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Low Grade Gliomas Modelling

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Abstract: ***Patient-specific models can be used to overcome imaging limitations, improve prognostic predictions, stratify patients, and assess treatment response in silico. The information gleaned from such models can aid in the construction and efficacy of clinical trials and treatment protocols, accelerating the pace of clinical research in the war on cancer. The aim of the study is to review the growing literature of patient-specific models to clinical neuro-oncology. It will also provide a forward-looking view on a new era of patient-specific mathematical neuro-oncology models.***

Keywords: glioma, mathematical modeling, patient, prediction

1. Introduction

Cancer is a complex disease which leads to the uncontrolled growth of abnormal cells, destruction of normal tissues and invasion of vital organs. There are different stages of tumor development with varying duration, starting from genetic changes at the cell level and finishing with detachment of metastasis and invasion. Tumor cell transport and proliferation are the main contributors to the malignant dissemination (1). Extensive research has been done to model cancerous growth, specially on solid tumors, in which growth primarily comes from cellular proliferation. It is far beyond the aim of the present paper to list exhaustively the many significant contribution in the topic. References (2-4) therein represent some of these contributions. Gliomas are diffusive and highly invasive brain tumors accounting for about 50% of all primary brain tumors and, unfortunately, the prognosis for patients with gliomas is very poor. Median untreated survival time for high grade gliomas ranges from 6 months to 1 year and even lower grade gliomas can rarely be cured. Theorists and experimentalists believe that inefficiency of treatments results from the high mobility of glioma cells. Additionally gliomas can exhibit very high proliferation rates. The understanding of malignant glioma growth still very less complete, mostly because gliomas proliferate as solid tumors and invade the surrounding brain parenchyma actively. Proliferation and specially migration of gliomas represent a very challenging problem from a mathematical viewpoint. Cancer research has been a fertile ground for mathematical modeling, beginning with the early concept of simple exponential growth of solid tumors doubling at a constant rate. The introduction of logistic or gompertzian growth (there is increased doubling time and decreased growth fraction as a function of time) allowed to slow the growth in the later stages. With the recognition that tumor cells might spread outside the grossly visible mass, invading locally and metastizing distantly, and that some cells die during the development process, the mathematical concepts necessarily became more complex than those used in the original simple models for solid tumors. The initial answer to the question of how to measure the growth of an infiltrating glioma was provided by Murray in the early 90s (5). He formulated the problem as a conservation law where the rate of change of tumor's cell population results from mobility and net proliferation of cells. Mathematical neuro-oncology (MNO) is a young and burgeoning field that leverages mathematical models to predict and quantify response to therapies. These mathematical models can form the basis of modern "precision medicine" approaches to tailor therapy in a patient-specific manner. Patient-specific models (PSMs) can be used to overcome imaging limitations, improve prognostic predictions, stratify patients, and assess treatment response in silico (6). The information gleaned from such models can aid in the construction and efficacy of clinical trials and treatment protocols, accelerating the pace of clinical research in the war on cancer. The aim of the study is to review the growing literature of PSM to clinical neuro-oncology. It will also provide a forward-looking view on a new era of patient-specific MNO.

2. Material and Methods

In this systematic review, we searched MEDLINE/PubMed and the Cochrane Database for studies regarding management of severe influenza cases. We searched peer-reviewed journals on infectious diseases and viral infection including influenza, hand-searched selected articles and also looked at the websites of the leading health authorities (e.g. WHO, CDC, HPA). To minimise the introduction of bias, no language or publication restrictions were applied.

3. Results and Discussion

Gliomas present a unique clinical challenge. In addition to intra- and inter-tumoral heterogeneity, these lesions are defined by their diffuse invasion of otherwise normal-appearing brain tissue peripheral to the imageable abnormality. This diffuse growth limits the clinical utility of neuroimaging in interpreting treatment response (7).

Mathematical models in medicine. Over the last several decades, much research has been devoted to understanding the physical and biological properties of gliomas in the effort to develop an extensive knowledge of this disease. Mathematical models are vital to many disciplines of science. Yet, compared to other scientific disciplines, there has been relatively little effort within neurosurgery or neuro-oncology to exploit such knowledge to form predictive systems that could accurately model or simulate the behavior of a malignant glioma. Such modeling could improve our sense of growth and invasive patterns and might translate into a useful clinical tool (8).

