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Research Paper

The Value of Apparent Diffusion Coefficient in Differentiating Metastatic from Benign Non Metastatic Axillary Lymph Nodes in Women with Breast Cancer

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ABSTRACT:

BACKGROUND:

Breast cancer is the most common woman cancer. Accurate diagnosis of metastatic axillary lymph node (ALN) have an important role because it controls the clinical therapeutic schedule and influence overall disease prognosis.

The development of MRI including DWI\ADC sequences improve the detection of axillary lymph nodes metastasis using the Brownian phenomena this represents an important non-invasive method with no need for contrast media.

OBJECTIVE:

To evaluate the role of the apparent diffusion coefficient in the differentiation between metastatic and benign non metastatic axillary lymph nodes.

PATIENTS AND METHODS:

A prospective cohort study was conducted at Oncology teaching hospital in Medical city teaching compass during a period of 10 months between January 2022 until November 2022.

Our study includes 58 women. MRI was performed using a 1.5 Tesla MRI using a dedicated bilateral sixteen channel breast coils. The mean ADC value were measured for axillary lymph nodes and results were compared with histopathological findings.

The optimal ADC cut off values were evaluated using receiver coefficient characteristic (ROC) curves.

RESULTS:

The histopathological examination reveals that 37.9% of examined lymph nodes were metastatic and 62.1% was non-metastatic.

The ADC value of the metastatic ALN was significantly lower than that of the non-metastatic ALN (0.78 x10–3 mm2/s vs 2.39 x10–3 mm2/s, P= 0.009).

The optimal cut-off ADC value for the discrimination between metastatic and non-metastatic lymph-nodes was 0.97x10–3mm2/s with sensitivity and specificity of 95.5% and 100% respectively, and accuracy of 98.3%. Positive predictive value and negative predictive value of ADC were 100% and 97.3% respectively.

CONCLUSION:

The ADC value obtain important role in prediction of axillary lymph nodes metastasis with a diagnostic accuracy of 98.3% in this study.

KEY WORDS: Breast cancer, axillary lymph nodes, magnetic resonance imaging, apparent diffusion coefficient.

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INTRODUCTION:

Breast cancer poses a significant threat to women's health and is the most prevalent form of cancer among female patients globally. A thorough examination of axillary lymph node (ALN) infiltration plays a vital role in the care of breast cancer patients, as it serves as a crucial predictive factor and impacts both clinical and treatment approaches. Therefore, it is imperative to accurately assess axillary lymph node metastases in newly diagnosed cases of breast cancer to determine cancer stage and plan appropriate treatment strategies[1,2].

Despite advancements, distinguishing between benign and metastatic lymph nodes through non-invasive methods remains challenging and can lead to delays in diagnosing metastatic risk [3].

Currently, sentinel node biopsy, often followed by axillary dissection, is a common practice during surgery. However, studies indicate that up to 70% of clinically non-metastatic breast cancer patients have no malignant axillary infiltration during dissection. Moreover, this surgical procedure carries risks of complications such as lymphedema, arm pain, infection, or seroma [4,5]. Preoperative examination techniques like magnetic resonance imaging (MRI), computed tomography, and ultrasonography provide limited qualitative and quantitative information on axillary nodal status, focusing on morphological features and nodal dimensions. However, these features have limitations in accurately distinguishing between metastatic and benign lymph nodes [6,7]. Diffusion-weighted imaging (DWI), a functional imaging modality, offers a promising alternative. DWI eliminates the need for gadolinium-based contrast agents and is commonly used in assessing breast tumors[8].

Diffusion-weighted imaging (DWI) is a functional imaging technique that does not require the use of intravenous contrast agents containing gadolinium. Its widespread application in assessing breast tumors underscores its utility and effectiveness in clinical practice[9].

Anatomy

The breast is a symmetrical organ that present in the front of the chest wall on both sides of the midline.

The Axillary Lymph Nodes

Gross Anatomy

There are five distinct groupings of axillary lymph nodes, namely the lateral (humeral), anterior (pectoral), posterior (subscapular), central, and apical nodes. The apical nodes hold a significant position as they serve as the central hub where all axillary lymphatic pathways converge [10].

