ORIGINAL RESEARCH

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Do Cerebral Blood Volume and Contrast Transfer Coefficient Predict Prognosis in Human Glioma?

INTRODUCTION: Noninvasive measurements of cerebral blood volume (CBV) and contrast transfer coefficient (K^{trans}) have potential benefits in the diagnosis and therapeutic management of adult glioma. This study examines the relationship between CBV, K^{trans}, and overall survival.

METHODS AND MATERIALS: Twenty-seven adult patients with glioma underwent T1-weighted dynamic contrast-enhanced MR imaging, and parametric maps of CBV and K^{trans} were calculated. The relationship of histologic grade, CBV, K^{trans}, age, sex, surgical resection, and use of adjuvant therapy to survival were analyzed by using the logrank method and Cox regression analysis. The Kaplan-Meier method for displaying survival curves was used. The relationship of factors such as comorbidity, elevated intracranial pressure, size of nonenhancing tumor, and peritumoral edema were not considered.

RESULTS: Both CBV ($P < .01$) and K^{trans} ($P < .01$) show a significant relationship to histologic grade. CBV ($P = .004$), K^{trans} ($P = .008$), and histologic grade ($P < .001$) all demonstrate a significant association with patient survival when analyzed individually. Cox regression analysis identified only histologic grade ($P < .01$) and K^{trans} ($P < .05$) as independent significant prognostic indicators. Examination of survival data from high-grade (III and IV) tumors demonstrated a linear relationship between K^{trans} and patient survival ($P < .01$).

CONCLUSION: This study suggests a direct relationship between K^{trans} and length of survival in high-grade gliomas, which could be of clinical importance. CBV relates directly to histologic grade but provides no independent prognostic information over and above that provided by grade. Further large prospective studies should be planned to test whether this observation holds true.

The formation of new blood vessels, referred to as angiogenesis, plays a fundamental part in tumor growth[1] The angiogenic process is driven by cytokines whose production is stimulated by hypoglycemia and hypoxia. In malignant gliomas, the most active cytokine is vascular endothelial growth factor (VEGF), which stimulates endothelial proliferation but also has a direct effect on endothelial membranes, directly increasing transendothelial permeability.[2,3] In higher-grade and more aggressive gliomas VEGF expression is increased.[4] This increase in angiogenic activity is identified during histologic examination by the presence of increased numbers of blood vessels with a concomitant increase in blood volume fraction.

A variety of imaging-based techniques has been developed to provide quantifiable biomarkers that reflect the extent and activity of angiogenesis within tumors.[5-20] Most of these techniques have been based on dynamic relaxivity contrast-enhanced MR imaging. Dynamic imaging of changes in contrast concentration allows the application of pharmacokinetic models to data analysis, which provide estimations of physiologic values such as regional proportional blood volume, blood flow, endothelial permeability surface area product, and the size of the extravascular extracellular space.[5-27]

Cerebral blood volume (CBV) maps can be calculated by 2 comparable methods,[11] by using either T2*-weighted or T1-weighted images.[28] CBV calculation is most commonly performed from dynamic T2*-weighted images with the use of a simple curve-fitting technique. To compensate for contrast leakage, modifications to the image acquisition and analysis approaches must be made[29] and, assuming that these precautions are taken, the technique is robust and reproducible.[30] A number of studies have shown CBV to correlate with the histologic grade of the glioma (ie, CBV directly increases with grade).[5-8,13-15,31-34]

The measurement of endothelial permeability, however, is more complex. Many groups have attempted to develop models for estimating the contrast transfer coefficient (K^{trans}) as a reflection of endothelial permeability.[21,22,24,25,27,34,35] All such models are based upon measuring the rate of contrast leakage between the vasculature and the extravascular, extracellular space. The concentration gradient across the endothelial membrane at any given time will reflect both the endothelial permeability and the rate of delivery of contrast agent into the vascular space. Thus, the transfer coefficient (K^{trans}) measurement reflects both permeability and flow.[36] Estimation of K^{trans} was initially designed to facilitate longitudinal studies of the effects of specific antiangiogenic drugs. This has been useful in drug development but has, as yet, found little or no direct application to clinical practice. This probably relates not only to the complexity of estimation and lack of availability of modeling software but also to a paucity of evidence as to the clinical value of K^{trans}.

Clinically several groups have studied the relationship between K^{trans} and histologic grade and have reached conflicting conclusions,[33,37,38] which seem to reflect wide variations in image acquisition and analysis methods. We have described a method for calculating K^{trans} from T1-weighted dynamic data that bases its analysis entirely on the first passage of the contrast bolus.[25,35,39] This technique gives comparable results to

Received June 27, 2005; accepted after revision August 30.

