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Visual inspection of MR relative cerebral blood volume maps has limited value for distinguishing progression from pseudoprogression in glioblastoma multiforme patients

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Abstract

Background: We examined whether visual interpretation of relative Cerebral Blood Volume (rCBV) colour maps made with dynamic susceptibility-weighted perfusion MRI, can reliably distinguish progressive disease (PD) from pseudoprogression (PsPD) in glioblastoma patients during treatment with temozolomide chemoradiation.

Methods: Magnetic resonance (MR) perfusion-weighted images were evaluated based on visual inspection of rCBV maps. Sensitivity and specificity was calculated to assess if rCBV can reliably differentiate between PD and PsPD, during standard chemoradiation therapy.

Results: Evaluation of dynamic susceptibility-weighted contrast-enhanced perfusion MRI by visual interpretation of rCBV maps did not differentiate PD from PsPD (sensitivity=72%; specificity=23%). Furthermore, the interpretation of the rCBV maps had no prognostic value regarding survival.

Conclusions: Qualitative rCBV-based dynamic susceptibility-weighted contrast-enhanced perfusion MRI does not reliably differentiate PD from PsPD, and is not prognostic for survival in glioblastoma patients during treatment with temzolomide chemoradiation.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common and most aggressive primary malignant brain tumor in adults. The standard treatment at initial presentation consists of maximal surgical resection followed by high-dose radiotherapy with concurrent oral chemotherapy (temozolomide [TMZ]) followed by six adjuvant courses of TMZ. There is no universally accepted standard second-line treatment for recurrent GBM, and for patients in (relative) good clinical condition, reoperation, reirradiation, alternative cytotoxic and targeted therapy regimens can be considered possible treatment options if a relapse is suspected.[1-3] Response monitoring using MRI after standard multimodality treatment in GBM patients has shown that 20-30% of patients develop an increase of contrast-enhancement on their first post-radiation MRI, in the absence of tumor progression, so-called pseudoprogression (PsPD).[4] This phenomenon may occur with or without new or progressive clinical symptoms. It is thought to be a treatment related reaction, due to alterations of the blood- brain barrier. In general, it has a self-limiting course without necessity to change therapy. Usually, PsPD occurs within 3 months after concurrent chemoradiation therapy.[5-8] Currently available data suggest a better clinical outcome in patients with PsPD, apparently due to a strong correlation with O6-methylguanine-DNA methyltransferase (MGMT) status, compared with patients with true early tumor progression and compared to patients with no PsPD, however, a significant survival benefit has yet to be established in larger patient cohorts.[5,8-11]

Evaluation of conventional MR imaging may be insufficient in differentiating PsPD from progressive disease (PD, i.e. tumor progression) in GBM patients. This may have important consequences for both expected prognosis and decisions on treatment adjustments.[4,6,12] Advanced MRI techniques may offer a noninvasive alternative for more accurate assessment of tumor response during treatment. One of these techniques is dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MRI, which is capable of quantifying vessel blood volume by assessment of the relative cerebral blood volume (rCBV), reflecting the degree of microvascular proliferation in tumor tissue.[13-15] It has been used for tumor grading, distinction of tumor progression versus treatment-induced changes and for prediction of survival in glioma patients, although larger studies are still needed to assess its utility and reproducibility.[16-27] Many studies have used quantitative rCBV analysis, while visual assessment of rCBV color maps is currently routinely used in daily practice. In brain metastasis, the visual assessment of perfusion-weighted imaging (PWI) analysis was unfortunately not reliable enough to predict (pseudo)progression.[28]

In clinical practice, radiological progression in combination with a high rCBV on perfusion MRI may in some patients result in a change of the treatment regimen based on presumed tumor progression. The radiological and clinical development during follow-up of these patients is therefore, highly relevant. The aim of the current study was to assess the value of routine assessment of rCBV color maps in GBM, to differentiate PsPD from PD.

