There are currently a number of considerations involved in the management of patients with LGGs, which, for the purposes of this discussion, will be defined as WHO Grade II gliomas. Advances in tumor biology, neuroimaging, and treatment paradigms have enabled the neurosurgeon to approach these patients with a better understanding of the disease entity and its natural history. However, many controversial issues remain unanswered. Diagnostic strategies previously considered reliable for patients with LGGs, including structural MR imaging and stereotactic biopsy, have more recently been shown to vary substantially with regard to specificity, sensitivity, and sampling error. Surgical management paradigms are also shifting, as mounting evidence now highlights the predictive value of volumetric tumor burden for patient survival, the role of greater extent of resection in reducing transformation rates, and the importance of eloquence in determining tumor resectability. Additionally, LGG-associated seizures are increasingly considered as a key determinant of quality of life, with electrocorticography being used as an effective surgical adjunct when seizures are medically refractory. Adjuvant therapies are also under renewed scrutiny. While the utility of radiation therapy is clear, the timing and type of chemotherapy remain somewhat uncertain, as does the role of new molecular therapeutics. Taken together, these innovations and controversies define the modern era of LGG management. Here, we review the current literature in an effort to highlight high-impact developments that are changing our view of LGGs, as well as the pivotal studies that should guide neurosurgeons as they consider these many issues.

Epidemiology

Low-grade gliomas are not uncommon, representing 15% of all primary brain tumors diagnosed in adults each year. They are most frequent among Caucasian men and typically affect patients at a younger age than high-grade gliomas (4th vs 6th decade of life). While LGGs are diffusely distributed along a variety of supratentorial regions, they have a particular predilection for the insula and supplementary motor area. In contrast, in adults these lesions rarely involve the cerebellum, brainstem, or spinal cord, as they commonly do in children. Most patients initially present with relatively good neurological function, and seizures are the most common symptom at presentation (80%). The only definite risk factor for LGG is previous exposure to ionizing radiation. Hereditary factors do not play a substantial role in the development of LGGs, although these tumors are more common in patients with

Abbreviations used in this paper: CBV = cerebral blood volume; DT = diffusion tensor; EORTC = European Organization for Research and Treatment of Cancer; FET = O-(2-\(^{18}\)F-fluoroethyl)-L-tyrosine; FLT = 3'-deoxy-3'-18F-fluorothymidine; fMR imaging = functional MR imaging; GFAP = glial fibrillary acidic protein; KPS = Karnofsky Performance Status; LGG = low-grade glioma; MGMT = O6-methylguanine-methyltransferase; mTOR = mammalian target of rapamycin; PCV = procarbazine/lomustine (CCNU)/vincristine; PDGF = platelet-derived growth factor; rCBV = relative CBV; RTOG = Radiation Therapy Oncology Group; UCSF = University of California at San Francisco.
neurofibromatosis Type 1 and Li-Fraumeni syndrome. Between 15% and 20% of individuals with neurofibromatosis Type 1 develop LGGs affecting the optic nerves, optic chiasm, and hypothalamus (optic pathway gliomas). Most of these gliomas are classified as WHO Grade I tumors, although Grade II LGGs can also occur in these locations.50

The etiology of LGGs in adults is largely unknown and is thought to be multifactorial; various genetic, infectious, and immunological factors have been implicated. Glioma epidemiology studies have revealed few consistent findings, possibly because of small sample sizes in individual studies and differences between studies in patients, tumor types, and methods of classification. Individual studies generally have lacked samples of sufficient size to examine interactions, but larger consortium efforts have outlined several potential risk factors for gliomagenesis and outcome.14 Data from the SEER (Surveillance, Epidemiology, and End Results) Program indicated that African Americans had similar or poorer survival than Caucasians,5 but those results were adjusted incompletely for important prognostic factors (for example, age at diagnosis, treatment patterns, and tumor histologies). After adjustment, African Americans had a 40% higher risk of death from low-grade tumors compared with non-Hispanic whites.31 Likewise, risks from specific neurocarcinogens have yet to be identified; however, the continued occurrence of brain tumor clusters leaves open the question of the extent and extent of their exposures. Observations of an association between drinking water and brain tumors suggest that ingestion of an environmental contaminant has an impact,2,6,149 perhaps from chlorinated sources like chloroethane, a byproduct of sewage treatment, or nitrate/nitrite contamination of drinking water supplies.

Recent epidemiological studies have also reported that adults with low-, as well as high-, grade gliomas are 1.5- to 4-fold less likely than controls to have allergies, which ranks the lack of allergies among the most consistent risk factors for glioma reported to date. In addition, an inverse relationship exists between IgE, a biomarker for atopic allergy, and glioma risk. Interestingly, the strongest IgE-glioma association has been observed among the least prevalent allergen—food IgE. Low- and high-grade glioma patients with elevated levels of IgE have been found to have an approximately 8 months longer survival than individuals with lower or undetectable levels, demonstrating the potential clinical significance of such correlates.89 The rise of cell phone use has also prompted concerns about its relationship with the formation of brain tumors, including gliomas. To date, no evidence supports this theory.10,94

Classification

Tumor histology remains the WHO’s current standard for diagnosing glioma grade and subtype (Fig. 1). As with all primary brain tumors, gliomas are classified according to their predominant cell type and graded based upon the presence or absence of necrosis, mitotic figures, nuclear atypia, and endothelial cell proliferation. While WHO Grade I and II lesions are both categorized as LGGs, they follow radically different clinical courses and, for the purposes of this review, we will focus on WHO Grade II oligodendrogliomas, astrocytomas, and oligoastrocytomas that occur in adults, as the greater management challenge. Among WHO Grade II astrocytomas, cellularity is moderately increased and nuclear atypia is occasional, but mitoses, endothelial proliferation, and necrosis are not present (although rare mitotic activity is permitted in a large specimen). The prognostic value of defining subcategories of gliomas based upon these features remains unclear, nevertheless 3 histological subtypes are described: fibrillary, gemistocytic, or protoplasmic neoplastic astrocytes define these subtypes, each embedded in a loosely structured and microcystic tumor matrix. Fibrillary astrocytomas, the most frequent variant, demonstrate low cellularity with minimal nuclear atypia. Neoplastic fibrillary astrocytomas are typically seen on a background of loosely structured tumor matrix that is extensively microcystic and expresses the intermediate filament marker, GFAP, diffusely. Gemistocytic astrocytomas are histologically characterized by plump, glassy, eosinophilic cell bodies of angular shape. These gemistocytes consistently express GFAP and the presence of abundant, compact glial filaments in the cytoplasm is also evident on electron microscopy. Interestingly, gemistocytic astrocytomas are reported to be more prone to histological upgrading (defined as transformation from a WHO Grade II glioma to a Grade III or IV) than other counterparts, raising the possibility that they are not biologically LGGs and may belong in the high-grade glioma category. Protoplasmic astrocytomas, the rarest histological subtype, contain small-bodied astrocytes with few processes and scant GFAP expression. Mucoid degeneration and microcystic formation are common characteristics as well.

