

Current concepts in the pathology and genetics of gliomas

Sarkar C, Jain A, Suri V

Department of Pathology, All India Institute of Medical Sciences, New Delhi, India

Correspondence to: Dr. Chitra Sarkar, E-mail: Sarkar.Chitra@gmail.com

Abstract

In recent years, there has been a marked improvement in our understanding of molecular genetics of gliomas. These advancements offer hope for development of tailored therapies targeting a tumor's unique molecular profile, and may also translate into improved classification and identification of newer prognostic markers. This review focuses on the neuropathological features of different types of glial neoplasms according to the World Health Organization classification, and the recent advances in their molecular biology with emphasis on the genetic mechanisms underlying tumor progression, diagnostic and prognostic markers and potential therapeutic targets.

Key words: Glioma, oligodendroglioma, astrocytoma, glioblastoma, 1p/19q deletion

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Introduction

Gliomas are the most common primary brain tumors of adults. Gliomas are classified by the World Health Organization (WHO), according to their morphological characteristics, into astrocytic, oligodendroglial, and mixed tumors. The first WHO classification of tumors of the nervous system was published in 1979,^[1] followed by revisions in 1993,^[2] 2000,^[3] and 2007.^[4] The present WHO classification is considered the gold standard for prognostication. Table I gives the classification of glial tumors with their incidence, age, and sex distribution.

It is unclear whether these tumors result from the transformation of an immature precursor or from the dedifferentiation of a mature glial cell.^[5] A number of prognostic and predictive factors are proposed for estimating the behavior of gliomas, including, clinical parameters, histological grading, proliferation indices, and molecular markers. Over the past 20 years, a number of chromosomal, genetic, and epigenetic alterations have been found to be associated with different histological types and malignancy grades of gliomas.

Genotype/phenotype correlation studies have identified early and late genetic alterations related

either to astrocytic or oligodendroglial phenotype. They complement the existing WHO morphological classification and provide additional prognostic markers such as 1p/19q deletion in oligodendrogliomas.

Neuropathology of astrocytic tumors

Pilocytic astrocytoma (WHO grade I)

Pilocytic astrocytomas are relatively circumscribed, slow growing, often cystic neoplasms, occurring in children and young adults, most commonly affecting the cerebellum followed by optic nerve and optic chiasma, hypothalamus, thalamus, basal ganglia, and brainstem.^[4,6] Histologically they are characterized by a biphasic pattern consisting of piloid areas with bipolar cells associated with Rosenthal fibers, and protoplasmic areas comprising of loosely textured multipolar cells with microcysts and eosinophilic granular bodies. Sometimes glomeruloid vascular proliferation may be observed, but it is not a sign of malignancy. These cells are strongly glial fibrillary acidic protein (GFAP) immunopositive. Proliferation indices are low with the MIB-1 labeling index (MIB-1 LI) ranging from 0-3.9% (mean 1.1%),^[7] however, due to overlap of this range with diffuse astrocytomas grade II (mean 2.3%), it is of little use in diagnosis.

Genetics: Relatively little is known about chromosomal

Table 1: Classification of gliomas according to WHO classification of tumors of the central nervous system^[4]

Glioma type	Grades	Name	Incidence (% of all brain tumors)	Age	Sex
Astrocytic tumors	Grade I	Pilocytic astrocytoma	5-6%	First 2 decades	1:1
		Subependymal giant cell astrocytoma	<1%	2-20	equal
	Grade II	Diffusely infiltrating astrocytoma	10-15%	30-40	1.18:1
	Grade III	Anaplastic astrocytoma	10-15%	45-50	1.1:1
	Grade IV	Glioblastoma multiforme	12-15%	45-75	1.26:1
Oligodendroglial tumors	Grade II	Oligodendroglioma	2.5%	40-45	1.1:1
	Grade III	Anaplastic oligodendroglioma	1.2%	45-50	1.1:1
Oligoastrocytic tumors	Grade II	Oligoastrocytoma	1.8%	35-45	1.3:1
	Grade III	Anaplastic oligoastrocytoma	1%	40-45	1.15:1
Ependymal tumors	Grade I	Subependymoma	0.7%	50-60	2.3:1
		Myxopapillary ependymoma	0.3%	20-35	2.2:1
	Grade II	Ependymoma	4.7%	<16, 30-40	1:1
	Grade III	Anaplastic ependymoma	1%	<16	1:1

