

Primary Brain Tumors: Characteristics, Practical Diagnostic and Treatment Approaches

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Abstract Primary brain tumors are classified according to the tissue of phylogenetic origin. Tumors arising from the neuroepithelium encompass a subgroup of neoplasms collectively referred to as “Gliomas”. Of this subgroup; astrocytomas are by far the most common. Astrocytomas are further subdivided by a four tier grading system based on The World Health Organization (WHO) classification where Grade I tumors represent the most benign and are able to be cured by surgical resection. Grade II astrocytomas are more infiltrative, but less aggressive than their more malignant counterpart Grades III and IV. However, due to their infiltrative nature grades II-IV are not cured by surgical extirpation. The most frequently used treatment regimen for malignant primary brain tumors include surgery for debulking or biopsy followed by postoperative radiation that is often combined with chemotherapy followed by 6 months of adjuvant chemotherapy. When paired with improved imaging and diagnostic modalities as well as new anti-angiogenic and molecular targeted therapies, the outcome for patients newly diagnosed with a malignant glioma has improved considerably. In addition, cancer stem cell research offers insight into the biology and pathogenesis of primary brain tumors. Currently, many studies implementing angiogenesis inhibitors and biologic modifiers offer encouragement for more patient participation in well-designed clinical trials for those patients who are eligible.

Keywords malignant gliomas • glioblastoma • oligodendroglioma • targeted therapies

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Introduction

Primary brain tumors are one of the most devastating diseases faced by modern medicine. Rare as compared to other cancers, they account for slightly greater than 1% of primary malignant cancers (Central Brain Tumor Registry of the United States (CBTRUS) 2005–2006). The latest published data compiled by CBTRUS estimated a total of 43,800 new cases of primary tumors of the brain and central nervous system (malignant and benign) diagnosed in the United States in 2006. They reported an incidence rate of 14.8 cases per 100,000 person-years with approximately one half malignant, constituting roughly 7.4 cases per 100,000 person-years. The American Cancer Society estimated that 18,500 new cases of primary malignant tumors of the brain and central nervous system were diagnosed in the United States in 2006 representing slightly greater than 1% of all primary malignant cancers diagnosed that year (CBTRUS 2005–2006).

It is estimated that in the United States alone, close to 13,000 people die yearly from a primary brain tumor, making malignant brain tumors among the top ten causes of cancer-related deaths in the United States (CBTRUS 2005–2006; Wrensch et al. 2002). Despite advances in surgery, radiation, and chemotherapy, these tumors still remain refractory to treatment as manifested by little change in the overall survival. In spite of the slow progress seen clinically, advances in the laboratory have provided a better understanding of the molecular and genetic aberrations that are believed to be the cornerstone in disease genesis, progression and treatment resistance providing the impetus for the development of newer and more effective therapies.

Primary brain tumors are classified according to the tissue of phylogenetic origin. Tumors arising from the neuroepithelium encompass a subgroup of neoplasms collectively referred to as “gliomas”. Gliomas represent approximately 40% of primary brain tumors (CBTRUS 2005–2006). Of this group, the most frequently seen in the clinical setting are astrocytomas, oligodendrogliomas, and oligoastrocytomas. Astrocytomas are further subdivided by a four-tiered grading system based on the World Health Organization (WHO) classification where the most benign are designated as grade I and the most malignant and aggressive are assigned higher grades of III and IV (Louis et al. 2007). Low grades are commonly referred to as WHO grade I or II and high grades as WHO grade III or IV. Tumor grade is essential when discussing treatment as well as prognosis, where the grade I tumors for the most part are well circumscribed, non-infiltrative and can be cured with complete surgical resection (Table 1). The tumors of higher grade infiltrate diffusely and are not amenable to cure by surgical resection alone. Thus, gliomas are often subclassified as localized or diffuse. This article addresses the characteristics of, and common chemotherapeutic regimens for, the most common types of tumors, and focuses on practical diagnostic and treatment approaches as well as on recent advances in adult primary brain tumors.

Table 1 WHO classification of astrocytic tumors and their characteristic features

WHO grade	WHO term	Histologic features	Age at diagnosis	Male/female ratio	Survival (years)
I	Pilocytic astrocytoma	Microcysts, Rosenthal fibers	10	1:1	Variable, Cures common
II	Diffuse astrocytoma	Mildly increased cell number or atypia	34	1.18:1	5 (2–12+)
III	Anaplastic astrocytoma	Mitoses, prominent atypia	41	1.8:1	2 (1–5)
IV	Glioblastoma multiforme	Necrosis, endothelial proliferation	53	1.5:1	1 (0.25–1.5)

Neuroepithelial Tumors

Localized Gliomas: Pilocytic Astrocytoma and Subependymal Giant Cell Astrocytoma (WHO Grade I, Low Grade Astrocytoma)

Astrocytomas classified as WHO grade I tumors are non-invasive, localized neoplasms. Most commonly seen in the clinical setting are the pilocytic astrocytomas and subependymal giant cell astrocytomas. Pilocytic astrocytomas can be seen either sporadically or as a manifestation of NF-1 or NF-2 while subependymal giant cell astrocytomas are found in the setting of tuberous sclerosis. Microscopically both are characterized by elongated cells with a small degree of nuclear atypia, cellular pleomorphism with occasional mitotic figures. Pilocytic astrocytomas on histologic sections reveal both microvascular proliferation and areas of sporadic necrosis, but in stark contrast to higher-grade tumors, these do not portend a poor prognosis and are felt to be more degenerative in nature. Anaplastic progression is a rare event seen in approximately 1% of cases (Tomlinson et al. 1994). In contrast to the pilocytic astrocytoma, malignant transformation has not been documented in the subependymal giant cell variant (Wiestler et al. 2000).

On T1-weighted Magnetic Resonance Imaging (MRI) scans, the pilocytic astrocytoma classically appears as a well-circumscribed isointense cystic tumor with a mural nodule, which is enhanced following the administration of contrast agents. While on T2-weighted imaging, the solid component may in some cases be hypointense to the gray matter similar to that of the cerebrospinal fluid (CSF). This can help distinguish radiographically a pilocytic astrocytoma from a medulloblastoma (Arai et al. 2006). Calcifications are rare and have been reported in 11% of pilocytic astrocytomas examined by Computerized Tomography (CT) scan (Lee et al. 1989). As for the subependymal giant cell astrocytoma, calcification is a common finding seen on CT scan. On MRI, they are generally isointense on T1-weighted and hyperintense on T2-weighted images. These tumors are commonly enhanced following the administration of contrast agents.

Both are successfully treated with surgery and usually do not require postoperative radiation or adjuvant chemotherapy; however, of note, the pilocytic astrocytoma has been associated with recurrence following incomplete resection and has shown a propensity to seed the leptomeninges (Brown et al. 1993; Tomlinson et al. 1994).

Diffuse Gliomas: Diffuse Astrocytoma, Oligodendroglioma, Oligoastrocytoma (WHO Grade II, Low Grade), Anaplastic Astrocytoma, Anaplastic Oligodendroglioma, Anaplastic Oligoastrocytoma (WHO Grade III, High Grade), and Glioblastoma Multiforme (WHO Grade IV, High Grade)

The most commonly encountered WHO grade II primary brain tumors are the diffuse gliomas consisting of the well-differentiated astrocytoma, oligodendroglioma, and oligoastrocytoma. Collectively, these grade II tumors are well-differentiated, hypercellular neoplasms with minimal cellular pleomorphism and nuclear atypia. Mitotic figures are rare with microvascular proliferation and absent necrosis. They have indistinct borders, infiltrating deep into the gray matter. On imaging, these tumors are hypointense to the brain on T1-weighted imaging and do not demonstrate enhancement following the administration of gadolinium. They are best visualized on the Fluid Attenuated Inversion Recovery (FLAIR) sequences where they appear as a hyperintense space-occupying mass which is the most sensitive imaging technique for all grade II diffuse gliomas.

Diffuse Astrocytoma (WHO Grade II, Low-Grade Astrocytoma)

Grade II astrocytomas arise from astrocytes and constitute anything from 15% to 25% of all gliomas. The peak age at presentation is between the ages of 30 and 39 years, with 10% diagnosed prior to the age of 20. Although histologically low-grade, these tumors almost always acquire the histologic, radiographic and clinical hallmarks of more malignant astrocytomas over time, 4–6 years after diagnosis, and are nearly always fatal. Median survival ranges from 2 to 10 years or more. The distribution between the sexes is more or less equal. The natural history of grade II astrocytomas is one of slow, indolent growth with the vast majority transforming into a higher-grade and more malignant phenotype. In keeping with their slow growth, the clinical presentation is often characterized by subtle and progressive behavioral changes (flattening affect, short-term memory deficits and difficulty with multi-step tasks), language and strength. However, the most frequent presentation is new onset seizure activity, which occurs in 50–90% of patients. Rarely, these tumors have been found incidentally on routine imaging for an unrelated condition, indicating that these tumors can remain silent for years.

