Neuro-Oncology Advances
4(1), 1–8, 2022 | https://doi.org/10.1093/noajnl/vdac032 | Advance Access date 09 March 2022

The impact of different volumetric thresholds to determine progressive disease in patients with recurrent glioblastoma treated with bevacizumab

Renske Gahrmann, Marion Smits, René Michel Vernhout, Walter Taal, Giorgios Kapsas, Jan Cees de Groot, Monique Hanse, Maaike Vos, Laurens Victor Beerepoot, Jan Buter, Zwenneke Hendrieke Flach, Bronno van der Holt, and Martin van den Bent

Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center, Rotterdam, The Netherlands (R.G., M.S., G.K.); Clinical Trial Center, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, The Netherlands (R.M.V., B.H.); The Brain Tumor Center at Erasmus MC Cancer Institute Erasmus University Medical Center, Rotterdam, The Netherlands (W.T., M.B.); Department of Radiology, University Medical Center Groningen, Groningen, The Netherlands (J.C.G.); Department of Neurology, Catharina Hospital Eindhoven, The Netherlands (M.H.); Department of Neurology, Medical Center Haaglanden, The Hague, The Netherlands (M.V.); Department of Internal Medicine, Elisabeth Tweesteden Hospital, Tilburg, The Netherlands (L.V.B.); Department of Oncology, VU University Medical Center, Amsterdam, The Netherlands (J.B.); Department of Radiology, Isala Clinics, Zwolle, The Netherlands (Z.H.F.).

Corresponding Author: Martin van den Bent, MD, PhD, Professor The Brain Tumor Center at Erasmus MC Cancer Institute Erasmus University Medical Center, Rotterdam, 's-Gravendijkwal 230, 3015CE, The Netherlands (m.vandenbent@erasmusmc.nl).

Abstract

Background. The optimal volumetric threshold for determining progressive disease (PD) in recurrent glioblastoma is yet to be determined. We investigated a range of thresholds in association with overall survival (OS).

Methods. First recurrent glioblastoma patients treated with bevacizumab and/or lomustine were included from the phase II BELOB and phase III EORTC26101 trials. Enhancing and nonenhancing tumor volumes were measured at baseline, first (6 weeks), and second (12 weeks) follow-up. Hazard ratios (HRs) for the appearance of new lesions and several thresholds for tumor volume increase were calculated using cox regression analysis. Results were corrected in a multivariate analysis for well-established prognostic factors.

Results. At first and second follow-up, 138 and 94 patients respectively, were deemed eligible for analysis of enhancing volumes, while 89 patients were included in the analysis of nonenhancing volumes at first follow-up. New lesions were associated with a significantly worse OS (3.2 versus 11.2 months, HR = 7.03, $P < .001$). At first follow-up a threshold of enhancing volume increase of ≥20% provided the highest HR (5.55, $p = .001$. At second follow-up, any increase in enhancing volume (≥0%) provided the highest HR (9.00, $p < .001$). When measuring nonenhancing volume at first follow-up, only 6 additional patients were scored as PD with the highest HR of ≥25% increase in volume (HR=3.25, $p = .008$).

Conclusion. Early appearing new lesions were associated with poor OS. Lowering the volumetric threshold for PD at both first and second follow-up improved survival prediction. However, the additional number of patients categorized as PD by lowering the threshold was very low. The per-RANO added change in nonenhancing volumes to the analyses was of limited value.

Key Points

- Early appearing new lesions indicate significantly poorer overall survival.
- Lowering the volumetric threshold for PD improves survival prediction.
- Nonenhancing abnormalities in glioblastoma have limited value for early follow-up.

