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Dorth, D. van; Jiang, F.Y.; Schmitz Abecassis, B.; Croese, R.J.I.; Taphoorn, M.J.B.; Smits, M.; ... ; Osch, M.J.P. van

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Influence of arterial transit time delays on the differentiation between tumor progression and pseudoprogression in glioblastoma by arterial spin labeling magnetic resonance imaging

Daniëlle van Dorth[1] | Feng Yan Jiang[2,3] | Bárbara Schmitz-Abecassis[1,4] | Robert J. I. Croese[5,6] | Martin J. B. Taphoorn[5,6] | Marion Smits[4,7,8] | Johan A. F. Koekkoek[5,6] | Linda Dirven[5,6] | Jeroen de Bresser[2] | Matthias J. P. van Osch[1,4]

[1]C. J. Gorter MRI Center, Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

[2]Department of Radiology, Leiden University Medical Center, Leiden, The Netherlands

[3]Department of Radiology, HagaZiekenhuis, Den Haag, The Netherlands

[4]Medical Delta, Delft, The Netherlands

[5]Department of Neurology, Leiden University Medical Center, Leiden, The Netherlands

[6]Department of Neurology, Haaglanden Medical Center, Den Haag, The Netherlands

[7]Department of Radiology and Nuclear Medicine, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands

[8]Brain Tumor Center, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence
Daniëlle van Dorth, C. J. Gorter MRI Center, Department of Radiology, Leiden University Medical Center, Albinusdreef 2, 2333ZA, Leiden, The Netherlands.
Email: d.van_dorth@lumc.nl

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Abstract

Arterial spin labeling (ASL) and dynamic susceptibility contrast (DSC) magnetic resonance imaging (MRI) have shown potential for differentiating tumor progression from pseudoprogression. For pseudocontinuous ASL with a single postlabeling delay, the presence of delayed arterial transit times (ATTs) could affect the evaluation of ASL-MRI perfusion data. In this study, the influence of ATT artifacts on the perfusion assessment and differentiation between tumor progression and pseudoprogression were studied. This study comprised 66 adult patients (mean age 60 ± 13 years; 40 males) with a histologically confirmed glioblastoma who received postoperative radio (chemo)therapy. ASL-MRI and DSC-MRI scans were acquired at 3 months postradiotherapy as part of the standard clinical routine. These scans were visually scored regarding (i) the severity of ATT artifacts (%) on the ASL-MRI scans only, scored by two neuroradiologists; (ii) perfusion of the enhancing tumor lesion; and (iii) radiological evaluation of tumor progression versus pseudoprogression by one neuroradiologist. The final outcome was based on combined clinical and radiological

Abbreviations: ASL, arterial spin labeling; ATT, arterial transit time; DSC, dynamic susceptibility contrast; EPI, echo planar imaging; FLAIR, fluid-attenuated inversion recovery; IDH, isocitrate dehydrogenase; PLD, postlabeling delay; WHO, World Health Organization.

follow-up until 9 months postradiotherapy. ATT artifacts were identified in all patients based on the mean scores of two raters. A significant difference between the radiological evaluation of ASL-MRI and DSC-MRI was observed only for ASL images with moderate ATT severity (30%–65%). The perfusion assessment showed ASL-MRI tending more towards hyperperfusion than DSC-MRI in the case of moderate ATT artifacts. In addition, there was a significant difference between the prediction of tumor progression with ASL-MRI and the final outcome in the case of severe ATT artifacts (McNemar test, $p = 0.041$). Despite using ASL imaging parameters close to the recommended settings, ATT artifacts frequently occur in patients with treated brain tumors. Those artifacts could hinder the radiological evaluation of ASL-MRI data and the detection of true disease progression, potentially affecting treatment decisions for patients with glioblastoma.

KEYWORDS
arterial spin labeling, arterial transit time, glioblastoma, perfusion MRI, pseudoprogression, tumor progression

1 | INTRODUCTION

Glioblastoma is a malignant primary brain tumor that is associated with poor median overall survival of approximately 15 months.[1] The current standard of care consists of radiotherapy with concomitant chemotherapy with temozolomide, followed by adjuvant treatment with temozolomide.[2] Radiochemotherapy can induce radiological abnormalities that mimic tumor recurrence, which is called pseudoprogression.[2,3] It is important to make the distinction between pseudoprogression and true disease progression, because in contrast to pseudoprogression, disease progression may require a change in the treatment regimen.[3,4]

Although both tumor progression and pseudoprogression can display enhancement on the 3D postcontrast T_{1w} scan and show hyperintense signal on the T_{2w} fluid-attenuated inversion recovery (FLAIR) scan, the underlying physiological processes are fundamentally different.[2] In the event of tumor progression, neo-angiogenesis leads to enhancement on the postcontrast T_{1w} scan and increased perfusion in the tumor. Also, tumor progression causes a hyperintense signal on the T_{2w} FLAIR scan because of infiltrating tumor.[5] On the other hand, in the event of pseudoprogression, there is a transient increase in vessel permeability, because the blood–brain barrier is damaged by the treatment. This leads to extravasation of contrast agent, causing enhancement on the postcontrast T_{1w} scan.[6–8] In addition, surrounding edema, inflammation of the tissue, and ischemia are potential causes of the hyperintense signal on the T_{2w} FLAIR scan.[5,6,9] Pseudoprogression is typically present within the first 3 to 6 months after treatment with radiotherapy, followed by spontaneous improvement or resolution.[7,10]

