ORIGINAL ARTICLE

Prognostic value of perfusion MR imaging in patients with oligodendroglioma: A survival study

Valeur pronostique de l’IRM de perfusion chez les patients avec oligodendrogliome : une étude de survie


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KEYWORDS
Perfusion MRI; Cerebral tumour; Oligodendroglioma; Survival prognosis

Summary
Objective. — The purpose of this study was to evaluate retrospectively whether cerebral blood volume measurement based on pretreatment perfusion MRI is a prognostic biomarker for survival in patients with oligodendroglioma or mixed oligoastrocytoma. Patients and methods. — Between 1998 and 2004, 54 patients (23 females and 31 males), aged 21–73 years, with oligodendroglioma (or mixed tumour) were examined prior to beginning treatment with dynamic susceptibility-weighted contrast (DSC) perfusion MRI during gadolinium first-pass. The relative cerebral blood volume (rCBV) was calculated by dividing the measurement within the tumour by the measurement of the normal-appearing contralateral region. The relative cerebral blood volume (rCBV) was calculated by dividing the measurement within the tumour by the measurement of the normal-appearing contralateral region. Patients were classified in two groups, grade A and grade B, according to the Saint-Anne Hospital classification and followed-up clinically and by means of MRI until their death or for a minimum of 5 years. Patients were also classified in grade II and grade III–IV, according to the World Health Organisation (WHO) classification, and were analysed with the same methods. Age, sex, treatment, tumour grade, contrast agent uptake, and rCBV were tested using survival curves with Kaplan-Meier’s method, and their differences were analysed using the log-rank test.

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Introduction

Oligodendrogliomas represent approximately 10% of primary cerebral tumours and 20% of gliomas. They originate from oligodendrocytes and affect preferentially young adults (mean age: 35 years) [1]. An epileptic seizure or non-specific neurological symptoms such as headaches are the usual mode of presentation of these tumours. Oligodendrogliomas are more responsive to chemotherapy than the other glial tumours [2], especially in the case of 1p/19q codeletion. Upon MRI imaging, low-grade lesions typically show homogenous low signal intensity on T1-weighted and high signal intensity on T2-weighted or FLAIR of cortico-subcortical topography; cystic and calcified components may be present. Higher-grade lesions correspond to either low-grade lesions that have progressed and present a localised high-grade area, or to lesions that were aggressive at initial examination with necrotic areas [3].

During perfusion first-pass MRI obtained during an intravenous bolus injection of gadolinium, tumoral neovascularisation [4,5] may be estimated using the relative cerebral blood volume (rCBV) measurement calculated by dividing the cerebral blood volume (CBV) measurement of the pathological region by that of the corresponding healthy region. This neovascularisation has been reported to be correlated to tumour aggressiveness [6].

A few published research papers [7—10] have investigated the prognostic value of rCBV in patients with glioma. A recent long-term follow-up study [11] has shown that rCBV at pre-treatment perfusion MRI is a useful prognostic biomarker for survival in patients with high-grade astrocytoma. In our study, factors affecting survival were assessed in patients with oligodendroglioma. To this end, a retrospective analysis of the medical records of 54 consecutive patients with oligodendroglioma (or mixed tumours) was conducted; patients were followed-up until death or for at least 5 years.

Patient and methods

Patients

Between 1998 and 2004, 54 patients (23 females and 31 males, aged 21 to 73 years [mean: 46.4 years]) were included in this retrospective study when they met the following inclusion criteria:

- histopathologically proven oligodendroglioma or mixed tumour;
- no history of brain tumour;
- performance of perfusion MRI prior to any surgery (stereotactic biopsy or resection);
- no chemotherapy or radiotherapy prior to perfusion MRI;
- survival time of at least 2 months after perfusion MRI.

Following diagnosis, patients were followed-up every 4 to 6 months by the neurosurgeon (after tumour resection), neuro-oncologist, or radiation oncologist depending on the initially proposed treatments, secondarily conducted treatments, or the progression of the lesion. Follow-up was both clinical and radiological, systematically including a control MRI. Follow-up was ensured within the multidisciplinary “brain tumour” team comprised of neuropathologists, neurosurgeons, neuro-oncologists, and radiation oncologists. The team met on a weekly basis, and all therapeutic decisions were based on consensus following analysis of the patient’s medical record.

Imaging

All MRI examinations were performed using a 1.5 Tesla scanner (Philip Medical System).

