Low-Grade Astrocytoma 4

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Low-grade astrocytomas reviewed in this chapter are grade 2 tumors according to the World Health Organization (WHO) classification [42], and correspond to grade 1 and 2 tumors of the Kernohan grading system [41] and to grade 2 tumors of the St Anne/Mayo classification [17]. They include fibrillary, protoplasmic, and gemistocytic astrocytomas [42]. In the literature, these histological entities are usually grouped together and referred to as 'low-grade gliomas'. Although this terminology is helpful in differentiating these tumors from higher grade gliomas which have a significantly different prognosis, grouping all histological subtypes together results in a heterogeneous group of tumors with different natural histories and therefore provides limited prognostic information. Various grading systems further complicate the overall picture.

Approximately 50% of newly diagnosed brain tumors are primary brain tumors of glial origin. Astrocytomas represent 26.6% of all newly diagnosed glial primary brain tumors [53]. This corresponds to 1500 to 1800 new cases of low-grade gliomas diagnosed in North America each year [18, 53]. Age-specific data show that low-grade astrocytomas constitute 15% of brain tumors in adults and 25% of brain tumors in children [26].

The etiology of low-grade gliomas is unknown. Except for patients with one of the phakomatoses, it has not been documented that genetic predisposition plays a role in the development of these tumors. There is no indication in the literature that low-grade gliomas are more prevalent in a specific ethnic or national group.

The only molecular genetic alteration consistently observed in otherwise healthy patients with low-grade astrocytomas is mutation of p53 [30]. The p53 gene is located at chromosomal location 17p13.1, and this site is often deleted in astrocytomas. The remaining copy of p53 is usually inactivated through a subtle mutation. The end product of this gene is a nuclear DNA-binding phosphoprotein that has transcriptional activity which is essential in the regulation of apoptosis and cell cycle progression. It has been shown that loss of normal p53 function promotes the accelerated growth and malignant differentiation of astrocytes [8, 103]. Astrocytomas are the only type of brain tumor to have significant p53 mutation rates. Some 50–60% of grade 2 and grade 3 astrocytomas exhibit p53 mutations, suggesting that this tumor suppressor gene inactivation is an early lesion among gene alterations associated with the development of malignant gliomas [98]. While 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 they arise from different genetic pathways. Other recurrent alterations observed in adult low-grade astrocytomas are gain of chromosome 7 and 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 are observed in isolated patients [76].

Pathology

In recent years, the critical progress in our understanding of gliomas has led to the distinction between circumscribed and infiltrating types of astrocytoma. Circumscribed and infiltrating astrocytomas display distinct characteristics in their morphological, clinical, radiological, and genetic features [20]. The current nosology of brain tumors considers infiltrating astrocytomas as diffuse and progressive gliomas that gradually accumulate more aggressive histological and molecular features [43]. 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 [42]. 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.

Intraoperative Evaluation

The fundamental purpose of the intraoperative evaluation or the 'frozen section' is to provide information for the surgeon which is needed to complete the surgical procedure. As in all cases submitted for intraoperative evaluation, a few critical steps facilitate the proper interpretation of infiltrating astrocytomas. The first step is the issue of sample adequacy and the studies needed for adequate interpretation of cytological and architectural detail. We believe the standard hematoxylin-eosin stain is sufficient for such an evaluation and should be adhered to until better and more detailed alternatives are discovered. Secondly, it is imperative to obtain intraoperative smears that provide the best venue for accurate interpretation of the cytological detail. Finally, intraoperative evaluation should never be considered as a substitute for a final diagnosis, and an adequate sample should always be saved for permanent sections. The pathologist should clearly communicate to the neurosurgeon that frozen sections always have the potential to require additional tissue. Frozen section requests made after completion of the surgical procedure are superfluous, or where additional tissue will not be available.

Frozen sections are particularly challenging for LGIA since there is a great tendency for the tissue to exhibit marked freezing artifact, often in the form of clear spaces and vacuoles. In addition, frozen sectioning greatly distorts the nuclear size and shape. It is also difficult to estimate the degree of cellularity and the relation of the cells to each other. Vacuolar artifacts may be difficult to distinguish from microcysts that are often filled with a faintly basophilic material. In most of these problems, the intraoperative smear proves to be an invaluable aid to the interpretation.

Grading of infiltrating astrocytomas during intraoperative evaluation is a nagging problem in surgical neuropathology. Particularly with the advent of more sophisticated treatment options that require intraoperative decisions, there is an increasing pressure for at least a tentative grading of the pathology material. The problem is often resolved if the surgical pathologist can 'unequivocally' identify the highest grade, but in the case of LGIA, it is best to evaluate histological features in the light of clinical and radiological evidence. For a more effective and appropriate evaluation of the intraoperative samples from LGIA, a visit to the operating room and a discussion with the neurosurgeon are invaluable.

