The Role of Diffusion Weighted Magnetic Resonance Imaging in Assessment of Axillary Lymph Node Metastasis in Patients with Breast Cancer Using Two Cut off Values

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Received: 12 August 2024
Accepted: 3 September 2024

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Abstract:

Background: Axillary lymph nodes (ALNs) metastasis is very important for the prognosis of breast cancer cases, affecting their survival rate but until now, tissue biopsy is the only golden standard for definite diagnosis. The current work evaluates the feasibility of Diffusion Weighted Magnetic Resonance Imaging (DW-MRI) in prediction of ALN metastasis in breast cancer.
Methods: A total of 300 ALNs were surgically excised from 30 women with confirmed as breast cancer. MRI with diffusion examination was performed and comparison between MRI findings with postoperative histopathology was done in lymph Nodes (LNs) with short axis diameter > 5 mm.
Results: By imaging It was found that MRI with diffusion had comparable accuracies with LNs > 5 mm in size (accuracy in both conditions was 59%). Also, accuracy of adherent diffusion coefficient is better when its cutoff point for malignant LNs ≤ 0.90 than ≤ 0.80 (65.3% vs.61.7%; respectively).
Conclusion: MRI is considering essential maneuver in preoperative LN evaluation of BC, MRI with diffusion and ADC values are showing accepted specificity and accuracy in LN assessment.

Keywords: Breast cancer, Axillary lymph nodes, Diffusion weighted magnetic resonance imaging, Adherent diffusion coefficient.

Background:

In 2024, the estimated numbers for breast cancer in the United States are as follows: Approximately 310,720 new cases of invasive breast cancer will be diagnosed in women. About 42,250 women and 530 men in the United States are expected to die from breast cancer. These statistics highlight the ongoing importance of awareness, early detection, and research efforts to combat breast cancer. Regular screenings and understanding risk factors remain crucial in improving outcomes for those affected by this disease [1]. In Egypt breast cancer accounts for 18.9 % of all cancer cases in Egypt (32.04 % in women and 2.2% in men), with an age-adjusted rate of 49.6 per 100,000 populations [2].

Recently, there has been a significant increase in the evaluation of ALNs in patients with breast cancer. Because the presence of metastasis in the ALNs is the only significant predictor of long-term survival in patients with early-stage breast cancer, accurate prediction and early diagnosis of the metastatic status of ALNs is critical for developing a treatment plan and grading for patients with early-stage breast cancer [3, 4].

MRI is considered as a non invasive method used for preoperative grading of metastatic ALNs which has high sensitivity and specificity. It can detect deep and contralateral lymph nodes. Its sensitivity and specificity for metastatic ALNs were higher than ultrasound and Computed tomography (CT) [5, 6].

DW-MRI assesses microscopic thermal motion of water molecules in biologic tissues, which is influenced by the interaction of water molecules with cellular membranes, macromolecules, variations in size of the extracellular extravascular space, the degree of cellular density, and motion of water molecules associated with blood flow in living tissues [7]. Apparent diffusion coefficient (ADC) can quantify the diffusion of water molecules; ADC value and ADC ratio were applied to distinguish metastatic from non-metastatic lymph node widespread [8]. This work was designed to detect the role of MRI with diffusion and ADC value in preoperative assessment of ALNs metastasis in breast cancer patients.

Methods:

Study setting & design:

A prospective cross-sectional study was conducted at South Egypt Cancer

Institute in the period between January 2018 and January 2020.

Participants and selection criteria:

30 patients enrolled in our study were newly diagnosed with breast cancer and confirmed histopathological and underwent surgery and axillary lymph node dissection (ALND) within block resection of ALNs on the ipsilateral side or sentinel lymph node biopsy (SLNB) was done within two weeks after axillary MRI examination.

