Glioblastoma (GB) is the most malignant and most common primary brain tumor in adults. It is characterized by rapid proliferation and highly aggressive and invasive growth into surrounding brain tissue. Vascular proliferation is a pathological hallmark of GB, which is among the most vascularized of all solid tumors. However, formation of new tumor vessels, also known as neovascularization, is highly defective, resulting in a dis-
organized vasculature with abnormal capillary bed topol-
ygy and increased blood-brain barrier permeability. Neovascularization in GB has high clinical relevance as it correlates with biological aggressiveness, degree of ma-

lignancy, clinical recurrence, and postoperative survival.

Despite ongoing progress in the therapeutic manage-

gment of GB, the prognosis remains poor, with an over-

all survival (OS) of 14–15 months after maximum radical 

cal and safe resection, concomitant radiochemotherapy, 

c and adjuvant chemotherapy. A main reason for the poor 

gnosis is the fact that GB treatment failure and recur-

rence are as yet inevitable and typically occur 6–7 months 

after surgery. Gross-total resection at repeat craniotomy 

of GB recurrence is associated with significantly longer 

OS compared with no surgery or subtotal resection and 

should, therefore, be performed whenever possible in 

patients with recurrent GB. However, early and reliable 
detection of GB recurrence is required to enable the most 

radical repeat resection of the tumor.

The diagnostic management of patients with GB is 

essentially based on MRI techniques. However, even ad-
canced MRI approaches, including measures of perfusion 

and blood volume as well as improved criteria, such as 

those provided by the Response Assessment in Neuro-

Oncology (RANO) group, are limited to reliably distin-
guishing active tumor tissue and tumor progression from 

reactive tissue and pseudoprogression, respectively. This 

ambiguity in GB recurrence detection requires repeated 

follow-up examinations that may result in loss of valuable 
time and further tumor progression. PET, especially with 

amino acid tracers, was recommended as a helpful adjunct 
to MRI for postoperative assessment of GB. PET, how-
ever, has several drawbacks, such as limited availability, 

requirement of an additional examination, and high costs. This makes PET less applicable for serial follow-up ex-

aminations in GB monitoring.

A novel MRI technique, termed vascular architectural 

mapping (VAM), provides deeper insight into tissue micro-

vasculature and tumor neovascularization. The physical 

basis for this MRI-based assessment of micro-

vascular structure is the sensitivity of gradient-echo (GE) 

and spin-echo (SE) MRI to magnetic susceptibili-

ties. As a result, the GE signals, which are commonly 

used in clinical routine MRI (cMRI) with perfusion, are 

dominated by larger vessel diameters (starting from 20 

μm, i.e., larger arterioles and venules), with reduced sen-
sitivity to the smaller microvascular range. In contrast, 

SE signals exhibit a peak sensitivity to the microvascu-

lature at a vessel diameter of around 10 μm, including cap-
i llaries and both small arterioles and venules. Importantly, 

neovascularization at an early stage is clearly dominated 

by very thin vascular structures, which are therefore hard-
l y detectable with the conventional GE perfusion MRI 
techniques used in cMRI protocols.

The purpose of this study was to evaluate the useful-

ness of VAM and SE perfusion MRI for the monitoring 
of GB patients after standard therapy. We investigated the 
diagnostic performance of cMRI and VAM for detection 
of tumor recurrence and quantitatively analyzed the fea-
tures of neovascularization of early- and progressed-stage 

GB recurrence.

**Methods**

**Patient Selection**

A consecutively and prospectively populated institu-
tional database was searched for patients who received 

follow-up MRI examinations after treatment of a GB (WHO grade IV) according to standard of care, i.e., maxi-

mal safe resection and radiotherapy with concomitant and 
adjuvant chemotherapy with temozolomide, between 

July 2015 and June 2019. Further inclusion criteria were 

1) age > 18 years and 2) available data obtained by use of 

our study MRI protocol from two or more follow-up 

examinations, if the cMRI data of the first follow-up re-

vealed no recurrence of the tumor. A total of 115 patients 

(49 women, 66 men; age 58.7 ± 12.0 years; range 29–81 

years) fulfilled these criteria, and the data from a total of 

374 follow-up MRI examinations were retrospectively 

evaluated in this study. The institutional review boards of 

the University of Erlangen and the University Clinic of St. 
Pölten approved this retrospective study. All patients gave 

written informed consent in accordance with the ethical 

standards of the Helsinki Declaration of 1975 and its later 

amendments. Written consent was obtained from all en-

rolled patients.

