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Research article

Application of arterial spin labeling perfusion MRI to differentiate benign from malignant intracranial meningiomas



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ABSTRACT

Purpose: Differentiating WHO grade I–III of meningioma by non-invasive imaging is challenging. This study investigated the potential of MR arterial spin labeling (ASL) to establish tumor grade in meningioma patients. **Material and methods:** Pseudo-continuous ASL with 3D background suppressed gradient and spin echo (GRASE) was acquired on 54 patients with newly diagnosed or recurrent intracranial meningioma. Perfusion patterns characterized in CBF color maps were independently evaluated by three neuroradiologists blinded to patient history, and correlated with tumor grade from histo-pathological review.

Results: Three perfusion patterns could be discerned by visual evaluation of CBF maps. Pattern 1 consisted of homogeneous hyper-perfusion of the entire tumor; pattern 2 demonstrated heterogeneous hyper-perfusion; pattern 3 showed no substantial hyper-perfusion. Evaluation of the perfusion patterns was highly concordant among the three readers (Kendall W = 0.9458, $P < 0.0001$). Pattern 1 was associated with WHO Grade I meningioma ($P < 0.0001$). Patterns 2 and 3 were predictive of WHO Grade II and III meningioma ($P < 0.0001$), with an odds ratio (OR, versus pattern 1) of 49.6 ($P < 0.01$) in a univariate analysis, and an OR of 186.4 ($P < 0.01$) in a multivariate analysis.

Conclusion: Qualitative evaluation of ASL CBF maps can help differentiate benign (WHO Grade I) from higher grade (WHO Grade II and III) intracranial meningiomas, potentially impacting therapeutic strategy.

1. Introduction

Meningiomas are the most common intracranial brain tumors [1,2]. Histologically, the vast majority of meningiomas are classified as benign lesions (Grade I), while the remaining 10–20% are more aggressive sub-types (atypical for Grade II, and anaplastic for Grade III) [1,3]. Recurrence rate increases from 6.9–19% for Grade I to 50–94% for Grade III meningiomas after surgical resection [1,4].

Differentiating malignant from benign meningiomas before surgery is important for both treatment planning and prognostic evaluation, especially when tumors are located at the skull base or other high-risk intracranial areas that do not allow easy surgical resection or even biopsy. Since many such tumors are observed with no treatment, or irradiated without definite tissue diagnosis, a non-invasive approach facilitating prediction of meningioma grade could benefit management.

Although meningiomas do have some identifiable features on conventional MR imaging, no specific feature has been found to be reliable

in predicting tumor grade [5,6]. Advanced perfusion MR imaging reflects characteristics of regional tumor angiogenesis and blood supply which is not available by conventional MRI. The measurement of maximal relative cerebral blood volume (rCBV, relative to the contralateral normal white matter) and corresponding relative mean time to enhancement (rMTE), markers derived from dynamic susceptibility contrast (DSC) perfusion MRI, have been shown useful in predicting meningioma grade [7].

Arterial spin-labeled (ASL) is an established MRI-based technique to measure blood flow without the use of a contrast agent. ASL has proven reliable and reproducible in the assessment of CBF in various pathological states. Correlation has been established between DSC- and ASL-derived metrics, including rCBV and CBF [8], and ASL perfusion imaging has been correlated with tumor blood vessel density in meningiomas [9]. However, the role of ASL-derived metrics as an imaging marker for differentiating benign from malignant meningiomas has not been studied in detail. In the current analysis, our purpose is to explore

Abbreviations: ASL, arterial spin labeling; GRASE, gradient and spin echo; DSC, dynamic susceptibility contrast; PWI, perfusion, weighted imaging; VEGF, vascular endothelial growth factor

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the potential of ASL perfusion imaging as a predictive marker of meningioma grade.

2. Material and methods

2.1. Patients

From an ongoing registry of patients diagnosed with meningioma from July of 2010 to May of 2015 at our medical center, subjects were selected who had imaging data collected with post-contrast MRI and ASL either pre-surgically or at tumor recurrence, and histologically confirmed diagnosis of meningioma after the surgery. Tumor grading information was collected from reports by board-certified pathologists for all patients. This retrospective study was approved by the Institutional Review Board with an informed consent waiver, and was HIPAA-compliant.

