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The use of advanced neuroimaging modalities in the evaluation of low-grade glioma in adults: a literature review

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Low-grade gliomas encompass a subgroup of cancerous glial cell growths within the central nervous system and are distinguished by their slow growth and relatively low malignant potential. Despite their less aggressive nature, these tumors can still cause significant neurological symptoms through the compression of surrounding neural and vascular structures and, in some instances, undergo malignant transformation. For these reasons, timely and appropriate evaluation and management of low-grade gliomas is critical. Medical imaging stands as a cornerstone for evaluating patients with low-grade gliomas because of its noninvasive nature and ability to provide a vast amount of information about the underlying lesion. With the growing number of neuroimaging techniques and their capabilities, there is a lack of clear guidance on which techniques to utilize for the assessment of low-grade gliomas and what their respective core use cases should be. In this literature review, the authors discuss in significant depth the available evidence pertaining to the use of advanced neuroimaging techniques in the evaluation and management of low-grade gliomas. Specifically, they review the specificity, sensitivity, accuracy, and use cases of magnetic resonance spectroscopy (MRS), perfusion MR imaging (perfusion MRI), diffusion tensor imaging (DTI), functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), as well as other emerging imaging techniques. They conclude that most of the advanced neuroimaging techniques are reliable in differentiating low- from high-grade gliomas, whereas MRS and DTI may further support molecular subclassification of the tumor. PET has been best employed for the purpose of tumor biopsy, whereas fMRI and DTI can be particularly valuable in preoperative surgical planning, as they delineate the functionally eloquent brain regions that need to be preserved during tumor resection. MRS, PET, SPECT, and perfusion MRI are best suited to monitor tumor progression, as their respective metrics closely correlate with the underlying metabolic activity of the tumor. Together, these techniques offer a vast amount of information and serve as tools for neurologists and neurosurgeons managing patients with low-grade gliomas.

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"Glioma" is a term representing a variety of cancerous growth patterns originating from the glial cells within the central nervous system.[1] The official 2021 World Health Organization classification of gliomas is robust and firmly rooted in histological, immunohistochemical, and molecular properties of the tumor.[2] A more simple and practical way to classify gliomas is by their grade, which reflects the degree of tumor differentiation, malignant potential, and likely clinical course.[3] "Low-grade" gliomas, corresponding to grades 1 and 2, include the more benign tumors with favorable prognoses, whereas "high-grade" gliomas, corresponding to grades 3 and 4, include the more malignant tumors that frequently require aggressive medical and surgical management. Regardless of the tumor grade or other defining characteristics, all gliomas need to be thoroughly evaluated, closely monitored, and appropriately managed.

The evaluation of gliomas is guided by neurological

ABBREVIATIONS ^{11}C-MET = carbon-11 methionine; ^{18}F-FDG = fluorine-18 fluorodeoxyglucose; ^{18}F-FET = fluorine-18 fluoroethyltyrosine; ^{99m}Tc-MIBI = technetium-99m sestamibi; ADC = apparent diffusion coefficient; BOLD = blood oxygen level–dependent; CEST = chemical exchange saturation transfer; Cho = choline; Cr = creatine; DTI = diffusion tensor imaging; FA = fractional anisotropy; FDI = fiber density index; fMRI = functional MRI; IMT = 3-[(123)I]iodo-alpha-methyl-L-tyrosine; MD = mean diffusivity; MRI = magnetic resonance imaging; MRS = MR spectroscopy; NAA = *N*-acetylaspartate; NIRS = near-infrared spectroscopy; PET = positron emission tomography; rCBV = relative cerebral blood volume; SPECT = single-photon emission computed tomography.

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examination, biochemistry, imaging, and, in instances in which a biopsy specimen is obtained, histopathological reports. All these methods are crucial in performing a comprehensive assessment of the pathological characteristics and likely clinical course of the underlying glioma. However, in modern medical practice, the role of imaging has become increasingly important because of its noninvasive nature and the wide spectrum of information it can provide. For instance, magnetic resonance imaging (MRI), which has been in use since the early 1980s,[4] can delineate the lesion, providing an understanding of its location, size, and growth pattern. The more recent advances in neuroimaging are facilitating an even more robust image-based assessment, offering information on metabolic activity, vascular perfusion, molecular composition, and tissue distribution within and around the area of the lesion. Together, these sequences can provide insight into the underlying grade of the evaluated glioma, its molecular subclassification, the likelihood of progression, the optimal resection margin if surgery is pursued, as well as the overall prognosis.

In this review article, we aimed to provide an overview of advanced neuroimaging modalities as they pertain to the evaluation of low-grade gliomas. More precisely, we discuss the literature on the accuracy, sensitivity, specificity, and use cases of MR spectroscopy (MRS), perfusion MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), as well as other emerging imaging techniques (Fig. 1).

