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Glioblastoma invasiveness may predict response to therapies with high or low blood brain barrier penetrability

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Introduction: Glioblastoma (GBM) is a very aggressive primary brain cancer, noted for its diffuse infiltration into surrounding normal–appearing brain. This particular nature makes GBM notoriously difficult to treat, as these diffusely invading cells cannot be resected surgically, are difficult to target with radiation therapy, and thus must be targeted with chemotherapy. However, this too presents a challenge, as these invading GBM cells reside beyond the dense tumour regions where angiogenesis causes disruption of the blood brain barrier (BBB) and allows drugs to more readily enter the central portion of the tumour. Thus, it is critical to determine predictors of drug distribution in individual patients' tumours and surrounding brain tissue to ensure the invading GBM cells are exposed to the therapy.

Objective: Determine predictors of drug distribution and effect from non-invasive imaging using minimal mathematical approaches.

Methods: Following experiments treating murine orthotopic patient-derived xenografts (PDXs) of GBM with various anti-tumour therapies, we compiled data from both the xenografts and the original patients from which the PDX lines were derived. This data included bioluminescence imaging (BLI), lamin–stained histological sections, and magnetic resonance imaging (MRI) from the PDXs, as well as patient MRIs and clinical data. Using the time series BLI data from PDXs, we developed and parameterized minimal differential equation models of PDX tumour growth for individual PDX lines, adjusted for lead time bias using a nonlinear mixed effects approach. This gave us an overall growth rate for each of the PDX lines across multiple subjects. Next, we compared these growth and invasion characteristics with therapeutic response in patients and PDX subjects to agents with different CSF to plasma ratios, indicating the degree of blood brain barrier penetrability of these drugs.

Results: Individual PDX lines have different growth kinetics, and recapitulate the kinetics observed in the original patients from which the lines are derived. Further, these growth kinetics appear to be correlated with differential drug response, with more diffusely infiltrating tumours responding better to drugs with higher CSF to plasma ratios.

Conclusion: While further work is needed to verify our results across more PDX lines, our results suggest that noninvasive imaging-based characterization of tumour invasiveness may be able to aid in matching patients to the best therapy for their individual tumours.

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