Clinical Review of Computed Tomography and MR Perfusion Imaging in Neuro-Oncology

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KEYWORDS

• Perfusion • Neuro-oncology • Glioblastoma • Fractional tumor burden

KEY POINTS

- Advanced perfusion imaging can offer enhanced evaluation of tumoral physiology to guide the diagnosis, intraoperative sampling, and grading of brain tumors.
- Perfusion imaging is useful when differentiating between tumor types and neoplastic and nonneoplastic conditions.
- Hemodynamic parameters obtained from perfusion imaging can guide clinical decision making for treatment-related processes, such as radiation necrosis.

INTRODUCTION

Neuroimaging plays an essential role in the initial diagnosis and continued surveillance of intracranial neoplasms, with multiple studies showing the utility of perfusion imaging in assessing tumor physiology and hemodynamics.[1] Although conventional MR imaging techniques are useful in evaluating the anatomy and structure of the brain, advanced imaging approaches can provide useful information about physiology and function not visible on the anatomic images.[2] Specifically, perfusion imaging can estimate cerebral blood flow (CBF) and cerebral blood volume (CBV) as markers of angiogenesis within intracranial tumors, can generate transfer constant (k-trans) as a permeability marker in tumors before and after treatment, and can help to distinguish between tumor and treatment effect in previously treated tumors. To date, the most useful perfusion parameters in the clinical neuro-oncology setting are CBF and CBV, which are acquired with exogenous contrast agents (eg, dynamic susceptibility contrast [DSC] MR imaging[3] and iodinated contrast-enhanced computed tomography [CT] perfusion imaging)[4] or without contrast agents (eg, arterial spin labeling [ASL] imaging).[2] In this article, we review the clinical relevance and implications of perfusion imaging in neuro-oncology and highlight promising perfusion biomarkers.

COMPUTED TOMOGRAPHY PERFUSION

CT perfusion provides information on brain hemodynamics by analyzing the first passage of an intravenous contrast bolus through the cerebral vessels. Raw images are acquired on a multislice CT scanner and are subsequently post-processed by software to generate hemodynamic perfusion maps. This permits quantitative and

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qualitative assessment of CBV and CBF (Fig. 1). CBV refers to the volume of blood within a given region of brain tissue and is measured in milliliters per 100 g of brain tissue. A closely associated and often interchangeably used term is relative cerebral blood volume (rCBV). This accounts for capillary permeability by measuring CBV relative to an internal control (such as the contralateral normal-appearing white matter) and is expressed as an overall ratio. CBF refers to the amount of blood per unit time passing through a given region of brain tissue and is measured in milliliters per 100 g per minute of brain tissue.[5] Fractional tumor burden (FTB) is a newer perfusion-derived metric and is defined as the volume fraction of tumor voxels higher or lower than a specified CBV threshold.[6]

An advantage of using CT perfusion over perfusion MR imaging is the linear relationship between iodine concentration and attenuation on CT, providing a more absolute measurement of vascular parameters.[5] CT also has the benefit of wider availability, faster scanning times, and lower cost compared with MR imaging.[4] CT can also be used in patients with contraindications to MR imaging, such as in those with medical implants. However, CT does require radiation exposure to the patient, which may be additive if serial imaging is needed. In addition, soft tissue resolution on CT is inferior to MR imaging.[4]

PERFUSION MR IMAGING

Perfusion MR imaging techniques take advantage of endogenous or exogenous tracers. With regards to exogenous agents, perfusion MR imaging is based on the concept of following an injected bolus of contrast agent over time, which is then used to investigate the perfusion characteristics of brain tumors. Contrast-enhanced perfusion imaging is accomplished with DSC and dynamic contrast-enhanced (DCE) imaging. With regards to endogenous agents, ASL imaging can be used; this technique magnetically labels spins using protons within arterial blood to estimate CBF.[7] In the next paragraphs, we briefly review the techniques of DSC, DCE, and ASL and highlight the clinically relevant parameters acquired from each technique for brain tumor imaging (Fig. 2).

Dynamic Susceptibility Contrast

DSC MR imaging uses a bolus tracking technique that is most frequently based on T2 (spin echo) or T2* (gradient echo imaging) effects before, during, and after administration of a gadolinium-based contrast agent.[8] In DSC imaging, injection of a contrast agent causes a transient drop in signal intensity reflective of the effects of the paramagnetic contrast agent. The spin echo technique has the advantage of minimizing brain, bone, and air interfaces and is more sensitive to signal changes from contrast material passage through small vessels. The main disadvantage of spin echo imaging is the requirement of a higher dose of contrast, which is needed to produce signal changes comparable with gradient echo imaging.[9] Gradient echo DSC is faster in terms of image acquisition and takes advantage of first-pass imaging and magnification

