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FULL PAPER

ADC histogram analysis of muscle lymphoma—correlation with histopathology in a rare entity

¹HANS-JONAS MEYER, MD, ²NIKOLAOS PAZAITIS, MD and ¹ALEXEY SUROV, MD

¹Department of Diagnostic and Interventional Radiology, University of Leipzig, Leipzig, Germany

²Department of Pathology, Martin-Luther-University Halle-Wittenberg, Halle, Germany

Address correspondence to: Dr Hans-Jonas Meyer
E-mail: Hans-Jonas.Meyer@medizin.uni-leipzig.de

Objective: Diffusion-weighted imaging is able to reflect histopathology architecture. A novel imaging approach, namely histogram analysis, is used to further characterize lesion on MRI. To correlate histogram parameters derived from apparent diffusion coefficient (ADC) maps with histopathology parameters in muscle lymphoma.

Methods: Eight patients (mean age 64.8 years, range 45–72 years) with histopathologically confirmed muscle lymphoma were retrospectively identified. Cell count, total nucleic and average nucleic areas were estimated using ImageJ. Additionally, Ki67-index was calculated. Diffusion-weighted imaging was obtained on a 1.5 T scanner by using the b-values of 0 and 1000 s mm⁻². Histogram analysis was

performed as a whole lesion measurement by using a custom-made Matlab-based application.

Results: All ADC parameters showed a good to excellent interreader variability. Cell count correlated well with ADCmean ($\rho = -0.76$, $p = 0.03$) and ADCp75 ($\rho = -0.79$, $p = 0.02$). Kurtosis and entropy correlated with average nucleic area ($\rho = -0.81$, $p = 0.02$, $\rho = 0.88$, $p = 0.007$, respectively). None of the analyzed ADC parameters correlated with total nucleic area and with Ki67-index.

Conclusion: ADC histogram analysis parameters can reflect cellularity in muscle lymphoma.

Advances in knowledge: Histogram parameters derived from ADC maps can reflect several different cellularity parameters in muscle lymphoma.

INTRODUCTION

Muscle lymphoma (ML) is a rare entity and accounts only for 0.1–1% of all extranodal lymphomas.¹ Histopathologically, most frequently, B-Non-Hodgkin lymphoma (NHL) occurs with diffuse large B-cell lymphoma as the most prevalent subtype.^{1,2} However, other subtypes such as natural killer lymphoma, T cell lymphoma, plasmacytoma as well as Hodgkin lymphoma have been described in the literature.¹

Due to its rare incidence, only few studies investigated imaging features of ML.^{3–5} Diffuse muscle enlargement is the predominant appearance of ML on imaging.^{1,3} Furthermore, on T_1 weighted images ML has similar signal intensity like the adjacent muscle and on T_2 weighted images, they appear slightly hyperintense.^{1,6}

Diffusion-weighted imaging (DWI) is an imaging technique to measure random water movement in tissues, which can be quantified with the apparent diffusion coefficient (ADC).^{5,7} It is postulated that the ADC value is directly associated with the cellularity of tissues because due to densely packed cells the free diffusion of the water molecules is hindered.⁷ Recently, an emergent analysis, namely

histogram analysis, was proposed to further characterize tumors.⁸ Every voxel of a region of interest (ROI) is issued to a histogram and, therefore, statistical analysis of the ROI is made possible. The provided parameters are percentiles, median, mode, as well as kurtosis, skewness and entropy. Presumably, the histogram analysis parameters are more sensitive than mean ADC values. For example, entropy, a parameter describing the heterogeneity of ADC values within an ROI, might also reflect the heterogeneity of the underlying histopathology architecture of tumors as it was shown for other tumors in some preliminary studies.^{8–10}

Correlation analysis between histopathology parameters and imaging features has lately been performed in different tumors.^{7–10} However, there was a distinct discrepancy between several tumors.⁷ For example, a good inverse correlation between cellularity and ADC values in glioma was found with a correlation coefficient of $r = -0.66$.⁷ Yet, only few studies investigated possible associations between cellularity and ADC values in lymphomas with inconclusive results.^{11–13} For example, in cerebral lymphomas an inverse correlation was found with a coefficient of $r = -0.52$,¹² whereas in another study no significant association was

identified.¹³ Furthermore, other authors did not find significant associations between cell count and ADC values in several B-NHL.¹¹

The aim of this study was to analyze possible associations between ADC histogram analysis parameters and histopathology features in MLs.

