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Echo-Planar MR Determination of Relative Cerebral Blood Volume in Human Brain Tumors: T1 versus T2 Weighting

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PURPOSE: Maps related to relative cerebral blood volume (rCBV) were generated with the use of the T1 effects produced by a low-dose bolus passage of gadopentetate dimeglumine. The T1 maps were evaluated in a tumor population and compared with rCBV maps obtained with T2-weighted measurements. **METHODS:** Imaging was performed in 19 patients with suspected intraaxial brain tumors. For the T1 rCBV maps, a low-dose bolus of contrast material was given during T1-weighted interleaved spin-echo echo-planar MR imaging. This was followed by a second injection during serial T2-weighted imaging for generation of the T2 rCBV maps. **RESULTS:** Among patients with low-grade lesions (n = 9), T1-based and T2-based rCBV maps showed comparably low rCBV in 7 subjects. In the other 2 patients, with confirmed tumor dedifferentiation, elevation of rCBV values was seen on maps obtained with both techniques. Among patients with high-grade tumors (n = 10), 4 had no evidence of recurrence and 6 did have tumor recurrence (confirmed by follow-up and positron emission tomography). In patients with the high-grade lesions exhibiting conventional contrast enhancement, lesions tended to have higher estimated values on T1 rCBV maps than on the T2 rCBV maps. **CONCLUSION:** Although the T1 rCBV maps showed less contrast as compared with the T2 rCBV maps, they provided diagnostic information that was comparable to the T2 rCBV maps in our series of 19 patients with primary brain tumors.

Index terms: Blood, volume; Brain, magnetic resonance; Brain, neoplasms; Magnetic resonance, flow studies

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With the introduction of ultrafast magnetic resonance (MR) imaging techniques, such as echo-planar imaging, it became possible to assess intracranial hemodynamics after administering an intravenous bolus injection of paramagnetic contrast material. MR imaging can thus serve as a sensitive measure of such pa-

rameters as relative cerebral blood volume (rCBV).

Recently, work has focused on the study of magnetic susceptibility contrast occurring when a paramagnetic agent is injected as a compact bolus (1-6). Dynamic susceptibility contrast signal changes can be directly related to tissue vascularization and blood volume (4, 7-9). Various approaches and recommendations to optimize sensitization to T2 contrast have been published (2, 6, 10-13), and initial clinical investigations have already been performed (9, 14, 15). The evidence shows that MR measurements of rCBV can potentially have the same clinical impact as measurements obtained with fludeoxyglucose F 18 (FDG) positron emission tomography (PET) (15).

However, there are certain obstacles to the use of T2-weighted maps, including the need for larger doses of contrast agent (5) injected by a

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power injector (15) and the potential pitfall of underestimating rCBV values owing to competing T1 effects in regions with a disrupted blood-brain barrier (15). However, T1 relaxivity changes (16) can also be used to calculate cerebral hemodynamics (17, 18). We evaluated a simple method of measuring rCBV that depends on transient T1 changes that occur when a bolus of contrast material passes through the brain.

The purpose of the study was to use T1 contrast to produce maps of relative rCBV and to compare these T1 rCBV maps with T2 rCBV maps in a group of patients with primary brain tumors.

Subjects and Methods

A total of 19 patients referred for contrast-enhanced MR imaging were included in the study. The 10 women and 9 men were 22 to 63 years old (mean age, 38 years). Seven patients were untreated, 5 underwent external-beam radiation therapy at least 10 weeks before the examination, 6 patients had combined surgery and radiation, and 1 patient with a low-grade lesion underwent resection alone. The patients were divided into two groups on the basis of whether they had a low-grade (group 1) or high-grade (group 2) tumor.

In group 1 (low-grade lesions, $n = 9$), four patients were untreated and five had either radiation therapy or surgery before the imaging study. Eight had had PET scans within 2 months of examination and in another eight, follow-up data were available. In group 2 (Daumas Duport grade 3 to 4 brain tumors, $n = 10$), two patients were scanned before treatment, two received radiation only, and the other six received a combination of surgery and radiation. All patients who had no recurrence of tumor on follow-up examinations had been treated surgically and by radiation therapy ($n = 4$). For a detailed summary of patients' data, see the Table.

Approval for the study was obtained by our Subcommittee on Human Studies. Informed consent was signed by all persons participating in the study. All patients underwent conventional precontrast T1-weighted and T2-weighted imaging and postcontrast T1-weighted imaging in addition to dynamic, enhanced echo-planar imaging. A standard head coil was used.

For T1-weighted data, a spin-echo echo-planar sequence was acquired with consecutive images at a repetition rate of 0.6 seconds per section (effective repetition time/echo time/excitations = $2 \times 300/20/1$, double-shot mosaic) for approximately 1.5 minutes. The data acquisition time for the echo train was 2×32 milliseconds. The T1 measurements were single section, with a thickness of 5 mm, a matrix of 256×128 , and a field of view of $40 \times$

20 cm. The injection of gadopentetate dimeglumine was administered after 15 seconds for baseline acquisition. The dose, which was based on theoretical calculations (16), was 0.02 mmol/kg body weight and was administered by fast manual injection into an antecubital vein and flushed by 15 mL of saline. Total injection time was less than 5 seconds.