2.2. MRI protocols

MRI scans were performed on a Siemens 1.5-T Avanto or 3.0T TIM Trio system (Erlangen, Germany) using a 12-channel head coil. The brain tumor imaging protocol was performed in the order of pre-contrast T1-weighted, T2-weighted, FLAIR, ASL, and post-contrast T1-weighted sequences. ASL scans were performed using a pseudo-continuous pulse sequence with background suppressed 3-D gradient and spin echo (GRASE) readout (labeling pulse duration 1.5 s, post-labeling delay 2 s, no flow crushing gradient, FOV = 22 cm, matrix size = 64 × 64, 26 5 mm slices, GRAPPA = 2, TE/TR = 22 ms/4000 ms, with 30 pairs of tag and control volumes acquired within 4 and a half minutes) [10,11]. Contrast-enhanced T1-weighted imaging were acquired after intravenous administration of Magnevist (Gadopentetate dimeglumine) at a dose of 0.2 ml/kg (0.1 mmol/kg) (Repetition time msec/echo time msec/inversion time msec, 1900–2000/2.33–3.52/900–1100; number of averages, 1–2; section thickness, 1.0 mm; matrix size, 256 × 256 mm).

2.3. ASL post-processing and evaluation

ASL images were corrected for motion, pair-wise subtracted between labeled and unlabeled images, and averaged to generate mean difference images, or CBF maps [10,11]. CBF maps of meningioma patients (n = 54) were visually evaluated by three independent readers (board-certified neuroradiologists with 5, 9 and 12 years of experience) blinded to patient history for focal perfusion abnormalities (hyper- or hypo-perfusion) in the tumor tissue, referenced by the post-contrast T1-weighted and T2/FLAIR sequences.

Quantitative analysis on meningiomas was performed in two ways: 1. Whole mount tumor tissue was segmented in the post-contrast T1-weighted imaging using MRICron program (University of South Carolina) and co-registered with ASL CBF map, with mean CBF values extracted from the whole tumor segmentation. 2. ROIs (3 × 3 pixels or 10.3 × 10.3 mm in size, n = 3 for each subject) were manually set in the tumor area showing the maximal perfusion ($_{\max}CBF_{\text{tumor}}$) by visual check on a transverse slice of the CBF map. A second set of ROIs (n = 3 for each subject) was drawn in the mirrored position in the contralateral hemisphere with normal brain tissue (Fig. 1 D, H, L). A Lesion-to-Normal Ratio ($R_{L/N}$) was calculated by dividing the mean values of $_{\max}CBF_{\text{tumor}}$ with the mean CBF values of the ROIs in the normal brain region. The ROIs were evaluated for eligibility independently by an experienced physician blinded to the results of the CBF map readings.

2.4. Statistical analysis

The inter-reader agreement in CBF map readings (hyper- versus hypo-perfusion in the tumor tissue) from three readers (n = 54

subjects × 3) was assessed using Kendall's Coefficient of Concordance (W). The W value was calculated to evaluate the degree of consensus.

A *t*-test was used to compare the means of $_{\max}CBF_{\text{tumor}}$ in meningiomas and the mean CBF values from ROIs in normal brain area within and between different perfusion patterns.

ASL CBF map readings in relationship with meningioma tumor grading were analyzed by using Fisher's exact test, as well as univariate and multivariate Cox proportional hazard models with covariates of age, tumor volume and derived CBF markers. In cases with disagreement on CBF map readings, the majority vote was applied by assigning the subjects to the group agreed by two (out of three) readers. 95% confidence intervals of the above covariates were calculated.

A *P*-value of 0.05 was accepted as statistically significant. Statistical analysis was performed with STATA software (version 12, 2012; STATA Corp, College Station, Texas).

3. Results

3.1. Patient characteristics

The mean age of the 54 enrolled patients (27 males, 27 females) at either the initial disease presentation or tumor recurrence was 55.7 ± 14.0 years, ranging from 19.1 to 88.5 years. By the time of the last assessment (March 15, 2016), 37 patients had pre-operative imaging, 17 patients were scanned at tumor recurrence. Histologically, 35 patients had tumors classified as WHO grade I, 19 were reported to have grade II and grade III meningiomas (14 of grade II, 4 of grade III, 1 of Grade II and III). The mean volume of high-grade meningiomas was significantly larger than that of grade I tumors ($P < 0.001$) (Table 1).

