Brain Tumors
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Brain Tumors

Edited by

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Preface

Exciting new developments and discoveries of the last two decades are beginning to shed light on the complex biology of brain tumors and are advancing our understanding of the cellular and molecular processes involved in their initiation, progression, and clinical and biological behavior. The disease process in brain tumors is quite complex and the resulting tumors are characterized by a high degree of biological and clinical diversity. Thus, despite the advances of the last two decades, prognosis for patients with malignant brain tumors remains abysmal. Significant progress in the diagnosis, treatment and, ultimately, prevention of these tumors will require both the timely harnessing of the advances in basic and clinical brain tumor research, and a continuing concerted effort at increasing our understanding of brain tumor biology, in particular, the molecular genetic changes and perturbations of cellular pathways involved in brain oncogenesis and which drive the biological and clinical behavior of the tumors. Brain tumor diagnosis and prognosis, which is still largely based on histopathology and other clinical criteria, will, in the future, acquire a significant molecular component, with the incorporation of knowledge of genes that are mutated, over-expressed, deleted, silenced, or functionally altered in the tumors. Treatment strategies for brain tumors, rather than being empirical, will be rationally developed based on an understanding of the cellular and molecular mechanisms and targets that have been activated, suppressed, or otherwise altered. The discovery of new therapeutics will employ novel paradigms of rational drug discovery that incorporate structural biology, genomics, proteomics, computational chemistry and high throughput approaches. Advances in genetic epidemiology and neuro-oncogenesis will lead to the definition of high risk genotypes and phenotypes and provide the basis for genetic counseling of individuals and populations at risk for brain tumors, and facilitate the development of brain tumor prevention strategies.

The goal of Brain Tumors is to bring together the major scientific advances and developments in important areas of brain tumor research of the last two decades. The explosion of knowledge in the neurosciences and in neuro-oncology that has marked this period make this a timely and much needed undertaking. The chapters, organized into three main sections, emphasize recent research advances, rather than a review of established knowledge. The first section is devoted to the molecular biology, genetics, epidemiology, and pathology of brain tumors, and includes chapters on molecular profiling, molecular pathology and classification, in vitro and in vivo brain tumor models, brain metastasis and progenitor cell biology. The second section focuses on the cellular and genetic pathways involved in brain oncogenesis, malignant progression, and therapeutic response. Individual chapters cover oncogenes and tumor suppressor genes, DNA damage and repair, invasion and migration, cell cycle, growth factors, signaling, apoptosis, and developmental biology. The final section covers areas relevant to brain tumor therapy, with chapters focusing on advances in pharmacological concepts, therapeutic modalities, novel therapeutic targets, rational drug design, gene and viral therapy, drug delivery, and the blood–brain barrier, immunotherapy, and brain imag-
Brain Tumors provides for the established brain tumor scientist and clinician, as well as, for the new investigator, graduate, or undergraduate student, a comprehensive, up-to-date guide to the critical research topics in the rapidly evolving area of neuro-oncology. The contributors of the chapters in this volume are all leaders at the frontiers of basic and clinical neuro-oncology research and practice whose work over the years has helped define the field. To each of them, I express my deepest thanks for a scholarly contribution that has resulted in a volume that is a major effort to better understand and ultimately eradicate, or at least minimize, human suffering from brain tumors.

Francis Ali-Osman, DSc
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I Epidemiology, Biology, Genetics, and Pathology
Epidemiology of Brain Tumors

Randa El-Zein, Melissa Bondy, and Margaret Wrensch

1. INCIDENCE AND RESEARCH INITIATIVES

1.1. Epidemiology

Brain cancer accounts for approx 1.4% of all cancers and 2.3% of all cancer-related deaths. The incidence of primary cerebral malignancies varies between 4 and 10/100,000 in the general population. This incidence tends to increase with age (4/100,000 up to the age of 12 yr; 6/100,000 up to the age of 35 yr; 18/100,000 up to the age of 55 yr; 70/100,000 up to the age of 75 yr).

In 2002, over 35,000 (approx 6 per 100,000) Americans were diagnosed with brain tumors (84). The annual death rate from the group of conditions so classified is some 13,000/yr. Currently, in part, owing to improved diagnostic methods, approx 16,800 brain tumor cases are diagnosed each year as malignant, with poor prognosis (3). However, even those cases that are classified as benign and are treatable, are significantly interfered with normal brain function that is essential for a normal life (3).

The continuing grim outlook for patients, the often devastating impact of even treatable low grade pediatric cancers and other benign disorders, as well as breakthroughs in genetic research, have given new impetus to brain cancer research.

Two types of epidemiologic studies, descriptive and analytical, have figured prominently in the notable recent increase in research effort in brain tumors. Descriptive studies characterize incidence, mortality, and survival rates associated with brain tumors by category of histologic tumor type and patient demography, such as age, sex, and geographic region. Analytic epidemiologic studies compare, in cohorts the risk of brain tumors in people with and without certain characteristics and histories, explore risk factors that can be implicated in the development of cancer.

A wide variety of risk factors, including diet, smoking, alcohol, occupation exposures, radiation, infections, allergies, head trauma, and family history are being intensively investigated for their role in brain tumors. In recent years, a greater focus is being directed at inherited polymorphisms in genes related to carcinogen metabolism, and DNA repair, as well as, gene environment interactions. The relative rarity of brain tumors makes the assembly of large cohort studies difficult and, therefore, most commonly these analytic studies use the case-control approach.

Though increasingly illuminating, epidemiologic studies of brain cancer lack consensus on the nature and weight of individual risk factors. Variations in study designs, population and information sources, measurement, and classification together cloud the research. Studies differ in methodologies such as those for selection of study subjects and determination of whether the subjects are representative, and the definition and selection of control groups. Studies vary in their reliance on proxy and historical information and the standards of precision and fullness that these must meet. They also face basic classification problems arising from the heterogeneity of primary brain tumors; inconsistencies
in histologic diagnoses, definitions, and groupings. In 1993, the World Health Organization (WHO) tumor classification was last updated but is not in universal use. This complexity is further compounded by difficulties in verifying past exposures.

