Original Article

DOI: 10.4274/haseki.galenos.2021.7545
Med Bull Haseki 2021;59:381-387

Diagnostic Value of Diffusion Magnetic Resonance Imaging in Detecting Malignant Axillary Lymph Nodes in Breast Cancer Patients

Betul Duran, Burcin Agridag Ucpinar

University of Health Sciences Turkey, Sisli Etfal Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey

Abstract

Aim: The prognostic value of apparent diffusion coefficient (ADC) measurement to detect axillary malignant lymph nodes in breast cancer is not clear. We aimed to investigate the prognostic importance of diffusion weighted imaging (DWI) in the differentiation of metastatic and non-metastatic lymph nodes.

Methods: Magnetic resonance imagings (MRIs) of 102 breast cancer patients were reviewed from the hospital PACS and automation systems between July 2018 and March 2021. Cortical thickness, short, long-axis diameters, long/short axis ratios and ADC measurements were done for ipsilateral and contralateral axillary lymph nodes. Univariate and multivariate regression analyses were performed.

Results: Pathology revealed that 64 patients had ipsilateral metastatic lymph nodes while 38 patients did not. When grouped into metastatic and non-metastatic groups, breast tumor size, mean diameter of the short axis, long axis and cortical thickness were significantly higher in the metastatic group. Ipsilateral metastatic lymph nodes' mean ADC values were significantly lower than non-metastatic ones with a calculated value of $0.972x10^{-3}$. The ipsilateral ADC value of the lymph node and loss of fatty hilum were the two significant factors to predict metastatic lymph nodes in multivariate analysis.

Conclusion: DWI is a valuable noninvasive tool in the diagnosis of metastatic axillary lymph nodes.

Keywords: Breast neoplasm, axilla, lymph nodes

Introduction

Breast cancer is the most common type of malignancy and the second most common cause of death among women in Turkey as well as in the world (1,2). The presence of lymph node metastasis is the most important prognostic factor for long-term and disease-free survival in patients (3,4). Axillary imaging of newly diagnosed breast cancer patients is currently done by either ultrasonography (US) or magnetic resonance imaging (MRI). MRI has advantages over US as being non-operator dependent, enabling it to evaluate even the deeply located lymph nodes and compare with contralateral axilla simultaneously. Conventional MRI features suspicious for metastatic axillary nodes are reported as cortical thickening, loss of fatty hilum, round shape and heterogeneous contrast enhancement after Gadolinium injection (5). Diffusion-weighted imaging (DWI) is an advanced functional MRI method that apparents the free motion of the water molecules in tissues (6). Apparent diffusion coefficient (ADC) can quantify the aforementioned motion of the water molecules and provide information about the microscopic cellular changes like cellular membrane integrity or cell proliferation (7,8).

So far, the prognostic value of ADC measurement of the lymph nodes in various malignities of head and neck, uterus and cervix have been shown (9). However, it is not clear whether it contributes to detecting axillary malignant lymph nodes in breast cancer. In the review of De Cataldo et al. (10) they concluded that DWI could be used in patients with low-intermediate risk of lymph node involvement. In another study of Liu et al. (11) they didn't find significant differences regarding ADC values of metastatic and nonmetastatic axillary lymph nodes in T1 and T2 stage breast cancer patients. In this study,

Address for Correspondence: Betul Duran, University of Health Sciences Turkey, Sisli Etfal Training and Research Hospital, Clinic of Radiology, Istanbul, Turkey
E-mail: betulduran_@outlook.com ORCID: orcid.org/0000-0001-8598-6814
Received: 19.06.2021 **Accepted:** 15.10.2021

we aimed to investigate the prognostic importance of DWI in the differentiation of ipsilateral metastatic and non-metastatic lymph nodes and determine the optimal combination of the MRI features to detect nodal status in breast cancer patients.

