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

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ABSTRACT

Background. We previously demonstrated that treatment assessment by volumetry using a 40% increase threshold for calling progression in recurrent glioblastoma treated with bevacizumab did not improve survival prediction compared to standard 2D methods. However, the optimal volumetric threshold for determining progressive disease (PD) has not been defined. We investigated a range of thresholds for enhancing and non-enhancing tumor volume increase in association with overall survival (OS).

Materials and 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 non-enhancing tumor volumes were measured at baseline, first (6 weeks) and second (12 weeks) follow-up on 3D T1w post-contrast and T2w-FLAIR images. 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 follow-up, 15 patients had a new lesion associated with a significantly worse OS (3.2 versus 11.2 months, HR=7.03, p<.001). At first follow-up (n=138), lowering the threshold of enhancing volume increase from ≥40% to ≥20% increased the HR (from HR=1.77, p=.010 to HR=5.55, p=.001), while only categorizing an additional 5 patients as PD. At second follow-up (n=94), lowering the threshold from ≥40% to ≥0% also increased the HR (from HR=3.02, p=.001 to HR=9.00, p<.001). Assessing the additional effect of measuring non-enhancing volume at first follow-up (n=89), the highest HR was found with ≥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 non-enhancing volumes to the analyses was of limited value even in the bevacizumab-treated group.

INTRODUCTION

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/or angiogenesis inhibitors. Recently, the United States Food and Drug Administration has given full approval for use of bevacizumab (Avastin®) in glioblastoma[2,3]. Angiogenesis inhibitors normalize the tumor vasculature, leading to a decrease in tumor enhancement on T1-weighted post-contrast images even in the absence of a true reduction of tumor activity.

The Response Assessment in Neuro-Oncology (RANO) criteria[4] expanded on the earlier MacDonald criteria[5] by incorporating non-enhancing 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 non-enhancing lesions, appearance of new lesions, or clear progression of non-measurable 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[6] and is originally based on breast cancer assessment on mammogram[7].

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 non-enhancing abnormalities, which are currently assessed only qualitatively with the RANO criteria. On the other hand, upon comparing 1D, 2D, and volumetric measures, high concordance between methods has been found, questioning the added value of the more demanding volumetric assessment[8-10]. All these 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[11], which foregoes the potential increased sensitivity of volumetric assessment. Some authors have used different volumetric cut-off values for PD, such as ≥25%[12], ≥15%[13], and ≥5%[14], suggesting that using lower thresholds could lead to a better survival prediction. Previously, a ≥25% increase of non-enhancing volumes has been proposed as the threshold to establish PD[10,15].

We aimed to determine whether lowering the volumetric threshold for PD in both enhancing tumor and non-enhancing abnormalities improves survival prediction and whether there is a preferred moment for first follow-up. We also evaluated the significance 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)[16,17]. 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 and Wick et al. 2016. The study endpoint in the current analysis was overall survival (OS), measured from the moment of follow-up (either first of second) to death from any cause.

Standardized MRI scans were performed at 6-week intervals and included pre- and post-contrast 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 non-enhancing volumes from respectively 3D T1w post-contrast 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[18]. Areas of necrosis, pre-contrast T1w hyperintensity, blood vessels, and dura were excluded. New enhancing and non-enhancing 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.

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)[19]. In the multivariate analysis p<.05 was considered significant.

We calculated the association between the appearance of a new lesion at first, i.e. 6 weeks' follow-up with OS. Both enhancing and/or non-enhancing 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 non-enhancing 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, HRs were calculated in strata of ≥40%, ≥20 – <40%, and ≥0 – <20% increase in enhancing volume and ≥25%, ≥10 – <25%, and ≥0 – <10% increase in non-enhancing volume (from now on referred to as strata 20-40% etc.). 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 non-enhancing volumetric analysis so that the added values of measuring non-enhancing volumes could be determined.

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

RESULTS

Patients

Patients without available 3D T1w post-contrast 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).

