

Letters to the editor

Is a prospective trial necessary to suggest a clinical relevance?

We would like to thank Dr Chamberlain for his comments on our article¹ and take this opportunity to respond to the issues he has raised. Radiological measurement of low-grade glioma (LGG) growth is a hot topic and clarification is required.

Firstly, we wish to emphasize that although not validated by a prospective trial, our calculation method (velocity of diametric expansion [VDE]) has been successfully reproduced in other institutions. Four other studies (107, 64, 21, and 21 patients in each, independent databases) demonstrated similar ranges of VDE (median 3.5–5.5 mm/y) using the ellipsoid approximation used in our study.^{2–5}

Secondly, our study reflects everyday clinical practice, where routinely one compares interval MR images. We have observed that the MR characteristics of LGG do not vary significantly between 1.5T and 3.0T synchronous MRIs (personal observation). Furthermore, it has been demonstrated that areas of high signal corresponding to an LGG are equivalent on both T2-weighted and fluid attenuated inversion recovery sequences.⁶ We acknowledge that a comparison study has never been performed to assess the equivalence of the 2 methods of volume measurements (segmentation vs ellipsoid approximation). However, measurements of VDE varied little between these techniques as reflected by: (i) a high coefficient of reliability at 0.824 ($n = 124$, personal observations) and (ii) the similarity of VDE measurements performed before (ellipsoid approximation) and after (segmentation) partial surgical removals.⁷

Thirdly, the time interval between MR examinations is indeed a crucial issue. One should bear in mind that the practical aim of our approach is the identification of “high-risk” LGG presenting with a VDE ≥ 8 mm/year (ie, an increase in the mean tumor diameter >1 mm over a 6-wk interval and >2 mm over a 3-mo period). We have previously proposed that the time interval between scans be determined on an individual basis, and according to the clinical condition of the patient.⁸

Finally, the choice of an 8 mm/year cutoff is not arbitrary; it fits clinical practice and reflects our previous finding that patients harboring an LGG with a VDE ≥ 8 mm/year have a clinical course in keeping with a more malignant glioma.^{9,10} We have demonstrated that VDE as a continuous predictor is an independent prognostic factor for overall survival, with a linear relationship between survival and VDE (hazard ratio, 1.09 per one unit increase in VDE; 95% CI, 1.06–1.12; $P = .001$) in a large series of 407 cases.¹⁰

We believe that the growth rate of LGG is a crucial prognostic variable, although we recognize the present study is limited by its retrospective nature. It adds clinically relevant information (without significant additional cost) together with the already known prognostic markers. Moreover, the demonstration of a growing LGG, even after partial surgical removal,⁷ challenges the clinical

relevance of a “progression-free survival” and of a “stable disease.” We agree that the issue of LGG growth on imaging requires further exploration in the context of prospective clinical trials and we expect that institutional groups involved in the study of LGG (RANO group, RTOG, EORTC) will incorporate this question in the design of future trials.

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See the letter by Chamberlain, on pages 1296.

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Does early identification of low-grade glioma growth impact outcome?

Dr Pallud and colleagues represent a vanguard research team in understanding glioma growth by serial anatomic MRI and the use of their novel radiographic methodology, that is, the determination of the velocity of diametric expansion (VDE) by ellipsoid approximation.¹ Several issues, however, temper enthusiasm for the incorporation of this radiographic method of low-grade glioma (LGG) growth into routine clinical practice as the authors suggest.

Firstly this method has never been assessed and validated in a prospective clinical trial, requirements that for example have been fulfilled for response assessment of high-grade gliomas using the Macdonald and RANO criteria.^{2,3} If treatment of LGG is to be determined by a VDE analysis, a prospective trial showing the benefit of this approach is relevant compared with the current standard practice of altering therapy at time of radiographic enhancement and presumed glioma de-differentiation to a higher grade or enlargement of the tumor by >25% as assessed by fluid attenuated inversion recovery or T2-weighted MRI.⁴

Secondly, routine clinical practice, at least in the United States, only rarely after radiographic demonstration of a presumed LGG follows patients with serial MRI. Rather these patients more often undergo resective surgery and after pathological and molecular assessment are considered for further therapy, most often radiotherapy (RT), particularly in the high risk LGG subgroup.⁵ The recently reported and data-mature RTOG 9802 trial demonstrated a significant survival benefit in patients studied defined as high risk (age >40 y or incompletely resected LGG) with the combined use of RT and PCV (procarbazine, lomustine, and vincristine) chemotherapy.⁶ This practice-changing RTOG study suggests that the majority of patients with LGG benefit from combined modality treatment in the up-front setting, a marked contrast to the watch and wait serial MRI assessment of Pallud et al.

Thirdly, this author is unaware of any data that indicate that treating radiographic progressive disease or a so-called more growth-aggressive LGG as defined by Pallud et al (VDE > 8 mm/y by serial MRI) results in an improved outcome with respect to either survival (overall or progression free) or quality of life. Clearly

the intent is to introduce more aggressive therapy (RT or chemotherapy) to alter outcome in a clinically meaningful manner, but it is uncertain if earlier treatment affects overall outcome in progressive LGG. Any benefit of earlier treatment may arguably be explained by a lead-time bias.

Pallud and colleagues are to be congratulated for continuing their efforts to define LGG based upon radiological growth characteristics and I look forward to their further research in this regard.

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