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Perfusion MRI-based differentiation between early tumor progression and pseudoprogression in glioblastoma and its use in clinical practice

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Abstract

Background. Early treatment effects in patients with glioblastoma are frequently discussed during multidisciplinary team meetings (MDTM), after which a decision regarding (dis)continuation of tumor-targeted treatment is made. This study examined whether a separate and systematic evaluation of perfusion MRI (pMRI) could impact such treatment decisions in the early stage.

Methods. This retrospective observational study evaluated the diagnostic accuracy for detecting early tumor progression of 4 different approaches including conventional MRI, pMRI with Arterial Spin Labeling (ASL), and/or Dynamic Susceptibility Contrast (DSC) MRI, and compared those to the MDTM evaluation in clinical practice.

Results. Sixty-five glioblastoma patients with clinical and radiological data until 9 months after irradiation were included. For all approaches, the sensitivity for detecting early true disease progression was poor to moderate (32%–62%). Area under the curve values were comparable (range 0.63–0.74), but highest for the MDTM evaluation (0.74). In the cases of inconclusive MDTM (26%), systematic pMRI evaluation showed a higher sensitivity compared to conventional MRI (respectively, 36% vs 0%), while the specificity was 100% for all MRI approaches. Multivariable regression analysis showed that a lower KPS score (OR = 0.84 [95% CI: 0.77–0.91]) and pMRI indicative of tumor progression (OR = 0.09 [95% CI: 0.02–0.52]) were independently associated with concluding tumor progression at the MDTM.

Conclusion. MDTM assessment in daily clinical practice has a higher diagnostic accuracy in distinguishing early tumor progression from pseudoprogression compared to a separate, systematic evaluation of pMRI. Systematic evaluation of pMRI might be helpful if the clinical MDTM assessment is uncertain.

Keywords

glioblastoma | multidisciplinary team meeting | perfusion MRI | pseudoprogression | tumor progression

Glioblastoma is a highly malignant primary brain tumor with a high mortality rate, characterized by an intrinsic aggressiveness and poor median survival of approximately 15 months.[1,2] Life-prolonging standard treatment in patients with newly diagnosed glioblastoma includes maximally safe surgical resection followed by radiotherapy (RT) with concomitant temozolomide (TMZ) and adjuvant TMZ. Magnetic resonance (MR) imaging with gadolinium contrast is considered the mainstay of radiological monitoring to evaluate the effect of tumor-targeted treatment. Reliable radiological assessment

of the tumor is needed to guide decisions on initiation or (dis)continuation of treatment. Radiologically, treatment-induced abnormalities, so-called pseudoprogression, are difficult to distinguish from real tumor growth.[3] On conventional MR imaging, pseudoprogression is observed in up to 30% of glioblastoma patients receiving RT, with a maximum occurrence around 3 months after treatment initiation at the time of the first radiological assessment.[4–6]

Perfusion MRI (pMRI), including Arterial Spin Labeling (ASL) and Dynamic Susceptibility Contrast (DSC), is one of the existing advanced MRI techniques that may help to differentiate between early tumor growth and pseudoprogression in patients with glioblastoma.[7] ASL measures tissue perfusion using endogenous blood water as a freely diffusible intrinsic tracer. Its noninvasive nature and ability to quantitatively measure tissue perfusion make ASL an attractive technique for clinical use. DSC MRI is the most commonly used pMRI technique in daily practice. Gasparetto et al.[8] showed the feasibility of the DSC-derived relative cerebral blood volume (rCBV) for discriminating treatment-related changes from tumor recurrence in malignant brain neoplasms. Another study[7] in brain tumors evaluated the diagnostic accuracy of quantitative ASL and DSC for the differentiation between tumor progression and pseudoprogression, where they found comparable areas under the receiver operating curves (ROC) for both techniques, indicating the value of ASL MRI as a noninvasive alternative for DSC perfusion imaging. Furthermore, de Godoy et al.[9] showed the added value of a multiparametric MRI model, including diffusion tensor imaging and DSC pMRI, over conventional MRI for identifying pseudoprogression in patients with glioblastoma. Despite these promising results, it remains challenging to establish the optimum threshold for discriminating tumor progression from pseudoprogression with these methods.[10]

Due to the complexity of the disease and its treatment, patients with glioblastoma are often discussed in multidisciplinary team meetings (MDTM) with experts in the field of treatment of patients with brain tumors.[11] In newly diagnosed patients, indications for diagnosis and first-line treatment are typically discussed. Patients with glioblastoma for whom treatment has been started can be reintroduced in the MDTM by the treating physician in case there is uncertainty about the effectiveness of treatment. This is typically the case when the distinction between tumor progression or pseudoprogression is difficult, impacting further treatment decisions. In the MDTM, both clinical and radiological parameters, including pMRI, are included in the decision. Previous research of Geer et al.[12] demonstrated the added value of pMRI for making decisions about the treatment strategy with more confidence compared to conventional MRI alone.

