Imaging Surveillance of Gliomas

Role of Basic and Advanced Imaging Techniques

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KEYWORDS

• Glioma surveillance • Advanced imaging • RANO • Perfusion imaging • Diffusion imaging • MR spectroscopy • 11C-Met-PET • FDG-PET

KEY POINTS

- The 2016 revised World Health Organization classification and grading system of gliomas includes additional information obtained from molecular biomarkers.
- Modified Response Assessment in Neuro-oncology (RANO) criteria divide treatment response in gliomas into complete response, partial response, progressive disease, and stable disease based on assessment of measurable and nonmeasurable lesions.
- Pseudoprogression is identified radiographically when tumors undergo growth similar to true disease progression defined by RANO criteria but occurring between 3 and 6 months' after treatment, typically with concurrent radiation treatment and temozolomide.
- Pseudoprogression has been shown to involve reduced relative cerebral blood volume (rCBV) on gadolinium-based dynamic susceptibility contrast perfusion magnetic resonance imaging scans in contrast with increase in the rCBV index in true progression.

INTRODUCTION

Gliomas are the most ubiquitous neoplasms of the central nervous system. According to the Central Brain Tumor Registry of the United States (CBTRUS), the reported average age-adjusted incidence rate for all benign and malignant central nervous system (CNS) tumors is 23.41, with glioblastomas being the most common malignant tumor. Glioblastomas account for 14.6% of all tumors of the CNS.[1] Before 2016, prognosis was based on the interpretation of hematoxylin-eosin–stained sections observed on light microscopy. The revised World Health Organization (WHO) classification and grading system of 2016 was based on the added information obtained from molecular biomarkers.[2,3] The major molecular markers that differentiate the histologic types of gliomas and their prognostic significance are summarized in **Table 1**.

Grading of gliomas combines the observed prognosis from histologic data and expected course of the tumors. Grade I tumors can be excised with low potential for recurrence. Grade II tumors show low levels of proliferative activity but are infiltrative with a potential to dedifferentiate to higher grades of the tumor. Grade III lesions show cellular atypia with higher proliferative indices and are frequently associated with recurrence. Grade IV tumors are associated with active

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Table 1
Molecular markers of gliomas and their prognostic significance

Molecular Marker	Implication for Follow-up Imaging and Treatment Strategies
IDH1 and IDH2 mutations	Marker for astrocytic tumors. IDH wild-type (without mutations) is associated with an aggressive course. IDH mutant tumors include diffuse and anaplastic astrocytic gliomas and oligodendroglial tumors
1p-19q codeletion	Confirming marker for oligodendroglial tumors if associated with IDH mutations
Alpha-thalassemia/mental retardation X-linked syndrome expression	Associated with IDH wild-type astrocytic tumors. Intermediate prognosis
TERT promotor mutations	IDH wild-type with TERT mutations is associated with poor prognosis
EGFR amplification	EGFR amplification and overexpression is seen in 40% of GBMs. EGFR-targeted therapies have led to a specific imaging techniques using PET-CT radiopharmaceuticals and experimental MR imaging contrast agents
MGMT promotor methylation	In the diagnostic schema for GBM, MGMT promoter methylation and IDH mutant GBMs denote better prognosis
Chromosome 7 gain and chromosome 10q loss	As in the TERTp mutations, the presence of this mutation is associated with poor prognosis in tumors that behave like GBMs
H3 K27M histone mutation	Identifier of diffuse midline gliomas, which are aggressive grade 4 tumors with no targeted therapies and universally poor outcomes

Abbreviations: CT, computed tomography; EGFR, epidermal growth factor receptor; GBM, glioblastoma; IDH, isocitrate dehydrogenase; MGMT, O^6-methylguanine-DNAmethlytransferase; MR, magnetic resonance; TERT, telomerase reverse transcriptase; TERTp, TERT promoter.

mitoses and a propensity for necrosis. Grade IV tumors are rapidly evolving tumors with a relentless progressive course and invariably have a fatal outcome.

TREATMENT AND RESPONSE ASSESSMENT OF HIGH-GRADE GLIOMAS

The International Society of Neuropathology established the Haarlem guidelines to consider how the molecular profile of a tumor can be incorporated into the current grading of tumors.[4] An understanding of this schematic diagnosis is essential because it reflects on the anticipated treatment protocols and hence the prognosis of the tumors.[5]

Preoperative functional imaging including tractography, precision surgical navigation techniques aided by magnetic resonance (MR) imaging studies, intraoperative MR imaging, ultrasonography, and 5-aminolevulinic acid are the investigative tools available to neurosurgeons to aid in maximizing tumor excision.[6] MR imaging remains the mainstay in the assessment of residual tumor in the immediate postsurgical period and early in the follow-up following surgery. Studies with and without contrast are recommended together with diffusion scans.[7]

Treatment Strategies

Surgical management is considered after radiographic assessment and determining the functional risks to the patient. The Karnofsky Performance Scale is often used to help make this determination. Although surgical intervention is needed to establish a diagnosis with biopsy, gross total resection reduces the bulk of tumor and is the goal before initiating pharmacotherapy. The age of the patient and the performance scores dictate the clinical outcomes.

