Low-Grade Astrocytomas

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5.1 Epidemiology

Glial tumors constitute approximately 50% of newly diagnosed primary brain tumors, with low-grade gliomas (LGG) accounting for approximately 15% of all brain tumors in adults [21]. The subset of tumors classified as LGG represents a heterogeneous group of tumors with astrocytic, oligodendroglial, ependymal, or mixed cellular histologies. In the adult population, the term LGG typically refers to the diffuse, infiltrating variety of tumors classified as World Health Organization (WHO) grade II lesions–specifically low-grade astrocytomas, oligodendrogliomas, or mixed oligoastrocytomas [33]. Among low-grade astrocytomas, the most common histologic subtypes are the fibrillary, protoplasmic, and gemistocytic variants. There is no indication in the literature that LGGs are more prevalent in a specific ethnic or national group.

Approximately 1,500 new cases of LGG are diagnosed in North America each year [15]. Age-specific data show that low-grade astrocytomas constitute 15% of brain tumors in adults and 25% of brain tumors in children [21]. Pediatric low-grade gliomas, which include cerebellar astrocytomas, optic pathway and hypothalamic gliomas, brainstem gliomas, and hemispheric low-grade gliomas, are discussed elsewhere in the text. These tumors demonstrate a slight male predominance and a biphasic age distribution with the first peak occurring during childhood (ages 6–12 years) and a second peak in adulthood (between the third and fifth decades). The median age of presentation in adults is 35 years.

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5.2 Clinical Presentation

LGGs typically arise in the frontal lobes, followed by temporal and parietal lobe lesions in order of decreasing incidence. Between 50 and 80% of patients present with seizures as their initial symptom, with the majority remaining otherwise neurologically intact [42]. Patients may present with or develop other signs and symptoms, which are largely dictated by the tumor's size and location. This includes signs and symptoms of raised intracranial pressure (headache, nausea, vomiting, lethargy, papilledema), focal neurological deficits (weakness, sensory disturbance or neglect, visual neglect, agnosia, aphasia), and impaired executive function (altered personality, disinhibition, apathy).

In some studies, seizures can accompany LGG presentation in up to 81% of patients [11]. Of the patients who presented with seizures, ~50% have uncontrolled seizures at the time of resection despite antiepileptic treatment. Partial seizure type, temporal location, and longer seizure duration also appear to predispose patients to poorer preoperative seizure control [11]. Careful consideration of a patient's seizure status is of paramount importance for LGG patients, as seizures significantly impact patients' quality of life. Beyond antiepileptic agents, surgical resection is an effective means of reducing seizure burden on patients with LGGs. Postoperatively, the factors associated with freedom from seizures are: gross total tumor resection, preoperative seizure history of <1 year, and nonsimple partial seizure type. However, continued use of antiepileptic drugs can be necessary, and in some patients, an additional operation may be required for persistent seizure activity. In our experience, optimal control of intractable epilepsy without postoperative anticonvulsants is possible when perioperative (i.e., extraoperative or intraoperative) electrocorticographic mapping of separate seizure foci accompanies the tumor resection. With most cases of epilepsy–those with occasional breakthrough seizures–mapping is not needed, but complete tumor resection is. When mapping is not used and radical tumor resection with adjacent brain is carried out, seizures occur less frequently, but most patients must remain on antiepileptic drugs [5].

5.3 Histology and Microscopic Features of Low-Grade Infiltrating Astrocytomas

5.3.1 Pathology

In recent years, low-grade astrocytomas have been categorized into the circumscribed and infiltrating subtypes, which differ in their morphological, clinical, radiological, and genetic features [19]. The current nosology of brain tumors considers infiltrating astrocytomas as diffuse and progressive gliomas that gradually accumulate more aggressive histological and molecular features [33]. The "infiltrating astrocytoma" without additional qualifiers is a WHO grade II neoplasm, even though the term can be used to identify all astrocytomas from grade II to IV. WHO grade II astrocytoma is synonymous with low-grade infiltrating astrocytoma (LGIA). "Astrocytoma, NOS" (not otherwise specified) is a highly vague and confusing term that should not be considered as a specific diagnostic entity. "Well-differentiated astrocytoma" is another vague term that should be avoided as a final diagnostic category.

5.3.2 Microscopic Features

An astrocytoma is traditionally described as a tumor resembling normal astrocytic cells. However, there is variability concerning the microscopic attributes of an astrocyte, and hence what an astrocytoma should look like microscopically. Nevertheless, the morphological features of cells recognized as fibrillary or protoplasmic astrocytes constitute the standards for defining an astrocytoma (Fig. 5.1).

Typically, low-grade infiltrating astrocytoma (LGIA) is hypercellular by a factor of two or more when compared with normal white matter. Recognizing the hypercellularity and the disruption of the architecture are the first clues to the diagnosis. Occasionally, the cell density may only minimally exceed that of normal white matter. In such cases, a correct diagnosis depends on the accurate interpretation of the cytological features. The microscopic nature of infiltrating astrocytomas is evident in their ability to penetrate the brain parenchyma and permeate among glia, neuronal cells, and axonal segments.