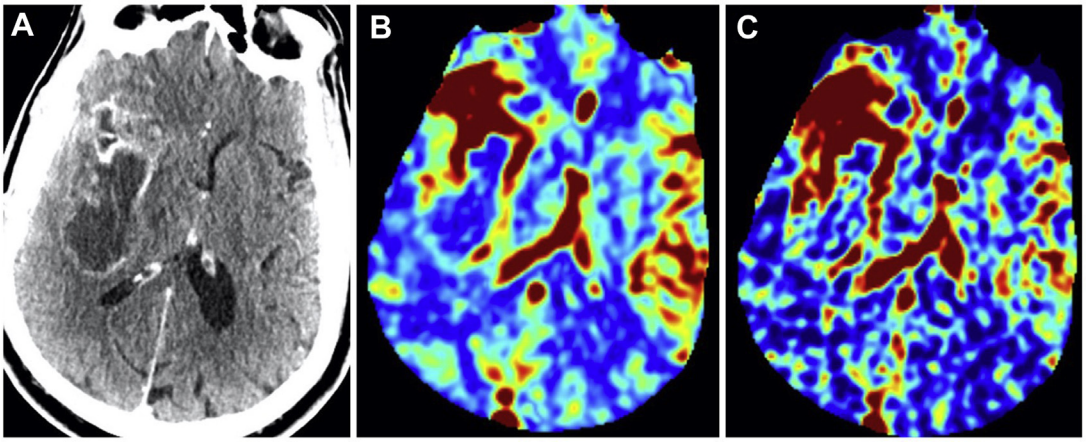

Fig. 1. CT perfusion in a 67-year-old man acquired for evaluation of stroke-like symptoms. (*A*) Postcontrast CT image shows a large peripherally enhancing necrotic mass in the right temporal lobe. (*B*) Post-processed cerebral blood flow and (*C*) cerebral blood volume images acquired from perfusion imaging show significantly elevated (*red color*) perfusion within the anterior and peripheral aspects of the mass. Histopathology following surgical resection revealed glioblastoma.

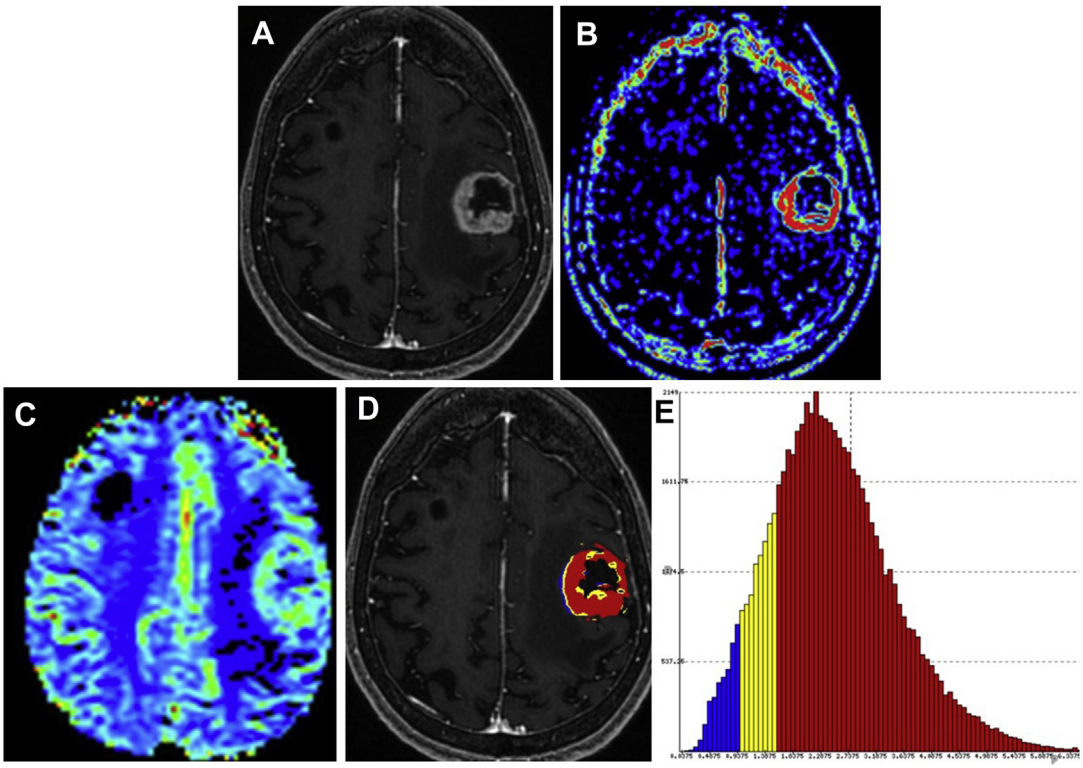

Fig. 2. A 70-year-old woman with a left frontal treatment-naive glioblastoma. (*A*) Postgadolinium three-dimensional (3D) T1-weighted MR image shows a large necrotic mass in the left frontal lobe. (*B*) K-trans map acquired from dynamic contrast-enhanced perfusion imaging shows elevated k-trans (*red color*) throughout much of the lesion. (*C*) CBV and (*D*) FTB images acquired from dynamic susceptibility contrast-enhanced perfusion imaging also show elevated CBV and FTB_{high}, respectively. (*E*) FTB histogram shows the distribution of contrast-enhancing voxels with low FTB (*blue*), intermediate FTB (*yellow*), and high FTB (*red*), with the greatest proportion of contrast-enhancing lesion voxels having high FTB.

of contrast-induced signal loss through susceptibility-weighted images. A disadvantage of this technique, however, is related to inherent susceptibility artifacts produced by blood, calcification, or larger vessels. Nonetheless, with either approach, contrast preloading, gamma variate curve fitting, or other leakage correction methods are commonly used to reduce T1 relaxation effects and to account for residual T2/T2* effects.[10,11] Much like CT perfusion, DSC allows for the calculation of multiple perfusion parameters, such as CBF, CBV, and FTB.[6]