Oligodendrogliomas occur in the white matter and cortex of the cerebral hemispheres and show a monotonous pattern on low power with occasional nodules of higher cellularity. The presence of low mitotic activity, vascular proliferation, and necrosis, including pseudopalisading necrosis, are insufficient by themselves to elevate the grade of WHO Grade II oligodendrogliomas, in contrast to WHO Grade II astrocytomas. The nuclei of oligodendrogliomas are round and regular, and clear perinuclear haloes are present in most paraffin-embedded specimens. This typical “fried egg” appearance is a formalin fixation artifact and is therefore not seen in frozen sections, smears, or rapidly fixed specimens. Oligoastrocytomas are a recognized category of LGGs, but are ill-defined, prone to neuropathologist subjectivity, and based on an unproven concept of dual differentiation of astrocytoma and oligodendroglioma as neoplastic processes.96 Histologically, they are defined by a mixture of cells, some with oligodendroglioma features, and others resembling diffuse astrocytomas. On standard H & E staining, oligoastrocytomas are composed of 2 distinct neoplastic cell types, resembling the tumor cells in oligodendroglioma and diffuse astrocytoma. Generally, these different cell types are intermingled, but occasionally a biphasic pattern is seen with relatively distinct, juxtaposed areas of oligodendroglioma versus astrocytoma phenotype.
Currently, there are no standardized immunohistochemical or molecular panels to distinguish oligoastrocytomas from other LGGs.

Molecular and Genetic Markers

Advances in our molecular understanding of LGGs represent arguably the greatest step forward in the field. The p53 pathway plays a crucial role in defining LGGs, as p53 mutations are the first detectable genetic alteration in two-thirds of low-grade diffuse astrocytomas that go on to transformation (Table 1). The p53 gene at 17p13.1 encodes a 53-kd protein that plays a role in several cellular processes, including the cell cycle, response of cells to DNA damage, cell death, cell differentiation, and neovascularization. After DNA damage, p53 is activated and induces transcription of genes such as p21Waf1 or Cip1. MDM2 binds to mutant and wild-type p53 proteins, thereby inhibiting the ability of wild-type p53 to activate transcription. Conversely, transcription of the MDM2 gene is induced by wild-type p53. In normal cells, this autoregulatory feedback loop regulates both the activity of the p53 protein and the expression of MDM2. The p14ARF gene product binds to MDM2 and inhibits MDM2-mediated p53 degradation and transactivational silencing. Conversely, p14ARF expression is negatively regulated by p53 and inversely correlates with p53 function in human tumor cell lines. Thus, loss of normal p53 function may result from altered expression of any of the p53, MDM2, or p14ARF genes.

The PDGF signaling pathway has been implicated in many aspects of low-grade gliomagenesis and glial development. Although PDGF can activate an array of downstream pathways, the extent to which PDGF signaling is directly responsible for or contributes to tumorigenesis remains unclear. In one study of 103 LGGs (WHO Grade II), PDGF receptor expression was found in 50% of the samples and correlated with a poorer prognosis. PDGF receptor and ligand overexpression also tend to be associated with p53 tumor suppressor loss and, together, have been implicated in the cascade of histological upgrading. The ability of PDGF to de-differentiate mature cells, keep glial cells from differentiating, or even promote cancer stem cells are important functions needing more investigation.

The molecular genetic signature of oligodendrogliomas at the DNA level is combined 1p and 19q losses, typically involving the entire chromosomal arm at both sites. Combined 1p/19q loss has been reported in 50%–80% of patients carrying a diagnosis of oligodendroglioma, with frequencies as high as 90% when using strict diagnostic criteria (Fig. 2). Unbalanced 1p/19q translocations have been reported and may also have prognostic value. Status with respect to 1p and 19q has been assessed using a variety of molecular techniques, including loss of heterozygosity, comparative genomic hybridization, quantitative microsatellite analysis, and fluorescence in situ hybridization. Initial results suggested that 1p/19q status is a predictive (in addition to prognostic) marker of response to PCV chemotherapy. Subsequent experience indicates that the therapeutic benefit of 1p/19q loss is not restricted to patients receiving PCV chemotherapy. Although no Class I evidence is yet available, preliminary studies suggest that patients with codeleted tumors respond favorably to temozolomide with improvements in overall and progression-free survival. Other studies have shown that patients with 1p/19q-loss oligodendrogliomas have improved progression-free survival and their tumors have more indolent behavior even before the initiation of treatment.

With respect to other LGG histologies, no consistent genetic abnormalities have been detected to indicate that oligoastrocytomas are distinct from oligodendrogliomas or astrocytomas. Between 30% and 50% of oligoastrocytomas are characterized by loss of chromosomes 1p or 19q. Interestingly, microdissection analysis of oligoastrocytomas reveals the loss of both alleles in all cells within each tumor, suggesting that oligoastrocytomas are monoclonal neoplasms originating from a single precursor cell, rather than representing combined tumors developing concurrently.