Although ASL and/or DSC are often incorporated in the MRI protocol for follow-up of glioma patients, not all centers have the required facilities and/or knowledge to correctly apply these techniques in clinical practice.[13] During the early stages of the disease, a correct and systematic assessment of pMRI could particularly be useful, when it is most challenging to distinguish pseudoprogression from true disease progression, which could immediately impact treatment decisions. In this study, we aimed to compare the diagnostic accuracy of a separate systematic and blinded evaluation of pMRI (including ASL and/or DSC) with the MDTM assessment from daily clinical practice for the detection of early tumor progression. In addition, the association of relevant clinical and radiological factors with the outcome of the MDTM assessment was studied.

Methods

Study Population

This retrospective, single-center observational study was conducted in accordance with local institutional review board regulations. Informed consent was obtained for all patients. Adult patients with histologically confirmed WHO grade 4 glioma according to the WHO 2021 criteria,[14] who received postoperative RT treatment from 2015 onwards, were eligible. For practical reasons, we use the term glioblastoma also for the few patients with astrocytoma isocitrate dehydrogenase (IDH)-mutant grade 4. Also, new or increased enhancement on the 3D T_{1w} post-contrast MRI scan compared to the post-surgery pre-RT scan had to be detected, indicating a suspicion of tumor progression. The presence of new or increased enhancement was confirmed by checking the radiology reports. In addition, pre- and post-RT ASL, DSC, FLAIR, and 3D T_{1w} post-contrast MRI scans had to be available, as well as a diagnosis regarding the presence or absence of tumor progression or pseudoprogression based on histopathology or adequate clinical and radiological follow-up (ie, sufficient follow-up data up to 9 months after the end of RT to assess whether there was tumor progression or pseudoprogression). Relevant sociodemographic-, clinical-, and treatment-related data were collected from the hospital medical charts.

MR Imaging

Pre- and post-contrast 3D-TFE T_{1w} (TE/TR = 5/10 ms, FOV = 220 × 175 mm^2, slice thickness = 1.0 mm), T_{2w} FLAIR (TE/TR = 125/11 000 ms, FOV = 220 × 175 mm^2, slice thickness = 5.0 mm), diffusion-weighted (TE/TR = 72/2700 ms, FOV = 220 × 220 mm^2, slice thickness = 5.0 mm), and perfusion images were acquired at a 3-T scanner (Philips Healthcare) as part of standard clinical routine 3 months post-RT, as well as 6 and/or 9 months post-RT. The ASL perfusion images were acquired either with a 2D pCASL protocol with 1650 ms labeling duration (LD) and PLDs of 1525 ms (first slice) – 2120 ms (last slice), or with a 3D pCASL protocol with 1800 ms LD and 1800 ms PLD. The other acquisition parameters were: TE = 16 ms (2D)/12 ms (3D), TR = 4.0 s (2D)/4.2 s (3D), flip angle = 90°, FOV = 240 × 240 mm^2, acquisition matrix = 78 × 78 (2D)/60 × 60 (3D), resolution = 3.0 × 3.0 mm^2 (2D)/4.0 × 4.0 mm^2 (3D), slice thickness = 7.0 mm (2D)/6.0 mm (3D). No vascular crusher gradients were used. The total scan time was 4:08 min (2D)/4:56 min (3D). For DSC perfusion imaging, a pre-bolus injection of 0.1 mL/kg body weight was administered before the standard dose of 0.2 mL/kg body weight gadoterate meglumine (Dotarem; Guerbet) using an MRI-approved power injector (Medrad; Bayer) at a rate of 5 mL/s with an injection delay of 14 s. The DSC images were acquired with a