Dynamic Contrast Enhancement

DCE MR imaging uses bolus tracking on T1-weighted imaging, where permeability characteristics of brain tumors are assessed. Advantages of DCE include acquisition with a lower contrast dose and better temporal resolution compared with that of T2- or T2*-weighted DSC imaging. This is because T1-weighted imaging-based DCE measures the relaxivity effects rather than the susceptibility effects of the injected dose of a paramagnetic contrast agent. The relaxivity effect refers to the generated signal of T1 shortening related to relaxation time, which is inherently stronger than susceptibility. Also, shorter injection times may result in better quantitation of CBV and CBF provided that the temporal resolution of the pulse sequence can allow for dynamic tracking of the injected contrast bolus over multiple time points to extract and estimate T1 signal and concentration.[9] However, DCE suffers from the necessity of advanced and complex pharmacokinetic modeling to account for the nonlinear relationship between the acquired signal intensity and contrast concentration. Nonpharmacokinetic model-based analyses with DCE have attempted to avoid this problem but have unclear physiologic and clinical basis and utility.[11]

Despite several choices for modeling, the Extended Tofts Model, which is a two-compartment model of the vascular and

extracellular-extravascular spaces, is frequently used in brain tumor imaging. In this model, the leakage of contrast is measured quantitatively and a triexponential enhancement curve is fitted to a theoretic model based on compartmental analysis.[12] This allows for many parameters to be obtained, such as the k-trans, volume of the extravascular extracellular space, and blood plasma volume.[5] Of these, k-trans has been the most widely used and investigated in clinical neuro-oncology. It is important to know that although k-trans is thought to be a marker of permeability, it is more reflective of blood flow in certain conditions. For example, in situations where there is high permeability, the flux of gadolinium-based contrast agent is primarily limited by flow and, therefore, k-trans primarily reflects blood flow. In situations where there is low permeability, the contrast leakage is limited in its ability to flow into the extravascular-extracellular space and, therefore, k-trans primarily reflects permeability.[13]

Arterial Spin Labeling

ASL imaging is a noncontrast technique that takes advantage of an endogenous tracer by magnetically labeling spins using protons within arterial blood.[7,14] The MR imaging sequence acquisition is built in such way that a delay allows the labeled water molecules to flow into the brain tissue and exchange with the brain tissue water, which results in small changes in the magnetization of the tissue water. When evaluated in conjunction with control (unlabeled) images, CBF images are generated after subtraction from the labeled images.[2] Although not yet widely used or established in clinical practice, this technique for acquiring cerebral perfusion offers several advantages over DSC and DCE, primarily because it does not require injection of a gadolinium-based contrast agent. Therefore, ASL is a promising technique for assessing perfusion in patients who have renal dysfunction or severe allergic reactions to gadolinium or who require frequent follow-up contrast-enhanced examinations.[3] However, widespread clinical applications of this method have been limited, in part because of longer acquisition times and sensitivity of the technique to patient motion.[9]

CLINICAL USE OF PERFUSION IMAGING IN NEURO-ONCOLOGY

Although conventional MR imaging is essential for the diagnosis and evaluation of brain tumors, it does not confer much information about tumor vascularity and physiology. Perfusion imaging is valuable because it is used to help grade tumors; differentiate between tumor types; differentiate tumors from nonneoplastic lesions; guide intraoperative sampling; and, most importantly, determine efficacy of treatment.[15] The initial differentiation between neoplastic and nonneoplastic lesions is difficult with conventional MR imaging, often requiring direct tissue sampling for diagnostic confirmation.[8] Perfusion imaging can help to distinguish between infectious and neoplastic lesions, as CBV of infection tends to be significantly lower than CBV of metastases or glioblastomas, likely reflective of their respective vascular densities.[16] However, there is potential for overlap between low-grade tumors and nonneoplastic lesions.[15] Thus, systematic incorporation of perfusion imaging as part of a multiparametric approach, potentially with MR spectroscopy, can aid in improving diagnostic confidence.[8,17]

Grading of Tumors

MR and CT perfusion imaging have shown to be helpful in determining the initial grade of gliomas based on increased or decreased tumor perfusion,[5] with studies showing that specific perfusion metrics correlate strongly with overall histopathologic grade.[18] These perfusion metrics can predict tumor behavior, because tumor aggressiveness and growth are associated with endothelial hyperplasia and endothelial neovascularization.[19] As such, it is not surprising that higher CBV correlates with lesion vascularity and higher tumor grade.[16] However, there is a substantial overlap of perfusion markers in tumors of varying grades and histology, which somewhat limits the discriminatory ability of perfusion imaging in certain tumor types and in differentiating between higher grades of tumors (eg, grade III and IV gliomas).[8] K-trans has shown promise in differentiating between low-grade (grade I) and higher-grade (grade II, III, or IV) tumors, although larger multicenter studies are still needed to validate its use in the clinic.[19]

