Measurement of apparent diffusion coefficient in discrimination of benign and malignant axillary lymph nodes

Ebru Yılmaz⁠¹A,B,E, Berrin Erok²A,B,C,D,E,F,G, Ali Önder Atca³C,F

¹Sarıyer Hamidiye Etfal Education and Research Hospital, İstanbul, Turkey
²Cihanbeyli State Hospital, Konya, Turkey
³Altınbas University School of Medicine Bahcelievler Medical Park Hospital, İstanbul, Turkey

Abstract

Purpose: We aimed to determine the contribution of the apparent diffusion coefficient (ADC) value in the detection of axillary lymph node metastasis.

Material and methods: Breast magnetic resonance of 58 patients, performed in the radiology clinic of our hospital between 2015 and 2017 were examined retrospectively, and 43 lymph nodes in 43 patients were included in the study. They were evaluated morphologically on T1W and T2W sequences, and the lymph nodes showing rounded shape, focal or diffuse cortical thickness of more than 3 mm, and partial or total effacement of fatty hilum were included in the study. Subsequently, their ADC values were measured.

Results: There were 43 lymph nodes, 20 of which were malignant and 23 of which were benign. While the mean ADC value of malignant axillary lymph nodes was 0.749 10⁻³ mm²/s (0.48-1.342), it was 0.982 10⁻³ mm²/s (0.552-1.986) for benign lymph nodes. When the ADC cut-off value was taken as ≤ 0.753 × 10⁻³ mm²/s, its discrimination power between benign and malignant axillary lymph nodes was as follows: sensitivity – 60%; specificity – 91.3%; accuracy – 76.7%; positive predictive value – 85.7%; and negative predictive value – 72.4%.

Conclusions: There was no significant difference between mean ADC value of 12 lymphadenopathies (LAP) associated with inflammatory breast diseases (granulomatous mastitis and acute suppurative mastitis) and mean ADC value of metastatic lymph nodes. However, the ADC value of lymph nodes showing thickened cortex due to systemic inflammatory diseases was over 1, and there was a statistically significant difference when compared with metastatic lymph nodes.

Key words: axillary LAP, breast cancer, diffusion-weighted imaging (DWI), apparent diffusion coefficient (ADC).

Introduction

The most important prognostic factor in breast cancer is whether or not the axillary lymph nodes include metastasis, and if so, the number of metastatic lymph nodes. When the five-year survival for patients with negative axillary lymph nodes is 82.8%, it decreases proportionally with the number of metastatic nodes [1-4]. The presence of metastatic lymph nodes alters the treatment modality and the surgical method. Therefore, preoperative diagnosis of nodal metastasis is extremely important. Axillary dissection is an invasive procedure which may be associated with complications reducing the quality of life [5,6]. The sentinel lymph node (SLN) procedure emerged to reduce unnecessary axillary lymphadenectomy, and the associated morbidity was shown to be successful in patients with breast cancer; however, when the literature was analysed, it was seen that the rate of false negativity was higher than expected. For this reason, preoperative radiological diagnosis of nodal metastasis with high accuracy is very important. To that end, the main imaging modality is ultrasound (US) imaging. On US the sensitivity and specificity is increased by using morphological criteria as a base in distinction of benign and malignant lymph nodes. In differentiation of
benign and malignant breast lesions, by making post-con- 
trast kinetic analysis in addition to morphological criteria 
in conventional magnetic resonance (MR) imaging, the 
sensitivity is increased to approximately 86-100%, but the 
specificity does not show a similarly high rate. Therefore, 
in order to increase specificity, additional sequences were 
sought [7,8]. It was shown that measurement of the ap- 
parent diffusion coefficient (ADC) obtained from diffusion- 
weighted sequences (DWI) added to conventional 
MR increases specificity and provides more accurate dif- 
ferentiation of benign and malignant breast lesions [7-11]. 
However, evaluation of axillary lymphadenopathies (LAP) 
with DWI is still under study. In our study, we aimed to 
determine the contribution of the ADC value to morpho- 
logical criteria evaluated with conventional MR imaging in 
the detection of nodal metastasis.

Material and methods

Breast MR of 58 patients, performed in the radiology cli- 
ic of our hospital between 2015 and 2017, were examined 
retrospectively, and the lymph nodes having focal or dif- 
cuse cortical thickness more than 3 mm were included in 
the study.

