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Advances in MR and PET imaging: Assessing Response in the Treatment of Low Grade Glioma

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Abstract

Following combined modality therapy for the treatment of low grade gliomas, the assessment of treatment response and the evaluation of disease progression are uniformly challenging. In this article, we review existing response criteria, and discuss the limitations of conventional MR imaging to distinguish between progression and treatment effect. We review the data on advanced imaging techniques including PET and functional MRI, which may enhance the interpretation of post-treatment changes, and enable the earlier assessment of the efficacy and toxicity of therapy in these patients with prolonged survival.

Introduction

In the era of combined modality therapy for the treatment of low grade gliomas (LGG) including surgery and radiation, and more recently, adjuvant chemotherapy,¹ the post-treatment management of patients with LGG has risen in complexity. Although the majority of patients ultimately succumb to the disease, survival may now be prolonged after treatment.^{2–6} The long natural history poses challenges both in monitoring the efficacy as well as the side effects of therapy. Assessing treatment response and evaluating for progression is uniformly challenging, and standardized metrics are still evolving.

In this article, we review the existing criteria for evaluating response and progression in patients with low grade glioma, clinical and radiographic aspects of follow-up with conventional MR imaging, and the fundamental challenges that exist in monitoring patients after treatment. We discuss the data regarding advanced imaging techniques including PET and MRI for distinguishing between treatment effect versus true disease progression, as well

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as the value of advanced imaging techniques for evaluating the late neurocognitive sequelae of treatment, which may ultimately be used to improve the therapeutic ratio for patients with low grade glioma treated in the era of combined modality therapy.

Clinical and Radiographic Assessment of LGG after Treatment

The assessment of treatment effect in patients with low grade glioma relies on a combination of clinical and radiographic factors. Practitioners involved in the care of patients with LGG should use a combination of neurologic status, corticosteroid use and MRI findings to determine subsequent management. At present, the standard of care for follow-up of LGG patients includes MR FLAIR or T2 weighted sequences, as LGG are predominantly non-contrast enhancing and are best seen on T2 and FLAIR images.⁷ Pre- and post-contrast T1 weighted MRI sequences should also be acquired to assess for malignant transformation, as the majority of patients will relapse with high grade glioma (HGG).

In both clinical trials as well as clinical practice, assessment of LGG after treatment entails the evaluation of tumor response as well as potential tumor progression. In assessing response and progression in LGG, two MRI findings should routinely be reported: the development or change in the enhancing component, and changes in the linear dimension of the non-enhancing component. For assessment of response, the pre-treatment scan should be used as a baseline examination; for progression, the nadir scan with the smallest lesion should be used for comparison⁸. Beyond this, however, multiple challenges exist in further assessing LGG after treatment, and standardized metrics to evaluate response and progression are still evolving.

Fundamental challenges exist in the assessment of response and progression after treatment of LGG. First, the response of LGG seen on MRI is often minor, and may underestimate the full extent of clinical benefit. Patients may experience significant improvement in seizure control or long-term disease control, even in the absence of a clear radiographic response. Progression is often quite difficult to assess, given the incremental growth rate of these tumors in the absence of malignant transformation.^{9,10} Small, asymptomatic increases in T2 or FLAIR changes may be difficult to interpret, and may represent a radiologic phenomenon rather than true progression. Second, the potentially anisotropic growth pattern of LGG may be difficult to measure. The most widely used approach of measuring linear one- or two-dimensional changes in tumor size or cross sectional area may not fully capture the complex regression or growth of an irregularly shaped tumor. Although quantitative metrics such as volumetric measurements of irregular tumors have been investigated, they have not been adopted in routine clinical practice.¹¹ In addition, the exact relationship between FLAIR signal used to define tumor margins and the histologic tumor borders has not been established.¹²

Imaging criteria for Response Assessment

Over the last 2 decades, standardized criteria for the evaluation of treatment response in glioma has evolved from the initial Macdonald criteria, which was of limited applicability in LGG due to its emphasis on regions of contrast enhancement as seen on MRI or CT, to the current RANO criteria for HGG, and the recently proposed RANO criteria for non-

enhancing LGG^{8,13–14} (Table 1). Like the Macdonald criteria, the RANO criteria assesses two-dimensional cross sectional tumor area, in addition to incorporating clinical status and corticosteroid use. Expanding on the Macdonald criteria, the RANO criteria also incorporates evaluation of non-enhancing regions seen on T2 or FLAIR in measuring treatment response, and recognizes increases in T2 or FLAIR as a result of radiation effect. The application of the RANO criteria in clinical trials of new therapies for patients with gliomas continues to evolve, but its widespread use in current clinical practice is uncertain. Moreover, it should be noted that none of these response criteria metrics have been conclusively shown to predict for survival outcomes.

