High-Grade Astrocytoma/Glioblastoma

7

Jon D. Weingart, Matthew J. McGirt, and Henry Brem

Contents

H. Brem (✉)
Department of Neurosurgery, The Johns Hopkins Hospital, 600 N Wolfe Street, Baltimore, MD 21287
e-mail: h.brem@jhmi.edu

7.1 Epidemiology

Malignant astrocytoma, glioblastoma multiforme (WHO grade IV), and anaplastic astrocytoma (WHO grade III) are still the most common primary cerebral neoplasms in adults. These highly invasive tumors have a strong predilection for cerebral hemispheres. Glioblastoma multiforme (GBM) comprises 80% of malignant gliomas. While malignant astrocytomas comprise only 2% of all adult tumors at a rate of 5 cases per 100,000 adults per year, their malignant nature makes them the fourth greatest cause of cancer death [4]. Malignant astrocytomas are associated with a slight male to female preference (1.6:1.0). The peak age at onset for GBM is in the sixth or seventh decade, whereas anaplastic astrocytoma (AA) usually presents in the fourth or fifth decade. GBM (0.2/100,000 per year) and AA (0.5/100,000 per year) rarely occur in children less than 14 years of age. While malignant astrocytomas occur less commonly in African-Americans, no national differences in incidence have been consistently demonstrated after racial and age correction. Recent evidence suggests that the incidence of GBM and AA have doubled over the past decade. While the significance of this observation is unclear, many believe this to be a result of the increased use of MRI and CT.

To date, malignant astrocytoma is not believed to be a familial disease. However, an increased incidence has been observed in multiple syndromes. Patients with Turcot's syndrome, familial colonic polyposis with frequent colon cancer, may develop malignant astrocytoma more frequently [17]. Low-grade astrocytomas occurring at higher frequencies in patients with tuberous sclerosis and neurofibromatosis type 1 and 2 may progress to malignant glioma. Patients with an autonomic-dominant inheritance of a germline mutation of

J.-C. Tonn et al. (eds.), *Oncology of CNS Tumors,*
DOI: 10.1007/978-3-642-02874-8_7, © Springer-Verlag Berlin Heidelberg 2010

Tp53, Li-Fraumeni syndrome, are predisposed to developing tumors of the breast, soft tissues, bone, blood, adrenal cortex, and brain, including malignant astrocytomas. Nevertheless, a clear genetic predisposition to malignant astrocytoma has yet to be found.

7.2 Symptoms and Clinical Signs

The symptomatic presentation of malignant astrocytomas can be divided into two, often coexistent categories: nonspecific symptoms of elevated intracranial pressure (ICP) and site-specific symptoms due to the location of tumor. Nonspecific symptoms include headache, drowsiness, visual obscurations, nausea, vomiting, nuchal rigidity, papilledema, and occasionally 6th nerve palsy. Site-specific symptoms vary by tumor location and include motor, sensory, visual, language, and speech disturbances. Hearing and gait abnormalities may also be seen. The rate of symptom onset, extent of nonspecific symptoms, and localization of site-specific symptoms can provide important information regarding the aggressiveness, location, and extent of disease.

The most common nonspecific symptom associated with malignant astrocytomas is headache, occurring in 77% of patients, and it is the initial symptom in 40% of patients with malignant glioma. Headaches resulting from malignant astrocytomas are often intermittent, deep and pressure-like, and are typically worse in the morning and improve throughout the day or with physical activity. Headache on awakening is thought to result from mild hypercapnia during sleep, resulting in cerebral vasodilation and transiently elevated ICP. The headache is most often nonlocalizing, but traction against meningeal structures may localize the pain to the side of the tumor.

Drowsiness is also frequently seen in patients with malignant astrocytomas, reflecting increased ICP. A depressed level of consciousness is seen at diagnosis in 40% of patients with malignant glioma and is a warning sign that the ICP may be nearing a critical level. Psychomotor retardation is the most common mental status change associated with malignant astrocytomas. Lack of persistence in routine tasks, faulty insight, emotional lability, forgetfulness, indifference to social practices, and blunted affect can be seen. Patients may also sleep for longer periods, often napping during the day. Frank confusion and dementia occur with more advanced disease and often accompany site-specific symptoms.

Both generalized major motor seizures and various focal seizures are observed in 29% of patients with malignant astrocytomas and occur less frequently in malignant astrocytomas versus all other glioma types (54%). A new onset seizure in a patient over 40 years of age should be considered indicative of a brain tumor until proven otherwise. Temporal lobe lesions often give rise to partial simple or complex (temporal lobe) seizures resembling petit mal attacks and may be associated with olfactory hallucinations, disorders of visual or auditory perception, or episodes of déjà vu. Epileptic progression from one body part to another, typical of Jacksonian lesions, may suggest a lesion of the motor or sensory cortex.

Site-specific symptoms are location dependent and a result of either irritation or destruction of functional brain. Tumors in silent brain areas produce symptoms by extension of edema into functional areas, which can be ameliorated by corticosteroids. An improvement in symptoms with steroids often predicts a more durable improvement with surgical debulking and subsequent decrease in regional ICP. Direct invasion of tumor into eloquent brain often results in loss of function and is most often irreversible. Focal neurological findings, especially motor weakness, are more frequently seen with malignant astrocytomas than low-grade gliomas. Some 42% and 14% of patients with GBM present with some degree of hemiparesis or hemianesthesia, respectively. Temporal lobe and motor cortex lesions have a higher incidence of seizures. Apathy, memory loss, and personality disturbances occur more often with frontal and temporal lobe lesions. Frontoparietal lesions are often associated with hemiparesis and sensory loss. Sensory changes typically include paresthesias, anesthesia, and dysesthesias. Parietal lesions more typically result in proprioceptive loss, decreased two-point discrimination, and astereognosis. Dominant posterior inferior frontal lobe or posterior parietotemporal lesions may result in an expressive or receptive dysphasia, respectively, that progresses to aphasia. While gait disturbances and ataxia are most often due to posterior fossa pathology, gait disturbances of apraxia can be seen with frontal lobe lesions. Bifrontal lesions can cause urinary incontinence [11].

7.3 Diagnostics

7.3.1 Synopsis

While radiographic assessment may be highly suggestive of malignant glioma, diagnosis and subsequent treatment planning still depend on tissue sampling in all cases. CT and MRI exquisitely define normal and pathological intracranial tissues. CT offers superior imaging of acute blood, intraglioma calcium, and bone, while MRI allows multiplanar assessment of volumetric size and tumor extension into adjacent tissues. On MRI, GBM classically presents with a central area of T1 hypointensity, representing necrosis, surrounded by a gadolinium-enhancing ring, representing active tumor (Fig. 7.1). Infiltrating tumor and marked edema are often present and visualized by T2 hyperintensity. The degree of enhancement, necrosis, hemorrhage, and associated edema is usually less prominent for AA (Fig. 7.2) [1]. While these radiographic characteristics are strongly suggestive of malignant astrocytoma, metastatic tumors, lymphomas, abscesses, and occasionally demyelinating diseases can have a similar appearance (Fig. 7.3). The advent of MR spectroscopy may now allow noninvasive differentiation in many of these problematic cases.

