ORIGINAL ARTICLE

Usefulness of the apparent diffusion coefficient for the evaluation of the white matter to differentiate between glioblastoma and brain metastases

L.A. Miquelini*, M.S. Pérez Akly, J.A. Funes, C.H. Besada

Área de Neurorradiología, Servicio de Diagnóstico por Imágenes, Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina

Received 20 January 2015; accepted 8 October 2015
Available online 30 May 2016

KEYWORDS
Diffusion magnetic resonance imaging; Glioblastoma; Metastasis; Brain

Abstract
Objective: To determine whether there are significant differences in the apparent diffusion coefficient (ADC) between the apparently normal peritumor white matter surrounding glioblastomas and that surrounding brain metastases.

Material and methods: We retrospectively reviewed 42 patients with histologically confirmed glioblastomas and 42 patients with a single cerebral metastasis. We measured the signal intensity in the apparently normal peritumor white matter and in the abnormal peritumor white matter on the ADC maps. We used mean ADC values in the contralateral occipital white matter as a reference from which to design normalized ADC indices. We compared mean values between the two tumor types. We calculated the area under the receiver operator characteristic curve and estimated the sensitivity and specificity of the measurements taken.

Results: Supratentorial lesions and compromise of the corpus callosum were more common in patients with glioblastoma than in patients with brain metastases. The maximum diameter of the enhanced area after injection of a contrast agent was greater in the glioblastomas (p < 0.001). The minimum ADC value measured in the apparently normal peritumor white matter was higher for the glioblastomas than for the metastases (p = 0.002). Significant differences in the ADC index were found only for the minimum ADC value in apparently normal peritumor white matter. The sensitivity and specificity were less than 70% for all variables analyzed.

Conclusions: There are differences in the ADC values of apparently normal peritumor white matter between glioblastomas and cerebral metastases, but the magnitude of these differences is slight and the application of these differences in clinical practice is still limited.

© 2015 SERAM. Published by Elsevier España, S.L.U. All rights reserved.

* Please cite this article as: Miquelini LA, Pérez Akly MS, Funes JA, Besada CH. Utilidad del coeficiente de difusión aparente en la evaluación de la sustancia blanca para diferenciar glioblastoma de metástasis cerebral. Radiología. 2016;58:207-213.

* Corresponding author.
E-mail address: arielmiquelini@gmail.com (L.A. Miquelini).

2173-5107/© 2015 SERAM. Published by Elsevier España, S.L.U. All rights reserved.
PALABRAS CLAVE
Difusión por resonancia magnética; Glioblastoma; Metástasis; Cerebro

Utilidad del coeficiente de difusión aparente en la evaluación de la sustancia blanca para diferenciar glioblastoma de metástasis cerebral

Resumen
Objetivo: Encontrar diferencias significativas en la sustancia blanca peritumoral aparentemente normal entre glioblastoma y metástasis cerebral mediante la valoración del coeficiente de difusión aparente (CDA).
Material y métodos: Se revisaron retrospectivamente resonancias magnéticas de 42 pacientes con histopatología de glioblastomas y 42 pacientes con metástasis cerebral única. Se realizaron mediciones de intensidad de señal en el mapa de CDA sobre la sustancia blanca peritumoral aparentemente normal (SBPAN) y la sustancia blanca peritumoral alterada (SBPALT). Se diseñaron índices normalizados de CDA utilizando valores medidos en la sustancia blanca occipital contralateral como referencia. Se compararon las medias para establecer diferencias entre ambos tipos de tumores. Se calculó el área bajo la curva (ROC) y se estimaron la sensibilidad y la especificidad para las mediciones realizadas.
Resultados: Los pacientes con glioblastoma presentaron con mayor frecuencia lesiones supratentoriales y compromiso del cuerpo calloso que los pacientes con metástasis cerebral. El diámetro máximo del área de realce tras la inyección de contraste fue mayor en los glioblastomas (p < 0,001). El valor mínimo de CDA medido en la SBPAN fue mayor en los glioblastomas que en las metástasis (p = 0,002). Solo se encontraron diferencias significativas en el índice de CDA para el valor mínimo de CDA en la SBPAN. Los valores de sensibilidad y especificidad fueron inferiores al 70% para las variables evaluadas.
Conclusiones: Existen diferencias en los valores del CDA de la SBPAN entre glioblastomas y metástasis, pero la magnitud de dicha diferencia es escasa y su aplicación en la práctica clínica aún es limitada.