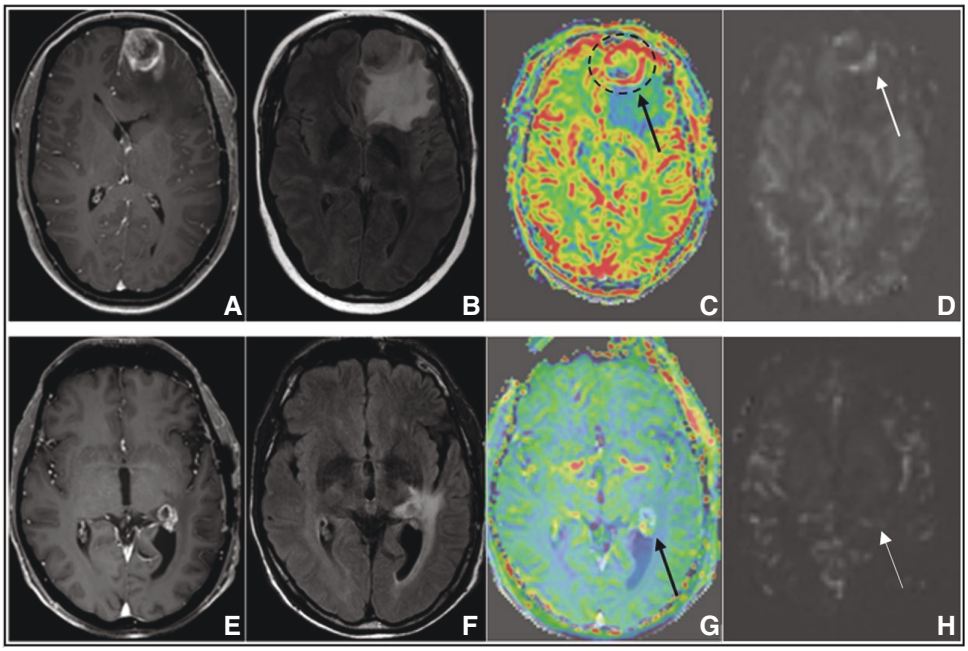

Figure 1. Example post-contrast T_{1w} images (A + E), T_2 FLAIR images (B + F), DSC-rCBV maps (C + G) and ASL-CBF maps (D + H) for 2 example cases with confirmed tumor progression (A–D; top) and pseudoprogression (E–H; bottom).

SE-EPI sequence and the following acquisition parameters: TE = 75 ms, TR = 1.6 s, flip angle = 90°, FOV = 240 × 210 mm^2, acquisition matrix = 93 × 93, resolution = 2.6 × 2.3 mm^2, slice thickness = 5.0 mm. The total scan time was 1:42 min. As part of the post-processing, leakage correction was applied using the Boxerman–Weisskoff approach.[15] Figure 1 shows example MR images for 2 subjects that were included in this study.

Radiological and Clinical Assessment

The postoperative pre-RT MRI of each patient was used to determine whether total resection (defined as no macroscopic residual enhancement on post-contrast T_{1w} MRI in the resection cavity) or partial resection had been performed. The postoperative pre-RT MRI was performed within 48 h after surgery. If biopsy was the surgical strategy, a postoperative MRI was performed as well.

After post-processing the MRI scans, a neuroradiologist blinded to the clinical follow-up and the final diagnosis of tumor progression retrospectively assessed the ASL, DSC, FLAIR, and 3DT_{1w} post-contrast scans at first follow-up, that is, 3 months after the end of RT. The ASL and DSC perfusion per enhancing lesion was assessed qualitatively and considered increased, normal, or decreased with respect to the contralateral tissue (for ASL, the option decreased was not included, since hypoperfusion is challenging to evaluate on ASL[16]). Besides the ASL and DSC perfusion, other factors considered were the presence of leptomeningeal disease, the tumor location, the amount and size of the lesions, the pattern of enhancement (nodular/patchy) on the post-contrast T_{1w} scan, and the hyperintense volume on FLAIR. These factors were included in the radiological assessment, where the conventional MRI, that is, post-contrast T_{1w} and the FLAIR, was used as reference scan. The radiological assessment was systematically performed by 4 different scan combinations (Figure 2): (1) Reference scan without perfusion; (2) Reference scan + ASL; (3) Reference scan + DSC; (4) Reference scan + ASL + DSC. For each combination, the outcome was scored on a 7-point Likert scale as: definite (1), probable (2), or possible (3) treatment-induced abnormalities, no preference for tumor progression, or treatment-induced abnormalities (4), or possible (5), probable (6), or definite tumor progression (7). The radiological assessment was performed in a research setting and could therefore be considered as a separate second review of the MR images besides the MDTM assessment, which is part of clinical practice. To what detail pMRI is included into the MDTM is not formalized and up to the involved clinicians.

The MDTM assessment score 3 months after RT was based on the combined clinical and radiological assessment during the MDTM. The clinical assessment incorporated factors such as age, surgery type, IDH mutation status, O^6-methylguanine-DNA methyl-transferase (MGMT) methylation status, KPS score, and treatment strategy. The MDTM consisted of at least an experienced neuro-oncologist, neuroradiologist, neuropathologist, and neurosurgeon and was part of the standard clinical procedure in our hospital. The MDTM score was based on a 5-point Likert scale defined as: definite (1) or probable (2) treatment-induced abnormalities, no preference for tumor progression, or treatment-induced abnormalities (3), probable (4) or definite (5) tumor progression.

