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TOPIC REVIEW & CLINICAL GUIDELINES

The role of imaging in the management of adults with diffuse low grade glioma

A systematic review and evidence-based clinical practice guideline

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Abstract

Question What is the optimal imaging technique to be used in the diagnosis of a suspected low grade glioma, specifically: which anatomic imaging sequences are critical for most accurately identifying or diagnosing a low grade glioma (LGG) and do non-anatomic imaging methods and/or sequences add to the diagnostic specificity of suspected low grade gliomas?

Target population These recommendations apply to adults with a newly diagnosed lesion with a suspected or histopathologically proven LGG.

Recommendation *Level II* In patients with a suspected brain tumor, the minimum magnetic resonance imaging (MRI) exam should be an anatomic exam with both T2 weighted and pre- and post-gadolinium contrast enhanced T1 weighted imaging.

Critical imaging for the identification and diagnosis of low grade glioma *Level II* In patients with a suspected brain tumor, anatomic imaging sequences should include T1 and T2 weighted and Fluid Attenuation Inversion Recovery (FLAIR) MR sequences and will include T1 weighted imaging after the administration of gadolinium based contrast. Computed tomography (CT) can provide additional information regarding calcification or hemorrhage, which may narrow the differential diagnosis. At a minimum, these anatomic sequences can help identify a lesion as well as its location, and potential for surgical intervention.

Improvement of diagnostic specificity with the addition of non-anatomic (physiologic and advanced imaging) to anatomic imaging *Level II* Class II evidence from multiple studies and a significant number of Class III series support the addition of diffusion and perfusion weighted MR imaging in the assessment of suspected LGGs, for the purposes of discriminating the potential for tumor subtypes and identification of suspicion of higher grade diagnoses.

Level III Multiple series offer Class III evidence to support the potential for magnetic resonance spectroscopy (MRS) and nuclear medicine methods including positron emission tomography and single-photon emission computed tomography imaging to offer additional diagnostic specificity although these are less well defined and their roles in clinical practice are still being defined.

Question Which imaging sequences or parameters best predict the biological behavior or prognosis for patients with LGG?

Target population These recommendations apply to adults with a newly diagnosed lesion with a suspected or histopathologically proven LGG.

Recommendation Anatomic and advanced imaging methods and prognostic stratification

Level III Multiple series suggest a role for anatomic and advanced sequences to suggest prognostic stratification among low grade gliomas. Perfusion weighted imaging,

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particularly when obtained as a part of diagnostic evaluation (as recommended above) can play a role in consideration of prognosis. Other imaging sequences remain investigational in terms of their role in consideration of tumor prognosis as there is insufficient evidence to support more formal recommendations as to their use at this time.

Question What is the optimal imaging technique to be used in the follow-up of a suspected (or biopsy proven) LGG?

Target population This recommendation applies to adults with a newly diagnosed low grade glioma.

Recommendations *Level II* In patients with a diagnosis of LGG, anatomic imaging sequences should include T2/FLAIR MR sequences and T1 weighted imaging before and after the administration of gadolinium based contrast. Serial imaging should be performed to identify new areas of contrast enhancement or significant change in tumor size, which may signify transformation to a higher grade. *Level III* Advanced imaging utility may depend on tumor subtype. Multicenter clinical trials with larger cohorts are needed. For astrocytic tumors, baseline and longitudinal elevations in tumor perfusion as assessed by dynamic susceptibility contrast perfusion MRI are associated with shorter time to tumor progression, but can be difficult to standardize in clinical practice. For oligodendrogliomas and mixed gliomas, MRS may be helpful for identification of progression.

Keywords Low grade glioma · Magnetic resonance imaging · Prognosis · Diagnostic specificity · Guidelines

Imaging rationale

Infiltrative low grade gliomas (LGG) are, diffuse, slow growing, intra-axial, primary brain tumors. They typically occur in individuals in the second to fourth decade of life [1–4] Histopathologically these tumors include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas, all of which are classified as grade 2 tumors by the World Health Organization (WHO). The natural history of these tumors is slow growth over time, with ultimate transformation to a higher grade tumor. Accurate diagnosis of these tumors (distinction of LGG from higher grade tumors) and subsequent appropriate management is critically important, and the contribution of imaging to both measures of diagnosis and prognosis is increasingly recognized.

LGG are typically identified on an anatomic MRI study as a non-enhancing mass lesion, hypointense on T1 weighted imaging and hyperintense on T2 and FLAIR imaging sequences. The relevance of imaging in the accurate diagnosis of LGG predates MR imaging technology, as tumor size, presence of calcification, and the presence or absence of contrast enhancement on CT have been recognized for decades as having relevance in predicting the histological classification of primary brain tumors [5]. However, the advent of MR imaging has not only increased the incidence of early diagnosis of LGG [1, 4], but also offered additional imaging sequences that could contribute to the non-invasive management of LGG. Nuclear medicine techniques including PET and SPECT imaging have also been increasingly considered as potential markers for diagnosis and prognostication in LGG.

For the purposes of these guidelines, we focus on patients with infiltrative, WHO II, LGG. Histopathologically these tumors include astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas, all of which are classified as grade 2 tumors by the World Health Organization (WHO). Distinguishing these histological subtypes and distinguishing LGG from higher grade tumors can impact decisions regarding prognosis and subsequent management. Particularly in situations where an extensive surgical resection is not possible (tumor infiltration of eloquent functional cortex, for example), the potential for inaccurate diagnosis is significant (quantified as high as 28 % in some series). Imaging methods including anatomic and physiologic sequences (diffusion and perfusion weighted MRI) as well as nuclear medicine techniques offer an adjunct to histopathological analysis and can help with sub-classification of LGG for diagnostic and prognostic measures. In addition, methods such as fMRI and diffusion tensor imaging (DTI) can aid in preoperative planning and aid in the achievement of a maximal safe resection when a tumor is located in functional cortex [6].

The purpose of this guideline is to assess the ability of the most widely used imaging techniques, primarily MRI and PET/radiotracer techniques, to accurately diagnose a LGG (distinguishing this from other tumor types, and from more aggressive primary brain tumors) while simultaneously aiding in the identification of subtypes of tumors for assistance with prognosis and management decisions. We also seek to identify the best imaging sequences for serial longitudinal follow up of suspected or biopsy proven LGG. This review has been structured so that the literature that focuses on each individual question (diagnosis, prognosis, and longitudinal follow-up) is subdivided based on the imaging techniques involved and divided broadly into magnetic resonance imaging based techniques and PET and SPECT radiotracers as outlined below.

MRI techniques

1. Anatomic Imaging sequences (T2, FLAIR, T1-pre and T1-post contrast, T2*/susceptibility weighted imaging SWI)
2. Perfusion weighted imaging (PWI)
3. Diffusion weighted imaging (DWI)/diffusion tensor imaging (DTI)
4. Magnetic resonance spectroscopy (MRS)

Nuclear medicine

1. [18F]Fluoro-deoxy-glucose (FDG) PET
2. [11C]Methionine (MET) PET
3. [18F]Fluoro-ethy L-tyrosine (FET) PET
4. [201]Thallium SPECT

The overall objectives of this guideline are:

1. To systematically review the evidence available for the imaging of adult patients with LGG.
2. To make recommendations based on this evidence for the role of imaging in the management of these patients specifically considering the role of imaging in:
   a. Diagnostic specificity (distinguishing LGG from higher grade tumors)
   b. Prognosis (identifying subtypes of LGG more likely to have an aggressive clinical course).
   c. Longitudinal management of patients with LGG

Imaging methodology

Literature review

The following databases were searched from 1990 to 2012 using low-grade glioma and surgery relevant search MeSH and non-MeSH search terms: PubMed (National Library of Medicine, http://www.ncbi.nlm.nih.gov) was searched using Endnote® (Thomas Reuters, Inc. http://www.endnote.com) using "ALL FIELDS" and entering "GLIOMA" AND "LOW GRADE" AND "IMAGING" without date limits for a broad initial search. Additional subsequent searches were performed searching "LOW GRADE GLIOMA" and other more specific imaging based terms including "MRI"/"MAGNETIC RESONANCE IMAGING", "CT"/"COMPUTED TOMOGRAPHY", "PET"/"POSITRON EMISSION TOMOGRAPHY", AND "DIFFUSION", "PERFUSION", "SPECTROSCOPY", "FDG", "FET", "MET", AND "SPECT". Potential references were restricted to manuscripts published in the interval between January, 1990 and December, 2012. The results were then hand searched based on the titles and abstracts to exclude laboratory only studies and titles not on topic. To answer our questions related to prognosis, terms of "DIAGNOSIS", "PROGNOSIS", and "NEOPLASM GRADING" were added to the search strategy. Similar search strategies were used to search additional databases including the Cochrane Database of Systematic Reviews, the DARE (Database of Abstracts of Reviews of Effect), and the Cochrane Central Register of Controlled Trials. This overall search strategy yielded a total of 1,297 unique citations.

Article inclusion and exclusion criteria

The 1297 citations were manually reviewed by the team with specific inclusion and exclusion criteria as outlined below. Four independent reviewers considered abstracted and/or full text data for each article and the two sets of data were compared for agreement by a third party. Inconsistencies were re-reviewed and disagreements were resolved by consensus. Citations that considered adult patients focusing on imaging in the diagnosis, prognostic or longitudinal evaluation of LGG were considered. We allowed that manuscripts could focus on a comparison of imaging features of LGG with high grade glioma or other tumor types. Abstracts that focused on a pediatric population, therapeutic studies, case reports noting imaging features of unusual tumor types, articles focusing on brainstem gliomas or spinal cord tumors, or those focusing on imaging and correlative histopathology markers as the primary subject were not included for review. This manual secondary review resulted in a list of 199 references that appeared best suited to answer the questions—those 199 references were pulled for formal paper review and possible inclusion in evidence tables to help answer the key questions outlined above.

