignant transformation in patients with LGG and might influence the timing of aggressive therapy.

### MR Imaging Protocol

Images were acquired with a 1.5-T system (Signa LX; GE Medical Systems, Milwaukee, Wis). Coronal fluid-attenuated inversion-recovery images (echo time msec/repetition time msec/inversion time msec, 161/8774/2192; section thickness, 5 mm; intersection gap, 1.5 mm), axial single-shot spin-echo echo-planar diffusion-weighted images with $b$ of 1000 sec/mm$^2$ (99.5/10 000; 5-mm contiguous sections), T2-weighted fast spin-echo images (104/6000; section thickness, 5 mm; intersection gap, 1.5 mm), and three-dimensional coronal spoiled gradient-echo images (6.4/14.4/650; 1.5-mm contiguous sections; 15° flip angle) were obtained. Subsequently, dynamic susceptibility-weighted contrast-enhanced perfusion images were acquired by using a single-shot gradient-echo echo-planar sequence (40/1200; flip angle, 90°; 128 × 92 matrix; 26 × 26-cm field of view; section thickness, 5 mm; contiguous sections) during the first pass of a 0.1-mmol bolus of gadoterate meglumine (Dotarem; Guerbet Laboratories, Paris, France) per kilogram of body weight injected at 5 mL/sec. After this, an additional bolus of 0.1 mmol/kg gadoterate meglumine was given,

**Published online before print**
10.1148/radiol.2532081623

**Radiology 2009;** 253:505–512

**Abbreviations:**
ADC = apparent diffusion coefficient
CI = confidence interval
LGG = low-grade glioma
rCBV = relative cerebral blood volume
ROC = receiver operating characteristic
SD = standard deviation
WHO = World Health Organization

**Author contributions:**
Guarantors of integrity of entire study, G.B.C., O.C., C.B., H.R.J.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; literature research, G.B.C., O.C., T.Y., H.R.J.; clinical studies, G.B.C., O.C., C.B., A.D.W., H.R.J.; statistical analysis, G.B.C., O.C., D.R.A., D.J.T., H.R.J.; and manuscript editing, G.B.C., O.C., D.R.A., C.B., D.J.T., T.Y., A.D.W., H.R.J.

Authors stated no financial relationship to disclose.

and additional three-dimensional spoiled gradient-echo images were obtained.

### MR Imaging Analysis

Two neuroradiologists (H.R.J. and G.B.C., with 16 and 6 years of experience in neurologic MR imaging, respectively) visually analyzed pre- and postcontrast spoiled gradient-echo images with a picture archiving and communication system (IMPAX; Agfa-Gevaert, Mortsel, Belgium) to assess for change in tumor enhancement characteristics between studies. Images were analyzed independently, and any discrepancies were resolved with consensus. Radiologic transformation was defined as the development of one or more new areas of contrast enhancement or as increase in previously stable baseline enhancement (in tumors with oligodendroglial elements) visible on two or more contiguous sections after intravenous administration of gadolinium-based contrast material.

Fluid-attenuated inversion-recovery images were analyzed on a workstation (Sunblade 150; Sun Microsystems, Mountain View, Calif) by using software (DispImage, version 4.9; Department of Medical Physics and Bioengineering, University College London, London, England) (14), and a semiautomated contouring technique was used by an observer (C.E.B., 6 years of experience in MR imaging), who was blinded to clinical details, to calculate tumor volumes at study entry and at 6 months (Fig 1).

Dynamic susceptibility-weighted contrast-enhanced perfusion images were processed offline by using software (Functool; GE Medical Systems). The beginning and end of the first-pass bolus was determined with inspection of time–signal intensity curves, and care was taken to exclude recirculation. For rCBV calculations, only the area under the curve of the first-pass bolus was considered. An observer (G.B.C. under supervision of H.R.J., with 3 and 10 years of experience in interpreting dynamic perfusion images, respectively), who was blinded to clinical and tumor volume results, placed at least six intratumoral regions of interest, each comprising 9 pixels, over areas showing the most elevated cerebral blood volume on color-coded rCBV maps. Care was taken not to include large intra- or peritumoral vessels, because these can confound perfusion measures (15) (Fig 2). The maximum tumor rCBV was expressed as a ratio of the highest rCBV value obtained from the intratumoral regions of interest to that obtained from a contralateral normal-appearing white matter region of interest. This approach has been previously shown to provide the best inter- and intraobserver reproducibility (10,16).