Exclusion criteria:

Patients had a history of any type of neoadjuvant chemo-, immune- or endocrine therapy, history of axillary surgery and/or recurrent axillary or breast malignancy. And usual MRI contraindications as heart pacemaker and claustrophobia

Image acquisition:

All MR examinations were performed with a 1.5-T unit clinical MR imaging system (Achieva) and commercially available phased array shoulder coils were used. Patients were imaged in the supine position, both conventional and DW imaging were obtained from upper thorax to axilla with the following sequences:

1-Axial and sagittal T1-weighted without fat suppression. (TR/TE 200/2.78, flip angle 70) 2-DW imaging, (TR/TE 6100/1100, flip angle 90) for all sequences field of view was 200×200 m^2, slice thickness 4 mm with no gap). 3-DW images were acquired at b values of 50, 500, 750 and 1000 sec mm² per axis in each patient with the diffusion-sensitization gradient along the readout, phase encoding, and section-selection directions with parallel acquisition techniques [9].

A maximum b value of 1000 sec/mm² was selected to prevent loss of signal in the axilla and to avoid image distortion and over estimation of ADCs. Advanced shimming, as supplied by the manufacturer, was also performed. ADC maps were generated by using the software built into our institute (3D Synapse) [9].

Image analysis:

All MR images were reviewed by three radiologists experienced in the breast MRI interpretation. They were blind to pathology and what about their experience.

Radiological information system / picture archiving and communication system workstation synapse 3D RIS/PACS; South Egypt Cancer Institute was used and when available, ultrasound findings from previous axillary assessment.

By using the T1 weighted imaging and short inversion time recovery (STIR), we calculate the short axis diameter of each lymph node. The lymph nodes with short axis diameter > 5mm assessed on T1-weighted images were subsequently identified on the DW images to detect the restricted and non-restricted LNs and calculate the mean ADC number of each. The qualitative assessment of the DW images was based on the DW signal intensity decay, restricted diffusion and the correlation between the lymph node signal intensity on the DW image (b = 50 sec/mm²) and the corresponding ADC map (fig.1).

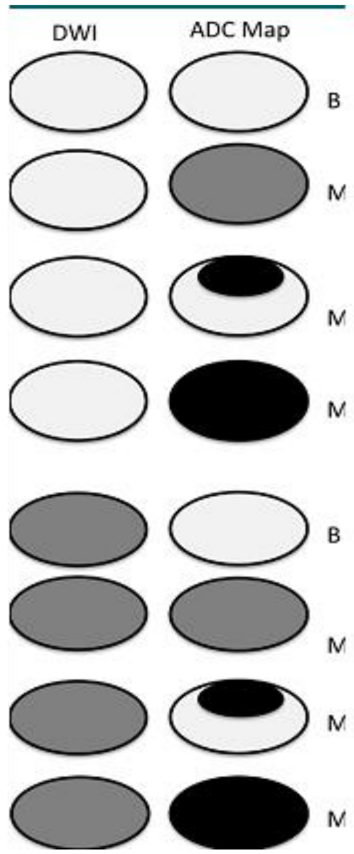

Figure (1): Diagram shows patterns of axillary lymph node signal intensity observed on DW images and ADC maps for qualitative analysis. B = benign, M = malignant [10]

LNs with homogeneous high or intermediate signal intensity on DW images compared with relatively less signal intensity at their respective location on ADC maps were considered metastatic while LNs with homogeneous high or intermediate signal intensity on DW images without a decrease in signal intensity on ADC maps were considered non-metastatic (figure2).