While the biology of LGGs is driven by genomic alterations that activate oncogenes and inactivate tumor suppressor genes, epigenetic alterations, such as gene silencing by promoter methylation, have now emerged as newly recognized factors in gliomagenesis. Methylation abnormalities are far more prevalent than expected and are particularly important in understanding LGGs, where...
frank genomic changes are less common than their high-grade counterparts. However, their exact role in driving LGG formation, as well as histological upgrading, remains unclear.\(^3\)

The DNA repair protein MGMT is a marker of high-grade glioma resistance to alkylating agents such as temozolomide. However, its applicability in similarly characterizing LGG patients remains controversial. In one study, methylated MGMT promoter was detected in 63 of 68 (92.6%) LGG patients and was a favorable predictor of progression-free survival as compared with unmethylated MGMT tumors treated with neoadjuvant temozolomide.\(^4\) Other studies, however, failed to show a significant association with patient outcome or tumor behavior,\(^9\) but raise the possibility that the methylation status of MGMT, as well as that of p14\(^{ARF}\) and PTEN, correlate with tumor grade and may constitute a unique pathway of glioma progression. Interestingly, recent work suggests that up to 80% of LGGs at risk for histological upgrading demonstrate PTEN methylation.\(^14\),\(^52\)

Efforts to identify other molecular markers of tumor progression have generated a number of potential targets, but most remain unvalidated in large, prospective series. For example, reduced expression of prostaglandin D(2) (PGD(2)) synthase (PGDS), an arachidonic acid metabolite produced by neurons and glia, is associated with LGG malignant progression, as well as poor patient survival.\(^10\) Similarly, the status of the phosphoinositide 3-kinase (PI3-kinase) signaling pathway has also been examined as a predictor of both LGG natural history and its likelihood to respond to conventional alkylating agents.\(^42\) In addition, cell cycle checkpoint proteins such as p21, p27, p14, p16, and p53 may serve as prognostic markers of histological upgrading, although in one study only the overall proliferative index was found to be predictive.\(^15\) Extracellular matrix glycoproteins, including tenascin-C, have also been examined as potential markers of LGG invasiveness.\(^6\)

The advent of gene-chip analysis has enabled genomic changes to be defined in the context of LGG histological upgrading. Associated chromosome imbalances include gains of 7q, 8q, and 22q, and losses of 1p, 13q, and 19q.\(^8\) Other studies have identified additional copy number aberrations for 5p, 9, and 19p, as well as losses
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on Xp. Deficient repair mechanisms for nucleotide mismatches, indicated by microsatellite instability, may also serve as an LGG prognostic factor, since microsatellite instability is often found at the time of histological upgrading. However, since biological systems comprise protein components resulting from transcriptional and posttranscriptional control, posttranslational modifications, and shifts in proteins among the different cellular compartments, all these properties cannot be analyzed by microarray systems at the RNA level. Therefore, recent work on LGG pathogenesis has also focused on proteome analysis, where high-resolution 2D gel electrophoresis allows separation and visualization of the protein contents of a cellular sample. Hierarchical clustering analysis demonstrates that LGG classification based on proteome profiling patterns can generate an accurate patient stratification that may be more clinically relevant than the conventional histological classification. In one analysis correlating proteomic analysis with histological grading and outcome, 25 identified proteins that spanned functional categories included signal transduction-related proteins, molecular chaperones, transcription and translation regulators, cell cycle-mediating proteins, extracellular matrix-related proteins, and cell adhesion molecules. Other analyses have identified several candidates already known to be associated with LGGs, including protein disulfide isomerase A3, the catalytic subunit of the cAMP-dependent protein kinase, and GFAP. However, other previously unrecognized protein signatures have also been discovered in the proteomics analysis of LGGs, including the T-complex polypeptide 1, a molecular chaperone; the ubiquitin carboxyl-terminal hydrolase, an enzyme responsible for the processing of ubiquitin precursors and of ubiquinated proteins; and dihydrolipoxidase reductase, an enzyme involved in the production of tetrahydrobiopterin that is an essential cofactor for phenylalanine, tyrosine, and tryptophan hydroxylases.

Based upon an initial genomic mutational analysis of glioblastomas, somatic mutations of the isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase 2 (IDH2) genes have been identified in the vast majority of LGGs, a subset of which progress to glioblastoma (that is, secondary glioblastoma). Interestingly, patients with a glioblastoma carrying an IDH1 or IDH2 mutation have a median overall survival of 31 months, which was significantly longer than the 15-month survival in patients with wild-type IDH1. In addition, an inverse association between IDH1 and IDH2 mutations and LGGs has been recently reported, with IDH1 mutations of the R132C type strongly associated with astrocytoma histology, while IDH2 mutations predominantly occur in oligodendroglial tumors. Although the role of the IDH pathways in gliomagenesis remains unclear, early evidence suggests they may define a unique road to glioma formation. Nevertheless, IDH mutations are increasingly being integrated into LGG prognostic categorizations, particularly since IDH1 mutations are associated with patients with better survival profiles. The combination of IDH mutational status and 1p/19q codeletion status represents a powerful set of prognostic indicators for LGG patients.

Historically, the neoplastic transformation of fully differentiated glia was widely assumed to be the only mechanism for gliomagenesis. Astrocytes and oligodendrocytes, once thought to be the sole dividing cells in the postnatal brain, were assumed to represent the cellular compartment susceptible to transformation. More recently, however, this hypothesis has been challenged by the discovery of germinal regions residing in the postnatal human brain, which may themselves serve as an origin of brain tumors. While LGGs share some of the morphological characteristics of mature astrocytes, recent studies have revealed a multitude of phenotypic and behavioral similarities between adult neural stem/progenitor cells and LGGs. A reappraisal of the classic gliomagenesis theory may lead to a more accurate picture of the LGG cell-of-origin and, at the least, prompt a much needed re-examination of the common assumptions underlying the field of LGG biology.

Clinical Presentation

Patients with LGGs present with signs and symptoms of disease related to direct parenchyma infiltration. Although the onset of symptoms can be subtle and insidious, when patients become symptomatic, seizure is the most common presenting sign, occurring in up to 80% of cases; this is probably due to the superficial localization and low growth rate of the tumor in many cases. Most patients are asymptomatic even if they have mass effect. Local tumor effects due to edema, hemorrhage, and intracranial hypertension are not common presenting features. Other, infrequent clinical presentations include headache, lethargy, and personality changes. In our view, incidentally found LGGs should be managed no differently than symptomatic lesions.

