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ADC Thresholds in the Discrimination of Indolent and Aggressive Orbital Adnexal Lymphoma

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1. Abstract

1.1. Aim: This study aims to determine whether ADC measurements allow discrimination of indolent (group A) from aggressive orbital lymphoma (group B) and how much ADC value can predict lymphoma subtype.

1.2. Methods: A retrospective two-armed cohort study including 32 Orbital Adnexal Lymphoma (OAL) lesions evaluated by conventional magnetic resonance image (MRI) and Diffusion Weighted Image (DWI) examination preceding histopathological lesion confirmation. DWI using single-shot echo-planar imaging with b factors of 0,400 and 800 sec/mm^2 were performed on 3 Tesla MRI unit. Lymphomas were grouped into indolent or aggressive histopathological subtypes according to the Revised European-American Classification of Lymphoid Neoplasms (REAL). The groups minimum, maximum and percentiles of ADC values of indolent were compared to those of aggressive lymphoma subtype. Multiple receiver operating characteristic curve (ROC) analysis was performed for predicting aggressive OAL.

1.3. Results: Of the 32 (OAL) cases, 23 (71.9%) were indolent and 9 (28.1%) were aggressive OAL subtypes. In general, ADC values were significantly higher in the indolent compared to the aggressive OL subtypes. (P<0.001). Extra-ocular muscles (P = 0.69) and globe involvement (P = 0.9) were not significant confounders for association of ADC to histological type. The area under curve (AUC) for ADC minimum was 94.4% and for ADC maximum was 81.6%. ADC minimum showed higher sensitivity and specificity than ADC maximum in revealing (OAL) subtypes.

1.4. Conclusions: ADC measurements are higher in indolent than in aggressive (OAL). ADC minimum has higher sensitivity and specificity than ADC maximum in (OAL) lesions. These concepts confirm and expand the knowledge on (OAL), revealing the importance of ADC minimum in discriminate indolent from aggressive OAL. DWI can be used to characterize (OAL) based on ADC values, having higher sensitivity and specificity to point the (OAL) subtypes.

2. Introduction

Orbital adnexal lymphoma (OAL) represents the most common lymphoproliferative disorder affecting the orbit, accounting from 6% to 20% of all orbital mass and about 2% of all lymphomas [1], mostly seen primarily in adults in the 50 to 70 year age group [2]. Clinical appearance does not allow a distinction between benign and malignant lymphoproliferative disease with the being biopsy remain the gold standard for accurate histological differentiation [3]. Based on the OAL subtypes, it is possible to plan and guide the appropriate treatment and to predict the prognosis, since low grade OAL is amenable to radiotherapy, while combined chemotherapy is indicated for high grade and disseminated lesions [4]. However, biopsy is often technically challenge mainly in lesions with difficult locations or in patients with systemic issues [5]. Different routine sequences using Positron emission tomography (PET) or gadolinium-enhanced MRI are optimal modalities to delineate and

to localize orbital masses, preceding biopsy with characteristics restricted pattern on Diffusion weighted images [6,7].

Recently, diffusion-weighted (DWI) MRI has been introduced as a non-invasive functional technique and valuable tool for the identification and characterization of orbital masses [6]. DWI-MRI can provide morphological and functional information regarding characterization of lymphomas using the apparent diffusion coefficient (ADC) [6,8]. Any architectural changes that affect the proportion of extracellular to intracellular water molecules will alter the apparent diffusion coefficient (ADC) of the tissue. In this context, the ADC value varies according to the microstructure and pathophysiological state of tissues [9], reflecting the dense cellularity and limited extracellular space of an aggressive neoplasm which can limit the random motion of water molecules in the tissues by means of ADC value [6,8]. Low values in the threshold ADC on DWI-MRI have been found helpful to discriminate lymphoma from other orbital lesions [3], with good sensitivity to distinguish malignant from benign lesions, and lymphomas from non-lymphoproliferative lesions [6,8], (OAL) from idiopathic orbital inflammatory pseudotumor [9,10]. The ADC can be useful for detection and stage, as well as for monitoring the response to chemotherapy [5,6,11,13-15]. However, to the best of our knowledge, only a few studies have compared the ADC value and tissue histology in (OAL) [6]. The role of ADC value for differentiation of histopathological OAL subtypes have not yet been studied and remains incompletely understood. The purpose of this study was to investigate whether ADC measurements allow discrimination of indolent from aggressive (OAL).

