Relative cerebral blood volume is a potential predictive imaging biomarker of bevacizumab efficacy in recurrent glioblastoma

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See the editorial by Pope, on pages 1046–1047.

Background. To analyze the relevance of dynamic susceptibility-weighted contrast-enhanced MRI (DSC-MRI) derived relative cerebral blood volume (rCBV) analysis for predicting response to bevacizumab (BEV) in patients with recurrent glioblastoma (rGB).

Methods. A total of 127 patients diagnosed with rGB receiving either bevacizumab (71 patients, BEV cohort) or alkylating chemotherapy (56 patients, non–BEV cohort) underwent conventional anatomic MRI and DSC-MRI at baseline and at first follow-up after treatment initiation. The mean rCBV of the contrast-enhancing tumor (cT1) as well as cT1 and fluid-attenuated inversion recovery (FLAIR) volumes at both time points were correlated with progression-free survival (PFS) and overall survival (OS) using Cox proportional hazard models, logistic regression, and the log-rank test.

Results. Baseline rCBV was associated with both PFS (hazard ratio [HR] = 1.3; \( P < .01 \)) and OS (HR = 1.3; \( P < .01 \)) in the BEV cohort and predicted 6-month PFS in 82% and 12-month OS in 79% of patients, whereas it was not associated with PFS (HR = 1.0; \( P = .70 \)) or OS (HR = 1.0; \( P = .47 \)) in the non-BEV cohort. Corresponding median OS and PFS rates in the BEV cohort for patients with rCBV-values less than 3.92 (optimal threshold from receiver operating characteristic [ROC] analysis of 12-month OS data) were 14.2 and 6.0 months, as compared to 6.6 and 2.8 months for patients with rCBV-values greater than 3.92 (\( P < .01 \), respectively). cT1 and FLAIR volumes at first follow-up were significant predictors of 6-month PFS and 12-month OS in the BEV cohort but not in the non-BEV cohort. Corresponding volumes at baseline were not significant in any cohort.

Conclusions. Pretreatment rCBV is a potential predictive imaging biomarker in BEV-treated rGB but not alkylating chemotherapy-treated rGB, which is superior to volumetric analysis of conventional anatomic MRI and predicts 6-month PFS and 12-month OS in 80% of BEV-treated patients.

Keywords: bevacizumab, cerebral blood volume, biomarker, glioblastoma, rCBV.

Angiogenesis is a hallmark of cancer, especially glioblastoma, which is the most malignant and common primary brain tumor in adults.1 This complex and highly adaptive biological process is regulated through several pathways, with vascular endothelial growth factor (VEGF) as one key factor promoting survival, proliferation, migration, and permeability of endothelial cells.2 This discovery has prompted considerable interest in antiangiogenic treatments with bevacizumab (BEV), a humanized monoclonal antibody to the vascular endothelial growth factor (VEGF)A, being the most commonly used antiangiogenic agent in the setting of recurrent glioblastoma (rGB).1,2 Although antiangiogenic treatment causes a rapid decline in the contrast-enhancing tumor (cT1), only a fraction of patients show a meaningful decline in tumor burden because radiographic response may result partly from normalization of abnormally permeable vessels and not always indicate a true antitumoral effect.3–5 Therefore, it is critically important to identify radiological biomarkers that can predict treatment response and aid patient selection.

Relative cerebral blood volume (rCBV) imaging, which is derived from dynamic susceptibility-weighted contrast-enhanced...
Magnetic Resonance Imaging

Images were acquired in the routine clinical workup using a 3 Tesla MR system (Magnetom Verio/Trio TIM, Siemens Healthcare) with a 12-channel head-matrix coil. Acquisition of the DSC-MRI sequence was performed as described previously.

