**Perfusion Magnetic Resonance Imaging to Assess Brain Tumor Responses to New Therapies**

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**Perfusion magnetic resonance imaging may improve the differentiation of recurrent intracranial brain tumor from posttreatment tumor necrosis.**

**Background:** Although magnetic resonance imaging (MRI) is effective in detecting the location of intracranial tumors, new imaging techniques have been studied that may enhance the specificity for the prediction of histologic grade of tumor and for the distinction between recurrence and tumor necrosis associated with cancer therapy.

**Methods:** The authors review their experience and that of others on the use of perfusion magnetic resonance imaging to evaluate responses of brain tumors to new therapies.

**Results:** Functional imaging techniques that can distinguish tumor from normal brain tissue using physiological parameters. These new approaches provide maps of tumor perfusion to monitor the effects of novel compounds that restrict tumor angiogenesis.

**Conclusions:** Perfusion MRI not only may be as effective as radionuclide-based techniques in sensitivity and specificity in assessing brain tumor responses to new therapies, but also may offer higher resolution and convenient co-registration with conventional MRI, as well as time- and cost-effectiveness. Further study is needed to determine the role of perfusion MRI in assessing brain tumor responses to new therapies.

**Introduction**

Conventional magnetic resonance imaging (MRI), despite its undisputed sensitivity in detecting and delineating the location of intracranial tumors, lacks specificity for the prediction of histologic grade of tumor and for the distinction between tumor recurrence and tumor necrosis produced by radiation or drug therapy. The correlation between the degree of MR enhancement of gliomas and their microscopic grade is imperfect; up to 38% of anaplastic astrocytomas do not enhance with gadolinium, which may contribute to the one quarter of these tumors reported as undergraded at stereotactic biopsy. Neuro-oncologic surgeons, medical neuro-oncologists, radiation therapists, and neuroradiologists have explored a variety of imaging techniques to address these concerns. Two considerations have made these studies of special importance: (1) the increased utilization of high-dose, small-field radiation therapy of proton, gamma knife, interstitial isotopic (brachytherapy) or nonisotopic sources have increased the likelihood that fully 50% of recipients will have mixtures of viable tumor and radiation necrosis within one year of treatment, and (2) materials have become available to modify the blood-tumor barrier and to provide a mechanism for the quick passage of chemotherapeutic drugs, viral vectors, and biologic response modifiers into tumors. These materials include “barrier modifiers” (such as arterially administered mannitol, bradykinin, and its analogue, RMP7), modulators of tumor neovascularity (including TNP470, penicillamine, and other “angiogenesis inhibitors”), and glucocorticoids and similar materials that may stabilize the blood-brain barrier (BBB).

"Physiological" imaging techniques, which can potentially differentiate neoplastic from nonneoplastic brain tissue based on functional rather than purely anatomic or structural parameters, have become an important area of investigation. These "functional" imaging modalities include not only the nuclear medicine methodologies such as 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET), methionine PET, tyrosine PET, and 201Tl-thallium single-photon-emission computed tomography (201Tl-SPECT), but also functional MRI methods such as MR spectroscopy, diffusion-weighted imaging, dynamic gadolinium-enhanced relative cerebral blood volume (rCBV) perfusion imaging, ultra-small superparamagnetic iron oxide susceptibility imaging, and noncontrast-enhanced, arterial, “spin-labeled” perfusion techniques.

The functional nuclear medicine techniques, which rely on the uptake and/or metabolism of a radioactive tracer to identify high-grade recurrent tumor components, generally have poorer spatial resolution and are less sensitive in the detection of small (<1.6 to 1.8 cm in diameter) lesions than are the MRI-based techniques. The likely resolution of these ligands is in the range of centimeters and is often qualified further by the close proximity of cerebral edema and foci of necrosis to tumor. Furthermore, the sensitivity-specificity of FDG-PET and 201Tl-SPECT in detecting postradiation treatment glioma recurrence have been reported to be as low as 81%:40%, and 69%:40%, respectively, with significant false-negative and false-positive examinations. One investigator has reported a 25% specificity of FDG-PET in the detection of recurrent glioma after radiation therapy. Methionine-, tyrosine-, and choline-labeled PET scanning are newer technologies that are based on amino acid membrane transport, protein synthesis, and phospholipid uptake. Although potentially more accurate than FDG-PET and 201T1-SPECT, these techniques are costly and as yet unproven.