3. Patients and Methods

This was a retrospective two-armed cohort study of (OAL) cases diagnosed at the Pathology and the Radiology Departments of King Khaled Specialist Eye Hospital, Riyadh - Saudi Arabia, from January 2015 to October 2019. The ethical and research board members of our institute approved this report (1250-R) and consent was waived due to the retrospective nature of the study. The tenants of Helsinki declaration were strictly followed at all steps of this research project.

Database search included all the suspected (OAL) patients who underwent satisfactory MRI images of at least 10mm axial length mass, with histopathological and immunohistochemical evaluation proven the (OAL) diagnosis. Cases of small lesions, located in other sites as conjunctiva, having history of biopsy, surgery, or treatment before imaging or poor MRI image quality were excluded.

3.1. Image exam technique

DWI was performed before contrast administration, obtaining images in axial plane using echo-planar spin-echo T2 (factor b of 0, 500 and 1000s/mm²) MR imaging was acquired using a 3 Tesla GE Discovery 750 superconducting MRI Scanner. Imaging parameters were as follows: TR/TE of 3200/81 mms, FOV of 20 × 22 cm, slice thickness of 3.0 mm, interslice gap of 1.0–2.0 mm, number of excitations of 6, matrix of 128 × 128, EPI factor of 128 and RF pulse bandwidth of 1200. The acquisition time for DWI was 2min 36s. ADC maps were automatically generated. DWI images were collected on a single workstation using commercial AGFA Enterprise Imaging workstation (IMPAX agility, Belgium) to calculate ADC values.

3.2. Image analysis

All MRI images were reviewed on a Picture Archiving and Communication System workstation. DWI images with b values of 0 and 800s/mm2 were carefully examined, and the signal intensity of the mass was assessed on images obtained at b=0s/mm2, b=800s/mm2 and on the ADC maps. The radiological evaluation was made by an expert neuroradiologist (SK), blinded to the final diagnosis. To achieve best results, at least five ROIs were selected in each examination[6,8,11] in concordance with T1 or T2 images. If cystic or necrotic content is present, ROI was placed to comprise only the solid component, avoiding the cystic-necrotic part by taking advantage of T2-weighted images. The region of interest (ROI) was manually drawn to encompass the entire cross-section of the lesion on ADC map image. The ADC value was measured directly on the parametric ADC maps by inline calculation. Distortion artifacts were carefully excluded from the ROI delimitation. Mean ADC value within the ROI was recorded as value ($\times 10^{-3}$ mm/s²).

3.3. Biopsy and histopathological exam

All included (OAL) cases underwent surgical biopsy by an experienced physician. The site of biopsy was the largest tumor region based on clinical presentation and MRI examination. The specimens were prepared for exam through routine sections of formalin-fixed, paraffin-embedded tissues, with slides stained by hematoxylin and eosin and then examined using binocular microscope (Zeiss, Germany). For labelling the exact subtype of (OAL), immunohistochemical (IHC) evaluation was carried out. In addition, flow cytometric and gene rearrangement analyses were performed to identify a monoclonal immunoglobulin band. Two co-investigators' pathologists (AM and HK) independently reviewed all specimen and classified according to the Revised European-American Classification of Lymphoid Neoplasms (REAL Classification) and divided according to the expected behaviour into either indolent or aggressive group OAL [1-17].

3.4. Statistical analysis

Data was collected on a spreadsheet of Microsoft XL® and subsequently transferred to the spreadsheet of Statistical Package for Social Sciences (SPSS Version 25.0, Chicago, IL, USA) for statistical analysis. The mean and SDV of minimum and maximum ADC values of indolent or aggressive histological subtypes were estimated. They were compared by presenting their difference of

mean, 95% confidence interval and two-sided P values. The histogram parameters, the ADC mean, 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentile of ADC values, ADC minimum, ADC maximum, skewness and kurtosis were calculated. The sensitivity vs (1- specificity) was plotted to determine the Area Under curve (AUC) by using graph facilities of SPSS 25. Receiver operating characteristic (ROC) curves were plotted to assess the diagnostic utility of identified variables and diagnostic models to evaluate diagnostic efficiency of the ADC values to differentiate in between certain groups, and threshold ADC values with highest accuracy were determined. A P<0.05 was considered as statistically significant.

