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Original Research

Repeatability and reproducibility of relative cerebral blood volume measurement of recurrent glioma in a multicentre trial setting

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Abstract ***Background:*** Measurement of relative cerebral blood volume (rCBV) with dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) is used extensively for brain tumour diagnosis and follow-up. The aim of this pilot study was to assess the robustness of rCBV measurement in patients with enhancing recurrent glioma in a European multicentre trial setting.

Methods: We included pre-treatment postcontrast T1 weighted (T1w) and DSC scans of 20 patients with recurrent glioma from 2 European Organisation for Research and Treatment of Cancer trials (26101 and 26091). Three reviewers independently placed a fixed circular region of interest of 70 mm^2 in the tumour area of highest rCBV ($rCBV_{max}$). To calculate the normalised $rCBV_{max}$ ($nrCBV_{max}$), three ROIs were placed in the anterior, middle and posterior centrum semiovale normal-appearing white matter of the contralateral hemisphere. After several months, each observer repeated the assessments blinded for initial findings. Repeatability and reproducibility were estimated with a mixed model. Each measurement was also classified according to 4 clinically meaningful categories.

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Results: Three patients were post hoc excluded from analysis because of lack of enhancing tumour. The mean $nrCBV_{max}$ repeatability was 49.5%, and reproducibility was 5.5%. In 14 of 17 patients, at least 2 reviewers classified the patient into the same category.
Conclusions: Our results indicate that a well-established review process needs to be applied upfront to assess perfusion in a multicentre trial setting. While awaiting further validation, we propose as a strategy to measure rCBV in the context of recurrent glioma trials to use two central reviewers and an adjudicator in case of disagreement.

1. Introduction

Dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) is widely used for brain tumour diagnosis and follow-up. Relative cerebral blood volume (rCBV) has been shown to correlate with tumour grade and overall survival and to differentiate tumour progression from treatment effects such as pseudoprogression and radiation necrosis [1,2]. With the advent of antiangiogenic treatment for primary brain tumours, there is even more interest in the measurement of tumour perfusion as a surrogate marker of angiogenesis to assess treatment effects [3,4].

DSC perfusion MRI relies on the T2- and T2*-shortening effects of gadolinium-based contrast media. Exact quantification of CBV is not possible with DSC MRI; hence, the term rCBV is used for semiquantitative assessment. The problem that remains is that measuring rCBV is highly operator dependent regarding two important aspects: determining the region of interest (ROI) that serves as a reference region to normalise the rCBV and determining the area of maximum rCBV in the pathological tissue. As yet, there is no agreed standardised method to measure the rCBV ratio. With the increasing publication of various threshold values, it is important to know to what extent user-dependent variability is an issue. This is even more pressing in the context of multicentre trials, if quantification of rCBV is to be used for assessing treatment effects.

The purpose of this pilot study was to assess intra- and inter-reviewer reliability of rCBV measurement in patients with enhancing recurrent glioma in a European multicentre trial setting.

2. Methods

2.1. Study population

We included patients from two recently concluded trials by the European Organisation for Research and Treatment of Cancer (EORTC) in recurrent glioma (EORTC26101 [5] and EORTC26091 [6]), providing a case mix of enhancing tumours of different grades. All relevant patient eligibility criteria and scanning procedures are listed in Supplements 1 and 2, respectively. A convenience sample of the baseline (i.e. before trial treatment) imaging studies which included DSC MRI of the first ten patients from each trial was considered for the present study. Both trials were approved by the internal review boards of the participating sites, and written informed consent was obtained from all included patients.

2.2. rCBV measurement

Measurements were performed using IB Neuro plugin (v1.1; Imaging Biometrics, LLC, Elm Grove, WI, USA) implemented in OsiriX (v5.7; Pixmeo Sarl, Geneva, CH) by three experienced neuroradiologists (M.B., M.S. and A.P.) independently, referred to as reviewers X, Y and Z (not in that order). Measurements using a case record form (Supplement 3) were performed twice by each reviewer, an average of 4.6 months apart (range, 2.4–11.1 months).