To overcome the limitations of structural clinical sequences in distinguishing between tumor progression and pseudoprogression, perfusion magnetic resonance imaging (MRI) has been demonstrated to be valuable.[3,6–12] Whereas the most commonly applied perfusion MRI technique is still dynamic susceptibility contrast (DSC) MRI, arterial spin labeling (ASL) MRI is increasingly recognized as a promising alternative, because it does not require exogenous contrast injection. The commonly used approach for ASL is a pseudocontinuous ASL (pCASL) sequence with a single postlabeling delay (PLD) of 1800 ms.[6,7,13] However, the resulting images could be affected by arterial transit time (ATT) delays.[14,15] In cases of ATT prolongation, not all labeled spins have arrived in the tissue at the time of imaging and are still residing within the arterial system. This results in an apparent signal increase in the larger vasculature, which could affect the interpretation of the ASL perfusion, that is, overestimation of local tissue perfusion. ATT artifacts are caused by changes in the vasculature that affect the blood circulation. Among those changes are radiation-induced vasculopathy, potentially leading to ischemic stroke and collateral flow.[16] Previous work has shown the influence of chemoradiation on some biomarkers for the tumor vasculature, such as K_{trans} and vascular endothelial growth factor,[17] however, the exact mechanism behind treatment-induced ATT artifacts remains unclear.

The presence of ATT artifacts implies that not all labeled blood has fully reached the brain tissue it would supply at the end and therefore certain regions might appear hypoperfused. For this reason, region-of-interest analysis might show an underestimation of the tissue perfusion,[14] which could thus affect the radiological evaluation of tumor progression versus pseudoprogression. ATT artifacts can therefore lead to local underestimation as well as overestimation of perfusion.

The purpose of this study was to investigate the influence of the ATT artifacts on (i) the visual assessment of ASL tumor perfusion (decreased, normal, increased) compared with DSC-MRI; (ii) the concordance in differentiation between tumor progression and pseudoprogression of ASL-MRI and DSC-MRI; and (iii) the accuracy of ASL-MRI scans at 3 months postradiotherapy for detecting tumor progression.

2 | METHODS

2.1 | Subjects

This retrospective single-center study was performed in accordance with local institutional review board regulations. Patient data were gathered over a period from January 2015 until February 2022. This study was part of a larger project, for which patients were eligible if they met the following criteria: (i) informed consent given (if alive); (ii) age 18 years or older; (iii) histologically confirmed glioblastoma according to the World Health Organization (WHO) 2016 classification[18] (WHO grade 4 glioblastoma isocitrate dehydrogenase [IDH]-wildtype, mutant or not otherwise specified); (iv) postoperative treatment with radiotherapy (and concomitant and adjuvant chemotherapy); (v) preradiotherapy and postradiotherapy MR imaging data available (only postradiotherapy data are used in this study, but availability of preradiotherapy data was an inclusion criteria for the larger project); also, image quality of the DSC and ASL data needed to be sufficient to be evaluated; and (vi) confirmation of the diagnosis of true tumor progression or pseudoprogression. This diagnosis was based on radiological follow-up data acquired at 3, 6, and/or 9 months postradiotherapy if available combined with the clinical course.[19] In case of re-resection, histopathology was the guiding principle for determining the outcome. Each individual patient record was retrospectively screened to collect this information, where also the decision from the multidisciplinary consultation was considered. This consultation was part of standard clinical procedures and consisted of an experienced neuro-oncologist, neuroradiologist, neurosurgeon, and neuropathologist.

2.2 | MR imaging

All patients were scanned at ~3 months postradiotherapy (mean 93 ± 24 days) and every 3 months thereafter at a Philips Achieva or Philips Ingenia 3-T scanner (Philips Healthcare), where the range for inclusion was set at 60 to 135 days postradiotherapy. The MRI scans were acquired as part of the clinical routine. Precontrast and postcontrast T_{1w} images were acquired using a 3D turbo field echo sequence, as well as 2D T_{2w} FLAIR images and diffusion-weighted images. ASL images were acquired with a 2D echo planar imaging (EPI) pCASL with 1650 ms labeling duration and PLDs of 1525 ms (first slice)–2120 ms (last slice). M_0 images were not acquired within this standard clinical protocol. Background suppression was used. The other acquisition parameters were: echo time (TE) = 16 ms, repetition time (TR) = 4.0 s, flip angle = 90°, field of view (FOV) = 240 × 240 mm^2, acquisition matrix = 78 × 78, resolution = 3.0 × 3.0 mm^2, and slice thickness = 7.0 mm. No vascular crusher gradients were used. The total scan time was 4 min 8 s. The DSC-MRI was performed with a spin echo-EPI sequence: 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, and slice thickness = 5.0 mm. For DSC, a prebolus 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, France) using an MRI-approved power injector (Medrad, Bayer, Germany) at a rate of 5 mL/s with an injection delay of 14 s. The total scan time for DSC was 1 min 42 s.

