

OLIGODENDROGLIOMA AND ANAPLASTIC OLIGODENDROGLIOMA: CLINICAL FEATURES, TREATMENT, AND PROGNOSIS

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Engelhard HH, Stelea A, Mundt A. Oligodendroglioma and anaplastic oligodendroglioma: clinical features, treatment and prognosis. *Surg Neurol* 2003;60:443–56.

BACKGROUND

Recent advances that have been made in diagnostic imaging, surgical technique, chemotherapy, molecular biology, and prediction of therapeutic response could have potential impact on the optimal diagnosis and treatment of patients with brain tumors, especially those with oligodendrogliomas. In this article, the topic of oligodendroglioma and anaplastic oligodendroglioma is reviewed, highlighting the new clinical developments.

METHODS

Information for this review was obtained by performing a Medline search for recent references using the term “oligodendroglioma.” The bibliographies of papers obtained also were checked for articles that could provide additional understanding of this disease and its current treatment.

RESULTS

The incidence of oligodendroglioma is increasing, most likely due to its improved recognition. Seizures and/or headaches are still common presenting features, and surgery continues to be the primary treatment. Positron emission tomography (PET) and molecular analysis of the surgical specimen are emerging as important diagnostic tools. Patients having either oligodendroglioma or anaplastic oligodendroglioma are likely to respond to chemotherapy. This has had an impact upon the timing of radiation therapy. Survival times are increasing, and patients can now be divided into prognostic subgroups based on the molecular features of their tumors. While procarbazine-CCNU-vincristine (PCV) chemotherapy has been the standard, other agents, notably temozolomide, are currently being tested.

CONCLUSIONS

The algorithm for diagnosing and treating patients with oligodendrogliomas has changed. Neurosurgeons need to be aware of the new developments so they can offer

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KEY WORDS

Brain tumor, chemotherapy, functional MRI, malignant glioma, oligodendroglioma, positron emission tomography, prognosis, radiation therapy, temozolomide.

Oligodendroglial tumors have generated much interest over the past decade, due to their heightened response to chemotherapy and ability to be divided into prognostic subgroups based on molecular biology (33,44,68,96). For the first time for a central nervous system (CNS) tumor, characterization of genetic alterations in the tumor tissue promises to be as important as histologic findings and clinical factors in defining appropriate therapy (10,33,96,111). Specifically, it has been confirmed by several clinical studies that losses of portions of chromosomes 1p and 19q are associated with the oligodendroglial phenotype and longer recurrence-free survival following radiation and/or chemotherapy (33,95). It is believed that these chromosome regions contain tumor suppressor genes, which when lost lead to the development and/or progression of the tumor.

Further studies have narrowed the chromosomal locations involved, and it has been reported that lesions at the loci 1p36 and 19q13.3 are related to the favorable therapeutic response (96). TP73 is a gene that is located at 1p36.3. It encodes for a protein that shares significant structural homology with the tumor suppressor p53 (30). However, not all oligodendrogliomas have 1p and 19q losses. Therefore, it is believed that there are multiple molecular pathways for the development of this type of tumor (44). In an alternative pathway, p16/CDKN2A deletion, 10q loss, and epidermal growth

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Received October 10, 2001; accepted January 27, 2003.

factor receptor (EGFr) amplification have been found; such patients have a poorer prognosis (33,44).

While molecular biologists have been intrigued with elucidating the pathogenesis of oligodendroglioma, neuropathologists have emphasized the importance of recognizing its key histologic features and therefore making the correct diagnosis (33). This is very important, since oligodendrogliomas are more responsive to chemotherapy than astrocytomas of comparable grade (35,95,96). The World Health Organization (WHO) has set guidelines for grading "pure" oligodendrogliomas according to a two-tier system. These tumors are called "pure" when they do not contain malignant astrocytes (23). The "garden variety" oligodendroglioma is a "well-differentiated" tumor, considered to be a grade II glioma. The more malignant "anaplastic oligodendroglioma" is a grade III glioma. Nuclear atypia and occasional mitosis can be seen in a WHO grade II oligodendroglioma, but marked mitotic activity, noticeable microvascular proliferation, and/or conspicuous necrosis are hallmarks of an anaplastic oligodendroglioma (33,76). An anaplastic oligodendroglioma may present *de novo* or "evolve" from a well-differentiated oligodendroglioma (59,100). According to a recent report from the Central Brain Tumor Registry of the United States (CBTRUS), 77% of oligodendrogliomas are low-grade and 23% are anaplastic (13).

In this article, the clinical features and current treatment options for pure oligodendroglial tumors—including both low-grade and anaplastic oligodendrogliomas—will be reviewed. The topic of mixed gliomas ("oligoastrocytomas"), which contain both neoplastic astrocytes and neoplastic oligodendroglia, will not be addressed here. The pathology and molecular biology of oligodendrogliomas (including the significance of the 1p and 19q chromosomal losses) have been discussed in detail in a previous issue of *Surgical Neurology* (33).

INCIDENCE, TUMOR LOCATION, AND SYMPTOMS

Oligodendrogliomas are the third most common type of glioma, traditionally thought to comprise 2% to 5% of primary brain tumors and 4% to 15% of gliomas (7,24,41,63,65,76,77,85). Recent evidence has indicated that these tumors are more common than once thought (19,23,68,100), and tumor data base analysis has confirmed that in the United States, the incidence of oligodendroglioma is increasing (49). It is believed that in the past, many tumors that were actually oligodendrogliomas were diagnosed to be various types of astrocytomas

(19,23,33). Also, with the improved brain imaging provided by magnetic resonance imaging (MRI), gliomas are being diagnosed more readily than in the past (49,55). The combination of these two factors, improved histologic recognition, and earlier diagnosis by magnetic resonance imaging (MRI) may account for the increased incidence (49,55).

