Assessment of perfusion in glial tumors with arterial spin labeling: comparison with dynamic susceptibility contrast method

H Cebeci a,∗, O Aydin a, E Ozturk-Isik b, C Gumus b, F Inecikli c, A Bekar d, H Kocaeli d, B Hakyemez a

a Department of Radiology, Uludag University Medical School, Bursa, Turkey
b Department of Biomedical Engineering, Yeditepe University, Istanbul, Turkey
c Department of Radiology, Kanuni Sultan Suleyman Educational and Research Hospital, Istanbul, Turkey
d Department of Neurosurgery, Uludag University Medical School, Bursa, Turkey

A R T I C L E I N F O

Article history:
Received 8 November 2013
Received in revised form 30 June 2014
Accepted 7 July 2014

Keywords:
Gloma
Dynamic susceptibility contrast perfusion imaging
Arterial spin labeling

A B S T R A C T

Purpose: Arterial spin labeling perfusion imaging (ASL-PI) is a non-invasive perfusion imaging method that can be used for evaluation and quantification of cerebral blood flow (CBF). Aim of our study was to evaluating the efficiency of ASL in histopathological grade estimation of glial tumors and comparing findings with dynamic susceptibility contrast perfusion imaging (DSC-PI) method.

Methods: This study involved 33 patients (20 high-grade and 13 low-grade gliomas). Multiphase multislice pulsed ASL MRI sequence and a first-pass gadopentetate dimeglumine T2*−weighted gradient-echo single-shot echo-planar sequence were acquired for all the patients. For each patient, perfusion relative signal intensity (rSI), CBF and relative CBF (rCBF) on ASL-PI and relative cerebral blood volume (rCBV) and relative cerebral blood flow (rCBF) values on DSC-PI were determined. The relative signal intensity of each tumor was determined as the maximal SI within the tumor divided by SI within symmetric region in the contralateral hemisphere on ASL-PI. rCBV and rCBF were calculated by deconvolution of an arterial input function. Relative values of the lesions were obtained by dividing the values to the normal appearing symmetric region on the contralateral hemisphere. For statistical analysis, Mann–Whitney ranksum test was carried out. Receiver operating characteristic curve (ROC) analysis was performed to assess the relationship between the rCBF-ASL, rSI-ASL, rCBV and rCBF ratios and grade of gliomas. Their cut-off values permitting best discrimination was calculated. The correlation between rCBV, rCBF, rSI-ASL and rCBF-ASL and gloma grade was assessed using Spearman correlation analysis.

Results: There was a statistically significant difference between low and high-grade tumors for all parameters. Correlation analyses revealed significant positive correlations between rCBF and rCBF-ASL (r = 0.81, p < 0.001). However correlation between rCBF and rCBF-ASL was weaker (r = 0.64, p < 0.001).

Conclusion: Arterial spin labeling is an employable imaging technique for evaluating tumor perfusion non-invasively and may be useful in differentiating high and low grade gliomas.

© 2014 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Brain tumors constitute one of the important disease group and frequently difficulties are encountered in imaging [1]. Gliom tumors are the most common primary neoplasms of the brain in adults, and histopathological distribution of gliomas were complex between low grade and high grade [2]. Histopathological grading of brain tumors which is achieved by surgical excision or stereotactic biopsy is crucial for optimal treatment planning [3].

Magnetic resonance (MR) imaging in particular is the most frequently used imaging modality to evaluate brain tumors. In addition to conventional MR sequences, advanced MR techniques found their place in clinical practice. Perfusion imaging, diffusion-weighted imaging, and MR spectroscopic imaging are the commonly used advanced MR imaging methods for brain tumor evaluation. These advanced techniques generate physiological data and information on chemical composition [1].

In general, contrast-enhanced conventional cranial MR imaging is mostly sufficient for intracranial tumor diagnosis. But there are some limitations, like nonspecificity of contrast enhancement. Enhancement after contrast agent reflects blood brain barrier disruption rather than a true assessment of tumor vascularity.
Especially, differential diagnosis between high and low-grade tumors and between radiation necrosis and recurrent tumors are challenges by using only conventional contrast-enhanced cranial MRI [4,5].

Recent advances in dynamic MR imaging have enabled the assessment of tumor vascularity quantitatively. Among various functional imaging techniques, perfusion MRI imaging is particularly sensitive in demonstrating microvasculature and tumor neovascularization. Clinical applications of perfusion MR imaging in brain tumor evaluation include assessment of tumoral grade, achieving guidance for stereotactic biopsy, differentiation between recurrent glioma and radiation necrosis, and determination of prognosis and response to treatment [4,5].