3.2. Evaluation of ASL CBF maps

ASL CBF maps of meningioma patients (n = 54) were visually evaluated by three board-certified neuro-radiologists blinded to patient history. Three perfusion patterns were characterized based on qualitative evaluation by the readers. Both pattern 1 and pattern 2 were characterized by the presence of hyper-perfusion in the tumor tissue, which could be identified by the bright areas in the CBF maps. A homogeneously hyper-perfused tumor body distinguished pattern 1 (Fig. 1A–D) from pattern 2, the latter demonstrated heterogeneously hyper-perfused tumor, with visible hyper-perfusion only in portions of the tumor (Fig. 1E–H). In comparison, pattern 3 corresponded to the absence of hyper-perfused tumor tissue and thus appeared on the CBF map as iso- or hypo-perfused in the region of the meningioma (Fig. 1I–L). Kendall's Coefficient of statistical analysis showed that evaluation of the perfusion patterns in CBF maps was highly concordant among the three readers ($W = 0.9458$, $p < 0.0001$). Based on majority vote by the readers, 33 of 54 patients (61.1%) had CBF maps of pattern 1, 11 patients (20.4%) had CBF map of pattern 2, and 10 patients (18.5%) had CBF map of pattern 3.

To confirm that the qualitative assessment of the readers corresponded to true differences in blood flow, a quantitative analysis was performed by using manual ROIs. Mean CBF values of tumor regions ($_{\max}CBF_{\text{tumor}}$) were significantly different (higher in patterns 1 and 2, lower in pattern 3) from mean CBF values of normal brain tissue in all three perfusion patterns. Comparison of $_{\max}CBF_{\text{tumor}}$ showed significant difference between patterns 1 and 3, as well as patterns 2 and 3, but not between patterns 1 and 2. Mean CBF values of ROIs in the normal brain tissue were not significantly different between the three patterns (Table 2).

3.3. Association of ASL perfusion patterns with meningioma grading

In 35 patients with Grade I meningiomas, 31 had CBF maps of pattern 1, 2 had pattern 2, and 2 had pattern 3. Grade II and Grade III meningiomas, individually, did not show correlation with any specific