For the T2 rCBV data, a long-echo-time echo-planar spin-echo sequence (1500/90/1) was used. The T2-weighted measurements were acquired with eight sections, with a thickness of 5 mm, a 2.5-mm intersection gap, a matrix of 256×128 , and a field of view of 40×20 cm. Gadopentetate dimeglumine was administered in a dose of 0.2 mmol/kg body weight after 15 seconds of baseline acquisition. Consecutive images were acquired for 55 seconds. The data acquisition time window was 64 milliseconds for each section, and the time between data points was 1.5 seconds. The second injection was administered approximately 10 minutes after the first one by a power injector at a rate of 5 mL/s into the same intravenous set.

Maps of rCBV were calculated from both series of images by means of a remote workstation. The data points used for baseline estimation and curve fitting were determined by region of interest (ROI) measurements on normal brain, selecting the data points before changes of the first pass were apparent. Changes in signal intensity occurring during the transit of the contrast material were converted into signal-intensity/time curves or T2 curves and delta R2 time curves during T2-weighted imaging. The area under the delta R2 curve, mapped pixel by pixel, was fitted by numerical fit to generate relative rCBV maps. The areas of high rCBV values were represented by bright gray shades, the areas of low rCBV by dark tones. This technique has been described in detail elsewhere (1, 8).

To estimate the contrast-to-noise ratio of the bolus effect, we measured peak signal drop for T2 (or rise for T1), and normalized the data to the standard deviation of the background noise of the raw image measured for a large ROI. ROI measurements were obtained in all patients both from reconstructed maps and from the raw images of tumor tissue as well as of white and gray matter contralateral to the tumor. ROIs were outlined manually in tumors at the regions of greatest signal change in the rCBV maps. The minimum size of an ROI was 8 pixels. Parameters calculated from the reconstructed rCBV maps consisted of measurements of rCBV values in the ROIs described above. Because these techniques provide only relative measurements of rCBV, we chose to calculate ratios of tumor/gray matter, tumor/white matter, and gray/white matter (Table).

For radiographic grading by means of visual impression, regions that appeared to have rCBV values larger than those of average normal gray matter were considered likely to be recurring tumor or tumor dedifferentiation. Regions that had lower rCBV values than those of normal gray matter were considered free of tumor recurrence.

Regional cerebral blood flow measurements in 19 patients with high-grade and low-grade brain tumors

Patient	Previous Therapy	rCBV Diagnosis		PET Diagnosis	Confirmation at Follow-up	T1 Maps		T2 Maps	
		T1	T2			Tumor/White Matter	Gray Matter/White Matter	Tumor/White Matter	Gray Matter/White Matter
Group 1 (low-grade tumors)									
1	None	Low grade	Low grade	Low grade	Yes	3.44	3.54	2.78	3.98
2	Radiation	Low grade	Low grade	Low grade	Yes	3.41	3.20	0.78	1.87
3	Radiation	Low grade	Low grade	High grade	Yes*	3.52	3.73	3.41	3.18
4	None	Low grade	Low grade	Low grade	Yes	0.93	2.99	0.91	2.86
5	None	Low grade	Low grade	Low grade	Yes	1.42	...	1.06	2.87
6	Surgery	Low grade	Low grade	Low grade	Yes	1.05	...	0.56	1.82
7	Surgery/ radiation	Low grade	Low grade	...	Yes	5.95	3.05	2.00	2.40
8	None	High grade	High grade	High grade	...	4.21	3.07	3.24	2.41
9	Radiation	High grade	High grade	High grade	Yes	10.10	3.29	4.71	2.00
Group 2 (high-grade tumors)									
10	None	High grade	High grade	No rec [†]	Yes	3.77	2.20	1.22	...
11 [‡]	Radiation	High grade	No rec	No rec	...	14.19	3.41	1.89	2.44
12	None	High grade	High grade	...	Yes	6.42	...	9.79	4.55
13	Radiation	High grade	High grade	High grade	...	6.74	2.68	1.69	2.69
14	Surgery/ radiation	High grade	High grade	High grade	...	10.58	...	6.18	1.82
15	Surgery/ radiation	High grade	High grade	High grade	Yes	3.44	3.29	...	2.38
16	Surgery/ radiation	High grade	No rec	No rec	Yes	...	8.71	...	2.75
17	Surgery/ radiation	No rec	No rec	No rec	Yes	...	3.34	...	2.86
18	Surgery/ radiation	No rec	No rec	No rec	Yes	...	6.90	...	3.18
19	Surgery/ radiation	No rec	No rec	No rec	3.30	...	5.83
						Average	3.78		2.88
						SD	1.7081		0.9933

Note.—No rec indicates no tumor recurrence.

* Elevation of FDG PET tracer uptake, but no change in size on follow-up MR studies 1 year later.

[†] At the time of the study, a small lesion was confirmed by surgery and at follow-up examination.

[‡] Marked rim enhancement (see Fig 5).