2.3 | Visual scoring of MR scans

The visual scoring of the ASL and DSC scans was performed by an independent and experienced neuroradiologist not involved in the clinical decision making of the patient. The scoring was based on the following three aspects:

1. The severity of ATT artifacts was scored on the ASL scans only. Severe ATT artifacts could be described as an angiography scan, where the label is still in the large vessels, while in the absence of ATT artifacts the ASL signal would be more homogeneously distributed throughout the cortex. The severity of the ATT artifacts was scored as a percentage between 0% and 100% with a step size of 5%. The ATT artifacts were scored by two experienced neuroradiologists in order to reduce observer bias. Figure 1 shows example ASL images with different levels of ATT artifacts severity based on the mean score of the two raters.
2. Perfusion score: lesion perfusion of both ASL and DSC scans was scored using the postcontrast 3D T_{1w} scan as anatomical reference. We considered multiple lesions per patient (a total of 97 lesions in 66 patients). The analysis was separated for nodular and patchy enhancing patterns within the lesions, because the pattern of enhancement has been shown to be associated with prognosis in patients with low-grade glioma.[20] The perfusion in the enhancing lesion was indicated as decreased, normal, or increased compared with the contralateral region (for ASL only, the options normal and increased were given, because hypoperfusion is notoriously difficult to assess[21]). Therefore, the options "decreased" and "normal" for DSC were merged to create a 2 × 2 table for the analysis.
3. Radiological score: ASL and DSC perfusion maps (cerebral blood flow and cerebral blood volume grayscale maps, respectively) were separately interpreted at patient level on a seven-point Likert scale ranging from 1 to 7, with 1 representing definite pseudoprogression and 7 representing definite tumor progression. The radiological scores were determined based on multiple features, one of which is the perfusion in the