Radiotherapy and chemotherapy are the next line of defense to mitigate the progression of

malignant gliomas. The age of the patient, extent of tumor resection, and the performance score play key roles in choosing the treatment paradigm before commencement of radiotherapy. MR imaging examinations performed after surgical resection are used to determine the extent of residual tumor (ie, gross tumor volume, based on the enhancing portions that remain in the surgical bed). T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences play key roles in the demarcation of the irradiated margin. Inclusion of this zone surrounding the tumor bed is defined as the clinical target volume.[6,8] Functional correlation using F^{18}-fluorodeoxyglucose (FDG)-PET is increasingly being advocated to accurately delineate metabolic activity beyond the enhancing margin of the tumor or included in the radiation field.[9,10]

Alkylating agents and nitrosourea compounds are the mainstay of cytotoxic chemotherapy for malignant gliomas. The oral alkylating agent temozolomide is the frontline chemotherapeutic agent for the treatment of astrocytic tumors such as diffuse astrocytomas, glioblastomas, and diffuse midline gliomas because of its favorable penetration through the blood-brain barrier, good safety profile, and documented favorable effect on the median progression-free survival (PFS) and median overall survival.[11]

Nitroureas are the second line of chemotherapeutic agents and include lomustine, carmustine, nimustine, and fotemustine. Of these agents, lomustine (together with procarbazine and vincristine) and carmustine (used as a wafer placed locally on the margins of the surgical cavity) have been used successfully with WHO grade III and IV gliomas and recurrent gliomas.[12,13]

Antiangiogenic agents inhibit vascular endothelial growth factors (VEGFs) and play an important role in the treatment of recurrent glioblastoma. The titular representative of this class of drugs, bevacizumab (Avastin, a synthetic monoclonal antibody that inhibits tumor neoangiogenesis by targeting VEGF), often results in misleading decrease in enhancement of the treated tumors, termed tumor pseudoresponse.[14]

Immunotherapy is an emerging frontier in the management of gliomas.[15] Several agents have been included in clinical trials and research is still ongoing. Immune checkpoint inhibitors primarily target immunosuppressive factors such as programmed cell death 1 ligand (PD-L1), cytotoxic T-lymphatic antigen-4 (CTLA-4), and indolamine 2,3-dioxygenase (IDO). Nivolumab and pembrolizumab are PD-L1 pathway inhibitors. Ipilimumab is an anti-CTLA-4 antibody currently approved by the US Food and Drug Administration (FDA). IDO in combination with temozolomide has shown promise in experimental studies. Dendritic cell vaccines are composed of dendritic cells generated in vitro and then loaded with tumor antigen developed from tumor lysate or cells cultured from surgical specimens. At present, only 1 vaccine (sipuleucel-T) has been approved by the FDA. Other immunotherapeutic options include cytokine therapy, adaptive cell therapy, and oncolytic viruses derived from strains of the herpes simplex virus, polio, and adenoviruses are under investigation. Large-scale population studies for assessing the efficacy of immunotherapy are ongoing.[16]

Response Assessment

MR imaging is essential for assessing treatment response and guiding management. The timing of serial imaging after the baseline pretreatment examination is important to assess structural changes in the brain. However, the temporal evolution of the changes is important and is taken into context relative to the patient's clinical status. The methodology used to measure response has evolved, but all of the following criteria are modifications from the WHO response criteria reported in 1981,[17] which measured tumors in 2 dimensions.

The Macdonald criteria

These criteria for glioblastoma treatment assessment in 1990[18] were established in clinical trials to standardize definitions of the imaging features combined with clinical assessments and the use of corticosteroids. Four criteria are summarized as follows:

- Complete response (CR): resolution of all enhancing lesions over 4 weeks without the concomitant appearance of new lesions. Patients needed to show clinical improvement with administration of corticosteroids.
- Partial response (PR): 50% or more decrease in the enhancement of all measurable lesions over 4 weeks without concomitant appearance of new lesions in patients and continued stability or improvement on reduced dosage of steroids.
- Stable disease (SD): clinical stability without features suggestive of progression of disease (PD), PR, or CR.
- PD: 25% or more increase in the enhancing lesions with or without appearance of new lesions, together with clinical deterioration.

The Macdonald criteria were limited for the following reasons. There was significant

interobserver variability in their application. This methodology also did not take into account the difficulty in measuring residual tumors with irregular contours and the presence of new areas of enhancement after resection. Assessment of multifocal disease was also not included in these criteria. In addition, antiangiogenic therapy masks any potential residual enhancing disease.[7,19]

AVAglio criteria

The Avastin In Glioblastoma (AVAglio) study (BO21990) criteria were developed primarily to address the limitations of the Macdonald criteria.[19] In addition to assessing PD, these criteria consider pseudoprogression based on the MR imaging features on T2 and FLAIR sequences. According to this scheme, the index lesions are defined as all measurable contrast-enhancing lesions with clear borders greater than 10 mm in diameter. These criteria also include assessment of small or irregularly shaped enhancing lesions and lesions that do not enhance. Nonindex lesions were recorded in present, absent, or unable-to-assess categories. These categories were then used to fortify the criteria for CR where the nonindex lesions disappeared for more than 4 weeks, for SD when these lesions showed no significant change, and for PD when there was unequivocal increase in the size of the nonindex lesion or presence of a new nonindex lesion.

Response assessment in Neuro-oncology criteria

Given that the Macdonald criteria were developed for assessment of only glioblastomas and relied on two-dimensional (2D) measurements and the administration of corticosteroids, it was increasing evident that the criteria were deficient in the assessment of transient increase in tumor enhancement (pseudoprogression), development of nonenhancing tumor during antiangiogenic treatment, and the changes in the enhancing characteristics during such therapy (pseudoresponse). This realization led to the development of the Response Assessment in Neuro-oncology (RANO) criteria[20] in 2010 and their modification in 2017.[21] The modified RANO criteria rely on specific MR imaging sequences to assess for treatment response. These sequences include three-dimensional (3D) T1-weighted precontrast, axial 2D FLAIR, axial 2D diffusion-weighted imaging (DWI), axial 2D T2-weighted imaging, and 3D T1-weighted postcontrast sequences. Lesions were classified as measurable and nonmeasurable. Measurable lesions are those with contrast enhancement, with clear margins, that are visible, and that are measurable in 2 or more axial sections. Measurements are performed in 2 perpendicular planes, each more than or equal to 10 mm in sections taken with interslice gaps of less than 5 mm. In those sequences where an interslice gap is greater than 5 mm, the minimum size of the lesions for both perpendicular measurements should be twice the sum of the slice thickness and interslice gap. Up to 5 target measurable lesions should be defined and ranked from largest to the smallest. Nonmeasurable lesions are those that do not meet the criteria of the measurable lesions, do not enhance, or lesions with poorly defined margins that cannot be measured with any degree of certainty.