**MRI Data Acquisition**

Follow-up MRI examinations were performed every 

3–4 months or on an unscheduled basis in case of clinical 
signs of tumor recurrence. MRI data acquisition was car-

ried out on a 3-Tesla whole-body scanner (Tim Trio, Sie-

mens) equipped with the standard 12-channel head coil. 
The cMRI protocol included, among others, the following 

two sequences: 1) a FLAIR sequence; 2) a single-shot dif-

fusion-weighted echo-planar imaging (DW-EPI) sequence 

(b = 0, 1000, and 2000 sec/mm²); 3) a dynamic suscepti-

bility contrast (DSC) perfusion MRI using a GE-EPI se-

quence (TR, 1740 msec; TE, 22 msec); and 4) pre– and 

post–contrast-enhanced (CE) T1-weighted (T1W) MRI. All 

sequences were performed in the axial orientation.

Additionally, for the VAM approach, a DSC perfusion 

MRI using an SE-EPI sequence (TR, 1740 msec; TE, 33 

msec) was performed in combination with a separate con-

trast agent (CA) injection. Both DSC perfusion exami-

nations were performed with 60 dynamic measurements 

and administration of 0.1 mmol/kg body weight gadoter-

de meglumine (Dotarem, Guerbet) as the CA at a rate of 

4 mL/sec using an MR-compatible injector (Spectris, Me-

drad). The first DSC-MRI was obtained by using SE-EPI 

DSC perfusion MRI because unwanted CA leakage oc-

curs to a lesser extent with this technique. Our strategies 

to minimize the probability of patient motions and differ-

ences in the time to first-pass peak, which may significant-

ly affect the data evaluation, were described previously.

Geometrical parameters were chosen that were identical 

for the 2 DSC perfusion sequences: in-plane resolution of 

1.8 × 1.8 mm, slice thickness of 4 mm, 29 slices, and 

geometrically autocalibrating partially parallel acquisition 

(Grappa) factor of 2. The additional acquisition time for 

the VAM approach, i.e., the SE-DSC perfusion sequence, 

was 2 minutes.
MRI Data Analysis

Analysis of cMRI data included calculation of maps of apparent diffusion coefficients from diffusion-weighted imaging (DWI) data as well as maps of cerebral blood volume (CBV) from the GE-DSC perfusion cMRI data via automatic identification of arterial input functions. Routine MRI data including these DWI and CBV maps were analyzed by at least two board-certified radiologists in consensus based on the updated RANO criteria for detection of recurrence of GB.

Analysis of VAM data was performed using custom-made MATLAB (MathWorks) software. VAM data post-processing consisted of 4 steps: 1) calculation of maps of microvascular CBV (μCBV) from the SE-DSC perfusion MRI data; 2) calculation of the so-called vascular hysteresis loop (VHL); 3) calculation of microvessel radius); and 4) calculation of the microvessel density (MVD) and vessel size index (VSI; i.e., the microvessel radius);18 and 4) calculation of the microvessel type indicator (MTI), which was previously defined as the area of the VHL with the sign of its rotational direction (i.e., a clockwise VHL direction was identified with a plus sign, and a counterclockwise with a minus sign). Based on previous studies, a positive MTI value (i.e., clockwise VHL) is associated with a vascular system that is dominated by arterioles, whereas a negative MTI value (i.e., counterclockwise VHL) is associated with venule- and capillary-like vessel components. For guidance of interpretation in the MTI maps, positive MTI values were assigned to warm colors and negative MTI values to cool colors. Consequently, maps of MTI enabled differentiation between supplying arterial (areas with warm colors) and draining capillary-venous (areas with cool colors) microvasculature. Furthermore, the more negative the MTI value, the stronger is the neovascular activity in the tumor. The VAM postprocessing was described in detail previously.