Approval was obtained from our hospital’s Ethics 
Board (date: 04.04.2018, decision: 20), and informed writ- 
ten consent was obtained from each patient.

At first, the lymph nodes were evaluated morpholog- 
ically on T1W and T2W images, and the lymph nodes 
showing rounded shape, focal or diffuse cortical thickness 
more than 3 mm, and partial or total effacement of fatty 
hilus were included in the study. After that, without know- 
ing about primary breast diseases, follow-up period, and 
pathological results, they were evaluated on DWI sequences 
and their ADC values were measured. The lymph nodes 
of 12 patients, which were apparent on conventional MR 
sequences, were not visualised on DWI possibly due to in- 
sufficient resolution especially for the nodes smaller than 
5 mm in diameter and motion artefact, so they were ex- 
cluded from the study. Additionally, because three patients 
had received neoadjuvant chemotherapy, they were also 
excluded from the study. As a result, a total of 43 lymph 
nodes in 43 patients were included in the study, and the 
mean age was 44.42 ± 12.15 years (26-73). Thirty-two out of 
43 patients had been diagnosed histopathologically by 
surgical excisional biopsy or thick needle biopsy, and the 
remaining 11 lymph nodes had been evaluated firstly as be- 
ign and during a one-year follow-up period at six-month 
intervals they were accepted as benign as they decreased in 
size and the cortical thickness returned to normal.

Magnetic resonance imaging

All examinations were performed with 1.5 Tesla (T) MRI 
equipment (GE Signa HDx, GE Medical Systems, USA) us- 
ing an eight-channel phased array breast surface coil. Care 
was taken to perform the breast MRI of pre-menopausal 
women between the 5th and 15th days of the menstrual cy- 
cle. Conventional contrast MRI images were obtained with 
the following technique: axial fat-suppressed T2-weight- 
ed turbo spin-echo (repetition time/echo time; TR/TE), 
4500 ms/97 ms, 330 mm field of view (FOV), number of 
excitations (NEX): 1, matrix, 384 × 512; slice thickness of 
3 mm with a 1 mm intersection gap and fat-suppressed 
T1-weighted (TR/TE, 720 ms/20 ms; 330 mm FOV, NEX: 
2, matrix, 320 × 320; slice thickness of 3 mm), and fat-sup- 
pressed 3D T1-weighted images (4.3 ms/1.4 ms; flip-angle, 
12°, a FOV of 320 mm; matrix, 307 × 512; signal average 1; 
slice thickness, 1.5 mm fast low-angle shot [FLASH]) with 
and without contrast. Sagittal fat-suppressed 3D T1-weight- 
ed images were obtained six minutes after contrast ma- 
terial injection in addition to axial dynamic contrast-en- 
hanced images. The contrast agent (Dotarem, Laboratoire 
Guerbet, Roissy, France) was administered at 0.2 mmol/ 
kg via automatic syringe, followed by 15-20 cc of saline 
for homogeneous distribution of the contrast substance. 
DWI echo-planar images (TR/TE 8500/70, FOV of 330 mm, 
matrix 192 × 192, NEX: 1, sectional thickness 4.5 mm with a 
1 mm intersection gap) were obtained in the axial plane 
before contrast administration. DWI were obtained by dif- 
fusion gradients between 0 and 1000 s/mm² b-values.

Apparent diffusion coefficient analysis

An ADC map was automatically constructed in a commer- 
cially available workstation. Mean ADC values of all lesions 
were automatically measured by using these maps according 
to the formula ADC = (lnS0 – lnS)/b (signal intensity val- 
ues are measured as S0 at b = 0 s/mm² and S at b = 1000 s/ 
mm²). Measurements were performed by placing a region of 
interest (ROI) of 0.5 mm diameter on lesions. ADC measure- 
ments were performed on enhancing or solid parts of the 
lesions identified in conventional sequences. The ROI did 
not include normal parenchymal tissue, or haemorrhagic 
or necrotic areas. One radiologist with experience in breast 
MRI evaluated the images and performed measurements of 
ADC and rADC values. A minimum of three ADC meas- 
urements were performed, and the lowest ADC value was 
accepted. The ADC value of the contralateral breast at the 
same level was also measured after ADC measurements 
were completed for the lesion and ROI of the same diam- 
eter was used. The rADC was calculated as the mass ADC 
value divided by the ADC value of adjacent parenchyma. In 
addition, the maximum diameters of the tumours on sagit- 
tal and axial planes were measured and the mean of these 
values were expressed as “mean maximum size”.