MR Spectroscopy

MRS is an advanced neuroimaging technique that utilizes a magnetic field to characterize the metabolic composition of the scanned tissue based on the radiofrequency of emitted electromagnetic signals.[5] It was introduced to the field of neuro-oncology in the late 2000s as a method of differentiating a tumor from a pseudotumoral lesion, as well as to provide insight into the underlying glioma grading.[6,7] According to a recent assessment by Shakir et al., the choline/creatine (Cho/Cr) ratio identified by MRS provides the most accurate assessment of glioma grade with a sensitivity of 83.3% and specificity of 93.7%.[8] However, other metabolite measurements have also proven to be useful in assessing glioma grade, including Cho/*N*-acetylaspartate (NAA), NAA/Cr, lactate, and lipid peaks.[7,9] Additionally, MRS has been shown to distinguish between glioma and nonglioma lesions based on the respective NAA/Cho and NAA/Cr ratios.[10] Furthermore, MRS may be a viable modality for guiding stereotactic tissue biopsy, as tumor regions with high Cho/NAA ratios are suggested to be best suited for histopathological assessment.[11]

MRS has also been increasingly investigated for its role

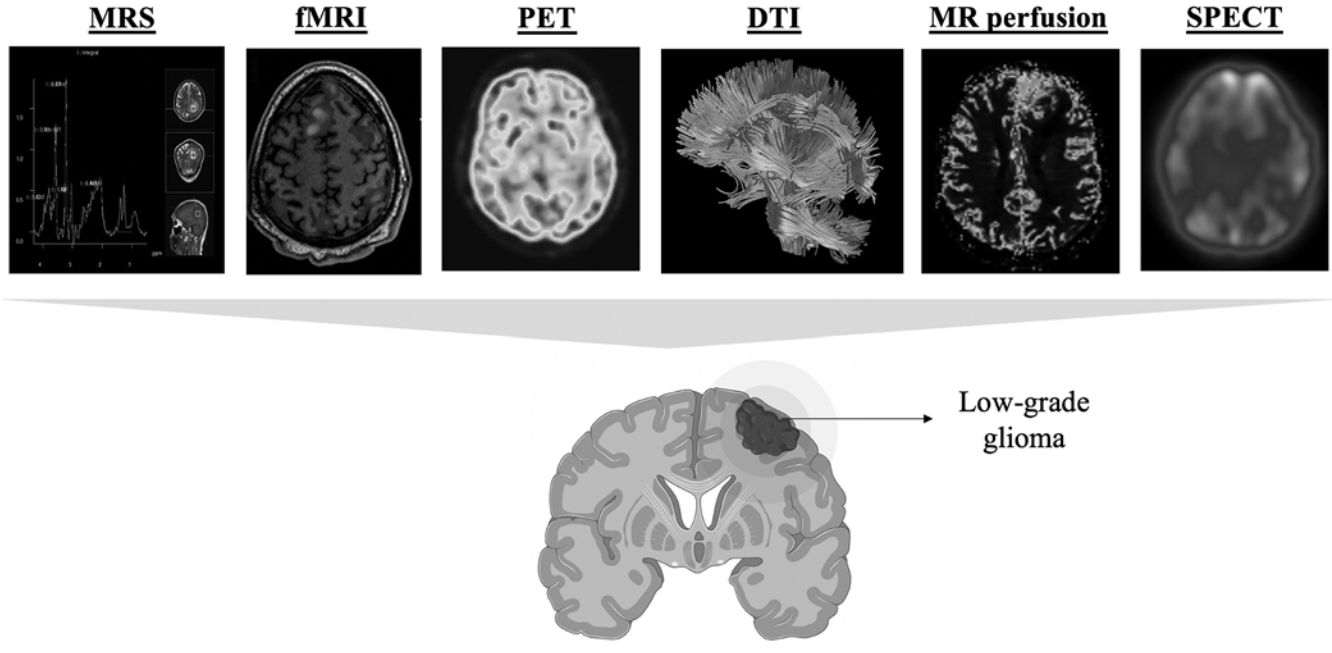

FIG. 1. A wide spectrum of advanced neuroimaging techniques has been used in the evaluation of low-grade gliomas. **MRS:** Case courtesy of Paresh K. Desai, Radiopaedia.org. From the case Primary CNS lymphoma. CC BY-NC-SA 3.0 Unported license (https://creativecommons.org/licenses/by-nc-sa/3.0/). **fMRI:** user:7mike5000/Wikimedia Commons/Public Domain. **PET:** Tomografia por Emisión de Positrones, © Juan Galan, published with permission. CC BY-SA 3.0 Unported license (https://creativecommons.org/licenses/by-sa/3.0/deed.en). Changes made: original four-color image converted to black and white. **DTI:** Healthy human adult brain viewed from the side, tractography. Dr. Flavio Dell'Acqua. CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Source: Wellcome Collection. **MR perfusion:** Case courtesy of Frank Gaillard, Radiopaedia.org. From the case Oligodendroglioma. CC BY-NC-SA 3.0 Unported license (https://creativecommons.org/licenses/by-nc-sa/3.0/). **SPECT:** Case courtesy of Frank Gaillard, Radiopaedia.org. From the case Posterior cortical atrophy. CC BY-NC-SA 3.0 Unported license (https://creativecommons.org/licenses/by-nc-sa/3.0/). **Low-grade glioma:** Created with BioRender.com.

in assessing tumor progression. A longitudinal measurement in 41 patients with low-grade glioma demonstrated increasing Cho/NAA concentrations in patients who had progression in their tumor grade, suggesting that MRS may be a viable surveillance tool in addition to traditional MRI follow-up.[12] Another study revealed that over the course of 1 year, a decrease in the Cho concentration within the center of the lesion is correlated to the reduction in tumor volume in patients treated with temozolomide, highlighting the value of MRS in monitoring the response to chemotherapy.[13] Furthermore, Cho/Cr measurements have shown 85.5% discrimination accuracy in differentiating between disease recurrence and radiation injury[14] and 84% discrimination accuracy in differentiating between disease recurrence and pseudoprogression. However, it should be noted that authors of a large meta-analysis of 445 patients across 18 studies concluded that the diagnostic performance of MRS for differentiating glioma recurrence from radiation necrosis is moderate.[15] Therefore, MRS findings should be combined with the results of other imaging techniques to ensure high diagnostic accuracy and to appropriately support clinical decisions.

