20 years of the Stupp protocol: confronting stagnation in glioblastoma therapy

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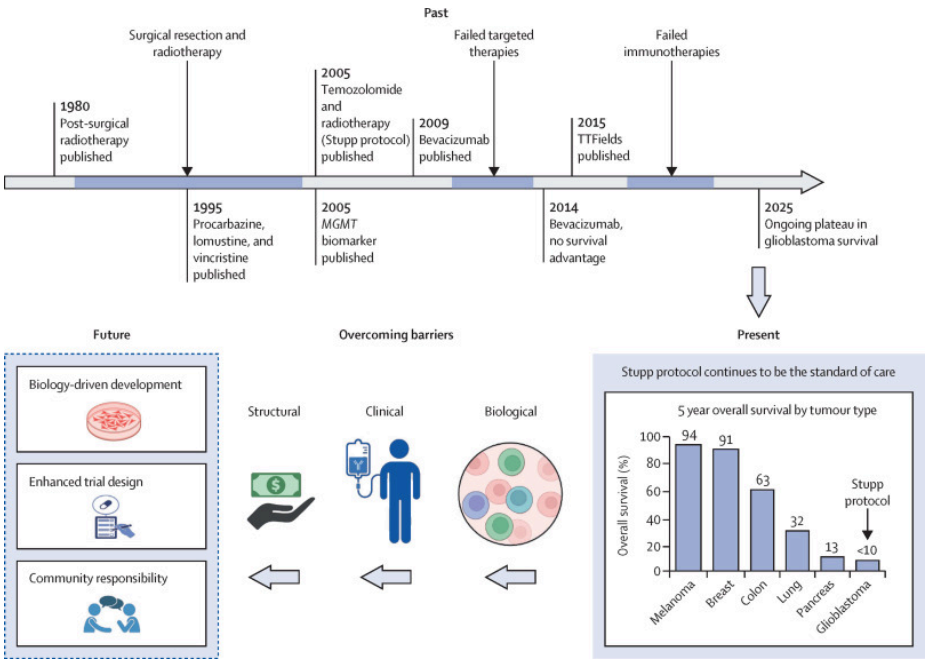
Mustafa KhasrawMustafa KhasrawCorrespondenceSend email to mustafa.khasraw@duke.eduAffiliationsThe Preston Robert Tisch Brain Tumor Center, Department of Neurosurgery, Duke University Medical Center, Durham, NC 27710, USASearch for articles by this authora Send email to mustafa.khasraw@duke.edu · Emma PristoEmma PristoAffiliationsThe Preston Robert Tisch Brain Tumor Center, Department of Neurosurgery, Duke University Medical Center, Durham, NC 27710, USASearch for articles by this authora · Roger StuppRoger StuppAffiliationsDepartments of Neurological Surgery, Neurology, and Medicine (Hematology/Oncology) and Northwestern Medicine Malnati Brain Tumor Institute of the Lurie Comprehensive Cancer Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USASearch for articles by this authorb



20 years ago, the combination of radiotherapy with concomitant and adjuvant temozolomide, also known as the Stupp protocol, transformed glioblastoma treatment. It was the first multimodal regimen to show a survival advantage in newly diagnosed glioblastoma and is the standard of care two decades later. The trial identified a biomarker (*MGMT*) to predict benefit from temozolomide; yet this represents only the beginning of what biologically informed patient selection could achieve. Advances in single-cell profiling, spatial imaging, and systems immunology are revealing fundamental determinants of glioblastoma behaviour, including dynamic cell states, lineage plasticity, metabolic constraints, and the role of the brain's resident and infiltrating immune cells. As these insights mature, they will offer a blueprint for developing therapies that are rational rather than empirical, aiming to target specific cellular programmes, modulate the immune microenvironment, or sensitise tumours to existing methods. Such mechanistic discoveries hold the potential to transform glioblastoma care from a uniform approach defined by chemotherapy tolerance to a precision strategy grounded in biology.