Statistical analysis

SPSS 25.0 (IBM Corporation, Armonk, New York, Unit- 
ed States) software was used for the analysis of variables. 
The conformity of normal distribution of data was evalu-
ated by Shapiro-Wilk test and homogeneity of variances by Levene. While comparing benign and malign groups with each other according to age-independent-samples t-test with Bootstrap results were used, and for long and short diameter and ADC comparison Mann-Whitney U test with Monte Carlo simulation technique was used. In the comparison of hilux situation with malignity Fisher exact test was verified by Exact results. Odds ratio with confidence interval was used in order to show how many more times the hilum situation affects malignity. The relationship between the classification with cut-off value calculated according to ADC variable and the real classification was defined by examination of sensitivity, specificity, positive predictivity, negative predictivity, diagnostic accuracy, and ROC (receiver operating curve) analysis. Quantitative variables were presented as mean ± SD (standard deviation), minimum-maximum and median (minimum/maximum), and categorical variables were presented as n (%). Variables were examined in confidence interval of 95%, and the significance level for the study was set as p < 0.05.

Results

In our study there were 43 lymph nodes, 20 of which were malignant and 23 of which were benign. The mean age of the patients with benign lymph nodes was 39.52 ± 9.54 years (26-61), and the mean age of the patients with malignant lymph nodes was 50.05 ± 12.60 years (27-73). The mean age of the malignant group was significantly higher than that of the benign group (p = 0.005) (Figure 1).

While the mean length of the long diameter of malignant lymph nodes was 15 mm (7-34), it was 14 mm (7-30) for benign lymph nodes. There was no statistically significant difference between the two groups (p = 0.492).

The mean length of the short diameter of malignant lymph nodes was 9 mm (5-23), and it was 8 mm (5-14) for benign lymph nodes. There was no statistically significant difference between the two groups (p = 0.539).

The mean ADC value of malignant axillary lymph nodes was 0.749 10⁻³ mm²/s (0.48-1.342), and it was 0.982 10⁻³ mm²/s (0.552-1.986) for benign lymph nodes. There was a statistically significant difference between the two groups (p < 0.001) (Figure 2).

When the ADC cut-off value was taken as ≤ 0.753 × 10⁻³ mm²/s, its discriminative power between benign and malignant axillary lymph nodes was as follows: sensitivity – 60%, specificity – 91.3%, accuracy – 76.7%, positive predictive value – 85.7%, and negative predictive value – 72.4% (Figures 3 and 4).

Discussion

Breast cancer is the most common type of cancer in women, and despite advances in diagnosis and treatment, it is the second most common cause of cancer-related deaths after lung cancer [12]. Being the most important prognostic factor, the presence of malignant axillary lymph nodes in breast cancer plays a critical role in staging, treatment planning, and long-term survival [1,13]. On mammography, the axillary region can be evaluated partially. Classi-
The diffusion weight factor (b value) shows the extent to which the sequence is sensitive to the diffusion. When the b value is low, perfusion and the T2 time affect diffusion, and the diffusion weight of the sequence decreases. The perfusion of malignant tumours is markedly higher than that of the benign ones, and so at low b values the ADC of malignant lesions were measured as higher than it is. However, if the b value is equal to or higher than 600 s/mm², the effect of perfusion is shown to be minimal and can be ignored [22]. Because, when the b value increases the spatial resolution decreases significantly, and when the b value decreases then the perfusion effect appears, in our study the b value was taken as 1000 s/mm².

ADC is the mathematical expression of diffusion obtained as a result of marking the signal losses on the map after the application of diffusion gradients. In order to obtain an ADC map two imaginings with and without diffusion gradient are performed. The ADC value is the negative logarithm of the signal ratios of these two images [23].

The ADC value of free water molecules at 37°C is reported to be 3.0 × 10⁻³ mm²/s. This value is taken as the reference point, and it is the value at which the diffusion is maximum. When there is restriction to diffusion the ADC value decreases [11].

