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REVIEW

Computational modeling of the WHO grade II glioma dynamics: principles and applications to management paradigm

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Abstract The advent of magnetic resonance imaging (MRI) has allowed the follow-up of tumor growth by precise volumetric measurements. Such information about tumor dynamics is, however, usually not fully integrated in the therapeutic management, and the assessment of tumor evolution is still limited to qualitative description. In parallel, computational models have been developed to simulate in silico tumor growth and treatment efficacy. Nevertheless, direct clinical interest of these models remains questionable, and there is a gap between scientific advances and clinical practice. In this paper, WHO grade II glioma will serve as a paradigmatic example to illustrate that computational models allow characterizing tumor dynamics from serial MRIs. The role of these dynamics for both therapeutic management and biological research will be discussed.

Keywords Glioma dynamics · Biomathematical modeling · Glioma surgery · Low-grade glioma

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Introduction

World Health Organization (WHO) grade II gliomas [15] are diffusely infiltrative and evolutive tumors affecting young adults that are, most of the time, revealed by seizures [23]. Their natural history comprises a first period of varying duration, during which the tumor grows slowly and infiltrates the brain parenchyma with isolated tumor cells [6, 7] that preferentially migrate along the white matter fiber tracts [16, 20]. Then, anaplastic transformation ineluctably occurs, hampering both functional and vital prognoses.

The efficacy and timing of oncological treatments remain controversial [19], and none of them are curative. It is widely agreed that surgery improves the prognosis of grade II gliomas [3, 11]. Other therapeutic options include radiotherapy [25, 29], which is known to increase progression-free survival, and chemotherapy [19], with rates of short-term responders between 31–61%.

Since patients are asymptomatic—except for epilepsy and insidious neuropsychological deficits—during the first

period of evolution, the tumor is essentially monitored by a magnetic resonance imaging (MRI) follow-up both prior to and after any oncological treatment. Thus, an accurate interpretation of the radiological evolution appears of utmost importance for the optimization of therapeutic management of grade II gliomas, and mathematical modeling could provide extra insights useful in clinical practice.

Measuring tumor growth on serial MRIs

Several methods have been proposed to quantify radiological glioma growth, especially for the contrast-enhanced areas in high-grade gliomas [4, 32]. The simplest one consists in a manual measurement of tumor diameters on successive MRIs [17]. In the particular case of grade II glioma, maximal visible abnormalities on MRI are seen on Flair sequences that usually best delineate the tumor [5]. The three largest tumor diameters (D_1, D_2, D_3) 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: $V = D_1 \times D_2 \times D_3/2$. Then, the mean tumor diameter (D_{mean}) is deduced from the volume: $D_{\text{mean}} = (2 \times V)^{1/3}$. 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 [2, 8]. 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 post-operative periods. In our retrospective series, we have measured, by the two methods, pre-operative tumor sizes in 96 Flair images (corresponding to 70 patients). The mean tumor diameter was 44.1 mm for the segmented method and 47.5 mm for the three-diameters method. Interestingly, the difference remained almost constant with increasing sizes. Consequently, average growth rates were 4.2 mm/year for the segmented method and 5 mm/year for the three-diameters method, corresponding to a difference of 0.8 mm/year. The measures performed on 192 Flair images for 119 patients in the post-operative period showed an average diameter of 36.4 mm with the simple method compared to 31.2 mm by segmentation. Overestimation was slightly increasing with tumor size. Thus, average growth rates were 8.2 mm/year with the three-diameters method versus 6.2 mm/year with the segmented one: tumor growth rates were slightly overestimated when tumor evolution was tracked by three-diameters measurements rather than volumetric segmentation.

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 [1], 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 [17, 22].

Modeling tumor growth curve

Why a model?

Figure 1 represents the quantified tumor evolution of an untreated and histologically proven grade II glioma over an 8-year period before any oncological treatment. Based on the first 3 years only, it is not possible to infer if an exponential or a linear law best fits the data. However, extrapolating future evolution using an exponential law clearly diverges from the actual tumor evolution, which appears to be better predicted using a linear law.