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conventional measurement techniques, allows simultaneous calculation of K^{trans} and CBV and has been extensively tested against both conventional methods and model data by using Monte Carlo simulations.[40] We have previously demonstrated strong relationships between both K^{trans}, CBV, and tumor grade by using this technique.[41]

Such studies confirm the validity of these parameters as surrogate biomarkers of tumor physiology but do not help us to understand the potential clinical value, if any, of these techniques. It is highly unlikely that these methods will ever be used to replace histologic tumor grading. The clinical question, therefore, is whether they provide additional information that could be of clinical value in diagnosis, classification, prediction of prognosis or guidance of therapeutic strategies.

This study is designed to examine the relationship between prognosis and 2 parametric indicators—CBV and K^{trans}. Histologic grade is currently the best indicator of survival in patients with glioma.[42-44] Patient age, use of adjuvant therapy, degree of surgery, and size of tumor have all also been shown, to a lesser extent, to have some prognostic value.[42-48] At the present time, only 2 studies have demonstrated a relationship between patient survival and parameters derived from dynamic MR imaging. These studies used estimations of CBV[31] and maximum tumor contrast uptake[16] in predicting patient survival. This study is the first to examine the relationship between calculated values of K^{trans} and prognosis.

Methods

Clinical Imaging

Twenty-seven patients with gliomas, of various grades, were recruited from 2 centers in the northwest of England and the Erasme Hospital in Belgium. All tumors were histologically confirmed as gliomas and graded according to criteria set out by the World Health Organization (WHO).[49] All patients gave informed consent. The Central Manchester Healthcare NHS Trust and Salford Royal Hospitals NHS Trust medical ethical committees and the ethical committee of Erasme Hospital approved the study. All patients with high-grade tumors (grades III and IV) were treated with corticosteroids before scanning, but none was receiving any other treatment. All MR imaging was performed before surgery (either for tumor resection or biopsy).

Imaging was performed on identical 1.5T MR systems (Philips Medical Systems, Best, the Netherlands) by using a birdcage head coil. Routine precontrast and postcontrast clinical imaging was performed according to local protocol. Three precontrast datasets were acquired for baseline T1 calculation by using a 3D T1-weighted fast field echo (T1-FFE; retention time [TR]/echo time [TE], 4.2/1.2 ms; field of view, 230 mm^2; matrix, 128 × 128; partition thickness, 6 mm with 3-mm overlap) using flip angles of 2°, 10°, and 35°. This was followed by a dynamic, contrast-enhanced acquisition series at a flip angle of 35°, consisting of 20 volume acquisitions with a temporal spacing of approximately 5 seconds. Gadolinium-based contrast agent (Gd-DTPA-BMA; Omniscan, GE Healthcare, Oslo, Norway) was injected as a bolus for 4 seconds at a dose of 0.1 mmol/kg of body weight after acquisition of the third image volume.

All imaging data were transferred from the scanners to an independent workstation (Sun Microsystems, Palo Alto, Calif) for analysis. Analysis was carried out with software written in house by using IDL (Interactive Data Language; Research Systems, Boulder, Colo). Regions of interest were defined by experienced radiologists (T.A.P. and S.J.M.) in one of the postcontrast datasets. Regions of interest were drawn on 3 consecutive sections through the middle of the tumor volume and were defined to contain all enhancing components of the tumor, specifically excluding nonenhancing areas. A vascular input function was measured on each patient from the vertical part of the superior sagittal sinus on the middle section of the scanned volume. A first-pass pharmacokinetic model was applied to calculate maps of K^{trans} and CBV as described by Li et al.[25,35,39]

Statistical Methods

Differences between patient age and measured parametric values for the individual tumor grades were tested by using an analysis of variance (ANOVA) to detect overall group differences with a posteriori pairwise testing by using Tamhane test assuming unequal variances. Values of K^{trans} and CBV were each used to categorize patients into 4 arbitrary quartile groups (group 1 [$n = 6$]; groups 2–4 [$n = 7$]). Survival between groups was compared by using logrank analysis to determine statistical significance of differences. Factors used in the logrank analysis included sex, histologic grade, K^{trans}, CBV, and the use of surgical resection. A separate analysis was also performed for grade IV tumors only. No such test was possible in patients with grade II tumors, because all survived and all fell into the same quartile groups for both K^{trans} and CBV. Similarly, logrank analysis could not be performed in grade III tumors because of the small sample size ($n = 4$).

The predictive value of individual parameters was assessed by using a Cox regression model. Parameters were analyzed in a forward stepwise manner entering variables based on the relative independent significance in the previous stage. The baseline comparatives for each variable were histologic grade II and the patient groups defined by the lowest quartile values of K^{trans} and CBV. The analysis was completed by stepwise removal of each individual parameter from the final model to detect significant independent associations that might be hidden by the order of data entry. This is of particular importance in this dataset, because preliminary data exploration showed that the relationship between survival and membership of classification groups defined by K^{trans} does not show a simple rank-order, linear relationship.[50]

Scatterplots of survival against measured values of K^{trans} were used to illustrate the relationship between these parameters (Fig 1). Because all patients with grade III and IV tumors had died by the end of the study, a simple linear regression was performed to examine the relationship between K^{trans} and survival.