ROI size and shape were predefined as a circular ROI of 70 mm^2. Each reviewer placed their own ROIs (Fig. 1). To calculate the normalised rCBV (nrCBV), three ROIs were placed in the anterior, middle and posterior centrum semiovale normal-appearing white matter (NAWM) of the contralateral hemisphere. These were superimposed on the postcontrast T1w images using National Institutes of Health–colour coding. The reviewers were encouraged to place multiple ROIs in the tumour to select the highest nrCBV ($nrCBV_{max}$). This method was previously shown to be most reproducible within and between reviewers [7].

One reviewer (M.S.) additionally measured enhancing tumour size as the product of bidimensional diameters [8] and noted any potential issues with assessing $nrCBV_{max}$. Patients with lack of clear tumour enhancement (n = 3) were excluded from the analysis as these did not fulfil the eligibility criteria of the study.

2.3. Statistical analysis

Statistical analysis was performed at EORTC-HQ (S.C.). Mean and standard deviation of the $nrCBV_{max}$ ROI were used for analyses. The natural logarithm of

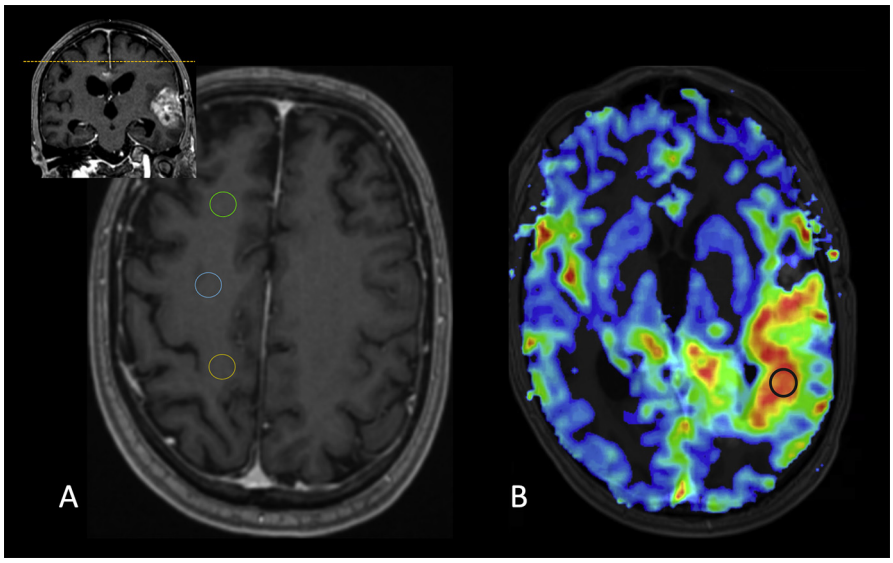

Fig. 1. Placement of ROIs in the (A) NAWM and (B) tumour to obtain the measurement of $nrCBV_{max}$. (A) On the anatomical imaging data, three ROIs were placed in the anterior, middle and posterior centrum semiovale, defined as the normal-appearing white matter (NAWM) of the hemisphere contralateral to the tumour at the level of one slice (±5 mm) superior to the lateral ventricles. rCBV was calculated with automated arterial input function detection using IB Neuro's proprietary algorithm and normalised to the average of the three NAWM ROIs. (B) Using a hotspot technique, an ROI was placed over the area of maximum nrCBV within the tumour, while care was taken to exclude blood vessels and grey matter. $nrCBV_{max}$, normalised highest relative cerebral blood volume; nrCBV, normalised rCBV; rCBV, relative cerebral blood volume; ROI, region of interest.

the mean $nrCBV_{max}$ was used as these transformed values were approximately normally distributed.

The repeatability coefficient (RC) and limits of agreement were calculated for each reviewer based on the two measurements of each patient's scan [9].

