Diagnostic accuracy of apparent diffusion coefficient value in differentiating metastatic form benign axillary lymph nodes in cancer breast

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Abstract Purpose: To detect axillary lymph node metastasis based on diffusion Weighted MR and apparent diffusion coefficient (ADC) in the known breast cancer cases.
Patient and methods: Forty-four patients were included in this study for preoperative MRI staging of the breast cancer and axillary lymph node assessment. The lymph node criteria (long/short-axis ratio, T2WI, DWI and ADC value) were included in the analysis. Images were obtained with diffusion sensitizing gradients of 0 and 750 mm²/s. The ADC was calculated.
Results: Thirty-two patients had metastatic axillary lymph nodes and 12 cases had no malignant LN involvement. There was no significant difference between both in S/L ratio, T2WIs & p = 0.079, respectively), while statistically significant difference between benign and malignant lymph nodes in both DWI and ADC mean values (p < 0.0001 & p < 0.007, respectively). The optimal ADC cut off value was ≤ 8 x 10⁻³ mm²/s for differentiation between benign and malignant lymph nodes with accuracy 96.7%, sensitivity 100%, specificity 87%, PPV 95.4% and NPV 100%.
Conclusion: Compared with lymph node size or routine magnetic resonance sequences, DWI and ADC are promising techniques for differentiating metastatic and non metastatic axillary lymph nodes in known breast cancer patients.

1. Introduction

Axillary lymph node involvement is the most common route of breast cancer metastases, and is an essential prognostic factor and an important determinant in the treatment of patients with breast cancer (1–4). Axillary lymph node dissection with histopathological examination of the surgical specimen is regarded as the gold standard for detecting involvement of the lymph nodes (1,2).
Axillary dissection is a separate procedure requiring hospitalization, general anesthesia, and a 1- to 2-week period of postoperative drain care (5,6). The effect of axillary lymph node dissection on long-term treatment results in invasive breast cancer is controversial; it is in fact frequently questioned because it is associated with high morbidity rates and neoadjuvant chemotherapy is already administered in aggressive local cancers (7).

With magnetic resonance imaging (MRI), computed tomography, and ultrasonography techniques, the preoperative assessment of axillary lymph node status is mainly based on the measurement of nodal dimensions, such as maximum long-axis diameter, short-axis diameter or long/short-axis ratio, but these techniques are somewhat limited. In addition, morphologic criteria (e.g., shape, thickened lobular cortex, displacement and/or absence of fatty hilum), enhancement patterns, and grouping of lymph nodes are further important parameters (8–11). All these criteria remain controversial, and recommendations for differentiation between metastatic and non-metastatic lymph nodes vary widely.

Diffusion-weighted imaging (DWI) facilitates the noninvasive characterization of various tissues on the basis of their water diffusion properties. Any architectural changes in the proportion of extracellular to intracellular water protons will alter the diffusion coefficient of the tissue (12–14), thus providing information about the biophysical properties of tissues in vivo. Quantitative measurement of apparent diffusion coefficient (ADC) could reflect the degree of restriction of diffusion of different tissues (15,16).

In the present study, we aimed to determine metastatic axillary lymph node involvement by a simple and noninvasive method with focus on the feasibility of DWI technique to detect metastatic lymph nodes in pathologically proven breast cancer patients.

2. Patients and methods

2.1. Patients

From July 2011 to April 2013, 48 consecutive patients (age range, 24–70 years) were included with histologically proven breast cancer and pre-operative MRI for staging and detection of axillary LN involvement. This study was approved by ethics committee of the University, and all patients gave written informed consent before being included. Four of these 48 patients were secondarily excluded for the following reasons: pulmonary metastases detected on MRI (n = 1), general health unsuitable for surgery (n = 1), cancelation of surgery by the patient (n = 1), and poor magnetic resonance (MR) image quality related to motion-artifacts (n = 1). Some cases had previous US examinations; we did not take these data and other morphological criteria into account or include them in statistical analysis.

