MANAGEMENT OF LOW GRADE ASTROCYTOMAS WORKSHOP

Biology of Low-Grade Astrocytomas

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Laboratory investigations into the biology of low grade astrocytoma have been relatively few in comparison to the extensive studies carried out on glioblastoma multiforme. In some cases it is not clear that the tissue lines employed in the experiments conform to the clinicopathologic behavior and morphology of truly low grade lesions. Nevertheless, some useful lessons can be learned under the assumption that there is a continuum or spectrum of change between well-differentiated and anaplastic astrocytomas. Although the morphologic characteristics of low grade astrocytomas are their best known features, recent investigations in regard to the prognostic importance of some of these variables and the relationship between subcellular organization and morphology have brought a new sophistication and complexity to our understanding of these matters.

In a recent study, 165 adult supratentorial well-differentiated and anaplastic astrocytomas were intensively studied for the potential prognostic influence of 9 morphologic and 25 clinicotherapeutic factors (37): glioblastomas were specifically excluded from the study. Highly significant factors included cell density, endothelial hyperplasia, number of mitoses and vessel frequency ($P < 0.001$); nuclear polymorphism, the presence of microcysts and vessel size were less significant ($P < 0.01$). The traditional classification of astrocytomas by histologic type (e.g. protoplasmic or gemistocytic) did not appear to be significant. Of course, the majority of astrocytic cells form cytoplasmic processes and the recent use of cDNA probes has demonstrated the localization of GFAP mRNAs along these processes (28). GFAP is a major constituent of astrocytic intermediate filaments and its appearance during neurogenesis corresponds to a reorganization of the cytoskeleton and eventually to a change in cell shape. In cultured cells, the appearance of GFAP is correlated with a transition from a highly motile cell to a fixed form. This is of interest because some glioblastomas do not exhibit strong GFAP staining and there appears to be a general increase in cell motility with tumor grade (20). Cell motility can also be correlated with the contractility of the microfiliament system and the appearance of certain ultrastructural changes.

In addition to GFAP, low grade astrocytomas stain positive for vimentin and to a variable degree for keratin; astrocytomas are negative for the other two classes of intermediate filaments, desmin and neurofilaments (7). Staining for vimentin and keratin appears to be independent of grade. Co-expression of vimentin and GFAP appears to be a uniform property of astrocytomas (14); normal mature astrocytes in the cerebral cortex usually fail to stain for vimentin, the expression of which usually precedes that of GFAP in glial development. Glioma cells appear to be capable of adapting their cyto-skeleton to the micro-environment since GFAP immunoreactivity is increased in cells invading collagenous tissue or the meninges (4). Immunoreactivity is also present in cells that are perivascular.

The expression of some cell surface antigens (such as A4) also appears to depend on the GFAP positivity of the cell (29). These findings lend further support to the notion that different tumor phenotypes may correspond to antigenic phenotypes of normal cells at distinct stages of glial differentiation. Together with the data on vimentin discussed above, these results support the concept that the cells in low grade astrocytomas are phenotypically equivalent to primitive or dedifferentiated astrocytes.

In addition to their constituent tumor cells and endothelial cells, low grade astrocytomas like glioblastomas demonstrate a variable degree of macrophage and lymphocyte infiltration. The presence or absence of perivascular infiltrates in tumors other than glioblastoma does not appear to have prognostic significance (37). The CD8 subset of T lymphocytes appears to be present to the same extent in both low and high grade tumors but macrophages are much less common in low grade astrocytomas (31). The HLA-DR antigen, a class II antigen needed for the presentation of processed antigen by macrophages to T lymphocytes for their activation is also present on only 35% of low grade tumor cells (31). Nevertheless, all the components necessary for immune mediated cell killing are present in low grade astrocytomas.

The histologic grade of astrocytomas has been correlated with DNA content and with various parameters related to the cell cycle and cell proliferation. Low grade tumors generally exhibit dipolid cell lines with relatively low S-phase fractions (47); the G2-M phase is also lower in well-differentiated tumors (6). In the more anaplastic tumors, an analysis of DNA content can sharpen the prognostic power of histologic grading. The total amount of DNA expressed as milligrams per gram of fresh tissue increases with tumor grade while the total amount of gangliosides decreases (13). Ganglioside composition is related to intercellular adhesion, receptor function and the regulation of cell growth. Although the total amount of gangliosides decreases in anaplastic tumors, the fraction of GD_3 increases. Aneuploidy is also associated with an increased expression of the proliferation-associated nuclear antigen p105, however dipoid cells in tumors appear to be heterogeneous in their expression of this antigen (10). Whether GD_3 or p105 can be used to improve tumor classification or whether they can serve as the targets of monoclonal directed therapy remains to be seen.

Anaplastic astrocytomas appear to be sensitive to a wide variety of growth promoting substances; some tumors can be shown to produce in an autocrine fashion the very substances to which they respond. The production of growth factors can be correlated with the presence of oncogenes and growth factor receptors. The amount of epidermal growth factor receptor (EGFr) and amplification of its gene can be correlated with the clinical aggressiveness of astrocytomas (23). The most important growth factor appears to be PDGF (platelet derived growth factor) and its expression is also increased in more malignant tumors. Internalization of the EDF receptor appears to be necessary for the mitogenic response to occur; the relatively dispersed surface receptors are collected into coated pits, internalized via endocytic vesicles and then distributed to Golgi and lysosomal structures for hormonal degradation. Human astrocytoma cells (1321N1) redistribute and internalize B-adrenergic receptors in parallel with EGFr (44). Human astrocytoma cells

(U 373) can also be shown to respond to interleukin (IL 1), fibroblast growth factor (FGF), and tumor necrosis factor (TNF) (22); other astrocytoma lines have been shown to respond to insulin binding and insulin-like growth factors, activation of dopamine receptors and PDGF (1, 21). Low grade tumors also produce growth factors; surprisingly the supernatant from astrocytoma cell cultures appears to stimulate endothelial cell growth to the same degree as the supernatant from glioblastoma cell lines (15).

