The value of apparent diffusion coefficient in predicting overall survival after the first course of bevacizumab and lomustine in recurrent glioblastoma

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SUBMITTED

ABSTRACT

Purpose: To investigate the value of apparent diffusion coefficient (ADC) histogram analysis to predict overall survival (OS) after the first treatment course of bevacizumab and/or lomustine in recurrent glioblastoma.

Materials and Methods: Patients (n=148) were included from the board-approved multicenter BELOB-trial and informed consent was acquired. Standardized MRI-scans from baseline and 6-week follow-up were retrospectively analyzed. Volumes of interest (VOIs) of enhancing and non-enhancing lesions were drawn on 3D T1w post-contrast and FLAIR images and co-registered with ADC-maps. Patients with missing MRI-data or small lesions (<0.2cm^3) were excluded. Unimodal ADC-histogram parameters were derived per VOI. From exploratory analyses of each histogram parameter performed in all treatment groups together, ADC_{min} was found to be most promising in predicting OS and was further analyzed using cox-regression analysis. The optimum cut-off value for predicting OS was determined in a multivariate analysis.

Results. Change in ADC_{min} in enhancing lesions was analyzed in 108 patients. A decrease of >27.5% resulted in significantly better OS when looking at all treatment arms together (HR=0.572, p=.007), both bevacizumab-treated groups (n=72) (HR=0.452, p=.002), and in the combination-treatment arm (n=38) (HR=0.287, p=.001). After correcting for WHO performance status, corticosteroid use, and baseline enhancing volume, results remained significant: HR=0.482 (p=.001), HR=0.415 (p=.001), and HR=0.250 (p<.001) respectively. No significant differences in OS were found in the monotherapy arms, nor in the non-enhancing lesions.

Conclusion. Decrease in ADC_{min} in enhancing recurrent glioblastoma treated with bevacizumab and lomustine was associated with significantly better OS.

Advances in knowledge:

- Response in terms of overall survival can be predicted by measuring change in ADC_{min} values from baseline to first follow-up in recurrent glioblastoma treated with bevacizumab combined with lomustine.
- Changes in ADC_{min} were only predictive for response in terms of overall survival in enhancing but not in non-enhancing lesions.

Implication(s) for patient care:

- Where response in recurrent glioblastoma treated with bevacizumab is difficult to determine on conventional imaging due to issues with pseudo-response, change in ADC_{min} can help to predict response in terms of improved overall survival after the first course of treatment.

Summary statement:

Change in ADC_{min} values measured in the enhancing portion of recurrent glioblastoma predicts improved overall survival at first follow-up after treatment with bevacizumab and lomustine when using a cut-off percentage change between -5% and -27.5% ($HR_{27.5\%}$=0.250, p<.001).

INTRODUCTION

Glioblastoma multiforme is the most common malignant primary brain tumor with a 5-year survival rate of only 5% despite intensive treatment[1,2]. Based on the results from two phase-II trials with bevacizumab (Avastin®, Genentech, San Francisco) and irinotecan[3,4], the United States Food and Drug Administration (FDA) approved the use of bevacizumab for second-line treatment in patients with recurrent glioblastoma in 2009. Bevacizumab is an angiogenesis inhibitor that specifically targets Vascular Endothelial Growth Factor (VEGF), resulting in the normalization of tumor blood vessels[5]. This reduces contrast-enhancement, edema, perfusion, and also diffusion[6-9].

Response assessment in glioblastoma is formulated in the Response Assessment in Neuro-Oncology (RANO) criteria, which are based on change in contrast-enhancement and/or non-enhancing abnormalities on T2-weighted (T2w)/Fluid attenuated inversion recovery (FLAIR) magnetic resonance (MR) imaging[10]. Decrease in contrast enhancement and edema in patients treated with bevacizumab may be actual tumor response or pseudo-response (i.e. decrease in vascular permeability only). The RANO do not discern the cause of the decrease and an imaging marker of true tumor response to bevacizumab is at present lacking. With diffusion weighted imaging (DWI), a quantitative measure of the magnitude of diffusion can be obtained, expressed as the apparent diffusion coefficient (ADC). Previous studies using histogram analysis of tumor ADC-values *at baseline* in patients treated with bevacizumab indicate that low values of ADC may be predictive for survival[11,12]. In bevacizumab-treated patients diffusion restriction has been observed *after treatment*, but the exact meaning of this finding is unclear[9,13].