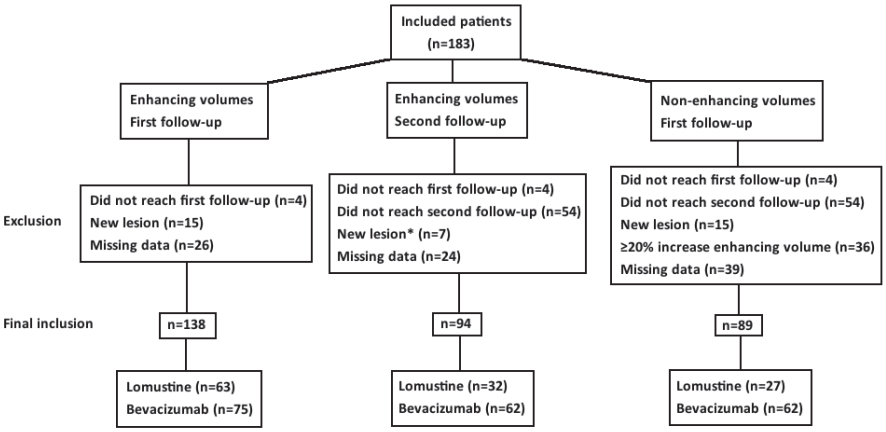

Figure 1. Flow diagram of all patients included from the BELOB and EORTC 26101 trials (n=183), reasons for excluding patients (in order) per analysis and number of patients included in the final analyses.

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 which 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.

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

	All treatment groups			Bevacizumab			Lomustine		
Parameters	**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

New lesions

At first follow-up (n=179), a new enhancing and/or non-enhancing lesion appeared in 15 patients (a more detailed description can be found in the ***Supplementary Files. Table S1*** and ***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 non-enhancing).

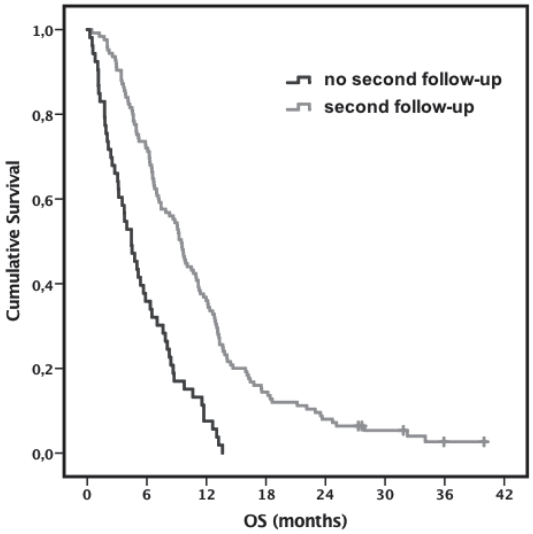

Figure 2. Kaplan-Meier curves of patients with and without a new lesion at first follow-up. The median overall survival (measured from first follow-up) was 2 versus 8.5 months, respectively.

Enhancing lesions

In all treatment groups combined, patients with a ≥ 40% increase in enhancing volume at first or at second 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. Within the threshold stratum of 20–40% increase, an additional 5 patients were categorized as PD at first follow-up, and 2 patients at second follow-up. When lowering the threshold to stratum 0-20% increase, 12 and 6 patients were additionally categorized as PD at first and second follow-up respectively. The highest HR at first follow-up was found with stratum 20-40% increase (HR=5.55, p=.001) and at second follow-up with stratum 0-20% increase (HR=9.00, p<.001) (see ***Table 2***).

Table 2. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values for the strata ≥40%, 20-40%, and 0-20% increase in enhancing volume at first and second follow-up in all treatment groups together and in the lomustine-treated group. Patient numbers with enhancing volume increase in the bevacizumab-treated group were insufficient for meaningful analysis.

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
	20-40	5	5.55	2.06-14.91	.001	2	-	-	-
	0-20	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
	20-40	4	-	-	-	2	-	-	-
	0-20	10	0.70	0.28-1.78	.46	5	10.70	3.45-33.17	<.001

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

Non-enhancing lesions

To determine the added value of measuring non-enhancing volume increase for response assessments, patients with PD based on increasing enhancing volume (at thresholds determined based on the highest HR found) were excluded from the analyses, i.e. stratum 20-40% at first follow-up. In all treatment groups together, the

Table 3. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values for ≥25%, stratum 10-25%, and stratum 0-10% increase in non-enhancing volume at first and second follow-up in all treatment groups together and in the bevacizumab-treated group. Patient number with non-enhancing volume increase in the lomustine-treated group was insufficient for meaningful analysis.

