ORIGINAL ARTICLE

Clinical Utility of the Diffusion Weighted Imaging (DWI) Ratio in Characterizing Primary Brain Neoplasms in Pediatric Patients: A 5-year Retrospective Study in a Tertiary Hospital in the Philippines

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ABSTRACT

Objective:
The goal of this study was to determine the accuracy of DWI ratio in characterizing primary brain tumors among pediatric patients in the Philippine General Hospital from January 2013 to July 2018.

Methods:
Magnetic resonance images of pediatric brain tumors were reviewed. Standardized ROI were placed at solid portion of the tumor that presented the highest signals on DWI (DWI T), at the normal appearing white matter of the contralateral frontal lobe (DWI WM), and at the normal-appearing homologous area of the ROI of the tumor in the contralateral hemisphere or adjacent region (DWI N). The DWI ratios were determined and analyzed. Data gathered were then subjected to statistical analysis to determine the accuracy of the DWI ratios.

Results:
Thirty cases of pediatric brain tumors were included in this study. Upon analysis, there was a significant difference in the median DWI(T/N) and DWI (T/WM) ratios between Grades II-IV neoplasms; with the Grade IV tumors exhibiting a higher median ratio compared to Grade II. There was significant difference in the median DWI (T/N) and DWI(T/WM) values between low- and high-grade neoplasms, with the median DWI (T/N) and DWI (T/WM) ratios significantly higher among those with high grade neoplasms.

Conclusion:
The DWI ratios presented relatively high sensitivity, high specificity, and relatively high diagnostic accuracies in grading or classifying pediatric intracranial tumors. This method shall be a useful additional non-invasive tool in the evaluation of tumor characteristics, which will guide clinicians in their therapeutic approach.

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INTRODUCTION

Neoplasms are abnormal and uncoordinated proliferation of tissues from certain organs, which may be from previously normal cells in the organ or may be from inherent vessels or connective tissues [1]. This abnormal process does not occur in specific sites only but can affect any part of the body. It is of particular importance when a primary neoplasm occurs intracranially since a patient with such a condition can present with a variety of neurologic manifestations, sometimes life-threatening in the acute setting. Worldwide, intracranial neoplasms are estimated to have an annual incidence of 10–17 per 100,000 population; this is comprised of either primary neoplasms or metastasis from distant sites [2]. Primary neoplasms can occur at any age, with most cases seen among children and older adults; metastasis, on the other hand, is more common in adults than in children [3].

Although clinical diagnosis is very important in such cases, the need for radiologic imaging is emphasized since it may provide a useful set of differential diagnosis, exclude alternative diagnoses, and identify complications, all of which may greatly impact management.

Computed tomography (CT) and magnetic resonance (MR) imaging are the most common imaging modalities being utilized for evaluation of intracranial neoplasms or tumors. Between the two, MR imaging is preferred due to its ability to provide excellent anatomic information and better tissue characterization to ionizing radiation without exposure [2,4–7]. In both modalities, it is important for radiologist to look for characteristics that can help direct the correct diagnosis, as close as it can be to the histopathologic diagnosis - the latter remaining as the gold standard in such cases. Tissue characteristics such as the presence of calcifications, fat, cystic components, contrast enhancement, and signal intensity in the different MRI sequences, can assist the radiologist in narrowing down the differential diagnosis [8].

MR imaging is now being widely used, especially in pediatric patients. The most common sequences used for such cases are the T1- and T2-weighted imaging (T1WI and T2WI, respectively). Contrast enhancement is likewise being utilized for improved tumor characterization. Brain tumors usually exhibit low signal intensity on T1WI and high on T2WI [9]. However, contrast-enhancement level does not always correlate with tumoral grade as tumors can exhibit variable enhancement regardless of benignity or malignancy [10]. As such, DWI is suggested being used as an alternative, non-invasive modality to tissue diagnosis. This MRI sequence probes water molecular diffusion over distances that correspond to typical cell sizes, as well as the diffusivity of water diffusion across membranes (structures that are an integral part of the cell architecture). The effect of these membranes is expected to increase once there is increasing cell density, as seen in tumors.[6] Present research on DWI ratio has all been conducted internationally. Grading tumors based on the method proposed will provide more objective approach to management, whether to do surgical approach or medical tumor debulking, and diagnosis without doing biopsies.

