# Chapter 14
# Glioblastoma: Physiopathology and Complications

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## ABSTRACT

*Glioblastoma is the most aggressive primary malignant brain tumor in adults. Complex genetic and molecular changes that cause unchecked cell proliferation, invasion of the surrounding brain tissue, and angiogenesis are the hallmarks of the physiopathology of glioblastoma. Although there are treatment options for this deadly tumor that include surgery, radiation, and chemotherapy, the blood-brain barrier and the tumor's infiltrative nature restrict their effectiveness, frequently leading to tumor recurrence and illness progression. To create new therapeutic approaches and enhance patient outcomes, it is crucial to comprehend the physiopathology of glioblastoma and its associated consequences. To improve treatment and quality of life for patients with glioblastoma, further research is required to clarify molecular causes, discover therapeutic targets, and address the difficulties provided by comorbidities.*

## INTRODUCTION

Glial cells are the supporting cells that surround and feed neurons in the brain, giving birth to the extremely aggressive kind of brain cancer known as glioblastoma (GBM); making up 50% of the glioma subtypes and more than 60% of all brain tumors (Aly et al., 2020).GBM generally only affects the Central Nervous System because of its fast development and the CNS's unique design, which is bordered by the blood-brain barrier and dura mater and lacks lymphatic channels (De Barros et al., 2019). GBMs can appear in the brain stem, cerebellum, and spinal cord, even though they mostly only happen in the brain. The four lobes of the brain—frontal (25%), temporal (20%), parietal (13%), and occipital (3%), account for sixty-one percent of all primary gliomas [American Association of Neuroscience Nurses (AANN),2014]

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(Ahmad et al., 2012). GBMs were once assumed to only come from glial cells, but data now reveals that they may come from a variety of cell types with characteristics resembling those of neural stem cells.

These cells are in various phases of development from stem cells to neurons to glia, with molecular changes in signaling pathways acting largely as a determinant of phenotypic variance rather than different cell types at the beginning (Ali et al., 2015). GBMs can be classed as primary, or de novo, emerging without a known predecessor, or secondary, where a low-grade tumor changes over time into a GBM. Most GBMs are primary, and patients with primary GBMs have worse prognoses than patients with secondary GBMs. Primary GBM patients more frequently have older ages (Ambartsumian et al., 2019). The age-adjusted incidence rate is 3.2 per 100,000 people on average (Fabi et al., 2004). A 5-year survival rate of 5% was recorded for GBM in the United States alone in 2016, where an estimated 12,120 patients received the diagnosis (Omuro et al., 2007). The incidence rises sharply after the age of 54 and peaks at 15.24 per 100,000 people between the ages of 75 and 84 years (Omuro et al., 2007). The median age of persons diagnosed with GBM has increased to 64 years over the past few decades as a result of the disease being more common in older people and people living longer in industrialized countries.

## GENETIC ANOMALIES AND MOLECULAR PATHWAYS DISCOVERED IN GBM

Tumour growth in GBM cells is aided by increased expression of cell surface membrane receptors that govern intracellular signal transduction pathways controlling proliferation and cell cycle abnormalities, including an increase in DNA repair proteins and aberrant cell death processes (Barzegar Behrooz et al., 2019). The Cancer Genome Atlas (TCGA) research network's comprehensive study of the genomic alterations revealed that the most frequently disrupted signaling cascades in GBM include modifications to pathways that are connected to receptor tyrosine kinase (RTK) signaling, TP53 pathway, CDK4/RB1 pathway.

### Receptor Tyrosine Kinase (RTK) Signaling in Glioblastoma

More than 80% of primary GBMs have mutations or amplifications of RTK, including the insulin-like growth factor receptor (IGFR-1), the basic fibroblast growth factor receptor 1 (FGFR-1), and the epidermal growth factor receptor (EGFR)(Bezecny, 2014). These structurally related proteins work together to control a convoluted signaling network that powers and controls numerous cellular processes. The RAS/MAPK pathway, which promotes cellular proliferation, differentiation, and migration in gliomas, and the PI3K/AKT/mTOR pathway, which primarily works to promote cell proliferation and survival by advancing the cell cycle and inhibiting apoptosis, are the two main signaling pathways used by RTK (Bezecny, 2014). PTEN, a tumor suppressor gene and an antagonist of this pathway, controls the activity of PI3K (Brown et al., 2017). A major contributor to resistance to EGFR therapies is PTEN loss, which is present in 36% of gliomas. Loss of PTEN may cause a dramatic upregulation of this pathway (Del Vecchio et al., 2013).

The majority of genetic alterations, which affect nearly 57% of GBM tumors, include EGFR mutations, rearrangements, alternative splicing, and focal amplifications (Gomez-Manzano et al., 1996). A classical subtype of GBM patient will almost always have EGFR amplification, whereas secondary GBMs are extremely uncommon to have this mutation (Sherr& Roberts, 1999). EGFR inhibitors, such as gefitinib and erlotinib, have sadly not been successfully introduced into clinical trials for patients

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