ASL-Perfusion for Intrinsic Brain Tumor Diagnosis. Analysis of 253 Patients.

Artem Batalov
Burdenko Neurosurgery Institute
Natal'ya Zakharova
Burdenko Neurosurgery Institute
Igor' Pronin
Burdenko Neurosurgery Institute
Artem Belyaev
Burdenko Neurosurgery Institute
Eduard Pogosbekyan
Burdenko Neurosurgery Institute
Sergey Goryaynov
Burdenko Neurosurgery Institute
Andrey Bykanov
Burdenko Neurosurgery Institute
Anastasiya Tyurina
Burdenko Neurosurgery Institute
Alexander Shevchenko (Alex20990222@gmail.com)
Burdenko Neurosurgery Institute
Pavel Nikitin
Burdenko Neurosurgery Institute
Alexander Potapov
Burdenko Neurosurgery Institute

Research Article

Keywords: MRI, pseudo-continuous labeling of arterial spins, pCASL, cerebral blood flow, CBF, tumor blood flow, TBF, glioma.

Posted Date: April 21st, 2021

DOI: https://doi.org/10.21203/rs.3.rs-428439/v1

Abstract

Purpose

The aim of the study was to evaluate the role of pseudo-continuous ASL-perfusion (pCASL-perfusion) in preoperative assessing of cerebral glioma grades.

Methods

The study group consisted of 253 patients aged 7 to 78 years with supratentorial gliomas (65 had low-grade gliomas (LGG), 188 – high-grade gliomas (HGG)). Maximal tumor blood flow (maxTBF) in small ROIs (20 mm^2 ± 10 mm^2) were evaluated by subsequently normalized tumor blood flow (nTBF) calculation which was compared with normal appearing white matter of center semiovale of the contralateral hemisphere.

Results

TBF and nTBF values were significantly differed in HGG and LGG groups, as well as grade II and grade III gliomas; grade III and grade IV gliomas ($p < 0.001$). ASL-perfusion has demonstrated both high sensitivity and specificity in differentiating LGG and HGG, grade II and grade III gliomas, but low sensitivity and specificity in distinguishing grade III and grade IV gliomas. We did not observe a significant difference in TBF in astrocytomas and oligodendrogliomas.

Conclusion

Current results demonstrate that 3D pCASL-perfusion is an effective diagnostic tool for preoperative differentiation of low and high grade gliomas.

Introduction

Gliomas are the most common type of primary brain tumors and comprise about 80% of all malignant brain neoplasms. Preoperative predicting glioma grades is important for development of an optimal treatment strategy and making a prognosis [1, 2].

It is well-known, that modern diagnostic modalities, like MR-perfusion, are more effective in detecting of brain tumors grades compared to the routine MRI [3, 4]. T2*MR-perfusion (dynamic susceptibility contrast) is the “gold standard” for assessing tumor blood flow [5–7].

Arterial spin labeling (ASL) is a non-invasive method of obtaining CBF (cerebral blood flow) maps. Some authors reporting on the use of pulsed ASL (PASL) and pseudo-continuous ASL (pCASL) marked that CBF

maps derived by ASL (ASL-CBF) were really helpful in detecting cerebral glioma grades [8–14, 15] and predicting prognosis of the disease [10, 16, 17]. Despite the fact that pCASL is an advanced ASL method compared to PASL and CASL [18–21], the recent data remain controversial. Some studies claim ineffectiveness of pCASL for glioma differentiation [4], while other papers, on the contrary, prove its informativity validate its virtue [22–26, 27, 28, 29–32]. pCASL sensitivity and specificity thresholds in differentiating LGG and HGG in the aforementioned studies vary considerably. Probably, these differences can be related to the methods of ROI detection and normalization technique of TBF.

The aim of the present study was to evaluate the potential of pseudo-continuous ASL-perfusion (pCASL-perfusion) in preoperative assessment of cerebral glioma grades. We suggest that measuring of maximal TBF and normalized TBF values using small ROI might be more informative for distinguishing cerebral gliomas.

Materials And Methods

The study group consisted of 253 patients (118 men and 135 women) aged 7 to 78 years (mean age 45 ± 15 years) with cerebral supratentorial glial tumors which were diagnosed and then surgically treated (tumor removal or stereotactic biopsy, chemo-radiotherapy) at Burdenko Neurosurgery Center from 2011 to 2018 (Table 1).

Table 1
Tumor distribution in the study group.

