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

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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 mm² ± 10 mm²) 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).

| Histopathological diagnosis            | Grade, WHO | N  |
|---------------------------------------|------------|----|
| Gangliolioma                          | 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 ms; TE – 9.8 ms; 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$^2 \pm$ 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$^2 \pm$ 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.

| Grade 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 mm² [23]. In contrast, we used smaller ROI size of 20 ± 10 mm² 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 mm³ in size and normalization was performed to the contralateral white matter.

Hales et al. (2019) used 50 mm² 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 glioma 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.

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**Declarations**

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**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.

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**Figures**

![ROC-curve](image)

**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