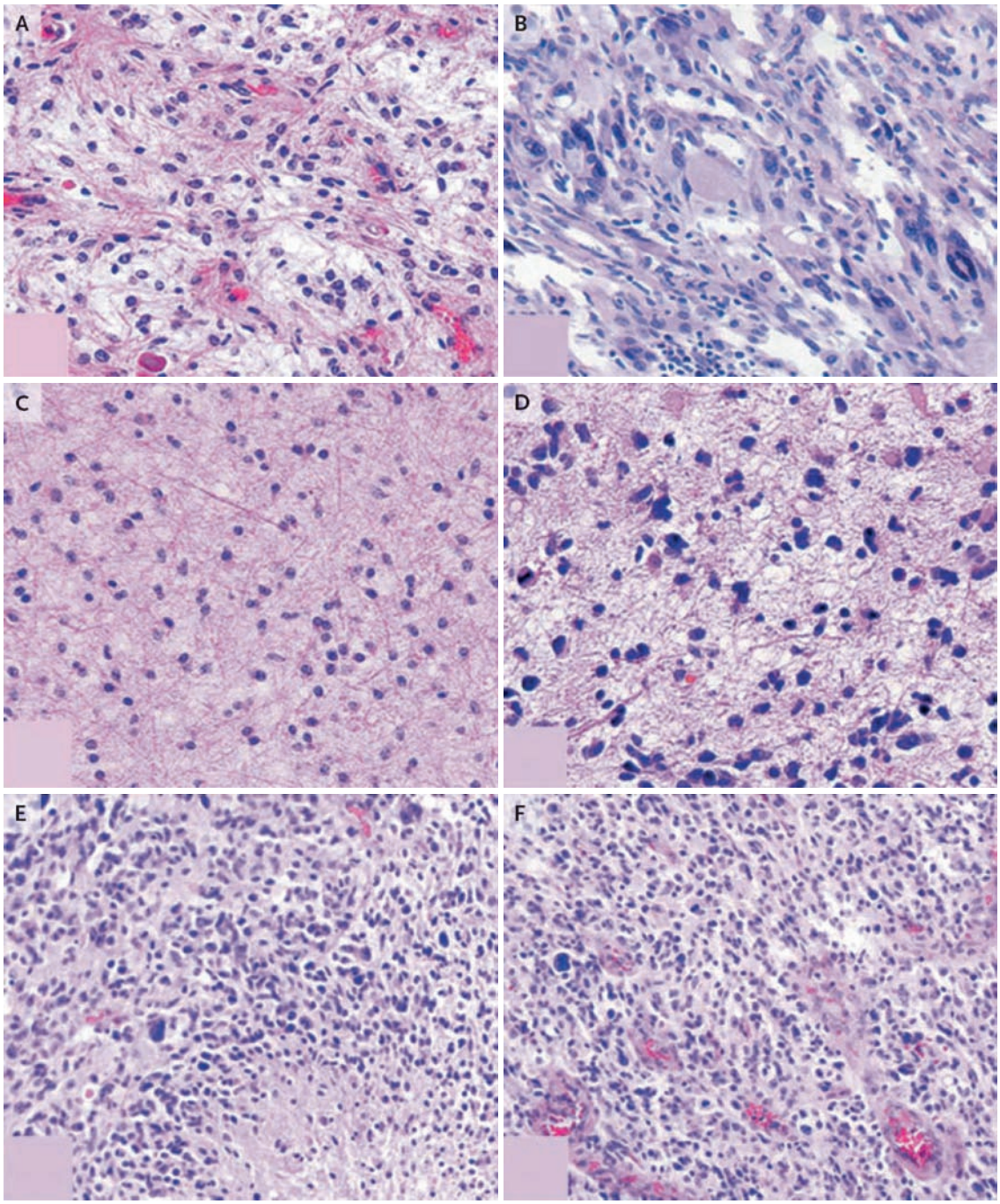

Fig. 5.1 Grades I–IV (World Health Organization) astrocytic tumors. Panels **a** and **b** show circumscribed astrocytomas. Pilocytic astrocytomas (panel a) are typically indolent, have a limited invasive capacity, and rarely undergo anaplastic progression. These tumors may have microvascular hyperplasia and cellular pleomorphism despite their designation as grade I tumors. Pleomorphic xanthoastrocytomas (panel **b**) are also relatively circumscribed and, despite their distinct, conspicuous cellular pleomorphism, tend to be low-grade (grade II) tumors with limited capacity for brain invasion. Panels **c** through **f** show diffuse-type astrocytomas, which have the capacity for dispersion into the surrounding brain and a high frequency of anaplastic progression. A grade II astrocytoma (panel **c**) is well differentiated, with mild-to-moderate nuclear pleomorphism. A grade III astrocytoma (panel **d**) has a high rate of cell proliferation, as indicated by the mitotic figures. These tumors commonly have a moderate degree of cellular pleomorphism and more heterogeneous cellularity. Glioblastoma multiforme, grade IV, is the most aggressive glial tumor and has the distinctive features of palisading or geographic necrosis (panel **e**) and conspicuous microvascular hyperplasia (panel **f**) in addition to marked cellular pleomorphism (adapted from [64])

The infiltrating astrocytomas have substantial nuclear hyperchromasia and pleomorphism. The nuclei often display striking irregularities with invaginations, sharp edges, and irregular contours. The chromatin is much coarser than that of normal astrocytes. Most astrocytic nuclei do not exhibit prominent nucleoli, or the nucleoli are rather indistinct within a markedly condensed chromatin. The size and shape of tumor nucleoli are quite variable among tumors as well as within a single specimen. Tumor cells occasionally display a fibrillary, eosinophilic cytoplasm. In paucicellular areas, the cytoplasm appears even more indistinct, and it may not be easy to associate the nuclei with the background fibrillarity.

Perinuclear haloes or the so-called fried-egg appearance of the cytoplasm can be seen in astrocytomas and does not necessarily imply an oligodendroglial component. Nevertheless, the prominence of such cells always raises the differential issue of oligodendroglioma or the dubious category of oligoastrocytoma.

The most common pattern for infiltrating astrocytoma is the microcystic pattern, which is a reliable indicator of an infiltrating low-grade glioma since it rarely occurs in reactive conditions. However, the microcystic pattern is not specific to LGIA and can also be observed in oligodendrogliomas and glioneuronal tumors.

LGIAs display secondary structures, such as perineuronal satellitosis, subpial or leptomeningeal spread. Although these features are helpful in defining a low-grade glial neoplasm, they are neither specific nor common in LGIA. Mineralizations (either as amorphous or concentric forms) can be seen in association with LGIA. These mineralizations often occur within the gray matter and are more typical of an oligodendroglioma than astrocytoma.

The histological definition of LGIA practically excludes the presence of mitoses [33]. The significance of a solitary mitosis in a fairly well-sampled tumor is still controversial. A recent study found a trend for a better prognosis for infiltrating astrocytomas with a single mitotic figure compared with frankly anaplastic astrocytomas. However, this trend could not be substantiated in multivariate analyses [51]. Nevertheless, it has been suggested that a single mitotic figure in a resection specimen may not impact the prognosis significantly, and some authors accept the presence of a solitary mitosis in a well-sampled grade II astrocytoma. In such cases, it is even more critical to be aware of the radiological, surgical, and clinical findings to interpret the biopsy better. In our opinion, it is not appropriate to view the microscopic features in isolation from the clinical and radiological data.

5.3.3 Immunohistochemical Features

The diagnosis of LGIA is primarily reached through routine H&E stains, and immunohistochemical stains can hardly make up for a poorly sampled specimen. Nevertheless, a number of immunohistochemical stains are useful adjuncts in the interpretation of LGIA. The commonly used antibodies for neurofilament protein (NF) aid in defining axons within the specimen and confirm the infiltrative nature of the tumor. Even though astrocytomas and astrocytes are strongly positive for GFAP, this antibody is often not helpful in determining the type and the grade of the neoplasm since the cells of many astrocytomas have little cytoplasm. In addition, the strongest GFAP positivity is seen in reactive rather than neoplastic astrocytes. The gemistocytic cells are often weakly positive for GFAP, and the staining is usually located in the periphery of the cytoplasm. In contrast, mini-gemistocytes of oligodendroglioma are strongly GFAP-positive. Staining for MIB-1 (Ki-67 antibody) is usually less than 2%, and a neoplasm with higher than 5% MIB-1 labeling should raise suspicions of a higher grade neoplasm. Despite extensive studies on the Ki-67 labeling index and its relation to grade and survival, changing the grade of the lesion based on the MIB-1 labeling index is not justified in the current WHO classification [78]. A significant percentage of LGIAs are immunoreactive for p53 [14, 82]. This is particularly predominant in gemistocytic astrocytomas [82].