and genetic aberrations in pilocytic astrocytomas. On comparative genomic hybridization of 48 pilocytic astrocytomas, chromosomal imbalances were observed only in seven tumors, most commonly a gain of 9q34.1-qter (three cases).^[8] The majority of pilocytic astrocytomas from patients with neurofibromatosis (NF) type 1 carry allelic losses at the NF-1 tumor suppressor gene locus 17q11.2.87. In contrast, sporadic cases rarely demonstrate this allelic loss and neither NF-1 mutations nor loss of NF1 mRNA expression have been demonstrated.^[9,10] This finding argues against an important role of NF1 in the tumorigenesis of sporadic pilocytic astrocytomas. In contrast to diffuse astrocytomas, allelic losses on 17p and mutations in the TP53 tumor suppressor genes are rare in pilocytic astrocytomas.^[9,11,12] However, one study employing the denaturing gradient gel assay detected TP53 mutation in seven out of 20 such tumors, suggesting that aberrations in p53-dependent growth control also contributes to the pathogenesis of pilocytic astrocytomas.^[13]

Diffuse astrocytomas (WHO grade II)

Diffusely infiltrating astrocytomas typically affect young adults and present as cerebral hemispheric masses, with the epicenter lying predominantly in the white matter, although cortical involvement is also common and may account for the seizures experienced by some of these patients.^[14] These tumors are characterized by a high degree of differentiation and slow growth, but have an intrinsic tendency for malignant progression to anaplastic astrocytomas and ultimately glioblastoma. Factors accounting for the variable time to progression have not been entirely worked out, although patient

age remains a powerful prognostic parameter, inversely associated with survival time.^[15] Histological examination reveals a moderately increased cellularity than in a normal brain, well-differentiated fibrillary or gemistocytic or rarely protoplasmic neoplastic astrocytes, with occasional nuclear atypia in a loosely structured, often microcystic tumor matrix. Grade II astrocytomas lack mitotic activity, endothelial proliferation, and necrosis. MIB-1 LI (usually < 4%) may provide useful information beyond that of simple mitosis counting, although there are no defined cut-off values, and there are significant methodological and interpretive differences among different laboratories.^[7] However, an MIB-LI > 5% has been said to constitute a threshold value for predicting shorter survival.^[16] GFAP immunoreactivity is strong in the gemistocytic and fibrillar variants, whereas, protoplasmic astrocytomas are only weakly positive.^[6] Vimentin and S-100 are also usually positive, but have relatively little diagnostic relevance.

Genetics [Figure 1]: About 60% of the diffuse astrocytomas carry mutations in the TP53 tumor suppressor gene at 17p13.1.^[17,18] Gemistocytic astrocytomas carry TP53 mutation in up to 80% of the cases.^[19] In most cases TP53 mutation is accompanied by loss of heterozygosity (LOH) on 17p resulting in a complete absence of the wild-type TP53 gene.^[6] Diffuse astrocytomas also frequently show elevated expression of platelet-derived growth factor receptor A (PDGFRA) and the corresponding ligand PDGFA.^[20,21] Overexpression of PDGFRA in diffuse astrocytic gliomas has been found preferentially in tumors showing LOH on 17p.^[22] The prognostic

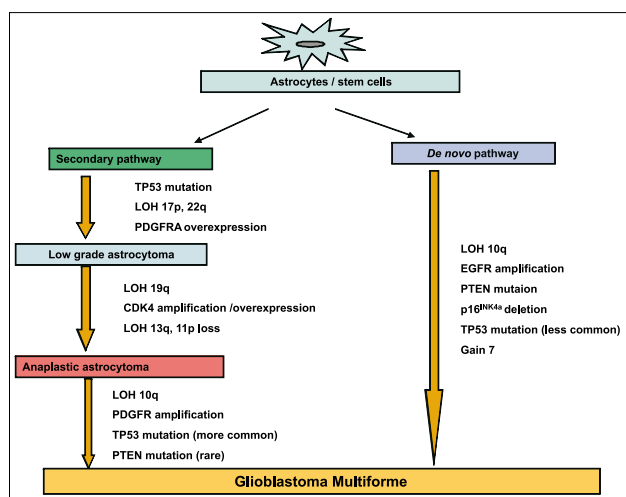


Figure 1: Genetic alterations involved in the development and progression of astrocytic tumors, (Modified from WHO 2007⁴)

significance of TP53 overexpression in diffuse astrocytomas is controversial. In a large retrospective study on diffuse astrocytomas, TP53 mutations were not associated with an overall change in the prognostic outcome.^[23]