Even with the increase, oligodendrogliomas are relatively uncommon, occurring at an incidence of less than 4 per 1,000,000 person-years (49). Oligodendrogliomas may occur at any age, but the initial diagnosis has two incidence peaks: 6–12 years and 35–44 years (15,109). Only about 7.5% are diagnosed in children, representing a small proportion (about 1%) of childhood brain tumors (75,83,94). Both males and females are affected, although the tumor is somewhat more common in males, with the male-to-female ratio ranging from 1.1 to 2.0 (65). In a study by Fleury et al on French glioma patients, it was concluded that these tumors had a peak incidence at 45–49 years when both genders were studied together. A gender difference was found for the incidence peak, however, when the sexes were analyzed separately. For males, the peak was at 45–49 years, while in females it was at 55–59 years (34). Other series have reported similar findings (76). While familial clusterings of oligodendrogliomas have been found, there is no clear pattern of inheritance from generation to generation nor any known genetic risk factors (70).

Anatomically, oligodendroglial tumors may occur anywhere oligodendrocytes are found. Like astrocytomas, their distribution has usually been found to be proportional to the normal distribution of their cell type within the central nervous system (CNS) (7,33,100). More than 90% arise in the supratentorial white matter, most commonly in the frontal (also the largest) lobe. Less than 10% occur in the posterior fossa and spinal cord (12,23,61,67,77,85,92). In a large study of 323 patients, which included oligodendrogliomas and anaplastic oligodendrogliomas, Ludwig et al (1986) found that the primary location was frontal in 55% of cases, temporal in 47%, parietal in 20%, occipital in 4%, cerebellar in 3%, and spinal in 1% (58). Several unusual primary locations (listed in Table 1) have been mentioned in the literature (3,11,22,29,39,60,62,66,78,94).

Oligodendroglial tumors have a tendency to invade the leptomeninges (33,76,100). A delayed occurrence of cerebrospinal fluid metastases (either leptomeningeal seeding or "drop metastases") probably occurs in 1% to 2% of cases (20,58,65,83,98,100). Oligodendrogliomas seem to be more likely to metastasize outside the CNS than

1 Unusual Primary Locations for Oligodendrogliomas

Thalamus
Cerebellopontine angle
Leptomeninges
Retina
Intraventricular (including fourth ventricle)
Brainstem
Septum pellucidum
Optic nerve
Multiple

other gliomas and have been reported to spread (although rarely) to bone, lung/pleura, and liver (57,65). One factor that could contribute to the increased occurrence of metastases is the longer survival of patients with oligodendroglioma, in comparison to patients with other malignant brain tumors (65). Interestingly, a recent study by Zlatescu et al found that molecular subtypes of anaplastic oligodendrogliomas arise preferentially in certain lobes of the brain, and have different patterns of growth (111). In their series of 64 cases, tumors with losses of chromosomes 1p and 19q occurred more frequently in the frontal lobes and more often showed widespread growth across the midline (111).

The symptoms for oligodendroglial tumors do not reliably distinguish them from other types. In most series, seizure has been the most common presenting symptom, ranging in incidence from 35–85% of patients (12,41,61,65,77,92). In a recent study by Liigant et al (2001), 53% of patients presented with seizures (56). This is in contrast to pre-CT era studies, in which 87-92% of patients presented with seizures (15,56). Daumas-Duport et al (1997) reported that 91% of their oligodendroglioma patients had seizures at some point (23). In Tice's study of pediatric and adolescent oligodendroglioma patients, 85% had seizures (94). Seizures from oligodendrogliomas may be generalized, simple partial, complex partial, or a combination (70).

Other presenting symptoms have included headaches, mental status changes, vertigo/nausea, visual complaints, and/or localized weakness (1,23,41,58,65,77,92). Classically, it has been observed that oligodendroglioma patients often experience symptoms (usually seizures) for a number of years prior to their diagnosis, which was definitively made after an apoplectic event such as a peritumoral hemorrhage. This situation has become less common with the increased availability and sensitivity of computerized tomography (CT) and MRI, which have lead to earlier diagnosis (55). Still, the average duration of symptoms prior to