© 2015 SERAM. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction
Brain metastases and glioblastomas are the most frequent encephalatous tumors in adults resulting both in approximately 70% of parenchymatous intracranial neoplasms.\(^1\) When it is a single metastasis, it is difficult to differentiate them from high-grade gliomas, since both their clinical manifestations and behavior in conventional magnetic resonance images (MRI) can be similar (both signal intensity in the basal study and the contrast enhancement pattern). On the other hand, the therapeutic strategies are different in both cases and this is why on certain occasions, biopsies are performed before initiating treatment, even with a known primary tumor. Nevertheless, biopsies are not the best option for some patients given their general functional condition or the location of the lesion in an eloquent area.\(^2,3\)

Both metastases and glioblastomas can show extensive peripheral edema: the former of vasogenic origin, while in glioblastomas it is secondary to the infiltration of neoplastic cells in the perilesion region. Vasogenic edema is the result of the alteration of the hematoencephalic barrier and the neocapillaries that allow the escape of endovascular proteins into the interstice, with the subsequent increase of osmotic pressure and also of the amount of extracellular water. The peritumoral edema in glioblastomas, in addition to the changes in fluids homeostasis, correlates to the infiltration of tumor cells in the fibers of the white matter.\(^4\) This is the difference that we have tried to identify through advanced MRI techniques such as spectroscopy (MRS), perfusion and diffusion through diffusion tensor with tractography (DTI) and apparent diffusion coefficient (ADC), since conventional MRI techniques do not allow us to identify the microscopic invasion of the adjacent white matter.\(^4,6\) Although advanced techniques are useful to reduce the differential spectrum of brain neoplasms, some authors have confirmed that the MRS has greater difficulties discriminating metastases from glioblastomas.\(^5,6\)

The physical concept of diffusion refers to the molecular movement of water, which results isotropic when the means is homogeneous or disorganized, without barriers, whereas in the tissues both the cellular membranes and some architectural characteristics of the interstice limit the free directionality of movement (diffusion) of these molecules. MRI diffusion techniques provide us with information on the movement of the water protons in normal or pathologic brain tissue. The ADC shows mobility of both inter- and extracellular free water fraction, and the signal is smaller when movement is restricted, and greater when it is facilitated, that is, the image will be hypointense or hyperintense, respectively. This is so in such a way that, for instance, it is used to infer tumor degree based on cellularity and the probable nucleus-cytoplasm index of mass from the value shown in the diffusion restriction.\(^2,7\)

Some studies have shown that there are no significant differences in the ADC measurements, in the tumor mass, between tumor metastases and glioblastomas.\(^8-10\) Others have proven that the ADC in the abnormal peritumoral white
matter (APWM), and the ADC gradient at this level help us discriminate between both etiologies.\textsuperscript{1,11-14}

Beyond the distinguishable findings in conventional sequences, the ADC values provide us with quantitative information about tumor cellularity and perilesion edema. Research has not provided, however, unanimous results when it comes to the capacity of diffusion-weighted images to differentiate metastases from glioblastomas.

In that sense, the goal of this study is to take a step forward in tumor evaluation by calculating ADC, not only in the tumor mass and the APWM, but also in the apparently normal peritumoral white matter (ANPWM), in an attempt to find significant differences in ADC signal intensity values to be able to discriminate brain metastases from glioblastomas.

Material and methods

Patients

Brain MRIs of patients with histopathologic diagnosis of glioblastoma or brain metastasis were evaluated between July 2009 and September 2014 in our hospital. The MRIs were performed before the biopsy, the latter obtained through biopsy or surgical resection.

The research project was approved by our Center Research Protocol Ethics Committee and no ethical objections to its publication were found. Due to this and the retrospective design of the study, the patients’ written informed consents were not obtained.

The sample calculation was performed using the software OpenEpi\textsuperscript{15} from the findings of a previous study\textsuperscript{14} by comparing two means based on the ADC sequence signal in the ANPWM of patients with glioblastoma or brain metastasis (0.75 ± 0.06 versus 0.71 ± 0.07), with a confidence interval of 95% and a 80% power; as a result a sample of 84 patients was obtained (42 of them with glioblastomas and 42 with brain metastases). A consecutive non-probability sampling was performed until the sample was obtained.