For assessment of reliability, a linear mixed model was used, and the intraclass correlation (ICC) was calculated as an indicator of consistency of repeated measures relative to the total variability of log-transformed mean $nrCBV_{max}$ among the included patients.

Finally, mean $nrCBV_{max}$ was categorised into four clinically meaningful categories: (1) reduced (mean $nrCBV_{max} < 1.0$); (2) minimally increased (mean $nrCBV_{max} = 1.0–2.5$); (3) moderately increased (mean $nrCBV_{max} = 2.5–5.0$) and (4) strongly increased (mean $nrCBV_{max} > 5.0$). Weighted Kappa coefficient and the exact 95% confidence interval (CI) were calculated to evaluate the agreement overall and per reviewer.

3. Results

3.1. Study population

All patients had been included in the trials at first tumour recurrence, and none had received anti-angiogenic treatment at this point. Of the 20 included patients, 3 (all with glioblastoma, 2 men, none using corticosteroids, all with biopsy/surgery at time of tumour recurrence) had no clearly enhancing lesion and were post hoc excluded from the analysis as per the eligibility criteria. The remaining 17 patients had been scanned at 5 different sites. Patient and disease characteristics are detailed in Table 1.

3.2. Data quality and measurements

Of the 17 patients available for analysis, 12 had assessable imaging data sets without any obvious issues (patients 1–12). The remaining 5 patients were retained in the analysis, but had the following issues: one patient had a mostly hemorrhagic lesion with the presence of extensive susceptibility artefacts (patient 13), and four patients had extensive white matter lesions in the contralateral centrum semiovale (patients 14–17). Four patients had multifocal brain lesions (patients 5, 10, 12 and 14). The median size of the largest lesion was 432 mm^2 (range, 120–2088 mm^2).

Mean $nrCBV_{max}$ measured by each of the three reviewers (X, Y and Z) at the first and second reviewing round is shown in Fig. 2. Mean $nrCBV_{max}$ was increased (>1.0) in all patients, except in one (patient 7), in whom one reviewer (Y) consistently measured a mean $nrCBV_{max}$ of < 1.0. This could not be explained by tumour multifocality or issues with raw data quality.

3.3. Repeatability and reproducibility

Fig. 3 indicates that there was no systematic bias in the measurement of mean $nrCBV_{max}$ (i.e. there was no significant difference of the mean difference) for each of the

Table 1
Patient and disease characteristics.

	All patients (N = 17)
Age at entry of trial, years	
Mean (standard deviation)	48 (12)
Range	23–67
Gender, N (%)	
Male	11 (64.7)
Female	6 (35.3)
Histologically confirmed diagnosis[a], N (%)	
Astrocytoma WHO grade II	6 (35.3)
Oligoastrocytoma WHO grade II	1 (5.9)
Astrocytoma WHO grade III	2 (11.8)
Oligodendroglioma WHO grade III	1 (5.9)
Glioblastoma	7 (41.2)
Number of brain lesions	
1	12 (70.6)
2	5 (29.4)
Prior chemotherapy given, N (%)	
No	8 (47.1)
Yes: temozolomide or other anticancer agent	9 (52.9)
Prior irradiation given, N (%)	
No	1 (5.9)
Yes: radiotherapy (total dose ≤65 Gy)	16 (94.1)
Biopsy/surgery at time of tumour recurrence, N (%)	
No	16 (94.1)
Yes	1 (5.9)
Corticosteroids intake, N (%)	
No	11 (64.7)
Yes: stable/decreasing dose for 7 days before baseline scan	6 (35.3)

WHO, World Health Organisation.
[a] Histopathological diagnosis was established at the time of initial diagnosis. Upon trial entry, tumours may have progressed to a higher grade.

reviewers. Repeatability was marginally acceptable for reviewer X (50%) and Z (66%; based on 16 patients because one measurement was missing from round 2), but unacceptable for reviewer Y (144%).

The linear mixed model (Table 2) shows high between-patient variance, indicating that the patient population is very heterogeneous. This leads to a high ICC for all reviewers because of the fact that the variability between or within reviewers does not exceed the variability of the patients themselves.