METHODS

Study Population

Patients included in this study were treated between January 2009 and December 2012 at the Department of Neuro-Oncology, Haaglanden Medical Center (The Hague, The Netherlands). Patients were eligible if they were diagnosed with histologically proven primary GBM (World Health Organization classification grade IV), were aged ≥18 years and had been treated with postoperative radiotherapy (60 Gy in 30 fractions of 2 Gy during 6 weeks) with concurrent TMZ (75mg/m^2/day), followed by (intention to treat with) six adjuvant TMZ cycles at a dose of 150-200 mg/m2 in a 5/28 schedule, according to the Stupp protocol.[29] Patients were included who had had (at least) finished the concurrent phase and had undergone MRI including PWI at the time of first radiological tumor progression or within 2 months thereafter. Radiological tumor progression was based on the Response Assessment in Neuro-Oncology (RANO) criteria (time of progression, T_p).[12] Based on the presumed diagnosis made by their treating neurooncologist at Tp, patients either continued or discontinued their initial treatment. Information was obtained concerning patient demographics (age, gender and survival), the type and extent of surgery performed, MGMT methylation status, Karnofsky Performance Status, time of suspected radiological and clinical progression, corticosteroid (dexamethasone) use and treatment regimens. Relative changes in (conventional) tumor measurements were used to assess tumor response or progression at follow-up MRI 3 months after Tp (T_{FU}). Research was conducted according to the principles of the Declaration of Helsinki, and according the regulations of the local medical ethics committee.

Definition of outcome variables

Suspected Radiological progression at T_p and radiological progression at T_{FU} (in comparison with T_p) were based on the RANO criteria[12], defined by an increase in size of the contrast-enhancing lesion and the T2/fluid-attenuated inversion recovery lesion and/or the presence of new contrast-enhancing lesion(s).

Progressive Disease (PD; i.e. tumor progression) was defined by either histologically proven tumor progression within 4 months after T_p, death within 4 months after T_p not caused by other (comorbid) conditions, or further radiological progression (on conventional MR imaging) at T_{FU} compared to T_p.

Pseudoprogression (PsPD) was defined by either pathological confirmation of necrosis without presence of viable tumor cells obtained by re-resection within 4 months after T_p, or stable or decreased (conventional) MRI abnormalities at T_{FU} compared to T_p.

Overall survival (OS) was defined as the interval between the date of initial surgery or biopsy and date of death.

Progression free survival (PFS) was defined as the interval between date of initial surgery or biopsy and date of clinical progression (derived from the RANO criteria, based on clinical status and use of corticosteroids).

MR Imaging

MRI studies were performed with a 1.5 Tesla system (Siemens, Symphony, Erlangen, Germany) and a 12-channel phased array head coil. Standard doses of 0.1 mmol/kg gadolinium were used for the contrast-enhanced images. The imaging protocol consisted of precontrast conventional axial T1-weighted, T2-weighted and fluid attenuated inversion recovery images followed by perfusion- weighted imaging/DSC MRI data and finally postcontrast axial T1-weighted images. DSC perfusion MR scans were acquired with a gradient-echo echoplanar imaging (GE-EPI) technique during the first pass of a standard dose bolus of gadolinium contrast. Before the PWI sequence, a prebolus (0,1 ml/kg) of gadolinium was injected to correct for leakage. Imaging parameters were: TR 2400ms, TE 46 ms, flip angle 70º Matrix 128 2, 6mm slice thickness 10% gap, 20 slices, field of view (FOV) 225 mm, fat saturation, EPI factor 112. During 50 consecutive EPI scans lasting 2 min, with a 10 s injection delay for baseline signal intensity measurements, an intravenous bolus injection of 20 ml of gadolinium at a flow rate of 4 ml/s followed by a 20 ml saline flush was administered. DSC data were transferred to a Siemens Numaris 4 workstation for postprocessing on which CBV values were displayed as a color-coded map. Conventional tumor size was defined as the product of the two largest perpendicular transverse-enhancing tumor diameters measured on a postcontrast T1-weighted image. MR perfusion-weighted rCBV color maps were independently scored based on subjective evaluations by two experienced neuroradiologists (REH, GJL), who were blinded to the clinical information and outcome. Discordant results between the radiologists were resolved by consensus. Adapted from Hoefnagels *et al*., we determined a subjective visual score of the rCBV color map.[30] For a reliable interpretation, the rCBV map was evaluated beside the conventional MR images to detect and account for magnetic susceptibility, motion, bolus timing and other artifacts. On visual inspection, lesions with a relative high rCBV compared to the contralateral normal appearing white matter and irrespective of areas indicative of necrosis were scored as 'high rCBV'. This was based on the presence of nodular highly vascularized areas within the contrast-enhanced lesion. In the absence of any high angiogenic intratumoral area a 'low rCBV' was scored.

