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# Multimodal imaging of gliomas in the context of evolving cellular and molecular therapies☆

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ABSTRACT

The vast majority of malignant gliomas relapse after surgery and standard radio-chemotherapy. Novel molecular and cellular therapies are thus being developed, targeting specific aspects of tumor growth. While histopathology remains the gold standard for tumor classification, neuroimaging has over the years taken a central role in the diagnosis and treatment follow up of brain tumors. It is used to detect and localize lesions, define the target area for biopsies, plan surgical and radiation interventions and assess tumor progression and treatment outcome. In recent years the application of novel drugs including anti-angiogenic agents that affect the tumor vasculature, has drastically modulated the outcome of brain tumor imaging. To properly evaluate the effects of emerging experimental therapies and successfully support treatment decisions, neuroimaging will have to evolve. Multimodal imaging systems with existing and new contrast agents, molecular tracers, technological advances and advanced data analysis can all contribute to the establishment of disease relevant biomarkers that will improve disease management and patient care. In this review, we address the challenges of glioma imaging in the context of novel molecular and cellular therapies, and take a prospective look at emerging experimental and pre-clinical imaging techniques that bear the promise of meeting these challenges.



**Contents**



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Key points

- High grade gliomas are heterogeneous and infiltrative, causing them to relapse after conventional standard therapies. New treatment approaches such as molecular and cellular therapies offer the perspective of a better personalized treatment.
- To provide clinicians with the appropriate information needed to efficiently deal with the treatment of gliomas, neuroimaging would benefit from an evolution from non-specific contrast based protocols to protocols that are oriented toward disease relevant and treatment specific biomarkers.
- Technological advances and the combination of imaging modalities, new contrast mechanisms and advanced data processing techniques will assist in addressing the challenges of tumor imaging in the context of emerging treatment approaches.

## 1. Introduction

Gliomas are brain tumors that arise from abnormally proliferating glial cells, which normally provide support and protection of neurons in the central nervous system. Glioblastoma (GBM), the focus of the present review, represents the most malignant form of gliomas with a mean patient survival after diagnosis of about 14 months [1]. Despite standard treatment involving surgical resection, radiation therapy and chemotherapy, only very few patients survive more than 5 years [2]. GBMs are highly heterogeneous; when tumors in different patients are compared, they vary in mutation status [3], in putative glial cell lineage, in epigenetic profiles and in histological appearance. Similarly, within single tumors, cell clones with different genetic profiles and even different ploidies co-exist within a microenvironment made up of varying non-neoplastic stromal cells, immune cells and extracellular matrix components. This heterogeneity represents a key challenge in tumor characterization and for the development of effective therapies. Data from high throughput molecular analyses attempts to define subclasses of GBM that differ by their genetic and epigenetic alterations, gene expression profiles, clinical aggressiveness, prognosis and response to treatment [4,5]. Although there is some discrepancy in currently proposed subclasses, the most recent work combines methylation profiles with specific genetic mutations and patient age group, to propose a classification into 6 distinct subgroups for pediatric and adult GBM [6]. Yet, these molecular classifications have so far not led to a diversification in treatment [7].

Initial diagnosis of GBM is largely based on magnetic resonance imaging or computed tomography, indicating the importance of

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