Update in the Treatment of High-grade Gliomas

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KEYWORDS

• Gliomas • Surgery • Radiation therapy • Chemotherapy

KEY POINTS

- As with other malignancies, recent advances in molecular diagnostics have advanced our understanding of high-grade gliomas and will influence their therapeutic management in the future.
- The role of temozolomide and radiation are being better defined in elderly patients with high-grade astrocytomas.
- The role of combined chemoradiation in grade III oligodendroglial tumors is becoming more established.
- The anti–vascular endothelial growth factor antibody, bevacizumab, is an important new agent in the treatment of recurrent high-grade astrocytomas.
- A combined multimodality approach is central to the management of most high-grade gliomas.

INTRODUCTION

This review focuses on updates of the treatment of high-grade gliomas, aggressive infiltrating neoplasms of the central nervous system (CNS). The authors highlight the key historical trials as well as other studies that represent important recent advances in the field. High-grade (grade III and IV) gliomas include both astrocytomas and oligodendrogliomas. A concerted multidisciplinary approach using several modalities in combination is often used in their treatment. This approach typically begins with a diagnostic and potentially therapeutic surgical procedure. Typically, this is followed by radiation therapy (RT) and often chemotherapy. The authors detail the specific approaches to each tumor subtype in the following sections.

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PATIENT EVALUATION OVERVIEW

Histology

Although molecular diagnostics for high-grade gliomas have undergone significant changes over the past few years, routine histology remains the gold standard of diagnosis. This point is reflected in updates to the most recent edition of the World Health Organization's (WHO) classification of CNS tumors.[1] Although many molecular details are discussed, they typically serve to refine rather than define a tumor by type. This review focuses on grade III and IV gliomas, but tumors of lower grade are mentioned when appropriate. This discussion is most important when comparing and contrasting the so-called secondary glioblastoma (GBM), high-grade tumors that arise in a stepwise fashion from tumors of lower grade, from the more common primary GBM, a tumor that begins as a high-grade neoplasm. The features that distinguish primary from secondary GBM are described by the WHO but, again, are not based on routine histology. This distinction is not routinely made but, as shown later, has become of more interest as molecular pathology further defines subtypes.

Oligodendrogliomas

Oligodendrogliomas are infiltrating tumors with round or ovoid nuclei and perinuclear halos, artifacts of tissue preparation. Microcalcification, microcysts, and chicken-wire vasculature are seen in some but not all cases. Oligodendrogliomas have 2 pathologic grades: II and III (anaplastic oligodendrogliomas [AO]). AO tumors are defined by prominent mitotic activity on routine histologic stains but not the MIB-1 labeling index, an antibody-based test of Ki-67 protein expression that is important in cell proliferation. Both endothelial proliferation and focal areas of necrosis may be seen in AO. Although certain molecular diagnostic features are frequently encountered in oligodendrogliomas, they do not define the tumor by the WHO diagnostic criteria. These features are discussed further later.

Astrocytomas

Astrocytomas typically share morphologic and histologic features characteristic of astrocytes, which may include immunohistochemical (IHC) staining for glial fibrillary acidic protein, a protein often expressed in reactive astrocytes. Infiltrating gliomas are of 3 pathologic grades: II, III, and IV. Anaplastic astrocytomas (AA), grade III, are distinguished from grade II astrocytomas by nuclear pleomorphism and the presence of mitoses. Although the WHO classification system allows for scant mitoses in grade II tumors, there is no clear cutoff distinguishing a grade II from a grade III tumor. Glioblastoma, previously termed *glioblastoma multiforme* by the WHO classification system, is a grade IV astrocytoma. It is differentiated from AA by the presence of either of the cardinal features of endothelial proliferation (often described as glomeruloid) and/or necrosis (often described as pseudopalisading). Gliosarcoma, large cell GBM, and gliofibroma are further subclassifications under the current classification system.

Mixed oligoastrocytomas

At times the distinction between oligodendrogliomas and astrocytomas is unclear. Distinct cell populations resembling either tumor type can be seen admixed in the same tumor leading to a histologic diagnosis of a grade II oligoastrocytoma or grade III anaplastic oligoastrocytoma (AOA). A separate histologic entity, GBM with oligodendroglial features (WHO grade IV) is also described. This pleomorphism raises questions about the cells of origin in these tumors, making room for the current thinking about both neural stem cells and brain tumor stem cells in glioma.[2] The underlying molecular features, described later, that allow for this histologic