Statistical methods

Differences between categorical factors were assessed by the Chi-Squared test (χ^2). For the association between continuous and categorical (nominal) factors, the Mann-

Whitney-U test was used. OS and PFS were evaluated according to the Kaplan-Meier method. The Log-Rank test was used to compare OS and PFS between patient groups (PD vs PsPD, and high vs low rCBV). Univariable and multivariable survival analyses were conducted using Cox proportional hazard models to identify prognostic factors for OS and PFS. Sensitivity and specificity were calculated to examine if the subjective rCBV map could reliably classify the clinical diagnosis (PD or PsPD). All data analyses were performed using IBM SPSS Statistics for Windows, version 20.0 (NY, USA). P-values less than 0.05 were considered to be statistically significant.

RESULTS

Patients Characteristics

Fifty-eight out of 200 consecutive adult patients with newly diagnosed GBM and adequate MR follow-up including PWI, who had been treated with concurrent TMZ chemoradiation followed by adjuvant TMZ between January 2009 and December 2012 were enrolled in the present study (Table 1). At the time of first increase of contrast-enhancement after concurrent chemoradiation (T_p), 23/58 (40%) patients continued their treatment with adjuvant TMZ because of suspected PsPD (based on both conventional and perfusion MR imaging and clinical performance). The remaining 35/58 (60%) patients were diagnosed with presumed PD and received a new type of therapy. A re-resection was performed in 12/58 (21%) patients. In total, 6/58 (10%) patients received no further treatment at the time of T_p: 2/6 patients did not continue current treatment because of ongoing thrombocytopenia and only underwent follow-up imaging, and in 4/6 patients there were no more treatment options due to worsening of their clinical condition. The majority of all patients (39/58; 67%) reached $T_p \leq 3$ months after completion of concurrent chemoradiation. T_p preceded clinical progression in 47/58 (81%) patients, with a median difference of 4 (range: 0-25) months.

PD and PsPD on follow-up

During follow-up, PD was diagnosed in 32/58 patients (55%), and PsPD was diagnosed in 26/58 patients at Tp (45%). Regarding the 32 patients with PD, 16 (50%) showed increase of the enhancing lesion or the appearance of new enhancing lesion(s) on T_{FU}, 10/32 patients (31%) had histologically proven tumor progression and 6/32 (19%) patients died within 4 months of T_p (not caused by other comorbid conditions) (Table 2). At T_{FU}, 24/26 (92%) patients demonstrated partial response or stable disease, based on the change in enhancing tumor size, and in 2/26 (8%) patients pathological examination revealed findings associated with treatment-related necrosis without viable tumor cells, resulting in 26 patients diagnosed with PsPD (Table 2). A decrease of Karnofsky performance status was found in 24/58 patients (41%). Of these 24 patients, 9 patients (38%) demonstrated

PsPD and 15 (63%) demonstrated PD. From the patients classified as having PsPD, 13/26 (50%) had a methylated MGMT promoter, whereas only 7/32 patients (22%) who were classified as having PD had a methylated MGMT promoter (p=0.08). Further analysis revealed that a majority of patients with PsPD (17/26; 65%) showed an early T_p (≤ 2 months), compared with PD patients (10/32 patients (31%), p=0.01). Only five of 26 PsPD patients developed PsPD after 3 months.

Table 1. Patient characteristics population (n=58)

Characteristic	
Male/female (n)	41/17
Median age at baseline (y)	60 (range 36-78)
Median KPS at baseline	90 (range 50-100)
Corticosteroid therapy at baseline (n)	
Yes	8 (14%)
No	47 (81%)
Missing	3 (5%)
Biopsy or resection at primary diagnosis (n)	
Biopsy	4 (7%)
Resection	54 (93%)
MGMT promoter methylation status (n)	
Methylated	20 (35%)
Unmethylated	30 (52%)
Missing	8 (14%)
Median number of adjuvant TMZ courses	6 (range 0-6)
T_p (n)	
0-3 months after concurrent chemoradiation	39 (67%)
3-6 months after concurrent chemoradiation	6 (10%)
>6 months after concurrent chemoradiation	13 (22%)
T_{fu} (n)	44 (76%)
Median tumor size at T_p (mm^2)	1642 (range 189-4025)
Therapy after T_p (n)	
Reoperation	12 (21%)
Reirradiation	1 (2%)
Chemotherapy	
TMZ	23 (40%)
Other	11 (19%)
Other	
Bevacizumab monotherapy	4 (7%)
Cediranib monotherapy	1 (2%)
None	6 (10%)

