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103. Aggressive Glial Neoplasms

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High-grade glial tumors, in particular anaplastic astrocytoma and glioblastoma multiforme, are the most frequent primary brain tumors in adults (1,2). They usually occur sporadically without identifiable familial tendency or environmental risk factors. Commonly arising in the deep white matter of the cerebral hemispheres, their removal without damage to eloquent brain areas poses a surgical challenge. Typically, these tumors present with headache, seizures, mental status or personality changes, signs and symptoms of increased intracranial pressure, hemiparesis, or other neurological deficit. Despite optimal current therapy, including surgery, radiation therapy, chemotherapy, and brachytherapy, high-grade gliomas are associated with a poor overall prognosis. The aim of clinical management is to achieve a longer progression-free interval and overall survival with preserved quality of life.

Epidemiology

Several domestic and foreign epidemiologic studies are in general agreement that the incidence of primary intracranial tumors in adults is between seven and 16 per 100,000 population (3–5). About half of these are primary tumors and half are metastatic. Neuroepithelial tumors, tumors arising from glial and/or neuronal elements, account for 50% to 60% of primary intracranial neoplasms in adults, and the vast majority of these are glial tumors (5). Of the neuroepithelial tumors, glioblastoma multiforme and anaplastic astrocytoma account for the vast majority, approximately 50% and 30%, respectively. In descending order, oligodendrogliomas (including anaplastic oligodendrogliomas), nonanaplastic astrocytomas, ependymal tumors, medulloblastomas and other less common tumors account for the other 20% of neuroepithelial tumors in adults. Thus, high-grade gliomas are the most common intracranial neoplasms in adults.

This chapter encompasses the pathology, clinical signs and symptoms, radiologic diagnosis, medical, surgical, and adjuvant (chemotherapeutic and radiotherapeutic) management of aggressive glial neoplasms. Included are the tumor types glioblastoma multiforme, anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic ependymoma, and mixed high-grade glial tumors (anaplastic oligoastrocytomas). In addition, novel agents and therapeutic modalities are discussed.

Pathology

Macroscopic features of high-grade glial tumors reflect their aggressiveness. The gross cut surface of glioblastomas shows a usually circumscribed appearance but often with ill-defined borders. The tumor itself is heterogeneous, with mottled areas of hemorrhage and necrosis (moth-eaten appearance). Often, there is marked necrosis and degeneration, which corresponds to the central area of low attenuation on computed tomography (CT) images. This central area is often surrounded by an irregular zone of denser, whiter tissue that corresponds to the area of higher attenuation and contrast enhancement on CT. Finally, there is a peripheral zone of lesser cell density, edema, and microscopic tumor infiltration that may be seen on T2-weighted magnetic resonance imaging (MRI) but often not on CT. This peripheral zone may vary in contour, with fingerlike projections extending from the main bulk tumor.

Anaplastic astrocytomas (WHO grade III) exhibit considerable variation in cellularity as well as morphologic heterogeneity (6). As a rule, compared to astrocytomas (WHO grade II), anaplastic astrocytomas exhibit greater cellularity, atypia, and the presence of multiple mitotic figures with a high degree of cellular pleomorphism but without necrosis or microvascular proliferation (Color Plate 29A). A subset of anaplastic astrocytomas show so-called "gemistocytes," or tumor cells with eccentrically placed pink cytoplasm on hematoxylin and eosin (H&E) staining.

Glioblastoma multiforme (WHO grade IV) has particular histological characteristics that differentiate it from lower-grade glial tumors (6): (a) hypercellularity; (b) mitoses; (c) nuclear atypia/pleomorphism; (d) pseudopalisading necrosis (i.e., curvilinear arrangement of tumor cells around a zone of necrosis); and (e) proliferation of vascular elements (microvascular proliferation). Importantly, marked variation in cellularity often is seen in different parts of the tumor, which can lead to misdiagnosis owing to incomplete sampling of the tumor. The primary characteristics distinguishing glioblastoma from anaplastic astrocytoma are necrosis and microvascular proliferation. A typical glioblastoma is shown in Color Plate 29B.

Anaplastic oligodendrogliomas comprise a subset of oligodendrogliomas with aggressive biologic behavior. These tumors, like anaplastic astrocytomas, appear either to arise from well-differentiated oligodendrogliomas or arise *de novo*. Hypercellularity, nuclear pleomorphism, high mitotic index, vascular proliferation, and necrosis characterize these tumors, like glioblastomas (7,8) (Color Plate 29C). The nuclei of oligodendrogliomas in general are more round and compact than the typically elongate nuclei of astrocytic tumors. GFAP-immunoreactive cells are seen in malignant oligodendrogliomas, but these cells lack the fine, GFAP-reactive processes of astrocytic tumors (9). Proliferative activity appears to be related to survival (10), as does the presence of specific genetic alterations. Mixed high-grade tumors can occur, with varying proportions of oligodendroglial and astroglial elements (anaplastic oligoastrocytoma) (Color Plate 29D).

Anaplastic progression of ependymomas is rare. Ependymomas show a characteristic pattern of perivascular rosetting, whereby tumor cells appear to encircle vessels, leaving a zone of processes between the vessel and the tumor nuclei. Anaplastic ependymomas (WHO grade III) are distinguished from ependymomas (WHO grade II) by hypercellularity, numerous mitoses, endothelial proliferation, and nuclear atypia (Color Plate 29E). Like anaplastic oligodendrogliomas, prognosis and time to tumor progression appear to be inversely correlated with mitotic and proliferative indices (11).