Lymphatic Pathways

The pectoral group of axillary nodes can be reached by the lymphatic vessels that travel along the side of the pectoralis major muscle. Lymphatic flow can be directed towards the apical nodes of the axilla by following pathways through or between the pectoralis muscles. As they pass through the pectoralis major muscle, the lymphatic channels often run alongside blood vessels, eventually leading to the parasternal (internal thoracic) lymph nodes [11].

Surgical Levels

Axillary lymph nodes are classified into three surgical levels:

- Level I: Located at the lower edge of the pectoralis minor muscle.
- Level II: Situated below and posterior to the pectoralis minor muscle.
- Level III: Found above and medial to the pectoralis minor muscle.[12]

Axillary nodal evaluation in breast cancer

- When diagnosing breast cancer in women, it is important to take note of any lymph nodes that appear round or irregular in shape, show a loss of fatty hila, or exhibit asymmetric cortical thickening. These characteristics should raise suspicion. Therefore, it is crucial to carefully document the quantity and position of these suspicious nodes, as well as any potential extra nodal extension.
- Accurate assessment of axillary nodal metastasis burden is essential for informing multidisciplinary team decision-making processes.[2]

DWI of lymph node metastases

Recent studies indicate that MRI, including diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) values, can be considered a valuable method for both diagnosing and quantitatively measuring various neoplasms [13,14]; Specifically, numerous studies have demonstrated significantly lower apparent diffusion coefficient (ADC) values in malignancies compared to benign lesions and normal tissues [15, 16].

The proposed functional mechanism suggests that metastatic lymph nodes invaded by tumor cells exhibit high cellularity, resulting in reduced extracellular and intracellular spaces. This restriction in space limits the mobility of water molecules, ultimately leading to a decrease in apparent diffusion coefficient (ADC) values. [17].

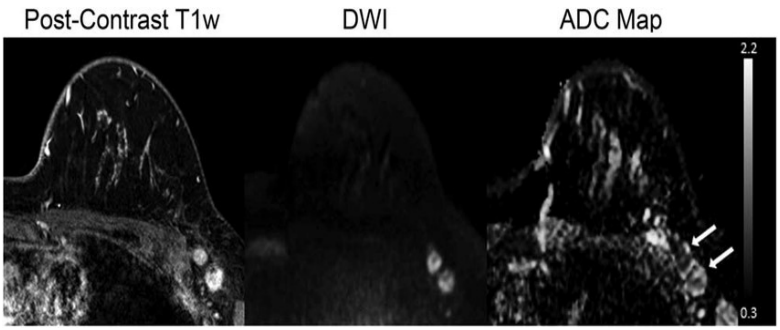

Figure 1: In this case of axillary lymph node metastasis of invasive ductal carcinoma in her left breast. The MRI revealed few abnormal axillary lymph nodes, which were confirmed to be infiltrated by cancer cells upon biopsy. These lymph nodes exhibited enhancement on post-contrast T1-weighted images and hyperintense signal intensity on diffusion-weighted imaging (DWI) with a b-value of 1000 s/mm^2, indicative of restricted diffusion. Additionally, the apparent diffusion coefficient (ADC) map showed low values, measuring 0.83 x 10^-3 mm^2/s for the anterior lymph nodes and 1.17 x 10^-3 mm^2/s for the posterior lymph nodes (indicated by arrows).[18]

AIM OF THE STUDY:

The aim of this study is to assess the role of the apparent diffusion coefficient in distinguishing between metastatic and benign non-metastatic axillary lymph nodes in Iraqi women with breast cancer across various age groups.

PATIENTS AND METHODS:

Study Design, Settings, and Data Collection Time

From January 2022 to November 2022, a prospective cohort study was carried out at an Oncology teaching hospital within the Medical City teaching campus, spanning a duration of 10 months.

Study Patients and Sample Size

This study includes 58 women, who were newly diagnosed with breast cancer and were referred for preoperative assessment by breast MRI.

Inclusion criteria:

- Newly diagnosed breast cancer patients with complete clinical data including histopathological results.
- patients who underwent preoperative MR examinations, including the axilla whithin a peroid of one to six weeks.