Results

Examples of typical T1-weighted and T2-weighted rCBV maps for low-grade and high-grade tumors are shown in Figures 1 through 3. The T1 relaxation effects allowed us to reconstruct rCBV maps in all subjects.

The mean signal change in T1-weighted raw data in our study group was 10% in normal gray matter, compared with 24% on the T2 rCBV maps in identical ROIs. The contrast-to-noise ratio (calculated in five subjects) was 3.1 (SD 0.8) for T1-weighted raw data and 7.5 (SD 1.6) for T2-weighted data.

To assess the contrast of tissues in various regions, ROIs were compared by ratios. The mean ratio of contralateral gray matter/white matter was 3.78 (SD 1.71) for T1 rCBV maps and 2.88 (SD 0.99) for T2 rCBV maps (see the Table). On the basis of a two-sample paired Student's *t* test for gray/white matter, the *P* value (T1 versus T2) was .083, and thus did not reach statistical significance. For low-grade tumors, the ratio of tumor/white matter was 2.29 (SD 1.28) for T1 rCBV maps and 1.59 (SD 1.19) for T2 rCBV maps. For the high-grade tumors, the tumor/gray matter ratio was 7.52

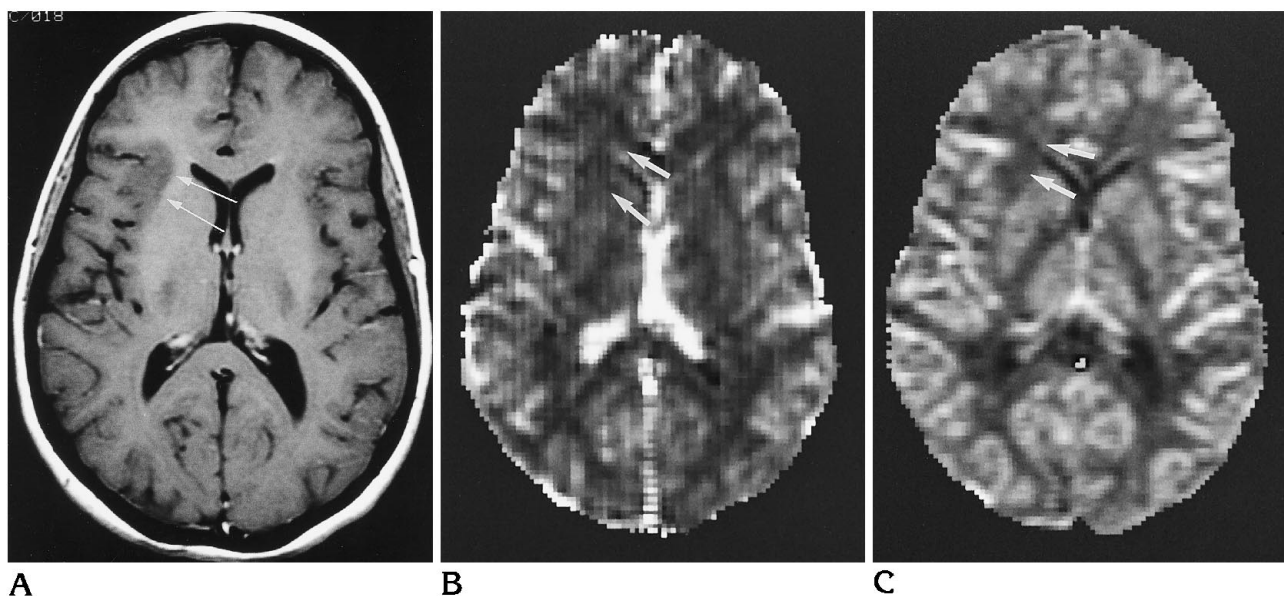


Fig 1. Low-grade glioma.

In conventional imaging, no contrast enhancement is seen on the T1-weighted postcontrast scan in the right frontal lesion (arrows) (A). As can be expected for this slowly progressing tumor, only a little blood volume (rCBV) is found in the region of the lesion on rCBV maps obtained with both T1 (B) and T2 (C) imaging methods. Although the contrast on the T1 rCBV map is limited, the same diagnostic information is reached. Venous structures and the choroid plexus are bright on the T1 rCBV map.

(SD 4.15) for T1 rCBV maps and 4.16 (SD 1.19) for T2 rCBV maps.

The typical low-grade lesions (group 1) had rCBV measurements below or equal to those of gray matter ($n = 8$), as expected for a slow-growing tumor (Fig 1). In comparing the lesion to gray matter ratio, we found the differences in the results of the T1 and T2 rCBV mapping methods were not statistically significant (paired t test $P = .35$). No gross contrast enhancement was noted by visual observation on the postcontrast T1-weighted images. Two patients, in whom low-grade tumors had initially been diagnosed, had markedly elevated blood volumes on both T1 and T2 rCBV maps, and thus were thought to have dedifferentiating lesions (Fig 4). Both patients had an FDG-PET study within 6 weeks of these MR findings that revealed local hypermetabolism, and, on follow-up studies, each had a high-grade tumor that was confirmed (one by surgery, one by follow-up PET scans). Neither had a marked T1-weighted enhancement in the conventional enhanced scan obtained after administration of the 0.2 mmol/kg dose of contrast material. The tumor ROIs for these patients (cases 8 and 9 in the Table) were taken from the area showing elevated rCBV. Overall, for low-grade lesions

(group 1), we saw no difference in tumor grading from rCBV measures between the T1-weighted and T2-weighted methods.