Methods

Study Design

This study was conducted in accordance with the 1964 Helsinki declaration and approval of the Ethics Committee of the hospital was obtained. Informed consent was waived. The cohort of the study was 114 newly diagnosed breast cancer patients at our radiology clinic who underwent preoperative breast MRI and US-guided ipsilateral axillary lymph node biopsy between July 2018 and March 2021. Patients who underwent axillary lymph node biopsy before breast MRI (n=4), patients whose DWI had artefacts which impede appropriate interpretation (n=2) and patients whose histopathological data couldn't be recollected (n=6) were excluded from this study. After inclusion and exclusion criteria were applied, 102 patients with 102 ipsilateral lymph nodes were enrolled in this study. All patients underwent tru-cut biopsy from breast masses and sentinel lymph node biopsy (SLNB) or axillary dissection from the ipsilateral axilla.

Breast MRI Protocol

All breast MRIs were acquired using 1.5 Tesla Siemens scanner (Avanto, Erlengen Germany) with patients positioned prone in an 8-channel breast array coil. The conventional MRI protocol was applied as T1 weighted fast spin echo axial sequence (TR = 650, TE = 112, Matrix 448 × 224, FOV = 320 x 320 mm, NEX = 1, Thickness = 3.0 mm) and pre- and post-contrast T1 weighted three-dimensional fat-suppressed axial sequence (TR = 485, TE = 10, Matrix 350 × 350, FOV = 320 x 320 mm, NEX = 1, FA = 10.0, Thickness 3.00). Images were taken before contrast administration and five times after contrast injection with 80s intervals. Gadopentetate dimeglumine contrast medium was injected with a dose of 0.1 mmol kg-1. Diffusion-weighted images [TR/TE = 1000/83, NEX = 2 and Thickness = 2 mm, FOV = 320 mm, Matrix 180x238] were obtained before contrast and ADC maps were attained. To interpret DWI, b0 and b1000 sn/mm^2 were used.

Evaluation of Conventional and Diffusion Weighted MRIs

All of the MRI images were analyzed and reported by consensus readings of two radiologists with 8 years and 4 years of experience in breast radiology. The interpreters were blinded to histopathological results. In conventional MRI sequences, presence or loss of fatty hilum, cortical thickness, long-axis diameter, short-axis diameter, long-axis to short-axis ratios were evaluated. While loss of fatty hilum was evaluated in precontrast T1 and T2 weighted images, other features were evaluated in precontrast T2 weighted images. The index lymph node was selected in consensus if there was no suspicious lymph node in axilla. While calculating ADC values, freely selected minimum size regions of interests (ROIs) were used and located to the cortex of each lymph node. Three measurements from the same and most suspicious lymph nodes were done and the minimum values were noted. Attention was given while placing ROIs not to include fatty hilar or adjacent soft tissues (Figure 1,2). The same calculation method was used to compare the contralateral axillary lymph nodes in normal morphology.

Histopathologic Evaluation

Histopathology results were obtained by fine needle aspiration biopsy of the most suspicious lymph nodes, SLNB or axillary curettage. In patients with suspicious metastatic lymph nodes in MRI images, care was taken to biopsy this lymph node. In patients with normal morphological lymph nodes, preoperative biopsy was not planned and SLNB was used as the histopathologic indicator.

Statistical Analysis

For statistical analysis, SPSS 15.0 for Windows program was used. Continuous data (short axis length, long axis length, long axis-short axis ratio, maximal cortical thickness, and ADC value) are given as mean, standard deviation, minimum, maximum, median, interquartile range. Categorical variables (sex, loss of fatty hilum) are