Exclusion criteria:

- Poor image quality or motion artefacts.
- Patients with small lymph nodes (dimension less than 6 mm).
- A history of any intervention before MRI examination (radiotherapy, chemotherapy, endocrine therapy or surgery).
- Patients without final histopathological diagnosis.

Administrative Approvals

Approvals were obtained from the Council of Iraqi Board of Medical Specialization and the Oncology Teaching Hospital in Baghdad Medical City.

Ethical Considerations and Official Approvals

Verbal permission was obtained from all patients before collecting data, and all informations were secured and used for research purposes only.

Equipment and Techniques

The MRI procedure was conducted with a Siemens Magnetom Aera system, specifically designed for breast imaging, operating at 1.5 Tesla. The patient was positioned in a prone position and a bilateral sixteen-channel breast coil was used.

Images Analysis and Interpretation

The breast lesion size was measured and the ipsilateral lymph nodes were evaluated morphologically firstly by T1 and T2 sequences for number, size, shape, loss of fatty hilum and cortical thickness, all lymph nodes more than 6 mm in shortest diameter were included.

ADC measurement:

After MRI examination completed, the DWI (p-value 800 s/mm^2) and ADC sequences are reviewed.

The largest and most suspicious lymph nodes was analysed by DWI and the mean ADC value was measured for lymph node by placing ROI (region of interest) area to involve most of cortex of suspicious lymph node with avoiding of central fatty hilum or central necrosis if present and the size of ROI has been chosen according to

the size of the lymph node with a minimum ROI area of 0.5 cm^2.

Histopathological Correlation

The conclusive histopathological findings were acquired through either fine needle aspiration or tru-cut biopsy, guided by ultrasound, targeting the same suspicious lymph nodes. Additionally, post-surgical results were obtained via sentinel lymph node biopsy or axillary curettage surgery.

Statistical Analyses

Statistical analysis was performed utilizing version 25 of the Statistical Package for Social Sciences (SPSS), presenting the data in terms of mean, standard deviation, and ranges. To evaluate the ability of ADC values to differentiate between metastatic and non-metastatic axillary lymph nodes, Receiver Operating Characteristic (ROC) analysis was employed. A threshold of $p < 0.05$ was considered to indicate statistical significance.

RESULTS:

Patient's Demographics:

Patients' age ranged from 22 to 67 years with a mean of 45.31 ± 10.35 years (Figure 2).

Histopathogical Results

According to the histopathological examination of the breast tumors and axillary lymph nodes, the metastatic ALN were found in 22 cases (37.9%) while the other 36 cases (62.1%) were with non-metastatic ALN (Figure 3).

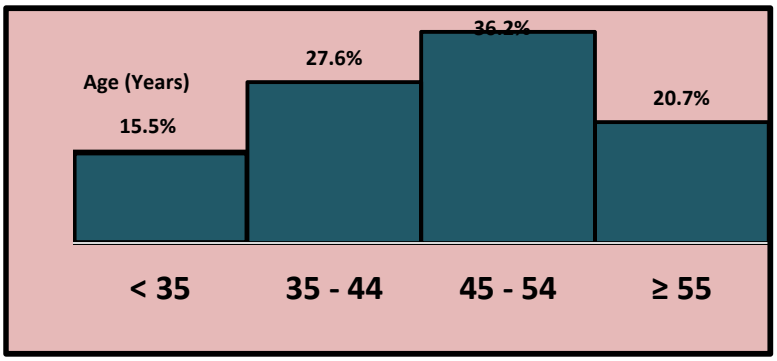

Figure 2: Distribution of the study patients according to age.

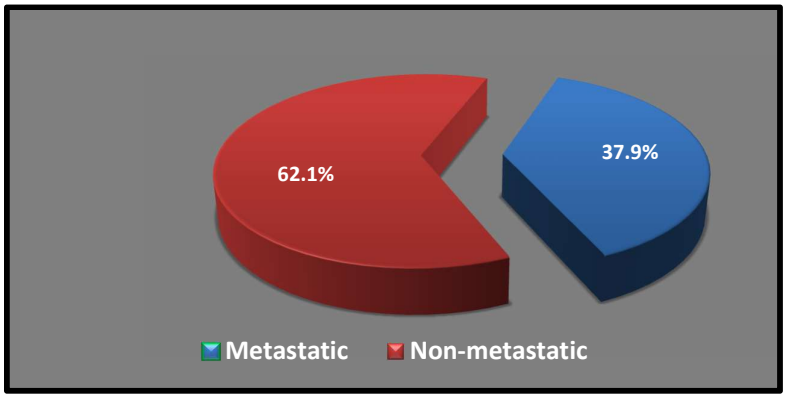

Figure 3: Axillary lymph node status of the biopsied tumors.