Study selection and quality assessment

Following broad screening for relevance, three independent reviewers evaluated citations and full text screening of potentially relevant papers using a priori criteria for data extraction on a standardized form. Disagreements were resolved with the involvement of a third reviewer, followed by primary re-review until agreement was achieved.

Evidence classification and recommendation levels

Both the quality of the evidence and the eventual strength of the recommendations generated by this evidence were graded according to a three-tiered system for assessing studies addressing diagnostic testing as approved by the American Association of Neurological Surgeons (AANS)/

Congress of Neurological Surgeons (CNS) Joint Guidelines Committee on criteria (Table 1). (Reference to intro/methods chapter needs to be added before publication). Imaging studies that considered markers of diagnostic specificity were reviewed using these guidelines, considering a histopathological diagnosis as a "gold standard".

In order to have class I evidence and/or a level I recommendation regarding imaging, data must be from one or more well-designed clinical studies in a diverse population using a "gold standard" reference test. Well-designed clinical studies should include a blinded evaluation appropriate for the diagnostic applications, sensitivity, specificity, positive and negative predictive values, and where applicable, likelihood ratios. Class II evidence and level II recommendations require that evidence be provided by one or more well-designed clinical studies of a *restricted* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios. For Class III evidence and/or a Level III recommendation, data is provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios.

Imaging series that consider these same markers with respect to prognosis were reviewed considering five technical criteria. If all five of these criteria are satisfied, the evidence is classified as Class I. If four out of five are satisfied, the evidence is Class II, and if less than 4 are satisfied, it is Class III:

- Was a well-defined representative sample of patients assembled at a common (usually early) point in the course of their disease?
- Was patient follow-up sufficiently long and complete?
- Were objective outcome criteria applied in a "blinded" fashion?
- If subgroups with different prognoses were identified, was there adjustment for important prognostic factors?
- If specific prognostic factors were identified, was there validation in an independent "test set" group of patients?

Conflict of interest

Low Grade Glioma Guidelines Task Force members were required to report all possible COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of Task Force Members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs.

Imaging scientific foundation

Overall, 65 publications met the eligibility criteria and are included in the evidentiary tables below. Tables 1-9 reference specific imaging modalities and the question of diagnostic specificity. Tables 10-13 reference prognosis, and tables 14-17 reference serial imaging. These included 16 publications focused on anatomic imaging sequences, 16 on MRI perfusion techniques, 7 on MR diffusion weighted imaging techniques, 7 on MR spectroscopy, 7 with mixed advanced MR imaging and 12 on PET and SPECT techniques. The details of this evidence are described in detail below.

Specifically as regards levels of evidence, although numerous series compared imaging markers with histopathology (as a gold standard) to consider diagnostic specificity, none were prospective continuous series in a large enough diverse population to classify the study as Class I. In cases where large series were able to show

Table 1 Classification of evidence on diagnosis

Class I evidence Level I (or A) recommendation	Evidence provided by one or more well-designed clinical studies of a *diverse* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class II evidence Level II (or B) recommendation	Evidence provided by one or more well-designed clinical studies of a *restricted* population using a "gold standard" reference test in a blinded evaluation appropriate for the diagnostic applications and enabling the assessment of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios
Class III evidence Level III (or C) recommendation	Evidence provided by expert opinion or studies that do not meet the criteria for the delineation of sensitivity, specificity, positive and negative predictive values, and, where applicable, likelihood ratios

Table 2 Diagnostic specificity: anatomic imaging

Author	Description of study	Data class	Conclusions
Nguyen et al. [11]	46 patients with pathologically proven glioma—retrospective consideration of preoperative anatomic MRI and correlation with tumor grade. Neuroradiology analsyis performed by two observers blinded to histopathological grade. Note this study also considered DCE imaging (this data considered elsewhere)	Class 2	Conventional imaging data provides Sens, Spec, PPV and NPV values of 97, 67, 92, and 86 % respectively
Kim et al. [10]	58 patients with cerebral astrocytoma evaluated prospectively with anatomic MR imaging and PASL. Sensitivity and specificity of PASL parameters compared with those seen with conventional imaging alone. Histopathology review blinded to image analysis data	Class 2	Sensitivity, specificity, PPV and NPV for diagnosis of HGG (compared with LGG) using anatomic imaging was 77, 73, 79, and 70 %, respectively
Law et al. [9]	Retrospective analysis of 160 subjects with biopsy proven glioma and preoperative imaging including anatomic, PWI and MRS MRI. Comparison of diagnostic sensitivity and specificity of anatomic imaging as compared with MRS and PWI. Neuroradiologists blinded to anatomic imaging data and to histopathology data performed the perfusion imaging analysis	Class 2	Anatomic imaging provides Sens, Spec, PPV, NPG for distinguishing HGG from LGG as 72.5, 65, 86, and 44 %
Mihara et al. [7]	In a population of 43 subjects with pathologically proven glioma, six anatomic imaging parameters were considered (by three neuroradiologists blinded to pathology) retrospectively for correlation to histopathologic diagnosis Multiple regression analysis used to compare imaging characteristics with histopathological diagnosis. No sensitivity or specificity data	Class 3	A semiautomated grading system allows improved non invasive tumor grading of LGG, AA and GBM, with maximum accuracy of 91, 83 and 88 % respectively, improved upon the sensitivity and specificity of qualitative anatomic diagnoses

statistically significant data with blinded comparisons, this sample size was most often the reason for downgrading of studies. This is not uncommon in imaging studies, where still technological limitations prevent the large sample sizes that would be required to provide class I evidence. Many series provided interesting and useful consideration of imaging biomarkers but did not review data in a blinded fashion, or were not able to provide enough statistical analyses to provide sensitivity, specificity or predictive data and were thus downgraded to Class III. In all of the studies that provided data regarding imaging markers and prognosis, only Class III evidence was achieved, largely because of a lack of test set for comparison, and again the relatively small sample size in these patient populations.

Imaging and diagnostic specificity: low grade glioma

Anatomic MR imaging

Most recent imaging studies do not specifically reference the diagnostic specificity of anatomic MR imaging sequences, although historically studies have considered aspects of anatomic imaging, particularly focusing on the presence or absence of contrast enhancement on CT or MR imaging studies. However, a total of four studies provide evidence for the use of anatomic imaging features in considering LGG diagnostic specificity. Two of these provide Class II evidence and two provide Class III evidence. A study by Mihara et al. [7] suggests that a semi-automated grading system taking into account anatomic imaging features allows improved noninvasive tumor grading of LGG, and high grade glioma (HGG) subtypes of anaplastic astrocytoma (AA) and glioblastoma (GBM), with maximum accuracy of 91, 83 and 88 % respectively, and that this improved upon the sensitivity and specificity of qualitative anatomic diagnoses. This study highlights the relevance of consideration of anatomic features supported by numerous reviews of LGG [1–3, 8], and offers Class III evidence suggesting that a T1 weighted MR sequence acquired following the administration of gadolinium (Gd) contrast is important for the establishment of a stratification for the purposes of diagnosis. The importance of inclusion of T1 + Gd and T2 weighted imaging is relatively established in the literature. A number of additional studies have evaluated the utility of anatomic imaging sequences including the use of T1 + Gd, T2 and FLAIR sequences in

Table 3 Diagnostic specificity: perfusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Nguyen et al. [11]	46 patients with pathologically proven glioma—retrospective consideration of preoperative anatomic and DCE MRI and correlation with tumor grade. Neuroradiology analysis performed by two observers blinded to histopathological grade	Class II	Ktrans can be a useful imaging parameter to discriminate between LGG and HGG. Conventional imaging data provides Sens, Spec, PPV and NPV values of 97, 67, 92, and 86 % respectively. Using Ktrans of >0.018 min (−1), Sens, Spec, PPV and NPV values of 89, 75, 94, and 62 % were measured respectively; inter-observer variability was measured with a k value of 0.76
Morita et al. [10]	17 patients with non-enhancing astrocytoma; DSC MRI performed prior to surgery retrospectively considered to determine whether PWI could assist with distinction between grade in nonenhancing gliomas. Not a blinded comparison	Class III	rCBV is significantly higher in high grade nonenhancing gliomas compared with low grade tumors. A cutoff of 0.94 yields a sensitivity of 91 % and specificity of 100 %. PPV/NPV data not provided/extractable
Narang et al. [26]	21 patients with preoperative perfusion CT and dx of OD compared retrospectively with 32 patients with astroglial neoplasms	Class III	Low grade OD show lower CBV compared with high grade OD, but these changes were a trend and not statistically significant. Perfusion CT not useful for grading OD. sensitivity/specificity data not discussed
Kim et al. [10]	58 patients with cerebral astrocytoma evaluated prospectively with anatomic MR imaging and PASL. Sensitivity and specificity of PASL parameters were compared with those seen with conventional imaging alone. Histopathology review blinded to image analysis data	Class II	Sensitivity, specificity, PPV and NPV for diagnosis of HGG (compared with LGG) using anatomic imaging was 77, 73, 79, and 70 %, respectively; for PASL parameter (tumor perfusion signal intensity) the same values were 82, 96, 97 and 81 % respectively; notation was made, however that inter-observer variability was measured with a k value of 0.72
Emblem et al. [25]	Prospective study of 52 patients with histologically confirmed gliomas and preoperative MR imaging with DSC MRI at 1.5. All study observers were blinded Histogram analysis (using four separate radiology analyses combined into a single mean histogram) used to consider HGG, LGG and ODG subtypes of LGG	Class III	Improved sensitivity and specificity for identification of OGD subtype of LGG using a histogram analysis (100 % sensitive and 91 % specific for oligodendrogliomas without LOH at 1p19q) from other tumor subtypes. Histogram analysis did not allow distinction of other tumor subtypes. No other sensitivity or specificity data provided for diagnostic specificity
Pauliah et al. [17]	25 patients with glioma assessed with DSC and DCE MRI prior to surgery. Retrospectively considered to see whether preoperative imaging could be used to distinguish LGG from HGG. Histopathologist blinded to imaging data	Class III	rCBV and rCBF can be used to discriminate between LGG and HGG. Sensitivity and Specificity data not provided in results/review
Chaskis et al. [27]	55 patients with newly diagnosed glioma prospectively considered with anatomic MR imaging and PWI; consideration of use of PWI in both biopsy and surgical resection as aids to improve biopsy targeting and preoperative diagnosis	Class III	Perfusion weighted imaging can be used in preoperative assessment of gliomas and used to guide biopsy; this aids in limiting the under diagnosis in situations of stereotactic biopsy. sensitivity/specificity data not provided
Ding et al. [21]	22 patients with histologically proven glioma prospectively underwent CT perfusion prior to surgery with consideration of rCBV and rPS as measured by CTP and correlation with tissue diagnosis (radiologist and histopathologists were blinded to comparison results)	Class III	rCBV and rPS (permeability map) can discriminate between LGG and HGG. Optimal rCBV and rPS to distinguish LGG from HGG were 3.78 and 5.04, respectively. Sensitivity and specificity of 100 and 83 % for LGG. PPV and NPV not calculated
Law et al. [20]	Retrospective consideration of 3 perfusion data analysis methods in 74 patients with gliomas considering diagnostic accuracy. Comparison made with histopathological diagnosis. Reviewers not clearly blinded to corresponding data types	Class III	rCBV is the best parameter for prediction of tumor grade; combination of rCBV and ktrans improves diagnostic specificity. Sensitivity and specificity data were obtained using ROC analysis