1.1.1. Age and Sex of Patients

The likelihood of different histologic types of brain tumor having different etiologic factors is suggested by age distribution and differences in site and histology of the tumors. For all primary brain tumors, although patient average age at onset is about 54 yr, there is a significant variation for each histological category. For example, the average age of onset for glioblastoma and meningiomas is 62 yr (84). In meningioma, the incidence increases with age, except for a slight decline in those 85 yr or older. In contrast, astrocytoma and glioblastoma peak in incidence at age 65 to 74 yr, whereas oligodendroglioma peaks at age 35 to 44 yr. Some of this variation may reflect differing diagnostic practices and access to diagnosis in different age groups. Much of the age-related tumor incidence increase may be accounted for by the duration of exposure required for malignant transformation, the number of genetic alterations required to produce clinical disease, or poorer immune surveillance with advancing age. An intriguing and incompletely explained feature of brain tumors is a peak in incidence in young children, which is not completely attributable to tumors of primitive neuroectodermal origin, which are primarily pediatric tumors.

In general, men experience higher rates of primary brain tumors than women, with the exceptions of meningiomas, which affect 80% more females than males, and tumors of cranial and spinal nerves, and the sellar region, which affect males and females almost equally (110). Gliomas affect about 40% more males than females (110). A New York State study showed that gender differences in glioblastoma appeared around the age of menarche, peaked near the age of menopause, and decreased thereafter, suggesting a protective effect of female hormones (85). Any comprehensive theory of the distribution and causes of brain tumors needs to include an explanation for the consistently observed age and gender differences.

As the incidence has become more accurately described a result of better and more consistent diagnosis and study designs approaching congruity, dramatic progress in the molecular classification of tumors opens the possibility of identifying etiologically homogeneous subsets of tumors. The accelerating characterization of potentially relevant genes has also created an opportunity to determine which of them might enhance susceptibility or resistance to brain tumors or etiologic environmental agents. Of special interest in carcinogenesis are proto-oncogenes, which initiate carcinogenesis by activating cell division, and suppressor genes that inhibit tumor growth and progression (120). Because such genes play a role in disease progression and sensitivity (or resistance) to radiation or drug treatments, knowledge from their study may result in feasible prevention strategies.

1.2. Histology and Molecular Genetics of Brain Tumor Types

Primary brain tumors are currently classified by histology and location. However, this classification is complicated by the potential ability of any of the cells of the nervous system to become cancerous, resulting in a mixture of cell types often seen in many brain tumors. Brain tumors have been further categorized by the WHO on the basis of their invasiveness or malignancy. The more invasive forms, which often show more frequent gene mutations, are given higher numbers. The relevant research findings on the individual brain tumors are summarized below.

1.2.1. Gliomas

Gliomas arise from the glial component of the nervous system and their cells provide an interface between neurons and brain fluids. They are the most common primary brain tumor and account for more than 40% of all central nervous system neoplasms with a peak incidence around age 60 yr (61). Despite the fact that gliomas are derived from astrocytes, oligodendrocytes, or ependymal cells, significant variations exist between them that may reflect the genes involved in their genesis (62). In
general, glial tumors are named after their putative cell type of their origin: viz., astrocytomas, oligodendrogliomas, and ependymomas.

1.2.1.1. ASTROCYTOMAS

Astrocytomas account for the majority of brain tumors, with an incidence in children of about 700 annually for low-grade forms, and approx 100 high-grade cases affecting the ubiquitous star-shaped cells that provide extensive structural and physiological support of neurons in the central nervous system (CNS). Astrocytic tumors comprise a wide range of neoplasms that differ in their location within the CNS, age and gender distribution, growth potential, extent of invasiveness, morphological features, tendency for progression, and clinical course. There is increasing evidence that these differences reflect the type and sequence of genetic alterations acquired during the process of transformation. The WHO has distinguished the following clinicopathological subtypes of astrocytomas:

a. WHO grade I, or pilocytic astrocytoma, the most common brain tumor in children and primarily a pediatric tumor, rarely undergoes neoplastic transformation. Even though the most benign of the astrocytomas, depending on location, they can interfere with vital sensory functions and often recur after apparently complete resection.

b. WHO grade II, or fibrillary astrocytomas account for 25% of all gliomas and are infiltrative in nature. Despite their relative lack of aggressive histologic features, low-grade astrocytomas in adults are fatal in the great majority of patients.

c. WHO grade III, or anaplastic malignant astrocytomas, are highly malignant gliomas and have an increased tendency to progress to glioblastoma.

d. WHO grade IV, diffuse astrocytoma or glioblastoma multiforme, is a highly malignant brain tumor and typically affects adults. This type of glioma has poor prognosis, in part, because the poorly defined tumor rapidly spreads to other regions of the brain. These are the most common intracranial neoplasm and account for more than 60% of all primary brain tumors.

The identification of genetic alterations in astrocytomas has led to the recognition that the nonrandom series of genetic changes reflects increasing malignancy and clinical grade (49). Several common, chromosomal alterations have been observed that are associated with changes in the expression of and/or function of several genes. For example, mutations in the p53 gene on chromosome 17p have been reported in 40% of astrocytic tumors of all grades. These mutations occur primarily in gliomas in young adults rather than children (47). Another gene whose loss or alteration occurs rarely in low-grade but frequently in high-grade tumors is the cyclin-dependent kinase N2 (CDKN2) or p16. Deletion of both copies of the CDKN2 gene on chromosome 9p is common in high-grade astrocytomas (115). In addition to deletions, rearrangements in the p16 gene have also been reported. Deletions of chromosome 10 (which harbors several tumor suppressor genes) (56), commonly occurs in higher grade astrocytic tumors. Loss of heterozygosity at 10q23 has been reported in approx 70% of glioblastomas. The tumor suppressor gene, MMAC1 or phosphatase tensin homolog (PTEN), on 10q is mutated in 40% of glioblastomas, but rarely mutated in low-grade gliomas. As a result, MMAC1 has been suggested to play an important role in progression from low-grade to high-grade gliomas (8).

Some chromosomal changes in gliomas often include both loss of tumor suppressor genes and activation of oncogenes, resulting in altered, often increased cell proliferation. The epidermal growth factor receptor (EGFR) gene is the gene most frequently amplified in malignant astrocytomas. The EGFR protein is a receptor for epidermal growth factor, an important proliferative stimulant for astrocytes. Amplification of a mutated EGFR allele has been found in approximately one-third of glioblastomas but absent in low-grade astrocytomas (55).

1.2.1.2. OLIGODENDROGLIOMAS

Oligodendroglioma develops from oligodendrocytes, which are cells that produce the lipid covering of the axons of nerve cells. This type of tumor occurs normally in the cerebrum, particularly in the frontal or temporal lobes, and is more common in adults than in children and in men more than
women. Oligodendrogliomas constitute 5–12% of all glial tumors and 5–7% of all intracranial tumors. They tend to grow slowly and demonstrate characteristic calcifications both in histological as well as on computed tomography and X-ray examinations. Although, clinically less aggressive than astrocytomas, oligodendrogliomas are invasive and can traverse into the cerebral spinal fluid (CSF). Oligodendrogliomas are capable of metastasizing and are often more difficult to remove surgically; however, they generally have a better prognosis and survival outlook than do other gliomas. Like other gliomas, oligodendrogliomas are graded between 1 and 4 depending on their malignancy and rate of growth.