Low grade astrocytomas and oligodendrogliomas are throught to arise through the dedifferentiation of adult cellular elements whereas glioblastomas may arise either "de novo" or through the further dedifferentiation of low grade tumors. Cavenee has recently presented a theory in which the profusion of a low grade astrocytoma to a glioblastoma is viewed as a sequence of three steps in which loss of genetic material results in the expression of recessive oncogenes, first on Chromosome 17 and subsequently on Chromosome 10. Rubinstein has estimated that 20% of glioblastomas have arisen in a preexisting astrocytoma (32). The highly variable and generally slow clinical course of low grade gliomas is paralleled by a relatively low proportion of actively dividing cells as demonstrated in vivo with the administration of radiolabelled thymidine (16). Low grade gliomas typically have a labelling index of less than 1%; this compares with a value of 5 to 15% for glioblastoma. Similarly, the S-phase fraction for glioblastoma, as measured by intravenous bromodeoxyuridine, is on the order of 5 to 20% and is less than 1% for low grade astrocyoma, ependymoma and mixed glioma (17). This labelling technique has also been used to determine that the growth fraction for low grade tumors is 2 to 6.7 % while it is 9.1 to 46.5% for malignant gliomas (46). Since the growth fraction is the percentage of cells in the total tumor mass actively engaged in cell proliferation, the majority of cells in a low grade tumor are metabolically quiescent and not actively engaged in the manufacture of nucleic acids or other proteins. Hypermetabolism in low grade tumors has also been demonstrated in vivo with positron emission tomography (PET) by measuring the ratio of ^{11}C-L-methionine uptake between tumor and surrounding brain. Malignant tumors have been shown to be hypermetabolic for protein synthesis (ratio = 1.79 ± 0.24) in comparison to low grade tumors (ratio = 1.08 ± 0.23); the difference between grade 2 and grade 4 astrocytomas is statistically significant ($P < 0.007$) (9).

Correlative observations in regard to the slow growth rate of low grade tumors include a relative paucity of mitotic figures on histologic examination and poor staining for Ki-67 antigen on frozen section (48). The latter is a nuclear protein associated with actively dividing cells in the G_1, S_1, G_2, and M phases of the cell cycle. The Ki-67 index in low grade astrocytoma is only 0 to 4.5% (mean = 1.0%) while it is 1.7 to 32.3% in glioblastoma (48). Flow cytophotometry of the nuclear DNA in grade 1 and 2 astrocytomas, oligodendrogliomas and piloid astrocytomas generally demonstrates a diploid chromosome content; hyperploidy and aneupoidy usually become evident after anaplastic change has become initiated (40). These findings probably have some bearing on clinical aggressiveness and growth rate since the degree of oncogene amplification and duplication as well as the production of associated growth factors and receptor proteins appear to be lower for astrocytoma than in glioblastoma (23).

As demonstrated by positron emission tomography, low grade gliomas possess blood flows, oxygen consumptions and glucose utilization rates comparable to adjacent non-neoplastic brain. Although there is no difference in tumor blood flow rates between low grade and high grade tumors (27), glucose consumption in 10 grade 3 and grade 4 tumors has been shown to be 7.4 $\pm$ 3.5 mg/100 gm tissue/min in comparison to 4.0 $\pm$ 1.8 mg/100 gm tissue/min for 13 grade 1 and 2 astrocytomas as measured with 2-^{18}F-2-deoxy-D-glucose (9).

Non-invasive clinical estimates of tumor doubling time and cell-cycling time have been obtained by sequential CT-scanning for glioblastoma, meningioma, acoustic schwannoma and some experimental tumors (33, 34); unfortunately, relatively little data of this type is available for low grade gliomas. In a study of four grade 2 or mixed astrocytomas, the estimated tumor doubling time was 937.3 $\pm$ 66.5 days in comparison to 48.1 $\pm$ 20.9 days for 11 glioblastomas ($P = 0.01$) (43). Clinical intuition would indicate that some tumors require many months or even a year or two to double in size; it is likely, therefore, that the production of daughter cells in the low growth fraction of these tumors is almost exactly balanced by the rate of cell loss and cell inactivation. Hoshino feels that many of the non-cycling or non-proliferating cells in low grade tumors may be mature cells that have left the cycling pool permanently (18); this situation contrasts with the non-cycling cells in glioblastoma that often re-enter the proliferating pool when environmental or nutrient conditions have changed. Hence, therapeutic strategies based on the relative susceptibility of actively cycling cells to ionizing radiation and chemotherapy are unlikely to be effective for low grade gliomas.

Perhaps the most cogent feature of the biology of these neoplasms is a highly variable and unpredictable progression in their degree of anaplasia. In a series of 72 grade I supratentorial astrocytomas treated with surgery and at least 3000 rads of radiation, only 14% of the tumors were unchanged in grade at the time of recurrence, 55.5% had become grade II lesions and 30.% had progressed to glioblastoma (25, 26). Tumors of intermediate grade at initial presentation ($N=65$) remained unchanged 55.4% of the time at recurrence and progressed to glioblastoma in 44.6% of the cases (25, 26). A similar evolution of low grade oligodendrogliomas has been described; in 23 recurrent grade I oligodendrogliomas, 15 of the tumors at reoperation became intermediate in grade and 2 progressed to glioblastoma (26); the authors concluded that the participation of transformed local astrocytes appeared to be essential for the development of malignancy in oligodendroglioma. In another study, 10 of 29 patients with pure oligodendroglioma suffered a recurrence; at reoperation or autopsy, 2 of the tumors were glioblastomas, 3 were mixed oligodendroglioma - grade 3 astrocytoma and 1 was a grade 2 astrocyoma (45). Only four of the ten tumors remained unchanged. Therefore, in about two-thirds of all astrocytomas an increase in malignancy is to be expected at recurrence, although the transformation of a low grade tumor to glioblastoma takes longer than the transformation of an intermediate grade astrocytoma. Even the pilocytic astrocytomas of childhood have some degree of malignant potential. In a series of 72 histologically benign cerebellar astrocytomas, three patients demonstrated spinal cord seeding through the subarachnoid pathway (38). A partially resected and irradiated cerebellar astrocytoma in a 13 year old

girl demonstrated malignant evolution at the primary site 28 years after treatment (4). The possibility of malignant transformation is a strong argument that a maximal therapeutic effort be made at initial presentation since virtually any therapy reserved for a subsequent glioblastoma is less likely to be successful than if initially applied to the more tractable low grade tumor, chemotherapy excepted.