Among the patients with high-grade lesions (group 2) 6 of the 10 T1 rCBV maps were consistent with recurrent or persistent tumor (Fig 3). Five of these were confirmed by follow-up MR imaging or PET, or both. One patient (case 11) had only subtle elevation of rCBV values on the T2 rCBV maps, which was not suggestive of recurrence, but there was marked elevation on the T1 rCBV map, which was graded radiographically as recurrence (Fig 5). PET scans in this case showed no evidence of hypermetabolism. In this subgroup of recurrent/persistent tumor, the mean ratios of tumor/white matter rCBV values were much higher on T1 (8.19) than on T2 (4.16) maps.

Four tumors in patients in group 2 showed no evidence of elevated rCBV values on either the T1 or T2 rCBV maps, despite exhibiting various amounts of conventional postcontrast enhancement. All these patients had been treated previously with radiation and surgery, and all showed hypometabolism on PET scans. Three of the four tumors proved negative for recurrence on available follow-up; no follow-up information was available for the fourth patient.

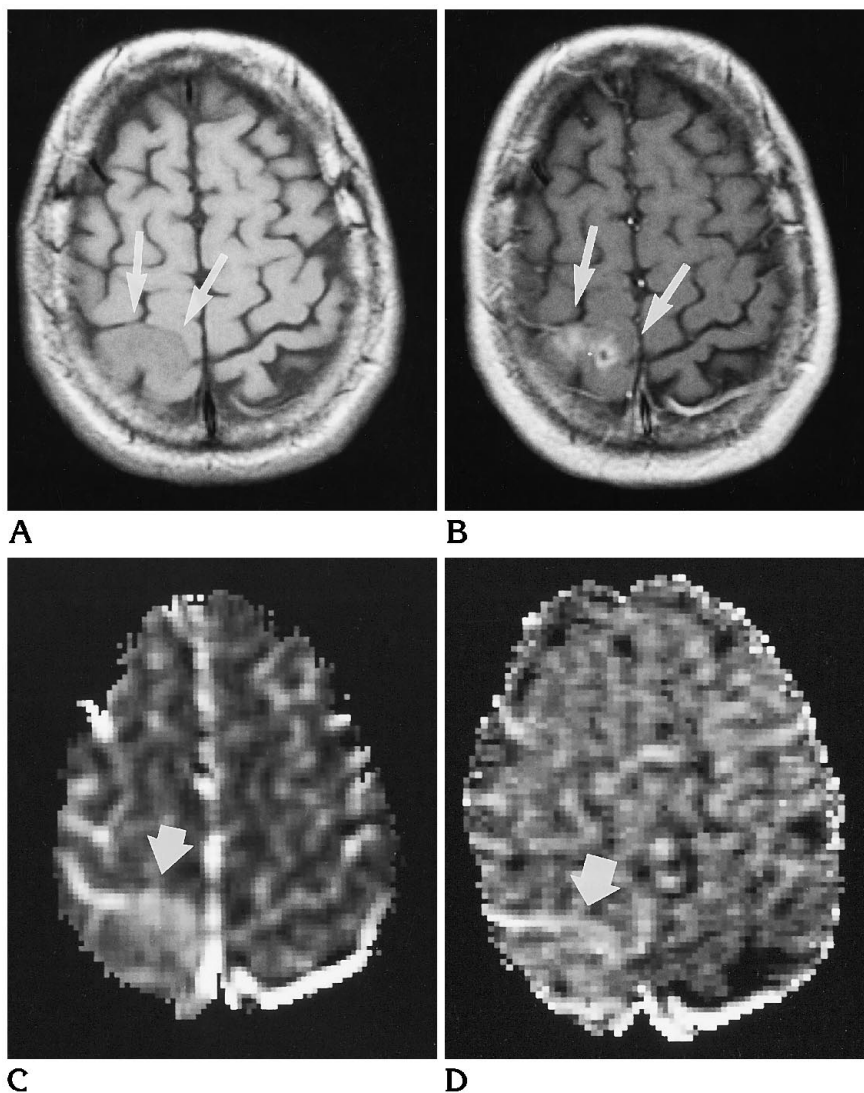


Fig 2. High-grade untreated glioma.

The tumor in the right central region is displayed on conventional precontrast (A) and postcontrast (B) MR images (arrows). Partial enhancement is seen on the T1-weighted postcontrast scan. Note the evidence of increased blood volume on the T1 (C) and T2 (D) rCBV maps (arrows). These regions of elevated rCBV values are consistent with high-grade glioma.