Histopathological diagnosis	Grade, WHO	N
Ganglioliоma	I	4
Papillary glioneuronal tumor	I	1
Pilocytic astrocytoma	I	5
Gemistocytic astrocytoma	II	1
Diffuse astrocytoma	II	39
Oligodendroglioma	II	14
Pleomorphic xantoastrocytoma	II	1
Anaplastic astrocytoma	III	44
Anaplastic oligodendroglioma	III	22
Anaplastic pleomorphic xantoastrocytoma	III	2
Glioblastoma	IV	118
Gliosarcoma	IV	2

In 65 of 253 patients low-grade gliomas were diagnosed (grade I-II WHO), high-grade gliomas – in 188 cases (grade III WHO – 68; grade IV WHO – 120).

MR-studies were performed on 3 Tesla MRI scanner General Electric Signa HD (GE Healthcare) with 8-channel head coil. Imaging included: T1 FSPGR BRAVO with isotropic voxel 1x1x1mm and no gap before and after contrast enhancement (or axial T1 weighted imaging with 5 mm slice thickness and 1 mm gap before contrast enhancement and postcontrast axial, sagittal and coronal T1 weighted images), axial T2 weighted images with 5mm slice thickness and 1 mm gap, T2-FLAIR with 5 mm slice thickness and 1mm gap, DWI ASSET with 5 mm layers and 1 mm gap, as well as 3D pCASL.

Tumor blood flow maps were obtained by processing 3D pCASL data using the following parameters: 3D FSE, 8-way spiral whole brain scanning with following reformation for 4mm slice thickness; FOV = 240x240 mm; matrix 128x128, ZIP 512; TR – 4717 мs; TE – 9.8 мs; NEX = 3; post-labeling detention (PLD) – 1525 ms; pixel bandwidth – 976.6 Hz/pixel. Scan duration 4 min 30 sec.

Postprocessing was performed with ReadyView (GE Healthcare). To assess tumor blood flow, ROI (region of interest) 20 mm^2 ± 10 mm^2 was chosen in the highest CBF zone (detected by color blood flow maps). Mean tumor blood flow (maxTBF) was then evaluated within this ROI. Normalization with intact white matter of center semiovale of the contralateral hemisphere was performed to exclude individual blood flow patterns by placing ROI of the same size (20 mm^2 ± 10 mm^2) in the centre semiovale like ROI in the tumor. Normalization was obtained by dividing the maximal TBF by CBF in centre semiovale in the contralateral hemisphere: nTBF = maxTBF/ CBFcent.semiov.

CBF maps were fused with structural images (T2WI, T2-FLAIR, postcontrast T1WI) by means of NeuroRegistration software (GE Healthcare) in all cases.

Statistical analysis was performed with R-project program (https://www.r-project.org), pROC library was used for ROC-analysis. We used nonparametric methods in this study. Between-group comparisons were performed using the two-tailed Mann–Whitney rank-sum tests; continuous dependences were evaluated using Spearman rank correlations.

Study Results

During our study there were obtained mean maximal tumor blood flow levels and mean maximal normalized tumor blood flow levels in gliomas of different grades. We found a significant difference ($p < 0.001$) in tumor blood flow for LGG (grade I + II) and HGG (grade III + IV), with higher TBF values being marked in high grade gliomas.

Maximal TBF levels and normalized TBF levels are summarized in Table 2.

Table 2
Maximal and normalized TBF values in tumors of different grades.

Ggrade WHO	Mean maxTBF, ml/100 g/min	Standard deviation	Mean nTBF	Standard deviation
I	36.51	15.46	2.33	1.03
II	30.80	14.20	1.69	0.71
III	122.85	85.09	6.77	4.53
IV	171.08	93.30	9.49	5.50
I + II	31.77	14.46	1.80	0.80
III + IV	153.64	93.13	8.51	5.32

ROC-analysis revealed sensitivity and specificity values of ASL-perfusion in the differential diagnosis of LGG and HGG. Data are summarized in Table 3 and Fig. 1.

ASL-perfusion exhibited both high sensitivity and specificity in distinguishing HGG and LGG. Threshold was determined as 64ml/100g/min for maximal TBF and 3.6 for normalized TBF. AUC > 0.95 for maximal TBF and normalized TBF.

Our study revealed distinct differences in TBF for low- and high-grade gliomas ($p < 0.001$). Spearman's correlation coefficient was 0.7 ($p < 0.001$), CI 95% (0.59–0.79) for maxTBF and tumor grade and 0.68 ($p < 0.001$), 95% (0.56–0.78) for nTBF and tumor grade.

Maximum values of TBF and nTBF turned out to be more homogeneous for low-grade gliomas (TBF = 31.77 ± 14.46 ml/100g/min; nTBF = 1.80 ± 0.80 ml/100g/min) than for high-grade gliomas (TBF = 153.64 ± 93.13 ml/100g/min; nTBF = 8.51 ± 5.53).