The final outcome of tumor progression or pseudoprogression was based on clinical and radiological follow-up data until 9 months (if available) after the end of

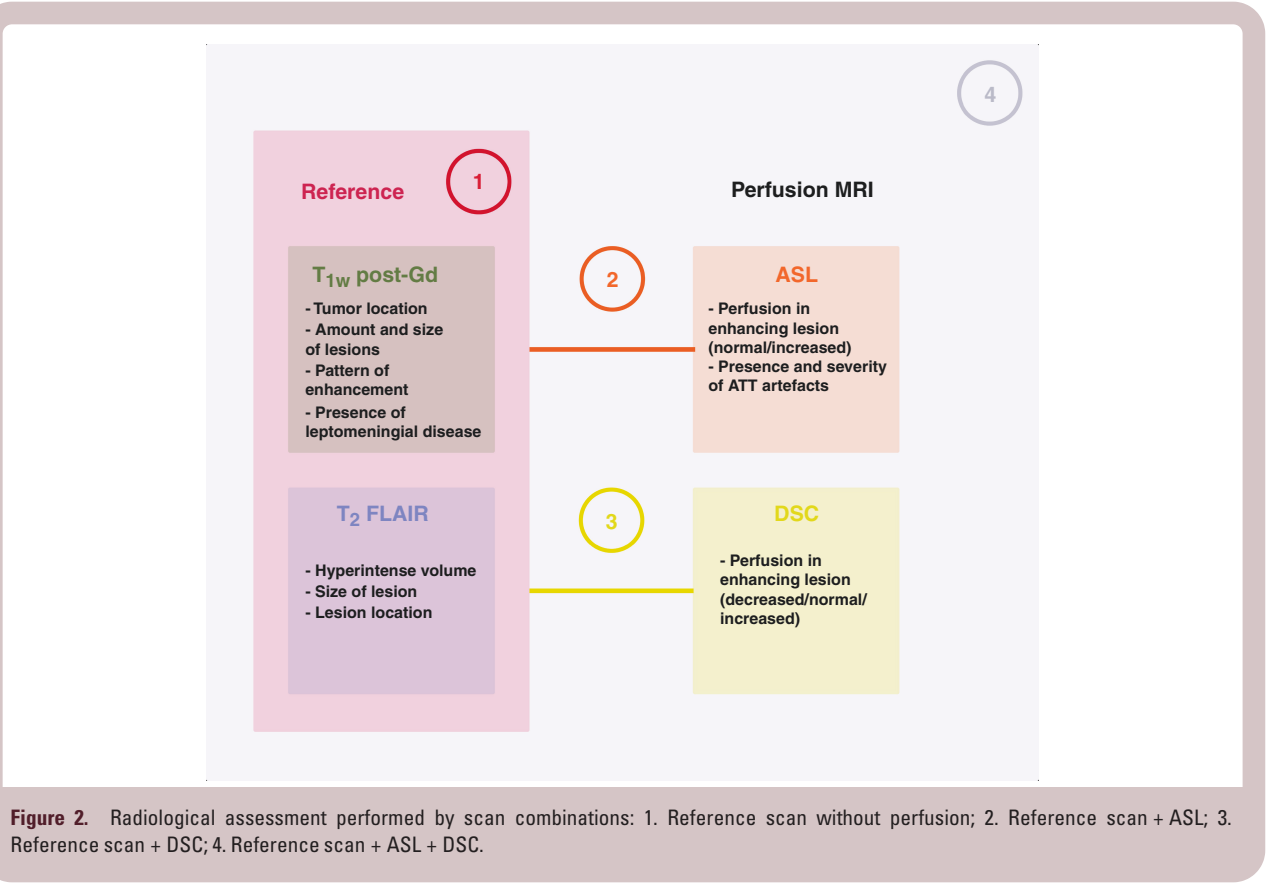

Figure 2. Radiological assessment performed by scan combinations: 1. Reference scan without perfusion; 2. Reference scan + ASL; 3. Reference scan + DSC; 4. Reference scan + ASL + DSC.

primary initiation of RT, where the evaluation was based on the modified RANO criteria.[17] In case survival did not extend to 9 months post-RT, the patient was assigned to final tumor progression if there was no other cause of death. The final outcome was defined as a binary statement "progression" or "no progression."

Statistical Analysis

The diagnostic accuracy was assessed by means of 2 × 2 tables, from which the sensitivity and specificity for detecting tumor progression were calculated. A Fisher's exact test was performed to investigate the association between the radiological assessment and the final outcome. For this part of the analysis, scores on the Likert scale for the MDTM score and radiological assessment were summarized into a binary variable, to make sure these scores were compatible with the binary decision-making in clinical practice. For the MDTM assessment, scores 1–3 were assumed no progression and scores 4–5 were assumed progression. For the radiological assessment, a similar approach was used, namely scores 1–4 were assumed no progression, while scores 5–7 were assumed progression. The results of the diagnostic accuracy analysis were visualized by means of an ROC curve, from which the area under the curve (AUC) values were calculated. In addition, the overall survival time was compared between the progressors and nonprogressors as indicated by the combined ASL and DSC pMRI assessment by means of a log-rank test. Kaplan–Meier curves were created to visualize the results.

Patients for whom the clinical assessment during the MDTM 3 months after RT was inconclusive (ie, score of 3 on the MDTM assessment, reflecting no preference for tumor progression vs treatment-induced abnormalities) were separately analyzed to investigate whether systematic assessment of pMRI could be helpful in those cases. The sensitivity and specificity for detecting tumor progression were again calculated from the 2 × 2 tables.