KPS Karnofsky Performance Status, *MGMT* O^6 –methylguanine-DNA methyltransferase, *TMZ* Temozolomide, T_p Time of first suspected radiological progression after chemoradiation, T_{fu} follow-up 3 months after Tp

Table 2. Criteria for Progressive Disease (PD) or Pseudoprogression (PsPD) at T_{FU} (n=58)

Progressive Disease (n=32)	**n(%)**
Radiological progression [a]	
Increase in size of enhancing tumor	13 (41%)
New lesions on post-contrast T1-weighted imaging	3 (9%)
Histological proven tumor [b]	10 (31%)
Death [b]	6 (19%)
Pseudoprogression (n=26)	
Radiological partial response (>50% decrease) [a]	5 (19%)
Radiological stable disease (0-50% decrease)[a]	19 (73%)
Histological proven necrosis [b]	2 (8%)

a) Relative change in tumor size based on the two largest perpendicular transverse-enhancing tumor diameters: T_{FU} compared with T_P
b) within 4 months after radiological progression (T_p)
Tfu: follow-up 3 months after Tp; Tp: time of progression

MR Perfusion Analysis

Concordant perfusion image results were found in 86% of the perfusion images (50/58) before the neuroradiologists reached consensus. On visual inspection of rCBV color maps, 43/58 lesions (74%) showed relative hypervascularity suggestive for viable tumor (high CBV) and 15/58 lesions (26%) showed no high vascularized intratumoral areas (low CBV), suggesting no viable tumor. No significant difference (p=0.66) in rCBV was found between patients with PsPD and PD; high rCBV was found in 20/26 patients with PsPD (77%) and in 23/32 (72%) of the patients with PD. MR images of a case of PD are shown in Figure 1, and of a case of PsPD in Figure 2. Sensitivity and specificity analyses were performed to calculate whether the rCBV color map in itself is capable of predicting PD. This showed a sensitivity and specificity of 72% and 23%, respectively. When the subgroup of patients with a histologically confirmed diagnosis of PD (n= 10/32) or PsPD (n=2/26) were evaluated, analysis of the subjective rCBV maps demonstrated a slightly better sensitivity (70%) and specificity (50%).