5.3.4 Ultrastructural Features

The ultrastructural examination of a LGIA is not undertaken for diagnostic purposes, and only to explain an unusual histological feature. The fine structure of the astrocytic cell bodies and the processes are fundamentally similar to those of normal or developing astrocytes. The nuclei often display marked chromatin condensation and irregularities. The astrocytomas differ in their less developed cell junctions and poorly formed peripheral processes. The processes often consist of small microvilli or pseudopod-like protrusions.

The cytoplasm of astrocytoma cells often contains little or no intermediate filaments, except in areas with increased cellularity [24]. The cytoplasm of gemistocytes is typically loaded with organelles and is sparse in intermediate filaments. The granular cell astrocytomas contain partially membrane-bound, dense bodies compatible with secondary lysosomes. The granular cells also contain intermediate filaments corresponding to GFAP [47], supporting their glial origin.

5.4 Conventional Neuroimaging Studies

The typical computed tomographic (CT) appearance is one of an either discrete or diffuse hypo- to isodense mass lesion, showing minimal or no enhancement with intravenous contrast. In approximately 15–30% of patients, however, tumor enhancement can be appreciated [41, 53]. Calcifications may also occur, particularly among oligodendrogliomas or mixed oligoastrocytomas. In addition, cystic changes may be seen with any histological subtype.

Magnetic resonance imaging (MRI) is the diagnostic procedure of choice for LGG, delineating the lesion as hypo- to isointense on T1-weighted images, and hyperintense on T2-weighted images (Fig. 5.2). Similar to CT scans, the majority do not show gadolinium enhancement on MRI. LGGs are intra-axial lesions, but do not typically exert significant mass effect on surrounding structures. They do, however, display a tendency to reside within and extend along white matter tracts (e.g., corpus callosum, subcortical white matter). Neuroimaging is not diagnostic, but may suggest a particular pathological subtype of LGG by virtue of the tumor's location and imaging characteristics. Oligodendrogliomas, for example, are frequently located within the frontal lobes, involve the cortex, and display calcifications, in contrast to other LGGs. Importantly, T1-weighted MRI with gadolinium may underestimate the extent of an LGG. The true extent is shown on the T2-weighted sequences, although on these sequences tumor extent and surrounding edema are indistinguishable. More recently, diffusion tensor MR imaging has been used as a surrogate marker of glioma infiltration [58, 59].

5.5 Emerging Neuroimaging Technologies

5.5.1 *Magnetic Resonance Imaging*

Continued improvement in the resolution of anatomic imaging and innovations in functional and physiological imaging modalities have the potential to improve our ability to diagnose, treat, follow, and predict outcome in LGG patients. The increasing use of 7-T MRIs (as compared the standard 1.5-T magnet) will provide more anatomic detail and exquisite cytoarchitectural data on intracranial lesions [16, 17]. Proton magnetic resonance spectroscopy (MRS) allows for the noninvasive assessment of metabolite levels within intracranial

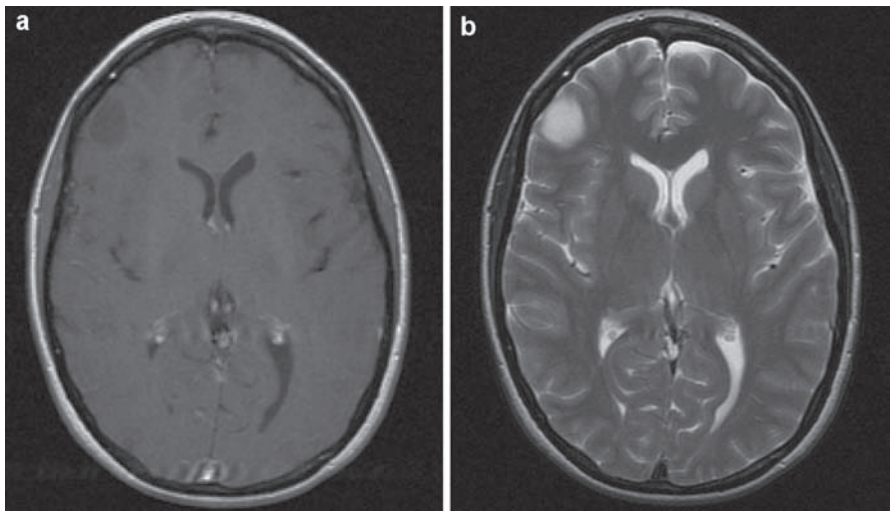

Fig. 5.2 T1-weighted, axial (**a**) and T2-weighted, axial (**b**) magnetic resonance imaging of a non-contrast-enhancing, low-grade astrocytoma in a 41-year-old female patient

lesions. Of particular interest are the metabolites N-acetyl aspartate (NAA), choline (Cho), creatine (Cr), and lipids. In contrast to normal brain, gliomas typically demonstrate a decrease in NAA and Cr levels and a rise in Cho levels, indicative of their proliferative potential, cellular heterogeneity, and high cell turnover. In general, higher grade lesions display higher Cho to NAA and Cho to Cr ratios than lower grade tumors. The utility and reliability of MRS in predicting tumor grade noninvasively are currently being evaluated [30, 43, 73], but do not supplant the need for tissue diagnosis. However, MRS may facilitate the identification of targets for surgical biopsy, focusing our attention on regions with elevated Cho peaks, suggestive of increased cellular proliferation and thereby regions of maximal tumor activity. In addition, MRS has proven useful in monitoring LGG patients following radiotherapy, as it can often distinguish between tumor recurrence and radiation necrosis.

Magnetic resonance techniques have also been developed for assessment of cerebral blood volume (CBV). A 2- to 3-min dynamic acquisition of T2-weighted images during intravenous injection of a bolus of Gadolinium-DTPA allows estimations of CBV. A voxel-by-voxel CBV map can be created by integrating the area under the dynamic contrast uptake curve and provides a relative measure of CBV with a spatial resolution of approximately $1 \times 2 \times 5\,mm^3$ or better. Magnetic resonance perfusion has already demonstrated utility in predicting histopathological diagnosis and tumor grade noninvasively [10, 22] (Fig. 5.3), and will likely play a role in selecting biopsy locations, evaluating treatment response, and differentiating treatment effects versus recurrent tumor.

