

# Association of Diffusion Weighted Magnetic Resonance Imaging Profile and Apparent Diffusion Coefficient Value with Brain Tumor's Histopathology

Hartati Rusmi Tri Wilujeng<sup>1</sup>, Anggraini Dwi Sensusiati<sup>2</sup>, M. Yamin Sunaryo Suwandi<sup>3</sup>

<sup>1</sup>Radiology Department, <sup>2</sup>Department of Neurology, <sup>3</sup>Department of Thoracic, Dr. Soetomo Teaching Hospital, Faculty of Medicine, Universitas Airlangga, Surabaya 60285, Indonesia

## Abstract

**Background:** Accuracy of preoperative brain tumor's histopathologic differentiation is very important to determine preoperative staging, intraoperative management and postoperative therapy. Diffusion weighted magnetic resonance imaging is an advanced technique developed as an important method for brain tumor assessment.

**Objectives:** This study aimed to investigate correlation between diffusion weighted imaging (DWI) profile and apparent diffusion coefficient (ADC) value with brain tumor's histopathology.

**Methods:** This study examined 86 subjects with brain tumors using magnetic resonance imaging and histopathology examination at Dr. Soetomo Teaching Hospital and evaluated DWI profile and ADC maps. The spherical ROI on ADC maps was placed on the solid part of the tumor to measure ADC value. Spearman's correlation test was conducted to determine correlation between DWI profile and ADC values with histopathological grading and types of brain tumor.

**Results:** There was a significant correlation between DWI profile and ADC values ( $p = 0.000$ ), as well as DWI and ADC values with histopathological grading and types of brain tumor ( $p = 0.000$ ). There was an inverse correlation between ADC value and histopathological grading. The higher the ADC value, the lower the brain tumor grade, while lower ADC value resulted in high tumor grade. The average ADC value of grade-1 meningiomas was  $1.061 \pm 0.257 \times 10^{-3} \text{ mm}^2/\text{sec}$ , pilocytic astrocytoma was  $1.301 \pm 0.107 \times 10^{-3} \text{ mm}^2/\text{sec}$ , glioblastoma multiforme was  $0.831 \pm 0.080 \times 10^{-3} \text{ mm}^2/\text{sec}$ , and medulloblastomas was  $0.600 \pm 0.078 \times 10^{-3} \text{ mm}^2/\text{sec}$ .

**Conclusion:** Evaluation on DWI profile and ADC value could provide additional information on conventional magnetic resonance imaging examination to determine histopathological grading and types of both intra and extra-axial brain tumors.

**Keywords:** ADC value, brain tumor, brain tumor histopathology, DWI.

## Introduction

Accurate brain tumor diagnosis has an important role in selecting an optimal therapeutic strategy due to the the influence of tumor natural course and grading on therapeutic approach of preoperative, intraoperative

and postoperative management. Conventional CT scan and MRI have limitations in differentiating intracranial lesions, with sensitivity, specificity, PPV and NPV of conventional MRI to determine high grade glioma. Therefore, many advanced MRI techniques are developed to improve the accuracy of preoperative brain tumor' histopathologic diagnosis <sup>1</sup>.

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### Corresponding Author:

Anggraini Dwi Sensusiati

E-mail: anggrainidwifkunar@yahoo.com

Diffusion weighted imaging (DWI) is an advanced MRI technique that is currently being developed as an

important method for assessing brain tumor<sup>2</sup>. In general, malignant tumors have large cell nuclei and exhibit high cell density. A study has shown that malignant tumors have low ADC values than benign tumors<sup>3</sup>. Therefore, one of the most prominent contributions of DWI is the differentiation between malignant and benign brain tumors. The sensitivity, specificity, PPV and NPV and ADC values of DWI in differentiation of high-grade brain tumors and lymphomas with low-grade glioma and non-neoplasm cases were 94.1%, 78.2%, 76.1% and 94.7%, respectively.

Recently, there has been no data on DWI profile and ADC of brain tumor which is associated with histopathology examination result, especially in Dr. Soetomo General Hospital, Surabaya, Indonesia. These data are important to show whether there is a difference with previous research. They also can be used as a reference in determining the diagnosis and characterization of preoperative brain tumor using MRI examination. Therefore, we aimed to examine correlation of DWI profiles and ADC values with histopathological outcomes in both postoperative patients with intra-axial and extra-axial brain tumors.

## Method

A retrospective study investigated correlation of DWI profile and ADC value with histopathology grading and type of brain tumor in post-brain tumor surgery patients at Dr. Soetomo Teaching Hospital, Surabaya, Indonesia. The subjects were patients with brain tumor who visited Neurosurgery Unit for head examination, surgery and histopathology examination.