Similar to the Macdonald criteria, the RANO criteria divide response into CR, PR, PD, and SD while incorporating additional features, as follows:

- CR: disappearance of all measurable and nonmeasurable lesions for at least 4 weeks. The patients are required to be off corticosteroids and should be clinically stable or improved since their baseline. The first MR study that shows these feature is termed the preliminary CR. Measurable lesions on any succeeding MR studies indicating unsustained response are termed preliminary PD (progression) or pseudoresponse. Durable CR is identified when the second scan shows continued absence of measurable lesions. Patients showing nonmeasurable lesions at baseline are best categorized as having SD.
- PR: defined as 50% or more decrease in measurable lesion, sustained for 4 weeks or more, with no progression of nonmeasurable lesions, and stable or improved nonenhancing FLAIR and T2 signals. Patients should be clinically stable, on reduced or unchanged dosage since baseline. No new lesions should be shown on follow-up studies.
- PD: defined as 25% or more increase in the product of perpendicular measurements or 40% increase in volume of the enhancing lesions in 2 successive scans. Measurements are compared with the baseline scan showing the smallest tumor measurement. This baseline study is termed the preliminary PD, and the first study that categorically shows the increase described earlier is termed the confirmed PD study. These criteria are applied 12 weeks or more after completion of radiotherapy. PD is also called when there are new lesions with clinical deterioration that cannot be attributed to radiation, ischemic injury, postoperative sequelae, demyelination, or infections. The findings also should not be attributable to changes in corticosteroid

dosage, adverse effects of medications, or seizures. Progression of nonmeasurable lesions is another criterion for PD.

- SD requires the patient to be clinically stable on a reduced or unchanged dose of steroids and without imaging criteria on the MR studies that qualify for other categories, such as CR, PR, or PD.

Immunotherapy response assessment for neuro-oncology criteria

With the advent of immunotherapy, the observed changes seen on imaging studies required reassessment of the criteria.[21] Therapy-induced changes showing increased dimensions of the lesions were deemed equivalent to PD. However, these patients remained clinically stable. Because this observed pseudoprogression was not similar to responses seen on standardized chemotherapies (Stupp protocol), patients were taken off these immunotherapy protocols. Modifications to the RANO criteria, Immunotherapy RANO (iRANO), take into account the adverse effects of immunotherapy and the occurrence of new enhancing lesions outside the radiation field. Clinical improvement on immunotherapy can be delayed, and repeat studies are needed to confirm stability or PD. Ideally, studies should be repeated 3 months or later after initiation of therapy as a baseline investigation. The principal diagnostic features of PD after immunotherapy include clinical deterioration caused by the primary tumor alone, or significant changes in measurable lesions after 6 months or more. If measurable changes are observed in a period less than 6 months after initiation of therapy, imaging at 3-month intervals is required to rule out pseudoprogression.

Pseudoprogression presumably occurs as a result of an immune-mediated inflammatory response or PD before treatment can take effect. In these cases, immunotherapy is not interrupted because of changes in lesion size provided that the patient does not show toxicity related to the ongoing therapeutic agent.[22]

Pseudoprogression and Assessment of Response to Combined Radiation and Alkylating Therapy

Pseudoprogression is identified radiographically when tumors undergo growth similar to true PD defined by RANO criteria but occurring between 3 and 6 months' after treatment, typically with concurrent radiation treatment and temozolomide. Unlike PD, pseudoprogression resolves spontaneously or improves without additional treatment. The incidence of pseudoprogression is reportedly around 36%,[23] making it a frequent occurrence in the treatment arc of gliomas. Pseudoprogression is thought to result from endothelial cell injury resulting from inflammation and upregulation of VEGF, leading on to increasing edema and vascular permeability.[24] Pseudoprogression is seen across the spectrum of low-grade and high-grade gliomas and has clinical implications in that manifestation of pseudoprogression is associated with better outcomes,[25] as is the presence of the O^6-methylguanine-DNAmethlytransferase (MGMT) promotor methylation.[26] The challenge of differentiating true tumor progression from pseudoprogression remains unresolved.[27]

Advanced imaging techniques

Advanced imaging techniques can play an important role in the differentiation of true tumor progression from pseudoprogression (**Figs. 1** and **2**). The temporal profile of treatment must be known to more accurately predict whether imaging changes represent PD versus pseudoprogression. The latter typically occurs within the first 3 months after completion of radiation treatment but has a range from a week to up to 6 months after treatment.[14]