Results

Patients included 9 women and 18 men, with a mean age of 52 years (age range, 33–75 years). There were 8 grade II, 4 grade III, and 15 grade IV tumors.

The measured values of both CBV and K^{trans} showed a clear trend to increase with increasing grade (Fig 2), and there were significant group differences for both K^{trans} ($P < .01$) and CBV ($P < .01$, ANOVA). Post hoc tests showed significant differences in K^{trans} between grade II and grade III ($P < .01$) and between grade II and grade IV ($P < .001$), but not between grade III and grade IV. There were also significant differences in CBV between grade II and grade IV ($P < .001$), but not between grade II and grade III or between grade III and grade IV.

Logrank tests showed significant differences in survival for histologic grade ($P < .0001$), K^{trans} ($P = .005$), and CBV ($P =$

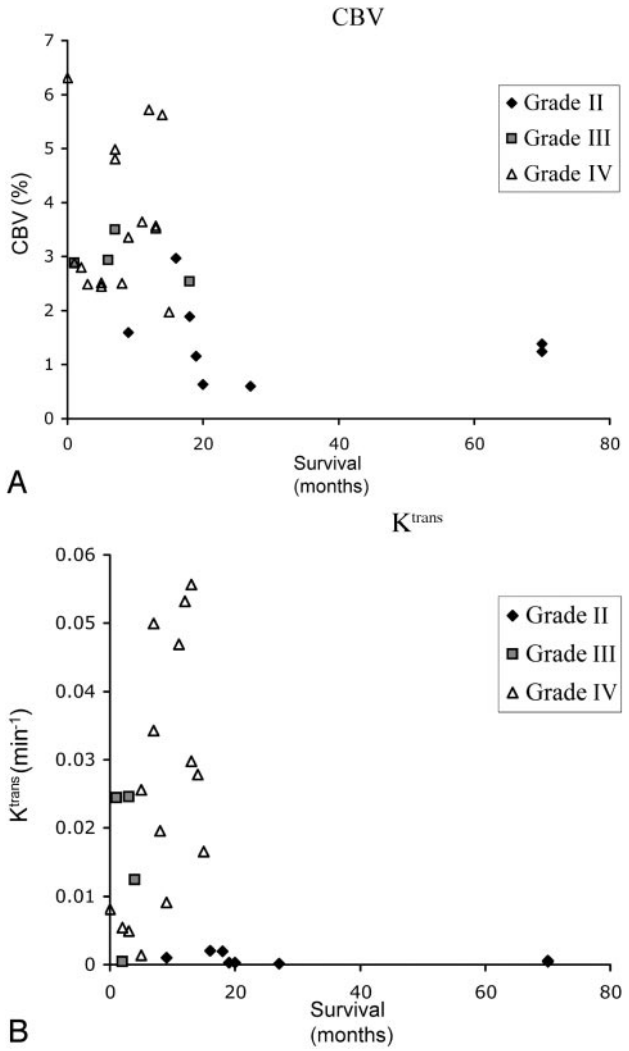

Fig 1. *A,* Cerebral blood volume (CBV) versus patient survival for tumor grades II–IV (WHO classification).

B, K^{trans} versus patient survival for tumor grades II–IV (WHO classification).

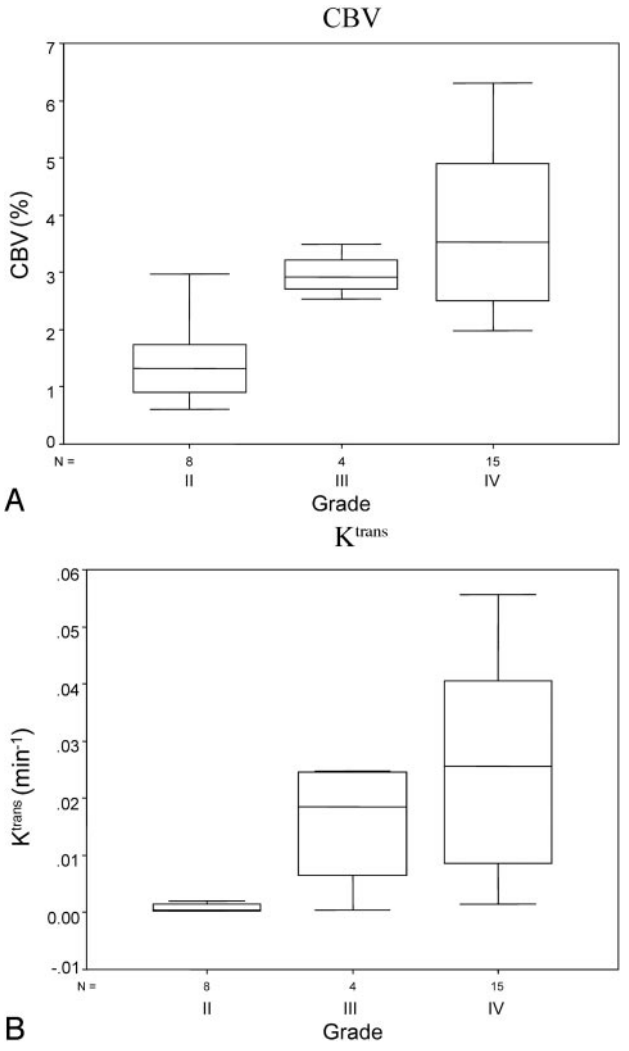

Fig 2. *A,* Boxplots showing median, interquartile range (box), and extreme values of cerebral blood volume (CBV) for tumor grades II–IV (WHO classification).