Finally, MRS may in some instances provide insight into the molecular characteristics of tumors. For example, an increase in d-2-hydroxyglutarate on MRS may indicate an IDH1 mutation,[16] whereas heavy expression of glutamate may imply a GLAST-expressing glioma.[17] Other potential applications of metabolite measurements to decode the underlying molecular mutations are conceivable but have yet to be formally evaluated.

Diffusion Tensor Imaging

DTI is an advanced imaging technique that uses the diffusion of water molecules to generate contrast on MRI-based images. The pattern of water diffusion can provide an understanding of the underlying dispersion of white and gray matter fibers within the brain, as well as any associated lesions that may be disrupting the normal distribution of the contrast. A DTI scan provides a range of metrics that describe the characteristics of neuronal tissue and underlying water dispersion, including the fiber density index (FDI), mean diffusivity (MD), fractional anisotropy (FA), and apparent diffusion coefficient (ADC).

The application of DTI in the evaluation of low-grade gliomas is broad. First, the metrics obtained through DTI can support the classification of glioma based on its grade. FDI and MD in the center of the glioma can help to differentiate between low- and high-grade gliomas with 81.3% and 91.4% accuracy, respectively.[18,19] Similarly, FA of the peritumoral area can predict the tumor grade with 80% accuracy.[19] In addition to evaluating tumor grade, DTI can provide insight into the molecular subtype of low-grade gliomas, with several studies suggesting that FA correlates with the IDH mutation status of the tumor and the presence of 1p/19q codeletion.[20]

DTI can also be used as an adjunct in both preoperative planning and intraoperative neuronavigation, as it outlines the location and integrity of white matter tracts. This facilitates planning of the surgical corridor, allowing the surgeon to strike the optimal balance between maximum resection and preservation of neurological function.[21] According to several studies, the use of DTI could be associated with greater Karnofsky Performance Status scores postoperatively, greater extent of tumor resection, and increased overall survival.[22] Coregistering DTI with MRI can further support the planning process and surgical navigation as a method for predicting the localization of critical white matter nerve functions.[23] The clinical benefit of such an approach has been reported by Ius et al., who showed better outcomes in cases in which MRI/DTI fusion was done as part of preoperative planning.[24] However, the anatomical accuracy of DTI-based tractography is not infallible,[25] with the lack of a standardized data analysis pipeline representing a major concern.[26] Therefore, it remains essential that, in addition to tractography, the surgeon relies on anatomical landmarks, electrophysiological assessment, and other imaging techniques to guide tumor resection.

Lastly, DTI has also been investigated as a tool in assessing the response to medical treatment. In one study, early changes in MD in response to temozolomide predicted the final volume change and the overall effectiveness of the therapy.[27] Similar observations have been noted in high-grade gliomas, with a predictable change in DTI metrics in response to other chemotherapeutic agents including bevacizumab and irinotecan.[28] Additionally, ADC and FA have been shown to discriminate between tumor progression and treatment-related abnormalities, warranting further research into DTI as a potential method of monitoring treatment response.[29]

Perfusion MRI

Perfusion MRI is a technique that involves the intravenous injection of gadolinium-based contrast, followed by a series of T2-weighted images. The accumulation of contrast within a lesion provides an indication of its vascularity, revealing valuable information about the likely pathological features of the lesion. Thus, it is particularly useful in delineating tissue vascularization and angioneogenesis in the context of brain tumors.

In relation to gliomas, perfusion MRI has been shown to differentiate between low- and high-grade gliomas with low to moderate accuracy. The ratio of tumoral cerebral blood flow to normal-appearing white matter (relative cerebral blood volume [rCBV]) was a sufficient metric to discriminate between low- and high-grade tumors with 83% sensitivity and 48% specificity, averaged across seven studies.[30] Similar findings were replicated in a large single-center study involving 33 patients, demonstrating that perfusion MRI provided benefit in evaluating the preoperative tumor grade.[31] While the accuracy of perfusion MRI grading is limited and varies across the literature, its diagnostic value remains higher than that of conventional MRI alone.[32]

Importantly, this technique has also been investigated in predicting malignant transformations of low-grade gliomas. A small study demonstrated that in patients with transforming low-grade glioma, perfusion MRI identified significant increases in rCBV up to 12 months before traditional contrast-enhanced T1-weighted imaging. This

was not the case in nontransforming gliomas, where the rCBV remained constant throughout the follow-up period.[33] However, its predictive value is likely limited because of a lack of standardized parameters and susceptibility to imaging artifact and should not be used as a stand-alone technique in monitoring disease progression.[34]

Functional MRI

fMRI is a neuroimaging technique that uses blood oxygen level–dependent (BOLD) signals to map out oxygen consumption throughout the brain. This technique has been widely used in research to gain a stronger understanding of the functional divisions of the brain, as well as the connectivity between different brain regions. However, fMRI is not commonly used in clinical practice, largely because of a high within- and between-subjects variability of the BOLD signal, as well as a lack of standardized acquisition and analysis techniques.[35]

Despite this important limitation, fMRI may provide some benefit in preoperative surgical planning. According to a meta-analysis of 68 observational studies, functional deterioration after glioma resection was less likely to occur when fMRI was performed preoperatively (OR 0.25, 95% CI 0.12–0.53), implying a both statistically and clinically significant benefit.[36] Another study specifically evaluating the benefit of fMRI for low-grade glioma resections revealed a very low incidence of postoperative complications with fMRI-guided resection, further validating its benefit in clinical settings.[37] However, the fMRI results should be carefully interpreted, as not all areas with an increased BOLD signal are critical for neurological function. Anatomical knowledge and previous outcomes should be used to gauge which areas remain safe to resect despite an increased BOLD signal to achieve optimal results.