Importance of the Study

Radiological treatment response in patients with recurrent glioblastoma is currently assessed using the 2D RANO criteria. Here we show that using an optimized volumetric threshold could improve survival prediction, but only in a limited number of patients. Additionally, new lesions appearing early after treatment (either enhancing or nonenhancing) are associated with significantly worse overall survival. We found that lowering volumetric thresholds (from the commonly used 40%) improved survival prediction in patients treated with lomustine. No added value was found by measuring nonenhancing volumes in this treatment group. In patients treated with bevacizumab, an increase was associated with worse overall survival, but only a small number of patients showed an increase in (non)enhancing volumes early after treatment. Despite the limited number of patients that would additionally be identified as progressive with a lower threshold, survival prediction does improve when applying a lower threshold for progressive disease.

Glioblastoma is the most common glioma in adults with an incidence of 0.6–3.7 per 100 000 persons per year. It has the worst survival rate of all gliomas with a 5-year survival of approximately 10% despite intensive surgical, radiotherapy, and chemotherapy treatment.[1] Recurrent glioblastoma are often treated with chemotherapy, and bevacizumab has been registered for this indication in several countries including the USA.[2] Angiogenesis inhibitors like bevacizumab normalize the tumor vasculature, leading to a decrease in tumor enhancement on T1-weighted postcontrast images even in the absence of a true reduction of tumor activity.

The Response Assessment in Neuro-Oncology (RANO) criteria[3] expanded on the earlier MacDonald criteria[4] by incorporating nonenhancing abnormalities into treatment response assessment. According to the RANO criteria, progressive disease (PD) is defined as ≥25% increase in the sum of products of perpendicular diameters of enhancing lesions, significant increase in nonenhancing lesions, appearance of new lesions, or clear progression of nonmeasurable lesions. Steroid dosage and clinical status are also taken into account. The threshold of ≥25% increase was obtained from the World Health Organization response criteria[5] and is originally based on breast cancer assessment on mammogram.[6]

Because of their irregular shape in three dimensions and the common presence of necrotic areas, it has been postulated that volumetric assessment of glioblastoma will improve response evaluation and survival prediction. In addition, volumetric methods can help quantify changes in nonenhancing abnormalities, which are currently assessed only qualitatively with the RANO criteria. Upon comparing 1D, 2D, and volumetric measures, high concordance between methods has been found, questioning the added value of the more demanding volumetric assessment.[7–9] Most studies extrapolated the RANO-based ≥25% increase in 2D areas to a ≥40% increase in volume ($4/3\pi r^3$), assuming a sphere-shaped tumor equally increasing in all directions,[10] which foregoes the potential increased sensitivity of volumetric assessment. Some authors have used different volumetric cutoff values for PD, such as ≥25%,[11] ≥15%,[12] and ≥5%,[13] suggesting that using lower thresholds could lead to a better survival prediction. Previously, a ≥25% increase of nonenhancing volumes has been proposed as the threshold to establish PD.[9,14]

We aimed to determine whether lowering the volumetric threshold for PD in both enhancing tumor and nonenhancing abnormalities improves survival prediction and whether there is a preferred moment for first radiological follow-up. We also evaluated the significance of the appearance of new lesions for the diagnosis of progression.

Methods

Patients

Included in this analysis were patients with first recurrence of glioblastoma treated in the phase II BELOB trial ($n = 148$; eligible patients) and the patients treated with lomustine at our institution in the subsequent phase III EORTC26101 trial ($n = 35$).[15,16] A previous publication by Gahrmann et al.[9] included all BELOB-trial patients and focused on differences between 2D and volumetric analyses. The current analysis includes volumetric analyses only and aims to determine the optimal volumetric threshold for determining PD. The total of 183 included patients had a mean age of 55 y (range 24–77 y). Patients from the BELOB trial were randomized to three different treatment arms: lomustine ($n = 46$), bevacizumab ($n = 50$), or both ($n = 52$); patients from the EORTC26101 trial were randomized to lomustine or bevacizumab plus lomustine. The 35 patients from the EORTC26101 trial were all treated with lomustine in the same way as in the BELOB trial with similar follow-up measures, and were added to obtain a balanced representation of lomustine and bevacizumab-treated patients. Patients were recruited between December 2009 and October 2011 and between October 2011 and October 2015 for respectively the BELOB trial and EORTC26101 trial. Patients had received no prior treatment with Vascular Endothelial Growth Factor (VEGF) inhibitors or nitrosoureas, were at least 18 years of age and had given informed consent according to national guidelines. Further study and patient details can be found in Taal et al. 2014[15] and Wick et al. 2016.[16] The study endpoint in the current analysis was

overall survival (OS), measured from the moment of follow-up (either first or second) to death from any cause.