Since not all patients seem to benefit from expensive treatment with bevacizumab, discerning the responders from the non-responders at an early stage is important to save costs and prevent possible side-effects in non-responders[14]. While progressive disease (PD) in bevacizumab-treated patients can be reliably established using the RANO criteria, a distinction between responders and non-responders when there is stable or decreased contrast enhancement is problematic due to the possibility of pseudo-response. The purpose of this study was to assess the value of ADC histogram analysis to predict overall survival (OS) after the first course (i.e. 6 weeks) of bevacizumab to obtain an indication of response at the very early stage after start of treatment.

METHODS

Patients

Patients from the Dutch institutional review board-approved BELOB trial (148 eligible patients), which is a phase II randomized controlled trial of first recurrence glioblas-

toma treated with either bevacizumab (Avastin, Roche) (n=50), lomustine (n=46) or a combination of both (n=52), were analyzed (Nederlands Trial Register, www.trialregister.nl, number NTR1929). Patients signed informed consent and were included between December 2009 and October 2011. No prior treatment with angiogenesis inhibitors or nitrosoureas had taken place, instead patients had been treated with surgery, radiotherapy and temozolomide. Details on the in- and exclusion criteria as well as the findings on the primary outcome from the trial are described elsewhere[15]. Earlier radiological analysis in this same patient population[16] did not include analysis of the DWI that were acquired during this study. All patients were above the age of 18, with a mean age of 55.9 years (range 24-77). Outcome measures were 6, 9 and 12-month OS and the proportion of patients with an objective response. In the current analysis OS was measured from first follow-up (i.e. 6 weeks) to death from any cause.

Data acquisition

Patients were treated in 14 different hospitals with follow-up which included MR scanning at 6-week intervals according to a standardized MR-protocol. Sequences scanned were: pre- and post-contrast 3D inversion recovery (IR) fast spin recovery gradient (FSPGR) T1-weighted (T1w) images with slice thickness and in-plane resolution ≤1mm, 3D T2w-FLAIR with slice thickness and in-plane resolution ≤1mm and fat-saturation, and transverse diffusion weighted images (DWI) with slice thickness of 3mm (no gap), in-plane resolution of 2mm, and b=0 and b=1000 s/mm^2. Due to differences in protocol implementation, voxel sizes of the DWI data differed between hospitals, ranging from 0.9x0.9x3.0mm to 2.0x2.0x6.0mm. Additionally, the protocol consisted of transverse 2D T2w, and dynamic susceptibility contrast perfusion imaging (selected sites only), not used for the current study.

Data post-processing

Enhancing tumor was segmented on T1w post-contrast images, and non-enhancing abnormalities on T2w-FLAIR images in BrainLab's I-Plan 4.0 Cranial using a semi-automated technique. The resulting volumes of interest (VOI) were categorized as enhancing and non-enhancing and assessed separately (***Figure 1***). T2w-FLAIR and DWI images as well as the VOIs were registered to the T1w post-contrast image per time-point with a non-linear registration technique using custom scripts in Matlab (R2014a) and Elastix[17]. During this registration the differences in voxel size and signal-to-noise ratio (SNR) between the different hospitals are taken into account (see ***Supplementary Files A*** for the parameter settings used in Elastix). To obtain a VOI for the non-enhancing lesion only, the enhancing lesion VOI was subtracted from the total non-enhancing VOI. ADC-maps were calculated from the DWI images and unimodal ADC-histogram parameters (mean, median, minimum, maximum, stan-

dard deviation, kurtosis and skewness) were computed from each VOI. A unimodal approach was chosen after visual inspection of histograms from 266 lesions at both baseline and first follow-up, which showed unimodal distribution in respectively 85% and 81% of cases. In case of multiple lesions in a single patient, histogram parameters were combined to obtain a single histogram per enhancing and non-enhancing VOI. VOIs <0.2cm^3 were excluded from analysis.

