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RETROSPECTIVE COHORT STUDY

Magnetic Resonance Imaging with Apparent Diffusion Coefficient (ADC) Mapping: A Diagnostic Tool for Differentiating Orbital Lymphomas from other Lesions

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Abstract

Purpose: To evaluate the utility of absolute and relative apparent diffusion coefficient (ADC and ADCr) in differentiating orbital lymphoma from other orbital lesions.

Design: Retrospective observational study.

Participants: Thirty-Three Patients (33) presenting with orbital masses.

Methods: Magnetic Resonance Imaging (MRI) studies were analyzed, with calculation of absolute ADC and ADCr values. Brainstem ADC measured on the same axial plane was used as the reference for ADCr calculation. ADC and ADCr values were compared between lymphoma and non-lymphoma groups using the Mann–Whitney U test.

Main Outcome Measures: Absolute ADC and ADCr values and their diagnostic performance.

Results: Lymphomas demonstrated significantly lower ADC and ADCr values compared to non-lymphoma lesions. Median absolute ADC was 0.65×10^{-3} mm²/s (Interquartile Range [IQR]: 0.59 - 0.70) in the lymphoma group and 1.32×10^{-3} mm²/s (IQR: 1.11 - 1.57) in the non-lymphoma group. Median ADCr values were 0.86 (IQR: 0.81 - 0.92) and 1.63 (IQR: 1.35 - 1.92), respectively ($p < 0.001$ for both comparisons). Using a cutoff value of 1.0, absolute ADC showed higher sensitivity, whereas ADCr demonstrated higher specificity, positive predictive value, and overall accuracy.

Conclusions: Absolute and relative ADC values are useful, non-invasive imaging parameters for differentiating orbital lymphoma from other orbital lesions. Relative ADC, using the brainstem as a reference tissue, may represent a valuable complementary approach by reducing interindividual variability and improving lesion discrimination.

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Introduction

The orbit is a complex anatomical space containing the globe and its adnexal structures, with close anatomical relationships to the skull base. The evaluation of orbital masses remains challenging because of the broad spectrum of possible etiologies, including inflammatory, benign, malignant, and metastatic lesions [1,2].

Magnetic Resonance Imaging (MRI) plays a central role in the assessment of orbital lesions because of its superior soft tissue characterization and absence of ionizing radiation. However, conventional MRI sequences may be insufficient for reliable lesion differentiation, leading to increasing interest in advanced imaging techniques such as Diffusion-Weighted Imaging (DWI) [1,3].

DWI evaluates the mobility of water molecules within tissues and indirectly reflects tissue cellularity and microstructural organization. Highly cellular lesions, such as lymphomas, typically demonstrate restricted diffusion with lower Apparent Diffusion Coefficient (ADC) values, whereas lesions with lower cellular density, cystic changes, or necrotic components tend to exhibit higher ADC values due to facilitated diffusion [2,4,5].

Despite its potential diagnostic utility, the clinical application of ADC remains limited by interindividual variability and differences related to MRI equipment and acquisition parameters. In this context, relative ADC (ADCr), calculated as the ratio between lesion ADC and a reference tissue ADC, has been proposed as a strategy to reduce measurement variability and improve reproducibility. However, there is still no consensus regarding the optimal reference tissue, and studies evaluating the use of ADCr in orbital lesions, particularly using the brainstem as a reference structure on the same axial plane, remain limited [6-8].

Therefore, the aim of this study was to evaluate the utility of absolute and relative ADC values in differentiating orbital lymphoma from other orbital lesions and to assess the potential applicability of the brainstem as a reference tissue for ADCr calculation.

Methods

Study design

This retrospective observational study was conducted at a tertiary cancer center. The study was approved by the institutional review board, and the requirement for informed consent was waived.

Participants

Patients with orbital masses who underwent MRI at our institution were retrospectively reviewed. Inclusion criteria were: age ≥ 18 years and availability of diffusion-weighted imaging. A total of 33 patients were included in the analysis.

MRI protocol

All patients underwent MRI examinations including diffusion-weighted imaging sequences. ADC maps were automatically generated by the MRI system software.