Standardized MRI scans were performed at 6-week intervals and included pre- and postcontrast 3D T1-weighted (T1w) inversion recovery (IR) fast spin gradient recalled echo (FSPGR) and 3D T2-weighted (T2w) Fluid Attenuation Inversion Recovery (FLAIR) imaging, all with a slice thickness and in-plan resolution ≤1mm. Scans from baseline, first, and second follow-up were included in this analysis.

Data Processing

Semi-automated segmentation techniques were used to obtain total enhancing and total nonenhancing volumes from respectively 3D T1w postcontrast and 3D FLAIR images. The BELOB-trial scans were segmented by R.G. in Brainlab iPlan 4.0 Cranial and the EORTC26101 scans were segmented by G.K. and R.G. using ITK-SNAP.[17] Areas of necrosis, pre-contrast T1w hyperintensity, blood vessels, and dura were excluded. All FLAIR-hyperintensities were included into a single segmentation, independent of possible etiology as this would have required unreliable differentiation by observation. New enhancing and nonenhancing lesions were scored by R.G. at the time of performing the segmentation. New lesions of any size were included and in case of unclear lesion origin, persistence or increase in size at the next available follow-up was taken into account according to the RANO criteria. Lesions were considered new when they appeared at some distance or adjacent to existing enhancing or nonenhancing abnormalities.

Statistical Analysis

Hazard ratios (HRs), 95% confidence intervals (CI), and *P*-values were calculated with Cox regression analysis. All results were corrected in a multivariate analysis for World Health Organization (WHO) performance status, steroid use at baseline, number of target lesions (0-1 versus ≥2), enhancing tumor volume at baseline, and predominantly frontal location if $P < .10$ in univariate analyses.[18] In the multivariate analysis $P < .05$ was considered significant.

We calculated the association between the appearance of a new lesion at first, ie, 6 weeks' follow-up with OS. Both enhancing and/or nonenhancing lesions of any size that remained stable or increased at the next follow-up were scored. As the appearance of a new lesion is considered unequivocal PD, these patients were subsequently excluded from the threshold analysis.

Analyses of enhancing and nonenhancing volume thresholds were performed in all treatment groups together, and subsequently in the lomustine-only treated and in the bevacizumab (with/without lomustine) treated groups separately at both first and second follow-up. To determine the association between increasing tumor volume and OS, patients were dichotomized using different thresholds, starting with ≥40%. For the lower-threshold calculations, which were ≥20% and ≥0%, we excluded those categorized as PD with higher threshold (respectively ≥40% and ≥20%) to determine whether these lower thresholds would improve survival prediction in these groups. The above mentioned thresholds were used to calculate HRs for increase in enhancing tumor volume. For volumetric increase in nonenhancing abnormalities patients were dichotomized using thresholds of ≥25%, ≥10%, and ≥0%. The threshold with the highest HR was considered the most predictive for OS. Patients with PD based on increasing enhancing volume were excluded from the nonenhancing volumetric analysis so that the added values of measuring nonenhancing volumes could be determined.

After scoring the presence of new lesions and after determining the optimal thresholds for both enhancing and nonenhancing volumes, we then compared our volumetric results to the original RANO scoring as performed in the BELOB and EORTC26101 trials. The discrepant cases were compared using an independent t-test.

All analyses were performed in SPSS Statistics, version 24 (Copyright IBM Corporation).