Standard MRI work-up systematically comprised at least one series of T2-weighted images (turbo spin echo, repetition time msec [RT]/echo time msec [ET] = 1500/70/45; field of view = 220 mm, matrix = 128 x 256, and slice thickness = 7 mm. Twelve axial slices parallel to the anterior commissure—posterior commissure (AC-PC) plane, covering the entire cerebral parenchyma were acquired every 2 seconds during 1 minute. A bolus injection of gadolinium (0.1 mmol/kg of Gd-DTPA) was started simultaneously to the data acquisition, at a rate of 6 ml/s, using an automatic injector (Spectris MR Injector; Medrad Inc.). After injection of the contrast agent, 20 ml of physiological saline solution were administered at a rate of 6 ml/s [12,13].

rCBV measurement

DSC perfusion MRI was processed on a workstation using a dedicated software (Philip Medical System). By using modelling related to the gamma function, the software reconstructs parametric maps of CBV for each slice. On the
different slices passing through the tumour, the regions of interest (ROI) of about a square centimeter were drawn in pathological and healthy areas according to the following rules, respectively:

- In pathological areas:
  - The ROI was drawn in the area where CBV was the highest [14] on the respective map, in confrontation with the T1-weighted images obtained after contrast injection at the same level to match with contrast agent uptake by the tumour,
  - Outside of the large vessels and the choroid plexus,
  - At a distance from the skull base and meningeal structures to avoid susceptibility artefacts;
- In healthy areas: A ROI was drawn on the contralateral white matter on the same slice in most of the cases. For the lesions located in the convexity, both ROIs were drawn in cortical or subcortical matter.

The ratio between maximum CBV in tumour tissue and CBV in the healthy contralateral hemisphere was established. The maximum rCBV ratio, equal to \( \frac{\text{CBV}_{\text{max}}}{\text{CBV}_{\text{normal}}} \), was considered representative of the lesion.

**Histopathological analysis**

Histopathological analysis was conducted on either biopsies taken in stereotactic conditions or surgical resection specimens. Tumour samples obtained by biopsy or surgical resection were analysed according to both the World Health Organisation (WHO) [15] and the Saint-Anne Hospital classifications [16]. The latter classification distinguishes two prognostic groups based on histological (endothelial hyperplasia) and imaging (contrast uptake on MRI or X scan) criteria: oligodendrogliomas grade A without endothelial hyperplasia and contrast uptake; oligodendrogliomas grade B with endothelial hyperplasia or contrast uptake on imaging. Anaplastic oligodendrogliomas (grade III in WHO classification) with nuclear atypia belong to grade B category in Saint-Anne Hospital classification. No cytogenetic study was conducted to investigate 1p/19q deletion status.

**Statistical analysis**

To assess the predictive value of perfusion indices for survival, the 54 patients were classified firstly in two groups, grade A and grade B in Saint-Anne Hospital classification, and then grade II and grade III—IV in WHO classification.

Taking into account the non-normal distribution of data, the Mann-Whitney’s U test, a non-parametric method, was conducted to evaluate the relationship between rCBV and the different tumour grades (grade A/grade B). Survival time was defined as the time period between the initial radiological investigation, including the perfusion study, and the date of death or last follow-up, taking into account that the follow-up period for surviving patients was at least 5 years, at July 31st, 2009.

Receiver operating characteristic (ROC) curve analysis allowed us to establish an optimal threshold value for rCBV when accounting the median survival time.

Several clinical and MRI factors were tested for their prognostic value relating to survival time, including age (<50 or ≥50 years), sex (male/female), type of treatment received (neurosurgical resection [absent/present], chemotherapy [present/absent], radiotherapy [present/absent]), tumour grade (grade A/grade B), contrast agent uptake (present/absent), and rCBV (below or above the optimal threshold value given by the ROC curve analysis).

For each of these factors survival curves were assessed using the Kaplan-Meier’s method, and their differences were analysed using the log-rank test. Cox proportional multivariate hazard model analysis was performed after adjusting for prognostic factors. A Chi² test was used to estimate between-group differences in 3-year survival rates. Statistical analyses were performed using SPSS version 15. \( P<0.05 \) was considered statistically significant.

All of the analysis mentioned above was performed again after using the WHO classification, i.e. regrouping the grade IIA and grade IIIB into a same group (grade II), and the grade III or IV into another one (grade III—IV).