LOCAL INVASIVENESS. Aside from high mitotic activity, the main cellular behavior of malignant glial cells is local tissue invasion. Macroscopic and microscopic infiltration of glioblastoma cells tends to occur along the path of deep white matter tracts, such as the corpus callosum (forming the "butterfly glioma"), anterior commissure, fornix, and internal capsule (12, 13).

Microscopic evidence of malignant cells can be found well beyond the gross radiographic margins of the tumor (14). Following surgical resection or radiation therapy, such microscopic tumor foci lead to eventual local recurrence, usually within 2 cm of the original lesion (1,15). Thus, even a wide margin of resection beyond the enhancing lesion seen on imaging studies may not encompass all of the neoplastic tissue (16).

Clinical Signs and Symptoms

High-grade glial tumors arise from elements of brain parenchyma (glial cells) and are thus intraaxial tumors. Most are intraparenchymal, but occasionally can have intraventricular or subarachnoid extension.

Two basic mechanisms account for clinical manifestations of glial tumors. First, regional parenchymal changes including compression, invasion, destruction, hypoxia, electrolyte derangements, and release of cytokines and free radicals alter the tissue microenvironment, disrupting the function of local normal tissue. The clinical correlate may take the form of irritation (e.g., tumor-associated epilepsy) often arising in a focus around the site of the tumor, or depression (e.g., focal neurological deficits related to the topographic functional brain area affected).

Tumors also lead to more diffuse intracranial changes, most commonly elevated intracranial pressure resulting from either the tumor volume itself but more commonly from secondary effects on brain, blood, or cerebrospinal fluid (CSF) volume. High-grade glial tumors in particular induce significant peritumoral vasogenic edema (17), which increases local brain volume. They may also cause venous obstruction or impairment of CSF flow or absorption depending on their size, location, and mass effect.

The clinical presentation of malignant gliomas commonly is divided into general neurological findings and focal neurological findings. General neurological symptoms and signs include headache, seizures without apparent focal onset, nausea, emesis, dysequilibrium, and changes in mental status. Headache, especially during the early morning hours, is the most common symptom, seen in over 70% of patients with brain tumors (18, 19). Second most common is seizures, found in approximately one third of patients (20,21). Tumor-associated emesis and dysequilibrium are probably related to increased intracranial pressure. Alteration in mental status is variable, from minor cognitive deficits to wholesale personality and cognitive changes with depression of consciousness. Papilledema, the most common sign of increased intracranial pressure, occurs in the majority of patients with intracranial neuroepithelial tumors and usually is bilateral. Other findings indicating increased intracranial pressure include abducens palsy and diplopia. Significant increased intracranial pressure may lead to subfalcine, transtentorial, uncal, or tonsillar herniation.

Localizing or focal neurological findings also can result from regional pathological alteration of brain function by a growing tumor. Focal signs include seizures and focal neurological deficits. The type of seizure (e.g., simple partial, complex partial, or generalized) can give a clue to the location of the tumor. Focal neurological deficits can result from interruption or de-

struction of nearly any pathway or nucleus depending on tumor location, and the presence of such a deficit can be of significant localizing value.

Imaging Studies

If clinical history, symptoms, and signs are suggestive of an intracranial tumor, then the next step in diagnosis is to obtain an imaging study with intravenous contrast enhancement. Important imaging characteristics include signal intensity; number of lesions; location, size, and shape; character of margins; pattern of contrast enhancement; and change over time with serial scans. These all help to determine the type and components of the lesion.

CT. CT scans of high-grade glial tumors are often distinctive. CT of glioblastoma multiforme (GBM) often shows a central area of low attenuation corresponding to necrosis. An area of high attenuation that enhances with contrast and corresponds to actively dividing, proliferating tumor cells surrounds this area. A third low-attenuation area around the tumor often is seen, representing tumor-associated vasogenic edema but also containing tumor cells (14,22).

There are several lesions that must be distinguished from gliomas on CT, including infarct, plaque, abscess, arteriovenous malformation (AVM), hematoma, and glial scar. Often these can be distinguished on imaging characteristics alone. For example, infarction appears as a sharply demarcated, wedge-shaped area of low attenuation that does not enhance. However, some lesions, such as demyelination plaques, may enhance with contrast. In addition, abscesses can appear as sharply demarcated regions of low attenuation surrounded by a contrast-enhancing wall, and thus may mimic the appearance of a glial tumor. Intraparenchymal contusions or resolving hematomas may have irregular shape and attenuation, and may enhance with contrast. Although clinical context should distinguish some of the possibilities, in some cases serial scans or MRI may be necessary.

Modern CT scanners can detect tumors less than 1 cm in diameter. However, false-negative CT scans in patients eventually shown to have tumors on follow-up scans have been reported (23,24); therefore, if there is still clinical evidence of possible tumor despite a negative CT scan, an MRI should be performed. It is also important to note that CT scan does not necessarily define the margin of neoplasm. High-grade astrocytomas may not enhance on CT scans, and tumor cells may extend outside the area of contrast enhancement on serial scans (14).

MRI. MRI is more sensitive than CT in the detection of intracranial mass lesions; therefore, it is the gold standard for detecting intracranial tumors. Several factors account for the superiority of MRI over CT: high contrast, lack of bone artifact (especially in posterior fossa lesions), resolution of tumor margins, and greater differentiation of discrete histological tumor components. Technical advantages of MRI over CT include multiplanar imaging, absence of iodinated contrast agents, and absence of radiation exposure; disadvantages include incompatibility with ferromagnetic medical devices and longer study time.

Most high-grade glial tumors are detectable as a hyperintense region of signal abnormality on T2-weighted MRI images. Most neuroepithelial tumors are visible on noncontrast T2-weighted MRI scans before they can be seen on contrast-enhanced T1-weighted images (25). Tumor-associated edema is hypointense on T1- and hyperintense on T2-weighted images. MRI may show a larger area of signal abnormality than CT for the same tumor because of the superior tissue contrast characteristics of MRI; however, tumor cells beyond areas of increased signal intensity on T2-weighted scans remain undetected.