Figure 2 represents the quantified tumor evolution of an untreated and histologically proven grade II glioma in a 4-year period before any oncological treatment, in which a tumor contrast-enhancement was noted on the last MRI. The actual tumor evolution appears to be well fitted using an exponential growth law. Such fitting suggests that tumor dynamic properties are unchanged during follow-up because tumor diameter/volume doubling times remain constant over the whole 4-year period. However, the occurrence of a

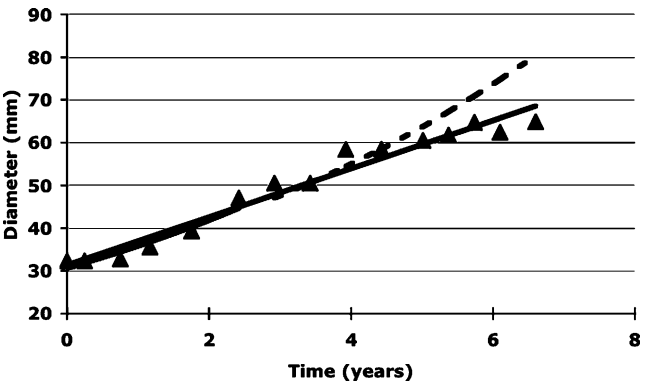

Fig. 1 Growth curve of tumor diameter for a patient harboring a WHO grade II glioma. Predicting the growth of the tumor after 3 years depends on the chosen model: the linear model best characterizes the future growth, while the exponential law overestimates it

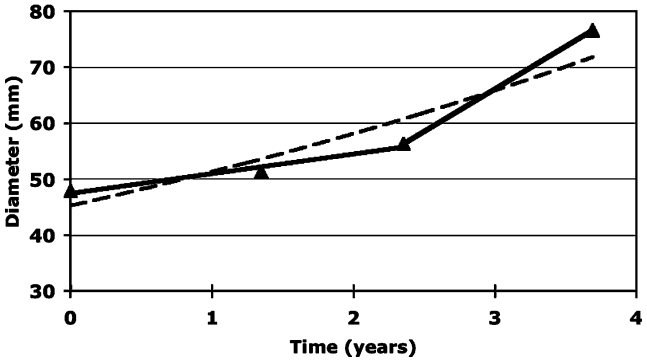

Fig. 2 Growth curve of tumor diameter for another patient. Fitting successive linear models to a tumor growth can reveal a change of biological behavior

contrast-enhancement in the natural history of a grade II glioma is highly suggestive of an anaplastic transformation and thus reflects a change of its biological behavior. An alternative solution would be to apply a linear law to fit the tumor evolution. Such modeling shows an initial low tumor growth rate (4 mm/year) before a break-up of the slope of the curve, with a higher tumor growth rate (8 mm/year) between the last two examinations. The observed changes of the slope of the curve are consistent with the changes of the tumor biological behavior suspected on the last MRI.

Thus, fitting the tumor evolution using different mathematical laws leads to different predictions in terms of future tumor growth or, alternatively, to different interpretations of the tumor biological behavior. The aim of mathematical modeling of grade II glioma is to describe correctly and accurately their actual growth in order to quantify for each tumor: (1) the further evolution with only two initial MRIs; and (2) the different biological phenomena underlying its dynamic behavior, through the determination of several parameters.

Mathematical modeling: *in silico* tumor growth

In its mathematical definition, a model is an equation describing the evolution of a variable of interest as a function of time. Such variable can be a number (tumor cells, tumor volume) or a function (tumor cell density in the brain parenchyma). Quantitative parameters can be introduced in the model, and their numerical values have to be adapted to each case. So, the ideal model could allow to: (1) adjust the different parameters so that the evolution of the variable best fits the clinical data; (2) give an interpretation of the parameters in terms of biological properties of the tumor; and (3) give to these parameters a clinical interest (prognostic factors, evaluation of treatment response,…).

Natural history of grade II glioma is a complex process, encompassing numerous biological changes that lead to an ineluctable anaplastic transformation with time. However, it is usually agreed that the extension of gliomas results, at the cellular level, from two essential mechanisms acting in various proportions: proliferation and migration [16–18]. Mathematical models translate these two characteristics into an equation. The variable in the equation is a coarse-grained tumor cell density (c), which represents the average concentration of tumor cells in each cubic millimeter of the brain. The generic form of the equation, initially introduced for high-grade gliomas [19–22], is the following:

$$\frac{\partial c}{\partial t} = \rho c + \nabla.(D\nabla c)$$

that is, evolution with time (δt) of tumor cell density (δc) at each position in the brain=proliferation (ρc)+diffusion [$\nabla.(D\nabla c)$].