Image analysis

Images were analyzed by a single experienced head and neck radiologist. Regions of interest (ROIs) were manually placed within the solid portions of the lesions to obtain ADC measurements, avoiding cystic, necrotic, hemorrhagic, or markedly heterogeneous areas whenever identifiable on MRI. ROI size was adapted according to lesion dimensions, with an effort to include the largest representative solid component while maintaining consistent placement criteria across cases.

For relative ADC (ADCr) calculation, an additional ROI was placed within the brainstem parenchyma on the same axial plane, avoiding adjacent cerebrospinal fluid spaces and visible artifacts whenever possible. ADCr was defined as the ratio between lesion ADC and brainstem

ADC.

Figure 1 illustrates ROI placement in both the orbital lesion and the brainstem on the ADC map of a representative lymphoma case. The obtained measurements were used for calculation of absolute ADC and ADCr values.

Statistical analysis

Statistical analysis was performed to compare absolute and relative apparent diffusion coefficient (ADC and ADCr) values between lymphoma and non-lymphoma groups. Continuous variables were expressed as median and Interquartile Range (IQR), given the non-parametric distribution of the data.

Group comparisons were performed using the two-tailed Mann–Whitney U test, with a significance level set at 5% ($p < 0.05$).

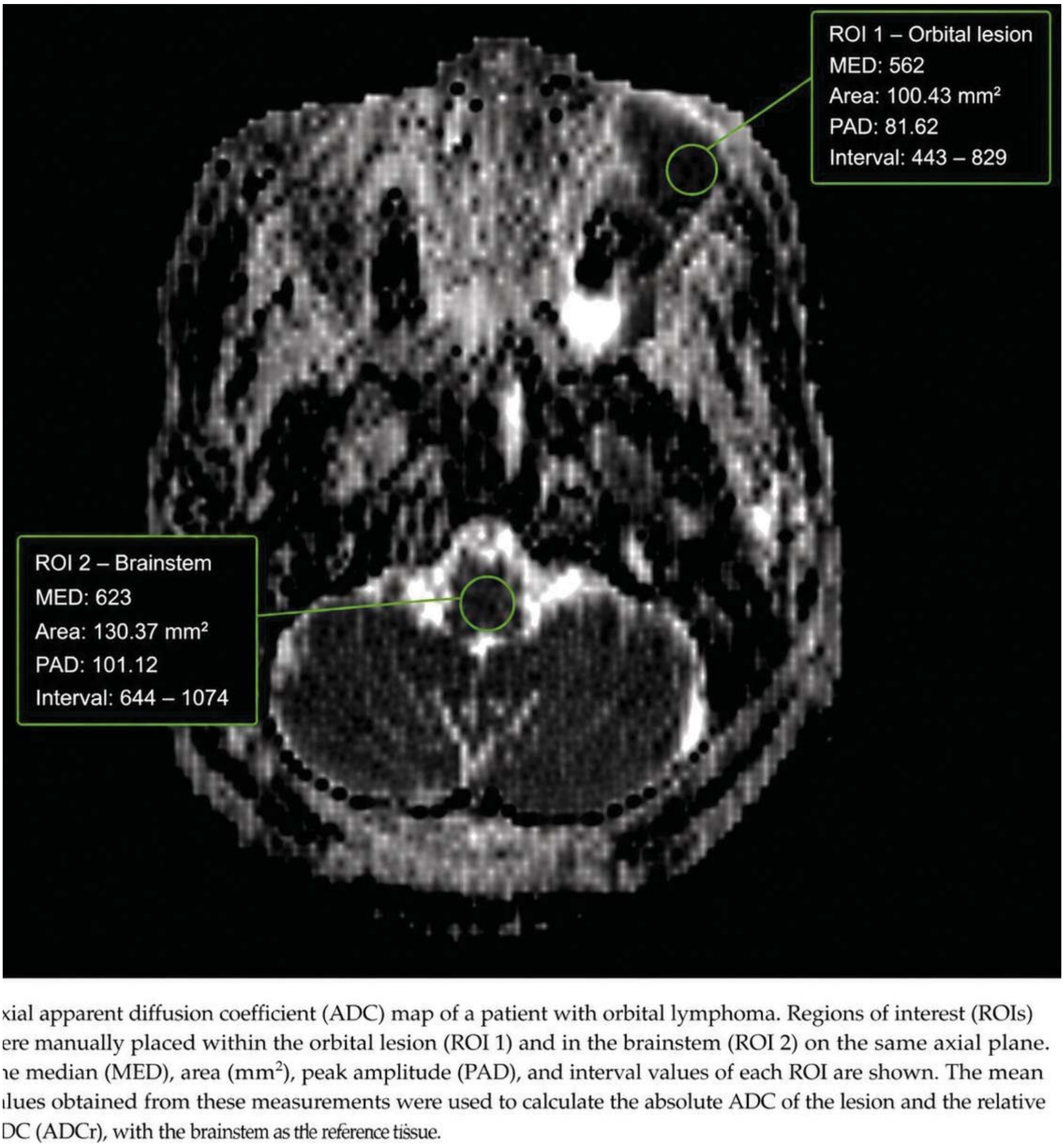

Figure 1 Region-of-interest placement for ADC measurement in orbital lymphoma.