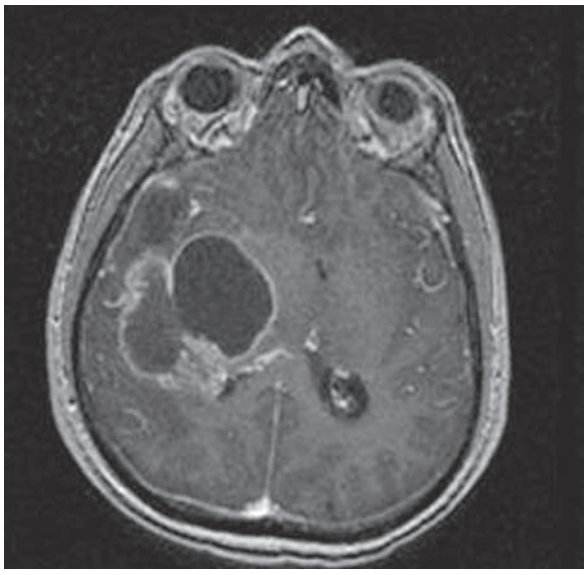

Fig. 7.1 Contrast-enhanced, T1-weighted MRI demonstrating classic radiographic signs of a GBM. A central area of low attenuation (necrosis) with multifocal and rim enhancement (active tumor) can be seen infiltrating the corpus callosum and is associated with mass effect and diffuse edema

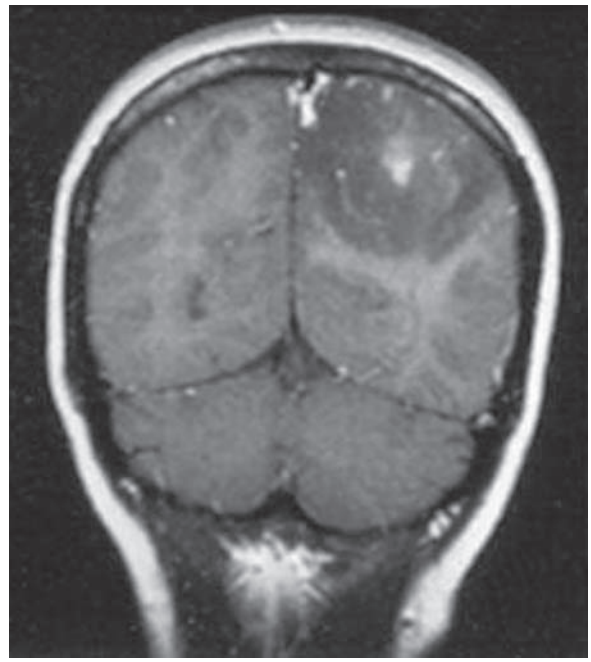

Fig. 7.2 Contrast-enhanced T1-weighted MRI of an anaplastic astrocytoma (*AA*). A low attenuation lesion with minimal enhancement on T1-weighted MRI with minimal to moderate edema on T2-weighted MRI is suggestive of AA (printed from [1] with permission)

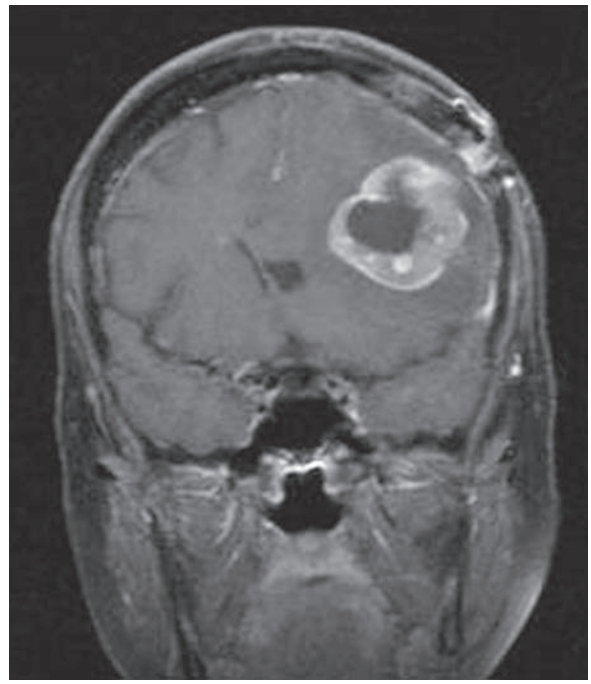

Fig. 7.3 Coronal contrast-enhanced T1-weighted MRI of a patient with a ring-enhancing left frontal lesion with mass effect and surrounding edema. Histopathological diagnosis was lymphoma

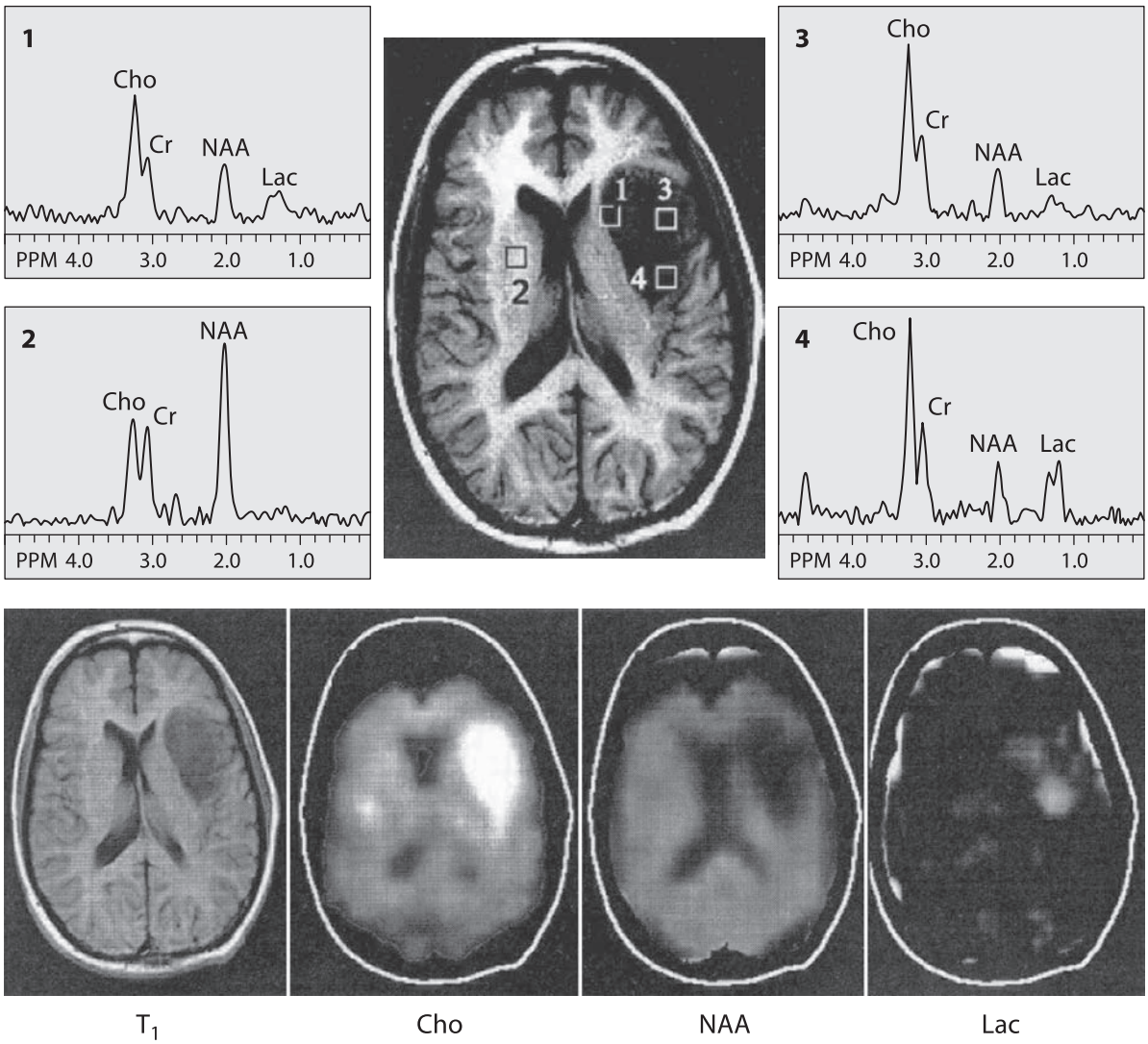

Fig. 7.4 MR spectroscopy of a glioblastoma. *Upper panel*: Single-pixel spectrographs (*1–4*) corresponding to regions sampled within tumor (*regions 1*, *3*, and *4*) and contralateral normal brain (*region 2*). Normal brain (*region 2*) contains high *N*-acetylaspartate (*NAA*) relative to choline (*Cho*) and creatine (*Cr*) and no lactate (*Lac*). All regions with tumor show elevated choline, elevated lactate, and diminished *N*-acetylaspartate relative to creatine. *Lower panel*: MR spectroscopic imaging of the same tumor depicting diffusely elevated choline, diffusely diminished N-acetylaspartate, and multifocally elevated lactate within tumor (printed from [11] with permission)

Nevertheless, the diagnosis remains dependent on tissue sampling in all cases (Fig. 7.4) [11].