TBF values in glioma grade I and grade II groups did not differ ($p > 0.05$). Nevertheless, we observed a significant difference for maxTBF and nTBF in glioma grade III and grade IV groups ($p < 0.001$). For glioblastoma group, maxTBF was 171.08 ± 93.30 ml/100g/min, nTBF was 9.49 ± 5.50, thus being significantly higher than in anaplastic astrocytomas and anaplastic oligodendrogliomas (TBF – 122.85 ± 85.09 ml/100g/min ($p < 0.001$), nTBF – 6.77 ± 4.53 ($p < 0.001$)).

However, ROC-analysis revealed relatively low diagnostic value of ASL-perfusion when distinguishing gliomas grade III and grade IV (Table 3, Fig. 2).

We also analyzed TBF in high-grade gliomas excluding anaplastic oligodendrogliomas. maxTBF for anaplastic astrocytomas was 123.37 ± 89.57 ml/100g/min and nTBF was 6.70 ± 4.59 and both parameters were significantly lower compared to those for glioblastomas ($p = 0.0004$ for maxTBF, $p = 0.001$ for nTBF). Despite of that, exclusion of anaplastic oligodendrogliomas did not result in higher sensitivity and/or specificity when distinguishing grade III and grade IV gliomas by ASL-perfusion. (Table 3).

Moreover, comparison of TBF and nTBF in diffuse astrocytomas and oligodendrogliomas, anaplastic astrocytomas and anaplastic oligodendrogliomas did not reveal any significant difference (all $p > 0.05$).

Grade III gliomas demonstrated significantly higher maxTBF and nTBF values than grade II gliomas ($p < 0.001$). According to ROC-analysis ASL-perfusion was proved to be highly informative in these tumors (Table 3). Exclusion of oligodendrogliomas and anaplastic oligodendrogliomas affected neither sensitivity nor specificity of the method.

Table 3
ROC-analysis of maxTBF and nTBF in differential diagnosis of brain gliomas.

		TBF	nTBF
HGGs and LGGs	**AUC**	0.954	0.951
	cutoff	64.0 ml/100 g/min	3.6
	Specificity	96.9%	98.5%
	Sensitivity	85.1%	80.9%
Grade II and Grade III tumors	**AUC**	0.923	0.921
	cutoff	44.8 ml/100 g/min	2.7
	Specificity	83.6%	90.9%
	Sensitivity	88.2%	77.9%
Grade III and Grade IV tumors	**AUC**	0.671	0.656
	cutoff	103.7 ml/100 g/min	4.7
	Specificity	54.4%	42.6%
	Sensitivity	76.7%	84.2%
Anaplastic astrocytomas and glioblastomas	**AUC**	0.677	0.664
	cutoff	114.4 ml/100 g/min	7.0
	Specificity	60.9%	60.9%
	Sensitivity	72.5%	62.5%

Discussion

Recent studies have demonstrated a high potential of PASL and CASL in differentiating high- and low-grade gliomas before surgery [8–14, 31]. Although ASL-perfusion is a relatively new method, it has already proved to be effective in diagnosis of cerebral gliomas. There is a number of studies establishing

a high correlation between tumor blood flow derived from ASL-perfusion and DSC-perfusion which is known as the “gold standard” in perfusion studies [33, 34].

Several recent studies were devoted to ASL-perfusion in differentiating cerebral gliomas. They showed contradictory results regarding sensitivity and specificity of this method in distinguishing LGG and HGG and TBF threshold values. An our opinion, these differences are the result of different approaches used for selecting ROI/VOI in TBF assessing as well as different methods of TBF normalization.

To measure TBF several study groups used large ROI covering almost all the tumor volume. Brendle et al. (2017) measured TBF in 63 patients with high- and low-grade gliomas using pASL and DCE, thus segmenting the whole tumor excluding large vessels and areas of necrosis. Also mean TBF was measured in particular volume. The authors did not find any significant difference in ASL-TBF parameter for HGG and LGG. ASL-TBF normalization was not the aim of their study.

Zeng et al. (2017) selected a slice with the highest TBF used color TBF maps. Using post-contrast T2-FLAIR the authors then chose ROI incorporating the whole tumor volume on the selected slice. Next ROI was transcribed on perfusion maps and afterwards, mean TBF was measured. ROI also included cystic components of the tumor, necrosis, hemorrhages characterized by low perfusion values and as such they could decrease the TBF [25]. The authors used pCASL and normalization was performed to contralateral grey matter.

Wang et al. (2019) used a dual approach for TBF measuring. Firstly, they chose a slice with the highest TBF according to color maps. Then on the slice they delineated the whole tumor volume in this slice in T2-FLAIR and measured mean TBF. Area with the highest TBF was selected on the slice and the ROI of 95–105 pixels was placed on it to get max TBF. The authors used pCASL and normalization was performed to contralateral grey matter. Maximal TBF was found to be associated with the highest sensitivity and specificity in distinguishing LGG and HGG.