Prognostic Factors

Although substantial heterogeneity exists when profiling LGG patient outcome, several clinical factors are known to be predictive. Chief among those is age over 40 years, a predictive factor identified in multivariate analyses from 2 large, prospective trials. Age at the time of LGG diagnosis is not only inversely correlated with time to progression, but the tumor proliferative index may be higher among those older than 40 years as well. Although the biology behind this association is unclear, one possibility is that age-related impairment of DNA repair mechanisms and the resulting acquisition of mutations may promote rapid progression after transformation occurs. Clinical presentation is another strong prognostic factor, as neurologically intact patients presenting with isolated seizures typically have a better performance status and overall prognosis. Patients with LGGs who present with seizures also tend to be younger and have smaller tumors than those without seizures, although patients with large tumors can present with seizures as well.

An LGG preoperative prognostic scoring system developed at UCSF assigns a prognostic score based upon the sum of points assigned to the presence of each of the 4 following factors (1 point per factor): 1) location of tumor in presumed eloquent cortex, 2) KPS score ≤ 80, 3) age >
of survival and a high rate of histological upgrading. Tumors with Grade 0 or 1 (97% 5-year survival) are considered low risk, while those with Grade 4 (56% 5-year survival) are considered high risk. This scoring system accurately predicted overall and progression-free survival in a multinstitutional population of patients with LGG. The overall survival for patients with oligodendrogliomas is typically 10–15 years, a better prognosis than for astrocytomas, which are associated with a survival of 5–10 years. Gemistocytic astrocytomas, a subtype of Grade II astrocytomas, are more aggressive than predicted by grade. Large tumors, nonlobar gliomas, and tumors that cross midline are associated with short duration of survival and a high rate of histological upgrading. Preoperative tumor burden is also associated with a reduced extent of resection, which in turn portends poorer outcome. Proliferative index has also been inversely related with LGG outcome, as has contrast enhancement.

Recent work in glioma outcomes research also suggests that more unconventional factors may play a role in LGG patient outcome. For example, among patients with nonanaplastic oligodendrogliomas, younger age and resection versus biopsy were significantly associated with better survival, as expected. Interestingly, however, those patients who were college graduates also showed significantly better survival in age-adjusted comparisons. Further consideration of impact of marital status, education, and other social factors on survival may be warranted, as these factors also appear to be significant in predicting outcome in patients with high-grade gliomas.

Efforts to synthesize LGG risk factors into distinct prognostic classes have led to 4 categories of patients: 1) younger patients (18–40 years of age) with a good performance status (KPS score ≥ 70) who have a poor performance status (KPS < 70) and older patients (> 40 years of age) with a good performance status and no contrast enhancement had a median survival of > 7 years; 3) older patients with a good performance status and with contrast enhancement had a median survival of < 4 years; and 4) older patients with a poor performance status had a median survival of only 12 months. It remains unclear, however, how extent of tumor resection impacts the predictive value of each category because it was not evaluated in that study.

Similarly, the EORTC (European Organization for Research and Treatment of Cancer) developed a prognostic scoring system based on 2 large, randomized, multicenter trials involving more than 600 patients. In their multivariate analysis, age > 40 years, astrocytic tumor type, tumor size > 6 cm, tumor crossing the midline, and neurological deficit at diagnosis were retained in the model. A favorable prognostic score was defined as no more than 2 of these adverse factors and was associated with a median survival of 7.7 years. The presence of 3–5 prognostic factors was associated with a median survival of 3.2 years (95% CI 3.0–4.0 years).

### Diagnostic Imaging

Although the emergence of 3-T magnets has improved image resolution considerably, 1.5-T MR imaging remains the gold standard for noninvasive identification and diagnosis of LGGs. Low-grade gliomas are characteristically homogeneously isointense to hypointense on T1-weighted images and hyperintense on T2-weighted images. The epicenter of low-grade astrocytomas is typically within the white matter, whereas oligodendrogliomas can be more superficial and will occasionally expand the adjacent gyrus. Contrast enhancement is uncommon but more often seen in oligodendrogliomas (25%–50%). Calcifications are apparent in 20% of lesions and are characterized by foci of high T1 and low T2 signals. Vasogenic edema and mass effect are uncommon due to the slow-growing nature of these tumors. Rarely, large LGGs will involve 3 or more cerebral lobes (gliomatosis cerebri). Diffusion tensor imaging has proven to be an essential adjunct to structural imaging for both preoperative planning and intraoperative neuronavigation. Specifional function can be determined using fMRI, although this technique remains too imprecise for complex functions such as language mapping, as their sensitivity (PET, 75%; fMR imaging, 81%) and specificity (PET, 81%; fMR imaging, 53%) remain suboptimal. For the identification of peritumoral language pathways, direct intraoperative stimulation mapping remains the gold standard. Intraoperative MR imaging is another operating room technology that may impact outcome of LGG surgery. Through real-time guidance, it allows for localization of tumors and their margins, and facilitates continuous assessment of surgical progress. Studies of patients who underwent LGG resection in an intraoperative MR imaging suite report encouraging results in terms of achieving greater extent of resection, which impacts outcome.

However, using standard structural imaging paradigms, the decision to presume low-grade histology on the basis of a nonenhancing lesion is a common mistake. For patients with supratentorial mass lesions that exhibit the typical imaging features of LGG, structural MR imaging has a false-positive rate as high as 50% when attempting to predict the histological diagnosis of astrocytoma. This risk of anaplasia in nonenhancing lesions increases significantly with patient age. Thus, in our opinion, observation of LGGs is not a prudent option and early tissue diagnosis is essential. These misleading imaging features are likely due to the intrinsic heterogeneity of LGGs, a characteristic evident on physiological imaging such as MR spectroscopy, which can demonstrate pockets of high-grade populations nested within the tumor stroma. Thus, stereotactic biopsies should be planned using MR spectroscopy guidance to target putative high-grade components in nonenhancing tumors.

Next-generation structural MR imaging technologies have recently focused on preoperatively delineating LGGs. Microscopic molecular movement of water in
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tumor tissue reflects tissue properties that include varying levels of structural alterations, tumor cellularity, and vasogenic edema. Diffusion-weighted MR imaging uses strong gradients to probe the structure of biological tissues at a microscopic level by measuring the Brownian motion of water molecules. Acquiring data with gradients in 3 directions allows the calculation of the apparent diffusion coefficient, while acquiring data with gradients in 6 or more directions allows the calculation of the apparent diffusion coefficient and the fractional anisotropy value. Recent work using these emerging imaging paradigms attempted radiographic prediction of specific LGG subtypes (Fig. 3). Interestingly, initial attempts demonstrated a significant difference in the apparent diffusion coefficient and fractional anisotropy values between patients with newly diagnosed Grade II oligodendrogliomas and astrocytomas, whereas patients with heterogeneous Grade II oligoastrocytomas had values that fell in between.69 Although the apparent diffusion coefficient has been suggested to correlate with cell density in a mixed population of glioma patients, it remains unclear whether this parameter is what drives its correlation with specific LGG subtypes.