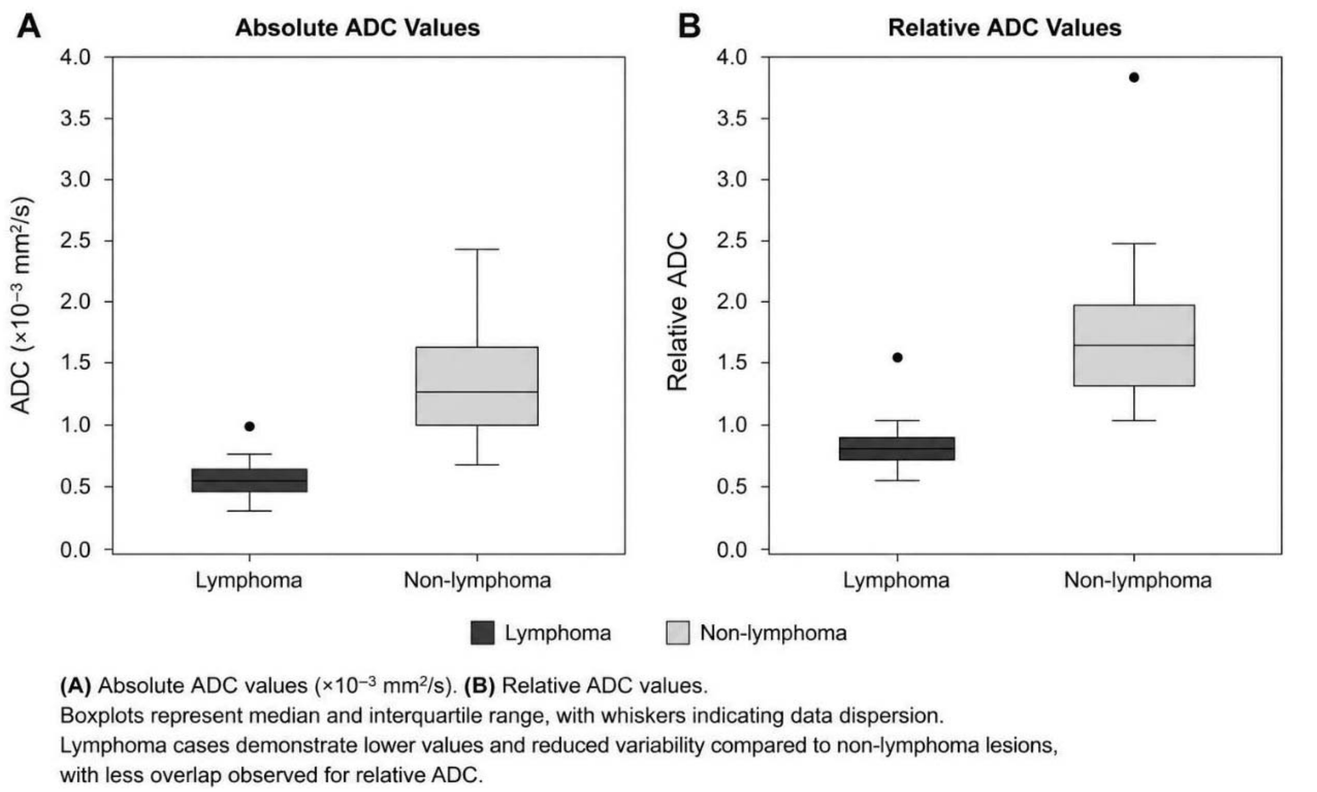

Figure 2 Distribution of absolute and relative ADC values in lymphoma and non-lymphoma lesions.

For exploratory assessment of diagnostic performance, a cutoff value of 1.0 was applied for both absolute ADC ($\times 10^{-3}$ mm^2/s) and ADCr, aiming to standardize the analysis. In the case of ADCr, this value corresponds to a physiological threshold at which lesion diffusion equals that of the reference tissue, with values below 1 indicating greater diffusion restriction relative to the reference tissue and, consequently, higher cellularity. For absolute ADC, the use of the same cutoff was purely exploratory, intended to allow direct comparison between parameters.

Based on this threshold, diagnostic performance measures, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, were calculated.

Results

A total of 33 patients with orbital masses were analyzed, including 17 patients (51%) with orbital lymphoma and 16 (49%) with non-lymphoma lesions.

Lymphomas demonstrated significantly lower absolute apparent diffusion coefficient (ADC) and relative ADC (ADCr) values compared to non-lymphoma lesions. The median absolute ADC was 0.65×10^{-3} mm^2/s (interquartile range [IQR]: 0.59 - 0.70) in the lymphoma group and 1.32×10^{-3} mm^2/s (IQR: 1.11 - 1.57) in the non-lymphoma group. For ADCr, median values were 0.86 (IQR: 0.81–0.92) in the lymphoma group and 1.63 (IQR: 1.35–1.92) in the non-lymphoma group.

Comparison between groups using the two-tailed Mann–Whitney U test demonstrated statistically significant differences for both absolute ADC ($U = 3.0$; $p < 0.001$) and ADCr ($U = 7.0$; $p < 0.001$).