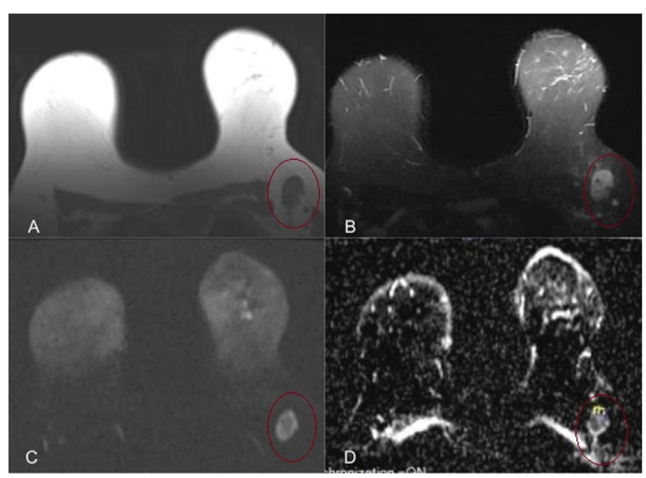

Figure 1. Sixty-eight year-old female patient diagnosed with invasive ductal carcinoma of the left breast with axillary metastasis. A) T1- weighted, B) T2- weighted, C) Diffusion -weighted imagings and D) ADC map. An enlarged metastatic lymph node is seen in the left axilla which shows prominent diffusion restriction
ADC: Apparent diffusion coefficient

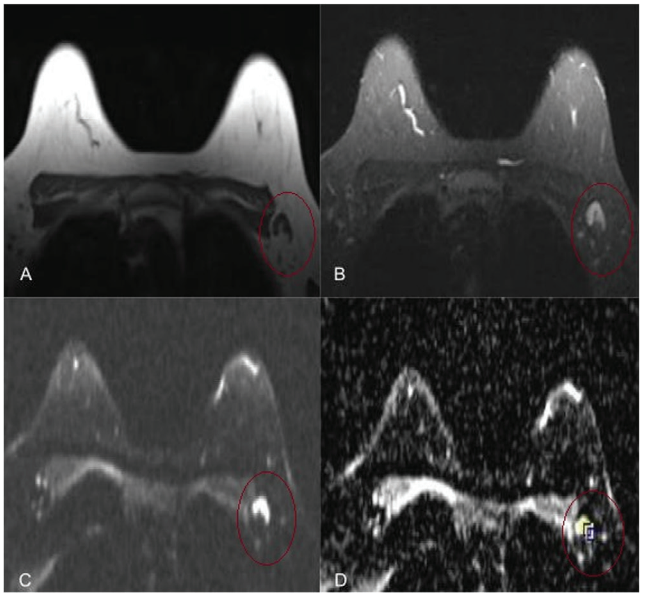

Figure 2. Forty-three year-old female patient diagnosed with tubular carcinoma of the left breast. There is a lymph node in the left axilla. A) T1-weighted and B) T2 weighted imaging) which is proven as reactive pathologically. No diffusion restriction is seen in C)DWI and D) ADC map

ADC: Apparent diffusion coefficient, DWI: Diffusion weighted imaging

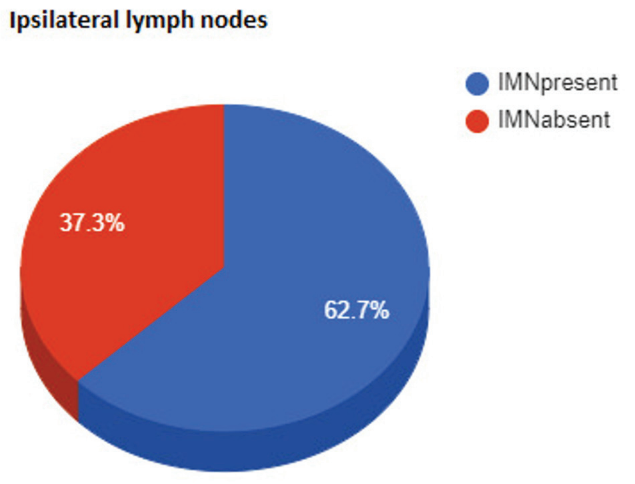

Figure 3. Schematic representation of ipsilateral metastatic nodes present (IMNpresent) and absent (IMNabsent) patients

given as numbers and percentage. Independent two-group comparisons were achieved with the Student's t-test when the numerical variables met the normal distribution condition, and the Mann-Whitney U-test was used when the condition was not met. Relationships between numerical variables were performed using Spearman correlation analysis since parametric test conditions were not met. To compare independent samples, the Wilcoxon test was used. To obtain cut-off values and compare the diagnostic performance of variables, receiver operating characteristics (ROC) was used. The optimal cut-off value was determined according to the highest Youden index (J), and the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated for each variable. Determinative factors were examined by logistic regression analysis. Statistical significance level of alpha was accepted as $p<0.05$.

