“Tumoral Pseudoblush” Identified within Gliomas at High-Spatial-Resolution Ultrahigh-Field-Strength Gradient-Echo MR Imaging Corresponds to Microvasculature at Stereotactic Biopsy¹

Gregory A. Christoforidis, MD
Ming Yang, MD
Amir Abduljalil, PhD
Abhik R. Chaudhury, MD
Herbert B. Newton, MD
John M. McGregor, MD
Clara R. Epstein, MD
William T. C. Yuh, MD
Sydeaka Watson, PhD
Pierre-Marie L. Robitaille, PhD

Purpose:

To use directed biopsy sampling to determine whether microvascular assessment within gliomas, by means of ultrahigh-field-strength high-spatial-resolution gradient-echo (GRE) magnetic resonance (MR) imaging at 8 T, correlates with histopathologic assessment of microvasculature.

Materials and Methods:

The study was institutional review board approved and HIPAA compliant. Informed consent was obtained. Thirty-five subjects with gliomas underwent 8-T and 80-cm MR imaging by using a GRE sequence (repetition time, 600–750 msec; echo time, 10 msec; in-plane resolution, 196 μ m). Haphazardly arranged serpentine low-signal-intensity structures, often associated with areas of low signal intensity within the tumor bed (“tumoral pseudoblush”) at MR imaging, were presumed to be related to tumoral microvasculature. Microvessel density (MVD) and microvessel size (MVS) ranked with a semiquantitative three-tier scale (high, medium, and low) relative to cortical penetrating veins were assessed from regions of interest identified at MR imaging and were compared with a similar assessment of stereotactic biopsy specimens by using Kendall τ_b . Tumor grade (high vs low) was compared with ultrahigh-field-strength high-resolution GRE MR analysis by using Pearson χ^2 . Discrepancies between 8-T and histopathologic assessment were identified and analyzed.

Results:

Ultrahigh-field-strength high-resolution GRE MR imaging and histopathologic assessment concurred for MVS ($P < .0001$) and MVD ($P < .0001$). World Health Organization classification tumor grade was associated with number ($P < .0005$) and size ($P < .0005$) of foci of microvasculature within the tumor bed at 8-T MR imaging. Radiation-induced microvessel hyalinosis mimicked tumor microvasculature at 8-T MR imaging. Potential confounders could result from radiofrequency inhomogeneity and displaced normal microvasculature.

Conclusion:

Microvasculature identified as a tumoral pseudoblush at ultrahigh-field-strength high-resolution GRE MR imaging without contrast material shows promise as a marker for increased tumoral microvasculature.

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¹From the Departments of Radiology (G.A.C.) and Health Studies (S.W.), University of Chicago Medical Center, 5841 S Maryland Ave, MC2026, Chicago, IL 60601; and Departments of Radiology (M.Y., A.A., C.R.E., W.T.C.Y., P.M.L.R.), Pathology (A.R.C.), Neurology (H.B.N.), and Neurological Surgery (J.M.M.), Ohio State University, Columbus, Ohio. Received April 19, 2011; revision requested July 11; revision received December 1; accepted December 28; final version accepted February 7, 2012. Address correspondence to G.A.C. (e-mail: gchristoforidis@radiology.bsd.uchicago.edu).

Histopathologic evidence for mitotic figures, necrosis, or vascular proliferation tends to classify gliomas as high grade (1). Burger et al (2) reported that vascular proliferation was the single most important histopathologic finding predictive of survival in a study of 1440 anaplastic astrocytomas. Because biomarkers predictive of high grade, including vascular proliferation, are often heterogeneously distributed within a glioma, nondirected biopsy or resection sampling may lack critical information to appropriately grade a glioma and may result in tumor undergrading. As a result, preoperative in vivo imaging localization of features suggestive of high grade, such as vascular proliferation within an astrocytoma, may play an important role to guide biopsy and thus facilitate appropriate diagnosis.