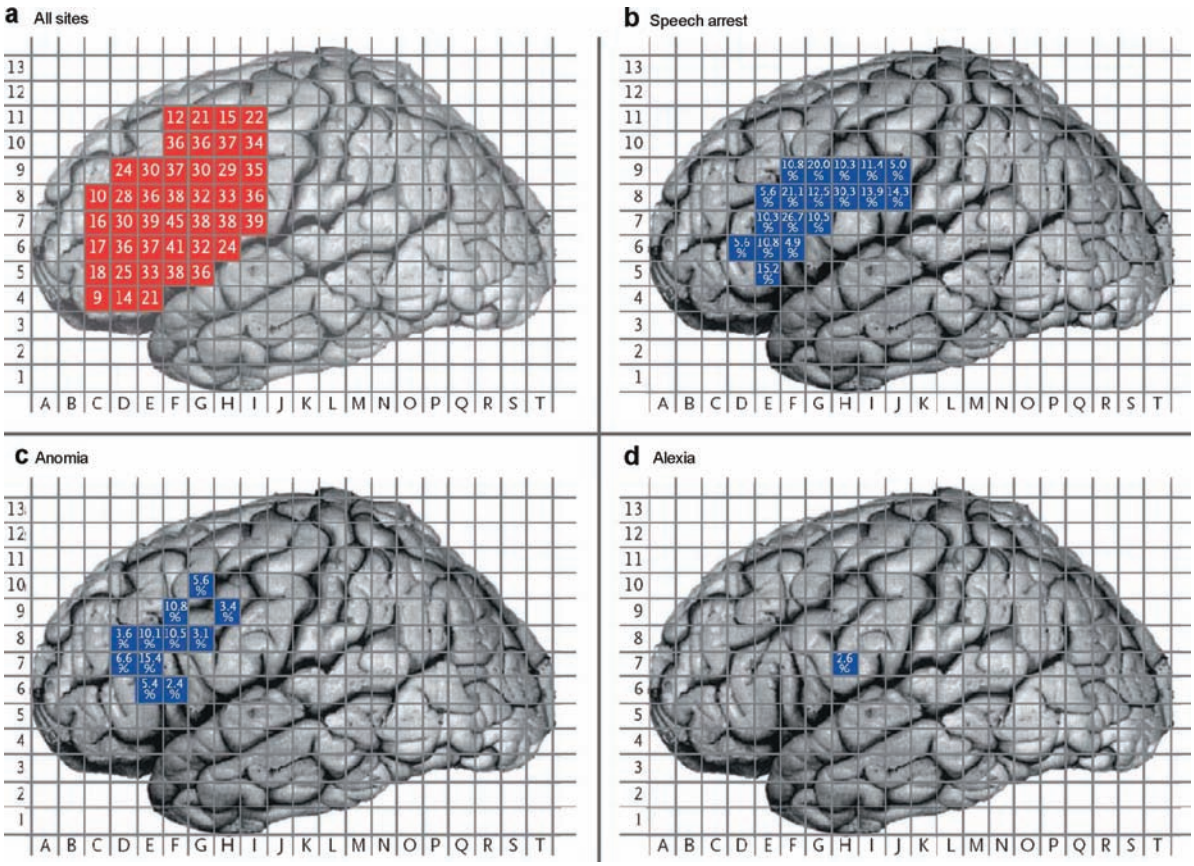

Fig. 5.3 Awake mapping results for 1,237 cortical sites stimulated in 151 glioma patients. The *red squares* denote the total number of sites that were stimulated, and the *blue squares* denote the total number of stimulations that induced speech dysfunction. A lateral view of the dominant-hemisphere cortex indicating the total number of stimulations per square centimeter of the frontal cortex is shown in panel **a**. The number of stimulations (*upper value*) and the percentage of total stimulations (*lower value*) that induced speech arrest (**b**), anomia (**c**), and alexia (**d**) are shown in each square centimeter of the frontal cortex (adapted from [66])

5.5.2 Positron Emission Tomography

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) are additional functional/metabolic imaging modalities that contribute to the diagnosis and management of LGG patients. These modalities supplement the characterization of tumor grade, as LGGs are typically hypometabolic compared with high-grade lesions. Preoperatively, these technologies are also used to identify motor- or language-related regions of cortical function, although with limited specificity. In addition to predicting tumor grade and preoperative planning, indications for the use of PET or SPECT in LGG include following patients for evidence of tumor recurrence or dedifferentiation [44].

5.5.3 Functional Imaging

Functional MRI is based on the increase in blood flow to local vasculature that accompanies neural activity in the brain. This results in a corresponding local reduction in deoxyhemoglobin, as the increase in blood flow occurs in the absence of a comparable increase in oxygen extraction. Thus, deoxyhemoglobin is used as an endogenous contrast-enhancing agent and serves as the source of the signal during fMRI. fMRI results can be consistent with electrophysiology, PET, cortical stimulation, and magneto-encephalography and are commonly used to provide preoperative functional and structural information for neurosurgery. Cortical stimulation, which remains the gold standard, is based upon local circuit disruption or activation and best identifies areas that are essential to language processing. In contrast, fMR imaging is an activation-based method that identifies all regions of the brain demonstrating activity related to a particular task, regardless of whether those areas are essential or supplementary. Consequently, areas that appear negative for language when cortical stimulation is used may still demonstrate fMR imaging activation, producing false-positive results. Decreased specificity may also be expected because fMR imaging is a perfusion-based method and does not directly detect neuronal activity.

5.5.4 Magnetoencephalography

Magnetoencephalography (MEG) has also been increasingly used for preoperative functional mapping. Compared with functional MR (fMR) imaging and positron emission tomography, MEG has the advantage of higher temporal resolution by directly measuring neuronal activation rather than indirect hemodynamic change. Previous studies have also suggested that MEG is more accurate than fMR imaging in identifying functional cortices that have been distorted by a nearby tumor. Overall, MEG is a robust and reliable functional imaging modality that is now used to identify the cortical location of motor and sensory pathways. Integrating MEG data with DTI information into a neuronavigational workstation directs the neurosurgeon towards potential functional sites that can be intraoperatively confirmed using stimulation mapping. Magnetic source imaging (MSI), which is based on the magnetoencephalographic detection of the late neuromagnetic field elicited by simple speech sounds [76], is another adjunct to mapping techniques that can be useful for mapping the somatosensory cortex and determining hemispheric dominance, and may serve as a replacement for the Wada test.