Dynamic susceptibility contrast perfusion

Apart from showing changes in the nonspecific enhancement pattern (often described as Swiss cheese or soap bubble) and increase in the size of the lesions,[28] pseudoprogression is thought to show reduced relative cerebral blood volume (rCBV) on gadolinium-based dynamic susceptibility contrast (DSC) perfusion MR imaging scans,[29] in contrast with increase in the rCBV index in true progression.[30] The increase in this index is attributed to increased neovascularity, impeded flow through the collateral vasculature of the tumor bed, and increased microvascular density. DSC is based on the variations in the T2 and T2* parameters following the passage of gadolinium through a given volume of cerebral tissue. The passage of gadolinium decreases the susceptibility signals from the baseline with comparative ratios of change in this parameter between a portion of the tumor and the contralateral normal-appearing brain forming the basis of this perfusion study. The range of threshold values for rCBV has been studied by several investigators for pseudoprogression and true progression. For pseudoprogression, the range of thresholds for mean rCBV is reported to be 0.9 to 2.15 and the range of values for the maximum cerebral blood volume (CBV) is 1.49 mL /100 grams to 3.10 mL /100 grams.[31] **Figs. 3** and **4** show how perfusion can play a role in the distinction between radiation-induced treatment changes from recurrent tumor. **Fig. 5** shows

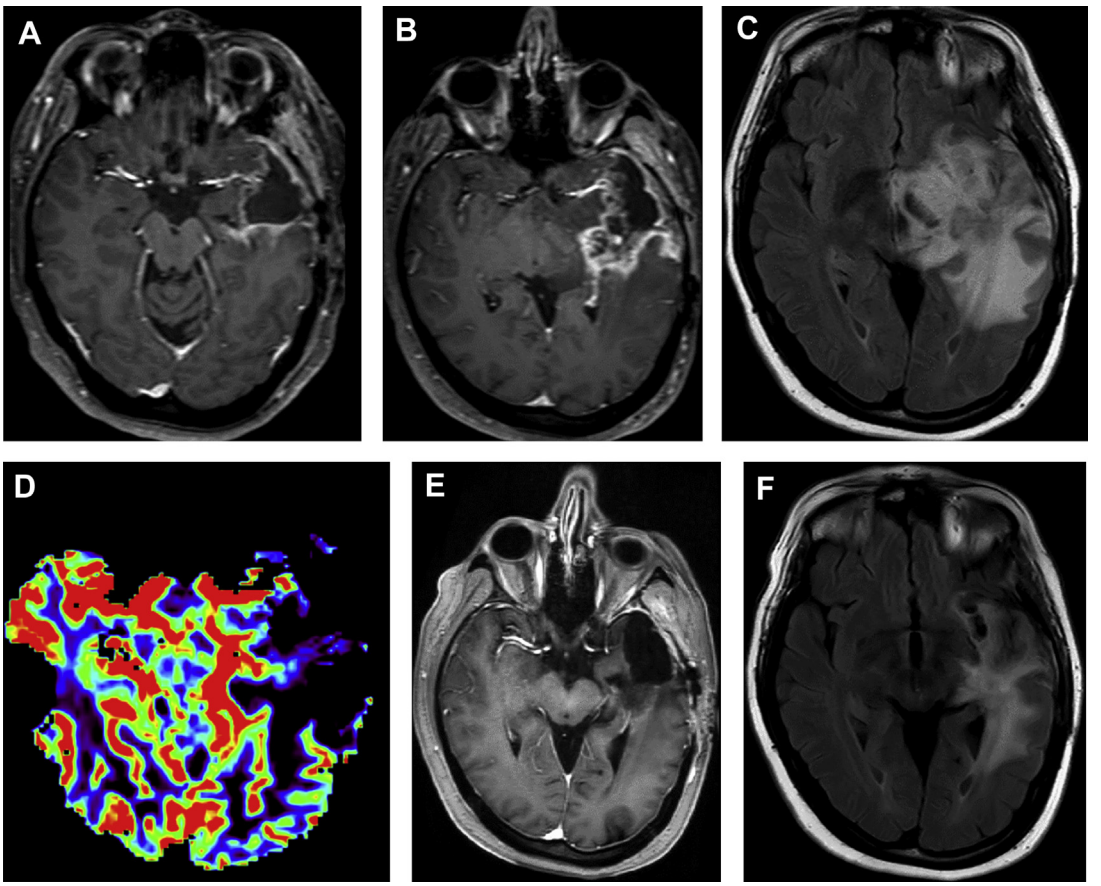

Fig. 1. A 41-year-old woman with new-onset spells was found to have a left frontal oligoastrocytoma and secondary left subinsular/temporal lobe glioblastoma (isocitrate dehydrogenase [IDH] mutant, MGMT methylated). MR imaging acquired after gross total resection and chemoradiation therapy with Temodar shows progressive changes from postresection study (*A*) to 3 months posttreatment examination (*B–D*) and at 6 months posttreatment (*E*, *F*). Postresection MR imaging shows a rim-enhancing cavity in the left temporal lobe (*A*). Three months after treatment with Temodar, progressive enhancement lining the surgical bed (*B*) and surrounding hyperintense FLAIR signal (*C*) is seen but without increased relative cerebral blood volume (rCBV) (*D*), suggesting a higher likelihood of pseudoprogression than true progression. At 6 months posttreatment, the enhancement (*E*) and the FLAIR signal (*F*) have diminished, confirming the initial suspicion of pseudoprogression.

how perfusion imaging can be helpful in interval assessment of tumors during the course of treatment.