The improved signal-to-noise ratio, possible with ultrahigh-field-strength magnetic resonance (MR) imaging, allows for the acquisition of high-spatial-resolution images of the central nervous system. One major advantage of gradient-echo (GRE) MR imaging has been its ability to delineate venous anatomy. The paramagnetic properties of deoxyhemoglobin, combined with the increasing magnetic susceptibility effects at higher field strengths, allow microvessels smaller than the acquired in-plane resolution to be resolved on T2*-weighted images. Indeed, microvessels with a diameter as small as 100 μm can be resolved at ultrahigh-field-strength GRE MR imaging by using an in-plane resolution of 196 μm in normal human brain and in glial tumors (3–6). Ultrahigh-field-strength high-resolution GRE MR imaging findings of enlarged and distorted microvasculature,

enlargement of draining veins, and adjacent signal intensity loss suggest increased microvascular proliferation within a tumor bed (3,4). Visibility of microvasculature identified at high-resolution GRE MR imaging in a nude mouse glioma model at 4.7-T MR imaging and in a Fischer rat F98 glioma model at 8 T has been shown to correlate with histopathologically identified increased microvascular density and hypoxia within the tumor bed (7,8). It should therefore be expected that ultrahigh-field-strength high-resolution GRE MR imaging can be used to help visualize foci with increased microvasculature within human brain tumors. These unique findings within primary brain tumors at ultrahigh-field-strength high-resolution GRE MR imaging without contrast agents cannot be identified at conventional 1.5-T MR imaging but have been demonstrated at conventional cerebral angiography (9–11). This study used directed biopsy sampling to determine whether microvascular assessment within gliomas, by means of ultrahigh-field-strength high-spatial-resolution GRE MR imaging at 8 T, correlates with histopathologic assessment of microvasculature.

Materials and Methods

Subjects

Male and female patients between 21 and 75 years old known to have a diagnosis of a primary brain tumor or suspected of having a primary brain tumor and considered for either biopsy or surgical excision were prospectively eligible to enter this study between November 2000 and January 2006. This study was institutional review board approved and Health Insurance Portability and Accountability Act compliant. Informed

patient consent was obtained. Patients were excluded if biopsy results were not consistent with tumor of neuroepithelial tissue origin or if stereotactic biopsy samples were not obtained or not properly labeled.

A total of 55 patients who met entry criteria initially agreed to undergo ultrahigh-field-strength high-spatial-resolution GRE MR imaging. Ten of these patients ultimately did not undergo imaging predominantly because they decided not to participate. An additional five patients either did not undergo stereotactic biopsy or their specimens were not properly labeled. An additional five patients who were initially thought to have a primary brain tumor ultimately had a singular metastasis. Thirty-five subjects with a mean age of 42.9 years (age range, 23–70 years) bearing biopsy-proved gliomas were therefore included in this study. There were 15 women with a mean age of 43.3 years (age range, 23–62 years) and 20 men with a median age of 42.7 years (age range, 24–70 years). World Health Organization (WHO) classification grades were used and included the following: WHO grade I, six biopsy samples in four

Advance in Knowledge

- This study confirms that increased microvasculature visualized within gliomas by using ultrahigh-field-strength high-spatial-resolution gradient-echo (GRE) MR imaging correlates with histopathologic evidence for higher microvascular density.

Implication for Patient Care

- The identification of tumoral microvasculature by using ultrahigh-field-strength high-spatial-resolution GRE MR imaging may serve to target potentially higher-grade foci within a tumor bed during biopsy planning.

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Abbreviations:

GRE = gradient echo
MVD = microvessel density
MVS = microvessel size
WHO = World Health Organization

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subjects; WHO grade II, 37 biopsy samples in nine subjects; WHO grade III, 26 biopsy samples in nine subjects; and WHO grade IV, 64 biopsy samples in 13 subjects. This included 13 astrocytic tumors (seven anaplastic astrocytomas, two pleomorphic xanthoastrocytomas, three juvenile pilocytic astrocytomas, one low-grade diffuse infiltrative astrocytoma), seven oligodendroglial tumors (two oligoastrocytomas, five oligodendrogliomas), three neuroglial tumors (one central neurocytoma, one ganglioglioma, one dysembryoplastic neuroepithelial tumor), 11 glioblastomas, and one medulloblastoma. Twenty-four patients underwent no prior surgery. Three underwent prior biopsy only, and eight underwent prior surgery and radiation treatment, of which four also underwent chemotherapy.

