Biology and Treatment of Malignant Glioma

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A large number of oncogenes have been identified as aberrant in gliomas, but only the erbB oncogene (gene encoding the epidermal growth factor receptor [EGFR]) is amplified in an appreciable number. The loss or

Primary brain tumors can occur at all ages but tend to cluster within two distinct peaks of age incidence: The peak occurs at 55 to 65 years of age in adults and from ages 3 to 12 in children. Approximately 15,000 new cases of adult central nervous system tumors are diagnosed each year,[1] and 11,000 deaths per year are attributed to these neoplasms. Although pediatric brain tumors are less numerous, with approximately 1,200 new cases each year,[2] they are now the leading cause of death from cancer in children.

Brain tumors affect the sexes differently. Glioma, the most common central nervous system tumor in adults, affects more males than females, and the reverse is true for meningiomas. Glioblastoma multiforme (GBM) is the most common glioma, followed equally by meningioma and astrocytoma. This discussion will be limited to gliomas occurring in adults.

A three-tiered classification system places well-differentiated astrocytomas at one end of the spectrum of malignancy, GBM at the other end, and anaplastic astrocytomas in the middle.[3] A newer classification system based on histology (Daumas-Duport) appears to correlate well with outcome.[4]

The World Health Organization (WHO) has used a modification of this system to define tumors according to their aggressiveness. Grade 1 gliomas are usually pilocytic astrocytomas occurring in young people; grade 2 gliomas include astrocytomas and oligodendrogliomas (mixed oligoastrocytomas); grade 3 gliomas consist of anaplastic astrocytomas and anaplastic oligodendrogliomas; and grade 4 gliomas are glioblastomas. Oligodendrogliomas have a somewhat better prognosis than astrocytomas of similar grade.

Biology of Gliomas

Gliomas are heterogeneous with regard to their cellular content. Karyotypically, the chromosomal complement of each cell type ranges from near diploid (2n) to hypotetraploid or hypertetraploid (4n) in chromosome number, and the distribution of cell types varies with each tumor.

**Astrocytomas**

Shapiro et al recently reviewed the cytogenetic characteristics of gliomas.[5] Of 68 astrocytomas in adults, 28 had normal karyotypes. Among those cases with abnormal karyotypes, the most common chromosomal abnormality was the loss of a single sex chromosome (X or Y), occurring in 25 cases. Chromosome 7, the only chromosome gained, was noted in eight cases. Chromosomal breakpoints are rare in low-grade astrocytomas. The most common molecular abnormality is a mutation of the p53 tumor-suppressor gene located on chromosome 17,[6] but this mutation occurs without structural changes and with or without loss of heterozygosity (LOH).[7]

**Anaplastic Astrocytomas**

Anaplastic astrocytomas are thought to evolve from astrocytomas. In the review by Shapiro et al, of 127 anaplastic astrocytomas, only 10 had normal karyotypes.[5] Chromosomal gain and chromosomal loss were frequent. The most common gain was of chromosome 7, with less frequent gain of chromosomes 19 and 20. Loss of chromosomes 10, 22, and a single sex chromosome were prominent. Loss of a sex chromosome occurred as an isolated event, whereas multiple chromosomal abnormalities were the rule with gains of chromosome 7 or loss of chromosome 10. Structural chromosomal abnormalities are not uncommon. More than 30% of anaplastic astrocytomas have mutation and/or deletion of the p53 gene.[8] The loss of p53 function, related to cell cycling through cyclin-dependent kinase (CDK), appears to account for some neoplastic behavior. When p53 is not mutated, in some cases there may be an amplification of another gene, murine double minute 2 (MDM2), which codes for a cellular protein that complexes with the p53 tumor-suppressor gene product and inhibits its function.[9]
Loss of heterozygosity for several other genes (CDK4, SAS, MTS-1) has been demonstrated in cases of anaplastic astrocytoma, but the frequency of these abnormalities is less than 5%. Analysis of more cases is needed to determine their significance.