Oligodendrogliomas characteristically exhibit loss of chromosomal regions on 1p and 19q13 and, less frequently, on 9q and 22 (97). Hoang-Xuan et al. (51) examined the molecular profile of 26 oligodendrogliomas (10 grade II and 16 grade III) and found that the most frequent alterations were loss of heterozygosity on 1p and 19q. These two alterations were closely associated, suggesting that the two loci may be involved in the same pathway of tumorigenesis. This study also showed that a combination of homozygous deletion of the $P16/\text{CDKN2A}$ tumor suppressor gene, loss of heterozygosity (LOH) on chromosome 10, and amplification of the $EGFR$ oncogene was present at a higher rate than previously reported (52). A statistically significant exclusion was noted between these three genetic alterations and the LOH on 1p/19q, suggesting that there are at least two distinct genetic subsets of oligodendroglioma. $EGFR$ amplification and LOH on 10q were significant predictors of shorter progression-free survival (PFS), thus characterize a more aggressive form of tumor whereas LOH on 1p was associated with longer PFS.

1.2.1.3. Ependymomas

These tumors develop from ependymal cells, which line the ventricles of the brain and the central canal of the spinal cord. Ependymomas may spread from the brain to the spinal cord via the CSF causing notable swelling of the ventricle or hydrocephalus. Ependymomas account for 4–6% of all brain tumors and occur mainly up to the age of 20 yr. In children, 30% of ependymomas appear before the age of 3 yr and are more aggressive than in adults. Nearly 90% of pediatric ependymomas are intracranial: they occur in supratentorial or posterior fossa locations, and only 10% are intraspinal. In contrast to the earlier mentioned tumors, low-grade ependymomas (grade I/II) develop metastases along the neuroaxis. The most commonly described genetic alterations in ependymomas are deletions of 17p and monosomy 22 (49).

1.2.2. Meningiomas

Meningiomas are regarded as benign tumors originating from endothelial cover cells of the meninges surrounding the brain. They account for 10–19% of all brain tumors. Meningiomas constitute a large proportion of tumors of the cranial base, so that the term “anatomic malignancy” is used in this region to denote meningiomas (in contrast to biologic malignancy). Age distribution of meningiomas is homogeneous; however, the disease occurs in less than 2% of children. At least 3000 new cases of meningiomas are diagnosed each year in the United States with a 2:1 predominance in women over men. The tumors occur over all age groups but generally peak at midlife. High-grade or malignant meningiomas are associated with deletions of loci on chromosome 1 and, to a lesser extent deletions on 6p, 9q, and 17p (49). Mutations in the $p53$ gene have also been reported in malignant meningioma.

1.2.3. Medulloblastomas

Medulloblastomas are malignant tumors originating from primitive or poorly developed cells, constitute 3–5% of all brain tumors, but as much as 25% of all brain tumors in childhood. The disease most commonly occurs between the ages of 3 and 8 yr, although occasionally, medulloblastoma are also observed in adults. Because of the median location of these lesions and their association with the fourth ventricle they are frequently accompanied by metastases to the ventricular system and the neuroaxis
Epidemiology of Brain Tumors

(25–45%), usually via the CSF. In 5% of cases, metastases are already present at the time of diagnosis. Although medulloblastoma is one of the most common pediatric malignancies, little is known of the outcome of long-term survivors of childhood medulloblastoma. Treatment of medulloblastoma with radiation has been implicated in the development of secondary malignancies. Chromosome 17p is a frequent site of deletions in medulloblastomas. Other, less frequent sites of deletions are 2p, 6q, 10q, 11p, 11q, and 16q (49).

1.2.4. Ganglioglioma

Gangliogliomas are tumors that contain both neurons and glial cells and usually occur in the temporal lobes and cerebral hemispheres. They are highly curable by surgery alone or by surgery combined with radiation therapy. Central gangliomas occur in 0.4–8% of children and 1% of adults and show no higher incidence either by sex or race. Most gangliogliomas are observed in patients younger than 30 yr. In 75–100% of cases gangliomas are manifested by epileptic seizures that occur long before alterations are seen on computed tomography (CT) or magnetic resonance imaging (MRI) (92). Among genetic alterations observed in ganglioglioma is loss of genetic material on the short arm of chromosome 9 and over-representation of partial or the whole chromosome 7. It has been recently reported that polymorphism in the tuberous sclerosis 2 (TSC2) gene may predispose to the development of sporadic gangliogliomas.

1.2.5. Schwannomas (Neurilemomas)

Schwannomas, usually benign tumors, arise from Schwann cells and often form near the cerebellum and in the cranial nerves responsible for hearing and balance (47). These benign tumors are twice as common in women as in men, and are most often diagnosed in patients between the ages 30 to 60 yr. Intracranial schwannomas account for approx 8% of primary brain tumors. The most common schwannoma is the acoustic neuroma, a tumor of the eighth cranial nerve, but these tumors can also occur on other cranial nerves. Malignant schwannomas originate from peripheral nerves and have a malignant course with recurrent disease and metastases developing early. Losses on 1p and gains on 11q have been detected in a few schwannomas, but no single consistent genetic alteration associated with schwannomas, other than a loss on 22q, has been found to date. Such changes have not been systematically searched previously.

1.2.6. Chordomas

Chordomas are relatively rare neoplasms arising from embryonic notochordal remnants and comprise less than 1% of intracranial neoplasms. They typically occur along the neuraxis, especially at the developmentally more active cranial and caudal ends, notably in the sphenocerebellar, sacrococcygeal, and vertebral locations. Twenty-five to 40% of chordomas occur in the skull base region. These tumors occur predominately in the 30 to 50 yr age range and show a slight predominance in men. They are amenable to treatment but stubbornly recur over a span of 10 to 20 yr. Genetic research into this disorder is underway. One study has detected chromosomal imbalances in chordomas and produced data suggesting that tumor suppressor genes or mismatch repair genes (located at 1p31 and 3p14) and oncogenes (located in 7q36) might be involved in chordoma genesis (101).