Functional MRI studies have a useful role not only in the evaluation of patients with acute cerebral infarction or neoplasm, but also in the noninvasive mapping of the human visual, motor, and language cortices for surgical planning. These data sets often can be the subject of topographic co-registration with high-resolution anatomic T1 MR images of the brain. Proton MR spectroscopy, in particular, has shown great promise in the noninvasive subclassification of malignant human brain tumors and is likely to develop into a clinically important modality. At the other extreme, MR diffusion-weighted imaging, despite its impressive role in the detection of hyperacute stroke and its selective ability to distinguish arachnoid cysts from epidermoid tumors of the central nervous system, has not otherwise proved beneficial in
This review focuses on the current status of perfusion MRI techniques in the evaluation of intracranial neoplasm.

Technical Background

Perfusion-weighted MR techniques, unlike those of MR angiography, which detect flow within large vessels, are sensitive to microscopic levels of blood flow. These techniques may or may not require the dynamic intravenous administration of an MR susceptibility contrast agent. Most of our current clinical experience is with gadolinium-based rCBV perfusion imaging. Both the ready availability and the T2 susceptibility effects of gadolinium, rather than the T1 shortening effects routinely associated with contrast enhancement, make gadolinium a suitable agent for use in perfusion imaging. Susceptibility here refers to the loss of MR signal, most marked on T2*-gradient echo-weighted and T2 (spin echo)-weighted sequences, caused by the magnetic field-distorting effects of ferromagnetic and, to a lesser degree, paramagnetic substances such as gadolinium.

In rCBV perfusion imaging, the T2 (or T2*) MRI signal drop within or across a brain region is caused by spin dephasing from susceptibility effects during rapid passage of a paramagnetic contrast agent (eg, gadolinium) through the capillary bed. The signal drop is used to compute the relative perfusion to that region. Theoretical and animal studies show that this signal drop depends on both the vascular concentration of contrast agent and the concentration of small (3 to 10 µm) vessels per voxel of tissue.27,28 rCBV maps are constructed using tracer kinetic principles by integrating the signal-time curve for each voxel. Maps are "relative" in that the arterial input function is not typically measured; hence, true quantitative volumes (cc blood/mL tissue/time) are not routinely calculated.29

It follows from the preceding discussion that the rCBV mapping technique, as introduced by Villringer et al,26 requires a sensitive and rapid, susceptibility (T2* or T2) scanning capability.14 Although echo-planar MRI systems, which utilize strong, rapidly switching magnetic field gradients, permit the fast, simultaneous acquisition of multiple axial T2*-weighted slices, more limited perfusion imaging can also be performed using standard gradient echo (T2*-sensitive) techniques on conventional MR scanners. Spin echo pulse sequences that characterize the microvasculature are more advantageous for imaging tumors than are gradient echo sequences, whose signal sampling incorporates artifact from the larger cerebral vessels.30 Rapid spin echo imaging, however, is convenient only with the more complex and expensive echo-planar systems.

To compute an rCBV map, the 9R2 (the change in T2 relaxation rate) vs time curve for each pixel in the imaged slice is numerically integrated (without correction for recirculation and potential T1 effects) at multiple time points extending from two seconds prior to injection, through to the end of the acquisition. In effect, a motion picture of T2 signal changes during the passage of gadolinium through tissue is used to create a single photographic image that characterizes this passage. The change in T2 relaxation is linearly proportional to the concentration of contrast material in tissue that itself is proportional to the blood supply to the tissue (Figs 1A-B).31

Precise CBV measurements (cc blood/mL tissue), as opposed to the "relative" CBV values described above, can be obtained by imaging a "control" region, typically a major intracranial vessel.32 Also, as the injected contrast material traverses large blood vessels and is diluted by passage into surrounding tissues, the resulting changes can be associated to calculate "maps" of true cerebral blood flow (CBF, cc blood/mL tissue/time). Preliminary clinical results with these techniques have been promising.33