Anaplastic astrocytoma (WHO grade III)

Similar to diffuse astrocytomas, anaplastic astrocytomas are preferentially located in the cerebral hemispheres, but occur in a slightly older age group. They are histologically characterized by nuclear atypia, increased cellularity and significant proliferative activity. Additional signs of anaplasia include multinucleated tumor cells and abnormal mitosis. Initially, the St. Anne-Mayo astrocytoma grading scheme, essentially adopted in the 1993 version of the WHO system, stated that even a single mitotic figure is sufficient to warrant an anaplastic or grade III designation.^[24] However, the “one mitosis” rule is questionable for large resection specimens, where it does not have the same dire implications as in a small biopsy. Survival times for anaplastic astrocytoma patients with solitary mitosis have been found to be similar to those of grade II astrocytoma patients,^[7,25] and later WHO classifications take the sample size into consideration, for defining the anaplastic features. The typical histological hallmarks of glioblastoma (microvascular proliferation and necrosis) are not yet present, but anaplastic astrocytomas tend to progress to secondary glioblastomas.^[6] MIB-1 LI is usually 5-10%, but may overlap with low grade diffuse astrocytoma as well as glioblastoma, and show considerable variation even within a given tumor.^[16,26,27]

Genetics [Figure 1]: Gains of chromosome 7 and TP53 mutations are similarly frequent in anaplastic astrocytomas as also in diffuse astrocytomas. In addition,

these tumors may carry deletions on chromosomes 6, 9p, 11p, 19q, and 22q. The target genes on 9p are the CDKN2A, p14^{ARF}, and CDKN2B tumor suppressor genes.^[28,29] A small fraction demonstrates amplification and overexpression of the CDK4 gene at 12q13-q1^[30], and this alteration occurs preferentially in tumors without CDKN2A deletion or mutation.^[31] In addition, a subset carries mutations in the retinoblastoma (RB1) gene.^[18,31] In contrast to glioblastomas (discussed a little later in the article), mutations of the PTEN gene on 10q23 are restricted to < 10% anaplastic astrocytomas and when present indicate a poor prognosis.^[32] Although detected with much less frequency than in grade IV tumors, epidermal growth factor receptor (EGFR) overexpression and / or gains of chromosome 7 in low grade (WHO II) and grade III astrocytomas are linked with shortened survival.^[33-35]

Glioblastoma Multiforme (WHO grade IV)

Glioblastoma multiformes (GBMs) are the most frequent and the most malignant primary brain tumors and occur typically in older adults, preferentially in the cerebral hemispheres. The clinical history is usually short (mostly <three months). Microscopically, glioblastomas are cellular, highly anaplastic tumors, which may be composed of cells of various morphologies including fibrillar and gemistocytic astrocyte-like cells, fusiform cells, small anaplastic cells, and pleomorphic multinuclear giant cells. Nuclear atypia is usually marked, and high mitotic activity, including atypical forms, is a prominent feature. The presence of pathological microvascular proliferation and / or necrosis is essential for the diagnosis. Microvascular proliferation often results in the formation of glomeruloid garland-like capillary structures. Vascular thromboses are also common. With respect to necroses, two types may be distinguished: (a) large confluent ischemic necrosis and (b) small, often multiple, irregularly shaped, band-like or serpiginous foci of necrosis, typically surrounded by glioma cells in a pseudopallisading pattern.^[6]

The WHO classification lists two glioblastoma variants, namely, the giant cell glioblastoma and the gliosarcoma. Giant cell glioblastomas are relatively well-circumscribed (which may account for somewhat better prognosis) and histologically comprise of bizarre highly pleomorphic multinucleated giant cells. Gliosarcomas are a rare variant of GBM, characterized by a biphasic tissue pattern with areas displaying phenotypic features of gliomas and sarcomas.^[6,36] In addition, the term “glioblastoma with oligodendroglial component” is suggested for those glioblastomas that contain areas with features generally associated with oligodendroglial differentiation; however, the histological criteria for the classification of these tumors are poorly defined,

making their differential diagnosis towards anaplastic oligoastrocytoma and ordinary glioblastoma a difficult and subjective issue. Nevertheless, it appears that glioblastoma with the oligodendroglial component may be associated with a better prognosis and a higher likelihood of a favorable response to adjuvant treatment than ordinary glioblastomas.^[36-39] The term 'small cell glioblastoma' refers to a subset of GBMs that show a highly monomorphic cell population, characterized by small, densely packed cells with mild hyperchromasia and modest atypia, long thin GFAP positive cytoplasmic processes, and markedly elevated MIB-1 LI.^[40]