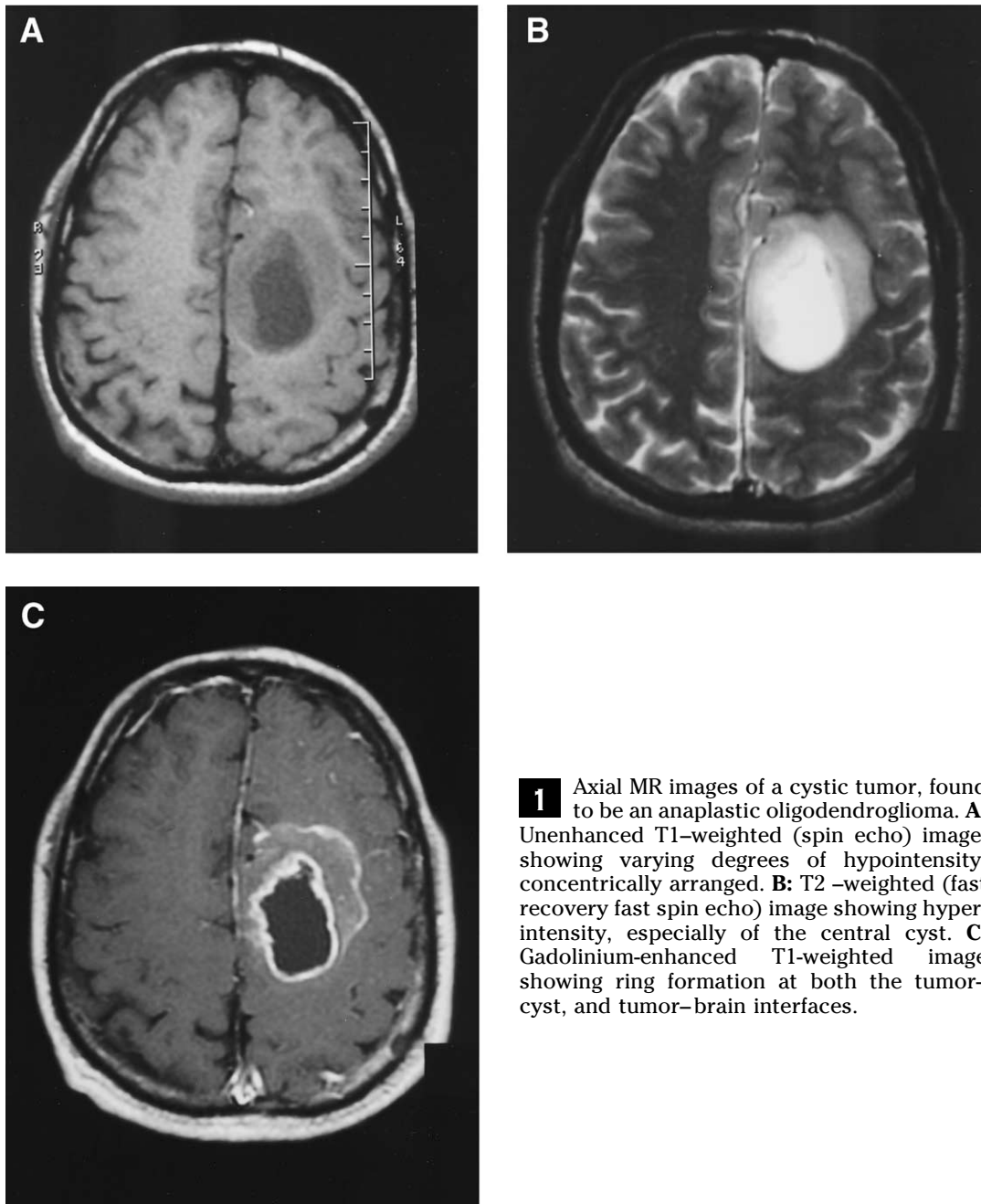
definitive diagnosis in relatively recent series has ranged from 2.9 months to 5 years, and even longer (23,65,67,75). Currently, the diagnosis of oligodendroglioma may still be made after an acute hemorrhage or following a decade of treatment for idiopathic seizures (42).

COMPUTERIZED TOMOGRAPHY, MR IMAGING, AND PET SCANS

As with other brain lesions, CT scans and especially MRI are used to determine the location and spatial configuration of the tumor. Findings on diagnostic imaging of oligodendrogliomas may be characteristic but are not pathognomonic (94,104). Oligodendrogliomas vary in their appearance and may occur in unexpected locations. Usually they are found in the cortex and/or subcortical white matter as mass lesions with fairly discrete margins (49% to 59%) (52). Typically on CT scan, oligodendrogliomas appear hypodense (57% to 70%) or isodense (61). Intraventricular oligodendrogliomas, although rare, have a tendency toward a hyperdense appearance (29). Oligodendrogliomas are typically described as enhancing poorly or not at all (61). Yet *some* degree of contrast enhancement has been reported to occur in 24–66% of cases (23,51,52,94,104). Peritumoral edema is usually mild or absent; cystic changes and tumor hemorrhages may also be seen (52). Due to their typically “peripheral” (i.e., cortical) location and slow-growing nature, oligodendrogliomas may cause calvarial erosion (52).

Oligodendroglioma is the intracranial tumor that develops calcifications most often, up to 90% in some series (29,51,52,104). Calcifications often present a coarse appearance; punctate or linear calcifications also may occur (52,104). CT shows the calcium deposits better than plain films or MRI (61,70). While calcification is common, it is not diagnostic for oligodendroglioma (29,51,52,104). Statistically, since astrocytomas may also calcify and are more common, a glioma with calcium deposits is more likely to be an astrocytoma than an oligodendroglioma (51).

On MRI, an oligodendroglioma is typically hypointense on T1-weighted images and hyperintense on T2-weighted images, often appearing fairly well demarcated and with little peritumoral edema (23,51,52,61). T2-weighted images may be even more sensitive than T1 for detecting tumor and in evaluating response to chemotherapy (28). MRI is more sensitive than CT for demonstrating parenchymal abnormalities and enhancement. With the widespread availability and increased sensitivity of MRI, it is likely that oligodendrogliomas (and other

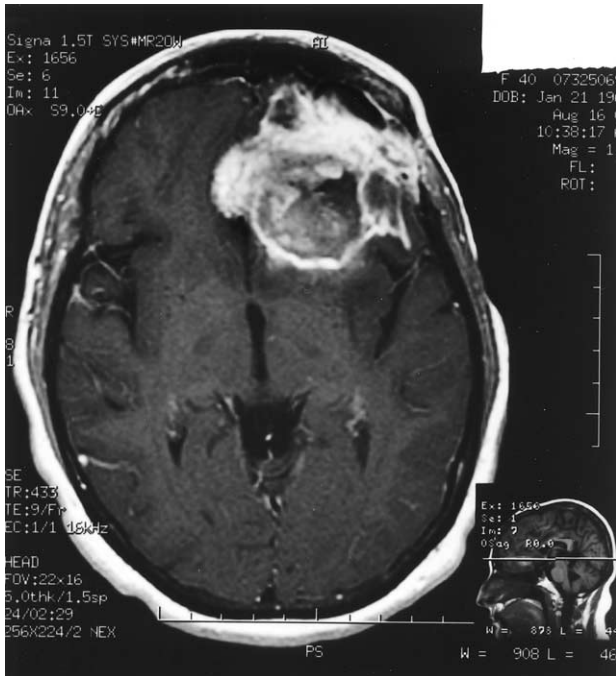


1 Axial MR images of a cystic tumor, found to be an anaplastic oligodendroglioma. **A:** Unenhanced T1-weighted (spin echo) image, showing varying degrees of hypointensity, concentrically arranged. **B:** T2-weighted (fast recovery fast spin echo) image showing hyperintensity, especially of the central cyst. **C:** Gadolinium-enhanced T1-weighted image showing ring formation at both the tumor-cyst, and tumor-brain interfaces.

types of tumors) are being diagnosed earlier. This may be one factor acting to increase the survival time calculation (55). Since intratumoral hemorrhage, areas of cystic degeneration, and/or calcifications may all be present, oligodendrogliomas may demonstrate a heterogeneous or “enigmatic” appearance (51). Like other glial tumors, oligodendrogliomas may spread through the corpus callosum and along the leptomeninges or ependyma (61,76).