Lastly, to provide insight into the relevance of radiological and clinical variables in the decision-making process, we evaluated which clinical and radiological variables were independently associated with the final outcome of the MDTM assessment. For this, a multivariable logistic regression model was constructed that included age, surgery type, IDH mutation status, MGMT methylation status, KPS score, chemotherapy, and pMRI evaluation. First, univariable analyses were performed to select the parameters for the multivariable model, and were considered eligible for inclusion if $P < .1$. All relevant variables were checked for multicollinearity before inclusion in the multivariable model, with a correlation > 0.6 considered an indication of multicollinearity. The statistical analyses were performed in SPSS using a significance level of $P < .05$.

Results

Patient Population

A total of 65 patients with glioblastoma were identified that met the inclusion criteria. Table 1 summarizes all relevant

Table 1. Sociodemographic and Clinical Characteristics of the Study Population

	Progression	No Progression
Total patients, *n* (%)	50 (77%)	15 (23%)
Male patients, *n* (%)	32 (64%)	8 (53%)
Age (mean years ± SD)	62 ± 14	54 ± 10
KPS, median (range)	90 (60–100)	90 (60–100)
Surgery, *n* (%)		
• Gross total resection	12 (24%)	5 (33%)
• Partial resection	25 (50%)	9 (60%)
• Biopsy	13 (26%)	1 (7%)
Radiotherapy (RT) dose + concomitant and adjuvant temozolomide (TMZ), *n* (%)		
• RT only (40–45 Gy)	12 (24%)	0 (0%)
• RT (40–45 Gy) +TMZ	5 (10%)	2 (13%)
• RT only (60 Gy)	0 (0%)	1 (7%)
• RT (60 Gy) +TMZ	33 (66%)	12 (80%)
O^6-methylguanine-DNA methyl-transferase (MGMT) methylation, *n* (%)	10 (20%)	8 (53%)
Isocitrate dehydrogenase (IDH) mutation status, *n* (%)		
• IDH mutation	2 (4%)	2 (13%)
• IDH wild type	36 (72%)	12 (80%)
• Unknown	12 (24%)	1 (7%)
Lesions per patient, median (range)	1 (1–4)	1 (na)

The characteristics are shown for both groups with and without true disease progression, which was determined based on clinical and radiological follow-up data until 9 months post-RT if available.

sociodemographic and clinical characteristics, separately for those with a final diagnosis of progression and no progression, as determined based on clinical and radiological follow-up data until 9 months after the end of RT. Most patients were male (62%), with a mean age of 60 ± 13 years and a good performance status (median KPS of 90). The majority of patients underwent partial or total (no macroscopic residual enhancement on post-contrast T_{1w} MRI) resection (52% and 26%, respectively) and most patients (80%) received concomitant and adjuvant TMZ in addition to RT. In 1 patient with tumor progression within the follow-up period of 9 months, treatment with lomustine was started. Re-resection was performed in 4 patients due to suspected tumor growth. In one of these patients, procarbazine, lomustine, and vincristine (PCV) chemotherapy was started. None of the patients received antiangiogenic treatment with bevacizumab. In 22 patients with tumor progression, it was decided to discontinue treatment and proceed to best supportive care, due to further clinical deterioration (deterioration in KPS < 70, $n = 18$) or undesirable side effects of treatment ($n = 4$).

Comparison of Assessment Approaches

The diagnostic accuracy of the 4 different radiological approaches to detect true tumor progression and the MDTM assessment is summarized in Table 2. The association with the final outcome was significant for the MDTM assessment as well as for DSC and the combination of ASL/DSC, with moderate sensitivity (range: 54%–62%). In general, the sensitivity for detecting true disease progression was poor to moderate considering all approaches (range: 32%–62%). Specificity ranged between 67% for radiological assessment with ASL to 93% for radiological assessment without perfusion. Although the sensitivity increased when adding pMRI to conventional imaging (32% for radiological assessment without perfusion vs 54%, 56% and 62% with DSC, DSC combined with ASL and ASL, respectively), the specificity was lower (93% for radiological assessment without perfusion vs 67%, 75%, and 80% with ASL, DSC, and combined ASL and DSC, respectively). Figure 3 shows the ROC curves of the different approaches of assessment, illustrating the diagnostic accuracy of the different approaches to detect tumor progression. The figure shows that the AUC values were comparable for the different radiological approaches (ranging between 0.63 and 0.68), though slightly higher for the MDTM evaluation (0.74). A separate sensitivity analysis was performed by excluding the few patients with astrocytoma IDH-mutant grade 4, which showed limited impact on the results.

The survival analysis showed that there was a significant difference in the median overall survival time between the progressors and nonprogressors as indicated by the combined ASL and DSC pMRI assessment (pMRI progression: median overall survival = 304 days; pMRI no progression: median overall survival = 442 days, $P = .008$). Supplementary Figure 1 shows the corresponding Kaplan–Meier survival curves.