Results

The mean patient age was 52.0±11.9 (range between 32 and 85). The most common pathological subtype was invasive ductal carcinoma (n=73, 71.57%) followed by invasive lobular carcinoma (n=9, 8.82%). FNAB or surgical final pathology revealed that 64 patients had ipsilateral the metastatic lymph nodes while 38 patients did not (Figure 1). Loss of fatty hilum was present in 38 ipsilateral lymph nodes (37.3%), whereas 64 (62.7%) of them had normal hilar structure.

When grouped into metastatic and non-metastatic ipsilateral lymph nodes, breast tumor size ($p=0.004$), mean diameter of the short axis ($p=0.001$), long axis ($p=0.003$) and cortical thickness ($p<0.001$) were significantly higher in metastatic group. There were no statistical differences between the age of the patients and long/short axis ratios between the two groups (Table 1)

Ipsilateral metastatic lymph nodes' mean ADC values were significantly lower than ipsilateral non-metastatic lymph nodes ($p<0,001$), as expected. The mean ADC value of contralateral lymph nodes was significantly higher in the ipsilateral metastatic lymph node group ($p<0,009$). There was a statistically significant difference in the metastatic lymph node group between ipsilateral and contralateral ADC values ($p<0.001$) whereas not in the non-metastatic group ($p<0.08$) (Table 2).

ROC curve analysis was performed and area under curves (AUC) were calculated for ADC values and each conventional MRI feature to predict metastatic ipsilateral lymph nodes. The highest Jouden indices and AUC values were calculated in ipsilateral ADC value and cortical thickness parameters (Figure 3). The cut of the value of ADC was found 0.972 x 10 -3 with 84.4% sensitivity and 86.8% specificity, 91.5% PPV, 76.7% NPV (J: 71.22, AUC: 0.929). The cut off value of cortical thickness was found 5.5 millimeters with 76.56% sensitivity and 81.58% specificity, 87,5% PPV, 67.39% NPV (J: 57.77 AUC: 0.828). The lowest AUC and sensitivity, specificity, PPV and NPV were observed in the long axis-short axis ratio (Table 3).

Fatty hilum loss was the only descriptive parameter in our study. The number of fatty hilum loss in lymph metastatic group lymph nodes was significantly higher than ones in the non-metastatic group. Even the sensitivity was relatively low (54.7%), the specificity (92.1%) and PPV (92.1%) were significantly high.

Multiple regression analysis was performed to investigate the effect of calculated cut-off value on other conventional MRI features. The ipsilateral ADC value of the lymph node and loss of fatty hilum were the two significant factors to predict metastatic lymph nodes (Table 4).

Discussion

Axillary lymph node status is the most important prognostic factor in newly diagnosed breast cancer patients (9). Detecting axillary metastasis in breast cancer patients is crucial as it has a primary role in staging and optimal treatment decision. The diagnostic values of physical examination, ultrasound-guided biopsy, mammography and ultrasonography were evaluated in the prediction of axillary involvement in breast cancer patients and the results were not satisfactory (12). Nowadays; SLNB is the gold standard technique with high sensitivity of 91.2% and high specificity of almost 100% for the detection of metastatic lymph nodes (13). However; it is an invasive procedure with possible complications.

At this point, as being a noninvasive alternative, conventional MRI with dynamic contrast enhancement

Table 1. Age, tumor size of the patients and short diameter, long diameter, long to short diameter ratio and cortical thickness parameters in ipsilateral metastatic and non-metastatic lymph nodes

	Lymph node status				
	Metastatic		Non-metastatic		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p*
Age	51.6±11.3	50 (43.25-59)	52.6±13.1	50 (42.75-61)	0.928
Tumor size	34.0±19.5	31 (20-40)	24.8±13.9	23.5 (15-29.5)	0.004
Short axis diameter	12.86±5.64	11 (9-17)	9.29±4.37	8.5 (6-11)	0.001
Long axis diameter	21.39±9.12	19 (14.25-27.5)	16.16±6.42	16 (12-18)	0.003
Long/short axis diameter	1.73±0.49	1.6 (1.43-1.87)	1.79±0.37	1.75 (1.55-2.02)	0.156
Cortical thickness	10.59±6.06	9 (6-14)	4.97±2.54	5 (4-5)	<0.001