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

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 non-enhancing volume increase. Analyses of non-enhancing volumes at second follow-up could not be performed for the same reason.

DISCUSSION

In this analysis of patients with recurrent glioblastoma, PD was determined based on the appearance of a new lesion, increasing enhancing volume, and increasing non-enhancing volume in association with OS. A new enhancing or non-enhancing 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.

After excluding all patients with PD based on the appearance of a new lesion or increase in enhancing tumor volume, an increase in non-enhancing 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 non-enhancing volumes was limited in this population.

HRs at second follow-up (i.e. after 12 weeks) were higher and more significant than those at first follow-up (i.e. 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. Slightly more bevacizumab-treated patients were categorized as PD when non-enhancing volume increase was taken into account, confirming a possible role for the RANO emphasis on non-enhancing volumes in bevacizumab-treated patients. In previous literature,

an increase in non-enhancing abnormalities has been described as a pattern of progression after anti-angiogenic treatment[20,21], but since our data is limited 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 non-enhancing abnormalities is during the entire course of anti-angiogenic treatment.

We measured total volume of either enhancing or non-enhancing lesions, which means that mixed responses were not considered. Mixed response is seen in a subset of patients[22,23], but we postulate that the outcome of these patients is determined by the overall volume increase or by newly appearing lesions. Measuring total non-enhancing 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[24], a decrease in non-enhancing 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[19]. The prognostic significance of the latter was conformed 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[25].

An important argument in favor of performing volumetric rather than 2D measurement is the lower inter- and intra-rater variability, which has previously been shown with (semi-)automated techniques. Unfortunately, volumetric measurement are still much more difficult to obtain than the commonly used 2D measures, and their added value for response assessment is disputed[8-10]. Despite the unclear added value when it comes to predicting survival, tumor volumes 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.

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 value of volumetric imaging (i.e. looking at enhancing and non-enhancing volume) in this treatment group.

In conclusion, new lesions, whether enhancing or non-enhancing, 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 non-enhancing volumes in patients treated with lomustine only. In the bevacizumab-treated group early increase in tumor size (either enhancing or non-enhancing) was found to be rare. Here, increasing lesions were also associated with poor outcome, whether enhancing or non-enhancing.

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. DA Grants Genentech's Avastin Full Approval for Most Aggressive Form of Brain Cancer. Genentech. Accessed December 5. http://www.gene.com/media/press-release/14695/2017-12-05/fda-grants-genentechs-avastin-full-appro.
4. 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.
5. 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.
6. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981;47(1):207-214.
7. 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.
8. Wang MY, Cheng JL, Han YH, Li YL, Dai JP, Shi DP. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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.
14. 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.
15. Gerstner ER, Chen PJ, Wen PY, Jain RK, Batchelor TT, Sorensen G. Infiltrative patterns of glioblastoma spread detected via diffusion MRI after treatment with cediranib. Neuro Oncol 2010;12(5):466-472.
16. Wick W, Gorlia T, Bendszus M, et al. Lomustine and bevacizumab in progressive glioblastoma. N Engl J Med 2017;377(20):1954-1963.

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

22. 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.

23. 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.

24. 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.