ADC maps were analyzed with in-house software (DispImage, version 4.9) (14). The tumor was contoured on each section of the $b = 0$ image by one observer (G.B.C.), and the saved regions were applied to the ADC map. Whole-tumor ADC histograms were produced as described in detail elsewhere (17) (Fig 3) and were normalized for the total number of tumor pixels and bin width. The following histogram parameters were extracted and used in statistical analysis: peak height, peak location, mean value, and 10th, 25th, 50th, 75th, and 90th percentile points.

### Statistical Analysis

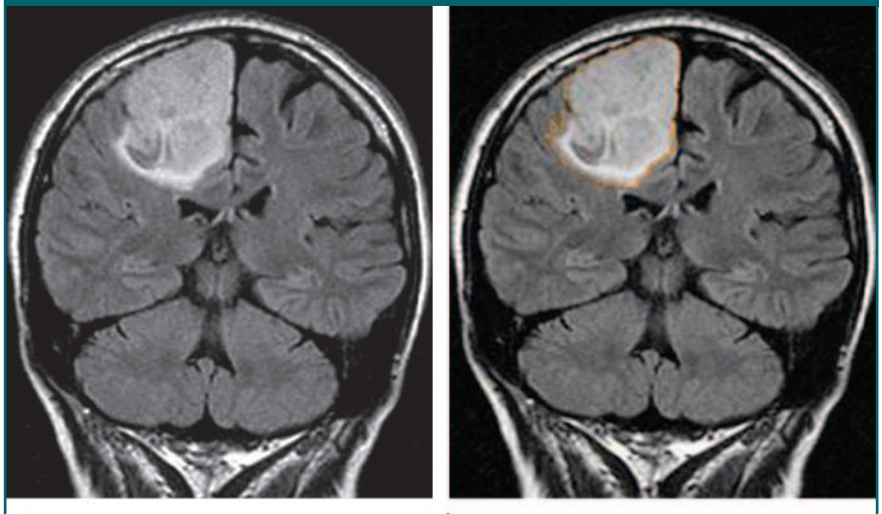
Analysis was performed (G.B.C., with contribution and supervision by D.R.A., O.C., and H.R.J.) by using software (Stata, version 9; Stata, College Station, Tex), and a $P$ value less than .05 was considered to indicate a significant difference.

*Short-term changes in MR imaging parameters.*—Wilcoxon signed rank test was used to analyze the difference in tumor volume, rCBV, and ADC between study entry and 6 months. Statistically significant change was indicated with a $P$ value less than .05.

*Predictors of time to transformation.*—Cox regression analysis was used with time (in years) from study entry to transformation. Stable patients were censored at last follow-up, with such censored patients contributing to the at-risk denominator of the analysis only at times prior to their last follow-up. The covariates at study entry were tumor volume, rCBV, ADC parameters, histologic findings, sex, and age. The analysis was then repeated and included data at study entry and changes in the first 6 months, with the following additional covariates: tumor growth and changes in rCBV. This procedure was first applied to all tumors and subsequently to the largest subgroup of pure astrocytomas.

*Predictors of time to death.*—The same analyses were repeated with time (in years) from study entry to death. In addi-

**Figure 1**



a. b.

**Figure 1:** **(a)** Coronal fluid-attenuated inversion-recovery MR image shows right frontal lobe low-grade astrocytoma. **(b)** Semiautomatic contouring (DispImage) for acquisition of tumor volume. The volume at study entry in this patient was 93.30 mL.

tion, the presence of treatment was added to the model as a covariate. This had not been considered a covariate for time to transformation analysis because patients received aggressive treatment only after malignant transformation. Patients alive at the time of latest follow-up were censored at that time (contributing to the analysis only at times prior to the last follow-up).

*Kaplan-Meier survival analysis.*— Kaplan-Meier curves were produced for the strongest predictors of time to transformation and of time to death. Receiver operating characteristic (ROC) analysis was applied to determine the best cutoff values for the variables that proved to be the strongest predictors. Kaplan-Meier survival curves and the log-rank test were then applied to compare the time to transformation and time to death in the two groups of patients defined by the cutoff. Differences between the two groups defined by the cutoff were tested by using the log-rank test.