4. Results

Thirty-two (OAL) cases fulfilled the criteria and were included in the present study. According to their histological behaviour, 23 (71.9%) were classified as indolent and 9 (28.1%) as aggressive subtypes. Twenty-one (91.3%) of the indolent OL, were extra nodal marginal zone B cell (MALT) lymphoma and two (8.7%) cases were of follicular lymphoma (FL). Among aggressive group, six (66.7%) had diffuse large B-cell lymphoma (DLBCL), two (22.2%) had Burkitt's lymphoma, and one (11.1%), T-cell lymphoma. Demographic profile and qualitative MRI orbital details of cases of indolent and aggressive OAL group are compared in (Table 1). Males were significantly more in indolent (86.4%) subgroup (Odd's Ratio = 7.1; P=0.02). The mean age of both groups was similar (P= 0.7). In the indolent subgroup, 18 (78.3%) were unilateral. Indolent type had longer duration of symptoms, but both were similar in other comparisons, such as no systemic involvement, no extraocular muscles or globe involvement in most cases (Table 1). The mean ADC indicate clear differences between histological subtypes, being ADC values significantly higher in the indolent compared to the aggressive OL subtype. (P<0.001). Both ADC minimum and ADC maximum values for indolent (OAL) cases were significantly higher than those of aggressive subtypes of OAL (P <0.001) (Table 2). Comparison of ADC values inside each group subcategory was not statistically significant (p=0.448). The lowest mean ADC value of indolent lesions was in MALT lymphoma and the highest mean ADC of aggressive lymphoma lesions was in B cell lymphoma (Figure 1,2). Regression analysis revealed extra-ocular muscles (EOM) and globe involvement of OAL correlated to ADC minimum and ADC maximum to type of lymphoma (REAL classification). EOM and globe involvement were not significant confounders in (OAL) and there was no correlation when the analysis was performed in each group separately (Table 3).

The OAL had median ADC of 0.51 (25% quartile 0.48) irrespective of patient age, sex, or histological subtypes (P <0.02). Analysis of percentile values showed the spread distribution of ADC minimum and maximum values, with a remarkable tendency of both ADC minimum and ADC maximum to be higher in indolent OL compared to the aggressive subtype. By generating and comparing the ROC curve, the ADC mean, ADC median, ADC10, ADC 25, ADC 75, and ADC90 did not reveal significant difference in the skewness between the two groups. Just few aggressive OAL cases resulted in skew deviation of results (Table 4).

Receiver operating characteristic curves were derived to determine the optimal ADC threshold for discrimination between indolent and aggressive (OAL), and the sensitivity, specificity, positive and negative predictive values were calculated. The area under curve (AUC) of ADC minimum and ADC maximum is given in (Figure 3,4). The AUC for ADC minimum was 94.4% and ADC maximum was 81.6%. With 85% specificity and 95% sensitivity, ADC minimum showed to be a reasonable predictor of histological (OAL) subtype (indolent vs aggressive). In contrast, ADC maximum had 80% sensitivity and 85% specificity and has less reliable predictability for histological subtype (OAL).

Table 1: Profile of OAL cases according to histological subtype

		Indolent		**Aggressive**		**Validity**
		Number	**%**	**Number**	**%**	
Gender	Male	19	86.4	4	44.4	OR = 7.1 P=0.02
	Female	4	18.2	5	55.6	
Age	Mean± SDV	54.2±22		51.2±12		*P=0.7*
Duration of symptoms	Median	8.5		3.0		*P = 0.016*
	IQ	4.0;12.0		2.0; 6.0		
Orbit involved	Right	15	65.2	3	33.3	OR = 5
	Left	3	13.0	6	66.7	
	Bilateral	5	21.7	0	0.0	
Systemic affection	Yes	4	18.2	3	33.3	P=0.06
	No	19	86.4	6	66.7	
Lymph node	Yes	5	22.7	3	33.3	OR = 0.4
	No	18	81.3	5	55.6	
Extraocular muscle involvement	Yes	8	36.4	3	33.3	P=0.4
	No	15	68.2	6	66.7	
Globe involvement	Yes	8	36.4	3	33.3	OR = 0.8
	No	15	68.2	6	66.7	