All subjects should meet the following inclusion criteria: (1) Patients with intra-axial and extra-axial brain tumors; (2) Having a complete and accessible medical record; (3) Having performed head MRI with contrast and DWI sequence; (4) Having performed surgery and histopathological examination of tumor tissue. We excluded subjects with the following criteria: (1) There was no MRI file or have not performed any DWI sequence; (2) Intratumoral bleeding; (3) Intratumoral inflammatory process.

Subjects were taken using consecutive sampling technique. We used GE Optima 360 1.5 Tesla MRI

machine. MRI examination protocol used head coil, while sequences made included T1WI using fast spin echo with Time repetition (TR) 250-750 ms and Time echo (TE) 10-20 ms (SE 250-750/10-20), T1WI + C, T2WI sequence (SE 4000-8000/100). DWI with b value of 1000 mm<sup>2</sup>/sec was performed on axial pieces. ADC is a reconstruction of the DWI sequence. ADC value measurement in ROI tumors was round with size of 20-30 mm<sup>2</sup>. It was placed in the denser area of the tumor that experienced signal intensity changes on DWI. ADC value measurement in normal brain parenchyma ROI had round shape of 20-30 mm<sup>2</sup>, and it was placed in white matter on the counter-lateral side of the lesion. Gadolinium-DPTA (Omniscan, GE Healthcare Inc.) media contrast was administered intravenously to all patients with a dose of 0.1 mmol/kg WW.

Data processing and analysis begin with an evaluation of MRI examination results conducted by two neuroradiologists (ADS) and (WFA) who did not know of tumor tissue's histopathological examination results. Decisions were made by means of agreement if there were any difference in MRI interpretation.

Descriptive analysis was conducted to obtain the sample's characteristics. We conducted Kappa test to determine interobserver variation on the interpretation of MRI head examination. Spearman's correlation test was then performed to determine the correlation between DWI profile and ADC values with grading and histopathology type in brain tumor. The confidence limit used was 95% (95% CI) with significant p value <0.05. The statistical calculations used SPSS software (SPSS, Inc. Chicago, IL).

## Results

We obtained 97 samples aged 1-82 years old, with average age of 33.39 years. Most subjects were found in the age group of 41-50 years (n = 24, 24.74%) followed by age group of 31-40 years (n = 23, 23.71%) and age group of less than 10 years (n = 21, 21.65%). Table 1 showed subjects's distribution by Tumor Histopathology. Table 1 showed subjects' distribution by tumor histopathology.

**Table 1. Subjects' Distribution by Tumor Histopathology**

| Histopathology                        | Frequency | Percentage (%) |
|---------------------------------------|-----------|----------------|
| Meningioma transitional               | 19        | 19.59          |
| Pituitary adenoma                     | 14        | 14.43          |
| Medulloblastoma                       | 9         | 9.28           |
| GBM                                   | 6         | 6.19           |
| Meningioma meningothelial             | 6         | 6.19           |
| Pilocytic astrocytoma                 | 6         | 6.19           |
| Schwannoma                            | 6         | 6.19           |
| Meningioma atypical                   | 4         | 4.12           |
| Meningioma microcystic                | 4         | 4.12           |
| Diffuse fibrillary astrocytoma        | 3         | 3.09           |
| Anaplastic ependymoma                 | 2         | 2.06           |
| Meningioma fibroblastic               | 2         | 2.06           |
| CNS PNET                              | 2         | 2.06           |
| Meningioma microcyst and angiomatous  | 2         | 2.06           |
| Adamantinoma craniopharyngioma        | 1         | 1.03           |
| Anaplastic astrocytoma                | 1         | 1.03           |
| Anaplastic oligodendroglioma          | 1         | 1.03           |
| Atheroma (dermoid cyst)               | 1         | 1.03           |
| Choroid plexus carcinoma              | 1         | 1.03           |
| Choroid plexus papilloma              | 1         | 1.03           |
| Ependymoma clear cell                 | 1         | 1.03           |
| Germinoma                             | 1         | 1.03           |
| Mature teratoma                       | 1         | 1.03           |
| Meningioma microcyst and transitional | 1         | 1.03           |
| Psammomatous meningioma               | 1         | 1.03           |
| Pilomyxoid astrocytoma                | 1         | 1.03           |
| Total                                 | 97        | 100            |