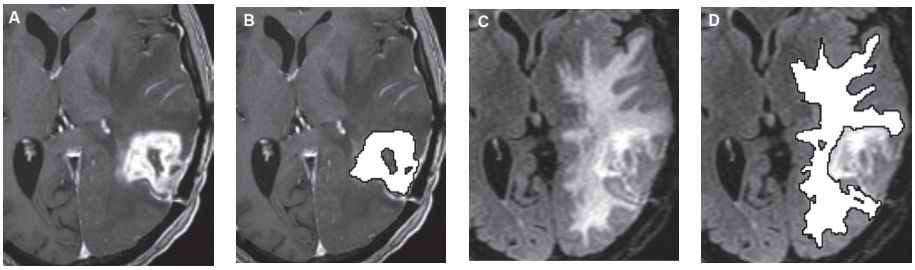

Figure 1 (A-D): 3D T1-weighted post-contrast and 3D T2w/FLAIR images without (**A, C**) and with (**B, D**) volumes of interest (VOI) in the same patient. The enhancing VOI was subtracted from the non-enhancing VOI to obtain the truly non-enhancing portion of the tumor.

Statistical analysis

All statistical analyses were performed using SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp. 2012). First, percentage change between baseline and first follow-up (i.e. 6 weeks after start of treatment) was calculated for each ADC histogram parameter. Exploratory analyses were then performed in the entire group of patients to determine which parameter(s) had potential value in establishing differences in OS. For every parameter, the group was dichotomized using its median. With cox regression analysis hazard ratios (HR) were obtained (significance level $p<.05$). Exploratory analyses were not performed in the separate treatment arms to avoid over-fitting, nor were threshold values chosen at this stage.

After determining which parameters were potentially useful in predicting OS, a range of cut-off values for percentage change measured in enhancing and non-enhancing lesions separately were tested in the entire group, in those treated with bevacizumab, and in all treatment arms separately. For the optimal threshold, results were corrected in a multivariate survival analysis (cox regression) for age, WHO performance status, corticosteroid use, and baseline enhancing volume (if $p<.10$ in univariate analysis).

In every patient, baseline and first follow-up scans had been performed in the same hospital on scanners from the same vendor. Four patients were scanned at different scanner field strengths between baseline and first follow-up (i.e. 1.5T and 3.0T). To assess the effect of differences in field strength, an additional analysis was

performed, correcting for differences in ADC values, using a factor of -9.79% to correct the values from the 3.0T scanner[18].

RESULTS

Patients

Out of 148 eligible patients, only those patients with 3D T1w post-contrast and/or T2w/FLAIR images were analyzed. In the analysis of enhancing lesions and non-enhancing lesions, respectively 108 and 99 patients were included (see ***Figure 2***).