Perfusion MR imaging methods exploit signal changes that accompany the passage of tracer through the cerebrovascular system. The tracer can be endogenous (arterial water) or exogenous (deuterium oxide, gadopentetate dimeglumine). Arterial spin labeling (ASL) MRI is a perfusion imaging method, which uses arterial blood water as a freely diffusible endogenous tracer [6]. One of the exogenous tracer methods of perfusion imaging is dynamic susceptibility contrast perfusion imaging (DSC-PI). In DSC-PI, rapid loss of MR signal on T2* weighted images is measured and then used to calculate the change in concentration of contrast material for each individual voxel [7].

The goal of our study was to determine the usefulness of ASL in evaluating the histopathological grade of cerebral gliomas and to compare findings with DSC-PI method.

2. Materials and methods

2.1. Patient population

This retrospective study included thirty-three patients with histopathologically proven gliomas (18 male, 15 female; age range = 17 to 74 years, mean age = 46.9 years) who had undergone perfusion MRI examination in our institute with both ASL and DSC perfusion imaging methods between January 2010 and May 2013. In total, we investigated twenty-high-grade and thirteen low-grade gliomas. Histopathological diagnosis was obtained with surgical excision or biopsies. The grading of gliomas was based on the 2007 World Health Organization brain tumor classification [8]. The study was approved by institutional ethical committee. The lesions were eighteen glioblastoma multiforme, one grade 3 astrocytoma, one gliosarcoma, eleven grade 2 oligodendroglioma, one dissembyloblastic neuroepithelial tumor (DNET), and one pilocytic astrocytoma.

2.2. Imaging protocol

All MR imaging examinations were performed on a clinical 3 Tesla MR imaging system (Philips Achieva 3T, Best, Netherlands) by using a 32 channel head coil. For conventional MR study, axial 3D turbo field echo (TFE) (TR/TE = 8.1/3.7 ms), axial T2-weighted turbo spin-echo (TSE) (TR/TE = 3000/80 ms), and axial post-contrast 3D-TFE images were acquired.

Multiphase ASL method was used in all patients. ASL-PI studies were performed after conventional MR sequences. ASL was capable of multisection image acquisition at multiple inversion time points (multiple TI) and was based on the EPSTAR pulsed ASL technique. On the basis of conventional MR imaging results, we selected 6 transverse sections through the tumor for our ASL studies. Image acquisition was done at 8 TI times. For the first slice, minimum inversion time was 300 ms, and subsequent inversion times were increased by 250 ms. The labeling slab thickness was 130 mm, and it was positioned at the level of upper cervical region. The imaging parameters for the ASL sequence were as follows: TR/TE = 250/16 ms, flip angle = 40°, FOV = 240 × 240 cm, matrix = 68 × 68, slice thickness/gap = 6/0.6 mm, number of dynamics = 30. A total of 2880 images, including 1440 labeled and 1440 control images, were obtained. The total acquisition time was 4 min and 8 s. ASL images were transferred to an off-line workstation (Philips Extended MR workspace, R.2.6.3.2, 2009) and subtraction images and rCBF maps were obtained.

DSC-PI was performed after ASL image acquisition by first passage contrast-enhanced T2-weighted single-shot gradient-echo echo-planar sequence. The parameters of the sequence were as follows: TR/TE = 1513/40 ms, flip angle = 75°, FOV = 224 × 224 mm, matrix = 96 × 95, slice thickness = 5 mm, slice gap = 0 mm, and total data acquisition time = 65 s. As a contrast material, 20 ml gadodiamide (Omniscan, Nycomed, Norway) was administered using an 18 ga IV catheter at a rate of 5 ml/s automatically (Spectris Solaris EP MR Injection System, Medrad) by the antecubital venous method. This was followed by 20 ml serum physiological liquid injection at nearly the same rate. After the perfusion MRI, contrast-enhanced T1-weighted 3D-TFE sequence was acquired.

2.3. Data processing

Image analysis was performed in Extended MR workspace (Version 2.6.3.2, 2009, Philips Medical Systems) with the special application tools “neuro perfusion” and “image algebra” for DSC-PI and ASL-PI, respectively. After evaluating the conventional MRI sequences, ASL and DSC images were evaluated and perfusion maps were created. Qualitative interpretation of lesions on perfusion images did not performed.

