Using Mathematical Modeling to Predict Survival of Low-Grade Gliomas

Ellsworth C. Alvord, Jr, MD, and
Kristin R. Swanson, PhD

Pallud and colleagues[1] have presented some interesting data concerning the long-term follow-up of low-grade gliomas, but why did they not pursue the implications of the mathematical model of glioma behavior that they championed in their previous work.[2] If they had, they would have seen that there can be no dichotomy, no distribution of velocities that "results in two groups," but rather a continuous gradation of velocities of glioma expansion contributing to survival differences. The two independent variables that Pallud and colleagues found to be statistically significant ($p = 0.034$), velocity and size, are exactly what the mathematical model predicts for survival. Actually, these two variables combine seamlessly to produce a predicted survival for each patient[3–5]; but in the available space and without access to the original data, we can illustrate only a sampling of predictions from the data provided in the manuscript (Table). For example, a tumor 80 mm in diameter would require only 2.5 years to grow enough to kill if expanding at 11 mm/year but would not yet have reached a fatal size within 11 years if only expanding at 2–3 mm/year.

A few questions require clarification. First, if "patients were excluded when an oncological treatment was administered,… or when anaplastic transformation occurred…histologically… or when a contrast enhancement appeared on MRI,"[1] who was left to die? Were all 143 patients "pure" low-grade gliomas until they died or were last seen alive?

Second, what was "time zero" in this study? That is, what is the relation between the time for "the median tumor volume (estimated on MRI before surgery)" and the time to the beginning of "the overall median duration of clinical follow-up since radiological diagnosis"?[1] Were there not magnetic resonance images on some patients being followed before any surgery (and after a radiological diagnosis), and were these excluded?

Third, rather than a p value of 0.619 for the "random histological review…in 40 cases (28%),"[1] would it not have been more interesting to review and compare all 22 cases in the "high-rate" group (ie, velocity > 8mm/yr) with the 16 cases in the lowest of the "low-rate" group (ie, velocity < 1mm/yr)? Can not neuropathology do better than to lump velocities of greater than 10-fold differences together?

Finally, we offer a suggestion: We prefer the phrase "velocity of radial expansion" (which is more euphonious and would be half that of "diametric expansion") to "growth rate" because the latter ambiguously implies proliferation, perhaps forgetting the cell loss factor, perhaps even including diffusion, whereas the mathematical model clearly separates net proliferation (ρ) and net dispersal or diffusion (D), the product of which relate to the velocity.[3–5]

Table. **Model-Predicted Survival Time (Years)**

Velocity (mm diameter/ year)	Size at Diagnosis (mm diameter)			
	20	40	60	80
1.5	58	45	31	18
2.5	35	27	19	11
3.5	25	19	13	7.7
4.5	19	15	10	6
5.5	16	12	8.5	5
7.0	12.4	9.6	6.7	4
11.0	7.9	6	4.3	2.5

Based on Pallud and colleagues'[1] data regarding the diameter of the gliomas at diagnosis and the velocity of diametric expansion.

Department of Pathology, Division of Neuropathology, University of Washington Medical School, Seattle, WA

References

1. Pallud J, Mandonnet E, Duffau H, et al. Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol 2006;60: 380–383.
2. Mandonnet E, Delattre J-Y, Tanguy M-L, et al. Continuous growth of mean tumor diameter in a subset of WHO grade II gliomas. Ann Neurol 2003;53:524–528.
3. Swanson KR. Mathematical modeling of the growth and control of tumors. PhD Thesis, University of Washington, Seattle, WA, 1999.
4. Swanson KR, Alvord EC Jr, Murray JD. Virtual brain tumors (gliomas) enhance the reality of medical imaging and highlight inadequacies of current therapy. Br J Cancer 2002;86:14–18.
5. Swanson KR, Bridge C, Murray JD, Alvord EC Jr. Virtual and real brain tumors: using mathematical modeling to quantify glioma growth and invasion. J Neurol Sci 2003;216:1–10.

Reply: Mathematical Modeling and Complexity of Biological Behavior of Low-Grade Gliomas

Johan Pallud, MD, Emmanuel Mandonnet, MD, PhD, and Laurent Capelle, MD

We thank Drs Alvord and Swanson, who proposed a refinement for prognostic significance of the velocity of diametric expansion (VDE) of World Health Organization grade II gliomas (G2G). We agree on the reality of a continuous gradation of velocities of glioma expansion,[1] but failed in practice to find conclusive prognostic value on an individual basis, even combined with tumor volume. This may be due to technical approximations in the VDE measurements. We rather believe that it reflects the complexity of biological behavior of G2G. Heterogeneous treatment effects and complex host–tumor relations could alter the correlation between VDE and survival. Moreover, the gradual acquisition of malignancy, which remains unpredictable, is another major factor explaining the differences of observed survivals with the predictions of a mathematical model restricted to G2G, as in the table submitted (which cannot yet integrate the anaplastic tumor fate or its sensitivity to treatments). Hence, a dichotomous classification, although unrepresentative of the actual individual biological behavior, appears the most useful parameter in practice.

Our take-home message was limited to "be aware that rapidly-growing gliomas, even if of pathological grade 2, can behave in practice more or less as anaplastic forms."[2] The