Glioblastoma multiforme can either develop by progression from less malignant gliomas (secondary glioblastomas) or, more frequently, develop rapidly in a *de novo* manner with no evidence of a previous lesion of lower grade malignancy (primary glioblastomas).^[41] Morphologically, primary and secondary glioblastomas cannot be distinguished. Clinically, secondary glioblastomas tend to occur in younger patients, below the age of 45 years, while primary glioblastomas account for the vast majority of glioblastomas in older patients. The prognosis of primary and secondary glioblastomas seems to be equally poor when adjusted for patient age.^[42]

In glioblastomas GFAP immunoreactivity is heterogeneous, with poorly differentiated and small anaplastic glioma cells being frequently negative. MIB-1 LI shows great regional variation with mean values ranging from 15-20%.^[23,33,43] Despite the wide range of proliferation indices observed, no association with the clinical outcome of GBM patients has been established.^[43]

Genetics [Figure 1]: In adults, at least two distinct molecular pathways leading to the development of GBM have been identified. Primary (*de novo*) GBM's frequently harbor amplification of the epidermal growth factor receptor (EGFR, 7p12), are associated with an older age of onset, and an aggressive clinical course. The majority of these tumors will express wild-type EGFR and / or variant mutant forms of the EGFR. The most common mutant form is designated EGFRvIII (also called de2-7EGFR or delta EGFR), which results from an in-frame deletion of exons 2 to 7, resulting in the loss of a portion of the extracellular domain of the receptor. In contrast, the evolution of secondary glioblastoma from the lower-grade precursor lesions is characterized by alterations of the p53 gene (17p13.1) and a more protracted clinical course.^[44-46] Although p53 mutation and EGFR amplification are generally mutually exclusive, occasional glioblastomas

harbor both alterations.^[46]

Primary glioblastomas also more frequently demonstrate the homozygous deletion of CDKN2A and p14^{ARF}, CDK4 amplification, MDM2 or MDM4 amplification, RB1 mutation/homozygous deletion, monosomy 10, and PTEN mutation. TP53 mutation is found in approximately 30% of primary GBMs^[36,47-50] Secondary GBMs carry TP53 mutation in more than 60% of the cases, while amplification of EGFR, MDM2 or MDM4, and PTEN are rare.^[51] Allelic losses on 19q and 13q, promoter hypermethylation of the RB1 gene, and overexpression of the PDGFRA are more common in secondary GBMs.^[36,47,52]

These data indicate that primary and secondary GBMs carry different genetic alterations. However, the functional consequences of the different alterations are similar, since they result in alteration of the same pathways, namely the p53, pRB1, PTEN/PI 3-kinase/Akt, and mitogen-activated protein kinase pathways.

In the GBM group also, as in diffuse astrocytomas, there is conflicting evidence as to whether or not p53 alterations independently correlate with patient survival, although they may indirectly impact prognosis in certain patient subgroups,^[23,53-58] such as, being a marker of age (more common in younger patients) and tumor biology.^[59] Therefore, knowledge of the presence of TP53 mutation appears to be of little clinical value. The predictive value of EGFR amplification in grade IV tumors is also unclear with different studies showing conflicting results.^[60-65] Mutations in EGFR and EGFRvIII variants are particularly common in malignant astrocytomas exhibiting a small cell phenotype, which behave as aggressively as primary glioblastomas, and EGFRvIII overexpression has been associated with poorer survival.^[14,66-68]

Second only to gains on chromosome 7, losses involving chromosome 10 are quite frequent in astrocytomas, limited mainly to high grade tumors.^[69,70] LOH 10q is the most frequent genetic alteration in glioblastomas and occurs in 60-80% of the cases.^[71-73] To date, most studies have identified 10q loss / monosomy 10 as an independent predictor of shorter patient survival.^[69,70,74-78] Several candidate tumor suppressor genes have been mapped to 10q, including PTEN (10q23), DMBT1 (10q25.5-26.1), and recently annexinVII (ANX7;10q21).^[69,72,73,79] The available data on PTEN alteration and survival of glioblastomas patients are heterogeneous. In several studies, PTEN mutations are not associated with prognosis of glioblastomas patients.^[32,54,77,80] Terada *et al.* identified LOH around PTEN as a predictor of less favorable

prognosis in a set of 40 astrocytomas (grades II-IV).^[81] Sano *et al.* reported that the PTEN mRNA level is an independent prognostic factor for glioblastomas patients with low PTEN transcript levels, having significantly shorter survival times.^[82]