Dynamic contrast-enhanced perfusion

This technique relies on the microvascular permeability in the extracellular extravascular space. It is essentially a T1-weighted sequence using spoiled gradient techniques in which concentration-time curves are generated to calculate several parameters. Of these, K^{trans} (the rate of transfer of contrast between the plasma and extracellular space) and Vp (plasma volume) are higher in true progression compared with radiation necrosis and pseudoprogression. A cutoff value of a mean Vp measurement of 3.7 min^{-1} yielded a sensitivity of 85% and specificity of 85% for pseudoprogression, and a K^{trans} greater than 3.6 min^{-1} had a specificity of 79% and a sensitivity of 69%.[32] Both gadolinium-based techniques do not at the present have well-defined, validated, and acceptable thresholds.[33]

Arterial spin labeling perfusion

These techniques can be applied to perfusion measurements without the use of gadolinium contrast. Arterial spin labeling (ASL) involves using a series of short radiofrequency pulses to tag a slab of flowing arterial blood in a pulsed or pseudocontinuous fashion. Subtraction of the labeled and tagged images removes the static tissue and thus the flowing blood is imaged. Given the known volume of the tagged tissue, perfusion parameters can be calculated. The inherent low signal/noise

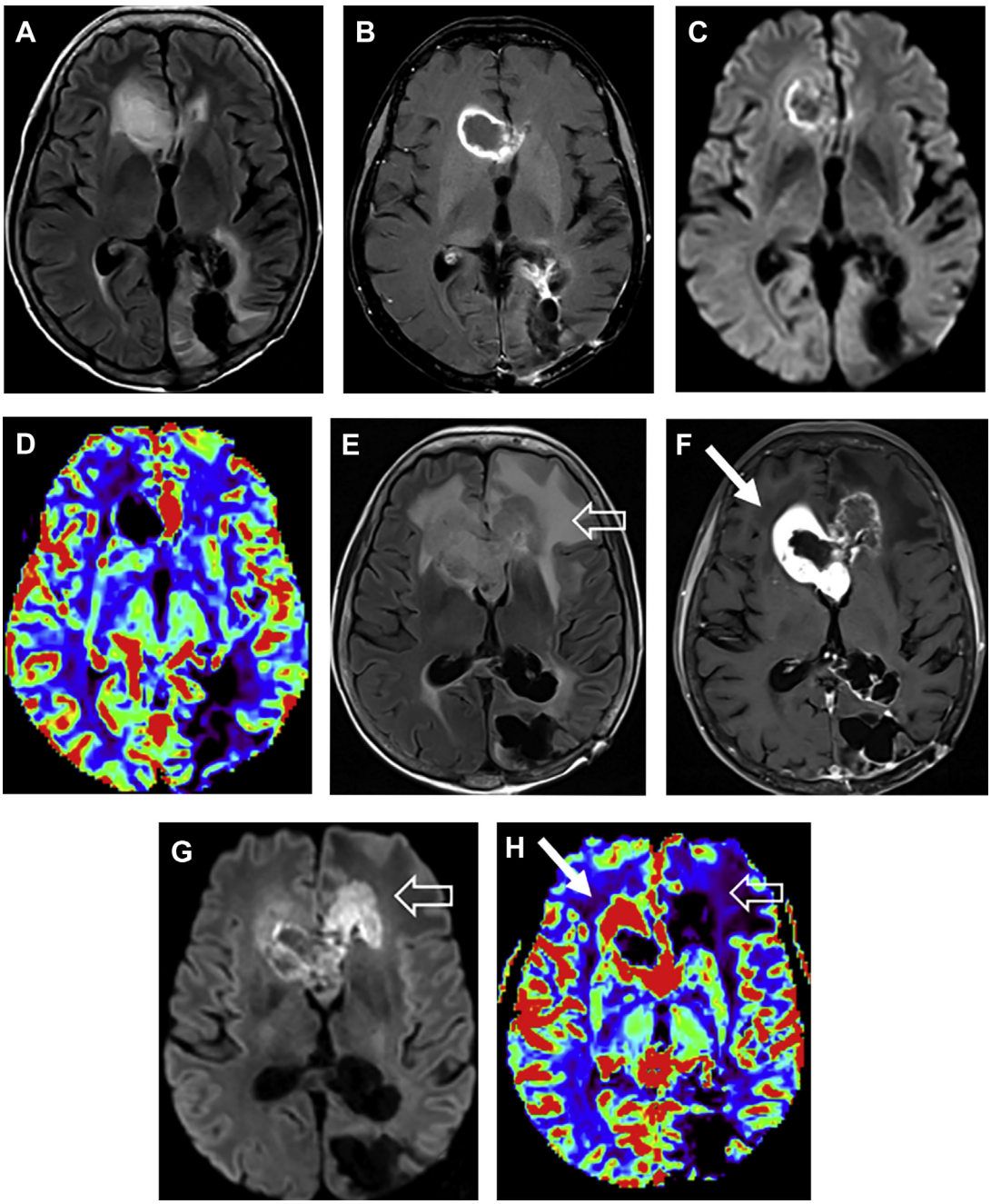

Fig. 2. A 52-year-old woman presented with blurred and double vision with headaches. A mass was identified in the left parieto-occipital region, which proved to be glioblastoma, IDH1 wild-type, MGMT positive. Despite surgical resection, radiation, and chemotherapy, radiographic stability was limited. MR imaging at completion of treatment showed hyperintense T2 FLAIR signal in the right frontal lobe (*A*) corresponding with a rim enhancing and central necrotic lesion in the right frontal horn (*B*). Limited rim of diffusion signal was seen along the periphery (*C*) with no increased rCBV (*D*). After 4 months, true progression is shown in 2 different ways. On the right, the frontal mass has grown, shows greater hyperintense signal and thicker rim enhancement (*solid arrow*, *F*), without significant change in diffusion in the right frontal region (*G*), but with significantly greater rCBV corresponding with the area of enhancement (*solid arrow*, *H*), suggesting progressive disease. Similar progressive disease is also shown in the left frontal lobe by significantly increased edema and restricted diffusion (*open arrow*, *G*) with increase in enhancement (*F*); however, perfusion MR imaging does not show increased rCBV (*open arrow*, *H*).