ADC value characteristic of normal brain parenchyma by age showed that the age <17 years old have mean  $0.865 \times 10^{-3} \text{ mm}^2/\text{sec}$  with SD 0.045 and the age >17 years old have mean  $0.820 \times 10^{-3} \text{ mm}^2/\text{sec}$  with SD 0.057. ADC value of WHO grade I tumor was  $1.152 \pm 0.042 \times 10^{-3} \text{ mm}^2/\text{sec}$ , WHO grade II was  $1.063 \pm 0.081 \times 10^{-3} \text{ mm}^2/\text{sec}$ , WHO grade III was  $0.865 \pm 0.080 \times 10^{-3} \text{ mm}^2/\text{sec}$ , WHO grade IV was  $0.603 \pm 0.065 \times 10^{-3} \text{ mm}^2/\text{sec}$ . ADC value of facilitated and restricted diffusions

in brain tumors were  $1.139 \pm 0.037 \times 10^{-3} \text{ mm}^2/\text{sec}$  and  $0.644 \pm 0.057 \times 10^{-3} \text{ mm}^2/\text{sec}$ , respectively. The average ADC value of facilitated and restricted diffusions in extra-axial brain tumor were  $1.138 \pm 0.042 \times 10^{-3} \text{ mm}^2/\text{sec}$  and  $0.642 \pm 0.083 \times 10^{-3} \text{ mm}^2/\text{sec}$ , respectively. The average ADC value of facilitated and restricted diffusions in intra-axial brain tumor were  $1.140 \pm 0.075 \times 10^{-3} \text{ mm}^2/\text{sec}$  and  $0.646 \pm 0.074 \times 10^{-3} \text{ mm}^2/\text{sec}$ , respectively.

**Table 2. Brain tumor characteristics by DWI profiles and ADC value**

| Brain Location  | Histopathology                          | WHO Grading | DWI Profile |             | ADC Value ( $\times 10^{-3} \text{ mm}^2/\text{sec}$ ) |       |
|-----------------|---|-------------|-------------|-------------|--|-------|
|                 |   |             | Restricted  | Facilitated | Mean   | SD    |
| Intra-axial     | Pilocytic astrocytoma                   | I           |             | Facilitated | 1.408  | 0.285 |
|                 | Diffuse fibrillary astrocytoma          | II          |             | Facilitated | 1.295  | 0.361 |
|                 | Anaplastic astrocytoma                  | III         |             | Facilitated | 1.440  |       |
|                 | Anaplastic oligodendroglioma            | III         |             | Facilitated | 0.970  |       |
|                 | Anaplastic ependymoma                   | III         | Restricted  |             | 0.728  |       |
|                 | CNS PNET                                | IV          | Restricted  |             | 0.430  |       |
|                 | Medulloblastoma                         | IV          | Restricted  |             | 0.596  | 0.864 |
|                 | GBM                                     | IV          |             | Facilitated | 0.831  | 0.209 |
| Extra-axial     | Psammomatous meningioma                 | I           |             | Facilitated | 0.812  |       |
|                 | Meningioma microcystic                  | I           |             | Facilitated | 0.940  |       |
|                 | Meningioma microcystic and angiomatous  | I           |             | Facilitated | 0.866  | 0.113 |
|                 | Meningioma microcystic and transitional | I           |             | Facilitated | 0.938  |       |
|                 | Meningioma meningothelial               | I           |             | Facilitated | 0.914  |       |
|                 | Meningioma transitional                 | I           |             | Facilitated | 0.979  | 0.129 |
|                 | Meningioma fibroblastic                 | I           |             | Facilitated | 1.079  | 0.142 |
|                 | Pituitary adenoma                       | I           |             | Facilitated | 1.045  | 0.304 |
|                 | Schwannoma                              | I           |             | Facilitated | 1.047  | 0.106 |
|                 | Adamantinoma craniopharyngioma          | I           |             | Facilitated | 1.660  |       |
|                 | Choroid plexus papilloma                | I           |             | Facilitated | 2.092  |       |
|                 | Pilocytic astrocytoma                   | I           |             | Facilitated | 1.194  |       |
|                 | Meningioma atypical                     | II          |             | Facilitated | 0.962  | 0.084 |
|                 | Pilomyxoid astrocytoma                  | II          |             | Facilitated | 1.408  |       |
|                 | Anaplastic ependymoma                   | III         | Restricted  |             | 0.710  |       |
|                 | Meningioma anaplastic                   | III         | Restricted  |             | 0.658  |       |
|                 | Choroid plexus carcinoma                | III         | Restricted  |             | 0.685  |       |
| CNS PNET        | IV                                      | Restricted  |             | 0.551       |  |       |
| Medulloblastoma | IV                                      | Restricted  |             | 0.605       | 0.033  |       |

Table 3 showed a significant correlation between DWI profile and ADC values ( $p = 0.000$ ). The DWI profile showed a significant correlation with histopathology grading ( $p = 0.000$ ), and ADC value significantly correlated with histopathology grading ( $p = 0.000$ ).