Results

Patients

Patients without available 3D T1w postcontrast and FLAIR images at relevant time points were excluded from the analyses. Additionally, patients that did not reach first ($n = 4$) or second ($n = 60$) follow-up were excluded from analyses at these time points (see Figure 1 for included patients per analysis).

The four patients that did not reach first follow-up within the trial had a median OS of 1.5 months measured from baseline to death. Another 60 patients did not reach second follow-up of whom the majority had been randomized to the lomustine-treated group ($n = 37$).

Univariate analyses (Table 1) showed associations between OS and WHO performance status (HR = 1.67, $P < .001$), steroid use at baseline (HR = 1.60, $P = .002$), predominantly frontal location (HR = 1.34, $P = .061$), and enhancing volume at baseline (HR = 1.02, $P < .001$). These variables were therefore included in the multivariate analysis. Number of target lesions and age were not associated ($P > .10$) with OS.

New Lesions

At first follow-up ($n = 179$), a new enhancing and/or nonenhancing lesion appeared in 15 patients (a more detailed description can be found in the Supplementary Table S1 and Supplementary Figure S1). The univariate HR for OS of the development of new lesions was highly significant (HR = 5.27, $P < .001$) and increased after correction for other variables in a multivariate analysis (HR = 7.03, $P < .001$). The median OS of patients with a new lesion at first follow-up was 2 months versus 8.5 months in patients without a new lesion (Figure 2). At second follow-up, 2 additional patients had developed a new lesion (1 enhancing and 1 nonenhancing).

Enhancing Lesions

In all treatment groups combined, patients with a ≥ 40% increase in enhancing volume at first or at second

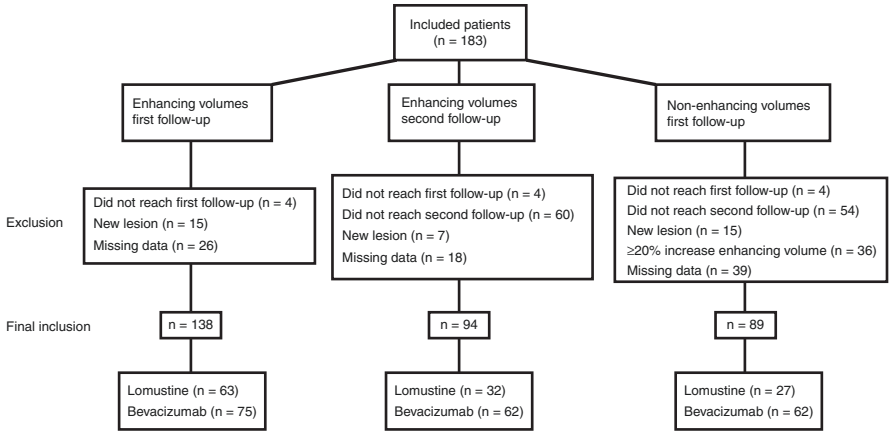

Figure 1. Flow diagram of all patients included from the BELOB and EORTC 26101 trials ($n = 183$), reasons for excluding patients (in order) per analysis and number of patients included in the final analyses.

follow-up had a significantly worse OS compared to those with less than 40% increase (HR = 1.77, $P = .010$ and HR = 3.02, $P = .001$, respectively) in the multivariate analysis. After excluding the 31 patients with ≥40% increase, the new threshold of ≥20% categorized an additional 5 patients as PD at first follow-up and 2 patients at second follow-up. After the exclusion of these patients and again lowering the threshold (to ≥0%) another 12 and 6 patients were categorized as PD at first and second follow-up respectively. The highest HR at first follow-up was found using a threshold of ≥20% (HR = 5.55, $P = .001$) and at second follow-up ≥0% (HR = 9.00, $P < .001$) (see Table 2).