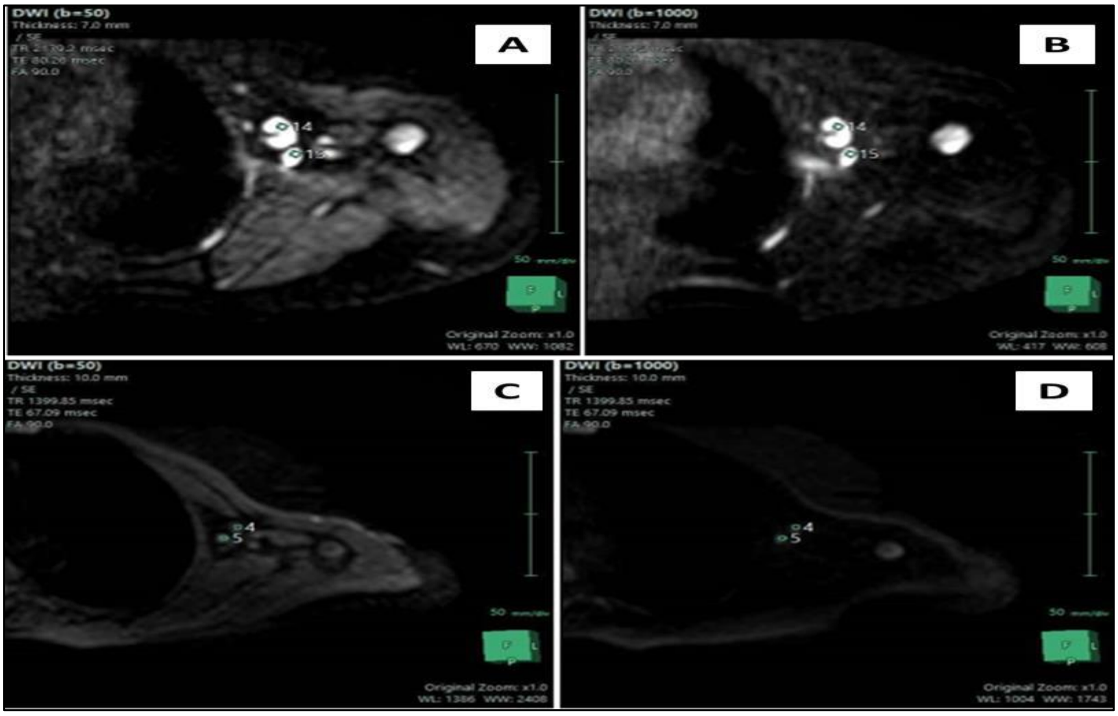

Figure (2): A-B) a case with DWI (b=50&b=1000) shows restricted left axillary LNs, C-D) a case with DWI (b=50&b=1000) show non-restricted left axillary LNs).

For quantitative assessment, mean ADC value was calculated for the restricted and non-restricted LNs at diffusion weighted imaging with cutoff 0.8 $\times 10^{-3}$ and another examination by cutoff 0.9×10^{-3} of the same group of patients. Regions of interest were placed on LNs identified on images obtained with a mean b value, and the software automatically marked with a cross the precise location on the ADC map. Then, a region of interest was manually traced independently by each observer on the ADC maps (We used elliptical region of interest with average 2 mm drawn at most hypointense area of LN on ADC map). The mean ADC derived from the lowest signal intensity averaged across images obtained with b values of (50, 500, 750 and 1000) sec/mm² was then calculated.

Statistical analysis:

Data was collected and analyzed by using SPSS (Statistical Package for the Social Science, version 20, IBM, and Armonk, New York). Continuous data was expressed in form of mean ± SD (Standard Deviation) while nominal data was expressed in the form of frequency (percentage).

Chi²-test was used to compare the nominal data of different groups in the study while student t-test was used to compare mean of different two groups. Receiver operating characteristic curve (ROC) was used to determine diagnostic accuracy of different MRIs findings in prediction of malignant LNs and grade-III breast cancer. Level of confidence was kept at 95% and hence, P value was significant if < 0.05.

Results:

Baseline data of studied women (table 1):

The study enrolled 50 patients with breast cancer. Their mean age was 61.87 ± 10.99 years with a range between 39 and 78 years. Out of them, 25 (83.3%) patients had intraductal carcinoma and only 5 (16.7%) patients had intralobular carcinoma.

Data expressed as mean (SD), frequency (percentage).