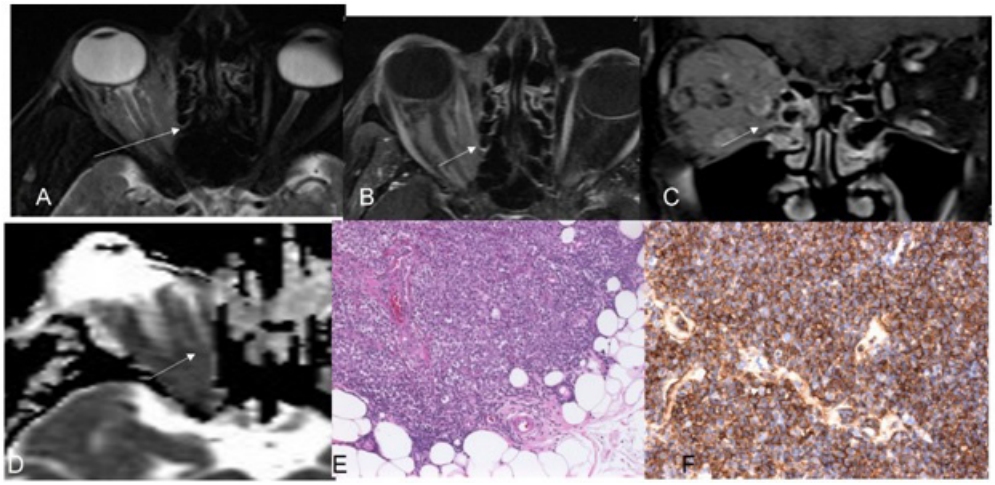

Figure 1(A-F): MR images in a 53-year-old female patient with Marginal Zone B-cell Lymphoma(indolent), A tumor mass in the right orbit (arrows): (A)It is isointense on T2-weighted image , difficult to be distinguished from the surrounding muscles tissue, it is Mild enhanced on post-contrast image (B); ill defined margins infiltrating the retro-orbital fat and extra-ocular muscles, encasing the optic nerve, displacing the globe anteriorly, yet no ocular infiltration. it is hypointense on ADC map with mean ADC value of $=0.75\times10^{-3}mm^2/s$ (D). Histopathological appearance using Hematoxylin & eosin stain of the tumor, which is composed of diffuse sheets of mature lymphocytes, and some plasma cells. The tumor infiltrates the orbital fibro-adipose tissue (E). The atypical lymphocytic infiltrate is predominantly of B-cell type expressing strong reactivity to CD20 (E,F)