Prior dynamic imaging, a 0.1 mmol/kg prebolus dose of gadoterate meglumine (Gd-DOTA, DOTAREM, Guerbet, France) was administered to diminish T1 effects that might result from agent extravasation. DSC-PWI was obtained with a T2*-weighted gradient-echo EPI sequence during bolus injection of a standard dose (0.1 mmol/kg) of intravenous gadoterate meglumine. Twenty-six to 28 slices with a thickness of 5 mm were acquired with fat suppression (TE = 36 milliseconds [ms], TR = 2220 ms, FA = 90°, field of view = 240 × 240 mm, image matrix = 128 × 128 mm). In total, 50–75 dynamic measurements were performed. Subsequently, postcontrast T1-weighted 3D magnetization-prepared rapid acquisition gradient echo (cT1; TI = 1100 ms, TE = 4 ms, TR = 1710 ms, and FA = 15°), and FLAIR (TI = 2400 ms; TE = 85 ms; TR = 8500 ms; section thickness, 5 mm; interslice gap, 5%) images were acquired.

Image Post Processing and Analysis

Postprocessing of DSC-MRI, cT1 and FLAIR data was performed with dedicated software (Olea Sphere v 2.3, Olea Medical). First, tumor segmentation on cT1 and FLAIR images at baseline and at first follow-up after BEV/alkylating chemotherapy treatment was performed according to a semiautomated region-growing segmentation method. This segmentation approach examines...
neighboring voxels of an initial seed point/voxel and determines whether the voxel neighbors should be added to the region of interest (ROI). Multiple seed points were used to account for multifocal or discontinuing lesions, and iteration of this process was performed on each slice of the cT1 images until the contrast-enhancing portion of the whole tumor was included, and macroscopic necrosis, cysts, and normal vessels were excluded from the segmented tumor. Similarly, segmentation of the tumor on FLAIR images was performed on each slice until the hyperintense FLAIR abnormality (excluding those resulting from obvious leukoaraiosis) was included. Tumor volume \( (\text{cm}^3) \) was calculated as the sum over all slices of (ROI area \( \times \) [slice thickness + gap]).

Postprocessing of DSC-MRI data included rigid-body registration to correct for motion artefacts. An arterial-input function (AIF) was determined automatically using cluster analysis techniques,\(^{14}\) and deconvolution of the AIF was performed using a time-insensitive block-circulant singular value decomposition.\(^{15}\) Mathematically leakage-corrected, whole-brain rCBV maps were generated by using an established tracer kinetic model applied to the first-pass data, with rCBV values computed pixel-by-pixel as the area under the concentration time curve (AUC) divided by the AUC of the AIF. (AIF pixels are assumed to be made of 100% blood if partial volume effects are neglected.)\(^{16}\) This approach eliminates the need to draw a reference ROI in the contralateral, nonaffected white matter for normalization of CBV values. Following automatic coregistration of rCBV maps with corresponding cT1 images that included the previously segmented cT1 ROIs, a mean rCBV (calculated as the mean of all individual rCBV voxels from the segmented tumor on cT1-images) was determined from both baseline and first follow-up after initiation of BEV/alkylating chemotherapy treatment.

### Statistical Analysis

Statistical analysis was performed using STATA version 12. Survival was calculated from initiation of BEV/alkylating chemotherapy treatment until death or last follow-up. Similarly, time to progression was calculated from initiation of BEV/alkylating chemotherapy treatment until tumor progression. Intragroup comparison of epidemiological, clinical, or imaging metrics between the BEV and non-BEV cohort was performed using a chi-square or 2-tailed \( t \) test. Spearman’s rank correlation was used to examine whether dexamethasone prescription had any impact on rCBV values (assessing the influence of both baseline dexamethasone prescription vs baseline rCBV and dexamethasone prescription at follow-up vs follow-up rCBV). The influence of rCBV, cT1 volume, or FLAIR volume (including initial, residual, or changes between baseline and first follow-up) on progression-free survival (PFS) and overall survival (OS) was assessed with Cox regression analysis. Kaplan-Meier estimates and the log-rank test were used to assess and compare PFS and OS rates. Specifically, patients in the BEV cohort and non-BEV cohort were dichotomized on the basis of an rCBV-threshold that maximized the sum of sensitivity and specificity as a cutoff calculated from receiver operating characteristic (ROC) analysis of 12-month OS data. Univariate logistic regression analysis was performed to assess the predictive value of rCBV, cT1 volume and FLAIR volume (including initial, residual, and changes between baseline and first follow-up) on 6-month PFS and 12-month OS. We performed cross-validation of logistic-regression models with the “leave-one-out” (jackknife) procedure because performance of a predictive model is overestimated when it is simply determined on the sample of subjects used to construct the model (ie, it does not indicate how well the model will do when used to make new predictions for data not previously examined). \( P \) values \(< .05 \) were considered significant.