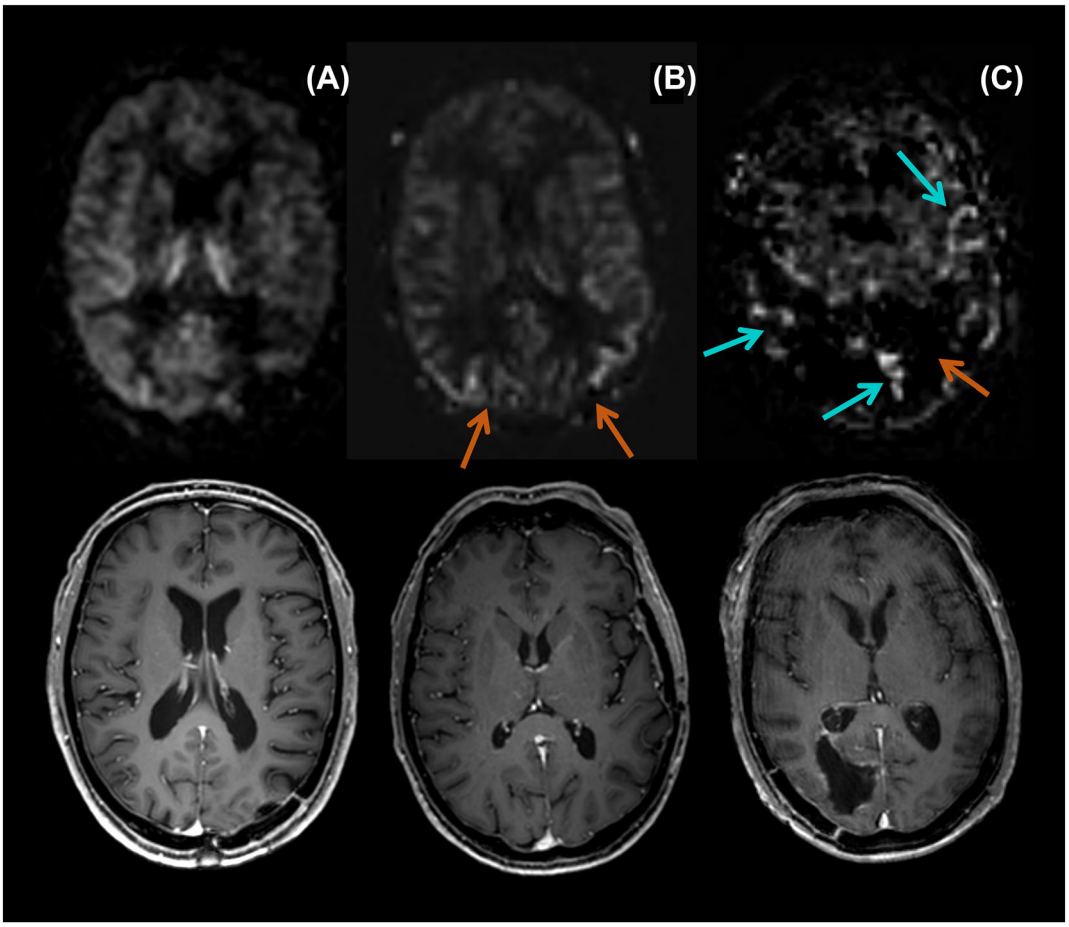

FIGURE 1 ASL images showing different levels of ATT artifacts severity (top row). The corresponding postcontrast T_{1w} scans are also shown (bottom row). (A) 57-year-old female with mild severity of ATT artifacts (20%); (B) 71-year-old male with moderate severity of ATT artifacts (55%); (C) 71-year-old female with high severity of ATT artifacts (85%). In (B), the posterior flow region seems less perfused (orange arrows), while also some of the cortex border zones display high signal intensity. In (C), tissue perfusion in the posterior flow region seems to be absent (orange arrow) and the signal in the large vessels is clearly visible (blue arrows). ASL, arterial spin labeling; ATT, arterial transit time.

tumor compared with the contralateral region. Other features included the presence of leptomeningeal disease, the tumor location, the number and size of the lesions, the pattern of enhancement (nodular/patchy) on the postgadolinium T_{1w} MRI scan, and the T_{2w} FLAIR hyperintensities.

2.4 | Statistical analysis

Groups were created based the severity of ATT artifacts. Mild ATT artifacts were defined as less than 30%, moderate ATT artifacts were defined as 30%–65%, and severe ATT artifacts were defined as 65% or greater.

To assess the differences in perfusion assessment (i.e., normal or increased) between the ASL and DSC scans, 2×2 tables were created. The McNemar test was used to investigate if there was a statistically significant difference between the ASL and DSC perfusion scores.

To investigate the radiological evaluation of the DSC and ASL scans on patient level, the concordance was calculated as the percentage of cases for which there was exact agreement between both methods. The concordance between the DSC and ASL scans in radiological score was statistically tested by a Wilcoxon signed-rank test for patients grouped based on the severity of ATT artifacts. Furthermore, a Levene's test was performed to study the variances in difference scores between ASL and DSC for the patients grouped based on the severity of ATT artifacts. Bland–Altman plots were used to visualize the differences. In addition, the correlation between the ASL and DSC scores was studied. Correlations were defined as very strong ($r > 0.8$), strong ($0.6 \leq r < 0.8$), moderate ($0.4 \leq r < 0.6$), weak ($0.2 \leq r < 0.4$), or very weak ($r < 0.2$).

Lastly, the association between the ASL radiological score at 3 months postradiotherapy and the final outcome (i.e., tumor progression or no progression) was determined based on 2 × 2 tables, and a McNemar test was calculated to determine if differences were statistically significant. For this part of the analysis, a binary scale was established because of the potential application in clinical practice. An ASL radiological score of 1 to 3 was considered no tumor progression, while a score of 4 to 7 was considered tumor progression. Furthermore, the sensitivity and specificity of the ASL radiological score to detect tumor progression were determined.

All statistical analyses were performed in R using a significance level of p of 0.05 or less.

3 | RESULTS

3.1 | Clinical information

For 84 patients, imaging data were judged, and 13 subjects were excluded because of too poor image quality to evaluate perfusion and/or ATT artifacts ($N = 11$) or missing perfusion data ($N = 2$). Therefore, a total of 71 patients with glioblastoma were eligible according to the inclusion criteria. However, one of the patients was scanned at 1.5 T, one of the patients was scanned with a 3D ASL acquisition, for one patient the enhancing lesion was too small to characterize the perfusion, and for two patients the lesion appeared to be nonenhancing on the postcontrast 3D T_{1w} scan postradiotherapy. Therefore, those five patients were excluded from this study, resulting in a study population of 66 patients with glioblastoma eligible for data analysis. Table 1 summarizes the demographic and clinical information.

3.2 | ATT artifacts

The interobserver agreement was 0.66 (Cohen's quadratic kappa, $p < 0.001$). For five of the patients, the difference between the two scores was 40% or higher. Therefore, a consensus score was determined by the two raters for those five patients. Without considering these outliers, the interobserver agreement increased to 0.79 (Cohen's quadratic kappa, $p < 0.001$). The correlation between the two observer scores was strong (Spearman's rho = 0.75, $p < 0001$). Figure S1 summarizes the ATT severity scores of the two raters. All of the 66 patients showed ATT artifacts according to the mean or consensus score of the two raters. Of those, 18 patients (27%) had severe ATT artifacts (i.e., a severity score of ≥ 65%). Figure S2 illustrates the differences of the ATT artifacts from a severity of 20% to 85%, as well as some examples of ASL and DSC-MRI perfusion maps.

TABLE 1 Clinical information.