7.3.2 Body

A diagnosis of malignant gliomas should be obtained by integrating clinical, radiological, and histopathological findings in all cases. While clinical presentation and radiological tumor characteristics allow a focused differential diagnosis, the definitive diagnosis remains dependent on tissue histology. High-grade gliomas must be differentiated from low-grade astrocytomas, metastases, primary CNS lymphomas, abscess, and multiple sclerosis plaques. The surgical procedure and its timing are based on the likely diagnosis, which is derived primarily from the radiographic appearance.

The radiographic appearance of a high-grade glioma is typically an irregular, heterogeneous lesion that is

poorly marginated from normal brain on noncontrasted CT or MRI (Fig. 7.1). Active malignant glioma cells appear hyperdense on CT, hyperintense on T1-weighted MRI, and enhance with contrast administration. Irregular ring enhancement (active tumor) typically surrounds areas of low or abnormal signal (necrotic tissue, proteinaceous fluid, and old blood). These nonenhancing areas of necrosis within the tumor reflect malignant behavior and rapid growth. Infiltration through white matter bundles, such as the corpus callosum, or into the ependyma or subarachnoid spaces is also suggestive of an aggressive astrocytoma, most typically GBM. GBMs are also commonly associated with prominent mass effect and edema. T2-weighted hyperintensity corresponds to both edema and infiltrating nonenhancing glioma that usually extends diffusely into the adjacent brain.

While these radiographic characteristics are strongly suggestive of malignant astrocytoma, lymphoma, metastatic tumors, and abscesses often cannot be differentiated from GBM on CT or MRI alone. However, subtle differences do exist. Despite having a central area of nonenhancement similar to GBM, metastases are more often round, well marginated, and have excessive edema relative to their size. Furthermore, metastases may be multiple, whereas GBM is usually a single lesion. Like GBM and metastasis, abscesses may have marked surrounding edema, mass effect, and intense enhancement. Abscesses are usually rounded with a smooth, thin-walled, enhancing rim with a nonenhancing center. The rim is characteristically hypointense on T2-weighted images. Compared with GBM, the enhancing wall is usually thinner; however, multiloculated abscesses may closely mimic a GBM with an irregular pattern. Although clinical correlation may strongly suggest a diagnosis in these difficult cases, biopsy and histological analysis are often needed to definitively differentiate these three lesions.

The characteristics of anaplastic astrocytomas (AA or grade 3 glioma) are radiographically more variable than GBM. Noncontrasted CT and MRI may resemble low-grade gliomas, but mass effect with AA is usually greater with more tumor heterogeneity. In contrast to GBM, the distribution of enhancement with AA is usually homogenous. Areas of necrosis are not present, and the degree of brain edema is variable.

Demyelinating diseases can present as a solitary mass with peripheral enhancement. Although a mass effect can be seen, there is often no mass effect or less than would be expected based on the size of the enhancement. Other differentiating features include minimal surrounding brain edema and minimal symptoms. When presented with this clinical scenario, additional tests, such as MR spectroscopy, are appropriate (Fig. 7.4) [11]. High-dose steroids will often result in resolution of the mass in as little as 1–3 weeks. Sarcoid can also mimic a glioma but tends to be very responsive to preoperative high-dose steroids.

MR spectroscopy has become increasingly utilized to differentiate malignant astrocytomas from non-neoplastic lesions, such as radiation necrosis, abscess, or demyelinating lesions. MR spectroscopy measures choline (marker of membrane turnover), creatine, and phosphocreatine (components of the energy pool); glutamate and glutamine (excitatory neurotransmitters); *N*-acetyl aspartate (NAA, marker of neuronal health); lactate (marker of anaerobic metabolism); and myo-inositol (a sugar phosphate). MR spectroscopy divides the image into voxels of interest. The composition within individual voxels can then be compared between the lesion of interest and normal brain. MR spectroscopy demonstrating elevated choline in relation to NAA or creatine suggests neoplasm, whereas the absence of elevated choline in a background of other lipids and lactate would suggest a non-glioma lesion (Fig. 7.4) [11]. MR spectroscopy may also be useful in differentiating the grade or aggressiveness of glioma. While a moderate choline elevation in the setting of modest NAA depression without increased lactate suggests low-grade glioma, marked elevation of choline, marked depression of NAA, and increased lactate strongly suggest malignant glioma. Nonetheless, almost all cases require tissue sampling. This can be done with a stereotactic biopsy or during an open resection. If there is concern that the abnormality may represent multiple sclerosis and a MR spectroscopy study is consistent with this, then repeat MRI scanning in 4–6 weeks is prudent.

7.4 Grading and Classification

7.4.1 Synopsis

Several grading systems have been formulated that rely solely on cytological and histological characteristics. Currently, the World Health Organization system is the most widely used and differentiates three grades of astrocytomas: WHO grade 2 (low-grade astrocytoma), WHO grade 3 (anaplastic astrocytomas), and

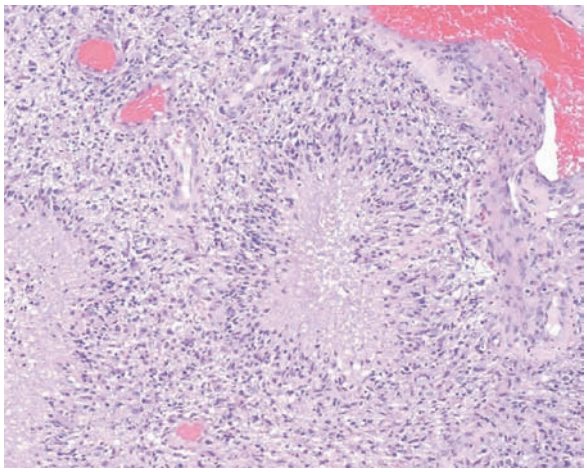

Fig. 7.5 Histopathology of glioblastoma multiforme (*GBM*) demonstrating classic features of GBM: palisading neoplastic cells around a zone of necrosis with vascular proliferation adjacent to the necrotic core

WHO grade 4 (glioblastoma multiforme). WHO grade 3 (AA) and WHO grade 4 (GBM) are considered malignant or high-grade gliomas. The spectrum from grade 2 to 4 is characterized by increased cellularity and pleomorphism, higher mitotic rate, and the presence of vascular proliferation and necrosis. The finding of vascular proliferation and necrosis is required for the diagnosis of grade 4 (Fig. 7.5) [3].

7.4.2 Body

Neoplasms arising from an astrocytic lineage form a large and heterogeneous group that can be divided into two groups of gliomas: fibrillary gliomas (astrocytoma, AA, GBM) and another more diverse group with distinct clinicopathological features (juvenile pilocytic astrocytoma, pleomorphic xanthrocytoma, and subependymal giant-cell astrocytoma). Current pathological classification systems rely solely on histological characteristics. Gliomas rarely metastasize beyond the CNS, and therefore, the tumor size, nodal status, and metastasis system used for systemic cancers are not applicable.

Fibrillary astrocytomas represent 80% of all astrocytic tumors. These tumors exist along a spectrum of well-differentiated tumors to highly anaplastic tumors. Several grading systems have been proposed and used in order to classify astrocytomas along this continuous spectrum. The WHO classification is the most widely accepted system. In this system, fibrillary astrocytomas are graded as 2, 3, or 4. These numbers correlate with the old modified Ringertz system of astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. In the literature and in practice, these terms are synonymous with each other, i.e., grade 2 = astrocytoma, grade 3 = anaplastic astrocytoma, and grade 4 = glioblastoma multiforme. In the WHO system, pilocytic astrocytomas are grade 1 lesions. However, they are not part of the continuum of fibrillary astrocytomas as they do not progress to a grade 2, 3, or 4.