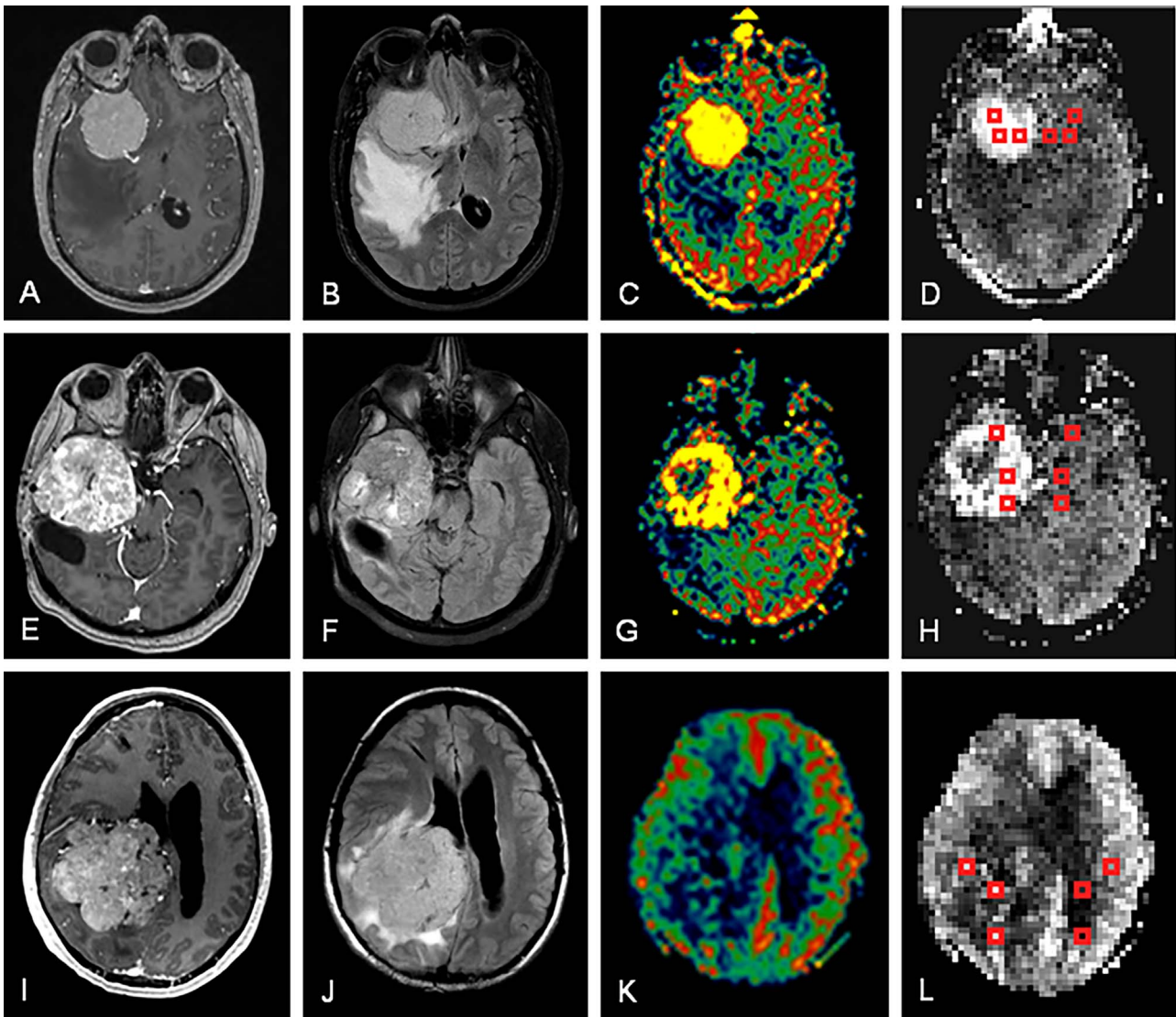


Fig. 1. Qualitative evaluation of ASL CBF maps in meningioma patients. Conventional MR imaging (T1-weighted post contrast imaging in A, E, I; T2/FLAIR in B, F, J) and ASL perfusion imaging (C, G, K) were visually evaluated by three independent readers. Three perfusion patterns can be characterized: pattern 1 and pattern 2 are characteristic of the presence of hyper-perfused tumor tissue, which can be identified by the bright areas in the CBF maps (C, G). Pattern 1 is further characterized by homogeneously hyper-perfused tumor (C) in comparison with heterogeneously hyper-perfused tumor region (G) in pattern 2. Pattern 3 corresponds to the absence of hyper-perfused tumor tissue, and usually appears as iso- or hypo-perfusion in the tumor area (K). CBF values are quantified by setting manual ROIs (empty squares 3 × 3 pixels in size) in both tumor and contralateral normal brain areas (D, H, L) ($n = 3$, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

perfusion patterns (Supplemental data). However, 17 of 19 patients with Grade II or Grade III tumors displayed CBF maps of either pattern 2 or pattern 3 (Table 3). Fisher's exact test demonstrated a significant association between CBF map of pattern 1 and Grade I meningioma, and CBF map of either pattern 2 or 3 with high-grade meningioma (Grade II and III) ($p < 0.0001$).

In a univariate Cox model, ASL CBF maps of pattern 2 and pattern 3 (versus pattern 1) were predictive of high-grade meningioma (Grade II and III) (Odds ratio = 49.6, $P < 0.001$). In the same model, tumor volume was also predictive of high-grade meningioma (OR = 1.02, $P < 0.01$). This predictive value was improved when larger tumor volume (tumor volume $> 20 \text{ cm}^3$) was added to the analysis (OR = 7.8, $P < 0.01$) (Table 4).

A multivariate Cox model showed that ASL CBF maps of patterns 2 and 3 (versus pattern 1) remained a significant predictor of high-grade meningioma (OR = 186.4, $P < 0.01$). In addition, $\text{maxCBF}_{\text{tumor}}$ was predictive of high-grade meningioma (OR = 1.05, $P = 0.043$), and larger tumor volumes ($> 20 \text{ cm}^3$) trended with high-grade tumors (OR = 12.27, $P = 0.08$) in the multivariate analysis (Table 5).