Differentiation Between Tumor Types

An important and often difficult diagnostic dilemma exists when differentiating between glioblastoma, solitary brain metastasis, and primary central nervous system lymphoma. This is because of their similar and often times overlapping appearance on conventional MR imaging, presenting as solitary and avidly enhancing lesions with peripheral T2 hyperintensity.[20] It is important to distinguish between these entities, because management (surgery and/or chemotherapy) is different.[20,21] A study by Neska-Matuszewska and colleagues[20] found that maximum CBV within the tumor core enabled discrimination of less

perfused primary central nervous system lymphomas from that of the more hyperperfused glioblastomas and metastases. When discriminating between glioblastoma and metastasis, maximum CBV within the perilesional zone was found to be most helpful. Increased CBV was observed within the peritumoral zones, reflecting the infiltrative and highly vascular nature of glioblastomas. Alternatively, decreased CBV was observed within the perilesional zone of metastases, reflecting regional vasogenic edema rather than nonenhancing infiltrative tumor.[20]

Differentiation Between Tumor and Nonneoplastic Conditions

On conventional imaging, aggressive neoplasms, such as a necrotic glioblastoma, may mimic and may be difficult to differentiate from other entities, such as a cerebral abscess, because these entities can appear as rim-enhancing lesions with regional edema.[22] Perfusion imaging is helpful in these cases, because higher-grade neoplasms tend to have increased neovascularity and capillary density and, therefore, higher CBV, whereas abscesses tend to have significantly lower CBV.[23] Other studies have found that neoplastic lesions also demonstrate higher CBV when compared with infectious lesions. For example, Floriano and colleagues[24] found that a rCBV value less than 1.3 yielded a 92.6% specificity for identifying infectious lesions, adding support for the use of perfusion imaging in distinguishing between infectious and neoplastic brain lesions.

Tumefactive demyelinating lesions can also mimic higher-grade neoplasms, given their aggressive appearance on structural MR imaging. However, it has been demonstrated that tumefactive demyelinating lesions have lower CBV than high-grade gliomas because of the absence of neoangiogenesis, a prominent feature of high-grade tumors.[5,8]

Tumor Sampling

Although the optimal management of low-grade gliomas is surgical resection, watchful waiting is reasonable in certain patients. With watchful waiting, imaging is used to ensure tumor stability over time. If tumor progresses on imaging or shows changes indicative of transformation to a higher-grade lesion (eg, new or increasing enhancement or perfusion), then intervention may be necessary. However, some higher-grade tumors may lack enhancement altogether.[25] In addition, the presence of contrast enhancement may not always indicate a higher-grade tumor because its presence is only reflective of a disrupted blood-brain barrier.[8] Furthermore, although nonenhancing tumors are more likely to be of higher grade in older patients, diagnosis of lower-grade tumors cannot be reliably made without a proper biopsy.[25]

Stereotactic guided biopsy is commonly used for sampling of tumor tissue (**Fig. 3**). However, because of the internal heterogeneity of brain tumors, sampling error remains a problem. Studies have shown that regions of increased CBV on perfusion imaging can help to guide biopsies in patients with gliomas. CBF and CBV maps are used to identify areas of maximum hyperperfusion within a lesion to guide intraoperative sampling, because these areas are most likely to yield diagnostic tissue representative of the highest grade component of tumor.[8,26] Beyond CBV, the use of FTB has shown the highest correlation with actual tumor content, further supporting that perfusion MR imaging can potentially reduce sampling error in histopathologic diagnosis and improve target selection for stereotactic biopsy.[27,28]

Distinguishing Between Tumor and Treatment Response

Perfusion imaging may serve as an early response marker of treatment efficacy. For example, CBV values may be more useful after initiation of cytotoxic therapy than enhancing tumor volume alone.[8] Bag and colleagues[29] found that higher post-treatment peritumoral CBV and CBF values in patients with newly diagnosed glioblastomas were associated with poor prognosis. Also, a greater than 5% increase in CBV correlated with poor overall survival when acquired 4 weeks after treatment was initiated.[29] Iv and colleagues[6] showed that FTB_{high} (defined as all contrast-enhancing lesion voxels with normalized rCBV >1.75) performed better than mean normalized rCBV, FTB_{low} (defined as all contrast-enhancing lesion voxels with normalized rCBV <1), and FTB_{mid} (defined as all contrast-enhancing lesion voxels with normalized rCBV between 1 and 1.75) in differentiating tumor from treatment effect in the recurrent glioblastoma setting and also impacted clinical decision-making.[6] These findings are likely related to the heterogeneity of tumor, which can have areas of high and low blood volume because of varying areas of angiogenesis and necrosis, whereas treated tissue typically has low blood volume.

Post-treatment Follow-up

In 1990, Macdonald and colleagues[30] published outlined criteria to evaluate malignant glioma response to treatment. The criteria consisted of two-dimensional measurements of enhancing