Table 3 continued

Author	Description of study	Data class	Conclusions
Hakyemez et al. [15]	33 patients with glioma who underwent DSC imaging prior to surgery were retrospectively considered to see whether preoperative imaging could be used to distinguish LGG from HGG. Not blinded analysis	Class III	rCBV and rCBF can be used to discriminate between LGG and HGG; statistically significant difference between these two groups for both imaging parameters. Cutoff value for rCBV of 2.0 and rCBF of 1.3 was suggested, yielding sensitivity and specificity of 100 and 91 %, respectively
Lev et al. [23]	Retrospective consideration of 30 subjects with preoperative PWI and tissue diagnosis. Consideration of how PWI aids in diagnostic specfiicity. Not blinded analysis	Class III	Elevated rCBV is a sensitive but not specific marker for high grade hitopathology (Sens, Spec of 96 %, 60 % for HGG vs LGG respectively): all HGG have rCBV above 1.5; notation that elevated rCBV can be seen in grade 2 ODG
Maia et al. [22]	Prospective consideration of perfusion weighted imaging in 21 patients with low and intermediate grade gliomas; consideration of whether PWI helped to reduce sampling error in biopsy. Not blinded analysis	Class III	An rCBV cutoff of 1.2 gave a sensitivity and specificity of 80 and 100 % respectively to help discriminate between diffuse low grade gliomas and other tumor types (higher rCBV suggestive of grade 2 ODG or AA)
Law et al. [9]	Retrospective analysis of 160 subjects with biopsy proven glioma and preoperative imaging including anatomic, PWI and MRS MRI. Comparison of diagnostic sensitivity and specificity of anatomic imaging as compared with MRS and PWI. Neuroradiologists blinded to anatomic imaging data and to histopathology data performed the perfusion imaging analysis	Class II	rCBV measures and metabolite ratios both individually and in combination improve the sensitivity and PPV when compared with conventional MR imaging alone in determining glioma grade. (Anatomic imaging provides Sens, Spec, PPV, NPG for distinguishing HGG from LGG as 72.5, 65, 86, and 44 %; rCBV threshold of 1.75 provides values of 95, 57, 87, and 79 %)
Warmuth et al. [13]	Retrospective consideration of ASL and DSC MRI in 36 subjects with histologically proven gliomas. Consideration of correlation of each imaging technique with histolopathological data (not blinded analysis)	Class III	ASL and PWI both allow for discrimination between HGG and LGG with improved accuracy over standard anatomic imaging parameters

distinguishing LGG from HGG, particularly as a baseline for comparison with more advanced imaging parameters. Specifically, in 2003, Law et al. [9] offered Class II data regarding anatomic imaging data and identified values for using anatomic imaging to distinguish HGG from LGG, measuring sensitivity, specificity, PPV and NPV as 72.5, 65, 86, and 44 %, respectively. Kim et al. [10] studied 58 patients with cerebral astrocytoma and noted (at the Class II level) that the sensitivity, specificity, PPV and NPV for diagnosis of HGG (compared with LGG) using anatomic imaging was 77, 73, 79, and 70 %, respectively. Nguyen et al. [11] found that conventional anatomic imaging data provides sensitivity, specificity, PPV and NPV values of 97, 67, 92, and 86 % respectively in a series of 46 patients with pathologically proven glioma in a third Class II series supporting the use of anatomic imaging, specifically T1 + Gd sequences in addition to non-contrast enhanced T1, T2 and FLAIR sequences in the diagnosis of LGG.

Perfusion weighted MR imaging

Nineteen studies meeting the inclusion criteria described above considered the utility of perfusion weighted imaging (PWI), also known as dynamic susceptibility contrast (DSC) imaging in distinguishing LGG from higher grade tumors and in the discrimination of tumor subtypes. A total of four of these studies [9–12] provided Class II evidence to suggest a benefit to perfusion weighted imaging in measures of diagnostic specificity, and the remaining fifteen provided Class III evidence. Fourteen studies considered PWI as an independent imaging parameter and five considered PWI in concert with other imaging parameters.

In 2003 Law et al. [9] considered 160 subjects with biopsy proven glioma and preoperative imaging including anatomic and PWI MRI retrospectively. A comparison was made between the diagnostic sensitivity and specificity of anatomic imaging as compared with advanced imaging sequences. Their results suggested that the derived DSC parameter of relative cerebral blood volume (rCBV) measures improve the sensitivity and PPV when compared with conventional MR imaging alone in determining glioma grade. An rCBV threshold of 1.75 provides sensitivity, specificity, PPV, NPG values of 95, 57, 87, and 79 % for distinguishing HGG from LGG. Warmuth et al. [13] performed a retrospective consideration of arterial spin labeling (ASL) and DSC MRI in 36 subjects with

Table 4 Diagnostic specificity: diffusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Jakab et al. [35]	40 patients with primary brain tumors considered retrospectively. DWI with b = 1000 considered in all patients and ADC compared with histological grade. Imaging data not blinded to histopathological analysis	Class III	Histogram analysis methods for DWI yielded separation of LGG from HGG with sensitivity and specificity of 88.5 and 85.7 %. PPV and NPV data not provided
Jolapara et al. [36]	38 patients with infiltrating glioma assessed retrospectively to compared ADC with histopathology data. No blinding of histopathology data from imaging data	Class III	LGG showed maximum FA values of < 0.4 with sensitivity and specificity of 100 %
White et al. [37]	34 subjects with primary brain tumors considered with DWI measures. Mean, Max and Min FA considered as measure to distinguish LGG from HGG. Imaging analysis blinded to histopathology diagnosis	Class III	FA max, FA range and SD max thresholds to distinguish LGG from HGG were 0.17, 0.0917, and 0.04 yielded sensitivity and specificity values of 92 and 78, 96 and 78 and 100 and 100 % respectively. PPV and NPV data not provided
Khayal et al. [31]	Retrospective analysis of 53 patients with histologically proven LGG. Consideration of DTI measures to distinguish subtypes of LGG. Imaging analysis not blinded to histological subtype	Class III	ADC and FA can be used to distinguish between LGG subtypes, although sensitivity and specificity data not provided
Alvarez-Linera et al. [28]	Prospective consideration of 54 patients with histologically proven HGG and LGG, considering DWI with standard and high b values in comparison with tumor grade. Neuroradiologist's assessment performed while blinded to pathological diagnosis	Class II	Notation made that inclusion of high b value diffusion measures (b = 3000) gives increased sensitivity/specificity than use of b = 1000 alone. Sensitivity, specificity, PPV and NPV values were 100, 10.5, 67.3 and 100 % for b = 1000 and 97.1, 94.7, 97.1, and 94.7 % for b = 3000
Lee et al. [34]	Retrospective analysis of 16 patients with imaging characteristics consistent with LGG on anatomic imaging (from overall population of 118 subjects with primary brain tumors) considered with DWI to see whether minimum ADC distinguishes LGG from HGG. Imaging analysis not blinded from histopathological grade	Class III	min ADC of 1.055 yielded best distinction of LGG from HGG (sensitivity and specificity of 87.5 and 79 %). PPV and NPV data not available
Tozer et al. [30]	Retrospective analysis of 27 patients with biopsy proven LGG—consideration of whether DWI metrics can distinguish between LGG subtypes of AC, OD, or OA. Imaging analysis not blinded from histopathological diagnosis	Class III	ADC histogram analysis can aid in the distinction between LGG subtypes. Sensitivity and specificity data not provided

histologically proven gliomas. They found that ASL and PWI both allow for discrimination between HGG and LGG with improved accuracy over standard anatomic imaging parameters. In 2004, Batra et al. [14] considered 22 patients with primary brain tumors prospectively with DSC MRI and found that rCBV was useful in distinguishing histopathological grade of non-contrast enhancing gliomas. Quantitative thresholds and sensitivity or specificity data were not suggested as aids to the implementation of the parameter in clinical practice. Hakyemez et al. [15] studied 33 patients with glioma who underwent DSC imaging prior to surgery retrospectively to see whether preoperative imaging could distinguish LGG from HGG and noted that rCBV and rCBF can be used to discriminate between LGG and HGG; a statistically significant difference between these two groups was noted for both imaging parameters. Cutoff values for rCBV of 2.0 and rCBF of 1.3 were suggested without a specific consideration of sensitivity and specificity. Fan et al. [16] considered PWI prospectively in 22 subjects with nonenhancing supratentorial gliomas. rCBV was considered as a method for identification of higher grade nonenhancing tumors. Higher rCBVs were described seen in solid and peritumoral regions of anaplastic gliomas, but not in LGG. Specific thresholds for diagnosis were not identified. Pauliah et al. [17] studied 25 patients with glioma, obtaining DSC and DCE MRI prior to surgery. They found that CBV and rCBF could be used to discriminate between LGG and HGG, although sensitivity and specificity data were not provided. In 2009, Arvinda et al. evaluated rCBV as a diagnostic