Discussion

In the normal brain, lanthanide chelates are limited to the intravascular space by the intact blood-brain barrier. A bolus injection of paramagnetic contrast agents, such as gadopentetate dimeglumine, leads to both T1 and susceptibility contrast effects. There are two major differences between the T1 and T2 rCBV maps. First, in the presence of leaky tissues, the T1 rCBV values overestimate blood volume whereas the T2 values underestimate blood volume. The high rCBV values on T1 rCBV maps of tumor pixels in high-grade lesions with blood-brain barrier disruption seen on conventional images may therefore be a reflection of how rapidly the contrast material leaks into the interstitial space, rather than being representative of true blood volume. Thus, at least partially,

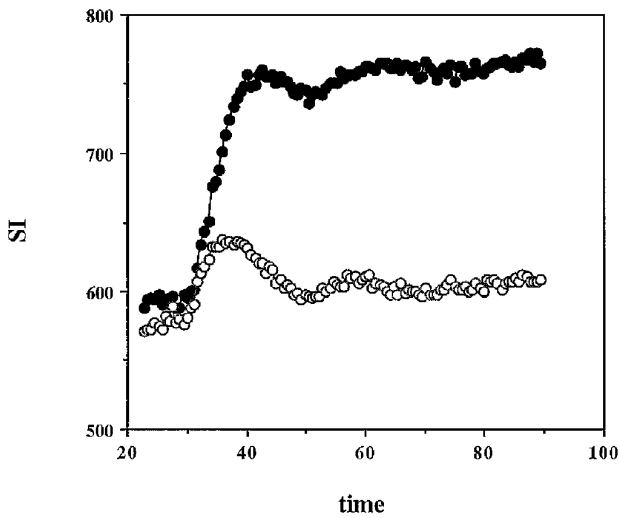
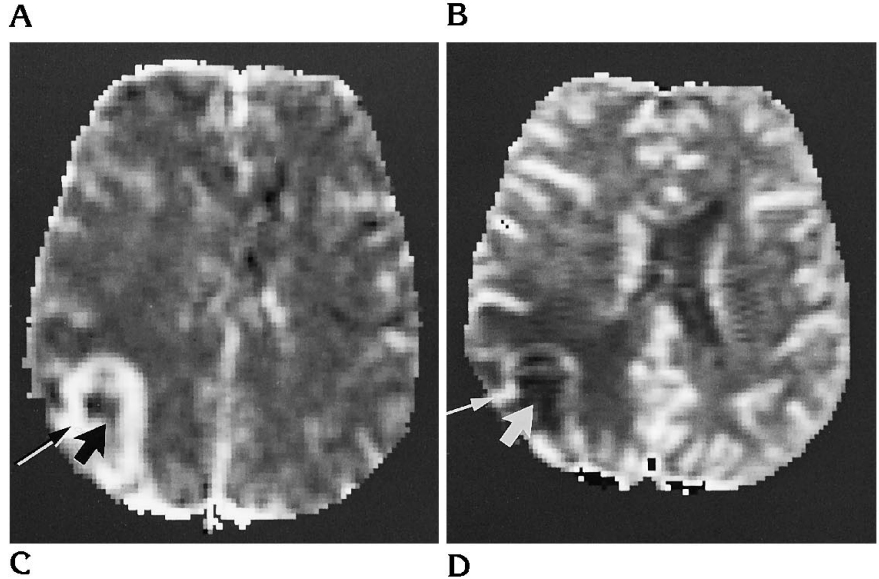
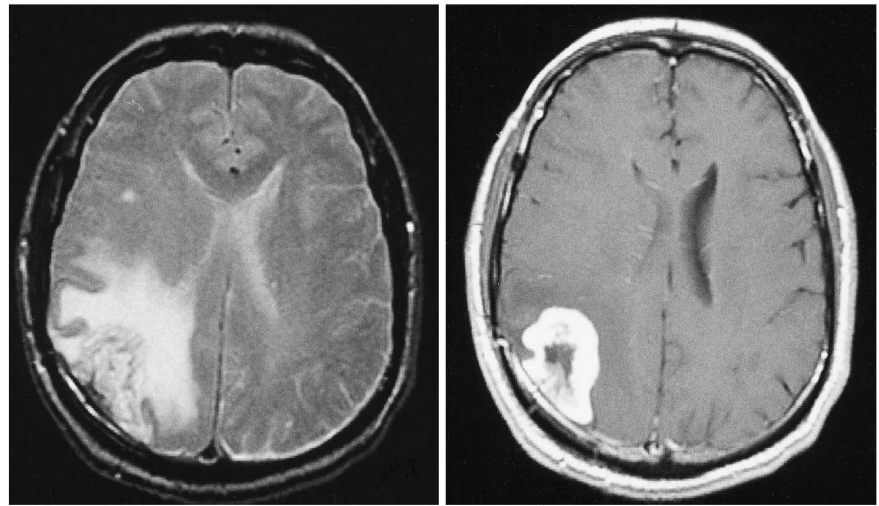
our blood volume value may be weighted toward a measure of the permeability/surface area product (19, 20) in cases of blood-brain barrier disruption. Although this permeability/surface product weighting may detract from our ability to define uniquely our T1 maps as rCBV weighted under all circumstances, the permeability/surface area product itself may have important pathophysiological importance in the evaluation of brain tumors.