METHODS AND MATERIALS

This retrospective study was approved by the local ethics committee and informed consent was waived. The radiological database of one university hospital was screened for ML. Inclusion criteria were MRI of the lesion including a DWI, as well as available histopathology specimens. Cases with invasion from adjacent bones or lymph nodes into the muscle were excluded from the study.

In total, eight patients were identified and included in this present study. The study sample consists of five females (62.5%) and three males with a mean age of 64.8 years (range 45–72 years). The histopathological diagnoses were diffuse large B cell lymphoma ($n = 3$, 37.5%), marginal cell lymphoma ($n = 2$, 25%), and T cell NHL, morbus Hodgkin and lymphocytic type lymphoma ($n = 1$, 12.5%, respectively)

MRI

In all cases, the identified tumors were investigated by MRI using a 1.5 T device (Magnetom Vision Sonata Upgrade, Siemens,

Erlangen, Germany). DW images were obtained with a multishot SE-EPI sequence (repetition time/echo time: 4700/61 ms; acquisition matrix: 128×83 ; flip angle 90° , b -values: 0 and 1000 s mm^{-1}).

All images were available in digital form and were analyzed by an experienced radiologist (AS) without knowledge of the histopathological diagnosis on a PACS workstation (Centricity PACS, GE Medical Systems, Milwaukee, WI). Figure 1 shows a representative case of the patient sample.

Histogram analysis

DWI data were processed with a custom-made Matlab-based application (The Mathworks, Natick, MA) on a standard windows operated system. On the ADC maps, a volume of interest was drawn at the tumor's boundary using all slices displaying the tumor (whole lesion measure). All measures were performed by two authors independently (AS and HJM). After this, the following parameters were estimated and given in a spreadsheet format: mean (ADCmean), maximum (ADCmax), minimum (ADCmin), median (ADCmedian), modus (ADCmodus), and the following percentiles: 10th (ADCp10), 25th (ADCp25), 75th (ADCp75), and 90th (ADCp90). Furthermore, histogram-based parameters kurtosis, skewness, and entropy were calculated. This approach was done previously in other similar studies.^{9,10}

Histopathology

For all lesions, bioptic material was available and was reanalyzed for this study blinded to the MRI imaging. All histopathological

Figure 1. Imaging findings and histopathological features of an intramuscular diffuse large B cell lymphoma. (a) T_2 weighted image showing a large lesion in the biceps brachii muscle (arrow). (b) Corresponding ADC map with drawn ROI inside the margins of the tumor. (c) The calculated ADC parameters are as follows (every parameter $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$): ADCmean = 0.96, ADCmin = 0.72, ADCmax = 1.41, p10 = 0.86, p25 = 0.89, p75 = 1.01, p90 = 1.09, ADC median = 0.95, ADC mode = 0.89. Histogram-based parameters are: kurtosis = 4.81, skewness = 0.80, entropy = 3.58. (d) The corresponding Ki67-stained specimen revealed a Ki 67 index of 98%. (e) The calculated cellularity was 3317 on hematoxylin-eosin specimen. ADC, apparent diffusion coefficient; ROI, region of interest.

