

Supratentorial Low-Grade Astrocytomas in Adults

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Summary: Approximately one-third of newly diagnosed primary glial tumors in adults are low-grade astrocytomas. With the development of more sensitive radiological techniques, these tumors are being detected earlier in their history, and thus the patients often have minimal or no neurological impairment. Low-grade astrocytomas are thought to have a good prognosis. However, their clinical behavior is variable and they often dedifferentiate to a more aggressive, high-grade glioma. Because of the lack of prospective, randomized studies, the role of surgery and radiation in the management of these lesions is controversial. We review the pathology, history, and clinical and radiological characteristics of low-grade astrocytomas and the clinical studies that examine the role of surgery and radiation therapy. Based on this review, the following recommendations are made: (1) treatment should be based on the histological type (astrocytoma, pilocytic astrocytoma, and gemistocytic astrocytoma); (2) magnetic resonance imaging is the modality of choice for diagnosis and surgical planning; (3) radical total resection should be attempted whenever safely possible; (4) multiple biopsies should be examined pathologically to avoid sampling errors; (5) patients with the astrocytoma histologic type who have a total resection can be followed clinically and with frequent magnetic resonance imaging scans, whereas those who have a subtotal resection should receive adjuvant radiation therapy in a conventional fractionated schedule with a dose of 4,500 to 5,500 rad to a limited volume of brain; (6) complete resections of pilocytic astrocytomas may be curative; (7) the benefit of radiation in patients with subtotally resected pilocytic astrocytomas is not well defined; (8) patients with gemistocytic astrocytomas should receive adjuvant radiation therapy regardless of the extent of resection, because of the high incidence of dedifferentiation to a high-grade glioma in these patients; and (9) lesions discovered as incidental findings can be managed conservatively by serial radiological observations. **Key Words:** Low-grade astrocytoma—Gemistocytic astrocytoma—Pilocytic astrocytoma—Radiation therapy.

In 1926, Bailey and Cushing (1) classified gliomas according to their histologic characteristics and correlated this classification with prognosis. Six years later, in Cushing's review of 2,000 brain tumors, he identified 164 cases of astrocytoma where the prog-

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nosis was better than for the glioblastoma multiforme (2). Over the next 20 years, numerous authors (3-9) reported their experience with what became known as benign or relatively benign astrocytoma. Today this "benign" astrocytoma is called "low-grade astrocytoma." The management of this tumor remains a controversial topic in neurosurgery.

About 50% of all new brain tumors diagnosed

each year are primary glial tumors. Of these, 30–40% are classified as low-grade astrocytomas. With improved neuroimaging, these tumors are detected and diagnosed earlier in the course of the disease. With earlier detection, the typical patient tends to be young with minimal or no neurologic impairment; often a seizure is the only symptom. We will explore the optimum treatment for these young, actively employed adults to maximize survival and quality of life.

The treatment options in low-grade astrocytoma include surgery and radiation therapy. Among surgical options, the effect of total gross removal, subtotal removal, or biopsy alone on survival is unclear. Similarly, the need for radiation therapy and whether it should be given postoperatively or at the time of recurrence remains subject to individual preferences. The persistence of these issues for 30 years can be attributed to the lack of long-term prospective studies evaluating therapies in a controlled manner. Therefore, we have to rely on retrospective reviews of varied clinical experiences to find general trends for optimal management of patients with low-grade astrocytomas. Morantz (10), in a recent review of the role of radiation therapy in cerebral astrocytoma, pointed out the difficulties in interpreting the available retrospective studies. Patient characteristics vary in terms of age, location of tumor, neurologic status, and extent of resection. Radiation treatment varies with respect to total dose, field size, and duration of therapy. We herein review what is currently understood about low-grade astrocytomas and provide guidelines for optimizing patient management.

PATHOLOGY

Accurate pathological diagnosis is critical in managing the patient with a low-grade astrocytoma. Within this general category, two histologic types, pilocytic and gemistocytic astrocytomas, behave differently and therefore need to be treated differently. Moreover, in many retrospective reviews (11–15), a significant percentage of tumors initially diagnosed as low-grade astrocytoma based on pathological examination are upgraded on reexamination to anaplastic astrocytoma or glioblastoma multiforme. Such patients are thus denied treatment that is more appropriate for high-grade tumors, that

is, systemic chemotherapy (16) or local treatments (17,18).

The Kernohan et al. classification (19) divides patients with gliomas into four grades; in this system, grades 1 and 2 are considered to be low-grade astrocytomas. The World Health Organization (WHO) (20), Burger and Vogel (21), Nelson et al. (22), Ringertz (23), and Rubinstein (24) classification systems divide gliomas into three categories: astrocytoma, anaplastic astrocytoma, and glioblastoma multiforme. In these three-tiered systems, low-grade astrocytomas are designated "astrocytoma." As pathologists may use any of these classification schemes, it is important to be familiar with all of them.

The Kernohan et al. system (Table 1) separates low-grade astrocytomas into two grades. Grade 1 tumors have an increased density of normal-appearing astrocytes. Tumors are classified as grade 2 when the cells show pleomorphism and hyperchromatism. The transition from grade 2 to grade 3 occurs when vascular endothelial proliferation is present. The significance of dividing low-grade astrocytoma into grades 1 and 2 has never been established. Daumas-Dupont et al. (25) from the Mayo Clinic, and others (23,26–29) have shown no survival difference between the two grades. Hence, many institutions have adopted one of the three-tiered systems described in Table 2, all of which use similar histologic criteria.

The low-grade tumors are mildly hypercellular with mild nuclear pleomorphism, rare mitoses, and no vascular endothelial proliferation (Fig. 1). Microcysts are commonly present. Evidence of vas-

TABLE 1. *Kernohan et al. (19) classification of astrocytic tumors*

Grade	Criteria
1	Increased cell density, no mitoses, no endothelial proliferation, no cellular pleomorphism
2	Appearance of pleomorphic changes in cells, increased cell density, no mitoses, no endothelial proliferation
3	Anaplastic changes found in at least half of cells in each microscopic field, mitoses present, increased cellularity, some endothelial proliferation, some regional necrosis
4	Cells demonstrate extensive anaplastic changes, marked increased cellularity, numerous mitoses, marked endothelial proliferation, and extensive necrosis

TABLE 2. *Histologic criteria of three-tiered astrocytic tumor classifications*

	Astrocytoma	Anaplastic astrocytoma	Glioblastoma
WHO classification (20)	Composed of normal fibrillary, protoplasmic, or gemistocytic astrocytes	Composed primarily of cells recognized as astrocytes, but areas of anaplastic transformation are present	Anaplastic-appearing glial tumor, high cellularity, necrosis with pseudopalisading
Ringertz classification (23)	Cells resemble normal astrocytes with mild nuclear abnormalities, infiltrative growth pattern, moderate hypercellularity	Infiltrative astrocytic tumor, moderate pleomorphism, mitoses, and vascular proliferation; no necrosis	High cellularity, frequent mitoses, marked pleomorphism, increased vascularity, and necrosis
Rubinstein classification (24)	Includes astrocytes, mild increase in cellularity, nuclear enlargement, and hyperchromasia; no necrosis or endothelial proliferation	Increased cellularity, nuclear irregularities, and hyperchromasia; vascular proliferation and mitoses present	Highly cellular; nuclear pleomorphism; many mitoses; endothelial proliferation; necrosis
Nelson et al. classification (22)	Cells resemble mature astrocytes; moderate increase in cell density; mitoses rare	Increased cellularity; cellular and nuclear pleomorphism; increased mitoses; vascular prominence; no necrosis	Features of anaplastic astrocytoma plus necrosis
Burger and Vogel classification (21)	Astrocytic tumor; mildly hypercellular; mild pleomorphism; no vascular proliferation or necrosis	Moderate hypercellularity and pleomorphism; vascular proliferation; no necrosis	Moderate to marked hypercellularity and pleomorphism; vascular proliferation; necrosis with or without pseudopalisading is key feature

cular endothelial proliferation indicates anaplastic characteristics and results in upgrading the tumor to a high-grade glioma.