For 17/65 (26%) of the patients, there was no preference for tumor progression vs treatment-induced abnormalities

Table 2. Diagnostic Accuracy of Tumor Progression for the Different Approaches, Including the Multidisciplinary Team Meeting Assessment and the 4 Different Radiological Evaluations

Approach of Assessment	Sensitivity	Specificity	PPV	NPV	*P*-Value From Fisher's Exact Test
Clinical practice					
MDTM assessment	62%	87%	94%	41%	.001*
Systematic radiological assessment					
Radiological assessment without perfusion	32%	93%	94%	29%	.090
Radiological assessment with ASL perfusion	62%	67%	86%	34%	.075
Radiological assessment with DSC perfusion	54%	75%	90%	34%	.037*
Radiological assessment with ASL and DSC perfusion	56%	80%	90%	35%	.019*

A Fisher's exact test was performed to compare the radiological assessment with the final outcome (gold standard). *$P < .05$. **Abbreviations:** ASL, Arterial Spin Labeling; DSC, Dynamic Susceptibility Contrast; MDTM, multidisciplinary team meeting; NPV = negative predictive value; PPV = positive predictive value.

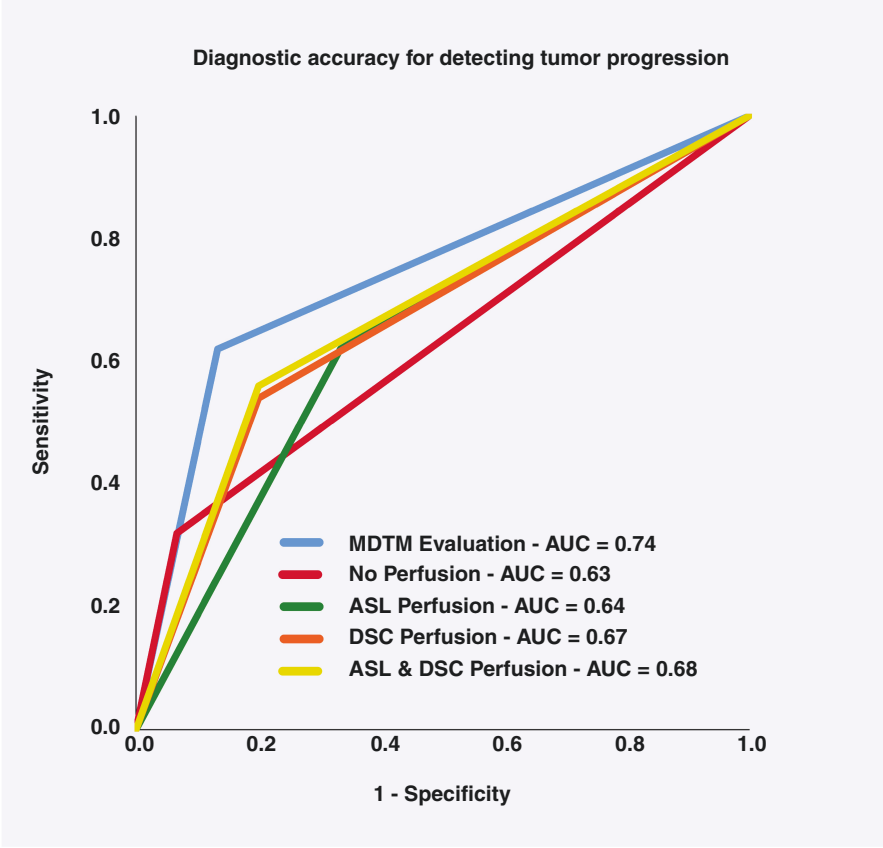

Figure 3. ROC curves illustrating the diagnostic accuracy to detect tumor progression of the 4 different radiological approaches and the MDTM assessment.

in the MDTM assessment. Table 3 summarizes the results separately for the radiological approaches in this subgroup. Although the sensitivity was low for all approaches (ranging between 0% and 36%), the specificity was 100%, meaning that there are no false positives. For the conventional MRI assessment, all uncertain cases were evaluated as having no progression. The increased sensitivity of pMRI compared to conventional MRI shows the potential of a systematic evaluation of pMRI to detect tumor progression in some cases ($n = 4$) where the MDTM assessment was inconclusive. Supplementary Tables 1–4 provide the 2 × 2 tables from which the sensitivity and specificity were derived.

Table 3. Diagnostic Accuracy to Detect Tumor Progression for the Different Radiological Approaches (Sensitivity and Specificity) for Patients Where the MDTM Assessment Was Inconclusive

Approach of Assessment	Sensitivity	Specificity
Conventional MRI	0%	100%
ASL MRI	36%	100%
DSC MRI	22%	100%
ASL + DSC MRI	36%	100%

Abbreviations: ASL, Arterial Spin Labeling; DSC, Dynamic Susceptibility Contrast; MDTM, multidisciplinary team meeting.