Table 1. Summary of the calculated histopathology and ADC histogram parameters

Parameter	Mean $\pm$ SD, range
Cell count	3097 $\pm$ 1696, 599–6334
Total area, μm^2	1531600 $\pm$ 955017, 524250–3258300
Average area, μm^2	585 $\pm$ 372, 203–1339
Ki 67 index, %	73 $\pm$ 42, 10–99
ADCmean, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.93 $\pm$ 0.10, 0.80–1.08
ADCmin, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.47 $\pm$ 0.16, 0.29–0.72
ADCmax, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	1.75 $\pm$ 0.40, 1.35–2.4
p10, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.72 $\pm$ 0.10, 0.61–0.87
p25, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.78 $\pm$ 0.09, 0.68–0.92
p75, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	1.05 $\pm$ 0.15, 0.84–1.34
p90, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	1.25 $\pm$ 0.31, 1.01–1.84
Median ADC, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.88 $\pm$ 0.08, 0.75–1.00
Mode ADC, $\times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$	0.83 $\pm$ 0.12, 0.69–1.01
Kurtosis	4.44 $\pm$ 2.59, 2.91–10.72
Skewness	0.86 $\pm$ 0.76, -0.01–2.39
Entropy	3.52 $\pm$ 0.37, 2.68–3.90

ADC, apparent diffusion coefficient; SD, standard deviation.

sections were digitalized using a research microscope Jenalumar equipped with a Diagnostic instruments camera 4.2 (Zeiss, Jena, Germany). In every case, routine hematoxylin–eosin slides were used to calculate cellular density. Thereby, two high-power fields (0.16 mm^2 per field, $\times 400$) were analyzed. The area with the highest number of positive nuclei was selected. Additionally, cell count, as well total and average nucleic areas were calculated for each tumor using ImageJ package 1.48v (National Institute of Health, Bethesda, MD) as described previously.^{9,10,13} Additionally, for seven cases, the proliferation index was estimated on Ki-67 antigen stained specimens using MIB-1 monoclonal antibody (Dako Cytomation, Glostrup, Denmark). The highest count of stained cells was used to estimate the Ki67-index.

Statistical analysis

Statistical analysis and graphics creation was performed using GraphPad Prism (GraphPad Software, La Jolla, CA). Collected data were evaluated by means of descriptive statistics $\pm$ standard deviation (absolute and relative frequencies). Spearman's correlation coefficient (p) was used to analyze associations between histogram parameters and histopathological parameters. Intraclass coefficients (ICC) were used for interreader variability of the imaging parameters. In all instances, p values < 0.05 were taken to indicate statistical significance.

RESULTS

The estimated histopathology and ADC histogram parameters are summarized in Table 1.

All ADC parameters showed good to excellent ICC, ranging from ICC = 0.653 for ADCmean to ICC = 0.990 for kurtosis (Table 2).

Table 2. Interreader variability of the investigated ADC histogram parameters calculated with ICC

Parameter	ICC
ADCmean	0.653
ADCmin	0.932
ADCmax	0.978
P10	0.767
P25	0.948
P75	0.908
P90	0.974
Median	0.900
Mode	0.809
Kurtosis	0.990
Skewness	0.980
Entropy	0.724

ADC, apparent diffusion coefficient; ICC, intra class coefficients.

The correlation analysis revealed statistically significant correlation between cell count and ADCmean ($p = -0.76$, $p = 0.03$) as well with ADCp75 ($p = -0.79$, $p = 0.02$). Kurtosis and entropy correlated both with average nucleic area ($p = -0.81$, $p = 0.02$, $p = 0.88$, $p = 0.007$, respectively, Figure 2). No ADC parameter correlated with total nucleic area and with Ki67-index (Table 3).

DISCUSSION

This study shows that ADC histogram analysis is able to reflect cellularity parameters in MLs. To the best of our knowledge, this is the first study of its kind.