Within the low-grade astrocytoma category, as stated above, pilocytic and gemistocytic astrocytomas should be considered separately because of their distinct clinical behavior. Pilocytic astrocytomas occur typically in children and are unusual in adults. There have been several reports (30–34) of pilocytic astrocytomas, both juvenile and adult type histology, occurring supratentorially in adults. Histologically, juvenile-type lesions are loosely structured and are composed of a mixture of bipolar and stellate astrocytes (21) (Fig. 2). Microcysts are often but not always present. The adult type, which consists primarily of elongated, bipolar cells, usually lacks microcysts and often contains calcifications. A characteristic feature of both adult- and juvenile-type tumors is the presence of conspicuous dark-staining bodies, called Rosenthal fibers (Fig. 2). Vascular endothelial proliferation is often a prominent finding in pilocytic astrocytomas (21), but, in contrast to other astrocytomas, this does not represent anaplastic change. Indeed, the pilocytic astrocytoma has the best prognosis of all low-grade astrocytomas in adults (32–35).

Gemistocytic astrocytomas are composed primarily of large plump astrocytes with abundant eosinophilic cytoplasm and one or more eccentric nuclei (21) (Fig. 3). They are regarded as a variant of the fibrillary astrocytoma. In the Kernohan et al. grading system (19), gemistocytic astrocytomas are classified as grade 2. Numerous series have demonstrated a poor prognosis for patients with these tumors since the tumors have a tendency to dedifferentiate into anaplastic astrocytoma or glioblastoma multiforme. In a recent review of the experience at the University of California at San Francisco, Krouwer et al. (36) found a 5-year survival rate significantly lower than that for other low-grade astrocytomas (23.8 vs. 50–60%). Low-grade astrocytic tumors with at least 20% gemistocytes were included in the group of patients with a poor prognosis. Based on these findings, Krouwer et al. (36) proposed that gemistocytic tumors should be classified and treated as anaplastic rather than low-grade astrocytomas.

CLINICAL FEATURES AND NATURAL HISTORY

The peak incidence of low-grade astrocytomas in adults is between ages 20 and 50. Males are affected

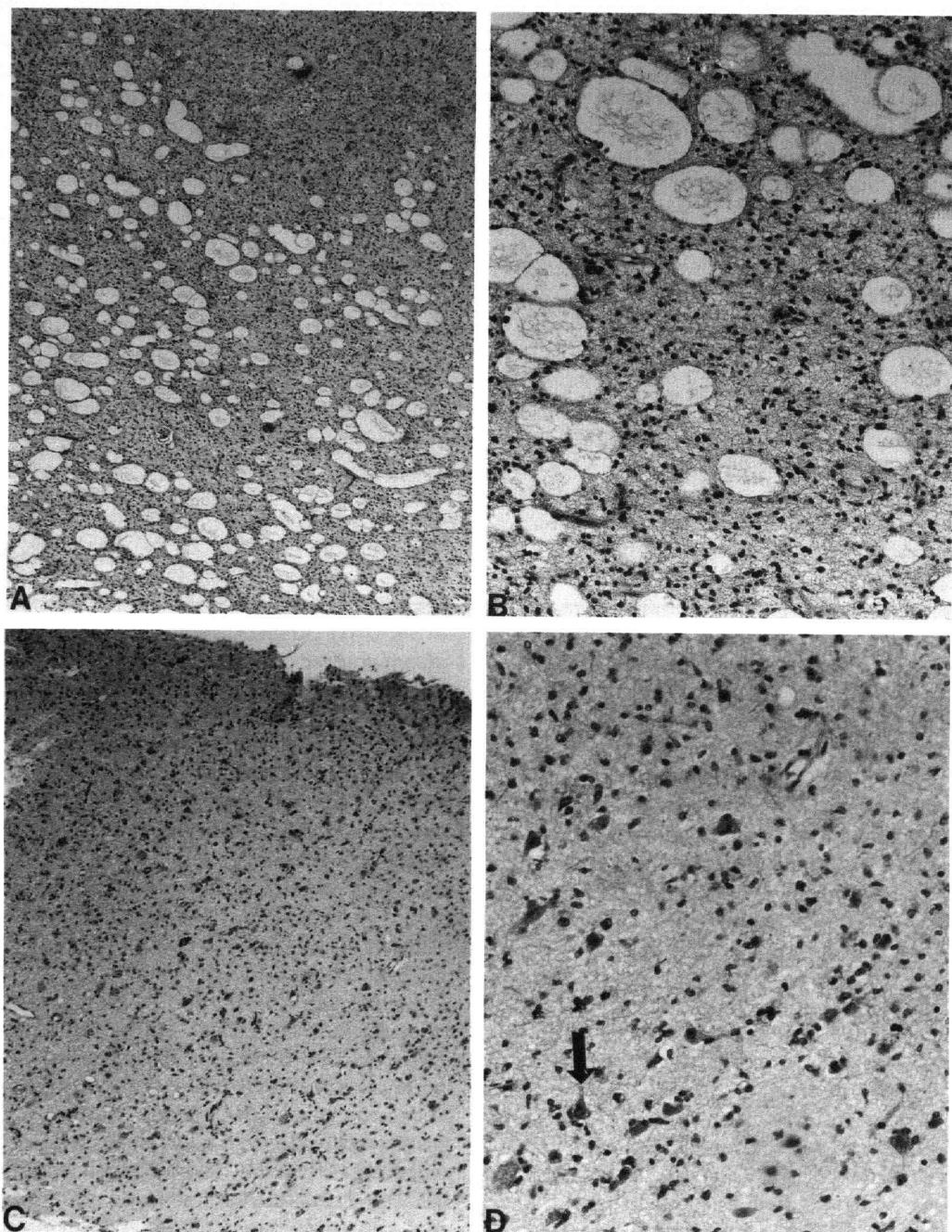


FIG. 1. Photomicrographs of two cases of low-grade astrocytoma. A: Case 1: mildly hypercellular specimen with obvious microcysts. Microcysts are a common finding in low-grade astrocytomas and are believed to represent a slow-growing lesion (H&E, $\times 4$). B: Case 1: higher magnification. Note the relatively uniform nuclei with no mitoses evident (H&E, $\times 16$). C: Case 2: area showing diffuse infiltration of cells. No evidence of vascular proliferation or necrosis is seen (H&E, $\times 4$). D: Case 2: higher magnification. Note relatively uniform nuclei and the perineuronal satellitosis (arrow) by the tumorous astrocytes (H&E, $\times 16$).