Lastly, independent component analysis of resting-state fMRI has shown a high success rate in differentiating gliomas from normal tissue, offering additional rationale for performing preoperative fMRI.[74] However, unlike many other imaging techniques, fMRI has not been shown to be of benefit in glioma grading and tumor surveillance.

Positron Emission Tomography

PET is a functional radiological technique that allows the visualization of intravenously injected positron-emitting isotopes. The injected isotopes and their relative uptake across the body provide insight into physiological function, including blood flow and metabolism. In the field of oncology, PET is widely used as a method of localizing and grading tumors, as well as tracking disease progression and response to treatment.[38]

In relation to low-grade gliomas, PET has been shown to have a wide range of viable use cases. First, it can support the identification and grading of an underlying tumor. In one study, ^{18}F-fluciclovine PET demonstrated very high sensitivity (97.5%) and specificity (95.5%) in differentiating low- and high-grade gliomas.[39] Another study demonstrated a differential uptake of carbon-11 methionine (^{11}C-MET) across high-grade gliomas, low-grade gliomas, and chronic nontumoral lesions, with an accuracy of 79% in differentiating between gliomas and nontumoral lesions.[40] Similarly, dual-phased fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET has shown 89.4% accuracy in predicting the proliferative activity of gliomas, making it a useful grading method.[41] Despite a wide range of isotopes demonstrating high levels of accuracy in grading and differentiating gliomas, it remains unclear which isotope is most effective and best suited for use in clinical practice.[42]

PET has also been investigated for monitoring progression and predicting survival in low-grade gliomas.[43] A study by Singhal et al. demonstrated that the tumor to mean standardized uptake value of ^{11}C-MET in low-grade gliomas was statistically significantly correlated with patient survival.[44] However, these authors did not observe the same trend with ^{18}F-FDG PET, which was shown to be a less reliable predictor of patient outcome. More recently, evidence has suggested that fluorine-18 fluoroethyltyrosine (^{18}F-FET) PET and 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (^{18}F-FDOPA) PET uptake may also be a predictor of tumor progression, disease recurrence, and unfavorable patient outcomes.[45,46]

Importantly, PET has also proved to be a valuable imaging modality in guiding stereotactic biopsy planning. Appropriate target selection is vital in obtaining a representative sample of tissue that can accurately guide further management. The use of PET tracers can identify the area of the tumor that is metabolically active, contains a high degree of proliferating cells, and provides an optimal sample for histopathological analysis.[47] A prospective study utilizing ^{18}F-FET PET showed that the diagnostic performance of the glioma biopsy was significantly higher when ^{18}F-FET PET and MRI were combined versus MRI alone (sensitivity: 93% vs 96%, specificity: 53% vs 94%, respectively).[48] Another study demonstrated that ^{18}F-FET PET can identify anaplastic foci in a low-grade glioma with a sensitivity of 92% and specificity of 82%.[49] In a similar vein, although less researched, PET tracers are also being investigated as a potential adjunct tool in surgery and radiation therapy planning for patients with gliomas.[50] However, a major limitation of PET-guided biopsy is that the tumor needs to be large enough to be detected via PET (i.e., > 0.7 cm in diameter) and requires coordination between tracer administration and scan acquisition time based on the compound half-life.[51]

Single-Photon Emission Computed Tomography

SPECT, like PET, is a nuclear imaging modality that allows for the assessment of tissue perfusion and metabolic uptake. It relies on the injection of a radioactive tracer, which binds to the evaluated tissue through a tissue-specific ligand. This radioactive isotope then emits gamma rays, which can be detected through a gamma camera.[52]

Overall, the value of SPECT in the evaluation of low-grade gliomas is not as thoroughly researched as other techniques. Like most of the discussed imaging modalities, SPECT has been shown to differentiate between low- and high-grade gliomas. For instance, in a study evaluating 61 patients with glioma, the technetium-99m sestamibi (^{99m}Tc-MIBI) SPECT index was significantly higher in high-grade gliomas than in low-grade gliomas.[53] Similar

results were found with the ^{99m}Tc-glucoheptonate (GHA) radiotracer, which differentiated low-grade gliomas, high-grade gliomas, and nonneoplastic lesions with moderate to high accuracy.[54]

SPECT may also be a viable tool in evaluating and predicting the progression of low-grade lesions. High uptake of thallium-201 on SPECT was associated with an increased likelihood of early disease progression, even if the tumor demonstrated low proliferative activity on histopathological examination.[55] Furthermore, 3-[(123)I]iodo-alpha-methyl-L-tyrosine (IMT) SPECT demonstrated high accuracy in differentiating between tumor progression and radiation injury with 94% sensitivity and 100% specificity.[56] These findings were replicated in another study in which IMT SPECT was clearly superior to ^{99m}Tc-MIBI SPECT and ^{18}F-FDG PET in differentiating between tumor progression and radiation injury.[57] A systematic review on the topic reached a similar conclusion, with SPECT being the most accurate imaging technique in differentiating tumor progression from radiation-induced injury.[58]

Finally, SPECT may be a useful follow-up method, as both ^{99m}Tc-GHA SPECT and nitrogen-13 ammonia (^{13}N-NH3) PET have proven valuable in identifying recurrent gliomas with an accuracy of 85.5% and 83.6%, respectively.[59] Regular surveillance SPECT may be a valuable adjunct to the regular clinic follow-up for patients in whom resection of a low-grade glioma was performed, with the understanding that it, like PET, exposes the patient to additional radiation.