5.6 Patient Outcome and Survival

Median overall survival for LGG patients is approximately 6.5–8 years [1, 31]. Published survival estimates for patients diagnosed with LGG range from 3 to over 20 years [1, 28, 32, 35, 38, 53, 55, 71, 79]. Overall, 5- and 10-year survival rates of ~70% and 50%, respectively, have been reported in the literature [36]. Interestingly, the clinical course of individual LGGs can demonstrate substantial heterogeneity, with certain lesions tending to behave more aggressively, while others follow a more indolent course. This diversity of clinical behavior is matched by the anatomic and histopathologic diversity inherent to LGGs. Not surprisingly, this contributes to the controversy among experts regarding the most appropriate strategy for treating this patient population. In a recent study, however, Smith et al. demonstrated that, after adjusting for the effects of age, KPS, tumor location, and tumor subtype, the extent of resection was a significant predictor of overall survival and tended towards predicting progression-free survival [74]. This volumetric extent of resection analysis revealed that patients with ≥90% resection had an 8-year overall survival of 91% and a progression-free survival of 43%, while patients with <90% resection had an 8-year overall survival of 60% and a progression-free survival of 21%.

5.7 Prognostic Factors

In light of this clinical heterogeneity, it has been particularly important to identify reliable prognostic factors and stratify LGG patients into low- and high-risk subgroups, allowing for the implementation of upfront treatment for lesions predicted to behave more aggressively. Additionally, reliable prognostic factors allow for the rational stratification of patients enrolled in clinical trials.

Clinical factors associated with improved LGG survival outcomes include: age less than 40 years at diagnosis, presence of seizures at diagnosis, the absence of additional neurological deficits at diagnosis, Karnofsky Performance Score (KPS) greater than or equal to 70, and Folstein Mini-Mental Status Examination (MMSE) scores greater than 26/30 [1, 8, 20, 29, 36, 55, 71, 75]. Imaging factors predictive of poor survival include: maximal tumor diameter greater than 5 to 6 cm and the presence of contrast enhancement [1, 71]. Increasingly, the extent of surgical resection has been found to be a significant predictor of outcome and/or progression-free survival among LGG patients (see Surgery section in Treatment Options). Furthermore, histopathological factors associated with better prognosis include an MIB-1 labeling index less than 8% and a histological diagnosis of either low-grade oligodendroglioma or oligoastrocytoma (especially if harboring chromosome 1p deletions, an indication of chemosensitivity and an indolent growth pattern) [55, 69, 71].

Dedifferentiation or malignant transformation is a well-described phenomenon observed in low-grade gliomas. In the literature, 13% to 86% of tumors initially diagnosed as low-grade recur at a higher histologic grade [3, 35, 42, 45, 49, 54, 75, 81]. Similar to its broad range of incidence, the time to malignant differentiation is also variable, ranging from 28 to 60 months [3, 42, 61, 70, 81]. However, the factors resulting in the transformation to a malignant phenotype are unclear, and the effect of treatment on this malignant transformation remains controversial. In one series, 58% of patients who did not initially undergo biopsy and treatment of a suspected low-grade glioma after diagnostic imaging studies eventually required surgery at a median interval of 29 months, and 50% of the tumors then showed anaplastic features [61]. Although a higher incidence of malignant transformation at the time of operation and shorter time to tumor progression were observed compared with that in patients who initially were operated on, the study concluded that no difference was observed in overall survival. Nevertheless, the timing of malignant transformation likely impacts patient outcome, and this phenomenon may be detected by more robust future studies. Furthermore, the extent of resection studies suggests that the natural history of malignant transformation can be altered by greater resection [74].

5.8 Genetic Expression Profile

The cause of LGG is unknown and, with the exception of patients with one of the phakomatoses, there is no defined genetic predisposition that leads to the development of these tumors. The only genetic alteration consistently observed in patients with low-grade astrocytomas is a mutation of p53 [27]. The p53 gene is located at chromosomal location 17p13.1, and this site is often deleted in astrocytomas of all grades. The remaining copy of p53 is usually inactivated through a subtle mutation. Since this gene is essential in the regulation of apoptosis and cell cycle progression, loss of normal p53 function promotes the accelerated growth and malignant differentiation of astrocytes [6, 85]. Astrocytomas are the only type of brain tumor to have significant p53 mutation rates. Between 50% and 60% of grade 2 and grade 3 astrocytomas exhibit p53 mutations, suggesting that inactivation of this tumor suppressor gene is an early lesion among gene alterations associated with the development of malignant gliomas [82]. Although some glioblastomas exhibit p53 mutations, a significant subset of them do not and instead have amplification of the epidermal growth factor receptor (EGFR) gene, suggesting that this subset arises from a different genetic pathway. Other common alterations observed in adult low-grade astrocytomas are gain of chromosome 7 and structural abnormalities, including double-minute chromosomes. Losses of chromosomes 10, 13, 15, 20, and 22 and structural rearrangements involving chromosomes 4, 11, 12, 13, 16, 18, and 21 have also been reported in patients [63].

Although p53 is only rarely mutated in oligodendrogliomas, more than one half of these tumors show a characteristic loss of the long arm of chromosome 1 and the short arm of chromosome 19. Because 1p and 19q loss, with rare exception, is not seen in astrocytic

tumors, the combination of p53 and 1p/19q analysis can distinguish an astrocytic from an oligodendroglial genotype in cases that are difficult to distinguish histologically. Similarly, most mixed oligoastrocytomas appear to segregate genetically into astrocytic or oligodendroglial genotypes, suggesting that such mixed tumors may not be a distinct biologic entity [62].

5.9 Treatment Options

5.9.1 Observation

It is increasingly uncommon for patients with the clinical presentation and imaging characteristics of LGGs to be followed with regular imaging without obtaining a histologic diagnosis at first presentation. Nevertheless, some practitioners still advocate this extremely conservative approach for patients felt to have deep-seated lesions or lesions located in the eloquent cortex for which surgery would have a higher risk. Although this strategy defers treatment-related risk and treatment-related costs for patients who remain asymptomatic, it may increase the risk of tumor progression, with subsequent development of new neurological deficits or intractable seizures, as well as the risk of malignant dedifferentiation of the lesion. Despite the best available evidence, one also must accept the fact that the initial presumptive diagnosis may be incorrect. Furthermore, tumor growth rates can be unpredictable and are often nonlinear, leading to sudden changes in tumor size that can drastically change the surgical landscape and turning an initially resectable or radioresponsive lesion into one that is difficult to remove safely or is more resistant to adjuvant therapies. An additional drawback to this approach is the psychological stress associated with not knowing with certainty what one is dealing with–possibly resulting increased distress and reduced quality of life for both the patient and caregiver.