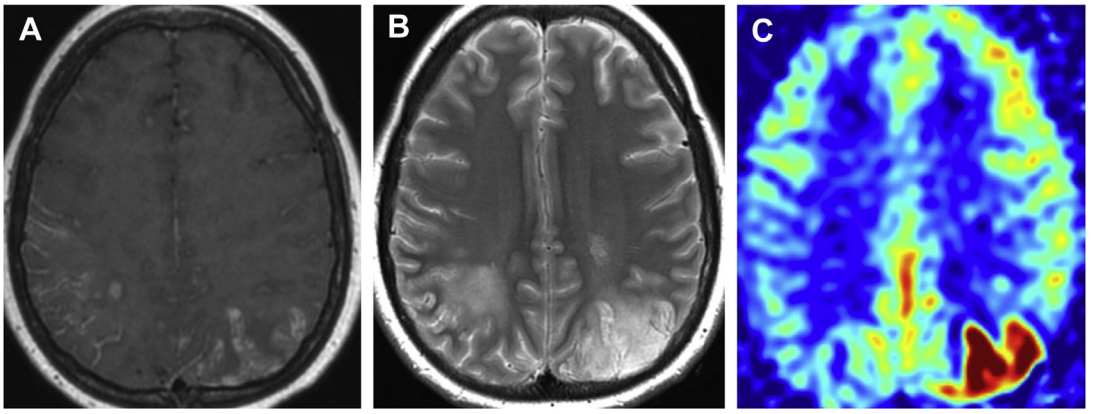

Fig. 3. A 29-year-old woman with history of an undifferentiated uterine sarcoma. (*A*) Postgadolinium 3D T1-weighted black blood image shows parenchymal and leptomeningeal enhancement within the parietal lobes bilaterally. (*B*) Extensive T2 signal is present in these areas. (*C*) Cerebral blood flow image acquired from arterial spin labeling perfusion imaging shows an area of high blood flow only in the left parietal lobe. Because the exact nature of these imaging findings was unclear in the context of progressive disease on serial imaging (not shown), persistent seizures, and unremarkable cerebrospinal fluid studies, intraoperative sampling was performed for tissue diagnosis. The biopsy was performed in the area of greatest perfusion. Histopathology revealed sarcoma metastases.

tumors using cross-sectional images, while incorporating neurologic status and corticosteroid use. With the development and growing use of antiangiogenic agents that drastically affected imaging findings, newer criteria have been made available for use when evaluating post-treatment response (Response Assessment in Neuro-Oncology [RANO] criteria). This construct is primarily used in the context of a clinical trial and in clinical research. The response assessment consists of measurements of contrast enhancement, progression or decrease (response) in size, durability of response, measurability, number of target lesions (up to five), and consideration and incorporation of corticosteroids, clinical status, and pseudoprogression. There are similar but different criteria for high-grade gliomas (RANO-HGG), low-grade gliomas (RANO-LGG), patients undergoing immunotherapy (iRANO), and brain metastases (RANO-BM), with multiple working RANO groups in progress.[31] A shortcoming of these criteria is the reliance on gadolinium enhancement, which is sensitive for tumoral changes but overall nonspecific when compared with other more advanced MR imaging sequences.[32] In addition to incorporating clinical findings with response criteria, clinicians today face the additional challenge of managing patients that have either new or established lesions seen on follow-up MR imaging.[33]

Pseudoprogression

A well-known phenomenon observed during the imaging surveillance of treated glioma patients is the increase in size of the contrast-enhancing lesion, or contrast-enhancing volume, followed by subsequent improvement or eventual stabilization. This initial increase in size and enhancement is termed pseudoprogression.[34] Pseudoprogression often appears several weeks or months after the initial treatment.[33] It reflects transiently increased contrast enhancement, which can often mimic tumor progression and can complicate evaluation using radiologic criteria for progression, because it represents an exaggerated response to therapy.[8,34] The cause of pseudoprogression is believed to be the result of transient interruption of myelin synthesis secondary to injury to primary oligodendrocytes, with studies suggesting an overall transient course with spontaneous recovery.[33] Although pseudoprogression is commonly seen after concomitant radiotherapy-temozolomide, it can also be seen after radiotherapy alone or in combination with chemotherapy. Pseudoprogression is seen in approximately 20% of patients treated with concomitant radiotherapy-temozolomide and is often seen in the 2- to 6-month period after chemoradiotherapy, with a median of approximately 3 months.[34]

Differentiation from progressive disease is a hallmark for avoiding premature trial failures in the setting of pseudoprogression and selecting timely alternate therapies.[8] The challenge in differentiating between pseudoprogression and progressive disease using conventional T1-weighted postcontrast MR imaging is because contrast enhancement is nonspecific and only a marker of blood-brain barrier disruption.[35,36] The inflammatory response in

pseudoprogression and angiogenic response in active tumor can demonstrate increased vascular permeability and contrast enhancement on MR imaging; therefore, it is often difficult to differentiate between these entities using conventional MR imaging alone. Perfusion MR imaging provides the advantage of quantifying blood volume, in addition to physiologic blow flow and permeability, which can provide a more discriminating diagnostic tool (**Figs. 4** and **5**).[35] For example, studies have found that an enhancing lesion with a normalized relative CBV ratio higher than 2.6 is suggestive of tumor recurrence, and a relative CBV value lower than 0.6 suggests nontumoral contrast-enhancing tissue. Overall, studies demonstrate that an increase in the relative CBV value favors tumor recurrence and a decrease favors pseudoprogression.[34] Another study by Young and colleagues[35] found that perfusion MR imaging estimates of blood volume and permeability can successfully identify pseudoprogression within a subgroup of patients that initially presented with radiographic worsening. This was characterized by lower perfusion parameters and overall higher permeability. This suggests that despite nearly identical appearances on conventional MR imaging, the addition of perfusion imaging may play an important role in the early diagnosis of treatment effects versus treatment failure.[35] Based on a recent 2017 meta-analysis of perfusion-weighted imaging in distinguishing treatment effect from tumor, perfusion imaging demonstrated promising accuracy.[11] A caveat is the heterogeneity of imaging techniques and highly variable proposed cutoff CBV values, which are potentially useful as a general guide. A particular threshold value that is optimized at a single institution might be more sufficient if applied consistently to a patient and subsequently followed over time.[11] Mean CBV may also be inadequate early in lesion evolution for observing the overall dominant or predicted behavior of tumor. As such, CBV trends or histograms identifying temporal and spatial variations may be more predictive.[8]