Although still somewhat controversial, contrast

enhancement (on CT and/or MRI) may indicate a more aggressive tumor (10,23,52,61,104). Enhancement may be either patchy or homogeneous. When *ring* enhancement is present (which is rare), it has been reported to herald a poor prognosis (10) (see Figure 1C). With contrast enhancement as a variable, Daumas-Duport et al have suggested a grading classification for oligodendrogliomas, which they found to be highly predictive of survival (23). In children and adolescents with oligodendrogliomas, calcifications, enhancement, and edema are seen



2 An anaplastic oligodendroglioma, recurrent in the frontal lobe, from a tumor that originally was a WHO grade II oligodendroglioma. The patient died within a few months despite re-resection, additional radiation therapy and chemotherapy.

less frequently than in adults (94). Representative imaging studies from patients with oligodendrogliomas are shown in Figures 1-3.

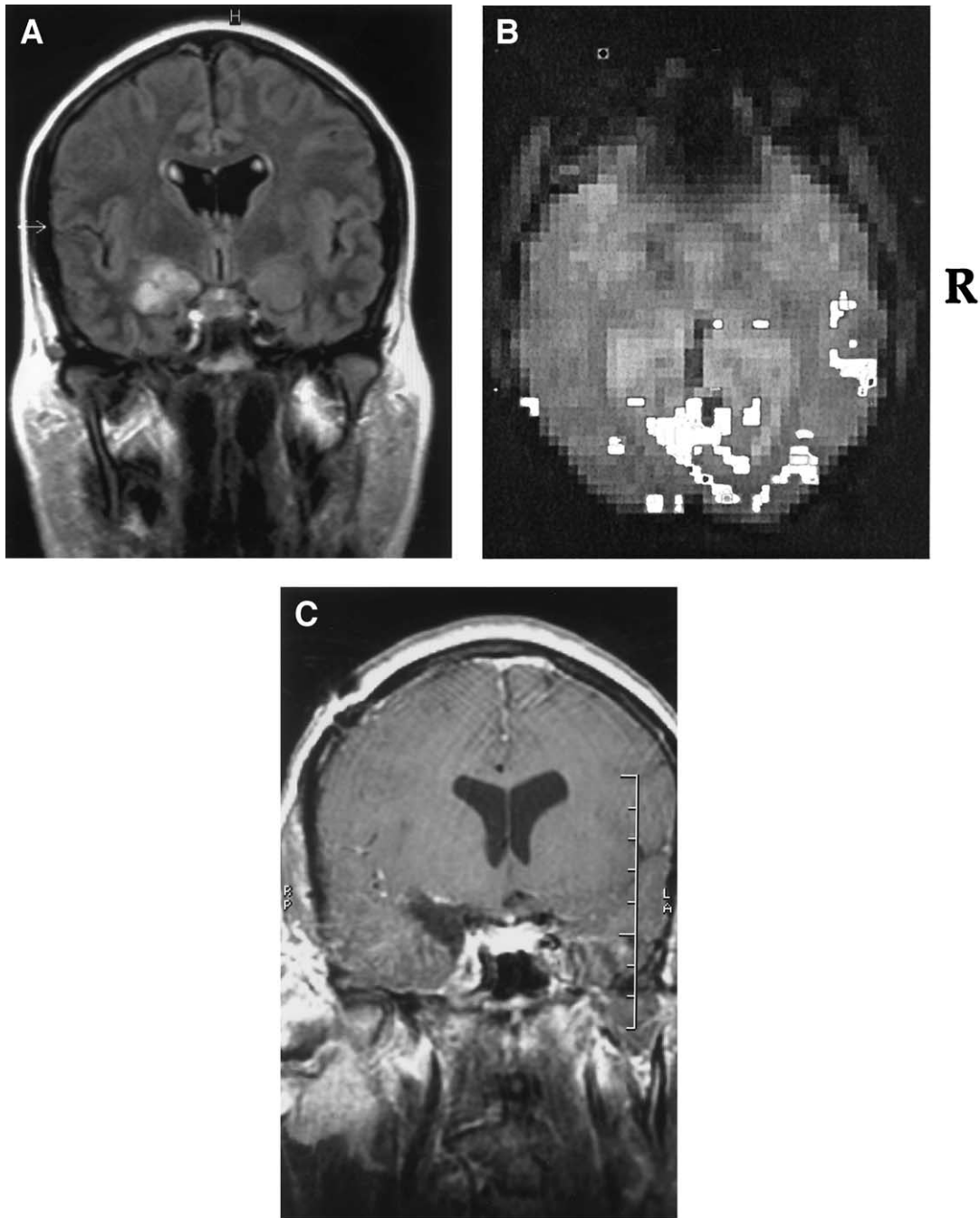
Preliminary studies are indicating that positron emission tomography (PET) may also provide valuable information for patients with oligodendroglioma or anaplastic oligodendroglioma. In general, brain PET can give quantitative information regarding glucose metabolism, blood flow, and amino acid metabolism (26,27,64,93). Fluorine-18 fluorodeoxyglucose (^{18}F -FDG) PET has been used as a tool in distinguishing scar, gliotic tissue, or necrosis from actively growing glial tumor (93,103). Carbon-11-methionine (^{11}C -MET) PET has been reported to be able to differentiate between low-grade astrocytoma and oligodendroglioma and to be useful in oligodendroglioma patients being followed for residual or recurrent tumor (27). PET might also be able to noninvasively grade oligodendrogliomas, i.e., distinguish between low- and high-grade tumors (26). Potential applications of PET for oligodendroglioma (especially when used in conjunction with MRI) are given in Table 2. In the future, PET may have increasing clinical importance in determining tumor location, grade, and progression.