None of the patient, disease or scan characteristics explained the heterogeneity between patients or between reviewers (Supplement 4).

For the categorical assessment (Table 3), the results were similar: intra-reviewer reliability was generally good (Kappa>0.6, for each reviewer), but CIs were large (Supplement Figure 1). The overall weighted Kappa was 0.66 (95% CI: 0.45, 0.88), which is similar to the results from the linear mixed model. In 7 of 17 patients, there was 100% 'categorical' agreement between and within reviewers, namely, patient 9 with mean $nrCBV_{max}$ >5; patients 3, 4 and 8 with a mean $nrCBV_{max}$ of 2.5–5 and patients 1, 5 and 10 with a mean $nrCBV_{max}$ of 1.0–2.5. In 14 of 17 patients, at least two reviewers classified the patient in the same category.

4. Discussion

In this multicentre, multi-observer pilot study, we found only modest repeatability and reproducibility of measuring perfusion in recurrent glioma. This was the

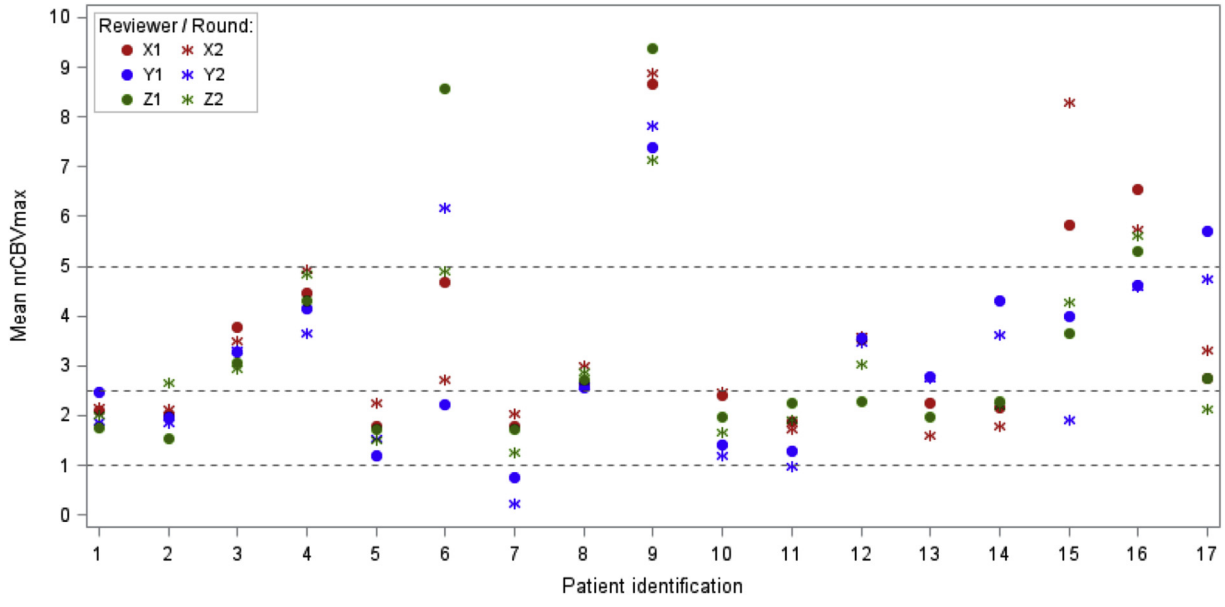

Fig. 2. Measurements of mean $nrCBV_{max}$ from the region within the tumour with the highest value per reviewer per round. The horizontal lines indicate the clinically relevant cut-off values of reduced, and minimally, moderately and strongly increased mean $nrCBV_{max}$. $nrCBV_{max}$, normalised highest relative cerebral blood volume.