Radiation Necrosis

Radiation necrosis and pseudoprogression are distinct entities on a spectrum of post-treatment enhancement.[8] In contrast to pseudoprogression, radiation necrosis typically appears months to several years after the initial treatment. Although its mechanism is not fully understood, it is thought to be characterized by increased vascular permeability with proinflammatory mediators and cytokines, mixed with quiescent tumor and necrosis, which results in edema and contrast enhancement that is difficult to distinguish from progressive disease on conventional MR imaging.[34] The area of necrosis results in a space-occupying lesion with mass effect and can result in neurologic dysfunction or sequelae,[33] which makes delineation between radiation necrosis and tumor progression a diagnostic challenge. Both entities often manifest as a mass-like lesion with regional edema and progressive enhancement on serial studies.[18] Often, conventional imaging is inconclusive and advanced MR imaging techniques are necessary.[2] This imaging dilemma is not uncommon, with a recent meta-analysis revealing that 36% of patients with an enhancing lesion on post-treatment MR have treatment-related changes, whereas true progression only occurred in 60% of the patients.[37,38]

In these cases, perfusion imaging has shown to be helpful (**Fig. 6**).[18] CBV measurements using

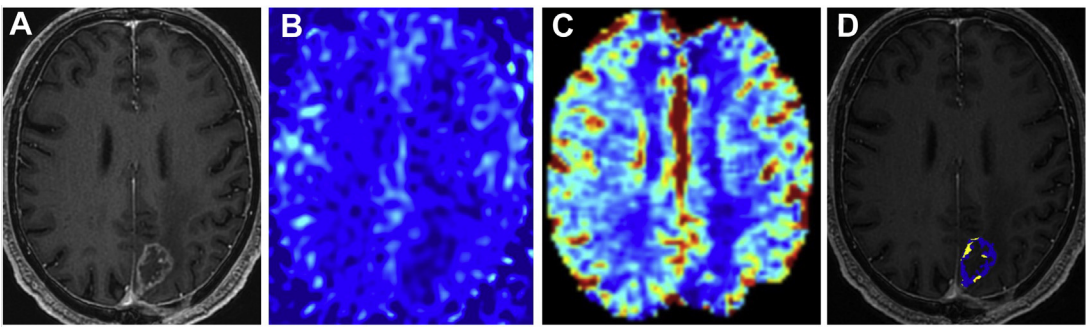

Fig. 4. A 65-year-old man with history of left posterior parietal glioblastoma previously treated with surgical resection and chemoradiation, presenting for follow-up 3 months after therapy. (*A*) Postgadolinium 3D T1-weighted image shows a heterogeneously enhancing lesion in the left posterior parietal lobe, at the site of previously treated glioblastoma. (*B*) Cerebral blood flow image from arterial spin labeling and (*C*) cerebral blood volume image from DSC imaging show low blood flow and volume, respectively, within the lesion. (*D*) Fractional tumor burden image from DSC shows primarily low fractional tumor burden (*blue*) within the lesion. Perfusion characteristics are suggestive of pseudoprogression (treatment effect). Nonetheless, the patient underwent surgical resection, and histopathology confirmed necrosis and reactive changes without tumor cells.

