Role of perfusion MRI in differentiating astrocytomas from solitary metastases and glioblastomas

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Aims and objectives

Perfusion studies have a fundamental role in the oncological imaging of central nervous system (CNS). The technique allows evaluation of angiogenesis, which, together with histological criteria such as cellularity, mitosis, pleomorphism, and necrosis, contributes to the definition of grading and patient survival [1].

In the study of gliomas, the role of perfusion-weighted imaging (PWI) is to evaluate and quantify the extent of neo-vascularization, and particularly the formation of new blood vessels from the pre-existing capillary network, a factor that affects the histopathological grade of astrocytomas [2].

According to Romano et al [3], several authors reported that the relative cerebral blood volume (rCBV) values correlate with the prognosis of low-grade glioma patients, and that they are more predictive of disease progression than histological evaluation; in particular, rCBV values larger than 1.75 point to neoplasia progression and clinical worsening. The calculation of the rCBV value has high importance also in the evaluation of disease progression and pseudo-progression for glioblastoma patients, thus avoiding unjustified treatment modifications [4].

The role of PWI in the study of cerebral metastases is based on the possibility of differential diagnosis with high-grade glial lesions: the management of these two tumors is different and can potentially affect the clinical outcome. In addition, it may call for further diagnostic tests in the search for the primitive tumor, as in the case of secondary cerebral lesions due to an unknown primitive tumor.

The histopathology of gliomas and metastases is very much different, as reported by Law et al [5]. Metastases do not present tumor cells infiltrating the adjacent edema, which is due to the rupture of the blood-brain barrier (BBB) producing capillary permeability followed by peri-lesional edema. On the other hand, the histopathologic appearance of low- and high-grade gliomas is different, since BBB can remain intact and in the peritumoral edema infiltrating tumor cells and neoplastic capillaries are present, thus leading to increased rCBV values.

Goal of the present paper is to evaluate the role of PWI-MRI of neoplastic tissues and of the peri-tumoral area by calculation of rCBV, in the differential diagnosis of glioblastomas, astrocytomas and solitary cerebral metastases, while having the retrospective histopathologic diagnosis.
Methods and materials

Inclusion criteria

From January 2013 to September 2014 49 patients between 40 and 63 years of age (median 51) were enrolled in the study after signing the informed consent. They were affected by grade IV (WHO) glioma of the CNS, astrocytoma (grade II-III) and singular cerebral metastases. Retrospective histopathologic diagnosis was available for all patients after brain stereotactic biopsy or surgical excision. Patients were divided in three groups: the first included 29 patients with glioblastoma multiforme, the second 9 patients with astrocytoma (grade II-III) and the third 16 patients with solitary cerebral metastases from lung tumor (Table 1).

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma multiforme</td>
<td>29</td>
</tr>
<tr>
<td>Astrocytoma (grade II-III)</td>
<td>9</td>
</tr>
<tr>
<td>Solitary metastasis</td>
<td>16</td>
</tr>
<tr>
<td>(from lung tumor)</td>
<td></td>
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</tbody>
</table>

Imaging

The MRI PWI pulses were acquired using a superconductive magnet (Achieva, software release 2.4.5) operating at 1.5 T (Philips, Best, the Netherlands), with updated gradients. The dynamic susceptibility contrast enhancement PWI (DSC-PWI) was obtained with a contrast medium bolus (1 M gadobutrol, Bayer-Schering, at a dose of 0.1 mmol/kg and an infusion rate of 5 mL/sec) using EPI T2* weighted sequences, shorter repeat time (RT), echo time (TE) 30 ms, flip angle 40°, field of view (FOV) 250 x 172 pixel, matrix dimensions 128 x 63, thickness 5 mm, 22 slices, dynamics 40, 1 mm interval, NSE 1, acquisition time 1 min 22 s.

PWI MR data were analyzed with a dedicated software (Philips NeuroPerfusion and FiberTrack software), using the arterial input function (AIF) in order to position the regions of interest (ROI) in the more visible region of the arterial vessel contralateral to the lesion, and then calculating the corresponding CBV color map. To assess the reproducibility of the ROI-based technique, a 'test-retest' reliability assessment was performed by measuring three times all ROI's for the first five patients.

ROI's were positioned by an experienced radiologist with the "hot spot" technique at the more vascularized areas, and for each enhanced tumor lesion (ENH/HYPER), peri-tumoral edema (HYPERp) and the contralateral normally-appearing white matter
(NAWM) were evaluated. The ratio between the CBV values of tumor tissue and the peritumoral area with the contralateral white matter was then calculated in order to normalize and reduce the measurement error. The criteria for the positioning of the ROI were as follows:

- The more solid portion inside the tumor area.
- The more homogeneous contrast enhancing or hyperintense or normal T2 signal areas (depending on the class of ROI’s).
- The avoidance of necrosis or hemorrhagic foci inside the ROI.
- ROI area of 10 mm$^2$, round in shape.

Statistical analysis

We used MEDcalc as software platform.

Test-retest reliability (R) was determined by means of repeated measurements. R is expressed by a number between 0 and 1. The value 0 indicates no reproducibility, the value 1 indicates perfect reproducibility. A value of R = 0.75 is usually considered the minimum requirement for a useful assessment [6]. Then statistical analyses were performed using Student’s t-test, a p value less than 0.05 was considered to indicate a statistically significant difference.