B, Boxplots showing median, interquartile range (box), and extreme values of K^{trans} for tumor grades II–IV (WHO classification).

.006; Fig 3). Logrank tests for grade IV tumors showed no residual significant differences between quartile groups defined by CBV. There was, however, a significant difference in survival in patients with grade IV tumors between those in K^{trans} groups 2, 3, and 4 ($P < .01$). Figure 4 shows the Kaplan Meier plot for these 3 patient groups in the grade IV tumor population.

Cox regression analysis of individual variables demonstrated significant relationships between overall survival and histologic grade ($P < .001$), CBV ($P = .004$), and K^{trans} ($P = .008$). The full forward stepwise regression analysis showed independent relationships only between survival and histologic grade ($P = .002$) and survival and K^{trans} ($P = .03$). Figure 5 shows scatterplots of the relationship between measured values of K^{trans} and survival in grade 3 and 4 tumors. There is a clear linear relationship between K^{trans} and survival, and linear regression analysis confirms a significant relationship ($\beta = 0.556$, $R^2 = 0.309$, $P < .01$).

Discussion

Many previous studies have shown strong relationships between histologic grade of glioma and CBV.[5-8,13-15,31-34] The relationship between K^{trans} and tumor grade is less clear, with a number of conflicting studies in the literature.[34,37,38] There is little published information regarding the relationship of these calculated parameters to patient prognosis and the role they may have in clinical practice, and histologic grade remains the best predictor of survival in patients with glioma.[42-44] Only 2 studies have demonstrated a relationship between patient survival and parameters derived from dynamic MR imaging. These studies demonstrated relationships between survival and CBV[31] and survival and maximum tumor contrast uptake.[16]

Three important observations can be made from the current study. First, histologic grade remains the most statistically significant predictor of prognosis when compared with CBV and K^{trans}. Second, CBV seems to correlate directly with patient survival, although the modified Cox regression shows this is simply a reflection of the relationship between CBV and tumor grade and has no additional prognostic value if histologic grading is performed. This is unsurprising, because many previous reports have identified a strong relationship between CBV and tumor grade.[5-8,13-15,31-34] Finally, K^{trans} demon-