Statistics

All data were expressed as mean ± SD. Areas of contrast enhancement on CE TIW images suspected as tumor recurrence were selected using manually defined regions of interest (ROIs). Additional ROIs were positioned in contralateral normal appearing white brain matter (cNAWM) and used as an internal reference. Imaging biomarker values for CBV, μCBV, MVD, VSI, and MTI were calculated for the ROIs. Based on evaluation of the imaging features seen on the cMRI and VAM data, respectively, obtained from all follow-up examinations during the whole study period, patient subgroups were retrospectively defined according to true-positive (TP), false-positive (FP), true-negative (TN), or false-negative (FN) results for detection of GB recurrence. The parameters for diagnostic performance (sensitivity, specificity, and accuracy) were calculated from these data. Additionally, the total tumor volumes were determined by CE TIW MRI for patients with recurrent GB.

Dedicated software (SPSS, IBM Corp.) was used for statistical evaluation. Differences in imaging biomarkers between subgroups of patients were determined using the general linear model method. A Dunnett T3 test was used as a post hoc procedure to be consistent with the assumption that homogeneity of variance was not met and for correction for multiple comparisons. Homogeneity of variance was tested using Levene’s test. Intraindividual differences in imaging biomarker values between lesions and cNAWM as well as in tumor volume between follow-up examinations were compared using a Wilcoxon signed-rank test. Significance of differences in tumor volume between patient subgroups was calculated using a Mann-Whitney U-test, and p values less than 0.05 were considered to indicate significance. Receiver operating characteristic (ROC) analysis was performed to calculate the area under the ROC curve (AUC) to determine the diagnostic performance of each imaging biomarker for GB recurrence detection.

Results

Of the 115 patients included in this study, 89 patients showed GB recurrence and 26 patients showed no recurrence during the study period. Treatment of the recurrent GB was initiated after detection in cMRI in accordance with clinical signs for recurrence and included a repeat craniotomy in 33 patients (37.1%), second-line monotherapy with the antiangiogenic drug bevacizumab in 26 patients (29.2%), a temozolomide rechallenge in 17 patients (19.1%), repeat radiation therapy or repeat combined radiochemotherapy in 10 patients (11.2%), and palliative care without further treatment of the tumor in 3 patients (3.4%).

Early Recurrence Detection in VAM

Recurrence of the GB was detected simultaneously by both cMRI and VAM data from the same examination in 61 patients (68.5% of all patients with recurrence). This subgroup of patients was termed “simultaneously TP.” An illustrative case for this subgroup is depicted in Fig. 1A. In the remaining 28 patients with recurrence of the GB during the study period, recurrence was detected earlier in VAM data of follow-up examinations whose cMRI data showed no evidence for recurrence, i.e., cMRI was FN. Therefore, this subgroup was termed “early TP in VAM & FN in cMRI.” In these patients, recurrence was detected in the cMRI data of the next follow-up (in 20 patients; illustrative case in Fig. 2) or the follow-up after (8 patients, Fig. 3). The time differences in detail were 147 ± 80 days (range 34–286 days). During this time period the increase in tumor volume on CE TIW MRI was statistically significant (p < 0.001), from 9.7 ± 11.1 cm³ (0.2–37.0 cm³) to 26.8 ± 22.4 cm³ (0.6–84.7 cm³). The degree of tumor volume increase ranged between a +13% and a 155-fold increase and showed a 10-fold increase on average. The tumor volumes at the early follow-ups, at which only VAM revealed evidence for GB recurrence, were additionally significantly smaller (p = 0.004) than the tumor volumes of the simultaneously TP subgroup (20.9 ± 21.0 cm³ [0.9–84.2 cm³]; Fig. 4A). No further FN results were found for cMRI, and no FN cases were found for VAM.
**FIG. 1.** A: Simultaneous TP detection of GB recurrence in both cMRI and VAM. cMRI, including anatomical sequences (CE T1W and FLAIR MRI) and macrovascular perfusion (CBV), and VAM biomarker maps of microvascular perfusion (µCBV), MTI, and MVD in a 54-year-old male patient clearly demonstrate recurrence of a GB. This patient received bevacizumab as second-line monotherapy. B: TN follow-up examination in both cMRI and VAM. The cMRI and VAM data of a 37-year-old female patient revealed pseudoprogression and no evidence for GB recurrence. This patient additionally showed no evidence for recurrence in the next 9 follow-up examinations carried out during the following 3 years.