Table 5 Diagnostic specificity: MR spectroscopy

Author	Description of study	Data class	Conclusions
Liu et al. [42]	33 patients with histologically proven gliomas were considered with MRS prior to surgery. DWI was used to guide placement of single voxel MRS ROI in consideration of Cho/Cr and Cho.NAA ratios for distinguishing HGG from LGG. Observers were not blinded to histopathology during the analysis	Class III	DWI guided single voxel MRS has potential value for the preoperative prediction of glioma grade. A threshold value of 2.01 for Cho.Cr yields a sensitivity, specificity, PPV and NPV of 86, 90, 95, and 75 % respectively. Threshold values of 2.49 for Cho/Naa and 0.97 for NAA/Cr were suggested as well with similar sensitivities. Cho/Cr was slightly better than the other two, however
Zeng et al. [40]	Prospective study of 39 subjects with primary brain tumors evaluated preoperatively with anatomic MR imaging and MRS. Correlations seen between MRS parameters and tumor grade were considered. Image analysis was not performed by reviewers blinded to pathology	Class III	Metabolite ratios of low grade gliomas were found to be significantly different than high grade gliomas using multivoxel 3D spectroscopy. The ratios Cho/Cr, Cho/NAA, and NAA/Cr were considered, with threshold values of 2.04, 2.20, and 0.72 found to be most sensitive based upon ROC analysis. Sensitivity, Specificity, PPV and NPVs for each respective anaysis were: Cho:Cr—84, 83, 91 and 71 %, Cho:NAA—88, 67, 85, and 73 %, and NAA:Cr—76, 67, 83 and 57 %
Senft et al. [39]	63 subjects with suspected primary brain tumors considered prospectively in the study. MRS and conventional MR imaging considered as measures to distinguish tumor type. Imaging measurements not blinded to histopathological diagnosis	Class III	Maximum Choline values were useful to distinguish LGG from HGG with threshold of 2.02 yielding sensitivity and specificity values of 86 and 78 %, respectively
Bulakbasi et al. [38]	49 subjects with brain tumors including 8 HGG and 12 LGG among other tumor types were prospectively considered with MRS prior to surgery. Correlations between imaging parameters and histopathology markers were considered. Imaging analysis was performed by observers not blinded to histopathology	Class III	ADC measured at tumor core combined with metabolite ratios from MRS were useful in distinguishing benign from malignant tumors. Specifically, increased Lactate/Cr ratios were useful in distinguishing between LGG and HGG. Sensitivity and specificity data were not provided

Table 6 Diagnostic specificity: diffusion and perfusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Liu et al. [19]	52 subjects with newly diagnosed gliomas, evaluated preoperatively with DTI and DSC imaging were considered retrospectively to see whether preoperative imaging could be used to distinguish LGG from HGG. Neuropathology review was considered in a blinded fashion in comparison with imaging data	Class III	Combination of FA mean and max values provide improved diagnostic accuracy in distinguishing LGG from HGG. Cutoffs for FA mean of 0.13 and for FA mx of 0.22 yielded sensitivity and specificity of 93 and 69 % (FA mean) and 100 and 77 % (FA mx). rCBV cutoff of 1.75 yields sensitivity and specificity of 60 % and 59 % (not felt to be as useful. PPV and NPV not available
Arvinda et al. [12]	51 subjects with histologically confirmed glioma retrospectively identified. All subjects had been valuated with DWI and PWI prior to surgery. Retrospectively imaging data compared with histopathology results (observers blinded to imaging data) to see whether preoperative imaging could be used to distinguish LGG from HGG	Class II	Threshold of 2.9 for rCBV and ADC of 0.98 were identified as determinants of HGG (compared with LGG) with sensitivity, specificity, PPV and NPV of 95, 94, 90, and 97 % for rCBV and 90, 87, 82, and 93 % respectively for ADC
Fan et al. [16]	DWI and PWI considered prospectively in 22 subjects with nonenhancing supratentorial gliomas. ACD and rCBV considered as ways to distinguish higher grade nonenhancing tumors	Class III	lower ADC seen in solid portions of anaplastic gliomas, but not in LGG; higher rCBV seen in solid and peritumoral regions of anaplastic gliomas, but not in LGG. Specific thresholds were not suggested

imaging parameter in 51 subjects with histologically confirmed glioma. A threshold of 2.9 for rCBV was identified as a determinant of HGG (compared with LGG) with sensitivity, specificity, PPV and NPV of 95, 94, 90, and 97 %. Morita et al. [18] reviewed 17 patients with nonenhancing astrocytoma analyzing their preoperative DSC MRI to determine whether PWI distinguish grade in nonenhancing gliomas. They found that rCBV was

Table 7 Diagnostic specificity: MR spectroscopy and diffusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Server et al. [29]	MRS and DWI considered prospectively in 74 subjects with histopathologically proven glioma. ADC and metabolite ratios were considered to determine whether these imaging parameters could be used to distinguish LGG from HGG. Imaging analysis was performed by observers blinded to each subject's histopathology data	Class II	DWI and MRS provide measures that can distinguish HGG from LGG. A threshold ADC of 1.07 and threshold values of 1.35 and 1.78 for peritumoral Cho/Cr and Cho/NAA ratios yielded sensitivity, specificity, PPV and NPV of 80, 60, 89, and 43 % (ADC), 83, 85, 42, and 98 % (Cho/Cr), and 100, 57, 23, and 100 % (Cho/NAA) for HGG, all suggesting that the combination of DWI and MRSI can increase the accuracy of preoperative imaging in determination of glioma grade
Zou et al. [41]	30 patients with supratentorial gliomas were prospectively evaluated with anatomic, DW and MRS MR imaging. The tumor grades determined using these three methods were compared with those given with histopathological analysis. Imaging analysis was performed by two neuroradiologists blinded to the pathology results	Class II	Differences between LGG and HGG were seen for Cho/Cr, NAA/Cr, and NAA/Cho ratio ($p < 0.0.01$) and ADC ($p < 0.01$). Threshold values for tumor NAA/Cr, NAA/Cho and ADC provided sensitivities, specificity, PPV and NPV that were improved compared with those suggested by anatomic imaging alone. NAA/Cho and ADC were the parameters which were found to contribute most significantly to the differences between the two groups

Table 8 Diagnostic specificity: MR spectroscopy and perfusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Spampinato et al. [24]	Retrospective study of 22 patients with oligodendroglioma who underwent both DSC and MRS imaging prior to surgery. Imaging parameters were correlated with tumor grade. No blinded analysis was performed	Class III	Statistically significant differences were seen between mean rCBV and choline/Cr ratios for LGG versus HGG. An rCBV threshold value of 2.14 provided the highest sensitivity and specificity (100 and 86 %). A Choline/Creatine ratio threshold of 2.33 offered the greatest sensitivity and specificity (100 and 83.3 %)
Batra et al. [14]	22 patients with primary brain tumors considered prospecitvely. DSC and MRS imaging considered in comparison with tumor grade. Analysis not blinded	Class III	rCBV, and Choline:Creatine ratios were felt to be useful in distinguishing histopathological grade of non-contrast enhancing gliomas. Thresholds and sensitivity/specificity data not suggested

significantly higher in high grade nonenhancing gliomas compared with low grade tumors, suggesting that a cutoff rCBV of 0.94 yielded a sensitivity of 91 % and a specificity of 100 %. In 2011, Liu et al. [19] considered PWI as a marker of diagnostic specificity in 52 subjects with newly diagnosed gliomas, noting that use of an rCBV cutoff of 1.75 yielded sensitivity and specificity values of 60 % and 59 % (they commented that they did not feel that the marker was as useful as others considered in their series).

While rCBV is the most common PWI parameter studied in consideration of diagnostic specificity for LGG, additional blood flow imaging methods have been applied to this question. Specifically, in 2006, Law et al. [20] performed a retrospective consideration of 3 perfusion data analysis methods in 74 patients with gliomas considering diagnostic accuracy. They found that rCBV was the best parameter for prediction of tumor grade; while a combination of rCBV and k-trans improved diagnostic specificity. Another less readily utilized perfusion imaging method is CT perfusion (CTP). Ding et al. [21] prospectively studied 22 patients with histologically proven glioma with CT perfusion prior to surgery. rCBV and rPS as measured by CTP were correlated with tissue diagnosis. rCBV and rPS (permeability map) could discriminate between LGG and HGG. An optimal rCBV and rPS to distinguish LGG from HGG were reported as 3.78 and 5.04, respectively. In 2008, Kim et al. [10] considered Pulsed Arterial Spin Labeling (PASL) as a methodology for considering blood flow parameters, evaluating 58 patients with cerebral astrocytoma prospectively with both anatomic MR imaging and PASL. The sensitivity and specificity of PASL parameters were compared with those seen with conventional imaging alone. Sensitivity, specificity, PPV and NPV for diagnosis of HGG (compared with