**Figure 2**

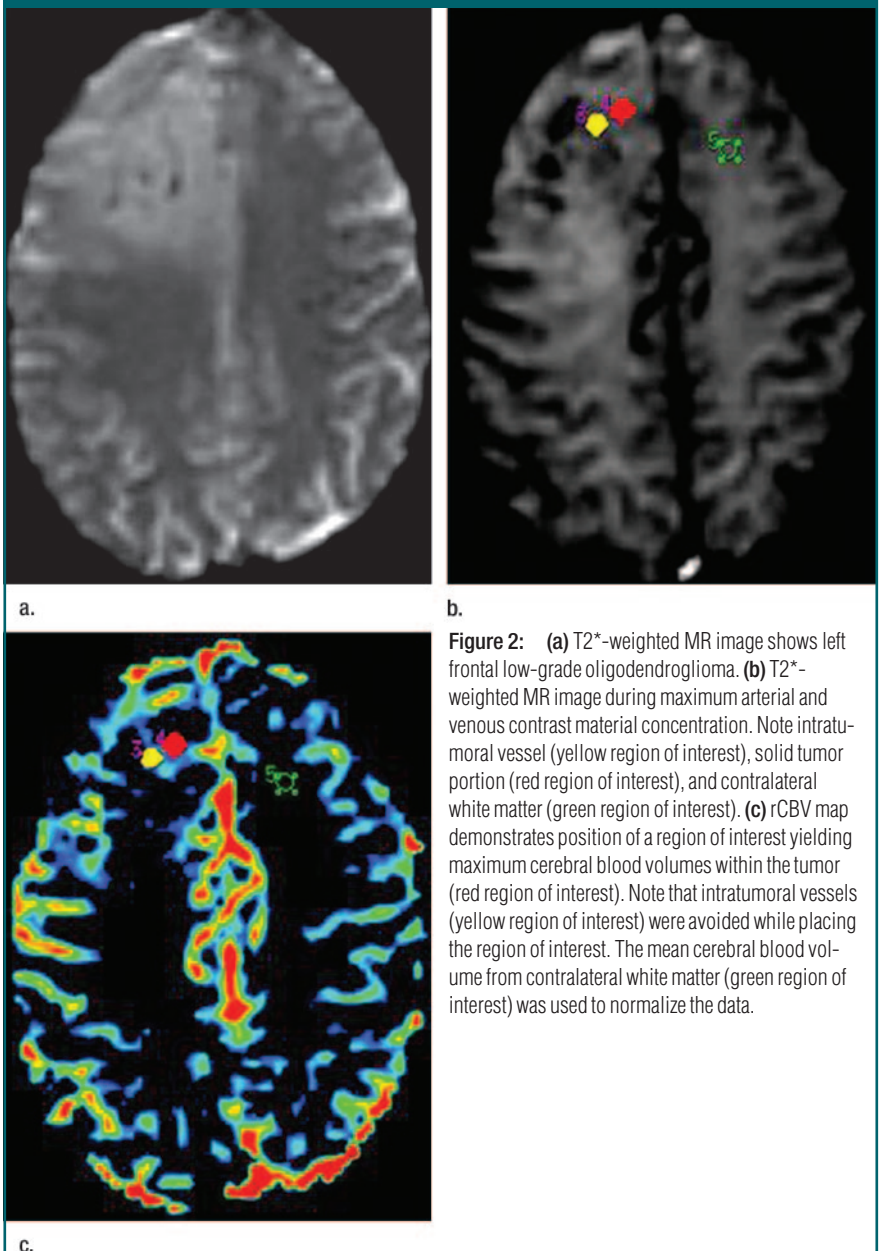



**Figure 2:** **(a)** T2*-weighted MR image shows left frontal low-grade oligodendroglioma. **(b)** T2*-weighted MR image during maximum arterial and venous contrast material concentration. Note intratumoral vessel (yellow region of interest), solid tumor portion (red region of interest), and contralateral white matter (green region of interest). **(c)** rCBV map demonstrates position of a region of interest yielding maximum cerebral blood volumes within the tumor (red region of interest). Note that intratumoral vessels (yellow region of interest) were avoided while placing the region of interest. The mean cerebral blood volume from contralateral white matter (green region of interest) was used to normalize the data.

## Results

### Patients

Demographic data are shown in Table 1. Two patients with histologic findings of WHO grade II astrocytomas were excluded, because they showed contrast enhancement on baseline MR imaging studies.

Thirty-four patients (22 men, 12 women; mean age, 42 years) with histologically proved WHO grade II gliomas (20 astrocytomas, eight oligodendrogliomas, and six oligoastrocytomas) were studied for a median follow-up of 2.6 years (range, 0.4–5.5 years). All 34 patients underwent MR imaging studies at 6 months after study entry.

Twelve (35%) of 34 patients remained stable during the follow-up period, 11 (32%) patients progressed but remained alive, and 11 (32%) patients died. The median length of follow-up was 2.2 years for the stable (range, 0.4–5.3 years) and 2.0 years for the progressive (range, 0.5–5.5 years) group of patients. Patients who died were radiologically followed up for a median of 2.0 years (range, 0.5–3 years) but were clinically studied for longer (median, 3.4 years; range, 1.0–4.8 years).