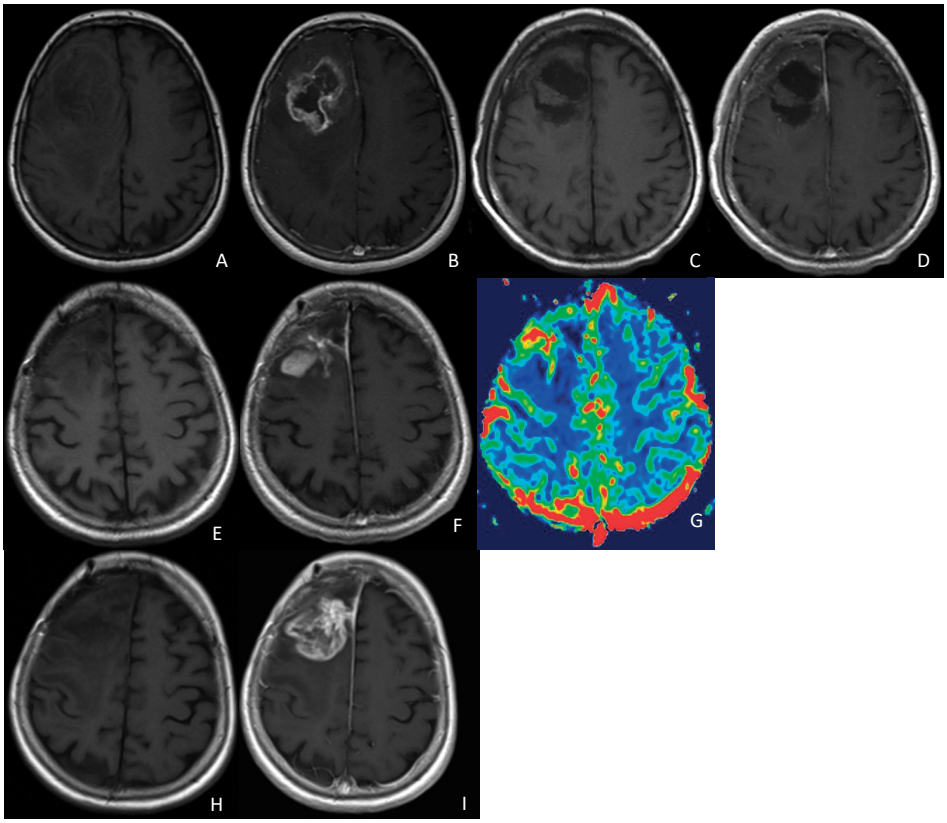

Figure 1. Progressive disease
A and B: pre-surgery T1-weigthed MR images pre- and post-contrast respectively. C and D: post-surgery T1-weigthed MR images pre- and post-contrast respectively. E and F: T1-weigthed MR images pre- and post-contrast respectively, showing TP 4 months after concurrent chemoradiation. G: rCBV perfusion map showing high rCBV within the contrast-enhanced lesion on visual inspection. H and I: T1-weigthed MR images pre- and post-contrast respectively at T_{FU}, showing an increase in the contrast-enhancing lesion consistent with PD. MR: magnetic resonance; PD: progressive disease; rCBV: relative cerebral blood volume; T_{FU}: follow-up 3 months after Tp; Tp: time of progression