The progression from grade 2 to 4 is characterized by increased cellularity, increased cellular atypia, increased mitotic index, and finally the appearance of vascular proliferation and necrosis. In general, necrosis is necessary for the diagnosis of a grade 4 lesion. The natural history of the fibrillary astrocytomas is for the lower grade lesions to progress to the grade 4 lesion (Fig. 7.6). The prognosis for the patient is directly related to the tumor grade at diagnosis, with median survivals of 8–10 years for grade 2, 2–3 years for grade 3, and 19 months for grade 4.

The MRI radiologic appearance of the tumor correlates well with the histopathology. Understanding this relationship is important in planning surgical intervention and in understanding the neurologic sequelae of surgery. Grade 2 lesions are usually isodense or hypodense on T1-weighted images and hyper-intense on T2-weighted images. The histopathology demonstrates a slight increase in cellularity, minimal atypia, and few if any mitoses. The grade 2 lesion is characterized as brain with infiltrated tumor cells. As this brain may retain neurologic function, plans to remove the tumor must be weighed against the risk of the potential neurologic compromise.

The high-grade astrocytomas, grades 3 and 4, are characterized by the presence of gadolinium enhancement on MRI (Figs. 7.1 and 7.2). However, 20% of nonenhancing primary brain tumors are in fact malignant gliomas by pathology. The grade 4 tumor usually has a central area that does not enhance, which represents necrotic tumor tissue. Although both grades 3 and 4 have surrounding edema, this finding is more prominent in the grade 4 tumor. Histopathologically,

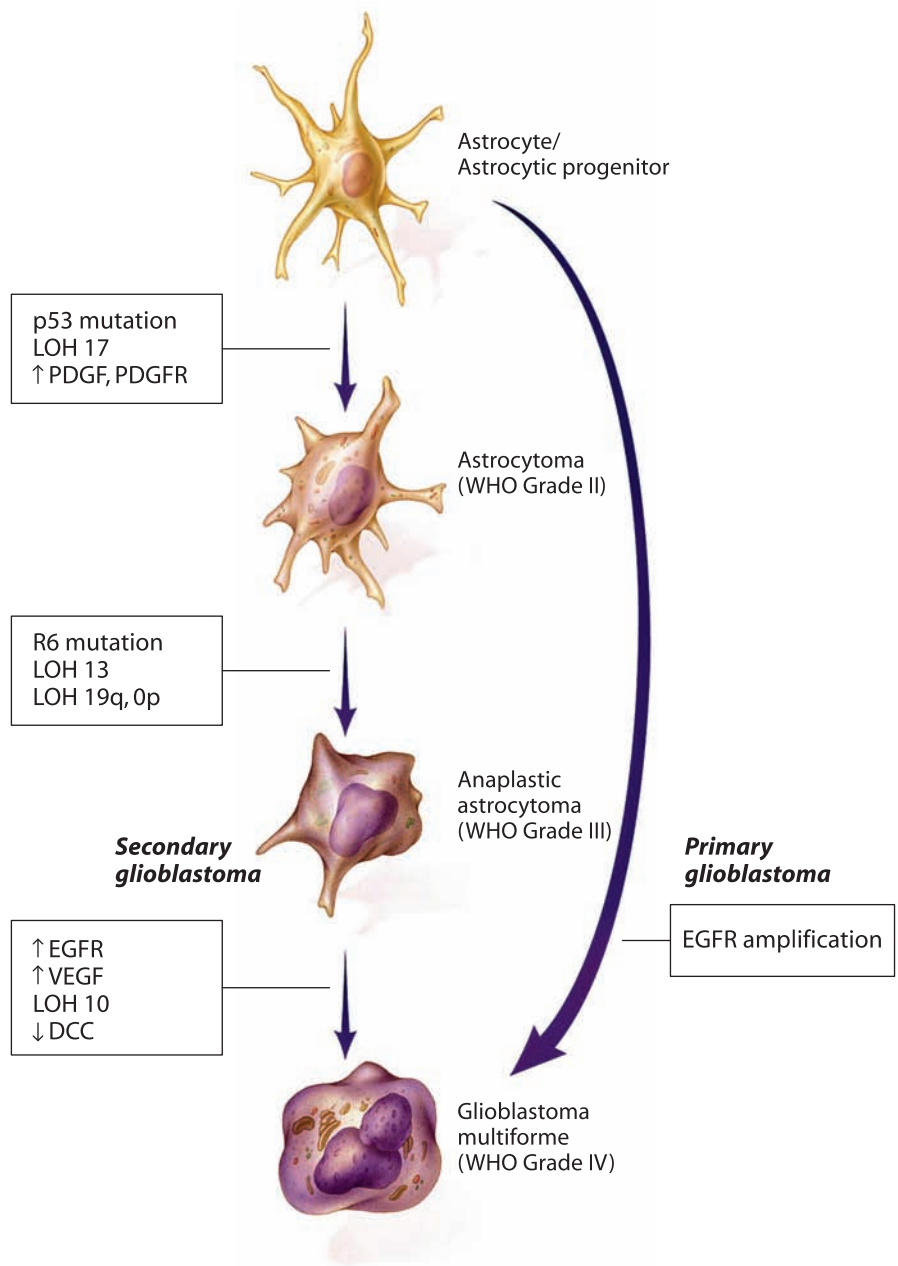

Fig. 7.6 Development and progression of astrocytic brain tumors. Malignant brain tumors can arise in one of two ways. Astrocytes can undergo genetic changes accompanied by upregulation of certain receptors, such as the platelet-derived growth factor (*PDGF*), endothelial growth factor receptor (*EGFR*), or vascular endothelial growth factor (*VEGF*). These progressive changes culminate in the formation of a glioblastoma. Alternatively, most primary glioblastomas arise de novo, without the need for gradual progression from an astrocytoma to a high-grade astrocytoma to a glioblastoma multiforme (illustration by Ian Suk, Johns Hopkins University)

the enhancing portion of the tumor seen on MRI represents pure tumor with no intervening brain. There is high cellularity, marked nuclear pleomorphism, mitoses, and necrosis. It is this enhancing portion of the tumor that is removed at surgical resection or is biopsied at stereotactic biopsy. The histopathology can vary in different regions of the tumor, which necessitates generous sampling at the time of surgery or biopsy. Tumors are generally graded by the highest grade tissue found since the higher grade tissue will determine the prognosis. For stereotactic biopsies, sampling error is a real concern and mandates close communication between the pathologist and the surgeon to maximize the chance of an accurate diagnosis.

Surgeons need always be wary when the tissue results of a biopsy are not consistent with the radiographic findings.

An important pathologic issue with high-grade gliomas is the tissue diagnosis of recurrent tumor. Treatment, including radiation and local chemotherapy, can alter the histopathology, making interpretation very difficult. In particular, the effects of treatment result in necrosis and changes in cellular morphology. Therefore, at the time of a second surgical procedure, a progressive or recurrent tumor requires the presence of viable tumor cells examined by the pathologist.

The degree of surgical resection of a primary brain tumor is an important prognostic factor in predicting the outcome of the disease and therefore the adjuvant therapy. It is therefore important to obtain a contrast-enhanced scan within 48 h so that an accurate assessment of the residual tumor can be made. Delayed scans are confounding because artifactual enhancement (secondary to surgery or radiation on local implants) may obscure the actual tumor that needs to respond to adjuvant therapy.