Second, owing to the physics of susceptibility-based contrast material on spin-echo images, spin-echo T2-weighted rCBV maps show a significant microvascular weighting (8). T1-weighted rCBV maps, like gradient-echo T2*-weighted susceptibility maps (21, 22), will exhibit sensitivity to the total vascular space, including the small and large vessels. This is

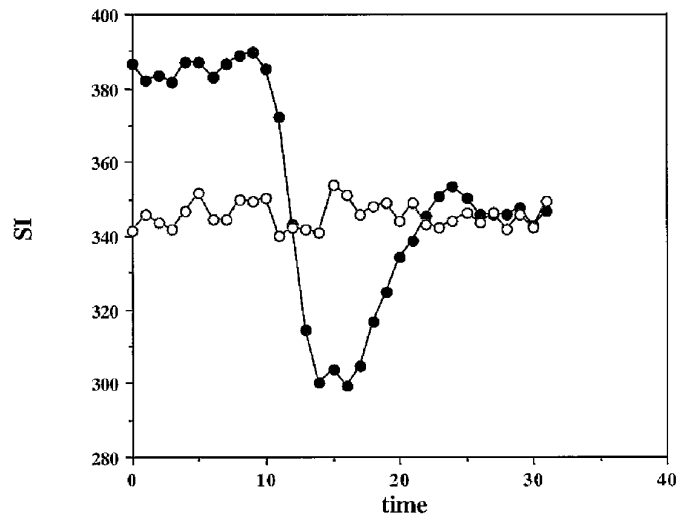
Fig 3. High-grade tumor (glioblastoma) after radiation therapy.

The T2-weighted conventional image (A) displays marked edema in the right posterior hemisphere, encircling a mass. The conventional T1-weighted image after injection of contrast material (B) shows rim enhancement 6 months after surgery and radiation therapy. Marked elevation in the rim of the rCBV values is seen on the T1 rCBV map (C) and only subtle changes are seen on the T2 rCBV map (*thin arrows*). Both maps show a decrease of rCBV values in the necrotic center (*thick arrows*). The difference in rCBV values between the two methods is caused by competing effects of first pass and leakage effects. These effects act synergistically in T1 reconstructions and antagonistically in T2 maps.

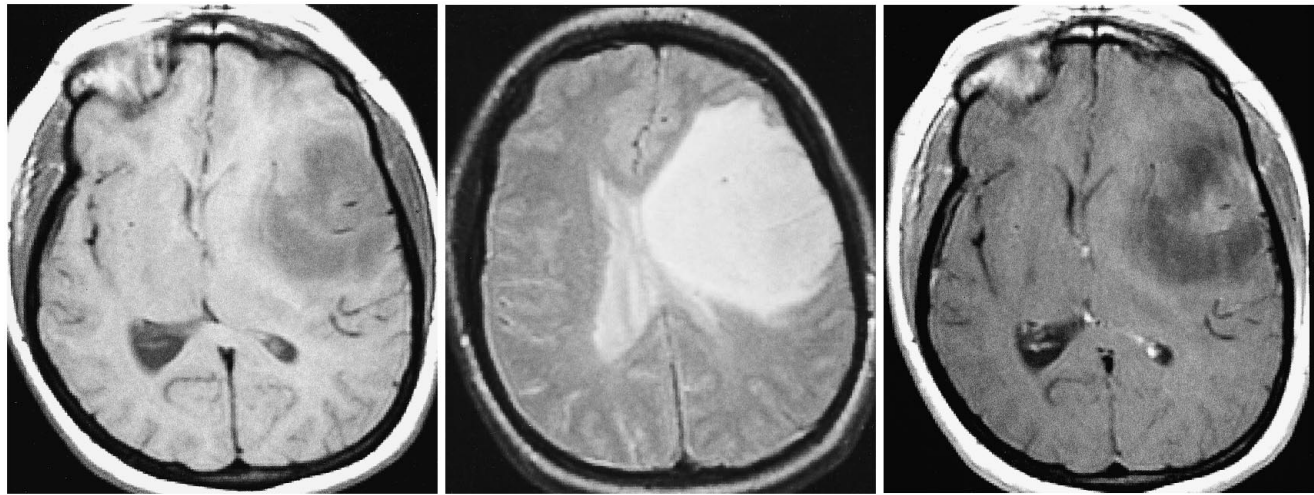
Signal intensity/time curves obtained from the T1 (E) and T2 (F) rCBV maps; the region of interest is indicated by the *thin arrows* in the rim of the lesion on C and D. The curve with *solid circles* represents the rim of the lesion; the curve with *open circles* represents the white matter.