### Results

Table 1 encompasses details on the analyzed imaging metrics. rCBV values at baseline were balanced between the BEV cohort (median, 4.3; range, 0.3–8.9) and non-BEV cohort (median, 3.2; range 0.6–12.8) \( (P = .22) \). In contrast, rCBV values at first-follow-up were significantly lower in the BEV cohort as compared with the non-BEV cohort (median change of \(-38\% \) with a median rCBV of 2.7 in the BEV cohort and \(+34\% \) with a median rCBV of 4.0 in the non-BEV cohort; \( P < .01 \), respectively). There was no significant association between rCBV values and dexamethasone prescription in any cohort at the time of baseline or follow-up MRI \( (P = .07 \) and .48 in the BEV cohort and \( P = .09 \) and .28 in the non-BEV cohort). Tumor volumes

| Table 1. Analyzed imaging metrics in the bevacizumab and non-bevacizumab cohorts |
|----------------------------------|-----------------|------------------|
| \( \text{rCBV}_{\text{baseline}} \)            | 4.3 (0.3–8.9)  | 3.2 (0.6–12.8)  |
| \( \text{rCBV}_{\text{first follow-up}} \)    | 2.7 (0.3–8.6)  | 4.0 (0.7–10.9)  |
| \( \text{rCBV change} \)                      | \(-38\% \) (–87% to +185%) | +34\% (–70% to +324%) |
| \( \text{cT1 volume}_{\text{baseline}} \)     | 8.3 (0.6–54.0) | 10.8 (0.2–60.8) |
| \( \text{FLAIR volume}_{\text{baseline}} \)  | 100.4 (7.5–384.5) | 86.2 (14.0–299.4) |
| \( \text{cT1 volume}_{\text{first follow-up}} \) | 4.1 (0.1–126.5) | 18.2 (0.4–91.8) |
| \( \text{FLAIR volume}_{\text{first follow-up}} \) | 62.0 (4.5–248.2) | 132.4 (28.7–326.6) |
| \( \text{cT1 volume change} \)                | \(-52\% \) (–99% to +375%) | +61\% (–68% to +2516%) |
| \( \text{FLAIR volume change} \)              | \(-40\% \) (–88% to +817%) | +22\% (–69% to +992%) |

Abbreviations: BEV, bevacizumab; cT1, contrast-enhancing T1; FLAIR, fluid-attenuated inversion recovery; rCBV, relative cerebral blood volume. Annotation: *group differences evaluated using a 2-tailed \( t \) test; tumor volumes are given in cm.
at baseline were well balanced between the BEV cohort and non-BEV cohort (median cT1 and FLAIR volumes of 8.3 and 100.4 in the BEV and 10.8 and 86.2 in the non-BEV cohort). In contrast, both cT1 and FLAIR volumes at first follow-up were significantly lower in the BEV cohort (median change of $-52\%$ and $-40\%$ to a median volume of $4.1\%$ and $62.0\%$) as compared with the non-BEV cohort (median change of $+61\%$ and $+21\%$ to a median volume of $18.2\%$ and $132.4\%$) ($P = .02$ for cT1 volume) ($P < .01$ for FLAIR volume as well as cT1 and FLAIR volume change).

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Fig. 1. Kaplan-Meier plot for overall survival (OS) and progression-free survival (PFS) (A and B) for all patients stratified by treatment administered (bevacizumab [BEV] vs non-BEV chemotherapy), (C and D) for patients in the BEV cohort stratified by the median baseline relative cerebral blood volume (rCBV), and (E and F) for patients in the non-BEV cohort stratified by the median baseline rCBV.
Progression-free Survival and Overall Survival