Challenges in Assessing LGG: Disease Progression versus Treatment Effect

A fundamental challenge facing practitioners and researchers alike is the difficulty in distinguishing between disease progression and treatment effect in patients who are treated with surgery and radiation therapy, with or without chemotherapy, for LGG. T2-weighted signal on follow-up MR imaging often persist even after successful treatment of LGG, and may not be distinguished from residual tumor on routine imaging. Moreover, treatment effect after radiation therapy, including local white matter changes and edema, may lead to T2 or FLAIR abnormalities that are also difficult to distinguish from tumor progression. Although typically in a characteristic periventricular or peritumoral distribution with sparing of the cortex and without mass effect, these treatment-induced changes may be difficult to distinguish from disease progression in the absence of advanced imaging.

The standard time-frame recommended for initial assessment of treatment response on follow-up MR imaging is a minimum of 3 months after completion of radiation therapy to help minimize the confounding effect of pseudoprogression, occasionally seen in LGG (although much more often in HGG). Often, serial imaging assessment with retrospective determination of imaging changes, in combination with clinical status and corticosteroid use, are necessary to determine progression versus treatment effect. In specialized centers, advanced imaging is under active investigation to help resolve this dilemma and shed further light on the biologic underpinnings of imaging findings after treatment.

Advanced Imaging for Evaluating Tumor Response

Given the limitations of conventional MRI, advanced imaging techniques including functional MRI and PET imaging may enable the evaluation of biological changes within the tumor and tumor microenvironment, allowing for early assessment of response or progression, and permitting the identification of effective treatment or the early discontinuation of ineffective therapy.

MRI

Recent advances in functional MRI techniques have led to a greater understanding of the tumor biology mediating treatment response. Beyond anatomic information, these functional MRI techniques provide non-invasive, in-vivo assessments of both tumor biology as well as

the surrounding environment, including tumor metabolism, tumor perfusion, vascular properties and angiogenesis, and ultrastructure and chemical composition of tumor microenvironment.¹⁵ With further validation, these tools may eventually be incorporated into clinical trials, potentially leading to wider use in general clinical practice.

Perfusion MRI

Dynamic susceptibility contrast (DSC) or dynamic-contrast enhanced (DCE) MRI acquired during the intravenous injection of a bolus of gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) measures regional tissue perfusion and vessel permeability. Relative cerebral blood volume (rCBV) can be derived from DSC images, e.g., an integral of the area under the contrast uptake curve, and is a measure of neovascularity that correlates with the amount of capillaries in subregions of tumor. A marker of tumor aggressiveness and growth rate, angiogenesis as detected by perfusion MRI has been correlated with histologic grade, response to treatment, and outcome in glioma, and is better defined by perfusion MRI than conventional T1 post-Gd imaging.^{16–23} In addition, abnormal vascular leakage of immature capillaries, seen with rapid tumor cell growth, may be estimated from perfusion MRI by quantifying vascular permeability using a compartmental pharmacokinetic model of contrast movement between the intravascular and extravascular spaces. The recruitment and synthesis of leaky vascular networks at the periphery of LGG as detected by perfusion MRI may represent an early feature of high-grade transformation, and relative CBV has been shown to correlate with progression-free and overall survival, where high rCBV > 1.75 independently predicted for a more rapid time to progression in study of 189 patients with LGG and HGG.^{22,23} In a study of 13 patients with biopsy-confirmed LGG observed with serial perfusion MRI after treatment with anti-epileptics alone, rCBV values increased in patients who ultimately developed high grade transformation seen on T1-contrast enhanced MRI. Patients without high grade transformation had relative stability of rCBV values, indicating that this metric may be used as an early indicator of malignant transformation in patients with LGG, preceding contrast enhancement seen on conventional T1 post-contrast imaging by 12 months or more.²⁴ These findings may potentially be used to distinguish between treatment effect and treatment-resistant or progressive regions of tumor following therapy. In a study of rCBV mapping in 59 patients with LGG and HGG following therapy, tumor progression was detected earlier by rCBV maps by a median of 4.5 months compared to conventional MRI, and 6 months compared to clinical assessment. It was thought to be more sensitive to small regional changes and thus potentially more useful in distinguishing viable tumor from treatment effect than standard imaging.²⁵ This technique may be especially useful in high-risk LGG subsets and possibly of less value in non-transforming LGG due to potential confounding with certain oligodendroglioma subtypes which may have abundant vasculature even in the absence of transformation.