Table 1: Baseline data of enrolled women

Total number	30
Age (year)	61.87 ±10.99
Age range	39-78
Histopathological type of intraductal carcinoma	41(83.3%)
Histological type of intralobular carcinoma	9 (16.7%)

MRIs' findings in the evaluated lymph nodes based on histopathology:

A total of 300 LNs were evaluated by MRI. Out of these LNs; 157 (52.3%) nodes

exceeded 5 mm in size. Frequency of mean ADC (≤ 0.8 x10^{-3}/s) and mean ADC (≤ 0.9 x10^{-3}/s) was significantly higher among malignant LNs (72% vs. 13.5%; p< 0.001) and (74% vs. 39%; p< 0.001), respectively. Regarding histopathological evaluation, 100 (33.3%) nodes were malignant.

Impact of mean ADC with cutoff point (≤ 0.8 x10^{-3}/s) in diagnosing malignant LNs (table 2, figure 3):

In examined LNs that were more than 5 mm in size, mean ADC (≤ 0.8 x10^{-3}/s) overall accuracy was 84% with AUC was 0.83. Figure 4

Table 2: Impact of mean ADC with cutoff point (≤ 0.8 x10^{-3}/s) in diagnosing malignant LNs.

Indices	SE	SP	PPV	NPV	AC	AUC	*P* value
LNs (> 5 mm)	80%	86%	75%	89%	84%	0.83	< 0.001

ADC: apparent diffusion coefficient; LNs: lymph nodes; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; AC: accuracy; AUC: area under curve

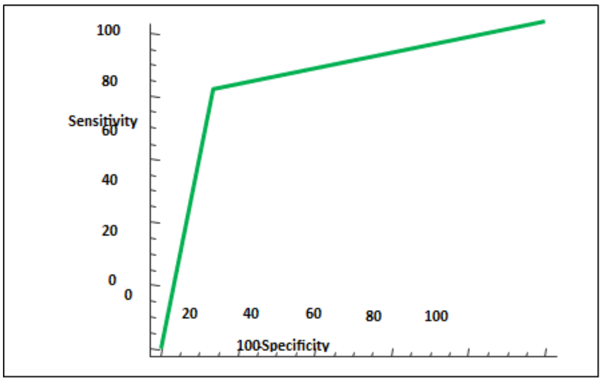

Fig. (3): Impact of mean ADC with cutoff point (≤ 0.8 x10^{-3}/s) in diagnosing malignant LNs

Impact of mean ADC with cutoff point (≤ 0.9 x10^{-3}/s) in diagnosing malignant LNs (table 3, figure5):

In examined LNs that were > 5 mm in size, mean ADC (≤ 0.9 x10^{-3}/s) had overall accuracy was 52.5% with AUC was 0.60. Figure 6

Table 3: Impact of mean ADC with cut off point (≤ 0.9 x10^{-3}/s) in diagnosing malignant LNs

Indices	SE	SP	PPV	NPV	AC	AUC	*P* value
LNs (> 5 mm)	79%	45%	42%	78%	52.5%	0.60	0.01

ADC: apparent diffusion coefficient; LNs: lymph nodes; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; AC: accuracy; AUC: area under curve

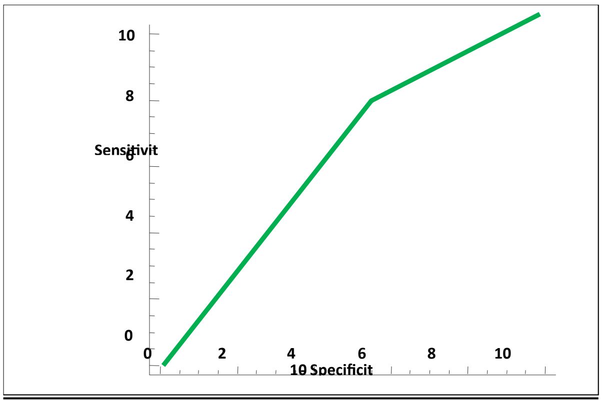

Fig. (5): Impact of mean ADC using cutoff point (≤ 0.9 x10^{-3}/s) in diagnosing malignant Lns

Impact of restricted diffusion in diagnosing malignant LNs (table 4,):

In examined LNs> 5 mm in size, restricted diffusion had overall accuracy was 58.6% with AUC was 0.51.