No patients received aggressive treatment before malignant transformation. Twenty-two (65%) of 34 patients received treatment during the study, which included surgery in eight patients, radiation therapy in 14 patients, and chemotherapy in eight cases. The median time from study entry to treatment was 2.17 years (range, 0.6–5.5 years).

### Short-term Changes in MR Imaging Parameters

There were significant changes in the mean values of tumor volume and rCBV between study entry and after 6 months ($P < .001$ for all). None of the ADC histogram parameters showed any sig-

nificant change. The means and standard deviations (SDs) of tumor volume, rCBV, and ADC for each time point and the change of these parameters within the first 6 months are given in Table 2.

### Predictors of Time to Transformation

*All tumors.*—By using variables available at study entry, tumor volume and rCBV were independent predictors of time to transformation. The risk of transformation during follow-up was 2.45 times higher per each additional SD of tumor volume at study entry (95% confidence interval [CI]: 1.38, 4.35; $P = .002$; SD = 32.3 mL) and was 1.73 times higher per each additional SD of rCBV at study entry (95% CI: 1.09, 2.74; $P = .01$; SD = 0.6). ADC histogram measures were not significantly different.

By using variables available at 6 months and according to Cox regression analysis with all the parameters available at 6 months (including the study entry data), change in tumor volume over 6 months (tumor growth) and rCBV at study entry were the only independent predictors of time to transformation. The risk of transformation during the study was 3.63 times higher per each additional SD of tumor growth within 6 months (95% CI: 1.75, 7.49; $P = .001$; SD = 7.1 mL) and was 1.75 times higher per each additional SD of rCBV at study entry (95% CI: 1.09, 2.82; $P = .02$; SD = 0.6). These results were independent of the other covariates in the model.

*Subgroup of pure astrocytomas.*—By using variables at study entry, the rCBV at study entry was the only independent predictor of time to transformation. The risk of transformation during follow-up was 12.99 times higher per each additional SD of rCBV at study entry (95% CI: 1.82, 92.75; $P = .001$; SD = 0.52).

By using variables available at 6 months (only astrocytomas included), changes in tumor volume over 6 months (tumor growth) was the only independent predictor of time to transformation: The risk of transformation during the study was 2.10 times higher per each additional SD of tumor growth within 6 months (95% CI: 1.05, 4.16; $P = .03$; SD = 6.19 mL).