Contrast enhancement is an important tool for distinguishing other pathologies seen on T2-weighted scans from intraaxial tumors. As with CT, tumor enhancement with contrast results from leakage of the contrast agent from tumor capillaries and accumulation in the extracellular space. Gadolinium-diethylenetriamine pentaacetic acid (Gd-DTPA) is the most commonly used contrast agent in MR imaging. A paramagnetic compound, it changes the MR relaxation times of adjacent protons, making areas of contrast accumulation bright on T1- or T2-weighted images. High-grade malignant gliomas usually enhance intensely with gadolinium, whereas less rapidly growing tumors, such as fibrillary astrocytomas, may not enhance (Fig. 1).

As for CT, other processes must be differentiated from tumor on MRI. Because many nonneoplastic lesions are also hyperintense on T2-weighted images, contrast enhancement on T1-weighted images provides more specific evidence of tumor. Hemorrhage is initially low-intensity on both T1- and T2-weighted images; as deoxyhemoglobin is converted to methemoglobin, several days later the area of hemorrhage becomes hyperintense on both sequences, followed by a chronic phase with T1-hypointensity and a rim of T2-hyperintensity.

The ability to follow a lesion over time with serial scans is of critical importance to the diagnosis of intracranial lesions on imaging studies. Enlargement and/or changes in imaging characteristics of a mass in association with clinical signs and symptoms may be pivotal in determining the nature of an intracranial mass lesion.

MAGNETIC RESONANCE SPECTROSCOPY AND FUNCTIONAL IMAGING. An adjunct to conventional neuroimaging techniques is proton magnetic resonance spectroscopy (MRS), which can be obtained during the same MR examination with little additional time. This technique allows detection of metabolite levels in specific brain voxels, thereby providing local physiological data in addition to anatomical imaging (Color Plate 30). MRS has shown potential in differentiating neoplasms from inflammatory and demyelinating lesions (26), as well as detecting progression of neoplastic disease and evaluation of response to radiation therapy (27).

The advent of functional magnetic resonance imaging (fMRI) provides additional information helpful in planning tumor resection tailored to individual patients. The ability to detect the small changes in blood volume and in intrinsic T2-weighted signal that occur in eloquent cortex during physiological activation (28) provides the potential for preoperative functional mapping of eloquent cortex (Color Plate 31). This information integrated with the anatomical information obtained from conventional MRI and intraoperative stimulation mapping data can allow for more precise and complete resection of tumor and the ability to avoid adjacent eloquent brain areas (29).

Another functional imaging modality is magnetic source imaging (MSI), which combines the temporal and spatial accuracy of magnetoencephalography (MEG) with the anatomical and pathological specificity of MRI (30). The resulting magnetic source image gives accurate knowledge of cortical functional organization, such as the late neuromagnetic field elicited by simple speech sounds (31). Like fMRI, this technique is useful for preoperative mapping of rolandic cortex and determining hemispheric language dominance (Color Plate 31).

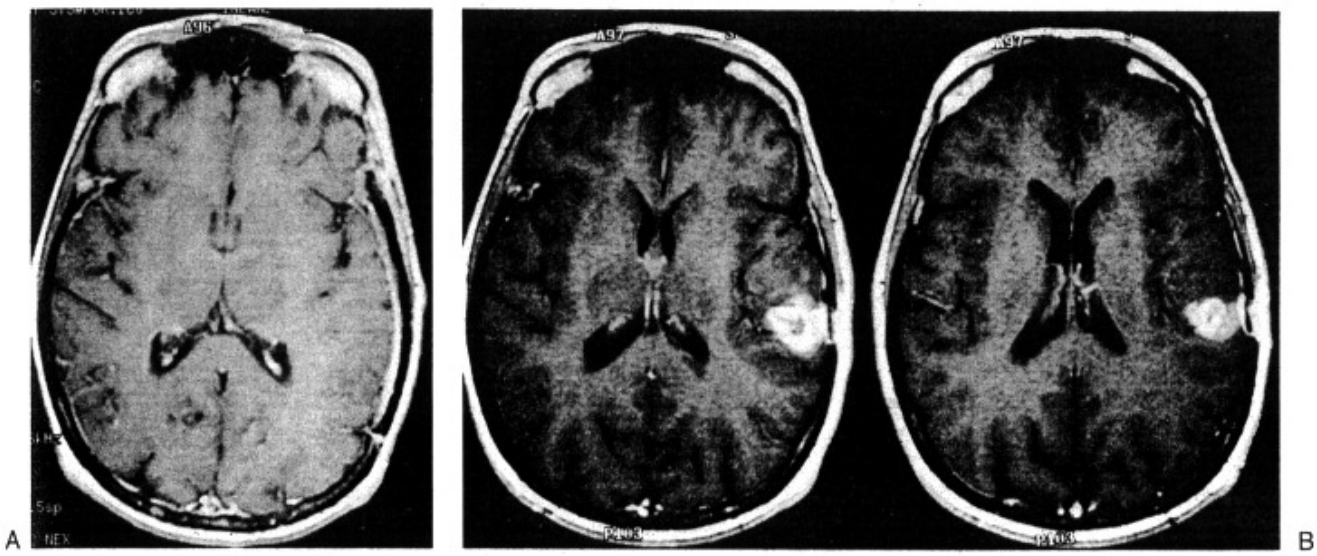

Fig. 1. T-1 weighted axial images without **(A)** and with **(B)** contrast showing marked contrast enhancement of a dominant hemisphere glioblastoma multiforme.