This research was conducted to determine the accuracy of DWI ratio in characterizing primary brain tumors among pediatric patients in the Philippine General Hospital from January 2013 to July 2018. Specifically, it is made to determine the association between DWI ratio of pediatric brain tumors with its histopathologic diagnosis and to measure the diagnostic ability of DWI ratio using receiver operating characteristic (ROC) curve in identifying low- or high-grade neoplasms.

METHODS

This was a retrospective study reviewing the MR images of pediatric patients scanned in a tertiary hospital in Manila, Philippines, who were referred for possible intracranial tumors from January 2013 to July 2018. All pediatric patients with primary intracranial tumors were included in this study (image acquired using 1.5 Tesla MR unit, Magnetom Essenza; Siemens, Germany). The sequences used were T1WI, FLAIR and DWI (B1000) sequences. The histopathologic diagnosis was then obtained. The age of the patient and sex were also gathered.

Excluded in this study were patients with no preoperative MR imaging, or those who have had previous radiation and/or chemotherapy before the MRI. Patients with tumors composed mainly of cysts and without measurable solid components, and patients with tumor bleeding and calcifications on MRI (evidenced by the presence of magnetic susceptibility on the included susceptibility-weighted imaging), will not be included likewise in this study. Also excluded are patients with imaging that do not have histopathologic diagnosis. This study has been approved by the institutional ethics board.

Review of the images of said patients was done with two of the advisers of the study, who are fellows of the Philippine CT-MRI Society. One adviser had more than 10 years in CT-MRI imaging while the other adviser had pediatric neuroradiology subspecialty training. Non-concordance between the two advisers would warrant repeat reevaluation of the case. If after review, there is still non-concordance, the sample is to be discarded. The radiologists were blinded regarding the tissue diagnosis of each case.

The signal intensity of selected regions of interest (ROIs) on DWI was obtained at the b1000 value. Three standardized ROI's measuring 25 ± 5 mm^2 were placed at the solid portion of the tumor that presented the highest signals on DWI (DWI_T), at the normal appearing white matter of the contralateral frontal lobe (DWI_{WM}), and at the normal-appearing homologous area of the ROI of the tumor in the contralateral hemisphere or adjacent region (DWI_N) (Fig. 1). In acquiring the measurements, the ellipse/circle ROI was copied and moved to the areas of interest to standardize the size of the tissue to be analyzed and avoid sampling errors. Using the formulae below,

$$DWI_{T/WM} = DWI_T / DWI_{WM}$$
$$DWI_{T/N} = DWI_T / DWI_N$$

the ratios $DWI_{T/WM}$ and $DWI_{T/N}$ were computed. When artifacts are present in the areas of interest, the ellipse/