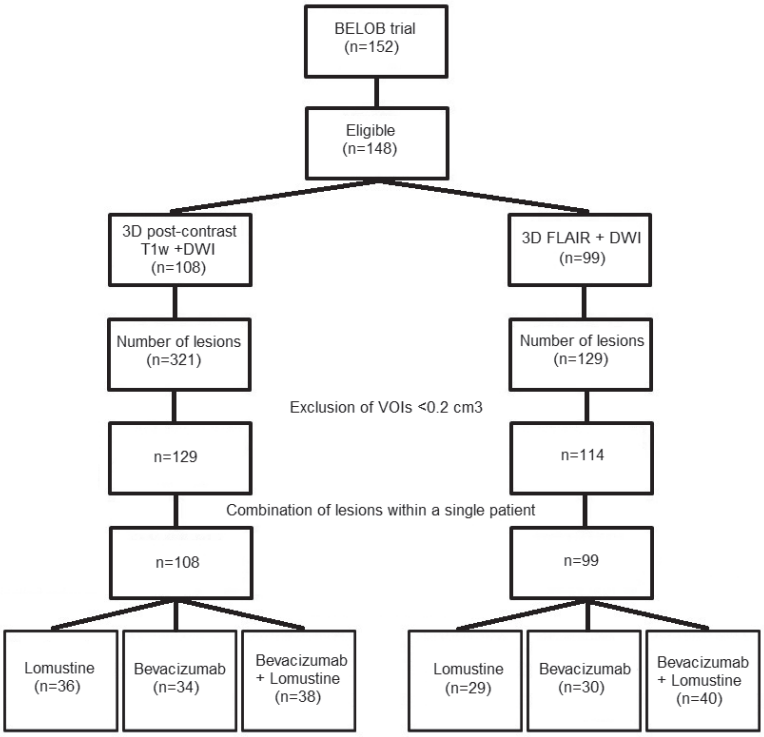

Figure 2: Flow diagram showing all patients included in the BELOB trial and those included in the final analyses. Patients with 3D T1weighted post-contrast (T1w+C) and 3D FLAIR scans at both baseline and first follow-up were included. Lesions <0.2cm^3 were excluded; if multiple lesions were present within a single patient, these were combined in a single volume of interest.

Histogram analysis

In the exploratory analysis, only skewness (ADC_{skew}) and minimum ADC (ADC_{min}) showed promise in predicting OS. Further exploration of the ADC_{skew} data showed inconsistent

findings due to multiple outliers. ADC_{min} did show consistent significant results and further cut-off values for percentage decrease of this parameter were tested (5%, 10%, 15%, 20%, 22.5%, 25%, 27.5%, 30%, and 32.5%) in enhancing and non-enhancing lesions separately (***Supplementary Files: Table S1*** and ***Table S2***). ***Figure 3*** shows an example of ADC_{min} histograms at baseline and first follow-up. Other histogram parameters explored did not show meaningful correlations with OS (data not shown).

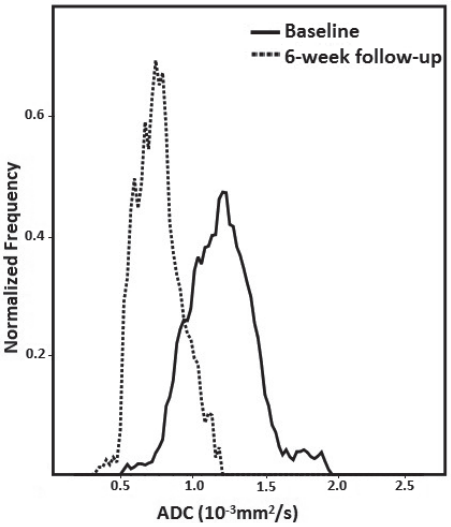

Figure 3: Apparent diffusion coefficient (ADC) histogram at baseline (**bold line**) and first follow-up at 6 weeks (**dotted line**) in an enhancing lesion of a patient treated with bevacizumab plus lomustine. Percentage change in ADC_{min} was -33.64% and the OS 13.3 months.

In enhancing VOIs (n=108), when assessing all treatment groups combined stratification of patients based on a decrease in ADC_{min} of 20% to 30% showed a significant difference in OS, with the most significant HR found with 27.5% decrease (HR=0.572, 95% CI 0.38-0.86, p=.007). This result remained significant after correcting for WHO performance status, corticosteroid use, and baseline enhancing volume (HR=0.482, 95% CI 0.32-0.74, p=.001), see ***Table 1***. In both bevacizumab-treated groups combined (n=72) stratification of patients based on decrease in ADC_{min} of 10% to 30% showed a significant difference in OS. The most significant HR was found with 27.5% decrease (HR=0.452, 95% CI 0.27-0.75, p=.003), which after correcting for covariates remained significant (HR=0.415, 95% CI 0.25-0.70, p=.001), see ***Table 2***. Upon further dividing the bevacizumab-treated groups into the bevacizumab-only and combined treatment arms, the significant differences were shown to originate from the combined treatment arm (n=38): stratification of patients based on decrease in ADC_{min} of 5% to 27.5% showed a significant difference in OS in this patient group. The most significant HR was again found with 27.5% decrease (HR=0.287, 95% CI 0.34-0.60, p=.001). Results remained significant after correcting for corticosteroid use (HR=0.250, 95% CI 0.12-0.54, p<.001), see ***Table 3***. The mean OS measured

Table 1: Univariate and multivariate assessment of the predictive value of >27.5% decrease in ADC_{min} in enhancing lesions in all treatment groups together (n=108)