**Glioblastoma Multiforme**

The incidence of GBM peaks in the mid-60s. Glioblastoma multiforme is the most malignant of the astrocytic tumors; median survival time of patients with this diagnosis is approximately 1 year (see below). This tumor is highly infiltrative, producing undifferentiated elements as a dominant feature, with high mitotic activity and necrosis. Vascular proliferation is invariably present, and the bromodeoxyuridine/Ki-67 labeling index is high. Although genetic instability of this tumor results in complex, nonuniform genetic changes, malignant gliomas of the astrocytic series show several significant nonrandom chromosomal changes. The review cited above identified 198 cases of GBM.[5] The most frequent numerical chromosomal changes were the gain of chromosomes 7 and 20 and the loss of chromosomes 10, 22, and a single sex chromosome. The gain of chromosome 20 was more evident in GBM than in anaplastic astrocytoma. Chromosomal losses were more prevalent than gains, with added loss of whole chromosomes 9, 13, and 14.

The proportion of tumors in males with loss of a single sex chromosome is approximately the same as in anaplastic astrocytomas. Of the 58 cases with loss of the Y chromosome, it was the only abnormality in half the cases, while the remaining cases lost a Y chromosome in addition to other clonal abnormalities.

Structural chromosomal abnormalities are common in glioblastomas; the most frequent occur in chromosomal arms 9p, 9q, 1p, and 6q, in which multiple breakpoints have been identified, often producing rearrangements. Double minute chromosomes containing amplified DNA occur in 25% to 50% of reported cases. Marker chromosomes occur in 30%. Because markers may represent selective retention of specific genes, their origin is being assessed with fluorescence in situ hybridization (FISH) techniques.[10]

### Significant Genetic Lesions

The largest body of molecular data for astrocytic tumors has been obtained from GBMs.[11] The frequency of p53 mutation and/or allelic loss is approximately the same in GBMs as in anaplastic astrocytomas, supporting the hypothesis that this DNA lesion occurs early in the evolution of gliomas.[6] Additional support for this theory comes from a study in which clonal expansion of a p53 mutation was demonstrated in the recurrent tumor.[12]

Other significant genetic lesions involve chromosome 7, which is overrepresented in the majority of GBMs. The genes encoding the epidermal growth factor receptor (EGFR) and the A-chain of platelet-derived growth factor (PDGF-A) map to chromosome 7. Both genes are amplified and/or overexpressed in GBMs.

Epidermal growth factor receptor amplification and/or gene rearrangement, occurring in 40% to 60% of GBMs, is frequently associated with the expression of truncated forms of the message and protein.[13] Overexpression of PDGF is less frequent, but its autocrine regulation suggests that, like EGFR, it could provide a selective growth advantage to tumor cells. Transforming growth factor-alpha (TGF-alpha) has approximately a 50% homology with EGF. Numerous tumors secrete TGF-alpha, including high-grade malignant gliomas. Transforming growth factor-beta has been found to inhibit certain immune reactions, and such inhibition may influence tumor growth.

Other abnormally expressed growth factors in gliomas include fibroblast growth factor (FGF) and insulin-derived growth factor (IGF). Although such growth factors are less common, each has been implicated as having an autocrine/paracrine growth stimulatory function in gliomas, suggesting that they contribute to the tumor's uncontrolled growth.[14]

The loss of the whole chromosome 10 has been reported in approximately 50% of the tumors reviewed, but allelic loss from 10p and 10q is even more common, occurring in 70% to 80% of the tumors. Although the identity of specific putative tumor-suppressor gene(s) remain(s) unknown, loss of at least two independent regions from chromosome 10 has been demonstrated, suggesting the existence of more than one tumor-suppressor gene.

