Clinical Imaging for Diagnostic Challenges in the Management of Gliomas: A Review

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ABSTRACT

Neuroimaging plays a critical role in the management of patients with gliomas. While conventional magnetic resonance imaging (MRI) remains the standard imaging modality, it is frequently insufficient to inform clinical decision-making. There is a need for noninvasive strategies for reliably distinguishing low-grade from high-grade gliomas, identifying important molecular features of glioma, choosing an appropriate target for biopsy, delineating target area for surgery or radiosurgery, and distinguishing tumor progression (TP) from pseudoprogression (PsP). One recent advance is the identification of the T2/fluid-attenuated inversion recovery mismatch sign on standard MRI to identify isocitrate dehydrogenase mutant astrocytomas. However, to meet other challenges, neuro-oncologists are increasingly turning to advanced imaging modalities. Diffusion-weighted imaging modalities including diffusion tensor imaging and diffusion kurtosis imaging can be helpful in delineating tumor margins and better visualization of tissue architecture. Perfusion imaging including dynamic contrast-enhanced MRI using gadolinium or ferumoxytol contrast agents can be helpful for grading as well as distinguishing TP from PsP. Positron emission tomography is useful for measuring tumor metabolism, which correlates with grade and can distinguish TP/PsP in the right setting. Magnetic resonance spectroscopy can identify tissue by its chemical composition, can distinguish TP/PsP, and can identify molecular features like 2-hydroxyglutarate. Finally, amide proton transfer imaging measures intracellular protein content, which can be used to identify tumor grade/progression and distinguish TP/PsP.

Keywords: Glioma, pseudoprogression, T2-FLAIR mismatch.

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Introduction

Neuro-oncologists commonly face diagnostic dilemmas prior to biopsy or resection, and at the time of new radiographic changes after chemoradiotherapy. When a mass is discovered, depending on the location, the clinician must decide between observation, biopsy (and biopsy target), or repeat resection. This decision can be difficult and involves a consideration of the extent of the lesion and involvement of eloquent cortex, whether the tumor is suspected to be high grade or low grade, and the molecular features of the tumor if these can be radiographically identified. Standard magnetic resonance imaging (MRI) is sometimes sufficient to resolve these dilemmas, for example, when there is a clear rim of enhancement suggesting a high-grade tumor. However, this is not always the case, for example, anaplastic astrocytomas do not always enhance but may be considered a high-grade tumor if they have wild-type isocitrate dehydrogenase (IDH). Advanced imaging modalities have therefore become an important adjunct tool for grading, choosing a biopsy site, and predicting molecular features.

Posttreatment radiographic changes present the clinician with the task of distinguishing tumor progression (TP) from pseudoprogression (PsP). PsP is fairly common with an estimated frequency of 31% in the largest study of 208 patients and is seen more commonly in O[6]-methylguanine-DNA methyltransferase (MGMT) methylated tumors.[1] Methylated tumors have a better prognosis and are more sensitive to DNA damage from both radiation and alkylating chemotherapy. PsP is felt to reflect a more robust treatment response and is associated with longer progression-free survival (PFS), whereas TP portends poor prognosis.[2] Of note, posttreatment biopsies seldomly reveal only progression or PsP, and a third of biopsies show a mixture of both, with no clear pathologic definition established.[3] Radiologic Assessment in Neuro-Oncology (RANO) criteria represent a significant improvement from MacDonald criteria but are frequently insufficient to guide decision-making in clinical practice, particularly for distinguishing TP/PsP (see Chukwueke et al[4] for a summary of the history and challenges of the RANO criteria for gliomas). The resulting uncertainty surrounding posttreatment MRI changes can result in delay of treatment or inappropriate termination of effective chemotherapy, unnecessary surgical interventions, and psychologic stress to patients and families. In this review, we will summarize how advanced imaging modalities can be used by the clinician to inform decision-making in the situations described above.