Interpretation of tissue previously utilized for a frozen section should also be done with great caution and with the understanding that artifacts in nuclear size and shape can cause misinterpretations. Post-frozen samples can mislead the interpreter to diagnose gliosis as glioma and cause misinterpretations about the grade and type of the tumors.

MacroscopicFeatures

The external appearance of LGIA largely depends on the extent of cortical involvement, in other words, the involvement of superficial structures. There may be little or no external abnormality in tumors that are seated deep within the cerebral hemisphere. In tumors involving the cortex, the gyri appear edematous, expanded, and slightly discolored. The infiltrative astrocytomas almost imperceptively blend with the brain parenchyma, and the boundaries are often difficult to define. In surgical and autopsy material, LGIAs cause gray-dusky discoloration of the white matter with a focal cystic appearance, and soft to gelatinous consistency. The cysts may be large enough to be noticed during surgery but are often small, and can be seen after examination of the cut surface of the pathology specimen. The outlines of the anatomical structures are typically effaced, and the boundary between the white matter and cortex becomes indistinct. In the brain stem, LGIA can expand the pons and medulla and fill the cerebellopontine angle or interpeduncular fossa. These tumors can also distort the fourth ventricle and encase the basilar artery.

Microscopic Features

An astrocytoma is traditionally described as a tumor resembling normal astrocytic cells [12]. 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.

Typically, 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.

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 do 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.

A rare pediatric type of infiltrating astrocytoma with a unique histological pattern has been termed bipolar angiocentric astrocytoma [96]. It is still not

clear whether this pattern represents a unique entity or a morphological variant of LGIA.

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.

Chondroid metaplasia or chondroid pattern is an extremely rare but striking finding in LGIA. The production of cartilage by neoplastic astrocytes may be related to their ability to secrete basement membrane material and other forms of mucopolysaccharides, which may become condensed to form a chondroid ground substance [40]. The chondroid cells in these metaplastic regions are also GFAP-positive [40].

The histological definition of LGIA practically excludes the presence of mitoses [43]. 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 [67]. 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 [12]. 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.

Neither the presence of necrosis nor of vascular proliferation is acceptable in LGIA. Nevertheless, it is rarely possible that LGIA might show focal necrosis due to vascular compression and ischemia. A rare LGIA that was inadvertently or deliberately subjected to radiation treatment can also present with necrosis. Accurate clinical information and knowledge of the biopsy site are often helpful to avoid overgrading such lesions.

Granular Cell Astrocytoma

Granular cell astrocytoma is a unique and rare form of infiltrating astrocytoma that has been recently described [9, 14]. This neoplasm is described as an infiltrating glioma that contains individual large, round cells or sheets of them packed with eosinophilic, PAS-positive granules. Most granular cell astrocytomas contain lymphocytic infiltrates, either perivascular or admixed with neoplastic cells, and often there is a transition to typical infiltrating astrocytoma. Granular cell astrocytomas can be grade II, but most reported cases are higher grade neoplasms [9].

Gemistocytic Astrocytoma

Some LGIAs primarily consist of plump cells with abundant eosinophilic, hyaline cytoplasm and an asymmetric array of short processes. These tumors are designated as 'gemistocytic astrocytomas'. Gemistocytic astrocytomas rarely occur in pure form and often coexist with the classical infiltrating astrocytoma pattern. Perivascular lymphocytic infiltrates, occasionally creating germinal centers, are common and typical for these neoplasms. Gemistocytic astrocytomas possess brightly eosinophilic bodies resembling the Rosenthal fibers in their highly fibrillary cytoplasm. However, typical Rosenthal fibers are not seen in these tumors. Gemistocytic astrocytomas also contain a second population of small astrocytic cells with hyperchromatic nuclei, mitoses, and a higher MIB-1 labeling index than the gemistocytic cell population. They are believed to represent the main proliferating element of this variant of astrocytoma [99]. Krouwer et al. [46] suggest that the presence of at least 20% gemistocytes in a glial neoplasm is a poor prognostic sign, irrespective of the pathological background. These authors also propose that gemistocytic astrocytomas be classified with anaplastic astrocytomas and treated accordingly [46]. The current WHO classification does not provide an automatic designation of grade III for gemistocytic astrocytomas [43]. Currently, there is little doubt that gemistocytic cells in infiltrating astrocytomas are neoplastic rather than reactive. The frequency of p53 mutations is significantly higher (approximately twofold) in gemistocytic astrocytomas than in other astrocytoma subtypes [44]. Further studies on the cytogenetics of gemistocytes confirm that the gemistocytic cells in most infiltrating astrocytomas are neoplastic [45].

A critical issue for gemistocytic astrocytomas is their distinction from oligodendrogliomas that typically contain plump cells known as 'minigemistocytes'. The 'minigemistocyte' has an eccentric, spherical, GFAP-positive cytoplasm, and GFAP staining can be even more pronounced than with typical astrocytic cells. True gemistocytes seen in astrocytomas are larger, more eosinophilic, and have less distinct cytoplasm with short processes. In contrast to the minigemistocyte, GFAP-positivity is confined to the periphery of the gemistocyte, while the central portion of the perikarya is weakly positive. There is a considerable overlap in the appearance of gemisto-

cytes and minigemistocytes, and neither is absolutely diagnostic of any specific entity.