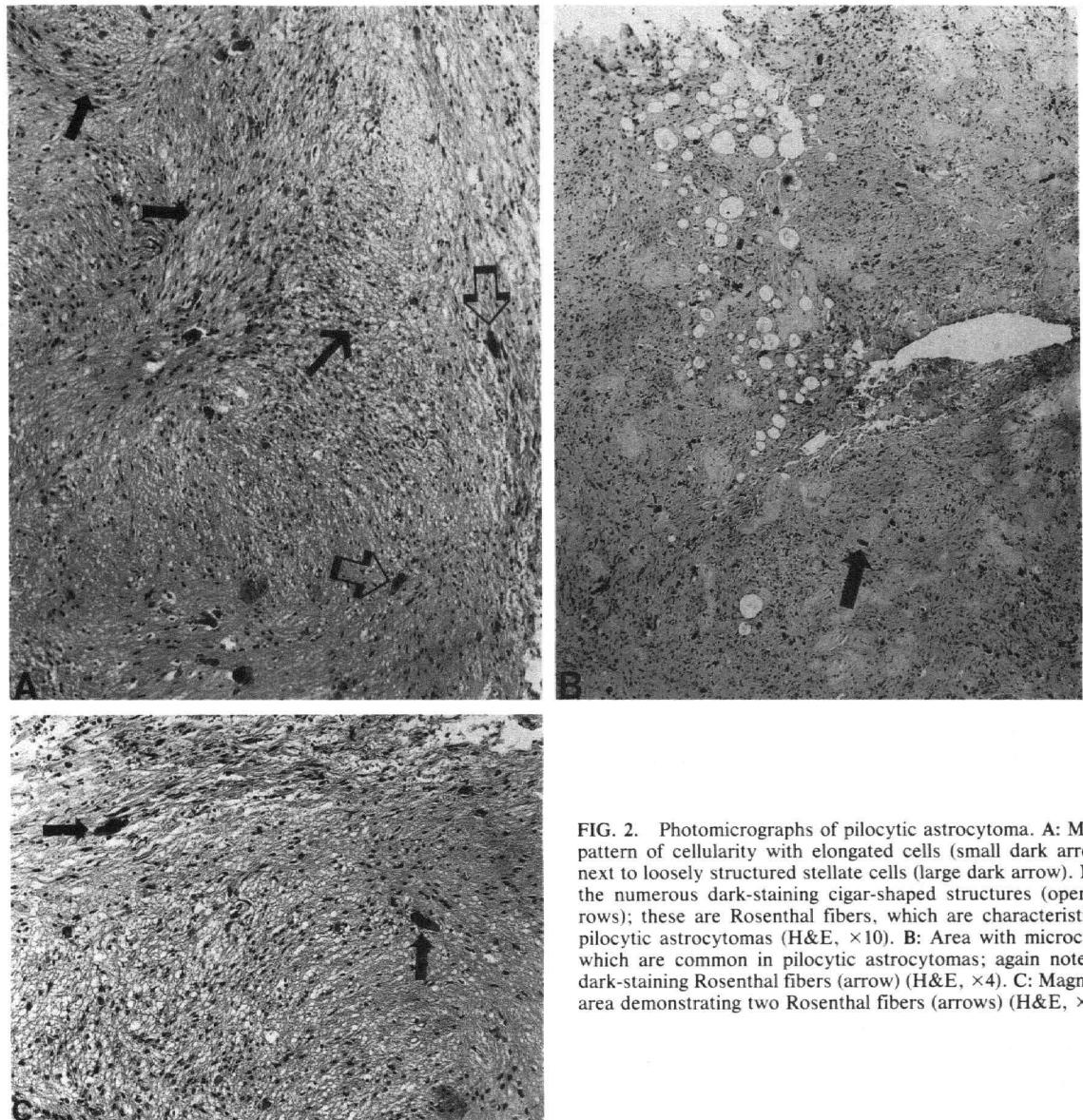


FIG. 2. Photomicrographs of pilocytic astrocytoma. **A:** Mixed pattern of cellularity with elongated cells (small dark arrows) next to loosely structured stellate cells (large dark arrow). Note the numerous dark-staining cigar-shaped structures (open arrows); these are Rosenthal fibers, which are characteristic of pilocytic astrocytomas (H&E, $\times 10$). **B:** Area with microcysts, which are common in pilocytic astrocytomas; again note the dark-staining Rosenthal fibers (arrow) (H&E, $\times 4$). **C:** Magnified area demonstrating two Rosenthal fibers (arrows) (H&E, $\times 16$).

slightly more frequently than females. These tumors are distributed between the different lobes according to their relative masses. Thus, low-grade astrocytomas are most common in the frontal lobe followed by the temporal, parietal, and occipital lobes. Other supratentorial locations include deeper structures such as the thalamus, hypothalamus, suprasellar region, and lateral ventricles. Locations

outside the supratentorial compartment include the cerebellum, brainstem, and spinal cord.

As with most intracranial lesions, symptoms of low-grade astrocytomas on presentation are site-specific. The most common symptoms are headache and seizure. Headaches, which are generally interpreted as a sign of increased intracranial pressure in patients with brain tumors, are usually site-

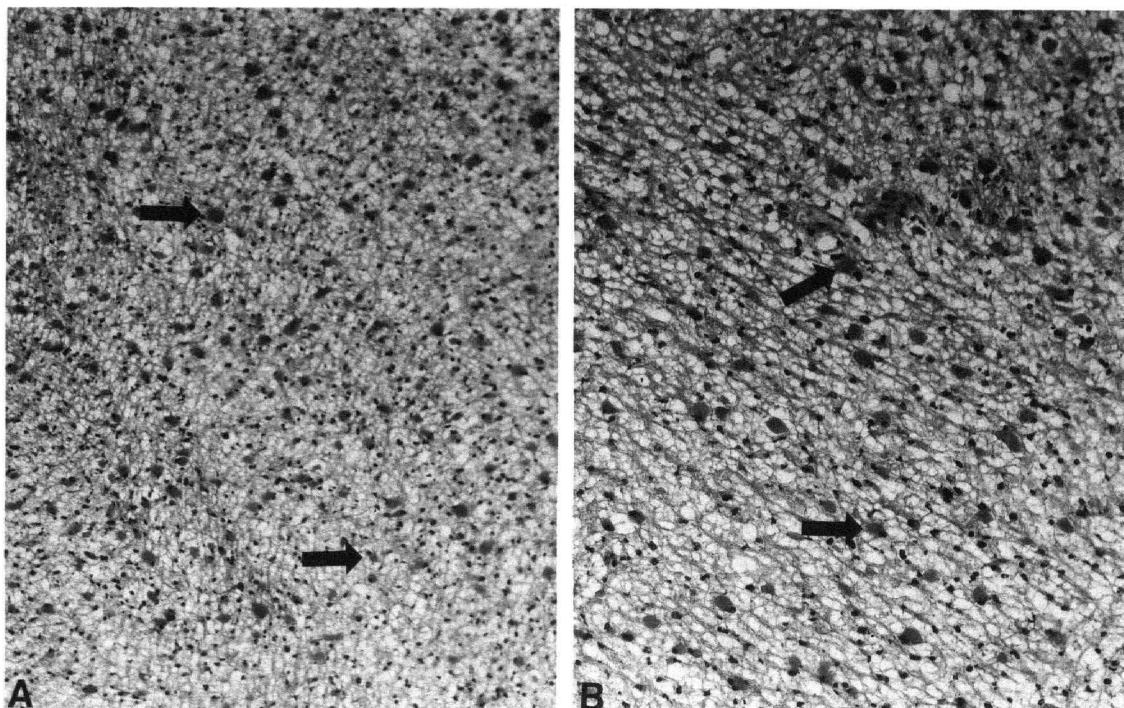


FIG. 3. Photomicrographs of a gemistocytic astrocytoma. A: Mildly increased cellularity with prominence of large cells, which are the gemistocytes (arrows) (H&E, $\times 10$). B: Higher magnification of gemistocytes (arrows). The gemistocyte is characterized by eccentrically placed nuclei and abundant glassy eosinophilic cytoplasm (H&E, $\times 16$).

specific in low-grade astrocytomas and are thought to be due to stretching of the dural nervous fibers overlying the affected brain. Seizures (focal, complex partial, or generalized) are the presenting symptom in as many as 65% of patients, and they are often helpful in localizing the site of the tumor. Objective neurologic deficits have been reported in up to 40% of patients at presentation, and these are related to the area of the brain where the lesion is located. An increasing number of these tumors are being discovered by modern imaging techniques in patients who are asymptomatic for the tumor itself but are being evaluated for migraine headaches or head trauma.

The natural history of these tumors is quite variable. For example, it is not unusual for a patient to have a long history of seizures prior to the diagnosis of a low-grade astrocytoma at the site of the seizure focus. On the other hand, in spite of a benign-appearing tumor, some patients follow a course similar to patients with high-grade gliomas. Indeed, in some cases both the radiologic and pathologic

characteristics change to those of high-grade glioma. Furthermore, radiation treatment frequently brings about a transient breakdown of the blood-brain barrier, which makes it difficult to distinguish malignant degeneration from changes expected from treatment. However, enhancement that is secondary to the radiation will resolve, whereas enhancement due to malignant degeneration will progress. The reason for the variability in behavior is not completely understood.

Growth kinetics and cell proliferation have been studied to explain the heterogeneity in tumor behavior. To calculate the percentage of cells proliferating in low-grade and high-grade gliomas, Zuber et al. (37) used an antibody against a nuclear antigen that is expressed specifically in proliferating cells. They found a significant difference in the percentage of proliferating cells, called the "labeling index," in low-grade astrocytomas (mean = 1.0%) compared with anaplastic astrocytomas (mean = 3.5%) and glioblastomas (mean = 11.1%). Two subgroups were identified within the low-grade group:

60% of the cases had a labeling index of less than 0.1% of cells and the remaining 40% had a labeling index of greater than 0.1%. The length of follow-up was insufficient for the authors to determine whether the difference in the labeling index reflected a different prognosis.

Hoshino et al. (38) used a monoclonal antibody against bromodeoxyuridine, which labels cells in the synthetic phase, to study the proliferative potential of low-grade astrocytomas. They identified two groups of tumors, those with greater than 1% labeling and those with less than 1% labeling, and found that the tumors with the higher labeling index had a significantly higher recurrence and mortality rate. From these results, they concluded that low-grade astrocytomas are not biologically uniform and that labeling of greater than 1% indicated a more aggressive tumor and poorer prognosis.