Table 9 Diagnostic specificity: PET

Author	Description of study	Data class	Conclusions
Singhal et al. [45]	102 patients with histologically confirmed glioma were studied with C-MET PET and FDG PET. These two imaging markers were considered as markers of diagnostic specificity (LGG versus HGG)	Class III	Both CMET PET and FDG PET showed an ability to distinguish between HGG and LGG
Kunz et al. [47]	55 patients with suspected primary LGG were considered prospectively with FET PET imaging. PET imaging measures were compared with histopathology to identify pure LGG tumors and distinguish them from tumors with heterogeneity (and regional higher grade tumor)	Class III	Regional elevation in FET uptake was found to correspond to focal regions of anaplasia or malignancy in histopathological analysis. No sensitivity or specificity data available
Calcagni et al. [48]	Prospective consideration of 32 subjects with brain tumors who underwent FET PET prior to surgery. SUV measures of FET uptake were correlated to tumor histology to determine ability to distinguish between LGG from HGG. Image analysis was performed by two researchers blinded to the histopathology data	Class III	Threshold values for early SUV and SoD yielded a parameter that distinguished LGG from HGG with sensitivity and specificity of 93 and 100 %. PPV and NPV data not available
Stockhammer et al. [44]	25 subjects with non-enhancing primary gliomas who underwent FDG PET prior to surgery were considered retrospectively. Reviewers of pathology and imaging data were not blinded to the comparison results	Class III	Elevated glucose utilization as measured by elevated FDG uptake corresponded to 1p/19q loss in subjects with WHO grade II tumors. No sensitivity or specificity data was available
Roessler et al. [45]	14 subjects with nonenhancing primary brain tumors considered preoperatively with XeCT were considered prospectively to see whether XeCT was useful in identifying anaplastic foci within tumors that would appear on anatomic imaging to be LGG. Image analysis was performed by reviewers not blinded to histopathology	Class III	XeCT may be useful in identifying foci of anaplasia within predominately LGG or identifying regional heterogeneity and OD components within LGG. No sensitivity or specificity data available
Delbeke et al. [43]	Retrospective consideration of 58 consecutive subjects with brain tumors who underwent FDG PET prior to surgery. Correlation between FDG uptake and tumor histology was considered. Reviewers not blinded to histopathological analysis	Class III	Threshold value of 1.5 (SUV) ratio for Tumor:WM was felt to yield the best distinction between LGG and HGG with sensitivity and specificities of 100 and 67 %. PPV and NPV not noted

Table 10 Prognosis: anatomic imaging

Author	Description of study	Data class	Conclusions
Brasil Caseiras et al. [64]	34 subjects with histologically proven LGG were followed prospectively in this case series to determine the effect of preoperative and pre-treatment imaging markers on prognosis and response to therapy	Class III	Six month tumor growth predicted outcome in patients with LGG better than parameters derived from DSC or DW imaging. Changes in tumor volume were measured by volumetric measures on FLAIR sequences
Bauman et al. [59]	401 subjects with LGG identified from three regional cancer centers. Clinical and anatomic imaging variables were correlated with prognosis as measured by overall survival	Class III	Enhancement on MRI and CT were found to be independently associated with an unfavorable prognosis as measured by OS
Schuurman et al. [50]	46 patients with supratentorial LGG were considered retrospectively to consider anatomic imaging and clinical variables and the impact on survival (as measured by 5 year survival). Case series	Class III	The presence of enhancement on preoperative CT was correlated with decreased overall survival
Shibamoto et al. [49]	101 subjects with supratentorial LGG were considered retrospectively and clinical variables and anatomic imaging markers were considers as markers of prognosis. Case series	Class III	On multivariate analysis, mass effect was the only significant imaging marker found to correspond to prognosis

Table 11 Prognosis: perfusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Dhermain et al. [53]	46 subjects with an initial diagnosis of LGG were considered prospectively to determine which clinical and anatomic imaging characteristics were predictive of prognosis (as measured by PFS)	Class III	Contrast enhancement was found to be an unfavorable factor with a hazard ratio of 3.0 for increased PFS. Microvascular leakage as measured by DSC imaging was also found to correlate to increased PFS with a hazard ratio of 7.3. Different prognostic subgroups (as measured by 2 year PFS) were noted for subgroups of patients with no MVL, MVL without CE, or MVL with CE, specifically 86, 57 and 19 % respectively
Caseiras et al. [54]	69 subjects with LGG were considered prospectively at 2 institutions and imaging parameters of rCBV were considered as markers of prognosis in this case series	Class III	A threshold rCBV value of 1.75 was used to discriminate between two groups of subjects, with elevated rCBV corresponding to poorer prognosis as measured by TTP
Law et al. [20]	35 subjects with LGG were considered retrospectively in this case series to determine whether DSC markers corresponded with patient prognosis as measured by TTP or death	Class III	A threshold rCBV value of 1.75 was used to identify subgroups of patients with distinct prognoses (subjects with rCBV <1.75 had a median TTP of 4620 days and lesions with rCBV >1.75 had a median TTP of 245 days

Table 12 Prognosis: MR spectroscopy

Author	Description of study	Data class	Conclusions
Hattingen et al. [52]	45 patients with LGG were evaluated with MRS prior to surgery and clinical variables as well as MRS parameters were correlated with prognosis as measured by overall survival, and TTP in this prospective case series	Class III	Contrast enhancement at diagnosis and the normalized creatine/phosphocreatine ratio were found to be correlated with prognosis, with an elevated tCR ratio and the presence of contrast enhancement correlating to decreased TTP

Table 13 Prognosis: PET

Author	Description of study	Data class	Conclusions
Singhal et al. [45]	102 subjects with glioma evaluated retrospectively to consider whether C-MET and FDG PET correlate with prognosis in this case series	Class III	Elevated Tumor to Normal ratios of tracer uptake for CMET PET corresponded to decreased overall survival with a threshold of 1.51 discriminating between groups in subjects with LGG
Smits et al. [56]	129 subjects with LGG were considered retrospectively in this case series to determine whether C-MET uptake could be considered as an independent predictor of prognosis in consideration with the EORTC criteria	Class III	In patients initially stratified as low or high risk based upon the EORTC criteria, elevated CMET uptake correlated with a poorer prognosis in both subgroups
Floeth et al. [57]	33 patients with LGG were considered prospectively to determine whether FET PET and MR imaging markers correlated to prognosis as measured by malignant transformation	Class III	Elevated baseline amino acid uptake on FET PET and a diffuse versus circumscribed tumor pattern on MRI were found to correspond to prognosis, with three subgroups identified: patients with circumscribed tumors without FET uptake, patients with circumscribed tumors with FET uptake, and patients with diffuse tumors with FET uptake. Statistically significant differences in TTP and OS were noted between these three groups with diffuse type and elevated FET uptake corresponding to worse prognosis
Ribom et al. [55]	89 subjects with LGG were considered retrospectively in this case series to determine whether C-MET PET corresponds to prognosis as measured by TTP and OS	Class III	Baseline C-MET PET was found to correspond to prognosis. Low CMET uptake was a favorable marker for survival along with olligodendroglioma subtype

Table 14 Serial imaging: anatomic imaging

Author	Description of study	Data class	Conclusions
van den Bent et al. [66]	Response assessment in neuro-oncology (RANO) group recommendation for imaging endpoints in LGG clinical trials	Class III	Minimum clinical protocol for LGG follow up should include FLAIR (to monitor for tumor growth) and T1 with and without contrast (to evaluate for progression to higher grade). MRS, DSC, volumetric MRI, and FDG or amino acid PET studies, while promising, require further evaluation in clinical trials and require development of tools for clinical implementation before they can be considered standard of care
Mandonnet et al. [63]	54 LGG patients treated with partial resection were followed by serial MRI with volumetric tumor estimates	Class II	After partial resection, LGGs grow at a rate of 4.3 mm/year (SD 3.2 mm/year), which is not statistically different than the rate of growth of untreated LGG
Soffietti et al. [74]	European Federation of Neurological Societies (EFNS) and European Association for Neuro-Oncology (EANO) task force report on management of LGG	Class III	Conventional MRI with and without Gd every 6 months is recommended for follow-up. Both DSC-MRI and FDG PET are useful for detecting malignant transformation and for differentiation of radiation necrosis from recurrence. MET PET may also be useful for treatment monitoring
Brasil Caseiras et al. [64]	34 patients with LGG underwent baseline and 6 month follow up MRI and were then followed for time to progression and time to death. Volumetric tumor measurements, average diffusion coefficient (ADC), and relative cerebral blood volume (rCBV) were compared	Class III	LGG volume growth over 6 months predicts transformation to higher grades; performs better than rCBV, ADC, age, and initial histology
Rees et al. [65]	27 untreated LGGs were followed with serial MRI	Class III	The overall risk of transformation to higher grade was 23 % per 6 months for this cohort. Total 3D tumor volume (but not increase in growth rate) predicted risk of transformation; for every 10 % increase in volume, transformation increased by 34 %
Shaw et al. [75]	Results of an RTOG multicenter Phase II observational trial	Class III	Young adults with LGG with GTR have a >50 % risk of recurrence in 5 years. Close follow up, including FLAIR MR imaging is recommended
Ricard et al. [62]	107 LGG patients treated with temazolomide (TMX) were followed by serial MRI with volumetric tumor estimates before, during, and after treatment	Class II	LGGs grow linearly prior to TMZ treatment (mean 4.7 mm/year). During TMZ, 92 % of patients initially had decreases in tumor size; regrowth resumed in a subset of patients despite continued TMZ. After TMZ discontinuation, 59 % of LGGs resumed growth at a rate similar to pre-TMZ
Pallud et al. [61]	143 LGGs were followed with longitudinal MRI prior to treatment. Pre-treatment tumor growth rates were correlated with survival	Class II	There is an inverse correlation between LGG growth rate and survival ($p < 0.001$; median survival >15 years for a growth rate <8 mm/year, median survival 5.16 years for a growth rate of 8 mm/year or more)
Mandonnet et al. [60]	27 patients with untreated LGG were followed with MRI for at least 2 years. Tumor volumes were estimated from the geometric mean of the largest diameters in three planes	Class III	Untreated LGG grow linearly over time with a mean of 4.1 mm/year (95 % CI 3.8–4.4 mm/year) regardless of initial size
Bauman et al. [51]	21 patients with LGG had volumetric tumor measurements based on CT	Class III	Regardless of method chosen for measuring LGG, CT volume changes did not predict clinical outcome
Afra et al. [58]	37 patients with LGG were followed with serial CE CT	Class III	Progression to anaplasia and/or GBM was associated with appearance or increase in contrast enhancement on serial imaging (100 % sensitivity and 77 % specificity)