E



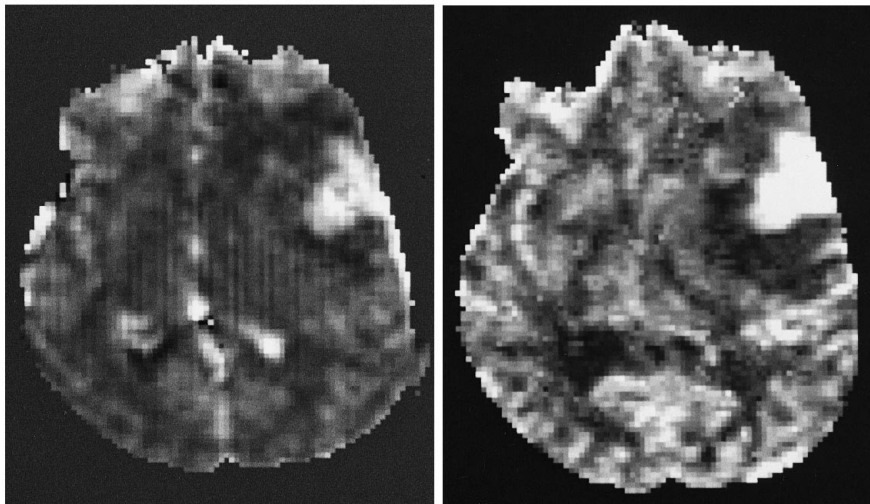
F



A

B

C



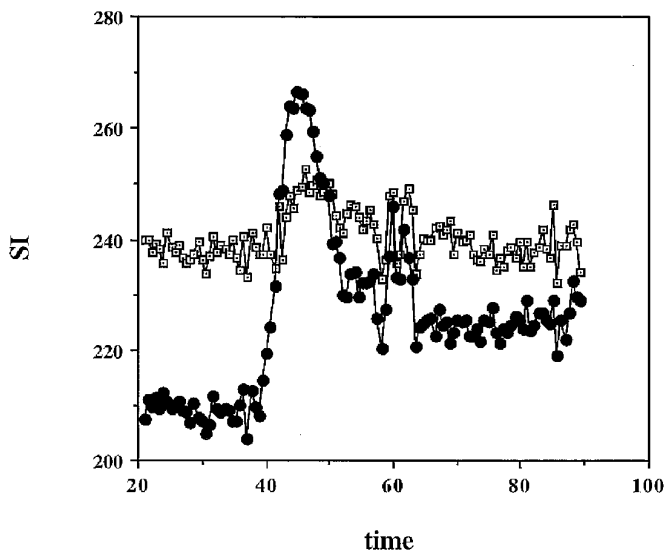
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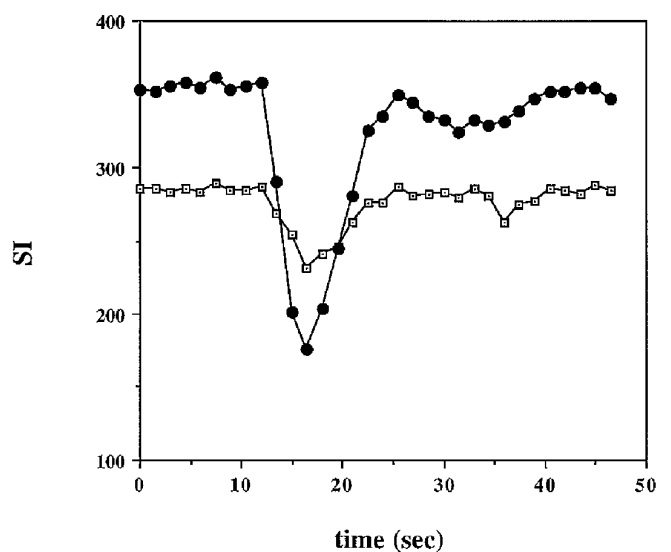
Fig 4. Low-grade dedifferentiating glioma.

In this tumor, although homogeneous in T2 signal intensity on T1-weighted (A) and T2-weighted (B) precontrast images, and with mild or minimal enhancement after contrast injection (0.2 mmol/kg) on the T1-weighted conventional scan (C), signs of elevated blood volume can be observed on both the T1 (D) and T2 (E) rCBV maps. Both maps depict clear separation of the low-grade and the dedifferentiated parts of the tumor (confirmed by findings on PET scans).

Signal intensity/time curves obtained from the T1 (F) and T2 (G) rCBV maps; the region of interest is the high-grade part of the lesion. The curve with circles represents the high-grade, dedifferentiating part of the tumor; the curve with squares represents the low-grade part of the tumor.