Medical Therapy

The role for medical management of high-grade glial tumors is quite limited. Other than cytotoxic chemotherapy (see the following), medical therapy is only used for palliation of tumor-induced neurological symptoms. The use of corticosteroids often provides rapid and dramatic symptomatic improvement (32). Neurological improvement after steroid therapy results from reduction of tumor-associated cerebral edema and mass effect (33). One proposed mechanism of steroid-induced reduction of peritumoral edema involves reduction in permeability of the capillary–endothelial cell junctions in the blood–brain barrier (BBB); however, steroid therapy palliates neurological symptoms but does not halt or slow tumor growth. In addition to steroids, patients presenting with tumor-induced seizures are placed on anticonvulsant medications. The use of prophylactic anticonvulsants in patients with no previous history of seizures undergoing surgery is common but controversial (34,35).

Surgical Therapy

Principles guiding appropriate surgical treatment of gliomas include tumor biopsy for the purpose of histological diagnosis, cytoreduction of tumor mass to the maximal extent consistent with optimal preservation of neurological function, and judicious implementation of adjuvant therapies tailored to the specific clinical situation.

BIOPSY. Diagnostic biopsy is most often accomplished by a closed stereotactic procedure performed with local anesthesia. Using image-guided stereotactic biopsy techniques, optimal acquisition of diagnostic tissue material can be obtained with a low rate of morbidity and mortality. In series from Toronto, Bernstein and colleagues have found that stereotactic brain biopsies are associated with a 6% overall complication rate, a 2% mortality rate (36), an 8% risk of failed biopsy owing to inadequate material for diagnosis (37), and a high rate of clinically silent hemorrhage postoperatively (38). These data are similar to other series (39–42). The diagnostic yield from stereotactic biopsies is likely to continue to improve as modern neuroimaging techniques permit targeting the most representative portions of intracranial tumors.

CHOICE OF PROCEDURE. The choice of operative procedure for resection of a neuroepithelial tumor depends on its location, size, gross characteristics, histological characteristics, radiosensitivity, and the preoperative neurological and medical condition of the patient. Contemporary neurosurgical methods, including frameless navigational systems, intraoperative imaging, ultrasonography, and functional mapping enable the neurosurgeon to achieve optimal cytoreduction of the tumor with minimal postoperative neurological morbidity.

NAVIGATIONAL SYSTEMS AND INTRAOPERATIVE IMAGING. The use of neuronavigation systems and intraoperative imaging modalities are of increasing importance in the treatment of malignant gliomas. A variety of neuronavigation systems have been developed to register the surgical target preoperatively with respect to surrounding brain structures and physical space using external fiducial markers. The intraoperative integration of a localization device with the stored preoperative registration information via a computer-based interface allows for frameless stereotaxy. The primary advantage is the ability to determine target trajectory independent of direct visualization. However, the success of intraoperative navigation is based on its accuracy in real-time mapping of tissue anatomy. Intraoperative changes involving displacement of brain and tumor tissue caused by surgical retraction, resection, and CSF leakage alter the accuracy of stereotactic localization based solely on preoperative imaging studies (43). Quantitative analysis of intraoperative cortical shift suggests that there may be a discrepancy of at least 1 cm in the registration of preoperative imaging studies to the surgical field (44).

Thus, in recent years intraoperative imaging using CT and

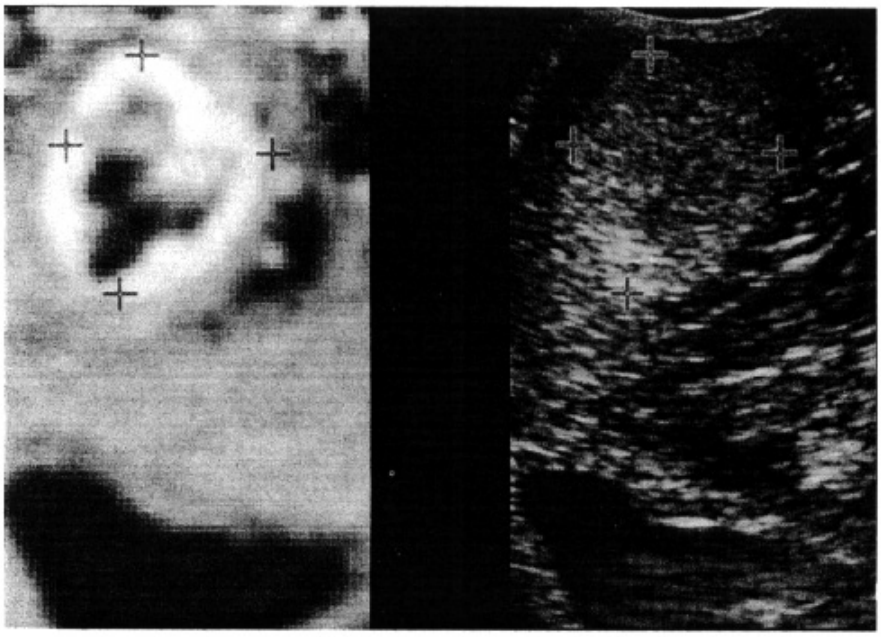

Fig. 2. (+) Signs outline the tumor margins as seen in intraoperative preresection real-time ultrasound imaging *(right)* and the Stealth navigation system *(left)*.

MRI has been developed at a few centers (45–48). The real-time images generated via intraoperative MRI allow the surgeon to assess intraoperative anatomy and thereby determine the extent of resection and/or modify the surgical approach, and eliminates the problem of brain shift. The use of intraoperative MR necessitates the use of MR-compatible surgical instruments made of ceramic or titanium.