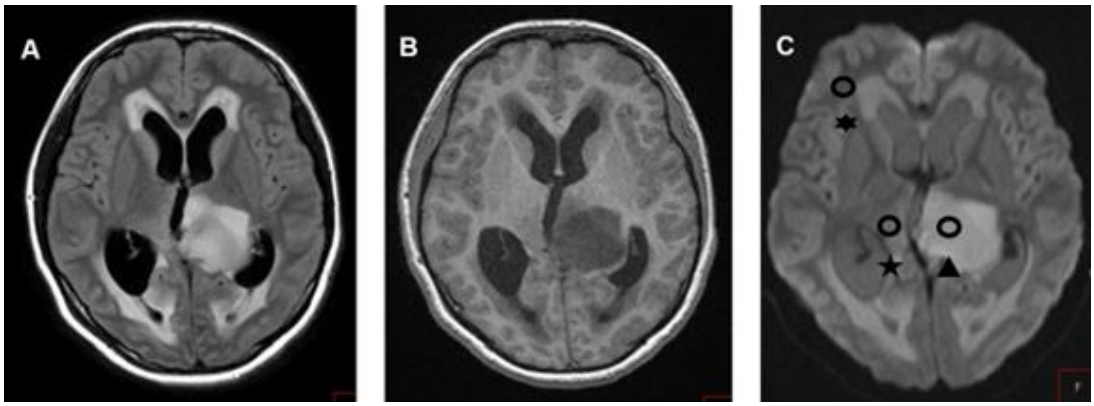

Fig. 1A–C Measuring signal intensities on DWI, with a tumor in the left thalamus (**A, B**). In order to obtain DWI values (**C**), three ROI's (black circles) are placed at the brightest solid portion of the tumor on DWI (▲), at the normal-appearing white matter of the frontal lobe (✶), and at the normal-appearing homologous area (★) of tumor ROI in the contralateral hemisphere on the axial DWI image. (Method adapted from Wu CC, et al., 2012) [4]

circle ROI was repositioned in areas without tumoral involvement, according to anatomical references.

Logistic regression was used to measure the association between DWI ratio and histologic diagnosis. Once computed, cases were categorized into low- or high-grade neoplasms, using $DWI_{T/WM}$ of 1.6 and $DWI_{T/N}$ of 1.5 as the cut-off values, with those equal to or less than the values considered as low-grade neoplasms. Categorizing into low or high-grade neoplasm is based on the 2016 WHO Classification of the Central Nervous System. Low-grade neoplasms include grade I and grade II, while high-grade neoplasms include grade III and grade IV [9]. After the initial analysis of the images, association was measured between the results and the histopathologic diagnosis to confirm whether the tumor grade.

Receiver operating characteristic (ROC) curve was used to determine the diagnostic ability of $DWI_{T/WM}$ and $DWI_{T/N}$ in identifying low- or high-grade neoplasms. The diagnostic ability was measured separately for $DWI_{T/WM}$ and $DWI_{T/N}$. The ROC curve was created by plotting the true positive rate (TPR) against the false positive rate (FPR) at various cut-off points of $DWI_{T/WM}$ and $DWI_{T/N.}$ An area of the ROC curve close to 1 suggests good diagnostic ability while an area close to 0 suggests poor diagnostic ability.

The test of normality of data was done using Shapiro-Wilk test. Since the data were not normally distributed, Kruskal-Wallis test was used to compare the median DWI ratios across the different tumor grades. Mann-Whitney U test was then used to compare the median DWI ratios between low-grade and high-grade neoplasms. Sensitivity and Specificity were calculated for $DWI_{T/WM}$ and $DWI_{T/N}$ in identifying low- or high-grade neoplasms.

Corresponding 95% confidence intervals were computed using Wilson Score Interval without continuity correction. The diagnostic accuracy was computed using the Youden Index (J), where,

$$J = \frac{\text{true positives}}{\text{true positives + false negatives}} + \frac{\text{true negatives}}{\text{true negatives + false positives}} - 1$$

to determine which cut-off points will yield the maximum predictive potential of $DWI_{T/WM}$ and $DWI_{T/N.}$

Encoding of needed data was done through Excel (Microsoft Office, USA) and all statistical tests used Stata 12.

RESULTS

Different cases of intracranial tumors included in this study were summarized in Table 1. Most of the included cases were low-grade gliomas; a few of these tumors were ependymoma and medulloblastoma.

Of the 52 pediatric tumor cases identified in MRI, 30 cases were included for analysis, given that 1 of the cases is that of tuberculoma, two have known histopathologic diagnosis but with unavailable MR images for review, and 19 which did not yield any available histopathologic results.

The DWI ratios were then computed and were categorized into low- or high-grade neoplasms, using $DWI_{T/WM}$ of 1.6 and $DWI_{T/N}$ of 1.5 as the cut-off values. Those equal to or less than these values were considered as low-grade neoplasms [4].