Immunohistochemical Features

In essence, the diagnosis of LGIA is primarily done on 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 unhelpful 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, minigemistocytes 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 [51, 91]. A significant percentage of LGIAs are immunoreactive for p53 [16]. This is particularly predominant in gemistocytic astrocytomas [97, 99].

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 [27]. 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 [59], supporting their glial origin.

Clinical Characteristics

It is important to obtain the past history and a physical examination, together with a thorough neurological examination preoperatively, for relevant details and information regarding the patient's general medical condition. Currently, with the help of better health care systems and advanced diagnostic technology, patients are diagnosed at an earlier stage of the disease. In a modern series, approximately half of the patients present with a seizure disorder, and half of the patients with a low-grade glioma appear neurologically intact [80].

The median age of patients with low-grade astrocytomas is approximately 35 years which is considerably lower than that of patients with higher grade gliomas. There is a biphasic age distribution with two peak incidences at 6–12 years and 26–46 years. Most studies have shown that males constitute between 55% and 65% of patients with low-grade astrocytomas [26]. This corresponds to a sex ratio of male-to-female incidence rates of approximately 1.5 [93]. The frontal lobe is the most common location, followed by the temporal and parietal lobes [105]. Low-grade astrocytomas may be lobar and relatively well-circumscribed or deep and diffusely infiltrating.

The most common presenting feature for patients with low-grade astrocytomas is seizures. One half to two-thirds of patients with low-grade gliomas present with seizures. Approximately 50% of the patients have headaches. In larger series and community-based studies, the presence of a brain tumor was detected in 8–30% of patients who presented with partial seizures, with age increasing the risk of epilepsy being caused by a tumor [37, 54, 102]. Together with gangliogliomas, the tumors reviewed in this chapter constitute gliomas that are most commonly associated with intractable epilepsy [37]. This fact is attributed to the characteristics of the tumor's growth pattern, with a higher seizure incidence being associated with relatively slowly growing tumors. In Penfield's series including 230 astrocytomas, low-grade gliomas were associated with epilepsy twice as frequently as glioblastomas [65]. The clinical course of 48% of 209 patients with hemispheric astrocytomas presented by Gonzales and Elvidge [24] was complicated by seizures.

Headache, lethargy, and personality change may be caused by the general increase in intracranial pressure. Papilledema may be present. Focal neurological deficits due to direct tumor infiltration or local pressure depend on the location of the lesion. Depending on the location of the low-grade glioma,

disinhibition, irritability, impaired judgment, abulia, apathy, motor and sensory loss, dysphasia, aphasia, anosognosia may be present. Tumors involving the parieto-occipital area may cause visual agnosias.

MRI and CT are the two neuroradiological tools that provide valuable diagnostic information. The diagnostic procedure of choice, however, is MRI due to its higher sensitivity in differentiating tumor tissue from normal brain. Although low-grade astrocytomas are often not associated with a significant mass effect, a mass effect upon the surrounding ventricular structures and cortical sulci is common, and in some cases a considerable mass effect may be seen in patients without a neurological deficit due to the slow-growth characteristics of these tumors. The typical CT image is a non-enhancing isodense or hypodense mass. Calcification may be detected in 15–20% of cases, and mild to moderate inhomogeneous contrast enhancement can be seen in up to 40% of all cases [78]. Cystic changes are not rare. On MRI, T1-weighted images reveal a isointense to hypointense non-enhancing mass which is hyperintense on T2-weighted images. Enhancement, when it occurs, is generally faint. In an earlier study, contrast enhancement was found to have no prognostic effect for patients with low-grade gliomas [87]. In contrast, more recent studies showed that enhancement has a negative effect on the time to progression and overall outcome [55, 69].

An adjunct to conventional neuroimaging techniques is magnetic resonance spectroscopy (MRS), which can be obtained during the same MR examination with little additional time. This technique allows the detection of metabolite levels in and around tumors, thereby providing metabolic data in addition to morphological imaging. Additional functional information may be obtained preoperatively with functional MRI and magnetic source imaging (MSI). This information integrated with the anatomical information obtained from conventional MRI and intraoperative stimulation mapping data can allow for more precise and complete resection of the tumor and enable the surgeon to minimize morbidity when operating in functionally eloquent brain areas [4].

Treatment and Outcome

Treatment options for diffuse astrocytomas at the time of initial diagnosis include observation, surgery in the form of biopsy or resection, and radiotherapy. The efficiency of chemotherapy is also being studied, mostly for recurrent tumors.