The inclusion criteria were: single brain lesions with anatomopathological diagnosis of glioblastoma or brain metastasis, brain MRIs with contrast and ADC map between July 2009 and September 2014 and presurgical images available in the PACS system. The exclusion criteria were: presence of hematic remains on the site of the signal intensity measurement on the ADC map; history of trauma or white matter diseases of a different origin (autoimmune, vascular or metabolic).

Magnetic resonance and image processing

The MRI studies were performed using three 1.5 T machines: Magnetom Avanto\textsuperscript{®} (Siemens, Munich, Germany, 2005), Achieva\textsuperscript{®} (Philips, Eindhoven, Holland, 2009) and Magnetom Essenza\textsuperscript{®} (Siemens, Munich, Germany, 2011). The ADC signal intensity measurements were taken directly on the map, in the ANPWM and the APWM, with ADC images and contrast and T1 images obtained from the machine: 4–5 mm thickness; 20% or 30% GAP; FOV of 320 × 230; matrix 128 × 128 or 112 × 89 or 140 × 140; RT/ET = 3600/94 or 2850/72 or 3200/98. Five mm thick TSE T1, T2 and FLAIR sequences on the axial plane; and axial GRE 5 mm thick, and volumetric post-contrast T1 sequences on the sagittal plane were examined too.

The signal measurements were taken directly on the ADC map. This methodology was chosen because the raw information of the DTI sequence was not available in the PACS system of our institution when the study was conducted. In addition, we consider it interesting to try the feasibility of a less complex form of ADC evaluation.

In order to take direct ADC intensity measurements, three regions of interest (ROI) were located with an area of 0.2 cm\textsuperscript{2} in the ANPWM, defined as such the peritumoral white matter without any signs of edema shown in FLAIR and T2 sequences, or enhancement after contrast injection. Measurements were taken of the anterior, medial, lateral or posterior white matter based on the tumor topography.

One ADC ANPWM index was used, measuring the ADC signal in the contralateral occipital white matter (COWM). Formulating: \[ \text{ADC signal in ANPWM/\text{ADC signal in ANPWM + ADC signal in the COWM}] \times 100 \]. An index was calculated using the minimum value of ADC in ANPWM (MinANPWM ADC index) and one index with the average of the three ADC measurements in ANPWM (Average ANPWM ADC index).

Secondarily, the ADC signal in the APWM was examined through one ROI adjacent to the edge of the post-contrast enhancement area (proximal APWM) and another ROI next to the peripheral edge of the APWM (distal APWM), and thus both ROIs were aligned on the axis with the largest visible surface of disturbed white matter, thus obtaining information from both ends of the APWM. Only one ROI was located in the APWM when its surface was too small to contain both ROIs. One APWM ADC index was also used by measuring the ADC signal in the COWM. Formulating: \[ \text{ADC signal in APWM/\text{ADC signal in APWM + ADC signal in the COWM}] \times 100 \].

The separation between ROIs was established at 3 mm with respect to the edge of the tumor mass and the edge of the APWM. The same distance was considered between them in the ANPWM (Fig. 1).

The measurements were taken by a researcher with 5 years of experience in radiology, who did not know the anatomopathological diagnosis.

Statistical analysis

The data were analyzed using the software SPSS\textsuperscript{®}. The median and the interquartile range (IQR) were used as measurements of distribution and central trend. The Fisher and the \( \chi^2 \) tests were used to establish the differences between dichotomous variables, and the Student \( t \) test was used for continuous variables. The measurement of ROC (receiver operating characteristic) curves was taken for variables referring to the signal intensity measurements in the ADC of the AVPWM and APWM, and that of derived indexes. The area under the curve was calculated and the sensitivity and specificity values were estimated for each of the variables. The level of significance was established at \( p \leq 0.05 \). The
odds ratio (OR) was used as association measurement, with confidence intervals of 95%. For the measurement of the OR of the continuous variables, univariate logistic regression tests were used.

Results

Ninety-eight cases of patients with glioblastomas and 85 cases of patients with metastases were analyzed until the estimated sample inclusion of 42 patients with glioblastomas and 42 patients with single brain metastases was obtained whose demographic data and certain topographic characteristics are shown in Table 1.

Fifty-six patients with glioblastomas and 43 patients with metastases were excluded. Fig. 2 shows the flow diagram with the reasons for exclusion. No patient was excluded due to the presence of hematic remains at the site of the measurement on the ADC map, nor due to the presence of other white matter conditions.

The average age was 62.8 (IQR 16.7) years. Forty-two patients (50%) were women.