Some investigators have attempted to subdivide patients with GBMs, assuming that different pathways depend on the genetic defects acquired in the formation of GBMs. Tumors that progress in a stepwise manner from low grade to more malignant anaplastic astrocytoma and then to GBM have a p53 mutation followed by allelic loss of chromosome 10. In contrast, GBMs that arise de novo demonstrate allelic loss on chromosome 10 and amplification of EGFR.[15,16] Other workers have attempted to determine whether subsets of genetic lesions are prognostically significant.[17]

One is still confronted with the problem of understanding the biology of those tumors that do not
appear to have the genetic lesions described above. An obvious source of such confounding data is tumor heterogeneity, which can be demonstrated by histology, cytogenetics, and molecular techniques.[18,20] Data to support the hypothesis that some genetic alterations may actually presage the frank appearance of histologic markers have been obtained from regional analyses of cytogenetic characteristics,[18] flow cytometric analysis of polyploidy and S-phase fraction,[18] LOH analysis,[19] and comparisons of primary and recurrent tumors from the same patient.[20] The presence or absence of a gene, chromosome, or chromosomal locus provides a clue as to the function that is missing or aberrant in a cell. However, any aberrant phenotype may result from several mechanisms rather than being mediated by a single gene. An example of this is the allelic loss associated with chromosome 9p. The p16 protein, which maps to this region, acts as a cell-cycle inhibitor of CDK4. However, recent studies have shown that aberrant cell-cycle control may arise from many different genetic lesions, including amplification of MDM2 or CDK4 (chromosome 12) and mutation of p53 (chromosome 17).

**Blood-Brain Barrier Alterations**

Finally, any discussion of the biology of brain tumors must include a comment on the environment of the tumor. The blood-brain barrier is substantially altered in malignant gliomas, although the “breakdown” is incomplete. One immediate consequence of the alteration in the blood-brain barrier induced by brain tumors is cerebral edema. The edema appears to be induced by a soluble factor(s) produced by gliomas, which increase(s) vascular permeability.[21] Edema is well treated by corticosteroid hormones.

**Treatment of Malignant Glioma**

Multimodality therapy—cytoreductive surgery, radiation therapy, and chemotherapy—has been utilized in one form or another in the treatment of malignant glioma for the past 25 years.[22] Much of this experience was a direct product of clinical research by individual institutions and cooperative group trials. We will briefly review each of the modalities, concentrating on recent results and controversies.

**Surgery**

The role of surgical resection in the treatment of malignant gliomas remains controversial even after 75 years of experience with primary malignant gliomas.[23] Surgery permits a pathologic diagnosis to be established while the patient is still alive. However, many physicians argue that current radiologic imaging methods, including computed tomography (CT) and magnetic resonance imaging (MRI), permit a malignant brain tumor to be diagnosed without the necessity for attempted tumor resection and, thus, avoid the risks of surgery. Although stereotactic biopsy usually provides enough tissue to make a diagnosis of primary glioma, the amount of tissue may be inadequate to grade the tumor.[24]

Stereotactic biopsy alone, or even small open craniotomy biopsy, denies a role for surgery as “anticancer” therapy. There is evidence that surgical reduction of tumor to very small residual amounts can prolong survival and permit patients to return to active lives. In one Brain Tumor Cooperative Group (BTCG) study, CT scans from brain tumor patients were studied at several times in their disease course and compared to ultimate outcome.[25] This study found no significant relationship between preoperative tumor size and prognosis. On the other hand, there was a very strong relationship between postoperative tumor size and survival, especially in patients with minimal or no residual enhancement.

There was a statistically significant ordering of tumor size, such that patients with very little residual enhancement (< 1 cm² in length × width area) had the longest survival, followed by those with tumors of 1 to 4 cm², and then by patients with tumors > 4 cm² (P = .0001). When the difference between preoperative and postoperative tumor size was evaluated, no significant relationship was discerned between the percentage of tumor removed and survival, although a trend toward longer survival was seen in patients whose tumors were reduced by ≥ 75%. Thus, the beneficial effect of surgery derives more from leaving the least amount of residual tumor possible and less from debulking.

In another similar study using postoperative MRI (on days 1 to 3 after surgery), a significant ordering of survival was associated with removal of more tumor.[26] Patients with postoperative residual contrast-enhanced tumor had nearly a sevenfold higher risk of death than did patients without residual tumor. Postoperative MRI was three times more accurate in defining the extent of surgical resection than was the surgeon’s estimate. Of note, 80% of the tumor recurrences emerged from contrast-enhanced remnants.
The Extent of Resection and Survival

Three consecutive Radiation Therapy Oncology Group (RTOG) trials reviewed the relationship between the extent of surgical resection and survival for glioblastoma.[27] Surgical resection was defined as total in 19%, partial in 64%, and biopsy-only in 17%. More extensive surgical resection was associated with statistically significant longer survival; the median survival of patients who underwent total resection was 11.3 months, as compared with 6.6 months for those who had biopsy only.