In ASL data processing, 48 subtraction images of the labeled and control images were obtained. A manually drawn elliptic region of interest (ROI) was placed on the solid and bright portion of tumor seen in subtraction images, which was assumed as having high perfusion. The signal intensity of the lesion was normalized with the symmetrical region on the contralateral normal hemisphere (rSI). A program was written in MATLAB (The Mathworks Inc., Natick, MA) for calculating the absolute cerebral blood flow from ASL images. First, thirty dynamics of each slice were averaged to increase SNR. Brain tissue was masked from the control images for each slice. Main magnetization (M0) was estimated for each pixel of the masked images using the T1 relaxation equation at different phases of control images using T1 value of blood (1.664 s). Thereafter, cerebral blood flow was calculated by taking into account the arterial blood flow [9]. The inversion efficiency (ε) was used as 0.95, T1 of tissue was used as 1.3 s, and the blood tissue water partition coefficient was taken as 0.9 for the whole brain.

For DSC data processing, arterial input function model was used. Middle cerebral artery (MCA) was selected as an arterial input for assessing CBF and CBV maps. For obtaining normalized values, the symmetrical region on the contralateral hemispher was accepted as reference like in ASL data processing.

2.4. Statistical analysis

Five perfusion MRI parameters, which were rCBV and rCBF obtained from DSC-PI and CBF, rCBF, and rSI values obtained from ASL were evaluated. The capability of these perfusion values and ratios about differentiating low and high-grade gliomas was investigated with Mann-Whitney ranksum test. Bonferroni multiple comparison correction was used, and a p value of less than 0.01 was considered as significant. The correlation between perfusion parameters obtained with DSC and ASL was assessed using Spearman correlation analysis.

Receiver operating characteristic curve analysis was used to evaluate the association between the perfusion values and the
grade of the glioma, as well as to calculate cutoff values permitting discrimination between high and low-grade gliomas.

3. Results

On conventional MRI findings, twenty-two out of thirty-three lesions had contrast enhancement. Nineteen of the enhancing lesions were high-grade, and 3 of them were low grade gliomas.

All the perfusion parameters obtained with ASL and DSC-PI were successful in the discrimination of low and high-grade gliomas (p < 0.001, using the Mann–Whitney rank sum test). There were significant differences between low and high-grade gliomas for all the parameters. The mean values of the parameters assessed in low and high-grade gliomas, and p values of the Mann–Whitney rank sum test are shown in Table 1. Figs. 1 and 2 show example cases of a low-grade and a high-grade glioma, respectively.

For ASL perfusion imaging parameters, a cut-off value of 2.10 and 2.19 for ASL-rCBF and ASL-rSI ratios, respectively (sensitivity %100, specificity %92.3), were the values for best discrimination. Fig. 3 shows the ROC curves for the perfusion parameters assessed in this study. As a result of the correlation analyses between perfusion parameters, a strong correlation between rCBV and ASL-rCBF (r = 0.81, p < 0.001) was found. However, the correlation between rCBF and ASL-rCBF was weaker (r = 0.64, p < 0.001). There was also a strong correlation between rCBV and ASL-rSI (r = 0.83, p < 0.001), ASL-rCBF and ASL-rSI (r = 0.76, p < 0.001), and ASL-rCBF and ASL-CBF (r = 0.79, p < 0.001).

On the basis of equal misclassification rates, a cut-off value of 1.80 and 1.36 for rCBV and rCBF ratios, respectively (sensitivity %100, specificity %84.6 for rCBV and sensitivity %100, specificity %76.9 for rCBF), best discriminated low and high-grade gliomas. Eleven of thirteen low grade tumors were grade 2 oligodendroglioma and two of eleven oligodendroglioma showed rCBV value higher than 1.80. None of high grade tumors had rCBV value of lower than 1.80. (Fig. 4)

4. Discussion

Glial tumors are the most common group amongst primary brain tumors. Tumoral angiogenesis is one of the most important factors for assessing grade of gliomas. Tumoral vascularity can be assessed non-invasively with various perfusion MRI applications.

Conventional MRI sequences are not very sensitive for grading gliomas. Contrast enhancement evaluated with conventional

Table 1
The age and sex distributions and perfusion parameters of low and high-grade gliomas.