Median OS and PFS rates were significantly higher in the BEV cohort (9.7 and 4.5 months, respectively) as compared with the non-BEV cohort (6.3 and 2.6 months, respectively) (P = .01 for OS and P < .001 for PFS) (Fig. 1A and B). Univariate Cox regression analysis demonstrated a significant association of baseline rCBV with PFS (hazard ratio [HR] = 1.33, P < .01) and OS (HR = 1.30, P < .01) in the BEV cohort, whereas there was no association with PFS (HR = 1.02, P = .70) or OS (HR = 1.04, P = .47) in the non-BEV cohort (Table 2). Using a cutoff of 3.92 (ie, the rCBV-value that maximizes the sum of sensitivity and specificity from ROC analysis of 12-month OS data), median OS and PFS rates for BEV-treated patients with a rCBV value of ≤3.92 were 14.2 and 6.0 months as compared with 6.6 and 2.8 months for BEV-treated patients with a rCBV value of >3.92 (P < .01, respectively) (Fig. 1C and D; Fig. 2).

The cT1 volume at baseline was not predictive of PFS or OS in the BEV cohort, whereas it was predictive of OS (but not PFS) in the non-BEV cohort on univariate Cox regression analysis. The FLAIR volumes at baseline were not predictive of PFS or OS in any cohort (Table 2).

Univariate Cox regression analysis also demonstrated a significant association of rCBV at first follow-up with PFS (HR = 1.34, P < .01) and OS (HR = 1.31, P < .01) in the BEV cohort but not in the non-BEV cohort, whereas the relative change in rCBV was not associated with PFS or OS in any cohort (Table 2).

Logistic Regression Analysis

We evaluated the predictive value of rCBV, cT1 volume, and FLAIR volume (including initial, residual, or changes between baseline and first follow-up) on 6-month PFS and 12-month OS (Table 3). Overall, 70%/89% of participants in the BEV/non-BEV cohort showed progression within 6 months, and 69%/86% of participants in the BEV/non-BEV cohort died within 12 month after treatment initiation.

For the BEV cohort, rCBV at baseline and first follow-up, as well as the cT1 and FLAIR volumes at first follow-up, were significant predictors of 6-month PFS and 12-month OS (Table 3). Overall, baseline rCBV demonstrated the best performance and correctly predicted 6-month PFS in 81.7% and 12-month OS in 78.9% of participants (P = .01 and <.001, respectively). None of the analyzed imaging metrics was a significant predictor of 6-month PFS or 12-month OS in the non-BEV cohort.

Following BEV-failure, the majority of participants received supportive care only (55% in the BEV cohort and 50% in the non-BEV cohort), whereas chemotherapy was administered

Table 2. Univariate Cox regression analysis for progression-free survival and overall survival

<table>
<thead>
<tr>
<th>Radiological parameters</th>
<th>Progression-free Survival</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEV Cohort</td>
<td>Non-BEV Cohort</td>
</tr>
<tr>
<td>rCBVbaseline&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; .01</td>
<td>1.33 (1.17–1.52)</td>
</tr>
<tr>
<td>rCBVfirst follow-up&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt; .01</td>
<td>1.34 (1.19–1.51)</td>
</tr>
<tr>
<td>rCBV change&lt;sup&gt;b&lt;/sup&gt;</td>
<td>.48</td>
<td>1.10 (0.74–1.65)</td>
</tr>
<tr>
<td>cT1 volumebaseline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.22</td>
<td>1.15 (0.92–1.45)</td>
</tr>
<tr>
<td>FLAIR volumebaseline&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.91</td>
<td>1.00 (0.97–1.03)</td>
</tr>
<tr>
<td>cT1 volumefirst follow-up&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; .01</td>
<td>1.28 (1.16–1.41)</td>
</tr>
<tr>
<td>FLAIR volumefirst follow-up&lt;sup&gt;c&lt;/sup&gt;</td>
<td>&lt; .01</td>
<td>1.07 (1.03–1.12)</td>
</tr>
<tr>
<td>cT1 volume change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>&lt; .01</td>
<td>2.26 (1.76–2.91)</td>
</tr>
<tr>
<td>FLAIR volume change&lt;sup&gt;d&lt;/sup&gt;</td>
<td>.02</td>
<td>1.22 (1.04–1.43)</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&lt;sup&gt;e&lt;/sup&gt;</td>
<td>.14</td>
<td>1.02 (0.99–1.04)</td>
</tr>
<tr>
<td>KPS&lt;sup&gt;f&lt;/sup&gt;</td>
<td>.18</td>
<td>0.87 (0.70–1.07)</td>
</tr>
</tbody>
</table>

Abbreviations: BEV, bevacizumab; CI, confidence interval; cT1, contrast-enhancing T1; FLAIR, fluid-attenuated inversion recovery; HR, hazard ratio; OS, overall survival; KPS, Karnofsky performance score; PFS, progression-free survival; rCBV, relative cerebral blood volume.