The MGMT (O6-methylguanine-DNA methyltransferase) gene is located on chromosome 10q26 and encodes a DNA-repair protein that removes alkyl groups from the O6 position of guanine, protecting the cells against alkylating agents. Methylation of promoter CpG islands results in loss of MGMT expression and is frequently seen in glioblastomas (45-75%) and has been shown to be associated with longer overall survival in patients with glioblastoma who have received alkylating chemotherapy with temozolomide.^[83-86] Also, irrespective of treatment, MGMT promoter methylation is considered an independent favorable prognostic factor for GBMs.^[84] Secondary GBM shows a higher frequency of MGMT promoter methylation than the primary GBM.^[83-84]

Several studies have been carried out in India on the biology, initiation, and progression of these tumors. Pathways for GBM have been worked out and correlation with outcome defined. The roles of c-myc, EGFR, and the Rb gene have also been studied in gliomas. A new genetic marker for astrocytic tumors located in the 17p13.3 region harboring several putative tumor suppressor genes, including HIC-1, has been shown for the first time. The correlation of these markers with tumor grade, proliferation, and apoptosis has been extensively evaluated.^[87-98]

Neuropathology of Oligodendroglial Tumors

Oligodendroglioma (WHO grade II)

These are diffusely infiltrating gliomas of adults, which can occur at any age or location, but are distinctly uncommon in children and are almost never encountered in the brainstem, cerebellum or spinal cord. The majority present as hemispheric masses in young to middle-aged adults, with the frontal lobe representing a favored location.^[14] Progression to anaplastic oligodendrogliomas does occur, but less frequently than in astrocytomas.^[99] Several studies have confirmed the WHO grading of oligodendroglial tumors as a significant predictor of survival.^[100-103] On histological examination, grade II oligodendrogliomas are diffusely infiltrating tumors of moderate cellularity, composed of monomorphic cells, with uniform round nuclei bland chromatin, clear perinuclear haloes on paraffin sections imparting a “fried egg” appearance, and a rich, branching capillary network reminiscent of “chicken wire”. It is important to

recognize that the “fried egg” appearance represents a formalin fixation artifact that is neither absolutely necessary for diagnosis nor is it encountered in frozen sections or rapidly fixed specimens. Other common, though slightly less specific findings include extensive cortical involvement, microcalcifications, mucin-rich microcystic spaces, and perineuronal satellitosis.^[14] There is no immunohistochemical marker available that allows the specific and sensitive recognition of oligodendroglial tumor cells. GFAP may be present in intermingled reactive astrocytes as well as in neoplastic oligodendroglial cells such as minigemistocytes and gliofibrillary oligodendrocytes. Other markers expressed are vimentin, S-100, and MAP-2, along with oligodendrocyte lineage specific transcription factors OLIG-1 and OLIG-2, but these are expressed in a vast majority of other gliomas. However, oligodendroglial tumors usually lack nuclear TP53 staining. The proliferation indices are low in grade II oligodendrogliomas (usually < 5%).^[99]

Anaplastic oligodendrogliomas (WHO grade III)

Oligodendrogliomas with focal or diffuse features of malignancy and less favorable prognosis fall in this group, and occur approximately seven to eight years later, on an average, than grade II oligodendrogliomas.^[100,104] They share, with WHO grade II oligodendrogliomas, a preference for the frontal lobe, followed by the temporal lobe. They may develop either *de novo* or by progression from pre-existing grade II oligodendrogliomas. The majority of tumor cells demonstrate features reminiscent of oligodendroglial cells, that is, rounded hyperchromatic nuclei, perinuclear haloes, focal microcalcification, and branching vascular pattern. Anaplastic features linked to malignancy in oligodendrogliomas are similar to those in astrocytic gliomas, that is, high cellularity, marked cytological atypia, high mitotic activity, microvascular proliferation and necrosis with or without pseudopalisading. Usually several of these features are present, but the diagnosis of grade III anaplastic oligodendroglioma requires the presence of either conspicuous microvascular proliferation and / or high mitotic activity. In doubtful cases, MIB-1 LI and clinicoradiological correlation may be helpful in assessing the prognosis.^[104] Gliofibrillary oligodendrocytes and minigemistocytes are frequent in anaplastic oligodendrogliomas, but are not of prognostic significance.^[105]

