Editorial

Prognosis in glioblastoma: insight gained from recent prospective trials

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Gittleman *et al*. report on the creation and independent validation of a nomogram estimating the survival of patients with glioblastoma multiforme (GBM) following chemoradiation therapy (CRT) (1). The nomogram was developed using three statistical approaches (cox proportional hazards regression, random survival forests, and RPA) from available data points of patients accrued to Radiation Therapy Oncology Group (RTOG) 0525, a clinical trial evaluating the benefit of dose-intensified temozolomide (TMZ) in patients with newly diagnosed GBM (2). The algorithm was validated in an independent population of patients who completed therapy on the RTOG 0825 clinical trial (2,3), which asked if the addition of bevacizumab to standard therapy for GBM improved survival. Neither of these randomized trials demonstrated a statistically significant difference in their primary endpoint (survival), so the inclusion of all patients in both cohorts is valid. The resultant nomogram provides an individualized tool for predicting 6-, 12-, and 24-month survival in patients with newly diagnosed GBM based on age, sex, performance status, extent of surgical resection, and O6-methylguanine-DNA-methyltransferaase (MGMT) methylation status.

We congratulate the authors on their use of existing prospectively collected data to create an updated and meaningful tool to be used by patients and clinicians. However, the nomogram is not without limitations. As noted by the authors, a major limitation of the nomogram is that it is only applicable to patients who met the inclusion criteria for, and were subsequently enrolled in, and completed concurrent chemoradiation on the RTOG 0525 trial from which it was built. The inclusion criteria for RTOG 0525 were restricted to patients from the United States with histologically confirmed GBM with favorable performance status (KPS ≥60). Since the nomogram was derived from a population consisting mostly of younger, Caucasian patients whom underwent surgical resection, it is not applicable to non-Caucasians, elderly, poor performance status patients, or patients having undergone biopsy alone.

Whether the current nomogram improves on previously published nomograms, including the nomogram by Gorlia *et al*. based on the EORTC-NCIC clinical trial and the recursive partitioning analysis (RPA) classification from the RTOG GBM database, is unknown (4,5). The current nomogram includes five prognostic factors: age, gender, performance status, extent of surgical resection, and MGMT status. In contrast, the two previously published nomograms are limited because they included fewer known prognostic factors and were not independently validated (4,5). The Gorlia *et al*. (EORTC-NCIC) nomogram incorporates three factors [MGMT status, performance status, and neurologic function as measured by mini-mental status exam (MMSE) score], while the RPA classification takes into account four factors (age, performance status, extent of resection, and neurologic function for three distinct prognostic groups). It is likely that the current nomogram is superior as it was built on a larger number of patients and is based on additional prognostic variables; however, no robust comparison testing the predictive accuracy of the various nomograms has been performed.

The addition of this nomogram will add value to the management of patients with newly diagnosed GBM. Not only can the nomogram be used in the multi-disciplinary care of patients to help them gain a more precise understanding of their prognosis, but also it may allow for a customized treatment approach based on individual patients' prognoses (i.e., considering hypofractionated radiotherapy in patients

with short survival expectancy). It should be noted that the nomogram only predicts survival out to 2 years. Younger patients with high performance status may likely want to know their probability of longer survival, as recent studies reveal a tail to the survival curve with some patients living longer than 2 years (6). Finally, the authors do not mention which other factors, if any, were evaluated in building the model and not ultimately incorporated into the final model. Beyond the variables included, there are several additional known factors that may have prognostic significance, but were not available in the RTOG dataset. Variables such as post-operative tumor volume, tumor location, MRI-perfusion, and IDH-1 along with yet-discovered genetic/epigenetic signatures could potentially lead to a more robust nomogram (7,8). In the future, nomograms will likely not only be more robust, but also include additional patient cohorts such as the elderly and those with poor performance status.

Overall, the authors have succeeded in developing a patient-individualized nomogram for estimating survival following surgical resection and adjuvant chemoradiation in generally young, healthy patients with GBM. The nomogram was independently validated using a second set of similar patients. While the prognostic factors included in the model have been demonstrated to influence survival in previously published reports, this is the first model to combine five factors into a single tool with clear implications for clinical practice. Future prospective studies may benefit from using this information for patient stratification.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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