Of course, the natural history and biological properties of low grade glial tumors do not support the concept that they are "benign" tumors to begin with. Scanlon and Taylor reported 5-year survival rates of 76% for 42 grade 1 astrocytomas and 58% for 92 grade 2 astrocytomas (35). Similarly, Wallner, et al reported a 61% 5-year survival rate for 29 patients with oligodendroglioma (45). The ten year survival rates for such "benign" tumors range from 20 to 50%. The 5-year survival rate for low grade astrocytoma calculated from 1366 patients is 48% (33a).

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Low-Grade Gliomas in Childhood

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Astrocytomas comprise about half of all pediatric brain tumors. The portion of the brain in which the tumor occurs is important in determining the eventual outcome, as is the degree of histologic malignancy. Tumors of the cerebellar hemispheres or vermis and tumors of the optic apparatus will almost always be histologically benign. This is also true of the majority of tumors arising in the brain stem. Often, though, despite the fact that astrocytomas may be histologically benign, site of origin and infiltration of surrounding vital structures precludes surgical resection. Pre-operative radiological imaging using CT or MRI scan with contrast agents is essential in determining the location and the operative approach to the lesion. Portable real time ultrasound in the operating room allows rapid and accurate intraoperative imaging to localize tumors and monitor the extent of resection. Other operative techniques which are useful are electrophysiological mapping of eloquent areas of the brain, and for deep-seated thalamic and hypothalamic gliomas CT-guided stereotactic biopsy is gaining popularity. Tumors located in non eloquent areas of the brain, such as the temporal lobe in the non-dominant hemisphere or the frontal pole, are managed by aggressive operation, and lobectomy may be appropriate. Technical improvements in instrumentation in the operating room, such as the ultrasonic surgical aspirator (CUSA) and laser, permit more aggressive resections than conventional techniques and with less morbidity.

The incidence of low-grade gliomas in childhood varies from different series. In our institution (The Children's Hospital of Philadelphia) in a 10-year period 462 brain tumors were operated upon primarily. Of these 227, or 49%, were astrocytomas with the great majority being of low grade, and only 32 were anaplastic. The largest single group were those in the cerebellum constituting 57 cases followed by 54 in the optic apparatus and diencephalon, 47 in the brain stem and 37 low-grade cortical tumors.

Management of Specific Lesions

Cerebellar Astrocytomas

The cerebellar astrocytoma, or juvenile astrocytoma of the cerebellus, remains the astrocytoma with the best prognosis. Therapy is primarily surgical excicion with the goal of total resection in all cases. Mortality should be low, on the order of 3-4%, and the major problems are acute hydrocephalus, respiratory problems due to manipulation of the brain

stem, and hemorrhage at the site of the resection. Appropriate neuroradiological studies should be obtained shortly after surgical excision and if large portions of residual tumor are seen and it is technically feasible to do so we recommend surgical re-exploration in the early post-operative period. Otherwise, the patient will be seen at regular intervals and have either a CT or MRI scan every 6 months for at least 5 years. In totally-resected tumors, we see no indication of radiation therapy unless histology reveals an anaplastic glioma. Recurrences should be treated with surgical excision, and radiation therapy should be considered when there is recurrence in spite of apparent total excision or when there is brain stem involvement. Many attempts have been made to correlate histological variants to final prognosis, but in our experience the best prognostic value is the ability of the surgeon to totally resect the lesion. There appears to be no difference in the prognosis for solid or cystic tumors or vermian versus hemispheric astrocytomas if complete surgical excision can be accomplished.

Thalamic tumors

Because of the lack of histological verification in many of these tumors in large series, it is impossible at present to accurately predict the outcome of these cases based on degree of malignancy. We recommend histological verification either by CT-guided stereotactic biopsy or by open craniotomy either by using a transventricular approach via the trigon or by means of a transcallosal approach. CSF shunts will be required in a large proportion of patients, and we favor the insertion of a biventricular shunt to prevent shifting due to blockage of the foramen of Monro.

Tumors of the Optic Apparatus and Hypothalamus

These tumors are controversial regarding management in the pediatric population. There has been enormous divergence of opinion, ranging from the extreme of suggesting that these tumors do not have the potential for growth and are truly hamartomas that should be left alone to series that demonstrate progression in a great majority of these cases eventually resulting in invasion of the entire optic tract to the occipital cortex. The advent of CT scan and MRI has demonstrated to our satisfaction that these tumors do progress and that there is no way to distinguish between the purely hypothalamic tumors and those that invade the optic chiasm. The natural history of this disorder is quite variable with some series showing a long-term stabilization with no treatment at all and others showing mortality of 40% at 10 years after diagnosis. Surgical intervention should be undertaken if there is a question about diagnosis, and biopsy is required for pathological examination.

In a child with thickening of the optic nerves and streaking along the optic radiations in the presence of neurofibromatosis, the presumption should be that of a

chiasmatic glioma and, in our opinion, pathological confirmation is not required. Large masses in the suprasellar region can occasionally be debulked, particularly if there is a large cystic component, and very often these patients will require biventricular shunting to control hydrocephalus.

