MATHEMATICAL MODELING OF GLIOMA PROLIFERATION AND DIFFUSION

Gliomas, the most common of primary brain tumors, are known for their widespread invasion of tissue near the gross tumor mass. My research was based on my mentor's focus on developing mathematical models for the growth of gliomas within the central nervous system (CNS). The model focuses on two key parameters: D, the spread of glioma cells to tissues within the central nervous system, and **ρ**, the net proliferation rate of glioma cells. The model was created to account for the fact that even after gross total resection of portions of the tumor detectable on magnetic resonance imaging (MRI) scans, invasive glioma cells are found in tissues surrounding the area of resection. Additionally, this model considers the location of the tumor within the CNS because tumor cells are known to diffuse at a faster pace in white matter compared to grey matter. As a result a more accurate prediction of the patient's longevity and the time period of the tumor's inevitable recurrence can be made. This accuracy will allow physicians to make improved diagnosis and treatment of gliomas, thereby extending the patients' survival.

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BACKGROUND

Gliomas account for an overwhelming 70% of the 22,500 new cases of adult malignant primary brain tumors diagnosed yearly in the United States.[1] Approximately 50% of all gliomas are glioblastomas, World Health Organization (WHO) grade IV astrocytomas, characterized by high rates of cell proliferation, wide diffusion, necrosis, and a 100% fatality rate within about one year despite extensive resection, irradiation, and/or chemotherapy.[2]

The malignancy of gliomas is demonstrated by the inability of even the most modern imaging technologies like computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) to detect invasive cells that have imbedded themselves in ''healthy'' tissues surrounding the bulk mass of the tumor.[3] As a result, it became apparent that it is necessary to have a method that allows us to assess tumor growth invisible to the imaging techniques in order to make more accurate predictions as to the tumor's effect on a patient's longevity before and after treatment of the visible tumor.

History of Bio-mathematical Modeling

Bio-mathematical modeling of tumors began with the discovery that cancerous cells generally proliferated in an exponential pattern. Tumors were understood to double starting with one cell and multiplying on to 2, 4, 8, 16, and so on.[4] For gliomas, this simple model grew complicated when researchers realized that glioma cells did not stay in a solid mass but that they diffused throughout the central nervous system.[5] Studies of cell growth led scientists to formulate complex models that demonstrated a detailed understanding of cellular kinetics. However, not until the 1990s was an equation established to quantify the net proliferation rate of invasive cells. Professor J.D. Murray provided the following equation written in words: rate of change of tumor cell concentration over time = net diffusion of tumor cells + net proliferation of tumor cells.[4]

The equation has been refined by the addition of a saturation term, $(1 - c/K)$, to the proliferation term. The addition of the cell proliferation limiting term allowed the model to consider the fact that tumor cells have a limiting density of packing in a fixed volume.

Swanson's lab developed the bio-mathematical model further by considering cell motility as a function of location in grey or white matter. Although no one is yet certain as to why gliomas react differently in different parts of the brain, it has been noted that glioma cells diffuse at a faster rate in white matter than in grey matter.[3] This difference in the motility rate of the cells can influence the rate of change of the tumor cell concentration. Therefore, the equation was modified to include x, the location of a glioma cells, as a variable of D, diffusion of the glioma cells. [3]

Because the coefficients are specific to each individual patient's tumor they allow a more accurate estimation of the patient's survival time without treatment and the extent of tumor invasion undetected by imaging techniques. And, since the bio-mathematical model can now be extended to simulate a patient's probable reaction to resection or chemotherapy,[4] physicians can tailor treatments to individual patients. Thus the quantitative study of gliomas aims at getting a

better understanding of the problem that this group of tumors presents and creating more precise simulations that will help improve patient outcome.

Methods and Materials

In order to determine the diffusion rate (D) and proliferation rate (ρ) of a specific patient's tumor, the difference between the volume of the tumor on two pre-treatment MRI images needed to be calculated by estimating the volumes of the tumor through 3 dimensional segmentation. Assuming the tumor is an idealized sphere with an equivalent volume, the tumor radii for both scans can be determined from which the radial velocity of the tumor's growth follows.[6] Next, the ratio D/ρ, a measure of the extent of the tumor's invasion below the clinically detectable threshold, is calculated from the difference between the size of abnormalities visible on T1Gd and T2 images at one time point. Using this ratio D/ρ along with Fisher's approximation, the edge of the tumor is regarded to invade at a constant velocity (v) where $v^2 = 4D\rho$. This velocity computation can be used to solve for a specific patient's D and ρ.

The extension of the model to incorporate chemotherapy is accomplished by subtracting G(t)c from Murray's original equation in which when $G(t)=k$ (k is a measure of the effectiveness of the treatment), chemotherapy is being administered.[4] However, to model resection of the bulk mass of the tumor, the area of the brain which is to be surgically resected is set to zero cell density in the simulation to indicate the cells removed by resection.

Results/Discussion

The model parameters quantify the overall biological aggressiveness of gliomas in terms of net invasion (D) and proliferation rates (ρ). The ratio D/ρ can be used to reveal the percentage of glioma cells below the thresholds of detection on MRIs.[2] D and ρ can also be used to discover the likely length of patient's survival time after treatment.[2] Additionally, while physicians tend to identify the grade of gliomas histologically, researchers might now be able to identify the grade of gliomas mathematically. Even within a given grade, a glioblastoma with a high ρ and a high D, for example, could be more aggressive than one with lower values for the model parameters.

If the tumor was proliferating quickly and there appeared to be a solid tumor mass visible on MRI scans, resection of the visible tumor could have a bigger impact than of a tumor that is more diffuse. However, even if gross total resection of the solid mass present on MRI was performed, the mathematical model may show that glioma cells have already diffused beyond the resection area with as much as 99% of the total glioma cells in the brain left behind after surgery. Therefore, while resection might elongate a patient's lifespan and reduce the effects of the tumor for a short period of time, it does not solve the problem.[4] Similarly, radiation therapy may not be as effective as previously believed. Some patients do respond positively to radiation therapy but others do not receive much relief, hinting that some tumor cells may be resistant to irradiation.[4] However, even if irradiation of the tumor visible on MRIs was successful, infiltrative tumor cells would still be present in brain tissue after treatment. Exposure of glioma cells to chemotherapeutic drugs is also another method through which the tumor cells are destroyed. But, a heavy exposure of the cells to the drugs does not necessarily mean tumor cell death because not all of the drugs given are delivered to the tumor as a result of the poor tumor vasculature.[4]

In Swanson et al,[6] a comparison was made between non-treatment model-predicted survival times and patients' actual survival times allowing estimation of the effectiveness of treatment in terms of the increase in survival over the model-predicted untreated survival time. This comparison provided an illustration that the mathematical model can be used to show that some patients might receive the same treatment but the results may not be as beneficial for one patient as they are for the other because the patients' tumor diffusion and proliferation rates may not be the same. As a result, quantifying the effects of treatment on glioma beforehand with consideration given to each tumor's individual D and ρ could help physicians assess the tumor growth rate.

In comparison to actual clinical data, the bio-mathematical model is able to make nearly accurate predictions regarding a patient's survival. Currently, when the model determines a patient's lifespan with and without treatment, it assumes that the patient is unaffected by age and poor neurological functioning.[6] The predicted lifespan and the tumor's response to treatment are then produced for an individual who, except for the glioma, can be considered healthy. But the near-accurate prognosis that the model provides means added understanding of a patient's individual case and, consequently, treatment that is more beneficial to the patient. Future work will focus on extending the model to account for radiation therapy, the presence of necrosis, and angiogenesis (formation of new blood vessels) among other factors.

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