All patients (n=108)						
Variables	**Univariate**			**Multivariate**		
	Hazard Ratio	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**P-value**
>27.5% decrease in ADC_{min}*	0.572	0.38-0.86	.007	0.482	0.32-0.74	.001
Age	1.003	0.99-1.02	.713			
WHO performance status	1.446	1.02-2.05	.039	1.424	0.94-2.16	.096
Corticosteroid use	1.551	1.05-2.28	.026	1.010	0.62-1.64	.968
Baseline enhancing volume	1.022	1.01-1.04	.006	1.026	1.01-1.04	.003

**ADC_{min} = minimum apparent diffusion coefficient; WHO = world health organization; CI=confidence interval*

Table 2: Univariate and multivariate assessment of the predictive value of >27.5% decrease in ADC_{min} in enhancing lesions in both bevacizumab-treated groups (n=72)

Both bevacizumab-treated groups (n=72)						
Variables	**Univariate**			**Multivariate**		
	Hazard Ratio	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
>27.5% decrease in ADC_{min}*	0.452	0.27-0.75	.002	0.415	0.25-0.70	.001
Age	1.005	0.99-1.03	.611			
WHO performance status	1.456	0.94-2.25	.090	1.417	0.85-2.36	.181
Corticosteroid use	1.677	1.04-2.69	.033	1.213	0.69-2.14	.503
Baseline enhancing volume	1.021	1.00-1.04	.038	1.017	0.99-1.04	.118

**ADC_{min} = minimum apparent diffusion coefficient; WHO = world health organization; CI=confidence interval*

Table 3: Univariate and multivariate assessment of the predictive value of >27.5% decrease in ADC_{min} in enhancing lesions in the combined treatment arm (i.e. lomustine and bevacizumab) (n=38).

Bevacizumab + lomustine (n=38)						
Variables	**Univariate**			**Multivariate**		
	Hazard Ratio	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
>27.5% decrease in ADC_{min}*	0.287	0.14-0.60	.001	0.250	0.12-0.54	<.001
Age	1.003	0.98-1.03	.836			
WHO performance status	1.329	0.74-2.40	.344			
Corticosteroid use	1.807	0.92-3.55	.085	2.139	1.07-4.29	.033
Baseline enhancing volume	1.015	0.99-1.04	.264			

**ADC_{min} = minimum apparent diffusion coefficient; WHO = world health organization; CI=confidence interval*

from first follow-up was 15.2 months in patients with a decrease in ADC_{min} ≥27.5% (n=24), versus 6.8 months in those with a decrease of ADC_{min} <27.5% (n=14). In the bevacizumab or the lomustine monotherapy group, no significant differences in OS were seen at any of the cut-off values. After correction for differences in scanner field strength between baseline and follow-up in four patients, stratification of patients based on the ADC_{min} percentage change in the enhancing lesions was unchanged. Kaplan-Meier curves of all patients together, both bevacizumab-treated groups, and the bevacizumab-treated groups separately using 27.5% decrease in ADC_{min} as a cut-off value are shown in ***Figure 4***.