**Results**

**Pathological and clinical data**

Tumour samples were obtained by biopsy or surgical resection. According to the WHO classification [15], tumours were classified in 31 oligodendrogliomas (or mixed tumour) grade II and 23 oligodendrogliomas (or mixed tumour) grade III—IV. According to the Saint-Anne Hospital classification [16], same samples were classified in 21 oligodendrogliomas (or mixed tumour) grade A (IIA) and 33 oligodendrogliomas (or mixed tumour) grade B (10 grade IIIB and 23 grade III—IV).

In total, 20 patients underwent immediate neurosurgical resection, of which 16 patients received complementary chemotherapy, two were treated with complementary radiotherapy, and the remaining two did not receive complementary treatments. Among the 34 patients who did not undergo surgical resection, 17 received chemotherapy, five received radiotherapy, nine received chemotherapy and radiotherapy, while three patients did not receive these treatments.

On conventional images, contrast uptake by the tumour was present in 26 of the 33 patients from grade B group, whereas it was absent in seven patients from grade B group (four grade IIIB and three grade III—IV). In the entire study population, the rCBV varied from 0.7 to 9.9 (median ± standard deviation: 1.7 ± 1.6), and the rCBV of grade A group (1.2 ± 0.4) was significantly lower than that of grade B group (2.5 ± 1.8; Mann-Whitney’s U = 168; \( P = 0.001 \)).

Similarly, when taking the WHO classification, the rCBV of grade II group (1.2 ± 0.6) was significantly lower than that of grade III—IV group (2.7 ± 2.0; Mann-Whitney’s U = 147; \( P = 0.000 \)).

**Survival analysis**

Of the 54 patients, 21 were still alive at the end of the study, at July 31st, 2009, all presenting a survival time of more than 5 years (1845 days). The median survival was 3800
days for the grade A group and 393 days for the grade B group, with a median survival of 1100 day (approximately 3 years) for the entire group. ROC analysis revealed that the optimal rCBV threshold value predicting 3-year survival was 2.2 (sensitivity = 89%; specificity = 59%), as shown in Fig. 1.

The relation between rCBV and survival time is illustrated in Fig. 2a and b. In the entire study population, the percentage of patients surviving 3 years was 50% (n = 27); the percentage of patients from grade B group surviving 3 years (11/33; 33.3%) was found to be significantly lower than that of patients from grade A group (16/21; 76.2%) (Chi² = 9.43; P = 0.002). A
similar statistical difference was found between patients with high rCBV (≥2.2) (6/22; 27.3%) and those with low rCBV (<2.2) (21/32; 65.6%) (Chi² = 7.67; \( P = 0.006 \)). These differences remained significant even after using the log-rank test that takes into account survival times at study end.

The survival curves in relation to tumour grade and rCBV are presented in Fig. 3. For grade B group tumours, survival had a trend towards a difference between patients with low rCBV and those with high rCBV (log-rank Chi² = 3.73; \( P = 0.053 \)). Contrarily, for grade A group tumours, rCBV had no significant effect on survival.

With respect to clinical findings and MRI data, prognostic factors identified in univariate analysis are listed in Table 1. These factors are: patient age (\( P = 0.004 \)), patient sex (\( P = 0.005 \)), tumour grade (\( P = 0.001 \)), contrast uptake by the tumour (\( P = 0.003 \)), and rCBV (\( P = 0.001 \)).

The results of multivariate Cox regression analysis are presented in Table 2. Of the aforementioned factors, tumour grade (grade A/grade B) was the most important prognostic factor (risk ratio = 2.70), followed by rCBV (risk ratio = 2.15), patient age (risk ratio = 2.10), and patient sex (risk ratio = 0.45). Contrast uptake was not found to be a prognostic factor in multivariate analysis. It suggests that rCBV could be useful to improve Saint-Anne classification.

When regrouping the patients using the WHO classification, only tumour grade (grade II/grade III–IV) and patient sex were found to be the independent prognostic factors by Cox regression analysis, with the risk ratio as 6.12 and 0.46 respectively. rCBV, patient age and contrast uptake by the tumour were washed out.

Illustrative cases are presented in Figs. 4–7.