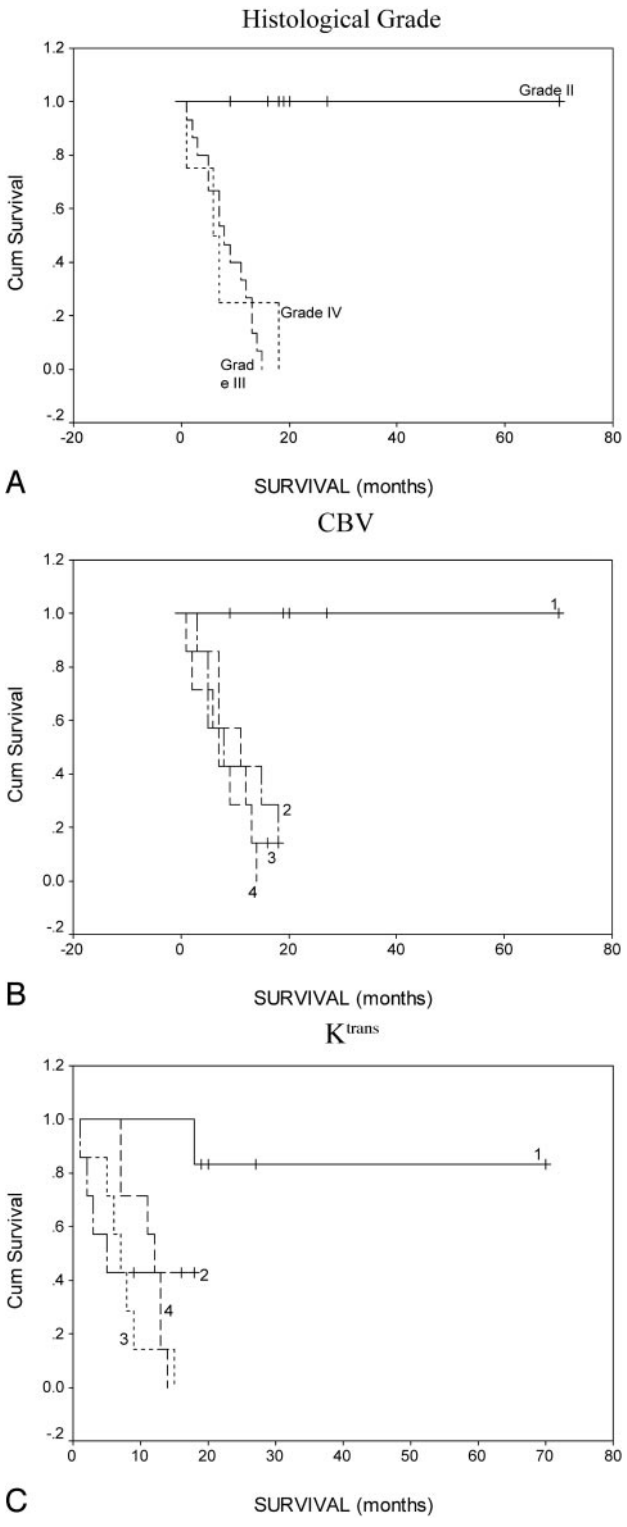

Fig 3. *A,* Kaplan Meier survival curve for histologic grade of tumor (according to WHO classification).

B, Kaplan Meier survival curve for arbitrary groups of cerebral blood volume (CBV), irrespective of grade (group 1 [$n = 6$]; range, 0.60%–1.60%; group 2 [$n = 7$]; range, 1.88%–2.54%; group 3 [$n = 7$]; range, 2.80%–3.53%; group 4 [$n = 7$]; range, 3.56%–6.31%).

C, Kaplan Meier survival curve for arbitrary groups of K^{trans}, irrespective of grade (group 1 [$n = 6$]; range, 0.00017–0.00054 minutes^{-1}; group 2 [$n = 7$]; range, 0.001–0.008 minutes^{-1}; group 3 [$n = 7$]; range, 0.009–0.025 minutes^{-1}; group 4 [$n = 7$]; range, 0.027–0.056 minutes^{-1}).

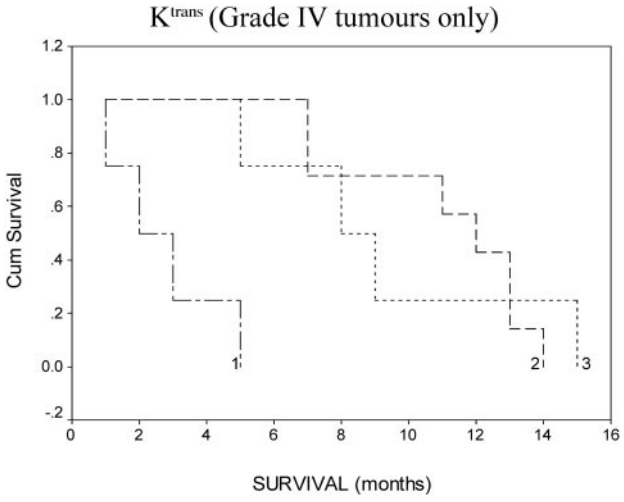

Fig 4. Kaplan Meier survival curve for arbitrary groups of K^{trans} in grade IV tumors only (group 1 [$n = 5$]; range, 0.0013–0.009 minutes^{-1}; group 2 [$n = 5$]; range, 0.016–0.029 minutes^{-1}; group 3 [$n = 7$]; range, 0.034–0.056 minutes^{-1}).

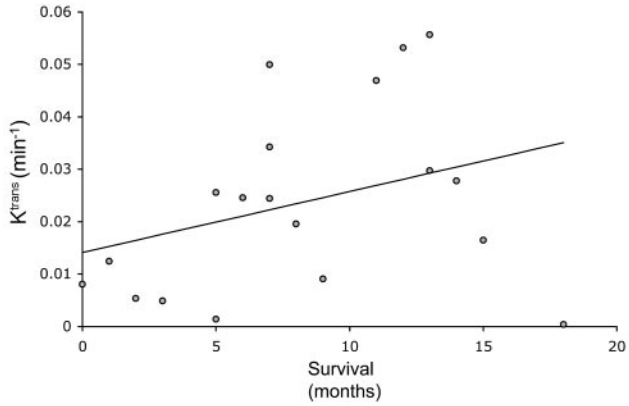

Fig 5. Relationship of K^{trans} with patient survival in high grade (III and IV) tumors. Linear regression shows increasing survival with increasing K^{trans} ($\beta = 0.556$; $R^2 = 0.309$; $P <$ .01).

strates a statistically significant relationship with prognosis, which is independent of tumor grade. This relationship is complex and nonlinear when all grades of tumor are considered in a group analysis. Clearly, low-grade tumors are associated with low values of K^{trans} and excellent survival; however, when only grade III and IV tumors are considered, a positive significant correlation can be demonstrated between K^{trans} and survival.