Genetics of Oligodendroglial Tumors [Figure 2]

The molecular abnormalities frequently associated with grade II oligodendrogliomas include (i) LOH for chromosomes 1p, 19q, and 4q, and (ii) overexpression of EGFR, PDGFR, and PDGF. Anaplastic oligodendrogliomas grade III more

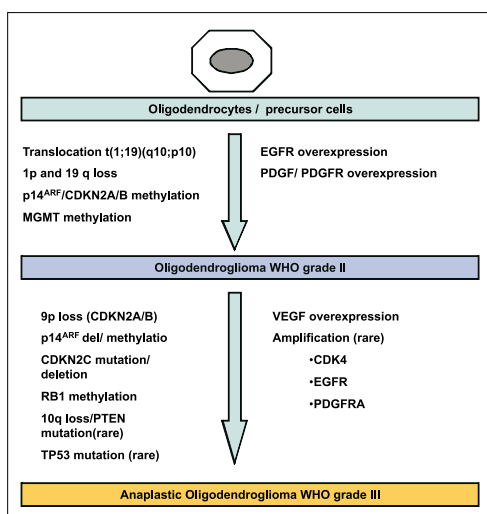


Figure 2: Genetic alteration in oligodendroglial tumors, (Modified from WHO 2007⁴)

frequently have (i) mutations / deletions of CDKN2A and CDKN2C, (ii) amplification of CDK4, EGFR, MYC, (iii) LOH for 1p, 19q, 9p, and 10q, and (iv) overexpression of vascular endothelial growth factor receptor (VEGFR).^[106-109]

LOH of 1p/19q: In 1994, Reifenberger *et al.* reported that allelic loss of chromosome 19q was detectable in 81% oligodendroglial tumors, of which approximately 75% also exhibited LOH at 1p locus.^[108] Subsequently several studies have confirmed that a combined loss of large chromosomal regions at these loci is the hallmark of oligodendroglial tumors. These structural lesions have been detected in up to 90% of the oligodendrogliomas.^[110-116] In adults, combined 1p and 19q LOH has been observed in up to 83% of pure oligodendrogliomas, 63% of anaplastic oligodendroglioma, 56% of mixed low-grade oligoastrocytoma, and 52% of anaplastic mixed oligoastrocytoma.^[117-119] The frequency of LOH 1p/19q is lower in anaplastic oligodendrogliomas, indicating a wider spectrum of genetic alterations leading to these tumors.^[120] Fuller and Perry found 1p/19q co-deletion to be highly associated with morphology: 84% in oligodendrogliomas, 15% in mixed oligoastrocytomas (MOAs) and 1% in astrocytomas ($P < 0.001$).^[121] Loss of 19q alone has been described in a smaller subset and is particularly common in MOAs.

To explain the mechanism of dual 1p/19q co-deletion, recently Griffin *et al.*^[122] and Jenkins *et al.*^[123] hypothesized that there occurs a balanced whole-arm translocation t(1;19)(q10;p10) between chromosomes 1 and 19 forming two derivative chromosomes, one composed of 1q and 19p, the other of 1p and 19q. Subsequent loss of der(1;19)(p10;q10) then results

in the simultaneous 1p and 19q loss observed in the oligodendroglioma, with retention of der(1;19)(q10;p10) seen in these cases. All informative markers on 1p/19q demonstrate that LOH makes the localization of relevant tumor suppressor genes difficult. Although the precise mechanism(s) relating to the whole chromosome arm loss of 1p and 19q to tumorigenesis remains a mystery, it is possible that: (1) haploinsufficiency of multiple genes is somehow sufficient without the need for a “second hit”, (2) epigenetic events such as hypermethylation of CpG islands are inactivating genes on the remaining copies of 1p and 19q, or (3) this cytogenetic signature is simply a marker of a specific glioma type, mechanistically unrelated to other, yet-to-be identified tumorigenic events.^[121]