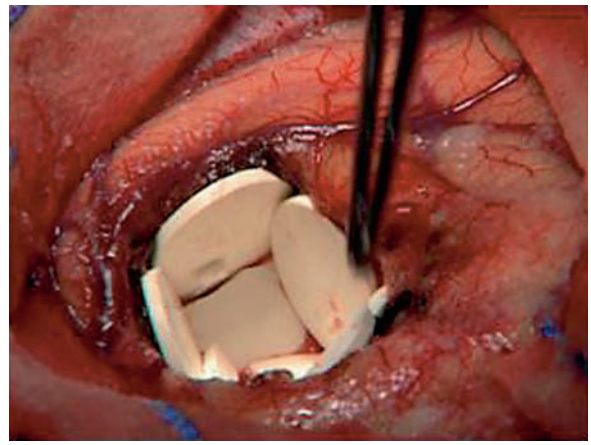

Fig. 7.7 Intraoperative view of a recurrent GBM resection cavity lined with biodegradable BCNU wafers

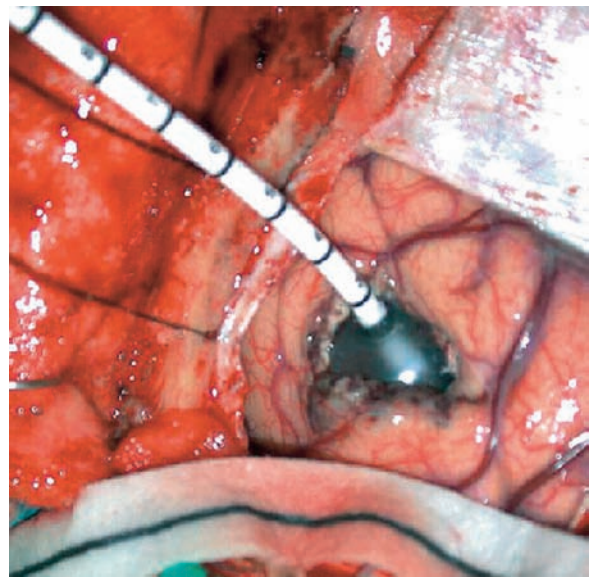

Fig. 7.8 Intraoperative photograph demonstrating Gliasite balloon within the resection cavity

7.4.3 Treatment

7.4.4 Synopsis

Patients with AA or GBM undergo surgery, either a stereotactic biopsy or a tumor resection. The goal of surgery is to establish the diagnosis and remove the enhancing portion of the tumor. The decision for a resection versus a stereotactic biopsy is based on the location of the tumor and its MRI appearance. A treatment option at the time of surgery is the implantation of chemotherapy (BCNU), in the form of impregnated polymer wafers (Gliadel) [19]. Following surgery, patients are treated with fractionated radiation therapy, often with temozolomide given concurrently. Temozolomide is then continued after the radiation therapy for up to 6 months [20].

Ninety percent of tumor recurrences are local, occurring within 2 cm of the original enhancing tumor. Treatment options include repeat surgery with or without local chemotherapy (Gliadel) (Fig. 7.7), standard chemotherapy regimens, brachytherapy with the Gliasite balloon (Fig. 7.8), or some combination of these. Whereas treatment at the time of initial presentation tends to be fairly consistent from patient to patient, treatment at the time of recurrence needs to be individualized based on the patient's disease status, performance status, and the tumor anatomy. Investigational treatments play an increasingly important role in the care of these patients at the time of tumor recurrence.

7.4.5 Body

7.4.5.1 Surgery

The role of surgery in the treatment of high-grade astrocytoma has often been debated. Historically, the value of surgery was in establishing the diagnosis and decreasing the size of the tumor mass by resection. As novel treatments have been developed, surgery has become important in the delivery of these treatments, such as Gliadel wafers, Gliasite balloon, and convection-enhanced delivery via intratumoral catheters.

The basic goals of surgery are tissue diagnosis, mass reduction, and tumor resection. Although the impact of resection on survival has been difficult to demonstrate in controlled trials, experience strongly supports the value of resection. Quality of life is certainly enhanced by resection in patients with increased ICP, mass effect, and brain edema. In the majority of patients, resection does not result in increased neurologic deficits due to the cytoarchitecture of the tumor. The enhancing portion of a high-grade glioma represents tumor cells without intervening brain. Therefore, the removal of this portion of the tumor can be carried out safely even in eloquent brain regions. The improved neuroimaging, intraoperative navigation techniques, intraoperative MRI, and preoperative and intraoperative functional mapping allow for better tumor resections with less neurologic morbidity.

In certain patients, aggressive tumor resection is not beneficial to the patient. Typically, tumors located primarily in the basal ganglia, thalamus, brain stem or corpus callosum are biopsied only. Lesions centered in the corpus callosum will sometimes have a large extension into one hemisphere, and resection may be beneficial in these circumstances to decrease the mass effect. In patients with diffuse infiltrating tumors, characterized by T2-weighted signal change only, which involve large areas of a hemisphere, biopsy is the procedure of choice. Deeper brain lesions are biopsied using CT- or MRI-guided stereotactic techniques. Open biopsy is appropriate for diffuse tumors located in the subcortical white matter. As sampling error and failure to obtain diagnostic tissue are risks of stereotactic biopsies, good communication with the pathologist during the procedure is important in establishing an accurate diagnosis.

In a recent review of 1,052 patients undergoing primary surgical resection of malignant astrocytoma, overall survival was closely correlated with the extent of resection regardless of WHO grade [12]. After primary resection of GBM, median overall survival was 13, 11, and 8 months when gross-total, near-total, or subtotal resection was achieved, respectively (Fig. 7.9). After primary resection of AA, median overall survival was

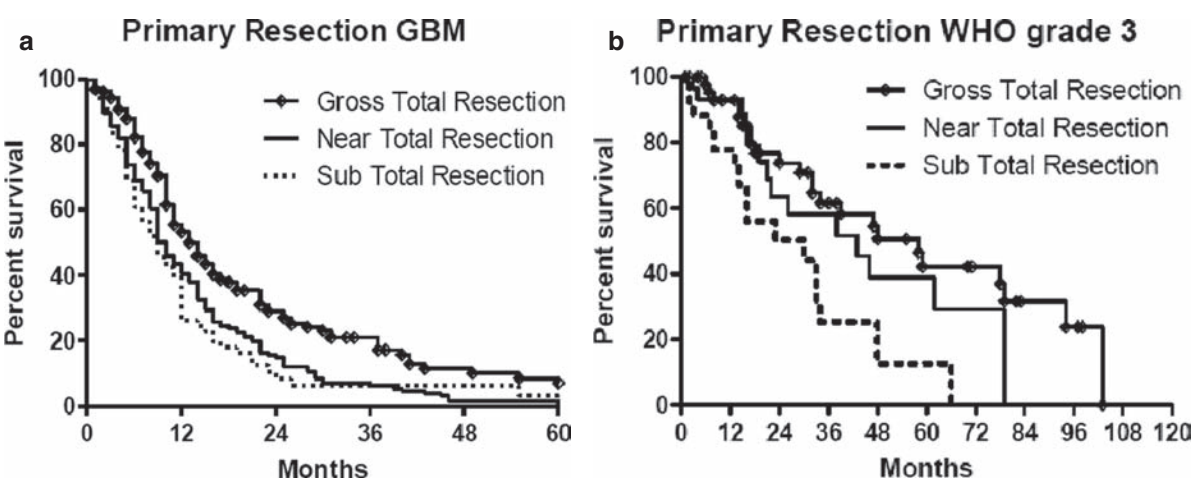

Fig. 7.9 Estimated Kaplan-Meier plot of survival after primary resection of (**a**) glioblastoma multiforme (*GBM*) or (**b**) anaplastic astrocytoma (*AA*). For both GBM and AA, patients receiving NTR ($p \leq 0.002$) experienced an independent survival benefit compared to patients receiving STR. Patients receiving GTR ($p \leq 0.05$) experienced an independent survival benefit compared to patients receiving NTR (gross total resection, *GTR* = no residual enhancement on MR; near-total resection, *NTR* = rim enhancement of resection cavity on MRI; subtotal resection, *STR* = residual nodular enhancement)