Little evidence exists to support this treatment strategy, although it has not been refuted, either. In one small, retrospective case-control study, no difference was observed in rates of malignant transformation, overall survival, or quality of life between patients initially observed as compared with immediate resection [61]. Similarly, in 30 patients presenting only with seizure, early versus late surgical resection did not affect overall survival [80]. Importantly, the small cohort number (<50) for both studies limits our ability to extrapolate these findings to a broader patient population.

Ultimately, the choice of management strategy must be guided by the entire clinical picture and surgeon's experience. If observation is chosen, disease progression may be detected based upon the onset of new neurological deficits, a change in seizure pattern or frequency, or simply an increase in lesion size and/or new enhancement on MRI.

5.9.2 Surgical Intervention

Operative strategies for patients with LGG include open surgical resection and open or stereotactic biopsy. The choice depends in part on the patient's clinical status, the anatomic location of the tumor, and the surgeon's preference. Goals of surgical intervention include establishing a diagnosis, treating neurological symptoms, decompressing mass effect, and tumor cytoreduction. Currently, the only agreed-upon surgical standard for adults with suspected or known supratentorial nonoptic-pathway low-grade gliomas is to obtain a tissue diagnosis before active treatment commences [57].

5.9.3 Biopsy

Stereotactic or image-guided biopsy can acquire tissue for histologic diagnosis in a minimally invasive fashion. This is particularly suitable for patients where open surgical resection is declined, deferred, or carries unacceptably high risks. The advantage of performing an early biopsy is that it allows for the identification of patients harboring more aggressive lesions, for which a course of observation alone may be inappropriate [39]. Additionally, the tissue can be analyzed for oligodendroglial characteristics, such as chromosome 1p loss.

In general, reported surgical risks associated with stereotactic biopsy in LGG patients have been low, with morbidity and mortality rates of less than 1% [40]. Mortalities occur as a result of intracranial hemorrhage, subarachnoid hemorrhage, or uncontrollable cerebral edema, although this generally is reported only among biopsies of high-grade lesions [4].

One pitfall of relying on stereotactic biopsy for tissue diagnosis is the possibility of misdiagnosis or inaccurate tumor grading due to tumor heterogeneity and diagnosis bias resulting from limited tumor sampling. The concordance between biopsy and open resection specimens is lower in patients with larger tumors [84], suggesting that multiple biopsies, which can be collected a single trajectory pass, may be useful in this subpopulation.

Diagnostic accuracy from image-guided biopsy may be improved by specific regional targeting of the biopsy site within the tumor mass. If the lesion demonstrates areas of focal enhancement on initial imaging, then including the enhancing region(s) in the biopsy is necessary. This strategy, however, is complicated by the fact that higher grade lesions may not always enhance on imaging. Preoperative planning of biopsy targets based on physiological imaging modalities (e.g., PET, SPECT, MRS) may increase the certainty of sampling the most aggressive portion of a particular tumor.

5.9.4 Surgical Resection

In the subset of patients with accessible LGG, suffering from symptoms of local mass effect, increased intracranial pressure, and intractable seizures, the role for open surgical resection is well-established. Resection serves several purposes in these circumstances, including alleviation of mass effect, cytoreduction, and diagnosis. Cytoreduction can also reduce cerebral edema and potentially improve radio- and chemosensitivity. The degree of tumor removal afforded by open surgical resection also offers the advantage of providing more tissue for histologic analysis, increasing the accuracy of pathological diagnosis. Theoretically, cytoreduction also reduces the number of tumor cells at risk of accumulating additional genetic aberrations, thereby reducing the risk of tumor progression and decreasing malignant transformation [74].

Open surgical interventions for the treatment of LGG are conducted using general neurosurgical principles of tumor surgery. Contemporary neurosurgical methods, including ultrasonography, functional mapping, frameless navigational resection devices, and intraoperative imaging techniques enable the neurosurgeon to achieve more extensive resections with less morbidity. Intraoperative ultrasonography provides real-time intraoperative data and is helpful in detecting the tumor, delineating its margins, and differentiating tumor from peritumoral edema, cyst, necrosis, and adjacent normal brain tissue. Although its use is limited by artifacts from blood and surgical trauma at the margin of resection, postresection tumor volumes based on intraoperative ultrasonography significantly correlate with those determined by postoperative MRI [23]. Similarly, intraoperative MR imaging may also allow for greater extent of resection, particularly when tumor-infiltrated tissue cannot be grossly distinguished from normal [13]. Stimulation mapping techniques are essential to minimize morbidity and to achieve radical resections of tumors located in or around cortical and subcortical functionally eloquent sites [66] (Fig. 5.4). For lesions in and around language pathways, awake mapping remains the gold standard for minimizing morbidity and maximizing the extent of resection. Intraoperative corticography can also be a useful adjunct, but is primarily reserved for patients with intractable epilepsy.

Despite the stated benefits for surgical resection, the role for surgery among LGG patients who are minimally symptomatic or asymptomatic remains somewhat controversial. Historically, this has been due, in part, to conflicting reports regarding whether the extent of resection actually confers any survival advantage for these patients. More recently, however, there is a growing body of evidence suggesting that more extensive resection at the time of initial diagnosis is a favorable prognostic factor. While most reports are retrospective, it is unlikely that the necessary prospective randomized studies will be conducted to address the role of extent of resection on outcome in low-grade glioma patients due to the relatively limited numbers of patients, the typically long survival times and a general lack of equipoise with regard to treatment options among care providers.

In the modern neurosurgical era, a number of studies have applied statistical analysis to examine the efficacy of extent of resection in improving survival and delaying tumor progression among low-grade glioma patients [2, 13, 26, 31, 36, 46, 48, 50, 52, 60, 67, 72, 74, 80, 83, 86] (Table 5.1). Five of these studies included volumetric analysis of the extent of resection [13, 32, 72, 74, 80]. Of the non-volumetric studies, 12 demonstrated evidence supporting extent of resection as a statistically significant predictor of either