Emerging Imaging Techniques

There is a broad spectrum of emerging imaging techniques that may prove valuable in the evaluation of low-grade gliomas. However, at this time, their respective diagnostic accuracy, as well as their test-retest variability, is yet to be fully evaluated and fine-tuned. In this section, we discuss selected techniques that are likely to play an increasingly important role because of the unique and important information they can provide about the underlying glioma.

Hyperpolarized ^{13}C MRI is an emerging molecular method that allows noninvasive investigation of in vivo metabolism in real time, providing insight into the extent of both glycolytic and oxidative phosphorylation within the tumor.[60] The technique has already been shown to be effective in differentiating IDH status and potentially supporting glioma surveillance.[61,62] While hyperpolarized ^{13}C MRI is likely to prove useful in the evaluation of low-grade gliomas, because of its novelty, the respective accuracy and use cases have yet to be fully investigated and established.

Imaging methods utilizing near-infrared spectroscopy (NIRS) could also prove to be valuable in the assessment of low-grade gliomas. NIRS is an optical spectroscopy method that employs infrared light to monitor oxygen metabolism.[63] A study published in 2016 demonstrated that NIRS can be used to visualize the glioma intraoperatively, potentially guiding tumor resection.[64] Furthermore, NIRS could support treatment monitoring and targeted drug delivery if the administered treatment is appropriately labeled with NIR fluorescence probes.[65]

^{23}Na MRI is another novel method that allows the estimation of tissue sodium concentration. The amount of sodium within the tumor has been correlated with the tumor proliferation rate[66] and may prove useful in the assessment of low-grade gliomas. However, at this time, the technique lacks sufficient specificity and sensitivity when used to evaluate complex tumor microenvironments.[67] Similarly, chemical exchange saturation transfer (CEST) imaging may facilitate the estimation of tissue pH, potentially providing an attractive metric to monitor proliferation rate, treatment response, and tumor progression.[68] Another CEST-based imaging technique is CEST amide proton transfer (APT) MRI, which may be of value in identifying molecular markers of glioma, including IDH, MGMT methylation status, 1p/19q deletion, and H3 K27M mutation status.[69]

Many other imaging techniques are emerging, but their validity and use cases have yet to be evaluated. At this rate, it is conceivable that soon neuroimaging will become the primary method of evaluating and, to an extent, managing low-grade gliomas.

Conclusions

In summary, there is currently a wide variety of advanced neuroimaging techniques that can facilitate and improve the management of low-grade gliomas. These techniques are particularly useful at present for the identification and grading of gliomas, pre- and intraoperative planning, disease surveillance, and the monitoring of treatment response. We have discussed these in significant depth and have provided a condensed overview in Table 1.

Currently, there is insufficient evidence to suggest that certain techniques are superior to others, and in practice, the use of multiple techniques may provide the most reliable and consistent results.[70,71] Most of the above-discussed techniques have shown reliable results in differentiating low- from high-grade gliomas but have had less success in identifying the exact grade (i.e., 1–4). Both DTI and fMRI may be particularly valuable in preoperative planning, as they delineate the functionally eloquent brain regions and patterns of connectivity that need to be preserved during tumor resection. However, both techniques carry inherent limitations, which are discussed within the respective sections of this review, and the use of additional intraoperative adjuncts remains highly encouraged. While MRS, PET, SPECT, and perfusion MRI can all be used to monitor tumor growth and visualize metabolic activity, the available evidence suggests that SPECT may be the most accurate imaging technique at distinguishing true progression, but this needs further support.[58] For the purpose of tumor biopsy, both PET and MRS have been explored, with limited data comparing the two. However, it is likely that the combination of the two techniques would yield optimal outcomes.[72] Finally, while both DTI and MRS have been shown to differentiate IDH mutation status, genetic testing and histopathological analysis remain the gold standard.[73]

The decision on whether, and to what extent, to employ these techniques in the evaluation and management

TABLE 1. Evidence-based use cases for advanced neuroimaging techniques in the evaluation and management of low-grade glioma

Imaging Technique	Brief Description	Use Case					
		Tumor Grading	Molecular Subclassification	Biopsy Planning	Resection Planning	Surveillance	Monitoring Response to Medical Treatment
MRS	Quantifies metabolite concentration	Yes	Yes	Yes	No	Yes	Yes
DTI	Identifies white & gray matter structures	Yes	Yes	No	Yes	No	Yes
Perfusion MRI	Quantifies cerebral blood flow	Yes	No	No	No	Yes	No
fMRI	Quantifies metabolic activity	No	No	No	Yes	No	No
PET	Quantifies metabolic activity using positron-emitting tracers	Yes	No	Yes	No	Yes	No
SPECT	Quantifies metabolic activity using radioactive tracer	Yes	No	No	No	Yes	No

of patients should be led by the practicing neurosurgeon, their familiarity with the established techniques, as well as the most recent scientific evidence. However, we strongly support the view that these techniques should, in some regard, be implemented in every physician's practice, as they offer a noninvasive method of collecting valuable information regarding the glioma and its clinical course with the significant potential to facilitate and improve the management of this patient population. We also encourage continued research in this area, as there is currently a lack of robust prospective studies comparing the relative diagnostic accuracy, sensitivity, and specificity of advanced neuroimaging techniques as they pertain to the management of low-grade gliomas. More definitive evidence will outline the optimal use cases for each method and support broader implementation of these modalities in neurosurgical practice.