2.2. Magnetic resonance imaging protocol and related dynamic data processing

Magnetic resonance imaging was performed on a 1.5 Tesla system (Philips, Achieva –Class B-USA) with the patient in the prone position and the breast suspended in 4 channel dedicated breast coil. After obtaining an axial localizer sequence, axial T1-weighted images [turbo-spin echo (TSE); repetition time (TR), 613 ms; echo time (TE), 9.1 ms; section thickness (ST), 3.5 mm], axial short T1 inversion recovery (STIR) sequences (TE: 9370 ms, TE: 70 ms, ST: 3.5 mm) were acquired [field of view (FOV): 400 × 350 mm].

For dynamic study a standard dose (0.1 mmol/kg) of contrast agent with gadolinium was injected through the antecubital vein in each patient immediately following the acquisition of precontrast series. Following the injection of contrast agent, 15 mL physiological saline flush was injected in each patient. After the contrast injection, DCE-MRI was performed with gradient-recalled sequences (TR, 4.4 ms; TE, 1.6 ms; flip angle, 12; FOV, 350 × 350 mm, 256 × 128; section thickness 1.5 mm with no section gap). Including those acquired during the precontrast period, a total of 7 series each consisting of 80 consecutive images were acquired. In every 51 s six subtracted images (image series achieved by subtracting the precontrast image from each series) were transferred to the mean curve analysis in the work station. After the dynamic study, sagittal late postcontrast fat-saturated T1-weighted TSE images (TR, 532 ms; TE, 4.01 ms; ST, 3.0 mm; FOV: 400 × 400 mm) were acquired in order to recheck and correlate the lesions and axillary lymph nodes.

DWI was performed using a diffusion-weighted echo planar imaging (EPI) sequence with spectral spatial fat suppression and parallel imaging (reduction factor = 2); TR/TE = 7000/71.5 ms, 3 NEX, matrix = 192 × 192, bandwidth = 1953 Hz/pixel, FOV = 36 cm, slice thickness = 5 mm, gap = 0. Diffusion gradients were applied in six directions with b = 0 and 750 s/mm², and the scan time was 160 s.

2.2.1. Measurements on MRI and image analysis

The axillary lymph nodes with the short-axis diameter equal to or greater than 5 mm were included in our study. The long-axis (L) and short-axis (S) diameters were measured on the corresponding maximum section of each lymph node on axial T2WI, respectively, and the long/short-axis ratio (L/S) was calculated. The signal intensity on T2WI and DWI (ST2WI, SDWI) of each selected lymph node was reported. The ADC maps were calculated on a pixel-by-pixel basis. We used the corresponding central slice of each lymph node on the ADC map, a round or elliptical region of interest (ROI) covering about 3/4 of the entire area of the selected lymph node attempting to avoid inclusion of the margins; while T2W imaging was used as the anatomical reference. The apparent diffusion coefficient (ADC) value was calculated for lymph nodes. The area of the ROI in the selected axillary lymph nodes was 25–150 mm², according to their different sizes. For ADC measurement, ROIs were placed in the LNs; all the values were averaged from three-time measurements and expressed as the mean ± standard deviation.

FNAB or/and true cut Biopsy were performed in dominant lymph node or nodes visualized in images in all cases. The dominant lymph nodes were identified according to the following criteria: asymmetric cortical thickening, cortical irregularity, cortical heterogeneity, hilar deformation and loss of fatty sinus, and loss of ovality (rounding).

2.2.2. Statistical analysis

Statistical analyses were performed by using Statistical Product and Service Solutions (SPSS, Version 15.0.1, Inc., Chicago,
IL). Differences of mean L/S ratio and the mean ADC values between the axillary malignant and non malignant lymph nodes were compared using independent t test. Fisher’s exact test was also used to assess the relationship between both groups’ signal intensity appearance on T2WI (SIT2WI) and signal intensity on DWI (SIDWI). A p value <0.05 was considered statistically significant.