1.3. Heritable Syndromes Associated With Central Nervous System Tumors

Original studies of CNS tumor associated syndromes and hereditary conditions associated with CNS tumors parallel in method and implication the studies of other congenital anomalies. These and follow-up studies associate astrocytoma with arteriovenous malformation of the overlying meninges, glioblastoma multiforme with adjacent arteriovenous angiomatous malformation and pulmonary arteriovenous fistula, congenital medulloblastoma with gastrointestinal and genitourinary system anomalies, and congenital ependymoma with multisystem anomalies (88).
CNS tumors commonly occur in association with Down’s syndrome, a disorder involving trisomy 21 and gliomatous tumors with syringomyelia (88). Mental retardation and brain cancer may also be associated, because children with astrocytomas had a mentally retarded sibling three times more frequently than controls ($p < 0.05$), and mentally retarded siblings, nieces, and nephews in families of adult males with brain tumors were seen 4.8 times more than in families of controls (64). The most frequently identified hereditary syndromes co-occurring with CNS tumors are described here.

1.3.1. Tuberous Sclerosis

Tuberous sclerosis (TSC), or Bourneville’s disease, is an autosomal dominantly inherited progressive disorder occurring in 1 per 6,000 live births. It is characterized by hamartomas of the skin, CNS, and kidneys (41,45), and results in sebaceous adenomas of the skin, muscle and retinal tumors, epileptic seizures, mental retardation, and nodes of abnormal glial fibers and ganglion cells in the brain (40). Its association with CNS tumors is anecdotal, although one hospital study reported 7 CNS tumors in 48 cases (15%) of TSC (59), another found 22 cases of subependymal giant-cell astrocytoma in 345 patients (6.4%) with tuberous sclerosis (2). Astrocytoma, ependymoma, and glioblastoma multiforme have been associated with tuberous sclerosis in up to 5% of cases (103,104,111). TSC displays genetic heterogeneity with two genes being linked to this condition, the first in 1993 is $TSC2$ mapping to 16p13 (The European TSC Consortium) and the second, $TSC1$ was mapped to 9q34 in 1997 (116). $TSC2$ is a large gene with at least 41 exons spanning approx 45 kb of genomic DNA and encodes the protein tuberin. $TSC1$ contains 23 exons spanning approx 40 kb of genomic DNA and encodes the protein hamartin (21). The majority (98% in $TSC1$ and 77% in $TSC2$) of mutations seen in both $TSC1$ and $TSC2$ are of a nature predicted to truncate the proteins, suggesting that these genes function as tumor suppressor genes (21). Further, loss of heterozygosity (LOH) at both the $TSC1$ and $TSC2$ loci have been observed in TSC hamartomas, suggestive of Knudson’s ”second-hit.” Of interest, intellectual disability has been more frequently associated with de novo mutation of $TSC2$ than $TSC1$ (58). Mosaicism has been reported, having important implications for molecular diagnostics.

1.3.2. Neurofibromatosis

Neurofibromatosis (NF-1), or von Recklinghausen’s disease, occurring in 1 of 3000 live births (27) has an autosomal dominant pattern of inheritance and is regarded by some as among the most common single-gene disorders. Paternal origin of the mutation was found in one study in 12 of 14 families (57), but single-gene etiology has yet to be firmly established, because the spontaneous mutation rate of large populations has been put at 50% (99). NF-1 constitutes 90% of all cases of neurofibromatosis and is manifested within the first 5 yr of life. It is characterized by cutaneous pigmentation (cafe-au-lait spots), multiple neurofibromas involving the skin and possibly deeper peripheral nerves and neural roots, The majority of NF-1 patients (94%) present with Lisch nodules or pigmented iris hamartomas (95) and experience optic nerve gliomas, astrocytomas, ependymomas, acoustic neuromas, neurilemmomas, meningiomas, and neurofibromas. Of NF-1 patients, 4–45% experience brain tumors (8,53,106). We recently reported that females with NF-1 are at a higher risk of developing neoplasia than males with NF-1 (1). We also found no elevated cancer risk in unaffected first-degree relatives, regardless of whether the proband had cancer or not. Our data suggested that the malignancy in the proband is not the result of a modifying gene that has a significant impact on general cancer risk (1). Within the past few years, the gene causing NF-1 has been identified and the protein encoded by this gene, neurofibromin, has been the subject of detailed investigation. Studies of tumors from NF-1 patients with homozygous deletions in the NF1 gene suggest a role for NF-1 as a tumor suppressor (118).

1.3.3. Neurofibromatosis Type 2

Neurofibromatosis type 2 (NF-2), or bilateral acoustic neurofibromatosis, occurs with one-tenth the frequency of NF-1. NF-2 is regarded as the central form of NF, occurring in 1 out of 50,000
persons and accounting for 10% of all NF. It is also an autosomal dominant inherited disease. In terms of molecular biology, there is a defect on chromosome 22. Meningiomas associated with NF-2 occur in 25% of cases. NF-2 presents the clinical characteristics of multiple tumors, usually schwannomas of the cranial and spinal nerve roots. Multiple ependymomas, meningiomas developing from arachnoidal cells in the cranial cavity and spinal canal, and spinal cord or brain stem astrocytic gliomas occur in individuals with NF-2. These are often low-grade malignancy but with devastating neurological effects (83). NF-2 is caused by a deletion in the long arm of chromosome 22 associated with meningiomas, gliomas, and spinal neurofibromas (102,122).

1.3.4. Nevoid Basal Cell Carcinoma Syndrome

Nevoid basal cell carcinoma syndrome (Gorlin syndrome), an autosomal dominant disorder, presents with multiple basal cell carcinomas arising early in life, jaw cysts, characteristic facies, skeletal anomalies, intracranial calcifications of the falx, and ovarian fibromas. The syndrome is associated with medulloblastoma (42). One in 200 patients with basal cell carcinomas (one or more) had the syndrome, but the proportion is much higher (one in five) among those in whom a basal cell carcinoma develops before age 19 yr. Only a few of the nevi grow and become locally invasive, and basal cell carcinomas do not develop at all in about 15% of affected persons. Radiation treatment can result in fresh crops of aggressive basal cell carcinomas and can lead to severe disfigurement. By linkage analysis it has been shown that the gene is located on chromosome 9q22.3-q31 (34). LOH at the chromosomal location examined, particularly in hereditary tumors, implies that the gene normally functions as a tumor suppressor and is homozygously inactivated (34,38).