Table 4: Impact of restricted diffusion in diagnosing malignant LNs

Indices	SE	SP	PPV	NPV	AC	AUC	*P* value
LNs (> 5 mm)	27%	75%	35%	66%	58.6%	0.51	0.89

ADC: apparent diffusion coefficient; LNs: lymph nodes; SE: sensitivity; SP: specificity; PPV: positive predictive value; NPV: negative predictive value; AC: accuracy; AUC: area under curve

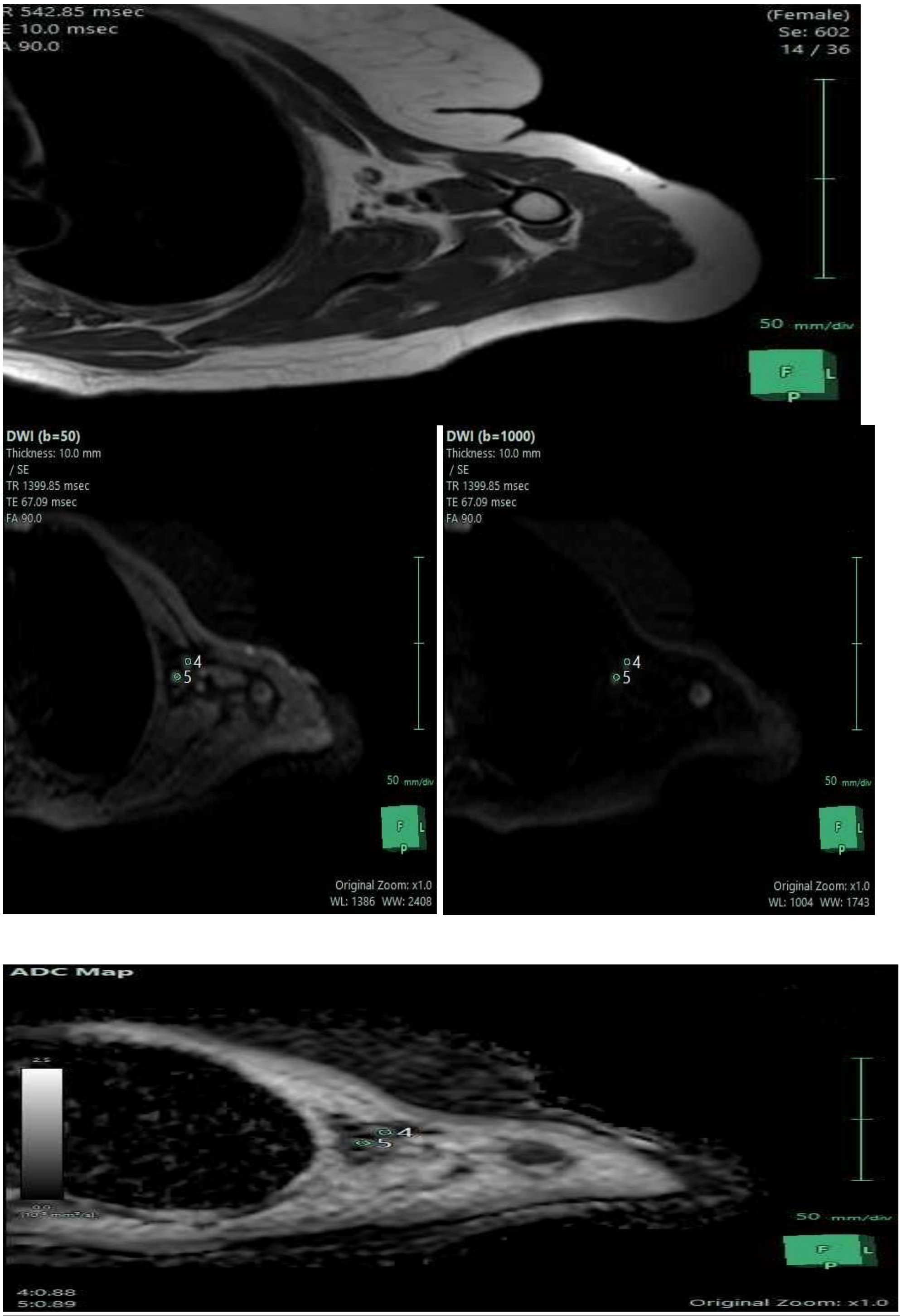

Fig.4 : 56 yrs old female patient presented with left breast mass and ipsilateral enlarged lymph nodes. MRI analysis of ipsilateral axilla (left axilla) using SYNAPSE 3D application detected multiple enlarged lymph nodes (7 LNs) of different shape and fatty hila by axial T1WI, DWI (b value 50 and 1000) show all of them restricted lymph nodes. ADC displayed 1suspicious lymph nodes and 6 benign lymph nodes using cut off value (0.8 $\times 10^{-3}$ mm^2 /s), while 5 suspicious lymph nodes and 2 benign lymph nodes detected at cut off value (0.9×10^{-3} mm^2 /s). By histopathology this case was IDC GII with total lymph node No was 17 LNs 1 of them were positive metastatic lymph nodes. A: T1 axial image. B c:DWI (b=50&b=1000) show non restricted left axillary LNs: D: ADC map


TR 400.0 msec
TE 10.0 msec
FA 90.0
(Female)
Se: 502
1 / 20
50 mm/div
F
L
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Zoom: x1.0
WL: 1070 WW: 1860
DWI (b=50)
Thickness: 7.0 mm
/ SE
TR 1634.01 msec
TE 80.26 msec
FA 90.0
1
2
50 mm/div
Original Zoom: x1.0
WL: 967 WW: 1647
DWI (b=1000)
Thickness: 10.0 mm
/ SE
TR 1399.85 msec
TE 67.09 msec
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Original Zoom: x1.0
WL: 1004 WW: 1743