In the lomustine-treated group, an analysis could be performed with thresholds of ≥40% and ≥20% increase in tumor volume. HRs were borderline significant at ≥40% (HR = 1.76, $P = .056$) and not significant at ≥20% increase at first follow-up; at second follow-up the highest significant HR was found with the ≥20% increase threshold (HR = 10.70, $P < .001$). The number of patients categorized as PD by increase in enhancing volume of the ≥0% stratum in the lomustine-treated group was insufficient for meaningful analysis.

The small number of patients with an increase in tumor volume within the bevacizumab-treated group was too small for meaningful analysis as only 2 patients showed an increase (≥0%) at first follow-up and 5 patients at second follow-up.

Nonenhancing Lesions

To determine the added value of measuring nonenhancing volume increase for response assessments, patients with PD based on increasing enhancing volume (at thresholds determined based on the highest HR found, ie, ≥20% at first follow-up) were excluded from the analyses. In all treatment groups together, the highest HR was found at a threshold of ≥25% at first follow-up (HR = 3.25, $P = .008$), categorizing 6 additional patients as PD. At the same threshold, the HR was also significant in the bevacizumab-treated group (HR = 5.04, $P = .002$) (see Table 3). The lomustine-treated group could not be analyzed because <5 patients were categorized as PD based on nonenhancing volume increase. Analyses of nonenhancing volumes at second follow-up could not be performed for the same reason.

Comparison with RANO

We then compared the 2D RANO evaluation with the optimal volumetric thresholds at first follow-up (ie, ≥20% increase in enhancing volume and ≥25% increase in nonenhancing volume). A total of 129 patients could be compared and in this group 18 discrepancies were found (9 patients were categorized as PD by RANO but not by volumetry and vice versa). When focusing on these discrepant cases no statistically significant difference in OS was found between the 9 patients classified as PD by 2D RANO but not volumetry (mean OS 7.1 months) and the 9 patients classified as PD by volumetry but not 2D RANO (mean OS 5.2 months), $t(16) = 1368$, $P = .190$. Most discrepancies were based on differences in scoring nontarget lesions (see Supplementary Table S2).

Discussion

In this analysis of patients with recurrent glioblastoma, PD was determined based on the appearance of a new lesion, increasing enhancing tumor volume, and increasing nonenhancing volume in association with OS. A new enhancing or nonenhancing lesion of any size at early follow-up was significantly associated with poor OS. When considering patients with increasing enhancing volumes, the majority of patients had an increase of ≥40%. Lowering the threshold to stratum 20–40% increase at first follow-up and to stratum 0–20% increase at second follow-up improved survival prediction, but only a small number of patients were additionally categorized as PD with these lower thresholds.

Table 1. Univariate Cox Regression Analyses of Variables With Potential Influence on Survival, Hazard Ratios (HRs), 95% Confidence Intervals (CIs) and *P*-values for all Treatment Groups Together and Bevacizumab- and Lomustine-Treated Patients Separately

Parameters	All treatment groups			Bevacizumab			Lomustine		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
WHO performance status	1.67	1.30–2.15	<.001	1.85	1.29–2.65	.001	1.49	1.01–2.12	.028
Steroid use	1.60	1.19–2.15	.002	1.52	1.02–5.56	.041	1.63	1.04–2.55	.032
Number of target lesions	1.09	0.79–1.52	.59	1.17	0.76–1.80	.48	1.07	0.63–1.79	.81
Predominantly frontal location	1.34	0.99–1.83	.061	1.26	0.84–1.90	.26	1.54	0.95–2.50	.078
Age	1.01	0.99–1.03	.16	1.01	0.99–1.02	.53	1.02	0.99–1.04	.13
Baseline enhancing volume	1.02	1.01–1.03	<.001	1.02	1.01–1.04	.012	1.02	1.01–1.03	.009

Overall survival is measured from randomization to death by any cause.

Figure 2. Kaplan-Meier curves of patients with and without a new lesion at first follow-up. The median overall survival (measured from first follow-up) was 2 versus 8.5 months, respectively.