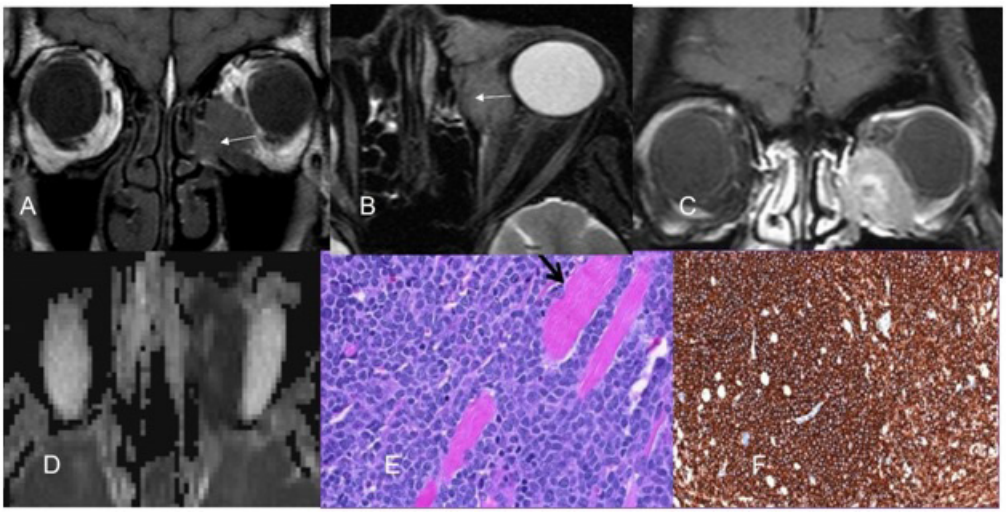

Figure 2(A-F): MR images in a 26-year-old Male patient with Diffuse large B- cell Lymphoma (aggressive) , A tumor mass in the left orbit (arrow): (A,B)It is isointense on T1 and T2-weighted image , it is Mild enhanced on post-contrast image (C); occupying left nasolacrimal sac ,possible partial infiltrating the tendinous insertion of the medial rectus ,displace the globe laterally without invasion. it is hypointense on ADC map with mean ADC value of $=0.64\times10^{-3}mm^2/s$ (D). Histopathological appearance using Hematoxylin & eosin stain of the tumor, which is composed of diffuse sheets of large atypical lymphocytes with frequent mitotic figures. The cells show high degree of pleomorphism and infiltrate the adjacent muscle fibres (black arrow). Almost all the lymphocytes show positive staining for CD20 (E & F

Table 2: Comparison of different ADC parameters of indolent to aggressive (OAL)

	ADC Minimum value (×10−3 mm/s2)		ADC Maximum value (×10−3 mm/s2)	
	Indolent (N = 23)	Aggressive (N = 9)	Indolent (N = 23)	Aggressive (N = 9)
Minimum	0.48	0.42	0.46	0.48
Maximum	0.96	0.64	0.94	0.66
5 percentile	0.48	0.42	0.46	0.48
10 percentile	0.53	0.42	0.46	0.48
25 percentile	0.59	0.44	0.63	0.49
50 percentile	0.64	0.45	0.74	0.52
75 percentile	0.74	0.48	0.83	0.57
90 percentile	0.82	-	0.92	-
95 percentile	0.94	-	0.94	-
Skewness ±SDV	1.03 ±0.48	2.32±0.72	-0.32± 0.48	1.29 ±0.72
Kurtosis ±SDV	2.05± 0.93	6.06± 1.4	-0.85±0.93	1.73± 1.4

Table 3: Regression analysis to evaluate the interaction of extraocular muscle and globe involvement to the correlation of ADC minimum and ADC maximum to type of lymphoma (WHO classification).

Coefficients[a]						
Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	.896	.076		11.769	.000
	European classification	-.178	.055	-.533	-3.237	.003
	EOM involvement	-.022	.056	-.068	-.400	.693
	globe INVOLVEMENT	.004	.033	.021	.124	.902
a. Dependent Variable: maximum adc						

Table 4: Characteristics of indolent and aggressive (OAL) according to ADC minimum and maximum value

	Indolent lymphoma (N = 23)		**Aggressive lymphoma (N =9)**	
	ADC Minimum	ADC Maximum	ADC Minimum	ADC Maximum
Minimum value	0.48	0.461	0.416	0.48
Maximum	0.96	0.94	0.64	0.66
Mean (SDV)	0.66 ± 0.11	0.71 ± 0.15	0.47 ± 0.07	0.54 ± 0.06
Skewness (SE)	1.03 (0.48)	-0.32 (0.48)	2.32 (0.72)	1.29 (0.72)
Kurtosis (SE)	2.05 (0.94)	-0.85 (0.94)	6.06 (1.4)	1.73 (1.4)