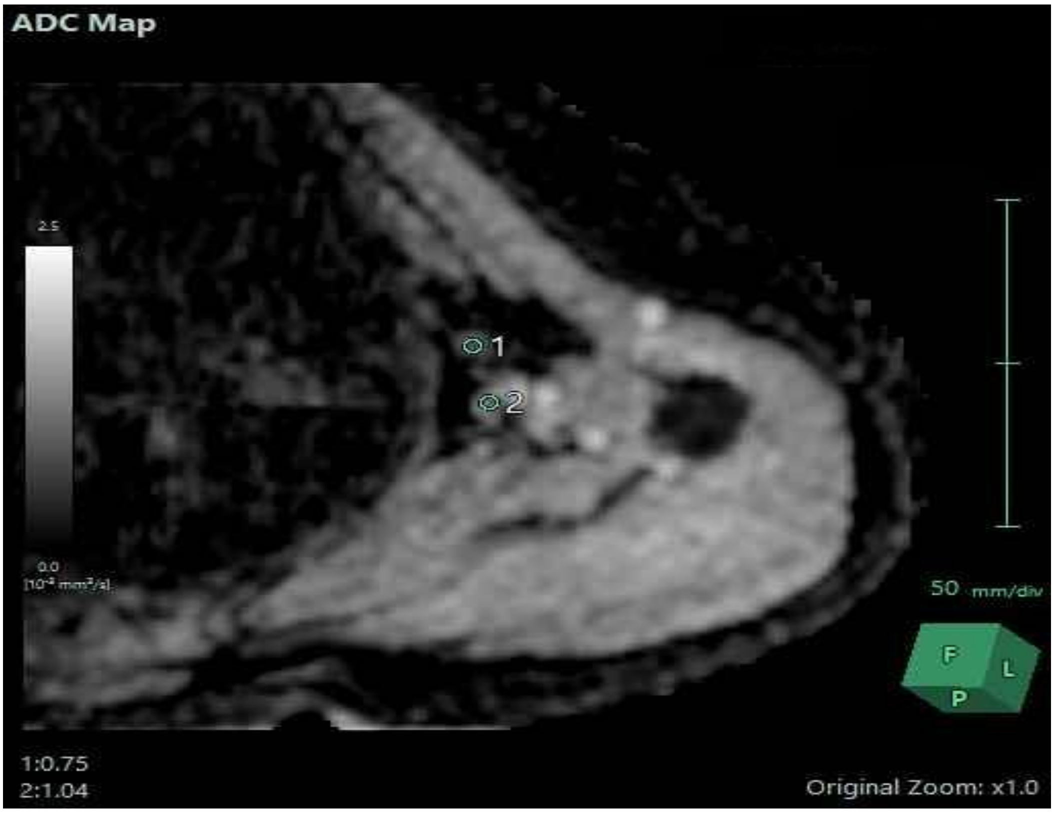

Fig 6: 59 yrs old female patient presented with left breast mass and ipsilateral enlarged lymph nodes. MRI analysis of ipsilateral axilla (left axilla) using SYNAPSE 3D application detected multiple enlarged lymph nodes (9 LNs) of different shape and fatty hila by axial T1WI.DWI (b value 50 and 1000) show 6 restricted lymph nodes and 3 non restricted lymph nodes. ADC displayed 6 suspicious lymph nodes and 3 benign lymph nodes using cut off value (0.8 $\times 10^{-3}$ mm^2 /s), while 7 suspicious lymph nodes and 2 benign lymph nodes detected at cut off value (0.9×10^{-3} mm2 /s). By histopathology this case was IDC GII with total lymph node No was 21 LNs 7 of them were positive metastatic lymph nodes.

Discussion:

Non-invasive, preoperative axillary imaging is needed in an attempt to reduce complication risks and minimize costs by avoiding unnecessary sampling [11]. In the current study, 300 LNs in patients with recently discovered malignant breast lesions were examined. The study was aiming at evaluating the role of DW - MRI, in the assessment of the ALNs status in patients with newly discovered breast cancer.

In current study we evaluate the accuracy of DWI in detection of the malignant lymph nodes using LNs with short axis diameter > 5 mm. Then the results are compared to the histopathological results (gold standard) after surgery (ALNs dissection).