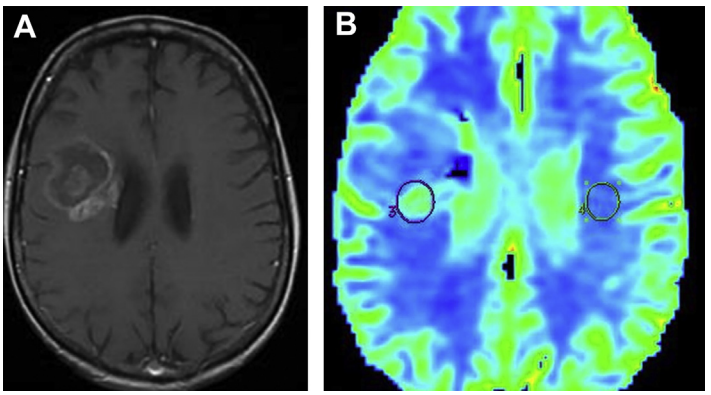

Fig. 3. A 65-year-old male patient with previously treated right frontal glioblastoma presented with new cognitive symptoms. T1 postcontrast MR imaging showed a new ring-enhancing lesion in the right frontal deep white matter (*A*) that could represent either radiation necrosis or recurrent tumor. (*B*) Corresponding perfusion map shows increased rCBV within the posterior enhancing wall, suspicious for tumor. Biopsy revealed tumor recurrence.

ratio of these perfusion techniques requires longer acquisition times and hypothetically is prone to motion artifacts. Echo planar sequences are required to acquire the ASL data and this adds to the distortion of images caused by high gradients. This technique is used primarily as an adjunct to DSC studies.[34] Note that the ASL sequences should be acquired before administration of contrast because the T1 shortening results in concomitant decrease in the ASL signal in the labeled and static images.

Diffusion-weighted imaging

DWI is uniformly included in the suite of conventional MR imaging sequences in almost all scanning protocols of the brain. Analysis of the apparent diffusion coefficient (ADC) was one of the first parameters used to differentiate tumor progression and pseudoprogression. Quantitative assessment of ADC maps has been shown to reflect treatment response,[35] with further studies involving generation of functional diffusion maps, which can serially assess changes in ADC values in designated voxels in a volume of treated tumor over a period of time.[36] Increasing ADC measurements on these maps indicated higher survival at 1 year, whereas decreasing ADC values indicated worsening course and poorer prognosis.[37] DWI is not sensitive in differentiating pseudoprogression and true progression, with contradictory findings of increased and decreased ADC values reported in both entities.[38,39]

Magnetic resonance spectroscopy

MR spectroscopy is another technique available for assessment of treatment response. N-acetylaspartate (NAA), total choline (tCho), and total creatine (tCr), lactate, and lipids are well-known metabolites relevant to clinical imaging. NAA is an indicator for neuronal viability, cellular

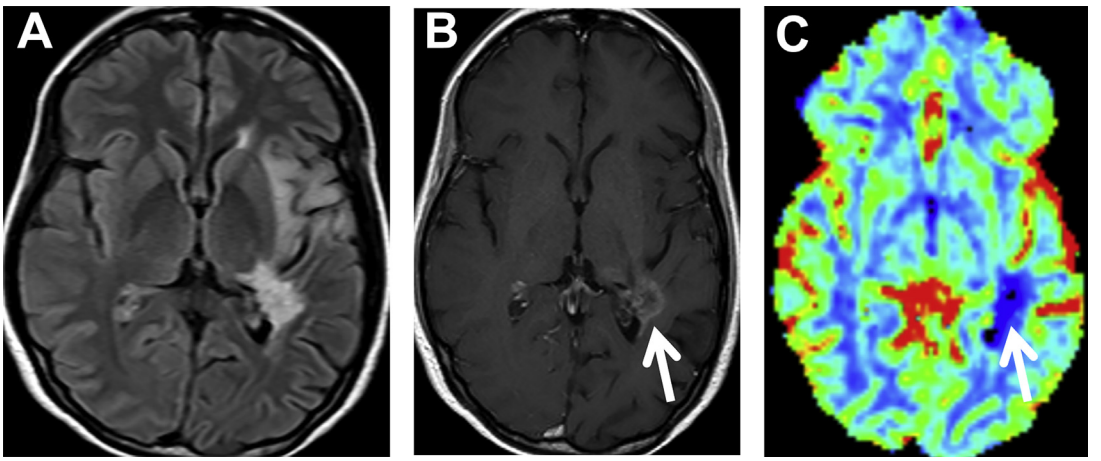

Fig. 4. MR imaging performed for surveillance in a 56-year-old man with previously resected and radiated oligoastrocytoma in the left temporal lobe (*arrows*) reveals new asymmetric FLAIR hyperintensity (*A*) and ring enhancement (*B*) within the left periatrial white matter. Although this could represent either radiation necrosis or recurrent tumor, the lack of increased rCBV on perfusion CBV map (*C*) favors the former as the likely diagnosis. This lesion was biopsied and was consistent with radiation-induced changes with no neoplastic cells.