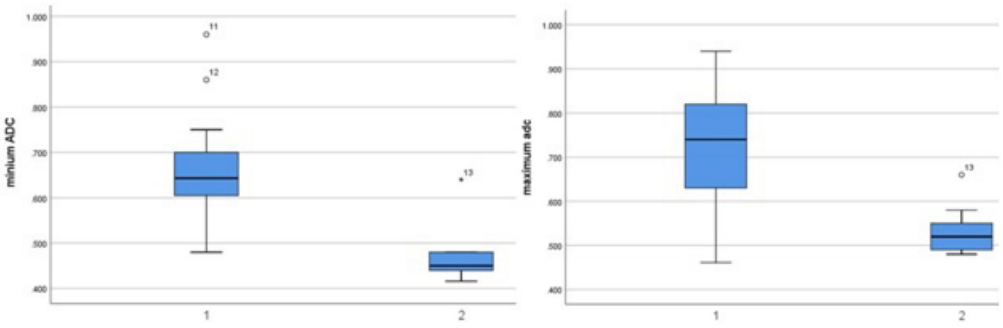

Figure 3: ROC of indolent and aggressive lymphoma.

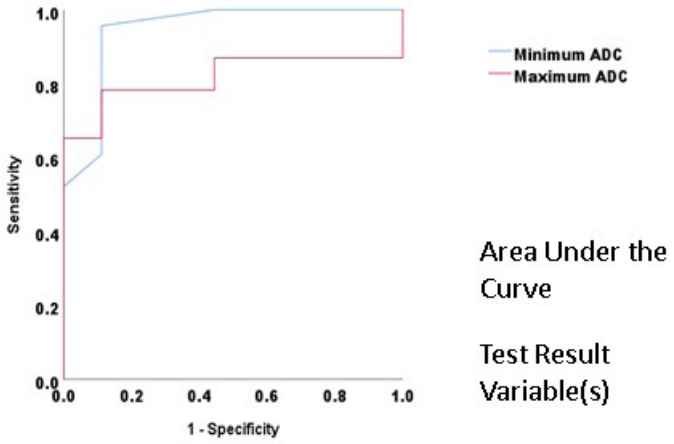

Figure 4: Test Results variability of Minimum and Maximum ADC

5. Discussion

In this study, we demonstrated that ADC values are valuable in predicting indolent versus aggressive subtypes of (OAL) and ADC minimum values are more reliable than ADC maximum in this exercise. We used in the present study an international acceptable histological classification, with the ratio of two subtypes of (OAL) in our cohort composed mainly of indolent OAL and all cases limited to the orbit, matching with others [1, 16-18]. DWI is a quickly non-invasive technique and does not require a contrast agent. Our study is suggesting whether DWI can be useful to differentiate indolent and aggressive (OAL) subtypes. Previous studies compared DWI in systemic lymphoma, showing ADC values can be useful to determine lesion aggressiveness, distinguishing inflammatory, benign, and malignant masses [19-21]. We explored possible correlation between the ADC value and (OAL) cellularity and it was possible to distinguish indolent from aggressive (OAL)

using ADC values, with significantly higher cellularity in almost all indolent subtype than that of aggressive (OAL). Malignant lymphomas are histologically composed by large cells, leading to effacement of the follicular architecture, with a relatively lower cellular density, angulated nucleus, increased nuclear atypia, mitotic figures, abundant macromolecular proteins, less extracellular space as well as increased extracellular vascularity, characteristics which can restrict diffusion space for water molecules in the extra and intra cellular compartments, resulting in reduced ADC values [6,10,11,20,21].However, highly malignant (OAL) can have high cellularity, leading to relative reduction in extracellular and intracellular diffusion spaces [14,22]. Systemic lymphomas have been shown significantly lower ADC values [22] but it is contradicted since ADC measurements can not discriminate DLBCL from follicular lymphoma [16,19,23] probably because there is no correlation between tumor ADC value and tissue cellularity in those cases [18, 20,21,24]. Discrepancies can happen because benign or malign orbital lesions can be hypercellular [9, 17, 18, 22] and ADC value is not solely a function of tumor cellularity, with other histological features such as cell size, nuclear atypia, macromolecules in cytoplasm, cellular organization, and extracellular matrix also influencing tissue diffusivity [8,16,22]. Another reason for discrepancies of ADC values can be the cell arranges in follicles related to physiological or structural components of different tissues, and differences between tumor areas in the same patient [17,19].

