ABSTRACT	TITLE	AUTHOR(S)	INSTITUTION	
#30	Computational reconstruction of glioblastoma surgical margins identifies molecular drivers of residual tumor recurrence	Shivi Kumar (1) Philip Moheno (2) Sweta Gupta (3) Leonardo Soto (4)	Mind Matters Foundation (1) University of California Berkeley (2) Stanford University School of Medicine (3) Harvard Medical School Mass Brigham (4)	Abstract

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Computational reconstruction of glioblastoma surgical margins identifies molecular drivers of residual tumor recurrence

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Introduction

Glioblastoma recurrence after maximal safe resection remains a major challenge in neurosurgical oncology, with residual infiltrative tumor cells frequently persisting beyond radiographically visible margins. Current surgical approaches rely primarily on anatomical visualization and histopathological evaluation, limiting the ability to predict which residual regions harbor aggressive tumor populations. This study developed a computational framework integrating surgical pathology, transcriptomic profiles, and invasion-associated molecular signatures to identify biological determinants of postoperative recurrence risk.

Methods

Publicly available glioblastoma datasets were integrated with molecular profiles from surgical specimens, including transcriptomic expression data, genomic alterations, and clinical outcomes. Computational analysis incorporated differential gene expression, pathway enrichment analysis, and molecular clustering to identify recurrence-associated tumor states. Spatially informed computational modeling was performed using tumor-margin characteristics to simulate residual disease behavior following resection.

Candidate recurrence-associated pathways were validated using in vitro patient-derived glioblastoma cell models. Tumor cells were cultured under three-dimensional extracellular matrix conditions, and invasion assays were performed to evaluate migration patterns associated with identified molecular signatures. Quantitative image analysis was used to measure invasion distance and cellular proliferation. Statistical analyses included false discovery rate correction, multivariable regression, correlation analysis, and survival modeling.

Results

Computational analysis identified a distinct residual disease signature associated with increased recurrence risk. Tumors demonstrating enrichment of stem-cell-associated and mesenchymal transition pathways showed significantly shorter progression-free survival compared with tumors lacking these signatures (median progression-free survival: 6.8 months vs. 11.4 months, hazard ratio 1.87, 95% CI 1.32–2.65, $p < 0.001$).

Pathway analysis identified increased activity in extracellular matrix remodeling, integrin signaling, and inflammatory pathways. In vitro validation demonstrated that high-risk molecular signatures correlated with increased invasion distance in three-dimensional cultures (high-risk group: 418 ± 72 μm vs. low-risk group: 241 ± 55 μm, $p < 0.001$).

Multivariable analysis demonstrated that the molecular recurrence signature remained independently associated with progression after adjustment for age, tumor grade, and molecular subtype (adjusted HR 1.74, $p = 0.004$).

Conclusions

This computational and in vitro study identifies molecular features associated with aggressive residual glioblastoma following surgical resection. Integrating surgical pathology with molecular modeling may provide a precision framework for predicting recurrence risk and guiding future margin-directed therapies.