A different approach was adopted for measuring TBF in other studies, including small-sized ROI/VOI. Lin et al. (2015) included solid component of the tumor picked on the slice with the highest TBF on the color maps [22]. ROI size was not specified in the paper. The authors did not use TBF normalization for the differential diagnosis in this paper.

Ma et al. (2017) used color maps to select the highest TBF and ROI was set to 50–60 mm^2 [23]. In contrast, we used smaller ROI size of 20 ± 10 mm^2 and performed normalization to the ROI within tumor in the mirror-like area of the contralateral hemisphere.

Hashido et al. (2020) used small VOI 162.8 mm^3 in size and normalization was performed to the contralateral white matter.

Hales et al. (2019) used 50 mm^2 ROI and normalization was performed to the contralateral grey matter.

The approach used by Xiao et al. (2015) was mostly close to the one we used: the researchers placed several 28–32 mm^2 ROI scattered within the whole tumor volume. Then ROIs with maximal TBF were picked for analysis [24]. Normalization was performed to CBF in the cerebellar white matter.

All the above mentioned papers were based upon pCASL technique.

Studies using small-size ROI and VOI demonstrated higher sensitivity and specificity in distinguishing LGG and HGG. According to meta-analysis performed by Alsaedi et al. (2019) maxTBF was proved to be more informative rather than meanTBF in differentiating cerebral glioma grades.

Our results coincide with the aforementioned studies, but demonstrate higher sensitivity and specificity in distinguishing LGG and HGG and much higher AUC. maxTBF for low-grade gliomas in our study group was much lower compared to other studies, and much higher for high-grade gliomas. The observed difference could be explained by different ROI selection for TBF measuring.

Our study is also different by nTBF: the difference was mostly defined by the site of normalization – we used center semiovale of the contralateral hemisphere.

TBF value comparison computed using pCASL in grade III and grade IV glioma groups was evaluated in a small number of studies due to small patient sample size. Zeng et al. (2017) [25] revealed a significant difference in TBF and nTBF values for these groups of patients, but they did not present ROC-analysis results and thus to evaluate ASL-perfusion effectiveness in differentiating cerebral gliomas grade III and grade IV. Wang et al. (2019) did not find any significant difference for TBF and nTBF in these two groups of patients.

In our study we used both absolute (TBF) and normalized (nTBF) maximal tumor blood flow and demonstrated higher sensitivity and specificity in distinguishing LGG and HGG. We found a significant difference in TBF for grade III and grade IV gliomas, although low sensitivity and specificity did not let us using ASL-perfusion for differentiating gliomas of grades III and IV. Importantly, excluding anaplastic oligodendrogliomas affected neither sensitivity nor specificity. We also failed to detect any statistically significant difference in TBF for diffuse astrocytomas and oligodendrogliomas as well as anaplastic astrocytomas and anaplastic oligodendrogliomas. On the contrary, in the study conducted by Zeng et al. (2017) exclusion of oligodendrogliomas and anaplastic oligodendrogliomas led to TBF lowering in glioma grade II and glioma grade III groups and statistically significant difference for this parameter in grade III and grade IV glioma groups. This can be explained by ROI selection method: we adopted the protocol for selecting small ROI in the highest TBF areas, whereas Zeng et al. (2017) delineated the whole tumor volume on the slice with maximal TBF.

It is well-known, that oligodendrogliomas are characterized by even higher microvascular density within the whole tumor volume [35]. Inclusion of the whole tumor volume on the slice in the measurement area results in the increased TBF on perfusion map in oligodendrogliomas. Our results suggest that

application of small ROI showed enable measuring maxTBF which is the same for astrocytomas and oligodendrogliomas.

Conclusion

pCASL with a small ROI used for measuring maxTBF and nTBF has demonstrated both high sensitivity and specificity in distinguishing high- and low-grade gliomas, as well as grade II and grade III gliomas.

The study was supported by the Russian Foundation for Basic Research (grant № 18-29-01018).

Declarations

Funding

The study was supported by the Russian Foundation for Basic Research (grant № 18-29-01018). No other funding was received for this study.

Conflict of interest

The authors declare that they have no conflict of interest.

Availability of data and material

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

Research concept and design - Pronin I.N., Potapov A.A., Batalov A.I.,

Collection and processing of material - Belyaev A.JU., Goryaynov S.A., Bykanov A.E., Tyurina A.N., Shevchenko A.M., Nikitin P.V.

Statistical data processing - Pogosbekyan E.L.

Writing a text - Batalov A.I.,

Editing - Pronin I.N., Zakharova N. E.