Significantly lower mean ADC observed in (OAL) subtypes than inflammatory orbital lesions can occur because the (OAL) have higher cellularity with uniformly small-sized atypical lymphocyte infiltrations and inflammatory lesions present with interstitial edematous changes, increasing ADC values [9,12,17,22]. Beyond DWI measurements can determine lesion aggressiveness, it is useful to monitor response to therapy, most likely because effective anticancer therapy changes tumor's microenvironment, resulting in increased diffusion of water molecules and ADC value [23-27]. Our ADC percentiles demonstrated that ADC minimum had a better discriminative power than ADC maximum to differentiate OAL. Histogram parameters of ADC map based on pixels' distribution can provide quantitative information about tumor heterogeneity, being significantly different in benign and malignant orbital tumor [16,17]. Low percentiles of ADC can be more effective in differentiate two lesions with distinct compactness or densely packed solid components within tumor tissues and high percentile of ADC value may be easily vulnerable to the cystic or necrotic components [6,17,18]. The better performance of ADC minimum in our study was reinforced by higher sensitivity/specificity than ADC maximum to predict indolent (OAL).

During the image acquisitions for exam, regions of interest (ROIs) in the tumor tissues were manually drawn and distortion artifacts were carefully excluded from the ROI delimitation, avoiding cystic/necrotic areas which can falsely identify heterogeneity of tumor tissues, elevating ADC value [14]. However, ROI measurement can present error from the non lesion signal in the scanning section due to the proximity of the orbital lesions to the other orbital structures as the eyeball [6,11]. (OAL) subtypes showed positive skewness. Skewness reflects the asymmetry of the histogram distribution. Pathologically, (OAL) consists of monomorphous sheets of lymphocyte, which would appear as a steep peak in histogram [3]. Positive skewness indicates most voxel values accumulating toward the lower end of the histogram [6,12]. The exclusion of the necrotic and cystic areas which have relatively higher ADC values from ROI, resulted in positive and similar skewness in both (OAL) subtypes.

In addition, we found significantly greater kurtosis in (OAL). Kurtosis reflects the degree of homogeneity of the tumors [12,14,16]. Even though malignant orbital tumors can have a significantly higher kurtosis than benign tumors [3,16], there was no significant difference in skewness and kurtosis between our two (OAL) subtypes probably because the homogeneity of OAL and the usual lack of extensive necrosis in lymphoma. Limitations for our study were the retrospective nature of the study, biopsy sites are usually selected by easy access and clinical feasibility and cellularity evaluation might not be the same one for ADC value measurement. Secondly, the relatively small sample size mainly in the aggressive (OAL), which may contribute to the inconspicuous difference in the differential utility of ADC histogram analysis. Combining histogram parameters derived from DWI for a larger group sample would be worth to better validate our results. Thirdly, the mean ADC value of the target tumors based on 2-dimensional ROI placed on a representative localized area of the tumor instead of covering the whole tumor, to overcome this limitation, future study would be rational to use whole-tumor volume of interest rather than localized ROIs for analysis to allow comprehensive measurement, avoiding sample bias and providing quantitative information about tumor heterogeneity despite of the homogeneity observed in the lymphomatous tumors. This method was not used to differentiate (OAL) in the current study, further volumetric ADC histogram analysis can be helpful to assess of tumor grade and

The current study did not stablish ADC threshold that can predict either indolent or aggressive (OAL) with high confidence. Future study using larger sample data can provide stronger evidence regarding relationship between ADC value with histological indices, including cellularity, tumor cell type, and pathological grade to differentiate (OAL) subtypes of lymphoma using DWI approach with independent verification of the processes that affect water diffusion (e.g. higher b values). The additional information provided by MRI-DWI may therefore improve staging, evaluation of lesion extent, to select the optimal site of biopsy identified by the area of marked low ADC value, where the lymphomatous site contains the highest malignancy grade cells, improving diagnostic accuracy, reducing the number of biopsies and patient mortality. Fur-

ther larger studies for the validation of the DWI-MRI to correlate the ADC value with the histological index, including degree of cellularity, tumor cell type, and pathological grade are needed. In conclusion, the present study revealed ADC percentiles are higher in indolent than in aggressive (OAL). ADC minimum has higher sensitivity and specificity than ADC maximum in (OAL) lesions and more reliable than ADC maximum

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