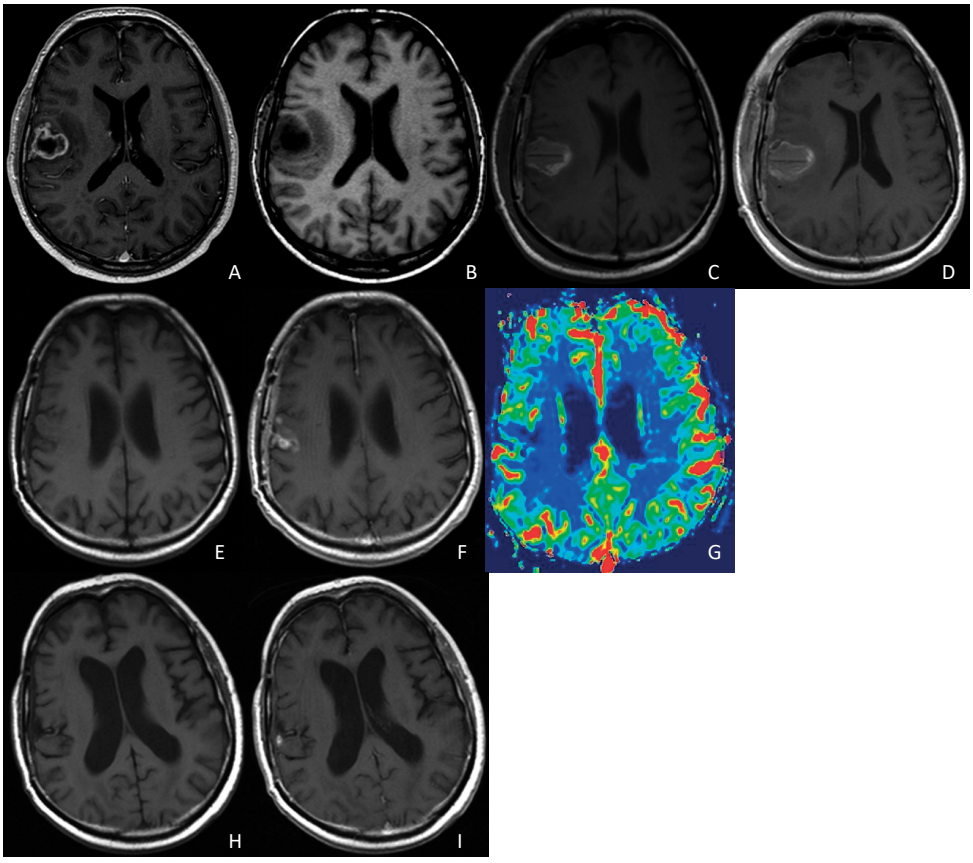

Figure 2. Pseudoprogression
A and B: pre-surgery T1-weigthed MR images pre- and post-contrast respectively. C and D: postsurgery T1-weigthed MR images pre- and post-contrast respectively. E and F: T1-weigthed MR images pre- and postcontrast respectively, showing TP 4 months after concurrent chemoradiation. G: rCBV perfusion map showing low rCBV within the contrast-enhanced lesion on visual inspection. H and I: T1-weigthed MR images pre- and postcontrast respectively at TFU, showing a decrease in the contrast-enhancing lesion consistent with PsPD. MR: magnetic resonance; PsPD:pseudoprogression; rCBV: relative cerebral blood volume; Tfu: follow-up 3 months after Tp; Tp: time of progression.

Progression free and overall survival

At the time of analysis, 57/58 (98%) patients were clinically progressive. Median PFS was 10.5 months (Table 3). Median PFS for the subgroup of patients with high rCBV was 9 months, whereas patients with low rCBV showed a median PFS of 14 (range 5-29) months (p=0.77). Median PFS for patients experiencing PD or PsPD was not statistically different: 9.5 months versus 12.5 months, respectively (p=0.86). In univariable analyses, MGMT status was significantly associated with PFS, with a median PFS of 17 (range 3-29)

months in MGMT promoter methylated patients versus 8.5 (range 3-37) months in MGMT promoter unmethylated patients (p<0.01). Median PFS was also significantly associated with (conventional) tumor size at T_p (<1642 mm2 vs ≥1642 mm2; 14.0 versus 6.0 months; p=0.04), and by the number of adjuvant TMZ cycles administered (<4 vs ≥4 cycles; 6.0 vs 14.5 months; p<0.01). Only MGMT promoter methylation status was independently associated with PFS in multivariable analysis (HR 0.36; p=0.03). At the time of completion of the study all patients had died. One patient had died due to aspiration pneumonia, though without signs of preceding clinical progression. For all patients, the median OS from baseline was 17 (range 4-42) months (Table 3).

Table 3. Median (Progression Free and Overall) survival times (n= 58)

Characteristic	PFS (months)	P - Value[a]	OS (months)	P-Value[a]
Median (range)	10.5 (2-37)		17 (4-42)	
MGMT promoter status		<0.01[b]		0.01[b]
Methylated	17 (3-29)		22 (6-38)	
Unmethylated	8.5 (3-37)		15 (4-39)	
PD or PsPD at T_{FU}		0.86		0.36
PD	9.5 (2-37)		15.5 (4-42)	
PsPD	12.5 (3-29)		19.5 (6-38)	
High or Low rCBV map at T_p		0.77		0.59
High rCBV	9 (2-37)		17 (4-42)	
Low rCBV	14 (5-29)		16 (8-32)	

Data are presented as median (range)
PFS Progression Free Survival; *OS* Overall Survival; *MGMT* O^6 –methylguanine-DNA methyltransferase; *PD* Progressive Disease; *PsPD* Pseudoprogression; *rCBV* relative cerebral blood volume; *Tfu* follow-up 3 months after Tp; *TP* time of progression
a) Log-Rank test
b) Statistical significant difference

Survival from the time of clinical and radiological progression (T_p) was 5 (range 0-29) and 9 (range 0-34) months, respectively. Median OS was similar for the subgroup with high rCBV and low rCBV, 17 (range 4-42) months versus 16 (range 8-32) months respectively (p=0.59). Median OS in patients with PD was 15.5 (range 4-42) months, whereas patients with PsPD had a median OS of 19.5 (range 6-38) months (p=0.36). In multivariable analyses, OS was independently associated with MGMT promoter methylation status (HR 0.48; p=0.03).