Male patients, *n* (%)	40 (61%)
Age at 3 months follow-up MRI (mean years ± SD)	60 ± 13
KPS, median (range)	90 (60–100)
Surgery, *n* (%)	
Resection	52 (79%)
Biopsy	14 (21%)
Radiotherapy dose, *n* (%)	
40 Gy	8 (12%)
45 Gy	11 (17%)
60 Gy	47 (71%)
Concomitant and adjuvant temozolomide chemotherapy, *n* (%)	53 (80%)
MGMT methylation, *n* (%)	18 (27%)
IDH mutation status, *n* (%)	
IDH mutant	4 (6%)
IDH wildtype	43 (65%)
Unknown	19 (29%)
Lesions per patient, median (range)	1 (1–4)

Abbreviations: IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Score; MGMT, O(6)-Methylguanine-DNA-methyltransferase; MRI, magnetic resonance imaging; SD, standard deviation.

3.3 | Lesion perfusion on ASL versus DSC images

Tables 2 and 3 show the 2 × 2 cross-tables summarizing the perfusion assessment of the lesions ($n = 97$) on ASL and DSC perfusion maps. Some lesions consisted of both nodular and patchy patterns of enhancement, which were separately included in the analysis. In total, 37 nodular and 69 patchy enhancing regions were analyzed. For patchy lesions, it was only in the case of moderate ATT severity that the McNemar test showed a significant difference between the ASL and DSC scores ($p = 0.023$), where ASL showed more hyperperfusion than DSC.

3.4 | Radiological evaluation of tumor progression versus pseudoprogression

In the presence of mild ATT artifacts, for 16/25 patients (64%), the radiological score showed agreement between ASL and DSC. In the case of moderate ATT artifacts, agreement was found in 15/23 patients (65%), while for severe ATT artifacts agreement was found in 11/18 patients (61%). In the presence of moderate ATT artifacts, ASL and DSC scores differed significantly (median 5 vs. 3, $p = 0.04$), while there was no statistically significant difference between ASL and DSC for mild or severe ATT artifacts (mild: median 5 vs. 3, $p = 0.11$; severe: median 5 for both ASL and DSC, $p = 0.58$).

Figure 2 illustrates the differences between the ASL and DSC radiological scores in the presence of mild, moderate, and severe ATT artifacts. Figure 2A,B show a larger spread in the difference score between ASL and DSC compared with Figure 2C. However, the difference in variances between the three groups was not significant according to Levene's test ($p = 0.49$).

Moreover, the correlation between the ASL and DSC radiological scores was studied to confirm the association between the radiological scores of ASL and DSC. Figure 3 shows a very strong correlation between the radiological evaluation on ASL and DSC scans for severe ATT

TABLE 2 Perfusion assessment on ASL and DSC MRI perfusion maps in nodular enhancing regions. In most cases, the ASL and DSC perfusion scores are similar (McNemar: $p = 1.0$, $p = 0.24$, and $p = 1.0$ for mild, moderate, and severe ATT artifacts, respectively).

	ASL normal	ASL increased
Mild ATT artifacts		
DSC normal	5	2
DSC increased	1	5
Moderate ATT artifacts		
DSC normal	2	3
DSC increased	0	10
Severe ATT artifacts		
DSC normal	2	0
DSC increased	1	6

Abbreviations: ASL, arterial spin labeling; ATT, arterial transit time; DSC, dynamic susceptibility contrast; MRI, magnetic resonance imaging.

TABLE 3 Perfusion assessment on ASL and DSC MRI perfusion maps in patchy enhancing regions. In the case of moderate ATT artifacts, the ASL score shows more hyperperfusion compared with DSC (McNemar: $p = 0.023$). For mild or severe ATT artifacts, the difference was not statistically significant (McNemar: $p = 1.0$ and $p = 0.61$, respectively).

	ASL normal	ASL increased
Mild ATT artifacts		
DSC normal	12	2
DSC increased	1	5
Moderate ATT artifacts		
DSC normal	10	7
DSC increased	0	9
Severe ATT artifacts		
DSC normal	13	3
DSC increased	1	6

Abbreviations: ASL, arterial spin labeling; ATT, arterial transit time; DSC, dynamic susceptibility contrast; MRI, magnetic resonance imaging.