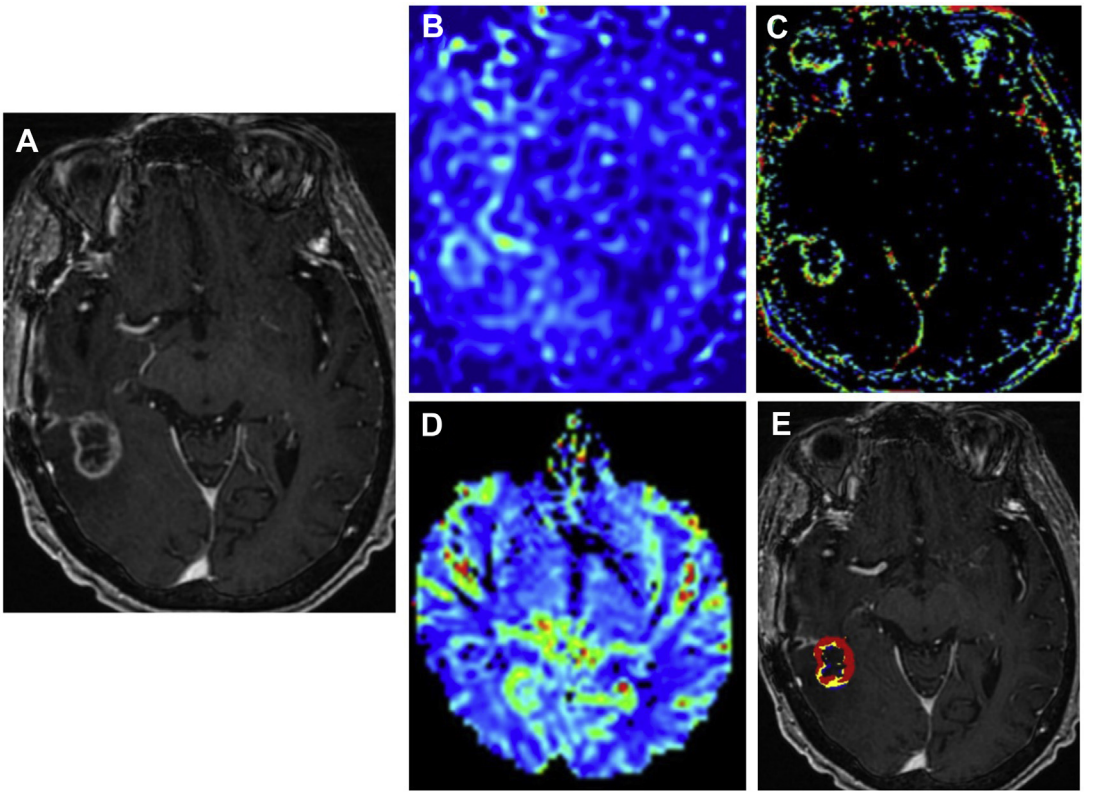

Fig. 5. A 70-year-old woman with history of right temporal glioblastoma, previously treated with surgical resection and chemoradiation, presenting for follow-up 2 months after therapy. (*A*) Postgadolinium 3D T1-weighted image shows a heterogeneously enhancing lesion in the right temporal lobe, at the site of the previously treated glioma. (*B*) CBF image from arterial spin labeling, (*C*) k-trans image from dynamic contrast enhancement, and (*D*) CBV image from dynamic susceptibility contrast-enhanced imaging show mild-to-moderately elevated CBF, k-trans, and CBV, respectively, within the lesion. (*E*) Fractional tumor burden image from DSC shows primarily high fractional tumor burden (*red*). Perfusion characteristics are suggestive of residual/recurrent tumor. The patient underwent surgical resection, and histopathology confirmed the diagnosis of residual/recurrent glioblastoma.

perfusion MR imaging may predict the status of contrast enhancing lesions and provide results similar to fluorodeoxyglucose (FDG)-PET with regards to differentiation between tumor recurrence and radiation necrosis.[39] In a study by Larsen and colleagues,[39] measurements of CBV were performed on patients with contrast enhancing lesions on MR imaging, which correlated well with FDG-PET examination findings. The lesions that regressed demonstrated lower CBV and generally corresponded to regions of decreased metabolism on FDG-PET (radiation necrosis). Lesions that progressed demonstrated higher CBV and corresponded to regions of higher metabolic activity on FDG-PET (tumor recurrence).[33] However, this is partially limited by the use of different CBV thresholds, which is dependent on the specific perfusion MR imaging protocol at a certain institution.[8] In a study by Barajas and colleagues,[40] perfusion MR imaging was retrospectively studied to determine whether a progressively enhancing lesion represented recurrent glioblastoma or radiation necrosis. The authors found that CBV tended to be significantly higher in tumor, and that significantly lower parameters were found in patients with radiation necrosis. As indicated by the findings of these studies, the ability of perfusion values to distinguish between radiation necrosis and tumor is caused by inherent differences in their hemodynamic characteristics, which is further supported by histologic studies that demonstrated that tumor vasculature was significantly elevated in tissue specimens obtained from the contrast-enhancing portions of glioblastoma.[18] Besides perfusion-weighted imaging, the addition of MR spectroscopy is helpful to differentiate between tumor progression and radiation necrosis, the latter of which demonstrates a