Association Between Radiological and Clinical Parameters and the MDTM Outcome

The univariable analysis showed significant associations of KPS score (OR = 0.85, 95% CI: 0.80–0.92, $P = .000$), MGMT methylation status (OR = 3.83, 95% CI: 1.17–12.53, $P = .026$), and pMRI evaluation based on ASL and DSC (OR = 0.15, 95% CI: 0.049–0.43, $P = .001$) with the outcome of the MDTM assessment ($P < .1$). Lower KPS score, unmethylated MGMT status, and a combined ASL and DSC pMRI score indicating tumor progression were associated with higher odds of concluding actual tumor progression in the MDTM assessment. None of these variables showed a correlation > 0.6, thus the assumption of no multicollinearity was met. Therefore, all 3 parameters identified with the univariable analysis were included in our final multivariable model. The multivariable regression analysis showed independent associations for KPS score (OR = 0.84, 95% CI: 0.77–0.91, $P = .000$) and radiological assessment based on combined ASL and DSC pMRI (OR = 0.09, 95% CI: 0.02–0.52, $P = .009$) with MDTM outcome. Thus, a lower KPS score and pMRI results indicating tumor progression were independently associated with concluding actual tumor progression during the MDTM assessment.

Discussion

This study compared the diagnostic accuracy of a separate systematic and blinded evaluation of ASL and DSC pMRI with the clinical and radiological assessment from daily clinical practice during the MDTM for the detection of early tumor progression in a cohort of patients with grade 4 glioma, mostly glioblastoma. The added value of this separate review of pMRI in cases of inconclusive MDTM was examined. Also, the association of relevant clinical and radiological factors with the MDTM outcome was analyzed, which to our knowledge has not been investigated before.

The most important findings include: (1) the sensitivity for detecting early true disease progression was poor to moderate for all evaluation approaches (32%–62%); (2) AUC values were comparable (range 0.63–0.74), but highest for the MDTM evaluation (0.74); (3) for the 26% of patients in whom the MDTM was inconclusive, systematic pMRI evaluation showed potential for identifying additional cases of tumor progression; (4) lower KPS score and pMRI results indicative of tumor progression were independently associated with the conclusion of tumor progression during the MDTM.

There was moderate sensitivity for detecting early tumor progression for all MRI approaches and the MDTM assessment (32%–62%). The sensitivity in this study was increased by adding pMRI to conventional MRI (from 32% with conventional MRI to 54%–62% with ASL and/or DSC added). The specificity ranged from 67% (ASL) to 93% (conventional MRI). The specificity decreased from 93% with conventional MRI to 67%–80% when combined with pMRI. The increased sensitivity due to the addition of the pMRI is in line with previous studies, in which an added value of DSC compared to conventional MRI was demonstrated in high-grade gliomas.[4,18,19] Although the literature on the value of ASL is scarce, this technique has shown to be equivalent to DSC in comparative studies for detection of progressive disease.[7,20] For the limited studies on ASL a sensitivity in the range of 52%–79% and a specificity in the range 64%–82% were reported, which is similar to what we have found in the current study. The reduced specificity when adding DSC pMRI to conventional MRI contradicts previous literature, in which the use of DSC pMRI resulted in an increased accuracy with sensitivity and specificity of 86% and 87%, respectively.[21] The current study, however, may be influenced by the relatively low negative predictive values, indicating there are quite some false negatives, reflecting conservative scoring. The diagnostic accuracy of the different MRI approaches, with and without pMRI, to detect tumor progression was quite similar with AUC values ranging from 0.63 to 0.68. The MDTM showed a slightly higher diagnostic accuracy of 0.74. The probable reason for this finding is that the MDTM takes into account both the clinical characteristics (eg, performance status, neurological symptoms, and age) of the patients at 3 months in addition to the radiological findings. Note that pMRI was part of the radiological information available to the MDTM, although we were unable to reconstruct to what extent information from the pMRI had played a role in the final conclusion of the MDTM. Previous studies have shown that there is a relationship between worsened clinical performance in case of tumor progression, as opposed to pseudoprogression, which can be asymptomatic.[2,22] This result was confirmed by our multivariable logistic regression analysis showing that both clinical and radiological parameters were considered in making the final diagnosis in the MDTM, as also shown in previous studies.[4,18,22,23]

In our study, it appeared that in 26% of the MDTM cases no definite diagnosis could be made as to whether there was tumor progression or treatment-related abnormalities.