SURGERY FOR OLIGODENDROGLIOMA AND ANAPLASTIC OLIGODENDROGLIOMA

Currently, surgery continues to be the mainstay of treatment for most patients with gliomas (1,8,70,81,86). Obtaining tissue is still essential for establishing an accurate diagnosis, and tumor resection can be used to reduce mass effect causing symptoms and neurologic deficits (35,70). Tumor resection may also allow a decrease in radiotherapy portal size and reduce sampling errors that may occur with biopsy alone (35). A fairly large cranial opening is often used to aid in brain decompression, facilitate exposure, and allow multiple trajectories to the tumor. Operative morbidity should be low but depends on tumor location. Use of preoperative functional MRI (fMRI), image-guided surgery ("stereotactic craniotomy"), and/or intraoperative MRI can be used to increase the amount of tumor that is safely resected (4,21,32,70). Intraoperative cortical mapping and/or awake surgery may occasionally still be useful in selected cases. Representative pre- and postoperative MR images from a left-handed patient who underwent surgery for a right temporal lobe oligodendroglioma are shown in Figure 3. In this patient, the combined use of noninvasive preoperative language mapping by fMRI and intraoperative frameless stereotaxy allowed an excellent tumor resection to be achieved while avoiding any postoperative language deficit.

At the time of surgery, even with frozen section diagnosis, it may not be possible to distinguish an oligodendroglioma from other intra-axial tumors (33). Intraoperatively, oligodendrogliomas may be soft or gelatinous masses of fleshy to pinkish-gray color with or without areas of gritty calcifications, cystic structures, hypervascularity, and/or hemorrhage. The tumor is usually located in the subcortical white matter and cortex and may invade the leptomeninges (33,100). Although oligodendrogliomas usually blend into normal brain, at times a more abrupt interface between the tumor and adjacent white matter may be found (21). Staying within the perceived confines of the tumor does not guarantee that a postoperative neurologic deficit will be avoided. A postoperative MRI should be performed with and without contrast within 24 hours of surgery (if possible) to assess for the amount of residual tumor and serve as a baseline for subsequent scans (68).

Most recent authors have stated that the surgical goal for oligodendroglioma should be gross total removal, if the tumor can be safely resected (4,21,45,68,80,81,91). Most reports have indicated that a more complete resection of tumor is associ-



3 MRI of a grade II oligodendroglioma of the right temporal lobe, before and after surgery. The patient was left-handed, and right-brain dominant. **A:** T2 diffusion-weighted image showing the tumor as a bright signal in the anterior and medial right temporal lobe. **B:** Functional MR image, generated using the language comprehension paradigm. This showed Wernicke's activation on the right side, in superior temporal gyrus, 2 cm above the tumor. **C:** Postoperative T1-weighted scan, showing resection of the tumor. The patient's speech comprehension was not adversely affected by the surgery.

ated with increased survival (4,12,25,38,43,48,50, 53,67,82,85), although a few clinical series have not been able to confirm this (40,67,92). Some of these studies looked at gross total versus subtotal versus partial resection, based on the operative report;

others compared gross total/subtotal resection versus partial resection/biopsy. In a recent study conducted by Allam et al (2000), it was concluded that as a group, oligodendroglioma and anaplastic oligodendroglioma patients with complete surgical exci-

2 Potential Uses of PET for Studying Patients With Possible or Known Oligodendroglial Tumors

- Initial evaluation of patients with gliomas
 - Determining tumor type
 - Determining degree of malignancy
- Guiding biopsy to sample most malignant area, or surgical resection of tumor
- Assessment of postoperative tumor burden
 - monitoring growth
 - monitoring conversion to anaplastic grade
- Discriminating tumor from radiation necrosis

sion had a higher 5-year progression-free survival in comparison to those who had biopsy or partial excision (75% versus 53%). Unfortunately, the number of patients included was small (37), and the operative mortality rate was high (14%) (1). Aggressive surgical resection in areas entailing significant risk of neurologic damage, however, should probably be avoided, since oligodendrogliomas usually respond to other therapies (see below).

Thorough surgical resection (when feasible) has also been advocated for patients with anaplastic oligodendrogliomas and recurrent oligodendrogliomas (59,68). In van den Bent's series, several patients underwent multiple craniotomies (98). In Streffer's series, 6 out of 7 patients with grade II tumors who underwent a second craniotomy had converted to a grade III tumor, a glioblastoma, or had leptomeningeal seeding (91). Reoperation seems to have a role in selected situations, when there is a reasonable potential for improving the function and life expectancy of the patient.

CLINICAL AND MOLECULAR PROGNOSTIC FACTORS: SURVIVAL

Several other clinical variables in addition to the extent of surgical resection, as discussed above,

have been reported to have prognostic value for patients with oligodendrogliomas. A list of prognostic factors for patients with oligodendrogliomas is given in Table 3. Age is one of the strongest predictors, with older age being associated with more aggressive tumors and worse prognosis. Patients younger than 40-45 years consistently have been found to experience a longer survival (12,36,40,50,58,67,74,82,85,86,109). Westergaard's study (1997) showed that patients younger than 20 years had a median survival of 17.5 years, while those older than 60 years survived a median of 13 months (107). In Giannini's study (2001), patients diagnosed under the age of 30 years had a 10-year survival of 75%, whereas for those over age 50 years, 10-year survival was 21% (40). Patients considered to be in a poor prognostic group (for example, one with a subtotal tumor resection) are often candidates for more aggressive treatment with radiation and/or chemotherapy.