Diagnostic Clues in Standard MRI

Standard MRI cannot reliably distinguish PsP from TP after radiation, except when new lesions clearly fall outside of the

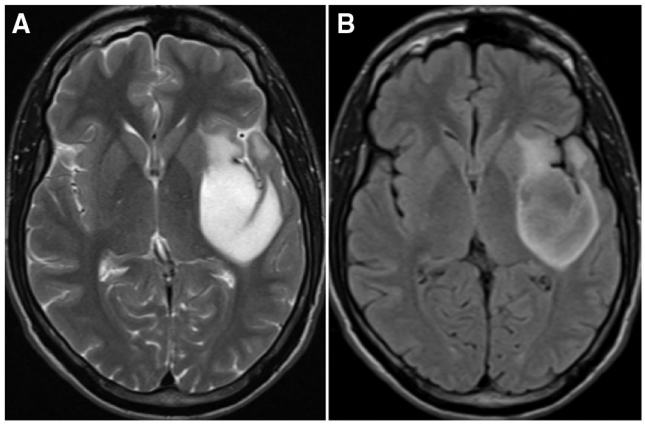

Fig 1. T2-FLAIR mismatch. A 36-year-old man with histologically proven isocitrate dehydrogenase mutant, 1p19q noncodeleted astrocytoma. On T2-weighted imaging (A), there is an area of homogenously hyperintense signal with signs of mass effect. On fluid-attenuated inversion recovery (B), a hypointense signal surrounded by a hyperintense peripheral rim is seen.

prior radiation treatment field, which is not routinely directly available for review. For example, PsP can manifest on MRI as increased fluid-attenuated inversion recovery (FLAIR) signal and enhancement along with mass effect, rendering it indistinguishable from the classic features of high-grade glioma. A large study of 321 patients whose initial posttreatment MRIs were systematically analyzed for 11 specific features found that only subependymal enhancement was predictive for TP, with 93% specificity, but only 38% sensitivity.[5]

Prior to treatment, one specific pattern on standard MRI deserves discussion, as it can be very useful in management of a newly discovered lesion. Mismatch between homogenously hyperintense T2-weighted signal and less-intense FLAIR signal, with a FLAIR-hyperintense peripheral rim (Fig 1), T2-FLAIR mismatch (T2FM) consistently demonstrates almost 100% specificity for IDH-mutant astrocytoma.[6,7] Importantly, this might not apply as reliably to tumors with enhancement or cystic components,[6] which can mimic this radiographic pattern in oligodendrogliomas.[8] Several false-positive cases of T2FM have been reported in pediatric-type gliomas, perhaps limiting the utility of the marker in this population.[9] While T2FM demonstrates high positive predictive value when employed judiciously, it is absent in 27% to 88% of IDH mutant astrocytomas, depending on criteria used, and the reason for this remains unknown.[6–8,10]

Diffusion Imaging

Diffusion-weighted imaging (DWI) uses multiple diffusion gradients to measure the magnitude of the random movements of water molecules, defined as the apparent diffusion coefficient (ADC). Visual inspection of DWI/ADC in gliomas is generally not informative, but by defining a region of interest (ROI), it is possible to generate a histogram from the sum of voxels. Minimum ADC values have been shown to inversely correlate with tumor grade in preoperative glioma.[11] Similarly, mean ADC ratios[12] and maximal ADC[13] values were lower in TP compared with PsP. Notably, these measures are highly dependent on the method used to define the ROI. More recently, high-*b*-value DWI was used to identify hypercellular tumors, and was a negative predictor of PFS.[14] ADC imaging is also a marker for epidermal growth factor receptor (EGFR) amplification, which is associated with increased angiogenesis.[15,16] There have been attempts to use ADC to distinguish high-grade from low-grade gliomas, and while there is some association, ADC was found to be inferior to dynamic contrast-enhanced (DCE) T1-weighted perfusion imaging.[17]

Diffusion tensor imaging (DTI) describes the magnitude of diffusion of water molecules as mean diffusivity (MD), and the directionality in a 3-dimensional plane as fractional anisotropy (FA). DTI allows visualization of tissue architecture, particularly white matter tracts. Because gliomas preferentially migrate along white matter tracts, DTI can be more sensitive for delineating the margins of involved parenchyma compared with regular MRI, a feature that can be helpful in surgical planning for resection as well as radiation planning.[18] For example, study of 31 patients demonstrated that DTI could reliably be used to predict invasion into the corpus callosum.[19] DTI has been reported to distinguish high- from low-grade gliomas,[20] and in particular the MD measured in the tumor bulk achieved an accuracy of 91.4%.[21] However, in studies comparing multiple modalities, measures of perfusion were superior for grading, and a multimodality algorithm was best.[22] While DTI makes the assumption that water diffusion assumes a Gaussian distribution, diffusion kurtosis imaging (DKI) accounts for the fact that the highly organized architecture of brain parenchyma results in a non-Gaussian distribution of water diffusion. DKI has been reported to be superior to DTI for glioma grading and prediction of Ki-67 and additionally DKI was able to distinguish IDH mutant from IDH wild-type tumors.[23]