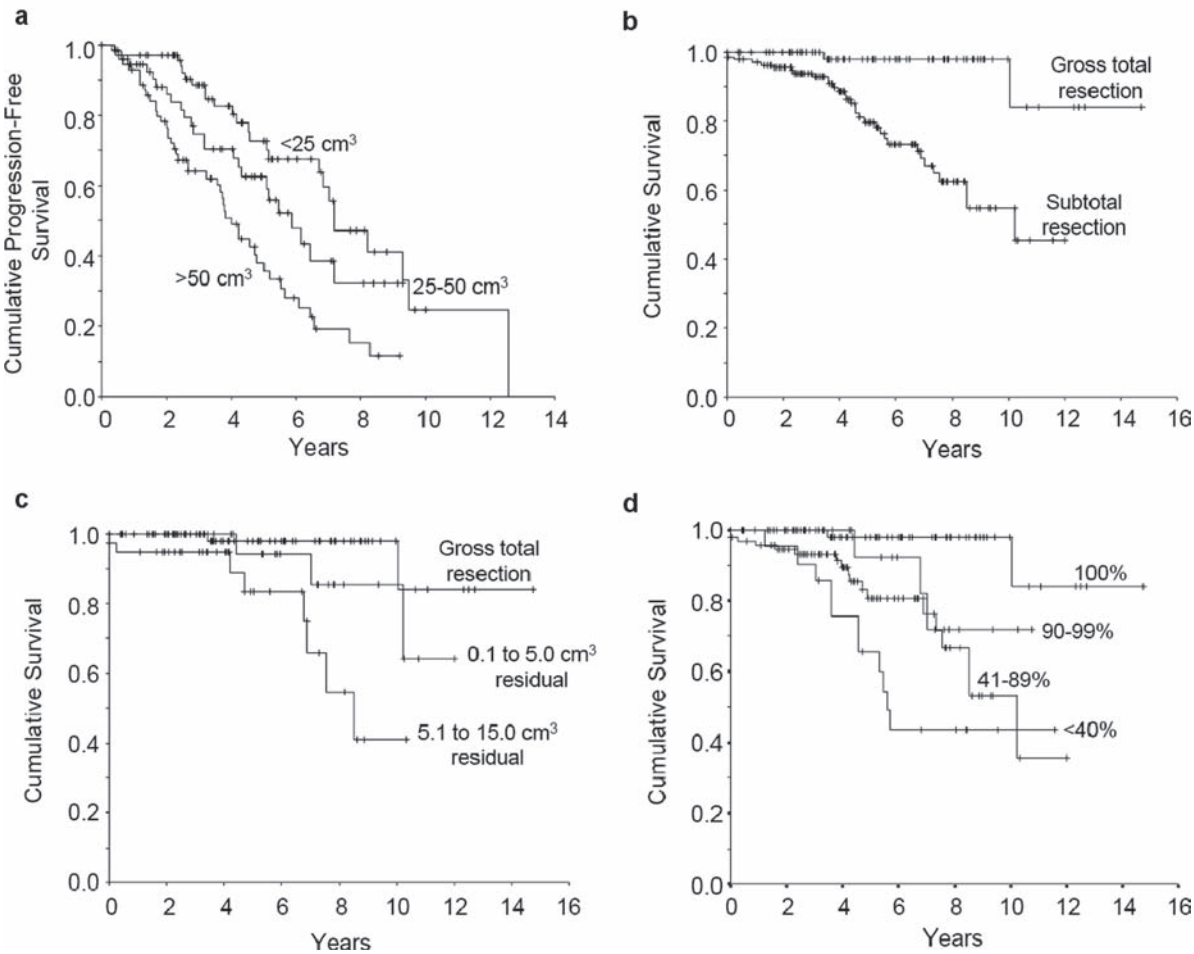

Fig. 5.4 Associations between low-grade glioma tumor burden and patient outcome. (**a**) Patients with larger preoperative tumor volumes have significantly shorter progression-free survival (Cox proportional hazards model based on log transformation of preoperative tumor volume, $p < 0.001$, HR = 2.711, 95% CI = 1.590–4.623). (**b**) Patients with complete resection of FLAIR abnormality (75 patients, two events) had a significantly longer overall survival compared with patients having any residual FLAIR abnormality (141 patients, 32 events) (HR = 0.094, 95% CI = 0.023–0.39, $p = 0.001$). (**c**) Patients with even small volumes of residual FLAIR abnormality demonstrated shorter overall survival compared with patients with no residual FLAIR abnormality (Cox proportional hazards model only including patients with ≤15 cm^3 of residual FLAIR abnormality, $p = 0.001$, HR = 1.166, 95% CI = 1.068–1.274). (**d**) Patients with a greater percentage of tumor resection had a significantly longer overall survival (Cox proportional hazards model, $p < 0.001$, HR = 0.972, 95% CI = 0.960–0.983) (adapted from [74])

5-year survival or 5-year progression-free survival. These studies were published from 1990 to 2005 and most commonly employed a combination of multivariate and univariate analyses to determine statistical significance. In most instances, extent of resection was defined on the basis of gross-total versus subtotal resection. However, in a recent volumetric LGG extent of resection analysis, Smith et al. demonstrate that a more aggressive resection does predict significant improvement in overall survival compared with a simple debulking procedure [74] (Table 5.2). Interestingly, predicted overall survival was shown to be negatively impacted by residual tumor volumes as small as 10 cm^3.

In light of this evidence, and in an effort to preoperatively estimate the respectability of LGG, Chang et al. generated a preoperative scoring system for the long-term prognostication of patients with hemispheric low-grade gliomas. Four variables (eloquence, age>50, KPS≤80, and diameter greater than 4 cm) were

Table 5.1 Nonvolumetric low-grade glioma extent of resection studies in the modern neurosurgical literature

Authors & year	No. of patients	Extent of resection (no. of patients)	5-Year progression-free survival			5-Year survival		
			5-Year progression-free survival (%)	Univariate *p* value	Multivariate *p* value	5-Year survival (%)	Univariate *p* value	Multivariate *p* value
Philippon et al. (1993) [69]	179	GTR (45) STR (95) Biopsy (39)	NA	NA	NA	80% 50% 45%	0.0002	< 0.01
Rajan et al. 1994 [70]	82	GTR (11) STR (30) PR (22) Biopsy (19)	NA	NA	NA	90% 52% 50% 42%	< 0.05	NS
Leighton et al. (1997) [36]	167	GTR (85) STR (23)	NA	NA	NA	82% 64%	0.008	0.006
Nakamura et al. (2000) [66]	88	Radical (43) Non-radical (45)	NA	NA	NA	NA	< 0.001	< 0.001
Shaw et al. (2002) [34]	203	GTR (29) STR (71) Biopsy (103)	NA	0.0137	NS	88 56 71	0.0116	0.0349
Yeh et al. (2005) [74]	93	GTR (13) STR (71) Biopsy (9)	84% 41% 41%	0.0073	0.002	92 52 52	0.0349	0.016

Source: Adapted from [65]

Table 5.2 Volumetric low-grade glioma extent of resection studies in the modern neurosurgical literature

Authors & year	No. of patients	Extent of resection (no. of patients)	5-Year progression-free survival			5-Year survival		
			5-Year progression-free survival (%)	Univariate *p* value	Multivariate *p* value	5-Year survival (%)	Univariate *p* value	Multivariate *p* value
Johannesen et al. (2003) [28]	993	GTR (173) STR (689) Biopsy (131)	NA	NA	NA	NA	NS	NS

Source: Adapted from [65]

predictive of survival on multivariate analyses and were therefore used for the scoring system, with the total score inversely proportional to predicted survival [12].