ML is a rare tumor entity comprising less than 1% of cases with lymphoma, with the majority of cases reported arising in

Figure 2. (a) The correlation coefficient between ADCmean and cell count is $p = -0.76$, $p = 0.03$. (b) The correlation coefficient between ADCp75 and cell count was calculated $p = -0.79$, $p = 0.02$. (c) Kurtosis is associated with average nucleic area $p = -0.81$, $p = 0.02$. (d) The correlation coefficient between entropy correlated and average nucleic area is $p = 0.88$, $p = 0.007$. ADC, apparent diffusion coefficient

Table 3. Correlation coefficients identified by Spearman analysis

Parameter	ADCmean	ADCmin	ADCmax	p10	p25	p75	p90	Median ADC	Mode ADC	Kurtosis	Skewness	Entropy
Cell count	$\rho = -0.76, p = 0.03$	$\rho = -0.10, p = 0.84$	$\rho = -0.14, p = 0.75$	$\rho = -0.50, p = 0.22$	$\rho = -0.50, p = 0.21$	$\rho = -0.79, p = 0.02$	$\rho = -0.69, p = 0.06$	$\rho = -0.48, p = 0.79$	$\rho = -0.11, p = 0.79$	$\rho = 0.67, p = 0.08$	$\rho = 0.31, p = 0.46$	$\rho = -0.07, p = 0.88$
Total area	$\rho = -0.57, p = 0.15$	$\rho = 0.02, p = 0.98$	$\rho = -0.24, p = 0.58$	$\rho = -0.14, p = 0.75$	$\rho = -0.03, p = 0.98$	$\rho = -0.38, p = 0.36$	$\rho = -0.26, p = 0.54$	$\rho = -0.05, p = 0.93$	$\rho = 0.31, p = 0.46$	$\rho = 0.02, p = 0.97$	$\rho = -0.36, p = 0.39$	$\rho = 0.62, p = 0.11$
Average area	$\rho = 0.12, p = 0.79$	$\rho = 0.20, p = 0.62$	$\rho = -0.07, p = 0.88$	$\rho = 0.16, p = 0.70$	$\rho = 0.29, p = 0.50$	$\rho = 0.33, p = 0.43$	$\rho = 0.38, p = 0.36$	$\rho = 0.26, p = 0.54$	$\rho = 0.29, p = 0.50$	$\rho = -0.81, p = 0.02$	$\rho = -0.50, p = 0.22$	$\rho = 0.88, p = 0.007$
Ki67	$\rho = 0.45, p = 0.30$	$\rho = 0.45, p = 0.30$	$\rho = -0.36, p = 0.44$	$\rho = 0.34, p = 0.44$	$\rho = 0.36, p = 0.44$	$\rho = -0.05, p = 0.91$	$\rho = -0.29, p = 0.56$	$\rho = 0.34, p = 0.44$	$\rho = 0.05, p = 0.91$	$\rho = 0.20, p = 0.66$	$\rho = -0.09, p = 0.84$	$\rho = -0.45, p = 0.30$

ADC, apparent diffusion coefficient.

The statistically significant correlations are highlighted in bold.

the lower extremity, particularly thigh and calf region.^{1,6} In the present study, several different lymphoma subtypes were investigated, with diffuse large B cell lymphoma, as the most prevalent type. Furthermore, we identified a high Ki67 expression and cellularity, which is also in good agreement.^{2,14}

Previously, only two studies analyzed ADC values of MLs.^{4,5} In a multicenter analysis, 14 lymphomas had a mean ADC value of $0.76 \pm 0.14 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, which was significantly lower than ADC values of muscle metastases and muscle sarcomas (mean ADC value of $1.28 \pm 0.24 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, and $1.82 \pm 0.63 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$, respectively).⁵ This finding might be caused by the high cellularity of lymphomas but no direct correlation analysis was performed in the former study to clarify this statement.^{4,5} In the present study, the mean ADCmean is slightly higher (mean $0.93 \pm 0.10 \times 10^{-3} \text{ mm}^2 \text{ s}^{-1}$) than in the previous study but, nevertheless, lower than of the other mentioned muscle tumors. Presumably, this finding might be explained by the fact that in the above-mentioned studies, the ADCmean was only calculated on one representative ROI, whereas in the present study a whole lesion measurement was performed.