References

1. Weller M, Wick W, Aldape K, et al. Glioma. *Nat Rev Dis Primers*. 2015;1:15017.
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251.
3. Mesfin FB, Al-Dhahir MA. Gliomas. In: *StatPearls* [Internet]. StatPearls Publishing; 2023.
4. Geva T. Magnetic resonance imaging: historical perspective. *J Cardiovasc Magn Reson*. 2006;8(4):573-580.
5. Gujar SK, Maheshwari S, Björkman-Burtscher I, Sundgren PC. Magnetic resonance spectroscopy. *J Neuroophthalmol*. 2005;25(3):217-226.
6. Majós C, Aguilera C, Alonso J, et al. Proton MR spectroscopy improves discrimination between tumor and pseudotumoral lesion in solid brain masses. *AJNR Am J Neuroradiol*. 2009;30(3):544-551.
7. Horská A, Barker PB. Imaging of brain tumors: MR spectroscopy and metabolic imaging. *Neuroimaging Clin N Am*. 2010;20(3):293-310.
8. Shakir TM, Fengli L, Chenguang G, Chen N, Zhang M, Shaohui M. 1H-MR spectroscopy in grading of cerebral glioma: a new view point, MRS image quality assessment. *Acta Radiol Open*. 2022;11(2):20584601221077068.
9. Chernov MF, Ono Y, Muragaki Y, et al. Differentiation of high-grade and low-grade gliomas using pattern analysis of long-echo single-voxel proton magnetic resonance spectroscopy ((1)H-MRS). *Neuroradiol J*. 2008;21(3):338-349.
10. Vuori K, Kankaanranta L, Häkkinen AM, et al. Low-grade gliomas and focal cortical developmental malformations: differentiation with proton MR spectroscopy. *Radiology*. 2004;230(3):703-708.
11. Wang Q, Zhang J, Li F, Chen X, Xu B. The utility of magnetic resonance spectroscopy in frame-less stereotactic needle biopsy of glioma. *J Clin Neurosci*. 2021;88:102-107.
12. Avalos LN, Luks TL, Gleason T, et al. Longitudinal MR spectroscopy to detect progression in patients with lower-grade glioma in the surveillance phase. *Neurooncol Adv*. 2022;4(1):vdac175.
13. Murphy PS, Viviers L, Abson C, et al. Monitoring temozolomide treatment of low-grade glioma with proton magnetic resonance spectroscopy. *Br J Cancer*. 2004;90(4):781-786.
14. Zeng QS, Li CF, Liu H, Zhen JH, Feng DC. Distinction between recurrent glioma and radiation injury using magnetic resonance spectroscopy in combination with diffusion-weighted imaging. *Int J Radiat Oncol Biol Phys*. 2007;68(1):151-158.
15. Zhang H, Ma L, Wang Q, Zheng X, Wu C, Xu BN. Role of magnetic resonance spectroscopy for the differentiation of recurrent glioma from radiation necrosis: a systematic review and meta-analysis. *Eur J Radiol*. 2014;83(12):2181-2189.
16. Branzoli F, Marjańska M. Magnetic resonance spectroscopy of isocitrate dehydrogenase mutated gliomas: current knowledge on the neurochemical profile. *Curr Opin Neurol*. 2020;33(4):413-421.
17. Corbetta C, Di Ianni N, Bruzzone MG, et al. Altered function of the glutamate-aspartate transporter GLAST, a potential therapeutic target in glioblastoma. *Int J Cancer*. 2019;144(10):2539-2554.
18. Davanian F, Faeghi F, Shahzadi S, Farshifar Z. Diffusion tensor imaging for glioma grading: analysis of fiber density index. *Basic Clin Neurosci*. 2017;8(1):13-18.
19. El-Serougy L, Abdel Razek AA, Ezzat A, Eldawoody H, El-Morsy A. Assessment of diffusion tensor imaging metrics in differentiating low-grade from high-grade gliomas. *Neuroradiol J*. 2016;29(5):400-407.
20. Aliotta E, Nourzadeh H, Batchala PP, et al. Molecular subtype classification in lower-grade glioma with accelerated DTI. *AJNR Am J Neuroradiol*. 2019;40(9):1458-1463.
21. Shalan ME, Soliman AY, Nassar IA, Alarabawy RA. Surgical planning in patients with brain glioma using diffusion tensor MR imaging and tractography. *Egypt J Radiol Nucl Med*. 2021;52(1):110.
22. Jung H, Shah A, Li G. Use of diffusion tensor imaging in the resection of gliomas. *Curr Surg Rep*. 2014;2:69.
23. Tamura M, Kurihara H, Saito T, et al. Combining pre-operative diffusion tensor images and intraoperative magnetic resonance images in the navigation is useful for detecting