Grade II astrocytic tumors have been divided into three types: fibrillary, protoplasmic and gemistocytic, with fibrillary the most common type and also the one that carries the best prognosis of the group. Conversely, the presence of a significant gemistocytic component of greater than 5% has been associated with a shorter time to progression and poorer prognosis (Krouwer et al. 1991). Microscopically, these tumors demonstrate a hypercellular, uniform population of well-differentiated astrocytes with minimal pleomorphism and nuclear atypia. Mitotic figures are rarely seen. Microvascular proliferation and necrosis are absent. Tumor borders are ill-defined, with individual neoplastic cells seen admixed with normal cortical neurons (perineuronal satellitosis). Microcystic change is seen, which is characteristic of low-grade astrocytic tumors, and is pathognomic, helping to differentiate a low-grade astrocytic tumor from reactive gliosis. Grade II astrocytomas have a Ki-67 index of less than 4% (Karamitopoulou et al. 1994; Montine et al. 1994).

The most common genetic abnormalities associated with grade II astrocytomas are deletions in the region of chromosome 17p13.1 corresponding to the locus for the tumor suppressor gene P53, overexpression of platelet-derived growth factor (PDGF) and its receptor (PDGFR), as well as allelic loss on chromosome 22q (Louis 1997). Although benign in appearance, approximately 50% of low-grade astrocytomas will transform into high-grade tumors (Laws et al. 1984; Pignatti et al. 2002; Soffietti et al. 2002). Despite the strong association with oligodendroglial neoplasms, it has been reported that approximately 11% of tumors fitting the histologic criteria of an astrocytoma possess allelic loss of chromosomes 1p and 19q (van den Bent et al. 2003c).

The imaging modality of choice is MRI, where they appear as a hypointense poorly defined mass on T1-weighted images that do not get enhanced following administration of gadolinium. FLAIR sequences reveal a hyperintense mass as compared to the surrounding brain.

Oligodendroglioma and Oligoastrocytomas (Grade II, Low-Grade Oligodendroglial Tumors)

Grade II oligodendroglial tumors like their astrocytic counterpart are well-differentiated, slow-growing neoplasms of the central nervous system. Compared to grade II astrocytomas, they are encountered less frequently. Older data report that they comprise approximately 4% of primary brain tumors (Mork et al. 1985). However, due to changing criteria and with the advent of 1p and 19q testing, the estimates have increased to as much as 20% (Coons et al. 1997). The natural history of low-grade oligodendroglial tumors is one of slow indolent growth with a favorable prognosis. The median survival ranges 6–10 years or more in many cases. Grade II oligodendroglial tumors occur most commonly in young adults and although presentation typically depends upon on the region of involvement, the most frequent symptom is seizures. It has a propensity to the frontal lobe or multilobular involvement in 50% of cases. Rarely, cerebrospinal involvement can be seen in tumors that are located in close proximity to the ventricular system. Because of dense, delicate

branching vasculature, spontaneous hemorrhage can occur and patients may present with acute neurological deficits including headache, confusion, lethargy and hemiparesis. Histologically, these tumors are well differentiated and demonstrate moderate cellularity with rare or absent mitosis. Tumor cells are seen infiltrating diffusely into the gray and white matter and classically have rounded nuclei with peri-nuclear halos, giving the pathomonic “fried egg” appearance on histologic sections. Foci of calcification can be seen along with a dense network of delicately branching blood vessels (“chicken wire”). Vascular proliferation and necrosis are absent. GFAP expression is scant in tissue sections unless there exists a significant astrocytic component. Ki-67 index is less than 5%.

Oligoastrocytomas contain varying proportions of both oligodendrocytes and astrocytes. Traditionally, neuropathologists have diagnosed oligodendrocytoma if the astrocytic or oligodendritic elements comprise 25% or more of the tumor tissue (Smith et al. 1983). However, any mixture of each tumor type is considered an oligoastrocytoma. This entity has a prognosis that lies somewhere between oligodendrogliomas and astrocytomas. Advances in genotyping and molecular analysis revealed that the loss of heterozygosity seen on the short arm of chromosome 1(1p) and the long arm of chromosome 19(19q) correlated with chemosensitivity and improved survival in patients with oligodendroglial tumors (Jenkins et al. 2006; Smith et al. 2000) (Fig. 1). Bauman and associates reported an improved prognosis

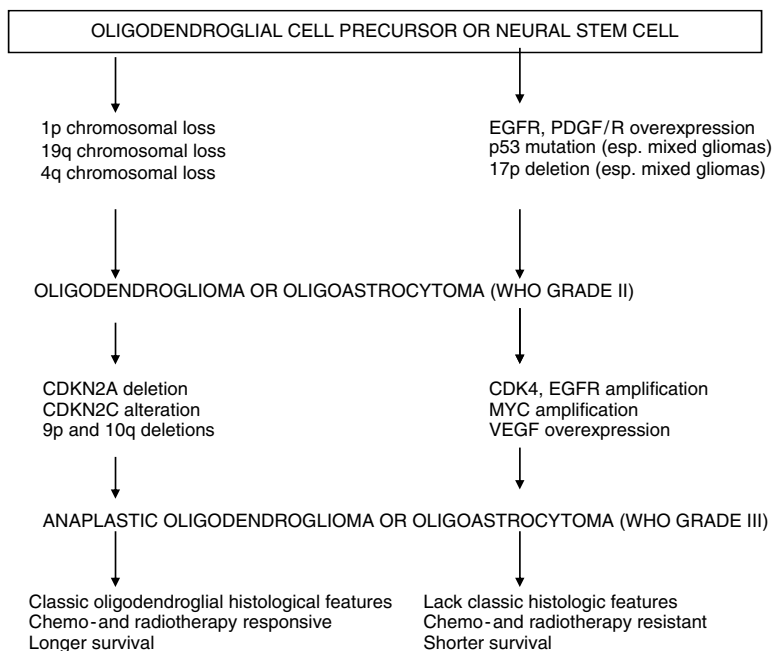


Fig. 1 Formation of oligodendroglial tumors, molecular markers, histological features, and therapeutic outcomes

in oligodendroglial tumors that possess loss of 1p either as a single deletion or in combination with loss of 19q (Bauman et al. 2000).

The radiographic appearance of grade II oligodendroglial tumors is indistinguishable from low-grade astrocytomas except for occasional calcifications that can be best seen on CT scan. Although not diagnostic, if calcification is present, it helps to distinguish oligodendrogliomas from astrocytomas. They, like their low-grade astrocytic correlate, are not enhanced following the administration of gadolinium on T1-weighted imaging. FLAIR sequences reveal a hyperintense lesion with ill-defined borders.

Treatment

Optimum treatment of patients with diffuse astrocytomas remains unsettled. Although a microscopic complete resection is probably impossible, an aggressive attempt to maximal surgical resection remains the mainstay of the treatment. More controversial are the nature and timing of the adjuvant therapy before or after the surgery. Some clinicians would advocate a watch and wait approach on asymptomatic patients without any definitive treatment (surgery or radiation therapy), while others may elect to treat with radiation therapy with and without chemotherapy following surgery. Based on the results of the five randomized clinical trials on patients with low-grade astrocytomas that are mainly composed of diffuse astrocytomas, Shaw et al. concluded that postoperative radiation improves time to tumor progression but not overall survival. They also noted that a low dose 5,400 cGy was as effective as higher doses and addition of chemotherapy did not improve progression-free or overall survival, except for causing more toxicity. They also identified a high-risk group of patients at age greater than 40 years who had subtotal resection (Shaw & Wisoff 2003). New data emerging from recent randomized studies suggest that observation only was a reasonable option for those patients who are in a low-risk group with age less than 40 years and had complete or near-complete resection. For high-risk patients (age great than 40 years who had partial resection or biopsy) who were randomized to radiation alone versus radiation and PCV (Procarbazine, CCNU and Vincristine) chemotherapy, the addition of PCV chemotherapy to radiation conferred survival and progression-free survival advantage and reduced risk of death and progression at beyond 2-year follow-up, suggesting possible benefit for chemotherapy in this group of patients (Shaw et al. 2006; Shaw et al. 2008).

A number of small trials using a variety of chemotherapeutic regimens including temozolomide and PCV have investigated the feasibility of neoadjuvant chemotherapy with some success. Although the response rates were encouraging and the prospect of delaying radiation and avoiding potential radiation toxicity or even surgery is attractive, a recommendation regarding this approach must await the results of randomized trials.

Perhaps the most significant factor in the diagnostic and therapeutic approach to oligodendroglial tumors has been the revelation that allelic loss on chromosome 1p

and 19q, as demonstrated by fluorescence in situ hybridization (FISH) techniques, is a strong predictor of response to radiation therapy and chemotherapy and also of longer overall survival. This understanding in molecular genotyping has helped to change the treatment algorithm in oligodendroglial tumors in recent years.