Annotation: given HR correspond to:
<sup>a</sup>one-unit increase in rCBV.
<sup>b</sup>1% change in rCBV.
<sup>c</sup>10 unit (10 cm<sup>3</sup>) increase in the tumor volume.
<sup>d</sup>1% change in tumor volume.
<sup>e</sup>1 year increase in age.
<sup>f</sup>10% increase in KPS.
for the majority of remaining cases (34% in the BEV cohort and non-BEV cohort, respectively) (Supplementary Table S3 encompasses detailed information on postprogression therapy). There was no significant difference in the probability of receiving postprogression therapy between participants in the BEV cohort and non-BEV cohort ($P = .81$).

**Discussion**

This study demonstrates that pretreatment rCBV analysis qualifies as a potential predictive imaging biomarker for BEV-treated rGB (but not for alkylating chemotherapy-treated rGB) that is superior to volumetric analysis of conventional anatomic MRI and correctly predicts 6-month PFS and 12-month OS in 80% of BEV-treated patients.

Several studies assessed the early changes in perfusion (by means of rCBV) and permeability (by means of the volume transfer constant [$K_{trans}$], an estimate related to microvascular permeability) on DSC and DCE-MRI for predicting response to BEV in rGB and produced controversial results. A study by Zhang et al showed that the early reduction in $K_{trans}$ (measured 96 h after treatment initiation) was neither associated with PFS nor OS. This was confirmed by a subsequent study of Verheoef et al showing that the extent of early reduction in rCBV or $K_{trans}$ (measured 4 days prior and 3 and 21 days following treatment initiation with BEV and dose-intense temozolomide) had no impact on disease outcome in recurrent high-grade gliomas.
grade glioma (including 15 rGB and 8 anaplastic astrocytoma cases). These 2 studies contradicted the results reported by Sorensen et al on cediranib (a pan-VEGF inhibitor) in 31 patients with recurrent GB. A greater reduction in $k_{\text{trans}}$ and a greater increase in rCBV (measured 1 day prior and 1 day after application of a single dose of cediranib) was associated with significantly longer OS and PFS. Overall, it is difficult to draw conclusions from these limited and heterogeneous patient populations that have, in part, contradicting results.

Verhoeff et al also evaluated perfusion and permeability prior to initiation of BEV treatment and showed that baseline rCBV was associated with OS. This initial observation was further strengthened in a recently published study by Schmainda et al who performed rCBV analysis prior to and at first follow-up after BEV treatment initiation in a rather heterogeneous population of recurrent high-grade gliomas (23 primary GBs, 4 secondary GBs, 6 anaplastic astrocytomas, and 3 anaplastic oligodendrogliomas). rCBV-analysis at baseline prior to BEV treatment stratified OS but not PFS, whereas rCBV analysis at first follow-up stratified both OS and PFS. The results from these promising initial studies with a more heterogeneous patient cohort, including both anaplastic gliomas as well as primary and secondary GBs, led to the present confirmatory series with a larger sample size, a control group, and a focus on primary rGB. With the results from the present study, we now provide evidence that pretreatment rCBV is not a prognostic, but rather a potential predictive, imaging biomarker for BEV-treated rGB because it was associated exclusively with treatment outcome in the BEV cohort (but not in the non-BEV cohort). These results are particularly important since there are currently—apart from the assessment of the lower Gaussian apparent diffusion coefficient (ADC) curve—which requires sophisticated postprocessing—no acceptable pretreatment imaging biomarkers for judicious selection of patients with rGB who may achieve maximum benefit from BEV. Therefore, it would be of interest to also determine if a combined analysis of rCBV and the lower ADC curve may further improve the stratification of patients in their response to BEV treatment.