white matter tracts during glioma surgery. *Front Neurol*. 2022;12:805952.
24. Ius T, Mazzucchi E, Tomasino B, et al. Multimodal integrated approaches in low grade glioma surgery. *Sci Rep*. 2021; 11(1):9964.
25. Schilling KG, Nath V, Hansen C, et al. Limits to anatomical accuracy of diffusion tractography using modern approaches. *Neuroimage*. 2019;185:1-11.
26. Schilling KG, Rheault F, Petit L, et al. Tractography dissection variability: what happens when 42 groups dissect 14 white matter bundles on the same dataset? *Neuroimage*. 2021;243:118502.
27. Castellano A, Donativi M, Rudà R, et al. Evaluation of low-grade glioma structural changes after chemotherapy using DTI-based histogram analysis and functional diffusion maps. *Eur Radiol*. 2016;26(5):1263-1273.
28. Paldino MJ, Desjardins A, Friedman HS, Vredenburgh JJ, Barboriak DP. A change in the apparent diffusion coefficient after treatment with bevacizumab is associated with decreased survival in patients with recurrent glioblastoma multiforme. *Br J Radiol*. 2012;85(1012):382-389.
29. van den Elshout R, Scheenen TWJ, Driessen CML, Smeenk RJ, Meijer FJA, Henssen D. Diffusion imaging could aid to differentiate between glioma progression and treatment-related abnormalities: a meta-analysis. *Insights Imaging*. 2022; 13(1):158.
30. Abrigo JM, Fountain DM, Provenzale JM, et al. Magnetic resonance perfusion for differentiating low-grade from high-grade gliomas at first presentation. *Cochrane Database Syst Rev*. 2018;1(1):CD011551.
31. Hakyemez B, Erdogan C, Ercan I, Ergin N, Uysal S, Atahan S. High-grade and low-grade gliomas: differentiation by using perfusion MR imaging. *Clin Radiol*. 2005;60(4):493-502.
32. Ghodsi SM, Khoshnevisan A, Arjipour M, et al. Diagnostic efficacy of perfusion magnetic resonance imaging in supratentorial glioma grading. *Iran J Radiol*. 2018;15(2):e13696.
33. Law M, Young RJ, Babb JS, et al. Gliomas: predicting time to progression or survival with cerebral blood volume measurements at dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging. *Radiology*. 2008;247(2):490-498.
34. Snelling B, Shah AH, Buttrick S, Benveniste R. The use of MR perfusion imaging in the evaluation of tumor progression in gliomas. *J Korean Neurosurg Soc*. 2017;60(1):15-20.
35. Specht K. Current challenges in translational and clinical fMRI and future directions. *Front Psychiatry*. 2020;10:924.
36. Luna LP, Sherbaf FG, Sair HI, Mukherjee D, Oliveira IB, Köhler CA. Can preoperative mapping with functional MRI reduce morbidity in brain tumor resection? A systematic review and meta-analysis of 68 observational studies. *Radiology*. 2021;300(2):338-349.
37. Hall WA, Liu H, Truwit CL. Functional magnetic resonance imaging-guided resection of low-grade gliomas. *Surg Neurol*. 2005;64(1):20-27.
38. Gallamini A, Zwarthoed C, Borra A. Positron emission tomography (PET) in oncology. *Cancers (Basel)*. 2014;6(4): 1821-1889.
39. Parent EE, Benayoun M, Ibeanu I, et al. [^{18}F]Fluciclovine PET discrimination between high- and low-grade gliomas. *EJNMMI Res*. 2018;8(1):67.
40. Herholz K, Hölzer T, Bauer B, et al. 11C-methionine PET for differential diagnosis of low-grade gliomas. *Neurology*. 1998; 50(5):1316-1322.
41. Ghany AF, Hamed MA. The diagnostic value of dual phase FDG PET CT in grading of gliomas. *Egypt J Radiol Nucl Med*. 2015;46(3):701-705.
42. Miyake K, Ogawa D, Okada M, Hatakeyama T, Tamiya T. Usefulness of positron emission tomographic studies for gliomas. *Neurol Med Chir (Tokyo)*. 2016;56(7):396-408.
43. Shah AH, Madhavan K, Heros D, et al. The management of incidental low-grade gliomas using magnetic resonance imaging: systematic review and optimal treatment paradigm. *Neurosurg Focus*. 2011;31(6):E12.
44. Singhal T, Narayanan TK, Jacobs MP, Bal C, Mantil JC. 11C-methionine PET for grading and prognostication in gliomas: a comparison study with 18F-FDG PET and contrast enhancement on MRI. *J Nucl Med*. 2012;53(11):1709-1715.
45. Jansen NL, Suchorska B, Wenter V, et al. Dynamic 18F-FET PET in newly diagnosed astrocytic low-grade glioma identifies high-risk patients. *J Nucl Med*. 2014;55(2):198-203.
46. Carapella CM, Villani V, Chiaravalloti A, et al. The potential role of 18F-FDOPA pet imaging in low-grade gliomas. *J Clin Oncol*. 2014;32(15 suppl):2091.
47. la Fougère C, Suchorska B, Bartenstein P, Kreth FW, Tonn JC. Molecular imaging of gliomas with PET: opportunities and limitations. *Neuro Oncol*. 2011;13(8):806-819.
48. Pauleit D, Floeth F, Hamacher K, et al. O-(2-[18F] fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. *Brain*. 2005; 128(Pt 3):678-687.
49. Kunz M, Thon N, Eigenbrod S, et al. Hot spots in dynamic (18)FET-PET delineate malignant tumor parts within suspected WHO grade II gliomas. *Neuro Oncol*. 2011;13(3): 307-316.
50. Clinical Trials: Investigating New Treatments. Mayo Clinic. Accessed December 15, 2023. https://www.mayo.edu/research/clinical-trials/cls-20314928
51. Erdi YE. Limits of tumor detectability in nuclear medicine and PET. *Mol Imaging Radionucl Ther*. 2012;21(1):23-28.
52. Yandrapalli S, Puckett Y. SPECT imaging. In: *StatPearls* [Internet]. StatPearls Publishing; 2023.
53. Baillet G, Albuquerque L, Chen Q, Poisson M, Delattre JY. Evaluation of single-photon emission tomography imaging of supratentorial brain gliomas with technetium-99m sestamibi. *Eur J Nucl Med*. 1994;21(10):1061-1066.
54. Alam SS, Junaid S, Ahmed SM. Evaluation of technetium-99m glucoheptonate single photon emission computed tomography for brain tumor grading. *Asian J Neurosurg*. 2016; 11(2):118-128.
55. Park KJ, Kang SH, Park DH, Cho TH, Choe JG, Chung YG. Usefulness of thallium-201 SPECT for prediction of early progression in low-grade astrocytomas diagnosed by stereotactic biopsy. *Clin Neurol Neurosurg*. 2012;114(3):223-229.
56. Henze M, Mohammed A, Schlemmer H, et al. Detection of tumour progression in the follow-up of irradiated low-grade astrocytomas: comparison of 3-[123I]iodo-alpha-methyl-L-tyrosine and 99mTc-MIBI SPET. *Eur J Nucl Med Mol Imaging*. 2002;29(11):1455-1461.
57. Henze M, Mohammed A, Schlemmer HP, et al. PET and SPECT for detection of tumor progression in irradiated low-grade astrocytoma: a receiver-operating-characteristic analysis. *J Nucl Med*. 2004;45(4):579-586.
58. Shah AH, Snelling B, Bregy A, et al. Discriminating radiation necrosis from tumor progression in gliomas: a systematic review what is the best imaging modality? *J Neurooncol*. 2013;112(2):141-152.
59. Khangembam BC, Singhal A, Kumar R, Bal C. Tc-99m glucoheptonate single photon emission computed tomography-computed tomography for detection of recurrent glioma: a prospective comparison with N-13 ammonia positron emission tomography-computed tomography. *Indian J Nucl Med*. 2019;34(2):107-117.
60. Wang ZJ, Ohliger MA, Larson PEZ, et al. Hyperpolarized ^{13}C MRI: state of the art and future directions. *Radiology*. 2019;291(2):273-284.
61. Chaumeil MM, Radoul M, Najac C, et al. Hyperpolarized (13)C MR imaging detects no lactate production in mutant IDH1 gliomas: implications for diagnosis and response monitoring. *Neuroimage Clin*. 2016;12:180-189.