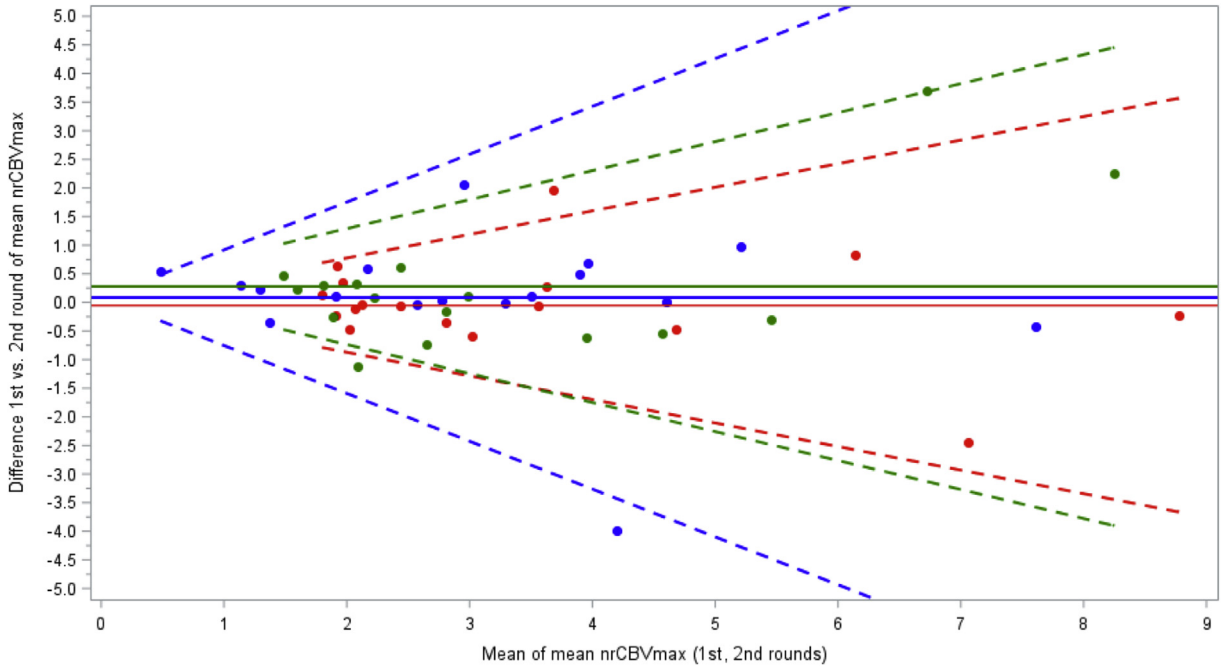

Fig. 3. Bland–Altman plot of the difference between the two reviewing rounds for each of the three reviewers. In red, reviewer X; in blue, reviewer Y and in green, reviewer Z. For each of the reviewers, the dashed lines indicate the limits of agreement (LOA); the solid lines indicate the overall mean of the differences of mean $nrCBV_{max}$ between test and retest for each of the reviewers. The repeatability coefficient RC_{ln} was defined as $1.96 \times SD_{ln}$, where SD_{ln} is the standard deviation of the difference of log-transformed mean $nrCBV_{max}$ between the two rounds of measurement. The LOAs were defined as mean of log-transformed mean $nrCBV_{max} \pm RC_{ln}$ and their 95% confidence interval (CI) being LOAs $\pm 1.96 \times \sqrt{(3 \times SD_{ln}^2/n)}$ where n is the number of patients reviewed. As the difference of two logarithms is equal to the logarithm of the ratio, the estimates (RC, LOAs, 95% CI for LOAs) can be back-transformed using exponential transformation. The different estimates correspond on the new scale to the ratio of one measurement (round 1) related to the other one (round 2). $nrCBV_{max}$, normalised highest relative cerebral blood volume; RC, repeatability coefficient.

Table 2
Reliability (linear mixed model, intraclass coefficient [ICC]).