**FIG. 2.** Early TP detection of GB recurrence in VAM data and FN result in cMRI. A: cMRI, including anatomical sequences (CE T1W and FLAIR MRI) and macrovascular perfusion (CBV), and VAM biomarker maps of microvascular perfusion (µCBV), MTI, and MVD of a 63-year-old male patient who was diagnosed with pseudoprogression in cMRI (no macrovascular hyperperfusion in CBV, red arrow), but showed evidence for recurrence in VAM data (microvascular hyperperfusion in µCBV and indication of neovascularization in MTI, but not in MVD, red arrows) at the initial follow-up examination. B: At the subsequent follow-up examination 142 days later the patient showed clear signs of recurrence in cMRI data, and progression of the recurrent GB in VAM data. The tumor volume had increased by 89%, from 15.6 to 29.4 cm³, within the 142 days. The patient received bevacizumab as second-line monotherapy.
FIG. 3. Early TP detection of GB recurrence in VAM data and FN result in cMRI. A: cMRI, including anatomical sequences (CE T1W and FLAIR MRI) and macrovascular perfusion (CBV), and VAM biomarker maps of microvascular perfusion (µCBV), MTI, and MVD of a 69-year-old male patient who was diagnosed with pseudoprogression in cMRI (no macrovascular hyperperfusion in CBV, red arrow) but showed evidence for recurrence in VAM data (microvascular hyperperfusion in µCBV and indication of neovascularization in MTI and MVD, red arrows) at both the initial follow-up examination (A) and the subsequent follow-up examination 122 days later (B). At the third follow-up examination another 95 days later (C), the patient showed clear signs of recurrence in cMRI data and progression of the recurrent GB in VAM data, respectively. The tumor volume had increased 39-fold, from 17.3 to 67.8 cm³, within these in total 217 days. The patient underwent repeat craniotomy with subtotal resection and histopathological analysis of tissue specimens revealed GB.

FIG. 4. A: Tumor volumes for the patient subgroups with an early TP result in VAM data and an FN finding in the cMRI data (VAM TP, cMRI FN, light gray box-and-whisker plot on the left) at the initial follow-up examination. The corresponding tumor volumes of the same patients at the subsequent follow-up with delayed TP result in cMRI (cMRI del. TP) are depicted in the dark gray box-and-whisker plot in the center. The dark gray box-and-whisker plot on the right depicts the tumor volumes for the patient subgroup with simultaneous (simultan.) TP findings in both cMRI and VAM data. ROC curves for differentiation of GB recurrence and pseudoprogression (B and C) illustrate diagnostic performance. B: Measures of macrovascular perfusion (CBV, black) and microvascular perfusion (µCBV, gray), C: Microvessel density (MVD, black), vessel size index (VSI, dark gray), and microvessel type indicator (MTI, light gray). MTI had the highest AUC (0.958) for detection of GB recurrence.
In the 26 patients who showed no recurrence during the study period, cMRI and VAM correctly revealed no recurrence (i.e., a TN result) for all follow-up examinations in 21 and 22 patients, respectively. An illustrative example for a TN result in both cMRI and VAM is depicted in Fig. 1B. However, FP results were found in 5 and 4 patients for cMRI and VAM, respectively. In all but 1 FP case, there correctly was no treatment of GB recurrence initiated, because clinical parameters showed no evidence for recurrence. The subsequent follow-up examinations of these patients (1 to 6 examinations over a time period of 4 months to 2 years) actually revealed no evidence for recurrence. Figure 5A and B illustrates imaging findings in a patient who showed clear signs for neovascularization in the initial follow-up in the VAM data but no obvious hyperperfusion in the cMRI data (Fig. 5A). The subsequent follow-up 4 months later (Fig. 5B) showed no signs for recurrence or progression and revealed that the initial findings were TN for cMRI and FN for VAM, respectively. The 1 FP case mentioned above, in which recurrence treatment was initiated, is depicted in Fig. 5C. In this patient, both cMRI and VAM data showed indications of recurrence. However, histological analysis of tissue specimens obtained during the repeat resection revealed radiation necrosis and no vital tumor tissue.