LGG) respectively using the PASL parameter (tumor perfusion signal intensity) were 82, 96, 97 and 81 % respectively; a notation was made that inter-observer variability was measured with a k value of 0.72. Nguyen et al. [11] considered 46 patients with pathologically proven glioma retrospectively to assess the correlation of anatomic and DCE MRI parameters with tumor grade. Their data suggested that K-trans can be a useful imaging parameter to discriminate between LGG and HGG. Using a K-trans threshold of >0.018 min (-1) yielded sensitivity,

Table 15 Serial imaging: perfusion weighted MR imaging

Author	Description of study	Data class	Conclusions
Voglein et al. [67]	20 LGG patients were included in a larger study of advanced imaging following glioma treatment. Tumor growth was compared to DSC and MRS	Class III	rCBF derived from DSC MRI outperformed MRS for the overall cohort. Small sample size limited full ananlysis of the LGG group as a subset
Danchaivijitr ret al. [68]	Longitudinal DSC MRI was performed in 13 treatment-naive LGGs; patients were followed for progression of disease	Class III	Increase in rCBV predicts high grade transformation of LGG and precedes development of contrast enhancement
Law et al. [20]	35 LGGs has baseline and longitudinal volumetric and DSC MRI	Class III	Elevated baseline rCBV in LGGs was associated with shoter time to progression. Change in rCBV and change in volumetric MRI were not found to be statistically significant for progression

Table 16 Serial imaging: MR spectroscopy

Author	Description of study	Data class	Conclusions
Hlaihel et al. [69]	Evaluation of advanced MRI for anaplastic transformation in 21 patients with oligodendroglioma or mixed glioma. Astrocytomas were not included in the study	Class III	MRS Cho/Cr ratio >2.4 was 80 % sensitive and 94 % specific for anaplastic transformation of oligodendroglioma or mixed glioma
Reijneveld et al. [70]	14 patients with suspected LGG underwent serial MRI including MRS	Class III	MRS was not useful in monitoring LGGs

Table 17 Serial imaging: PET and SPECT imaging

Author	Description of study	Data class	Conclusions
Arbizu et al. [71]	23 new and recurrent high and LGG (8) patients were selected to undergo MET PET based upon MRI findings	Class III	87.5 % of patients had a larger mass defined by MRI than by MET PET. Biopsies were obtained in this area in two LGG patients: histology for one patient was "dysplasia" and for the 2nd patient was LGG. A larger sample size is needed before an additive role for MET PET in LGG can be confirmed
Imani et al. [72]	Six LGG and six Grade III glioma patients with MRI suggestive of recurrence underwent MRS and FDG PET. Outcomes determined by biopsy (if available) or longitudinal imaging	Class III	Sensitivity and specificity of FDG for recurrence was 100 and 67 % respectively; for MRS it was 100 and 33 % respectively
Santra et al. [73]	34 LGGs were studied an a total cohort of 81 patients with previously treated glioma. Patients with MRI suspicious for recurrence underwent FDG PET and were then followed for survival	Class III	Regardless of initial glioma grade or size of the recurrent tumor, tumoral FDG uptake greater than normal grey matter was the most significant predictor of shortened survival

specificity, PPV and NPV values of 89, 75, 94, and 62 % respectively; inter-observer variability was measured with a k value of 0.76.

Maia et al. [22] performed a prospective study of PWI in 21 patients with low and intermediate grade gliomas and found that an rCBV cutoff of 1.2 gave a sensitivity and specificity of 80 and 100 % respectively to help discriminate between diffuse LGGs and other tumor types (higher rCBV was suggestive of grade 2 oligodendroglioma (ODG) or AA). Lev et al. [23] also demonstrated the finding of elevated rCBV in grade 2 ODG, finding that an elevated rCBV is a sensitive but not specific marker for high grade noting that in there series all HGGs had an rCBV above 1.5 with the caveat that elevated rCBV was also seen in grade 2 ODG. In 2007, Spampinato et al. [24] specifically considered 22 patients with ODG who underwent DSC imaging prior to surgery. Statistically significant differences were seen between mean rCBV values for low grade versus high grade ODG. An rCBV threshold value of 2.14 provided the highest sensitivity and specificity (100 % and 86 %). Emblem et al. [25] considered 52 patients with histologically confirmed gliomas and preoperative MR imaging with DSC MRI prospectively. Histogram analysis was used to consider HGG, LGG and ODG subtypes of LGG. The

authors noted improved sensitivity and specificity for identification of the OGD subtype of LGG using a histogram analysis (100 % sensitive and 91 % specific for ODG without LOH at 1p19q) from other tumor subtypes, although their histogram analysis did not allow distinction of other tumor subtypes. Narang et al. [26] used CTP to compare 21 patients a diagnosis of ODG with 32 patients with low grade astroglial neoplasms, finding that low grade ODG showed a lower CBV compared with high grade OD, but that these changes were a trend and not statistically significant. Thus perfusion CT cannot be suggested as useful for diagnosing ODG noninvasively.

Chaskis et al. [27] considered 55 patients with newly diagnosed glioma prospectively with anatomic MR imaging and PWI and examined whether the addition of PWI aided in making the diagnosis of tumor grade. They found that PWI could be used in preoperative assessment of gliomas and suggested that the method ought to be used to guide biopsies as the imaging technique might aid in limiting under-diagnosis in stereotactic biopsy.

Diffusion weighted MR imaging

Twelve studies meeting the inclusion criteria described above have specifically considered the utility of diffusion weighted imaging (DWI) in the discrimination of LGG from higher grade tumors and in the discrimination of tumor subtypes. A total of four of these studies [12, 19, 28, 29] provided Class II evidence to suggest a benefit to diffusion weighted imaging in measures of diagnostic specificity, and the remaining eight provided Class III evidence. Seven studies considered DWI as an independent imaging parameter and five considered DWI in concert with other imaging parameters.

Specifically, Fan et al. [16] considered DWI prospectively in 22 subjects with nonenhancing supratentorial gliomas. The derived parameter of apparent diffusion coefficient (ADC) was considered as a way to distinguish higher grade nonenhancing tumors. Lower ADCs were seen in solid portions of anaplastic gliomas, but not in LGG. Specific quantitative thresholds were not suggested. Tozer et al. [30] performed a retrospective analysis of 27 patients with biopsy proven LGG and considered whether DWI metrics can distinguish between LGG subtypes of AC, OD, or OA. Their data suggested that ADC histogram analysis could aid in the distinction between LGG subtypes, although detailed quantitative data regarding sensitivity and specificity were not calculated. Khayal et al. [31] performed a retrospective analysis of 53 patients with histologically proven LGG. They considered the use of DWI measures to distinguish subtypes of LGG. Their results suggested that DWI parameters of apparent diffusion coefficient (ADC) and fractional anisotropy (FA) can be used to distinguish between LGG subtypes, although sensitivity and specificity data were not provided. Arvinda et al. [12] considered 51 subjects with histologically confirmed glioma. All subjects had been evaluated with DWI prior to surgery. Imaging data was compared with histopathology results. A threshold of 0.98 for mean ADC was identified as useful in discriminating HGG from LGG, with sensitivity, specificity, PPV and NPV values of 90, 87, 82, and 93 % respectively noted. Server et al. [29] prospectively considered 74 subjects with histopathologically proven glioma. DWI parameters measures were considered to determine whether ADC could be used to distinguish LGG from HGG. A threshold ADC of 1.07 yielded sensitivity, specificity, PPV and NPV values of 80, 60, 89, and 43 % (ADC), suggesting that DWI can be a beneficial addition to preoperative imaging in determination of glioma grade.

Alvarez-Linera et al. [28] prospectively considered 54 patients with histologically proven HGG and LGG, acquiring diffusion weighted imaging sequences using both standard and high b values and correlating ADC metrics with tumor grade. The b-value is a mathematical factor used in designing of diffusion weighted imaging sequences [32]. The b value summarizes the influence of magnetic gradients on the diffusion images [33]. The higher the b value, the stronger the diffusion weighting [33]. The authors found that inclusion of high b value diffusion measures ($b = 3000$ s/mm^2) gave increased diagnostic sensitivity/specificity when compared with measurements made with $b = 1000$ s/mm^2 alone. Lee et al. [34] performed a retrospective analysis of 16 patients with imaging characteristics consistent with LGG on anatomic imaging (from overall population of 118 subjects with primary brain tumors). These patients' DWI sequences were analyzed to see whether quantitative ADC measures (specifically minimum ADC values within the tumor) distinguished LGG from HGG. A minimum ADC threshold value of 1.055 yielded the best distinction of LGG from HGG (sensitivity and specificity of 87.5 and 79 %) in this small series of subjects. In Jakab et al. [35], preoperative DWI sequences from 40 patients with primary brain tumors were considered retrospectively. ADC measures were compared with histological grade. Histogram analysis methods yielded separation of LGG from HGG with a sensitivity and specificity of 88.5 and 85.7 %, respectively.

In 2011 Liu [19] retrospectively considered 52 subjects with newly diagnosed gliomas to see whether preoperative DWI could be used to distinguish LGG from HGG. Their results suggested that the FA parameter has diagnostic utility, reporting that a combination of FA mean and max values provided improved diagnostic accuracy in distinguishing LGG from HGG. Fractional anisotropy is a scalar value between zero and one that describes the degree of

anisotropy of a diffusion process being measured with DWI. A value of zero means that diffusion is isotropic, or that it is unrestricted with complete freedom of water movement in all directions (or restricted equally in all directions). Increasing values indicate relative inequality in restriction of movement. Cutoffs for an FA mean of 0.13 and for an FA max of 0.22 yielded sensitivity and specificity measures of 93 and 69 % (FA mean) and 100 and 77 % (FA max) when distinguishing LGG from HGG. Also in 2011, Jolapara et al. [36] compared ADC with histopathology data in 38 patients with infiltrating glioma retrospectively, and found that a threshold for FA max measures of 0.4 LGG distinguished LGG from HGG with a sensitivity and specificity of 100 %. White et al. [37] retrospectively reviewed 34 subjects with primary brain tumors and considered DWI parameters of mean, maximum and minimum FA as measures to distinguish LGG from HGG. They reported that FA max, FA range and SD max thresholds of 0.17, 0.0917, and 0.04 distinguished LGG from HGG, yielding sensitivity and specificity values of 92 and 78, 96 and 78 and 100 and 100 % respectively.