Dedifferentiation, the change of a slow-growing astrocyte to a rapidly proliferating astrocyte, within a low-grade astrocytoma has also been proposed to explain the heterogeneity of these tumors. Low-grade astrocytomas are thought to contain many noncycling cells. Hoshino (39) evaluated the growth within gliomas by administering ^3H -thymidine i.v. before resection. The ^3H -thymidine labels the DNA that is replicating. As the cell continues to divide, the ^3H -thymidine is diluted and becomes undetectable. Tumor tissue obtained at autopsy was examined for residual ^3H -thymidine-labeled cells. Low-grade astrocytomas harbored labeled cells 2.5–7 years after being injected with ^3H -thymidine, indicating that these cells had left the cycling pool. This suggests that low-grade astrocytomas biologically grow at a very slow rate and that the well-established progression of a low-grade astrocytoma to a high-grade glioma (11–14) is not an inherent characteristic of the cell that makes up the low-grade astrocytoma. Rather, the malignant change appears to be the result of dedifferentiation. In support of this concept, Muller et al. (12) reported a series of patients whose initial pathological diagnosis was low-grade astrocytoma. At the time of recurrence, 14% of the cases remained low-grade, 55% had progressed to anaplastic astrocytoma, and 30% had progressed to glioblastoma. The average time to recurrence was 31 months.

An alternative explanation for progression in grade of low-grade astrocytomas is that, because of sampling errors, the area of the tumor examined did

not include the area with anaplastic characteristics. In support of this, Scherer (8) studied at autopsy the hemispheres of 18 patients purportedly with low-grade astrocytomas. He found 13 patients with foci of anaplasia. Similarly, Russell and Rubinstein (40) examined 55 autopsy cases of patients previously diagnosed with low-grade astrocytoma and found that 53% of these cases had areas of anaplastic change. Whether sampling error or dedifferentiation explains the anaplastic change cannot be definitively known. In either case, the importance of these findings is their effect on patient management. Since residual tumor can become more aggressive, if residual tumor is present, further therapy should be directed toward preventing progression or expression.

RADIOLOGICAL CHARACTERISTICS

Computed tomography (CT) and magnetic resonance imaging (MRI) have revolutionized the diagnosis of intracranial masses. Their impact on low-grade astrocytoma is earlier detection and better delineation in patients with minimal symptoms.

On CT, low-grade astrocytomas are classically hypodense with minimal surrounding edema or mass effect (Fig. 4). When contrast is administered 60–70% of these tumors will not enhance (41). The prognostic significance of enhancement in these tumors, which is due to breakdown of the blood-brain barrier, is not clear. Since enhancement almost always occurs in high-grade gliomas, enhancement in low-grade gliomas has been correlated with more aggressive, malignant tumors. Corroborating this, Piepmeier (42) in 1987 found in his review of low-grade astrocytomas that enhancement carried a poor prognosis. His group included children and adults with astrocytomas, pilocytic astrocytomas, and mixed astrocytomas-oligodendroglomas. In contrast, however, Silverman and Marks (43) reviewed 22 patients with low-grade astrocytomas diagnosed between 1974 and 1977. These patients all had subtotal resections and received 5,000–6,000 rad postoperatively. Eight of the 22 patients had enhancement on the preoperative CT scan. At the 4-year follow-up, no significant differences in survival were found between the enhancing and non-enhancing groups. With these two opposite conclusions, no definitive statements can be made regarding the prognostic value of enhancement.

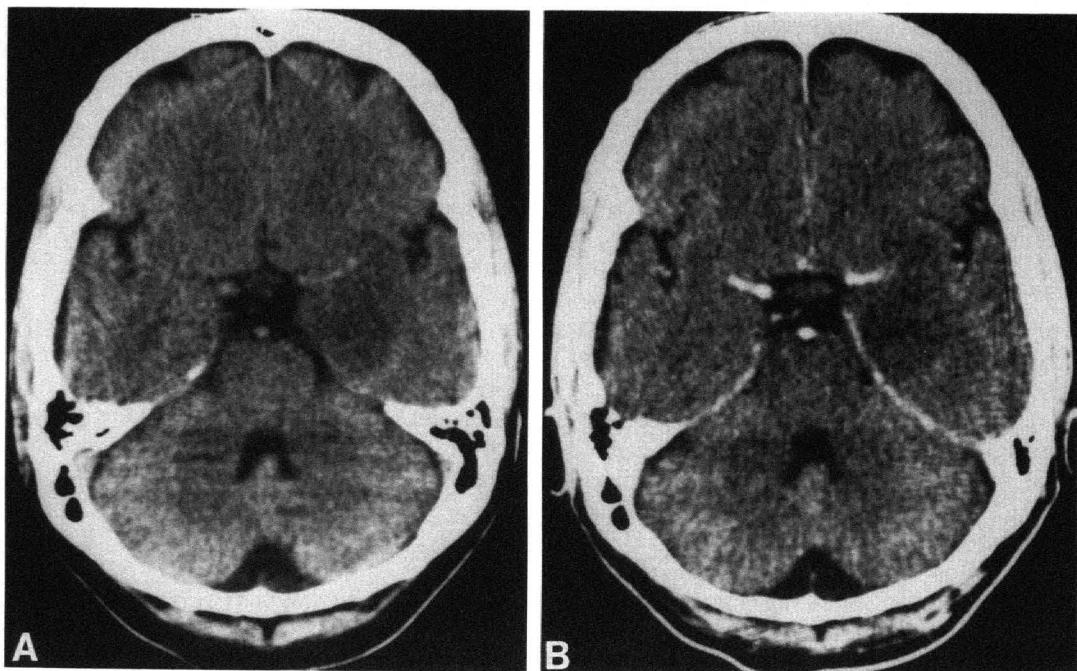


FIG. 4. Axial CT images of low-grade astrocytoma. A: Noncontrast scan demonstrating low-density area in left medial temporal lobe with minimal mass effect. B: Enhanced CT image showing no enhancement of the tumor.

Because of the lack of enhancement on CT, MRI has been very helpful in delineating these lesions. Characteristically, the lesions are isodense or hypodense to surrounding brain on T1-weighted images (44,45) and bright on T2-weighted images (Fig. 5). As in CT, there is minimal mass effect or surrounding edema. Because gadolinium is more sensitive than CT contrast, a higher percentage of these tumors will enhance on MRI than on CT. The enhancement pattern with gadolinium is usually patchy and irregular (46,47). Axial, coronal, and sagittal projections are useful to localize the mass and plan the best surgical approach. Kelly et al. (48) demonstrated, using serial stereotactic biopsies, that isolated tumor cells extend at least as far as the high signal on the T2-weighted image. Since contrast enhancement cannot delineate many of these lesions, MRI is the neuroimaging modality of choice to assess the extent of resection and to follow the patient for recurrence or progression.

In contrast to diffuse astrocytomas, pilocytic astrocytomas characteristically show strong enhancement on both MRI and CT (Fig. 6) (49). Pilocytic astrocytomas are usually sharply demarcated and appear isointense or hypointense on noncontrast

CT or T1-weighted MRI images and hyperintense on T2-weighted images. These tumors may be solid or have an associated cyst. The majority of pilocytic astrocytomas arise in the area of the third ventricle, but they can be found in the cerebral hemisphere.

With the availability of CT and MRI, cerebral angiography, once considered the test of choice in the diagnosis of astrocytomas, is rarely used today. Angiography is still occasionally utilized to visualize the superficial cortical veins in preparation for a particular surgical approach or to outline major intracranial vessels when an intimate relationship of the tumor with those vessels is suspected. In the future, MRI angiography may provide this information noninvasively.