The diffusion component of the equation is usually assumed to follow a "passive diffusion" process (i.e., random walk of cells, also called Brownian or Fickian process) in which tumor cells tend to move from regions of higher cell density towards regions of lower cell density. The speed of tumor cell diffusion into the brain parenchyma is controlled by the parameter D. Passive diffusion does neither model cell migration (i.e., active motion of cells), which predominantly follows the white matter fiber tracts, nor tumor cell invasion (i.e., destruction of the extracellular matrix). In the present model, glioma cell migration is thus reduced to the simplest mathematical form of spreading, which does not reflect the actual complexity of this active process.

If the diffusion term was skipped out, tumor growth would be exponential. The parameter ρ indeed controls the effective cell cycle time. Indeed, if all cells were dividing, the cell cycle time would be equal to $\ln(2)/\rho$ (which is also the volumetric doubling time). Despite its common use [10, 24], there is no evidence of the appropriateness of the exponential model for gliomas. Gliomas are highly infiltrative tumors, and tumor cells extend far beyond MRI-defined abnormalities, even in cases of grade II gliomas [13, 14, 21, 30]. It is usually admitted that tumors appear on MRI only for cell densities above 8,000 cells/mm^3. Thus MRI underestimates the actual spatial extension of a glioma, and numerous tumor cells will not appear inside the MRI-defined abnormalities. Consequently, even if the total number of tumor cells is growing exponentially, the growth curve of the tumor volume observed on MRI is expected to be a cubic curve, and volumetric doubling times measured on MRI could be meaningless in this context.

Predictions provided by simulations

Within some approximations, an analytical solution of the proliferation–diffusion equation predicts that *the velocity of*

diametric expansion is constant [12, 31]. In other words, the mean tumor diameter evolves linearly with time. The velocity of diametric expansion (i.e., the slope of the diameter growth curve) is equal to $4\sqrt{(D\rho)}$, hence depending on both D and ρ. We insist on the fact that this linear growth rate is valid only for the diameter. Indeed, the volume will evolve with time as the cube of the diameter, and no simple parameter quantifies the volumetric growth rates.

Thus, if the product $D\rho$ relates to the kinetics of tumor growth, *the ratio D/ρ is linked to the spatial extent of the radiologically nonvisible part of the tumor* [28]. It is commonly admitted that MRI-visible tumor concerns only areas of cell density above 8,000 cells/mm^3. Computational simulations allow decreasing arbitrarily this visibility threshold under 8,000 cells/mm^3, thus seeing "the immerged part of the tip". The ratio D/ρ determines its extent (see Fig. 3). This is the so-called concept of "virtual imaging" [26]. Unfortunately, to the present date, there is no way to validate this virtual imaging [1].

Translating grade II glioma dynamics to clinical practice

Measuring diameter growth rates

The first study of spontaneous tumor growth was carried out by mean tumor diameter measurements on successive MRIs in a selected series of 27 patients carrying a grade II glioma and followed before any oncological treatment [17]. It was in good agreement with a linear evolution of the mean tumor diameter over time and quantified the velocity of diametric expansion at an average rate of 4 mm/year (see Fig. 4). These results were confirmed using the same conditions on a larger series of 143 patients, which showed individual velocities of diametric expansion ranging from 1 to 36 mm/year with an average rate of 4.4 mm/year [22].

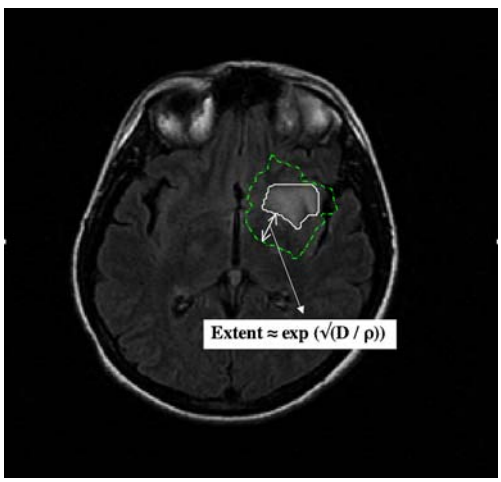

Fig. 3 The ratio D/ρ. The two contours come from the simulation of a patient case. The *thick white contour* corresponds to the threshold of cell density visible on MRI. The *dotted line* is the contour corresponding to a cell density five times smaller than the threshold. The higher the ratio D/ρ, the higher is the distance between these two contours