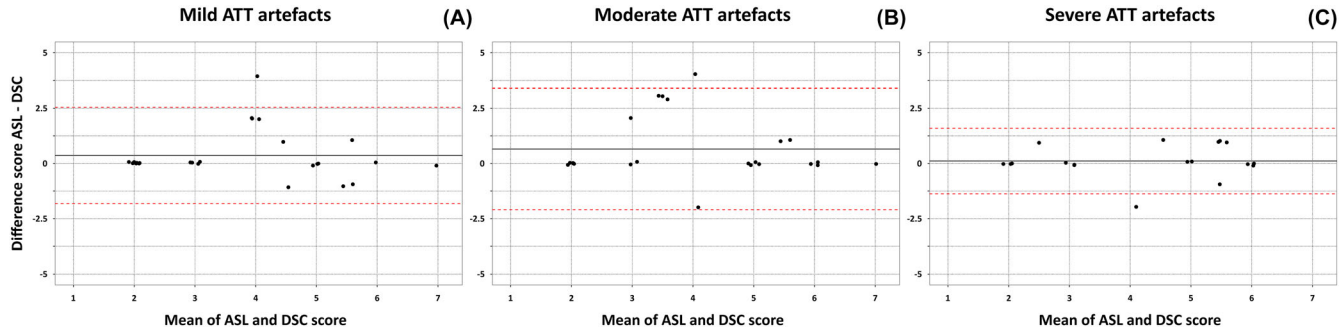

FIGURE 2 Bland–Altman plot (+/− 1.96 SD) showing wider limits of agreement in the difference score between the ASL and DSC scans for (A) Mild, and (B) Moderate ATT artifacts, while for (C) Severe artifacts, there are smaller limits of agreement for the difference score between the ASL and DSC scans. ASL, arterial spin labeling; ATT, arterial transit time; DSC, dynamic susceptibility contrast; SD, standard deviation.

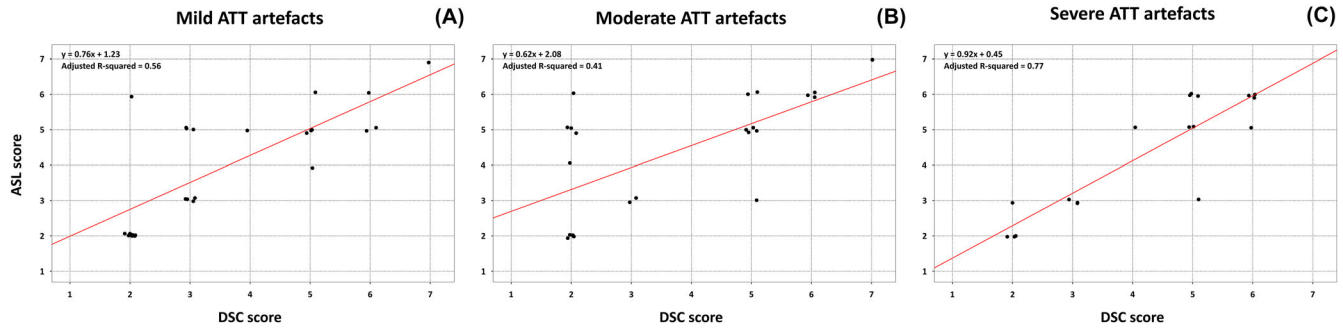

FIGURE 3 Correlation between scores on ASL and DSC scans in patients with (A) Mild ATT artifacts (Spearman's rho = 0.75, $p < 0.001$), (B) Moderate ATT artifacts (Spearman's rho = 0.68, $p < 0.001$), and (C) Severe ATT artifacts (Spearman's rho = 0.85, $p < 0.001$). ASL, arterial spin labeling; ATT, arterial transit time; DSC, dynamic susceptibility contrast.

artifacts (Spearman's rho = 0.85), whereas for mild and moderate ATT artifacts the correlation was strong (Spearman's rho = 0.75 and 0.68, respectively).

3.5 | Association between ASL radiological score and tumor progression

Sixty-four of 66 patients could be included for the comparison of the ASL radiological evaluation and the tumor progression based on follow-up data until 9 months. For two patients, no decision was possible because of termination of treatment (as a result of cardiac issues) or that insufficient follow-up data were available. For all 64 patients included in this part of the analysis the data were available up to 3 months postradiotherapy, where for 40 of those patients data were available up to 6 months, and for 30 of those patients data were available up to 9 months. The results showed that 49/64 patients had tumor progression, whereas 15/64 patients had no progression. Table 4 shows the 2 × 2 cross-tables summarizing the comparison between the ASL radiological score and the final outcome of tumor progression. The number of patients with tumor progression was 15/24 (63%) in the group with mild ATT artifacts, 18/22 (82%) in the group with moderate ATT artifacts, and 16/18 (89%) in the group with severe ATT artifacts. The McNemar test showed a significant difference between the ASL prediction at 3 months postradiotherapy and the final outcome with respect to tumor progression in the presence of severe ATT artifacts ($p = 0.041$), whereas for mild or moderate ATT artifacts the difference was not significant ($p = 1.0$ and 0.22, respectively). The sensitivity for detecting tumor progression was lowest for severe artifacts (63%) compared with moderate (72%) and mild (67%) ATT artifacts, although the differences were small. On the other hand, the specificity was highest for severe ATT artifacts (100%) compared with moderate (75%) and mild (56%) ATT artifacts. Table **S1** summarizes the results for DSC-MRI, where it can be seen that the sensitivity for detecting tumor progression is higher for ASL-MRI compared with DSC-MRI in the case of mild or moderate ATT artifacts. Tables S2 and S3 summarize the comparison between the ASL prediction at 3 months postradiotherapy and the final outcome with respect to tumor progression on the lesion level, where the results were analyzed for both nodular and patchy lesions separately. It was shown that for patchy lesions, there was a significant difference between the ASL radiological score and the final outcome in the case of severe ATT artifacts ($p = 0.023$), while for mild or moderate ATT artifacts the difference was not significant

TABLE 4 ASL radiological score based on imaging at 3 months postradiotherapy versus the outcome tumor progression based on clinical and radiological follow-up until 9 months postradiotherapy. The McNemar test showed a significant difference between the ASL radiological score and the final outcome only for severe ATT artifacts ($p = 0.041$), while for mild or moderate ATT artifacts the difference was not significant ($p = 1.0$ and 0.22, respectively).