The presence of a neurologic deficit at the time of initial diagnosis also has been reported to predict a poor outcome (12,24,38,107). Daumas-Duport et al found a median survival time of 2.5 years in oligodendroglioma patients with neurologic deficits at diagnosis versus 11 years for patients without deficits (24). An initial presentation consisting of seizures has been found to be associated with a better prognosis and for predicting a positive response to chemotherapy (5,36,98). Other favorable features include a frontal lobe location and higher functional performance status (1,24,50,54,82). Bowers et al recently published their data on 20 children with low-grade oligodendrogliomas who were treated with aggressive surgery. Radiation therapy and chemotherapy were withheld until the time of radiographic or clinical progression (6). Of the prognos-

3 Prognostic Factors for Oligodendroglioma

FAVORABLE FOR PROGNOSIS	POOR PROGNOSIS
Clinical Variables	
Younger age	Older age
Frontal location	Contrast enhancement
Absent neurologic deficit at diagnosis	Neurologic deficit at diagnosis
Initial presentation with seizure	
Higher performance status (eg Karnofsky score)	Poor performance status
More extensive surgical resection	Inability to resect safely
Radiation therapy (if incompletely resected)	
Pathologic/Molecular Features	
WHO Grade II histology	WHO Grade III (anaplastic) histology
Lower proliferative activity (Ki-67; %S)	Higher proliferative activity
	Increased angiogenesis
	p16/CDKN2A deletion, 10q loss
	EGFr amplification
	Increased p53

tic variables studied, only location in the parietal lobe was associated with subsequent tumor progression (6). Data from a large national study is currently being analyzed to confirm the validity of these prognostic factors [Engelhard H, Piepmeier J, Olson J, Stewart AK. The Commission on Cancer's Brain Tumor Study for the Year 2000: Information for Neurosurgeons. Presented at the Annual Meeting of the Congress of Neurologic Surgeons, Boston, Massachusetts, November 1999].

The WHO histologic criteria (i.e., determining whether the tumor is an oligodendroglioma versus anaplastic oligodendroglioma) have been shown to have a strong predictive value for survival (25,40,54,108). Histologic features reportedly associated with a worse prognosis have included necrosis, high mitotic activity, increased cellularity, nuclear atypia, cellular pleomorphism, and microvascular proliferation (i.e., angiogenesis) (25,33,36,38,40,74,79,85,88). In Giannini's study, among the histologic features analyzed, vascular changes including endothelial proliferation and endothelial hypertrophy had the strongest association with poor survival (40). In a recent histologic study by Vaquero et al, which included 26 patients with low-grade oligodendrogliomas, a vascular endothelial surface area index (VESI) was determined based on CD-34 immunostaining. Determining the VESI is essentially a way to quantify tumor angiogenesis and correlates with contrast enhancement on CT scans. Patients with a VESI <15 showed a 5- and 10-year survival of 100% and 71%, respectively, versus 50% and 0% for patients with a VESI > 15 (101). Alternative grading systems (to the WHO criteria) have been developed for oligodendrogliomas, based both on histology and imaging criteria. The imaging feature that is used is the presence or absence of contrast enhancement on MRI or CT (19,24,35). Contrast enhancement is an indicator of poorer prognosis (10,70,73).

Molecular markers present in oligodendroglioma tumor specimens now also have been confirmed to have prognostic value (33). Molecular markers currently seem to be more important for oligodendroglioma than for any other brain tumor. Allelic loss (i.e., "loss of heterozygosity") on chromosome arm 1p (especially if accompanied by loss on 19q) appears to be strongly associated with the oligodendroglial phenotype and to also be an independent predictor of response to chemotherapy (with or without radiation therapy) and survival, both in high- and low-grade oligodendrogliomas (10,35,46,89,95). Assessment of proliferative activity within the tumor is another predictive tool (18). In a number of studies, Ki-67 labeling indices for

patients with oligodendrogliomas (as determined using the MIB-1 antibody) have been evaluated. Higher labeling indices (indicating higher proliferation) were associated with poorer prognosis (33,79,82). Other molecular markers that have reported to have prognostic value have included topoisomerase II α , cyclooxygenase isoenzyme-1, p16 and, especially, p53 mutations in anaplastic oligodendrogliomas (33,46).

The degree to which the study of molecular prognostic factors has changed the thinking about these patients can be illustrated by an example. Recent studies, if confirmed, would tell us that a patient with an anaplastic oligodendroglioma that displays both 1p and 19q losses would be predicted to have a radiographic response to PCV chemotherapy (see below) and a 95% chance of surviving 5 years. The same patient, with a histologically identical tumor but without 1p and 19q losses, yet having a CDKN2A gene deletion instead, would be expected to be less responsive to chemotherapy and have a survival of approximately 2 years (10,71). To date, only specialized laboratories can provide such (molecular) information. Yet even with all the prognostic information available, it can still be difficult to accurately predict survival for an individual oligodendroglioma patient. One reason for this is the threat of conversion to a more anaplastic tumor, often a glioblastoma, refractory to all treatment (Figure 2).

Survival times from recent reports are already significantly longer than in studies from a decade ago. In a study of 44 patients with pure supratentorial oligodendrogliomas and anaplastic oligodendrogliomas conducted by Prayson et al (2000), there was a 5-year survival of 71% and a 10-year survival of 63% (74). Henderson and Shaw (2001) reported 5- and 10-year survivals of 73% and 49% for oligodendroglioma and 63% and 33% for anaplastic oligodendroglioma (43). In another study by Giannini et al (2001), which included 124 oligodendroglial tumor patients, the overall survival at 5 and 10 years was 62% and 38%, respectively (40). Other studies have had similar results (2,36,38,48,53,80). Leonardi and Lumenta recently reported 5- and 10-year survivals of 78.9% and 44.1% for oligodendroglioma but only 23.8% and 0.05% for anaplastic oligodendroglioma (54). Olson et al (2000) recently reported a median survival time of 16.7 years in their series of oligodendroglioma and mixed glioma patients (67). Available clinical studies are sometimes difficult to compare because the patients included vary in their histologic diagnoses and treatment received.