MR spectroscopy

Proton MR spectroscopy (MRS) permits the regional assessment of tissue metabolites that reflect tumor metabolism, cell membrane turnover and proliferation, neuronal integrity, and necrosis. Regional concentrations of metabolites including choline (Cho), creatine (Cr), lactate (Lac) and lipid can be estimated to determine tumor extent in the pre-treatment setting, providing prognostic information prior to therapy. Elevation of choline

concentration, possibly representing higher cell membrane turnover, correlates with proliferative markers such as Ki-67, and raised creatine/phosphocreatine correlates with reduced progression-free survival in both LGG and anaplastic glioma.^{26–28} In a study of 12 patients with LGG treated with temozolomide alone, a significant reduction in the mean choline signal was observed at 12 months post-treatment compared to baseline. The reduction of tumor choline/water signal paralleled tumor shrinkage and appeared to reflect response to chemotherapy.²⁹

In another study of 14 patients including LGG, an increase in the Lac/Cr ratio in contrast-enhancing tumor regions during chemotherapy was associated with reduced progression-free survival. An increase in the Cho/Cr ratio in the “normal-appearing brain” adjacent to non-enhancing tumor during treatment was also associated with decreased progression-free survival.³⁰ Following treatment after radiation therapy, some studies suggest that an increase in choline-containing compounds versus increased lactate or lipid concentrations may be used to distinguish recurrence from radiation necrosis, respectively^{31–34} (Figure 1). In a study of 26 consecutive patients undergoing postoperative radiation with or without chemotherapy for a range of glial neoplasms, MRS had a positive-predictive value of 91.6% and a negative-predictive value of 100% in distinguishing recurrence from radiation necrosis, and to identify tumor transformation.³² More recently, the ability to identify mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) using MRS to non-invasively detect the accumulation of 2-hydroxyglutarate (2HG) metabolite has raised the exciting possibility of using MRS as an imaging biomarker of recurrent disease or response to therapy in patients with gliomas.^{35–37}

Diffusion MRI

Diffusion-weighted imaging (DWI) can measure water mobility in the intracellular and extracellular space, which varies with cellular density and the tumor microenvironment, including cellular and extracellular tissue structure, viscosity of the medium, and tortuosity of the extracellular space. Apparent diffusion coefficient (ADC) maps are derived from diffusion-weighted images, providing an assessment of water diffusion properties in brain tissue, and these measurements may be serially compared before, during and after treatment to estimate prognosis and treatment response. Whereas unaltered ADC may reflect treatment-resistance, the transient cell swelling resulting from necrosis or focal ischemia may lead to decreased ADC suggesting treatment response. Eventually, an increase in ADC may be seen with progression when cells undergo apoptosis leading to cell shrinkage and phagocytosis.³⁸ Quantitative analysis may be undertaken by creating parametric response maps that enable the regional assessment of MR parameters both within and around tumor, which have shown predictive value 3 weeks after treatment start of later radiographic response in a population with a mixed population of primary brain tumors.³⁸ This method has also shown predictive value of early treatment response in transformed LGG, reflecting changes at the cellular level before morphologic changes may occur.

Using a combination of functional imaging parameters rather than a single technique may better distinguish recurrence versus treatment effect in patients treated with multiple modalities for LGG. In a study of 15 patients with gliomas including LGG with suspected

progression after radiation, a multiparametric scoring system combining minimum ADC ratio, maximum rCBV ratio, and maximum Cho/Cr and Cho/N-acetyl-aspartate (NAA) peak-height ratios appeared to improve overall diagnostic accuracy in distinguishing progression from post-radiation change beyond each technique alone.³⁹ Additional data supports the use of perfusion and multi-voxel MRS parameters over DWI alone for distinguishing recurrent glioma from post-radiation injury in a series of 40 cases that included patients with LGG.⁴⁰

PET

An increasing interest in advanced PET imaging to monitor the effects of treatment has led to a number of promising techniques using newer radiotracers that highlight the metabolic activity of gliomas. PET analysis permits the quantitative localization of enzyme or transporter expression by measurement of the respective enzyme or transporter substrate, allowing visualization of a variety of molecular processes such as increased metabolism or cell proliferation. It is of note that the interpretation of advanced PET findings requires appropriate selection of cutoff thresholds based on different regions of the brain that may not have uniform uptake.