Ethics approval

This retrospective and prospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval was granted by the Ethics Committee of "FEDERAL STATE AUTONOMOUS INSTITUTION N.N. BURDENKO NATIONAL

MEDICAL RESEARCH CENTER OF NEUROSURGERY OF THE MINISTRY OF HEALTH OF THE RUSSIAN FEDERATION" (Date 16.12.16/No. 12/2016).

Consent to participate

Informed consent was obtained from all individual participants included in the study. Informed consent was also obtained from the parent and / or legal guardian of the minors who participated in the study.

Consent for publication

Patients signed informed consent regarding publishing their data and photographs.

References

1. Soffietti R, Baumert B, Bello L et al. Guidelines on management of low-grade gliomas: report of an EFNS-EANO* Task Force. *Eur J Neurol*. 2010;17(9):1124-1133. doi:10.1111/j.1468-1331.2010.03151.x
2. Weller M, van den Bent M, Hopkins K et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastoma. *The Lancet Oncology*. 2014;15(9):e395-e403. doi:10.1016/s1470-2045(14)70011-7
3. Nguyen T, Cron G, Perdrizet K et al. Comparison of the Diagnostic Accuracy of DSC- and Dynamic Contrast-Enhanced MRI in the Preoperative Grading of Astrocytomas. *American Journal of Neuroradiology*. 2015;36(11):2017-2022. doi:10.3174/ajnr.a4398
4. Roy B, Awasthi R, Bindal A et al. Comparative Evaluation of 3-Dimensional Pseudocontinuous Arterial Spin Labeling With Dynamic Contrast-Enhanced Perfusion Magnetic Resonance Imaging in Grading of Human Glioma. *J Comput Assist Tomogr*. 2013;37(3):321-326. doi:10.1097/rct.0b013e318282d7e2
5. Knopp E, Cha S, Johnson G et al. Glial Neoplasms: Dynamic Contrast-enhanced T2*-weighted MR Imaging. *Radiology*. 1999;211(3):791-798. doi:10.1148/radiology.211.3.r99jn46791
6. Law M, Yang S, Babb JS et al. Comparison of cerebral blood volume and vascular permeability from dynamic susceptibility contrast enhanced perfusion MR imaging with glioma grade. AJNR Am J Neuroradiol. 2004;25(5):746–55.
7. Law M, Young R, Babb J et al. Gliomas: Predicting Time to Progression or Survival with Cerebral Blood Volume Measurements at Dynamic Susceptibility-weighted Contrast-enhanced Perfusion MR Imaging. *Radiology*. 2008;247(2):490-498. doi:10.1148/radiol.2472070898
8. Chawla S, Wang S, Wolf R et al. Arterial Spin-Labeling and MR Spectroscopy in the Differentiation of Gliomas. *American Journal of Neuroradiology*. 2007;28(9):1683-1689. doi:10.3174/ajnr.a0673
9. Fudaba H, Shimomura T, Abe T et al. Comparison of Multiple Parameters Obtained on 3T Pulsed Arterial Spin-Labeling, Diffusion Tensor Imaging, and MRS and the Ki-67 Labeling Index in Evaluating

Glioma Grading. *American Journal of Neuroradiology*. 2014;35(11):2091-2098. doi:10.3174/ajnr.a4018