Positron emission tomography (PET) can provide additional information on the biological nature of astrocytomas and may aid in distinguishing different grades of tumor. $[^{18}\text{F}]$ Fluorodeoxyglucose (FDG) has been used to investigate the metabolic activity of low-grade and high-grade astrocytomas. Low-grade astrocytomas are characteristically hypometabolic. Although DeChiro et al. (50) demonstrated that FDG can distinguish grades 1 and 2

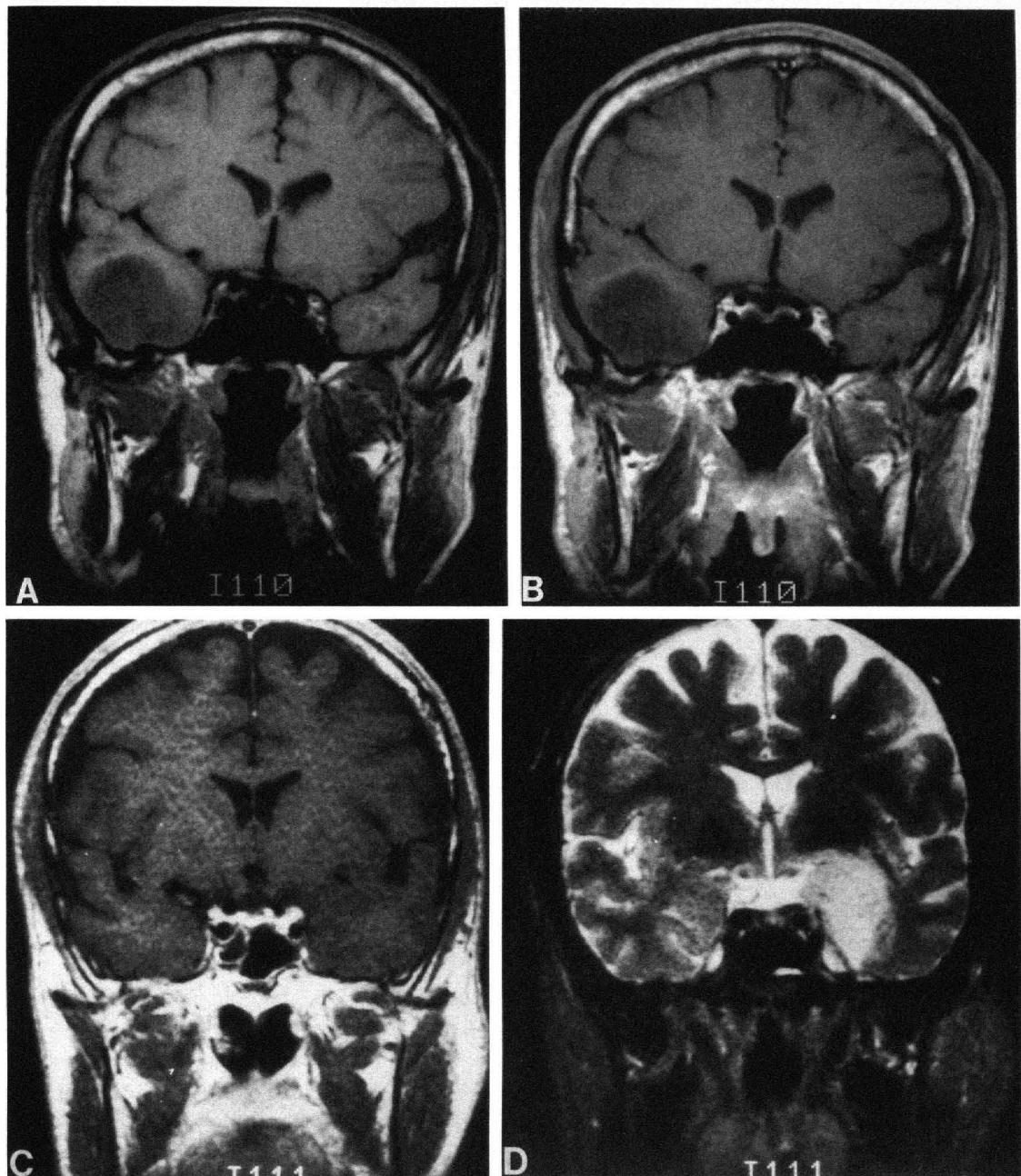


FIG. 5. MRI scans of low-grade astrocytoma. A: Case 1: noncontrast, T1-weighted image of right temporal lobe mass. Note the low density of the lesion, with no mass effect. B: Case 1: T1-weighted image after administration of gadolinium, demonstrating no enhancement. C: Case 2: T1-weighted image demonstrating left-temporal-lobe hypodensity with no mass effect. D: Case 2: T2-weighted image demonstrating the characteristic bright signal outlining the tumor.

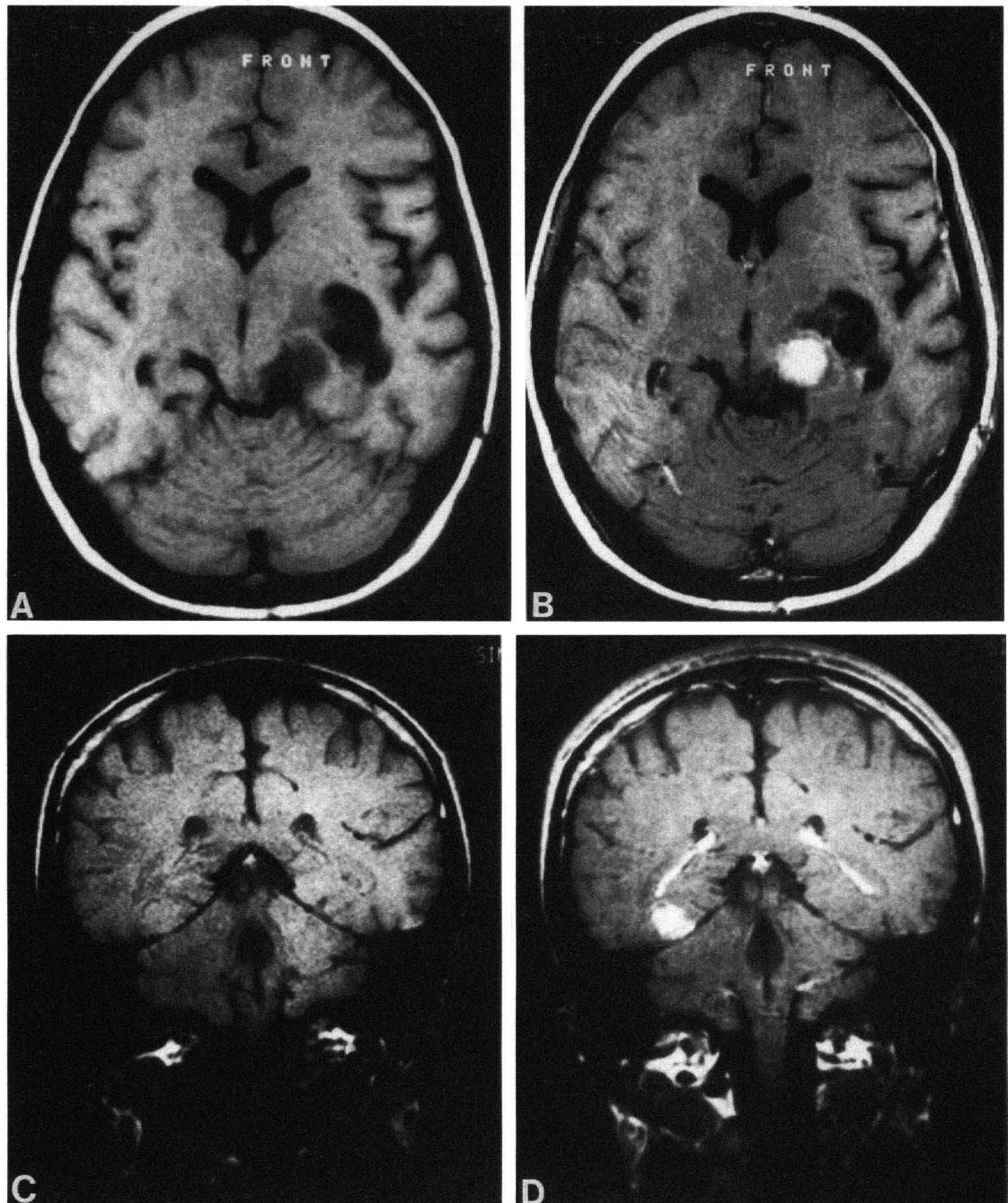


FIG. 6. MRI scans of pilocytic astrocytoma. A: Case 1: noncontrast T1-weighted image demonstrating a hypodense area in the left thalamic region. B: Case 1: gadolinium-enhanced T1-weighted image demonstrating strong enhancement of the tumor. C: Case 2: noncontrast T1-weighted image demonstrating the isodensity of this posterior temporal tumor. D: Case 2: gadolinium-enhanced T1-weighted image demonstrating strong enhancement of the tumor.

tumors from grades 3 and 4 tumors, the prognostic implications of PET scanning in low-grade astrocytomas remain to be determined. Francavilla et al. (51) used PET with FDG in 12 patients whose astrocytomas progressed from low grade to high grade. All patients had focal areas of hypermetabolism within the tumor similar to the hypermetabolism found in high-grade tumors. Three of the 12 patients had PET scans with FDG before the progression of their tumors. The initial scans in these three patients showed a hypometabolic tumor without areas of hypermetabolism. Thus, the progression from low-grade to high-grade astrocytoma resulted in a portion of the tumor changing its metabolic activity. Serial PET scanning with FDG may be useful for monitoring these patients for tumor progression to a higher grade. PET may also play a role in managing patients with lesions discovered as incidental findings. If an FDG PET study were consistent with a high-grade lesion, the threshold for diagnostic and therapeutic intervention would be lower.