The emergence of physiological imaging techniques has indeed added a new dimension to LGG diagnosis and targeting.28 Proton MR spectroscopy is another evolving modality, which identifies the distribution of cellular metabolite levels. Five classes of molecules are generally observed in brain spectra: N-acetylaspartate; free choline and choline-containing compounds, including phosphocholine and glycerophosphocholine; creatine and phosphocreatine; lactate; and lipid. Using MR spectroscopy, typical spectra of LGG include a dominant choline peak (reflecting increased membrane synthesis) with low-intensity N-acetylaspartate (reflecting decreased neuronal elements) and no quantifiable lipid or lactate (suggesting an absence of necrosis or hypoxia, respectively, both features of high-grade gliomas). The choline peak may be associated with cellular density and cellular proliferation, thereby improving selection of targets for biopsy. Normalized creatine/phosphocreatine levels of LGGs are a significant prognostic factor for progression-free survival, as well as malignant progression–free survival.54 Newly introduced 3D techniques allow whole anatomical regions to be quantified metabolically, correlating well with the region of T2 hyperintensity, as well as with tumor extension along white matter tracts.108 Three-dimensional MR spectroscopy may also have the potential to evaluate the proliferative activity of LGGs and identify potentially more aggressive clinical behavior.39 There is less convincing evidence, however, that MR spectroscopy is sufficient for monitoring and follow-up of patients with suspected LGG.117 In some instances, MR spectroscopy can also be used to discriminate radiation necrosis from tumor progression, as well as to monitor treatment progress.23

Among low-grade astrocytomas, measurement of relative cerebral blood volume (rCBV) derived from dynamic susceptibility-weighted perfusion contrast-enhanced MR imaging (DSC-MR imaging) correlates well with tumor behavior and patient survival.83 For these tumors, rCBV specifies regional tumor vascularity and correlates with expression of vascular endothelial growth factor, 2 critical factors driving tumor growth.84 Most low-grade astrocytomas demonstrate slightly higher rCBV than normal tissue (1.5), with an increase in rCBV (1.75–2.0) indicating the evolution of a more aggressive tumor and often preceding the emergence of enhancement.85 Low-grade astrocytoma rCBV measurements also correlate well with time to progression, raising the possibility that DSC-MR imaging can predict the risk of transformation.25 In contrast, however, low-grade oligodendrogliomas have a paradoxically high rCBV, confounding the strict reliabil-

Fig. 3. Physiological imaging of LGGs. Physiological imaging profiles for WHO Grade II oligodendrogliomas (A), oligoastrocytomas (B), and astrocytomas (C). Apparent diffusion coefficient (ADC) maps demonstrate normal-appearing white matter (green), pink regions characteristic of oligodendrogliomas, and blue values characteristic of astrocytomas. Similarly, physiological MR imaging modalities can identify histologically specific profiles on the basis of the choline-to-NAA index (CNI), as well as fast spin echo (FSE), FLAIR, and normalized MR perfusion (nPH) signatures. nADC = normalized ADC.


Biopsy and the Utility of Integrated Metabolic Imaging

Surgical options for LGG are limited to biopsy versus resection. Stereotactic needle biopsy can obtain tissue for diagnostic purposes, but there is a risk of sampling error. In one recent study, overgrading of WHO Grade II tumors occurred in 11% of cases and undergrading of WHO Grade III gliomas in 28%. Thus, histopathological diagnosis of LGG with only stereotactic biopsy comes with substantial risk of inaccuracy, particularly for tumors with low proliferative activity or for mixed gliomas. At present, indications for biopsy of presumed LGGs are: 1) diffuse lesion, such as gliomatosis, and 2) patients unable to undergo a definitive operation for medical reasons.

Given the potential diagnostic inaccuracies associated with stereotactic biopsy, the operative integration of new imaging modalities shows promise in improving the sensitivity and specificity of LGG biopsy. Additional use of metabolic data for target selection can potentially increase both the diagnostic efficacy and safety of stereotactic brain biopsies. Previous reports noted significant improvement of its diagnostic yield if guidance with FDG, l-methyl-11C-methionine, FET, 18F-choline and 11C-choline PET, or 201thallium SPECT was used. These techniques, which range in diagnostic yield from 80% to 100%, have drawbacks, including radiation exposure, excessive time requirements, poor anatomical resolution, technological complexity, and financial expense, which limit their general use. Alternatively, 1H-MR spectroscopy is a noninvasive and sensitive study that can be performed at the time of routine MR imaging. For LGGs, the diagnostic yield of 1H-MR spectroscopy—supported stereotactic tissue sampling approaches 100%. Thus, the integration of metabolic imaging modalities into the stereotactic biopsy procedures greatly improves the reliability of this approach in correctly identifying and grading LGGs.

Surgery and the Value of Extent of Resection

In the past 2 decades, mounting evidence in the literature suggests that a more extensive resection of LGG is associated with a more favorable life expectancy. In addition to providing longer overall survival, more aggressive resections of LGGs can also influence the risk of histological upgrading, raising the possibility that a surgical intervention can alter the natural history of the disease. These associations are evident not only within the general hemispheric LGG population but also for specific LGGs limited to certain subregions, such as insular LGGs. An overall review of the modern neurosurgical literature reveals 16 studies that have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among patients with LGG (Table 2). Four of these studies included volumetric analysis of extent of resection. Of the nonvolumetric studies, 8 demonstrated evidence supporting extent of resection as a statistically significant predictor of either 5-year survival or 5-year progression-free survival. These studies were published from 1990 to 2010 and most commonly employed a combination of multivariate and univariate analyses to determine statistical significance. Interestingly, all 3 negative nonvolumetric studies evaluated 5-year survival only, without examining the impact on aggressive resection on progression-free survival.