Perfusion Imaging

Tumor neovascularization is correlated with glioma grade and inversely correlated with outcomes. Vascular perfusion imaging often can provide information about grade, prognosis, and distinguish TP/PsP. Dynamic susceptibility contrast (DSC) MRI relies on reduced susceptibility signal due to the transit of gadolinium and allows calculation of relative cerebral blood volume (rCBV) within an ROI that can then be analyzed in several different ways. One method is to include all tumor voxels and calculate a mean rCBV, which is straightforward but averages out potentially important signal from tumor heterogeneity. Another approach is histogram analysis from which multiple measures may be considered (minimum, maximum, mode, etc). Alternately, if a large dataset is available in order to preemptively validate a cutoff value, voxels can be thresholded to this value and then analyzed either as a mean or as a histogram, to avoid including potentially healthy tissue that may skew the results. Using a histogram approach, Kong et al reported that $rCBV_{max}$ could be normalized to the corresponding contralateral brain location and demonstrated higher rCBV ratios in TP compared to PsP, achieving a sensitivity of 81.5% and specificity of 77.8% in a prospective cohort of 90 patients.[24] Other studies using methodologies similarly found that rCBV distinguishes TP/PsP, with Barajas et al[25] using mean rCBV with a 5% threshold cutoff, and Gasperetto et al using a 20% cutoff.[26]

DCE T1-weighted perfusion MRI imaging (DCE-MRI) is an alternate method that relies on the T1 shortening property of gadolinium, and is a good measure of vascular permeability.

This method can be combined with values like rCBV derived from DSC in order to more accurately distinguish TP/PsP.[27] A novel thresholding method was reported by Hu et al,[28] who subtracted pregadolinium voxel values from postgadolinium in order to create a mask of enhancing voxels, which was then used to define the ROI. Their method not only distinguished TP/PsP but also correlated with overall survival (OS). Other approaches emphasize dynamic measures of contrast such as maximum slope of enhancement, which in one study achieved a 95% sensitivity and 78% specificity for distinguishing TP/PsP.[29] These methodological differences highlight the challenge of standardization across institutions.

A limitation of perfusion imaging has been the porous nature of the blood brain barrier (BBB) in gliomas, leading to potentially confounding gadolinium extravasation.[30] This is highlighted by reports that correction for contrast extravasation is required to establish correlations between rCBV values and tumor grade.[31] An alternative to gadolinium-based contrast agents is the superparamagnetic iron oxide nanoparticle ferumoxytol, whose large size (750 kDa) minimizes leakage through defective endothelium. Ferumoxytol therefore is less sensitive to disruption of the BBB and remains limited to the intravascular compartment.[32] In one study of 7 patients with TP, gadolinium-contrasted MRI resulted in artefactually low rCBV measures, whereas ferumoxytol-contrasted MRI correctly measured high rCBV in all 7 patients.[33] A subsequent study by the same group demonstrated that in posttreatment MRI changes, rCBV measures using ferumoxytol were strongly predictive of OS, and low rCBV in this group showed a hazard ratio of .098 ($P = .004$). Additionally, the authors showed that mismatched cases with high rCBV using ferumoxytol and low rCBV using gadolinium had OS that closely matched the OS of tumor progressors, suggesting that the rCBV values generated using ferumoxytol were indeed correct.[34] Subsequently, their group used ferumoxytol-contrasted MRI to distinguish progression from PsP in 56 patients with GBM, and then followed them according to RANO criteria.

