

Recurrent Glioblastoma: Where we stand

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Abstract

Current first-line treatment regimens combine surgical resection and chemoradiation for Glioblastoma that provides a slight increase in overall survival. Age on its own should not be used as an exclusion criterion of glioblastoma multiforme (GBM) treatment, but performance should be factored heavily into the decision-making process for treatment planning. Despite aggressive initial treatment, most patients develop recurrent diseases which can be treated with re-resection, systemic treatment with targeted agents or cytotoxic chemotherapy, reirradiation, or radiosurgery. Research into novel therapies is investigating alternative temozolomide regimens, convection-enhanced delivery, immunotherapy, gene therapy, antiangiogenic agents, poly ADP ribose polymerase inhibitors, or cancer stem cell signaling pathways. Given the aggressive and resilient nature of GBM, continued efforts to better understand GBM pathophysiology are required to discover novel targets for future therapy.

Key words: Chemotherapy, glioblastoma multiforme, glioma, targeted therapy, temozolomide

Introduction

Glioblastoma multiforme (GBM) is one of the most aggressive primary brain tumors, with a grim prognosis despite maximal treatment. Advancements in the past decades have not significantly increased the overall survival of patients with this disease. The recurrence of GBM is inevitable, its management often unclear and case dependent. In this report, the authors summarize the current literature regarding the natural history, surveillance algorithms, and treatment options of recurrent GBM. In addition, they provide brief discussions regarding current novel efforts in basic and clinical research. They conclude that although recurrent GBM remains a fatal disease, the literature suggests that a subset of patients may benefit from maximal treatment efforts.

Glioblastoma multiforme is a World Health Organization Grade IV tumor that represents 15–20% of all primary intracranial tumors.^[1] It is the most malignant astrocytic tumor, with histopathological features that include cellular polymorphism, brisk mitotic activity, microvascular proliferation, and necrosis. The current standard of care for patients with newly diagnosed glioblastoma was established in 2005, following the pivotal trial by the European Organization for the Research and Treatment of Cancer/National Cancer Institute of Canada Clinical Trials Group, in which concurrent temozolomide (TMZ) (75 mg/m²/d for ≤7 weeks) and radiotherapy followed by 6 maintenance cycles of adjuvant chemotherapy (150–200 mg/m² on 5-d therapy every 28 d) improved progression-free survival (PFS) and OS.^[2]

Despite advances in imaging techniques and multi-modal treatment options, the overall prognosis of patients with GBM remains grim. The median duration of patient survival is estimated to be between 12 and 18 months with maximal treatment, but those without any intervention die soon after diagnosis.^[3,4] So far, very few cases of curative outcome or long-term survival have been reported.^[5-7] In a large retrospective study, Scott *et al.*,^[6] estimated that 2.2% of the cohort survived for >2 years. Overall, the 5-year survival rate is <10%, with a final mortality rate of close to 100%.^[8,9]

Glioblastoma has an unfavorable prognosis mainly due to its high propensity for tumor recurrence. It has been suggested that GBM recurrence is inevitable after a median survival time of 32–36 weeks.^[10,11] The natural history of recurrent GBM, however, is largely undefined for the following reasons: (1) Lack of uniform definition and criteria for tumor recurrence; (2) institutional variability in treatment philosophy; and (3) the heterogeneous nature of the disease, including location of recurrence and distinct mechanisms believed to contribute to known subtypes of GBM.

The criteria used to define recurrent GBM remain ambiguous due to the varied presentation of new lesions. First, the infiltrative nature of GBM cells makes it difficult to eliminate microscopic disease despite macroscopic gross-total resection. Studies have shown that GBM recurrence most often occurs in the form of a local continuous growth within 2–3 cm from the border of the original lesion.^[12-14] Choucair *et al.*,^[15] reported that more than 90% of patients with glioma showed recurrence at the original tumor location and that multiple lesions developed in 5% after treatment. Second, although less common, GBM may also recur through the development of new parenchymal lesions that fail to exhibit continuous growth patterns, intraventricular spread, or dissemination.^[12] Baumann *et al.*,^[16] have shown that uncommon relapse patterns are more prevalent in midline tumors and tumors that infiltrate both hemispheres. Finally, in an attempt to preserve neurological function and maintain patient QOL, subtotal resections are sometimes performed when tumors infiltrate eloquent areas of the brain. Tumor recurrence is also defined by the appearance of residual tumor growth on imaging studies or the manifestation of new clinical symptoms. The term “tumor recurrence” is frequently used synonymously with “tumor progression” because of the spectrum from which new lesions can develop.

Diagnosis of Progression

Serial neuroimaging remains the primary monitoring tool for glioblastoma. Standard magnetic resonance imaging (MRI) contrast studies though beneficial for monitoring, may be misleading and confounding the recurrence even strictly adhered to McDonald criteria^[17] in first couple of months it becomes difficult to differentiate recurrence from pseudoprogression using T2-weighted, T1-weighted gadolinium, fluid-attenuated inversion-recovery (FLAIR)^[18] sequence of MRI. Pseudo progression is featured in 20–30% patient treated with concurrent radiation cum TMZ followed by adjuvant TMZ.^[19,20] Radionecrosis also appears earlier in patients

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