SUPPLEMENTARY FILES

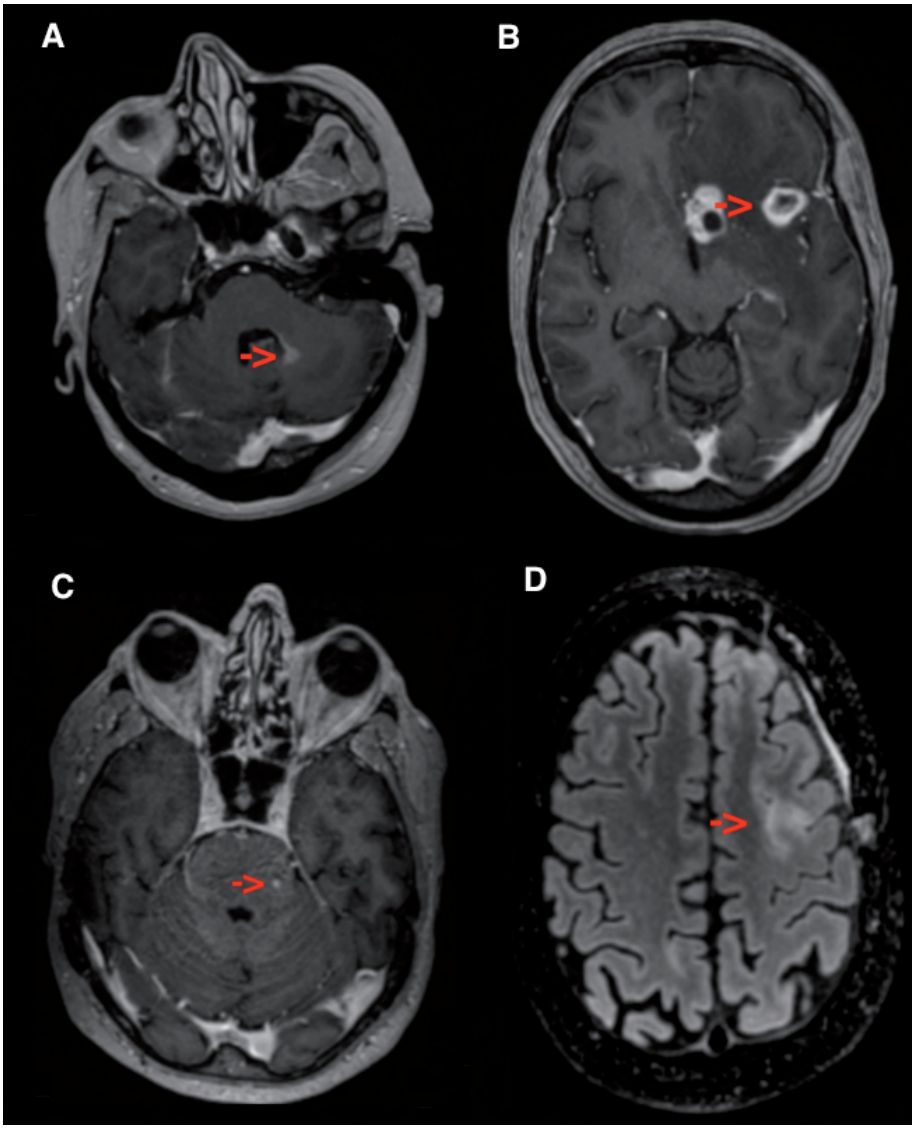

Figure S1. Examples of new lesions found at first follow-up. New enhancing lesions found in patients 046 (**A**), 071 (**B**), and 087 (**C**) and a new non-enhancing lesion found in patient 137 (**D**). Additional information on these patients can be found in ***TableS1***.

Table S1. Characteristics of all patients with a new lesion at first follow-up (n=15). Enhancing and non-enhancing lesions of any size were included. OS=overall survival.

Trial	Patient	Treatment	Enhancing or non-enhancing lesion	Volume (cm^3)	Max axial diameter (mm)	OS (days)
BELOB	004	Bevacizumab	Enhancing	0.773	22.1	61
	004		Non-enhancing	0.142	11.4	
	028	Bevacizumab	Enhancing	0.019	6.73	220
	029	Lomustine	Non-enhancing	1.044	17.3	57
	046	Bevacizumab+lomustine	Enhancing	0.217	10.9	43
	071	Lomustine	Enhancing	1.388	17.7	32
	085	Lomustine	Enhancing	0.023	4.77	35
	087	Bevacizumab	Enhancing	0.016	3.10	114
	092	Bevacizumab	Enhancing	0.014	5.34	61
	100	Lomustine	Enhancing	0.022	2.58	198
	127	Bevacizumab	Enhancing	0.014	2.50	77
	137	Bevacizumab	Non-enhancing	2.042	22.4	54
	151	Bevacizumab	Non-enhancing	0.828	15.3	86
	151		Non-enhancing	0.328	6.60	
EORTC26101	161	Lomustine	Enhancing	0.14	5.79	251
	180	Lomustine	Non-enhancing	14.02	62.0	39
	189	Lomustine	Enhancing	0.03	4.22	96
	189		Enhancing	0.06	3.00	