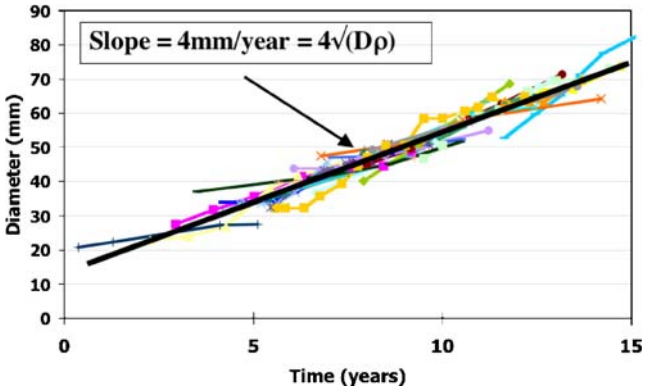

Fig. 4 Linear growth rates of 27 untreated patients harboring a WHO grade II glioma. The growth of mean tumor diameter is correctly fitted by a linear regression (average growth rate=4 mm/year, range of individual growth rates=2–8 mm/year). Growth rate of tumor diameter determinates the product $D\rho$

Initial dynamics as a prognosis factor

In this latter study, there was a strong statistical influence of individual tumor growth rates on survival [22]: the clinical outcomes of histologically proven grade II gliomas growing faster than 8 mm/year were similar to those of anaplastic gliomas (see Fig. 5).

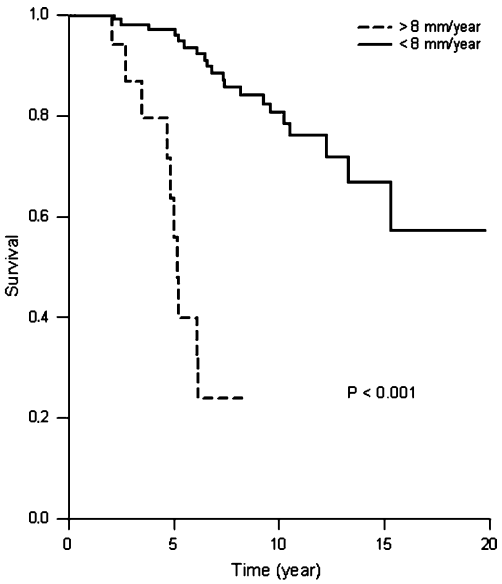

Fig. 5 Prognostic value of MRI growth rates on a series of 143 patients harboring a WHO grade II glioma. Patients with growth rates higher than 8 mm/year have a worse prognosis, similar to patients with high-grade glioma

Implications for management paradigm

Therapeutic management of grade II gliomas remains a matter of debate, especially regarding: (1) the need of an immediate initial histological diagnosis; (2) the timing of the different treatment modalities; (3) the impact of surgery on the natural history of the tumor; and (4) the exact efficacy of chemotherapy. Historically, when a grade II glioma was diagnosed, the commonly accepted strategy was a "wait and see" approach after an initial histological diagnosis by biopsy, due to the supposed indolent nature of such tumors. The recent better understanding of the natural history of grade II glioma together with an optimization of the benefit-to-risk ratio of surgery [9, 10] and chemotherapy [19] have led to a renewed interest in earlier and more aggressive treatments.

Based on the aforementioned results, *we propose*, in a case of a suspected grade II glioma on MRI, *to perform systematically a second* MRI *3 months after the first one and before any treatment*. Three months would be a reasonable delay to detect with confidence (even with three-diameters measurements) fast-evolving tumors (that is, more than 8 mm/year). Moreover, delaying treatment by 3 months is not expected to worsen the prognosis: such an assertion has been proven for radiotherapy [29] and seems to be acceptable for surgery and chemotherapy.