	No progression	Progression
Mild ATT artifacts		
ASL no progression	5	5
ASL progression	4	10
	Specificity = 56%	Sensitivity = 67%
Moderate ATT artifacts		
ASL no progression	3	5
ASL progression	1	13
	Specificity = 75%	Sensitivity = 72%
Severe ATT artifacts		
ASL no progression	2	6
ASL progression	0	10
	Specificity = 100%	Sensitivity = 63%

Abbreviations: ASL, arterial spin labeling; ATT, arterial transit time.

($p = 0.68$ and $p = 0.13$, respectively). For nodular lesions, there were no significant differences between the ASL radiological scores and the final outcome for mild, moderate, and severe ATT artifacts ($p = 0.25$, $p = 1.0$, and $p = 0.48$, respectively).

4 | DISCUSSION

This study investigated the presence of ATT artifacts on ASL imaging in patients with glioblastoma, the influence of ATT artifacts on the perfusion assessment and radiological evaluation of the ASL perfusion maps, and the influence of those artifacts on the accuracy of ASL-MRI at 3 months postradiotherapy for detecting tumor progression. The main findings of this study were: (i) in all of the patients with glioblastoma scanned with pCASL, ATT artifacts were observed; (ii) the perfusion assessment showed that ASL scores tended more towards hyperperfusion than DSC in the case of moderate ATT artifacts; (iii) for moderate ATT artifacts, the radiological evaluation of tumor progression differed significantly between ASL and DSC-MRI; and (iv) in the presence of severe ATT artifacts, the prediction of ASL-MRI acquired at 3 months postradiotherapy significantly differed from the final outcome with respect to tumor progression.

First, it should be recognized that even when using settings close to the recommended settings by the ISMRM Perfusion study group,[13] in a large number of patients, ATT artifacts were observed. When using ASL, a compromise has to be reached between a sufficiently long PLD time to allow the labeled spins to arrive at their destination in tissue/tumor, and the signal-to-noise ratio (SNR) of the measurement that is decreasing with increasing delay times due to T_1 relaxation of the label. Alsop et al.[13] provided recommended settings for pCASL to achieve the optimal trade-off between risk of vascular artifacts and SNR. However, our results illustrate that the possible presence of ATT artifacts is still a highly relevant phenomenon that radiologists should be aware of when interpreting ASL perfusion scans. The perfusion assessment showed that in most cases the ASL and DSC maps agreed, and when this was not the case, the ASL perfusion was scored higher (i.e., indicative of hyperperfusion) compared with the DSC perfusion (Tables 2 and 3), although this was only significantly different for moderate ATT artifacts and patchy lesions. The radiological evaluation of tumor progression versus pseudoprogression showed a statistically significant difference in the agreement between the scoring of DSC and ASL in the case of moderate ATT artifacts, whereas for mild or severe ATT artifacts the difference did not reach statistical significance. Figure S3 supports this finding, because the largest discrepancies between ASL and DSC were found in the severity range of 20%–55%. However, some care with interpretation is needed because of the small group sizes, which might have affected the statistical power.

The correlational analysis showed that the neuroradiologist tended slightly more towards the diagnosis of tumor progression when using ASL compared with DSC (Figure 3). This agrees with the tendency of ASL perfusion scores towards hyperperfusion and also with a higher sensitivity for detecting tumor progression compared with DSC-MRI, especially for mild and moderate ATT artifacts.

For ASL-MRI, there was a significant difference between the radiological score at 3 months postradiotherapy and the final outcome of tumor progression in the presence of severe ATT artifacts, while for mild or moderate ATT severity the difference was not statistically significant. This finding might imply that severe ATT artifacts affect the radiological evaluation of the ASL scans, as would be expected from previous literature highlighting the impact of the ATT delay on ASL perfusion imaging.[15,22,23] This finding highlights the importance of considering the ATT artifacts

in clinical decision making. The presence of severe ATT artifacts appeared to lower the sensitivity, although not the specificity, of the ASL radiological score for detecting tumor progression. Additionally, the sensitivity and specificity were moderate, suggesting that the clinical utility of ASL-MRI at 3 months postradiotherapy for detecting true disease progression can still be improved further.

The strength of this study is the extensive amount of follow-up data available for a large number of patients, which made it possible to include the final clinical outcome in our analysis. In many hospitals, ASL perfusion MRI has only recently been introduced, which make data as presented in our study rare. Moreover, no reports have been published on the influence of ATT artifacts on the interpretation of ASL perfusion MRI in the follow-up of patients with glioblastoma. Our findings thus constitute an important addition to the existing literature.