1.3.5. Turcot’s Syndrome, Gardner’s Syndrome, and Familial Polyposis

Turcot’s syndrome, Gardner’s syndrome, and familial polyposis are characterized by adenomatous polyps, have been associated with medulloblastoma and glioblastoma (24,70). Because of their marked similarity, some authorities consider Turcot’s syndrome, Gardner’s syndrome, and classical adenomatous polyposis variations of a single genetic defect. Investigators associate chromosome 5q with these three syndromes (9,25,70). Familial adenomatous polyposis (FAP) is an autosomal dominant disorder that typically presents with colorectal cancer in early adult life secondary to extensive adenomatous polyps of the colon. Polyps also develop in the upper gastrointestinal tract and malignancies may occur in other sites including the brain and the thyroid. Helpful diagnostic features include pigmented retinal lesions known as congenital hypertrophy of the retinal pigment, jaw cysts, sebaceous cysts, and osteomata.

1.3.6. Sturge-Weber Syndrome

Sturge-Weber Syndrome (SWS) is an inherited neurocutaneous syndrome characterized by sporadic occurrence; distribution of lesions in an asymmetrical pattern; variable extent of involvement; lack of diffuse involvement of entire body and or an organ; almost equal sex ratio; facial and leptomeningeal angiomas; and, frequently, facial and optical port-wine lesions. The true prevalence of this disease is unknown. One in 200 individuals are born with a Port Wine Stain (PWS) in the United States. The incidence of SWS is thought to be 8–15% in live births with an associated PWS. The sporadic occurrence of SWS and distribution of lesions in a scattered or asymmetrical pattern suggests the occurrence of a somatic mutation in an otherwise essential gene, leading to mosaicism for the mutation. Computer-assisted tomography and MRI of SWS cases show cerebral lobar atrophy, brain calcification, choroid plexus enlargement, and venous abnormalities (82).

1.3.7. Von Hippel-Lindau Disease

Von Hippel-Lindau disease (VHL), an autosomal dominant multi-system disorder, involves cerebellar hemangioblastoma of the CNS and visceral organs, retinal angiomas, pancreatic cysts, and benign and malignant renal lesions (69). VHL genetic research indicates that it is underdiagnosed, i.e., more common than previously thought and possibly one of the most common of the familial
cancers. Age at onset of diagnosis varies from early childhood up through the eighth decade of life. Affected individuals will have one or more manifestations including hemangioblastomas of brain (especially cerebellum) and spinal cord; endolymphatic sac tumors, retinal angiomas, renal cell carcinomas and cystic masses, pheochromocytomas, epididymal cystadenomas, pancreatic islet cell tumors, cystadenomas and cysts; and an adenocarcinoma of the pancreas has been reported. Angioma pressure in the brain or spinal cord may press on nerve or brain tissue and cause symptoms such as headaches and may weaken the walls of blood vessels causing damage to surrounding tissues. Blood leakage from angiomas in the retina can interfere with vision. Cysts and tumors, benign or cancerous, may also grow around angiomas, occurring beyond the CNS in the kidney, pancreas, liver, or adrenal glands. Several studies link VHL disease to the short arm of chromosome 3. This arm has two commonly deleted sites 3p13-14.3 and 3p25-26 (29,102,125). Genetic heterogeneity has not been observed in VHL and a single gene for this syndrome was identified in 1993 using positional cloning strategies (67). Loss of the wild-type allele in VHL component tumors has been reported, and is consistent with a tumor suppressor gene function (26). A wide spectrum of germline mutations have been identified in VHL patients including missense and nonsense point mutations, microdeletions, micro-insertions, splice site, complex rearrangements (including inversions), whole gene and gross deletion (109). Mutations are scattered along the entire gene and “hotspots” have been reported, most because of de novo events in unrelated families at hypermutable sequences such as CpG dinucleotides (96). Founder mutations have also been reported (15). Given the heterogeneity of mutation type, it has recently been reported that by using a combination of molecular techniques mutations can be identified in nearly 100% of VHL families (109).

1.4. Familial Associations of Brain Tumors

In addition to the association of hereditary syndromes with CNS tumors, investigation of brain cancer etiology focuses on families of CNS tumor patients aggregating CNS and other cancers (35,71–74,112). Tumors of patients and their relatives in these “cancer families” are histologically and biologically similar and well documented, though the precise relationship between genetics and CNS neoplasms remains unknown (111). Methodologic constraints unfortunately limit the authority of many of these studies. They are also obscured by the confounding factor of common familial exposure to environmental agents potentially contributing to neoplasia induction, but they consistently report the presence of similar brain or other tumors in siblings (31,35,87), and the cancer family syndrome (71–74,76–77). With regard to etiology, two possible explanations of family occurrence emerge: (1) a genetic factor may in itself cause family clustering of CNS tumors, or (2) a hereditary vulnerability to exposures may produce the clusters.

1.4.1. CNS Tumors Among Twins

A challenge to studies of heritability of brain tumors is the lack of concordance CNS tumors in twins. Neither increased risk nor histological congruence has been proven in twin studies (46,63,87). Norris and Jackson (90) found 54 solid tumors and 21 brain cancers in a review of 145,708 twins and singletons born between 1940 and 1964, but no evidence of concordance of CNS neoplasms in these twins. Results from a study of 556 twins with cancer suggest that there is not in general a strong constitutional genetic component for childhood cancers other than retinoblastoma (16). In another study, data on 44,788 pairs of twins listed in the Swedish, Danish, and Finnish twin registries were analyzed in order to assess the risks of cancer at 28 anatomical sites for the twins of persons with cancer. Results indicate that inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms and that the environment has the principal role in causing sporadic cancer (91).

1.4.2. CNS Tumors Among Siblings

Seeking epidemiological information, investigators have long collected information on siblings of cancer patients, and from the first, this information has indicated sibling’s higher risk of cancer from genes. Early surveys finding sibling concordance for brain tumors or siblings with different types of
cancer were challenged because of small numbers \( (73,87) \) although larger studies have supported a genetic hypothesis. Farwell and Flannery \( (35) \) traced the cancer histories of relatives of 643 patients in the Connecticut Tumor Registry matching them with sex, age, and birthplace, and discovered a significantly higher risk of brain cancer in case siblings. Another large study \( (31) \) reviewed over 20,000 cases from the Marie Curie/Oxford Survey of Childhood Cancers in England, Scotland, and Wales, and identified 11 sibling pairs with brain tumors and 21 sibling pairs with dissimilar cancers.