Pulsed continuous arterial spin labeling (pCASL) is a measure of perfusion that is relatively insensitive to porous BBB. Unlike the other methods reviewed above, pCASL does not require a contrast agent. Rather, blood is "labeled" by a radiofrequency pulse and continuous labeling in a defined plane that inverts or saturates the water molecules in blood, creating contrast that is leveraged as an indirect measure of blood flow in the area of interest.[35] pCASL has been reported to have increased sensitivity (94%) compared with DCE-MRI (71%) and may be particularly useful for distinguishing tumor from radiation necrosis.[36] This technique may also be used to stratify for PFS[37] and can be used in conjunction with other advanced imaging techniques to distinguish TP/PsP.[38] However, use of pCASL is limited by low signal to noise ratio and low resolution.

Positron Emission Tomography

Positron emission tomography (PET) measures positrons emitted from administered radiotracers, which typically contact electrons only a very short distance from their emission point, on the order of 1 mm. Contacted electrons are annihilated, producing photons travelling in opposite vectors that are, respectively, detected by the scanner and from which the initial point of annihilation can be calculated. The resulting overall spatial resolution of PET scanners is about 5 mm.[39]

The most widely used radiotracer is 18-fluorodeoxyglucose (FDG), a glucose analog that is a direct measure of metabolic rate. Standardized uptake value can be compared between the region of the tumor and a reference region to semiquantitatively measure metabolic activity, thereby differentiating low- and high-grade gliomas.[40] The Warburg effect predisposes toward glucose metabolism in high-grade gliomas as in other tumors, and therefore, they are highly FDG avid.[41] FDG avidity also correlates with overall cell density.[42] However, because the brain has intrinsically high rates of glucose metabolism (particularly in gray matter), the distinction in FDG avidity between normal brain parenchyma and low-grade glioma is less reliable. In retrospective studies, metabolic activity by FDG PET was correlated with OS independent of other prognostic factors.[43] In a retrospective study of 59 patients with glioma, FDG uptake was significantly lower in IDH1-mutant gliomas, and, for those with IDH1 wild-type tumors, increased FDG uptake predicted decreased survival.[44] Finally, a meta-analysis found FDG PET to be a promising method for detecting recurrent glioma, with sensitivity 0.77 and specificity 0.78.[45] It has been suggested that this distinction can be leveraged to identify anaplastic transformation in a previously histologically low-grade tumor that shows high FDG avidity.[43]

Standard FDG PET is unreliable for distinguishing TP from metabolically active processes seen in PsP that are presumed to be inflammatory.[46] However, serial imaging after FDG injection and at a delayed time point can distinguish TP/PsP. While active tumors show increased uptake in delayed imaging (Fig 2), inflammatory lesions retain stable or decreasing FDG uptake over time (Fig 3).[47] Thus, serial FDG PET imaging is superior to single timepoint imaging for distinguishing TP/PsP.

Radiolabeled amino acids are preferentially taken up in proliferating cells and have been studied for distinguishing TP from PsP. [11C]-Methionine (MET) uptake correlates with glioma grade,[48] vascularity,[48] and rCBV.[48,49] In a study of hybrid MET-PET/MRI versus MRI for progression versus PsP, MRI had 86.1% sensitivity and 71.4% specificity compared with 97.1% sensitivity and 93.3% specificity for MET-PET/MRI.[50] A direct comparison of MET versus FDG PET imaging obtained on the same day concluded that MET was more reliable in identifying recurrent tumor than FDG,[51] and this has been confirmed by subsequent meta-analysis.[52] Combining MET-PET and DCE perfusion imaging modalities similarly demonstrated significantly increased sensitivity and specificity for identifying TP.[37] Nonetheless, the clinical use of MET is complicated by its short half-life of 20 minutes, requiring an onsite cyclotron and precise coordination of its administration.[53]

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) detects specific metabolites in a defined ROI. Tumor tissue has an MRS signature of elevated choline due to increased cell density and total cell membrane, and decreased NAA due to decreased neuronal content. Necrosis has an MRS signature of elevated lipid and lactate peaks, but in contrast with solid tumor tissue, choline levels may be lower due to the absence of intact cells. For this reason, it is important to be aware of necrotic areas when choosing an ROI for analysis.[54,55] TP has a higher choline/creatinine ratio compared to PsP in recently resected glioblastoma, and in one study could correctly categorized 27 of 28 patients.[56] A meta-analysis reviewed 55 studies and a total of 1,174 patients