Within the brain, conventional ¹⁸F-fluoro-deoxy-D-glucose (¹⁸F-FDG) PET is of less value due to the high level of uptake in the normal brain. Newer amino acid radiotracers including ¹¹C-methionine (¹¹C-MET) and ¹⁸F-fluoro-ethyl-tyrosine (¹⁸F-FET) improve the contrast between the tumor lesion and background brain tissue, and may help resolve regions of viable tumor by detecting increased transport into tumor cells as well as tumor vasculature. The transport of ¹¹C-MET by type L amino acid carriers occurs at the level of the blood-brain barrier, reflecting proliferative activity and microvessel density of glioma cells, with eventual incorporation into proteins. Recent studies have shown that ¹¹C-MET PET may more reliably detect tumor progression compared to treatment effect or radiation necrosis with a sensitivity of 75% and specificity of 75%.^{41–44} In a study of 11 patients with non-enhancing LGG treated with temozolomide and imaged at 3–6 month intervals with ¹⁸F-FET-PET and conventional MRI, the time to maximal volume reduction was 8 months using ¹⁸F-FET-PET and 15 months using conventional MR alone, suggesting deactivation of amino acid transport as an early event in response to chemotherapy.⁴⁵

The incorporation of nucleosides into DNA is another measure of cellular proliferation that may be non-invasively assessed with PET. In untreated patients, increased uptake via ¹⁸F-fluorothymidine (¹⁸F-FLT) PET has been shown to predict for decreased overall survival. In both the pre- and post-treatment setting, FLT uptake has been used to distinguish low-grade and high-grade tumors and correlate with Ki-67, tumor progression and survival. It has not been as well studied as the amino acid tracers in differentiating recurrent tumor from radiation necrosis or other treatment effect in patients with LGG. There are conflicting reports about its ability to distinguish between tumor recurrence and radiation necrosis compared to ¹⁸F-FDG PET.^{46–49}

Advanced Imaging for Evaluating Treatment Effect on Normal Tissue

Understanding the changes in normal brain tissue that are associated with long-term neurocognitive outcome after cranial irradiation is essential to improving the therapeutic ratio for patients with LGG who may live for many years after treatment. These changes, although not evident on conventional MRI or CT, may be detected using functional MRI. Using MR spectroscopy, one study demonstrated metabolic changes in irradiated normal brain as early as the third week of radiation in patients with stable LGG compared to baseline, and changes in Cho/Cr were correlated with radiation dose and volume both during and 1 month after radiation. Moreover, progressive decline in NAA/Cr 6 months after RT was observed, possibly indicating progressive neuronal damage.⁵⁰ Other changes including microvessel injury detected by DCE MRI are seen early during the course of radiation therapy, and changes in vascular volumes and blood brain barrier permeability correlate with changes in verbal learning and recall 6 months after radiation in patients with stable disease.⁵¹ With even longer follow-up beyond 10 years, white matter hyperintensities and global cortical atrophy in patients undergoing radiation for LGG may be seen that are associated with worsened cognitive function in multiple domains including executive functioning, information processing speed, and attentional functioning.⁵²

Diffusion tensor MRI is particularly helpful for distinguishing early changes in normal white matter induced by radiation, which are correlated with delayed changes in neurocognitive outcome. These findings have been demonstrated in a variety of patient populations with intracranial tumors, receiving local field or whole brain radiation. The particular sensitivity of structures within the limbic circuit, known to be involved in cognitive functions such as learning and memory, was demonstrated in a prospective study of 10 patients undergoing conformal external beam radiation for low grade or benign brain tumors (Figure 2). Serial diffusion tensor MR imaging pre-treatment, during radiation, and up to 78 weeks after starting radiation were acquired and correlated with neurocognitive outcomes and quality of life assessments in patients with stable tumors.⁵³ The authors observed an increase in perpendicular diffusivity 3 weeks into radiation in the parahippocampal cingulum, which correlated with radiation dose. Early cingulum longitudinal diffusivity changes predicted for changes in verbal recall scores after radiation, suggesting that diffusion tensor imaging may serve as an early biomarker of late neurocognitive effects after treatment.