Imaging

Ultrahigh-field-strength high-spatial-resolution GRE MR imaging was performed with an 8-T and 80-cm MR imaging system (Magnex-GE, Abingdon, England) equipped with a console (Avance; Bruker, Billerica, Mass) interfaced with gradient amplifiers (Techon; Crown International, Elkhart, Ind) and by using a custom-built radiofrequency front end. A modified four-channel quadrature transverse electromagnetic transmit-and-receive coil was tuned to the head of each subject at 340 MHz. A conventional two-dimensional T2*-weighted GRE sequence was used (repetition time, 600–750 msec; echo time, 10 msec; flip angle, 22.50°; matrix, 1024 × 1024; field of view, 20 cm; section thickness, 2 mm; intersection gap, 3 mm). Eighteen to 20 cross-section sections covering the region of tumor were acquired in 12 minutes with an in-plane resolution at 196 μ m. These parameters were derived from a solution to the Bloch equations for the spoiled GRE sequence and from preliminary 8-T relaxation parameter estimates. Ultrahigh-field-strength high-resolution GRE MR imaging preceded 1.5-T MR imaging for stealth navigation.

Stereotaxis

During the immediate preoperative period, subjects underwent frameless

stereotactic 1.5-T MR imaging (Signa; GE Healthcare, Milwaukee, Wis) by using 10 scalp fiducial markers. Regions of interest identified at ultrahigh-field-strength high-resolution GRE MR imaging intended for biopsy were coregistered to 1.5-T MR images used for frameless stereotactic navigation (StealthStation; Surgical Navigation Technologies, Louisville, Colo). The StealthStation system allows reconstruction and resampling of an acquired three-dimensional 1.5-T data set in such a manner so as to align imaging plane and section thickness of 8-T images. Anatomic landmarks identified on both the 8-T and 1.5-T images were used to align imaging planes between 8-T and reconstructed 1.5-T images on the basis of relative distances from the nearest three anatomic landmarks. The sections were reviewed, and the stereotactic coordinates were established for each biopsy site (Fig 1). By using the frameless biopsy arm and a stereotactic biopsy needle, specimens were then taken from previously chosen sites that represented possible increased or decreased microvasculature as suggested at ultrahigh-field-strength high-resolution GRE MR imaging within the area of planned tumor resection. The biopsy specimens were labeled, and their location within the ultrahigh-field-strength high-resolution GRE MR imaging section was recorded. The accuracy of the stereotactic method used was tested on a phantom model and was found to be within 0.05–1.91 mm. Error due to brain shift was minimized by reviewing biopsy sites with the surgeon and obtaining samples early during the surgery.

Assessment of Tumor Microvasculature

Ultrahigh-field-strength high-resolution GRE MR images of each subject's brain tumor were prospectively reviewed by two radiologists (G.A.C., M.Y.) who were blinded to biopsy results for haphazardly arranged serpentine low-signal-intensity structures within the tumor bed at ultrahigh-field-strength high-resolution GRE MR imaging that were suspected to represent microvasculature, as previously described (3,4) (Figs 1–3).

Regions of interest thought to represent hemorrhage within the tumor bed in which biopsy was performed were not considered part of the analysis (Fig 4). Both radiologists had 1 year of previous experience evaluating ultrahigh-field-strength high-resolution GRE MR images for microvasculature in humans as well as rodents. Both radiologists agreed on a final assessment for both microvessel density (MVD) and microvessel size (MVS). Regions of interest, with or without microvasculature, identified on phase and magnitude ultrahigh-field-strength high-resolution GRE MR images were selected from each tumor bed and ranked with a semiquantitative three-tier scale based on MVS and MVD. Tumoral MVD was graded as low (grade 1), medium (grade 2), or high (grade 3) relative to the density of penetrating veins within gray matter. MVS was graded as small (grade 1) when invisible (Fig E1 [online]), medium (grade 2) when equal to or smaller than cortical penetrating veins, or large (grade 3) when larger than cortical penetrating veins (Fig 3). The results were then compared with histopathologic analysis. In an effort to help analyze discrepancies between histopathologic and 8-T imaging assessment of microvasculature, signal-to-noise ratio and contrast-to-noise ratio were assessed for each image. In addition, images and histopathologic findings were reviewed for presence of blood products and necrosis, which were considered potential mimickers for microvasculature. Interobserver agreement for MVS and MVD between two observers (M.Y., G.A.C.) was tested on 50 regions of interest chosen by one observer and compared with observations by a second observer who was blinded to the first observer's assessment. The results were then compared by using a weighted κ statistic, revealing κ of 0.960 for MVD and 0.975 for MVS (12).