Radiation therapy in these cases is also quite controversial since there is no clear-cut evidence that these tumors are radiosensitive. Because of their location, it is quite likely that the treatment itself will produce sequelae particularly in the neuroendocrinological area and in learning disabilities. In our own institution, chemotherapy with actinomycin-D and vincristine has resulted in stabilization or regression of disease in 80% of the patients.

In summary, therapy in these cases will include close follow up and opthalmological evaluations with CT scan and MRI in stable cases and a trial of chemotherapy in the slowly-progressive gliomas, especially in young children. Radiation therapy should be reserved for older children with rapid tumor enlargement or deterioration of vision.

Astrocytoma of the Cerebral Hemispheres

The treatment of the low-grade astrocytoma of the hemisphere is operative resection with the goal of obtaining gross total excision. The use of the ultrasonic aspirator and intraoperative ultrasound is of great help. A particularly favorable prognosis is justified in those cases of cystic pilocystic astrocytoma of the hemisphere. This is a peculiar tumor seen primarily in children and young adults and is analogous to the cystic cerebellar astrocytoma. The most frequent presentation is convulsions. The overall survival in these cases should be very similar to the cerebellar astrocytoma and should have an 85% 10-year survival rate. A peculiar subgroup of tumors in the cerebral hemispheres is the ganglioglioma. These occur primarily in children and have a very favorable prognosis. They are characterized by a low-density mass on the CT scan often confused with cerebrospinal fluid. They are cortical or subcortical in location. They should not be radiated after total gross resection.

Giant Cell Astrocytomas

These occur primarily in the wall of the lateral ventricles, particularly in the region of the foramen of Monro and produce obstructive hydrocephalus. They can be huge and extremely vascular, making surgical excision very difficult. In a few of these cases, the tumor will degenerate into a malignant, very aggressive anaplastic glioma. Shunting is frequently necessary because of obstruction of the CSF pathways and can be very difficult because many ventricular compartments may require different proximal catheters.

This remains one of the most difficult areas of treatment. The majority of brain stem gliomas in childhood are infiltrating within the substance of the pons and medulla and are not amenable to surgical therapy. There are a small number of cystic astrocytomas with small mural nodes which can be safely operated upon and which carry a better prognosis. Likewise, those that are largely exophytic with large masses in the region of the IVth ventricle which can be safely removed to the floor of the IVth ventricle, also carry a somewhat better outlook.

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Supratentorial Low Grade Gliomas in Adults

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Introduction

Roughly 40% of all gliomas are low-grade (3, 11, 14, 32, 38, 40). Some remain queiscent for many years, while others grow and/or may undergo malignant transformation. Modern imaging allows diagnosis of these lesions at a size much smaller than those for which published management data apply. Consequently, their optimal management is not established. The following report attempts to summarize available information about this disease and formulate a reasonable approach to its management.

Pathology

Low grade gliomas include grades I and II astrocytomas of the Kernohan (20) and Daumas-Duport (8) classifications, 'astrocytoma' of the World Health Organization and most oligodendrogliomas (2, 37). 'Mixed' low grade gliomas contain both astrocytic and oligodendroglial neoplastic cells. Up to 40% of oligodendrogliomas contain neoplastic astrocytes (37). It is unclear whether this effects prognosis. However, it is possible that astrocytomas with oligodendroglial cells are less aggressive than pure astrocytomas (33).

The topography of low grade gliomas is significant with regard to therapeutic considerations. With the exception of pilocytic astrocytomas, they consist of a core of tumor tissue surrounded by neoplastic cells which infiltrate relatively normal brain. Infiltration can be quite extensive and may extend beyond the T2 intense margins as seen on MRI scan (18). This has significant implications regarding surgical treatment, particularly when it is entirely possible that infiltrating tumor cells may infiltrate brain that continues to function normally. In contrast, pilocytic astrocytomas generally have more compact margins with less infiltration, rendering them more operable.

Epidemiology

The location of supratentorial low grade astrocytomas roughly parallels the mass of brain white matter. About 80% occur in the frontal and temporal lobes. The data on oligodendrogliomas suggest that they have a predilection for the frontal lobes, with about 60% in this location (34). The median age of patients with low-grade gliomas is 35 to 40 years. Pilocytic astrocytomas afflict patients in their early teens. Males are diagnosed at a

slightly higher rate than females, comprising 55 - 65% of patients with low grade astrocytomas and up to 75% of patients with oligodendrogliomas (6, 16, 33, 34).

Low grade gliomas affect the brain by compression secondary to tumor mass and by alteration of the biologic milieu in the region of infiltrating tumor cells. Prior to modern neuroimaging, these tumors often attained large sizes with common clinical characteristics being seizures (66%), focal deficit (51%), headache (44%) and personality changes (16%). Only 39% of these patients had a normal exam (22). Since the advent of CT and MRI, up to 85% of patients have a normal exam, reflecting earlier diagnosis (30). Many of these lesions are diagnosed after a single seizure and the concept of "duration of symptoms" prior to diagnosis is not valid. It is this combination of early diagnosis plus a poorly understood natural history that makes definitive therapy difficult.

Imaging Studies

Neuroimaging of low-grade gliomas basically consists of CT and MRI. Non-pilocytic low grade astrocytomas may occasionally show a faint irregular uptake of contrast, but are usually non-enhancing. CT contrast enhancement may indicate foci of higher grade tumor (18) and a strongly enhancing lesion should be viewed suspiciously. MRI is more sensitive than CT in detecting these lesions. They appear hyperintense on T2 weighted scans and are lucent with a T1 pulse sequence. However, it is known that neither CT nor MRI can accurately delineate the margins of these tumors (18). Pilocytic astrocytomas are unique in that they often homogeneously enhance, which is a reflection of microvascularity and not malignancy. In terms of enhancement, gadolinium and iodine based agents behave similarly.