In the modern literature, the largest analysis with volumetric quantification demonstrates a survival benefit for hemispheric LGGs, even at the 10-year mark. More aggressive resection predicted significant improvement in overall survival compared with a simple debulking procedure. For patients who undergo gross-total resection, the 10-year survival rate approaches 100%, but the survival rate decreases incrementally as extent of resection approaches 40%. Furthermore, a significantly improved overall survival was predicted even when pushing near the limits of complete resection. For a 100% resection versus a 50% resection, the hazard ratio for risk of mortality was also significantly reduced. Predicted overall survival was negatively influenced by residual tumor—even with volumes on the order of 10 cm³. Although other studies have also suggested an association between greater resection and improved outcome, none has offered the resolution to demonstrate the benefit of resecting the last few cubic centimeters, a step that may require the use of sophisticated mapping techniques. Collectively, these data argue strongly in favor of achieving a maximal resection of LGGs.

Histological Upgrading

Histological upgrading of LGGs is a special consideration for these patients, as it carries a dramatically worse prognosis. Interestingly, the documented incidence of LGG transformation ranges from 17% to 73% in clinical studies published over the past 15 years, suggesting a high level of variability. Definition of the timing of this phenomenon is equally elusive, as reported median intervals range from 2.1 to 8 years.
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**TABLE 2: Neurosurgical literature on extent of resection of LGG***

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Methodology</th>
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<th>Benefit</th>
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* Since 1990, 16 studies have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression in patients with LGG. Gray rows indicate reports demonstrating a survival benefit for greater extent of resection. The overall trend favors the value of greater extent of resection in improving patient outcome. Abbreviations: NA = not assessed; OS = Overall Survival; PFS = Progression-Free Survival; Pts = Patients.

10.1 years based upon studies published in the past 15 years.23,76,82,88,127,132 Authors of several recent studies have examined histological upgrading in the context of extent of resection, reasoning that the risk of progression increases with tumor burden. In a study of hemispheric LGGs, greater preoperative tumor volume was significantly associated with shorter malignant progression-free survival,132 suggesting that tumors that are larger at presentation may have an inherently faster growth rate, and thus recur faster in the setting of a subtotal resection. Tumor growth rates were also studied among 143 consecutive cases of LGG in adults; a median survival of 5.16 years was associated with a growth rate of 8 mm/year or more and a median survival of more than 15.0 years was seen with a growth rate of less than 8 mm/year or more and a median survival of more than 10.1 years based upon studies published in the past 15 years.23,76,82,88,127,132 Among 143 consecutive cases of LGG in adults; a median survival of 5.16 years was associated with a growth rate of 8 mm/year or more and a median survival of more than 15.0 years was seen with a growth rate of less than 8 mm/year or more and a median survival of more than 10.1 years based upon studies published in the past 15 years.23,76,82,88,127,132

Others have also evaluated LGG growth rate, demonstrating that sequential measurement of LGG volume allows accurate determination of growth rates and identification of patients whose tumors are at high risk for early transformation.106 Six-month tumor growth may also predict outcome in patients with LGG better than parameters derived from perfusion- or diffusion-weighted MR imaging.106 Similarly, within the insula, the interval to malignant progression of Grade II gliomas is longer in patients who have undergone greater resections.124 As with hemispheric LGGs, the volume of residual tumor in the insula serves as a predictor of histological upgrading. Thus, these studies represent a potential shift in our concept of aggressive glioma resection, as the ability to manipulate the natural history of these tumors makes a case for earlier intervention and argues against the validity of a simple biopsy procedure or a wait-and-watch approach.

**Mapping Functional Pathways**

The principle that patient outcome improves with greater extent of resection must be tempered by the potential for functional loss following a radical resection. To this end, not only do MR imaging–based neuronavigational techniques facilitate greater resection, but embedding of DT imaging–based tractography can prevent inadvertent resection of adjacent subcortical pathways.136,154 In a recent study of 238 glioma patients randomized to DT imaging–based or traditional MR imaging–based neuronavigation without DT imaging, postoperative motor deterioration occurred in 32.8% of control cases, whereas it occurred in only 15.3% of the study cases.154 Among the LGG cases in this study, the findings did not impact patient survival, but demonstrated the utility of this technology in maximizing tumor resection while minimizing morbidity. Similarly, for patients with gliomas that are located within or adjacent to the rolandic cortex and, thus, the descending motor tracts, stimulation mapping of cortical and subcortical pathways enables the surgeon to identify these descending motor pathways during tumor removal and achieve an acceptable rate of permanent morbidity in these high-risk functional areas.21,41,62 In a recent study in which complete resection was performed in 46.1% of LGG cases, new immediate postoperative motor deficits were documented in 59.3% of patients in whom subcortical motor tracts were identified intraoperatively.
and in 10.9% of those in whom subcortical tracts were not observed. However, permanent deficits were observed in 6.5% and 3.5%, respectively.21 Another study of subcortical motor pathways in 294 patients who underwent surgery for hemispheric gliomas, 14 patients (4.8%) had a persistent motor deficit after 3 months. Interestingly, patients whose subcortical pathways were identified intraoperatively were more likely to develop an additional transient or permanent motor deficit (27.5% vs 13.1%).67 In another study with an 87% gross-total or subtotal resection rate, the overall neurological morbidity was 5% after using cortical motor mapping.48 Thus, collectively the recent literature suggests that intraoperative motor mapping can safely identify corridors for resection, as well as define the limits of tumor resection.

Importantly, prediction of cortical language sites through classic anatomical criteria is inadequate in light of the significant individual variability of cortical organization, the distortion of cerebral topography from tumor mass effect, and the possibility of functional reorganization through plasticity mechanisms. A consistent finding among all cortical language stimulation studies has been significant individual variability.122 Specifically, speech arrest is variably located and can go well beyond the classic anatomical boundaries of the Broca area for motor speech.123 This variability has also been further confirmed by studies designed to preoperatively predict the location of speech arrest based upon the type of frontal opercular anatomy.124 Similarly, for temporal lobe language sites, the distance from the temporal pole to the area of language function can vary from 3 to 9 cm.29 Neural plasticity mechanisms also introduce an element of unpredictability to functional pathway localization. The capacity for the brain to reorganize itself is critical for the process of functional recovery following CNS injury. Interestingly, lesions such as LGGs can induce large-scale functional reshaping. This reorganization is thought to explain why slow infiltrative LGGs within the eloquent cortex do not induce detectable neurological deficits40 and must be anticipated when reoperating on patients with LGGs within or near functional pathways.199