TREATMENT: INSIGHTS FROM THE LITERATURE

Therapy can have an impact on the outcome of patients with low-grade astrocytomas, but the extent and type of treatment are not well-defined. In this section, the available literature on treatment for supratentorial low-grade astrocytomas in adults is reviewed. The histologic types, pilocytic and gemistocytic astrocytomas, are addressed separately.

Astrocytoma

In 1966, Uihlein et al. (52) reviewed 88 patients from the Mayo Clinic diagnosed with grade 1 or 2 astrocytomas between 1955 and 1959, all of whom had subtotal resections. They found no difference in survival at 5 years between those who received radiation and those who did not. However, when the group receiving radiation was divided into greater or less than 3,500 rad, the 5-year survival in the group receiving higher doses was significantly better. This suggested that the amount of radiation administered is important.

Leibel et al. (53) reviewed the experience at the University of California at San Francisco with treat-

ment of low-grade astrocytomas treated between 1942 and 1967. Of 147 patients, 100 had tumors in the cerebrum; the majority of these occurred in the fourth and fifth decades of life. Leibel et al. found a significant benefit to administering 5,000–5,500 rad to patients who had subtotal resection (35 vs. 23% 5-year survival in nonirradiated group). Fourteen of the 147 patients were thought to have had a complete resection; of these, three were adults who remained free of disease at 8, 12, and 12.5 years postoperatively.

Laws et al. (11) reviewed the Mayo Clinic experience with low-grade astrocytomas from 1935 to 1964. Of 461 patients, 409 were adults (>20 years old). The 5-year survival for patients 0–19 years old was 83%; for patients 20–49 years old, it was 35%; and for patients older than 50 years, it was 12%. These results emphasize the importance of distinguishing adults from children when considering prognosis and treatment options; studies that include adults and children will give the false impression that adults have a better survival than occurs in reality. Laws et al. found that gross total removal (5-year survival = 61%) was better than subtotal removal (5-year survival = 44%) or biopsy alone (5-year survival = 32%). Radiation therapy was not strongly associated with improved survival. However, patients receiving more than 4,000 rad (5-year survival = 49%) survived longer than the combined group of patients receiving less than 4,000 rad or no radiation (5-year survival = 34%).

Medberry et al. (54) reported the results on 50 adult patients with low-grade astrocytomas treated with radiation at the Naval Hospital (Bethesda, MD, U.S.A.) during the years 1960–1986. Eight patients had a gross total removal, 30 patients had a subtotal resection, and 12 patients had biopsy only. Doses of radiation varied between 3,420 and 6,480 rad. Actuarial survival rates for the entire group were 45% at 5 years and 32% at 10 years. Medberry et al. found that survival decreased with each decade of life, with the most notable decrease in patients over 40 years old. Radiation doses greater than 5,000 rad were associated with better outcomes. In this group of patients, all of whom received radiation, extent of surgical resection did not influence survival. Interestingly, 10 patients were treated with surgery alone during the time of this review but were not included in the paper; 6 of these 10 patients underwent gross total removal.

One of these six died of intercurrent disease at 68 months. The other five are all alive 6.5–21.5 years later. The four patients who had incomplete resections and no radiation all died within 6 years.

Soffietti et al. (14) reported 85 low-grade astrocytomas in adults who underwent surgery between 1950 and 1982 at the University of Torino in Italy. The extent of resection was studied according to surgeon's description of total removal (100% of tumor volume), subtotal removal (greater than 50%), partial removal (less than 50%). Patients in whom only a biopsy was performed were not included in the study. The patients who had a total resection (19 of 85) had a 5-year survival of 51%, while those with a subtotal resection (49 of 85) had a 5-year survival of 23.5%. Those with partial removal (13 of 85) had a 5-year survival of 0%. Only 32 patients had radiation treatment, and 21 of them received less than 4,000 rad. The extent of resection in these 32 patients was not provided. At 3 years, survival was better in the small group receiving more than 4,000 rad than in the group receiving less than 4,000 rad and the group receiving no radiation. Twenty-four patients had a histologically proven recurrence; 79% of these had progressed to either anaplastic astrocytoma or glioblastoma multiforme. Soffietti et al. concluded that the extent of resection was important and proposed that the rationale for radiation therapy was to destroy undetected anaplastic foci or prevent dedifferentiation.

Shaw et al. (35) reported the Mayo Clinic experience with low-grade astrocytoma from 1960 to 1982. Patients of all ages as well as those with pilocytic astrocytomas were included. Of 167 patients, 126 had nonpilocytic astrocytomas; more than 90% of these were adults. Survival rates were similar regardless of the extent of resection, with 52% 5-year survival and 23% 10-year survival. Survival was improved with high-dose radiation, and the following respective 5- and 10-year survival rates were obtained: for patients receiving more than 5,300 rad, 68 and 39%; less than 5,300 rad, 47 and 21%; no radiation, 32 and 11%. Twenty-three patients had gross total or radical subtotal resection; of these, 19 had tumor progression and died. The pathology of the recurrences was not reported.

Piepmeier (42) in 1987 reported on 60 patients with supratentorial low-grade astrocytomas treated at Yale-New Haven Hospital between the years 1975 and 1985. This collection of patients was the

most recent group reported up until 1987. CT scanning was used for diagnosis, preoperative planning, and postoperative management. Seven of the 60 patients had mixed astrocytoma-oligodendrogloma, and three patients had pleomorphic xanthoastrocytoma. More than 80% of patients were adults. Eighty percent of patients had normal neurological exams. Ninety percent presented to medical attention after having a seizure.

Piepmeier (42) selected the 50 patients with astrocytoma histology and evaluated them independently. Nineteen had total resection, 17 had radical subtotal resection, and 13 had biopsy only. There was one surgical death. Of the 26 patients receiving postoperative radiation treatment (5,000–6,000 rad), 5 had had total resection, 13 had had radical subtotal resection, and 8 had had biopsy only. Piepmeier analyzed the effects of age, CT enhancement, extent of surgical resection, and radiation on patient survival. In the 50 patients, age and CT enhancement were the only significant factors influencing survival. The mean survival for patients over 40 years old was 4.85 years; in patients under 40 years old, it was 8.47 years. If the tumor enhanced on CT, the mean survival decreased from 7.94 to 3.92 years. Extent of resection did not influence survival. Mean survival was 8.47 years in patients with total resections, 7.22 years in patients with subtotal resections, and 6.24 years in patients having biopsies only. Analysis of the effect of radiation therapy on survival in the 50 patients as a group, as well as within each surgical subgroup, did not reveal any significant benefit of radiation. The mean survival in the 26 patients who were irradiated was 6.51 years compared with 8.51 years in the 23 patients not irradiated. The mean survival within each resection subgroup of patients receiving radiation versus patients not receiving radiation was as follows: total resection, 7.65 versus 5.10 years; subtotal resection, 6.34 versus 9.58 years; and biopsy only, 6.01 versus 6.67 years. At the time of the report, 14 of the 50 patients had died from their tumor. Even though no benefit of radiation or surgery was found, these survival results are encouraging, as survival was generally better than in previously reported retrospective studies; however, this report was published only 2 years after the last patients were treated.

As Vertosick et al. (13) stated in their analysis of low-grade astrocytomas since CT, improved sur-

vival today may be secondary to earlier diagnosis. By intervening earlier in the natural history of the disease, survival results may appear better, though the treatment may not significantly improve the eventual outcome. Hence, patients should be followed longer before the true impact of surgery or radiation can be determined. Longer follow-up is clearly needed in Piepmeier's group of patients before the value of surgery or radiation in the treatment of low-grade astrocytomas can be evaluated fully (42).

North et al. (55) reviewed the experience at Johns Hopkins from 1975 to 1984, a similar period to Piepmeier's study (42). Seventy-seven cases of low-grade supratentorial astrocytoma were reviewed; 52 (66%) of the cases were adults and 9 (12%) of the cases were pilocytic. Recognizing that this was not a homogeneous group, North et al. found that patients who had gross total or subtotal resections fared significantly better than those with biopsies alone. Five-year survival values for these groups were as follows: gross total resection, 85%; subtotal resection, 64%; and biopsy, 43%. Similar to other studies, age was an important prognostic factor in the adult population. The 5-year survival in the 20–50-year-old group was 53% compared with 32% in patients older than 50. As 66 of the 77 patients received radiation, conclusions on the impact of radiation on survival could not be made. However, within the group receiving radiation, patients receiving between 4,500 and 5,900 rad had a significantly higher 5-year actuarial survival than patients receiving less than 4,500 rad or greater than 5,900 rad.