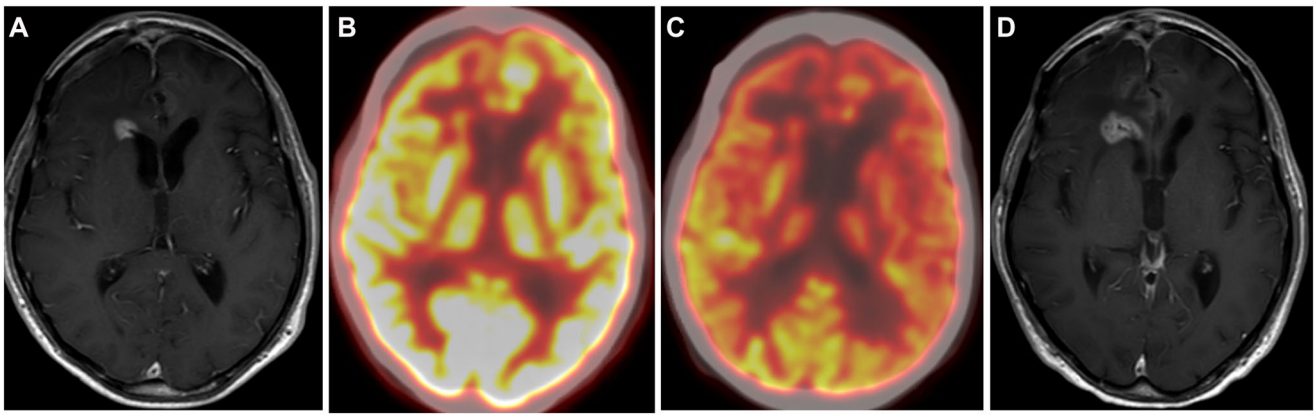

Fig 2. Tumor progression identified by delayed PET imaging. A 60-year-old man with bifrontal grade III anaplastic oligodendroglioma. One year following resection and chemoradiation, postgadolinium T1-weighted imaging showed enhancement along the inferior right margin of the resection cavity along the right frontal horn (A). PET imaging 1 hour after 18-fluorodeoxyglucose administration revealed focal increase in uptake in the target lesion (B). Delayed acquisition at 4 hours showed 18-fluorodeoxyglucose uptake did not decrease over time relative to normal brain structures (C), suggesting recurrent tumor rather than pseudoprogression, subsequently confirmed four months later (D).