In the optimal situation, the density of small blood vessels in brain tissue is proportional to the concentration of gadolinium within those vessels. However, in high-grade brain tumors that are growing rapidly or have been treated with radiation, there often exist fragile vessels that are highly permeable and "leak" contrast. In this situation, the T2 signal properties of gadolinium are distorted by other T1 effects, resulting in falsely low rCBV values. Thus, in leaky regions of severe BBB breakdown, standard rCBV imaging does not adequately categorize capillary beds with increased microvascularity.34-35 We routinely compensate for this leaky effect by using a mathematical correction algorithm and injecting a small dose of gadolinium prior to the administration of the study dose in order to "saturate" the leaky regions.36 Other solutions include increasing scan repetition time at the expense of lengthening total scan time and/or reducing the number of slices, or using other contrast agents such as sprodiamide (dysprosium).14,26,34,36-39 In one pilot study of nine patients,40 dysprosium rCBV maps more accurately discriminated between radiation necrosis and recurrent brain tumor than did gadolinium rCBV maps, and both techniques provided better discrimination than did FDG-PET.40 Yet another approach to obtaining more accurate perfusion measurements in regions of marked BBB breakdown is the construction of perfusion maps using so-called "spin-labeled" techniques, which do not require the administration of intravenous contrast (Fig 2). These T1-based, absolute flow methods, such as the EPISTAR (echo-planar imaging and signal targeting with alternating radio frequency) pulse sequence, involve the tagging of incoming spins with either a continuous or single inversion recovery pulse, followed by imaging a distal slice.41,42 These techniques involve long imaging times (6 to 8 minutes per slice), decreased spatial resolution compared with T2* rCBV maps, and the inability to image after gadolinium administration.43 In 13 subjects (8 with high-grade gliomas, 3 of these 8 with marked increased BBB permeability), this technique appeared superior to uncorrected gadolinium rCBV imaging in characterizing the microvascularity of "leaky" brain, and closely mirrored the results of FDG-PET scanning.44
rCBV maps can also be acquired using a low-dose bolus of intravenous contrast during T1-weighted echo-planar imaging. Although these "T1 maps" have poorer contrast-to-noise ratios than corresponding T2-weighted CBV maps, in preliminary investigations they have provided similar diagnostic information. In such maps, the effect of BBB "leakiness" is exaggerated.45

Clinical Utility of rCBV Brain Tumor Imaging

Anaplastic astrocytoma and glioblastoma are characterized by proliferation of arterioles, capillaries, and venules that can be demonstrated by staining with Factor VIII stains and also characterized by overexpression of endothelial growth factors such as epidermal growth factor and vascular endothelial growth factor.

Susceptibility-based perfusion imaging is concerned with this microscopic, capillary level blood flow,26,46 potentially useful for the clinician would be tumor characterization by MRI, which provides a surrogate marker of tumor vasculature and thus tumor grade. Targeting of biopsy sites using MR-based guidance systems would provide for sampling of areas of malignant glioma transformation (high vascularity) within otherwise benign glioma (low vascularity), while improving identification of changes in tumor vessels as a result of therapy with angiogenesis inhibitors, biologic response modifiers, and genetic vectors with the ability to reduplicate in endothelial cells. Theoretically, rCBV maps might serve as the basis for conformal or three-dimensional radiation treatment planning for hypervascular foci of tumor, as distinguished from euvascular deposits, both within malignant gliomas.47

For purposes of noninvasive tumor grading, multiple studies have demonstrated the utility of both dynamic susceptibility rCBV mapping and FDG-PET scanning in localizing regions of high-grade glioma (Fig 3).14,47,48 This is a function of the increased vascularity and metabolism of grade III and IV gliomas as compared with lower-grade neoplasms.16,49-52 In a histologic correlation study of 19 patients with gliomas, foci of maximal tumor CBV were associated with high mitotic activity and vascularity but not with cellular atypia, endothelial proliferation, necrosis, or cellularity.14

It is well known that glial tumors that do not enhance with gadolinium may still contain anaplastic or malignant features. Significantly, high CBV foci can be found in nongadolinium-enhancing tumors. In a series of 15 patients, low-grade tumors were found to have homogeneously low CBV, whereas high-grade tumors were heterogeneous, with both low and high blood volume components.53 A regional tumor CBV value more than double that of normal white matter highly correlated with high-grade astrocytoma (grade III or IV), whereas tumor with a maximum value less than 1.5 that of white matter was typically a low-grade neoplasm.53