### 1.4.3. CNS Tumors and Cancer Family Syndrome

In addition to studies of twins and siblings, the results of other studies of family pedigrees of brain and other tumor patients have been consistent with a dominantly inherited disorder \( (73) \). Li et al. \( (75) \) described this cancer family syndrome in 24 kindred that had both childhood and adult onset cancers of diverse sites. Fourteen \( (9\%) \) of the 151 cancers that occurred before age 45 yr were brain tumors. The Li-Fraumeni Syndrome has since been linked to a \( p53 \) mutation on chromosome 17p in some families \( (79) \).

Additional evidence for a brain tumor family syndrome comes from many epidemiologic comparisons of family medical histories of brain tumor cases with those of controls. These reports show a relative risk of 1–1.8 for any cancer in families of brain tumor cases and a relative risk of brain tumors in these families of 1–9 \( (13,17,23,31,46,64,87,94,100,124) \). Two case-control studies further suggest that risks for other types of cancer may be elevated in family members of brain cancer patients. One study found elevated risk of leukemia and liver cancers and another observed elevated breast and respiratory tract cancer \( (17,124) \). Relatives of children with brain tumors have also been reported to be at increased risk for colon cancer, whereas families with colon polyposis experience elevated frequencies of gliomas \( (13,24,77,117) \). Also of interest are reports of familial clustering of brain tumors with Hodgkin’s disease \( (5) \).

#### 1.4.3.1. Familial Aggregation

A multigenerational history of disease in a family could suggest, aside from genetics, the possibility of common environmental exposures. This possibility is further indicated by the variable findings of familial aggregation where studies report ranges of brain tumors in relatives of cases from nearly one to ten \( (11,48,80,123) \). Although sibling and twin studies cast doubt on the hypothesis of a simple genetic etiology, that aggregation was not only because of chance and was the result of a set of factors, as shown in a family study of 250 children with brain tumors \( (11) \). Segregation analysis found aggregation as a result of multifactorial inheritance. A polygenic model best explained occurrence patterns of brain tumors in another study employing segregation analyses of more than 600 adult glioma patients’ families \( (28) \). Segregation analyses of 2141 first degree relatives of 297 glioma families did not reject a multifactorial model, but an autosomal recessive model provided the best fit \( (81) \). The study estimated that 5\% of all glioma cases were familial. Grosman et al. \( (44) \) showed brain tumors can occur in families without a known predisposing hereditary disease and that the pattern of occurrence in many families suggest environmental causes.

Discovery that some families with the hereditary Li-Fraumeni cancer family syndrome inherited mutated \( p53 \) led to studies revealing the importance of \( p53 \) in many human cancers including brain tumors \( (89) \). Li et al. \( (74) \) reported in a population-based study of adults who had developed glioma, that more cases with \( p53 \) mutant tumors than controls had first-degree relatives with cancer \( (58\% \text{ vs } 42\%) \), and more cases had a previous cancer \( (17\% \text{ vs } 8\%) \). Germ-line \( p53 \) mutations occur more often in patients with multifocal glioma, glioma, and another primary malignancy, or in those with a family history of cancer than in patients with other brain tumors \( (65) \). Currently, research in this area is focused on determining the frequency of \( p53 \) mutations in tumors and on correlation between specific \( p53 \) mutations and specific exposures. Alterations in other important cell-cycle regulators in tumors, such as \( p16, \text{ Rb, and MDM2} \) are also being evaluated. One study designed to identify germ-line mutations in genes mutated, deleted, or amplified in sporadic gliomas showed no evidence of germ-line mutations of \( CDK4, p16, \text{ and } p15 \) \( (39) \).
1.4.3.2. Metabolic Susceptibility: Polymorphisms (Common Variations) in Genes Relevant to Cancer Causation or Prevention

Because evidence suggests that inherited rare mutations are a factor in only a small proportion of primary brain tumors, investigators are turning their attention to common polymorphisms in genes that, in concert with environmental exposures, might influence susceptibility to brain tumors or make the tumors more aggressive. Alterations conferring susceptibility to brain and other tumors could occur in genes that affect oxidative metabolism, detoxification of carcinogens, DNA stability and repair, or immune response. Genetic polymorphisms' influence on susceptibility to carcinogenic exposures has been studied primarily in relation to tobacco smoking, but recent advances in genetic technology permit the epidemiologic evaluation of polymorphisms potentially relevant to other cancers.

Elxepuru-Camiruaga et al. (33) first showed that cytochrome p450 2D6 (CYP2D6) and glutathione transferase theta (GSTT1) were significantly associated with an increased risk of brain tumor. Kelsey et al. (60) found that GSTT1 null genotype was associated only with an increased risk of oligodendroglioma. Trizna et al. (114) found no statistically significant associations between the null genotypes of GSTM1, GSTT1, and CYP1A1 and risk of gliomas in adults, but observed a nearly two-fold increased risk for rapid N-acetyltransferase acetylation and a 30% increased risk for intermediate acetylation. However, that finding was not confirmed in another case-control study of adults with glioma (93). Chen et al. (22) showed that patients with oligoastrocytoma were 4.6 times (95% CI 1.6–13.2) as likely as controls to have AA or AC vs CC genotype in nucleotide 8092 of ERCC1 (22). However, the odds ratio of those genotypes was about the same in patients with glioblastoma and controls. Although this variant is a silent polymorphism (i.e., does not lead to an amino acid change), it might affect ERCC1 messenger ribonucleic acid (mRNA) stability, and the same polymorphism leads to an amino acid substitution of lysine to glutamine in a nucleolar protein and T-cell receptor complex subunit. Using the same populations as those reported by (20,22) Caggana et al. found the AA genotype (C to A polymorphism [R156R]) of ERCC2 to be statistically significantly more common than the CC or CA genotypes in patients with glioblastoma, astrocytoma, or oligoastrocytoma than in controls. This variant is also a silent polymorphism, suggesting that another gene linked to it may account for the associations observed. Moreover, as genotyping data from blood tests were not available for those patients with the poorest survival in this population-based study of gliomas, it is not certain whether these polymorphisms were related to survival or to etiology. Further work is clearly warranted to confirm or refute these provocative findings. Larger studies may be needed as chance can play a role in falsely identifying or failing to identify associations especially when sample sizes are small.