Steiger et al. (15) from Berne, Switzerland, reported 50 adult patients with supratentorial nonpilocytic astrocytoma who underwent surgery between 1984 and 1988. Forty-two of the 50 patients presented with a seizure. Thirty-two patients underwent gross total resection, 4 subtotal resection, and 14 a stereotactic biopsy. Stereotactic biopsy required a series of biopsies through the mass so that the center and periphery of the tumor were sampled. During open procedures where there was a question about the extent of resection, frozen-section specimens were taken from the margins. The resection was extended if necessary and feasible depending on the surrounding parenchyma. The tumor margin was classified as well-delineated or diffusely infiltrating by the pathologist, based on

whether the transition from tumor to normal brain occurred within 10 mm or more. Thus, every effort was made to determine the character of the tumor at its border. The follow-up ranged from 8 to 69 months (mean, 22 months). Tumors recurred in 5 of the 32 patients who had gross total resections; 4 had progressed to a higher grade. For all 5 recurrences, the tumors had been originally classified as diffusely infiltrating at the border. Tumors in 27 of the 32 patients who underwent gross total resection had originally been classified as diffusely infiltrating and 5 were classified as well-delineated; none of the latter patients had a recurrence. Of the 18 patients who had subtotal resections or stereotactic biopsies, 5 had tumor recurrences; 4 of these tumors had been classified as diffusely infiltrating. No pathologic examination at the time of recurrence was reported. Steiger et al. concluded that the frequency of recurrence is higher in patients with subtotal resections. Their data also suggest that tumors found to be diffusely infiltrating at the margin are more likely to recur.

Vertosick et al. (13) reported 25 adult patients with low-grade supratentorial astrocytomas treated between 1978 and 1988 at the University of Pittsburgh. Twenty-three (92%) of these patients presented with a seizure only. Five patients had their tumors debulked and the remaining 20 patients had tumor biopsies. Eighteen patients received more than 5,000 rad of radiation. The median survival for this group of 25 patients was 8.2 years. In 14 of the 25 patients, tumor recurred and the pathology changed to a high-grade glioma. Interestingly, the median time to dedifferentiation in the patients receiving radiation was 5.4 years, compared with 3.7 years in the group not irradiated. Although this difference did not reach statistical significance, it suggests that radiation is beneficial.

Considering all of the above retrospective studies together, several conclusions can be drawn. First, age is an important prognostic factor; young adults consistently fared better than older adults. Second, low-grade astrocytomas do recur and, in a high percentage of patients, progress to high-grade gliomas. Whether this represents dedifferentiation or residual anaplastic foci, the important conclusion is that patients with residual tumor after resection should receive adjuvant therapy. Although several reports did not show a significant advantage of radiation, the general impression is that radiation is beneficial.

and that 4,500 rad is the minimum dose. Whether patients with gross total resections should be irradiated is not clear from the above reports. Third, there is convincing evidence that some patients survive for long periods after total resection but that tumors recur in other patients. It is unclear whether those patients whose tumors recur after total resection actually have residual microscopic tumor at the margin. Nevertheless, based on the information available, total resection when feasible is in the best interest of the patient.

An increasing number of low-grade astrocytomas are being discovered as incidental findings. The role of surgery or radiation has not been determined in this group of patients. Therefore, a conservative course of serial observation may be appropriate.

Pilocytic Astrocytoma

Pilocytic astrocytomas are included in most low-grade astrocytoma series. Similar to children, adults with this diagnosis have a very good prognosis. Indeed, the 5-year survival is significantly better than for other low-grade astrocytomas. For this reason, pilocytic astrocytomas should be considered separately.

In 1963 Schisano et al. (34) from Stockholm reported the largest series of adult patients with pilocytic astrocytoma. They reviewed 42 cases treated from 1926 to 1957: 39 had a mural nodule associated with a cyst and 3 were solid tumors. Thirty-five of the 42 patients underwent complete resection and 13 of these received radiation postoperatively. Thirty-four of the 42 patients were alive at the time of the report, and only three deaths occurred secondary to recurrent tumor. Twenty-five of the 27 patients who have been followed for more than 10 years had a complete resection. Other studies (30-35) demonstrated similar survival results, with virtually 100% survival with complete resection of the tumor. Schisano et al. did not comment on the value of radiation, as only three patients were irradiated.

Shaw et al. (35) in 1989, reporting on the Mayo Clinic experience with low-grade astrocytomas from 1960 to 1982, analyzed 41 patients with pilocytic astrocytomas. Survival was 100% at 10 years in those patients who had a complete resection, but it dropped to 95% at 5 years and 84% at 10 years for subtotal resection and 44% at 5 and 10 years if only a biopsy was performed. In the subtotal and biopsy

groups (31 patients), those receiving radiation (27 patients) survived longer, although the difference between groups did not reach statistical significance.

In summary, pilocytic astrocytomas in adults have an excellent prognosis. Total resection can be curative. Radiation in patients with complete resections is not necessary, and currently there is only suggestive evidence that radiation is beneficial in patients with subtotal resections.

Gemistocytic Astrocytoma

Anecdotal reports have indicated that gemistocytic astrocytomas behave differently from other low-grade astrocytomas. Krouwer et al. (36) reported on 28 cases from the University of California at San Francisco treated from 1976 to 1989. Diagnosis of gemistocytic astrocytoma required the presence of more 20% gemistocytes/high-power field. Eighteen patients had recurrence of tumor. The 5-year survival was 23%. As all of these patients underwent radiation, no conclusions could be drawn about its value. All four who underwent total resection of their tumor were alive at the time of the report (survival: 2, 5, 6, and 9 years). All 5 patients who only had a biopsy died (at 10 weeks, 1 year, 1.25 years, and 3 years from tumor progression; one died of a pulmonary embolus). Krouwer et al. concluded from this review that extent of resection is important and that aggressive postoperative therapy is indicated.

SURGICAL OPTIONS

Total resection should be the goal in all surgery for low-grade astrocytomas. The feasibility of total resection depends on the location of the tumor and the function of the surrounding brain. When lesions are confined to silent areas, every effort should be made to achieve a complete resection. T2-weighted MRI images should be studied preoperatively to determine the extent of tumor involvement. When the tumor does not reach the cortical surface, the least destructive path of exposure should be planned, circumventing the eloquent cortical areas. Resolution or improvement in neurologic deficits with preoperative steroids suggests that pressure rather than neuronal destruction is contributing to the deficit. In these cases, permanent neurologic improvement following surgical decompression is possible.

Identification of the tumor once the dura is opened can be difficult; often the only clue is a swollen, discolored gyrus. Both intraoperative ultrasound and stereotactic craniotomies are helpful in this regard. Ultrasound can assist with localizing the tumor, determining its depth, and assessing for residual tumor or blood at the end of the resection. The introduction of stereotactic techniques allows very accurate localization and resection of various lesions. The application of such techniques to low-grade astrocytomas is limited somewhat by the characteristic lack of enhancement of these lesions on CT. As the stereotactic frames become MRI-compatible, this technique will allow accurate localization and resection of low-grade astrocytomas. Once identified, these lesions are firm and tougher than normal white matter and often have a grayish discoloration. The tumor margins can be identified better by use of a microscope, and the ultrasonic aspirator and laser aid in gentle removal of the tumor. Often a plane can be developed between the gliotic white matter and the tumor. With blunt dissection, this plane can be used to separate the tumor edges from the surrounding parenchyma. Internal debulking of the central portion of the tumor can be of great assistance in its removal.

Goerss et al. (56) and Kelly et al. (57,58) at the Mayo Clinic have developed a computer-assisted stereotactic system with a stereotactically directed carbon dioxide laser to attack deep-seated intracranial lesions. Low-grade astrocytomas as well as pilocytic astrocytomas have been treated with this system (59). Fifteen patients with grade 2 astrocytomas and five patients with grade 1 astrocytomas were resected stereotactically. The volume resected correlated with the high signal on T2-weighted MRI images. Nine of the 15 patients with grade 2 tumors were neurologically intact preoperatively; of the six who had preoperative deficits, four showed improvement postoperatively. Six of the 15 showed no neurological changes, and five had new neurological deficits that were thought to be the direct result of resection of intact, functional parenchyma. Kelly (59) concluded that stereotactic resection in low-grade astrocytomas should be reserved for tumors located in nonessential areas because of the risk of postoperative neurologic deficit.