- If the mean diameter growth exceeds 2 mm within 3 months, we then propose to start oncological treatment immediately, as it would be the case for a high-grade glioma. Follow-up should be strengthened accordingly.
- If the mean diameter growth is about 1 mm within 3 months, surgical resection could then be proposed, especially if the residual tumor could be predicted to be less than 10 cm^3 [3, 11, 18]. If surgery is refuted, a third MRI could be performed 6 months after the first one. This would offer a more accurate estimation of the pretreatment dynamics. Measuring precisely tumor dynamics will be indeed helpful for the interpretation of oncological treatment efficacy [24]: patients can then serve as their own control. For example, let us consider a patient with a pretreatment growth rate about 4 mm/year. Let us assume that the lesion is stable under chemotherapy, that is, growth rate falls to 0 mm/year: such a breakdown in the diameter growth curve should be considered as a form of response.

Perspectives

The next challenge to be solved by biomathematicians will be the so called "inverse problem", that is, to determine for each patient, from two or more serial segmented MRIs, its couple of parameters D and ρ, allowing the best fit between simulation and the actual tumor evolution. Such an achievement would open the way to [1]:

- Tailor therapies individually. In particular, surgical indication could be adapted according to this ratio: gross total removal would be less efficient for tumors with high versus low values of D/ρ [27], and in the latter cases even more than the former, it is expected that supra-complete resection (beyond the visible margins on MRI) could greatly increase the progression-free survival [27].
- Correlate these dynamic parameters with molecular analysis of the tumor. Indeed, there is growing evidence that gliomas behave biologically as a complex system. The understanding of their behavior requires a multiscale approach, combining macro-, micro-, and nano-scopic scales. Such correlations have been already reported for volumetric doubling times, histological grade, and DNA ploidy [4]. Correlations between diametric expansion and 1p19q status have also been observed: 1p19q deletion was significantly associated with lower velocities of diametric expansion [24]. It is quite probable that the analysis of the data provided by micro-arrays of DNA or RNA would be greatly facilitated by correlations with homogeneous groups of patients for D and ρ.

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Comments

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Mandonnet and colleagues demonstrate in this article how computational models based on an analysis of serial MR investigations may help in the characterization of tumor growth. They provide highly valuable information and perspective, how the information on tumor dynamics obtained by serial MR investigations might be integrated in a therapeutic regimen of low-grade gliomas.

The largest tumor diameters in the three orthogonal planes were determined to estimate the tumor volume in subsequent imaging. An ellipsoid approximation was used to deduce the mean tumor diameter which was monitored over the time course. Algorithmic tools, allowing a semi-automatic segmentation in which the user can segment a complexly shaped glioma in a 3D volume dataset without being forced to manually segment the whole tumor in every single slice, are under development and should help to refine the parameters which are necessary to precisely evaluate the growth dynamics of a tumor. The crucial value of high-quality MR scans preferably performed with identical parameters in the repeated investigations cannot be overemphasized. It will be highly interesting to see how the precise knowledge of patient individual tumor dynamics will influence the clinical management of the disease in the future.

James Rutka, Toronto, Canada

Mandonnet et al. have utilized serial high-resolution MR images and computational models to examine the growth rates of low-grade gliomas. The mathematical formulae used to calculate tumor volume over time are given. They show in several cases how reliable such modeling can be. They allude to the clinical information that can be derived from such predictions and how patient management may be affected over time.

This type of analysis makes a few assumptions. One of the most important is that tumor growth rate is constant over time. While this may be the case in the majority of instances, unquestionably, exceptions to this rule will arise. Several years ago, Hoshino and colleagues used the labeling index of human low-grade gliomas to predict tumor growth rates and patient survival [1–3]. These studies required intravenous infusion of bromodeoxyuridine prior to surgery and then an analysis of the labeling index from tumor specimens taken at surgery. In some of his studies, Hoshino used the labeling index data along with computed tomography scanning over time to predict rate of tumor recurrence. This was applied, however, mostly to meningiomas [4].

The value of the work by Mandonnet et al. is that the information derived is based on non-invasive imaging techniques. As techniques evolve for us to analyze the cellular composition of human brain

tumors, as for example with MR spectroscopy, it is conceivable that a combination of data derived non-invasively will be used to predict for tumor growth with as much precision as is possible.

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