### Table 1 Prognostic factors in patients with oligodendroglioma.

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Number of patients (total ( n = 54 ))</th>
<th>Survival rates(^a) (%)</th>
<th>( P ) value(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>31</td>
<td>64.5</td>
<td>0.004</td>
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<tr>
<td>≥50</td>
<td>23</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>31</td>
<td>38.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>65.2</td>
<td></td>
</tr>
<tr>
<td><strong>Tumour grade</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade A</td>
<td>21</td>
<td>76.2</td>
<td>0.001</td>
</tr>
<tr>
<td>Grade B</td>
<td>33</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td><strong>Neurosurgical resection</strong></td>
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<td></td>
</tr>
<tr>
<td>Present</td>
<td>20</td>
<td>60.0</td>
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<tr>
<td>Absent</td>
<td>34</td>
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<td></td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>42</td>
<td>54.8</td>
<td>0.216</td>
</tr>
<tr>
<td>Absent</td>
<td>12</td>
<td>33.3</td>
<td></td>
</tr>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>19</td>
<td>36.8</td>
<td>0.162</td>
</tr>
<tr>
<td>Absent</td>
<td>35</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td><strong>Contrast uptake by tumour</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>26</td>
<td>34.6</td>
<td>0.003</td>
</tr>
<tr>
<td>Absent</td>
<td>28</td>
<td>64.3</td>
<td></td>
</tr>
<tr>
<td><strong>rCBV</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2.2</td>
<td>32</td>
<td>65.6</td>
<td>0.001</td>
</tr>
<tr>
<td>≥2.2</td>
<td>22</td>
<td>27.3</td>
<td></td>
</tr>
</tbody>
</table>

rCBV: relative cerebral blood volume.

\(^a\) Calculated in regard to a 3-year survival.

\(^b\) Analyses based on log-rank test.
Discussion

Based on our study results, rCBV at pretreatment perfusion MRI appears to be an independent prognostic biomarker for survival in patients with oligodendroglioma. In accordance with previous studies, we reported that rCBV was a more relevant prognostic factor for survival than contrast uptake by tumour tissues in a population of gliomas of a different nature and different grades [9,11]. In a recent study, Hirai et al. [11] established that rCBV, with a threshold value of 2.3, was a useful prognostic factor for survival in patients with high-grade astrocytoma. A more recent study [17] revealed that rCBV was found to have a prognostic value in a 20-patient series with low-grade astrocytoma. Even in a study population including 189 patients with high-grade glioma or low-grade glioma, rCBV was also detected as an independent predictor for clinical outcome [10]. In this context, we thought it might be interesting to evaluate whether rCBV was a useful prognostic factor for survival in patients with oligodendroglioma (oligodendroglioma and mixed oligoastrocytoma), using a similar statistical approach than that used in the study by Hirai et al.

Median survival time significantly differed in grade A group patients (3800 days or approximately 11 years) in comparison to that in grade B group patients (393 days or approximately 1 year). For grade A group patients, the median survival of 11 years observed in our study is very close to that observed by Daumas-Duport et al. [16]. Because more than 60% of the patients in grade A group were survival at the end of this study, the median survival time for this group was then estimated as a mathematic extrapolation.

When taking the WHO classification, the median survival time for patients of grade II group was 3800 days, which was significantly longer than that of grade III–IV group (342 days).
Figure 6  Forty-two-year-old women: left anterior and paramedian frontal lesion extending into the corpus callosum, with moderate focal contrast enhancement (a, b). On the parametric map for cerebral blood volume (CBV), there is significant angiogenesis; relative cerebral blood volume (rCBV) = 2.8 (c, d). Grade B (grade II according to the WHO classification) oligodendroglioma (biopsy). Following chemotherapy, a marked regression of the lesion is noted, with contrast enhancement and signs of neovascularisation (e, f).

In a comparative analysis of rCBV in patients with low-grade astrocytoma or other low-grade oligodendroglioma, Cha et al. reported that rCBV values were significantly higher in patients with oligodendroglioma in comparison to those with astrocytoma [18]. These high values observed in patients with so-called low-grade oligodendroglioma (grade II according to WHO classification) suggest the fact that grade II tumours with endothelial proliferation should not be mixed up, in terms of prognosis, with oligodendroglioma without proliferation or contrast agent intake.

Considering the 3-year survival for our patient population, ROC curves allowed us to establish a rCBV threshold value of 2.2, which is very close to that reported by Hirai et al. for high-grade astrocytomas [11]. This result again suggests that all oligodendrogliomas with high rCBV value should be regarded as high-grade tumours. As shown in Fig. 2a, all the patients with rCBV superior to 2.2 were in grade B group, while there were some grade B oligodendrogliomas whose initial rCBV was inferior to such threshold. None of grade A group patient had a tumoral rCBV superior...