Previous studies found a statistically meaningful relationship between high signal intensity on DWI and metastatic ALNs [11, 16, 17]. However, it has been reported by previous study, that both inflammatory and malignant LNs have high signal intensity on DWI that make it difficult to identify [7]. This was inconsistent with the current study.

In the current study, obtained mean ADC values were significantly lower for metastatic ALNs than non-metastatic type and many other prior studies had nearly similar results [7, 11, 17, 19, 20]. While using mean ADC with cutoff point ($\leq$ 0.8 $x10^{-3}$/s), specificity in diagnosis of malignant ALNs was 86.5%, overall accuracy was 61.7% while using mean ADC with cutoff point ($\leq$ 0.9 $x10^{-3}$/s), specificity in diagnosis of malignant ALNs was 61%, overall accuracy was 65.3%

In study of De Cataldo et al. using cutoff value of the mean ADC $0.8\times 10{-}3$mm2/s, specificity for diagnosing metastatic ALNs was 86% [21]. Also, in study of Zaitonetal et al. using cutoff value of the mean ADC 0.8×10^{-3}mm2/s. they found that the specificity for diagnosing metastatic ALNs was87% and accuracy was 96.7% [18].

Another study using the cutoff value of mean ADC for discriminating benign from malignant was 0.904×10^{-3} mm^2/s with specificity of 88.9% and accuracy of 91.8% [22]. Anabel M. Scaranelo et al. was using the cut value of mean ADC was 0.959 $x10^{-3}$ mm^2/s with specificity of 77%, and accuracy of 80% [23]. Luo et al., using cutoff $<0.89 \times 10^{-3}$ mm^2/s with specificity of 88.2 % and accuracy of 86.1 % [24].