In order to determine the test discriminating capacity, the area under the ROC curve (AUC) was evaluated. The ROC curve for a non-significant test is a diagonal that passes through the origin with AUC = 0.5. We also calculated the diagonal accuracy of peritumoral edema.
Results

A test-retest reproducibility of $R = 0.76$ was obtained, thus indicating that the procedure of ROI's positioning was quite reproducible.

The mean rCBV values for tumor tissue (ENH/HYPER) were 2.85, 1.59 and 2.40 for glioblastomas (Fig. 1), astrocytomas (Fig. 2) and metastases (Fig. 3), respectively.

No statistically significant difference between the rCBV of tumor tissue of glioblastomas and metastases was observed ($p = 0.20$, AUC = 0.51). On the other hand, statistically significant differences were observed for the rCBV of tumor tissue of glioblastomas and astrocytomas ($p = 0.017$, AUC = 0.68), and metastases and astrocytomas ($p = 0.035$, AUC = 0.73).

The mean rCBV values for peri-tumoral edema (HYPERp) were 1.06, 0.75, and 0.74 for glioblastomas, astrocytomas and metastases, respectively. No statistically significant difference for the rCBV of peri-tumoral edema between glioblastomas and astrocytomas ($p = 0.17$), and between metastases and astrocytomas ($p = 0.48$), was observed. The difference between the rCBV of peri-tumoral edema of glioblastomas and metastases was statistically significant ($p = 0.037$, AUC = 0.62), with a cut-off value 1.24, sensitivity 33% and specificity 94% (Fig. 4).
Fig. 1: Left temporo-parietal glioblastoma: a) Pink ROI positioned in the hypervascularized (rCBV = 15) solid tissue (ENH/HYPER); white ROI in the peri-lesion area (rCBV = 6) (HYPERp); blue ROI in the contralateral normal appearing white matter (rCBV = 5) b) rCBV map c) FLAIR sequence showing the solid tissue and the hyperintense, peri-lesional area d) Sequence after administration of contrast medium; the solid tissue is soaking with contrast medium and surrounds a necrotic area

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Fig. 2: Grade II astrocytoma of the right hippocampus: a) Pink ROI in the hypovascularized tissue (rCBV = 1); blue ROI in the peri-lesional area (rCBV = 6); white ROI positioned in the contralateral white matter (rCBV = 12) b) rCBV map c) FLAIR sequence showing the hyperintensity of the solid tissue d) No soaking is observed after contrast medium administration

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Fig. 3: Metastasis from ovarian tumor in correspondence of right corona radiata: a) White ROI in the hypervascularized 'donut' (rCBV = 14); pink ROI in the peri-lesional edema (rCBV = 2); blue ROI positioned in the contralateral white matter (rCBV = 7) b) rCBV map c) FLAIR sequence that clearly shows the peri-lesional edema d) Sequence after contrast medium administration showing the soaking 'donut' with central necrosis

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Fig. 4: AUC graph; 0 = rCBV for metastases, 1 = rCBV for glioblastomas (HYPERp)

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Conclusion

In agreement with other studies [5-6, 9, 19-20], this study found that statistically significant differences exist between rCBV values of peri-tumoral area of metastases and those of glioblastomas.

The mean rCBV value in this study for peri-tumoral edema of glioblastoma (1.06) is in agreement with that (1) described by Blasel [20], who got sensitivity 96%, specificity 64%, positive predictive value 68% and negative predictive value 95% in the differential diagnosis between metastasis and glioblastoma. With the statistical calculation of the ROC curve we obtained an AUC value of 0.62 that confirms the significance of the study since the cut-off value (1.24) has specificity 94%, though limited by the low sensitivity (33%).

The mean rCBV in this study for peri-tumoral edema of metastases (0.74) is lower than Blasel's (rCBV = 1) and is similar to the mean rCBV (0.84) obtained by Chiang [9]. In our study there was no statistically significant difference for rCBV of tumor tissue between metastases and glioblastomas (p = 0.2, AUC = 51%), similar to what Hakyemez reported [6]; the mean rCBV values found in this study for glioblastoma lesion tumor tissue (2.85), as well as for the metastatic one (2.40), fall in the range calculated in [6].

Statistically significant differences were observed for the rCBV of lesion tumor tissue between glioblastomas and astrocytomas (p = 0.017, AUC = 0.68) and between metastases and astrocytomas (p = 0.035, AUC = 0.73). These findings are probably due to the fact that in the astrocytoma group both grade II and grade III were present. Anyway, the mean rCBV value for astrocytomas (1.59) is similar to the cut-off value of 1.7 that reportedly permits the differential diagnosis between grade II and III astrocytomas [10].

The fact that in this study no statistically significant difference for the rCBV of peri-tumoral edema between glioblastomas and astrocytomas (p = 0.17), and between metastases and astrocytomas (p = 0.48) may be due to the difficulties in positioning ROI's in the evaluation of low-grade glial lesions and in discriminating the peri-lesional boundaries. One major bias of this ROI-based technique is that it was not always possible to define a standard ROI with fixed and reproducible area. A second limitation was the use of echo-planar sequences which are sensitive to and influenced by large vessels CBV, while DCE-T1wPWI is more sensitive to microcirculation. We adopted the pre-bolus correction to reduce the contrast extravasation on T2* signal and to saturate areas with high vascular permeability. The rCBV values were normalized by use of the contralateral normal-appearing white matter: potential errors in positioning this ROI, involving white matter, grey matter, or both, may have occurred.

However, even with the above limitations and the reduced number of patients, the present study positively evaluated the use of DSC-PWI in the differential diagnosis of
glioblastomas and solitary metastases, adding scientific confirmation to the work of other authors [3-5, 12, 21-22].
References