POSTOPERATIVE TREATMENT FOR LOW-GRADE OLIGODENDROGLIOMA

Oligodendrogliomas, like other glial tumors, have a propensity to deeply infiltrate the brain. The extent to which the neoplastic cells have migrated cannot be accurately delineated by current imaging techniques. Therefore, while surgical treatment is very important, patients with oligodendrogliomas are rarely cured by surgical resection, even if all identifiable tumor has been removed (38,106). In the vast majority of cases, the tumor slowly but inexorably progresses. If the residual tumor burden has been below the threshold of clinical detection, at the time it reappears, this could be termed a "recurrence." Recurrences are usually seen at the operative site (55). For patients with low-grade tumors, this may not happen for many years. Unfortunately, however, patients usually die from progressive disease or from conversion to a higher-grade tumor (Figure 2) (91). Because of this, localized (partial brain) radiation therapy has been used in the past following surgery for adults with low-grade oligodendrogliomas. In children, radiation therapy is typically withheld whenever possible, particularly in patients 3 years of age and younger (2,55).

Despite its frequent use, the evidence supporting the efficacy of radiation therapy for low-grade oligodendroglioma is mixed. Several studies have failed to demonstrate a benefit to adjuvant radiation therapy in these patients (50,67,92,107). However, the bulk of the available literature indicates that radiation therapy prolongs survival, especially if the tumor has only been partially resected (2,38,47,82,84,85,86,105,106). For example, in the study by Gannett et al, oligodendroglioma patients treated with surgery and postoperative radiation therapy had a median survival time of 84 months versus 47 months for those treated with surgery alone (38). Yet since these patients are expected to survive a relatively long time, the potential toxicities of adjuvant radiation therapy need to be carefully considered. Detrimental effects in long-term survivors following radiation therapy have included personality changes, memory loss, dementia, hypopituitarism, and radiation necrosis with mass effect (53,67). Abnormalities of gait, coordination, and balance may also occur (35). In the series of Olson et al, which included 77 oligodendroglioma patients, 21% developed radiation therapy-induced cognitive changes and 15% developed radiation necrosis (67). However, in general, the risk of serious radiation therapy-induced sequelae is acceptably low. Strict attention to limiting the total radiation dose, daily fraction size (i.e., hyperfractionation),

4 Components of Standard "PCV" Chemotherapy (adapted from Ref. 59.)

DRUG	SCHEDULE AND DOSAGE	FREQUENCY OF DELIVERY
Procarbazine	Days 8-21: 60 mg/m ² /day, orally	
CCNU (Lomustine)	Day 1: 110 mg/m ² , orally	Every 8 weeks
Vincristine	Days 8 and 29: 1.4 mg/m ² *, IV	Every 6 weeks

*Maximum is 2.0 mg.

and the volume of normal brain irradiated using three-dimensional conformal and intensity-modulated techniques help to minimize the incidence of and severity of potential sequelae (35,43,47).

Controversy exists regarding whether radiation therapy should be administered postoperatively or reserved for later, either after chemotherapy or at the time of tumor progression (38,43,45,53,67,71,84,91). Significantly, recent studies (including a randomized trial) have indicated that delayed radiation therapy is as effective as postoperative therapy in treating low-grade oligodendrogliomas if minimal residual tumor is present (43,53). In other words, the length of survival was not found to be adversely affected if the radiation therapy was given in a delayed fashion (43,53). Thus, based on the available data, a strong argument exists for delaying radiation therapy until tumor progression is detected. The extent of residual tumor may figure into this decision; yet, since chemotherapy is likely to produce a clinical response even for low-grade oligodendroglioma (see below), one option is to postpone the use of radiation therapy in favor of chemotherapy, even when obvious residual tumor is present (16).

Regarding the use of chemotherapy for low-grade oligodendrogliomas, responses have definitely been seen in patients treated with procarbazine, lomustine (CCNU), and vincristine sulfate ("PCV" chemotherapy; see Table 4) either before or after radiotherapy (63,69,90,91,95,98). Approximately 60% to 65% of patients respond to PCV chemotherapy, with a median response duration of 1-1.5 years (45,96). Many neuro-oncologists are now giving chemotherapy before radiation therapy (i.e., "neoadjuvant chemotherapy") in order to postpone the adverse side effects of radiation therapy (described above) (16,63,68,69). As with radiation therapy, chemotherapy may be associated with clinically significant adverse effects. Numerous side effects of PCV therapy have been reported, as listed in Table 5 (8,35,41,63,98). In a report by Olson et al, 46% of

5 Reported Side Effects of “PCV” Chemotherapy

Gastrointestinal
nausea
constipation
hepatotoxicity
vomiting
abdominal pain
anorexia
Neurological
numbness or paresthesias
neuropathy
seizures
weakness
encephalopathy
intracranial hemorrhage
Hematologic
neutropenia
thrombocytopenia
General/other
fatigue
pneumonia and other infections
rash

patients treated with PCV chemotherapy developed myelosuppression (67). Temozolomide, a newer (“second generation”) alkylating agent, is currently being tested in clinical trials as an alternative or supplement to PCV chemotherapy, with promising results (16,45,96). It may be more convenient and better tolerated than other chemotherapeutic regimens. Ultimately, most oligodendroglioma patients receive both chemotherapy and radiation therapy. Patients undergoing both treatments have been reported to survive longer than patients treated with either radiation or chemotherapy alone (2,91).

POSTOPERATIVE TREATMENT FOR ANAPLASTIC OLIGODENDROGLIOMA

For anaplastic oligodendrogliomas, most authors advocate the use of postoperative radiation therapy (2,48,54,59,85), although again some studies (which usually include patients with both oligodendrogliomas and anaplastic oligodendrogliomas) have not been able to demonstrate a benefit (50,107). PCV chemotherapy (Table 4) has been shown to be effective and is currently the most commonly used chemotherapy regimen used for treating anaplastic oligodendrogliomas (8,48,69,91, 98). In the landmark study by Cairncross et al, a tumor response (i.e., size reduction) was found in 75% of recurrent anaplastic oligodendroglioma patients treated with PCV; many of the responses were judged as complete (albeit temporary) (8). Subsequent studies confirmed the efficacy of this treatment (48,69,91,98). Like low-grade oligodendrogliomas, about two-thirds of patients with anaplastic oligodendrogliomas will respond to PCV

chemotherapy, and a median response duration is 1–1.5 years (95). Chemotherapy also is being used increasingly as the first postoperative treatment for anaplastic oligodendroglioma, with radiation being delayed until tumor progression (5,35,68,69,91). The combination of radiotherapy and PCV chemotherapy is presumably superior to either treatment alone (48,91,98). It has been suggested that a time lapse of at least 1 week should separate the two treatments (35).

