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

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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 non-enhancing 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 non-enhancing 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 non-enhancing 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 non-enhancing volumes to the analyses was of limited value.

Keywords: GBM | bevacizumab | RANO | volumetry
Key Points

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

Importance of 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 non-enhancing) 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 non-enhancing 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.
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. Recurrent glioblastoma are often treated with chemotherapy, and bevacizumab has been registered for this indication in several countries including the USA. Angiogenesis inhibitors like bevacizumab 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 expanded on the earlier MacDonald criteria 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 and is originally based on breast cancer assessment on mammogram.

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. Upon comparing 1D, 2D, and volumetric measures, high concordance between methods has been found, questioning the added value of the more demanding volumetric assessment. Most studies extrapolated the RANO-based ≥25% increase in 2D areas to a ≥40% increase in volume (4/3πr³), assuming a sphere-shaped tumor.
equally increasing in all directions, which foregoes the potential increased sensitivity of volumetric assessment. Some authors have used different volumetric cut-off 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 non-enhancing 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 non-enhancing 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 55y (range 24-77y). 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\textsuperscript{15} and Wick et al. 2016\textsuperscript{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 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 $\leq1\text{mm}$. 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\textsuperscript{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 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. Lesions were considered new when they appeared at some distance or adjacent to existing enhancing or non-enhancing 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. 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, 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 non-enhancing 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 non-enhancing volumetric analysis so that the added values of measuring non-enhancing volumes could be determined.

After scoring the presence of new lesions and after determining the optimal thresholds for both enhancing and non-enhancing 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 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 Figure1 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 (Table1) 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 non-enhancing lesion appeared in 15 patients (a more detailed description can be found in the Supplementary Files. TableS1 and FigureS1). 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 (Figure2). At second follow-up, 2 additional patients had developed a new lesion (1 enhancing and 1 non-enhancing).

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. 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 Table2).

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.

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, i.e. ≥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 Table3). 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.

Comparison with RANO

We then compared the 2D RANO evaluation with the optimal volumetric thresholds at first follow-up (i.e. ≥20% increase in enhancing volume and ≥25% increase in non-enhancing volume). A total 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
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 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. 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 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\(^{19,20}\), but since our data is restricted to the early period of follow-up, we are unable to determine if this pattern 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\(^{21,22}\), but we postulate that the outcome of these patients is determined by the overall volume increase or by newly appearing lesions. Measuring total 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\(^{23}\), 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\textsuperscript{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 \( \geq 25\% \) 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\textsuperscript{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 non-target lesions.

An important argument in favor of performing volumetric rather than 2D measurement is the greater inter- and intra-rater variability found using 2D methods\textsuperscript{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\textsuperscript{7,9}. Recent studies on fully automated approaches suggest that with the advance of technology this may become standard\textsuperscript{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 cut-off 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 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


FIGURE CAPTIONS

**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.

**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.
TABLES

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.

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>Lomustine</th>
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<tr>
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<td>p-value</td>
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<td>1.30-</td>
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<td>1.19-</td>
<td>.59</td>
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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.

<table>
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<tr>
<th>Treatment groups</th>
<th>≥40% increase in volume</th>
<th>≥20% increase in volume</th>
<th>≥0 increase in volume</th>
<th>First follow-up (n=138)</th>
<th>Second follow-up (n=94)</th>
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<tr>
<td></td>
<td>n</td>
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<td>95% CI</td>
<td>p-value</td>
<td>n</td>
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<td>-</td>
<td>-</td>
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<tr>
<td>0</td>
<td>10</td>
<td>0.70</td>
<td>0.28-1.78</td>
<td>.46</td>
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Table 3. Hazard ratios (HRs), 95% confidence intervals (CIs), and p-values at thresholds ≥25%, ≥10% and ≥0% increase in non-enhancing volume at first and second follow-up in all treatment groups together and in the bevacizumab-treated group.

<table>
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<th>HR</th>
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<tr>
<td></td>
<td>≥0%</td>
<td>4</td>
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</table>
Figure 1

Included patients (n=183)

Enhancing volumes
First follow-up

Did not reach first follow-up (n=4)
New lesion (n=15)
Missing data (n=26)

Exclusion

Final inclusion

n=138

Lomustine (n=63)
Bevacizumab (n=75)

Enhancing volumes
Second follow-up

Did not reach second follow-up (n=60)
New lesion (n=7)
Missing data (n=18)

n=94

Lomustine (n=32)
Bevacizumab (n=62)

Non-enhancing volumes
First follow-up

Did not reach first follow-up (n=4)
New lesion (n=15)
>20% increase enhancing volume (n=36)
Missing data (n=39)

n=89

Lomustine (n=27)
Bevacizumab (n=62)
Figure 2

Cumulative Survival

OS (months)

- new lesion
- no new lesion