Although not the primary focus of this work, the number and size of foci with increased microvasculature identified on ultrahigh-field-strength high-resolution GRE MR images were compared with tumor grade. The number of foci found in each tumor bed was tabulated and placed in one of four

categories as follows: those that had no foci, one focus, two to four foci, and more than four foci. Similarly, the diameter of the largest focus of increased microvasculature within each tumor was measured and placed in one of four categories (0 cm, <0.5 cm, 0.5–1.0 cm, and >1.0 cm). The number and size of the foci with increased microvasculature were then compared with tumor grade by using contingency analysis.

Histopathologic Analysis

Biopsy specimens from regions of interest were evaluated by using reticulin stains and hematoxylin-eosin stains. Tumoral microvasculature, based on microvascular density and size, at histopathologic examination was graded as high, medium, or low relative to normal white matter and gray matter by an experienced neuropathologist (A.R.C.). These results were then compared with microvascular assessments made with 8-T MR imaging. Biopsy specimens were also reviewed for presence of hemosiderin and necrosis. Hemosiderin deposition and necrosis could potentially create a susceptibility effect similar in appearance to microvasculature (Fig 4). All histopathologic analysis occurred after ultrahigh-field-strength high-resolution GRE MR analysis was completed.

Statistical Analysis

Contingency tables were generated comparing MVD and MVS for ultrahigh-field-strength high-resolution GRE MR and histopathologic assessment of directed biopsy specimens. Significance was calculated by using Kendall τ_b , a rank-based statistic that exploits the ordinal nature of the data and includes an adjustment for clustering (13). Kendall τ_b values range from -1 (perfect negative association) to 1 (perfect positive association). A value of 0 would be obtained in the presence of two quantities exhibiting no overall ordinal relationship. Statistical tests assume a t distribution with $n - 1$ degrees of freedom, where n is the number of clusters. Calculations for Kendall τ_b were performed in software (Stata, release 12, 2011; Stata, College Station, Tex) by using the somersd function in the somersd package. This

Figure 1

Figure 1: (a) Axial gadolinium-enhanced T1-weighted MR image in 24-year-old man with history of blurry vision, headaches, and papilledema associated with an intraventricular mass. (b) Axial ultrahigh-field-strength high-resolution GRE MR image shows stereotactic biopsy site of a focus suggestive of high microvasculature that was shown at histopathologic assessment to represent a high degree of microvascular density, with microvessels similar in size to cortical draining veins within a WHO grade II central neurocytoma. (c) MR image shows serpentine flow voids and surrounding signal intensity loss within the biopsy site (tumoral pseudoblush). (d) Ultrahigh-field-strength high-resolution GRE MR image from an adjacent section within the tumor 2 cm beneath the biopsy site shows associated enlarged tributary to the thalamostriate vein (arrowheads) coursing medial to lateral in and out of the imaging plane. This information can assist stereotactic biopsy planning because damage to this vessel can result in substantial bleeding.

method was applied to the assessment of size and density given clustering by patient ($n = 35$) and glioma type ($n = 11$). Discrepancies between 8-T and histopathologic assessment of MVD were identified and analyzed.

Contingency tables were generated comparing tumor grade identified at

histopathologic examination with ordinally categorized number and size of foci identified at ultrahigh-field-strength high-resolution GRE MR imaging. Significance of association was calculated by using Pearson χ^2 analysis. A P value less than .05 indicated a significant difference.