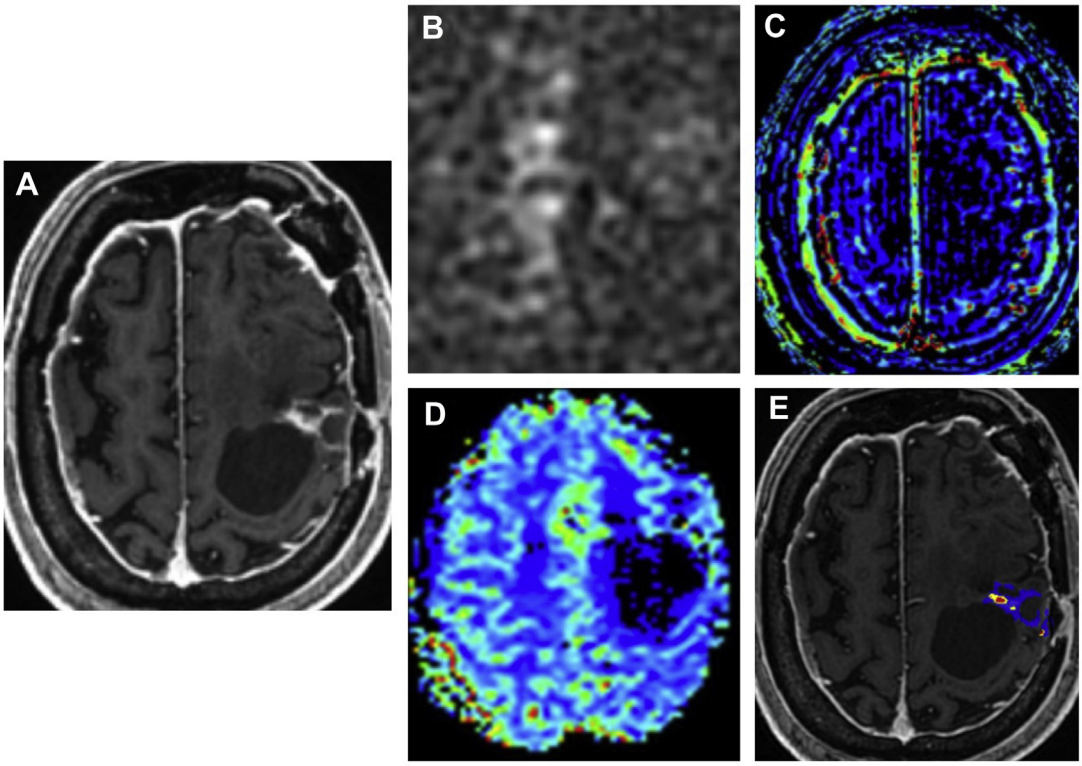

Fig. 6. A 72-year-old man with history of brain metastases from non–small cell lung cancer and previous treatment of a dominant left frontal metastasis with surgical resection and stereotactic radiosurgery, more than 4 years prior. (*A*) Postgadolinium 3D T1-weighted image shows a heterogeneously enhancing lesion in the left frontal lobe, at the site of the previously treated metastasis. (*B*) Arterial spin labeling images were suboptimal because of poor labeling. (*C*) K-trans image acquired from dynamic contrast-enhanced imaging and (*D*) CBV image acquired from dynamic susceptibility contrast-enhanced imaging show no increase in k-trans and CBV, respectively, within the lesion. (*E*) Fractional tumor burden image from DSC shows primarily low fractional tumor burden (*blue*) within the lesion. Perfusion features are suggestive of radiation necrosis (treatment effect). Nonetheless, the patient underwent a surgical resection, and histopathology revealed radiation necrosis and extensive gliosis without neoplasm.

high lipid/lactate peak, low N-acetylaspartate (NAA) peak, and a low choline peak as compared with normal brain parenchyma and pretreatment brain tumor.[2]

Pseudoregression (Pseudoresponse)

The advent of antiangiogenic therapy has led to often deceptive improvements in imaging findings, termed pseudoregression or pseudoresponse. This consists of relative decreases in contrast enhancement and peritumoral edema and is noted in up to 25% to 60% of the patients.[41,42] The most common agents used in these treatments are bevacizumab, which is a recombinant antibody, and cediranib, a receptor tyrosine kinase inhibitor. Additionally, pseudoregression may be associated with several other immunotherapeutic treatment agents, which are currently being studied.[31]

It is thought that the rapid radiographic response related to pseudoregression represents a direct action on blood vessel permeability rather than a true antitumor effect.[2] Typically, these findings are evident after several days, and can coincide with a transient improvement of clinical symptoms. However, the decrease in contrast enhancement in cases of pseudoregression is not associated with a decrease in tumor or overall survival.[43] Despite the shortcomings of conventional techniques, perfusion MR imaging can demonstrate areas of persistent increased perfusion values within the responsive lesion.[41]

Furthermore, studies have shown that the information provided by perfusion imaging can provide valuable information about changes in vascular function during therapy, which may aid in the identification of patients who are more likely to respond to prior therapies, or as an early indicator of patient

response to antiangiogenic therapy. A study by Essock-Burns and colleagues[44] emphasized two parameters derived from perfusion maps: peak height, defined as the maximum increase in relaxivity of the greatest gadolinium influx, which is used as an estimate of vascular density; and percent signal recovery defined as the relative return to baseline of the signal intensity-time curve reflective of the bolus through a voxel, which is used as an estimate of leakage. These parameters were chosen in lieu of relative CBV because they did not require extensive curve fitting.[44] The study found that those with true response demonstrated a decrease in peak height and an increase in percent signal recovery which was attributed to an improvement in vessel permeability caused by antiangiogenic treatment. However, other studies demonstrate conflicting results, with a study by Stadlbaeur and colleagues demonstrating that changes in CBV were not significant enough to be suitable for differentiation between a true response and pseudoresponse.[41,45] A further confounder in the assessment of response is the tendency for antiangiogenic agents to promote progression of nonenhancing disease, thought be secondary to selection of a more invasive tumor subtype that does not require angiogenesis.[2]

SUMMARY

Through the years, there has been increased clinical utility of perfusion techniques using CT and MR imaging. These techniques have the potential to overcome the shortcomings of conventional MR imaging and can offer better approaches to tumor grading and provide physiologic information to aid advanced biopsy techniques. Furthermore, perfusion MR imaging is helpful to distinguish tumor from treatment-related processes, such as radiation necrosis, pseudoprogression, and pseudoregression.[41] Although the heterogeneity of image acquisition and processing techniques across sites remains a significant hurdle, the use of perfusion imaging in neuro-oncology has thus far proven to be promising.

CLINICS CARE POINTS

- Advanced perfusion imaging can offer enhanced evaluation of tumor physiology and hemodynamics to establish diagnosis, grade tumors, guide intraoperative sampling, and monitor therapeutic efficacy.
- Perfusion imaging is useful to differentiate between tumor types and between tumor and nonneoplastic conditions, such as infection or demyelination.
- Physiologic parameters obtained from perfusion imaging can help to identify treatment-related processes, such as radiation necrosis, pseudoprogression, and pseudoregression, and can help to guide clinical decision-making.

DISCLOSURE

The authors have nothing to disclose.

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