After excluding all patients with PD based on the appearance of a new lesion or increase in enhancing tumor volume, an increase in nonenhancing volumes of ≥25% was significantly associated with poorer OS. However, only 6 out of 89 patients (5 of whom were treated with bevacizumab) were categorized as PD and thus the added value of considering nonenhancing volumes was limited in this population.

HRs at second follow-up (ie, after 12 weeks) were higher and more significant than those at first follow-up (ie, after 6 weeks). This effect can be largely attributed to the lower number of patients included at second follow-up, as many had already reached PD (based on either radiological or clinical parameters) prior to this evaluation point. This complicates the comparison of these two evaluation points. In the lomustine-treated group many patients had reached radiological PD after 6 weeks, while in the bevacizumab-treated group enhancing tumor volumes did not increase much even after 12 weeks follow-up.

While results found in the lomustine-only treated group were similar to those found in all treatment groups together, results from the bevacizumab-treated group are more difficult to interpret as only a small number of patients showed an increase in enhancing tumor volume at 6 and 12-week follow-up. The value of measuring enhancing volumes in bevacizumab-treated patients, therefore, appears relatively low in early follow-up, although early increase in enhancing volume under bevacizumab might indicate treatment failure. In lomustine-treated patients the value of measuring enhancing tumor volumes is quite clear. Slightly more bevacizumab-treated patients were categorized as PD when nonenhancing volume increase was taken into account, confirming a possible role for the RANO

Table 2. Hazard Ratios (HRs), 95% Confidence Intervals (CIs), and *P*-values at First and Second Follow-up in all Treatment Groups Together and in the Lomustine-Treated Group Separately Using Thresholds of ≥40%, ≥20 and ≥0 Increase in Enhancing Tumor Volume

Treatment groups	≥% increase in volume	First follow-up ($n = 138$)				Second follow-up ($n = 94$)			
		n	HR	95% CI	*p*-value	*n*	HR	95% CI	*p*-value
All	40	31	1.77	1.15–2.72	.010	12	3.02	1.57–5.79	.001
	20	5	5.55	2.06–14.91	.001	2	-	-	-
	0	12	1.01	0.54–1.90	.97	6	9.00	3.32–24.42	<.001
Lomustine	40	30	1.76	0.99–3.16	.056	8	3.63	1.33–9.87	.012
	20	4	-	-	-	2	-	-	-
	0	10	0.70	0.28–1.78	.46	5	10.70	3.45–33.17	<.001

emphasis on nonenhancing volumes in bevacizumab-treated patients. In previous literature, an increase in nonenhancing abnormalities has been described as a pattern of progression after anti-angiogenic treatment,[19,20] but since our data is restricted to the early period of follow-up, we are unable to determine if this patterns of progression is more common in the bevacizumab-treated patients at later stages, and hence what the true value of volumetric assessment of nonenhancing abnormalities is during the entire course of anti-angiogenic treatment.

We measured total volume of either enhancing or nonenhancing lesions, which means that mixed responses were not considered. Mixed response is seen in a subset of patients,[21,22] but we postulate that the outcome of these patients is determined by the overall volume increase or by newly appearing lesions. Measuring total nonenhancing volume could also have confounded results, as these volumes include tumor, effects due to earlier treatment, and edema. As bevacizumab is a known edema-relieving agent,[23] a decrease in nonenhancing volume in this group is expected at early assessment.

The benchmark for increase in volume was overall survival, considered the gold standard in oncology trials and the ultimate measure of patient benefit. Results were corrected for several known prognostic variables, including baseline enhancing tumor volume.[18] The prognostic significance of the latter was confirmed in our dataset. Initial tumor size is also important to take into account when measuring change in size as an increase of ≥25% has a more profound effect in an already large tumor compared to a small tumor. Large tumors are not only associated with a worse OS, but with worse overall clinical condition as well.[24]

Comparing the volumetric method to the RANO criteria showed some discrepancies, underlining the need for additional research for determining the optimal method for measuring progressive disease (and treatment response) in larger groups. Discrepancies found seemed mainly caused by the scoring of PD based on new or increasing nontarget lesions.