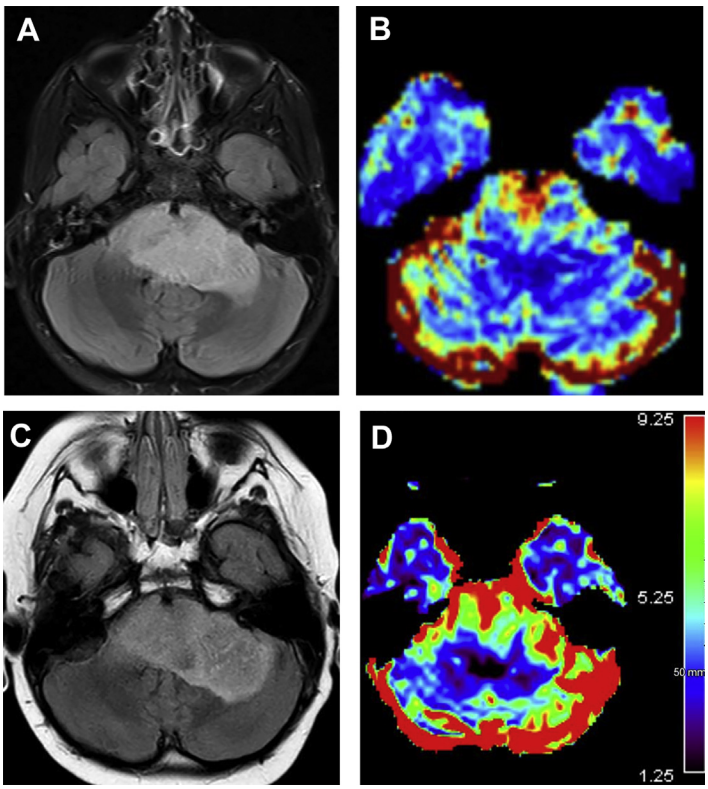

Fig. 5. A 6-year-old girl with diffuse intrinsic pontine glioma was enrolled in a clinical trial. Initial FLAIR image (*A*) and corresponding CBV map (*B*) show significant expansion and FLAIR hyperintensity of the pons and left middle cerebellar peduncle with increased rCBV parameters primarily in the pons. Repeat MR imaging after multiple cycles of chemoradiation shows further increase in extent of FLAIR hyperintensity along the left (*C*) and significant increase in rCBV in both the pons and left middle cerebellar peduncle (*D*) suggesting neoplastic PD.

proliferation is measured relative to the peak of tCho, tCr is related to the cellular energy turnover, lactates are a measure of anaerobic metabolism, and lipids are representative of necrosis and cell death. Given these basic presumptions, high-grade gliomas are associated with increased tCho and tCr peaks. Pseudoprogression has been shown with low choline peaks and increased lactate and lipid peaks together with a measured Cho/NAA ratio of less than or equal to 1.4.[40,41] Radiation necrosis is associated with expected broad peaks representing lipid, lactates, and amino acids. Radiation necrosis is seen to be represented by reduced NAA peaks. Increase in the ratio of Cho/Cr and Cho/NAA, and decrease in the NAA/Cr ratio, is considered to indicate PD or tumor recurrence.[22]

F^{18}-fluorodeoxyglucose PET scan

Monitoring response by FDG-PET is limited by its availability and the related logistics of preparation and administration of the radiotracer. In the past, it was thought that increased standardized uptake values (SUVs) in FDG-PET studies were correlated with decrease in the overall survival and vice versa; however, the advent of newer agents, such as 18F-flourothymidine PET (FLT-PET), has changed the perception that PET has limited use in the assessment of treatment response. FLT-PET has shown promise in that a persistent early decrease in SUV values is a predictor of long-term survival, and conversely an SUV increase to baseline pretreatment levels heralds a poor prognosis. Variations in the FLT-PET technique include dynamic imaging, and this technique has been used to measure the efficacy of treatment regimens.[42,43] Radiolabeled amino acids have been used as PET radiotracers. 11C-methionine (Met) PET in combination with FGD-PET is considered to be the gold standard.[44] 11C-Met-PET has been used to differentiate between tumor recurrence and radiation necrosis, with the former showing uptake of the tracer.[45]

Pseudoprogression and Immunotherapy

Patients having immunotherapy may undergo increase in size and enhancement, which may be related to a phase in time when the tumor is unresponsive to the treatment or may be a manifestation of localized inflammation termed a flare phenomenon. MR perfusion studies have been used to distinguish inflammation from true progression,[46,47] as has MR spectroscopy, because a lipid peak is thought to be associated with increase in lipids, which act as substrates to natural killer

cells.[31,48] In the study by Stenberg and colleagues,[46] the investigators concluded that increased rCBV that corresponded to the contrast-enhancing lesion supported the diagnosis of recurrent malignant tumor and that a mismatch showing a volume of rCBV increase smaller than that of contrast enhancement could be identified in particularly aggressive tumor growth. In another study, by Vrabec and colleagues,[47] the investigators were able to show that the maximum lesional rCBV ratios and minimum ADC values in the contrast-enhancing area could serve as potential radiologic markers in differentiating between recurrent tumor growth and immune therapy–induced inflammatory response.

Pseudoresponse and Assessment of Response to Antiangiogenic Therapy

Pseudoresponse is a term for apparent decrease in the size and enhancement of a tumor, being treated by antiangiogenic therapy, on conventional MR imaging sequences in the absence of true treatment effect. Pseudoresponse is thought to occur secondary to stabilization of the blood-brain barrier early in the treatment with agents that target the VEGF signaling pathway. Bevacizumab, a monoclonal antibody that binds to the endothelial growth factor-A, which in turn inhibits neoangiogenesis, and cediranib, which inhibits a VEGF receptor tyrosine kinase, are the 2 principal agents used in clinical practice. Treatment by VEGF inhibitors is marked by significant early response to therapy but without corresponding overall survival. Rebound enhancement is seen in tumors when the patient is on a drug holiday, which again proves that the response is a manifestation of the stabilization of the blood-brain barrier. It is pertinent to note that there is often a concomitant increase in the nonmeasurable perifocal FLAIR hyperintense signals, which may indicate a shadowed progression.[49]

DSC perfusion has been studied as a potential tool for improving the identification of nonenhancing tumor compared with FLAIR signal images, which show both tumor and treatment response as bright signal. Although initial studies showed that decreased rCBV in bevacizumab-treated glioblastoma can distinguish vasogenic edema from infiltrative tumor and correlates with PFS, later studies showed that 8-week changes in rCBV were nonpredictive of overall survival.[14,19,22] Hence, the ability of posttherapy rCBV changes to predict overall survival probably depends on when the imaging is performed after treatment, and the overall role of DSC perfusion in this setting is still being investigated.