Surgery

The extent of the surgical resection and its timing are still controversial in the management of diffuse astrocytomas, mainly due to a lack of conclusive studies addressing these issues. In the literature, there are reports questioning the value of immediate treatment when an imaging study suggests a low-grade glioma [75]. Although there is no class 1 evidence in favor of early intervention, there is also no study showing an outcome benefit for patients when treatment is deferred. Furthermore, there are several potential risks that the patients would be exposed to by delaying surgery, including the risk of malignant degeneration, probability of developing irreversible neurological deficit, and a more persistent seizure disorder refractory to medical treatment.

Dedifferentiation or malignant transformation is a well-described phenomenon observed in low-grade gliomas. In the literature, 13–86% of tumors initially diagnosed as low grade recur at a higher histological grade [5, 47, 55, 58, 61, 69, 89, 94, 100]. Similar to its broad range of incidence, the time to malignant differentiation is also variable, ranging from 28 to 60 months [5, 55, 75, 81, 94]. However, the factors resulting in the change to a malignant phenotype remain unclear. In a recent study investigating the relationship between anaplastic transformation and the patient's age, a strong inverse relationship was found between the age at initial diagnosis and time to progression to a higher grade glioma [81]. The effect of treatment on malignant transformation is controversial. In Recht et al.'s [75] 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. Although a higher incidence of malignant transformation at the time of operation and shorter time to tumor progression were observed compared with those in patients who were initially operated upon, the authors stated that no difference was observed in terms of survival [75]. The opposite was found in a series of 53 hemispheric low-grade gliomas volumetrically analyzed regarding recurrence patterns [5]. The risk of recurrence, either as low grade or at a higher histological grade, was minimized when less residual tumor volume was present postoperatively. The residual tumor volume was found to be more important than the percentage of resection in predicting the histological phenotype of recurrence. In addition, time to tumor progression was longer with more extensive resections associated with a smaller volume of residual tumor [5]. Additional studies evaluating the role of residual tumor volume on survival provided inconclusive results [48, 57].

The surgical treatment of diffuse astrocytomas consists of several different approaches depending on the patient's clinical condition and the surgeon's preferences. The surgical intervention may range from a simple stereotactic biopsy to obtain a tissue diagnosis to an extensive resection coupled with seizure surgery in patients with diffuse astrocytomas associated with intractable epilepsy. Surgical intervention is the essential treatment modality in the management of low-grade gliomas, and the main goals are histological diagnosis and reducing the tumor bulk in order to decrease intracranial pressure, improve neurological deficit, prevent malignant dedifferentiation, and obtain seizure control.

Stereotactic techniques or frameless methods, i.e., neuronavigation, have a lower morbidity and mortality, i.e., 1.2–6.4% [1, 7], than open surgical approaches; however, with the exception of computer-assisted stereotactic resections, they only serve the aim of obtaining a tissue diagnosis. Therefore, the use of stereotactic biopsy is limited to a subgroup of patients harboring suspected low-grade glial tumors depending on the characteristics of the lesion, e.g., depth, small size, multiplicity, diffuseness, or the patient's clinical condition. An incorrect pathological diagnosis is not uncommon for tumors of glial origin, and the misdiagnosis usually consists of misinterpreting a high-grade tumor as a low-grade glioma. Although the incidence of this problem varies in different series, it may be significantly reduced by serial sampling along the entire radius of the lesion and beyond. Close collaboration with an experienced neuropathologist is essential for the diagnostic efficiency of stereotactic biopsies. There are no randomized studies examining the prognostic effect of stereotactic biopsy followed by radiation therapy for the initial management of patients with diffuse astrocytomas. Retrospective, non-randomized studies including selected patients do not show any substantial benefit in terms of overall survival for patients who receive a biopsy followed by radiotherapy when compared with those patients who receive conventional surgical resections [52, 69, 85, 86].

Computer-assisted stereotactic resections are helpful for tumor resection in certain locations that are technically challenging and associated with high morbidity rates. This technique, by providing images of lesions in triplanar format and by accurately referencing the data to either a stereotactic frame or the patient's surface anatomy, permits the neurosurgeon to plan precisely an approach that minimizes injury to critical neural structures. As an example, perioperative mortality for radical resection of gliomas in and around the thalamus now approaches zero with modern techniques [90]. Unnecessary brain resection and retraction are also minimized.

Contemporary neurosurgical methods, including ultrasonography [6, 39], functional mapping [36], frameless navigational resection devices, and intraoperative imaging techniques [104], enable the neurosurgeon to achieve more extensive resections with less morbidity. Intraoperative stimulation mapping of cortical and subcortical tissue in and around a tumor will identify functional tissue, and its preservation will minimize the risk of permanent postoperative deficit. It has been shown that resection of tumors located near or within functional brain areas may not be safe even if the surgeon remains within the boundaries of the macroscopically obvious tumor. In addition to its use to determine functional cortical sites, stimulation mapping is the only available method that provides reliable identification of descending subcortical motor, sensory, and language tracts. Hemispheric gliomas located within or adjacent to functional areas, such as the Rolandic cortex, supplementary motor area, corona radiata, internal capsule, and uncinate fasciculus, constitute the major indications for intraoperative motor mapping. Due to the tendency of infiltrative gliomas to invade underlying white matter tracts, it is important to identify both cortical motor sites and their descending pathways. Regardless of the gross appearance and consistency of the tumor, functional tissue may also reside within the mass itself and must be identified with stimulation mapping before definitive resection.