**Figure 3**

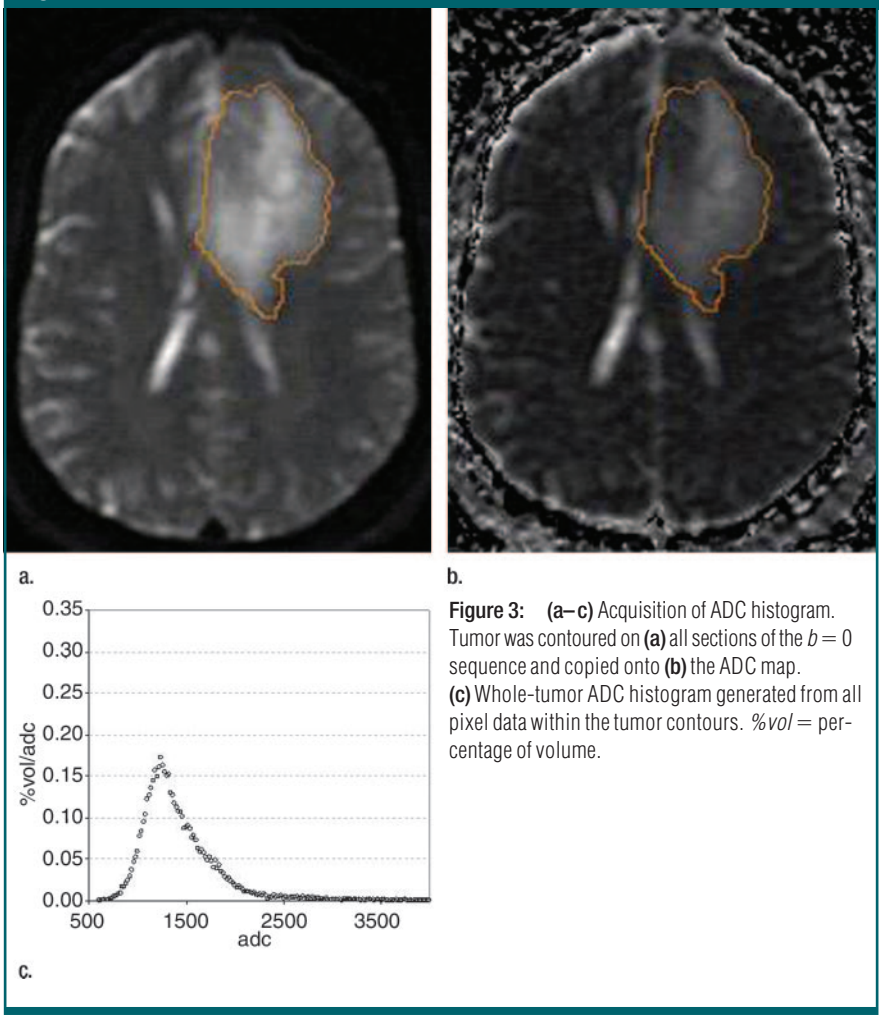



**Figure 3:** **(a–c)** Acquisition of ADC histogram. Tumor was contoured on **(a)** all sections of the $b = 0$ sequence and copied onto **(b)** the ADC map. **(c)** Whole-tumor ADC histogram generated from all pixel data within the tumor contours. *%vol* = percentage of volume.

### Predictors of Time to Death

*All tumors.*—Tumor volume at study entry was the only independent predictor of time to death: The risk of dying at any time during the study was 6.05 per each additional SD of tumor volume at study entry (95% CI: 1.77, 20.68; $P = .004$; SD = 32.3 mL).

*Subgroup of pure astrocytomas.*—Tumor volume at study entry remained the only independent predictor of time to death: The risk of dying at any time during the study was 8.18 per each additional SD of tumor volume at study entry (95% CI: 1.15, 57.99; $P = .03$; SD = 35.3 mL).

### Kaplan-Meier Survival Analysis

This analysis was performed by using tumor growth within 6 months and tumor volume at study entry, because these were the best independent predictors of time to transformation and to death, respectively.

The ROC curve showed a tumor growth of 6.21 mL in 6 months to be associated with the highest accuracy for predicting transformation (sensitivity: 83.3%; specificity: 83.3%; positive predictive value: 83.3%). By using this threshold, the mean time to transformation was 3.91 years (95% CI: 2.81, 5.02) for patients with tumor growth less than 6.21 mL in 6 months, compared with 1.82 years (95% CI: 1.38, 2.27) for patients with tumor growth greater than or equal to 6.21 mL ($P = .003$) (Fig 4).

The ROC curve showed a study entry tumor volume of 83.14 mL to be associ-

**Table 1**

**Demographic Data and Baseline MR Imaging Parameters in Patients**

| Patient No./ Age (y)/Sex | Histologic Finding* | Admission Volume (mL) | rCBV† | Median ADC ($\times 10^{-6}$ mm$^2$sec$^{-1}$) | Outcome‡ | Years of Follow-up |
|---|---|---|---|---|---|---|
| 1/30/M | A | 77 | 0.94 | 1749.5 | S | 0.4 |
| 2/60/F | A | 47.5 | 1.14 | 1307.5 | S | 1.1 |
| 3/38/M | A | 79.1 | 0.8 | 1491.5 | S | 2 |
| 4/29/F | A | 43.8 | 1.18 | 1767.5 | S | 2.7 |
| 5/32/M | A | 20.1 | 1.61 | 1256.5 | S | 2.9 |
| 6/57/F | A | 72.3 | 1.49 | 1275.5 | S | 4.3 |
| 7/32/M | A | 42.9 | 1.42 | 1843.5 | S | 1.6 |
| 8/39/M | A | 30.8 | 1.79 | 1364.5 | S | 0.6 |
| 9/29/M | A | 66 | 0.7 | 1724.5 | S | 3.7 |
| 10/51/M | A | 93.3 | 2.46 | 1215.5 | P | 0.5 |
| 11/37/M | A | 77.1 | 0.99 | 1289.5 | P | 5.6 |
| 12/34/M | A | 58.7 | 1.56 | 1643.5 | P | 1.9 |
| 13/52/M | A | 40.4 | 1.37 | 1151.5 | P | 1.7 |
| 14/56/M | A | 84.2 | 1.04 | 1169.5 | D | 2.9 |
| 15/58/M | A | 169.3 | 2.24 | 1122.5 | D | 1 |
| 16/29/F | A | 59 | 2.38 | 1674.5 | D | 4.2 |
| 17/41/M | A | 136.9 | 1.04 | 2013.5 | D | 2.2 |
| 18/47/F | A | 75 | 1.09 | 1466.5 | D | 4.8 |
| 19/35/M | A | 64.8 | 0.91 | 1669.5 | D | 4.2 |
| 20/30/M | A | 106.7 | 1.91 | 1504.5 | D | 4.1 |
| 21/63/F | O | 38.9 | 1.47 | 1322.5 | S | 3.5 |
| 22/30/F | O | 45.6 | 2.02 | 1131.5 | P | 3.1 |
| 23/57/M | O | 132.2 | 1.94 | 1205.5 | P | 3.6 |
| 24/56/M | O | 72 | 2.53 | 1229.5 | P | 4.6 |
| 25/28/F | O | 24.4 | 2.81 | 978.5 | P | 1.2 |
| 26/24/M | O | 44.6 | 1.59 | 1241.5 | P | 2 |
| 27/53/F | O | 94.9 | 1.84 | 1569.5 | P | 2.1 |
| 28/36/M | O | 71.6 | 3.51 | 1291.5 | P | 1.36 |
| 29/37/F | OA | 105.4 | NA | 1369.5 | S | 1.5 |
| 30/69/M | OA | 37.4 | 1.94 | 1169.5 | S | 5.3 |
| 31/25/M | OA | 84.6 | 1.28 | 1149.5 | D | 1.6 |
| 32/48/M | OA | 83.1 | 1.26 | 1450.5 | D | 3 |
| 33/42/F | OA | 101 | 1.91 | 1342.5 | D | 3.8 |
| 34/65/F | OA | 92.3 | 1.28 | 1649.5 | D | 4 |