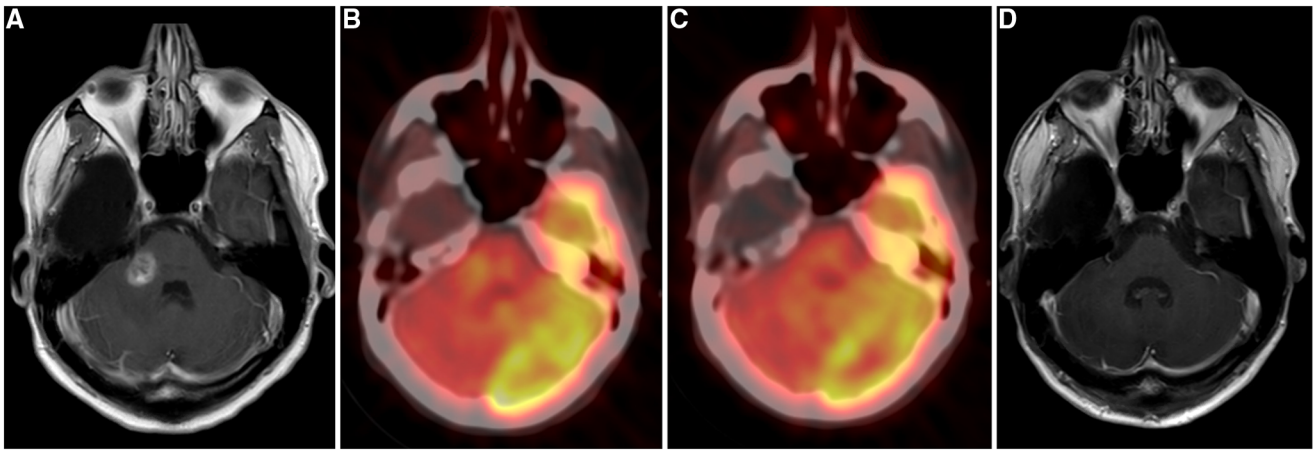

Fig 3. Radiation necrosis identified by delayed PET imaging. A 41-year-old man with grade III anaplastic astrocytoma. Two years after resection and chemoradiation, the patient was found to have an enhancing lesion along the right brachium pontis on postgadolinium T1-weighted imaging (A). At 1 hour, there was mild focal uptake (B) that decreased on delayed imaging at 4 hours after 18-fluorodeoxyglucose administration (C), suggesting radiation necrosis. Seven months later, postgadolinium T1-weighted imaging revealed decreased enhancement in the original area (D).

with high-grade gliomas after chemoradiation and compared sensitivity and specificity for distinguishing TP/PsP based on anatomical MRI (5 studies, 166 patients), ADC (7 studies, 204 patients), DSC perfusion (18 studies, 708 patients), DCE perfusion (5 studies, 207 patients), and MRS (9 studies, 203 patients). The performance of MRS was superior to other modalities, with pooled sensitivity of 91% and specificity of 95% for tumor.[57] To our knowledge, this is the most comprehensive comparison of individual advanced imaging approaches, although it did not include amide proton transfer (APT) or PET. Of note, some groups have proposed multiparametric scoring algorithms using DWI, rCBV, and MRS for improved diagnostic accuracy.[58]

2-Hydroxyglutarate (2-HG) is an oncometabolite produced by IDH mutant tumors,[59] which has a characteristic peak on MRS.[60] In a study of 30 patients with gliomas, detection of elevated 2HG by MRS perfectly correlated (100%) with IDH1/2 mutation.[61] A recent prospective study of 136 patients followed 2-HG levels over repeated scans throughout treatment. Using a cutoff of 1 mM 2-HG, the authors reported 100% sensitivity and 88% specificity for IDH mutation subsequently confirmed by histology, and of patients who were unable to undergo resection, a molecular diagnosis could be established in 67% by MRS. Impressively, the authors were able to measure a rapid increase in 2-HG concentration in tumors under observation at the time of their progression.[62] Therefore, clinicians may find it useful to track 2-HG levels in low-grade gliomas under observation, to identify progression even in the absence of classic features on standard MRI.

Amide Proton Transfer

APT was initially developed as a method for measuring intracellular protein content by leveraging the amide backbone of polypeptides.[63] Increased APT resonance can result from a combination of increased amide (protein) content or increased amide proton exchange rate. In tumor tissue, this effect is a by-product of increased intracellular pH that catalyzes amide proton exchange. Studies have demonstrated increased APT-weighted (APTw) signal in glioma compared with unchanged