3. Results

In the present study the patients’ age ranged from 24 to 70 years (mean 54 years). Among the 44 cases, dominant lymph nodes were evaluated consisting of 32 (72.7%) metastatic and 12 (27.2%) non malignant lymph nodes. Of thirty-two metastatic cases, 8 (25%) of the cases were bilateral and unilateral in 24 (75%) of the cases, while non malignant lymph nodes were bilateral in 3 cases and unilateral in 9 cases. The pathological results for 32 malignant breast cases were as follows: 21 invasive ductal carcinoma, 10 diagnosed as lobular carcinoma, and 1 medullary carcinoma. Regarding the 12 benign cases 5 of them were inflammatory and the other 7 cases were non specific enlargement.

The mean values of L/S ratio for the axillary benign (Fig. 1) and metastatic (Figs. 2 and 3) lymph nodes were 2.1 ± 0.12 mm, 1.6 ± 0.13 mm, respectively (table 1). Depending on the S/L ratio between the malignant and benign LNs there was no statistically significant difference. Depending on the signal intensity criteria on T2WI and signal-intensity of the LNs in DWI, there was no significant difference between the signal intensity of benign and metastatic LNs on T2 WI (p = 0.079), however, there was a statistically significant difference between non malignant and malignant LNs (p < 0.001) in DWI (Figs. 1 and 2, respectively).

The mean value of the ADC for the axillary metastatic LNs (Figs. 2 and 3) is lower (0.79 ± 0.23 × 10^{-3} mm²/s) than mean AD values for benign lymph nodes (1. 42 ± 0.57 × 10^{-3} mm²/s) (fig. 1). The difference between the two groups was statistically significant (Table 1).

In this study, statistical analysis of our results showed that optimal ADC cut off value for differentiation between benign and malignant lymph nodes is < 8 × 10^{-3} mm²/s with accuracy 96.7%, sensitivity 100%, specificity 87%, PPV 95.4% and NPV 100%.

4. Discussion

Preoperative detection of axillary lymph node metastases is desirable because in many settings it may allow a surgeon to bypass sentinel lymph node biopsy (SLNB) and proceed directly to complete axillary lymph node dissection (ALND), sparing patients an additional operative procedure and expediting their progression through their cancer treatment course (17).

DCE-MRI is now performed routinely in patients newly diagnosed with breast cancer at many institutions in preoperative evaluation as it had advantages over sonographic evaluation of the axilla which include the ability to compare directly axillary lymph nodes in question with the contralateral axilla and decreased dependence on operator experience. Unlike the evaluation of primary tumors on MRI, enhancement kinetics features have not proven useful for discrimination of abnormal nodes because many normal nodes exhibit kinetics features typical of breast malignancy (e.g., delayed washout) (18).

As a simple, fast, non-invasive and non-contrast tool, diffusion weighted imaging (DWI) has been the most potential representative of fMRI in LN mapping in recent years (13,15).

We found that no statistically significant difference between malignant and benign LNs depending on the S/L ratio,
similarly Stets et al. (3) and Michel et al. (4), stated that inaccurate differentiation between the metastatic and benign LNs depending on the LN size and this criteria gave is low sensitivity in the diagnosis of metastatic nodes (53–62%). Moreover, Obwegeser et al. (19) reported that, in histological analysis of 1249 axillary lymph nodes in 71 patients with breast cancer, 13.7% of metastatic nodes were 5–9 mm in short-axis diameter. Also we found, there was no statistical difference between axillary non metastatic and metastatic lymph nodes, regarding their signal intensity on T2WI, in agreement with the results obtained by Som (20).

In the present study the high signal intensity nodes on DWI were significantly higher than those on T2WI, the malignant
LNs were shown with marked high signal intensities on DWI that made it easy to identify. Similar to Wang et al. (21) findings in their study on rabbit models, stated that statistical significant difference comparing the signal intensity on T2 WI and DWI between inflammatory and malignant LNs groups.

On the contrary Vandecaveye et al. (22), found that the visual assessment of DWI to differentiate the axillary inflammatory from metastatic lymph nodes was rather a difficult task, as in some cases both groups’ lymph nodes showed high signal intensities on DWI. The ADC values calculated from DWI can provide quantitative analysis of microscopic water diffusivity in the target tissues and can completely exclude the T2 shine-through effect.