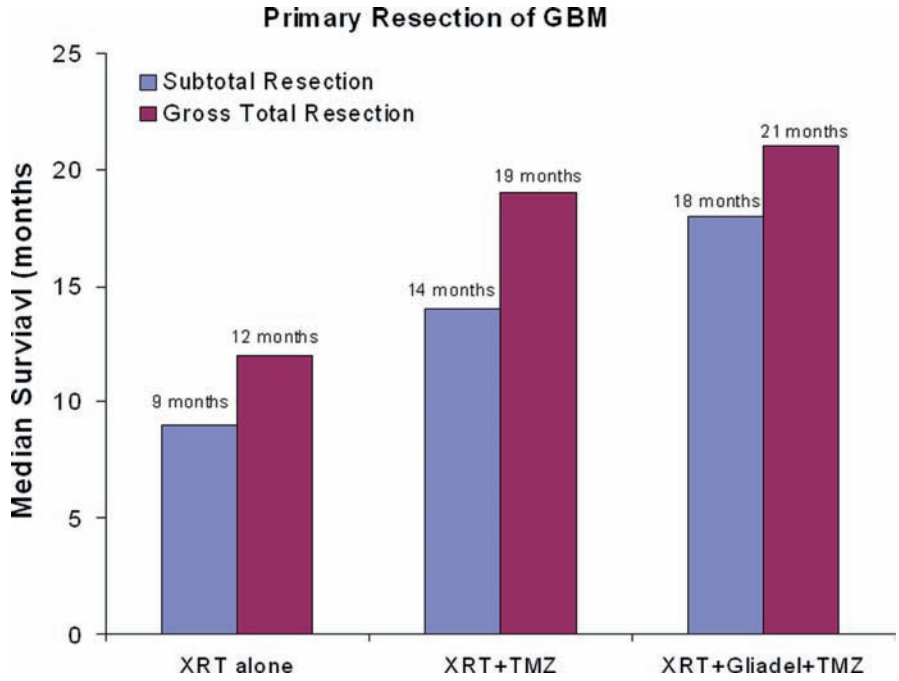

Fig. 7.10 Median survival after gross total resection (*GTR*) or subtotal resection (*STR*) of glioblastoma multiforme. GTR was associated with an increased median survival regardless of choice of adjuvant therapy in the Johns Hopkins 10-year experience (*XRT*, external beam radiation therapy; *TMZ*, temozolomide via Stupp protocol)

58, 46, and 34 months when gross-total, near-total, or subtotal resection was achieved, respectively (Fig. 7.9). In our experience with 700 consecutive cases of surgically treated GBM, we have observed prolonged survival when gross-total resection was achieved independently of whether Gliadel wafers, concomitant temozolomide, or both were utilized (Fig. 7.10).

Adjuvant treatment can be initiated at the time of surgical resection with the implantation of Gliadel wafers. Gliadel wafers, a polymer-based drug delivery system that provides sustained local release of BCNU, has been evaluated in three randomized, prospective, placebo-controlled phase III trials [2, 18, 19]. Gliadel was approved in 1996 for use in patients with recurrent GBM. This approval was based on a phase III prospective, randomized, placebo-controlled trial conducted in 222 patients at 27 centers. Results showed a median post-treatment survival of 31 weeks for patients treated with BCNU polymer versus 23 weeks for blank polymer (hazard ratio 6.67, $p = 0.006$). In the subgroup of patients with glioblastoma, the 6-month survival was increased 60% in the BCNU polymer group (64% vs 44%, $p = 0.02$). There were no clinically significant adverse effects attributable to the BCNU-loaded polymers [9].

To evaluate whether the treatment was effective as initial therapy in combination with radiation therapy, Valtonen et al. reported a prospective, randomized, placebo-controlled study of BCNU polymers or placebo as part of initial treatment, followed by standard radiotherapy. Thirty-two patients were enrolled in the study and equally divided between the groups, and all completed the study. All placebo patients had glioblastomas. Median survival was 58.1 weeks for the Gliadel group versus 39.9 weeks for placebo (hazard ratio 0.27, $p = 0.012$). When considering only the 27 patients with glioblastomas, median survival was 53.5 weeks with Gliadel and 39.9 weeks with placebo (hazard ratio 0.28, $p = 0.008$). Moreover, of six patients alive at 2 years, five were in the Gliadel group (31% 2-year survival vs 6% for the control group), and four of them had glioblastomas. At 3 years, 25% of patients in the Gliadel group were alive compared with 1 of 16 in the control patients.

Westphal et al. [19] carried out a 340-patient, randomized, prospective trial using Gliadel as the initial therapy. They reported a median survival of 13.9 months versus 11.6 months for those patients treated with surgery and radiation (hazard ratio 0.73, $p < 0.05$). At 3 years, 9.2% of patients with Gliadel were alive compared with 1.7% of controls. A meta-analysis of the GBM population of the Westphal and Valtonen study showed a significant improvement in survival for GBM patients (hazard ratio 0.75, $p = 0.034$).

These studies strongly suggest that Gliadel is safe and effective as an initial therapy. Based on the cumu-

lative evidence above, Gliadel was approved for use as the initial treatment in the USA by the FDA on 25 February 2003, and in Europe in 2004.

7.4.5.2 Radiotherapy

Radiation therapy is a critical component of the treatment plan for patients diagnosed with high-grade astrocytomas. Attempts to alter radiation schedules, change fraction size, or increase the dose have not demonstrated added benefit. Recently, clinical trials have shown a survival benefit by combining temozolomide with radiation therapy [15]. Other new approaches to enhance and expand the role of radiation include brachytherapy with the Gliasite balloon, stereotactic radiosurgery, a second course of radiation, and the use of radiation sensitizers.

Fractionated radiotherapy has been shown to extend survival in multiple randomized trials. The treatment regimen involves 30–33 treatments at 180–200 rads/treatment for a total dose of 5,400–6,000 rads. Patients with a very poor prognosis can be treated in a more rapid fashion in order to complete the course of radiation more quickly. This treatment regimen involves 300 rads/day in 17 treatments. Patients are treated with ten treatments over 2 weeks. The last seven treatments are given after a week off. In a retrospective study looking at 219 patients treated in this way, outcomes were as expected when the patients were assigned to six prognostic groups identified in a recursive partitioning analysis by the RTOG. These findings suggested that this shortened regimen results in a similar survival to the standard regimens [9].

Concomitant temozolomide and radiotherapy have recently been shown to be superior to radiation alone. A randomized phase III trial reported a significant improvement in the progression-free survival and overall survival in patients diagnosed with GBM. The study enrolled 573 patients from 85 centers. Patients treated with both temozolomide and radiation had an increased median survival of 15 months compared with 12 months with radiation only. Furthermore, the 2-year survival was 26% in patients treated with both temozolomide and radiation and 8% in patients treated with radiation only. These findings have now resulted in temozolomide being used in combination with radiation therapy as the initial treatment regimen for most patients diagnosed with glioblastoma [15].

Stereotactic radiosurgery has been utilized to increase or to boost the dose to a portion of the radiation field in the newly diagnosed patient. In the recurrent tumor setting, this modality is being employed to treat focal-enhancing recurrences. However, there is no study that has demonstrated a statistically significant benefit in terms of tumor control or increased survival.

Intracavitary brachytherapy using the Gliasite balloon is a novel approach to delivering additional radiation to the brain surrounding a tumor cavity (Fig. 7.8). Approved by the FDA as a device to be used in this fashion, the Gliasite balloon is being used in both recurrent and newly diagnosed settings. The balloon is sized and implanted at the time of resection. Several weeks later, an 125I solution is injected into the balloon via an attached port. The radiation material and the balloon are removed 4–5 days later [16]. A study of 24 recurrent GBM patients treated in this way had a median survival after Gliasite brachytherapy of 9 months.

Finally, a second course of radiation for patients with recurrent tumors is offered to some patients. The rationale is that the expected survival even with a treatment benefit from the second course of radiation is not long enough if patients suffer the morbidity of additional radiation on normal brain function.