More recently, we retrospectively reviewed the rCBV studies of 32 consecutive patients who received dynamic perfusion imaging for evaluation of untreated brain tumors. Using a normalized rCBV regions of interest (ROI) cutoff ratio of 1.5, 13 of 13 astrocytomas were correctly categorized as high grade. Three of these high-grade tumors did not enhance with contrast. Alternative stereotactic biopsy sites were suggested by additional nonenhancing, high rCBV foci in 7 of the 13 cases. Of the 9 low-grade astrocytomas, 7 were correctly classified on the basis of their ROI values, including one potentially false-negative-enhancing lesion. One of the 2 falsely high rCBV foci in a second demonstrated enhancement. Of 8 oligodendrogliomas, 4 of 4 high grade and 2 of 4 low grade had elevated rCBV. The sensitivity and specificity of rCBV imaging for detecting native high-grade glioma components, based on the above, were 100% and 69%, respectively.54 In fact, no high-grade tumor in our study had a normalized rCBV ROI value less than 1.5. These results are similar to those reported by others who, using FDG-PET scanning in 58 untreated patients, reported 100% sensitivity and 67% specificity in differentiating high-grade from low-grade gliomas (applying a tumor-to-white matter FDG uptake ratio cutoff of 1.5).55

As would be expected, highly vascular tumors such as meningiomas, oligodendrogliomas, and vascular metastases such as renal cell carcinoma and melanoma have high rCBV relative to gray and white matter. Conversely, densely packed tumors with high nuclear-cytoplasm ratio (eg, medulloblastoma and lymphoma), in our experience, demonstrate low rCBV.53 This low relative CBV in lymphoma and other "small, round, blue-cell" lesions has also been observed by other groups (personal communications, S. Cha). Thus, rCBV mapping may be of limited value in grading lymphoma and medulloblastoma patients. Caution must also be exercised in imaging extra-axial lesions, as the increased permeability secondary to the lack of BBB in meningiomas could theoretically cause falsely low rCBV measurements due to T1 gadolinium "leakage" effects.56

Caution must additionally be exercised in generalizing the results of studies involving untreated vs treated patients, although similar imaging considerations should apply to both pretreatment and posttreatment populations. Shortly after radiation therapy, particularly of proton or gamma-knife origin, there may be increased permeability of BBB. At intervals up to years after radiation, vessel injury changes may appear, with endothelial cell damage, hyalinization of vessels, and ultimately their occlusion or diminished permeability.57,58 That angiogenesis determines blood flow, metabolism, and growth rate of residual or recurrent tumor in irradiated tumor beds has been demonstrated in experimental models.50,51 The sensitivity of cells to radiation therapy associated with alterations in the micromilieu (eg, microvascularity, oxygenation, pH) of an irradiated region has been termed the "tumor bed effect." The tumor bed effect has clinical relevance with regard to metastatic rate and timing of recurrence. In a study of "tissue-isolated" human tumor xenografts in nude rats,59 therapeutically relevant parameters of the metabolic micromilieu largely depended on the efficacy of tumor circulation. High metabolic rates, concomitant with high blood flow values, coincided with rapid tumor growth. rCBV imaging, along with other noninvasive methods, could permit monitoring of the local microcirculation, supplementing clinical and histologic staging. Indeed, CBV maps have proven capable of following changes in the microcirculation of lymphoma in response to corticosteroid treatment.60
A potentially confounding factor in the interpretation of posttreatment rCBV images is the blood volume lowering effect of treatments on normal brain tissues. In one series of 41 examinations of 19 patients with grade II astrocytoma compared with 13 patients studied after whole-brain irradiation, a reduction in mean blood volume within the tumors from 12.2 to 6.5 mm$^3$/100 g after fractionated conformation radiotherapy was observed, although there was no consistent pattern in different patients. Outside the target volume, absolute reduction in CBV in both gray and white matter was not significant (mean drops of 9.2 to 7.4 and 4.4 to 4.1, respectively). After whole-brain irradiation, however, the reduction in blood volume of both gray (6.3) and white (3.1) matter was significant. Local decreases in CBV without concomitant changes in BBB permeability (important if the indicator-dilution model assumptions, which underlie the calculation of rCBV maps, are to remain valid) are also known to occur with both chemotherapy and aging.