Kelly (59) recently reported 45 computer-assisted stereotactic resections on 42 patients with pilocytic astrocytomas; three patients had two procedures

because of growth of residual tumor after the first computer-assisted stereotactic resection. The mean age of this group of patients was 18 years (range, 3-37 years). The indications for surgery in this group were (a) ventricular obstruction with increased intracranial pressure; (b) imminent ventricular obstruction; (c) residual and enlarging tumor following previous surgery; (d) progressive enlargement of tumor on CT; (e) progressive neurologic deficit; and (f) medically intractable seizures. Twenty-four of the 42 patients had deep-seated tumors in the thalamic-basal ganglia area. Eight patients had cerebellar lesions. Twenty-seven patients had a preoperative neurologic deficit. After surgery (45 procedures), 24 patients showed improved neurology, 17 patients showed no change, and 4 patients showed worse condition. One patient died 10 days after surgery. Thirty-four of the 42 patients had no enhancement of their postoperative scan. Kelly (59) recommends a conservative approach in patients with deep-seated pilocytic astrocytomas who are doing well, reserving computer-assisted stereotactic resection for patients showing signs of mass effect.

Regardless of how the tumor is removed, multiple specimens should be evaluated pathologically to avoid misdiagnosis because of sampling errors. Efforts should be made to evaluate the margin of the resection. Biopsies of the walls of the resected area can provide important information about the extent of resection and need for further therapy.

DIRECTIONS FOR THE FUTURE

Determining which low-grade astrocytomas are likely to progress to a higher grade will result in better patient management. Efforts in this direction are proceeding in several research areas, two of which were considered above: cell proliferation studies, as by Hoshino et al. (38), and correlation of tumor infiltration at the margin with recurrence, as by Steiger et al. (15). Two promising new areas are examination of growth factor expression in gliomas and cytogenetic studies of gliomas.

Growth factors have been implicated in controlling glial proliferation (60). Maruno et al. (61) reported a difference in growth factor expression between high- and low-grade astrocytomas. One of the low-grade astrocytomas was found to express the growth factors found in the higher grade tumors, and the possibility that this expression represents a

tendency to anaplastic differentiation remains to be explored. Low-grade astrocytomas differ cytogenetically from their high-grade counterparts. Chromosomal abnormalities have been found consistently in high-grade astrocytomas (62-64). Griffin et al. (65) studied 10 low-grade astrocytomas and found that eight had normal karyotypes, while two had chromosomal abnormalities. Whether chromosomal abnormalities or expression of certain growth factors in low-grade astrocytomas will identify a group of patients at risk for anaplastic progression will require correlating clinical outcome with the presence of these abnormalities in large numbers of patients.

Currently, radiation is the only adjuvant therapy offered to patients with low-grade astrocytomas. Three prospective randomized trials to investigate the efficacy of radiation treatment in low-grade astrocytomas are under way (Table 3). The results of these trials should provide more definitive information on the role of radiation therapy.

Finally, novel approaches to treatment of tumors, including astrocytomas, are on the horizon. First, angiogenesis, which is the growth of new blood ves-

sels, is required for tumor expansion (66). Inhibition of this process could potentially limit tumor growth. Second, sustained local delivery of potential inhibitors or other antineoplastic agents directly to the tumor bed is possible with the use of biodegradable polymers (67).

CONCLUSIONS

Low-grade astrocytomas are not a homogeneous group of tumors. Three histological diagnoses are relevant to patient management: astrocytoma, pilocytic astrocytoma, and gemistocytic astrocytoma. The three histologic types show different clinical behavior, which has implications for treatment. Thus, optimum management of low-grade astrocytomas begins with accurate pathological diagnosis.

The tumors, particularly the astrocytoma type, have an extremely variable natural history. The results of Hoshino et al. (38) that DNA replication labeling of bromodeoxyuridine of greater than 1% indicates a worse prognosis and of Steiger et al. (15) that tumors classified as diffusely infiltrating have a higher recurrence rate and worse prognosis provide

TABLE 3. *Study schema for prospective randomized trials in patients with low-grade astrocytomas*

1. Mayo-NCCTG (North Central Cancer Treatment Group) Study	Pilocytic astrocytoma	Register	Observation
	Gross total resection		
	Radical subtotal resection		
	Subtotal resection		
	Pilocytic astrocytoma	Randomize to	5,040 cGy/28 fractions localized brain radiation
	Biopsy only		or
	Ordinary astrocytoma		6,480 cGy/36 fractions localized brain radiation
	Any extent of resection		
	Oligoastrocytoma		
	Any extent of resection		
2. EORTC (European Organization for Research and Treatment of Cancer) Studies	Oligodendrogloma		
	Any extent of resection		
	Ordinary astrocytoma	Randomize to	Observation or 5,400 cGy/30 fractions localized brain radiation
	Less than total resection		
	Oligoastrocytoma		
3. BTG-RTOG (Brain Tumor Cooperative Group-Radiation Therapy Oncology Group) Study	Less than total resection		
	Oligodendrogloma		4,500 cGy/25 fractions localized brain radiation
	Less than total resection		or 5,940 cGy/33 fractions localized brain radiation
	Ordinary astrocytoma	Randomize to	Observation or 5,400 cGy/30 fractions localized brain radiation
	Any extent of resection		
	Oligoastrocytoma		
	Any extent of resection		
	Oligodendrogloma		
	Any extent of resection		

evidence that there is heterogeneity within low-grade astrocytomas. Currently, no criteria exist to select patients who will do poorly. Prognostic factors that require consideration are age and extent of resection. Younger adults survive longer than do older ones. Patients with complete resections have the best chance of long-term survival. However, in some patients with complete resection, tumors will recur and become high-grade tumors.

Whether the progression to malignant tumors is due to dedifferentiation or residual anaplastic foci does not affect patient care. In both cases, residual abnormal cells lead to tumor recurrence and progression. Patients with residual tumor should be treated by radiation. Evidence from the literature demonstrates improved survival when radiation is given to patients with residual tumor. Patients with complete resection may be followed clinically and radiographically, with adjuvant therapy being withheld until the time of recurrence.

Pilocytic tumors are unusual in adults. They have the best prognosis and complete resection can be curative. Surgical removal may be very challenging as they are often deep-seated in the region of the third ventricle. Computer-assisted stereotactic procedures can be used to obtain a complete resection. The benefit of radiation when residual tumor remains is unresolved.

Gemistocytic astrocytomas have the worst prognosis. Again, complete resection is optimal for the patient. As these lesions behave very aggressively and have a high propensity to progress to high-grade tumor, adjuvant radiation should be administered in all cases.

For optimal management of low-grade astrocytomas, the following recommendations can be made: (a) treatment should be based on the histologic type of low-grade astrocytoma (astrocytoma, pilocytic astrocytoma, or gemistocytic astrocytoma); (b) MRI, the T2-weighted image in particular, is the imaging modality of choice to determine the extent of the tumor and to follow the progress of the tumor; (c) radical total resection should be attempted whenever safely possible; (d) multiple biopsies should be performed during open or stereotactic procedures to provide ample histological material and avoid sampling errors and misdiagnosis; (e) patients in the astrocytoma group who have a total resection can be followed clinically and with frequent MRI scans; (f) patients in the astrocytoma

group with subtotal resections should receive adjunctive radiation therapy in a conventional fractionated schedule with a dose of 4,500–5,500 rad to a limited volume of brain; (g) when the histologic diagnosis is pilocytic astrocytoma, every effort should be made to achieve a complete resection; computer-assisted stereotactic resection is an option when these tumors are deep-seated; (h) subtotal resections of pilocytic astrocytoma should be followed very closely clinically, as the benefit of radiation in this group is only suggestive; (i) gemistocytic astrocytomas should be treated aggressively; regardless of extent of resection, these patients should receive adjuvant radiation therapy and be considered for chemotherapy or experimental protocols; and (j) astrocytomas discovered as incidental findings can be managed conservatively by serial observation; PET scanning may be beneficial for decision-making. However, the general oncology principle of early intervention with minimal tumor burden may be applicable in this group of patients. Future clinical studies are needed to answer this question.

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