4. Discussion

Currently no standard or advanced imaging technique can reliably distinguish meningioma grade [12]. Perfusion, diffusion and MR spectroscopy have all been investigated as potential methods to add value to standard imaging in the assessment of meningiomas [12]. Most perfusion studies of central nervous system tumors have focused on the use of quantitative parameters, such as rCBV and CBF, as markers of histopathological grade, therapy response and clinical outcome [13–15]. In the present study, a qualitative examination of CBF maps was conducted in a patient cohort with meningioma, and its potential for predicting meningioma tumor grade was analyzed.

Using pseudo-continuous arterial spin labeling CBF maps, three perfusion patterns were observed in patients with meningiomas with good inter-rater agreement. Perfusion pattern 1 was highly associated with grade I tumors, whereas perfusion patterns 2 and 3 were associated with grade II and III meningiomas. The perfusion patterns of meningiomas in relation to tumor grading were further examined in univariate and multivariate Cox models. In both models, ASL CBF maps

Table 1
Patient Clinico-radiologic Characteristics.

Characteristic	WHO Grade I (N = 35)	WHO Grade II & III (N = 19)	Total (N = 54)	P value ^a
Male (%)	16 (59.3%)	11 (40.7%)	27	–
Female (%)	20 (74.1%)	7 (25.9%)	27	–
Primary Tumor (%)	26 (70.3%)	11 (29.7%)	37	–
Recurrent Tumor (%)	10 (58.8%)	7 (41.2%)	17	–
Age ^b	54.5 ± 13.1	57.8 ± 15.7	55.7 ± 14.0	0.42
Whole Brain CBF ^c	42.2 ± 10.9	40.5 ± 10.9	41.6 ± 10.9	0.59
Whole Tumor CBF ^c	71.8 ± 45.1	71.7 ± 62.5	71.8 ± 51.4	0.998
maxCBFtumor ^c	126.4 ± 69.8	96.0 ± 99.8	115.8 ± 81.8	0.20
Mean Control CBF (ROI) ^c	40.4 ± 11.8	40.6 ± 11.4	40.5 ± 11.5	0.96
Tumor Volume ^d	25.6 ± 30.1	84.8 ± 72.7	47.2 ± 56.9	0.0005

^a WHO Grade I versus higher grade (WHO Grade II and III), *P* < 0.05 denotes statistical significance.

^b In years, shown as mean ± SD.

^c In ml/100 g/min, shown as mean ± SD. For quantification of Whole Brain CBF, N = 52; for Whole Tumor CBF, N = 44 (28 for Grade I, 16 for Grade II and III); for ROIs, N = 52 (34 for Grade I, 18 for Grade II and III).

^d In cm³, shown as mean ± SD, N = 44 (28 for Grade I, 16 for Grade II and III).

of patterns 2 and 3 (versus pattern 1) were predictive of high-grade meningioma.

Three perfusion patterns were consistently observed in both primary and recurrent meningiomas (Supplemental data), and showed good correlation with tumor grades. Disagreement of ASL map reading was observed in 10.8% (4/37) of the primary tumors and 11.8% (2/17) of the recurrent tumors, respectively. Quantitatively, CBF of primary meningioma was not significantly different from that of recurrent whether assessed by ROIs or whole tumor measurement (Supplemental data). Moreover, no difference in the whole brain CBF was demonstrated between subjects with primary vs recurrent meningioma (Supplemental data). Given these findings, recurrent meningiomas were included in our current analysis to increase the power of the study.

Numerous efforts have been spent on differentiating meningioma tumor grades with perfusion metrics. A positive correlation between CBV and VEGF expression [16], and potentially an association between rCBV and cell proliferation (Ki-67 index) [17] has been shown in meningioma, although the association of Ki-67 with higher perfusion is disputed [18]. ASL CBF measurements have been shown to correlate with DSC metrics in meningiomas as well as microvessel area on histologic specimens [19]. There also is a relationship between meningioma subtype (angiomatous, meningo-epithelial, fibrous) and perfusion [9]. In that report the authors do not specify whether their method of continuous ASL could be used to differentiate meningioma grade.