As already noted, pilot studies have suggested that both mathematically corrected gadolinium-based rCBV maps and dysprosium maps have greater sensitivity and specificity than do FDG-PET scans in evaluating for recurrent glioma in irradiated tumor beds (Fig 4). Our recent work supports this contention. Of 45 consecutive post-high-grade glioma resection patients treated with proton-beam irradiation at our institute between 1992 and 1996, 26 met entry criteria of (1) presentation with newly progressive MRI findings suspicious for tumor recurrence, (2) pathological or clinical proof of diagnosis at time of presentation, and (3) availability of concurrent rCBV ± FDG-PET scans performed at presentation. Representative ROIs were selected from each of 28 discrete enhancing foci suspicious for tumor recurrence; their rCBV values were normalized to those of corresponding contralateral uninvolved regions (Figs 5 and 6). The 28 ROIs included 17 foci of recurrent tumor and 11 foci of necrosis. Their normalized rCBV ROI values clustered around 1.0 for the necrosis cases and were either very high (>1.5, indicating high tumor vascularity) or very low (<0.7, indicating high permeability areas of marked BBB breakdown) for the recurrent gliomas. Interestingly, the low rCBV ROI value recurrences occurred exclusively in the high (>55 cobalt Gy equivalent) photon radiation dose fields. Using the above cutoff values, 10 of 11 necrotic foci and 14 of 17 tumor foci were correctly categorized ($P<0.0001$), which corresponds to a sensitivity and specificity of approximately 78% on the fitted receiver operating characteristics (ROC) curve. Direct visual inspection of both the rCBV maps and the available FDG-PET scans proved significantly less accurate than the use of quantitative ROIs in distinguishing necrosis from recurrence; the sensitivity and specificity of both the PET and the rCBV qualitative visual evaluations were approximately 65% and 45%, respectively.

What do these results mean? Certainly, the finding of elevated rCBV in regions of high-grade recurrence is to be expected, but how are the reduced rCBV values found in the recurrences at the high-photon dose fields to be explained? The answer, although still under investigation, may be related to the failure of the mathematical "correction" algorithm to compensate for the synergistic damage to the BBB (with consequent marked increase in vascular permeability) caused by superimposed high-grade recurrent tumor and high-dose photon-beam radiation, resulting in severe focal underestimation of rCBV during map construction. The severe focal signal loss observed, however, may also be the result of exaggerated susceptibility artifacts. These could arise, as before, from the summed effects of proton-beam-induced damage to the tumor bed (with accompanying susceptibility effect due to hemosiderin deposition from microhemorrhage) and superimposed susceptibility effects due to high-grade tumor recurrence. This hypothesis is supported by a recent paper suggesting that lesion susceptibility artifacts detected on T2*-weighted images are associated with preoperative glioma grade ($P<0.05$), possibly due to iron-binding compounds present within malignant gliomas. Only a small percentage of the high-grade tumors with susceptibility artifact reported in that study were found at biopsy to contain hemosiderin, proving that the observed correlation was not solely a...
A trend toward early detection of recurrent tumor has also been reported using rCBV imaging. In one proton-beam treated patient we studied serially, an elevated rCBV at the corpus callosum predicted recurrence six weeks before any abnormality could be discerned on conventional MRI (Fig 7). Similarly, in an earlier pilot study of serial perfusion imaging carried out by our group, some rCBV images were observed to become “positive” for glioma recurrence before either FDG-PET or conventional MR images became positive, although the number of patients involved was not sufficient to establish significance. Other groups have had an analogous experience comparing rCBV mapping to \(^{201}\)Tl-SPECT. In a serial study of 59 patients (191 studies), tumor progression was detected by rCBV maps earlier than MRI in 32% of the studies (earlier by a median of 4.5 months, \(P<0.01\)), earlier than \(^{201}\)Tl-SPECT in 63% (median 4.5 months, \(P<0.01\)), and earlier than clinical assessment in 55% (median 6 months, \(P<0.01\)). Of interest, in 82% of studies with positive MRI but negative SPECT, the lesions were smaller than 1.5 cm.

Conclusions

In summary, rCBV MRI of brain tumors not only is feasible, but also offers clinically relevant physiological data not obtainable by conventional MRI. In untreated gliomas, rCBV imaging has a high negative predictive value; the absence of elevated blood volume effectively excludes high-grade tumor, regardless of the enhancement characteristics of the lesion. For posttreatment brain tumors, the situation is more complex, but there is good evidence that perfusion MRI has advantages over both conventional MRI and more established functional imaging techniques.

Additional studies are required to define the role of perfusion MRI as an endpoint to assess brain tumor responses to diverse therapies, including brachytherapy, boron neutron capture therapy, fractionated conventional radiation dosing schedules and, most recently, genetic-based treatments involving retroviral vectors. Perfusion MRI offers the promise of improved detection of recurrent disease, which could lead to more efficient use of imaging resources and, potentially, to decreased tumor morbidity. Perfusion MRI techniques are likely to be at least as sensitive and specific as radionuclide-based techniques, and they offer the added advantages of higher intrinsic resolution, convenient co-registration with conventional MRI, and time- and cost-effective imaging in a patient population that already receives frequent follow-up conventional MRI studies.

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