Cortical language localization, through object-naming and reading, is variable in each individual and does not follow any reproducible pattern across the population. The traditional concept regarding the cortical representation of language function involves an anterior language site, Broca's area (posterior part of the inferior frontal gyrus), and a posterior site, Wernicke's area (perisylvian in the temporoparietal cortex). This concept was challenged by some early studies in which electrical cortical stimulation was used. In addition, dominant temporal-lobe resections guided by standard neurosurgical landmarks – that is, restricting the temporal lobe resections to within 4 cm of the temporal tip and limiting the removal of the superior temporal gyrus – have been associated with permanent postoperative language deficits. A negative stimulation mapping may not provide the necessary security to proceed confidently with the resection. Therefore, it is essential to document where language is located, as well as where it is not located, if feasible. This is also the reason for having a generous exposure, not only to maximize the extent of resection but also to minimize the possibility of obtaining negative data. It has been shown that the distance of the resection margin from the nearest language site is the most important factor in determining recovery from preoperative language

deficits, the duration of postoperative language deficits, and whether the postoperative language deficits are permanent. Significantly fewer permanent language deficits occur if the distance of the resection margin from the nearest language site is >1 cm.

Reviewing the four prospective, randomized studies currently available for diffuse astrocytomas in adult patients, age, histology, and tumor size appear to be generally accepted prognostic factors influencing the outcome [19, 34, 71, 83]. The prognostic effect of the surgical intervention is controversial, however [38]. The majority of low-grade gliomas seen in adults are located in the cerebral hemispheres, and their natural history is significantly different than their pediatric counterparts. The trend in the literature, unfortunately, has been to include all low-grade gliomas into the series regardless of the age group and location, making the data difficult to interpret. A review of the literature from 1970 to 2000 shows that in recent years, i.e., 1990s, there was a noticeable increase in the number of studies that support more extensive resections along with a decrease in the number of reports showing no difference in terms of outcome [2, 3, 19, 29, 31, 33, 35, 47, 48, 50, 56, 57, 60, 61, 66, 68–70, 74, 77, 79, 82, 84, 85, 86, 88, 89, 92, 101]. All of these studies are non-randomized except for two [19, 35], and in all studies, the extent of resection was determined by non-volumetric methods, mostly depending on the surgeon's intraoperative estimate.

Studies with a distinct subgroup of patients who had a macroscopically gross total resection of their tumor [2, 29, 47, 56, 57, 60, 61, 66, 68–70, 74, 79, 85, 89, 101] found a statistically significant effect of the extent of surgery on survival. Results of studies in which gross total resections were combined with less than total resections [3, 19, 31, 33, 35, 48, 50, 77, 82, 86, 88, 92] were also consistent with an improved survival observed in patients with a higher degree of resection. Although longer 5-year survival rates were observed for patients who undergo a more extensive resection, the difference of survival benefit was less pronounced compared with those patients who received a gross total resection. However, there was no indication that more extensive resections were associated with a less favorable outcome.

There are few studies that simultaneously excluded pediatric patients and pilocytic and gemistocytic histologies, which have a significantly different prognosis, and included more than 75 patients [48, 68, 74, 89, 92]. Despite the fact that these 5 studies are all retrospective and non-matched, they are the most homogeneous series that are available in the literature regarding patient population and histologic characteristics. The prognostic effect of extent of resection was found to be statistically significant in univariate analysis in every study. In multivariate analysis, however, the extent of resection was a significant independent factor in 4 of these 5 series [48, 68, 89, 92].

Within the last few years since 2001, five new studies have addressed the issue of extent of resection for diffuse astrocytomas as it relates to outcome. Two of these studies [71, 83] are prospective and randomized, and although they were not designed to evaluate the extent of resection specifically, both had this parameter as a variable in their statistical analysis. The volume assessments, however, were not volumetric. In both studies, extent of resection was found to be a statistically significant predictor of outcome in univariate analysis, but not in multivariate statistics [71, 83]. The results of these studies will be discussed further later in this chapter. In the remaining 3 retrospective studies, the extent of resection had a significant prognostic impact for low-grade tumors [28, 32, 49].

The surgical management of patients with low-grade gliomas and seizures is controversial. Surgical options include focal excision of the tumor alone, radical tumor resection without electrocorticography, and a radical resection with seizure foci mapping. In patients with low-grade gliomas who are under complete seizure control preoperatively or those who have an occasional seizure on medication, seizure control with or without the need for postoperative anticonvulsants is often achieved only with radical tumor resection.