The nature of the relationship between K^{trans} and survival in high-grade tumors is both unexpected and counterintuitive. The prognosis of patients with high-grade gliomas shows a strong significant positive correlation with measured values of K^{trans} (ie, patients with higher values of K^{trans} showed improved survival). One might expect that more aggressive tumors with poorer prognosis would demonstrate increased angiogenic activity and therefore increased levels of blood flow and endothelial permeability, cumulatively expressed as increases in K^{trans}. When the gliomas group is considered as a whole, there is some validity in this prediction, with low-grade tumors showing very low or unmeasurable values of K^{trans} associated with long survival. In high-grade tumors, however, we have demonstrated the opposite trend and can only spec-

ulate why this unexpected relationship is seen. Such speculation is complicated by the lack of specificity of the K^{trans} measurement such that the observations could represent improved survival associated with high endothelial permeability or blood flow, or both. It is difficult to relate an improved survival to any mechanism related entirely to changes in endothelial permeability, because the major factor known to directly influence permeability is local VEGF expression. This is known to be higher in more vascular and hence (or so it is commonly assumed) more aggressive tumors. A positive relationship between blood flow and survival might be explained by improved drug delivery; however, none of our patients received adjuvant therapy. Flow-related improvements in tumor tissue oxygenation could also produce an improvement in radiation therapy response, which has been well documented in a variety of tumor types.

This study has a number of limitations that must be considered when attempting to interpret the observations described above. The main limitation is the relatively small sample size and the existence of multiple covariant factors that could also affect survival. Some potential covariants could not be included in the analysis because of the small sample size. For example, we have made no attempt to compensate for variations in the health status, intracranial pressure, or use of concurrent medications in individual patients. Similarly, we have not considered all of the imaging data available and assessment of factors such as nonenhancing tumor size and volume of edema could help explain the relationship between K^{trans} and survival. In addition some of the factors included in the analysis may demonstrate sample bias—for example, the decision to undertake tumor resection may be based largely on its position and size so that the use of resection does not act as a truly independent factor.

The findings described here clearly indicate the need for a large-scale prospective study to examine the potential clinical value of K^{trans} and other parametric variables calculated from DCE-MR imaging. Unfortunately, because of the potential variability in treatment regime and the number of cofactors that need to be included in the analysis, it is not possible to perform a formal power calculation to predict the necessary size of such a study. A group multiple correlation estimation based on the current sample size of patients, including all noncategorical variables (K^{trans}, CBV, and age), however, predicts a requirement for a minimum sample population of 55 high-grade tumors to detect a 60% improvement in survival at a significance level of 5% with 80% power. Taking into account the important categorical variables (grade, use of radiation therapy, use of surgical debulking, and use of adjuvant chemotherapy) would increase this requirement, although no model exists to allow accurate calculation of the sample size increase required. If the study were to be limited to only grade IV tumors, however, assuming that these constitute approximately 80% of cases, radiation therapy usage is assumed to be at a high level (>90%), and surgical debulking rates run at around 40% (which is typical at this center), one could estimate a sample size requirement of $55/(0.8 \times 0.6 \times 0.9)$. This would allow confident detection of pure prognosis-related effects of CBV and K^{trans} in grade IV tumors treated with radiation therapy alone. This approach to sample size calculation is actually overly simplistic and represents a "best case scenario" that would be complicated by inclusion of other new variables and changes in treatment strategy. Nonetheless, it indicates the need for a prospective cohort study of at least 128 nonsurgically treated patients with high-grade tumors and follow-up to death. The potential value of these techniques in clinical management—but, more important, in the development of principled approaches to the design of imaging based trials of therapeutic agents—is such that we believe a large-scale study of this type forms an essential next step in the assessment of dynamic contrast-enhanced MR imaging in human gliomas. Detecting similar differences in grade III tumors with no radiation therapy but with surgical debulking would require a sample size larger than 6000, making such a study impractical.

In conclusion, this small study suggests a possible direct association between K^{trans} and length of survival in patients with grade IV gliomas that may be of considerable clinical importance. CBV is directly related to histologic grade and does not provide any independent prognostic information over and above histologic information. We conclude that a large-scale prospective study of dynamic contrast-enhanced–MR imaging in glioma management is both timely, essential, and warranted on the basis of our observations.