Intraoperative ultrasonography also provides real-time intraoperative data and is helpful in detecting the tumor; delineating its margins; and differentiating tumor from peritumoral edema, cyst, necrosis, and adjacent normal brain. Although its use is limited by artifact from blood and surgical trauma at the margin of resection, it has been shown that postresection tumor volumes based on intraoperative ultrasound are significantly correlated with those determined by postoperative MRI (49). The most important use of intraoperative ultrasound may become real-time re-registration of preoperative images to correct for intraoperative brain shift (50,51) (Fig. 2).

INTRAOPERATIVE STIMULATION MAPPING. Intraoperative functional brain mapping using cortical stimulation also provides important real-time data to guide the surgeon in identifying eloquent cortical and subcortical areas (52), allowing preservation of function during tumor resection, thus minimizing morbidity (52,53) (Fig. 3). This is especially important given the marked interindividual differences in localization of function (54). Cortical stimulation mapping is accomplished by placing a bipolar electrode (5-mm spacing) on the surface for several seconds with current amplitude of 2 to 16 mA. Cold Ringer's lactate should be available for immediate irrigation of the stimulated cortex should focal motor seizures arise (55). Mapping of both cortical and subcortical sites can provide critical information regarding localization of motor, sensory, and language tracts (53).

EXTENT OF RESECTION. The degree of cytoreduction achieved as measured by extent of resection appears to correlate with outcome. Patients with gross total resection live longer than those with partial resection who in turn live longer than those who have biopsy only (56,57). A further consideration is that partial resection often is accompanied by significant postoperative edema surrounding residual tumor tissue along with increased neurological morbidity (58).

The association between extent of resection and longer survival for patients with high-grade malignant gliomas is controversial, similar to low-grade gliomas for which the prognostic effect of extensive surgery is not well defined but appears to have a positive effect on outcome (59–61). The controversy is mainly caused by lack of randomized studies addressing the issue and the inconsistent and less than objective methodology used in determining extent of resection. In a retrospective study of preoperative and postoperative tumor volumes in 92 patients with GBM, extent of tumor removal and residual tumor volume were significantly correlated with median time to tumor progression and median survival (62). In this study, greater resections did not compromise the quality of life and patients without any residual disease had a better postoperative performance status than those patients who received less than total resections.

REOPERATION. Reoperation for recurrent tumor growth after operative and adjuvant therapy often is necessary. Clinical deterioration or tumor progression on serial imaging studies despite surgery and postoperative adjuvant therapy constitutes treatment failure, and these cases should be considered for reoperation.

The goal of reoperation remains maximal cytoreduction with minimal neurological morbidity (63). Early studies showed poor outcome in patients who underwent reoperation for malignant gliomas; one study of patients with anaplastic astrocytoma or

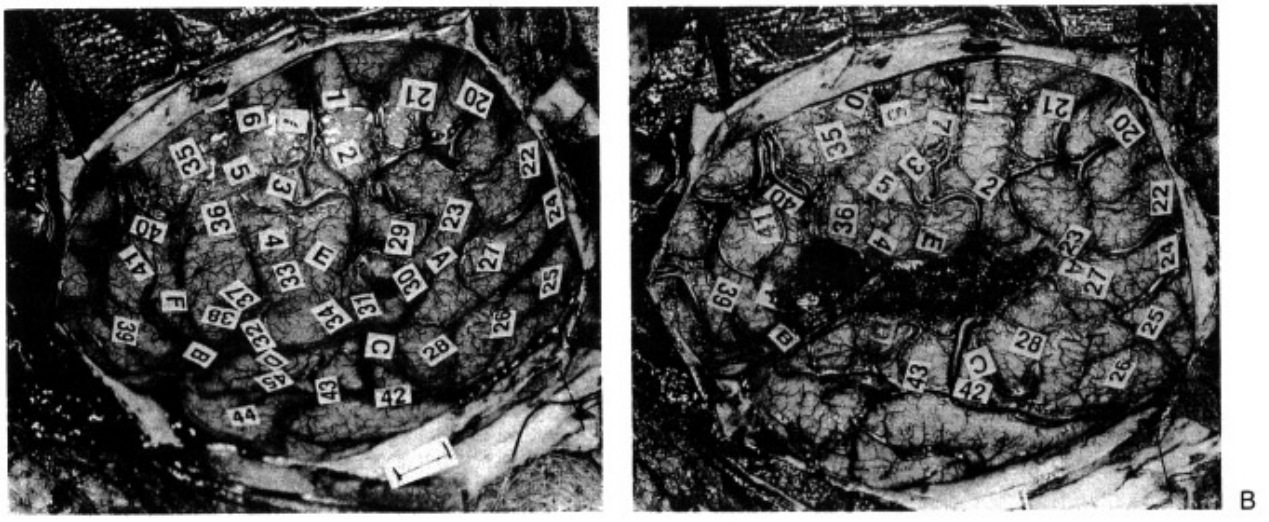

Fig. 3. Preresection **(A)** and postresection **(B)** intraoperative view of the case described in Fig. 1. Intraoperative stimulation of *25* and *28* resulted in anomia.

glioblastoma multiforme reported median survival after reoperation of only 14 weeks with a median total survival of 62 weeks (64). However, a more recent study showed a median survival of 37 weeks after reoperation and median total survival of 91 weeks (65). Reoperation is clinically reasonable when lengthened survival of acceptable quality is the likely result of surgery. Thus, it should be performed when a patient whose tumor characteristics, age, and preoperative performance status suggest the potential for a favorable outcome; of note also is that studies of patients who survive longer than 5 years nearly all have undergone reoperation as a cornerstone of therapy (66).