In most of the studies conducted in the literature, patients with diagnosis of invasive breast carcinoma were taken as a study group and by comparing ADC values of axillary lymph nodes, its contribution to differentiation of malignant and benign lymph nodes was investigated [24-26]. In the study conducted by Kim et al. [24] the ADC value for metastatic lymph nodes was 0.91 × 10⁻³ mm²/s and it was 1.27 × 10⁻³ mm²/s for benign lymph nodes; in the study of Razek et al. [25] the ADC value for metastatic lymph nodes was 1.08 × 10⁻³ mm²/s and it was 1.15 × 10⁻³ mm²/s for benign lymph nodes; in the study of Chung et al. [26] the ADC value for metastatic lymph nodes was 0.69 × 10⁻³ mm²/s and it was 1.04 × 10⁻³ mm²/s for benign lymph nodes; and in the study conducted by Hazanzadeh et al. [27] the ADC value for metastatic lymph nodes was 0.824 × 10⁻³ mm²/s and it was 1.098 × 10⁻³ mm²/s for benign lymph nodes. In these studies, the ADC values were significantly lower in metastatic lymph nodes.

When water molecules are placed in a container, they undergo Brownian motion without any obstacles. This motion, which is not restricted by anything, is called free diffusion [21]. The DWI value shows the level of diffusion of water molecules in tissues. The diffusion of water in tissues was restricted basically by cell membranes and cellularity of the tissue. When the cell membranes are destroyed, water molecules move freely or when the cellularity increases, which means the number of cell membranes increases (in tumoral processes) the motion of water molecules restricted [11]. In order to measure diffusion in tissues, before and after 180° RF pulses, two gradients having equal force and time (diffusion gradients) are applied in EPI sequences. These gradients should be strong enough to determine the movement dependent on diffusion. The diffusion weight factor (b value) shows the extent to which the sequence is sensitive to the diffusion.
primary breast disease, and then their ADC values were measured without knowing about primary breast disease, follow-up period, and pathology results [29].

Morphologically the most common cause of malignant-looking LAP is inflammatory pathologies. In the study conducted by Wang et al. [30] no significant morphological difference was established between the lymph nodes that underwent a change due to metastasis and inflammatory pathologies. In our study, there were 12 LAPs associated with inflammatory breast diseases (pathologically proven nine granulomatous mastitis and three acute suppurative mastitis), and their mean ADC value was \(0.868 \times 10^{-3} \text{mm}^2/\text{s}\). No statistically significant difference was found when compared with mean ADC value of metastatic axillary lymph nodes. However, in the lymph nodes with thickened cortex associated with systemic inflammatory diseases, the value of ADC was over \(1 \text{mm}^2/\text{s}\) and there was a statistically significant difference when compared with mean ADC values of metastatic axillary lymph nodes.

In the study conducted by Wang et al. [30] and Vandacavaye et al. [31] the signal of both the malignant and inflammatory lymph nodes was hyperintense on DWI, and it was specified that they were not differentiated from each other by using DWI signal. In also our study, all the lymph nodes showed hyperintensity on DWI in accordance with the literature.

The main limitations of our study are: the limited number of patients, exclusion of lymph nodes with diameter less than 5 mm, even if they have rounded shape and effaced hilum because of not being rounded shape and effaced hilum because of not being visualised on DWI, and the validity of the cut-off DC value only for the imaging protocols performed with the b values defined for our device.

### Conclusions

ADC values of axillary lymph nodes secondary to systemic inflammatory processes have been found over \(1 \times 10^{-3} \text{mm}^2/\text{s}\) and were significantly higher when compared with the ADC values of metastatic LAP (Figure 5), and the malignant-benign distinction could be made. However, in the axillary LAP associated with inflammatory pathologies of the breast, like granulomatous mastitis and acute suppurative mastitis (Figure 6), there was no significant difference between their ADC values, and the malignant-benign distinction could not be made. We believe that this information will be obtained more accurately and reliably in studies conducted with larger patient series.

### Disclosure

The authors declare no conflicts of interest.

---

**Figure 5.** 10 × 7 mm right axillary lymphadenopathies with diffuse cortical thickening, seen as hyperintense on diffusion-weighted imaging and hypointense on apparent diffusion coefficient (restricted diffusion) (ADC: 0.584 × 10^{-3} \text{mm}^2/\text{s}) (pathology: carcinoma metastasis from ipsilateral breast)

**Figure 6.** 14 × 12 mm sized left axillary lymphadenopathies with rounded shape, seen as hyperintense on diffusion-weighted imaging and hypointense on apparent diffusion coefficient (restricted diffusion) (ADC: 0.768 x 10^{-3} \text{mm}^2/\text{s}) (pathology: reactive hyperplasia associated with acute suppurative mastitis in the ipsilateral breast)
References