Table 1 Summary of included pediatric tumors done from January 2013 to July 2018

Disease	WHO Grade	Number	%
Ependymoma	II	5	16.7
Low-grade glioma	II	11	36.7
Non-germinomatous pineal gland tumor	II	1	3.3
Non-specific high-grade glioma	III	1	3.3
Anaplastic ependymoma	III	1	3.3
Medulloblastoma	IV	5	16.7
Glioblastoma	IV	2	6.7
Germ cell tumor	IV	2	6.7
Non-germinomatous germ cell tumor	IV	1	3.3
CNS embryonal tumor	IV	1	3.3
Total		30	100

There was a significant difference in the $DWI_{T/N}$ ratio between Grades II-IV neoplasms. Group IV exhibits a higher ratio compared to Group II; however, the ratios between Groups II and III, and III and IV were not significantly different. (Table 2)

Table 2 Median $DWI_{T/N}$ per WHO Tumor grade

Grade (n)	Median $DWI_{T/N}$ (Range)	p-value
II (17)	1.2 (0.5–1.9)	0.0119
III (2)	1.5 (1.5–1.6)	
IV (11)	1.8 (0.4–3.5)	

There was also a significant in the median DWI tumor:white matter ratios of Grades II-IV neoplasms (p-value=0.0150). Post-hoc analysis again showed that Group IV had significantly higher median $DWI_{T/WM}$ values than Group II. There were no significant differences in the median value of $DWI_{T/WM}$ between Groups II and III, and between Groups III and IV. (Table 3)

Table 3 Median $DWI_{T/WM}$ per WHO Tumor grade

Grade	Median $DWI_{T/WM}$ (Range)	p-value
II	1.3 (0.6–1.9)	0.0150
III	1.4 (1.4–2.0)	
IV	1.8 (0.5–3.2)	

The categorization of cases into low- or high-grade neoplasms was based on the 2016 WHO Classification of the Central Nervous System. Grades I and II were considered low-grade neoplasms, while Grades III and IV were considered high-grade neoplasm. There was a significant difference in the median $DWI_{T/N}$ values between low- and high-grade neoplasms (p-value = 0.003). Median $DWI_{T/N}$ was significantly higher among those with high-grade neoplasms. (Table 4)

Table 4 Median $DWI_{T/N}$ per WHO Classification of CNS Tumors

Classification (n)	Median $DWI_{T/N}$ (Range)	p-value
Low (17)	1.2 (0.5–1.9)	0.003
High (13)	1.7 (0.4–3.5)	

Table 5 showed a statistically significant difference in the median DWI tumor:white matter ratios between low- and high-grade neoplasms (p-value=0.004). The values were found to be higher among high-grade neoplasms (WHO Grades III and IV).

Table 5 Median $DWI_{T/WM}$ per the WHO Classification of CNS Tumors

Classification	Median $DWI_{T/WM}$ (Range)	p-value
Low	1.3 (0.6–1.9)	0.004
High	1.8 (0.5–3.2)	

It was also observed that the $DWI_{T/N}$ ratio had a relatively high sensitivity (69.23%) and high specificity (82.35%). The diagnostic accuracy of using DWI tumor:normal-appearing homologous area ratio in assessing low- and high-grade neoplasm was relatively high, with a computed accuracy of 76.67%. (Table 6)

Table 6 Diagnostic accuracy of $DWI_{T/N}$ in classifying low- and high-grade pediatric tumors

	Low $DWI_{T/N}$	High $DWI_{T/N}$
Low-grade neoplasm	14 (82.4%)	3 (17.6%)
High-grade neoplasm	4 (30.8%)	9 (69.2%)
Sensitivity	69.23% (95% CI = 42.37–87.32%)	
Specificity	82.35% (95% CI = 58.97–93.81%)	
Diagnostic Accuracy	76.67% (95% CI = 59.07–88.21%)	

On the other hand, it was observed that $DWI_{T/WM}$ had a relatively high sensitivity (61.54%) and a high specificity