The question arises as to why malignant oligodendroglial cells are chemosensitive, whereas malignant astrocytes (to date) are not. Neoplastic oligodendroglial cells may have more difficulty repairing DNA damage and thus be more susceptible to cytotoxic drugs that alkylate DNA (71). Significantly lower levels of the DNA repair protein O⁶-methylguanine-DNA methyltransferase have been found in oligodendrogliomas than in astrocytic tumors (87). Another hypothesis is that p53-mediated apoptosis may be activated in oligodendrogliomas after exposure to cytotoxic agents (71). The positive response seen in oligodendroglioma patients also sheds light on the issue of whether or not systemic chemotherapy can cross the blood-brain barrier (or alternatively, whether there are adequate “gaps” in the barrier) (31,95). Chemotherapy must be able to reach malignant gliomas; otherwise, such a response (on the part of oligodendrogliomas) would not be possible.

A recurrent oligodendroglioma is often an anaplastic oligodendroglioma or glioblastoma multiforme (85,91). In the future, PET studies may be able to diagnose the tumor grade noninvasively (see above). For patients with progressive or recurrent oligodendroglioma or anaplastic oligodendroglioma, radiation and/or PCV chemotherapy is given—whichever the patient has not already received. In a recent study by Veninga et al (2001), it was concluded that reirradiation can be considered a treatment option for patients in good condition with recurrent gliomas, including oligodendrogliomas (102). Previously irradiated patients seem to be as likely to respond to PCV therapy as those who have not received radiation therapy (5). PCV chemotherapy has been used with some response even when there has been leptomeningeal seeding (91). In a recent report, “intensified” PCV therapy with stem cell support was used to treat six patients with recurrent or progressive anaplastic oligodendrogliomas; two of the six patients had a complete response and four of six had a partial response, with progression-free survival lasting from 18 to >39 months (110). Patients with recurrences who have not received PCV chemotherapy are likely to re-

respond to PCV, even if they have been given other agents. Relapses usually occur in 12-34 months (72,90). A second course of PCV may or may not be beneficial (72,91).

Carboplatin has been used to treat recurrent oligodendroglioma with some responses (37), as has etoposide (VP-16) and cisplatin (72,91). Oligodendroglial tumors also have been shown to be partially sensitive to other second-line chemotherapeutic agents, including melphalan, thiotepa, paclitaxel, and other nitrosoureas (14,71,91,105). High-dose thiotepa with bone marrow or peripheral blood stem cell transplantation has been attempted with some responses but also significant toxicity (9,21,68). Interferon- β has been used in the treatment of anaplastic oligodendrogliomas (105). Second-line or "salvage" chemotherapy treatments, which are attempted after standard treatment (i.e., PCV) have failed and are in need of further study. Temozolomide has been used with some success as "salvage" chemotherapy for patients with recurrent anaplastic oligodendrogliomas (16,17,97,99).

CONCLUSIONS

Over the past decade, advances in imaging, surgical technique, histologic diagnosis, radiation delivery, and chemotherapy have combined to improve the prognosis for patients with oligodendroglioma and anaplastic oligodendroglioma. Advances linking imaging to the operating room, including the use of frameless stereotaxy and fMRI, have provided surgeons with additional tools for increasing the extent of surgical resection and reducing operative morbidity. The possible utility of radiosurgery, for instance, in a patient with a local recurrence of an oligodendroglioma is still an open question.

In the past, fractionated radiation therapy was the main nonsurgical treatment for patients with oligodendrogliomas. While radiation still plays a role, its use has changed for two reasons. First, patients having either oligodendroglioma or anaplastic oligodendroglioma are likely to respond to chemotherapy. The observation that oligodendrogliomas are chemosensitive has been one of the more significant developments in "medical" neurooncology in recent years. Standard chemotherapy has consisted of "PCV," but other agents, especially temozolomide, are currently being tested. Second, studies have seemed to indicate that patients receiving delayed radiation fare as well as those receiving it postoperatively. Increasingly, therefore, given the potential for adverse side effects, radiation therapy is being delayed until tumor recurrence, especially if a gross total tumor resection has

been achieved. Until additional studies settle this issue, the timing of radiation therapy should be made on a case-by-case basis, considering factors including the extent of resection; the location of the tumor; and the patient's age, functional status, and occupation.

While it is better to achieve a gross total resection of an oligodendroglioma, given the expected response to chemotherapy, aggressive initial surgical resection in areas entailing significant risk of neurologic deficit should probably be avoided. Our philosophy is to perform the maximal safe resection, utilizing every available surgical tool. Even with aggressive multimodality therapy and the improved survival times, oligodendrogliomas ultimately are expected to recur, and malignant progression at the time of recurrence is common. Additional clinical trials are needed for patients with recurrent, progressive, and/or anaplastic oligodendrogliomas and given the clear differences in biology and response to treatment, such studies should no longer group oligodendrogliomas with other types of gliomas (35,95). In the near future, it is hoped that continued advances such as expanded use of PET data, improved molecular characterization, and more effective and less toxic chemotherapeutic agents will produce further clinical improvements for these patients.

The authors sincerely thank Dr. Marc Chamberlain (University of Southern California) for his review of the manuscript and Dr. Fady Charbel (University of Illinois, Chicago) for contributing Figure 3. Dr. Stelea is a Visiting Scholar in The Department of Neurosurgery at the University of Illinois, Chicago.

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