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Response assessment in high-grade glioma: tumor volume as endpoint

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See article in this issue by Gahrmann et al., pp. 853–861.

Glioblastomas are typically irregular in shape, often growing along postoperative cavities, ventricles, and transhemispheric tracts. These characteristics, along with variations in slice orientation and slice thickness during imaging acquisition, make accurate quantification of tumor size difficult. Currently, treatment response in glioma trials most commonly employ the Response Assessment in Neuro-Oncology (RANO) criteria,[1] which specify 2D bi-diameter product measurements of enhancing lesions in determining tumor progression. While this approach is relatively simple to implement, there is significant inter-observer variability in estimating tumor size using a 2D method.[2,3] Volumetric approach by calculating pixel volumes within regions of interest outlined by tumor margins can address the shortcomings of linear methods, although currently the process of tumor volume segmentation is done manually or semi-automatically, requiring significantly more time compared with linear measurements. Therefore, to use tumor volume measurement as a standard endpoint in clinical trials, it is important to demonstrate that significant advantages exist in volumetric approach over the current 2D RANO criteria.

Gahrmann et al aimed to address this important question by retrospectively evaluating the imaging data from the multicenter randomized phase II BELOB trial.[4] This trial randomized patients with recurrent glioblastoma into 3 arms receiving bevacizumab or combination treatment with lomustine and bevacizumab. The first 2 posttreatment MRIs (at 6 and 12 wk) were reviewed to determine progression using the RANO criteria as well as several predefined volumetric criteria. The authors concluded that there is no significant difference among the criteria when correlating the progression status with overall survival at both time landmarks. This result is concordant with that from a prior study by Boxerman et al where 2D and volumetric measurements of enhancing and fluid attenuated inversion recovery (FLAIR) lesions 8 and 16 weeks posttreatment were compared in the single-arm Radiation Therapy Oncology Group (RTOG) 0625 trial.[5] In addition to analysis of a larger patient sample size (N = 148) than previous work, Gahrmann et al made comparison to the full RANO criteria for all 3 different treatment arms in the BELOB trial.

Among the volumetric criteria investigated in this study, T1 subtracted tumor volume was evaluated to assess whether this approach would improve the sensitivity in depicting tumor during anti-angiogenic treatment. In this treatment setting, the enhancing characteristics of tumor can be affected by the effect of treatment on vascular permeability making contrast enhancement much more subtle, if any. Intrinsic T1 hyperintense lesions are also commonly found in areas of tumor following treatment as a result of mineralization. These physiological alterations brought significant challenges in measuring tumor size using standard T1-weighted imaging. By subtracting pre- from postcontrast T1-weighted images, Ellingson et al found improved quantification of tumor volume with better prediction of patient outcome in the single-arm phase II BRAIN trial.[6] Interestingly, analysis of the BELOB trial revealed that the subtracted enhancing volume did not perform better than other volumetric criteria, including non-subtracted volume in the bevacizumab-treated groups. Nevertheless, this result will need further validation in trials adopting standardized MRI protocol to allow generation of accurate T1 subtraction maps.

To address the problem of tumor detecting using contrast-enhanced imaging for patients receiving anti-angiogenic treatment, one important addition to the current RANO criteria is the inclusion of qualitative evaluation of the tumor using FLAIR in determining tumor progression. Compared with the Macdonald criteria, the addition of evaluating FLAIR lesions qualitatively in the RANO criteria appeared to demonstrate comparable performance in predicting outcome of the phase II BRAIN trial.[7] Since a volumetric approach can potentially improve the accuracy of quantification of FLAIR lesions, Gahrmann et al also compared progressive disease criteria with and without FLAIR volume measurements. The result did not show a significant difference after addition of FLAIR evaluation, which is not surprising given previous results on the value of volumetric FLAIR evaluation, including those reported by Boxerman et al in the analysis of the RTOG 0625 trial. One important caveat when evaluating non-enhancing tumor using FLAIR is the coexisting FLAIR

abnormality not related to tumor, including areas of edema and gliosis. This presents a significant challenge in quantifying tumor volume on FLAIR imaging, making such approach less sensitive to growing tumor compared with qualitative evaluation when readers can detect focal changes when reviewing longitudinal scans. Finally, the analysis of the BELOB trial focused on the first 2 posttreatment scans where non-enhancing tumors tend to appear circumscribed and rapidly enlarging.[8] It remains unclear whether volumetric evaluation will have an advantage in quantifying slower-changing progressive tumor at later posttreatment time points.

The volumetric criteria defining tumor progression in this study included a 40% increase cutoff for contrast-enhancing lesions measured on postcontrast T1-weighted imaging, and a 25% cutoff for non-enhancing lesions measured on FLAIR imaging. These values have been examined in prior studies of tumor volume but have not been confirmed as optimal thresholds. While lower threshold values can potentially increase the sensitivity of detecting a smaller degree of tumor size change that may be relevant in predicting subsequent clinical outcome, future work will be needed to explore the threshold limit while considering the measurement variability of volumetric approach.

At present, measuring brain tumor volume remains laborious even with the best available software tools. The current analysis by Gahrmann et al comparing volume-based criteria with the RANO criteria using data from a prospective trial of recurrent glioblastoma treated with bevacizumab is an important effort in validating the clinical value of the volumetric approach. One potential advantage of the volumetric method that was not evaluated in this study is inter-observer variability, which is expected to be lower than the 2D method. Nevertheless, the finding that volumetric evaluation during the first 2 posttreatment time points did not result in substantial improvements over the current standard suggests caution as to its use in this setting.

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