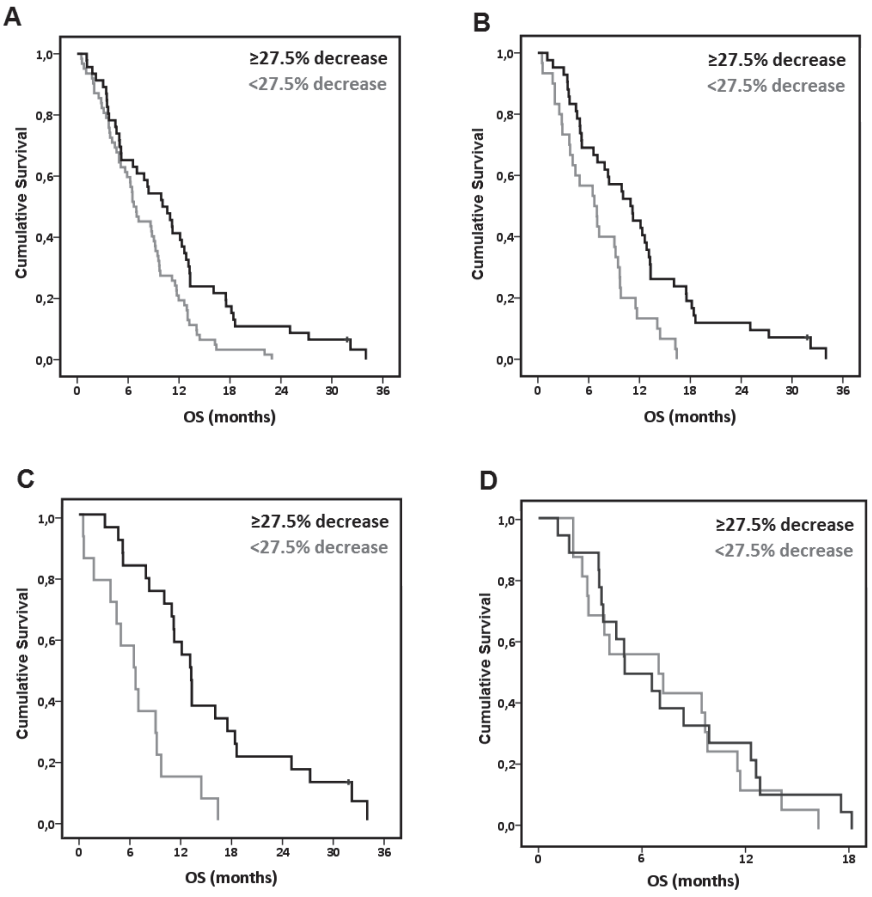

Figure 4 (A-D): Kaplan-Meier with 27.5% decrease of minimum apparent diffusion coefficient (ADC_{min}) as a cut-off value in enhancing lesions (data from table 1), for all treatment groups together (**A**), for both bevacizumab-treated (bevacizumab monotherapy and bevacizumab plus lomustine combined treatment) groups (**B**), for the bevacizumab plus lomustine group (**C**), and the bevacizumab monotherapy group (**D**).

In non-enhancing lesions (n=99) (***Supplementary Files: Table S2***) there were no significant differences in OS after stratification of patients based on any of the ADC_{min} percentage change values.

DISCUSSION

In the context of the phase II BELOB-trial, we found that patients treated with bevacizumab and lomustine for recurrent glioblastoma had a significantly better OS, i.e. an indication of response, when there was a decrease of ADC_{min} in enhancing lesions after the first course of treatment than in those who didn't show such a decrease. The optimum cut-off value for establishing response was 27.5% decrease in ADC_{min}. In patients treated with bevacizumab or lomustine monotherapy, or in non-enhancing lesions, an association between ADC changes and OS was not seen.

The significant difference in OS based on ADC_{min} was seen when patients from all treatment arms were combined as well as when all bevacizumab-treated patients were considered. These findings seemed to be driven by the combined treatment arm, as no significant effects were found in the monotherapy groups. Considering the BELOB-trial survival data, published previously[15], patients treated with bevacizumab plus lomustine showed a better OS then those treated with bevacizumab or lomustine alone. This result was however not reproduced in the subsequent phase III trial EORTC 26101[19], possibly indicating differences between patient samples. We must therefore consider the possibility that our results are specific to the BELOB-trial population. However, the observed changes could also indicate true tumor response in a subset receiving combination treatment. Our results will need to be externally validated in order to generalize these. It should be noted that while exploratory analyses were performed in the same population as the test population, they were performed within the entire patient group without optimization for a specific treatment arm nor was a specific threshold value established at this stage.

Because of tumor heterogeneity, changes in diffusion may differ between tumor regions[20]. Measures such as ADC_{mean} and ADC_{median} are therefore less insightful when considering lesions as a whole. Aside from ADC_{min}, skewness also showed promise, but in our analysis there were so many outliers in the ADC_{skew} data that this parameter was considered unreliable.