Boxplot analysis (Figure 2) showed lower median values and reduced variability in the lymphoma group for both parameters, whereas non-lymphoma lesions exhibited higher values, greater dispersion, and the presence of outliers. This wider distribution in the non-lymphoma group likely reflects the heterogeneous composition of these lesions. Notably, ADCr showed less overlap between groups compared to absolute ADC, suggesting improved discriminatory performance.

In the exploratory analysis of diagnostic performance using a standardized cutoff value of 1.0 for both parameters, absolute ADC demonstrated higher sensitivity, whereas ADCr showed higher specificity, positive predictive value, and overall accuracy. These findings suggest that ADCr may provide more consistent differentiation between lymphoma and non-lymphoma lesions. Detailed diagnostic performance metrics are summarized in table 1.

Discussion

In this study, both absolute Apparent Diffusion Coefficient (ADC) and relative ADC (ADCr) demonstrated good discriminatory performance in differentiating orbital lymphoma from non-lymphoma lesions. Lymphomas consistently showed lower ADC and ADCr values, as well as a more homogeneous distribution, compared to the broader and more variable range observed in non-lymphoma lesions.

These findings are consistent with the known biological behavior of lymphomas, which are characterized by high cellularity and reduced extracellular space, leading to restricted diffusion and lower ADC values. In contrast, non-lymphoma lesions, including inflammatory and non-lymphomatous neoplastic processes with lower cellular density or necrotic components, tend to present higher ADC values due to facilitated diffusion [1,5].

An important observation was the reduced variability of ADC and ADCr values among lymphoma cases. This more homogeneous pattern may reflect more uniform histological characteristics of lymphomas compared to the heterogeneous nature of non-lymphoma lesions, which encompass a wide spectrum of pathological entities with distinct imaging features [1,6,7].