MRI characteristics of breast tumor and axillary lymphnodes

The MRI characteristics are summarized at (Table 1).

Table 1: Clinical characteristics of the studied breast tumors and axillary lymph nodes.

Clinical Characteristics	No. (n= 58)	Percentage (%)
Tumor Side		
Right	37	63.8
Left	21	36.2
Histological Type		
IDC	47	81.0
Lobular Carcinoma	6	10.3
DCIS	3	5.3
Adenocarcinoma	1	1.7
Sarcoma	1	1.7
Site of Lymph Node		
Ipsilateral	48	82.8
Contralateral	10	17.2
Shape of Lymph Node		
Oval	47	81.0
Round	11	19.0
Loss of Fatty Hilum		
Yes	12	20.7
No	46	79.3

Table 2: Distribution of study patients by axillary lymph nodes status and clinical characteristics of breast tumors.

Tumor Characteristics	Axillary Lymph Node		Total (%) n= 58	P- Value
	Metastatic (%) n= 22	Non-metastatic (%) n= 36		
Tumor Side				
Right	5 (23.8)	16 (76.2)	21 (36.2)	**0.095**
Left	17 (45.9)	20 (54.1)	37 (63.8)	
Histological Type				
IDC	17 (36.2)	30 (68.3)	47 (81.0)	**0.241**
Lobular Carcinoma	4 (66.7)	2 (33.3)	6 (10.3)	
Other	1 (20.0)	4 (80.0)	5 (8.7)	
Site of Suspicious Lymph Node				
Ipsilateral	21 (43.8)	27 (56.2)	48 (82.8)	**0.045**
Contralateral	1 (10.0)	9 (90.0)	10 (17.2)	
Shape of Lymph Node				
Oval	11 (23.4)	36 (76.6)	47 (81.0)	**0.001**
Non oval	11 (100.0)	0 (0)	11 (19.0)	
Loss of Fatty Hilum				
Yes	12 (100.0)	0 (0)	12 (20.7)	**0.001**
No	10 (21.7)	36 (78.3)	46 (79.3)	

This study found that means of tumor size and number of the metastatic ALN were significantly higher than non-metastatic ALN (Table 3).

Table 3: Comparison of certain tumor characteristics between metastatic and non-metastatic axillary lymph nodes.

Tumor Characteristics	Axillary Lymph Node		P – Value
	Metastatic Mean ± SD	Non- metastatic Mean ± SD	
Tumor Size (mm)	34.22 ± 16.05	25.02 ± 11.43	0.013
Number of Lymph Node	5.32 ± 1.88	3.97 ± 1.54	0.004
Short Axis (mm)	13.71 ± 4.59	8.44 ± 2.58	0.001
Long Axis (mm)	19.83 ± 2.82	15.08 ± 4.14	0.007
Cortical Thickness (mm)	3.94 ± 0.81	2.01 ± 1.32	0.032

Diagnostic performance of ADC values

The comparison of ADC value revealed that ADC value of the metastatic ALN was significantly lower than that of the non-metastatic ALN (0.78 x10–3 mm2/s vs 2.39 x10–3 mm2/s, P= 0.009) (Table 4).

Table 4: Comparison of ADC value between metastatic and non-metastatic lymph nodes.

Clinical Parameter	Axillary Lymph Node		P – Value
	Metastatic Mean ± SD	Non- metastatic Mean ± SD	
ADC (10^{-3} mm2/s)	0.78 ± 0.13	2.39 ± 0.77	0.009

CUT-OFF ADC VALUES

Receiver operating characteristic (ROC) curve analysis was constructed for ADC value as predictors of metastatic ALN. The optimal cut-off ADC value for the discrimination between metastatic and non-metastatic lymph-nodes was $0.97x10^{-3}$mm2/s.This cut-off value obtained a sensitivity and specificity of 95.5% and 100% respectively, with accuracy of 98.3%. Positive predictive value and negative predictive value of ADC were 100% and 97.3% respectively (Figure 4) and (Table 5).