Positron emission tomography (PET) can detect a malignant focus within a tumor due to its increased glucose metabolism (10, 29). Low grade gliomas are "cold", that is, exhibit little or no glucose uptake. Malignant transformation of a low grade glioma can be detected early by PET as a "hot spot" within the tumor. We make use of this important capability of PET in following our patients with low grade gliomas.

Natural History

The natural history of low-grade gliomas is unclear. It is known that these tumors grow slowly and that many will eventually require some attempt at therapy. However, the optimal therapy and its timing is poorly understood. Currently, the best indication of the natural history of this tumor is the results of series of patients either not treated or minimally operated and not radiated. Weir and Grace (40) found an average survival of 5 months after diagnosis for patients receiving only a biopsy. In similarly treated patients, Mundinger and Weigel found 5 and 10 year survivals of 17% and 6% respectively (27).

Shaw et al found 5 and 10 year survivals of 32% and 11% respectively, while Liebel et al found survivals of 19% and 11% for patients with minimally treated low grade astrocytomas (23, 34). Soffietti et al reported no 5 year survivors after subtotally resected low grade gliomas (38). From these data, an estimate of survival without treatment after diagnosis of low grade glioma would be 15% - 30% at 5 years and around 10% at 10 years. It must be pointed out that because of the lack of CT, by today's standards most of these patients were diagnosed relatively late in the course of their disease. Earlier diagnosis using CT or MRI would, of course, result in improved survival figures without necessarily reflecting improved treatment. This may account for Piepmeier's report of an average survival of 6.7 years after biopsy alone (30). Unfortunately, he did not account for pilocytic histology, which can favorably bias series of low grade gliomas (21, 34). It is likely that 50% of these patients live 5 years or more after diagnosis without treatment (34).

Results of Surgery Without Radiation

Effective treatment of this tumor should improve the course of the disease in comparison to the natural history. Traditionally, therapy has been surgery, usually followed by radiation. This, however, has been for relatively large tumors causing significant mass effect. Today's patient is more likely to have a small lesion diagnosed by CT or MRI after a seizure, a situation for which there is not good treatment data.

As stated above, non-pilocytic astrocytomas can extend far beyond image-defined tumor margins and possibly infiltrate functioning brain. Such topography raises the question of whether surgery is a justifiable. However, it seems reasonable to offer surgery in an effort to reduce mass effect, reduce tumor burden for adjuvant therapies and to reduce the potential for malignant transformation (17). Available data suggest that in some patients, surgery favorably affects outcome. In 1975, Liebel reported 100% 5 and 10 year survivals after gross total removal of low grade astrocytomas (23). In general, however, the experience of other authors is less encouraging, with 5 and 10 year survival of 15 - 40% and 10% respectively after resection not followed by radiation (1, 9, 23, 34, 39). Extent of removal has correlated weakly with outcome and in particular, lobectomy does not improve results (21, 22). It seems reasonable, however, that if surgery is performed resection should be as complete as is safely possible.

There is little information on the management of predominantly oligodendroglial tumors. For patients operated and not irradiated, 5 and 10 year survivals of 31% and 25% respectively were reported in 1964 (35) but were 81% and 54% respectively in a 1980 series (6). Pilocytic astrocytomas are much more benign such that after "total resection" and no radiation, ten year survival exceeds 80% (28, 34).

Results of Surgery Followed by Radiation

The role of radiation in treatment of low grade gliomas is not as well-defined as it is in the treatment of malignant gliomas. The infiltrative nature of these tumors requires that large areas of functioning brain be irradiated. This, in combination with long-term survival, increases the probability of symptomatic radionecrosis, which may occur in up to 7% of patients receiving more than 5500 cGy (15). Doses less than 5000 cGy are probably not adequate (34). Standard technique is to deliver 5000 to 5500 cGy to the region of the tumor, avoiding whole brain irradiation (25).

Using death as the endpoint, postoperative radiaiton therapy appears to improve outcome after any extent of low-grade astrocytoma resection (23). The results of radiation therapy as reported in several large series are summarized in TABLE 1. The 5 and 10 year survivals following subtotal resection and radiation of low grade astrocytomas are 40-68% and 35-39% respectively (1, 9, 34, 39). These results are strongly suggestive of a beneficial effect of postoperative radiation for what were probably relatively large low grade astrocytomas. Patients receiving postoperative radiation for oligodendrogliomas have a 5 and 10 year survival of 83-100% and 45-55% respectively (6, 33, 35). While this represents a better survival than for patients with low grade astrocytomas, it is not clear that radiation improves results over operation alone for oligodendroglioma (see above). There is little data regarding postoperative radiation for pilocytic astrocytomas. Shaw et al found in a small group of patients that after subtotal resection, the 5 year survival was 85% for radiated vs. 50% for non-irradiated patients (34). Patients felt to have complete resections were not radiated and 10 year survival exceeded 80% (34).

Prognostic Factors

There are certain parameters related to the patient and tumor characteristics that seem to have prognostic value. It seems that oligodendroglial histology is a favorable factor. The overall 5 and 10 year survival for patients with oligodendrogliomas is 50-60% and 42% respectively, while that for low grade astrocytomas is 41-51% and 23-33% respectively. Patients with pilocytic astrocytomas fare best with overall 5 and 10 year survivals of 85% and 79% respectively (23, 34, 35 & TABLE 1). Depending on the grading system, tumor grade is important. Under the Kernohan or Daumas-Duport system, those patients with grade I tumors do better than those with grade II. Patients with Kernohan grade I and II have a 3 year survival of 62.5% and 14.3% respectively (20). Patients with Daumas-Duport grade I and II have 5 year survivals of 85% and 50% respectively (7, 34). Other histologic factors such as variability in tumor vascularity and gemistocytic histology may predict a worse prognosis (34, 38). Among patients with oligodendrogliomas, those with tumors displaying necrosis have a 5 year survival of 40% versus 65% for those without necrosis (2).