10. Furtner J, Bender B, Braun C et al. Prognostic Value of Blood Flow Measurements Using Arterial Spin Labeling in Gliomas. *PLoS ONE*. 2014;9(6):e99616. doi:10.1371/journal.pone.0099616
11. Furtner J, Schöpf V, Schewzow K et al. Arterial Spin-Labeling Assessment of Normalized Vascular Intratumoral Signal Intensity as a Predictor of Histologic Grade of Astrocytic Neoplasms. *American Journal of Neuroradiology*. 2013;35(3):482-489. doi:10.3174/ajnr.a3705
12. Kim H, Kim S. A Prospective Study on the Added Value of Pulsed Arterial Spin-Labeling and Apparent Diffusion Coefficients in the Grading of Gliomas. *American Journal of Neuroradiology*. 2007;28(9):1693-1699. doi:10.3174/ajnr.a0674
13. Warmuth C, Günther M, Zimmer C. Quantification of Blood Flow in Brain Tumors: Comparison of Arterial Spin Labeling and Dynamic Susceptibility-weighted Contrast-enhanced MR Imaging. *Radiology*. 2003;228(2):523-532. doi:10.1148/radiol.2282020409.
14. Wolf R, Wang J, Wang S et al. Grading of CNS neoplasms using continuous arterial spin labeled perfusion MR imaging at 3 Tesla. *Journal of Magnetic Resonance Imaging*. 2005;22(4):475-482. doi:10.1002/jmri.20415
15. Morana G., Tortora D., Staglianò S., Nozza P., Mascelli S., Severino M., Piatelli G., Consales A., Lequin M., Garrè M., Rossi A., Pediatric astrocytic tumor grading: comparison between arterial spin labeling and dynamic susceptibility contrast MRI perfusion. *Neuroradiology*. 2018;60(4):437-446. doi:10.1007/s00234-018-1992-6
16. Qiao X, Ellingson B, Kim H et al. Arterial Spin-Labeling Perfusion MRI Stratifies Progression-Free Survival and Correlates with Epidermal Growth Factor Receptor Status in Glioblastoma. *American Journal of Neuroradiology*. 2014;36(4):672-677. doi:10.3174/ajnr.a4196
17. Rau M, Braun C, Skardelly M et al. Prognostic value of blood flow estimated by arterial spin labeling and dynamic susceptibility contrast-enhanced MR imaging in high-grade gliomas. *J Neurooncol*. 2014;120(3):557-566. doi:10.1007/s11060-014-1586-z
18. Pronin IN, Fadeeva LM, Podoprigora AE, et al. Arterial Spin Labeling (ASL): method of cerebral blood flow visualisation and quantification. Diagnostic radiology and radiotherapy 2012;3(3):64-78 [In Russian]
19. Fernández-Seara M, Edlow B, Hoang A, Wang J, Feinberg D, Detre J. Minimizing acquisition time of arterial spin labeling at 3T. *Magn Reson Med*. 2008;59(6):1467-1471. doi:10.1002/mrm.21633
20. Garcia DM, De Bazelaire C, Alsop D. Pseudo-continuous flow driven adiabatic inversion for arterial spin labeling. Proc Int Soc Magn Reson Med. 2005;13:37-50.
21. Wong E. New developments in arterial spin labeling pulse sequences. *NMR Biomed*. 2013;26(8):887-891. doi:10.1002/nbm.2954
22. Batalov A, Zakharova N, Pogosbekyan E et al. Non-contrast ASL perfusion in preoperative diagnosis of supratentorial gliomas. *Voprosy neirokhirurgii imeni NN Burdenko*. 2018;82(6):15. doi:10.17116/neiro20188206115

23. Lin Y, Li J, Zhang Z et al. Comparison of Intravoxel Incoherent Motion Diffusion-Weighted MR Imaging and Arterial Spin Labeling MR Imaging in Gliomas. *Biomed Res Int*. 2015;2015:1-10. doi:10.1155/2015/234245
24. Ma H, Wang Z, Xu K et al. Three-dimensional arterial spin labeling imaging and dynamic susceptibility contrast perfusion-weighted imaging value in diagnosing glioma grade prior to surgery. *Exp Ther Med*. 2017;13(6):2691-2698. doi:10.3892/etm.2017.4370
25. Xiao H, Chen Z, Lou X et al. Astrocytic tumour grading: a comparative study of three-dimensional pseudocontinuous arterial spin labelling, dynamic susceptibility contrast-enhanced perfusion-weighted imaging, and diffusion-weighted imaging. *Eur Radiol*. 2015;25(12):3423-3430. doi:10.1007/s00330-015-3768-2
26. Zeng Q, Jiang B, Shi F, Ling C, Dong F, Zhang J. 3D Pseudocontinuous Arterial Spin-Labeling MR Imaging in the Preoperative Evaluation of Gliomas. *American Journal of Neuroradiology*. 2017;38(10):1876-1883. doi:10.3174/ajnr.a5299
27. Kong L, Chen H, Yang Y, Chen L. A meta-analysis of arterial spin labelling perfusion values for the prediction of glioma grade. *Clin Radiol*. 2017;72(3):255-261. doi:10.1016/j.crad.2016.10.016
28. Wang N, Xie S, Liu H, Chen G, Zhang W. Arterial Spin Labeling for Glioma Grade Discrimination: Correlations with IDH1 Genotype and 1p/19q Status. *Transl Oncol*. 2019;12(5):749-756. doi:10.1016/j.tranon.2019.02.013
29. Hashido T, Saito S, Ishida T. A radiomics-based comparative study on arterial spin labeling and dynamic susceptibility contrast perfusion-weighted imaging in gliomas. *Sci Rep*. 2020;10(1). doi:10.1038/s41598-020-62658-9
30. Hales P., d'Arco F., Cooper J., Pfeuffer J., Hargrave D., Mankad K., Clark C. Arterial spin labelling and diffusion-weighted imaging in paediatric brain tumours. *NeuroImage: Clinical*. 2019;22:101696. doi:10.1016/j.nicl.2019.101696
31. Alsaedi A., Doniselli F., Jäger H., Panovska-Griffiths J., Rojas-Garcia A., Golay X., Bisdas S. The value of arterial spin labelling in adults glioma grading: systematic review and meta-analysis. *Oncotarget*. 2019;10(16):1589-1601. doi:10.18632/oncotarget.26674
32. Fu J, Li L, Wang X, Zhang M, Zhang Y, Li Z. Clinical utility of arterial spin labeling for preoperative grading of glioma. *Biosci Rep*. 2018;38(4). doi:10.1042/bsr20180507
33. Arisawa A., Watanabe Y., Tanaka H., Takahashi H., Matsuo C., Fujiwara T., Fujiwara M., Fujimoto Y., Tomiyama N. Comparative study of pulsed-continuous arterial spin labeling and dynamic susceptibility contrast imaging by histogram analysis in evaluation of glial tumors. *Neuroradiology*. 2018;60(6):599-608. doi:10.1007/s00234-018-2024-2
34. Morana G., Tortora D., Staglianò S., Nozza P., Mascelli S., Severino M., Piatelli G., Consales A., Lequin M., Garrè M., Rossi A., Pediatric astrocytic tumor grading: comparison between arterial spin labeling and dynamic susceptibility contrast MRI perfusion. *Neuroradiology*. 2018;60(4):437-446. doi:10.1007/s00234-018-1992-6