A comparison between our study and previous studies is problematic, because of differences in patient populations (with varying number of recurrences or inclusion of grade III glioma), post-processing methods, treatment (bevacizumab monotherapy and/or combined therapy groups), and measured time-points (pretreatment-only; different follow-up). In a recent publication, Ellingson et al. conclude that *pre-*

treatment diffusion histogram analysis can be predictive in recurrent GBM treated with angiogenesis inhibitor monotherapy[21]. Here, we focused on determining the response *after* treatment, which is known to be problematic in the context of anti-angiogenic agents due to issues with pseudo-response. We specifically looked at the first moment of follow-up after start of treatment, assessing *change* in ADC from baseline to first follow-up, considering an early response assessment most relevant for treatment decisions. There are a few other studies assessing changes from baseline to first follow-up. These measured volumes of foci with low ADC values within T2w/FLAIR abnormalities[22-24], sometimes by means of a graded functional diffusion map (fDM)[25]. In these studies, low ADC_{min} at baseline and larger volumes of areas with low ADC values predicted a worse outcome.

Low ADC is hypothesized to reflect regions of high cellularity within the tumor[25], which is consistent with worse outcome as established in previous studies[22-24]. Our seemingly contradictory results can be explained in light of the changes occurring after bevacizumab-treatment specifically. Anti-angiogenic treatment normalizes tumor vasculature leading to a decrease in enhancement, perfusion, and ADC[7-9]. Diffusion restriction could be the result of hypoxia, but could also be due to a reduction in blood volume. The decrease in ADC in those treated with both bevacizumab and chemotherapy may thus reflect a strong anti-angiogenic treatment induced anti-tumoral effect, resulting in better OS as an indication of treatment response. In patients not treated with bevacizumab, diffusion restriction likely corresponds with hypercellularity[26], thus showing a negative impact on survival.

ADC changes in non-enhancing lesions were not predictive of OS. The T2w/FLAIR abnormalities in recurrent glioblastoma are generally a combination of non-enhancing tumor, edema, and treatment effects. Given the heterogeneity of the T2w/FLAIR abnormalities it is possible that differential effects were obscured.

Aside from the need to validate our findings in a different cohort, other limitations are the retrospective nature of the study, and the fact that these patients were all derived from a phase II trial.

In conclusion, we found that decreasing ADC_{min} in enhancing tumor from baseline to first follow-up in patients with recurrent glioblastoma treated with bevacizumab and lomustine predicted OS using a cut-off percentage change between 5 and 27.5% with a significantly better OS found in those with decreasing ADC_{min}. These results indicate that the assessment of ADC may have a role in predicting response after the first course of combined bevacizumab and lomustine treatment, but given the fact that findings are derived from data acquired in the context of a phase II trial, external validation in a wider cohort is required before these can be generalized to all patients treated with bevacizumab in combination with lomustine.

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SUPPLEMENTARY FILES

A: Parameter settings used in Elastix

Parameter settings "rigid" component
(FixedInternalImagePixelType "float")
(MovingInternalImagePixelType "float")
(FixedImageDimension 3)
(MovingImageDimension 3)
(UseDirectionCosines "true")
(Registration "MultiResolutionRegistration")
(Interpolator "BSplineInterpolator")
(ResampleInterpolator "FinalBSplineInterpolator")
(Resampler "DefaultResampler")
(FixedImagePyramid
"FixedSmoothingImagePyramid")
(MovingImagePyramid
"MovingSmoothingImagePyramid")
(Optimizer "AdaptiveStochasticGradientDescent")
(Transform "AffineDTITransform")
(Metric "AdvancedMattesMutualInformation")
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(AutomaticTransformInitialization "true")
(HowToCombineTransforms "Compose")
(NumberOfHistogramBins 32)
(ErodeMask "false")
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3.0e+038 3.0e+038 3.0e+038 3.0e+038 -1 -1 -1)
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Table S1: Findings in all enhancing lesions (n=108) for all treatment groups together, both bevacizumab-treated groups together, and the bevacizumab-treated groups separately (i.e. bevacizumab + lomustine and bevacizumab-only). Hazard ratio's (HRs), 95% confidence intervals (CI) and p-values per percentage decrease in ADC_{min} at first follow-up.