Surgery

Like for the majority of brain tumors, surgery for resection or biopsy for diagnosis is the initial step in the management of diffuse low-grade gliomas. Pathology is of both prognostic and therapeutic significance. Historically, there has been a debate over the extent and timing of surgery and some of the issues still remain unsettled. Due to the infiltrative nature, resection even when thought complete, does not result in cure. Since the extent of removal does not alter the natural progression of the disease, it was uncertain whether a complete resection should be undertaken versus stereotactic biopsy for diagnostic purposes only. Proponents for resection argued that although sub- or gross total resection does not offer a curative result, a feasible debulking should be attempted in order to secure a larger tissue sample providing a more accurate diagnosis. Support of this view came from a study conducted by Jackson and colleagues in which 81 patients with a diagnosis of grade II astrocytoma underwent biopsy for diagnosis followed by craniotomy with a gross total or subtotal resection. Results revealed that in 38% of cases, the tumor grade was changed from the original grade obtained at biopsy (Jackson et al. 2001). Advances in neuroimaging, along with the implementation of neuro-navigational systems, have improved the delineation of tumor margins and, when combined with better neuro-anesthesia and cortical mapping, a more detailed resection can be undertaken safely.

In addition, the benefits of surgical resection include decreasing the tumor burden, resulting in less edema, especially in high-grade gliomas, and mass effect, which in some patients may provide palliation of neurologic symptoms such as seizure activity. Today, most neurosurgeons reserve biopsy as the procedure of choice for deep-seated lesions (i.e., tumors involving the brainstem or thalamus) or tumors involving eloquent cortex (insula cortex on the left, speech area, motor strip). Therefore, gross or subtotal resection is usually recommended so long as the neurologic function can be preserved.

In relation to overall survival, there is no clear evidence that supports or refutes either approach; however, Berger and colleagues utilized computer imaging analysis in the pre-operative and postoperative settings to determine tumor volume as it related to recurrence and time to progression in 53 patients with diffuse low-grade gliomas. Results from the study provided evidence that the extent of resection had a significant impact on the incidence of recurrence and time to progression during a mean follow-up of 54 months. None of the patients who had received a complete resection ($N=13$) had recurrence during the mean follow-up period. In contrast, recurrence was seen within the mean follow-up period in patients who had received an incomplete resection, with tumor volume postoperatively lesser or greater than 10 cm³ (Berger et al. 1994).

For asymptomatic patients who have a low-grade appearing mass on contrast imaging, a watch and wait approach has been adopted by some clinicians. In general, if this approach is undertaken, it is suggested that supportive studies such as positron emission tomography (PET) scan or magnetic resonance spectroscopy be performed to rule out the potential high-grade tumors (Ginsberg et al. 1998). Still, this watch and wait approach can cause the burden and anxiety associated with ongoing clinical and radiographical surveillance, the uncertainty of diagnosis and the possibility that an abrupt change in tumor behavior may result in significant clinical and neurological symptoms or a tumor that is less amenable to aggressive resection. As a consequence, the most aggressive feasible surgical intervention constitutes the usual initial therapy.

Like for grade II astrocytomas, there exists controversy regarding the role of extensive surgical resection for grade II oligodendroglial tumors, with most of the studies being retrospective or post hoc analysis. There exist several uncontrolled studies supporting resection as it relates to a prolonged disease-free interval and overall survival (Berger et al. 1994; Celli et al. 1994). In contrast, studies by Kros and colleagues reported no statistically significant survival benefit in patients receiving a resection (Kros et al. 1994). Regardless of the predictive value, most neuro-oncologists support resection, when feasible, to improve the neurologic status as well as to provide confirmation of histology based on the observation that a proportion of non-enhancing lesions, radiographically presumed to be low-grade, were later proven to be of a higher grade in up to 30–40% on tumor tissue obtained following resection (Ginsberg et al. 1998).

Radiation Therapy

Radiation therapy has been part of the standard treatment for low-grade astrocytomas for decades; however, again, the timing of administration is still not well defined. To address this issue, a large randomized collaborative study was undertaken by the European Organization for Research and Treatment of Cancer (EORTC) and the Brain Tumor Working Group of The Medical Research Council of the United Kingdom. This study accrued 311 patients into two groups. The cohorts were well matched for the extent of tumor resection and were randomized into patients who would receive immediate radiation following surgery (within 8 weeks of operation) and those who would be observed, delaying radiation until time of tumor progression. Each cohort was treated with the standard radiation dosing schedule of 54 Gy over 6 weeks. Results reported a statistically significant increase in the 5-year progression-free survival in patients receiving radiation therapy in the immediate postoperative setting (55%) versus those in the observation group (34%). However, the results showed no difference in the overall survival between the two groups. Of note was the fact that those treated with radiation had improvement in seizure control, as compared to the observation group. Unfortunately, no other formal measures of quality-of-life or neuro-cognitive function were performed (Karim et al. 2002; van den Bent et al. 2005).

Conversely, in a retrospective study conducted by Leighton and colleagues, 167 patients with a diagnosis of a supratentorial low-grade astrocytoma were randomized into two groups. Eighty (48%) of the 167 patients received immediate postoperative radiation therapy while 87 (52%) had therapy delayed until the time of progression. Results reported that the delayed radiation group had significantly improved 5- and 10-year progression-free survival rates (84% and 70% respectively) compared to the group receiving immediate radiation (62% and 35% respectively). However, one notable bias of the study was that those in the delayed cohort had more favorable prognostic features at the onset compared to the immediate radiation group (Leighton et al. 1997).

Accordingly, a study performed by the Radiation Therapy Oncology Group (RTOG) selected patients aged 40 years and under who had undergone complete resection as gauged by the operating neurosurgeon and had good prognostic indicators for observation only. The overall survival rate at 5 years was 93% with a progression-free survival rate of 50%. Unfavorable patients (age > 40 and had subtotal resection or biopsy) received radiation therapy or radiation therapy and PCV chemotherapy and the study showed no overall survival advantage, with the addition of PCV to radiation therapy in the initial median follow-up of 4 years. Five-year PFS was poor in all three arms ranging from 39% to 61%. Only half of the favorable patients were disease-free at 5 years. Both progression-free survival rate and median progression-free survival time were noted to be better with the addition of PCV, but not significantly (Shaw et al. 2006). In their final report with a longer 5.9-year median follow-up time, they stated that improved progression-free survival rate, but not overall survival rate, was seen between years 0 and 2 for patients receiving radiation therapy and PCV versus radiation therapy alone. However, beyond 2 years, the addition of PCV chemotherapy to radiation therapy conferred both a significant overall survival rate and progression-free survival rate advantage, and reduced the risk of death by 48% and progression by 55%, suggesting a delayed benefit for chemotherapy in the unfavorable group of patients (Shaw et al. 2008).

A treatment algorithm for the use of radiation versus observation in low-grade astrocytomas can be used on a case-by-case basis to stratify patients according to age (40 years or less), pathology, percentage of MIB-1 or Ki-67 indices, as well as size and amount of residual tumor.

As for grade II oligodendroglial tumors, although radiation is an effective treatment affording long progression-free periods, there exists no definitive multi-center randomized controlled clinical trial addressing the value of radiation alone on overall survival in patients with low-grade oligodendroglial tumors.

In general, for all low-grade gliomas, most clinicians agree that it is acceptable to withhold radiation until the time of progression in young otherwise healthy patients who have no neurologic deficits, low MIB-1 or Ki-67 indices and received a complete or near-complete resection. In contrast, patients with extensive disease, significant residual tumor after resection or those with significant neurologic deficits and high MIB-1 or Ki-67 indices should be considered for radiation or chemotherapy or even combined radiation and chemotherapy based on recent study results.

Chemotherapy

The role of chemotherapy in the treatment of grade II astrocytomas also remains to be defined. At present, there have been no definitive randomized studies addressing this issue. Most of the studies focusing on the use of chemotherapy as initial treatment have been done in the pediatric population, in part due to the deleterious effects of radiation on the developing brain. Most neuro-oncologists would agree that in light of their indolent growth and long natural history, observation only is a reasonable option in a young patient harboring a grade II astrocytoma. However, in the setting of an enlarging low-grade tumor, upfront chemotherapy is a reasonable option in a young otherwise healthy patient. First, it delays the neurocognitive side effects, which is a well-known trepidation associated with radiation therapy. Secondly, radiation-related toxicity is avoided. Lastly, the size of the tumor may be reduced decreasing the size of the radiation field, thereby limiting radiation damage to normal structures. These advantages must be weighed against the possible bone marrow toxicity inherent with many of the standard drugs used today. Therefore, the optimal drug would have superior bioavailability, cross the blood–brain barrier and have a favorable toxicity profile. Temozolomide is one such agent. The introduction of temozolomide has changed the scope of brain tumor therapy. In a study performed by Brada and associates, temozolomide was used in the neoadjuvant setting in patients with enlarging low-grade gliomas. Tumor stabilization was seen for both tumors of oligodendroglial and astrocytic lineage (Brada et al. 2003). Regarding the chemosensitivity of grade II astrocytomas, approximately 11% of histologically appearing low-grade astrocytomas harbor deletions of chromosomes 1p and 19q. This genetic aberration is associated with the chemosensitivity seen in gliomas of oligodendroglial lineage (Smith et al. 1999).