Radiation Therapy

Radiation therapy is one option for the treatment of patients with low-grade glioma. Other options include postoperative observation or chemotherapy. The role of radiation has been controversial for many decades, with physician and patient bias supporting the decision to treat once the diagnosis is made, or to defer therapy until further tumor progression or symptoms occur, prompting the need for intervention. Retrospective, single-institution reviews seemed to suggest a benefit for the use of radiation therapy at the time of the initial diagnosis. Fortunately, over the past few years, a number of prospective clinical trials have been reported which should be helpful as guidelines for treatment decision.

In general, treatment is reserved for patients with symptomatic residual disease despite optimal surgical resection or for patients who are felt to have high-risk features. Further studies are needed to fully define 'high-risk' features, but the current hypothesis is that patients over the age of 40 with residual disease represent a subset of cases in which earlier intervention may be warranted. These recommendations are based upon three prospective studies done over the last 10 years [34, 35, 83]. The studies were designed

to address two specific questions: Is there a radiation dose that might improve survival, and does early intervention with radiation improve the outcome compared with observation. A fourth study was also conducted which sought to evaluate the survival impact of chemotherapy in addition to radiation [19].

The European Organization for Research and Treatment of Cancer (EORTC) conducted two prospective studies in adults with low-grade glioma, which included astrocytoma, oligodendroglioma, and mixed oligoastrocytoma [34, 35]. EORTC protocol 22845 randomized 311 patients to postoperative observation versus postoperative radiation (54 Gy), while EORTC 22844 randomized 379 patients to high-dose (59.4 Gy) versus low-dose (45 Gy) radiation. The two studies were conducted simultaneously, with similar eligibility and stratification factors. No survival benefit was seen with high-dose radiation compared with low-dose radiation, and perhaps more importantly, no survival benefit was seen when radiation was used postoperatively compared with patients who were followed by observation alone. The 5-year overall survival rate for observation was 66% compared with 63% after radiation with 54 Gy, 58% for low-dose radiation of 45 Gy, and 59% for 59.4 Gy. There was no difference in the 5-year progression-free survival rate when comparing the low-dose (47%) versus higher-dose radiation (50%). However, there was an improvement in the 5-year progression-free survival in patients randomized to radiation (44%) compared with patients who were observed (37%). The conclusions from these two large prospective studies support the notion that a survival benefit does not exist when radiation is used in the initial treatment of adults with low-grade glioma, although there does appear to be a difference in progression-free survival.

The Southwest Oncology Group (SWOG) conducted a small, prospective, randomized study of radiation alone (55 Gy) versus radiation plus adjuvant chemotherapy using the single agent lomustine (CCNU) [19]. This study included adult patients with subtotally resected or biopsied astrocytoma, oligodendroglioma, or mixed oligoastrocytoma. Only 60 patients were randomized. There appeared to be a trend toward better median survival with chemotherapy (7.4 years) compared with radiation alone (4.45 years), but the 10-year survival rate was 40% for radiation alone compared with radiation plus CCNU (20%). Thus, this study also suggests that more therapy is not necessarily better.

Finally, the North Central Cancer Treatment Group (NCCTG) along with the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Group conducted a large phase-3 study in adult patients with newly diagnosed low-grade glioma (astrocytoma, oligodendroglioma, and oligoastrocytoma), randomizing patients to high-dose (64.8 Gy) versus low-dose (50.4 Gy) radiation [83]. As with the EORTC 22844 trial, no survival benefit was seen with the higher dose of radiation. There appeared to be a higher incidence of neurotoxicity at 5 years with the higher dose strategy (10% rate) than the lower dose radiation (2% rate). The 5-year overall survival rate was 72% and 65% with low-dose radiation and higher dose radiation, respectively. Important negative prognostic factors included age >40 years, tumor size larger than 5 cm, and astrocytoma histology. Extent of resection was an important prognostic factor in the EORTC 22844 study.

RTOG recently completed accrual to a large, randomized, phase-3 study comparing radiation alone versus radiation plus adjuvant chemotherapy using procarbazine, CCNU, and vincristine (PCV) in patients with high-risk features, which they defined as age >40 years or any age with less than a gross-total resection. Patients aged less than 40 years with a gross-total resection were followed by observation. The results of this study have not been analyzed but will be of interest, and will hopefully add further information about prognostic subgroups and the impact of the combination of radiation and chemotherapy. Other randomized studies are ongoing in the EORTC as well. These new studies will be of great interest not only for the outcomes data, but also for the results of tissue correlation studies that will compare biologic factors in the outcomes analysis. Molecular pathology and genetic characterization of tumors will hopefully become as important as age, histology, and extent of resection as prognostic factors. The goal of these studies will ultimately allow specific stratification of patients towards treatment more likely to improve survival with minimal risk.