There was a wide difference in the mean and cutoff value of mean ADC between the different studies. Some studies have shown that this difference of the mean ADC value is affected by several factors, such as the magnetic field, MRI acquisition parameters, location, size and area of region of interest (ROI) and patient age [18, 25].

Previous studies reported opposite results; in their studies, the mean ADC value of metastatic ALNs was higher than that of non-metastatic ones [26, 27]. These results may be explained by the difference in the histological types, the variation within lymph nodes at the cellular level and also heterogeneous ROI. In the necrotic tissue cell density is low, so the mean ADC value becomes higher. Like study of Fereshteh, Fariborz et al. [22], we examined LNs more than 5 mm only, we found that high signal intensity at DWI had specificity 75% and accuracy 58.6% in detection of malignant LNs. Examined LNs less than 5 mm high signal intensity at DWI had specificity 63% and accuracy 59.1% in detection of malignant LNs.

Examined LNs more than 5 mm using mean ADC with cut off point (≤ 0.8 $x10^{-3}$/s) nodes like in study of Fatma Zaiton,et al. specificity was 86% and accuracy was 84% in detection of malignant LNs [18].

We also examined lymph nodes less than 5 using mean ADC with cutoff point (≤ 0.8 $x10^{-3}$/s) specificity was 87% and accuracy was79.6% in detection of malignant LNs. Using mean ADC with cutoff point (≤ 0.9 $x10^{-3}$/s) when we examine all lymph nodes of any size like in the study of Anabel M. Scaranelo et al. [9], specificity was 86.5% and accuracy was 65.3%.

We examined LNs more than 5 mm using mean ADC with cutoff point (≤ 0.9 $x10^{-3}$/s) like in the study of Fereshteh, Fariborz et al. [22], specificity was 86% and accuracy was 52.5% in detection of malignant LNs.

In order to define the importance of MRI evaluation of ALNs as a replacement for SLNB, differentiation between minimal and more advanced nodal disease must be clear. Future studies should strongly consider the use of node-by-node analyses of the ALNs to test whether axillary MRI can help to replace SLNB.

The current study had some limitation incudes; MR evaluations were performed without using an axillary coil, which led to limited evaluation of the axillary anatomy. Therefore, use of coils for ALNs is recommended for better evaluation. Secondly, all patients were treated surgically by ALND, but the precise correlation of the visualized and/ or interpreted lymph node within this study is limited. We had to cooperate with pathologists to evaluate the size of histopathological positive resected nodes.

Conclusion:

MRI with diffusion and ADC values are promising imaging methods which can assess metastatic ALNs in breast cancer with higher sensitivity, specificity and accuracy with high accuracy of mean ADC cutoff value range (≤ 0.8 $x10^{-3}$/s _ ≤ 0.9 $x10^{-3}$/s).

Abbreviations:

Axillary lymph nodes (ALNs)
Diffusion Weighted Magnetic Resonance Imaging (DW-MRI)
Lymph Nodes (LNs)
Short Axis Diameter (SHORT AXIS DIAMETER)
Computed Tomography (CT)
Apparent Diffusion Coefficient (ADC)
Axillary Lymph Node Dissection (ALND)
Sentinel Lymph Node Biopsy (SLNB)
Invasive Ductal Carcinoma (IDC)
Invasive Lobular Carcinoma (ILC)
Short Inversion Time Recovery (STIR)
Statistical Package for the Social Science (SPSS)
Standard Deviation (SD)
Receiver operating characteristic curve (ROC)
Area Under Curve (AUC)
Sensitivity (SE)
Specificity (SP)
Positive Predictive Value (PPV)
Negative Predictive Value (NPV)
Accuracy (AU)
Breast Cancer (BC)
Region Of Interest (ROI)

Competing Interests:

There were no competing interests in this manuscript.

Author's contributions:

S,H collected the data and performed the statistical analysis and the design of this study, D,F, H,Y carried out the analysis and interpretation of the data and participated in the design of this study and H,K revised the data and participated in the coordination of the manuscript.

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