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# The Changing Management of Low-Grade Astrocytomas and Oligodendrogliomas

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Modern classifications of brain tumors are based on the work of Bailey and Cushing [1] first published in 1926. Primary central nervous system (CNS) tumors consist of a diverse range of pathological entities, each harboring a varied and distinct clinical course. Primary CNS tumors may be classified as gliomas or nongliomas. Low-grade gliomas represent approximately 11% of the primary CNS tumors diagnosed each year in the United States and Canada [2]. Of all low-grade gliomas, only a grade-1 astrocytoma, such as a pilocytic astrocytoma, can be considered truly benign. Grade-2 gliomas, while classified pathologically as low grade, are not benign because they are capable of malignant dedifferentiation. Although typically more indolent than their high-grade counterparts, they may be associated with increasing neurological disability and are ultimately fatal. Patients with low-grade gliomas have median survivals in the range of 5 to 7 years, with considerable individual variation [3]. Optimum treatment for patients with low-grade gliomas is unknown and the management strategies remain controversial. Common options include early and extensive surgery followed by radiotherapy, and a conservative approach of "watch and wait," where treatment is postponed until patients become symptomatic or have radiographic tumor progression. Greater awareness of the toxicities of both radiotherapy and chemotherapy, and the potential morbidity of surgery for patients whose survival is protracted, has led to the increasing tendency to defer treatment for as long as possible. With advances in molecular biology, improved and more accessible radiologic techniques, and both new chemotherapeutic and molecular targeted therapies, the therapeutic options for patients with low-grade gliomas is likely to change soon.

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## EPIDEMIOLOGY AND ETIOLOGY

Low-grade gliomas typically arise in young to middle-aged adults. The median age at diagnosis is approximately 35 years [4–9]. Males appear at increased risk for this disease, reportedly constituting 55% to 65% of all patients with low-grade glial tumors [5,6]. Low-grade gliomas are also more common in Caucasians [10]. Low-grade gliomas are distributed in a manner relative to proportions of the cerebral mass, and are consequently most likely to develop within the frontal, parietal, or temporal lobes. Involvement of the insula or supplementary motor area is more common in low-grade than high-grade gliomas [11]. The cerebellum, brainstem, and spinal cord are unusual sites in adults, although the brainstem is a common site in children [12].

It is believed that most CNS tumors arise from acquired somatic mutations of genes involved in control of cell growth and proliferation. Gliomas may rarely be inherited as part of a familial disease and examples include type-1 neurofibromatosis, Turcot's syndrome, Gorlin's syndrome, and Li-Fraumeni syndrome [13]. The etiology of sporadic gliomas is unknown. Environmental factors, such as chemical, biological, or physical agents that cause DNA damage, are possible neurocarcinogens, although discrete environmental factors have not been linked consistently with these diseases. However, exposure to vinyl chloride and ionizing radiation is associated with the development of primary brain tumors. Low-dose radiation treatments, once used to treat childhood skin disorders, and radiotherapy for childhood cancers and leukemia, remain risk factors for the development of CNS tumors [14]. Several studies have explored the impact of N-nitroso compounds in the environment as causative of brain tumors. Though suggestive in animal models, human case control studies have not implicated tobacco smoke, alcohol, or cured meats in the genesis of brain tumors [15–20]. Interestingly, one case-controlled study has linked paternal occupational exposure to polycyclic aromatic hydrocarbons preconception to an increased risk of all childhood CNS tumors [21]. Although viruses can cause CNS tumors in animal models, and JC virus, BK virus, simian virus 40, and herpes cytomegalovirus have been isolated from human CNS tumor tissue [22,23], no causative role for viruses in human gliomagenesis has been demonstrated.

## CLASSIFICATION

The World Health Organization (WHO) classification segregates gliomas into four discrete morphologic groups with distinct prognoses and treatment recommendations [24]. Grade-I tumors are biologically indolent while grade-IV tumors are highly aggressive. The diagnostic grade of a tumor is based on the grade of the most malignant portion sampled. Table 1 summarizes the WHO classification of low-grade gliomas.

Low-grade astrocytic tumors can be diffusely infiltrating or well circumscribed. Pleomorphic xanthoastrocytoma, pilocytic astrocytoma, and giant-cell astrocytoma have a circumscribed growth pattern and are characterized by slow growth and indolent behavior. These tumors are distinct from infiltrating