* A = astrocytoma, O = oligodendroglioma, OA = oligoastrocytoma.

† NA = Not available due to technical problems.

‡ D = death, P = progressive, S = stable.

ated with the highest accuracy for prediction of death (sensitivity: 66.67%; specificity: 79.17%; positive predictive value: 75%). By using this cutoff, we found a mean survival time of 5 years (95% CI: 4.52, 5.48) for patients with tumor volumes less than 83.14 mL compared with 3.04 years (95% CI: 2.32, 3.76) for patients with tumor volumes greater than or equal to 83.14 mL ($P = .0001$) (Fig 5).

## Discussion

The most noteworthy feature of our study was the prospective comparison of several MR imaging variables as predictors of outcome in patients who did not undergo disease-modifying treatment until malignant transformation was diagnosed.

Tumor growth over 6 months was the strongest predictor of the time to transformation for all tumors, as well as for the subgroup of astrocytomas. When only the single-time-point measurements at study entry were considered, tumor volume proved to be the best independent predictor for the entire study cohort, whereas rCBV was the best predictor for pure astrocytomas. Tumor volume was the only independent predictor of time to death. On the basis of our calculations, patients with a tumor volume exceeding 83.14 mL were highly likely to die within 5 years of presentation.

Our results are broadly in keeping with previous studies on tumor volume and growth in LGG. A retrospective study (18) of low-grade astrocytomas and oligoastrocytomas over a 9-year period showed preoperative tumor volume to be the strongest predictor of overall survival and malignant transformation, but all patients were treated surgically prior to malignant transformation.

**Table 2**

**Values at Each Time Point and Tumor Growth within the First 6 Months**

| Parameter | Volume (mL) | | Maximum rCBV | | ADC 50th Percentile ($\times 10^{-6}$ mm$^2$sec$^{-1}$) | |
|---|---|---|---|---|---|---|
| | Mean ± SD | Median* | Mean ± SD | Median* | Mean ± SD | Median* |
| Study entry | 73.1 ± 32.3 | 73.1 (20.1–169.3) | 1.6 ± 0.6 | 1.5 (0.7–3.5) | 1407.9 ± 240.7 | 1353.5 (978.5–2013.5) |
| 6 months | 81.8 ± 35.2 | 81.9 (22.0–186.8) | 2.22 ± 0.8 | 2.0 (1.2–4.6) | 1387.4 ± 258.9 | 1319.5 (978.5–2013.5) |
| Change (6 months − study entry) | 8.8 ± 7.1 | 9.2 (11.9–23.4) | 0.5 ± 0.4 | 0.3 (0.1–1.8) | −5.5 ± 74.7 | 00 (−246.0–180.0) |

* Data in parentheses are ranges.

**Figures 4, 5**

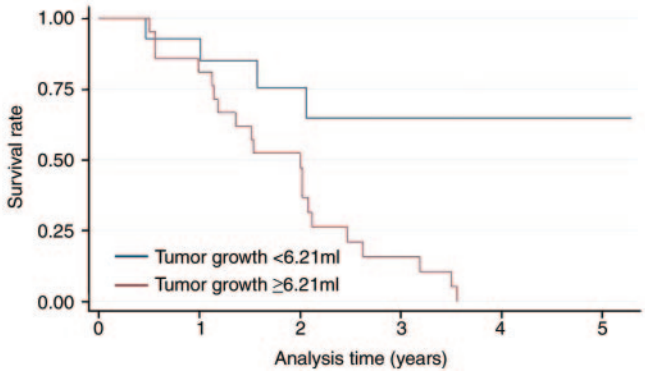



**Figure 4:** Graph shows comparison of time to progression between groups with small (<6.21 mL) and large (≥6.21 mL) tumor growth within 6 months. Patients with small tumor growth had a mean time to progression of 3.91 years (blue curve), whereas patients with large tumor growth had a mean time to progression of 1.82 years (red curve).