Among our patients lower ADC values were always observed in metastatic lymph nodes and there was a statistically significant difference in the ADC mean values between metastatic and non-metastatic axillary LNs. We use the optimal \( \leq 8 \times 10^{-3} \, \text{mm}^2/\text{s} \) ADC cut off value for differentiation between benign and malignant lymph nodes and this optimal cut off recorded high accuracy 96.7%, sensitivity 100%, specificity 87%, PPV 95.4% and NPV 100%. Near to our findings Kim et al. (23) reported that ADC value can help to differentiate malignant from benign LNs in predicting nodal metastasis in head and neck cancer. Using threshold value of 0.85 \( \times 10^{-3} \, \text{mm}^2/\text{s} \), the accuracy, sensitivity and specificity of ADC value for differential diagnosis are 91.0%, 91.3% and 91.1%, respectively. They stated the reasons for a more powerful diagnostic ability of DWI than other size-dependent imaging methods because, normal size LNs with micrometastasis are evaluated correctly and another is hyper plastic benign nodes are appropriately excluded. Also, Ilg et al. (24) found that, the ADC values of malignant lymph nodes were significantly lower than the benign ones \( (p = 0.001) \), but they used 1.22 \( \times 10^{-3} \, \text{mm}^2/\text{s} \) as the cut-off ADC value, and reported a sensitivity of 75.6% and a specificity of 71.1%.

On the other hand Wang et al., 17 had reported sensitivity, specificity and accuracy, which were 86.2%, 79.3%, 81.2%, when the rADC value (ADC lesion/ ADC reference site) was chosen as 0.80.

Further studies with a large number of subjects will increase confidence in the results of DWI and guide physicians involved in diagnosis, treatment and follow up of breast cancer patients.

In conclusion: DWI and ADC values had high accuracy for differentiating axillary non metastatic (benign) from metastatic lymph nodes.

Conflict of interest
None declared.

References


### Table 1
Comparison of the results of the mean value for the lymph node S/L ratio, T2WI, DWI signal intensity and mean ADCs of the metastatic and non malignant.

<table>
<thead>
<tr>
<th>MRI criteria</th>
<th>Malignant (n = 32, %)</th>
<th>Non malignant (n = 12, %)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mean S/L ratio</td>
<td>1.6 ± 0.13</td>
<td>2.1 ± 0.12</td>
<td>( p &lt; 0.140^b )</td>
</tr>
<tr>
<td>SIT2WI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypointense</td>
<td>2/32, 6.2</td>
<td>6/12, 50</td>
<td>( p = 0.079^a )</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>28/32, 87.5</td>
<td>5/12, 41.6</td>
<td></td>
</tr>
<tr>
<td>Heterogeneous</td>
<td>2/32, 8.6</td>
<td>1/12, 8.3</td>
<td></td>
</tr>
<tr>
<td>SI-DWI (B = 750)</td>
<td></td>
<td></td>
<td>( p &lt; 0.0001^a )</td>
</tr>
<tr>
<td>Hyperintense</td>
<td>31/32, 96.8</td>
<td>1/12, 8.3</td>
<td></td>
</tr>
<tr>
<td>Hypointense</td>
<td>1/32, 3.1</td>
<td>11/12, 91.6</td>
<td></td>
</tr>
<tr>
<td>Mean ADC ( (x10^{-3} , \text{mm}^2/\text{s}) )</td>
<td>0.79 ± 0.23</td>
<td>1.42 ± 0.57</td>
<td>( p &lt; 0.007^b )</td>
</tr>
</tbody>
</table>

L/S = long/short-axis ratio, SI-T2WI = signal Intensity on T2WI, SI-DWI = signal intensity diffusion-weighted imaging ADC = mean apparent diffusion coefficient p value < 0.05 was considered statistically significant.

\( ^a \) Fisher’s exact test.
\( ^b \) Independent-t test.