Furthermore, because functional tissue can be located within the tumor nidus, the standard surgical principle of debulking tumor from within is not always safe.131 In the largest reported series of cases in which intraoperative language mapping was used in resection of gliomas, 4 (1.6%) of 243 surviving patients had a persistent new language deficit at 6 months after surgery. Among LGG cases, the gross-total resection rate was 51.6%, suggesting that intraoperative language mapping remains the most effective technique for maximizing resection while minimizing language morbidity.123 In a recent LGG study designed to identify prognosticators of survival and tumor progression, 4 variables (areas of eloquence, patient age > 50 years, KPS score ≤ 80, and lesion diameter > 4 cm) were predictive of survival on multivariate analysis and were incorporated into a scoring system (the UCSF Low-Grade Glioma Scoring System27) that was externally validated.24 Importantly, the predictive value of tumor eloquence made evident in this study demonstrates the need for mapping functional pathways whenever an LGG is presumed eloquent.

Surgical Seizure Control

Seizures play an important role in postoperative quality of life for patients with LGGs, and seizure control, alongside survival and progression-free survival, is an important end point to consider for those undergoing resection. Patients with supratentorial LGGs have a higher incidence of seizures than do patients with high-grade gliomas. Patients with LGGs also suffer from a number of neuropsychological problems that are aggravated by the severity of epilepsy and intensity of its treatment.27 The pathophysiological mechanism causing epileptic seizures in these patients is unclear, but several studies suggest that seizures rarely originate from the mass lesion itself and instead originate from adjacent brain tissue. The factors associated with freedom from seizures were gross-total resection, preoperative seizure history of less than 1 year, and nonsimple partial seizure type (Fig. 5).23 Consequently, many surgeons advocate the use of intraoperative electrocorticography during LGG resection to identify and facilitate resection of adjacent cortical seizure foci.81,135 although some work suggests that gross-total resection alone can lead to durable seizure control in some cases.26 Nonetheless, because LGGs are often diffuse and difficult to delineate, the high likelihood of subtotal tumor resection supports the need to map independently and fully resect single or multiple epileptogenic areas for optimum seizure control in patients who have medically refractory epilepsy.12 Others have also compared glioma patients undergoing “lesionectomy” with patients who had “seizure surgery,” defined as removal of adjacent mesial temporal or frontal lobe brain tissue (that is, “lesionectomy plus”). The results also supported the value of targeting broader territories, as patients who underwent the more extensive procedure had greater than 95% reduction in seizure frequency, compared with approximately 50% in patients who only had tumor resection.133

Lesions adjacent to mesiotemporal structures often result in secondary epileptogenicity in the same region. For these patients, MR imaging evidence of hippocampal atrophy is predictive of unsatisfactory seizure outcome after tumor resection and therefore temporal lobectomy plus amygdalohippocampectomy with intraoperative corticography is associated with optimal seizure control. Similarly, for patients with no MR imaging evidence of hippocampal atrophy and temporal lobe LGGs, intraoperative electrocorticography and deep electrode monitoring are indicated as well.80 Importantly, when patients are initially seizure free after surgery, seizure recurrence is associated with tumor progression.26,109 Although poorly understood, one proposed alternative to more extensive surgery for seizure control is utilization of stereotactic radiosurgery for mesiotemporal tumors.126 Longer duration of a tumor-related seizure disorder, however, is a negative prognostic factor for postoperative seizure control following resection, again emphasizing the importance of early microsurgical intervention.26 This avoids the development of multiple seizure foci, which is known to occur when patients continue to have seizures for several years without successful control. It should be emphasized that for patients with occasional seizures (1–2 per year) or
those with complete control on antiepileptic medications, there is no known benefit from intraoperative electrocorticography during microsurgical resection.26

**Adjuvant Treatment for LGG**

The determination of adjuvant treatment of LGG is still challenging and is based mainly on the best definition of prognostic factors. While watchful waiting remains an option for patients with low-risk LGGs, the optimal treatment has yet to be defined for those at risk for rapid progression and histological upgrading. In a recent prospective trial of 111 RTOG LGG patients, preoperative tumor diameter ≥ 4 cm, astrocytoma/oligoastrocytoma histological type, and residual tumor ≥ 1 cm according to MR imaging each were predictive of significantly higher recurrence rates.129 Many clinical trials are evaluating adjuvant treatments stratified by these risk groups.

**Chemotherapy With Temozolomide and PCV**

The role of chemotherapy for LGG remains to be defined. Several recent studies have explored upfront treatment (that is, immediately following resection) of newly diagnosed LGGs with chemotherapy using either PCV or temozolomide.15,18,58,134 Collectively, these Phase II trials provide little conclusive evidence for clinical efficacy in terms of overall survival, although measuring response in the absence of contrast enhancement is a challenge. In select instances, preliminary evidence suggests that temozolomide is associated with improved quality of life, better seizure control, and longer progression-free survival.15,100,111 Furthermore, in a limited trial involving 16 patients with low-grade oligodendroglioma, data suggesting improved tumor control rates was also reported for the use of PCV chemotherapy.134 However, whether there is a true advantage in treating patients with upfront chemo-therapy compared with initial radiotherapy is currently under investigation. Consequently, it remains controversial whether upfront chemotherapy should be offered to LGG patients, although for patients with bulky disease or neurological deficits, this is a reasonable strategy prior to implementation of radiotherapy.

For the methylating agent temozolomide, early data suggests that the best responders, if any, appear to be patients with oligodendrogliomas and mixed oligoastrocytomas. Combined 1p/19q loss of heterozygosity is significantly associated with a higher rate of and longer response to temozolomide.64 The EORTC study 26971 on first-line temozolomide chemotherapy demonstrated this with a reported 50% response rate for patients with recurrent oligodendroglioma.132 Dose-intensive continuous dosing schedules have also been investigated and were proven to be feasible.17,68 Using a prolonged temozolomide schedule, patients with progressive or recurrent LGGs also have an overall response rate of 30% and a progression-free rate of 56.7%.138

Among PCV chemotherapy trials, the RTOG study 9802 randomized high-risk patients (age > 40 years or subtotal resection) to postoperative radiotherapy with or without subsequent adjuvant PCV. After stratification by age, histology, KPS score, and presence or absence of contrast enhancement, patients were randomized to either radiotherapy alone (54 Gy) or radiotherapy followed by 6 cycles of standard-dose PCV. With a median follow-up of more than 4 years, no advantage for the administration of PCV was evident, even in the group of high-risk LGG patients.11 Ongoing clinical trials are evaluating the role of concurrent and adjuvant temozolomide for high-risk patients with LGG.