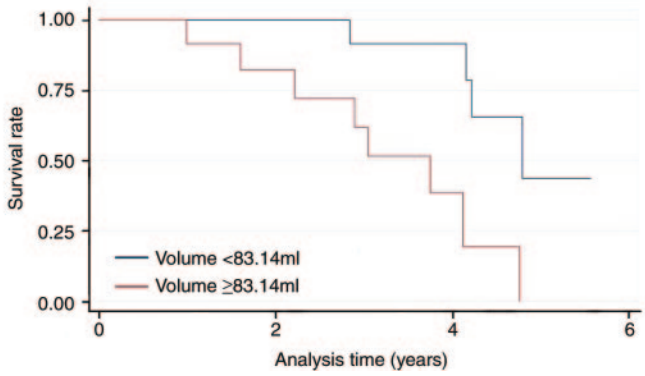



**Figure 5:** Graph shows comparison of survival between groups with small (<83.14 mL) and large (≥83.14 mL) tumor volume at study entry. Patients with small tumor volume had a median survival time of 4.80 years (blue curve), whereas patients with large tumor volume had a median survival time of 3.76 years (red curve). Note that, after almost 5 years of follow-up, all patients with large tumor volumes would probably be dead, whereas more than 40% of patients with small tumor volumes would still be alive.

A retrospective study (8) of 143 patients over a 12-year period demonstrated an inverse correlation between growth rates of LGG and patient survival. The time interval between successive MR imaging studies varied widely from 3 to 219.3 months (mean, 33.4 months) in this study, which included predominantly oligodendrogliomas and linear measurements to determine growth.

A recent prospective study (6) of untreated LGG, which included a subset of the patients studied here, showed higher average annual growth rates and baseline tumor volumes in tumors undergoing malignant transformation during a 3-year observation period than in those tumors not undergoing malignant transformation.

Our current data showed that rCBV was also a predictor for time to tumor progression. This accords with a previous study on LGG (11), demonstrating a negative correlation between pretreatment rCBV and time to progression. The majority of the patients in this latter study, which also included children, had undergone resective surgery and/or radiation therapy at the time of initial diagnosis.

The importance of baseline rCBV as a predictor for time to tumor progression increased in the subgroup of pure astrocytomas where it was more significant than baseline volume (but remained less significant than 6-month tumor growth).

Low-grade oligodendrogliomas tend to have higher rCBVs than low-grade astrocytic tumors (19). This feature can be a confounding factor and may explain the fact that in the entire cohort of the current study, which consisted of mixed LGGs, rCBV was a less powerful predictor than baseline tumor volume (whereas the opposite pertained to the subgroup of pure astrocytomas, as mentioned above).

When comparing rCBV measurements with other parameters in our study by using Cox regression analysis, tumor growth within 6 months proved to be a stronger predictor for time to transformation than rCBV, both for the entire cohort as well as for the astrocytoma subgroup.

Investigators of a recent longitudinal MR perfusion study of LGG (20), which included a small subset of patients studied here, analyzed perfusion data over a longer time period and found rCBV to increase mainly 12 months prior to malignant transformation, which is likely to reflect neoangiogenesis in evolving aggressive tumor components. The above considerations of tumor histologic conditions apart, it may therefore well be that the predictive value of rCBV measurements for patient outcome increases nearer the time of transformation, but this will have to be confirmed with further studies.

We did not find significant changes in ADC measurements within 6 months, and none of the ADC parameters proved to be a useful predictor of malignant transformation. This is not entirely unexpected, because ADC has been, on the whole, less promising than rCBV in differentiating between low- and high-grade tumors (9). There are no published data on the predictive value of ADC measurements in LGG. However, preoperative ADC measurements in high-grade (12) tumors appear promising in predicting patient prognosis.

## Method Considerations

We used fluid-attenuated inversion-recovery images for tumor volume measurement, because these are more sensitive to subtle glioma tumor volume change than T2-weighted images (21).

Of the statistical parameters used, time to transformation is clinically more relevant than time to death with a greater potential influence on treatment strategy. Time to death reflects tumor biology less clearly than time to transformation, because other factors such as treatment-related morbidity and mortality can affect survival.

## Study Limitations

The intersection gap of 1.5 mm on the fluid-attenuated inversion-recovery images used for volume measurements might lead to less precise measurements

than contiguous sections, but the tumor volumes probably were big enough to consider the possible effect of partial volume to be negligible.