<table>
<thead>
<tr>
<th>Sex (%male)</th>
<th>Low grade (n = 13)</th>
<th>High grade (n = 20)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rCBV</td>
<td>41.5 ± 15</td>
<td>51.3 ± 15.6</td>
<td>0.17</td>
</tr>
<tr>
<td>rCBF</td>
<td>0.89 (0.43–0.80)</td>
<td>4.15 (2.7–7.14)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rCBF ASL</td>
<td>0.96 (0.22–2.14)</td>
<td>2.55 (1.54–5.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>rSI ASL</td>
<td>0.93 (0.54–2.29)</td>
<td>4.87 (2.21–21.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CBF ASL</td>
<td>8.1 (4.6–117)</td>
<td>23.65 (6.8–186)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow; rCBF ASL, relative cerebral blood flow obtained with ASL; rSI ASL, relative signal intensity obtained with ASL; CBF ASL, cerebral blood flow obtained with ASL.

Fig. 1. A 53 years old woman diagnosed with oligodendroglioma grade 2. Conventional T2W (A), T1W (B) and postcontrast T1W (C) MR images, show a large, nonenhancing mass in the left frontal lobe. CBV (D) and CBF (E) maps of DSC-PI and ASL subtraction image (F) show hypoperfusion in tumoral lesion.
**Fig. 2.** A 65 years old woman diagnosed with glioblastome multiforme. T1W (A) and postcontrast T1W (B) MR images show a large, enhancing mass in the right frontal lobe. CBV (C) and CBF (D) maps from DSC-PI, ASL subtraction image (E) and CBF map (F) from ASL-PI show hyperperfusion in tumoral lesion.

**Fig. 3.** Receiver operating characteristic curves for, DSC-rCBV and DSC-rCBF, rCBF-ASL, rSI-ASL and CBF-ASL.

Please cite this article in press as: Cebeci H, et al. Assessment of perfusion in glial tumors with arterial spin labeling; comparison with dynamic susceptibility contrast method. Eur J Radiol (2014), http://dx.doi.org/10.1016/j.ejrad.2014.07.002
sequences means disturbance of blood brain barrier, not exactly the vascularization [3]. On the other hand, there are quite a few nonenhancing high-grade tumors. Radiological tumoral grade of nonenhancing malignant gliomas may be assumed as lower, possibly resulting in wrong treatment approaches [10]. In this study, 3 out of thirteen low grade tumors were enhancing and 1 out of twenty high grade gliomas was nonenhancing. Our results suggest that enhancement is not a reliable factor for determining tumoral grade, similarly with previous results.

Previous studies reported that DSC-PI provided useful information about glioma grading [3,10]. More recently, some studies suggested that ASL is also capable of differentiating low and high-grade gliomas [11–12]. Our findings confirm those of previous studies showing a strong positive correlation between the degree of elevated perfusion parameters and tumor grade [13–16].

rCBV calculated out of DSC-PI is commonly used in in evaluating perfusion in brain tumors, but some studies also used rCBF for grading gliomas [3]. According to our results, both rCBV and rCBF were significantly different between low and high-grade gliomas. However, the cutoff value of 1.80 for rCBV had a higher specificity than the cut of value of 1.36 for rCBF. DSC-PI provides both rCBF and rCBV data, but ASL can only result in an rCBF estimate. Although there have been some animal experiments to measure CBV with ASL, there has not been a measurement of CBV with ASL in clinical practice yet [12].

DSC perfusion imaging is the most commonly used modality for perfusion assessment in clinical practice. On the other hand, ASL is a promising technique that does not require contrast agent injection. According to our results, ASL perfusion parameters, which were relative signal intensity and relative cerebral flow, could differentiate low and high-grade tumors. Absolute CBF values obtained with ASL was also capable of differentiating tumoral grade, but we think relative values were more reliable. To our knowledge, there is no consensus about the absolute CBF values calculated out of ASL of low and high-grade gliomas.

Warmuth et al. [10] reported strong positive correlation between CBF measurements on DSC and ASL perfusion maps. Pulsed ASL method with a single TI point was used in their study. But, this may lead to serious errors due to the sensitivity of CBF measurements to arterial transit times [17]. Bolus saturation sequences such as QUIPSS II were developed to render ASL less sensitive to transit time, but if the arterial transit time is wide, image acquisition in multiple TI points and modelling CBF might solve this problem. Another study that compared DSC and ASL perfusion imaging was done by Hirai et al. [12] for 24 gliomas at 3T. They also found an agreement between DSC and ASL.