An important argument in favor of performing volumetric rather than 2D measurement is the greater inter- and intrarater variability found using 2D methods.[25] However, volumetric measurement is still more difficult to obtain than the commonly used 2D measures, and their added value for response assessment is disputed.[7–9] Recent studies on fully automated approaches suggest that with the advance of technology this may become standard.[26,27] Tumor volume does more accurately reflect the—enhancing—tumor size than 2D measurement. Especially in heterogeneous tumors such as glioblastoma this could be useful. Furthermore, from such a volume of interest, other measures such as Apparent Diffusion Coefficient (ADC) and relative Cerebral Blood Volume (rCBV) can also be determined, facilitating a more integrated approach to tumor assessment, which would potentially improve survival prediction further. That however still required agreed upon cutoff values for the definition of response and progression.

The main limitation of our study is the relatively small sample size of bevacizumab-treated patients showing progression of enhancing lesions at this early assessment time point. Assessment at later time points and/or a larger sample size is desirable to further determine the

Table 3. Hazard Ratios (HRs), 95% Confidence Intervals (CIs), and *P*-values at Thresholds ≥25%, ≥10%, and ≥0% Increase in Nonenhancing Volume at First and Second Follow-up in all Treatment Groups Together and in the Bevacizumab-Treated Group

		First follow-up ($n = 89$)			
Treatment groups	≥% increase in volume	*n*	HR	95% CI	*p*-value
All	25	6	3.25	1.37–7.70	.008
	10	5	1.88	0.72–4.86	.196
	0	8	0.63	0.28–1.39	.248
Bevacizumab	25	5	5.04	1.80–14.08	.002
	10	2	-	-	-
	0	4	-	-	-

value of volumetric imaging (ie, looking at enhancing and nonenhancing volume) in this treatment group.

In conclusion, new lesions, whether enhancing or nonenhancing, appearing early after the start of treatment were clearly associated with poor outcome. While only a small additional number of patients would be categorized as PD with volumetric thresholds lower than the commonly applied 40% increase, survival prediction did improve, and therefore lowering the threshold should be considered. We found no added value for measuring nonenhancing volumes in patients treated with lomustine only. In the bevacizumab-treated group early increase in tumor size (either enhancing or nonenhancing) was found to be rare. Here, increasing lesions were also associated with poor outcome, whether enhancing or nonenhancing.

Supplementary material

Supplemental material is available at *Neuro-Oncology Advances* online.

Keywords

bevacizumab | GBM | RANO | volumetry

Funding

This project was not supported by external funding.

Conflict of interest statement. There are no conflicts of interest to report.

Authorship statement. Collection of data: W.T., J.C.G., M.H., M.V., L.V.B., J.B., Z.H.F., M.B., G.K. Statistics: R.M.V., B.H. Supervision and writing: M.S., M.B. Analysis and writing: R.G. No unpublished papers cited.

