Neuroimaging and Genetic Influence in Treating Brain Neoplasms

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KEYWORDS

• High-grade gliomas • Glioblastoma • Gene expression • Radiogenomic • Treatment response • Prognosis • Outcome • Pseudoprogression

KEY POINTS

- The inability of the traditional histopathologic brain neoplasm classification to define prognosis and treatment response determined the development of the genomic classification of brain neoplasms and radiogenomics.
- The major clinical importance of this molecular classification is that the same histopathologic type of brain tumor, glioblastoma multiforme, has different treatment response based on the molecular subtype classification.
- The same histopathologic tumor may differ in the molecular component and demonstrate different clinical behavior and outcome.
- Gene characteristics might be a better predictor of key outcomes than histopathologic classification.
- MR imaging findings may be correlated with molecular mutations of brain neoplasms and glioblastoma molecular subtypes.
- Radiogenomics is the combination of imaging and gene expression characteristics of brain neoplasms that has the potential to give insight into tumor biology.
- The major clinical importance of molecular classification of brain tumor, especially glioblastoma, is the capacity to evaluate treatment response, patient outcome, and prognosis.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor in adults. They account for 50% to 60% of all astrocytic gliomas, with an incidence of around 5 cases per 100,000 patients per year. Despite significant advances in treatment with aggressive multimodal therapy, GBM remains a deadly disease with a dismal prognosis, with a 2-year overall survival less than 10% and a median overall survival duration of 16 to 17 months.[1,2] The current standard of care is based on targeted surgical resection followed by concomitant radiation therapy and temozolomide (TMZ) treatment.[1,2] In recurrent cases, this treatment regimen is commonly followed by antiangiogenic therapy.[3] Nevertheless, after this new therapy approach, only a slight increase in overall survival has been observed, improved from 10 months to 16 to 17 months.

The identification of molecular genetic biomarkers has considerably increased the current understanding of glioma genesis, prognosis,

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evaluation, and treatment planning. Recent publications have pointed out that gene characteristics might be better predictors of key outcomes than histopathologic classification. Genetic and cellular features of high-grade glioma aggressiveness influence MR imaging. The heterogeneous aspect depicted by MR imaging can be secondary to underlying differences in intratumoral tissues and genetic expression patterns.[4] Improvement in treatment strategies has largely been based on the substantial progress in the identification of genetic alterations or profile in GBMs, which may enable the development of more individualized and specifically targeted therapy.

RADIOGENOMICS

An intriguing characteristic of glial brain tumors is their phenotypic variety. No isolated genetic event accounts for gliomagenesis, but rather the cumulative effects of several alterations that operate in a concerted manner and are responsible for the phenotypic and genotypic heterogeneity of these tumors. Radiogenomics can be referred to as a combination of imaging and gene expression and has the potential to give insight into tumor biology, which is harder to obtain from other techniques alone.

Glioblastoma was the first human cancer sequenced by The Cancer Genome Atlas (TGCA) network effort, resulting in a comprehensive characterization of the mutational spectrum of this neoplasm.[2,5,6] TCGA is a project supervised by the National Cancer Institute and the National Human Genome Research Institute to catalog genetic mutations responsible for cancer, using genome sequencing. It is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of genome analysis technologies. The overarching goal is to improve the ability to diagnose, treat, and prevent cancer (https://wiki.nci.nih.gov/display/TCGA/The+Cancer+Genome+Atlas). The TCGA project has been established to generate a comprehensive catalog of genomic abnormalities driving tumorigenesis.[7]

Microarray is a tool used to characterize genomewide gene expression based on messenger RNA levels. This technique has been used to assess the correlation between gene-expression levels, MR imaging features, and outcome in GBM patients. Radiogenomics has been defined as the combination of imaging features and gene expression and has the potential to give insight regarding tumor biology, which may in turn be important to predict management and outcome.[8,9]

GENETIC EVALUATION OF BRAIN TUMORS

Great strides have been made in the characterization of regional GBM genetic expression patterns. Because of integrated genomic analysis, molecular classifications have been proposed with the intent of providing more uniform neoplasm subclasses from a biological standpoint. Imaging correlates of gene expression may provide important insight into brain tumor biology. Continued genomic sequencing may contribute to patient selection for trials and to developing more specific targeted therapies.

O^6-Methylguanine-DNA Methyltransferase

Epigenetic silence of the DNA repair O^6-methylguanine-DNA methyltransferase (MGMT) by promoter methylation is associated with a loss of its expression and has been related to longer overall survival in patients with high-grade gliomas.[10] Those patients treated with concomitant radiation therapy and alkylating agents, such as TMZ, have higher median survival (21.7 months) and 2-year survival (46%) rates when compared with those with unmethylated tumors.[11] Alkylating agents are highly reactive drugs that cause cell death by binding to DNA. MGMT inhibits the killing of tumor cells by alkylating agents by encoding a DNA repair protein to reverse alkylation at the DNA O^6 position of guanine, thereby averting the formation of lethal crosslinks.[12] A promoter controls MGMT activity, and methylation silences the gene in the neoplasm and thus diminishes DNA-repair activity. Through this mechanism, MGMT causes resistance to alkylating drugs (**Fig. 1**).

Methylation of the MGMT promoter in gliomas can be a useful predictor of tumor responsiveness to alkylating agents.[12] MGMT promoter methylation is an independent favorable prognostic factor that has been associated with longer survival in patients with newly diagnosed high-grade glioma after TMZ chemotherapy. Patients whose tumor contained a methylated MGMT promoter benefited from TMZ, whereas those with unmethylated tumors showed less benefit. Thus, MGMT methylation status may allow the selection of patients most likely to benefit from alkylating therapy. For those patients with unmethylated MGMT, alternative treatments using drugs with different mechanisms of action or methods of inhibiting MGMT should be used.[10]

The level of MGMT varies widely among different tumor types as well as among various samples of the same type of neoplasm. Approximately 30% of gliomas lack MGMT,[12] which may increase tumor sensitivity to alkylating treatment. High levels of MGMT in cancer cells may create