**Quantitative Evaluation of Imaging Biomarkers**

The values for the imaging biomarkers of cMRI (i.e., macrovascular CBV) and VAM (i.e., µCBV, MVD, VSI, and MTI) for the patient subgroups are summarized in Table 1. Macrovascular CBVs in patients with an FN finding in cMRI were significantly lower (p < 0.001) than those in both subgroups with TP findings in cMRI (“simultan TP” and “delayed TP” in Table 1), but were not significantly different from CBV values in TN and FP patients, as well as in cNAWM. These findings provided quantitative confirmation for absence of macrovascular hyperperfusion in early GB recurrence. CBV values for patients with FP findings in cMRI were significantly lower (p < 0.05) than the values in both subgroups with TP findings in cMRI, and were not significantly different from the CBV values in cNAWM. As it turned out, this FP finding was mostly associated with small spots of high CBV from large vessels within the hyperintense region on the CE T1W MR images that were misinterpreted as GB recurrence.

The values of µCBV, MVD, and MTI in patients with...
early TP findings in VAM were significantly lower (p < 0.05 for µCBV; p ≤ 0.001 for MVD and MTI) than the values in the other 2 subgroups with TP findings in VAM (Table 1) and were significantly higher than the values in the TN and FP cases as well as in cNAWM. These findings provide quantitative confirmation for microvascular hyperperfusion in early GB recurrence and a continued increase in neovascular activity during progression of the tumor. Biomarker values for FP cases in VAM, however, were not significantly different from values in the subgroups with TP findings in VAM and were significantly different from the values for cNAWM. This was a quantitative confirmation that there was indeed neovascular activity within the hyperintense region on the CE T1W MR images, but it remained unclear why no recurrent GBs have developed in the further disease course of these patients. Finally, we found that VSI was not useful for detection of GB recurrence, because we found no significant differences when comparing the subgroup values with each other or with the cNAWM values.

### Diagnostic Performance of Biomarkers for GB Recurrence Detection

The findings of the quantitative analysis were confirmed by both the parameters for diagnostic performance and the ROC curve analysis results. Sensitivity, specificity, and accuracy for detection of GB recurrence were 0.685, 0.808, and 0.713 for cMRI, and 1.0, 0.846, and 0.965 for VAM, respectively. ROC curve analysis (Fig. 4B and C) revealed that MTI had the highest AUC (0.958; p < 0.001) for detection of GB recurrence, followed by the VAM biomarkers MVD (AUC 0.919; p < 0.001) and µCBV (AUC 0.912; p < 0.001), with very similar diagnostic performance. Macrovascular CBV showed slightly inferior diagnostic performance (AUC 0.866; p < 0.001), and VSI had the worst diagnostic performance for GB recurrence detection (AUC 0.614; p = 0.069).

### Discussion

In the present study, we extended our cMRI protocol for monitoring of GB patients with an approach for assessment of microvascular perfusion and architecture. Our main findings were threefold: 1) VAM allowed for early detection of GB recurrence, prior to cMRI; 2) early GB recurrence showed microvascular but no macrovascular hyperperfusion; and 3) VAM showed superior diagnostic performance compared with cMRI.

### Early GB Recurrence Detection With VAM

We demonstrated that our VAM approach can provide additional information about tumor vasculature and neovascularization that is complementary to the information from routine perfusion MRI and may be helpful for early detection of GB recurrence. For tumors with very small volume (1–2 mm³), the supply of oxygen and nutrients from neighboring capillaries via vascular cooption is sufficient because the diffusion distance of oxygen is 100–200 μm. To grow beyond this size, generation of new blood vessels toward the tumor, i.e., neovascularization, is required. Mathivet et al. observed a progres-
sive increase in vessel diameters during GB development in an orthotopic mouse model. VAM focuses precisely on these very thin vascular structures from early neovascularization and thereby closes the information gap in data from clinical routine perfusion MRI, which has very limited sensitivity to microvasculature. The reason for this is the high sensitivity of the SE-DSC perfusion MRI for microvessels with a diameter around 10 μm. This phenomenon has been well known in MR physics since the 1990s but was not applied in routine clinical use until now. Here, we demonstrated that the VAM approach is compatible with cMRI protocols and requires only 2 minutes of extra time for data acquisition.