	X	Y	Z[a]	All
Between-patient variance (σ_p^2)	0.238	0.436	0.243	0.250
Within-patient/reviewer variance (σ_ε^2)	0.022	0.104	0.034	0.108
Between-reviewer variance (σ_o^2)	–	–	–	0.006
ICC (95% CI)	0.92 (0.80, 0.97)	0.81 (0.59, 0.93)	0.88 (0.72, 0.95)	0.69 (0.50, 0.83)

Linear mixed model was defined as follows: $\ln(Y_{ij}) = \beta_0 + p_i + r_j + \varepsilon_{ij}$ where Y_{ij} is the estimated mean of $nrCBV_{max}$ for patient I by reviewer J, β is a fixed intercept parameter and p_i (patient random effect), r_j (reviewer random effect) and ε_{ij} (error) are independent random effects which are normally distributed with mean 0 and variances σ_p^2, σ_r^2 and σ_ε^2, respectively. The large difference between reviewer Y and reviewers X and Z indicates the need for a complete linear mixed model with reviewer as a random factor. With this model (final column: 'All'), variability between patients was still high (0.250), but variability within patients/reviewers increased substantially, resulting in a decrease of ICC to 0.69. This can again be mainly attributed to the high repeatability coefficient of reviewer Y. The ICC is the proportion of measurement error that is not associated with reviewer error and is defined as $ICC_{ln} = \sigma_p^2/(\sigma_p^2 + \sigma_r^2 + \sigma_\varepsilon^2)$.

[a] Reviewer Z, in some cases, reported the average of multiple hotspot measurements.

case for absolute and categorical measurements of mean $nrCBV_{max}$. These findings could not be unequivocally attributed to the reviewer, patient or scan characteristics. On the other hand, most patients were classified in the same category by two reviewers.

Perfusion imaging is widely used in current clinical practice of glioma imaging and is also of considerable interest in the context of clinical trials. As a semi-quantitative parameter of tumour physiology, rCBV is a potential *in vivo* biomarker of the biological effect of treatment. For a perfusion measurement—in terms of rCBV—to be used as a biomarker, however, it needs to not only reflect the biological mechanism or clinical condition but also be quantitative, reliable and robust. To assess response, it is adamant that an observed change due to treatment is greater than the intrinsic and extrinsic variability of the biomarker in the absence of treatment. The Quantitative Imaging Biomarkers Alliance initiative stipulates that to this end an assessment of all sources of variability is required [10]. These include acquisition, physiology and post-processing.

In terms of acquisition, Shin *et al.* [11] reported high reliability and reproducibility of quantitative DSC perfusion using a bookend approach, which includes T1 mapping for calibration with a fully automated post-

Table 3
Categorical assessment of $nrCBV_{max}$.

			Round 1												
			X	Y	Z[a]	X	Y	Z[a]	X	Y	Z[a]	X	Y	Z[a]
			<1			1–2.5			2.5–5			≥5		
Round 2	X	<1	**0**			0			0			0		
	Y			**1**			1			0			0	
	Z[a]				**0**			0			0			0
	X	1–2.5	0			**8**			0			0		
	Y			0			**4**			1			0	
	Z[a]				0			**6**			1			0
	X	2.5–5	0			0			**6**			0		
	Y			0			0			**7**			1	
	Z[a]				0			2			**4**			1
	X	≥5	0			0			0			**3**		
	Y			0			1			0			**1**	
	Z[a]				0			0			0			**2**

Bold value represents agreement between round 1 and round 2.
$nrCBV_{max}$, normalised highest relative cerebral blood volume.
[a] Reviewer Z, in some cases, reported the average of multiple hotspot measurements. For the second round, one measurement is missing from reviewer Z.

processing pipeline in a scan–rescan study. Caseiras *et al.* [12] also demonstrated the robustness of acquiring rCBV in a dual institutional setting by showing differences in progression free survival (PFS) when patients were stratified according to an rCBV threshold value of 1.75. Assessing both within-scanner and physiological variations, Jafari-Khouzani *et al.* [13] established high to excellent repeatability of dual-echo DSC perfusion with scanning being performed 1–5 days apart. In this study, user bias was explicitly avoided by using a single rater and then copying the ROIs to all images. The coefficient of variation was found to be below 11%.