This study has some limitations that need to be discussed. First, the perfusion scans were acquired as part of the standard clinical routine, where for some of the patients the perfusion data were missing or the image quality was too poor to score (due to, e.g., incorrect labeling). Therefore, those patients were excluded during our quality check. In this study, the patients were scanned with a 2D ASL sequence, in which the labeling duration was shorter than recommended (1650 ms vs. the recommended 1800 ms) and the PLD varied over the slices (from 1525 ms for the lowest up to 2120 ms for the highest slice). Although this results in a different effective PLD per slice, the variation in PLD intrinsically accounts for the differences in arrival time in the craniocaudal direction. These settings are probably slightly more sensitive towards ATT artifacts, but the difference with the recommended settings should still be considered small. Furthermore, it should be stated that such a 2D readout has less intrinsic vascular crushing than 3D sequences and might therefore show more intravascular signal. Please note that the recommendations are to not suppress vascular signal by means of crusher gradients, so as to provide the clinician with all the available information. This emphasizes, once again, that the reporting radiologists should be aware of the risk of ATT artifacts when interpreting ASL perfusion scans.

Second, the current scoring could be perceived as subjective; however, the ASL images were scored by two raters to reduce observer bias. In addition, by providing example images (Figure S2), we have ensured that this scoring can be reproduced by other researchers. In the end, the percentage scale was summarized into three groups (i.e., mild, moderate, and severe ATT artifacts), which should only lead to some variation around the cut-off values.

Another limitation of this study is that for comparison of radiological scores between ASL and DSC, the latter can only be considered a pseudogold standard. DSC-MRI can underestimate perfusion when leakage effects are dominating. This drawback is minimized by using a predose and by incorporating leakage correction using the Boxerman–Weisskoff approach[24] in the postprocessing procedure. The clinical outcome was considered as the true gold standard.

In addition, while the full range of radiological scores was used for comparison between ASL-MRI and DSC-MRI, the scores were binarized for the last part of the analysis that addresses the relationship with the final outcome. The latter allows for a decision comparable with clinical practice, in which each case is marked as either progression or pseudoprogression. On the other hand, when comparing the radiological scores from ASL-MRI and DSC-MRI, using as much of the data as possible is preferred to allow for detailed insight into the data and prevent losing useful information.

Another limitation is the low numbers of patients within each of the ATT severity groups, which has impacted our statistical analysis, although the group sizes were comparable.

Finally, we relied heavily on visual inspection of the perfusion scans, which is inherently observer dependent. For the perfusion assessment, a quantitative approach to determine the cerebral blood flow and cerebral blood volume from the ASL and DSC scans would be an option, but in our center this is not part of the conventional way in which perfusion scans are considered in clinical decision making. Furthermore, the visual analysis showed agreement between the perfusion methods in most cases; therefore, we anticipate that quantitative analysis would supply limited added value.

Further research and clinical evaluation of multi-PLD sequences that allow correction for the ATT artifacts would be highly recommended, although this would require more complex postprocessing and acquisition methods, which makes this technique cumbersome for clinical application. Velocity-selective ASL would be another option to reduce the sensitivity for transit time delays,[25] although it is currently not available as a CE-marked product sequence on any MRI scanner, which limits its widespread implementation and use. Previous work[26] has provided an approach to identify ATT artifacts in clinical practice by using the spatial coefficient of variation as an approximation for the ATT artifacts. The disadvantage of this approach is that it requires advanced postprocessing not widely accessible in clinical practice.

5 | CONCLUSIONS

This study shows that ASL perfusion MRI is frequently subjected to ATT artifacts in patients with glioblastoma and that such artifacts can impact the radiological evaluation of ASL perfusion MRI scans. For mild to moderate ATT artifacts, the evaluation of ASL-MRI scans at 3 months postradiotherapy seems to tend more towards hyperperfusion, while also being more sensitive for detecting tumor progression compared with DSC-MRI. However, severe ATT artifacts may impact the diagnostic value of ASL-MRI scans at 3 months postradiotherapy for detecting true disease progression. Therefore, the role of ASL perfusion MRI to differentiate between tumor progression and pseudoprogression in patients with

glioblastoma needs to be further evaluated; for example, a comparison between single-PLD and multi-PLD sequences would add valuable information.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Daniëlle van Dorth https://orcid.org/0000-0001-7535-8072
Feng Yan Jiang https://orcid.org/0000-0002-4967-3412
Bárbara Schmitz-Abecassis https://orcid.org/0000-0003-1776-4560
Robert J. I. Croese https://orcid.org/0000-0003-2378-4525
Martin J. B. Taphoorn https://orcid.org/0000-0001-9949-4722
Marion Smits https://orcid.org/0000-0001-5563-2871
Johan A. F. Koekkoek https://orcid.org/0000-0002-3648-9616
Linda Dirven https://orcid.org/0000-0001-9157-9895
Jeroen de Bresser https://orcid.org/0000-0003-0759-8407
Matthias J. P. van Osch https://orcid.org/0000-0001-7034-8959

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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