As for grade II oligodendroglial tumors with their more favorable prognosis, some clinicians may consider deferring initiation of chemotherapy until time of progression, especially following a complete or near-complete resection. If a watch and wait approach is undertaken after surgical removal, the patient may be followed clinically with serial contrast MRI every 2–3 months initially (Smith et al. 2000; Smith et al. 1999). Historically, PCV regimen has been widely used as a treatment option for patients diagnosed with an oligodendroglioma. One study reported encouraging responses (1 partial response, 1 complete response and 2 stable diseases) with longer than 14 months progression free survival in a small cohort of patients (number: 4) diagnosed with a low grade oligodendroglial tumor treated with PCV as preirradiation therapy. PCV, given as salvage therapy after radiation treatment failure and as a first-line therapy with radiation therapy, also was found to be highly effective with excellent responses. Other studies reported similar favorable progression free survival when given as neoadjuvant therapy. Recently, Lebrun and colleagues treated 33 patients with newly diagnosed low grade symptomatic oligodendrogliomas. They noted that 90% of patients were progression free at 1 year and the survival rates at 2, 5 and 10 years were found to be 85%, 75% and 50%, respectively. These results suggest that radiation therapy could be postponed to delay cognitive side effects of irradiation (Lebrun et al 2007).

At present, the available clinical data reveal that grade II oligodendroglial tumors with deletions of 1p and 19q respond equally to both temozolomide and PCV with the former having a more favorable toxicity profile. Van den Bent et al. reported a response rate of more than 50% in patients with an oligodendroglioma treated with temozolomide as first-line therapy at recurrence (van den bent et al. 2003a). Additionally, temozolomide was shown to be an effective second-line therapy in patients following failure of PCV treatment (van den Bent et al. 2003b). Hoang-Xuan et al. treated 60 patients with a grade II oligodendrogliomas and oligoastrocytomas with temozolomide. The study documented both a significant radiographic and clinical improvement. The median time to maximum tumor response was 12 months, with some responses seen after the tenth month of treatment. There was a significant association between 1p loss and temozolomide chemosensitivity seen in 26 patients in whom molecular analysis was performed (Hoang-Xuan et al. 2004).

Malignant Gliomas: Anaplastic Astrocytoma, Anaplastic Oligodendroglioma, Anaplastic Oligoastrocytoma (WHO Grade III, High Grade), and Glioblastoma Multiforme (WHO Grade IV, High Grade)

Malignant gliomas are characterized by a group of highly malignant neoplasms derived from an astrocytic or oligodendroglial lineage. They include the anaplastic astrocytoma (AA), glioblastoma multiforme (GBM), anaplastic oligodendroglioma (AO), and anaplastic oligoastrocytoma (AOA), the GBM being the most common malignant glioma comprising slightly more than half of all malignant gliomas. In 2006 alone, an estimated 18,500 cases of malignant brain tumors were diagnosed in the United States (CBTRUS 2005–2006). Unfortunately, these tumors have an inherent capacity to infiltrate into distant areas of the brain, rendering little chance for cure. The role of radiation therapy for malignant gliomas has been well established as it clearly demonstrated a survival benefit in many randomized trials. However, the role of chemotherapy in malignant gliomas remained elusive. Multiple clinical trials utilizing single or various combination chemotherapy regimens that were conducted in the past have been mostly negative with only a modest benefit at best. These negative results were mainly felt to be due to the small number of patients in each trial, different treatment regimens, lack of effective drugs that can penetrate the blood–brain barrier, patient populations and outcome measures. To increase statistical power, a number of meta-analyses were performed and each has demonstrated a small but clear improvement in survival benefit from chemotherapy, especially with anaplastic gliomas. Historically, most of chemotherapeutic agents were nitrosourea-based as their lipid solubility allowed them to cross the blood–brain barrier. In addition, the timing and sequencing of chemotherapy in relation to radiation therapy has not been well defined until recently, when a landmark phase III randomized trial conducted by EORTC and National Institute of Canada (NCIC) demonstrated a clear survival benefit of combined radiation therapy and chemotherapy with temozolomide over radiation therapy alone in newly diagnosed patients with GBM (Stupp et al. 2002).

Histologic criteria of high-grade gliomas include hypercellularity, cellular pleomorphism, nuclear atypia, and microvascular proliferation with individual tumor cells infiltrating into the normal brain parenchyma. Necrosis is pathomonic for grade IV astrocytomas (GBM) according to the WHO grading system. Imaging reveals contrast enhancement, albeit on rare instances a malignant glioma may exhibit no or minimal enhancement following the administration of contrast agents. On T1-weighted non-contrast images they appear as a hypointense mass surrounded by low attenuation, representing vasogenic edema. Although all can have an identical radiographic appearance, a lesion delineated by a thick, irregular rim of enhancement surrounded by a central area of necrosis is most characteristic of a GBM. In comparison to heterogeneously enhancing lesions seen on malignant astrocytomas, anaplastic oligodendrogliomas appear homogeneously enhancing on contrast and the presence of ring enhancement appeared to be associated with a poor prognosis (Cairncross et al. 1998).

The most frequently used treatment regimen for malignant gliomas includes surgical intervention for debulking or biopsy, if sub- or gross total resection cannot be achieved, for diagnosis, followed by postoperative radiation, which is often combined with chemotherapy. The chemotherapeutic options in the treatment of malignant gliomas that are mostly chemo- and radiation-resistant have been limited in the past with only modest survival benefit except for anaplastic oligodendrogliomas. However, with the advent of the recent success in treating newly diagnosed glioblastomas with combination radiation and chemotherapy approach, improved diagnostic and imaging modalities, better understanding of molecular genetics such as 1p, 19q chromosomes, methyl-guanyl-methyl-transferase (MGMT) promoter methylation and epidermal growth factor receptor (EGFR) status, and the introduction of new antiangiogenic agents and molecular targeted therapies, significant progress has been made in the diagnosis and management of malignant gliomas in recent times. Currently, many clinical trials implementing angiogenesis inhibitors, biologic modifiers and cancer stem cell research are being actively investigated and participation in a well-designed trial should be encouraged for those patients who are eligible.

Anaplastic Astrocytoma (Grade III Astrocytoma) and Glioblastoma Multiforme (Grade IV Astrocytoma)

Anaplastic astrocytomas and GBM are classified as WHO grade III and WHO grade IV tumors respectively. GBM, in contrast to anaplastic astrocytoma, can originate de novo (Primary GBM) or transform from a pre-existing lower-grade tumor (Secondary GBM) (Fig. 2). This paradigm purports that primary glioblastomas arise in older patients (mean age of 53 years) and are driven by a key mutation producing EGFR amplification, whereas secondary glioblastomas occur in a younger population (usually 45 years or less) and evolve from lower-grade through a sequential accumulation of genetic alterations starting with a p53 mutation. The incidence of high-grade gliomas increases with age. Anaplastic astrocytomas are seen most frequently

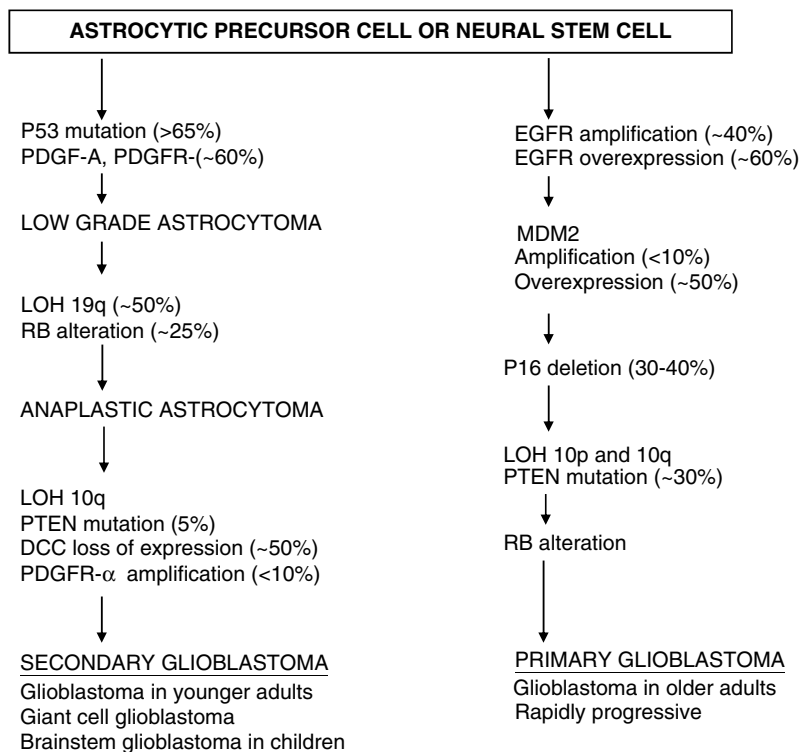


Fig. 2 Formation of primary and secondary glioblastomas and their molecular markers

between the fourth and fifth decades (median age at diagnosis, 41 years) while GBMs are seen from the fifth to the seventh decades (median age at diagnosis, 53 years). The average survival from time of diagnosis has been reported to be between 24 and 36 months for grade III and between 9 and 15 months for grade IV astrocytomas. However, patients with primary glioblastomas appear to have shorter median survival, and patients with secondary glioblastomas have longer median survival. Once these malignant gliomas recur, less than 50% of patients will survive more than a year.