Whatever the mechanism of tumorigenesis, oligodendrogliomas are the first CNS neoplasms in which a genetic signature, namely, 1p and 19q deletion, has been associated, with outcome and response to chemotherapy.^[121,124-127] LOH for 1p and 19q has correlated with the response to chemotherapy and increase in overall survival.^[101,119,128,129] A five-year survival rate of 95% has been observed for those with deletions versus 65% for those without deletions. Those with deletions also have a longer overall survival of 172 months vs. 105 months without deletions.^[101,130] In a series of 39 patients with anaplastic oligodendroglioma, nearly all of the 70% cases with positive response to procarbazine, lomustine, and vincristine (PCV) chemotherapy exhibited LOH 1p/19q. Another study confirmed the association of LOH 1p/19q and prolonged overall survival in oligodendrogliomas WHO grade II, while no survival advantage was observed in patients with oligoastrocytomas or glioblastomas with LOH 1p/19q.^[119] Studies indicate a similar outcome in patients with LOH 1p/19q treated at the time of diagnosis with both PCV chemotherapy and radiotherapy or only with chemotherapy.^[131] Other recently published studies support this positive correlation between LOH 1p/19q and survival.^[132-136] Two recent phase III prospective trials, namely, RTOG 9402 (Radiation therapy oncology group) and EORTC 26951 (European organization for research and treatment of cancer) have included correlative analyses of 1p and 19q deletions in tumor specimens of anaplastic oligodendrogliomas and anaplastic oligoastrocytomas. Both involved radiation therapy along with PCV chemotherapy in the treatment protocol. The RTOG 9402 study showed that LOH for either 1p or 19q was a significant independent prognostic variable correlating with the outcome ($p = 0.01$). In EORTC 26951, a significant difference in survival was also observed for patient

with 1p/19q loss as compared to those without deletions ($p = 0.003$).^[137-140] The findings from these two phase III studies, the largest to date on newly diagnosed oligodendrogliomas, suggest that there is no improvement in survival with the addition of PCV to RT, and the timing of the PCV with respect to RT is also irrelevant. It was also interesting to note in these prospective studies that 1p and 19q deletions are associated with improved outcome, regardless of treatment. Thus, combined loss of 1p and 19q identified a favorable prognostic group in both studies, which appeared independent of the treatment arms. Irrespective of whether a patient was treated with RT alone or with PCV and RT, the survival was better if the patient had 1p/19q deletions. Giannini *et al.*^[141] in their recent study on refining the correlation among histopathology, 1p 19q deletion, and clinical outcome in intergroup RTOG trial 9402 found that (i) overall survival (OS) of patients with classical features of oligodendrogliomas was significantly longer than for patients without these features ($P < 0.0001$) and they were not affected by necrosis, (ii) Classic oligodendroglial morphology was highly associated with 1p 19q deletion, present in 80% of classic for oligodendroglioma (CFO) and in only 13% lacking classic features of oligodendroglioma (NCFO), (iii) On multivariate analysis, both classic oligodendroglial morphology and 1p 19q deletion remained significantly associated with progression free survival (PFS) and OS, (iv) Patients with CFO, treated with PCV-plus-RT, showed a trend toward increased survival compared with CFO treated with RT ($P = 0.08$).

Given the significance of these findings, it is not surprising that many institutions have initiated testing for 1p/19q deletions, for prognostic information that this testing provides, and some clinicians are basing treatment decision on these markers. It is also unclear if the more favorable clinical outcome associated with these molecular changes is simply due to a better response to treatment or other inherent molecular characteristics yet to be elucidated.^[127] In a recent review on the clinicopathological aspects of 1p / 19q status, Aldape *et al.*^[142] concluded that it is an important marker in oligodendrogliomas and its loss is associated with classic oligodendroglioma histology as well as improved prognosis. Thus, the combined 1p / 19q marker will continue to be a clinically useful marker of prognosis and could potentially be incorporated into the diagnostic criteria in the future.

Other genetic alterations and prognosis [Figure 2]:

The incidence of TP53 mutation in oligodendroglial tumors is not as frequent as in astrocytomas, remaining within the range of 10-20%.^[98,119] It has been noted

that TP53 mutations were almost exclusively found in oligodendrogliomas without 1p loss. LOH 10q, frequently seen in glioblastomas has been observed in up to 58% of anaplastic oligodendrogliomas, and associated with a poorer outcome in some studies, but not in others.^[143-145] An inverse association between LOH 10q and LOH 1p/19q has frequently been noted.^[131,135,146,147] PTEN on 10q23.31 is frequently mutated in glioblastomas and altered in 3-10% of grade III oligodendrogliomas.^[143,147-149] In an analysis of 72 oligodendrogliomas, 10 q was identified in 14 of 67 (21%), including the PTEN and DMBT1 regions. PTEN gene alterations have been associated with poorer survival in oligodendrogliomas, even in patients with chemotherapy sensitive tumors.^[150]

Alterations of chromosome 9p have been encountered in oligodendrogliomas, albeit at a lower frequency than is typical for high-grade astrocytic lesions.^[108,135,146,148,151,152] Likewise, deletions of p16 have been associated with anaplasia and worsened survival.^[132,153-155] Another negative molecular indicator for overall survival and anaplastic oligodendrogliomas has been found to be CDKN2A/p16 deletion.^[156] However, only small groups of patients have as yet been analyzed regarding these genetic alterations.

