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Original article

Role of Diffusion MRI in Mediastinal lymphoma (Diagnosis, Initial Staging and Response to Treatment)

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Abstract

Background: Lymphoma is a kind of blood cancer that begins in lymphocytes, white blood cells that are part of the lymphatic system. The lymphatic system is part of the immune system and helps fight infection. This study's objective was to detect role of diffusion MRI in the algorithm of diagnosis of mediastinal lymphoma and assessment of post therapeutic response. **Methods:** Cross sectional study was conducted to patients with mediastinal lymphoma diagnosed by CT and biopsy and admitted in Benha University Hospital from 1st November 2022 to 31th September 2023 (10 months). **Results:** ROC analysis was done for ADC to distinguish between Hodgkin and non-Hodgkin lymphoma patients. It revealed a significant AUC of 0.828 (P = 0.003), with a 95% confidence interval ranging from 0.661 – 0.995. The best cutoff point was ≤0.887, at which sensitivity, specificity, PPV, and NPV were 63.6%, 100%, 100%, and 82.6%, respectively. For ADC to distinguish between Hodgkin and non-Hodgkin lymphoma in mediastinal masses, It revealed a significant AUC of 0.875 (P = 0.02), with a 95% confidence interval ranging from 0.671 - 1. The best cutoff point was ≤ 0.887, at which sensitivity, specificity, PPV, and NPV were 75%, 100%, 100%, and 75%, respectively. For ADC to predict treatment response, It revealed a significant AUC of 0.894 (P < 0.001), with a 95% confidence interval ranging from 0.762 – 1.0. The best cutoff point was> 1.165, at which sensitivity, specificity, PPV, and NPV were 91.7%, 88.9%, 84.6%, and 94.1%, respectively. **Conclusions:** DWI MRI is a promising functional technique in diagnosis of Hodgkin and non-Hodgkin lymphoma and assessment of response to treatment with significant statistic difference between ADC values of lymph nodes and mediastinal mass in Hodgkin and non-Hodgkin lymphomas.

Keywords: Diffusion MRI; Mediastinal lymphoma; diagnosis; initial staging; response to treatment

Introduction

Computed Tomography (CT) and Positron Emission Tomography (PET) are two common non-invasive methods used to examine pulmonary nodules or masses with high diagnostic accuracy, but these two methods have increased radiation exposure and the sensitivity of PET-CT is low in nodules smaller than 20mm, so another non-invasive method is required in the differential diagnosis of lung masses to avoid unnecessary biopsies that cause many risks and complications **(1).**

MRI is a powerful tool for research and specific clinical applications, although Computed Tomography (CT) remains the gold standard for imaging of lung pathomorphology in cancer patients. The advantages of MRI over CT are not only limited to the lack of ionizing radiation but also combines excellent soft tissue contrast and functional information, it allows for multiple and repeated measurements and can be used to assess motion and perfusion of thoracic organs (**2**).

Diffusion weighted MRI detects the random motion of water molecules in the biological tissues; this is called "Brownian motion" and helps in characterization of tissue microstructural changes. Water diffusion is changed in various disease processes reflecting physiological and morphological tissue criteria such as cell density and tissue viability.

This can be quantified by Apparent Diffusion Coefficient (ADC) value (**3**).

ADC relates to the molecular transitional movement of water molecules. Decrease ADC values correlates with increased tumor cellularity which tends to restrict water diffusion (**4).**

Although DWI has been used to differentiate malignant and benign lesions in several other locations, there are few studies about the intrathoracic lesion characterization (**5**).

The clinical application of pulmonary MRI was limited due to physical motion artifacts and technical limitations. However, with the development of technology in recent years, MRI has become a clinically feasible method for specific pulmonary problems**.** Lymphoma represents one of the most common tumors in mediastinum approximately 10–15% of all masses (**6).**

This study aimed to detect role of diffusion MRI in the algorithm of diagnosis of mediastinal lymphoma and assessment of post therapeutic response.