Kelly and Hunt argue that there is little benefit to attempting major resection in elderly patients, although the patients in their study who underwent resection always showed a survival advantage over those whose tumors were merely biopsied.[28] All such retrospective studies are subject to the criticism that the extent of attempted resection depends on the condition of the patient at the time of surgery (age, tumor location, clinical state), and that favorable conditions usually lead the surgeon to attempt a greater resection. Therefore, in such studies, it is not clear that the extent of surgery is as important to survival as are the more favorable prognostic variables.

Nevertheless, these results support the surgical removal of the largest possible tumor volume that can be done safely. There is little justification in performing biopsy alone or limited resection of accessible tumors. If the surgical resection is confined to the tumor itself, it rarely induces a major new neurologic defect. On the contrary, patients are frequently able to return to a full, active life without the need for large doses of corticosteroids to ameliorate incapacitating symptoms.

Radiation Therapy

The proper portals and doses of radiation for brain tumors have changed with the advent of better imaging techniques. The BTSG first reported in controlled studies that postoperative whole-brain radiation therapy increases patient survival over surgery alone.[29,30] Other data showed that patients receiving 5,500 to 6,000 cGy of radiation live significantly longer than those receiving ≤ 5,000 cGy.[31]

In the aforementioned BTSG study of CT scanning,[25] patients with no tumor enhancement after radiation therapy had better survival than those with residual tumor. Patients with larger tumors that shrank by > 50% survived longer than those whose tumors shrank < 50% or those whose tumors actually increased in size.

One BTSG study compared entirely whole-brain radiation therapy with whole-brain plus partial coned-down radiation in patients with malignant glioma.[32] There was no statistical difference in survival between the groups, indicating that reduction of part of the radiotherapy to the tumor volume is as effective as full whole-brain irradiation. Neither increased fractionation of radiotherapy (twice daily) nor addition of the radiosensitizer misonidazole confers any survival advantage over conventional postoperative whole brain radiotherapy and carmustine (BCNU [BiCNU]).[33] Focal radiotherapy techniques include interstitial implantation of radioactive seeds (brachytherapy) and radiosurgery.

Brachytherapy

Prolonged survival has been reported in patients with recurrent malignant gliomas who were treated with temporarily implanted iodine-125 sources.[34] A BTSG phase III trial (BTCG 87-01) randomized newly diagnosed patients to receive either (1) postoperative temporary iodine-125 seed implantation in the residual tumor bed, followed by standard external-beam radiotherapy plus IV BCNU; or (2) external radiotherapy plus BCNU, without seed implantation. The purpose of this controlled trial was to test in newly diagnosed patients the potential survival value of adding 60 Gy in the form of brachytherapy to the 60 Gy delivered by external irradiation. The study was closed in April 1994, when accrual reached 299 patients.

Preliminary review of the results demonstrated that patients who received iodine-125 seeds lived longer than those who did not receive seeds, although the difference did not quite reach statistical significance. About 50% of the patients underwent reoperation in both the implanted and the nonimplanted groups. Patients with recurrent tumor lived longer after resection if the recurrence was due to radiation necrosis (mostly from seeds) than if tumor was present at recurrence. The incidence of biopsy versus tumor resection was approximately equal in the two groups, thus indicating that the difference in survival was not related to the extent of tumor resection at the time of failure. The study suggests but does not prove that brachytherapy extends survival beyond that achievable with external radiotherapy alone.