*by Mann-Whitney U test, SD: Standard deviation, IQR: Interquartile range

Table 2. Mean and Median ADC values of ipsilateral metastatic and non-metastatic lymph nodes and the contralateral lymph nodes of all patients

	Lymph node status				
	Metastatic		Non-metastatic		
	Mean ± SD	Median (IQR)	Mean ± SD	Median (IQR)	p*
Ipsilateral ADC ($x10^{-3}$)	0.77±0.19	0.76 (0.62-0.90)	1.17±0.20	1.15 (1.07-1.31)	<0.001
Contralateral ADC ($x10^{-3}$)	1.27±0.21	1.27 (1.09-1.40)	1.15±0.18	1.12 (1.04-1.27)	0.009
p**	<0.001		0.080[a]		

*Ipsilateral ADC p<0.001 by 2-sample t-test, Contralateral ADC p=0.009 by Mann-Whitney U test, **by Wilcoxon test, [a] There was no significant difference only when ipsilateral and contralateral ADC values were compared in non-metastatic group, SD: Standard deviation, IQR: Interquartile range, ADC: Apparent diffusion coefficient

Table 3. Calculated Area under curve, confidence interval, p-value, cut-off value. Youden index, sensitivity, specificity, positive predictive value and negative predictive value of each variable

Test result variable (s)	AUC	95% CI		p	Cut-off value	Youden index	Se (%)	Sp (%)	PPV (%)	NPV (%)
Primary tumor size	0.673	0.567	0.779	0.004	24.5	16.12	63.49	52.63	68.97	46.51
Cortical thickness	0.828	0.746	0.910	<0.001	5.5	57.77	76.56	81.58	87.5	67.39
Short axis diameter	0.701	0.599	0.804	0.001	9.5	30.37	70.31	60.53	75.00	54.76
Long axis diameter	0.670	0.565	0.775	0.004	16.5	25.61	65.63	60.53	73.68	51.11
Long axis/short axis diameter	0.421	0.306	0.535	0.183	1.696	11.02	53.13	57.89	68.00	42.31
Ipsilateral ADC ($x10^{-3}$)	0.929	0.018	0.124	<0.001	0.972	71.22	84.38	86.84	91.53	76.74

ADC: Apparent diffusion coefficient, AUC: Area under curve, CI: Confidence interval, Se: Sensitivity, Sp: Specificity, PPV: Positive predictive value, NPV: Negative predictive value stands out to evaluate the nodal status. Preoperative conventional MRI gives the opportunity to staging, detecting and measurement of axillary lymph nodes and evaluation of morphological features like cortical thickness, shape, fatty hilum obliteration, and contrast enhancement (14,15). In recent years; DWI has been added to routine breast MRI protocols to increase diagnostic performance. DWI is widely used in diagnosis and treatment response in breast cancer (16-18). The value of DWI in axillary lymph node evaluation is still controversial.

Table 4. Multiple regression analysis of the features to predict metastatic lymph nodes

	p	OR	%95 CI (min-max)	
Ipsilateral ADC ($x10^{-3}$) <0.972	<0.001	77.896	11.838	512.588
Loss of fatty hilum	0.006	65.541	3.260	1317.507
Cortical thickness	0.736	0.920	0.568	1.492
Short axis diameter	0.542	0.736	0.275	1.973
Long axis diameter	0.289	1.409	0.748	2.653
Long/short axis diameter	0.304	0.053	0.000	14.281

CI: Confidence interval, OR: Odds ratio, Min-max: Minimum-Maximum

This study showed the diagnostic performance of DWI and conventional MRI characteristics of ipsilateral lymph nodes to predict malignancy in breast cancer patients. Regarding conventional MRI characteristics; long axis, short axis and cortical thickness of the malignant lymph nodes were significantly higher in the metastatic group. The ratio of long axis to short axis sizes did not differ between groups. In previous studies, no significant correlation was found between lymph node diameter and the presence of metastasis (19-22). However, Atallah et al. (23) and Yoshimura et al. (24) found that metastatic lymph nodes had larger long-axis size with a threshold of 12 and 10, respectively. In our study, we calculated the short and long-axis diameters as 9.5 mm and 11.5 mm. In another study, these values were found 9.3 and 11.3 mm which are very similar to our results (9). We found that the cortical thickness was the best diagnostic parameter among conventional MRI features. Kim et al. (9) and Scaranelo et al. (25) also found the maximal cortical thickness as the most discriminative parameter among conventional MRI features.