Patients and Methods

Cross sectional study was conducted to patients with mediastinal lymphoma diagnosed by biopsy and admitted in Benha University Hospital.

Approval code: MS.1.11.2022

Study time:

The field work was carried out during the period from 1st November 2022 to 31th September 2023 (10 months).

Target population and sample size:

The study conducted to patients with mediastinal lymphoma diagnosed by biopsy and admitted in Benha University.

Inclusion criteria

Patient diagnosed to have mediastinal lymphoma by CT guided biopsy and histopathological analysis with the ability of the patient to lie supine.

Exclusion criteria

Contraindication to MRI e.g. Patients with pace maker, cochlear implants, cerebral aneurysm clips, ocular met allic foreign body, bullets or gunshots near great vessels or vital organs.

MRI technique

Patients were subjected to MR scanning sequences which areT1W1, T2WI, T2 STIR and DWI including quantitative DWI analysis (ADC measurement). Respiratory gating has been used in all patients.

Administrative and Ethical design:

Ethical consideration:

- After approval from Research Ethics Committee of Benha Faculty of Medicine which was obtained.
- Informed written consent was taken from all patients before participation.
- An official permission from the administrators of Benha University Hospitals to conduct this study was obtained.

Statistical methods

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality, quantitative data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared according to lymphoma type or treatment response using the independent t-test or Mann-Whitney U test for normally and non-normally distributed quantitative variables, respectively. Categorical data were compared using the Chi-square or Fisher's exact test. ROC analyses were done for ADC to predict non-Hodgkin lymphoma and treatment response. The areas under the curve with their 95% confidence intervals, best cutoff points, and diagnostic indices were calculated. ADC values were compared according to affected lymph nodes using the Mann Whitney U test. Multivariate logistic regression analyses were done to predict non-Hodgkin lymphoma and treatment response. The odds ratios with 95% confidence intervals were calculated.

All statistical tests were two-sided. P values less than 0.05 were considered significant.

Results

A significant difference was observed in the ADC values between Hodgkin and Non-Hodgkin lymphoma cases. The median ADC value for Hodgkin lymphoma was notably higher (1.266) than that for non-Hodgkin lymphoma (0.631) (P = 0.002)***(Table 1).***

In mediastinal masses, a significant difference was observed in the ADC values between Hodgkin and non-Hodgkin lymphoma masses. The median ADC value for Hodgkin lymphoma masses was significantly higher (1.089) than that for non-Hodgkin lymphoma masses (0.627) (P = 0.002)**.**

Responders exhibited significantly higher ADC values (median = 1.976) than non-responders (median = 0.959) (P < 0.001)**.**

ROC analysis was done for ADC to distinguish between Hodgkin and non-Hodgkin lymphoma patients. It revealed a significant AUC of 0.828 (P = 0.003), with a 95% confidence interval ranging from 0.661 – 0.995. The best cutoff point was ≤0.887, at which sensitivity, specificity, PPV, and NPV were 63.6%, 100%, 100%, and 82.6%, respectively ***(Table 2).***

ROC analysis was done for ADC to distinguish between Hodgkin and non-Hodgkin lymphoma in mediastinal masses. It revealed a significant AUC of 0.875(P = 0.02), with a 95% confidence interval ranging from 0.6ٷ1 - 1. The best cutoff point was ≤ 0.887, at which sensitivity, specificity, PPV, and NPV were 75%, 100%, 100%, and 75%, respectively ***(Table 3).***

ROC analysis was done for ADC to predict treatment response. It revealed a significant AUC of 0.894 (P < 0.001), with a 95% confidence interval ranging from 0.762 – 1.0. The best cutoff point was> 1.165, at which sensitivity, specificity, PPV, and NPV were 91.7%, 88.9%, 84.6%, and 94.1%, respectively ***(Table 4).***