The use of a standardized cutoff value of 1.0 for both ADC and ADCr provided a simple and practical approach for differentiating between groups. Although this threshold was selected primarily for standardization and exploratory purposes, it demonstrated a relatively clear separation between lymphoma and non-lymphoma lesions in most cases. Previous studies have proposed similar threshold values for ADC in orbital lesions. Sepahdari, et al. [4] suggested a cutoff around 1.0×10^{-3} mm²/s for differentiating malignant from benign lesions, while ElKhamary, et al. [5] reported a lower threshold of approximately 0.8×10^{-3} mm²/s. Additionally, Mundhada, et al. [2] proposed a classification system using a cutoff of 1.04×10^{-3} mm²/s, with intermediate values between 1.04 and 1.22×10^{-3} mm²/s. Similarly, Koontz and Wiggins reported that lesions with normalized ADC ratios below 1 were typically malignant in head and neck imaging studies using the medulla as an internal control.[8] Taken together, these findings support the concept that ADC thresholds fall within a relatively consistent range, reinforcing the potential clinical applicability of the cutoff value adopted in the present study.

Variability in reported ADC values and discriminatory thresholds across different

Table 1. Diagnostic performance of absolute ADC and relative ADC (ADCr) in differentiating orbital lymphoma from non-lymphoma lesions using a cutoff value of 1.0

Parameter	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Absolute ADC	94.1	81.3	84.2	92.9	87.9
Relative ADC (ADCr)	88.2	100.0	100.0	88.9	93.9

Abbreviations:
PPV = positive predictive value; NPV = negative predictive value.

studies and imaging protocols remains a recognized limitation in diffusion-weighted imaging, potentially affecting the reproducibility and routine clinical applicability of ADC measurements [8].

The use of relative ADC may represent an important advantage in clinical practice, as it accounts for variations related to scanner parameters and patient-specific factors [7,9,10]. In this study, the brainstem was used as the reference tissue due to its relative structural homogeneity, central location, and feasibility for reproducible ROI placement on the same axial plane as the orbital lesion. Norris, et al. [7] suggested the use of an internal reference structure, such as the brainstem, to normalize ADC measurements and potentially reduce inter-scanner variability; however, robust validation data regarding its reproducibility and diagnostic reliability remain limited. Similarly, Koontz and Wiggins proposed the medulla as an internal control to minimize variability related to scanner models, magnetic field strength, and diffusion acquisition parameters, reinforcing the potential utility of normalized ADC ratios in head and neck imaging.[8] However, there is still no consensus regarding the optimal reference tissue for ADCr calculation, particularly in orbital lesions.

Despite these findings, some limitations should be considered. The relatively small sample size and retrospective design limit the statistical robustness and generalizability of the results. In addition, the non-lymphoma group was heterogeneous, encompassing inflammatory, benign, and malignant lesions with distinct histopathological characteristics and imaging patterns, which likely contributed to the broader distribution and partial overlap of ADC values observed between groups.

The proposed cutoff should be interpreted as exploratory rather than as a definitive threshold for clinical application. Moreover, no Receiver Operating Characteristic (ROC) curve analysis was performed, limiting a more comprehensive evaluation of diagnostic performance. ADC measurements were performed by a single experienced radiologist, and interobserver variability was therefore not assessed. Future prospective studies with larger and more homogeneous cohorts are needed to validate these findings.

In conclusion, diffusion-weighted magnetic resonance imaging, through the analysis of ADC values, may be useful in differentiating orbital lymphoma from other orbital lesions. Lymphomas demonstrated lower absolute and relative ADC values, reflecting their high cellularity and restricted diffusion. Relative ADC, using the brainstem as a reference tissue, showed potential to improve lesion discrimination by reducing interindividual variability. However, partial overlap between groups limits the use of a single cutoff as a definitive diagnostic threshold, highlighting the need for integrated clinical and imaging assessment. Overall, ADC, particularly in its relative form, may represent a valuable complementary tool for improving diagnostic assessment in orbital masses.

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Conflict of interest

The authors declare no conflicts of interest.

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