Adjuvant Therapies

Adjuvant therapies are defined as postsurgical therapies designed to decrease the likelihood of recurrence after operative treatment of tumors or those used to treat recurrences that arise. Chemotherapy, external beam radiation therapy, and brachytherapy are the three principal types of adjuvant therapy. Currently, most protocols for the treatment of aggressive glial neoplasms in adults combine surgery with postoperative external beam radiation therapy and carmustine or vincristine chemotherapy.

RADIATION THERAPY. Radiation therapy has been the adjuvant therapy of choice for the treatment of malignant gliomas for many years (67). In the past, patients were treated with large fields of low-energy x-rays with poor penetration, leading to substantial irradiation to normal tissue. Today, three-dimensional treatment planning based on modern CT and MRI techniques permits delivery of a full dose of radiation to the tumor with minimal irradiation of normal tissue.

EXTERNAL BEAM RADIATION THERAPY. External beam radiation therapy for brain tumors is carried out with high-energy, or megavoltage x-rays produced by a linear accelerator. These x-rays deliver increasing dose with depth up to a few centimeters and the dose decays thereafter in approximately exponential fashion. Various beam configurations are analyzed with respect to their isodose configurations at the target site and optimal dosimetry is calculated. Radiation is thought to kill cells primarily by means of DNA damage. As the intent of radiation therapy is to destroy tumor tissue with minimal effect on normal tissue, in practice the dose-limiting factor is always the susceptibility of normal tissue to radiation damage. Radiation injury to normal brain tissue may be manifest as acute or delayed neurological sequelae, cognitive dysfunction, diffuse white matter injury, or outright radiation necrosis. These adverse effects may be limited by fractionation of the overall dose into multiple sessions. Multiple clinical trials have demonstrated improved survival for patients receiving radiation therapy, and current data support treating malignant glioma with conformal stereotactic external beam radiotherapy to a total dose of 60 Gy in 30 fractions (68). Higher doses have not demonstrated increases in survival (68). Optimal outcome is obtained with close cooperation between the radiation oncologist, neurosurgeon, and neuroradiologist.

RADIATION SENSITIZERS. Chemicals that modify radiation sensitivity have been used in the attempt to increase the therapeutic effect of standard radiation therapy. One example is the halogenated pyrimidine bromodeoxyuridine (BrdU), which incorporates into DNA of cycling cells in place of thymidine, enhances DNA strand breaks caused by radiation therapy and inhibits DNA repair (69). However, despite encouraging phase 2 results with BrdU (70), in phase 3 trials no survival advantage was seen and the study was closed (71).

Oxygen-mimetic radiosensitizers have been developed because areas of tumor hypoxia are thought to convey radioresistance. The nitroimidazole etanidazole (72) and cytotoxic sensitizer tirapazamine (73) have been studied in phase I and II trials, respectively, but no clear evidence of efficacy has been established yet.

BRACHYTHERAPY. Interstitial or intracavitary implantation of radioactive sources (brachytherapy) permits local delivery of high doses of radiation. Brachytherapy has been used primar-

ily in the control of recurrent malignant gliomas (74), which are likely to recur locally (15). Isotopes commonly used for brachytherapy include iridium-192, iodine-125, and phosphorus-32. The rationale for use of brachytherapy is that local sources can deliver a larger radiation dose to the tumor volume while sparing surrounding tissue. Modern stereotactic techniques permit accurate placement of radioactive sources, and combined with computer-based planning systems allow for manipulation of isodose distributions to minimize dose to surrounding normal tissue. Median survival of GBM patients treated with brachytherapy at two centers is approximately 19 months (75,76). Hyperthermia is another possible local treatment as an adjunct to interstitial brachytherapy (77).

STEREOTACTIC RADIOSURGERY. Stereotactic radiosurgery has evolved considerably since its introduction by Leksell (78). Radiosurgery involves the use of numerous narrow collimated beams of radiation stereotactically directed to converge at a specific intracranial target. Three types of radiation have been used: gamma rays, produced by the radioactive decay of ^{60}Co ("gamma knife" radiosurgery); high-energy x-rays produced by linear accelerators; and charged particles such as protons produced by cyclotrons. Radiosurgery usually involves attaching a stereotactic frame on the patient, delineating the target on radiologic images, treatment planning by displaying isodose contours on these images, registering the frame and patient, and irradiating the target. Doses delivered during radiosurgery typically are lower than those delivered by fractionated radiation therapy but have greater effect because the entire dose is delivered in a single session to a highly limited target field.

Results of several long-term retrospective studies support the idea that the addition of radiosurgery prolongs median survival in the postoperative treatment of GBM (79–81). In general, radiosurgery may be used as adjuvant therapy following resection and for recurrences or disease under a certain size (e.g., <3 cm). Prospective, randomized trials are underway to help define more precisely the role of radiosurgery in the treatment of patients with GBM.

RADIOIMMUNOTHERAPY. Another approach is to deliver radiolabeled monoclonal antibodies directed at tumor-specific antigens to increase the tumor-specific radiation dose. Several groups have investigated this technology using either intravenous or intracavitary routes of administration of immunoglobulins. One study delivered intravenous ^{125}I-labeled antiepidermal growth factor antibodies, with a median survival of 13.5 months in the treatment group (82). A recent study using intracavitary delivery of ^{131}I-labeled antibodies to tenascin via Ommaya reservoir demonstrated a promising outcome in a subset of patients (83).