As being the only descriptive parameter; fatty hilum loss was observed in 3 (7.89%) cases among the non-metastatic group and 35 (54.69%) cases among the metastatic group. Fatty hilum loss showed the highest specificity (92.1%) that loss of fatty hilum is the best parameter to exclude the metastatic lymph nodes. This result was concordant with the literature (9,24,26).

In this study, the cut-off ADC value of the ipsilateral lymph node <0,972 $X10^{-3}$ showed highest sensitivity (84.3%), specificity (86.4%), PPV (91.53%) and NPV (76.74%) to predict the nodal status. In terms of ADC value measurement, our results were concordant with the literature (27-29). Guvenc et al. (27) found the cut-off value of ADC value as 0.985 $X10^{-3}$ mm^2/sec with a sensitivity of 83%, specificity of 98%, PPV of 95%, and NPV of 93%. They calculated the AUC for ipsilateral lymph nodes as 0.96. Kim et al. (9) founded the threshold ADC value of 253 lymph nodes in 252 breast cancer patients as 0.986 × 10^{-3} mm^2/sec with sensitivity, specificity, PPV, and NPV values as 75.8%, 83.9%, 72.6% and 86.0%, respectively. Fornasa et al. (29) reported the sensitivity and specificity to be 82.22% and 82.35%, respectively. These results are similar to our percentages that show the reproducibility of ADC measurement in axillary lymph nodes.

We found a significant difference between ipsilateral metastatic lymph nodes and contralateral non-metastatic ones that; ipsilateral metastatic lymph nodes had lower ADC value (mean ± SD: 0.77±0.19 × 10^{-3}) than contralateral non-metastatic group (mean ± SD: 1.27±0.21 × 10^{-3}). Another study conducted by Ramirez et al. (30) found a similar result. The multivariate logistic regression analysis showed that ADC value lower than 0.972 ×10^{-3} and loss of fatty hilum had the strongest associations with axillary metastasis (Table 4). In the study conducted by Guvenc et al. (27) they also found the strongest associations with lower ADC value (<0.985×10^{-3}) and axillary metastasis.

Study Limitation

Our study has some limitations. First of all; due to its retrospective design, the study results couldn't be utilized in clinical diagnosis. A prospective study with a larger number of patients would reveal more trustworthy results. Secondly; all the ADC calculations were obtained by two radiologists by consensus MRI readings which resulted in lack of information about interobserver variability. Lastly; we performed institutional standard protocol to obtain MRIs. As a known dilemma, the calculated ADC values are affected by the scanning parameters (TR and TE) and b value used for DWI. Even so, we believe that this study will contribute to literature regarding the high diagnostic value of diffusion-weighted imaging of axilla in breast cancer patients.

Conclusion

Diffusion-weighted imaging is significantly valuable in the noninvasive diagnosis of metastatic axillary lymph nodes in breast cancer. In terms of conventional MRI parameters, higher values of the short axis, long axis diameters and loss of fatty hilum are significantly correlated with axillary metastasis. Lower ADC value and loss of fatty hilum had strongest associations with axillary metastasis. Therefore; DWI should be included in routine MRI protocols in breast cancer staging, since ADC values of the ipsilateral lymph nodes could help to differentiate the metastatic ones in order to prevent unnecessary biopsies.

Authorship Contributions

Concept: B.D., B.A.U., Design: B.D., Data Collection or Processing: B.D., B.A.U., Analysis or Interpretation: B.D., B.A.U., Literature Search: B.D., Writing: B.D., B.A.U.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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