MR spectroscopy

MR spectroscopy, using both single voxel and multivoxel methods, has been applied to the question of diagnostic specificity in LGG. In 2003, Bulakbasi et al. [38] reported data from the study of 49 subjects with brain tumors including 8 HGG and 12 LGG who were prospectively evaluated with MRS prior to surgery. Specifically, metabolite ratios from MRS were noted to be useful in distinguishing benign from malignant tumors, and increased Lactate/Cr ratios were useful in distinguishing between LGG and HGG. Sensitivity and specificity data were not provided. Subsequent studies have not focused on this parameter as a marker of diagnostic specificity in LGG.

In 2004, Batra et al. [14] considered Choline:Creatine ratios in 27 patients with primary brain tumors. Choline:Creatine ratios were noted to be useful in distinguishing the histopathological grade of non-contrast enhancing gliomas, however quantitative thresholds and sensitivity or specificity data were not provided. When Spampinato et al. [24] evaluated 22 subjects with ODG prior to surgery with MRS, they found statistically significant differences between mean choline/Cr ratios for LGG versus HGG. A choline/creatine ratio threshold of 2.33 offered the greatest sensitivity and specificity for distinguishing among tumor grades (100 and 83.3 %). Senft et al. [39] studied 63 subjects with suspected primary brain tumors with MRS prior to surgery. They found that maximum Choline values were useful in distinguishing LGG from HGG with threshold of 2.02 yielding sensitivity and specificity values of 86 and 78 %. When Zeng et al. [40] considered 39 subjects who had undergone multi-voxel MRS prior to surgery for primary brain tumors, they found that metabolite ratios of LGGs were significantly different than HGGs. The ratios Cho/Cr, Cho/NAA, and NAA/Cr were considered, with threshold values of 2.04, 2.20, and 0.72 found to be most sensitive based upon ROC analysis. Sensitivity, Specificity, PPV and NPVs for each respective analysis were: Cho:Cr—84, 83, 91 and 71 %, Cho:NAA—88, 67, 85, and 73 %, and NAA:Cr—76, 67, 83 and 57 %. Server et al. [29] collected MRS prospectively in 74 subjects with histopathologically proven glioma. Metabolite ratios were considered to determine whether these imaging parameters could be used to distinguish LGG from HGG. Threshold values of 1.35 and 1.78 for peritumoral Cho/Cr and Cho/NAA ratios yielded sensitivity, specificity, PPV and NPV of 83, 85, 42, and 98 % (Cho/Cr), and 100, 57, 23, and 100 % (Cho/NAA), suggesting that MRSI can increase the accuracy of preoperative imaging in determination of glioma grade. Zou et al. [41] also considered MRS in 30 subjects with supratentorial gliomas. Differences between LGG and HGG were seen for Cho/Cr, NAA/Cr, and NAA/Cho ratios. Thresholds for tumor NAA/Cr and NAA/Cho provided sensitivity, specificity, PPV and NPV values that were improved compared with those suggested by anatomic imaging alone. NAA/Cho was the MRS parameter found to contribute most significantly to the differences between the two groups. Liu et al. [42] used DWI to guide placement of a single voxel MRS study in 33 patients with histologically proven gliomas, considering Cho/Cr and Cho/NAA ratios to distinguish HGG from LGG. This methodology was felt to be useful, with a threshold value of 2.01 for Cho/Cr yielding a sensitivity, specificity, PPV and NPV of 86, 90, 95, and 75 % respectively. Threshold values of 2.49 for Cho/Naa and 0.97 for NAA/Cr were suggested, with similar sensitivities. Cho/Cr was felt to be the best diagnostic parameter of the three.

PET and SPECT imaging

Nuclear medicine tracers have also been considered in evaluation of patients with LGG. As far back as 1995, Delbeke et al. [43] considered FDG PET as a diagnostic marker in 58 consecutive subjects with brain tumors. Correlation between FDG uptake and tumor histology was considered. Their series suggested that a threshold value of 1.5 standard uptake value (SUV) ratio for tumor: white matter WM yielded the best distinction between LGG and HGG with sensitivity and specificities of 100 and 67 %. PPV and NPV was not noted. Stockhammer et al. [44] considered FDG PET in 25 subjects with nonenhancing primary gliomas. Elevated glucose utilization as measured

by elevated FDG uptake corresponded to 1p/19q loss in subjects with WHO grade II tumors. Singhal et al. [45] considered FDG PET along with CMET PET in 2012 in 102 patients with histologically confirmed glioma. Both CMET PET and FDG PET showed an ability to distinguish between HGG and LGG.

Although historically, FDG PET has been a focus of metabolic imaging, additional tracers have also been considered in small series. Roessler et al. [46] considered Xenon SPECT CT in 14 subjects with nonenhancing primary brain tumors to see whether XeCT was useful in identifying anaplastic foci within tumors that appeared, on anatomic imaging to be LGG. Their results suggested that XeCT may be useful in identifying foci of anaplasia within predominately LGG or identifying regional heterogeneity and OD components within LGG, however no quantitative thresholds or sensitivity or specificity data were provided. Kunz et al. [47] evaluated 55 patients with suspected primary LGG prospectively with FET PET imaging. FET PET imaging measures were compared with histopathology to identify pure LGG tumors and distinguish them from tumors with heterogeneity (and regional higher grade tumor). Regional elevation in FET uptake was found to correspond to focal regions of anaplasia or malignancy in histopathological analysis. No sensitivity or specificity data were provided. Calcagni et al. [48] also considered FET prospectively in 32 subjects with brain tumors, noting that Threshold values for early SUV and SoD yielded a parameter that distinguished LGG from HGG with sensitivity and specificity of 93 and 100 %. All of the referenced studies considering PET tracers and diagnostic specificity offered only Class III evidence in support as to the integration of these tracers into clinical practice.

Imaging and prognosis: low grade glioma

Anatomic MR imaging

Features on both CT and MR imaging have long been recognized as predictive of prognosis for LGG. These have included findings of overall tumor size measurements, anatomic location, and specific imaging features. Four referenced studies considered this and offer Class III evidence related to the inclusion of anatomic imaging sequences in consideration of prognosis. Specifically, in 1993, Shibamoto et al. [49] retrospectively considered 101 subjects with supratentorial LGG; clinical variables and anatomic imaging markers were considered as markers of prognosis. In this series, using multivariate analysis, mass effect was the only significant imaging marker found to correspond to prognosis. Schuurman et al. [50] considered 46 patients with supratentorial LGG retrospectively to evaluate anatomic imaging and clinical variables and their impact on survival (as measured by 5 year survival). In this series, the presence of enhancement on preoperative CT was correlated with decreased overall survival. In 1999, Bauman et al. [51] identified 401 subjects with LGG from three regional cancer centers. Clinical and anatomic imaging variables were correlated with prognosis as measured by overall survival. Enhancement on MRI and CT were found to be independently associated with an unfavorable prognosis as measured by overall survival. Hattingen et al. [52] considered anatomic imaging parameters in 45 patients with LGG prior to surgery, imaging parameters were correlated with prognosis as measured by overall survival, and time to progression. Contrast enhancement at diagnosis correlated with prognosis, with the presence of contrast enhancement correlating to decreased TTP. In 2009, Dhermain et al. [53] considered 46 subjects with an initial diagnosis of LGG prospectively to determine which clinical and anatomic imaging characteristics were predictive of prognosis (as measured by PFS). Contrast enhancement was found to be an unfavorable factor with a hazard ratio of 3.0 for increased PFS. Brasil Caseiras et al. [64] also considered anatomic imaging and prognosis in 34 subjects with histologically proven LGG, noting that six month tumor growth (as measured by volumetric changes on FLAIR sequences) predicted outcome in patients with LGG better than parameters derived from DSC or DW imaging.

Perfusion weighted MR imaging

Three studies offer Class III evidence to suggest that Perfusion Weighted Imaging can play a role in providing non-invasive predictors of prognosis for patients with LGG. In 2006, Law et al. considered whether PWI parameters were associated with prognosis in LGG [20]. 35 subjects with LGG were considered retrospectively in this case series to determine whether DSC markers corresponded with patient prognosis as measured by time to progression (TTP) or death. A threshold rCBV value of 1.75 was used to identify subgroups of patients with distinct prognoses (subjects with rCBV <1.75 had a median TTP of 4620 days and lesions with rCBV >1.75 had a median TTP of 245 days. Caseiras et al. [54] considered 69 subjects with LGG prospectively at 2 institutions. rCBV was considered as a marker of prognosis. Again, a threshold rCBV value of 1.75 was used to discriminate between two groups of subjects, with elevated rCBV corresponding to poorer prognosis as measured by TTP. Dhermain et al. [53] also considered the DSC parameter of microvascular leakage (MVL) as a marker of prognosis, noting that MVL was found to correlate to increased PFS with a hazard ratio of 7.3. Different prognostic subgroups (as measured by 2 year PFS) were

noted for subgroups of patients with no MVL, MVL without contrast enhancement (CE), or MVL with CE, specifically 86, 57 and 19 % respectively.

MR spectroscopy

In 2008, Hattingen et al. [52] considered MRS in 45 patients with LGG prior to surgery, and clinical variables as well as MRS parameters were correlated with prognosis as measured by overall survival, and time to progression. The normalized creatine/phosphocreatine ratio were found to be correlated with prognosis, with an elevated CR/Phosphocreatine ratio correlating to decreased TTP, offering limited Class III evidence to support the potential for the use of MRS in consideration of LGG prognosis.