35. Guo H, Kang H, Tong H, et al. Microvascular characteristics of lower-grade diffuse gliomas: investigating vessel size imaging for differentiating grades and subtypes. *Eur Radiol*. 2019;29(4):1893–1902. doi:10.1007/s00330-018-5738-y.

Figures

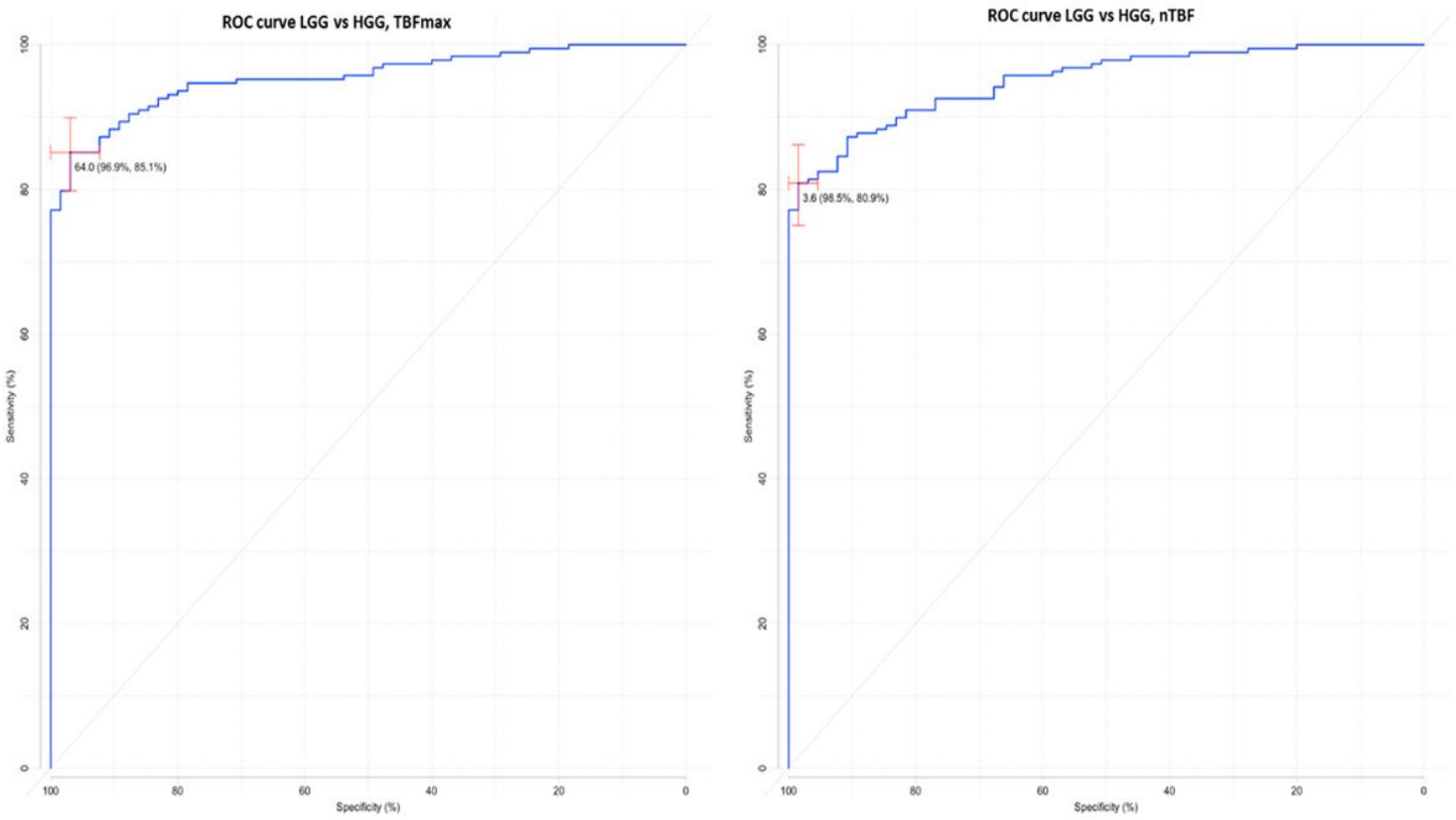

Figure 1

ROC-curve. Comparison of maxTBF (a) and nTBF (b) in HGGs and LGGs

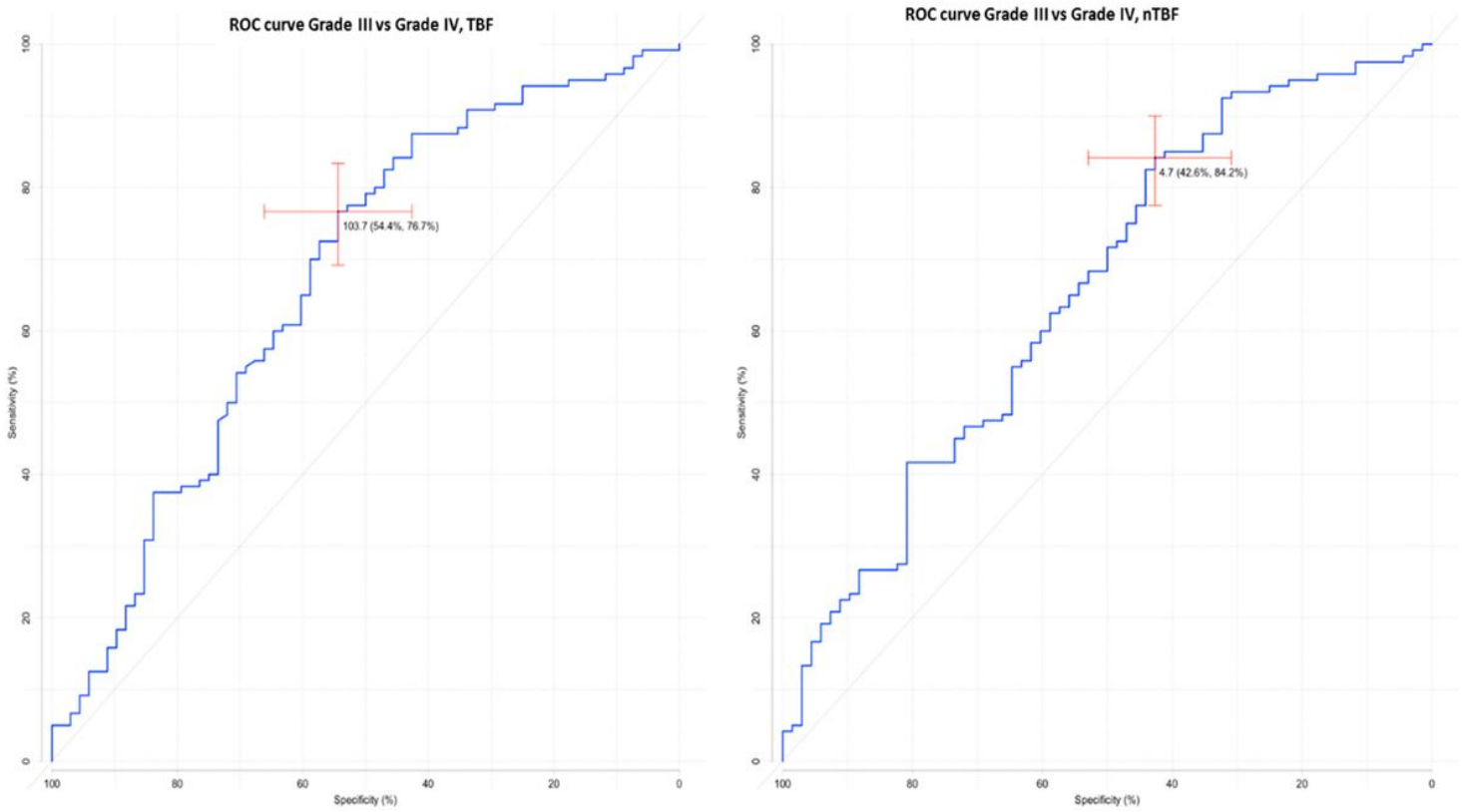

Figure 2

ROC-curve. Comparison of maxTBF (a) and nTBF (b) in Grade III and Grade IV tumors