**Table 3. Correlation of DWI Profile and ADC Value with Brain Tumor's Histopathology Grading**

| Location    | WHO Grading | DWI Profile | ADC Value ( $\times 10^{-3}\text{mm}^2/\text{sec}$ ) |       |
|-------------|-------------|-------------|--|-------|
|             |             |             | Mean   | SD    |
| Intra-axial | I           | Facilitated | 1.130  | 0,450 |
|             |             | Restricted  | -  | -     |
|             | II          | Facilitated | 1.185  | 0.109 |
|             |             | Restricted  | -  | -     |
|             | III         | Facilitated | -  | -     |
|             |             | Restricted  | 0.684  | 0.113 |
|             | IV          | Facilitated | -  | -     |
|             |             | Restricted  | 0.578  | 0.120 |
| Extra-axial | I           | Facilitated | 1.408  | 0.087 |
|             |             | Restricted  | -  | -     |
|             | II          | Facilitated | 0.940  | 0.120 |
|             |             | Restricted  | -  | -     |
|             | III         | Facilitated | 1.205  | 0.138 |
|             |             | Restricted  | 0.728  | 0.195 |
|             | IV          | Facilitated | -  | -     |
|             |             | Restricted  | 0.619  | 0.470 |

Spearman's correlation between ADC value and brain tumor location ( $r = 0.119$ ;  $p = 0.227$ )

Spearman's correlation between ADC value and DWI profile ( $r = .563$ ;  $p = .000$ )

Spearman's correlation between WHO grading and DWI profile ( $r = .930$ ;  $p = .000$ )

Spearman's correlation between ADC value and WHO grading ( $r = .514$ ;  $p = .000$ )

Table 4 showed a significant correlation between ADC value and histopathology of brain tumors ( $p = 0.000$ ).

**Table 4. Correlation of ADC Value and Brain Tumor’s Histopathology**

| WHO Grading | Histopathology                        | ADC Value (x 10 <sup>-3</sup> mm <sup>2</sup> /sec) |       |
|-------------|---------------------------------------|---|-------|
|             |                                       | Mean  | SD    |
| I           | Pilocytic astrocytoma                 | 1.301   | 0.107 |
|             | Choroid plexus papilloma              | 2.092   | 0.195 |
|             | Adamantinoma craniopharyngioma        | 1.660   | 0.195 |
|             | Schwannoma                            | 1.047   | 0.080 |
|             | Pituitary adenoma                     | 1.045   | 0.056 |
|             | Meningioma fibroblastic               | 1.080   | 0.138 |
|             | Meningioma transitional               | 0.979   | 0.045 |
|             | Meningioma meningothelial             | 0.914   | 0.195 |
|             | Meningioma microcyst and transitional | 0.938   | 0.195 |
|             | Meningioma microcyst and angiomatous  | 0.866   | 0.195 |
|             | Meningioma microcyst                  | 0.940   | 0.138 |
|             | Psammomatous meningioma               | 0.812   | 0.195 |
| II          | Ependymoma clear cell                 | 0.585   | 0.195 |
|             | Diffuse fibrillary astrocytoma        | 1.295   | 0.138 |
|             | Pilomyxoid astrocytoma                | 1.408   | 0.195 |
|             | Atypical meningioma                   | 0.962   | 0.098 |
| III         | Anaplastic meningioma                 | 0.658   | 0.195 |
|             | Anaplastic astrocytoma                | 1.440   | 0.195 |
|             | Anaplastic oligodendroglioma          | 0.970   | 0.195 |
|             | Anaplastic ependymoma                 | 0.719   | 0.138 |
|             | Choroid plexus carcinoma              | 0.685   | 0.294 |
| IV          | Medulloblastoma                       | 0.600   | 0.078 |
|             | GMB                                   | 0.831   | 0.080 |
|             | CNS PNET                              | 0.491   | 0.138 |

Spearman’s correlation between ADC value and brain tumor’s histopathology (r = .563; p = .000)

**Discussion**

In this study, the average value of normal brain parenchyma’s ADC white matter in age group less than 17 years was 0.865±0.045 x 10<sup>-3</sup> mm<sup>2</sup>/sec, while 0.820±0.057 x 10<sup>-3</sup> mm<sup>2</sup>/sec for age group more than 17 years. This value was higher than the normal value found in a study conducted by Thomas study (0.75±0.03 x 10<sup>-3</sup> mm<sup>2</sup>/sec) <sup>4</sup>.