Promoter hypermethylation of MGMT (O6-methylguanine-DNA methyltransferase) on 10q26.3 has been observed in 60-80% of oligodendroglial tumors, and an association with 1p / 19q status and tumor grade is reported.^[157,158]

Neuropathology of Oligoastrocytic tumors

Mixed Oligoastrocytoma (WHO grade II)

Mixed Oligoastrocytoma (MOA) are diffusely infiltrating gliomas composed of a mixture of two distinct neoplastic cell types, morphologically resembling the tumor cells in oligodendrogliomas and diffuse astrocytomas of WHO grade II.^[159] They usually develop in middle-aged individuals (35-45 years), preferentially in cerebral hemispheres.^[100,160,161] Of all the gliomas, MOAs remain the most difficult to define, are least reproducible, and most likely to receive discordant diagnoses from expert neuropathologists around the country.^[14] Nevertheless, the WHO recognizes two basic patterns, (1) a biphasic ("compact") variant, where the two elements are spatially distinct, and (2) an intermingled ("diffuse") variant, where the cell types are interspersed. The former, though more often illustrated, is far less common than the latter. A diffuse admixture of GFAP positive minigemistocytes and gliofibrillary oligodendrocytes with an oligodendroglial component should not be confused as oligoastrocytoma instead of oligodendroglioma. Only tumors in which fibrillary,

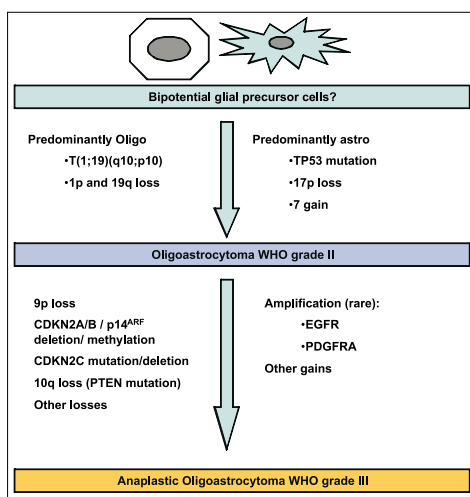


Figure 3: Genetic alterations and the development of oligoastrocytic tumors, (Modified from WHO 2007⁽⁴⁾)

protoplasmic or classic gemistocytic astrocytic cells are present, in addition to the oligodendroglial tumor, qualify as oligoastrocytoma.^[159] Both the components show the same immunoreactivity patterns as 'pure' oligodendrogliomas and astrocytomas, respectively. GFAP and vimentin expression are more consistently found in the astroglial component, while they are variably expressed in oligodendroglial tumor cells. About one-third demonstrate nuclear p53 overexpression.^[162] MIB-1 LI is usually low ($< 6\%$).^[163]

Anaplastic Oligoastrocytoma (AOA) (WHO grade III)

As with other high grade gliomas, AOA occur at a higher age (mean age 44 years).^[164] They are predominantly hemispheric. AOA are oligoastrocytomas with histological features of anaplasia, including nuclear atypia, cellular pleomorphism, high cellularity, and high mitotic activity. In addition, microvascular proliferation may be present.^[159] MIB-1 LI correlates with the presence of anaplastic features. The presence of necrosis in AOA, in contrast to AO, has been seen to be associated with a significantly worse prognosis. Even though prognosis of patients with AOA is better than classical glioblastomas, AOA with necrosis according to some authors should be classified as 'glioblastoma with oligodendroglial component'.^[37,164,165]

Genetics of oligoastrocytic tumors [Figure 3]

The molecular genetic alterations underlying oligoastrocytomas resemble those of oligodendrogliomas and astrocytomas. About 30-50% of oligoastrocytomas (predominantly nontemporal) are characterized by combined loss of $1p$ and $19q$, while 30% (predominantly temporal) carry the TP53 mutations, with both these alterations being mutually exclusive.^[108,109,112,116] As for oligodendrogliomas, a

combined $1p / 10q$ loss is associated with favorable prognosis.^[166,167] In AOA, $1p$ loss alone has been seen to be an independent marker of improved progression and free and overall survival.^[166]

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