7.4.5.3 Chemotherapy

In the past, most patients were treated with systemic chemotherapy at the time of tumor recurrence or following radiation as part of the patient's primary adjuvant treatment. For GBM, this occurred in the absence of any statistically significant benefit in any individual, controlled clinical trials. For AA, the combination of procarbazine, CCNU, and vincristine was found to be beneficial in several noncontrolled studies. Recently, when this combination was evaluated in a randomized, controlled fashion in patients with high-grade gliomas who were treated with the chemotherapy regimen following radiation compared with patients treated with radiation alone, no significant difference in survival was demonstrated for patients with AA or GBM [14]. Recent trials have focused on temozolomide, an oral alkylating agent, at the time of recurrence and at initial treatment for patients with GBM and AA. In 162 patients with refractory, recurrent AA who had failed a nitrosourea procarbazine combination, temozolomide

treatment resulted in a 9% complete response rate and a 13% partial response rate. When tested in patients with recurrent GBM in a phase II study compared with procarbazine, the median progression-free survival was 12 weeks with a progression-free survival at 6 months of 21%. Based on these findings, temozolomide has been approved for use in patients with recurrent AA who have failed a nitrosourea procarbazine regimen [20].

Stupp and colleagues reported the first evidence that systemic chemotherapy may play a definitive role in prolonging survival for patients with malignant astrocytoma [15]. Oral temozolomide given concomitantly with postoperative radiation followed by up to 6 monthly cycles of adjuvant temozolomide increased median survival by 2.5 months compared to adjuvant radiation alone. This recent phase III trial showing the benefit of combining temozolomide and radiation has resulted in the routine adoption of temozolomide in the initial treatment of GBM at many institutions [15].

Epigenetic silencing of the MGMT (O6-methylguanine -DNA methyltransferase) DNA-repair gene by promoter methylation compromises DNA repair and has been associated with prolonged survival in GBM patients. Hegi and colleagues demonstrated that the MGMT promoter was methylated in 45 % of 206 cases of malignant atsrocytoma [8]. In patients with MGMT methylation, concomitant temozolomide was associated with a 21.7 month median survival and a 6.4-month prolonged survival when compared to surgery plus radiation alone. This 6.4-month temozolomide survival benefit was superior to the 2.5-month benefit in median survival reported by Stupp [15], suggesting that this subgroup of tumors (MGMT silenced) represents increased susceptibility to concomitant temozolomide [8]. For this reason, the majority of patients will have already received temozolomide at the time of recurrence. Chemotherapy options for these patients will include a variety of agents, such as BCNU, procarbazine, CPT-11, and cisplatin, which have been used in this patient population but have not been shown to be statistically beneficial in controlled trials. Other options for patients include participation in investigational chemotherapy and immunotherapy trials.

More recent studies suggest that combining Gliadel wafers with postoperative radiation therapy and temozolomide (via Stupp protocol) is safe and may result in improved overall survival. In a series of 33 consecutive patients treated with this multi-modality therapy, a median survival of 21.3 months was observed [13]. Similarly, an interim analysis of a multicenter phase II study reported an 18.6-month median survival with combined Gliadel plus TMZ therapy [10]. In a nonrandomized comparison of patients receiving gross-total resection of their GBM, Gliadel with adjuvant radiation and temozolomide was associated with a 1.7-month increase in overall survival versus postoperative radiation and temozolomide alone [13].

7.4.6 Recurrent Tumors

The clinical problem of tumor recurrence arises in virtually all patients with this diagnosis. As patients are followed every 2–3 months with serial MRI scans, tumor progression is often documented before symptoms appear. As the intensity of treatment has increased, in particular local treatments, differentiating tumor recurrence versus treatment effect or treatment necrosis has become an important and difficult diagnostic dilemma. This is most problematic when the MRI change is increased enhancement around the original tumor cavity in the absence of mass effect. Although MRI spectroscopy and PET scans have been employed to differentiate tumor from treatment effect, these have not been found to be completely reliable. Often tissue obtained via stereotactic biopsy or open biopsy/resection is necessary. Given the problem of sampling error with stereotactic biopsy, open biopsy/resection is often preferred.

For patients with focal recurrences, surgical resection is an option. Additional treatment can be administered locally at the time of resection or systemically following surgery. Local treatments administered at the time of surgery include implantation of Gliadel wafers or brachytherapy using the Gliasite balloon. Systemic chemotherapy is an option with or without surgical resection. Initial drug options include temozolomide or BCNU. A number of other single agents, such as procarbazine, CPT-11, or carboplatin, have been used with only anecdotal reports of treatment response.

7.5 Prognosis/Quality of Life

The overall prognosis for patients with high-grade gliomas remains poor. For GBM, surgical resection following radiation therapy results in median survival

of 50 weeks. The recent advances with Gliadel and temozolomide have resulted in extending the median survival, but neither offer long-term control for most patients. Age and Karnofsky Performance Scores (KPS) are the factors that have the strongest association with survival.

Patients with high KPS at presentation, in general, continue with high KPS throughout surgery and radiation treatment. Dexamethasone is used, perioperatively and during radiation, to counteract the symptoms that arise from the brain edema associated with high-grade gliomas. Typical doses are 4–8 mg of dexamethasone four times a day. Doses as high as 20 mg every 4 h can be used on patients with high ICP due to brain edema. In these circumstances, dexamethasone has a profound effect on reducing patient symptoms and improving the quality of life. Following surgery and radiation therapy, dexamethasone should be tapered, as over time the side effects secondary to the steroids begin to detract from quality of life.

Recurrences occur primarily locally in the region of the original site of the presentation. This recurrence pattern has resulted in new approaches, such as Gliadel and convection-enhanced delivery, directed locally at the tumor site. Common patterns of spread include white matter tracts, in particular the corpus callosum. As local tumor control improves, distant recurrences are now developing. Because of the almost 100% recurrence rate, close radiological follow-up every 2 to 3 months is useful in the management of these patients in terms of treatment decisions and prognosis counseling. In addition to the enhancing portion of the tumor, attention should also focus on the signal change on FLAIR and T2-weighted images, as changes seen on these MRI sequences can also represent progressive disease.

7.6 Follow-Up/Specific Problems and Measures

An important management issue in patients with high-grade gliomas is the interpretation of the follow-up images after surgery and radiation therapy. With the intensification of therapy with these patients, MRI changes can be related to the treatment itself and not to tumor progression. For the first 3 months following radiation therapy, increased enhancement is often seen on follow-up images. Similar changes are now being seen 3 months to 1 year after treatment. Differentiating tumor verses treatment effect is critical as patients may receive unnecessary treatment, and furthermore, apparent benefits of some treatment may be overstated.

There are no diagnostic studies that differentiate recurrence versus treatment effect in a consistent manner. Clues on imaging studies include an enhancement pattern that surrounds the original tumor site and lacks nodularity. Often there is minimal or no mass effect associated with changes caused by treatment effect. Surrounding brain edema can be minimal or quite significant and will respond to steroids if present. MRI spectroscopy and PET scanning can be employed and may be helpful in suggesting recurrence versus treatment effect. In patients where treatment effect is suspected and the symptoms are minimal, increased steroids and repeating the MRI scan in 4–6 weeks are appropriate. Obtaining tissue is the gold standard, and this is recommended in cases where the risk of surgery is acceptable, and the outcome will alter treatment. Because of the difficulty in identifying active tumor in these cases, open surgery with adequate tissue sampling is superior to stereotactic biopsy. If treatment effect is found at surgery, additional anti-tumor treatment would not be appropriate. Hyperbaric oxygen and steroids are used in this scenario.

The use of local chemotherapy with Gliadel implanted at the time of surgery at initial diagnosis and recurrence has increased with its approval by the FDA. Up to eight wafers are placed along the walls of the tumor cavity with Surgicel used to cover them. The Surgicel should overlap onto the cortex and intervening white matter in order to hold the wafers in place. Irrigation fluid can be used to fill up the cavity, although this is not required. A water-tight dual closure is absolutely necessary as infections in the setting of Gliadel are closely associated with CSF leaks. The high-dose chemotherapy may impede the dural closure, and therefore it is very important for the surgeon to utilize techniques to reduce the risk of a CSF leak. The use of fibrin glue and dural grafts are encouraged when necessary.