1.4.4. Mutagen Sensitivity

Cytogenetic assays of peripheral blood lymphocytes have been extensively used to determine response to genotoxic agents. The basis for these cytogenetic assays is that genetic damage reflects critical events in carcinogenesis in the affected tissue. To test this hypothesis Hsu et al. (54) developed a mutagen sensitivity assay in which the frequency of in vitro bleomycin-induced breaks in short-term lymphocyte cultures is used to measure genetic susceptibility. We have modified the assay by using γ-radiation to induce chromosome breaks because radiation is a risk factor for brain tumors and can produce double-stranded DNA breaks and mutations (12). It is believed that mutagen sensitivity indirectly assesses the effectiveness of one or more DNA repair mechanisms. The following observations support this hypothesis. First, the relationship between chromosome instability syndromes and cancer susceptibility is well-established (19). Patients with these syndromes also have defective DNA repair systems (119). Furthermore, patients with ataxia telangiectasia, who are extremely sensitive to the clastogenic effects of X-irradiation and bleomycin, differ from normal people in the speed with which aberrations induced by these agents are repaired but not in the number of aberrations produced (50).

γ-Radiation induced mutagen sensitivity is one of the few significant independent risk factors for brain tumors (12). DNA repair capability and predisposition to cancer are hallmarks of rare chromo-
some instability syndromes, and are related to differences in radiosensitivity. An in vitro study showed that individuals vary in lymphocyte radiosensitivity, which correlates with DNA repair capacity \((12)\). Therefore, it is biologically plausible that increased sensitivity to \(\gamma\)-radiation results in increased risk of developing brain tumors because of an individual’s inability to repair radiation damage. Bondy et al. \((12,14)\) have shown that lymphocyte mutagen sensitivity to \(\gamma\)-radiation is significantly associated with a risk of glioma. The mutagen sensitivity assay has also been shown to be a risk factor for other cancers such as head and neck and lung cancers suggesting that sensitivity to the mutagen is constitutional \((50)\), especially that the breaks are not affected by smoking status or dietary factors (micronutrients) \((108)\).

### 1.4.5. Chromosome Instability

A number of chromosomal loci have been reported to play a role in brain tumorigenesis because of the numerous gains and losses in those loci. For example, Bigner et al. \((7)\) reported gain of chromosome 7 and loss of chromosome 10 in malignant gliomas and structural abnormalities involving chromosomes 1, 6p, 9p, and 19q; Bello et al. \((4)\) reported involvement of chromosome 1 in oligodendrogliomas and meningiomas; and Magnani et al. \((78)\) demonstrated involvement of chromosomes 1, 7, 10, and 19 in anaplastic gliomas and glioblastomas. Loss of heterozygosity for loci on chromosome 17p \((37)\) and 11p15 \((105)\) have also been reported.

There is little data on chromosomal alterations in the peripheral blood lymphocytes of brain tumor patients. Information on such changes might shed light on premalignant changes that lead to tumor development. We demonstrated that compared with controls, glioma cases have less efficient DNA repair, measured by increased chromosome sensitivity to gamma radiation in stimulated peripheral blood lymphocytes \((12)\). This inefficiency was shown to be an independent risk factor for glioma \((12)\). Recently, we investigated whether glioma patients have increased chromosomal instability that could account for their increased susceptibility to cancer \((32)\). Using fluorescent in situ hybridization methods, background instability in these patients was measured at hyperbreakable regions in the genome. Reports indicate that the human heterochromatin regions are frequently involved in stable chromosome rearrangements \((30,66)\). Smith and Grosovsky \((107)\) and Grosovsky et al. \((43)\) reported that breakage affecting the centromeric and pericentromeric heterochromatin regions of human chromosomes can lead to mutations and chromosomal rearrangements and increase genomic instability. Our study demonstrated that individuals with a significantly higher level of background chromosomal instability have a 15-fold increased risk of development of gliomas \((32)\). A significantly higher level of hyperdiploidy was also detected. Chromosome instability leading to aneuploidy has been observed in many cancer types \((68)\). Although previous studies have demonstrated the presence of chromosomal instability in brain tumor tissues \((86,98,121)\), our study was the first to investigate the role of background chromosomal instability in the peripheral blood lymphocytes of patients with gliomas \((32)\). This suggests that accumulated chromosomal damage in peripheral blood lymphocytes may be an important biomarker for identifying individuals at risk of developing gliomas.

### 2. DIRECTIONS FOR FUTURE STUDIES

Primary malignant brain tumors clearly represent a heterogeneous group of diseases. Therefore, a workable consensus on classification and increased use of molecular tumor markers in concert with improved surveillance and registration are necessary to characterize homogeneous subgroups of the many heterogeneous categories of primary brain tumors. For example, the recently elucidated distinction between de novo and “progressive” glioblastomas has significant implications for epidemiologic research \((61)\). This concept and others reinforce the notion that glioblastoma multiforme is not one but probably many diseases that must be distinguished if progress is to be made in determining etiology.

Molecular characterization of tumors may help to disentangle causes of subtypes of glioma by enabling researchers to group tumors with similar molecular lesions. Use of rapidly developing tech-
nology to examine arrays of either gene or protein expression may help enormously to categorize tumors into more homogeneous groups with regard to lesions of etiologic or prognostic importance. A major challenge to interpreting this information will be deciphering which alterations represent early changes of potential etiologic significance, and which represent later changes that may have serious prognostic consequences. Genetic and molecular epidemiologic methods to collect and define pertinent subject data from well-defined source populations and to follow-up subjects for recurrence and survival, might help to make sense of the complex information about tumor molecular alterations.

The descriptive epidemiology of brain tumors suggests that a major task is to formulate and evaluate explanations for the consistently observed gender and ethnic differences for glioma and meningioma. Among the most provocative clue to the etiology of primary brain tumors in adults is the characteristic gender difference, with glioma being more prevalent among men and meningioma among women. The glaring absence of analytic epidemiologic research into risk factors for meningioma provides little information to hypothesize reasons for the female preponderance other than the probable importance of hormonal factors. Furthermore, very few studies of glioma have shed any light on gender and ethnic differences in occurrence of these tumors, despite the extensive research of gliomas.

Further analytic studies of environmental factors (viruses, radiation, and carcinogenic or protective chemical exposures through diet, workplace, or other sources), when combined with incorporation of potentially relevant polymorphisms that might influence susceptibility, may help us understand this devastating collection of diseases. Multicenter studies or sharing of data between ongoing studies might be needed to obtain sufficient numbers of cases to compare subgroups of subjects with specific molecularly defined tumor types. Studies of potentially relevant polymorphisms, viral factors, other infectious agents, and immunologic factors are promising understudied areas for further etiologic research. Moreover, as currently established or suggested risk factors probably account for a small proportion of cases, novel concepts of neurocarcinogenesis may be required before we are able to discover a more comprehensive picture of the natural history and pathogenesis of brain tumors. With the rapid pace of discovery of meaningful tumor markers and susceptibility genes, this is an ideal time for neurosurgeons, oncologists, pathologists, and epidemiologists to forge new collaborations within and between their institutions and professional organizations to design and conduct meaningful epidemiologic research into the causes of primary brain tumors.