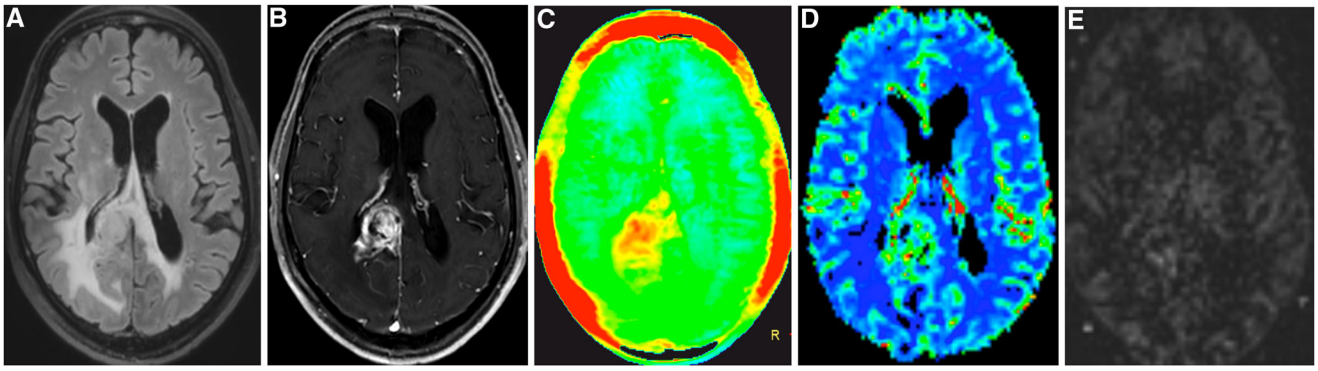

Fig 4. Progression confirmed by multiple advanced imaging modalities. A 50-year-old man with previously treated right parietal isocitrate dehydrogenase nonmutated glioblastoma who developed headache and nausea 12 months after chemoradiotherapy. A new area of abnormality on fluid-attenuated inversion recovery (A) is seen in the right splenium with enhancement (B) and mass effect. This area also shows increased amide proton transfer signal (C) and increased perfusion by both dynamic contrast-enhanced MRI (D) and arterial spin labeling (E). Subsequent imaging showed an enlarging mass and the patient went on to salvage therapy.

or decreased APTw signal in treatment effect.[64] A single center prospective study followed 32 patients with serial imaging over 6 months, comparing TP, which was defined as an increase in radiographic size of the lesion over 6 months, with tumor stabilization or regression attributed to treatment effect. APTw mean intensities were almost twofold higher in PT compared with PsP, and a cutoff of mean APTw of 2.42% generated 85% sensitivity and 100% specificity.[65] A subsequent report from the same group paired MRI with biopsy, allowing for comparison of APTw signal intensity with histopathology from the same location. The authors reported a positive correlation between APTw signal intensity and tumor histopathology, as well as cellularity and proliferation index, and generated an ROC with 85.1% sensitivity and 94.1% specificity for identifying TP. However, one major limitation of APT is that blood products can independently increase APT signal, potentially confounding the results.

APTw imaging may also be predictive of grade and critical prognostic factors. Togao and Honda reported that in 36 patients with a histologically proven glioma, APT signal intensity was elevated in high-grade gliomas and there was a positive correlation with Ki-67.[66] A retrospective analysis of 27 patients showed increased APTw signal in IDH wild-type tumors compared with IDH mutant tumors,[67] as confirmed in a second cohort of patients with glioblastoma.[68] Other independent groups have confirmed these results, reporting an association between increased APTw signal with high-grade histology, worse clinical outcomes, and IDH mutant status,[68,69] but no association with MGMT methylation status.[69] In summary, APTw imaging can help distinguish tumor from treatment effect, especially when used in combination with other imaging modalities (Fig 4).[70]

Pseudoresponse to Vascular Therapies

Despite failing to improve OS in randomized trials in glioblastoma, bevacizumab is still in use for management of glioma. Bevacizumab is a vascular endothelial growth factor (VEGF) receptor antibody that results in decreased endothelial permeability and peritumoral edema as well as contrast extravasation. This has been termed pseudoresponse, since bevacizumab decreases enhancement but this is not necessarily indicative of tumor regression or improved survival.[71] Similar effects have been noted with the pan-VEGF tyrosine kinase inhibitor cediranib,[72] and may also occur with corticosteroids due to their vascular effects. Overall, these effects are most confounding for measures of perfusion, except ferumoxytol based rCBV measures that are relatively insensitive to the effects of VEGF inhibitors. Other modalities including MRS and APT are less sensitive to targeting VEGF. Of note, bevacizumab treatment has been associated with DWI-positive T1 hyperintense lesions that on histology are revealed to be calcified areas of necrosis, and which clinically are associated with improved survival.[73]

Conclusions

In summary, we have reviewed a selection of imaging modality approaches that can offer helpful information to assist the clinicians facing challenging decisions in glioma management. Major areas of need continue to be noninvasive prediction of molecular features, as well as choosing biopsy site or extent of resection in preoperative management. In postoperative management, distinguishing progression versus PsP is the major challenge. For distinguishing PsP, the authors recommend a combined approach that includes perfusion imaging, APT, and MRS or PET, with awareness of the limitations of each so that they can be applied in a personalized fashion to individual patients to be most informative. Future studies are needed to explore multimodality advanced imaging algorithms that can be standardized across institutions and ideally become incorporated into clinical trials.

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