With regard to post-processing, at least two aspects need to be considered: the post-processing software or algorithms that are used to estimate rCBV and the methodology of rCBV measurements, which includes the definition and placement of the ROIs and which is generally rater dependent. Several studies have shown that differences in software or applied algorithms are a large source of variability of measured values [14,15]. We used post-processing software that was previously used successfully in a clinical trial context similar to ours and which incorporates methodology to correct for well-known issues such as contrast leakage [16].

ROI placement, both within the tumour and for reference measurement in the NAWM, is highly variant in the published literature. In a single-centre study of 22 patients, Jung *et al.* compared several methods of normalised CBV measurement and reported very high ICCs, both for intra- and inter-rater assessment (0.997 and 0.98–0.99, respectively) [17]. A major difference with our study is that mean normalised CBV was measured for the entire tumour. Their assessment therefore relied more on tumour segmentation than on identification of $rCBV_{max}$. Owing to intratumoural heterogeneity, however, the definition and placement of the ROI to capture the area of highest rCBV is critically important [3]. Wetzel *et al.* [7] assessed several methods to this end and found clinically acceptable intraobserver and interobserver reproducibility (ICC = 0.71) of maximum rCBV measurement. A major difference with our study is that Wetzel *et al.* provided their three reviewers with rCBV maps for placing tumour ROIs that were already normalised by a single reviewer, rather than having all reviewers place the ROIs in the NAWM for normalisation. The measured variation of NAWM measures in their study was 20%, which is an important source of variability that was thus not taken into account. In a very recent study by Anzalone *et al.*, two reviewers independently calculated rCBV ratios in 94 patients with newly diagnosed glioma of different grades and reported a high ICC of 0.86, using methodology very similar to ours. Clearly, there was a difference in the patient population (newly diagnosed versus recurrent tumour), and it is also conceivable that a setting of two reviewers from the same institution is different from ours, with three reviewers in three different institutions. Most importantly, though, there is only an *apparent* discrepancy between our study and those published previously: we also found high ICCs (0.69–0.92), but noted that this is due to the fact that the variability between or within reviewers does not exceed the variability of the patients themselves.

An important implication of modest reproducibility and repeatability of rCBV measurement is that the effect size for reliable assessment needs to be large. Several studies have specifically addressed this. In a phase I assessment of an antiangiogenic agent, Akella *et al.* [3] defined thresholds for treatment effect in a multicentre setting of 4 participating sites with 1.5T scanners from multiple vendors and a single observer. Decreases of 8–36% were observed in patients with response, and conversely, increase was observed in progression. The findings were very variable with substantial intratumoural heterogeneity. Jackson *et al.* [18] reported that a minimum change of 15% in nrCBV was required to confidently detect group differences. The CIs of repeat measurements within a single patient were much wider, such that the minimum change required at the individual patient level was about 25%. Jafari-Khouzani *et al.* found an RC, reflecting how much change should occur to be considered significant, of as much as 42% in the individual patient.

A further important implication is that the various published threshold values cannot be applied directly to individual patients in a clinical setting nor to groups of patients in the context of a clinical trial. Even when using broad categories of $nrCBV_{max}$ values such as in our study, there was considerable disagreement between and within raters. On the other hand, most patients were classified in the same category by two of the three reviewers.

Based on our findings, we propose as a strategy for the use of $nrCBV_{max}$ in clinical trials that measurements

are performed by two central reviewers and that a third reviewer is used as an adjudicator in cases of disagreement (Fig. 4). It cannot be stressed enough that although perfusion MRI is a relatively simple technique, it requires strict protocols, careful acquisition, accurate contrast agent dosing and injection rate, image timing and image post-processing and analysis for quantification.