Radiosurgery, either by gamma knife or linear accelerator, has been shown to be effective in the treatment of arteriovenous malformations, small primary and metastatic brain tumors, and benign brain tumors, such as meningiomas and acoustic neuromas. Its investigational use in the treatment of gliomas has been addressed in several reports. In one trial, 37 patients received radiosurgery (1,000 to 2,000 cGy) to residual contrast-enhancing tumor after treatment with conventional
external-beam radiation therapy.\[35\]. Local recurrence still occurred, but overall survival time may have been prolonged. Of the 37 patients, 7 (19\%) required reoperation at a median time of 5 months after radiosurgery to remove necrotic tumor.

Another study of the value of radiosurgery in patients with malignant gliomas revealed little additional survival benefit over that reported for external-beam radiotherapy.\[36\]

A major problem with radiosurgery (as with brachytherapy) is bias in the selection of patients for treatment. Curran et al pointed out that radiosurgery-eligible patients live longer than radiosurgery-ineligible patients, when neither group actually receives radiosurgery.\[37\]

Radiosurgery may be of benefit in a small group of good-prognosis patients with small tumors.\[38\]

The RTOG is performing a randomized trial (RTOG 9305) that is similar to the BTCG interstitial radiotherapy study. This study is randomizing patients with supratentorial malignant gliomas, Karnofsky performance score ≥ 60, and postoperative residual disease ≤ 4 cm in greatest diameter to treatment with either radiosurgery followed by external radiotherapy (60 Gy) and BCNU or radiotherapy and BCNU alone.

**Chemotherapy**

In 1983, the BTSG reported that surgery plus radiation therapy and BCNU chemotherapy significantly adds to the survival of patients with malignant glioma, as compared with surgery plus radiation therapy without chemotherapy.\[39\]

High-dose methylprednisolone does not prolong survival.\[39\]

Both procarbazine (Matulane) and streptozotocin (Zanosar) have demonstrated effectiveness similar to that of BCNU.\[33,39\] BCNU alone is as effective as BCNU followed by procarbazine, or BCNU plus hydroxyurea followed by procarbazine plus teniposide (VM-26 [Vumon]).\[32\]

Intra-arterial (IA) BCNU is no more effective than IV BCNU and substantially more toxic.\[40\]

Serious toxicity induced by IA BCNU included irreversible encephalopathy and/or visual loss ipsilateral to the infused carotid artery. In the same study, fluorouracil did not influence survival. Neuropathologically, IA BCNU produced white matter necrosis.\[41\]

Intra-arterial cisplatin (Platinol) is safer than BCNU administered by the same route but is no more effective than another nitrosourea, PCNU.\[42\]

Over the past several years, there has been increasing interest in the use of targeted interstitial drug delivery using biodegradable microspheres and wafers. In a multicenter controlled trial, 222 patients with recurrent malignant gliomas who required reoperation were randomly assigned to receive surgically implanted biodegradable polymer discs containing 3.85% of BCNU (Gliadel) or discs containing placebo.\[43\]

Median survival of the 110 patients who received BCNU polymers was significantly longer than that of the 112 patients who received placebo polymers (31 vs 23 weeks). Because BCNU is readily administered intravenously, a comparative study between BCNU-containing wafers and IV BCNU would help define the role of wafers containing this drug. However, studies of wafers containing other agents that do not readily enter brain tumors would be of greater interest.

In addition to these controlled survival-based clinical trials, a large number of agents have also been tested in response-based studies in glioma patients.\[44\]

To date, however, no drug has been found to be more effective than the nitrosoureas. The combination of procarbazine, CCNU, and vincristine (PCV) has become a popular chemotherapeutic regimen for malignant glioma, and may be more effective than BCNU alone.

Of the malignant gliomas, GBM responds least well to chemotherapy, anaplastic astrocytoma better, and, according to recent studies, oligodendrogliomas may be most chemosensitive.\[45,46\]

Future therapeutic strategies include both conventional chemotherapy and gene therapy.

