Simulating patterns of recurrence following ischemia in brain tumors

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Background: Recurrence of Glioblastoma Multiforme

Glioblastoma Multiforme (GBM) is the most aggressive primary brain tumor with median survival of 14 months from diagnosis. Following resection, GBM recurrence most often occurs locally but can recur distally. Experimentally, hypoxia has been seen to drive infiltrative growth of glioma cells, but its clinical effects are not well understood.

However, a recent paper demonstrated that GBM patients with perioperative ischemia are more likely to recur distally than those without, 61% vs. 19% [1]. While this is convincing evidence that hypoxia is involved in generating distant recurrences, it does not fully answer the question regarding the difference between tumors that do or do not recur distally. We hypothesize that individual tumor growth kinetics may provide another part of the answer to this question.

To investigate this question we utilized a previously developed spatio-temporal biochemical model for glioma proliferation and invasion that encapsulates the complex interactions between tumor tissue and vasculature. We simulated multiple tumors defined by their growth kinetics as well as differing extents of perioperative ischemia.

Methods: The PIHNA Model

The Proliferation Invasion Hypoxia Necrosis Angiogenesis (PIHNA) models five quantities: normoxic tumor cells, hypoxic tumor cells, necrotic cells, vascular cells and angiogenic factors [2].

The PIHNA model uses partial differential equations to simulate the proliferation and invasion of a GBM on a realistic brain geometry. Cell populations can interact, proliferate, decay and migrate, see the schematic below.

- Normoxic cells proliferate and migrate, whereas hypoxic cells only migrate. Normoxic cells become hypoxic and in turn necrotic in regions of low vasculature.

We have simulated the realistic case of a gross total resection that clears imageable densities of the tumor on T1Gd MR images with a proximal ischemic event. An example can be seen on Figure 1. Various levels of vessel occlusion and conversion rates have been simulated (see Figure 2). The conversion rate can be thought of as how resistant cells are to a decrease in vasculature.

- Low Ischemia: The location of the first reappearance on T1Gd MR scans following resection and proximal ischemia (with the regions in Figure 1). Various diffusion and proliferation rates were simulated. Less aggressive tumors tend to recur locally (blue). Faster growing tumors will recur distally (red), outside the ischemic region. Increasing the severity of the ischemia shifts this behavior but keeps the overall trend. If the tumor is resistant to low vasculature, it will remain more normoxic and is more likely to recur locally.

Results: Key Drivers of Distal Recurrence

The model suggests that a distant recurrence is controlled by a number of factors:

- Severity of ischemia
- Tumor invasiveness
- Tumor cell proliferation
- Extent of resection
- Resistance of cells to a decrease in vasculature

- The model suggests that more aggressive tumors are more likely to recur distally, while nodular tumors are more likely to recur locally, see Figure 2 and above schematic. This effect is shifted by the level of ischemia present.

References