Cancer is an inherently multi-scale process and different types of models adequately describe different aspects of the proliferation and spread of gliomas. All of the time and spatial scales of glioblastoma are important, from individual cell interactions to the role nutrients and brain geometry play on the tumor (9).

Measuring tumor growth on serial MRIs.
Several methods have been proposed to quantify radiological glioma growth, especially for the contrast-enhance areas in high-grade gliomas (10). The simplest one consists in a manual measurement of tumor diameters on successive MRIs (11). In the particular case of grade II glioma, maximal visible abnormalities on MRI are seen on Flair sequences that usually best delineate the tumor (12). The three largest tumor diameters (D1, D2, D3) according to the three reference orthogonal planes (axial, coronal, and sagittal planes) can be measured using printed as well as digitized MR images. An estimation of the tumor volume (V) is calculated by the ellipsoid approximation: V ¼ D1 _ D2 _ D3=2. Then, the mean tumor diameter (Dmean) is deduced from the volume: Dmean ¼ ð2 _ VÞ1=3.

Finally, the glioma growth curve can be represented by the evolution of the mean tumor diameter with time. Despite the advantages of this simple and rapid method, its limit, with respect to full 3D tumor segmentation, is well known: the ellipsoid approximation overestimates the volume, the overestimation increasing with a more irregular contour of the tumor. The influence of this methodological issue on the evaluation of the response to radiotherapy or chemotherapy has also been investigated, the rate of responders differing between 1D, 2D, or 3D measurements (13). However, it remains unknown to what extent the difference between the two methods can affect the estimation of growth rates for both the pre-and postoperative periods.

In summary, the gold standard in measuring grade II glioma evolution on MRI is the 3D segmentation on Flair images. Despite recent advances in automated segmentation algorithms (14), manual segmentation is still the reference method, but it is a time-consuming task. For many applications, the approximation given by the three-diameters measurement offers a simple and effective way to estimate growth rates. Actually, all present clinical data on grade II glioma dynamics relied on this method. Furthermore, few methods have been adapted to heterogeneous DLGG segmentation. The focus of early methods was on contrast enhanced and homogeneous tumors and while glioblastomas have been mostly studied in the recent years. Current metrics of therapeutic response rely on observable changes to clinical imaging (15), ignoring the underlying growth dynamics of the tumor. Further, the current standard of care leaves few treatment options and may over-treat patients with slow growing tumors. Patient-specific mathematical modeling provides a novel means of developing UVCs for each patient's tumor and provides predictive insight into prognosis, treatment response, and optimal treatment design. The future of patient-specific modeling and application depends on asking questions that mathematical models can realistically answer with data that can be obtained from patients either non-invasively or infrequently (16).

PSM must be validated and incorporated into clinical trials to become broadly and directly applicable to patient care. Advantages of a patient-specific modeling approach include: a) Identification of individualized tumor proliferation and inva- sion rates or other kinetic information about an individual patient's tumor b) Development of methods for quantifying and predicting response to therapy – alone and also with respect to UVCs pro- vided by model predictions c) More informed treatment planning and response assessment tools that compare each patient's tumor growth against its own virtual control.

4. Conclusion

Despite an extensive amount of work dedicated to brain tumor segmentation, the problem remains difficult and segmentation results are often not satisfactory. Generalization of the existing methods to several kinds of tumors (or pathologies) is often difficult. Additionally, many methods are based on the use of different image modalities which are not systematically available in a clinical setting. Despite the need of a prior training phase, machine learning methods offer a flexible and efficient way of capturing the tumor's properties that are not limited to intensity values.

These advantages directly address a number of key unmet challenges in clinical neuro-oncology. In the coming years we antic- ipate a continued expansion of peer-reviewed journals dedicated to mathematical oncology, coordinated with increased funding for research in the area. Recently, Cancer Research has added a special section devoted exclusively to mathematical oncology. By producing individualized virtual tumors that predict disease progression in the absence of treatment, patient-specific modeling can contribute to the ongoing dialog regarding the design of appropriate response criteria (Wen et al., 2010), provide a means to perform virtual clin ical trials to assess the likely benefit of novel neurotherapeutics, and move neuro-oncology toward individualized treatment plans optimized for maximum benefit.

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