Anaplastic Oligodendroglioma and Anaplastic Oligoastrocytoma (Grade III Oligodendroglioma and Grade III Oligoastrocytoma)

For the most part, the treatment of anaplastic oligodendroglial tumors parallels the therapies utilized in malignant astrocytomas. Surgery with resection or biopsy is the initial step in treatment. However, unlike anaplastic astrocytomas, because of known unique chemosensitivity associated with deletions on chromosomes 1p and 19q, upfront chemotherapy can be considered prior to radiation for young otherwise healthy patients with anaplastic oligodendroglioma who have no neurologic deficit and who had a complete or near-complete resection. For patients with anaplastic

oligoastrocytomas, upfront radiation therapy is usually recommended. The role of combining chemotherapy with radiation therapy for non-GBM patients has not been fully established although this approach has been widely adopted based on the Stupp trial that showed a survival benefit in the most highly aggressive GBM patients.

Treatment

Surgery

Surgery is the foundation in the initial treatment for malignant gliomas which includes biopsy for tissue diagnosis, and sub- or gross total resection. The benefits of surgical resection include decreased tumor burden, mass effect and requirement for steroids. In addition, it can provide a more accurate tissue diagnosis than biopsy and may improve neurologic deficits. Unfortunately, due to their diffusely infiltrative nature, complete resection of malignant gliomas is not possible. A few trials have reported an increase in progression-free survival associated with a gross total resection. However, because these studies were based on a small population, no definitive recommendation could be made (Lacroix et al. 2001).

Radiation

Radiation is an effective therapy providing a survival benefit in patients with malignant gliomas and is generally administered up to a total dose of 59.4–60 Gy over a 6–7-week period. Historically, radiation therapy has been shown to improve survival benefit in patients with malignant gliomas. In addition, a study of newly diagnosed GBM patients performed by Stupp et al., a combined approach consisting of radiation and temozolomide chemotherapy showed a significant improved survival than radiation therapy alone (Stupp et al. 2002). Although the trial was conducted in patients with glioblastoma multiforme only, this combined approach has been widely adopted as the preferred therapy of choice in the treatment of most types of malignant gliomas. As for recurrent disease, re-irradiation can be performed to an area not previously irradiated. For long-term survivors who received radiation in the past, usually 10 years and beyond, re-irradiation can be considered in selected cases. For a focal recurrence at a site initially irradiated, the application of stereotactic radiosurgery can be considered.

Chemotherapy

The role of radiation therapy for malignant gliomas has been well defined as it clearly showed a survival benefit in previous trials. Until recently, the role of chemotherapy in the treatment of malignant gliomas, especially GBM, has been

limited with most of the previous trials showing negative survival benefit. The standard management for malignant gliomas has been maximum cytoreduction of tumor through maximum debulking followed by radiation therapy. Traditionally, one of the nitrosoureas has been used as adjuvant therapy following radiation therapy or at the time of recurrence after radiation failure and it only showed a modest antitumor activity. However, recent combined radiation therapy with daily low-dose temozolomide followed by 6 months of monthly temozolomide chemotherapy has shown to improve 2-year survival over radiation alone and this shifted the whole treatment paradigm for GBM, and, to some extent, for other malignant gliomas towards a combination radiation and chemotherapy approach.

Unlike astrocytic tumors, oligodendrogliomas and oligoastrocytomas are often extremely sensitive to radiation and chemotherapy, especially nitrosourea-containing regimens like PCV, and temozolomide. Some of the most important recent achievements in neuro-oncology have arisen from advances in molecular genetics, which significantly enhanced our understanding of chemosensitivity and drug-resistant mechanism. A molecular genetic analysis of 39 patients with anaplastic oligodendroglioma by van den Bent et al. suggested that allelic loss (or loss of heterozygosity) of chromosome 1p is a significant predictor of chemosensitivity whereas combined loss involving chromosomes 1p and 19q significantly correlated with chemotherapy and radiotherapy responsiveness and with longer recurrence-free and overall survival. This molecular signature (codeletion of 1p and 19q) was also predictive of a complete radiographic response to PCV chemotherapy (van den bent et al. 2003a). As a result of these findings, 1p and 19q testing has become common and in some centers it is incorporated into treatment algorithms for patients with oligodendroglial tumors (Hoang-Xuan et al. 2004).

Unlike GBM, the timing and sequencing chemotherapy for newly diagnosed anaplastic oligo- or oligoastrocytomas in relationship to radiation therapy remain unsettled. Cairncross et al. conducted a phase III trial comparing PCV chemotherapy followed by radiation therapy to radiation therapy alone in this population and it showed a similar median survival time for both groups at 3 years (4.9 years after PCV plus radiation therapy versus 4.7 years after radiation therapy alone) except the increased toxicity in PCV followed by the radiation therapy group. However, the subset analysis of the results showed that patients with tumors lacking 1p and 19q (46%) compared with tumors not lacking 1p and 19q had longer median survival times (>7 years versus 2.8 years, respectively; $p < 0.001$) and longer progression-free survival was most apparent in this subset (Cairncross et al. 2006). A recent phase III trial by Wick et al. compared radiation therapy versus chemotherapy in patients with newly diagnosed anaplastic gliomas that included anaplastic astrocytomas, anaplastic oligodendrogliomas and anaplastic oligoastrocytomas, and the results showed no difference in time to treatment failure or overall survival between patients started on radiation therapy versus those started on chemotherapy (either PCV or temozolomide). At occurrence of unacceptable toxicity or disease progression, patients in the radiation therapy were treated with one of the chemotherapies and patients in chemotherapy arms with radiation therapy. Histologically, patients with anaplastic astrocytoma had a worse time to treatment failure than those with anaplastic

oligodendrogliomas or AOAs who shared the same favorable risks and clinical course. The favorable impact of an oligodendroglial component was as strong as detection of loss of heterozygosity on chromosome arms of 1p and 19q in the tumor tissue. These deletions on chromosomes 1p and 19q and hypermethylation of the MGMT promoter provided a large risk reduction for time to treatment failure and, similarly, for progression-free survival, irrespective of histology and randomized group (Wick et al. 2008).

The chemotherapy drugs used in the treatment of malignant gliomas is similar. At present, the most commonly used standard agents are temozolomide, the nitrosoureas (e.g., BCNU, CCNU), platinum compounds (e.g., carboplatin, cisplatin), high-dose tamoxifen, a nonsteroidal anti-estrogen with antiangiogenic properties that inhibits the activity of protein kinase C, erlotinib for EGFR positive malignant glial tumors or combination PCV regimen for oligodendroglioma. Most of the newer drugs that have shown wide-spectrum antitumor activity in systemic cancers, such as taxanes (paclitaxel and docetaxel), and the topoisomerase inhibitors (topotecan and irinotecan), unfortunately, have produced only infrequent or marginal responses in most patients with brain tumors.

Molecular targeted therapies such as anti-VEGF (vascular endothelial growth factor), EGFR, and mTOR (mammalian target of rapamycin) analogs, immunotherapies, gene therapies, tumor vaccines and cancer stem cell researches are being actively investigated, and participation in a well-designed clinical trial would certainly be appropriate for any eligible patient in this situation.

Temozolomide

Temozolomide is an imidazotetrazine derivative of the alkylating agent dacarbazine and undergoes chemical conversion at physiologic pH to the active species 1-triazenoimidazole-4-carboxamide (MITC). The active metabolite works by forming a methyl diazonium cation that methylates the DNA at position N⁷ of guanine, N³ of adenine and O⁶ of guanine on the DNA molecule. The end result is interference with DNA replication. The effectiveness of temozolomide is modulated by the level of MGMT which is associated with hypo- or hypermethylation of the promoter or an intact DNA mismatch repair system. Derangements in either can confer resistance. For example, low expression of MGMT or hypermethylation of the promoter has been associated with a favorable response. Similarly, the DNA mismatch repair pathways must be at a normal functional capacity to confer temozolomide toxicity (Cahill et al. 2007). Temozolomide is 100% bioavailable and readily crosses the blood–brain barrier to achieve a CSF concentration that is approximately 40% of plasma. Temozolomide has the most favorable hematologic toxicity profile, with leukopenia and thrombocytopenia being the most common. Fatigue, nausea and vomiting are also frequently seen but are mild. Temozolomide in the adjuvant setting is dosed orally at 150–200 mg/m²/day for 5 days every 28 days. The administration of temozolomide with food results in a 33% decrease in the C_{max} with a 9% decrease in the AUC. Therefore, it is recommended that temozolomide be taken

without food. Data support postoperative single-agent temozolomide in the adjuvant setting after radiation. In a phase III randomized trial conducted by Stupp et al., patients treated with radiation concurrent with daily low-dose temozolomide followed by adjuvant temozolomide given for 5 days every 28 days for 6 months had an increase in median survival from 12.1 months in the control group to 14.6 months in the treatment group. The overall survival at 2 years with this regimen increased from 10% with radiation therapy alone to 26.6% with a combination approach (Stupp et al. 2002). At longer follow-up, this combination regimen continued to show survival benefit at 3 and 4 years (16.7% and 12.9% respectively) compared to radiation therapy alone (4.3% and 3.8% respectively) (Mirimanoff et al. 2007). There have been numerous efforts to optimize the response rate seen with temozolomide. Metronomic dosing schedules, extended administration of maintenance therapy beyond 6 months, or combining temozolomide with other novel drugs are currently under investigation.