CHEMOTHERAPY. Many trials of cytotoxic chemotherapy for malignant brain tumors have been reported over the last three decades. The primary group of chemotherapeutic agents currently used for malignant gliomas are the nitrosoureas, including carmustine and lomustine. Nitrosoureas are lipid-soluble and readily cross the BBB. Their mode of action is incompletely understood, but their antitumor activity is likely related primarily to the formation of DNA interstrand crosslinks. Like other alkylating agents, nitrosoureas are myelosuppressive, and platelet and leukocyte counts must be closely monitored. Dosage adjustments are based on nadir blood cell counts. Other agents shown to have at least some activity against human gliomas include procarbazine, vincristine, hydroxyurea, carboplatin, etoposide, cyclophosphamide, and high-dose tamoxifen (84). The following is a summary of evidence regarding chemotherapy for each histological subtype of malignant glioma, for recurrent gliomas, and a discussion of novel therapies.

Glioblastoma Multiforme. An early outcome review of a large series of patients with glioblastomas treated from 1950s to 1980s demonstrated that median survival in the chemotherapy and radiation group was only 3 weeks longer than the group treated with radiation therapy alone (85). However, routine use of the nitrosoureas increased survival in the 1980s (86). Although use of nitrosoureas alone is inferior to radiation therapy alone (67), a recent metaanalysis of 16 studies published between 1975 and 1989 involving more than 3,000 patients concluded that combined therapy with radiation and chemotherapy increased survival compared to radiation therapy alone (86).

Standard therapy usually includes carmustine (BCNU) or procarbazine (Matulane), lomustine (CCNU), and vincristine (Oncovin) together (PCV). Studies comparing BCNU versus PCV in the treatment of glioblastoma multiforme have failed to consistently demonstrate a survival advantage to the three-drug regimen (87,88).

Anaplastic Astrocytoma. Specific information regarding efficacy of adjuvant chemotherapy for anaplastic astrocytoma is limited because most studies of chemotherapy for malignant glioma include both anaplastic astrocytoma and glioblastoma multiforme. However, the standard adjuvant therapy for patients with newly diagnosed anaplastic astrocytoma is nitrosourea-based. Some evidence indicates that PCV (procarbazine, lomustine, vincristine) chemotherapy may be superior to carmustine alone in treating anaplastic astrocytomas but this is controversial (87–89).

Anaplastic Oligodendroglioma and Mixed Oligodendroglial Tumors. Anaplastic oligodendrogliomas and anaplastic mixed oligoastrocytomas have been shown to respond especially well to PCV chemotherapy (90,91). Cairncross and colleagues demonstrated that the allelic loss of chromosomes 1p and 19q predicted response to chemotherapy and longer survival in patients with anaplastic oligodendrogliomas (92), establishing a molecular marker for chemosensitivity in these tumors. Indeed, increasingly neoadjuvant (i.e., preradiation) chemotherapy with PCV is being used in treating pure or mixed anaplastic oligodendrogliomas since up to 70% of patients may respond (93,94). In addition, salvage therapy with PCV may be effective in patients progressing after radiotherapy (93).

Anaplastic Ependymoma. The role of chemotherapy in ependymal tumors is poorly defined. Although some evidence suggests that there may be better response with platinum-based than with nitrosourea-based regimens for intracranial ependymoma (95), little data exist on the role of chemotherapy in anaplastic ependymomas.

Recurrent Glioma. The optimal treatment for recurrent glioma (anaplastic astrocytoma and glioblastoma) is unclear. The difficulty in evaluating efficacy of treatments in this patient population is emphasized in a recent systematic metaanalysis of 1,415 patients with recurrent gliomas (96). Temozolomide, an imidazotetrazine derivative that exerts its antitumor effect by DNA methylation, has shown good response in patients with recurrent anaplastic astrocytoma (97) and has received recent approval by the FDA for treatment of recurrent anaplastic astrocytomas. Temozolomide is also under study as therapy for

recurrent glioblastoma multiforme (98) and as neoadjuvant therapy for patients with newly diagnosed AA (99). Carmustine-impregnated biodegradable polymers (Gliadel wafers) have shown some efficacy in prolonging survival in patients undergoing repeat surgical resection (100), and based on this have received FDA approval for treatment of recurrent glioblastoma multiforme. A recent study also suggests that carmustine polymers may prolong survival when given at the time of primary operation (101).

STRATEGIES TO IMPROVE CHEMOTHERAPY DELIVERY. Several strategies have been used in the attempt to improve local delivery of chemotherapeutic agents to the tumor tissue. These include intraarterial chemotherapy (102), hyperosmolar BBB opening (103), and high-dose chemotherapy (104). None of these yet have been shown to provide any clinical benefit and have significant associated toxicity. For example, a randomized study of patients with newly diagnosed high-grade glioma found no benefit to intracarotid versus intravenous carmustine, and intraarterial administration produced significant neurological toxicity (105). High-dose myeloablative chemotherapy with thiotepa followed by bone marrow rescue has been used in the treatment of recurrent aggressive oligodendroglioma, but is associated with 20% mortality (106).

NEWER THERAPIES. Advances in understanding of the molecular biology of gliomas have led to the development of novel forms of chemotherapy. One novel target is type I topoisomerase, an enzyme critical for DNA replication and transcription. Irinotecan (CPT-11), which inhibits topoisomerase I, has shown activity as a single agent (107). Other newer agents target tumor invasion, signal transduction, and angiogenesis. For example, marimastat, a matrix metalloproteinase inhibitor that inhibits enzymes known to be involved in tumor invasion, is in phase III trials for patients with newly diagnosed GBM (108). Leflunomide (SU-101), which inhibits the PDGF (platelet-derived growth factor) signaling pathway, known to be upregulated in a subpopulation of human gliomas, has shown activity in phase I and II trials (109). Tamoxifen, an inhibitor of protein kinase C at high concentrations, has demonstrated efficacy for a subset of patients with recurrent gliomas (110). The angiogenesis inhibitor thalidomide has shown activity in phase II trials (111).