(88.24%). The diagnostic accuracy of using the DWI tumor:white matter ratio in assessing low- and high-grade neoplasms was also relatively high, with a computed accuracy of 76.67%. (Table 7)

Table 7 Diagnostic accuracy of $DWI_{T/WM}$ in classifying low- and high-grade pediatric tumors

	Low $DWI_{T/WM}$	**High $DWI_{T/WM}$**
Low-grade neoplasm	15 (88.2%)	2 (11.8%)
High-grade neoplasm	5 (38.5%)	8 (61.5%)
Sensitivity	61.54% (95% CI = 35.52–82.29%)	
Specificity	88.24% (95% CI = 65.66–96.71%)	
Diagnostic Accuracy	76.67% (95% CI = 59.07–88.21%)	

DISCUSSION

Magnetic resonance diffusion-weighted imaging has been helpful in studying water mobility in normal brain tissue, cerebral infarction, multiple sclerosis, brain tumors and brain abscesses, and to differentiate between arachnoid cysts and epidermoid cysts and other diseases.[11] In the case of brain tumors, routine contrast-imaging studies alone may provide all the necessary information needed to differentiate between benign and malignant neoplasms.

Diffusion-weighted imaging (DWI) is one of the MR sequences utilized in determining hyperacute and acute infarcts in the first 6 hours after ictus, as it uses the diffusivity of the water molecules in the infarcted brain cells. The same principle can be used in the assessment of brain tumors, wherein signal characteristics are based on the alterations of the cellularity and of the extracellular spaces within the tumor. This specific procedure may provide qualitative and quantitative assessments of water diffusivity in brain tumors [5].

In most studies, pathological alteration of water diffusion in the brain tissues is illustrated by apparent diffusion coefficient (ADC) mapping. Most institutions use the ADCs to determine neoplastic density and proliferation indices. A previous study showed low ADC values in pediatric brain tumors suggesting high-grade hypercellular tumors, such as medulloblastoma, primitive neuroectodermal tumor, and glioblastoma; low-grade gliomas usually show high ADC values. However, there remains a considerable overlap of the ADC values between high- and low-grade tumors in both pediatric and adult patients, resulting in the limited clinical value of ADC for tumor grading [5]. As such, an ADC map alone is not totally sufficient in predicting the type and grade of intracranial neoplasms [2].

The use of DWI, particularly the DWI ratio, is another proposed and studied method in determining whether an intracranial tumor is high- or low-grade neoplasms. DWI ratio, is computed using the following formulae:

$$DWI_{T/WM} = DWI_T / DWI_{WM}$$
$$DWI_{T/N} = DWI_T / DWI_N$$

where DWI_T is the signal intensity value of the tumor, DWI_{WM} is the signal intensity value of the white matter of the contralateral frontal lobe, and DWI_N is the signal intensity value of the homologous contralateral normal brain tissue [4].

In a 2012 study, a higher DWI ratio ($DWI_{T/WM}$) was seen in high-grade gliomas. On the other hand, a lower DWI ratio was noted in low-grade tumors. This can be explained by the greater cellularity and fewer extracellular space in high-grade tumors, such as glioblastoma and lymphoma. In previous studies, homologous area in the contralateral hemisphere of the tumor was identified and used to determine the DWI ratio. Presently, cut-off values of 1.6 for $DWI_{T/WM}$ and 1.5 for $DWI_{T/N}$ have been used in pediatric neuro-oncological practice [4]. In this study, a significant difference in the DWI ratios of low- and high-grade tumors when comparing the DWI ratios between the tumor and the contralateral frontal lobe white matter and of the tumor with normal-appearing homologous area was determined. These results were congruent with the study by Wu, et al. in 2012 [4]. With a relatively high sensitivity and a high specificity, both the $DWI_{T/WM}$ and $DWI_{T/N}$ provided relatively high diagnostic accuracies in classifying low- and high-grade neoplasms, particularly gliomas. The results of this study indicate that a lower DWI ratio suggests a low-grade intracranial neoplasm, while a higher DWI ratio suggests otherwise.