By identifying early changes in irradiated normal brain using advanced MR imaging that correlate with late normal tissue injury, it may be possible to tailor treatment in order to reduce long-term neurocognitive toxicity, particularly in the era of combined modality treatment for LGG. Whether reliable changes in patients with true tumor progression can be identified and distinguished from the bystander effects in normal tissue remains an active area of investigation.

Future Directions

Moving forward, biologic-based imaging in combination with molecularly targeted agents may be used to assess treatment response, providing earlier endpoints reflecting treatment effect, or even treatment toxicity. Because overall survival assessment takes many years to

ascertain, earlier endpoints for evaluating new therapies will continue to evolve and will be incorporated into clinical trials. Likewise, characterizing treatment-related changes that impact long term function and neurocognitive outcome in these patients in whom prolonged survival is expected may enable further refinement of therapies to reduce toxicity, and will increasingly form the basis of new therapeutic recommendations in this disease.

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Figure 1.

(A) T1-Gd MRI at baseline (left) and 80 months post-RT (right) of a 14 yo female patient with diffuse astrocytoma who underwent stereotactic biopsy and definitive radiation followed by alkylating chemotherapy. (B) Representative voxel within the enhancing lesion (left) and MRS spectrum demonstrating elevated Cho peak, decreased NAA peak and small lactate peak (right). (C) ¹¹C-MET PET demonstrating increased uptake in lesion. (D) Image of biopsy specimen of lesion demonstrating viable tumor cells consistent with recurrent disease. Adapted from Nakajima et al.³¹ Copyright permission pending.

Figure 2.

The patient was a 43 yo male with grade 2 gemistocytic astrocytoma of the right temporal lobe treated on a clinical protocol with definitive radiation to 59.4 Gy and adjuvant temozolomide who remained without disease progression at last follow-up. Top panel shows pre-RT T2/FLAIR MRI (left) and overlying radiation dose distribution (right). Middle panel shows fractional anisotropy (FA) maps, a measure of anisotropic diffusion that reflects overall white matter fiber integrity, pre-RT (left) and 18 months post-RT (right). Bottom panel shows an enlarged view of the area within the white boxes; right and left cingulum outlined in white. FA declined by 30% in the right cingulum, and by 1% in the left. The patient experienced a significant decline of 5 standard deviations in delayed recall at 18 months compared to pre-RT.

Table 1

Updated Response Assessment Criteria for Low Grade Glioma: Response Assessment in Neuro-Oncology Working Group (RANO)

Response	Criteria
Complete Response	Requires all of the following compared with baseline scan: <ol style="list-style-type: none"> 1 complete disappearance of the lesion on T2/FLAIR imaging (if enhancement had been present, it must have resolved completely) 2 no new lesions; no new T2/FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement 3 patients must be off corticosteroids (or on physiologic replacement doses only) 4 patient is stable or improved clinically
Partial Response	Requires all of the following compared with baseline scan: <ol style="list-style-type: none"> 1 50% decrease in the product of perpendicular diameters of the lesion on T2/FLAIR imaging for 4 weeks 2 no new lesions, no new T2/FLAIR abnormalities apart from those consistent with radiation effects, and no new or increased enhancement 3 same or lower dose of corticosteroids compared with dose at baseline scan 4 patient is stable or improved clinically
Minor Response	Requires all of the following compared with baseline scan: <ol style="list-style-type: none"> 1 decrease in area of nonenhancing lesion on T2/FLAIR between 25–50% 2 no new lesions, no new T2/FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement 3 same or lower dose of corticosteroids compared with dose at baseline scan 4 patient is stable or improved clinically
Stable Disease	Requires all of the following: <ol style="list-style-type: none"> 1 does not qualify for complete response, partial response, minor response or progression 2 stable area of nonenhancing abnormalities on T2/FLAIR 3 no new lesions, no new T2/FLAIR abnormalities apart from those consistent with radiation effect, and no new or increased enhancement 4 same or lower dose of corticosteroids compared with dose at baseline scan 5 patient is stable or improved clinically
Progression	Any of the following: <ol style="list-style-type: none"> 1 any new lesion or increase of enhancement (radiological evidence of malignant transformation); 2 25% increase of T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not attributable to radiation effect or to comorbid events 3 clear clinical deterioration not attributable to other causes apart from tumor or changes in corticosteroid dose 4 failure to return for evaluation as a result of death or deteriorating condition, unless caused by documented non-related disorders