Tumor immunotherapy is another area of development. Tumor vaccines using cells engineered to secrete cytokines aim to boost host immunity against tumor-specific antigens with minimal effect on surrounding tissue, and this has shown promise in animal models (112,113). In another approach, recombinant toxins target tumor-associated antigens via a tumor-specific binding protein (e.g., antibody or growth factor) linked to a toxic moiety to combine tumor selectivity with increased potency (114). For example, because transferrin receptors are expressed on rapidly dividing cells, one approach uses a conjugate of human transferrin fused to a diphtheria toxin (TF-CRM107) to potently kill glioblastoma cells, which has shown efficacy in some patients (115).

Gene therapy also has been considered as a potential adjunct treatment for malignant gliomas. One approach is to transfer an exogenous gene into tumors that confers susceptibility to a given agent. For example, transfer of the gene that encodes the herpes simplex virus enzyme thymidine kinase (HSV-TK) followed by administration of the antiviral drug ganciclovir should in theory destroy rapidly proliferating cells that take up the viral gene (116). The first clinical trial using vector-producing cells was reported in 1997 (117). Fifteen patients with progressive recurrent malignant brain tumors were studied and an antitumor response was detected in five of the smaller tumors; however, gene transfer to tumors was limited. A subsequent study using a similar approach resulted in transient tumor control with limited effect on survival (118). Using a protocol based on a more efficient new vector construct, two phase I/II clinical trials in adult patients, a European-Canadian study (119) and a United States study were initiated. In the former trial, clinical benefit was marginal, although the treatment method was found to be feasible and sufficiently safe (119). A third phase I study using the modified vector was conducted on pediatric patients with recurrent malignant supratentorial tumors and concluded that the method may be used with satisfactory safety in select patients (120). Although this approach is promising, improved gene delivery vectors are needed to affect a sufficient proportion of tumor cells.

Conclusion

Prognosis remains poor despite intensive basic and clinical study of malignant gliomas. Factors influencing the clinical course of malignant gliomas include histological grade, age, neurological status, extent of resection, and radiation therapy (121,122). It is hoped that advances in noninvasive diagnosis, surgical technology and adjuvant treatment together with novel therapies derived from cellular and molecular understanding of glial tumorigenesis will significantly improve the clinical outcome from these devastating lesions.

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104. Surgery for Glial Neoplasms within the Brain

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Primary brain tumors represent one of the most devastating events that can befall any individual. Likewise, craniotomy for tumor removal, adjuvant chemotherapy, and radiation therapy all represent highly significant departures from everyday life and are also associated with significant morbidity. Glial neoplasms are by far the most common primary brain neoplasm, accounting for approximately 40% to 60% of all primary brain tumors and occurring in approximately 4.1 to 5.7 per 100,000 population per year (1,2). Gliomas come in two peaks according to age-incidence, one in childhood consisting mostly of brainstem gliomas and cerebellar astrocytomas and a second in the fifth and sixth decades, containing a much larger percentage of aggressive tumors including anaplastic astrocytoma and glioblastoma multiforme (GBM).

Surgery for glial neoplasms largely coincides with the earliest historical evidence for craniotomy (3). The first resection of a glioma reported in the literature, however, was performed by Rickman Godlee in 1884 on a patient with an oligodendroglioma in rolandic cortex and focal motor seizures (4). Interestingly, Cushing initially advocated external decompressive craniotomy for the treatment of all gliomas, but by his later years had converted to gross total resection as the primary therapy, believing that removal of tumor itself had a positive impact on patient survival (5). Even as the modern era of neurosurgery enters the 21st century—with the advent of improved tumor markers to produce more accurate histology and molecular understanding of gliomas, imaging-guided stereotactic biopsy to improve early diagnosis of gliomas, and the development of more refined techniques of intraoperative guidance and localization to improve resection of tumor versus normal brain—there remains little consensus regarding the overall management of patients harboring glial neoplasms (6,7).

Classification of Gliomas

Historically, this lack of consensus has arisen in large part from difficulty in classifying these lesions (8,9). Cushing and Bailey first classified tumors in the late 1920s based on the presumed embryonic cell type of origin. Several decades later, however, Kernohan concluded the opposite, that gliomas arise from adult glial phenotypes via dedifferentiation, and thus can be classified as astrocytomas, oligodendrogliomas, and ependymomas. He classified gliomas into four grades of anaplasia on the basis of *amount* of pleomorphism, *number* of mitoses, *degree* of necrosis, and *amount* of vascular proliferation, recognizing that histopathological criteria have prognostic significance (10).

This system was codified by the World Health Organization (11), with grade assigned according to the predominant cell type found within the tumor (i.e., grade 1 = "pilocytic" astrocytoma; grade 2 = "fibrillary" and "gemistocytic" astrocytoma; grade 3 = "anaplastic" astrocytoma, and grade 4 = "glioblastoma"). Oligodendroglial tumors were assigned to grade 2 (oligodendrogliomas and oligoastrocytomas) and grade 3 (anaplastic oligodendrogliomas). Many institutions, however, have adopted some modification of the Daumas-Duport ("Mayo-St. Anne") system, which is based on more objective presence or absence of relevant histopathological features (nuclear atypia, mitoses, necrosis, and endothelial hyperplasia). In this system, grade is assigned on a scale of 1 to 4 according to the number of relevant features present, rather than subjective *amount* and *degree* of such findings (12).

In addition to evaluating tumor cell morphology, gliomas can be typed according to the topography of tumor cells in the brain (13,14). Correlation of sequential stereotactic biopsy results