Microvascular but No Macrovascular Hyperperfusion in Early Recurrence

Our quantitative analysis of cMRI and VAM imaging biomarkers demonstrated that early recurrence of GB is dominated by formation of small vascular structures, as already known and previously shown for untreated GB. CBV of the macrovasculature in early GB recurrence was found not to be significantly different from both pseudoprogression and cNAWM but was significantly lower than the CBV of progression-stage GB recurrence. On the other hand, μCBV, MVD, and MTI values for early-stage GB recurrence were significantly higher than the values for both pseudoprogression and cNAWM. Therefore, conventional GE-DSC perfusion MRI alone is not useful for detection of early-stage GB recurrence, and SE-DSC perfusion MRI should be considered for future modifications of the RANO criteria.

Superior Diagnostic Performance of VAM

Repeat craniotomy is the first and best option for treating GB recurrence, but this treatment requires early and reliable recurrence detection. In this study, repeat craniotomy was possible in 33 of 89 patients (37.1%) after (partly delayed) detection of GB recurrence in cMRI. For the remaining 56 patients with GB recurrence, only the second best alternatives for GB recurrence treatment (e.g., bevacizumab therapy) were available. The low percentage of repeat craniotomies demonstrates that the cMRI methods for GB patient monitoring were not sufficiently accurate. The accuracy of cMRI (0.713) was clearly lower than that of VAM (0.965). Detection of early-stage GB recurrence with VAM was associated with a significantly smaller volume than detection with cMRI. However, it has to be established in future studies whether the detection of smaller-volume tumors is associated with a higher resection rate and an OS benefit.

The diagnostic performances of μCBV, MVD, and MTI were very similar in terms of AUC of ROC analyses. This opens the door for the application of our VAM approach in the clinical routine because μCBV can be easily calculated from SE-DSC perfusion MRI data and requires no sophisticated postprocessing software tools.

Study Limitations

A limitation of our VAM approach is the requirement for additional DSC-MRI perfusion sequences (SE-DSC) and a second CA injection. On the other hand, this ensures that the routine GE-DSC perfusion MRI sequence is kept unchanged regarding spatial and temporal resolution. However, our approach allows the acquisition of VAM data with high signal-to-noise ratio, high spatial resolution, and coverage of the whole brain, which is mandatory for MR perfusion examinations performed with cMRI. These features are especially important for detection of small or multicentric lesions. The commonly used combined simultaneous GE-SE-DSC perfusion sequence, however, does not meet these requirements because of insufficient spatial coverage (maximum of 12 sections) and resolution, which necessitates performing the routine perfusion separately and consequently requires a further CA injection. Additionally, the combined simultaneous GE-SE-DSC perfusion sequence was performed with a double dose or more of CA, which resulted in the application of up to a triple dose. Furthermore, this study was limited due to its retrospective design. Prospective clinical trials are necessary to investigate the clinical usefulness and potential OS benefit of VAM for patients with recurrent GB.

Conclusions

This study demonstrated that the targeted assessment of microvascular features using the VAM technique provided valuable information about early neovascularization activity in recurrent GB that is complementary to the information provided by perfusion imaging in cMRI and may be helpful for earlier and more precise monitoring of patients suffering from GB. Our VAM approach is compatible with existing MRI protocols for routine clinical diagnosis of GB recurrence, and an extension of this technique is straightforward if VAM data postprocessing remain limited to the calculation of μCBV.

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Disclosures

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Author Contributions
Conception and design: Stadlbauer, Oberndorfer. Acquisition of data: Stadlbauer, Dörfler, Heinz, Oberndorfer. Analysis and interpretation of data: Stadlbauer, Eyüpoglu, Zimmermann, Oberndorfer. Drafting the article: Stadlbauer. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Stadlbauer. Statistical analysis: Stadlbauer, Zimmermann. Administrative/technical/material support: Stadlbauer, Oberndorfer. Study supervision: Stadlbauer, Buchfelder, Dörfler, Heinz, Oberndorfer.

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