Regarding associations between cellularity and ADC values in lymphoma, Barajas Jr et al¹² identified an inverse correlation between ADC values and cell count in cerebral lymphomas. However, Schob et al¹³ could not reproduce this finding. Furthermore, Wu et al¹¹ investigated diffuse large B cell lymphoma and follicular lymphoma and also did not find a correlation between ADC and cell count. In the present study, an inverse correlation could be obtained between ADCmean, ADCp75 and cell count. Presumably, these two ADC parameters can reflect histopathology architecture in ML the best.

Interestingly, kurtosis and entropy were very strongly associated with average nucleic area. A similar finding was not reported to date. Kurtosis reflects the peakedness of the histogram distribution and measures the shape of the probability distribution.⁸ It is difficult to ascertain why this parameter reflects the average nucleic area in lymphoma. However, previously, it has been shown that kurtosis of ADC values was associated with chemotherapy response in ovarian cancer¹⁵ and was able to predict nodal status in thyroid cancer.⁹ Therefore, this parameter might be strongly associated with histopathology. Regarding entropy, this parameter displays the irregularities in a histogram and is therefore, recognized for allowing describing the variation of a parameter in a distribution.⁸ The strong correlation with average nucleic area might be explained as follows: if there is more variance in average nucleic area, the entropy increases and vice versa. Furthermore, some previous reports showed that ADC entropy was associated with expression of p53 in cervical cancer¹⁰ and tumor stages in gastric cancer.¹⁶ For muscle imaging, Corino et al¹⁷ investigated 19 soft tissue sarcomas and identified that entropy features were significant higher in the high-grade group and thus, displaying the greater heterogeneity of high-grade tumors. Recently, in a similar study by Kim et al¹⁸ investigating 40 myxoid containing sarcomas, the high-grade tumors showed significantly higher texture features than the low-grade ones. However, in cerebral lymphomas, entropy did not correlate with

histopathology features.¹⁹ This finding might indicate that cerebral lymphomas and MLs are significantly different in their architecture and, therefore, show also different correlations between ADC-derived parameters and histopathological features.¹⁹

Ki67 index is most used proliferation index in clinical practice.¹⁴ High expression of Ki67 is associated with a poor survival in lymphoma as shown in a recent meta-analysis.¹⁴ In the present study, no correlation could be identified between ADC histogram parameters and Ki67. As mentioned above, there were inconclusive data about associations between ADC values and Ki67 index in lymphomas.²⁰ For instance, Schob et al¹³ identified a statistically significant correlations between different ADC values and Ki67, whereas other authors did not.²¹

Our findings might explain some phenomena described previously. For example, it could be shown that different lymphoma subtypes show different ADC values. In fact, indolent lymphomas have significantly lower ADC values than other lymphomas.²² Moreover, ADCmean was associated with overall survival.²² This can be explained with lymphomas with a lower ADC value have higher cellularity and higher Ki67 expression and are, therefore, of a more aggressive tumor behavior. Clearly, further researches are needed to answer, whether ADC values can be used as a direct surrogate parameter in these patients. According to Mayerhoefer et al²³ DWI showed almost as good results as the current gold-standard FDG-PET/CT in the assessment of treatment response in lymphomas. Thus, DWI might be a feasible replacement of FDG-PET without any radiation exposure for patients.

A very important factor for translation of imaging parameters into clinical routine is their reliability. As seen, all calculated ADC parameters showed good to excellent ICC indicating their robustness and the possibility for clinical usage. This is in good agreement of the literature, in which especially whole tumor measurements showed a good interreader variability.²⁴⁻²⁶

There are several limitations of this study to address. Firstly, it is a retrospective study with possible concordant bias. However, the histopathology and imaging were analyzed blinded to each other. Secondly, and to admit the most important limitation is the small patient sample. This is caused by the rare incidence of this entity. Thirdly, the histopathology performed for this analysis only reflected a small part of the tumor, whereas the MRI was measured as a whole lesion measurement. However, lymphomas tend to be a homogenous tumor and, therefore, the biotic site might be good comparable with the whole tumor, which minimize this limitation.

In conclusion, this study identified significant correlations between cellularity and histogram parameters derived from ADC maps in ML.

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