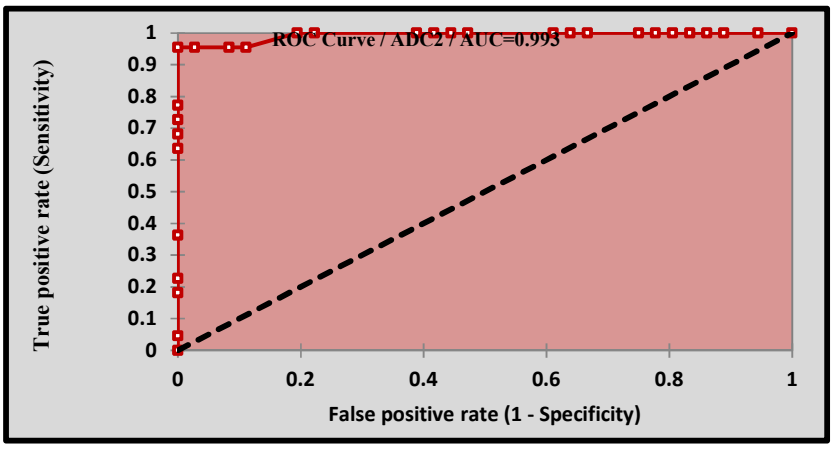

Figure 4: ROC curve of ADC in diagnosis of metastatic ALN in breast tumors.

Table 5: Diagnostic accuracy of ADC in predictions of metastatic ALN.

Clinical Parameters	Cut-off value	SN	SP	PPV	NPV	Accuracy
ADC (10^{-3} mm2/s)	0.97	95.5%	100%	100%	97.3%	98.3%

Case no.1:

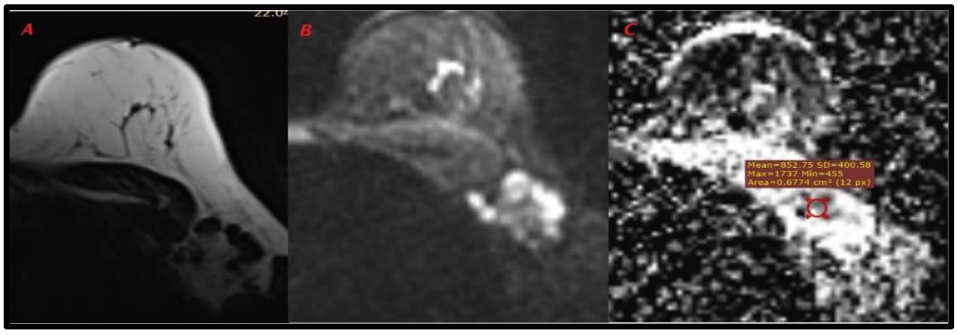

Figure 5: MRI images of a 40 years old female with recent diagnosis of left lobular carcinoma of the breast, A: T2WI, B: DWI 800s/mm2 and C: ADC with mean ADC value measurement. The most suspicious lymph node measure 20x21 mm, rounded in shape with loss of fatty hilum, mean ADC value = 0.852x10-3 mm2\sec, the histopathological result show metastasis to lymph nodes.

Case no.2:

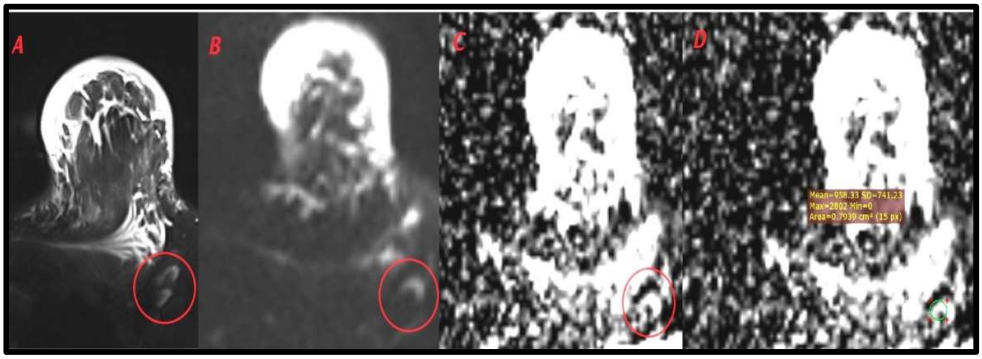

Figure 6: MRI images of a 38 years old female recently diagnosed with invasive ductal carcinoma of the left breast, A : T1WI, B: DWI 800s/mm2, C: ADC and D: mean ADC value measurements, the largest one was 18.4x9.2 mm, oval in shape with preserved fatty hilum, cortical thickness was 2.1 mm and mean ADC value = 0.958x10-3 mm2\sec, the histopathological results show non metastatic reactionary lymph nodes.

DISCUSSION:

The infiltration of breast cancers from local lesions into the surrounding lymph nodes represents a well-recognized transition from a non-metastatic state to a metastatic state. This progression is a pivotal factor influencing staging, treatment planning, and long-term survival outcomes. Moreover, it significantly impacts the necessary medical and surgical management strategies [19-21].

Recent studies have demonstrated that diffusion-weighted imaging (DWI) coupled with apparent diffusion coefficient (ADC) values serves as a valuable approach for both diagnosing and quantitatively assessing malignant tumors. Furthermore, the utilization of diffusion-weighted imaging alongside Magnetic Resonance Imaging (MRI) has been shown to enhance diagnostic precision in distinguishing

between benign and malignant nodes [77,78]; Various studies have consistently shown markedly reduced ADC values in malignant tumors compared to benign lesions and healthy tissues.

In this current study which included 58 female patients with breast cancer, 22 of them with metastatic ALN and 36 with non-metastatic ALN, the mean ADC value of the two groups are compared, the mean ADC value of malignant lymph nodes is 0.78 $x10^{-3}$ mm^2/s which is lower than mean ADC value of benign (non-metastatic) lymph nodes which is found as $2.39x10^{-3}$ mm^2/s (P-value <0.009). The optimal cut-off ADC value for the discrimination between metastatic and non-metastatic lymph-nodes was 0.97 x $x10^{-3}$ mm^2/s. Hence, ADC value < 0.97 $x10^{-3}$ mm^2/s is a predictor for metastatic ALN with a sensitivity and specificity of 95.5% and 100% respectively.

Table 6: Summary of the studies that evaluate the ADC value of ALN.

Authors	year	Study group	Cut off value	Specificity	Sensitivity
This study	2022	58	0.97 $x10^{-3}$ mm^2/s	100%	95.5%
Betul et al(22)	2021	102	0.972 x 10^{-3} mm^2/s	86.8%	84.4%
Fereshteh et al(23)	2017	50	0.904×10^{-3} mm^2/s	88.9%	87.0%
Mahmoud et al [24]	2016	30	$1x10^{-3}$ mm^2/s	91.67%	100%
Dalia et al[25]	2021	77	0.95 × 10^{-3} mm^2/s	63.3%	76.6%
Camilla et al[26]	2020	107	0.8×10^{-3} mm^2/s	82.6%	85.96%

Limitations of our study:

1. The axillary regions were not included routinely by the operators in the field of view in the DWI sequence
2. The poor resolution of the DWI sequence for the small axillary lymph nodes (less than 6 mm in shortest dimension).

CONCLUSIONS AND ECOMMENDATION:

CONCLUSION:

1. The ADC value has important role in prediction of axillary lymph nodes metastasis with a diagnostic accuracy of 98.3% in our study.
2. The ADC value of the metastatic ALN is significantly lower than that of the non-metastatic ALN (0.78 $x10^{-3}$ mm^2/s vs 2.39 $x10^{-3}$ mm^2/s, P= 0.009).
3. The cut of value in discrimination between metastatic and non-metastatic ALN is $0.97x10^{-3}$ mm^2\sec.

Recommendation:

MRI study with included DWI and ADC is recommended in preoperative assessment of ALN in newly diagnosed breast cancer patients to minimize unnecessary axillary dissection and its complications.

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