References

1. Wyllie AD. **Growth and neoplasia.** In: MacSween N, Whaley K. *Muir's textbook of pathology.* 13th ed. London: Edward Arnold; 1992;355–410
2. Plate KH, Breier G, Weich HA, et al., **Vascular endothelial growth factor is a potential tumour angiogenesis factor in human gliomas in vivo.** *Nature* 1992; 359:845–48
3. Dvorak HF, Brown LF, Detmar M, et al. **Vascular permeability factor/vascular endothelial growth factor: an important mediator of angiogenesis in malignancy and inflammation.** *Int Arch Allergy Immunol* 1995;107:233–35
4. Chaudhry IH, O'Donovan DG, Brenchley PEC, et al. **Vascular endothelial growth factor expression correlates with tumour grade and vascularity in gliomas.** *Histopathology* 2001;39:409–15
5. Warmuth C, Gunther M, Zimmer C. **Quantification of blood flow in brain tumors: comparison of arterial spin labeling and dynamic susceptibility-weighted contrast-enhanced MR imaging**. *Radiology* 2003;228:523–32
6. Sugahara T, Korogi Y, Tomiguchi, et al. **Perfusion-sensitive MR imaging of gliomas: comparison between gradient-echo and spin-echo echo-planar imaging techniques.** *AJNR Am J Neuroradiol* 2001;22:1306–15
7. Ludemann L, Grieger W, Wurm R, et al. **Comparison of dynamic contrast-enhanced MRI with WHO tumor grading for gliomas.** *Eur Radiol* 2001;11: 1231–41
8. 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; 24:1989–98
9. Hacklander T, Hofer M, Reichenbach JR, et al. **Cerebral blood volume maps with dynamic contrast-enhanced T1-weighted FLASH imaging: normal values and preliminary clinical results.** *J Comput Assist Tomogr* 1996;20:532–39
10. Fuss M, Wenz F, Essig M, et al. **Tumor angiogenesis of low-grade astrocytomas measured by dynamic susceptibility contrast-enhanced MRI (DSC-MRI) is predictive of local tumor control after radiation therapy.** *Int J Radiat Oncol Biol Phys* 2001;51:478–82
11. Bruening R, Kwong KK, Vevea MJ, et al. **Echo-planar MR determination of relative cerebral blood volume in human brain tumors: T1 versus T2 weighting.** *AJNR Am J Neuroradiol* 1996;17:831–40
12. Aronen HJ, Perkio J. **Dynamic susceptibility contrast MRI of gliomas.** *Neuroimaging Clin North Am* 2002;12:501–23
13. Aronen HJ, Gazit IE, Louis DN, et al. **Cerebral blood volume maps of gliomas: comparison with tumor grade and histologic findings.** *Radiology* 1994;191: 41–51
14. Sugahara T, Korogi Y, Kochi M, et al. **Correlation of MR imaging–determined cerebral blood volume maps with histologic and angiographic determination of vascularity of gliomas.** *AJR Am J Roentgenol* 1998;171:1479–86
15. Sugahara T, Korogi Y, Shigematsu Y, et al. **Value of dynamic susceptibility contrast magnetic resonance imaging in the evaluation of intracranial tumors.** *Top Magn Reson Imaging* 1999;10:114–24
16. Wong ET, Jackson ER, Hess KR, et al. **Correlation between dynamic MRI and outcome in patients with malignant gliomas**. *Neurology* 1998;50:777–81