Similar to malignant astrocytomas, temozolomide has also been used in the treatment of oligodendroglial tumors. A recent preliminary study in a small population of newly diagnosed patients harboring oligodendroglial tumors, a response rate of 70% was reported with a median follow-up of 13.7 months (range 3–37 months) (Taliani et al. 2004). A similar response was also seen in the recurrent anaplastic oligodendroglioma and AOA patients who failed radiation and PCV chemotherapy. Chinot et al. reported that 8 out of 46 patients had a complete response (16.7%) and 13 patients (27.1%) had a partial response. An additional 19 patients (39.6%) had a stable disease. For complete and partial responders, mean overall survival was 13.1 months and median progression-free survival was 16 months (Chinot et al. 2001).

Nitrosoureas

Nitrosoureas are non-ionized and highly lipophilic, readily cross the blood–brain barrier and act as an alkylating agent inhibiting DNA. Many different nitrosourea analogs have been studied in the past, but BCNU and CCNU are the only two drugs that are currently available in the treatment of malignant gliomas.

BCNU (Carmustine)

BCNU (1,3-bis 2-dichloroethyl-1-nitrosourea) is a nitrosourea that, for the past few decades, has served as the first-line chemotherapeutic agent for the treatment of malignant gliomas until the introduction of temozolomide (Parney & Chang 2003). Due to its poor oral bioavailability, BCNU is given intravenously at a standard dose of 200 mg/m² every 6 weeks to a total treatment dose of approximately 1,400 mg. Dose-limiting toxicities include nausea, fatigue, myelosuppression and pulmonary fibrosis. A study performed by Walker and colleagues, investigated treatment with BCNU following radiation. Results documented a modest improvement in the median survival (Walker et al. 1978). Several other studies utilizing a nitrosourea-containing regimen also showed a modest survival benefit (Deutsch et al. 1989;

Fewer et al. 1972). In regard to the BCNU-impregnated wafer (Gliadel), only marginal benefit was seen following implantation within the surgical cavity following resection (Westphal et al. 2003; Westphal et al. 2006).

BCNU has been used in combination with other compounds such as Thalidomide, an antiangiogenic agent, in the treatment of recurrent malignant glioma. In a study by Fine and colleagues, BCNU was combined with daily thalidomide in a small group of patients with recurrent malignant glioma that showed a modest clinical and radiographic response (Fine et al. 2000).

CCNU (Lomustine)

Unlike BCNU, CCNU is an orally administered nitrosourea. Although it can be administered alone for the treatment of malignant gliomas, it has been commonly used in combination with other drugs such as Procarbazine and Vincristine (PCV regimen) for the treatment of oligodendroglioma or oligoastrocytoma. CCNU is given at 110 mg/m² every 6 weeks. CCNU is the preferred treatment option over BCNU for patients with poor venous access or those who prefer outpatient treatment. Its efficacy is felt to be similar to that seen with BCNU; however, no randomized trial comparing responses has been performed. The toxicity profile also parallels BCNU.

Platinum Compounds

Of all the platinum-based compounds, carboplatin is the preferred drug for the treatment of malignant gliomas due to its better tolerability and toxicity profile.

Carboplatin

Carboplatin is a platinum-based compound that inhibits DNA synthesis by forming intrastrand cross links (Shaw et al. 2006). Similar to BCNU, it has poor bioavailability and is best given intravenously. Carboplatin is dosed to an AUC of 5–7 every 4 weeks (Parney & Chang 2003). Carboplatin is for the most part well tolerated. Side effects included nausea, fatigue and myelosuppression, particularly thrombocytopenia. Response has been variable. Yung et al. reported an overall response rate of 48% with a median time to progression of 26 weeks (Yung et al. 1981). Warnick and associates demonstrated either stabilization or response in 50% of patients with recurrent malignant glioma. Median time to progression and median time of survival were reported at 19 and 38 weeks, respectively (Warnick et al. 1994).

PCV (Procarbazine, CCNU, Vincristine)

PCV has been proven as an effective regimen in the treatment of oligodendroglioma. Historically, PCV has been widely used as a treatment option for patients

diagnosed with an oligodendroglioma. Cairncross and McDonald initially reported on the positive response seen in oligodendroglial tumors following treatment with PCV (Cairncross & Macdonald 1988). The standard dose of the three-drug regimen is given every 6 weeks. On day 1, CCNU is given orally at 110 mg/m², Procarbazine orally at 60 mg/m²/day on days 8 through 21 and Vincristine is given intravenously at a dose of 1.4 mg/m² (maximum of 2.0 mg) on days 8 and 29. This treatment regimen has been confirmed to be effective by several studies and has been accepted as the standard of care in the treatment of oligodendroglial tumors until the introduction of temozolomide.

The PCV regimen has been also studied as a treatment for oligoastrocytoma. A retrospective study done by Kim et al. showed a high response rate to this regimen. In a total of 32 patients studied, 25 patients were AOAs and the remainder were cases of anaplastic oligodendrogliomas. The overall objective response rate for the entire group was 91%. More specifically for the AOA cohort, the objective response rate was reported at 89% (Kim et al. 1996). The toxicity profile of the PCV regimen includes hematologic, gastrointestinal and peripheral neuropathy (vincristine) as well pulmonary fibrosis (CCNU).

Tamoxifen

Tamoxifen is an anti-estrogenic agent most commonly used in the treatment of breast cancer. Administered at high dose it is believed to have an anti-glioma effect through the inhibition of protein kinase C. Tamoxifen, when given at high dose has shown a modicum of efficacy in treating recurrent malignant gliomas. In a small study by Couldwell et al., a 25% response rate with disease stability was noted in 19 patients following treatment with high-dose Tamoxifen (Couldwell et al. 1996). The usual recommended dose is 120 mg twice per day.

Molecular Targeted Therapy

Bevacizumab (Avastin)

Bevacizumab is a monoclonal antibody formed against human VEGF-A. Bevacizumab has shown significant response in patients with recurrent high-grade glioma. Vredenburgh et al. conducted a phase II study of bevacizumab plus irinotecan in 35 patients with recurrent GBM. The 6-month progression-free survival in all 35 patients was 46%. The 6-month overall survival was 77%. Twenty out of the 35 patients had at least a partial response (Vredenburgh et al. 2007). Cloughsey et al. reported a phase II randomized, non-comparative trial investigating Bevacizumab alone versus in combination with irinotecan in recurrent or refractory GBM. Results showed tumor responses in 26% of the 85 patients treated with Avastin alone and the median duration of response was 4.2 months (Cloughsy et al. 2008). Other investigators studied forty-eight heavily pretreated recurrent glioblastoma

patients with bevacizumab as a single agent. Responses were observed in 20 percent of patients with a median duration of 3.9 months. Of 19 patients treated with bevacizumab plus irinotecan at progression, there were no objective radiographic responses. They concluded that single-agent bevacizumab has significant biologic and antiglioma activity in patients with recurrent glioblastoma multiforme (Kreisl 2009). Based on these two encouraging trial results, bevacizumab was approved as a single agent treatment for recurrent glioblastoma multiforme in 2009. The role of irinotecan in combination with bevacizumab is unclear. As a single agent, irinotecan has shown no efficacy in recurrent malignant glioma (Batchelor et al. 2004; Prados et al. 2006). Further studies are needed to define the role of irinotecan in combination with bevacizumab.

Erlotinib (Tarceva)

Erlotinib is one of the small molecule tyrosine kinase receptor inhibitors (TKRI) and functions to prevent activation of the EGFR. EGFR is a transmembrane receptor tyrosine kinase that is involved in the development of the nervous system by promoting proliferation of multipotent neural stem cells (Burrows et al. 1997). Overactivity of the EGFR is associated with uncontrolled cell proliferation, angiogenesis, invasion and inhibition of apoptosis. EGFR amplification is a common molecular aberration in primary GBM (de novo GBM) (Zhu et al. 1999). Studies investigating Erlotinib as a single agent in recurrent GBM have revealed conflicting results (Brandes et al. 2008; Mellinghoff et al. 2005). Haas-Kogen et al. conducted a phase I trial in 52 patients with progressive high-grade glioma. Erlotinib was given as a monotherapy or in combination with temozolomide. The study concluded that patients with recurrent GBM harboring high EGFR expression and low levels of phosphorylated AKT had a better response to erlotinib than those patients with low EGFR expression and high phosphorylated AKT (Haas-Kogen et al. 2005). In contrast, a study performed by Lassman et al. reported no correlation between EGFR amplification and response to Tarceva in vivo (Lassman et al. 2005).