Table 2
Assessment of ASL CBF values^a in meningiomas by manual ROIs.

	maxCBF _{tumor} ^b	Control ^c	P Value (t-test) ^d	R _{L/N} ^e
Perfusion Pattern 1 (N = 31)	141.9 ± 72.6	42.6 ± 11.2	< 0.0001	3.39 ± 1.72
Perfusion Pattern 2 (N = 11)	130.1 ± 81.4	37.5 ± 6.4	< 0.01	3.46 ± 1.87
Perfusion Pattern 3 (N = 10)	19.4 ± 9.6	37.1 ± 15.8	< 0.01	0.54 ± 0.19
P Value (t-test, pattern 1 vs 2) ^d	0.66	–	–	0.90
P Value (t-test, pattern 1 vs 3) ^d	< 0.0001	0.22	–	< 0.0001
P Value (t-test, pattern 2 vs 3) ^d	< 0.001	0.93	–	< 0.0001

^a In ml/100 g/min.

^b Maximal CBF values from ROIs in tumor tissue.

^c CBF values from ROIs in contra-lateral hemisphere.

^d *P* < 0.05 denotes statistical significance.

^e Lesion to normal ratio.

Table 3
Association of ASL perfusion patterns with pathology grade in meningioma.^a

Perfusion Patterns	WHO Grade I	WHO Grade II & III	Total	
CBF Pattern 1	31	2	33	PPV ^d 93.9%
CBF Patterns 2 & 3	4	17	21	NPV ^e 81.0%
Total	35	19	54	
Sensitivity:	88.6% ^b			
Specificity:	89.5% ^c			

^a Fisher's exact test, *P* < 0.0001.

^b For association of CBF pattern 1 with WHO grade I.

^c For association of CBF patterns 2 and 3 with WHO grade II and III.

^d Positive predictive value (PPV).

^e Negative predictive value (NPV).

Table 4
Univariate analysis: predictor of high-grade^a histopathology.

Predictors	Odds Ratio (SE)	95% Confidence Interval	P-value ^b
Male	1.9 (1.1)	[0.59, 5.8]	0.29
Age ≥ 75yr ^c	2.3 (2.0)	[0.41, 12.6]	0.35
CBF Patterns 2 & 3 vs. 1	49.6 (44.2)	[8.6, 284.7]	< 0.001
maxCBFtumor ^d	0.99 (0.004)	[0.99, 1.00]	0.21
R _{L/N} ^e	0.76 (0.14)	[0.53, 1.08]	0.13
Whole tumor CBF ^f	0.98 (0.027)	[0.94, 1.03]	0.58
Tumor volume ^g	1.02 (0.0087)	[1.0, 1.04]	0.007
Tumor volume > 2 ^g	7.8 (5.9)	[1.79, 34.1]	0.006

^a WHO grade II and III.

^b *P* < 0.05 denotes statistical significance.

^c N = 6 for age ≥ 75yr, N = 38 for age < 75yr.

^d Mean CBF values of ROIs in tumors, in ml/100 g tissue/min, N = 52.

^e Lesion to normal ratio, N = 52.

^f Mean tumor CBF from whole mount tumor segmentation, N = 44.

^g In cm³, N = 22 for Tumor volume > 20, N = 22 for Tumor volume ≤ 20.

Table 5
Multivariate analyses: predictor of high-grade^a histopathology.

Predictors	Odds Ratio (SE)	95% Confidence Interval	P-value ^b
Male	1.3 (1.5)	[0.14, 13.0]	0.80
Age ≥ 75yr ^c	2.3 (6.0)	[0.02, 347.8]	0.74
CBF patterns 2 and 3	186.4 (333.7)	[5.58, 6225.4]	0.003
R _{L/N} ^d	0.16 (0.16)	[0.02, 1.18]	0.073
maxCBFtumor ^e	1.05 (0.02)	[1.00, 1.09]	0.043
Tumor volume > 20 ^f	12.27 (17.60)	[0.74, 204.01]	0.08

^a WHO grade II and III.

^b *P* < 0.05 denotes statistical significance.

^c N = 6 for age ≥ 75yr, N = 38 for age < 75yr.