17. Wong JC, Provenzale JM, Petrella JR. **Perfusion MR imaging of brain neoplasms.** *AJR Am J Roentgenol* 2000;174:1147–57
18. Cha S, Knoff EA, Johnson G, et al. **Intracranial mass lesions: dynamic contrast-enhanced susceptibility-weighted echo-planar perfusion MR imaging.** *Radiology* 2002;223:11–29
19. Lev MH, Rosen BR. **Clinical applications of intracranial perfusion MR imaging.** *Neuroimaging Clin North Am* 1999;9:309–31
20. Petrella JR, Provenzale JM. **MR perfusion imaging of the brain: techniques and applications.** *AJR Am J Roentgenol* 2000;175:207–19
21. Tofts PS, Brix G, Buckley DL, et al. **Estimating kinetic parameters from dynamic contrast-enhanced T(1)-weighted MRI of a diffusable tracer: standardized quantities and symbols.** *J Magn Reson Imaging* 1999;10:223–32
22. Johnson G, Wetzel SG, Cha S, et al. **Measuring blood volume and vascular transfer constant from dynamic, T(2)*-weighted contrast-enhanced MRI.** *Magn Reson Med* 2004;51:961–68
23. Vonken EP, van Osch MJ, Bakker CJ, et al. **Simultaneous quantitative cerebral perfusion and Gd-DTPA extravasation measurement with dual-echo dynamic susceptibility contrast MRI.** *Magn Reson Med* 2000;43:820–27
24. Zhu XP, Li KL, Kamaly-Asl ID, et al. **Quantification of endothelial permeability, leakage space, and blood volume in brain tumors using combined T1 and T2* contrast-enhanced dynamic MR imaging.** *J Magn Reson Imaging* 2000;11:575–85
25. Li KL, Jackson A. **New hybrid technique for accurate and reproducible quantitation of dynamic contrast-enhanced MRI data.** *Magn Reson Med* 2003;50:1286–95
26. Roberts TP. **Physiologic measurements by contrast-enhanced MR imaging: expectations and limitations.** *J Magn Reson Imaging* 1997;7:82–90
27. Weisskoff RM, Boxerman JL, Sorensen AG, et al. **Simultaneous blood volume and permeability mapping using a single Gd-based contrast injection.** In: *Proceedings of the Society of Magnetic Resonance, Second Annual Meeting*; 1994 Aug 6–12; San Francisco, Calif. Berkeley, Calif: Society of Magnetic Resonance; 1994:279
28. Hacklander T, Reichenbach JR, Modder U. **Comparison of cerebral blood volume measurements using the T1 and T2* methods in normal human brains and brain tumors.** *J Comput Assist Tomogr* 1997;21:857–66
29. Kassner A, Annesley D, Zhu XP, et al. **Abnormalities of the contrast re-circulation phase in cerebral tumors demonstrated using dynamic susceptibility contrast-enhanced imaging: a possible marker of vascular tortuosity.** *J Magn Reson Imaging* 2000;11:103–13
30. Jackson A, Kassner A, Zhu XP, et al. **Reproducibility of T2* blood volume and vascular tortuosity maps in cerebral gliomas.** *J Magn Reson Imaging* 2001;14:510–16
31. Lev MH, Ozsunar Y, Henson JW, et al. **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** [published erratum appears in *AJNR Am J Neuroradiol* 2004;25(3):B1]. *AJNR Am J Neuroradiol* 2004;25:214–21
32. Knopp EA, Cha S, Johnson G, et al. **Glial neoplasms: dynamic contrast-enhanced T2*-weighted MR imaging.** *Radiology* 1999;211:791–98
33. Shin JH, Lee HK, Kwun BD, et al. **Using relative cerebral blood flow and volume to evaluate the histopathologic grade of cerebral gliomas: preliminary results.** *AJR Am J Roentgenol* 2002;179:783–89
34. Law M, Yang S, Babb JS, et al. **Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast-enhanced perfusion MR imaging with glioma grade.** *AJNR Am J Neuroradiol* 2004;25:746–55
35. Li KL, Jackson A. **Simultaneous mapping of blood volume and endothelial permeability surface area product in gliomas using iterative analysis of first-pass dynamic contrast enhanced MRI data.** *Br J Radiol* 2003;76:39–50
36. Jackson A, Grayson GC, Li KL, et al. **Reproducibility of quantitative dynamic contrast-enhanced MRI in newly presenting glioma.** *Br J Radiol* 2003;76:153–62
37. Provenzale JM, Wang GR, Brenner T, et al. **Comparison of permeability in high-grade and low-grade brain tumors using dynamic susceptibility contrast MR imaging.** *AJR Am J Roentgenol* 2002;78:711–16
38. Roberts HC, Roberts TPL, Brasch RC, et al. **Quantitative measurement of microvascular permeability in human brain tumors achieved using dynamic contrast-enhanced MR imaging: correlation with histologic grade.** *AJNR Am J Neuroradiol* 2000;21:891–99
39. Li KL, Zhu XP, Waterton J, et al. **Improved 3D quantitative mapping of blood volume and endothelial permeability in brain tumors.** *J Magn Reson Imaging* 2000;12:347–57
40. Haroon HA, Buckley DL, Patankar TA, et al. **A comparison of Ktrans measurements obtained with conventional and first pass pharmacokinetic models in human gliomas.** *J Magn Reson Imaging* 2004;19:527–36
41. Patankar TA, Haroon HA, Mills SJ, et al. **Is volume transfer coefficient (K^{trans}) related to histological grade in human gliomas***? AJNR Am J Neuroradiol* 2005;26:2455–65
42. Bauman G, Lote K, Larson D, et al. **Pretreatment factors predict overall survival for patients with low-grade glioma: a recursive partitioning analysis.** *Int J Radiat Oncol Biol Phys* 1999;45:923–29
43. Scott CB, Scarantino C, Urtasun R, et al. **Validation and predictive power of Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis classes for malignant glioma patients: a report using RTOG 90–06.** *Int J Radiat Oncol Biol Phys* 1998;40:51–55
44. Pignatti F, van den Bent M, Curran D, et al. **Prognostic factors for survival in adult patients with cerebral low-grade glioma.** *J Clin Oncol* 2002;20:2076–84
45. Fazeny-Dorner B, Wenzel C, Veitl M, et al. **Survival and prognostic factors of patients with unresectable glioblastoma multiforme.** *Anticancer Drugs* 2003;14:305–12
46. Kreth FW, Berlis A, Spiropoulou V, et al. **The role of tumor resection in the treatment of glioblastoma multiforme in adults.** *Cancer* 1999;86:2117–23
47. Paszat L, et al. **A population-based study of glioblastoma multiforme.** *Int J Radiat Oncol Biol Phys* 2001;51:100–07
48. Stewart LA. **Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials.** *Lancet* 2002;359:1011–18
49. Kleihues P, Burger PC, Scheithauer, et al. **The WHO classification of tumors of the nervous system.** *J Neuropathol Exp Neurol* 2002;61:215–25; discussion 226–29
50. Collet D. *Modeling survival data in medical research*. New York: Chapman and Hall; 1994