The histological characteristics of the glioblastomas and the metastases are described in Table 2. The most common primary tumor associated with the presence of brain metastasis was lung cancer (35.7%), followed by breast cancer (21.4%) and colon cancer (9.5%).

The infratentorial location of the lesion was more common in metastases (11.9%) than in glioblastomas (2.4%).

The mass maximum diameter with post-contrast enhancement was greater in glioblastomas than in metastases (p = 0.0001). Fig. 3 shows the measurement of the largest diameter assessed in one tumor.

The involvement of the corpus callosum occurred more frequently in glioblastomas (p = 0.048).

The minimum ADC value as measured in the ANPWM was greater in glioblastomas than in metastases (p = 0.002).

The ADC indexes for the minimal ADC value measured in the ANPWM were calculated for the average of the three ADC measurements in the ANPWM and the two ADC measurements taken in the APWM (Table 3). Significant differences

### Table 1 Results of the analysis of basic demographic, topographic and data, size included.

<table>
<thead>
<tr>
<th></th>
<th>Glioblastoma (n=42)</th>
<th>95% CI</th>
<th>Metastasis (n=42)</th>
<th>95% CI</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age (years)</td>
<td>63.9</td>
<td></td>
<td>61.3</td>
<td></td>
<td>0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (#, % males)</td>
<td>23, 55.3</td>
<td></td>
<td>19, 44.7</td>
<td></td>
<td>0.5</td>
<td>1.2</td>
<td>0.8-1.8</td>
</tr>
<tr>
<td>Location (#, % infratentorial)</td>
<td>1, 2.4%</td>
<td></td>
<td>5, 11.9%</td>
<td></td>
<td>0.007</td>
<td>10</td>
<td>1.4-74.7</td>
</tr>
<tr>
<td>Involvement of the corpus callosum (#, %)</td>
<td>3, 7.1%</td>
<td></td>
<td>1, 2.4%</td>
<td></td>
<td>0.048</td>
<td>1.1</td>
<td>0.99-1.3</td>
</tr>
<tr>
<td>Average diameter of the enhancement area (mm)</td>
<td>50.7</td>
<td>45.8-55.62</td>
<td>35.7</td>
<td>31.45-39.95</td>
<td>0.0001</td>
<td>1.06</td>
<td>1.03-1.1</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; OR, odds ratio.

![Figure 1](image1.png)  
**Figure 1** Example of measurements on the ADC map, axial plane. Glioblastoma; 65-year-old woman. (A, B) ROI of proximal and distal location at the ANPWM, respectively. (C–E) ROI located at the ANPWM. (F) ROI located at the COWM. The red line outlines the ANPWM-APWM transition. The green line excludes the left lentiform nucleus core.

![Figure 2](image2.png)  
**Figure 2** Flow diagram of final inclusion of patients.
Usefulness of the ADC for the evaluation of the white matter

**Table 2** Percentage of histological types in glioblastomas and metastases.

<table>
<thead>
<tr>
<th>Histology of glioblastomas</th>
<th>Histology of metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% classic</td>
<td>Lung 15 (35.7%)</td>
</tr>
<tr>
<td>7.1% with olygodendrocitic component</td>
<td>Breast 9 (21.4%)</td>
</tr>
<tr>
<td>2.4% large cells</td>
<td>Colon 4 (9.5%)</td>
</tr>
<tr>
<td></td>
<td>Esophagus 3 (7.1%)</td>
</tr>
<tr>
<td></td>
<td>Melanoma 3 (7.1%)</td>
</tr>
<tr>
<td></td>
<td>Kidney 3 (7.1%)</td>
</tr>
<tr>
<td></td>
<td>Others 5 (12%, endometrium 1, bladder 1, gastric 1, germinal 1, undifferentiated 1)</td>
</tr>
</tbody>
</table>

**Figure 3** Example of measurement of maximum diameter on a T1-weighted sequence with contrast, sagittal plane. Metastasis of lung adenocarcinoma. 59-year-old woman.

were only found in the ADC index for the ADC minimal value in the ANPWM. Fig. 4 is a box-and-whisker diagram for the estimated normalized indexes. A non-significant difference is observed between the median and the extreme values in the glioblastoma group with respect to metastasis in all indexes evaluated.