Figure 7  Sixty-four-year-old women: ventricular lesions with nodular contrast enhancement at the left corpus callosum level (a, b). On the parametric map for cerebral blood volume (CBV), significant angiogenesis is observed at the level of the small nodule (relative cerebral blood volume [rCBV] = 2.8) and a general increase in rCBV at the level of the corpus callosum splenium (c, d). Grade B (grade II according to the WHO classification) oligodendroglioma (biopsy). Rapid tumour progression occurred during the following months.
to the threshold value of 2.2. When using the WHO classification (Fig. 2b), there were two gliomas from grade II group with rCBV superior to 2.2; and some gliomas from grade III–IV group with initial rCBV inferior to 2.2.

The univariate analysis conducted on age, sex, contrast uptake, tumour grade, and rCBV provided remarkable results. Independent from rCBV, which was found to be a prognostic factor, tumour grade and contrast uptake were identified as prognostic factors for survival. In our study, patient age was found to be a significant prognostic factor, which was not the case in Hirai’s et al. study on astrocytomatas. Contrarily, as was the case in Hirai’s et al. study, sex was also identified as a significant prognostic factor for survival, with women having a longer survival than men, reflected by a median survival of 3800 days for women and 550 days for men. The similar difference was also indicated in other studies of high-grade gliomas and may be explained by hormonal or X chromosome-genic factors, but it was not suggested in patients with low-grade gliomas.

The different administered treatments, often given in association (surgery and chemotherapy), were not found to be discriminators in terms of survival. It should be mentioned, however, that our patient population was not well suited for this type of analysis as patients received several complementary treatments, often given concomitantly during patient follow-up.

Multivariate analysis determined the following independent factors of prognosis by order of importance: tumour grade (with a distinction between grade A and grade B), rCBV (with a threshold value of 2.2), patient age (with a threshold value of 50 years), and sex (female/male). Contrast uptake was not found to be an independent prognostic factor in multivariate analysis. It suggests that rCBV could be useful to improve Saint-Anne classification.

Our study has a number of limitations regarding design and image analysis.

Therapeutic treatment options and their chronology were not taken into account. In fact, the entire study population was seen by our multidisciplinary “brain tumour team” comprising neuroradiologists, surgeons, radiation oncologists, and neuro-oncologists. This team decided on the best therapeutic strategy to be implemented for each patient at the initial stage and following tumour progression.

It should also be mentioned that there are always possibilities of error regarding the tumour grading based on biopsies, which do not necessarily reflect the entire lesion. In our series, seven lesions were graded as B on histological examination, which revealed endothelial proliferation, whereas MRI did not reveal any significant contrast uptake. For these seven lesions from grade B group without tumoral contrast uptake, four of which were graded as IIb, the rest three were graded as III–IV. As Ginsberg et al. already indicated that some grade II oligodendrogliomas enhance and some grade III lack contrast enhancement.

From a methodological perspective, the positioning of the ROI may be subject to discussion, as it was shown to be operator-dependant. However, there appears to be consensus that ROI, of a square centimetre, positioned at the level of maximum CBV in the pathological region and the contralateral apparently healthy white matter allows for the rCBV measurement which is considered representative and reproducible for tumoral neovascularization. In the study on oligodendrogliomas, which tumoral topography is often cortical or subcortical, it sounds appropriate to draw the ROI on the mirrored region in contra-lateral hemisphere, which should also include the cortex. And it has been well respected in our series, sometimes when the lesion located at the convexity level (Fig. 5). The operator’s experience, the accomplishment of parametric map of CBV as well as the MR imaging, which may undoubted influence the measurements according to the ROI position, were taken into account.

Regarding rCBV measurement, several authors propose correction methods for extravasation of contrast medium or recommend another model than that derived from gamma function, using the deconvolution of the first pass curve by the arterial entry function. However, deconvolution methods are highly sensitive to arterial input function (AIF) selection, i.e. location and acquisition type. In fact, relative estimation of brain perfusion using interhemispheric ratios on perfusion maps calculated without AIF selection, is a well-known method, demonstrated to be robust and reproducible. In clinical practice and research, many studies in neuro-oncology were conducted using gamma-variate fitting correction, even recently.

In conclusion, this long-term follow-up study (5 years or more for patients who were still alive 5 years after diagnosis) involving 54 patients with oligodendroglioma or mixed oligoastrocytoma demonstrated that the rCBV was a useful independent prognostic biomarker for survival in this patient population while using the Saint-Anne Hospital classification. Moreover, our study findings support the usefulness of this classification, which separates in terms of survival oligodendrogliomas grade A and oligodendrogliomas grade B.

Conflict of interest statement
Nothing declared.

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References
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