ADC maps were thought to be sensitive to the assessment of the presence of viable tumor in the background of pseudoresponse; however, studies have revealed that this does not occur.[50] A pretreatment ADC threshold of 1.24 μm^2/ms reportedly predicts an improved overall survival in patients with recurrent glioblastoma undergoing antiangiogenic treatment,[51] but this remains to be validated on larger trials.

Amino acid PET studies have exploited the fact that tumor viability is linked to increased demand for carbon. Therefore, the potential use of FET-PET and 3,4-dihydroxy-6-[18F]-fluoro-L-phenylalanine (18F-FDOPA) PET to show recurrent tumors previously treated with bevacizumab has been explored.[51,52]

TREATMENT RESPONSE ASSESSMENT AND SURVEILLANCE OF LOW-GRADE GLIOMAS

Diffuse low-grade gliomas (LGGs) are slow-growing indolent lesions, but approximately 70% have the potential for anaplastic transformation within 5 to 10 years of diagnosis.[53] In accordance with the revised 2016 WHO classification, the term low-grade glioma commonly includes grade II gliomas. These tumors often show little to no enhancement and are hyperintense with well-defined margins. However, these tumors require continued surveillance because they have infiltrative margins and can progress to grade II to IV tumors. With higher grades, these tumors are known to have poorer outcomes.[54]

Assessment of LGGs is challenging because they singularly lack the features of aggressive enhancement, which forms the bedrock of stratification by the Macdonald classification.[53] Furthermore, the imaging findings of these tumors are poorly correlated with clinical presentations with respect to quality of life and cognition. PFS is the parameter often used in clinical trials to assess the efficacy of therapeutic agents. Given these limitations, the RANO working group formulated separate and detailed criteria for treatment response in these patients. The criteria are[55]:

- CR: complete disappearance of the original lesion on T2 or FLAIR MR imaging sequences and the absence of any new lesions or imaging abnormalities other than those attributable to treatment. Patients should be clinically improved or stable and off steroids or on physiologic replacement doses only. CR status should be sustained for at least 4 weeks.
- PR: a greater than 50% decrease in the product of the perpendicular diameters on T2 or FLAIR MR imaging sequences without new

lesions, sustained for at least 4 weeks. Clinically, the patient should be stable or improved and there should be no increase in baseline steroid requirements.
- Minor response: a response of greater than 25% but less than 50% in the product of the perpendicular diameters on T2/FLAIR MR imaging sequences without new lesions. Clinically, the patient should be stable or improved and there should be no increase in baseline steroid requirements.
- SD: no change in imaging that meets the requirements for response (complete, partial, or minor) or progression. Clinically, the patient should be stable and there should be no increase in baseline steroid requirements.
- PD: progression based on imaging requires the development of new lesions, radiologic evidence of transformation to a high-grade glioma (increase in contrast enhancement), or a 25% increase in size on T2 or FLAIR MR imaging sequences of a nonenhancing lesion on stable or increasing doses of corticosteroids that is not attributable to treatment effect. Alternatively, progression is defined based on clinical criteria that include definite clinical deterioration that does not have other causes or to decreasing doses of corticosteroids.

The key point in the advanced imaging assessment of LGG includes accurate assessment of tumor growth rate by using velocity of diametric expansion (VDE). VDE is obtained by calculating a mean tumor diameter (MTD) and volume by segmentation of the tumor on axial images and then using linear regression of the MTD over time.[55] Before anaplastic conversion, LGG shows linear growth of VDE of 4 mm/y.

Advanced Imaging in Low-Grade Gliomas

Apart from assessment of growth, LGG also shows the following, which are important for appropriate surveillance strategies[56]:

- LGG has lower cellularity (ADC_{min}), angiogenesis ($rCBV_{max}$), capillary permeability (K^{trans}), and mitotic activity (Cho/Cr) than high-grade glioma.
- Initial low ADC_{min} with high CBV_{max} and K^{trans} values is consistent with poor prognosis.
- A gradual increase in Cho/Cr ratio and $rCBV_{max}$ values is well correlated with tumor progression.
- Critical distortions in quantifying parameters can be minimized by proper region of interest selection and voxel-based assessment.
- Quantitative multiparametric MR imaging can either improve the diagnostic accuracy of conventional MR imaging or provide a better assessment.

SUMMARY

It is important to keep updated with the latest recommendations for serial assessment of both high-grade gliomas and LGGs. Although conventional imaging-based metrics continue to be heavily used for surveillance of gliomas, there is an increasing role of advanced imaging modalities such as perfusion imaging in helping detect early recurrences and in prognostication.

CLINICS CARE POINTS

- The diagnosis of recurrence or progression of high grade gliomas is an essential aspect of management of these tumors.
- Treatment strategies are dependent on the accurate diagnosis of progressive disease and pseudoprogression.
- Advanced imaging techniques may be helpful in differentiating true progression and pseudoprogression.
- Advances in treatment have resulted in distinct changes in imaging morphologies of the tumors especially on MR studies which are the mainstay in the diagnosis and follow up of these lesion.

DISCLOSURE

The authors have nothing to disclose.

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