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A meta-analysis of arterial spin labelling perfusion values for the prediction of glioma grade

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AIM: To investigate the ability of arterial spin labelling (ASL) perfusion parameters to distinguish high-grade from low-grade gliomas.

MATERIALS AND METHODS: The PubMed and EMBASE databases were systematically searched for relevant articles published up to September 2015. Studies that evaluated both high- and low-grade gliomas using ASL were included. The random effect model was used to calculate the standardised mean difference (SMD) of maximum mean absolute tumour blood flow values ($aTBF_{max}$, $aTBF_{mean}$) and maximum mean relative tumour blood flow ($rTBF_{max}$, $rTBF_{mean}$) between high- and low-grade gliomas.

RESULTS: Nine studies encompassing 305 patients with high- and low-grade gliomas, met all inclusion and exclusion criteria and were included in the study. Compared with low-grade gliomas, high-grade gliomas had a significant increase in all ASL perfusion values: $aTBF_{max}$ (SMD=0.70, 95% confidence interval [CI]: 0.22–1.19, p=0.0046); $aTBF_{mean}$ (SMD=0.86, 95% CI: 0.2–1.52, p=0.01); $rTBF_{max}$ (SMD=1.08, 95% CI: 0.54–1.63, p=0.0001) and $rTBF_{mean}$ (SMD=0.88, 95% CI: 0.35–1.4, p=0.0011).

CONCLUSIONS: The current study results indicate that tumour blood flow from ASL differs significantly with respect to the glioma grade. Despite some limitations, there is evidence that ASL may be useful to distinguish high- and low-grade gliomas. Further larger-scale studies are necessary to examine the utility of ASL to distinguish tumour grade.

Introduction

Gliomas are the most common primary brain tumours in adults,[1] and a precise diagnosis is important because the adjuvant therapy after surgery and prognosis differ considerably according to tumour grade.[2] Conventional morphological imaging technologies are usually limited in grading gliomas. For example, enhancement is not a reliable factor for determining tumoural grade.[3,4] Perfusion imaging is the commonly used advanced imaging method for the evaluation of brain tumours.[5,6] Currently, two major types of imaging methods are available to evaluate brain tumour perfusion. One is dynamic susceptibility contrast (DSC) perfusion imaging and the other is arterial spin labelling (ASL).

One practical advantage of ASL technique is that it relies on endogenous tracers, such as water molecules, and can be

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repeated many times in patients with renal failure.[7,8] Several recent clinical studies have highlighted ASL techniques as helpful in the differential diagnosis of brain tumours; for example, low-grade gliomas from high-grade gliomas, and gliomas from other type of tumours.[9–13]

Clinically established methods for quantitative perfusion measurements usually include absolute tumour blood flow (aTBF) and relative tumour blood flow (rTBF), which is the normalisation of the aTBF values in relation to mean values in normal appearing regions. Some studies have investigated the value of TBF to distinguish high- from low-grade gliomas, but the findings have been incongruent. For example, Warmuth *et al.*[14] demonstrated that mean ($aTBF_{mean}$) and maximum aTBF ($aTBF_{max}$) values were significantly higher in high-grade than in low-grade brain tumours. Cebeci *et al.*[15] reported significant positive correlations between rCBV from DSC and rCBF from ASL, and they considered relative values from ASL were more reliable. In contradistinction, Roy *et al.*[16] demonstrated that ASL-derived absolute CBF values were not significantly different between histopathologically proven high- and low-grade glioma, even after normalising these values from the contralateral regions. They concluded that despite the advances in the technical developments of ASL, the currently available ASL method still suffers from interpatient variability.[16]

To the authors' knowledge, the efficiency of ASL to distinguish between high-grade and low-grade gliomas has not been evaluated quantitatively. Therefore, the main objective of the present study was to conduct a quantitative meta-analysis of the existing literature to determine the statistical consensus of aTBF, and rTBF in distinguishing the tumour grade of gliomas.

Materials and methods

Search strategy

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.[17] A systematic search was performed in the PubMed and EMBASE for relevant publications from inception to September 2015. The search terms were as follows: ("arterial spin labelling" or "arterial spin labelling" or "arterial spin labelled" or "ASL") AND ("glioma" or "brain neoplasm" or "brain tumour" or "brain tumour"). There was no language restriction. Additionally, the references of selective articles were searched manually to identify potentially relevant studies that were not identified in the previous searches. Two authors independently performed the search, reviewed all eligible articles, and excluded obviously irrelevant studies by reading titles, abstracts, and keywords. The full text of each article was obtained when one or both reviewers were unsure or recommended review of the full text of the article.

Inclusion and excluded criteria

The inclusion criteria were as follows: (1) ASL was used to measure perfusion values of both high-grade (WHO grade III–IV) and low-grade gliomas (WHO gI–II); (2) histopathological analysis was used as the reference standard; (3) patients had no radiotherapy, surgery, or chemotherapy before ASL; (4) studies reported aTBF values and/or the rTBF values were available for effective calculation; (5) the number of patients should be at least eight; (6) no data overlapped between studies, if studies had the same or overlapping data, only the largest study was included in the final analysis. Studies were excluded based on the following criteria: animal studies, abstracts, reviews, case report, letters, editorials, comments, and conference proceedings. Articles that did not provide adequate information to allow the calculation of values were also excluded.

Data extraction and quality assessment

The final articles were assessed independently by the same two authors. For each included study basal characteristics (authors, year of publication, and country of origin), patient characteristics (mean age, sex, and number and type of gliomas), and technical aspects (imaging field strength, ASL techniques, reference standard, and the method for TBF measurement) were noted. The $aTBF_{mean}$, $aTBF_{max}$, mean rTBF ($rTBF_{mean}$), and maximum rTBF ($rTBF_{max}$) values were tabulated as mean values and SDs. $aTBF_{max}$ was obtained by placing a region of interest (ROI) in the apparent maximum TBF region and average several ROIs within the tumour to create the $aTBF_{mean}$. rTBF values were evaluated by normalising aTBF values to reference regions:

$rTBF_{max} = aTBF_{max}$/reference value and

$rTBF_{mean} = aTBF_{mean}$/reference value.

Reference regions may be normal-appearing grey matter, white matter, the contralateral mirrored region, or the global mean value. Data were recorded at the patient level, when possible. Each reviewer extracted study information on a standardised Microsoft Excel spreadsheet. Discrepancies were resolved by consensus.

The same two reviewers independently assessed the quality of each article using the modified Quality Assessment of Diagnosis Accuracy Studies (QUADAS-2) score tool,[18] which consisted of 14 questions answered "yes", "no", or "unclear". Disagreements between the two investigators were resolved by consensus, and if disagreement persisted, a third reviewer made the ultimate decision.

Statistical analysis

The mean difference (MD) of $aTBF_{mean}$ and $aTBF_{max}$ and the standardised mean differences (SMDs) of $aTBF_{mean}$, $aTBF_{max}$, $rTBF_{mean}$, and $rTBF_{max}$, between high-grade and low-grade gliomas were calculated and used as effect-size statistics. The SMD is the standardised difference between two means and can be calculated as the difference between the high- and low-grade glioma groups divided by the

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