Figure 2

Figure 2: (a) Axial ultrahigh-field-strength high-resolution GRE MR image in 58-year-old woman with left leg numbness and weakness due to a right parietal lobe glioblastoma near the central sulcus. Box indicates area enlarged in (b) MR image that shows stereotactic biopsy sites where specimens were taken from foci (A, B, C) outlined by arrowheads. (c) At histopathologic assessment, focus A was found to harbor low microvasculature (not shown). Focus B from an area of tumoral pseudoblast represented an area of high microvascular density and large microvascular size with endothelial proliferation (arrowheads). (Hematoxylin-eosin stain; original magnification, $\times 200$.) Focus C revealed hemorrhagic necrosis (not shown).

Results

Correlation of Microvasculature at 8-T Imaging to That at Histopathologic Assessment

Both microvascular density and size of microvessels relative to normal cortical vessels at high-resolution GRE 8-T MR imaging correlated to MVD and MVS identified with histopathologic stains at 133 directed biopsies in 35 patients (Tables 1, 2). Thirty-two biopsies came from the eight patients who underwent prior treatment. Disagreement was found in two of 32 regions of interest for

MVS and in one of 32 for MVD. These were rated as medium MVS or MVD at histopathologic examination and high MVS or MVD at ultrahigh-field-strength high-resolution GRE MR imaging.

Discrepancies between MR imaging findings and histopathologic findings from directed biopsies were reviewed. For MVD, discrepancies were attributable to oligodendrogliomas whose concentrated fine vascular structures were considered to be high density, but small vessels at histopathologic examination were not visualized at ultrahigh-field-strength high-resolution GRE MR imaging. Furthermore, ultrahigh-field-strength high-resolution GRE MR imaging was not able to facilitate discrimination of radiation-induced microvascular change

from neovascularity. Although visibility of microvasculature at 8-T MR imaging was predictive of increased microvascular density and size at pathologic examination, microvascular visibility did not always imply higher tumor grade. Discrepancies for tumor grade shown in Tables 3 and 4 predominantly occurred in low-grade tumors (Fig E2 [online]) and in radiation necrosis (Fig E3 [online]). Hemosiderin deposition and normal vascular structures were sometimes difficult to distinguish from microvasculature. In general, tumoral microvasculature was distinguishable on the basis of the serpentine pattern associated with tumoral microvasculature. Hemosiderin deposition typically had a more pronounced and focal pattern with “blooming” (Fig 4). Normal vascular structures could be traced to the draining vein and lacked the serpentine and haphazard pattern associated with tumoral microvasculature. Finally, experience accumulated during this work suggests that normal but displaced vasculature may require careful scrutiny to distinguish from de novo microvasculature arising within a tumor.

Signal-to-noise ratio and contrast-to-noise ratio were not normally distributed according to the Shapiro-Wilk test ($W = 0.89$ for signal-to-noise ratio and $W = 0.89$ for contrast-to-noise ratio). Median signal-to-noise ratio for tumor signal versus noise was 15.8 (quartile range, 11.4–24.1). Median contrast-to-noise ratio for tumor-to-vein signal was 12.6 (quartile range, 8.54–20.5). Medians were skewed below the means for both signal-to-noise ratio and contrast-to-noise ratio. Neither signal-to-noise ratio nor contrast-to-noise ratio explained discrepancies between MR imaging evaluation of microvasculature and histopathologic findings.

Correlation of Microvasculature to Tumor Grade

In 35 gliomas, tumor grade classified as low (WHO I or WHO II) and high (WHO III and WHO IV) correlated to the number of foci of microvasculature within the tumor bed and size of the largest focus of increased microvasculature within the tumor bed (Tables 3, 4). Discrepancies between tumor grades in

Figure 3

b.

a.

c.

Figure 3: Data in 55-year-old woman with visual changes and headache. **(a, b)** Axial ultrahigh-field-strength high-resolution GRE MR images reveal foci with a high degree of microvascular density and large size (arrowheads in **b**). Box indicates area enlarged in **b**. **(c)** Histopathologic findings show that stereotactic biopsy of this focus revealed a high degree of microvascular density and large microvessels with endothelial proliferation (arrowheads), which corroborates MR imaging findings. (Reticulin stain; original magnification, $\times 200$.)

biopsy guidance, with diminished potential for undergrading of a tumor, as well as monitoring response to treatments targeting microvascular proliferation and confirmation of microvasculature identified on perfusion-based studies.