F



G

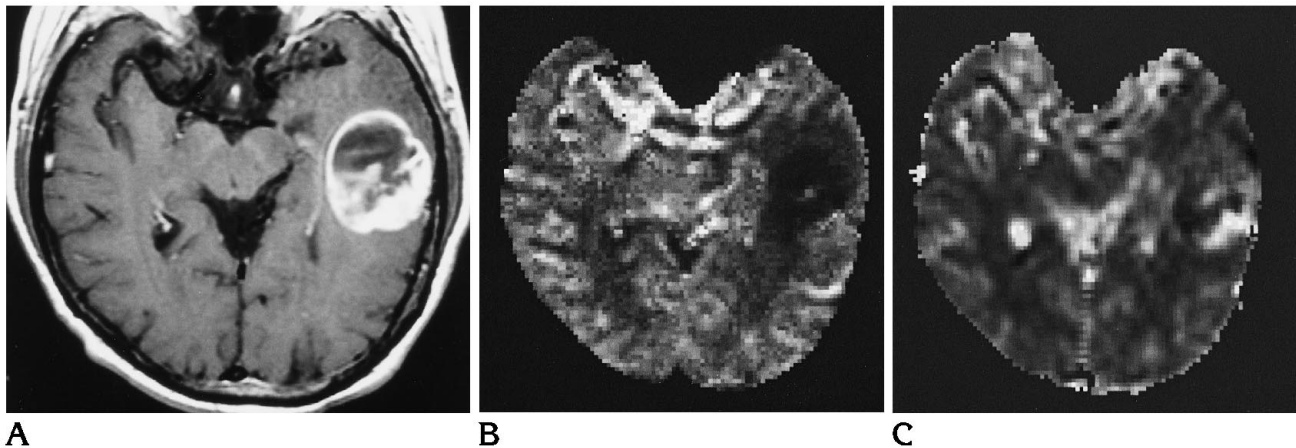


Fig 5. Recurrence of a glioblastoma after treatment with external beam and local radiation.

T1-weighted postcontrast conventional MR image (A) shows a mass in the left temporal lobe, with marked rim enhancement. Owing to competing effects of the first pass and immediate leakage into the interstitial space, the rCBV values of the T2 map (B) are partly below those of gray matter in the left temporal region. The T1 rCBV map (C) shows a marked elevation of blood volume in the posterior part of the lesion (recurrence was confirmed by follow-up examination).

apparent in the visual appearance of the maps (eg, Fig 1). In this respect, we would anticipate that the T1-based rCBV maps would more closely correlate with blood volume maps made by using traditional radionuclide techniques (such as with cobalt-11 PET imaging). Whether sensitivity to the total vascular or microvascular space confers a specific advantage in evaluating brain tumors was not definitely determined in this initial study, and will require further investigation specific to the clinical question asked (eg, recurrence versus necrosis). Nevertheless, this study does suggest that important physiological information is contained in T1 rCBV maps.

Several other points distinguish the T1-based and T2-based methodologies. From an economic standpoint, the most important is the large difference in the contrast dose required for each: the T1 rCBV maps require about one tenth the contrast agent as the T2-based methods do. However, this comes at a loss of about one half the contrast-to-noise ratio in the raw data, a difference that cannot be narrowed through use of additional contrast agent, owing to T1 saturation effects. The use of a smaller bolus with the T1 rCBV method confers the additional advantage of a narrower, better-defined bolus, a property that may be of importance in efforts to extract regional cerebral blood flow information from first-pass data. Finally, the use of a short repetition time limited the number of sections we could acquire relative to the longer repetition time of the T2-weighted sequences (about 2 to

3 versus 8 to 10). The use of an inversion recovery sequence may improve this number in the future.

Despite the smaller T1 effect, the first-pass signal change seen in all patients was sufficient to allow reconstruction of the maps and to provide diagnostic information. With the use of relaxation contrast, however, some extraaxial tissue became bright and could potentially be mistaken for tumor regrowth. The strong gray/white matter contrast, observed on T1 rCBV maps (see Table), may in part be explained by a partial volume effect, including small cortical vessels with high rCBV values in the gray matter ROIs.

Low-grade lesions with intact blood-brain barriers were reliably differentiated with both methods. This was also true for the two low-grade lesions with malignant change. In the high-grade group, different values between T1 and T2 rCBV maps were apparent. Despite these quantitative differences in the rCBV values they did not cause a change in grading in our series during direct comparison, although one diagnosis remains indeterminate (case 11). Theoretically, one would anticipate that in settings of blood-brain barrier disruption without tumor (eg, radiation necrosis) there would be a tendency for the T1 rCBV maps to cause elevated rCBV measurements. Our series suggests that, in at least some patients, this may not always be the case (cases 16, 17, and 18). This is possibly due to the more limited blood-brain barrier permeability seen here, leading to small

first-pass extraction fractions and thus limiting the elevation of rCBV values. In contrast, T2 rCBV maps tended to underestimate the apparent rCBV values in the presence of a blood-brain barrier breakdown, and may show false-negative findings in the event of an active tumor recurrence (15).

There is a clear need to correct both methods for these effects. In cases of high capillary permeability, other techniques may be needed to correct more aggressively for blood-brain barrier breakdown. For T2 rCBV mapping, these might include a larger contrast material preload to eliminate T1 effects when using T2 rCBV methods (15) and the use of contrast agents with minimal relaxivity enhancement (eg, iron oxide) (23). For both T1 rCBV and T2 rCBV techniques, the use of macromolecular (intra-vascular) agents (24) would minimize the effects of blood-brain barrier breakdown. Both techniques may also benefit from the use of more sophisticated postprocessing algorithms, which measure permeability/surface area product directly and then correct for its effects on the rCBV map (19). These corrections are expected to contribute most in lesions with moderate enhancement.

As for the clinical impact of T1 rCBV maps, it is assumed that prognostic tools like rCBV maps are most likely to be useful in providing additional information to further differentiate untreated (25–27) or treated (28–33) brain lesions. Data from this pilot study showed similar results as obtained in the better-established T2 rCBV studies. Further investigation will be needed to define better the precise role that T1 rCBV maps can play in the evaluation of primary brain tumors.

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