Thus, mounting evidence in the modern neurosurgical literature suggests that a more extensive surgical resection may be associated with a more favorable life expectancy for LGG patients [65]. More aggressive resections for low-grade gliomas also affect the risk of malignant transformation [74], as well as take advantage of an opportunity to treat the disease when the neoplasm is at its earliest stage of evolution.

5.9.5 Radiotherapy

Traditionally, radiotherapy for LGG patients employed whole-brain irradiation techniques, with or without a local boost to the tumor bed. Advances in imaging and dose-delivery systems have led to the development of numerous modalities for delivering precise radiotherapy doses limited to the tumor and its immediate surroundings. Recently, several randomized, controlled trials have generated class I data to guide decisions regarding radiotherapy for LGG patients.

The European Organization for Research and Treatment of Cancer (EORTC) published the first prospective, randomized clinical trial (EORTC 22844) addressing whether LGG exhibited a dose response to radiotherapy [32]. In this study, 379 adult patients with LGG were randomized to receive either a low-dose regimen of 45 Gy over a 5-week period or a high-dose regimen of 59.4 Gy over 6.6 weeks, following either open surgical resection or biopsy. After a median follow-up of 74 months, patients in the low- and high-dose groups did not differ in overall 5-year survival (58% vs. 59%, $p = 0.73$) or PFS (47% vs. 50%, $p = 0.94$).

A similar randomized trial addressing the question of whether a dose response to radiotherapy exists for LGG glioma patients was published by Shaw et al. in 2002 [71]. This trial (NCCTG 86-72-51) was organized jointly by the North Central Cancer Treatment Group (NCCTG), Radiation Therapy Oncology Group (RTOG), and the European Cooperative Oncology Group (ECOG). From 1986 to 1994, 203 patients were randomized to receive either a low-dose (50.4 Gy over 28 fractions) or a high-dose (64.8 Gy over 36 fractions) radiotherapy regimen. Similar to the EORTC 22844 study, no dose response was seen after a median follow-up of 6.4 years. Additionally, patients in the high-dose group were found to have a significantly increased risk of developing radionecrosis. As a result of these and other studies, the accepted dose range for LGG patients receiving radiotherapy is approximately 50–54 Gy in 1.8 Gy fractions.

To determine the benefit of early versus delayed radiotherapy in LGG patients, another prospective trial (EORTC 22845) randomized patients to receive either early radiotherapy (54 Gy over 6 weeks) or observation alone following initial surgical resection or biopsy [79]. Interim analysis and long-term follow-up both demonstrated no benefit to early radiation in terms of overall survival. A significant increase in progression-free survival was seen in the early radiotherapy group versus observation alone (4.8 years vs 3.4 years, respectively, $p = 0.02$). Based on these results, it was concluded that withholding radiotherapy until the time of disease progression is a safe and effective strategy, as it demonstrated no adverse impact on overall survival. The absence of any difference in overall survival between the two arms of the trial was attributed in part to the effectiveness of radiation given as a salvage strategy upon disease progression.

The rationale for delaying radiotherapy in patients with LGG is based in part on a desire to avoid iatrogenic radiotherapy-induced side effects, such as delayed cognitive impairment, neuroendocrine dysfunction, radionecrosis, tumor dedifferentiation, and induction of secondary malignancies. However, these concerns may need to be reassessed in light of the advances in the field of radiotherapy, the change in strategy from whole-brain irradiation to focused-dose delivery, and modern studies suggesting that the risk of adverse events is lower than reported historical studies [34, 77]. Currently, however, there is no evidence to indicate that stereotactic radiosurgery is effective in treating low-grade gliomas.

5.9.6 Chemotherapy

The recognition of the responsiveness of oligodendroglial tumors to chemotherapy, as well as the identification of chromosomal markers predicting increased chemosensitivity, has helped to renew interest in employing chemotherapy in the management of LGG patients with other histopathologies [9]. The most commonly used chemotherapeutic regimens in adult LGG patients are temozolomide initially and procarbazine, CCNU, and vincristine (PCV) for tumors that fail to respond to temozolomide.

An early randomized study by the Southwest Oncology Group looked at the utility of treating LGG patients with single-agent CCNU following radiotherapy [18]. This study found no added benefit of including CCNU in the treatment regimen. In addition, patients in the CCNU arm commonly developed hematologic side effects related to chemotherapy.

The efficacy of temozolomide, an oral alkylating agent in treating LGG patients, is currently a mainstay of adjuvant treatment, but also under scrutiny in a variety of studies. Several small studies have explored the use of temozolomide as the initial post-surgical therapy for low-grade gliomas, utilizing temozolomide in place of fractionated radiotherapy either immediately after surgery or when the tumor has progressed [7, 25, 37, 56]. Response rates, when minor responses are included, range from 31% to 61%. While follow-up is short, median time to progression ranges from 31 months to >36 months [7, 37]. Brada et al. conducted a phase 2 trial assessing the role of temozolomide as a

primary chemotherapeutic agent in LGG patients previously treated with surgery alone [7], concluding that temozolomide does have single-agent activity against LGG and may help control seizures in this patient population as well. Studies have also demonstrated efficacy of temozolomide in treating patients with progressive LGG [68]. Importantly, temozolomide is administered orally and has a very favorable side effect profile, allowing for its use in a variety of clinical scenarios.

5.10 Conclusions

While low-grade gliomas are more indolent than their high-grade counterparts, their associated clinical course is by no means benign. In an effort to delay the inevitable progression towards malignancy, aggressive LGG resection is supported by a growing body of literature and can improve patient outcome, but should not be pursued at the expense of patient quality of life. Such a strategy minimizes the chances of misdiagnosis due to sampling error and can immediately relieve symptomatic mass effect, obstructive hydrocephalus, and neurological deficit. Greater extent of resection is also correlated with improved survival and reduces the risk of malignant transformation. Conservative therapy or observation is not recommended at this time. Furthermore, radiation therapy should be withheld until progression, although chemotherapeutics such as temozolomide may be useful as an up-front treatment. This approach necessitates precise delineation of the structural and functional tumor margins using a combination of preoperative imaging modalities, intraoperative mapping techniques, and functional mapping.

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