Multivariate logistic regression analysis was performed to predict non-Hodgkin lymphoma. It revealed that ADC was a significant predictor for non-Hodgkin disease. One unit increase in ADC was associated with an 89.3% risk reduction of non-Hodgkin disease (OR = 0.107, 95% CI = 0.013 – 0.864, P = 0.036), controlling for age and gender**.**

Multivariate logistic regression analysis was performed to predict response to treatment. It revealed that ADC was a significant predictor for treatment response. One unit increase in ADC was associated with a 93.2% risk reduction of non-response (OR = 0.068, 95% CI = 0.01 – 0.469, P = 0.006), controlling for age and gender**.**

Table (1) ADC value according to type of lymphoma

		Hodgkin (n = 19)	**Non-Hodgkin (n = 11)**	**P-value**
ADC ($x10^{-3}$ mm^2/s)	Median (range)	1.266 (0.895 - 3.151)	0.631 (0.512 - 1.983)	**0.002***

*Significant P-value; ADC: Apparent Diffusion Coefficient

Table (2) ROC analysis of ADC to differentiate Hodgkin and non-Hodgkin disease

ROC characteristics	
AUC	0.828
95% CI	0.661 – 0.995
Best cutoff	≤0.887
Sensitivity	63.6%
Specificity	100%
PPV	100%
NPV	82.6%
P-value	**0.003***

*Significant P-value; AUC: Area under the curve; 95% CI: 95% confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

Table (3)ROC analysis of ADC to differentiate Hodgkin and non-Hodgkin disease in mediastinal masses

ROC characteristics	
AUC	0.875
95% CI	0.671 – 1.0
Best cutoff	≤0.887
Sensitivity	75%
Specificity	100%
PPV	100%
NPV	75%
P-value	**0.02***

*Significant P-value; AUC: Area under the curve; 95% CI: 95% confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

Table (4) ROC analysis of ADC to predict response to treatment

ROC characteristics	
AUC	0.894
95% CI	0.762 – 1.0
Best cutoff	>1.165
Sensitivity	91.7%
Specificity	88.9%
PPV	84.6%
NPV	94.1%
P-value	**<0.001***

*Significant P-value; AUC: Area under the curve; 95% CI: 95% confidence interval; PPV: Positive predictive value; NPV: Negative predictive value

Discussion

As regard to ADC according to the lymphoma type, there is statistic significant difference between ADC values in LN (p = 0.003).

This result was in agreement with **Sabri et al., (7**) study, in which ADC range in non-treated Hodgkin lymphoma was 0.774 to 1.4, while ADC range in non-treated ono-Hodgkin lymphoma was 0.476 to 0.668.

In their study, there was statistically significant difference of ADC values in lymphoma case presented by mediastinal masses with and without chemotherapy.

While on other hand **Rezk et al., (8)** stated regarding the pathological subtypes of mediastinal lymphoma, that there were no statistically difference between the ADC average value of Hodgkin lymphoma and non-Hodgkin lymphoma in these studies but the ADC value of non-Hodgkin lymphoma was lower than Hodgkin lymphoma. These findings may be attributed to limited study on relatively small sample size.

As regard to the mediastinal masses, a significant difference was observed in the ADC values between Hodgkin and non-Hodgkin lymphoma masses. The median ADC value for Hodgkin lymphoma masses was significantly higher (1.089) than that for non-Hodgkin lymphoma masses (0.627) (P = 0.002).

ADC according to treatment response showing significantly higher ADC values (median = 1.976) in responders than non-responders (median = 0.959) (P < 0.001)**.**

Out of twelve patients with MRI done after starting chemotherapy sessions; eight patients were diagnosed as Hodgkin lymphoma (66.666%), and four patients were diagnosed as non-Hodgkin lymphoma (33.33%). ADC range in treated Hodgkin lymphoma cases presented with residual lymph node presentation was 1.05 to 3.6 with ADC average 1.580. ADC range in treated non-Hodgkin lymphoma cases presented with lymph node presentation was 0.72 to 2.6 with ADC average 1.102, while ADC mean in one case presented with mass was 1.29**.**

All of the eleven cases with mediastinal masses had the epicenter of the mass in the anterior mediastinum; which agrees with **Shahrazad et al., (9)** who stated that mediastinal lymphoma usually occur in the anterior mediastinum.