Other Neuroepithelial Tumors

Ependymoma

Ependymomas are neuroepithelial tumors that originate from the ependymal lining of the ventricular system and from remnants of the central canal of the spinal cord. They comprise approximately 3–9% of CNS tumors. Although they are seen most frequently in childhood where they make up 8–10% of pediatric brain tumors, they are also found in adults except with a much lower frequency of 1–3%. In adults, approximately 75% originate from within the spinal canal. The WHO has classified these tumors into grade I ependymoma (myxopapillary ependymoma and

subependymoma), grade II ependymoma (with tanycytic, cellular, papillary, and clear cell variants) and grade III anaplastic ependymoma (Louis et al. 2007).

Grade II ependymomas lack anaplastic features such as cellular pleomorphism, nuclear atypia, vascular proliferation or necrosis. Unlike other gliomas, there is scant evidence of the association of ependymomas with the oncogenic virus SV40. Studies documenting the presence of SV40 DNA in human cancers have been reported (Cabone et al. 2003). These cancers include mesothelioma, osteosarcoma and ependymoma. The classic ependymoma on histopathologic examination possesses both glial and epithelial features with neoplastic cells surrounding blood vessels, forming the characteristic perivascular pseudorosettes. This is the pathomonic feature of the tumor. The imaging characteristics of the classic ependymoma are of a heterogeneous solid mass filling the fourth ventricle (posterior fossa ependymoma) or the cerebral hemisphere. The mixed signal is due to the presence of hemosiderin, blood, necrosis or calcification that is often associated with this neoplasm. Administration of gadolinium yields homogeneous or non-homogeneous enhancement. Ependymomas can, on rare instances, present as a non-enhancing mass (Furie & Provenzale 1985). Astrocytomas and medulloblastomas can mimic radiographically a supratentorial ependymoma and fourth ventricular ependymoma, respectively (Lee et al. 1989).

Treatment

Surgery is the mainstay in the treatment of low-grade (WHO grade I and II) ependymoma. In patients presenting with an incidental radiographic finding of a presumed ependymoma, a watch and wait approach can be undertaken in patients with no neurologic deficits; however, complete resection may also be attempted. Surgery is also recommended for recurrent disease. Radiation is the adjuvant therapy of choice in patients in whom the tumor is located in areas where complete resection is not possible. Local field radiation therapy to a tumor dose of 54–59.4 Gy is recommended. Since intracranial ependymomas can disseminate throughout the neuro-axis, contrast imaging of the craniospinal axis or examination of CSF cytology is recommended. However, despite the potential for spinal dissemination, craniospinal radiation therapy is not advised when the disease is localized only to the brain (Chamberlain 2003; Moynihan 2003). At present, chemotherapy has no defined role in the treatment of low-grade ependymomas outside the clinical trial setting.

Management of anaplastic (WHO grade III) ependymomas parallels its low-grade counterpart, with surgery as the mainstay of treatment. As with low-grade ependymomas, evaluation of the extent of central nervous system involvement using CSF cytology and contrast craniospinal MRI is carried out to rule out metastasis or leptomeningeal disease. There appears to be a strong association between the extent of surgical resection and the outcome. For anaplastic ependymoma, the treatment paradigm consists of surgical debulking with an attempt at a gross total

resection followed by postoperative radiation to a total dose of 59.4 Gy to the brain with 35 Gy to the spine. At present, there is no defined role for chemotherapy in the adjuvant setting for recurrent anaplastic ependymoma. The largest studies investigating the use of chemotherapy in recurrent grade III ependymoma have been performed within the pediatric population. In regard to the adult population, most of the earlier studies involving adjuvant chemotherapy in recurrent anaplastic ependymoma have been disappointing; however, in a small study by Soffietti and colleagues a 43% response rate in adult patients with a recurrent anaplastic ependymoma was reported (Soffietti et al. 1989).

Non-neuroepithelial Tumors

Meningioma

Meningiomas comprise a group of extra-axial neoplasms of the nervous system that arise from the arachnoidal cap cells of the meninges. For the most part slow-growing and indolent, they constitute approximately 20% of intracranial tumors. Although these tumors can arise anywhere along the neuro-axis, the most common sites include falcine/parasagittal, over the cerebral convexity, medial sphenoid wing, along the olfactory groove, the sella and parasellar regions, posterior fossa, spinal cord and rarely intraventricular. The most consistent etiologic factor is prior cranial irradiation (Ron et al. 1988; Wrensch et al. 2002). Meningiomas have a slight female preponderance and most commonly afflict older individuals usually between the sixth and eighth decades of life; however, when seen in young patients or in multiple form, workup for neurofibromatosis type II should be undertaken. The histologic classification for meningiomas is a tiered grading system developed by the WHO (Louis et al. 2007). The WHO grading system classifies meningiomas according to the predominate histologic appearance and degree of malignancy, with grade I being the most benign and grade III the most aggressive. The vast majority of meningiomas are grade I tumors, which are considered benign and for the most part curable following gross total resection. There are several subtypes of grade I meningiomas, with the most common being the meningothelial, fibrous and transitional. Grade II meningiomas or atypical meningiomas differ from the lower-grade ones by the presence of at least three of the following characteristics: increased cellularity, small cells with a high nuclear to cytoplasmic ratio, cells demonstrating patternless growth, and areas of necrosis. Anaplastic meningiomas designated as grade III are the most aggressive, demonstrating more frank malignant features. These features include: abundant mitosis, nuclear pleomorphism, infiltration into the underlying brain and necrosis. Like for the majority of primary brain tumors, MRI with contrast is the imaging modality of choice where meningiomas appear as an extra-axial space-occupying mass that appears hypo- to isointense to the brain on T1-weighted non-contrast imaging. Following the administration of intravenous contrast agents, meningiomas enhance homogeneously. The most characteristic

finding on contrast MRI is the presence of the “dural tail” which is a thin linear tail of enhancement extending from the point of dural attachment to the main body of the mass.

Treatment

Surgery

Surgical resection is the mainstay of treatment for meningiomas at initial diagnosis and at recurrence. Overall survival and likelihood of tumor recurrence is based on both the extent of tumor resection and the histologic grade. The completeness of tumor resection is graded according to the Simpson scale. The Simpson scale correlates 10-year survival with the extent of tumor resection. Similarly, histologic grade is also used as a predictor of recurrence. In a study performed by Jaaskelainen et al., the recurrence rate at 5 years was investigated in 936 patients diagnosed with an intracranial meningioma who had undergone a complete resection. The 5-year recurrence rate for grade I (benign) was 3%, with 38% and 78% for grades II (atypical) and III (anaplastic/malignant), respectively (Jaaskelainen et al. 1986). Accordingly, in a study investigating the 5- and 10-year survival rates in patients with atypical versus anaplastic meningioma, the 5-year survival rate was reported as 95% and 64.3%, with the 10-year survival rates of 79% and 34.5%, respectively (Palma et al. 1997).

Radiation

The role of radiation in the initial treatment of meningiomas is mostly limited to tumors adjacent to vital structures where surgical resection is not felt to be a good option. As for recurrent disease, most likely seen with atypical or anaplastic tumors, radiation is the treatment modality of choice to areas of inoperable recurrent disease. Unlike for recurrent glioma, stereotactic radiosurgery can play a significant role in treating areas of disease at initial diagnosis or at recurrence where an attempt at surgical resection is believed to be risky.

Chemotherapy/Immunotherapy

The role of chemotherapy in the treatment of meningiomas remains unclear and is still evolving. Chemotherapy is most commonly applied in patients with high-grade tumors in the setting of inoperable disease following recurrence after radiation therapy. Although no one agent or group of agents has shown a dramatic response, there are three agents that have shown modest activity in refractory or recurrent cases. These agents are recombinant interferon alpha-2beta (IFN-alpha-2b), hydroxyurea, and most recently somatostatin.

Recombinant Interferon (IFN-alpha-2b)

IFN-alpha-2B is a recombinant immunomodulating agent that has shown modest activity in the setting of recurrent or refractory meningioma. The precise mechanism of action is unclear, but disease stabilization and partial responses have been recorded. In a study performed by Kaba and colleagues, six patients with recurrent or inoperable meningiomas (two benign, one atypical, three malignant) were treated with IFN- α at a dose of 4 million units (MU)/m²/day 5 days a week. The treatment was well tolerated and results reported four patients with stable disease and one patient showing a partial response (Kaba et al. 1997). Similarly, Muhr et al. treated 12 patients with IFN- α at a subcutaneous dose of 1.5–5 MU. Five out of the 12 patients had disease stabilization ranging from 9 months to 8 years (Muhr et al. 2001).