Treatment	All treatment groups (n=108)			Both bevacizumab-treated groups (n=72)			Bevacizumab + lomustine (n=38)			Bevacizumab-only (34)			Lomustine-only (n=36)		
ADC_{min} % decrease	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
5	0.781	0.52-1.17	.230	0.609	0.36-1.05	.074	0.361	0.16-0.81	.013	1.110	0.52-2.36	.787	1.653	0.84-3.26	.147
10	0.731	0.49-1.09	.122	0.571	0.34-0.96	.038	0.386	0.18-0.82	.014	0.956	0.47-1.94	.901	1.627	0.82-3.23	.165
15	0.725	0.49-1.08	.112	0.571	0.34-0.96	.038	0.386	0.18-0.82	.014	0.956	0.47-1.94	.901	1.900	0.91-3.95	.086
20	0.647	0.43-0.97	.032	0.528	0.32-0.88	.016	0.356	0.17-0.75	.007	0.917	0.46-1.84	.807	1.583	0.73-3.44	.246
22.5	0.641	0.43-.095	.027	0.528	0.32-0.88	.016	0.356	0.17-0.75	.007	0.917	0.46-1.84	.807	2.350	0.88-6.30	.089
25	0.597	0.40-0.89	.011	0.482	0.29-0.80	.006	0.329	0.16-0.69	.003	0.820	0.41-1.65	.577	2.772	0.94-8.17	.064
27.5	0.572	0.38-0.86	.007	0.452	0.27-0.75	.003	0.287	0.34-0.60	.001	0.820	0.41-1.65	.577	2.772	0.94-8.17	.064
30	0.664	0.48-0.99	.040	0.585	0.36-0.95	.032	0.531	0.27-1.05	.070	0.754	0.38-1.52	.429	2.772	0.94-8.17	.064
32.5	0.746	0.50-1.12	.147	0.698	0.44-1.12	.135	0.663	0.34-1.30	.230	0.901	0.45-1.81	.768	2.772	0.94-8.17	.064

ADC_{min} = minimum apparent diffusion coefficient

Table S2: Findings in all non-enhancing lesions (n=99). Results from all treatment groups together, both bevacizumab-treated groups together, and the three separate treatment arms, i.e. bevacizumab + lomustine, bevacizumab-only and lomustine-only. Hazard ratio's (HR) and their 95% confidence intervals (CI) with corresponding p-values per percentage decrease in ADC_{min} at first follow-up.

Treatment	All treatment groups (n=99)			Both bevacizumab-treated groups (n=70)			Bevacizumab + lomustine (n=40)			Bevacizumab-only (30)			Lomustine-only (n=29)		
ADC_{min} % decrease	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
5	0.737	0.49-1.11	0.145	0.685	0.41-1.14	0.143	0.571	0.29-1.13	0.106	0.852	0.39-1.85	0.686	1.289	0.61-2.74	0.511
10	0.727	0.49-1.09	0.121	0.675	0.42-1.09	0.110	0.681	0.36-1.30	0.243	0.631	0.30-1.32	0.223	1.734	0.76-3.98	0.195
15	0.818	0.54-1.24	0.339	0.767	0.48-1.24	0.279	0.776	0.41-1.48	0.441	0.616	0.29-1.31	0.207	2.093	0.86-5.08	0.102
20	0.841	0.54-1.32	0.448	0.795	0.48-1.33	.0380	0.855	0.43-1.68	0.650	0.865	0.30-1.55	0.365	2.207	0.82-5.98	0.119
22.5	0.775	0.48-1.24	0.291	0.699	0.41-1.20	0.197	0.814	0.41-1.63	0.560	0.567	0.22-1.50	0.252	2.207	0.82-5.98	0.119
25	1.120	0.65-1.92	0.680	1.116	0.61-2.06	0.724	1.214	0.55-2.68	0.630	1.067	0.40-2.86	0.897	1.725	0.51-5.87	0.383
27.5	1.418	0.81-2.48	0.218	1.452	0.77-2.74	0.248	1.780	0.77-4.12	0.176	1.067	0.40-2.86	0.897	1.725	0.51-5.87	0.383
30	1.342	0.73-2.47	0.343	1.312	0.65-2.67	0.453	1.509	0.62-3.66	0.363	1.315	0.38-4.50	0.663	1.725	0.51-5.87	0.383
32.5	1.250	0.65-2.42	0.506	1.165	0.53-2.57	0.704	1.199	0.42-3.42	0.734	1.315	0.38-4.50	0.663	1.725	0.51-5.87	0.383

ADC_{min} = minimum apparent diffusion coefficient