Shaw and colleagues have shown that age is important to the extent that it relates to histology and is probably not a strong primary determinant, particularly for pilocytic astrocytomas (34). The issue of CT and MRI contrast enhancement is confusing since there is no way to distinguish between increased microvascularity which is not an indication of malignancy (7) and abnormal blood-brain barrier which indicates malignancy. Authors have reported that contrast enhancement is and is not important, however, strong enhancement should alert one to the possibility of malignancy (18, 30, 33, 36). It is relatively well established that the worse a patient's preoperative neurologic status, the worse the outcome of surgery (21, 22, 38). However, a focal deficit in an alert patient may not be deleterious (38). Operative mortality for low-grade gliomas has been stable over the last 20 years at under 5%.

The importance of extent of tumor removal continues to be an issue. In general, radical resection of large tumors offers improved survival over little or no resection (23, 38). However, there are excellent reviews that suggest extent of removal is of no significance (30, 34). It probably depends on the timing of the resection such that debulking of a large tumor causing mass effect improves survival as compared to not operating such a large lesion. The effect of early operation for very small low grade gliomas is unknown. Performance of lobectomy has not been found to enhance survival (21, 22, 30). Postoperative neurologic status is strongly related to survival, particularly 5 year survival (21, 38).

Surgical Technique

Currently, the two most common surgical procedures employed in the management of low grade gliomas is standard craniotomy for tumor resection and diagnostic stereotactic biopsy. The latter is becoming more common as the lesions are diagnosed earlier, while the role of craniotomy is becoming less well-defined.

Stereotactic Biopsy

It is common today for patients to have a single seizure which prompts an MRI showing a small T2 intense lesion in the supratentorial space. These patients should be approached with the intention of not worsening their neurologic condition. This goal is ideally attained by a diagnostic stereotactic biopsy and the use of anticonvulsants. Stereotactic biopsy is extremely safe and has been shown to be relatively accurate in the diagnosis of low grade gliomas (5). Taking a series of samples through the tumor lessens the chances of sampling error (18). Today there is little justification for performing a craniotomy for the purpose of obtaining a biopsy of such a lesion.

Craniotomy

Available data regarding the results of resection of low grade gliomas pertain mostly to those tumors that had attained a large enough size to cause significant mass effect and/or focal deficit. Debulking seems appropriate for those tumors causing deleterious mass effect or for patients with intractable seizures. About 50% of low grade gliomas eventually undergo malignant transformation (21, 31, 38) and it makes sense that reduction of tumor volume would reduce the incidence of malignant transformation, but there are no data to support this. Along the same lines, it would seem reasonable that tumor volume reduction would enhance the effect of radiation, but, again, there are no relevant data. It must be remembered that pilocytic astrocytomas are minimally infiltrative, making surgical resection more feasible and possibly curative (34).

A standard craniotomy can be used to resect these lesions. The bone opening should cover the intended resection limits. The tumor should be removed from within its borders, watching for normal brain as tumor is removed. Given the impossibility of removing all infiltrating tumor cells, it is reasonable to stop resection when the brain begins to appear relatively normal. Conservative resection is sensible around eloquent brain. Electrophysiologic mapping may be of some assistance near vital brain regions (12).

Stereotactic Resection

If tumor "edges" can be demarcated on CT or MRI scan, interactive stereotactic imaging can assist in the planning and performance of the operation. Most commercial stereotactic systems can be used to guide a craniotomy, making it possible to use smaller skin incisions and craniotomies and to operate more confidently near important brain. Kelly has reported on the technique of stereotactic "volume resection" in which a volume of tissue (tumor) is removed using a computer reconstructed display of the lesion in an interactive fashion (19). The technique is to remove the desired tissue volume by dissecting around the margins, thus perserving the preoperatively defined stereotactic relationships (19). The benefit of this procedure in terms of survival is not known, but in our hands, it has resulted in shorter hospital stays and a more comfortable convalescence for the patient.

Recurrence and Malignant Transformation

Local recurrence is due to continued growth of residual tumor or to malignant transformation. The latter eventually occurs in 13% to 85% of patients (13, 21, 24, 26, 31,

38), with the most commonly reported incidence being around 50% at a median time of 31-56 months (13, 36). We have begun to use PET to follow patients with low grade gliomas because PET can detect small foci of hypermetabolism, signalling emergence of malignancy. Once there is malignant transformation, management should be much more aggressive. The treatment of recurrence depends on the tumor grade. If clinical and imaging studies (including PET) suggest no malignant transformation and the patient is stable, careful observation is prudent. If the recurrent tumor causes symptomatic mass effect, it should be debulked. If studies suggest malignant transformation, aggressive therapy is indicated. We manage these latter patients by confirmational biopsy followed as indicated by interstitial brachytherapy and stereotactic resection.

Discussion

The optimal management of supratentorial low grade gliomas is not established. Modern neurosurgeons are often consulted for management of very small lesions in asymptomatic patients; very different from the patients upon which most of the published data are based. There are no clear guidelines about how to manage these small lesions and some authors feel there is no role for surgery (4). On the other hand, there are those that report no recurrence after complete tumor resection (23). Ideal management currently lies somewhere between these extreme approaches. Above all, the surgeon should aim not to hurt the patient. Debulking of a lesion causing mass effect seems reasonable and postoperative radiation appears to benefit those patients with partially resected large tumors (TABLE 1). Patients with pilocytic astrocytomas do extremely well and total removal results in long-term good results (34). In patients with non-pilocytic gliomas, good prognostic factors include normal preoperative neurologic status, oligodendroglial elements, grade I as opposed to II, pathology and possibly young age.

In conclusion, patients with large tumors causing symptomatic mass effect, with enlarging tumors on sequential studies, with intractable seizures or with malignant recurrences are surgical candidates. Surgery for other reasons remains less well founded. Radiation therapy appears to benefit patients after partial resection of large tumors. Determination of optimal therapy awaits the results of proper prospective, randomized trials.

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Table 1

Survival after Subtotal Resection Alone

vs.