The ROC curves were calculated for the minimal ADC value of the ANPWM: 0.68; the ADC value in the proximal and distal APWM, respectively: 0.56 and 0.57, and for the ADC MinANPWM index: 0.64. Fig. 5 shows the ROC curve of the ADC minimal value in the ANPWM. With a cutting point of 70.75 sensitivity (67%) and specificity (65%) could be obtained. The rest of the variables studied obtained values below 60% in both sensitivity and specificity.

**Table 3** Results of signal intensity and indexes derived from the measurement of the ADC of both the ANPWM and the APWM.

<table>
<thead>
<tr>
<th></th>
<th>Glioblastomas (n = 42)</th>
<th>Metastases (n = 42)</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC at the proximal APWM (intensity)</td>
<td>1464.7</td>
<td>1119–1810.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC at the distal APWM (intensity)</td>
<td>1365.7</td>
<td>1076.1–1655.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal ADC at the ANPWM (intensity)</td>
<td>740.4</td>
<td>678.5–802.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADC index at the MinANPWM</td>
<td>46.9 (1.9)</td>
<td>46.3–47.5</td>
<td>0.27</td>
<td>1</td>
<td>0.99–1.002</td>
</tr>
<tr>
<td>ADC index at the proximal APWM</td>
<td>62.7 (6.4)</td>
<td>60.8–64.6</td>
<td>0.06</td>
<td>1.2</td>
<td>0.9–1.4</td>
</tr>
<tr>
<td>ADC index at the distal APWM</td>
<td>61.2 (5.5)</td>
<td>59.5–62.9</td>
<td>0.5</td>
<td>0.96</td>
<td>0.87–1.07</td>
</tr>
</tbody>
</table>

95% CI, 95% confidence interval; MinANPWM, ADC minimal value at the ANPWM; OR, odds ratio; APWM, abnormal peritumoral white matter; ANPWM, apparently normal peritumoral white matter.
in the former corresponds to fiber infiltration of white matter by tumor cells. On the other hand, the study done by Kono et al. could not find any significant differences in the ADC values in the APWM between these two tumor types. As an interpretation of this finding we could say that the microstructural lesion of the ANPWM secondary to cellular invasion in glioblastomas is accompanied proportionally by greater extracellular edema than infiltrative tumor load and that this one is enough to cause the signal to drop on the ADC map.

**Main limitations of this study**

Among the shortcomings of this work, it could be considered that the direction of the diffusion gradient might not be adequately representative of the anatomic trend of tumor cell dissemination.

The study has some limitations. A possible limitation is the fact that we took a direct measurement of the ADC signal on a workstation using conventional image interpretation software even though this modality has been used by other researchers. This modality was chosen because the raw information of the DTI sequence was not available in the system used in our institution. On the other hand, it was interesting to consider the feasibility of a less complex modality for measuring the ADC in the differential evaluation of glioblastomas and metastases being more similar to other measurements taken in clinical practice through ROI.

Another limitation of this work was the fact that it did not have anatomopathological data on the involvement of the ANPWM also attributed to its retrospective design. The selection of the cuts to be assessed and the placement of the ROI was discretionary and totally based on the observer’s own interpretation. It would be helpful to develop a systemized modality to standardize measurements and reduce mistakes on this stage. Finally, we used the COWM to normalize measurements. The COWM might not be the place of choice as reference since its measurement did not describe a normal curve of distribution. Another reference topography could be considered to measure the normal white matter, just like other authors have done.

It should be considered that the homogeneity of the results obtained could be affected by the use of different MRI machines, despite the use of the COWM to normalize measurements.

On the other hand, we also considered as a further weakness the small size of sample used in this work.

In sum even though we found significant differences in the ADC signal intensity in the ANPWM between glioblastomas and metastases, the extent of such difference disappears when the data is normalized, and its application in clinical practice is still limited, due to the low sensitivity and specificity to establish differences between these two entities.

**Ethical disclosures**

**Protection of human and animal subjects.** The authors declare that no experiments were performed on humans or animals for this investigation.
Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Authorship

1. Manager of the integrity of the study: LM, MPA, JF and CB.
2. Study idea: LM, MPA, JF and CB.
3. Study design: LM and MPA.
4. Data mining: LM and MPA.
5. Data analysis and interpretation: LM, MPA, JF and CB.
6. Statistical analysis: MPA.
7. Reference search: LM.
8. Writing: LM, MPA and JF.
9. Critical review of the manuscript with intellectually relevant remarks: JF and CB.
10. Approval of final version: LM, MPA, JF and CB.

Conflict of interests

The authors declare no conflict of interests associated with this article whatsoever.

References