However, the low sample size gathered in this study particularly in the homogeneity of the identified tumor grades, may not be statistical enough to generate a universal conclusion on the utility of the DWI to determine tumor grade. Determining the ADC values of pediatric intracranial tumors would still be of benefit, as seen in previous published studies where low ADC values in pediatric brain tumors suggest high-grade hypercellular tumors, such as medulloblastoma, and high ADC values suggest otherwise [4]. However, an ADC map alone is not sufficient in predicting the type and grade of intracranial neoplasms. A study in 2017 by Hyun Woo Goo, et al. showed a considerable overlap of the ADC values between high- and low-grade tumors in both pediatric and adult patients, resulting in the limited clinical value of ADC for tumor grading [5]. The information derived from determining the DWI ratio, on the other hand, may provide additional information to clinicians and surgeons.

The determination of the DWI ratio may be limited particularly after interventions (i.e. radiation, chemotherapy, or surgery) and which is beyond the scope of this study. This is to avoid potential confounding factors for tissue diffusion. Also, tumors with mostly cystic contents and patients with tumor bleeding and calcifications may provide inaccurate measurements on DWI. A prospective approach may provide improved results, considering that some of the possible cases that could have been included in this study did not have histopathologic results and did not have prior imaging studies for review.

CONCLUSION

The DWI ratios presented a relatively high sensitivity, high specificity, and relatively high diagnostic accuracies in grading or classifying pediatric intracranial tumors. This method shall be a useful additional non-invasive tool in the evaluation of tumor characteristics, which will guide clinicians in their therapeutic approach.

REFERENCES

1. Atlas of Pathology. Neoplasia (Tumor) [Internet]. Atlas of Pathology website. 2016 [cited 2017 June 15]. Available from: http://www.pathologyatlas.ro/tumors-neoplasia.php
2. Lavra F, Scartozzi M, Zaccagna F, Cartocci G, et al. Advanced magnetic resonance imaging in the study of primary intracranial brain tumors in adults: a state of art review. J Xiangya Med 2017;2:56.
3. American Brain Tumor Association. Brain Tumor Statistics. ABTA website. 2014 [cited 2017 June 15]. Available from: http://www.abta.org/about-us/news/brain-tumor-statistics/
4. Wu CC, Guo WY, Chen MH, Ho DM, et al. Direct measurement of the signal intensity of diffusion weighted magnetic resonance imaging for preoperative grading and treatment guidance for brain gliomas. JCMA [Internet]. 2017 [cited 2017 June 15]. Available from: https://www.sciencedirect.com/science/article/pii/S1726490112002225
5. Goo HW, and Ra Y. Advanced MRI for Pediatric Brain Tumors with Emphasis on Clinical Benefits. Korean J Radiol 2017;18(1):194–207.
6. Chedia S, Todua F. Differentiation between benign and malignant meningiomas using diffusion and perfusion MR imaging. Georgian Med News 2012;(206):16–22.
7. Maier SE, Sun Y, Mulkern RV. Diffusion Imaging of Brain Tumors. NMR Biomed 2010;27(7):849–64.
8. Smithuis R, and Montanera W. Brain Tumor – Systematic Approach. Radiology Assistant [Internet]. 2008 [cited 2017 June 15]. Available from http://www.radiologyassistant.nl/en/p47f86aa182b3a/brain-tumor-systematic-approach.htm
9. Louis DN, Perry A, Reifenberger G, von Deimling A, et al. The 2016 World Health Organization Classification of the Tumors of the Central Nervous System. Acta Neuropathol 2016;131(6):803–20.
10. Koob M, Girard N. Cerebral tumors: Specific features in children. DIII [Internet]. 2014 [cited 2017 June 15]; 95(10):965–83. Available from https://www.sciencedirect.com/science/article/pii/S2211568414002101
11. Kono K, Inoue Y, Nakayama K, Shakudo M, et al. The role of diffusion-weighted imaging in patients with brain tumors. AJNR Am J Neuroradiol 2001; 22(6):1081–88.