**Treatment of Low-Grade Glioma**

The advent of CT and MRI has had a substantial impact on our ability to diagnose and follow brain tumors. Patients with low-grade gliomas may present only with a single seizure, but the tumor is readily seen as a T2 mass on MRI. However, with earlier diagnosis has come unresolved therapy questions, some of which are discussed below. **Low-Grade Astrocytomas of the Cerebral Hemisphere**

Adults with low-grade astrocytomas of the cerebral hemisphere generally have a good prognosis, with expected survival of 3 to 7 years. Increasingly, patients with low-grade astrocytomas present with a single seizure, and the tumor is found on MRI. In one study, neither CT nor MRI was accurate enough to diagnose or grade such tumors.\[47\]

Of 20 patients diagnosed by imaging studies who underwent stereotactic biopsy, only 10 (50\%) had low-grade astrocytomas, whereas 9 (45\%) had anaplastic astrocytomas and 1 (5\%) had encephalitis. Thus, surgical biopsy is necessary to diagnose and especially to grade the tumor.

Therapy for patients with low-grade astrocytomas includes resection, irradiation, and chemotherapy, but there has been controversy over when to treat patients and with which of these modalities. Removal may be curative, but when residual tumor is present after attempted resection, the patient
may benefit from radiation therapy.

Laws et al analyzed 461 cases of supratentorial low-grade astrocytoma.[48] Age was the most important prognostic indicator; 83% of patients under age 20, but only 12% of patients age 50 and over, survived 5 years. Other important prognostic variables included postoperative neurologic deficit, altered consciousness, type of surgery (actually, extent of resection), date of treatment (worse before 1949), and tumor site (frontal/temporal worse).

The authors concluded that resection offers the best hope for cure, or at least is associated with the longest survival. Radiation therapy appeared to be valuable primarily in patients over age 40 who had more extensive tumors.

In a review of 221 patients treated at the University of Washington, Berger et al also found that the extent of surgical resection influences outcome.[49] When the tumors were totally resected, there was no recurrence (mean follow-up, 54 months). Postoperative residual tumors of < 10 cm³ were associated with a 14.8% recurrence rate at 50 months, while larger residual tumors were associated with a 46% recurrence rate at 30 months (P = .002). Furthermore, 46% of patients with residual tumors > 10 cm³ had a histologically higher grade at recurrence. Radiotherapy, age, and histologic subtype were not predictive of recurrence.

The role of radiation therapy in the treatment of low-grade astrocytoma remains controversial. Shaw et al[50] updated the Mayo Clinic experience of Laws et al, dividing the cases into those treated between 1960 and 1974 and between 1975 and 1982.[4] They also utilized the new Daumas-Duport classification, which allowed patients originally considered to have Kernohan grade I or II tumors, which have the same prognosis, to be divided into four grades with different prognoses. On multivariate analysis, four variables were found to predict survival. Of these, the most important was the classification into pilocytic astrocytoma vs ordinary astrocytoma (including astrocytoma and mixed oligoastrocytoma). The pilocytic astrocytomas had 5- and 10-year survival rates of 85% and 79%, respectively, while the ordinary astrocytomas had 5- and 10-year survival rates of 51% and 23%, respectively.

Patients with ordinary astrocytomas who received at least 53 Gy of radiotherapy had 5- and 10-year survival rates of 68% and 39%, respectively, while corresponding figures for those receiving < 53 Gy were 47% and 21%, respectively, and for those undergoing resection without radiation therapy the survival rates were 32% and 11%, respectively. One cannot draw definitive conclusions from these data because of the retrospective nature of the study, although the data do support the notion that patients with incompletely resected ordinary astrocytomas should receive radiation therapy.

Soffietti et al noted that, in 85 patients with well-differentiated astrocytomas, total tumor removal produced a 5-year survival rate of 51.3%, while only 23.5% of those who underwent subtotal resection were alive at 5 years, and no patient who underwent partial resection survived longer than 5 years.[51]

Vertosick et al reviewed their experience with 25 patients with well-differentiated astrocytomas, concluding that such patients live longer than they used to, in part, because of the earlier diagnosis possible with modern imaging. They questioned the need for surgical resection.[52]

One study from Paris failed to document a decisive role for radiation therapy.[53] At 5 years, 80% of patients whose tumor was totally removed were alive, as compared with 50% who had incomplete removal and 45% who underwent biopsy alone. Of those who did not receive radiotherapy, 65% were alive at 5 years, as compared with 55% of those given radiotherapy.