We used ROC analysis to determine the thresholds for our Kaplan-Meier survival curves. ROC curves do not provide a CI, and the exact optimal threshold determined from the ROC analysis of our data set may not be generalizable to a different population. Further studies are required to determine an optimal binary threshold that could be used in clinical practice.

In conclusion, tumor growth within 6 months was better than baseline volumes, rCBV, or ADC in predicting time to malignant transformation in untreated LGGs and was independent of other parameters, including histologic findings.

## References

1. Johannesen TB, Langmark F, Lote K. Progress in long-term survival in adult patients with supratentorial low-grade gliomas: a population-based study of 993 patients in whom tumors were diagnosed between 1970 and 1993. J Neurosurg 2003;99:854–862.
2. Claus EB, Horlacher A, Hsu L, et al. Survival rates in patients with low-grade glioma after intraoperative magnetic resonance image guidance. Cancer 2005;103:1227–1233.
3. van den Bent MJ, Afra D, de Witte O, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomised trial. Lancet 2005;366:985–990.
4. Mihara F, Numaguchi Y, Rothman M, Sato S, Fiandaca MS. MR imaging of adult supratentorial astrocytomas: an attempt of semiautomatic grading. Radiat Med 1995;13:5–9.
5. Pierallini A, Bonamini M, Bozzao A, et al. Supratentorial diffuse astrocytic tumours: proposal of an MRI classification. Eur Radiol 1997;7:395–399.
6. Rees J, Watt H, Jäger HR, et al. Volumes and growth rates of untreated adult low-grade gliomas indicate risk of early malignant transformation. Eur J Radiol doi: 10.1016/j.ejrad.2008.06.013. Published online July 14, 2008.
7. Mandonnet E, Delattre JY, Tanguy ML, et al. Continuous growth of mean tumor diameter in a subset of grade II gliomas. Ann Neurol 2003;53:524–528.
8. Pallud J, Mandonnet E, Duffau H, et al. Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol 2006;60:380–383.
9. Cha S. Update on brain tumor imaging: from anatomy to physiology. AJNR Am J Neuroradiol 2006;27:475–487.
10. Law M, Yang S, Wang H, et al. 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 2003;24:1989–1998.
11. Law M, Oh S, Babb JS, et al. Low-grade gliomas: dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging—prediction of patient clinical response. Radiology 2006;238:658–667.
12. Higano S, Yun X, Kumabe T, et al. Malignant astrocytic tumors: clinical importance of apparent diffusion coefficient in prediction of grade and prognosis. Radiology 2006;241:839–846.
13. Murakami R, Sugahara T, Nakamura H, et al. Malignant supratentorial astrocytoma treated with postoperative radiation therapy: prognostic value of pretreatment quantitative diffusion-weighted MR imaging. Radiology 2007;243:493–499.
14. Plummer D. Dispimage: a display and analysis tool for medical images. Rev Neuroradiol 1992;5:489–495.
15. Brasil Caseiras G, Thornton JS, Yousry T, et al. Inclusion or exclusion of intratumoral vessels in relative cerebral blood volume characterization in low-grade gliomas: does it make a difference? AJNR Am J Neuroradiol 2008;29:1140–1141.
16. Wetzel SG, Cha S, Johnson G, et al. Relative cerebral blood volume measurements in intracranial mass lesions: interobserver and intraobserver reproducibility study. Radiology 2002;224:797–803.
17. Tozer DJ, Jager HR, Danchaivijitr N, et al. Apparent diffusion coefficient histograms may predict low-grade glioma subtype. NMR Biomed 2007;20:49–57.
18. Mariani L, Siegenthaler P, Guzman R, et al. The impact of tumour volume and surgery on the outcome of adults with supratentorial WHO grade II astrocytomas and oligoastrocytomas. Acta Neurochir (Wien) 2004;146:441–448.
19. Cha S, Tihan T, Crawford F, et al. Differentiation of low-grade oligodendrogliomas from low-grade astrocytomas by using quantitative blood-volume measurements derived from dynamic susceptibility contrast-enhanced MR imaging. AJNR Am J Neuroradiol 2005;26:266–273.
20. Danchaivijitr N, Waldman AD, Tozer DJ, et al. Low-grade gliomas: do changes in rCBV measurements at longitudinal perfusion-weighted MR imaging predict malignant transformation? Radiology 2008;247:170–178.
21. Connor SE, Gunny R, Hampton T, O'Gorman R. Magnetic resonance image registration and subtraction in the assessment of minor changes in low grade glioma volume. Eur Radiol 2004;14:2061–2066.