**Radiation Therapy**

Radiation therapy is used postoperatively for many patients with LGG. The EORTC study 22845 revealed an advantage for immediate postoperative radiotherapy in terms of progression-free survival (5.3 vs 3.4 years), but not for overall survival, among LGG patients.141 The factors that influence the timing of radiation therapy relate to speed of progression and the possibility of late toxicity to normal brain. Higher doses of radiation (> 45–50 Gy) have also failed to demonstrate an improved outcome and are associated with increased late toxicity.65 Furthermore, any benefit on initial tumor control may be outweighed by potential late toxicity.10 In an ongoing international study (EORTC 22033–26033), LGG patients with high-risk disease or with progressive tumors are randomized to primary radiotherapy or primary chemotherapy with low-dose temozolomide for up to 1 year (12 cycles). In addition to clinical factors, these patients are stratified according to 1p status, and their tissue will also be surveyed for other molecular markers of interest in the hope of generating a predictable profile for radiation response. Beyond fractionated radiotherapy, stereotactic radiosurgery has also been raised as a possibility for treating LGGs, although no data exist to support this strategy beyond small, retrospective case series.3,51,55,20,78 At present, there appears to be no conclusive evidence that radiotherapy is indicated.
following biopsy or subtotal resection of a LGG. It should be reserved for the setting of recurrent disease.

**Molecular Targeting**

Recent evidence suggests the Akt-mTOR pathway may play a role in the development of LGGs. PTEN, a negative regulator of the phosphoinositide 3-kinase (PI3K) signal transduction pathway, is methylated at its promoter region in more than 50% of Grade II astrocytomas, oligodendrogliomas, and gliomas of mixed histological characteristics. Sitting downstream of PI3K is the mammalian target of rapamycin (mTOR), a serine/threonine kinase that phosphorylates downstream effectors involved in protein biosynthesis, ribosome biogenesis, and the transcription of genes crucial to cell growth (Fig. 6). The mTOR pathway is frequently upregulated in a variety of neoplasms and has been targeted for therapeutic intervention, with rapamycin showing some antitumor activity in PTEN-deficient glioblastoma. When activated, this pathway amplifies protein transcription, intensifies cell growth, halts apoptosis, and portends a worse prognosis in cases of LGG. More recent evidence implicates PTEN promoter methylation, and, therefore, mTOR activation, in the malignant progression of LGGs. The enrichment for hypermethylation in high-grade recurrences also suggests that this epigenetic modification and PI3K-mTOR pathway upregulation plays a crucial role in the biology of LGGs, as evidenced by correlation of the S6 protein in the mTOR pathway with patient survival. Clinical trials examining the effects of mTOR inhibitors are currently underway, including a Phase II study of everolimus alone for recurrent LGGs (UCSF-H7858–32860–01).

**Current Management Paradigm**

In the modern era, LGG management is more aggressive, multimodal, and nuanced than years past (Fig. 7). Initial assessment begins with an anatomical MR imaging to define the margins and extent of tumor infiltration. Once an LGG is suspected, diffuse lesions are examined with physiological imaging modalities that enable suspected higher-grade sites within the tumor to be stereotactically biopsied. Should pockets of Grade III or IV histology be identified, the lesion is treated as a high-grade glioma with radiation and chemotherapy. If the tumor is histologically low grade, then temozolomide (irrespective of 1p/19q status) is suggested, with subsequent evidence of radiographic progression examined through additional stereotactic biopsy.

For a focal lesion, defined as a mass that is confined to 1 or 2 lobes and has discrete margins on FLAIR imaging, a combination of physiological imaging, functional imaging, and DT imaging tractography are useful prior to resection. The patient’s seizure status must also be accounted for, as those with medically refractory seizure can benefit from intraoperative electrocorticography, while others with occasional breakthrough seizures may not require electrocorticography (lesionectomy-plus). Comprehensive preoperative imaging will also identify the extent of the tumor’s eloquence. The impact of functional sites adjacent to or within the tumor should be assessed in terms of likely extent of resection. For eloquent tumors where < 50% extent of resection is anticipated, frameless biopsy using physiological imaging is recommended, followed by appropriate adjuvant therapy. For eloquent tumors where > 50% extent of resection is anticipated, intraoperative mapping paradigms should be employed. In cases in which postoperative imaging demonstrates
gloss-totel resection, patients are monitored with serial imaging; in cases in which imaging demonstrates subtotal resection, patients should either undergo reoperation (in cases in which the resection was not limited by function) or temozolomide therapy (in cases in which the resection was limited by function). Subsequent evidence of progression is then treated with radiation-based therapy.

**Conclusions**

For the neurosurgeon, LGGs represent an opportunity to intervene early and impact outcome in several ways. Advances in molecular markers, diagnostic imaging, operative techniques and technologies, and adjuvant therapies have collectively pushed the envelope toward improved quality of life and survival. Stereotactic biopsy remains a source of sampling error, but can be enhanced through metabolic imaging. Extent of resection has been increasingly shown to correlate with improved outcome, as well as with better seizure control and reduced histological upgrading rates. While the exact roles and timing of radiation and chemotherapy remain to be defined, the value of upfront therapy has yet to be established, although there may be a role for temozolomide in a subset of patients with postoperative bulky disease. Recent advances in our molecular understanding of the disease may open new avenues for novel therapy, including mTOR inhibitors currently in trial. Nevertheless, significant challenges remain—chief among them the substantial clinical and biological heterogeneity that still exists within the LGG classification. Such limitations not only emphasize the need for further investigation into the tumor subsets, but also the value of clinical studies examining the factors that determine tumor recurrence and transformation.

**Disclosure**

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Author contributions to the study and manuscript preparation include the following. Conception and design: Berger, Sanai. Acquisition of data: Sanai. Analysis and interpretation of data: all authors. Drafting the article: Berger, Sanai. Critically revising the article: all authors.

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