PET and SPECT imaging

Four studies offer Class III evidence to support the potential for the consideration of nuclear medicine tracers in consideration of LGG prognosis. Specifically, in 2001, Ribom et al. [55] retrospectively considered 89 subjects with LGG to determine whether C-MET PET corresponded to prognosis as measured by time to progression and overall survival. Baseline C-MET uptake was found to correspond to prognosis. Low CMET uptake was a favorable marker for survival. In 2008, Smits et al. [56] identified 129 subjects with LGG who had undergone C-MET PET prior to surgery. They asked whether C-MET uptake could be considered as an independent predictor of prognosis in conjunction with the EORTC analyses. In patients initially stratified as low or high risk based upon EORTC criteria, elevated CMET uptake correlated with a poorer prognosis in both subgroups. Finally, Singhal et al. [45] evaluated 102 subjects with glioma who had undergone C-MET and FDG PET prior to surgery retrospectively to consider whether uptake of these two radiotracers correlated with prognosis. They found that Elevated Tumor to Normal ratios of tracer uptake for CMET PET corresponded to decreased overall survival with a threshold of 1.51 discriminating between groups in subjects with LGG.

Floeth et al. [57] evaluated 33 patients with LGG prospectively to determine whether FET PET correlated to prognosis as measured by time to malignant transformation. Elevated baseline amino acid uptake on FET PET and a diffuse versus circumscribed tumor pattern on MRI were found to correspond to prognosis, with three subgroups identified: patients with circumscribed tumors without FET uptake, patients with circumscribed tumors with FET uptake, and patients with diffuse tumors with FET uptake. Statistically significant differences in TTP and OS were noted between these three groups with diffuse type and elevated FET uptake corresponding to worse prognosis.

Imaging and serial imaging follow-up studies: low grade glioma

Anatomic MR imaging

Almost all of the data for anatomic, longitudinal imaging of LGGs is based upon Class III evidence (10 of 11 studies). A single study provides Class II evidence for use of anatomic imaging in serial follow up studies. Initial studies of LGG imaging examined small single-institution cohorts with CT [51, 58]. With CT, new tumoral contrast enhancement over time was associated with progression to higher grade [58] but volumetric tumor measurements were not [59]. Once MR became widely available, its superior tissue contrast enabled quantitative studies of glioma growth. Using a volume estimate derived from the geometric mean of the 3 largest diameters on T2 and FLAIR, using standard 2D imaging, in a series of 27 patients with LGG Mandonnet and colleagues demonstrated that untreated LGGs grow linearly over time, with a mean of 4.1 mm/year (95 % confidence interval [CI] 3.8–4.4 mm/year) [60]. The same group then followed with a Class II study considering a larger cohort of 143 patients and demonstrated an inverse correlation between LGG growth rate and survival ($p < 0.001$), with a median survival of greater than 15 years when the growth rate was less than 8 mm/year but only 5.16 years for a growth rate of 8 mm/year or greater [61]. Similar findings were seen when considering volumetric measures prior to and following treatment with temazolamide (TMZ); in a Class II study of 107 patients with LGG, pre-treatment tumor growth was 4.7 mm/year [62]. 92 % of patients in this study had a decrease in tumor size during TMZ treatment, but after discontinuation of TMZ, 59 % of LGGs grew at a rate similar to untreated LGGs. Similarly, for patients with partial resections of LGGs, growth of the residual tumor is $\sim$4.3 mm/year, based on a Class II study of 54 LGGs treated with surgery only [63]. These studies collectively support the use of volumetric measures of LGG prior to and serially following diagnosis and/or treatment in the management of LGG.

In a Class III comparison of volumetric tumor growth to ADC and rCBV, Brasil Caseiras et al. [64] found that LGG volume growth over 6 months predicted transformation to higher grade and out performed patient age, initial histology, ADC and rCBV as predictors. However, in another Class III study of 27 untreated LGGs, Rees et al. [65]. found that the total 3D tumor volume (but not an increase in growth rate) predicted transformation; for every 10 % increase in volume, transformation increased by 34 %.

None of the Class II or Class III LGG longitudinal studies have addressed the question of how often to obtain

imaging. The Response Assessment in Neuro-Oncology (RANO) group published a guideline for clinical trials of LGGs in 2011 [66]. Their recommendation is consistent with the findings of this manuscript—a minimum examination should include T2/FLAIR and T1 pre and post-Gd. Other options, such as MRS, DSC, DTI, FDG or other nuclear medicine studies may be helpful, but require development of better clinical tools before they can become widely implemented and, being based primarily on Class III evidence, require multicenter clinical trials with larger cohorts before their value can be formally assessed.

Perfusion weighted MR imaging

Three Class III studies have been published examining longitudinal PWI in LGGs cohorts of less than 40 patients each. In a mixed study of 20 LGG patients as well as other tumor types, relative cerebral blood flow (rCBF) outperformed MRS, but analysis was limited by the small sample size [67]. In a study of 13 LGGs patients, Danchaivijit detected an increase in rCBV over time preceding the development of contrast enhancement in LGGs [68]. However, in a slightly larger study of 35 LGGs, only baseline rCBV and not change in rCBV or change in volume was associated with shortened time to progression [20]. Additional studies with larger cohorts and standardized methods for perfusion estimation are needed.

Diffusion weighted MR imaging

No longitudinal studies of diffusion in untreated LGGs have been reported.

MR spectroscopy

Two small studies (Class III) of longitudinal MRS have been reported for LGG. Hlaihel found that in a study of 21 patients with olidgodendroglioma or mixed glioma, MRS was 80 % sensitive and 94 % specific for anaplastic transformation of LGG [69]. However, in a study of 14 patients with suspected LGG, Reijneveld et al. did not find an added value for MRS [70]. Additional studies with larger cohorts are needed in this area as well.

PET and SPECT imaging

Class III evidence supports continued research into the role of nuclear medicine studies in patients with LGGs. Currently, studies have selected patients for PET based upon MRI findings suspicious for transformation, such as marked interval growth or new contrast enhancement. Since MR has been the basis for entry into the PET studies, full comparisons of the two methods cannot be performed at present. Arbizu et al. [71] studied 8 untreated LGG patients with MET PET as part of a larger cohort, and 2 of these patients went on to have histology. However, in one case, an area of tissue was MR negative but MET PET positive was found to have glioma cells; as long as surgical resection is the mainstay of therapy for LGG, imaging techniques to better determine pre-surgical extent of tumor should be investigated. In another small series which included 6 patients with LGG, Imani et al. [72] compared FDG PET to MRS for LGG recurrence and found FDG to have greater specificity than MRS. Finally, in an intriguing study by Santra et al. [73] found that LGGs which had FDG uptake greater than grey matter (i.e. which behaved more like HGG on FDG PET) had shortened survival compared to patients with LGG which were not hypermetabolic. Again, larger studies are needed to better evaluate the potential of these approaches.

Imaging summary and discussion

The introduction of first CT and subsequently MR imaging has transformed the way we diagnose and treat LGGs. It has increased our awareness of these tumors, and allows early identification of asymptomatic lesions. Anatomic imaging remains critical to the identification of these tumors, but increasingly, advanced imaging methods including functional and physiologic imaging have impacted the way we manage this tumor type.

With respect to anatomic imaging, numerous authors have recognized that the addition of contrast enhanced images assist aid in the distinction of low grade from higher grade primary brain tumors and to identify progression to a higher grade over time. If a lesion is suspected, an MRI that includes anatomic T2, FLAIR and T1 weighted images, along with T1 weighted images acquired after the administration of contrast is necessary to begin to characterize a lesion as a possible LGG. In further evaluation of a suspected LGG, particularly if a complete resection of visible tumor is not anticipated, significant Class III evidence and a few series with Class II evidence suggest a benefit to volumetric tumor assessment, even using mean diameters from 2D imaging, and the addition of diffusion and perfusion weighted sequences to aid in the identification of possible tumor heterogeneity.

Performance of MR spectroscopy and PET imaging has been suggested to have relevance in some preliminary pilot studies, but there is not enough evidence to recommend the inclusion of either in standard diagnostic imaging protocols at this time as further investigation as to best metabolite ratios for consideration as well as best PET tracers and their role need to be further investigated.

With respect to consideration of advanced imaging as a prognostic imaging marker in LGG, the literature has a few

series examples of Class III evidence that suggest a role for PWI in distinguishing different classes of LGG in terms of prognosis, but these imaging parameters, at this time, should not be relied upon, in isolation, as markers of prognosis for patients. In settings where PWI and DWI can be obtained as a part of a routine tumor protocol imaging, these sequences can, however, have utility in the diagnostic workup and management of this patient population, and having a baseline understanding of tumor characteristics can be useful when questions arise as to later management with questions of progression, recurrence, or radiation change. If these sequences are not available and a complete resection of visible tumor is possible then the aspects of tumor heterogeneity that are identified with physiologic imaging may be less critical.

Conclusions and key issues for future investigation

Importantly, with consideration of all of these physiologic and advanced imaging sequences, differences in image acquisition, processing and analysis are not considered in these series. There is a paucity of literature addressing questions that arise with regard to complexities of data analysis when considering patients at multiple sites. Differences in scanner type, in image acquisition protocols, and in analysis methodologies may impact the quantitative measures obtained for different imaging parameters; this may account for some of the differences seen in threshold values, particularly in MRS and PWI measures. Larger, multi-site studies considering these markers as indicators of diagnosis and of prognosis will be beneficial (and are critical) to the standardization of integration of advanced imaging parameters into clinical practice. Ultimately, it appears that it would be very reasonable to consider perfusion and diffusion weighted imaging markers in larger, multi-site, studies of prognosis and diagnostic specificity in LGG. Prospective studies considering these sequences in larger populations may lead to series that allow for class I diagnostic or prognostic evidence for this population. Ultimately this approach may also be reasonable for PET and MRS parameters, although additional series might be useful to identifying the best PET tracers or specific MRS parameters to be chosen for integration into larger scale LGG trials., The integration of imaging markers as secondary endpoints in larger clinical trials will foster their ultimate translation to standard aspects of the management of patients with LGG.

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Complicance with ethical standards

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