DISCUSSION

At the moment of 'first radiological progression', in other words, a growing enhancing lesion on standard MR images, it would be very useful to be able to predict the subsequent clinical course. We assessed in a group of 58 homogeneously treated GBM patients whether DSC perfusion MRI may predict a PsPD or PD course, and whether abnormalities on rCBV colour maps may have overall predictive value. In our study, the detection of nodular high perfusion areas on the rCBV map (i.e. 'high rCBV') did not reliably predict a subsequent PD course (sensitivity and specificity of 72% and 23%, respectively). Twenty-nine out of 58 patients (50%) were misclassified based on evaluation of the rCBV maps: 9 patients with a PD course demonstrated a low rCBV at Tp and more interestingly 20 patients with a PsPD course had demonstrated high rCBV abnormalities at Tp. The possible mechanisms underlying this under- and overestimation of rCBV might include the following: GBM is a heterogeneous lesion with a possible mixture of tumor and (avascular) radiation-induced necrosis; beside endothelial injury, therapy-induced lesions can show vascular abnormalities, such as telangiectasis.[25] These vascular abnormalities may result in an increased rCBV within the necrotic lesion; rCBV assessment of cortical areas is difficult. rCBV in the cortical area is higher than that in the white matter and, subsequently, can lead to confusion in interpretation. Also, lesions are often located on the junction of gray and white matter. Since the rCBV map has a lower resolution than the conventional MRI, this might result in discussion whether the area of high perfusion is due to progression of the tumor in the white matter, or representing the normal surrounding gray matter; artefacts due to focal hemorrhage.

In our analyses, no significant association was found between abnormalities found on rCBV color maps and (overall and progression free) survival. As such, rCBV-based DSC perfusion MRI was not prognostic for survival.

Based on the criteria applied in this study, a PD course after Tp was seen in 55% of our patients, while a PsPD course was seen in 45% of patients with presumed radiological progression (T_p). This percentage of patients with PsPD is higher than reported in literature, which will be related to the selection of patients with radiological progression according to the RANO criteria, instead of including all patients after chemoradiation. In our study population, we detected a survival benefit favoring the PsPD group. The presence of methylation of the MGMT promoter in GBM had been found to be strongly associated with PsPD.[5] We indeed found that patients with PsPD had more often methylated MGMT promoter than patients with PD (50 vs 22%, p=0.08) and MGMT promoter methylation status was independently associated with both OS and PFS.

A limitation of the current study is the methodology of perfusion MR analysis, which was based on visual inspection, instead of using quantitative rCBV measurements or measurement of the parametric response map. However, the applied visual interpretation technique of perfusion MRI resembles routine daily clinical practice, and is therefore

highly relevant. Furthermore, different therapy modalities were applied in patients once they had experienced (presumed) radiological progression and this difference may have influenced subsequent MRI results at T_{FU}. Nevertheless, these considerations also hold true in daily clinical practice. Finally, the interval of 3 months (T_{FU}) after radiological progression (T_P) to define PsPD is arbitrary, but in accordance with other literature on this topic. Also, given the aggressive nature of GBMs, we hypothesized that PD would result in further radiological progression within 3 months of first radiological progression (or death within 4 months).

In conclusion, with a reported relatively high incidence of PsPD after concurrent TMZ chemoradiation in GBM patients, a timely and reliable differentiation of PsPD and true PD is crucial for appropriate treatment decision making, both in daily clinical practice and in clinical trials. Unfortunately, in this retrospective study, we found that qualitative scoring of DSC MR perfusion rCBV maps did not reliably differentiate PsPD from PD and is not a prognostic factor for survival in GBM patients treated with TMZ chemoradiation. Currently, we are planning to perform analyses with a revised quantitative rCBV measurement technique to substantiate our findings. If the prognostic value of perfusion MRI (rCBV) indeed seems to be limited in GBM patients treated with TMZ chemoradiation, this may obviate the use of this imaging modality in this setting.

Practice points

- Pseudoprogression (PsPD) is increasingly encountered in patients with glioblastoma multiforme (GBM) since the introduction of chemoradiation with temozolomide (TMZ)
- Evaluation of conventional MR imaging can be insufficient in differentiating PsPD from PD in glioma patients
- Dynamic susceptibility-weighted contrast-enhanced (DSC) perfusion MRI is capable of quantifying vessel bloodvolume by assessment of the relative cerebral blood volume (rCBV), reflecting the degree of microvascular proliferation in tumor tissue
- Qualitative rCBV-based DSC perfusion MRI does not reliably differentiate PsPD from PD in patients treated with TMZ chemoradiation
- Qualitative rCBV-based DSC perfusion MRI is not prognostic for survival in GBM patients treated with TMZ chemoradiation

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