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Parameter sensitivity investigation of a mathematical model of glioma angiogenesis via Latin hypercube sampling.

Malignant glioblastoma multiforme (GBM) is a relatively rare cancer with a very poor prognosis. It is unique among cancers in that the tumors are quite diffuse and infiltrative, but do not metastasize out of the CNS. This diffuse nature, as well as its location in the brain, presents many challenges for treatment and disease monitoring. Following the development of anti-angiogenic agents in the past few years, there has been much hope that this form of treatment might make great strides in the treatment and management of malignant glioma, but clinical response to date has been disappointing. Patients often show a strong initial response on MRI, with imageable tumor receding relatively soon following treatment initiation. However, after some time they all progress, often with more diffuse, wide-spread disease than prior to anti-angiogenic treatment. To better understand the role of angiogenesis and anti-angiogenic therapy in GBM patients, we have created a proliferation-invasion-hypoxia-necrosis-angiogenesis (PIHNA) mathematical model of glioma growth with angiogenesis and have adapted it to simulate anti-angiogenic therapy. Based on our clinically validated, extensive work with the proliferation-invasion (PI) model of glioma growth (1, 2, 3) this model was developed to simulate the effects of hypoxia on vascular recruitment in glioma. It has been correlated with FMISO PET imaging data (4), and provides a basis from which we can better understand the effects of anti-angiogenic treatment on vascular recruitment, as well as the tumor environment. Here we present our use of a sensitivity analysis technique incorporating latin hypercube sampling (LHS) to vary parameters against each other and determine which parameters in the model have the most significant influence on hypoxic burden and how treatment parameters fit in. This knowledge allows us to better assess the significance of anti-angiogenic therapies on tumor growth patterns and give insight into the relationships between these factors and the tumor microenvironment to enhance combat and control of the disease.

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