Subtotal Resection plus Radiation Therapy

(%)

	No Radiation		Radiation	
	5 year	10 year	5 year	10 year
Fazekas et al	13		54	
Liebel et al	19	11	46	35
Stage et al	20		40	
Shaw et al	32	11	68	39
Bouchard et al	38		49	

The Role of Radiation Therapy in the Treatment of Low Grade Astrocytomas

Robert A. Morantz, M.D.

Perhaps the most important question in the treatment of low-grade astrocytoma is the issue as to whether or not post-operative radiation therapy should be used as an adjunctive form of therapy. The answer to this question should be relatively easy to come by. Ideally, such an answer would be forthcoming from what is probably our most powerful tool for scientifically answering clinical questions such as this one -- the randomized, controlled, prospective clinical trial. In this case, one would have to carry out a multi-group, long-term (perhaps as long as ten years) study in which two large groups of patients (containing individuals who are balanced with respect to important variables such as age, tumor location, histologic classification, etc.) were treated identically in every respect (i.e. extent of operation, use of steroids, etc.) except that one group received an exactly specified course of radiation therapy and the other group did not. Whether there was a statistically significant difference in the length and/or quality of survival between these two groups could then be determined. Such a study has never been completed, although at the present time such studies are being carried out by several cooperative groups within this country and Europe.[1,2,3] Unfortunately, the results of these endeavors will not be available for many years to come.

Because no single neurosurgeon's experience is adequate to answer properly how patients with low-grade astrocytoma should be optimally treated post-operatively, and the results of present cooperative trials are not available, we are faced with the question of how to presently manage this group of patients. The imperfect present day solution would seem to be a review of the major studies in this area to see whether they can furnish any guidance.

What is immediately apparent in carrying out such a review, however, is that the reports previously published have almost universally not satisfied even the minimal criteria that could be set forth for a study that could properly answer this question. More specifically, the previous studies have been retrospective analyses in which the irradiated and nonirradiated groups of patients have not been similar in important characteristics (e.g., age, Karnofsky rating, etc.). The pathological classification of the lesions has been different (e.g., varying numbers of Grade I and II tumors, etc.). The location and size of the tumors have been different, and the extent of operation has not been uniform (e.g., biopsy vs. complete resection). Finally, the parameters of the treatment being tested (i.e., radiation therapy) have not been standardized with respect to total dose, duration of therapy, field size, etc.

There has been a recent report on the use of interstitial permanent irradiation with low-intensity ^{125}I in patients with low grade astrocytomas.[4] Although this report on 45 patients is encouraging, there is not yet enough experience to evaluate the effectiveness of this technique. Thus, the following literature review is a summary of those series where treatment has been with post-operative external beam radiation therapy. It will mention several older major series but concentrate on the recent literature on this subject.

In 1975, Leibel et al.[5] reviewed the experience at the University of California at San Francisco in the treatment of astrocytoma. They found 147 patients who were treated at their institution between 1942 and 1967. If the patients who had complete resection of their lesion were excluded from the analysis, there was a clear-cut increased survival in the group undergoing radiation therapy (i.e., 5-year survival of 19 vs. 46%; 10-year survival of 11 vs. 35%). Based on their analysis, patients with complete removal of their tumor did well even if they did not receive radiation therapy, and patients with cerebellar lesions also did well irrespective of whether radiation therapy was given. Finally, they indicated that the quality of life was acceptable in the long term survivors and that there were no instances of radiation damage in those who experienced long term survival.

Weir and Grace[6] in 1976 studied 107 patients with Grade I and II supratentorial astrocytomas treated in the Province of Alberta, Canada, between 1960 and 1970. They analyzed the patients with respect to prognostic factors that might be related to survival and found that young age, clinical grade at operation (i.e. Grade I > Grade II), and the addition of radiation therapy were correlated with an increased survival.

In 1984, Laws et al.[7] used the patient population at the Mayo Clinic to review 461 astrocytoma patients treated between 1915 and 1975. These cases were selected from a much larger group of patients and represented only those with supratentorial tumors who survived at least 30 days postoperatively and for whom follow up data were available. Multiple prognostic factors were analyzed for possible correlation with an increase in survival. He found that the age of the patient was the most important variable and surpassed all others in its positive correlation with long term survival. In addition, he interpreted the data as supporting radical operation and a beneficial effect of radiation therapy only in those patients with poor prognostic factors (e.g. older age); his data have been interpreted by Sheline, however, as showing a survival advantage for the irradiated group if we consider only those receiving > 4000 rads as having been adequately irradiated.[8]

In 1985, Garcia and coworkers[9] undertook a retrospective study of 86 adults treated at Washington University between 1950 and 1979. Although the number of patients with well-differentiated astrocytomas was small, they found that those with a juvenile pilocytic type did well regardless of treatment and did not require radiation therapy, a conclusion that has been confirmed in other recent studies.

In 1987, Piepmeier[10] reviewed the records of 60 patients with low grade astrocytomas seen at the Yale-New Haven Hospital between 1975 and 1985. In this retrospective review, there was no significant difference found in survival between those patients who received radiation therapy in addition to surgery and those who did not. What is important in this study is that all patients who were irradiated received between 50 to 60 Gy delivered over five to six weeks to fields that were constructed by using CT scanning to include the tumor plus a wide margin of surrounding brain. One caveat expressed by the author, however, was that since the patient population reviewed in this paper was treated over the last decade, the mean follow up time was slightly less than five years and thus this may have been insufficient time to allow a potential effect of radiation to become evident. However, it should also be noted that most previous studies which did indicate a beneficial effect of radiation therapy did so mainly at five years, with such beneficial effect decreasing at ten years and longer.

In 1988 Medbery et al[11] reviwed 60 patients with low grade astrocytomas who were treated at the Bethesda Naval Hospital between 1960-1986. The series compared 50 patients who received post operative radiation therapy and 10 patients who did not. Although the numbers are small, there appeared to be a survival advantage at 5 years for those patients with incompletely resected lesions who received radiation therapy.