Hydroxyurea

Hydroxyurea is a ribonucleotide reductase inhibitor that arrests cells in the S phase and initiates apoptosis in meningioma cells. When administered at 20 mg/kg/day, a modest tumor response has been reported (Mason et al. 2002; Newton 2007).

Somatostatin

Somatostatin has demonstrated antitumor activity on meningioma cells in vitro. Although the mechanism of action requires further elucidation, somatostatin receptors, especially the sst2A subtype, are present in most meningiomas. In a recent small study performed by Chamberlain and colleagues, 16 patients diagnosed with a recurrent intracranial meningioma were treated monthly with a sustained released analog of somatostatin (Sandostatin LAR). In all patients, the expression of the somatostatin receptor was documented prior to treatment. Results reported a partial response rate of 31% and an overall 6-month progression-free survival of 44% (Chamberlain et al. 2007). Similarly, Fisher and associates treated seven patients with monthly Sandostatin administered at 20–30 mg/month. Again, all were documented to have expression of somatostatin receptors. Both a clinical and a radiographic response were seen in four out of the seven patients (Fisher et al. 2006). The treatment option for recurrent disease is limited. Currently, somatostatin analog, molecular targeted therapy targeting PDGF, c-kit and VEGF are investigated.

Primary Central Nervous System Lymphoma

Primary Central Nervous System Lymphoma (PCNSL) is a rare form of non-Hodgkins lymphoma that afflicts the central nervous system. PCNSL is extremely chemo- and radiation therapy sensitive and has a potential to cure. The incidence of

PCNSL has been estimated at 1:100,000 persons per year and has risen considerably over the past two decades from approximately 0.5% to 6% of all primary brain tumors (Miller et al. 1994; Schabet 1999). The advent of immunosuppressive drugs for organ transplant patients and an aging population have contributed to the increased incidence. The rising incidence was also partly attributed to the outbreak of the Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome HIV/AIDS. However, since the introduction of the Highly Active Antiretroviral Therapy (HAART) regimen utilized in the treatment of HIV/AIDS, the incidence of PCNSL within this population has decreased.

Unlike other gliomas, because of extreme chemo- and radiation sensitivity of the PCNSL, a simple biopsy is sufficient for diagnosis. Aggressive surgical resection is usually reserved for patients with a life-threatening mass effect. Radiation therapy has been the mainstay of treatment as it demonstrated high initial response rates including complete resolution of tumors but, invariably, they tend to recur with poor outcome. The overall survival following radiation therapy is less than 2 years. High-dose methotrexate alone or in combination with other agents yields complete resolution of tumor in 65–75% of patients with a long-term survival of 4 years in most studies (DeAngelis et al. 1992; Glass et al. 1994).

Standard combination (multiagent) chemotherapy followed by radiation therapy increased toxicity and long-term neurocognitive deficits without improvement in survival over radiation therapy alone. High-dose methotrexate alone provides response rate and overall survival comparable to radiation therapy and combination chemotherapy regimens (Batchelor et al. 2003). In addition, at a dose of 8 g/m², high-dose methotrexate alone can achieve therapeutic concentrations in brain tissue and CSF, possibly obviating the need for intrathecal administration of chemotherapeutic agents, which are frequently administered with combination chemotherapy regimens for PCNSL. Transient disruption of the blood–brain barrier with mannitol to enhance drug delivery to the central nervous system has also shown some benefit.

Grossly, PCNSL are well-circumscribed deep-seated lesions. The vast majority (approximately 98%) are of B-cell origin. Approximately 2% are derived from T-cell lymphoma (Grant & Isaacson 1997). Microscopically, PCNSL reveals large rounded cells with round nuclei and prominent nucleoli, demonstrating an angio-centric growth pattern. This feature is described as diffusely infiltrating individual tumor cells or aggregates forming neoplastic peri-vascular cuffs. These peri-vascular neoplastic cuffs when seen in association with an increase in perivascular reticulin fibers is the hallmark of PCNSL (Nelson 1999).

MRI is the imaging modality of choice. On T1-weighted non-contrast imaging, PCNSL is an iso- to hypointense mass surrounded by hypointense vasogenic edema. Following the administration of intravenous contrast, PCNSL demonstrate marked homogeneous enhancement, although ring-like enhancement can be seen especially in immunocompromised individuals. Lesions are most frequently solitary or can be multiple enhancing masses found adjacent to the ventricle (peri-ventricular) or involving deeper-seated structures such as the basal ganglia, thalamus, or corpus callosum (butterfly lesion). Leptomeningial or ependymal involvement has been reported to occur in approximately 12% of

cases (Rosenthal et al. 1995). Traditionally, extensive staging workup except for CSF studies and neuro-ophthalmologic examination was not felt to be warranted as most body CT scans were negative (Batchelor & Loeffler 2006). However, a recent single institutional study suggests the benefit of staging and re-staging PCNSL patients with body fluorodeoxyglucose (FDG)-PET scan. Workup utilizing traditional staging did not reveal systemic lymphoma. In 8% of patients, however, body FDG-PET was the only abnormal diagnostic study suggestive of systemic lymphoma. In addition, out of a total 49 PCNSL patients, 15% studied with FDG-PET had systemic malignancy, with 4% being other than lymphoma (Mohile et al. 2008). Although the number of studied patients was small, based on these interesting findings, FDG-PET may play a role in the staging workup of patients with PCNSL.

Treatment

Surgery

As for other intracranial tumors, surgery is the initial step in treatment. If radiographic findings are highly suggestive of PCNSL, a simple biopsy for diagnosis would be sufficient as PCNSL are extremely chemo- and radiation sensitive such that extensive debulking is not warranted. However, in instances of life-threatening or severe neurologic deficits resulting from mass effect, surgical debulking can be considered. Unlike gliomas, the administration of pre-operative steroids is discouraged. Steroids such as dexamethasone and prednisone activate the endogenous steroid receptors, which trigger the apoptosis cascade within malignant lymphocytes and thus should be withheld if possible until after a histologic diagnosis has been confirmed. Corticosteroids have been reported to render complete or partial remissions in 15% and 25% of PCNSL patients, respectively, but in most cases, as with gliomas, their response is usually short-lived and they tend to recur invariably.

Radiation

Since PCNSL is an extremely radiosensitive neoplasm, radiation has been the mainstay of treatment for newly diagnosed PCNSL in the past. Unfortunately, the recurrence rate is significantly high, and is reported at 61% (Nelson et al. 1992). Despite initial complete resolution of tumor in most patients, survival following whole-brain radiation seldom exceeds 2 years. The median survival rate was 11.6 months and the 5-year survival rate was less than 50% (less than 15% in an elderly population that had poor clinical and neurological performances) (Nelson 1999). In patients presenting with intraocular PCNSL, both eyes require treatment even in the presence of monocular disease (Hormigo & DeAngelis 2003). Due to the high incidence of recurrence following radiation therapy and associated

neurocognitive deficits frequently seen in long-term survivors, the popularity of this modality as first-line treatment following surgery has fallen out of favor, especially when a similar response or improved long-term survival could be achieved with high-dose methotrexate alone. However, in patients who are poor candidates for chemotherapy or who are resistant to chemotherapy, radiation is an option.

Chemotherapy

High-Dose Methotrexate

Most newly diagnosed patients are treated with upfront chemotherapy (usually methotrexate alone or a methotrexate-containing combination regimen) with deferred radiation. Methotrexate is the agent of choice and when given in combination with other agents or as monotherapy in high dose, it is associated with significant resolution of disease in a majority of the patients with a median survival approaching 4 years (Celli et al. 1994; DeAngelis et al. 1992). In a study by Batchelor and colleagues, intravenous methotrexate at 8 g/m² alone provided response rates comparable to what was achieved with combination regimens consisting of radiation and chemotherapy (Batchelor et al. 2003). Methotrexate achieves therapeutic CSF concentration when given at high dose (8 g/m²), providing a benefit that possibly can obviate the need for intraventricular or intrathecal administration and its associated side effects and Ommaya reservoir placement (Glantz et al. 1988). This strategy to give methotrexate alone may avoid radiation-related neurocognitive deficits which are common in patients who are older than 60 years and may appear as early as 12 months following radiation therapy.

Rituximab

Rituximab is a human/murine chimeria anti-CD-20 monoclonal antibody used as a single agent in patients with PCNSL. Rituximab is a large antibody and under normal conditions has limited CSF penetration; however, in the presence of a disrupted blood–brain barrier and administered in high concentrations, rituximab can attain therapeutic CSF levels. Pels and associates reported a 50% response rate following systemic administration of rituximab in patients with PCNSL (Pels et al. 2003). This is similar to recent data that reported a 40% response in recurrent or refractory PCNSL (Batchelor et al. 2008). Because of the concern for poor CSF penetration, some authors advocate intraventricular/intrathecal administration through an Ommaya reservoir (Pels et al. 2003).

Other investigators studied rituximab in combination with temozolomide, topotecan, iburimumab (zevalin), high-dose Ara-C and high-dose chemotherapy with autologous stem cell rescue, with varying success. Continuous effort to further improve response rate and overall survival in this potentially curative CNS malignancy is warranted.

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