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Where size matters: imaging-based biomarkers for patient stratification

Bradley J. Erickson and Evanthia Galanis

Division of Neuroradiology (B.J.E.) and Division of Medical Oncology (E.G), Mayo Clinic, Rochester, Minnesota

Corresponding author: Bradley J. Erikson, MD, PhD, Mayo Clinic, 200 First Street SW, Rochester, MN 55905 (bje@mayo.edu).

See the article by Ellingson et al. on pp. 89–98.

Ellingson et al[1] are to be commended for organizing and executing a very large study that retrospectively analyzes imaging and outcome data in 497 patients with recurrent glioblastoma (GBM). Their analysis for the first time identifies imaging biomarkers of prognostic significance in recurrent GBM, which, in addition to clinical (ie, age) and molecular (ie, O^6-DNA methylguanine-methyltransferase promoter methylation status, isocitrate dehydrogenase mutation status)[2] prognostic markers, should be taken into consideration in clinical trial design. The authors provide a convincing rationale for stratifying patients with recurrent GBM based on tumor burden and for controlling this variable in clinical trials. Their data could also help explain the difficulty in reproducing promising findings deriving from single-arm trials conducted in select academic centers (where enrolling patients with smaller tumors could result from a referral bias) versus testing the same experimental approaches in larger studies conducted in the community setting. Although other prognostic factors such as tumor grade and performance score are routinely controlled in trial eligibility criteria, with the exception of a limited number of immunotherapy trials, tumor volume has generally not been taken into consideration either as an eligibility or a stratification factor in clinical trial conduct. The present analysis is still based on retrospective collection of clinical trial and single institution data, however, while lacking uniform clinical, molecular, and genetic data on all patients: prospective validation of tumor volume as a prognostic factor in future randomized recurrent GBM trials is warranted and should be strongly encouraged.

This study also raises additional questions. The selection of 15 cc as the threshold for analysis deserves some commentary and possibly further investigation. The median tumor size was 15.3 cc and was the basis for selecting 15 cc (of enhancing tumor volume including central necrosis) as the threshold for "small" versus "large" tumors. While not unreasonable, it would be interesting to perform a sensitivity analysis to investigate whether decreasing or increasing that cutoff would increase the separation between groups. For instance, one could consider creating a relative risk plot of tumor volume versus OS. From this plot one could evaluate whether there are nonlinear effects, and perhaps then decide whether categorizing the tumor volume would better fit the data than using a continuous linear form as was done in the Ellingson paper.[1] If cutoffs are needed, one could do a sensitivity analysis on a subgroup (ie, use part of the data to search for optimal cutoff) and internal validation analysis (ie, use the rest of the data to validate the cutoff). For the sensitivity analysis, multiple methods could be used, including quantiles (these authors just used median), a search based on *P*-values versus hazard ratios, or recursive partitioning methods. For validation, more advanced methods could be considered, such as cross-validation or bootstrap validation.

These considerations notwithstanding, the authors did perform subgroup analysis that further supports the importance of volume, showing that subjects with volumes less than 5 cc did better than those with volumes of 5–15 cc. Although compelling, this does not establish 15 cc as the optimal threshold. Importantly, when this threshold was applied to subgroups treated with either conventional cytotoxic or anti-angiogenesis agents, it retained its significance. The prognostic importance of tumor volume was lost in the cohort of patients who failed bevacizumab (n = 70), however, possibly reflecting the importance of the infiltrative nonenhancing tumor component in these patients and highlighting the difficulty in developing prognostic biomarkers in subgroups with especially dismal outcome.

Overall these data support that 15 cc can be used as a stratifier for therapy trials in recurrent GBM patients who have not failed bevacizumab. It would also have been interesting to analyze the data by separating the enhancing and the necrotic components. The majority of subjects in the study went on to be treated with anti-angiogenic agents; since these agents are designed to reduce vascularity of tumors, it may be that the volume of enhancing tumor (without the necrotic component) would be a more powerful predictor, but a different threshold value would almost certainly be needed in this case. The ability to distinguish necrosis from surgical cavity can also be challenging, and it is possible that the tumors that were very large to start with, and therefore had large residual resection cavities at recurrence, were also the ones most likely to progress. This does not refute the authors'

fundamental conclusion that volume is an important stratifier, but it might help advance our understanding of the mechanism—for instance, that larger tumors might also have properties that make them less susceptible to agents used for recurrence.

How the tumor volume is measured is always of relevance and deserves some comment. In this analysis, the authors applied a subtraction technique to define the enhancing tumor and then filled any nonenhancing component (the necrosis) to produce a final volume. This technique has been described elsewhere,[3] and reproducibility has been shown to be good. Increasingly, clinical trials and clinical practice should adopt methods where such contrast-enhancing volumes can be reliably assessed. Because patients do experience recurrence with disappointing frequency, they will often move from standard practice approaches to clinical trials and sometimes back and forth several times. In order to get the best clinical assessment and research findings, it is important that clinical practice and clinical trial practice be as harmonious as possible. From that perspective, the adoption of standardized brain imaging methods required for clinical trials such as the recently developed standardized Brain Tumor Imaging Protocol[4] should be strongly considered by clinical practices. Vendors should be encouraged to provide efficient processing methods so that clinical practices can implement the same tools in practice as in research. The latter would also facilitate the seamless incorporation of prognostic or predictive imaging biomarkers from clinical trials into standard-of-care clinical practice and optimize patient management.

There is an intuitive sense that larger tumors bode ill for patients. Ellingson et al have now shown that this is likely true for patients with recurrent glioblastoma. While one can consider further refinements to this work, it would seem prudent to include lesion volume as a stratification factor in planning clinical trials.

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