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Editorial

Advances in glioblastoma: Is there light at the end of the tunnel?

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Glioblastoma, the most aggressive primary brain tumour in adults, continues to represent one of the greatest therapeutic challenges in neuro-oncology. Despite decades of research, outcomes remain dismal, with a median overall survival of approximately 14–16 months following standard-of-care treatment consisting of maximal safe resection followed by radiotherapy with concurrent and adjuvant temozolomide.[1] The near-universal recurrence of glioblastoma underscores the urgent need for novel therapeutic strategies and a paradigm shift in disease management. The central question remains: are recent advances sufficient to suggest a meaningful turning point?

Refining the surgical and radiotherapeutic backbone

Surgical resection remains the cornerstone of glioblastoma management, with the extent of resection consistently correlating with survival. Advances in intraoperative imaging, fluorescence-guided surgery (5-ALA), and functional mapping have improved the safety and completeness of resection.[2] However, surgery alone is insufficient due to the highly infiltrative nature of glioblastoma.

Radiotherapy continues to play a pivotal role, yet recurrence within the irradiated field occurs in nearly 90% of patients within two years.[3] Adaptive radiotherapy provides an opportunity to modify the target volume based on serial imaging and is under investigation. Techniques such as stereotactic radiosurgery (SRS) and hypofractionated stereotactic radiotherapy (SRT) allow precise targeting while minimising toxicity.[4] However, optimal patient selection, dose fractionation, and long-term neurotoxicity remain unresolved issues. Role of advanced radiotin technique like proton therapy remains under investigation. Reirradiation, once considered high risk, has emerged as a feasible option in selected patients.[5]

Chemotherapy and antiangiogenic therapy: Incremental gains:

Temozolomide remains the backbone of systemic therapy, particularly in patients with O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation.[1] Alternative regimens, including dose-dense or metronomic schedules, have been explored but with limited success.[6]

Antiangiogenic therapy, particularly bevacizumab, initially generated enthusiasm due to radiographic response and improved progression-free survival. However, robust evidence has failed to demonstrate a meaningful overall survival benefit.[7] The Cochrane review by Khasraw *et al*[7] highlights the limitations of antiangiogenic strategies, emphasising transient benefits and the development of resistance.

These findings reinforce the notion that targeting a single pathway in a biologically heterogeneous tumour like glioblastoma is unlikely to yield durable results.

Immunotherapy: Promise tempered by complexity:

The success of immune checkpoint inhibitors in other malignancies has spurred interest in their application to glioblastoma. However, results have been largely disappointing. The recent Cochrane review evaluating anti–PD-1 and anti–PD-L1 therapies found insufficient evidence to support their routine use

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in glioblastoma.[8] Several factors contribute to this limited efficacy, including the heterogeneity of tumour and microenvironment cells, low mutational burden, inadequate pharmacokinetic properties of agents, and the presence of the blood-brain barrier.[9] Nevertheless, ongoing trials exploring combination approaches—such as checkpoint inhibitors with vaccines, radiotherapy, or oncolytic viruses—offer cautious optimism. Emerging immunotherapeutic strategies include dendritic cell vaccines, CAR-T cell therapy targeting Epidermal Growth Factor Receptor variant III (EGFRvIII), and tumour lysate-based vaccines.[10] While early-phase trials have shown signals of activity, these approaches remain investigational.

Targeting tumour biology: Molecular and cellular insights:

Advances in molecular profiling have transformed our understanding of glioblastoma, revealing its profound heterogeneity. The identification of key molecular subtypes and pathways, including epidermal growth factor receptor (EGFR) amplification, changes in cyclin and cyclin-dependent kinases (CDK), retinoblastoma, and p53 pathways, has provided potential therapeutic targets.[11] However, translating these insights into effective therapies has proven challenging.

One of the more intriguing avenues is the modulation of autophagy, a cellular process involved in tumour survival and resistance. Preclinical and early clinical studies suggest that both activation and inhibition of autophagy may have therapeutic potential, depending on the context.[12] This duality reflects the complexity of glioblastoma biology and highlights the need for precision approaches.

Similarly, theranostics, tumour metabolism, epigenetic regulation, and the glioma stem cell niche are being actively investigated.[13-16] These areas may offer opportunities for disrupting tumour resilience and recurrence.

Tumour treating fields and emerging technologies

Tumour treating fields (TTF), a non-invasive modality delivering low intensity, intermediate frequency (200 Hz), alternating electric fields, have demonstrated a survival benefit when combined with temozolomide in newly diagnosed glioblastoma.[17] Despite logistical challenges and patient compliance issues, TTF represents one of the few recent interventions to show a positive phase III outcome. Technological advances, including artificial intelligence–guided imaging, radiomics, and liquid biopsy approaches, are also poised to enhance diagnosis, treatment planning, and monitoring. These tools may enable earlier detection of recurrence and more adaptive therapeutic strategies.

Recurrent glioblastoma: The unmet frontier:

Management of recurrent glioblastoma remains particularly challenging, with no established standard of care. Median survival for recurrent disease is 6-9 months. Options include reresection, reirradiation, chemotherapy, and enrolment in clinical trials.[4,6] The review by Aldoghachi *et al*[6] emphasises the need for multimodal strategies tailored to individual patient characteristics. Importantly, patient selection and quality-of-life considerations are critical in this setting.

Barriers to progress: Biological and clinical realities

Several fundamental barriers continue to impede progress in glioblastoma namely, (*i*) Inter and intra-tumoral heterogeneity, with a lack of a single driver mutation leading to therapeutic resistance; (*ii*) Blood-brain barrier, limiting drug delivery; (*iii*) immunosuppressive microenvironment, reducing immunotherapy efficacy; (*iv*) Adaptive resistance mechanisms, enabling tumour survival

These challenges necessitate integrated approaches that combine modalities rather than relying on single-agent therapies.

Is there light at the end of the tunnel?

The answer is nuanced. While no single breakthrough has dramatically altered the prognosis of glioblastoma, incremental advances across multiple domains—surgical techniques, radiotherapy, molecular targeting, and emerging therapies—collectively suggest progress. The future of glioblastoma management likely lies in personalised, multimodal therapy, guided by molecular profiling and adaptive treatment strategies. Collaborative research, innovative trial designs, and integration of translational science into clinical practice will be essential.

Rather than a sudden breakthrough, hope may emerge gradually—through the convergence of incremental innovations that, together, reshape the therapeutic landscape.

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