Recht et al found that the overall survival of a group of 26 patients who were not operated on for a newly diagnosed supratentorial nonenhancing mass lesion on CT or MRI was similar to that of another group of 20 patients who were treated immediately.[54] The overall median survival of both groups was 84 months.

Winger et al addressed the issue of malignant transformation of low-grade glioma and its relationship to overall survival.[55] In their study of 285 patients with malignant gliomas, they noted that those with a prior history of low-grade glioma lived significantly longer after the diagnosis of anaplastic glioma than those in whom anaplastic glioma arose de novo. Thus, early irradiation of low-grade gliomas may extend overall survival.

One concern about irradiating the brains of patients with low-grade gliomas is the potential for radiation damage in a population expected to live long enough to experience it. One report suggests that such damage is uncommon, in that specific cognitive deficits were not encountered in patients so treated.[56]

**Oligodendrogliomas**

Oligodendrogliomas occur mostly in middle-aged adults, although there is also a small peak in incidence in children (6% to 8% of patients are 15 years of age or younger). The most common
clinical manifestation is seizures, and many of the tumors demonstrate calcification on routine skull films or CT scans. Several reports have related survival to grading of oligodendrogliomas; grading is historically related to the number of mitoses and degree of necrosis in one study,[57] and to endo-thelial proliferation, necrosis, maximal nuclear/cytoplasmic ratios, maximal cell density, and pleomorphism in another study.[58,59]

The role of radiation therapy in the treatment of oligodendroglioma is not established. Lindegaard et al found that 108 irradiated patients had a significantly better median postoperative survival time than did 62 patients who did not receive radiotherapy (38 vs 26.5 months; \( P = .039 \)).[60] Radiation therapy was most beneficial in patients who underwent subtotal resection; it was less clearly valuable in patients whose tumors were thought to have been totally resected. This was also true of the series of Shaw et al, in which patients receiving subtotal resection plus radiotherapy lived longer than those undergoing resection alone. This was a retrospective series, however, and patients often were not treated with radiation.[61] Similarly, Bullard et al found no statistical difference in survival between patients treated with radiation therapy (37 patients) and those who underwent surgery without radiation therapy (34 patients).[62]

Shaw et al reviewed their experience with mixed oligoastrocytomas in 71 patients, noting that tumor grade (Kernohan) was most strongly associated with survival.[63] The 60 patients with grades 1 and 2 tumors had a median survival of 6.3 years and 5- and 10-year survival rates of 58% and 32%, respectively, as compared with a 2.8-year median survival and 5- and 10-year survival rates of 36% and 9%, respectively, in 11 patients with grades 3 and 4 tumors. Age < 37 years, gross total resection, partial-brain radiation, and radiation dose \( \geq 5,000 \) cGy were associated with improved survival.

A large series of patients reported by Celli et al yielded slightly different results.[64] Only three variables correlated positively with survival: benign histology, recent operative period (ie, after 1977), and postoperative radiotherapy therapy. Subgroup analysis found that radiotherapy prolonged survival in patients with neurologic deficits only but not in those who presented with seizures and negative neurologic status. The authors suggested that different clinical presentations correspond to different stages in the natural history of the disease, and that radiation results vary with the tumor \(^{\text{type.}}\)

Finally, there is increasing evidence that oligodendrogliomas may be sensitive to chemotherapy.[45,46] Several controlled trials of chemotherapy are underway.

**Conclusions**

Primary brain tumors, especially gliomas, represent an especially difficult therapeutic challenge for several reasons: (1) The brain is so unforgiving in its response to tumor and therapy; (2) the tumor cells themselves are so unstable and develop resistance so easily; and (3) the tumor's environment is so far removed from the therapist's tools. Advances in understanding the biology of both tumor and brain cells promise to lead to new therapeutic approaches for these tumors.

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**Addendum**

Since the submission of this article, the putative tumor-suppressor gene located at 10q23-24 has been identified by two independent groups and has been designated MMAC1[65] or PTEN[66]. The protein encoded in this region contains significant homology to the catalytic domain of protein phosphatases and to the cytoskeletal proteins, tensin and auxilin.


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