In 1989, Shaw et al[12] once again reviewed the patients at the Mayo Clinic and reported on 167 patients, of whom 139 or 83% received radiation therapy with a mean tumor dose of 5000 rads. The 5 year survival rate for those receiving high dose (>5300 rads) radiation therapy was 68%, while it was 47% for those who received low dose irradiation (<5300 rads) and 32% for those were not irradiated. The comparable 10 year survival rates were 39%, 21% and 11%. In contrast to this data for the Grade I and II astrocytomas indicating a beneficial effect of radiation therapy, they found the post operative irradiation was not associated with an improved survival in the patients with "pilocytic" astrocytomas.

Finally in this same year (1989), Hirsch et al[13] reported on 22 pediatric patients (i.e., 15 years or younger) who were operated upon for Grade I or II astrocytomas. None of these patients was initially given radiation therapy. Since only 3 recurrences (8%) were seen in the entire group of 42 patients (which included 8 patients with oligodendroglioma and 12 patients with oligoastrocytoma), the authors concluded that post operative radiation therapy should not be given in pediatric patients with low grade cerebral gliomas.

As indicated in the literature review above, the majority but certainly not all of the major English language studies have found that radiation therapy is beneficial when added to surgery in the treatment of cerebral astrocytoma. One must, however, be extremely cautious in interpreting the retrospective data from these reports. As indicated previously, it is mandatory to take into account the various prognostic factors that may be present to differing degrees in the two groups of patients that are being compared. Age, functional

status of the patient, extent of surgical removal, and pathological grade (i.e., Grade I or II) are at least some of the important variables that must be known. In almost none of the studies reviewed is this information readily available. In addition, all of these studies suffer from being retrospective analyses in which the two groups are not strictly comparable with respect to various selection factors or even the treatment given. Consequently, any conclusions reached must be considered only tentative until the proper studies are carried out.

It is possible that future advances in technology will allow us to select a sub-group of patients with low-grade astrocytomas who should receive post operative radiation therapy. Procedures that are just now being perfected will allow us to directly measure the proliferative potential of low-grade astrocytomas using immunohistochemical techniques such as either in vivo[14] or in vitro[15] labeling with bromodeoxyuridine (BUDR) or labeling with the monoclonal antibody Ki-67.[16] Preliminary data would appear to reveal a correlation between a poor prognosis and an increase in proliferative potential. Furthermore, a recent study of 12 patients with low-grade astrocytomas who underwent PET scanning with (18F) fluorodeoxyglucose (FDG) indicated that malignant change may be associated with a focal area of hypermetabolism that develops within an area that in general is hypometabolic.[17] If this is confirmed, then perhaps only those patients whose tumors have a labeling index above a certain level or who have a hypermetabolic area on PET scanning should receive radiation therapy.

The issue of whether radiation therapy should be utilized in these patients is not one that can be taken lightly. In patients with anaplastic astrocytomas or glioblastoma multiforme, it is quite probable that the relatively short survival time prevents the long-term deleterious effects of radiation therapy from becoming evident. This would not be the case in this group of patients, who have a 5-year survival rate of approximately 40% and a 10-year survival rate of perhaps 20%.

There has been a recent report of seven patients who developed malignant gliomas after radiation therapy that had been administered previously for other conditions.[18] A literature review by these authors indicated that 37 such cases have been documented, and that there was a tendency toward a younger age in the patients who experienced this complication. Although the reported incidence of radiation necrosis varies widely, a recent study indicates its presence in 9% of a series of 76 patients treated with whole brain irradiation for various intrinsic brain tumors[19]. In this regard, it is of interest that a review of 371 irradiated brain tumor patients by Marks and Wong[20] found the incidence of radiation necrosis to be 1.5% at 5500 rads, 4% at 6000 rads, and to increase substantially for higher doses. It is also generally accepted that the risk of untoward sequelae from radiation therapy is greater after whole brain radiation therapy than after more localized treatment.

Conclusions

Because the proper prospective, randomized study has not yet been done, the optimal treatment of the low-grade astrocytoma remains controversial, and thus dogmatic statements as to proper management should be avoided. Nevertheless, until more definitive data becomes available, we may draw certain tentative conclusions:

1. An attempt should be made to obtain pathological confirmation of the nature of a supratentorial lesion that is seen on CT or MRI scans and has at least some of the features of an intrinsic brain tumor.

2. Consistent with sound neurosurgical judgment as to postoperative sequelae, an attempt should be made to carry out gross total removal of a hemispheric astrocytoma or to remove as much tumor as possible.

3. In the case of such a gross total surgical removal, and even in its absence in the case of the cerebral pilocytic astrocytoma, radiation therapy can be withheld and the patient carefully followed with periodic CT and/or MRI scans. If the lesion does not show definite evidence of recurrence, then radiation therapy should be withheld. If the cerebral low-grade astrocytoma is present in a pediatric patient (ie., 15 years or younger) then radiation therapy should be withheld and the patient carefully followed with CT and/or MRI scans.

4. It is likely that within the near future new techniques utilizing monoclonal antibodies, PET scanning, etc., will allow us to select a sub-population of patients who would most likely benefit from post operative radiation therapy.

5. At the present time, however, in cases where total removal cannot be accomplished, post operative radiation therapy seems warranted.

6. Such radiation therapy should be given in a conventional fractionation schedule to a dose not exceeding 55 Gy. This radiation therapy should be given to a limited volume as determined by the CT/MRI scans rather than to the whole brain.

7. Such a treatment regimen may be expected to yield a 5-year survival of approximately 40% and a 10-year survival of up to 20%, although a more precise estimate of survival time can be made if the particular prognostic variables (especially age) of the individual patient are known.

8. The results of several multigroup, long term, prospective, randomized studies of this important question are eagerly awaited.

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