We found a significant correlation between DWI profile and ADC value (p = 0.000). The average ADC value in DWI profile of facilitated and restricted diffusions in brain tumor were 1.139±0.037 x 10<sup>-3</sup> mm<sup>2</sup>/sec and 0.644±0.057 x 10<sup>-3</sup> mm<sup>2</sup>/sec, respectively. In another study, ADC value less than 1.0-1.1 x 10<sup>-3</sup> mm<sup>2</sup>/sec indicated a restricted diffusion of water molecules <sup>5</sup>. Nevertheless, we found no significant correlation between ADC value and brain tumor location. The value of facilitated and restricted diffusions in intra-

axial and extra-axial brain tumors showed no significant difference.

MRI is a highly sensitive imaging modality for evaluating brain tumors, but conventional MRI has limitations to differentiate histopathologic types of most brain tumors. In this study, we found a significant relationship between ADC value and tumor histopathology grading ( $p = 0.000$ ). This finding was consistent with a study that found higher ADC value led to LGG (WHO I, II), while lower ADC value led to HGG (WHO III, IV). These findings were consistent with a study that found low ADC value led to atypical or malignant meningiomas compared with benign<sup>6</sup>.

Increased mitotic processes, necrosis, high cytoplasmic nucleus ratios and increased disturbed cell growth patterns are found in high-grade meningiomas, causing restricted diffusion of water molecules seen in DWI. On the other hand, benign meningiomas show little representation of a coherent histological organization, because they are composed of oval-shaped neoplastic or spindle cells that form threads, fascicles, cords, or nodules, which force water molecules to move relatively isotropic<sup>1</sup>. The location of pituitary adenoma could be affected by the air-induced susceptible artifacts in the sinuses and surrounding bones resulting in varying results on the evaluation of ADC values, but no data supporting this possibility has been obtained<sup>7</sup>. On the other hand, PCL as a hypercellular tumor has been reported to have lower ADC values significantly greater than HGG and metastatic tumors<sup>1</sup>. A study reported that lymphoma and metastasis' ADC values were lower than glioma<sup>8</sup>.

A study ( $n = 76$ ) reported ADC tumor metastasis was  $0.72 \times 10^{-3} \text{ mm}^2/\text{sec}$  (using b-value of  $1,000 \text{ mm}^2/\text{sec}$ )<sup>9</sup>. On the other hand, another study ( $n = 21$ ) reported ADC tumor metastasis values ranging from 0.35 to  $1.37 \times 10^{-3} \text{ mm}^2/\text{sec}$ , with an average of  $0.79 \pm 0.23 \times 10^{-3} \text{ mm}^2/\text{sec}$  (using b-value of  $1,000 \text{ mm}^2/\text{sec}$ ). Nevertheless, the study found no significant correlation between ADC tumor metastasis score and GBM<sup>10</sup>.

A study reported that  $\text{ADC}_{\min}$  value measured by multiple ROI was a significant preceptor for differentiating PCL with glioblastoma, with an optimal cutoff value of  $0.72 \times 10^{-3} \text{ mm}^2/\text{sec}$ . The obtained average value of ADC glioblastoma and PCL were  $0.79 \pm 0.20 \times 10^{-3} \text{ mm}^2/\text{sec}$  and  $0.51 \pm 0.17 \times 10^{-3} \text{ mm}^2/\text{sec}$ , respectively<sup>11</sup>. However, there is limited analysis of

ADC sample values with histopathology ependymoma and heterogeneous morphology and tumors, therefore the results of this group are not fully reliable and further research is needed<sup>12</sup>.

Brain tumor is an abnormal growth of cells in the brain. Magnetic resonance imaging (MRI) is an advanced diagnostic tool that enables us to visualize anatomical details more clearly so superior in detecting abnormalities in the soft tissues of the brain<sup>13</sup>. Neoplasia refers to the growth of new cells that are different from the growth of cells around it<sup>14</sup>. Image segmentation has been popularly performed for researchers in the field of Biomedical, Informatics Engineering, and Statistical Computation<sup>15</sup>.

## Conclusion

ADC value measurement in both extra-axial and intra-axial brain tumors was a significant predictor of grading differentiation and histopathologic types of brain tumor. Clinicians could use this diagnostic method for comprehensive action planning and management of brain tumor cases.

**Ethical Clearance:** The study protocol was approved by the ethics committees of Dr. Soetomo Teaching Hospital, Surabaya, Indonesia.

**Conflict of Interest:** No conflict of interest reported from this research

**Source of Funding:** This research funded individually.

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