Ideal patients for Gliadel use are those with solitary lesions in whom a near gross total resection of the enhancing tissue is possible. Patients with large amounts of visible tumor left at the end of surgery can have significant problems with brain edema as tumor cells die because of the local release of BCNU. Patients with tumor crossing the corpus callosum or distant from the resection cavity are not appropriate candidates. Placement of Gliadel in the setting of a small ventricular opening is acceptable. If the surgeon has concerns

about migration of the polymer into the ventricular system, then the polymer should not be used. Exposure of the ventricular cerebrospinal fluid to the BCNU released by the polymer does not result in BCNU toxicity.

Postoperatively, patients should be maintained on steroids for several weeks and may initially need higher doses than usual. The wafers can be seen on MRI images, hyperdense on T1-weighted images and dark on T2-weighted images. The hydrophobic component of the wafer can take months to absorb and can be seen on reoperation. There is no BCNU in this polymer remnant. The interpretation of post-treatment imaging is critical as there is a local treatment effect. Within the first 3 months, there is often increased enhancement around the margin of the tumor cavity. This enhancement can at times appear quite significant and suggest progressive tumor or abscess. In these circumstances, serial imaging is helpful in differentiating progressive tumor versus treatment effect. Changes related to the Gliadel will diminish over time. Air within the tumor cavity can also be seen for a number of weeks after treatment. In the initial experience, there was a concern that this represented infection, and the patients were explored. However, no infection was found in these cases. Therefore, when air is found within the tumor cavity, close follow-up and correlation with other clinical signs should be used to guide treatment decisions. Finally, the rim of enhancement around the cavity can persist indefinitely in some patients. Although it is not clear what this represents, observation with serial MRI scans is all that is necessary. Additional treatment should be withheld until the enhancement pattern increases.

7.7 Future Perspectives

Significant advances in imaging and surgical techniques have allowed for more rapid precision diagnosis and initial therapy of high-grade astrocytomas. Advances in radiation and chemotherapy have led to newer and better methods of treating these patients with less morbidity. However, in the future greater attention needs to be paid to predicting the response to individualized therapies and to overcoming the tumors' resistance mechanisms. For example, MGMT promoter methylation can be identified and is associated with increased responsiveness to alkylating agents [5]. Studies are underway to see if blocking resistance enzymes by agents such as O6-benzylguanine will further enhance the benefit of newly approved treatments using Gliadel and temozolomide [6]. Combination therapies will likely improve the outcomes [7].

In the future, it is conceivable that neuro-oncologists will first sample the tumor, evaluate its sensitivity and genetic characteristics, and then design the most individually appropriate therapy. Future advances in anti-angiogenesis therapy and immunotherapy will likely improve the outcome for these patients. Encouraging improvements in median survival and increasing percentage of patients with prolonged survival have occurred because of clinical trials testing new paradigms. The current approach of aggressively treating patients with the best possible therapies as well as offering innovative clinical trials will likely lead to further improvements in clinical outcomes.

References

1. Bohan E. (2002) Brain tumors. In: Barker E (ed) Neuroscience nursing-spectrum of care, 2nd ed. Mosby, St. Louis, MO, pp. 269–301
2. Brem H, Piantadosi S, Burger PC, Walker M, Selker R, Vick NA, Black K, Sisti M, Brem S, Mohr G, Muller P, Morawetz R, Schold SC, and the Polymer-Brain Tumor Group. (1995) Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. Lancet 345:1008–1012
3. Burger PC, Scheithauer BW, Vogel FS. (2002) Surgical pathology of the nervous system and its coverings, 4th ed. Churchill Livingstone, New York
4. Davis F et al (1998) Survival rates in patients with primary malignant brain tumors stratified by patients age and tumor histology type: an analysis based on surveillance, epidemiology, and end results (SEER) data, 1973–1991. J Neurosurg 88:1–10
5. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, Baylin SB, Herman JG. (2000) Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. New Engl J Med 343(190):1350–1354
6. Friedman HS, McLendon RE, Kerby T, Dugan M, Bigner SH, Henry A, Ashley DM, Krischer J, Lovell S, Rasheed K, Marchev F, Seman AJ, Cokgor I, Rich J, Stewart E, Colvin OM, Provenzale JM, Bigner DD, Haglund MM, Friedman AH, Modrich PL. (1998) DNA mismatch repair and O6-alkylguanine-DNA alkyltransferase analysis and response to Temodal in newly diagnosed malignant glioma. J Clin Oncol 16(12): 3851–3857
7. Guruangan S, Cokgor I, Rich JN, Edwards S, Affronti ML, Quinn JA, Herndon JE, Provenzale JM, McLendon RE, Tourt-Uhlig S, Sampson JH, Stafford-Fox V, Zaknoen S, Early M, Friedman AH, Friedman HS. (2001) Phase I study of GliadelTM

wafers plus temozolomide in adults with recurrent supratentorial high-grade gliomas. Neuro-Oncol 3(4):246–250
8. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R. (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med Mar 10;352(10):997–1003
9. Kleinberg L, Slick T, Enger C, Grossman S, Brem H, Wharam MD, Jr. (1997) Short course radiotherapy is an appropriate option for most malignant glioma patients. Int J Radiat Oncol Biol Phys 38(1):31–36
10. La Rocca RV, Hodes J, Villanueva WG, Vitaz TW, Morassutti DJ, Doyle MJ, et al (2006) A Phase II study of radiation with concomitant and then sequential temozolomide (TMZ) in patients with newly diagnosed supratentorial high-grade malignant glioma who have undergone surgery with carmustine (BCNU) Wafer Insertion. Eleventh Scientific Meeting of the Society for Neuro-Oncology
11. Laterra J, Brem H. (2002) Primary brain tumors in adults. In: Asbury A, McDonald I, McKhann G, Goadsby P, McArthur J (eds) Diseases of the nervous system: clinical neuroscience and therapeutic principles, 3rd ed. Cambridge University Press, Cambridge (Chap 87), pp. 1431–1447
12. McGirt MJ, Chaichana KL, Gathinji M, Attenello FJ, Than K, Olivi A, Weingart JD, Brem H, Quinones-Hinojosa AR (2009) Independent association of extent of resection with survival in patients with malignant brain astrocytoma. J Neurosurg 110(1):156–162
13. McGirt MJ, Than K, Weingart J, Chaichana K, Attenello F, Laterra J, Kleinberg L, Grossman S, Brem H, Quinones-Hinojosa A.(2009) Gliadel (BCNU) wafer plus concomitant temozolomide therapy after primary resection of GBM. J Neurosurg 110(3):583–588
14. Medical Research Council Brain Tumour Working Party. (2001) Randomized trial of procarbazine, lomustiine, and vincristine in the adjuvant treatment of high-grade astrocytoma: a medical research council trial. J Clin Oncol 19(2):509–518
15. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO. (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med Mar 10;352(10):987–996
16. Tatter SB, Shaw EG, Rosenblum ML, et al (2003) An inflatable balloon catheter and liquid 125I radiation source (GliaSite Radition Therapy System) for treatment of recurrent malignant glioma: multicenter safety and feasibility trial. J Neurosurg 99:297–303
17. Tod DW et al (1981) A family affected with intestinal polyposis and gliomas. Ann Neurol 10:390–392
18. Valtonen S, Timonen U, Toivanen P, Kalimo H, Kivipelto L, Heiskanen O, Unsgaard G, Kuurne T. (1997) Interstitial chemotherapy with carmustine-loaded polymers for high-grad gliomas: a randomized double-blind study. Neurosurgery 41(1):44–49
19. Westphal M, Hilt DC, Bortey E, Delavault P, Olivares R, Warnke PC, Whittle IR, Jaaskelainen J, Ram Z. (2003) A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. Neuor-Oncol 5(2):79–88
20. Yung WKA, Patros D, Yaya-Tur R, Rosenfeld SS, Brada M, Friedman HS, Albright R, Olson J, Chang SM, O'Neill AM, Friedman AH, Bruner J, Yue N, Dugan M, Zaknoen S, Levin VA. (1999) Multicenter Phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. J Clin Oncol 17(9):2762–2771