This pilot study has a few limitations. First, we only included patients with recurrent enhancing tumour, in which perfusion is expected to be high. We focused on these patients as increased perfusion is of most clinical relevance. However, this does mean that tumours with low perfusion are underrepresented, so we cannot make any inferences on reproducibility or repeatability in low-grade or low perfusion tumours. Second, one of the reviewers deviated from the protocol by reporting the average rather than the maximum ROI measurement. This reviewer's performance was not notably worse than the others'. Third, of the 20 included patients, 3 were post hoc excluded because they did not fulfil the inclusion criterion of the presence of an enhancing lesion. This reduced our intended sample size, but does not invalidate our findings. This pilot study requires further validation; its findings serve to design larger confirmatory studies with prospective collection and assessment of imaging data as well as appropriate sample size and statistical design [19].

5. Conclusion

To the best of our knowledge, we report on the first multicentre, multi-observer study taking into account all aspects of variability in measuring maximum nrCBV in enhancing recurrent glioma. Despite carefully designed standardised operating procedures, repeatability and reproducibility in this pilot study were only modest, even when broad categories of rCBV measurements were considered. While awaiting further validation, we propose that for clinical trials, all aspects of perfusion MRI are standardised and recorded, imaging quality is carefully scrutinised and a central review is performed with two raters and an adjudicator in cases of disagreement. Importantly, rCBV thresholds derived from the published literature should be applied with the greatest care to individual patients with glioma.

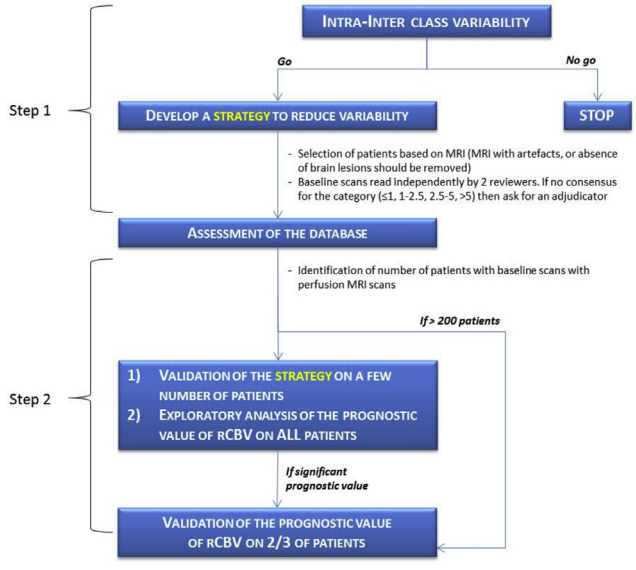

Fig. 4. Strategy for the assessment of the prognostic value of rCBV. MRI, magnetic resonance imaging; rCBV, relative cerebral blood volume.

Conflict of interest statement

No financial relationships directly related to the study are reported. Outside the context of the present study, the following relationships are reported: Dr. Smits receives compensation (paid to institution) as independent reviewer for Parexel Ltd for EORTC-1410 and received speaker fees (paid to institution) from GE Healthcare and travel compensation from Quantib BV and GE Healthcare; Dr. Bendszus reports personal fees from Vascular Dynamics, grants and personal fees from Novartis, personal fees from Roche, grants and personal fees from Guerbet, grants from Siemens, grants from Hopp Foundation, grants from Stryker, grants from Medtronic, personal fees from Teva, grants and personal fees from Codman, grants and personal fees from Bayer, personal fees from Boehringer Ingelheim and personal fees from B. Braun, outside the submitted work; Dr. Postma has speaker agreements with Bayer and Siemens; Dr. Clement's institution receives a research grant from MSD; Dr. Wick has participated in a speaker's bureau for and has received research funding from MSD, received research funding from Apogenix, Boehringer Ingelheim, Genentech, Roche and Pfizer and has a consultant relationship with BMS, Celldex and Genentech/Roche and Dr. Van den Bent receives study support and honoraria from Roche. Ms. Collette, Dr. Dhermain, Dr. Hagenbeek,Dr. Liu and Prof. Heiland report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.03.007.

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