Imaging methods currently used to assess glioma microvasculature do so by evaluating perfusion within the tumor bed, by using dynamic contrast material-enhanced or arterial spin-labeling techniques, thus providing functional or physiologic insight into microvascular density. Relative cerebral blood volume maps created by using MR imaging, and more recently computed tomography, indirectly help measure microvascular density and MVS (11,14,15). Dynamic contrast-enhanced MR imaging may help evaluate vascular permeability, which has been shown to correspond to endothelial proliferation (15). In contrast, distinction, ultrahigh-field-strength high-resolution GRE MR imaging helps assess

Figure 4

a.

b.

Figure 4: **(a)** Axial ultrahigh-field-strength high-resolution GRE MR image shows area of profound signal intensity loss due to susceptibility effect within a glioblastoma (arrowheads). **(b)** Histopathologic findings show that stereotactic biopsy of this area of signal intensity loss revealed hemorrhagic necrosis associated with fibrinoid change and occluded vessels. (Hematoxylin-eosin stain; original magnification, $\times 200$.)

Tables 1 and 2 included a central neurocytoma (Fig 1), a juvenile pilocytic astrocytoma (Fig E2 [online]), a pleomorphic xanthoastrocytoma, and a ganglioglioma. These tumors are typically low-grade tumor types known to be highly vascular but without histopathologic evidence for neovascularity.

Discussion

In the current study, tumoral pseudo-blush identified at ultrahigh-field-strength high-resolution GRE MR imaging corresponded to histopathologically proved foci of microvasculature and was predictive of tumor grade. Correlation of pseudo-blush with microvasculature may facilitate

visibility of microvasculature within gliomas, thus providing an anatomic assessment of glioma microvasculature, rather than a dynamic assessment. The distinction lies in the fact that ultrahigh-field-strength high-resolution GRE MR imaging provides direct visualization of microvasculature, while dynamic susceptibility imaging provides a dynamic examination of perfusion status. Ultrahigh-field-strength high-resolution GRE MR imaging relies on paramagnetic deoxyhemoglobin to create local magnetic

Table 1**Association of MVD at Histopathologic Examination and Ultrahigh-Field-Strength High-Resolution GRE MR Imaging**

MR Imaging Analysis	Histopathologic Analysis			Total
	Low	Medium	High	
Low	26	9	2	37
Medium	1	12	10	23
High	0	5	68	73
Total	27	26	80	133

Note.—Data are number of biopsies. Kendall τ_b association adjusted for patient clustering was 0.783 ($P < .0001$); Kendall τ_b association adjusted for glioma type clustering was 0.795 ($P < .0001$).

Table 2**Association of MVS at Histopathologic Examination and Ultrahigh-Field-Strength High-Resolution MR Imaging**

MR Imaging Analysis	Histopathologic Analysis			Total
	Low	Medium	High	
Low	36	2	0	38
Medium	0	7	3	10
High	0	11	74	85
Total	36	20	77	133

Note.—Data are numbers of biopsies. Kendall τ_b association adjusted for patient clustering was 0.856 ($P < .0001$); Kendall τ_b association adjusted for glioma type clustering was 0.874 ($P < .0001$).

field inhomogeneity, which leads to a faster loss of phase coherence and selective shortening of the T2 relaxation time. This allows for identification of vessels smaller than the in-plane resolution of the image. There is some evidence to suggest that signal intensity loss adjacent to areas of increased microvascular visibility may correspond to foci of hypoxia attributable to deoxyhemoglobin and vasodilatation (8). Unlike most dynamic imaging methods assessing microvasculature, ultrahigh-field-strength high-resolution GRE MR imaging does not require intravenous contrast material. Cerebral blood volume maps at lower field strength rely on the conversion of signal intensity to changes in T2 or T2* relaxation rate, which is in turn proportional to the concentration of contrast material. Limitations of cerebral blood volume assessment by using these methods result, to a large degree, from signal-to-noise and blood-brain barrier disruption. Algorithms have been developed