^d Lesion-to-Normal Ratio, calculated by dividing the mean CBF values of tumor ROIs with the mean values of the ROIs in the normal brain area, N = 52.

^e Mean tumor CBF values from manual ROIs, in ml/100 g tissue/min, N = 52.

^f In cm³, N = 22 for Tumor volume > 20, N = 22 for Tumor volume ≤ 20.

Thus the current report is, to our knowledge, the first to differentiate meningioma tumor grades by using ASL.

Some studies suggest increased CBV is associated with higher tumor grade in meningioma [18], whereas others have found increased CBV associated with grade I meningioma [7,20]. The potential relationship between neo-angiogenesis, CBV, CBF and tumors grade in meningioma is complex. The majority of Grade I meningioma express VEGF and are highly vascular [21]. Therefore, there may not be a close correlation between increasing tumor grade and hyper-perfusion in meningioma (as exists, for example, in glioma [22]). In fact, the isoforms of VEGF expressed in higher grade meningioma (121 and 165) appear to induce vascularization patterns in mouse xenograft models that may have reduced or more variable blood flow [23] due to heterogeneous microvessel eruption, vessel dilation and hemorrhage [24]. In contrast, grade I meningioma express VEGF isoform 189 that in xenograft models induces intense angiogenesis consisting of small, more homogenous microvessels [25], associated with higher microvessel density and greater tumor perfusion than other VEGF isoforms [23]. Furthermore, different histological subtypes of grade I meningioma demonstrate differences in ASL-derived CBF [19]. Thus, future studies are needed to more fully characterize the impact of isoform-specific VEGF expression as well as meningioma subtype/grade on MR-based perfusion metrics.

Using a *qualitative* approach, our current study shows a homogenous hyper-perfusion pattern correlates with benign meningiomas (Grade I), suggesting different mechanisms and patho-physiological functions of angiogenesis may occur in meningiomas compared to gliomas. This is further supported by the observation that hypo-perfusion (as seen in pattern 3), previously reported to be a marker for better clinical outcome in glioma [15], correlates with high-grade meningiomas with poor prognosis. Angiogenesis in both meningioma and glioma is known to share a common signaling pathway mediated by vascular endothelial growth factor (VEGF) [16,26,27]. However, this common pathway could be regulated by numerous cellular events which generate different downstream phenotypes. For example, signaling crosstalk is possible between the VEGF pathway and epidermal growth factor receptor variant III (EGFRvIII), and this receptor variant is found to be a driver of glioblastoma aggressiveness by promoting invasion and angiogenesis via activation of Src pathways [28]. In comparison, the expression of EGFRvIII is not seen in meningiomas [29]. It is possible that these diversified molecular mechanisms may result in differentiation of imaging phenotypes between meningiomas and gliomas.

The characterization of different perfusion patterns in meningioma could prove useful for clinical management, especially when tumors are located at the skull base or other high-risk areas that do not facilitate easy surgical resection or even biopsy. Such tumors often lead to blinded treatment without definitive histopathological diagnosis. Given the correlation between ASL perfusion imaging patterns and meningioma WHO grade, it could be beneficial to evaluate tumors with CBF maps as a non-invasive approach, easily performed by visual inspection, so that non-surgical treatments (such as radiotherapy versus stereotactic radiosurgery) could be reasonably chosen, or optimized (in the case of radiation dosage) to achieve maximal effectiveness.

Our study was limited by a small patient cohort consisting of both newly diagnosed and recurrent meningiomas. For this mixed cohort, information on histological subtypes and examination of histological markers such as VEGF was lacking, limiting our ability to explore the underlying mechanisms that may contribute to the formation of the observed perfusion patterns. The potential value of perfusion patterns of CBF maps as a predictor of meningioma grading requires verification in prospective studies with larger sample size. Although three perfusion patterns were identified and supported by data from quantitative analysis using ROIs, a more comprehensive quantitative approach, such as histogram analysis, could potentially yield further classifiers of predictive significance.

5. Conclusion

Qualitative evaluation of ASL CBF maps provides a promising method, with high inter-observer reliability, that differentiates benign from malignant intracranial meningiomas.

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Conflict of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejrad.2017.10.005>.

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