References

1. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomized phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol.* 2009;10(5):459–466.
2. Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. *Oncologist* 2009;14(11):1131–1138.
3. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol.* 2010;28(11):1963–1972.
4. Macdonald DR, Cascino TL, Schold SC, Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* 1990;8(7):1277–1280.
5. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47(1):207–214.
6. Hayward JL, Carbone PP, Heusen JC, et al. Assessment of response to therapy in advanced breast cancer. *Br J Cancer.* 1977;35(3):292–298.
7. Wang MY, Cheng JL, Han YH, et al. Measurement of tumor size in adult glioblastoma: classical cross-sectional criteria on 2D MRI or volumetric criteria on high resolution 3D MRI? *Eur J Radiol.* 2012;81(9):2370–2374.
8. Warren KE, Patronas N, Aikin AA, Albert PS, Balis FM. Comparison of one-, two, and three-dimensional measurement of childhood brain tumors. *J Natl Cancer Inst.* 2001;93(18):1401–1405.
9. Gahrmann R, van den Bent MJ, van der Holt B, et al. Comparison of 2D (RANO) and volumetric methods for assessment of recurrent glioblastoma treated with bevacizumab—a report from the BELOB trial. *Neuro Oncol* 2017;19(6):853–861.
10. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst.* 2000;92(3):205–216.
11. Boxerman JL, Zhang Z, Safriel Y, et al. Early post-bevacizumab progression on contrast-enhanced MRI as a prognostic marker for overall survival in recurrent glioblastoma: results from the ACRIN 6677/RTOG 0625 Central Reader Study. *Neuro Oncol* 2013;15(7):945–954.
12. Radbruch A, Lutz K, Wiestler B, et al. Relevance of T2 signal changes in the assessment of progression of glioblastoma according to the Response Assessment in Neurooncology criteria. *Neuro Oncol* 2012;14(2):222–229.
13. Gzell CE, Wheeler HR, McCloud P, Kastelan M, Back M. Small increases in enhancement on MRI may predict survival post-radiotherapy in patients with glioblastoma. *J Neurooncol.* 2016;128(1):67–74.

14. Gerstner ER, Chen PJ, Wen PY, et al. Infiltrative patterns of glioblastoma spread detected via diffusion MRI after treatment with cediranib. *Neuro Oncol* 2010;12(5):466–472.
15. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. *N Engl J Med.* 2017;377(20):1954–1963.
16. Taal W, Oosterkamp HM, Walenkamp AM, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB trial): a randomized controlled phase 2 trial. *Lancet Oncol.* 2014;15(9):943–953.
17. Yushkevich PA, Piven J, Hazlett HC, et al. User-guided 3D active contour segmentation of anatomical structures: significantly improved efficiency and reliability. *Neuroimage* 2006;31(3):1116–1128.
18. Gorlia T, Stupp R, Brandes AA, et al. New prognostic factors and calculators for outcome prediction in patients with recurrent glioblastoma: a pooled analysis of EORTC Brain Tumour Group phase I and II clinical trials. *Eur J Cancer.* 2012;48(8):1176–1184.
19. Iwamoto FM, Abrey LE, Beal K, et al. Patterns of relapse and prognosis after bevacizumab failure in recurrent glioblastoma. *Neurology* 2009;73(15):1200–1206.
20. Norden AD, Young GS, Setayesh K, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. *Neurology* 2008;70(10):779–787.
21. Pope WB, Lai A, Nghiemphu P, Mischel P, Gloughesy TF. MRI in patients with high-grade gliomas treated with bevacizumab and chemotherapy. *Neurology* 2006;66(8):1258–1260.
22. Kreisl TN, Lassman AB, Mischel PS, et al. A pilot study of everolimus and gefitinib in the treatment of recurrent glioblastoma (GBM). *J Neurooncol.* 2009;92(1):99–105.
23. Ananthnarayan S, Bahng J, Roring J, et al. Time course of imaging changes of GBM during extended bevacizumab treatment. *J Neurooncol.* 2008;88(3):339–347.
24. Wood JR, Green SB, Shapira WR. The prognostic importance of tumor size in malignant gliomas: a computed tomographic scan study by the Brain Tumor Cooperative Group. *J Clin Oncol.* 1988;6(2):338–343.
25. Berntsen EM, Stensjøen AL, Langlo MS, et al. Volumetric segmentation of glioblastoma progression compared to bidimensional products and clinical radiological reports. *Acta Neurochir.* 2020;162:379–387.
26. Kickingereder P, Isensee F, Tursunova I, et al. Automated quantitative tumour response assessment of MRI in neuro-oncology with artificial neural networks: a multicentre, retrospective study. *Lancet Oncol.* 2019;20(5):728–740.
27. Chang K, Beers AL, Bai HX, et al. Automatic assessment of glioma burden: a deep learning algorithm for fully automated volumetric and bidimensional measurement. *Neuro Oncol* 2019;21(11):1412–1422.