To conclude, primary brain tumors probably stem from multiple exogenous and endogenous events. To date, the few proven causes (i.e., inherited genetic syndromes, therapeutic ionizing radiation giving rise to brain lymphomas) account for only a small proportion of cases. Brain malignancies are devastating diseases, but there is hope that a continuing explication of their cause and biologic course and new concepts about neuro-oncogenesis might emerge to advance the study of brain tumor epidemiology and the possibilities for prevention and cure.

REFERENCES


Epidemiology of Brain Tumors


1. INTRODUCTION

1985 marked the first reporting of a specific gene alteration in a human central nervous system (CNS) tumor: epidermal growth factor receptor (EGFR) gene amplification in glioblastoma (43). Since that time, a relatively short period by most standards, neuro-oncology research has revealed many genetic abnormalities that indicate consistent genotype-phenotype associations for the various cancers that are collectively referred to as CNS tumors. This chapter reviews the established CNS tumor genotype associations, and discusses resulting molecular biologic consequences as well as the clinical implications of these genetic alterations.

2. TYPES OF GENE ALTERATIONS IN CANCER

2.1. Oncogenes

As is the case for all human cancers, the genes that are altered in CNS tumors can be grouped into two general categories: (1) oncogenes and (2) tumor suppressors (37). The protein products of oncogenes promote cell proliferation and/or promote other characteristics important to tumor growth, such as invasion, angiogenesis, and resistance to apoptosis. Oncogenes can be activated by increasing the synthesis of their corresponding protein, in normal form, or by alteration of corresponding protein function through gene mutation.

In nervous system tumors, oncogene activation occurs almost entirely by gene amplification. Gene amplification causes an increase in number of a specific gene within a cell, and invariably results in a corresponding increased expression of the gene’s encoded protein. In nearly all instances, CNS tumor gene amplifications have been revealed by Southern analysis; a technique in which DNA probes for specific genes reveal elevated gene copy number in tumor DNAs (83).

2.2. Tumor Suppressor Genes

As might be suspected from their name, proteins encoded by tumor suppressor genes (TSGs) inhibit cell growth. Their identification has resulted largely through the application of two molecular genetic methods. One of these is linkage analysis that relies upon subtle DNA sequence variations (polymorphisms) between chromosome homologs that allow one to “track” the segregation pattern of a disease-predisposing gene through multiple generations of an affected family (96). In a study of such families, the chromosomal proximity of a polymorphic variant to a cancer-predisposing gene is indicated by the consistency of its co-segregation with the occurrence of cancer within a family. This approach has been useful in identifying and/or associating tumor suppressor genes, such as TP53,
(NF2), and (VHL), with their respective cancer syndromes: Li-Fraumeni (TP53), neurofibromatosis type 2 (NF2), and von Hippel-Lindau (VHL) disease (see Subheading 3.3).

The other approach that has been extensively used for TSG identification is deletion mapping. Deletion mapping is performed through loss of heterozygosity (LOH) analysis (41), in which the patterns of DNA fragments from restriction enzyme digestions or polymerase chain reactions (PCRs) are compared in a patient’s normal and tumor DNAs. Loss of a restriction or PCR fragment-length allele in a tumor DNA sample indicates a genetic alteration directed at the deletion of a TSG. By applying a battery of mapped probes (markers) from a chromosome of interest, one can limit the chromosomal location of a TSG by determining the smallest common region of deletion among a panel of similar tumors. This type of analysis has been applied extensively to brain tumors and has revealed several associations between detectable chromosome losses and tumor histopathology.

3. MALIGNANT ASTROCYTOMAS: A DETAILED GENETIC DESCRIPTION

Given the combined concerns of malignant astrocytoma frequency and mortality, it is perhaps to be expected that the details of genetic alterations in these tumors would be the most extensive among the CNS cancers. Although it is likely that additional gene alterations of importance will be discovered in malignant astrocytomas, it is also possible that most and perhaps all of the high-frequency activation/inactivation targets have been identified. Regardless of the possible discovery of additional high-frequency gene alterations, there is sufficient information on hand to provide a reasonably thorough account of genetic events that promote the development of these tumors.

3.1. Oncogene Alterations in Malignant Astrocytoma: EGFR

The vast majority of CNS tumor oncogene alterations have been identified in malignant astrocytomas, and in most instances oncogene activation is accomplished through gene amplification. The most frequent oncogene alteration in CNS tumors is amplification of the, EGFR (12,43,98). EGFR encodes a transmembrane tyrosine kinase that is activated by its binding of epidermal growth factor (Egf), transforming growth factor alpha (TGF-α), as well as other growth factor ligands. The aforementioned discovery as well as specificity of EGFR amplification in glioblastoma, or grade IV astrocytoma, has stood up well over the years, although this gene alteration is also observed in grade III anaplastic astrocytoma at a lesser frequency (12,98). Occurrences of EGFR amplification in other types of CNS tumors are at best rare events, and consequently the detection of this gene alteration is predictive of high malignancy grade astrocytoma.

In approximately two-thirds of the tumors having EGFR amplification, amplified genes undergo intragene deletion rearrangements that result in the overexpression of mutant Egf receptors (20). The most common EGFR mutant, Egfr-vIII, is known to have constitutive, ligand-independent tyrosine kinase activity, as well as an extended half-life that stimulates cell proliferation and enhances the tumorigenicity of human glioma cells in nude mice (13,14,54). Furthermore, the activity of this mutant has been shown to promote tumor angiogenesis (17), as well as to confer tumor resistance to programmed cell death by increasing Bcl-XL expression (51).

EGFR amplification and/or overexpression have been evaluated as prognostic indicators in multiple glioma series, and the majority of these studies suggest that increased EGFR gene dosage and high level Egf receptor expression are not predictive of patient survival for glioblastoma patients (58,92). However, a recent report indicates that analysis of this gene alteration may be a useful if also considered in the context of patient age (78), whereas another study suggests that detection of Egf receptor mutants in glioblastoma may help predict their differential clinical behavior (16).

3.2. Other Oncogene Activations in Astrocytomas

Additional oncogenes whose amplification have been observed in patients with malignant astrocytomas include MYCN (4), CDK4 and MDM2 (27,67), CCND1 (27), and MET (19), the latter of which, like EGFR, is a member of the family of tyrosine kinase growth factor receptors. The reported