Despite the straightforward results of the present study, we must acknowledge that the retrospective nature of the present study has certain limitations regarding patient selection and distribution of epidemiological and clinical characteristics between the BEV cohort and non BEV cohort. Specifically, one potential confounding issue is the phenomenon of early or delayed radiochemotherapy treatment-related imaging changes (ie, pseudoprogression/radiation necrosis), which presents as increasing lesion volume or new contrast enhancement on MRI suggestive for tumor progression. Because the enhancement seen in pseudoprogression/radiation necrosis can be mistaken for tumor progression, patients may be routed to BEV as treatment for tumor recurrence that has been observed to decrease the permeability of not only tumor-related leaky vasculature but also of radiation-induced leaky vasculature. The absence of histological confirmation, which would be the gold-standard for ruling out pseudoprogression/radiation necrosis, is another limitation of the present study. However, considering the available literature on rCBV-thresholds that are suggestive of radiation necrosis (rCBV < 1.5–1.8), it is rather unlikely that the long-term survival in our study was related to the presence of radiation necrosis (median rCBV of 2.5 for patients surviving >12 months following BEV treatment).

A methodological limitation of the present study was the use of 2 different MR systems; despite comparative assignment of patients to the different scanner types and identical sequence parameters, results might have been biased without

### Table 3. Univariate logistic regression analysis for predicting 6-month progression-free survival and 12-month overall survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>6-month Progression-free Survival</th>
<th>12-month Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BEV Cohort</td>
<td>Non-BEV Cohort</td>
</tr>
<tr>
<td></td>
<td>$P$ Value*</td>
<td>Correctly Classified</td>
</tr>
<tr>
<td>CBV$_{\text{baseline}}$</td>
<td>&lt;.01</td>
<td>81.7%</td>
</tr>
<tr>
<td>rCBV$_{\text{first follow-up}}$</td>
<td>&lt;.01</td>
<td>77.5%</td>
</tr>
<tr>
<td>FLAIR volume$_{\text{baseline}}$</td>
<td>.86</td>
<td>n.s.</td>
</tr>
<tr>
<td>cT1 volume$_{\text{baseline}}$</td>
<td>.42</td>
<td>n.s.</td>
</tr>
<tr>
<td>FLAIR volume$_{\text{first follow-up}}$</td>
<td>.92</td>
<td>n.s.</td>
</tr>
<tr>
<td>FLAIR volume$_{\text{first follow-up}}$</td>
<td>.01</td>
<td>74.7%</td>
</tr>
<tr>
<td>cT1 volume$_{\text{change}}$</td>
<td>.04</td>
<td>67.6%</td>
</tr>
<tr>
<td>FLAIR volume$_{\text{change}}$</td>
<td>.05</td>
<td>67.6%</td>
</tr>
<tr>
<td>cT1 volume$_{\text{change}}$</td>
<td>.02</td>
<td>71.8%</td>
</tr>
</tbody>
</table>

Abbreviations: BEV, bevacizumab; CT1, contrast-enhancing tumor; FLAIR, fluid-attenuated inversion recovery; n.s., not significant; OS, overall survival; PFS, progression-free survival; rCBV, relative cerebral blood volume.

Annotation: * logistic regression was performed with the “leave-one-out” (jackknife) cross-validation procedure.
the use of additional normalization of rCBV-maps (eg, Gaussian normalization). Whether all of these limitations influenced the analyzed outcome measures remains to be proven. Post hoc analysis of DSC-MRI from the ongoing EORTC-26101 trial, which compares BEV + lomustine with lomustine alone in patients with rGB at first recurrence, may allow prospective validation of whether rCBV is a predictive imaging biomarker in the setting of BEV-treated rGB.

In conclusion, we have demonstrated the potential utility of pretreatment rCBV analysis as a predictive imaging biomarker for BEV-treated rGB (but not for alkylating chemotherapy-treated rGB), which is superior to volumetric analysis of conventional anatomic MRI and correctly predicts 6-month PFS and 12-month OS in 80% of BEV-treated patients. Thus, pretreatment rCBV analysis deserves validation in prospective randomized trials because it may allow judicious preselection of patients who could obtain maximum benefit from BEV-treatment.

**Supplementary Material**

Supplementary material is available at Neuro-Oncology Journal online (http://neuro-oncology.oxfordjournals.org/).

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