62. Autry AW, Gordon JW, Chen HY, et al. Characterization of serial hyperpolarized ^{13}C metabolic imaging in patients with glioma. *Neuroimage Clin*. 2020;27:102323.
63. Cui X, Bray S, Reiss AL. Functional near infrared spectroscopy (NIRS) signal improvement based on negative correlation between oxygenated and deoxygenated hemoglobin dynamics. *Neuroimage*. 2010;49(4):3039-3046.
64. Lee JY, Thawani JP, Pierce J, et al. Intraoperative near-infrared optical imaging can localize gadolinium-enhancing gliomas during surgery. *Neurosurgery*. 2016;79(6):856-871.
65. Li J, Ling J, Yao C. Recent advances in NIR-II fluorescence based theranostic approaches for glioma. *Front Chem*. 2022; 10:1054913.
66. Nagel AM, Bock M, Hartmann C, et al. The potential of relaxation-weighted sodium magnetic resonance imaging as demonstrated on brain tumors. *Invest Radiol*. 2011;46(9):539-547.
67. Poku LO, Phil M, Cheng Y, Wang K, Sun X. ^{23}Na-MRI as a noninvasive biomarker for cancer diagnosis and prognosis. *J Magn Reson Imaging*. 2021;53(4):995-1014.
68. Jiang S, Wen Z, Ahn SS, et al. Applications of chemical exchange saturation transfer magnetic resonance imaging in identifying genetic markers in gliomas. *NMR Biomed*. 2023; 36(6):e4731.
69. Ellingson BM, Bendszus M, Sorensen AG, Pope WB. Emerging techniques and technologies in brain tumor imaging. *Neuro Oncol*. 2014;16 Suppl 7(7 Suppl):vii12-vii23.
70. Hasan AMS, Hasan AK, Megally HI, Khallaf M, Haseib A. The combined role of MR spectroscopy and perfusion imaging in preoperative differentiation between high- and low-grade gliomas. *Egypt J Radiol Nucl Med*. 2019;50(1):72.
71. Lin K, Cidan W, Qi Y, Wang X. Glioma grading prediction using multiparametric magnetic resonance imaging-based radiomics combined with proton magnetic resonance spectroscopy and diffusion tensor imaging. *Med Phys*. 2022;49(7): 4419-4429.
72. Grech-Sollars M, Vaqas B, Thompson G, et al. An MRS- and PET-guided biopsy tool for intraoperative neuronavigational systems. *J Neurosurg*. 2017;127(4):812-818.
73. Li Y, Qin Q, Zhang Y, Cao Y. Noninvasive determination of the IDH status of gliomas using MRI and MRI-based radiomics: impact on diagnosis and prognosis. *Curr Oncol*. 2022;29(10):6893-6907.
74. Huang H, Lu J, Wu J, et al. Tumor tissue detection using blood-oxygen-level-dependent functional MRI based on independent component analysis. *Sci Rep*. 2018;8(1):1223.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tiefenbach, Lu, Haider, Komotar, Shah. Acquisition of data: Tiefenbach, Lu, Shah. Analysis and interpretation of data: Tiefenbach, Ivan, Komotar. Drafting the article: Tiefenbach, Lu, Haider. Critically revising the article: Lu, Palejwala, Haider, Ivan. Reviewed submitted version of manuscript: Lu, Metzler, Haider, Ivan, Komotar. Approved the final version of the manuscript on behalf of all authors: Tiefenbach. Statistical analysis: Komotar. Administrative/technical/material support: Metzler, Haider. Study supervision: Shah.

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