Radiation frequently will be necessary in patients with low-grade glioma. Older, newly diagnosed patients with larger tumors or any patient with symptomatic lesions should be considered for radiation. The alternative approach is to use chemotherapy in an attempt to defer the need for radiation (see below). In general, radiation is given to a dose of 50–54 Gy, in 1.8 to 2.0 Gy fractions, to a focal field with 2-cm margins. Whole brain radiation is rarely indicated and can cause significant neuro-cognitive deficits over time. This is especially relevant in older patients who appear to have less tolerance to radiation-associated injury. Younger patients, who may live for decades, are also at greater risk for late radiation effects. The volume of brain irradiated, total dose given, as well as tumor location may play a role in the development of late radiation effects. Unfortunately, there are limited prospective data concerning the scope and degree of neurotoxicity in long-term survivors treated with radiation. Improved techniques now exist for radiation treatment planning which

make it possible to limit normal brain exposure to higher dose radiation, and hopefully these advances will minimize the potentially negative impact of radiation-associated injury.

With the results thus far presented in the literature, a practical approach to the patient with low-grade glioma would be to consider prognostic factors and make specific recommendations based upon age, extent of resection, tumor location, and presence of symptoms related to the residual disease. One could strongly consider the option of observation, particularly in the setting of a younger patient with a gross-total resection of disease. Observation of the older patient with gross-total resection is also an option, although the risk of earlier progression may be higher compared with younger patients. More frequent scanning may be indicated in this setting. Younger patients (age <40 years) with partially resected disease, who are without significant symptoms, could also be given the option of observation as well, as no survival benefit has been demonstrated with early intervention using radiation. This is not to state categorically that radiation is not indicated, as there may appear to be some benefit in progression-free survival. Some patients and physicians may feel that the potential to defer growth is an appropriate reason to choose radiation early. In this setting, the risks of radiation need to be weighed against this non-survival benefit. Smaller lesions in non-eloquent areas of the brain would seem to offer less long-term risk, and thus may be a situation where radiation would be a reasonable approach. Younger patients with symptomatic disease, despite optimal surgery, could be given the option of radiation or perhaps chemotherapy and, as noted previously, should consider enrollment into clinical trials. Older patients with residual disease with or without symptoms appear to represent the highest-risk group for early progression and should be considered for treatment. Whenever possible, enrollment into clinical studies should be encouraged, given the uncertainty of specific therapies on survival outcomes within patient subgroups.

Chemotherapy

Management options for adults with low-grade astrocytomas (LGA) include observation, surgery, radiation, or chemotherapy, but there is no well-established standard approach. Patients who have undergone a complete radiographic resection of their tumor are often followed with surveillance MRI scans and treated upon progression. Patients who have undergone subtotal resections have been treated with radiation therapy in the past. However, there is now a trend to avoid up-front radiation based on an EORTC study that suggests there is no survival benefit [34]. Adjuvant chemotherapy after radiation has not typically been given. However, RTOG is conducting a study that addresses the question of a possible benefit with this approach. In this trial, patients over 40 or those with incompletely resected low-grade tumors will receive radiation with or without procarbazine, CCNU, and vincristine (PCV).

The role of chemotherapy in adult patients with LGA has not been extensively investigated. This section will focus on the use of chemotherapy in the treatment of adults with LGA and the relevant clinical studies that have been completed or are presently being conducted.

In the available literature describing the use of chemotherapy for low-grade gliomas in adults, there are differences in trial methodology that can confound an interpretation of the results. Most studies are retrospective and have a mixture of low-grade histologies included in them. Patients may also have had different prior therapies before receiving chemotherapy, i.e., radiation. Chemotherapy in adults with LGA has most commonly been used as a salvage treatment for post-radiotherapy progression [10, 13, 22]. However, in many instances, it is not clear that the tumor has remained low grade at progression since tissue confirmation has not been obtained. Up-front chemotherapy has been used primarily to treat children in order to avoid the potential long-term deleterious effects of radiation [21, 72].

To date, there has only been a single published, randomized trial to assess the role of chemotherapy in patients with low-grade astrocytomas. SWOG conducted a prospectively randomized study to evaluate the addition of CCNU to radiation therapy for the treatment of low-grade gliomas. This study included grade I or II astrocytomas that were pilocytic astrocytomas, gemistocytic astrocytomas, mildly anaplastic astrocytomas, mixed gliomas, oligodendrogliomas, and gangliogliomas [19]. Fifty-four patients were randomized after incomplete resection to receive radiation or radiation in combination with CCNU. There was no statistically significant difference in survival time seen between the two groups. The median survival for patients who received radiation alone was 4.5 years, and for patients who received irradiation plus CCNU, the median survival was 7.4 years (p=0.7). Other clinical factors that impacted survival in this study were age, functional status, and extent of resection.