Noguchi et al. [11] compared percent signal intensity (%SI) and histopathological microvessel area in 35 brain tumor patients. A positive correlation was observed between ASL signal intensity and histopathological microvascular area, and they reported that %SI on ASL reflected tumoral vascularity in brain tumors. In agreement with these results, our study showed standardized signal intensity (rSI) on ASL could differentiate low and high-grade gliomas, and it was highly correlated with rCBF on DSC perfusion imaging ($r = 0.83, p < 0.001$).

Also rSI measurements were highly correlated with rCBF for ASL data ($r = 0.90, p < 0.001$).

According to these results, we suggest that measuring signal intensity on ASL subtraction image may be valuable for grading gliomas, although, it does not provide a CBF estimate.

Another study that supports this opinion was done by Kimura et al. [5] for a group of meningioma patients. According to their results, there was also a strong correlation between %SI and histopathological data for continuous ASL ($r = 0.91, p < 0.001$), but correlation between rCBF and histopathological data was weaker ($r = 0.61, p < 0.001$).

---

Please cite this article in press as: Cebeci H, et al. Assessment of perfusion in glial tumors with arterial spin labeling; comparison with dynamic susceptibility contrast method. Eur J Radiol (2014), http://dx.doi.org/10.1016/j.ejrad.2014.07.002
Lev et al. [18] investigated glial tumor grade and DSC-PI rCBV threshold and confounding effect of elevated rCBV of oligodendrogliomas. They found rCBV of 1.5 threshold value for best discrimination low from high grade gliomas, whereas our threshold value for rCBV was 1.80. Our results were consistent with Lev et al. about confounding effects of oligodendrogliomas. So that two low grade oligodendrogliomas showed rCBV value of higher than threshold and also other perfusion parameters of both DSC-PI and ASL-PI were higher than threshold for these two low grade oligodendroglioma.

No need of intravenous contrast agent injection is the major advantage of ASL, which makes ASL easy repeatable. ASL may also be useful in patients with renal failure, because they may be at risk for contrast-related nephrogenic systemic fibrosis, and in children for whom the intravenous rapid bolus injection of contrast agents may be difficult [12]. However, over 20 years after development of first ASL sequences, ASL still has not been utilized in routine clinical practice. Low signal to noise ratio (SNR) is the major cause of this issue. Therefore, ASL technique needs multiple repetitions for higher SNR, which causes longer imaging times. This study had some limitations. Contrast enhancement seen in most of the high-grade tumors may have lead to an underestimation of rCBV and rCBF values in DSC perfusion imaging. Also, CBF measurement in ASL was hard in some regions due to low SNR. This effect was especially significant in posterior fossa lesions. Low spatial resolution (3.5 × 3.5 × 6 mm) and limited imaging plane (6 sections, 3.9 cm total width) were other technical limitations of ASL imaging. Although, this study included quite a few patients, there were no grade 2 astrocytomas in the low-grade group and eleven out of thirteen lesions were grade 2 oligodendrogliomas. However, all lesions in this study had histologically proven diagnoses, and all MR imaging examinations were done at a high magnetic field of 3T. SNR is higher in high magnetic field thus leading decreased motion artifacts compared to 1.5T. ASL image acquisition at multiple sections at multiple time points was also an advantage of this study.

Motion artifacts were detected in perfusion MR images especially ASL-PI images because of low temporal resolution. Magnetic susceptibility artifacts in echo-planar imaging were prominent at bone-air interfaces and around operation materials. However, none of the tumors studied was markedly distorted by these artifacts.

5. Conclusion

Both perfusion MRI techniques, ASL and DSC, were successful in discriminating low and high grade gliomas. DSC is more commonly used in routine clinical practice and is a widely accepted method for perfusion imaging in the brain. Despite this fact, ASL is a promising perfusion imaging method having the advantage of being non-invasive. According to the results of this study, perfusion parameters obtained by these two techniques were positively correlated. DSC has the advantage of high SNR and lower imaging time, and could be preferred in diseases with delayed arterial transit time, like atherosclerosis. However, a relatively newer non-invasive perfusion method, ASL, may obtain results that are in good agreement with DSC perfusion imaging, and it may be a useful alternative method for evaluating the perfusion of glial tumors, especially for patients with contraindications to contrast agents.

Conflict of interest statement

We confirm that there are no actual and potential conflicts of interest associated with this publication and there has been no financial support for this work.

References


Please cite this article in press as: Cebeci H, et al. Assesment of perfusion in glial tumors with arterial spin labeling; comparison with dynamic susceptibility contrast method. Eur J Radiol (2014), http://dx.doi.org/10.1016/j.ejrad.2014.07.002