According to ROC analysis of ADC to differentiate between Hodgkin and non-Hodgkin disease revealed a significant AUC of 0.828 (P = 0.003), with a 95% confidence interval ranging from 0.661 – 0.995. The best cutoff point was ≤0.887, at which sensitivity, specificity, PPV, and NPV were 63.6%, 100%, 100%, and 82.6%, respectively**.**

According to ROC analysis of ADC to differentiate between Hodgkin and non-Hodgkin disease in mediastinal masses, It revealed a significant AUC of 0.٨٧٥ (P = 0.0٢), with a 95% confidence interval ranging from 0.6٧1 - 1. The best cutoff point was ≤ 0.887, at which sensitivity, specificity, PPV, and NPV were 75%, 100%, 100%, and 75%, respectively**.**

This is agrees with **Lin et al., (10)** who stated that functional information provided by diffusion MRI are potentially helpful in assessment of response to treatment. **Littooij et al., (11)** stated that ADC measurements could be a valuable for the differentiation between viable and non-viable residual lesions.

ROC analysis was done for ADC to predict treatment response. It revealed a significant AUC of 0.894 (P < 0.001), with a 95% confidence interval ranging from 0.762 – 1.0. The best cutoff point was> 1.165, at which sensitivity, specificity, PPV, and NPV were 91.7%, 88.9%, 84.6%, and 94.1%, respectively**.**

According to the prediction of non-Hodgkin disease, multivariate logistic regression analysis was performed to predict non-Hodgkin lymphoma. It revealed that ADC was a significant predictor for non-Hodgkin disease. One unit increase in ADC was associated with an 89.3% risk reduction of non-Hodgkin disease (OR = 0.107, 95% CI = 0.013 – 0.864, P = 0.036), controlling for age and gender**.**

According to the prediction of treatment non response, Multivariate logistic regression analysis was performed to predict response to treatment. It revealed that ADC was a significant predictor for treatment response. One unit increase in ADC was associated with a 93.2% risk reduction of non-response (OR = 0.068, 95% CI = 0.01 – 0.469, P = 0.006), controlling for age and gender**.**

In agreement with **Broncano et al., (12**) who stated that, MRI DWI can be used as a reliable non-invasive technique that can differentiate between benign and malignant tumors including those of the mediastinum. This also consistent with **Abou Youssef et al., (13)** who stated that the ADC values of malignant mediastinal lesions are significantly lower than those of benign lesions and determined cut-off ADC values to differentiate the two.

De Paepe et al., (14) stated that DWI may be used as a response marker very early during treatment for lymphoma.

In two cases who had received chemotherapy, there was a residual anterior mediastinal mass lesion that was considered as residual lymphoma; however their ADC values were 2.6 and 2.7, suggesting benign nature rather than lymphoma residual. The possibility of thymic hyperplasia was considered and was proved by histopathology.

In agreement with **Zhen et al., (15)** who stated that thymus hyperplasia following chemotherapy can occur in both children and adults, but occurs most often in children, adolescents and

young adults. It can occur in various types of tumors including lymphoma.

In agreement with **Ibrahim et al., (16)** who stated that DWI MRI can differentiate benign from malignant mediastinal masses and can differentiate lymphoma from sarcoidosis in the setting of mediastinal and hilar lymphadenopathy.

5. Conclusion

We concluded that DWI MRI is a promising functional technique in diagnosis of Hodgkin and non-Hodgkin lymphoma and assessment of response to treatment with significant statistic difference between ADC values of lymph nodes and mediastinal mass in Hodgkin and non-Hodgkin lymphomas.

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