Temozolomide, an oral alkylating agent, is now being investigated in several trials for patients with progressive low-grade gliomas. In a study published by Quinn et al., temozolomide was administered at 200 mg/m^2 daily for 5 consecutive days to 46 patients with progressive low-grade gliomas [73]. Histologic types included in this cohort were astrocytoma, oli-

godendroglioma, mixed glioma, and pilocytic astrocytoma. Some 35% of the patients had astrocytomas. The median period of follow-up was 11.2 months. Some 15% of the patients had undergone prior radiation and 22%, prior chemotherapy. The objective response rate for all histologic types was 61%, with an additional 35% having stable disease. The median progression-free survival was 22 months. In the 16 patients with astrocytomas, the overall objective response rate was 69% (31%, 5/16 complete response and 38%, 6/16 partial response). Of the astrocytoma patients 25% (4/16) had stable disease for an overall response rate of 94%.

Pace et al. have also looked at temozolomide in patients with progressive low-grade gliomas [62]. Forty-three patients were enrolled in this study. Tumor types included grade II astrocytomas, oligodendrogliomas, and mixed gliomas. Patients began therapy at the time of documented radiographic progression. Thirty patients had previously received radiation. Sixteen patients had already been treated with PCV chemotherapy. Temozolomide was administered at 200 mg/m^2 daily for 5 consecutive days. They observed 4 complete responses and 16 partial responses for an objective response rate of 47%. Seventeen patients had stable disease, making the overall response rate 86%. Median length of response was 10 months. Progression-free survival at 12 months was 39.6%.

Viviers et al. assessed the efficacy of temozolomide in patients with stable or progressive low-grade gliomas [95]. Patients in this study had no antitumor therapy other than resection. Twenty-five patients were enrolled (18 grade II astrocytoma and 7 oligodendroglioma). All patients had radiographic residual disease at study entry. Of the 12 patients who received a minimum of 6 cycles, an overall objective response rate of 67% was seen.

Based on these studies, it is apparent that temozolomide is an effective therapy for patients with recurrent or progressive low-grade gliomas. This raises the question of a role for this agent in patients with newly diagnosed low-grade gliomas. Currently, a single-institution phase-II investigation is being conducted at UCSF that will address this question. In this study, newly diagnosed patients will be treated with temozolomide as the primary therapy after an incomplete resection. The goals of this study are to determine the efficacy by radiographic response criteria and time until disease progression.

Other chemotherapy regimens that have been investigated in adults are carboplatin and PCV. Christina et al. treated 22 patients with progressive low-grade gliomas using carboplatin[15]. Carboplatin was given at 560 mg/m2 every 4 weeks. The maximum response was stable disease in 12 patients (55%). The 3-year progression-free survival was 20%. Median follow-up was 28 months. Carboplatin in combination with vincristine has been used often to treat children with low-grade gliomas [63, 64].

The reported data using the PCV regimen have predominantly involved patients with low-grade oligodendroglioma and oligoastrocytoma, which is outside the focus of this review [11].

The best management for adult patients with low-grade gliomas has not been defined. And the only clear role for chemotherapy in adults with LGA is in the setting of postradiation progression. In those patients with gross totally resected tumors, it is advisable to just observe after surgery, reserving further therapy until tumor progression. At the time of progression, both radiation and chemotherapy may be considered. Investigations also show that chemotherapy can be used effectively in some patients with progressive tumors that have not been previously treated. Postoperative high-risk patients (those over 40 and those with significant residual disease) having stable tumors may also receive radiation or chemotherapy. There is an emerging trend to forgo or delay radiation and use chemotherapy in this setting. The efficacy of this approach is currently being evaluated in a single-institution phase-II trial using temozolomide.

Conclusion

Despite a better prognosis when compared with higher grade glial tumors, low-grade glioma patients have a median survival of 5–10 years and a 10-year survival rate which ranges from 5% to 50% [19, 23, 25, 31, 48, 55, 68, 69, 86, 94]. Some 50–75% of the patients will eventually die of their disease. Within the last 10 years, several studies analyzing the prognostic impact of tumor resection on outcome have revealed lower recurrence rates and improved overall survival with radical resection. Moreover, aggressive resection minimizes the chances of misdiagnosis as a result of sampling error and also relieves symptomatic mass effect, obstructive hydrocephalus, and neurologic deficit. Our standard practice is radical resection whenever feasible. This approach requires precise delineation of both the tumor margins and functional regions of involved and adjacent brain. A combination of methods, including intraoperative navigation techniques, intraoperative ultrasonography, cortical and subcortical functional mapping may be used to minimize the incidence of morbidity. Adjuvant postoperative therapy is usually not required in the treatment of localized, low-grade gliomas resected with minimal or no residual tumor volume. The patient is followed with sequential imaging, and recurrence is treated with another operation and irradiation, chemotherapy, or both. Overall, the management of low-grade gliomas is still controversial, and

practice parameters are ill-defined. This is caused by our limited knowledge regarding the natural history of this entity, and lack of high-quality evidence supporting various treatment options.

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