to mathematically correct for contrast material leakage, but this still remains a confounder for this method (16). Furthermore, cerebral blood volume maps have been shown to result in upgrading microvasculature within oligodendrogliomas, which did not appear to be the case with ultrahigh-field-strength high-resolution GRE MR imaging. On the other hand, for microvasculature identified at ultrahigh-field-strength high-resolution GRE MR imaging as a tumoral pseudoblush, distinction between microvascular changes due to radiation and those due to tumoral neovascularity could not be done. With this in mind, ultrahigh-field-strength high-resolution GRE MR imaging and dynamic contrast-enhanced MR methods may complement each other when assessing tumoral microvasculature. It is possible that methods described in this study can translate to lower field strengths by using susceptibility-based sequences; however, this is speculation at this point.

Discrepancies between ultrahigh-field-strength high-resolution GRE MR imaging and histopathologic findings represent general limitations of 8-T microvascular imaging. Certain low-grade tumor types (eg, pilocytic astrocytoma) are known to be highly vascular but without neovascularity, which results in a discrepancy between ultrahigh-field-strength high-resolution GRE MR and histopathologic tumor grade assessment. In addition, a distinction between radiation-induced microvasculature and tumoral microvasculature was not ascertained in this study. This indicates that although microvasculature may be defined at ultrahigh-field-strength high-resolution GRE MR imaging, this does not always indicate the presence of neovascularity. Furthermore, normal but displaced vasculature near or within the tumor may be confused with tumoral microvasculature. One way to help avoid this confusion is to be familiar with the course of local venous vasculature and to follow drainage pathways. Although familiarity with the expected venous vasculature can serve to avoid such confusion, differentiation between tumoral and normal vasculature presents a challenge for image interpretation.

Certain limitations with ultrahigh-field-strength high-resolution GRE MR imaging may affect the overall quality of any one image. Radiofrequency inhomogeneity represents a challenge at very high field strengths. Radiofrequency inhomogeneity and dielectric effects may lead to variations in signal-to-noise ratio even within a single section. One potential solution to this problem may be the use of multiple radiofrequency sources (17,18). The presence of susceptibility artifacts entails another challenge. This problem arises from inhomogeneity near air-tissue interfaces, most notably near sinuses and mastoids, limiting the value of high-resolution GRE 8-T imaging near the skull base. Improvements in spatial resolution can also help assess microvascular visibility. The intravenous administration of ultrasmall superparamagnetic iron oxide (USPIO) can help improve vascular conspicuity. USPIO is an intravascular contrast agent with negligible leakage across the blood-brain

Table 3

Association between Number of Foci of Increased Microvasculature and Tumor Grade

MR Imaging Analysis	Tumor Grade		Total
	Low	High	
0 foci	7	0	7
1 focus	1	0	1
2–4 foci	1	5	6
>4 foci	4	17	21
Total	13	22	35

Note.—Data are numbers of gliomas ($P = .0005$, Pearson χ^2 test).

Table 4

Association between Size of Largest Focus of Increased Microvasculature and Tumor Grade

MR Imaging Analysis	Tumor Grade		Total
	Low	High	
0 cm	7	0	7
0–0.5 cm	1	0	1
0.5–1 cm	3	10	13
>1 cm	2	12	14
Total	13	22	35

Note.—Data are numbers of gliomas ($P = .0005$, Pearson χ^2 test).

barrier for the first 30 minutes after administration and has been shown to improve microvascular visibility in a glioma model (8). Currently, the United States Food and Drug Administration considers imaging at ultrahigh field strengths (7 T and higher) investigational, without substantial risk up to 8 T, and has yet to approve it for clinical use.

In conclusion, increased microvascular density and size identified as a tumoral pseudoblush sign at ultrahigh-field-strength high-resolution GRE MR imaging correspond to increased microvascular density and size at histopathologic assessment, and thus it shows promise as a new imaging biomarker for microvasculature without the use of contrast reagent. The presence of this sign may serve as a potential site to guide biopsy and may provide insight for tumor grade.

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