For these cases, a higher sensitivity was observed for pMRI compared to the conventional MRI, while for both approaches the specificity was 100%. This could indicate that some clinical factors pointed at tumor progression, while conventional MRI scans did not support this diagnosis, thus the MDTM was inconclusive. However, pMRI confirmed the suspicion of tumor progression in some of the patients and thus might be helpful in cases for which the clinical assessment is uncertain by finding some additional cases of progression that could not be detected by the standard clinical procedures. This could be an important finding to avoid unnecessary aggressive interventions such as reoperations, which are sometimes chosen when there is doubt about the diagnosis, before additional tumor treatment follows histopathological confirmation.[9,23] In addition, in case of pseudoprogression, continuation of treatment with chemotherapy with TMZ can be considered, as the treatment-induced abnormalities are expected to disappear without change of treatment regimen.[23] This is in line with the findings of Geer et al.,[12] where they showed an improved confidence for decision-making by adding pMRI to the radiological evaluation. Furthermore, the treatment strategy was changed in some of the subjects due to the addition of pMRI, which highlights its added value in assessing treatment efficacy.

One of the strengths of this study is the homogeneous patient population of only patients with glioblastoma. Moreover, follow-up data were gathered until 9 months, which seems to be an adequate time frame to obtain a reliable outcome marker of tumor progression vs pseudoprogression, since the mRANO criteria recommend to use the 6 months follow-up evaluation to determine the outcome in case of any uncertainties at the 3 months follow-up evaluation. Nevertheless, a histological diagnosis is still considered the gold standard. In addition to conventional MRI sequences, both ASL and DSC perfusion scans were available for analysis. The use of ASL is especially beneficial due to its noninvasive nature, that is, it allows perfusion imaging without the need for intravenous contrast agent injection (or less contrast agent, since some contrast agent is still needed for the post-contrast T_{1w} scan) or complicated post-processing. However, ASL is not widely implemented as part of the standard clinical routine. The DSC scans were acquired by the use of a SE-EPI sequence, which is not according to the consensus recommendations,[24] although this was according to clinical practice in the hospital where the inclusions took place at the time before the recommendations were published. A limitation of the current study is the lack of quantitative radiological information (ie, rCBV). However, the previous study by Kerkhof et al.[10] showed that the optimum rCBV to distinguish between tumor progression and pseudoprogression remains challenging, though this study was performed in patients with brain metastases. In addition, the order in which the MR images were assessed might have introduced some bias in the evaluation of the perfusion maps. This bias could be mitigated in further studies by randomizing the order in which the MR images are assessed or by performing the scoring procedure across multiple sessions. A further limitation is the final outcome of tumor progression or pseudoprogression, which is not independent from the MDTM assessment. However, multiple factors were considered to define the final outcome, such as data on overall survival and clinical and radiological follow-up information from the medical files. Furthermore, there is a possibility of the tumor progressing after the time point of 3 months post-RT assessment, which affects the sensitivity of the assessment at the 3 months time point for detecting tumor progression. At a later time point, there is way more information to make this decision; thus, the decision is made with much more certainty when incorporating follow-up data up to 9 months. Nevertheless, there was only a small number of patients with a final diagnosis of "no tumor progression," which also impacted our results.

Empirical research shows that MDTMs do not always live up to their positive expectations.[11] The goal of the MDTM is to ensure that all patients receive quality care from well-trained professionals, going through 3 main communicative phases: exploration, discussion, and conclusion. Previous research showed that some MDTMs follow a different structure than others.[25] It is also not indicated within the exploration phase to what extent an observation plays a role in the decision-making process. This makes it impossible to determine with certainty to what extent the radiological findings, including pMRI, have influenced the final outcome, although some insights could be obtained from our multivariable logistic regression model. Even though one could argue that the pMRI assessment and the MDTM are not independent, since pMRI is part of the MDTM evaluation, the MDTM also incorporates important clinical features that are shown to be important for predicting the outcome. Furthermore, the setting in which the MDTM and pMRI assessment was performed differed, that is, a global evaluation of pMRI together with clinical information was compared to a systematic evaluation of pMRI in a research setting. By systematically evaluating the pMRI scans, the way the MDTM evaluates early tumor progression may be improved. Changing compositions of the MDTM and also of the neuroradiologists who assess the scans could have influenced the results. Regarding the treatment strategy, it was found in a previous study[26] that concomitant RT with TMZ was associated with pseudoprogression in glioblastoma. However, in our study most patients showed tumor progression and therefore we did not find evidence that supported this finding. In addition, the use of dexamethasone (or other corticosteroids), which can reduce the inflammatory response in pseudoprogression due to its anti-inflammatory property,[5] might have influenced the radiological evaluation. However, due to the retrospective nature of this study, it was not possible to analyze and correct for these factors separately, because there were many fluctuations in use and dosage within patients.

Conclusion

The MDTM assessment has the highest diagnostic accuracy in distinguishing early tumor progression from pseudoprogression, in which the performance status of the patient and pMRI results are most informative. A

separate, systematic evaluation of pMRI might additionally be helpful if the MDTM assessment is uncertain. In future studies, it should be investigated which factors play a role in the final decision-making during the MDTM and to what extent.

Supplementary material

Supplementary material is available online at *Neuro-Oncology Practice* (https://academic.oup.com/nop/).

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Conflict of interest statement

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