Diagnostic value of MRI for predicting axillary lymph nodes metastasis in newly diagnosed breast cancer patients: Diffusion-weighted MRI

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Received 4 December 2015; accepted 16 March 2016
Available online 4 April 2016

Abstract Objective: Non-invasive preoperative detection of axillary nodal metastasis is beneficial for the outcome of breast cancer patients. We aimed to determine the value of DW MRI, ADC and their combination with MRI morphological criteria in detecting axillary metastasis.

Methods: We included recently diagnosed forty breast cancer patients. MRI morphological criteria, signal intensity on DWI, and ADC value were assessed and compared between metastatic and non-metastatic LNs using histopathological findings as reference standard. Sensitivity, specificity, PPV, NPV and accuracy for each variable and cutoff value of ADC were evaluated.

Results: No statistically significant difference between metastatic and non-metastatic LNs in short axis diameter or L/S ratio (p value: 0.87 and 0.82 respectively); however, loss of fatty hilum, high signal intensity on DWI and low ADC value were significant with increasing sensitivity on their combination. The mean ADC was 0.96 ± 0.9 mm²/s for metastatic and 1.53 mm²/s for non-metastatic LNs.

Keywords: Breast cancer; Axillary nodal metastases; Diffusion weighted MRI.
1. Introduction

Determining the axillary lymph node status is a crucial factor in treatment planning and prognosis determination in patients with breast cancer (1). Therefore, it is very important to preoperatively detect the lymph node metastasis. However, the accuracy of preoperative diagnosis of nodal metastasis is still challenging (2,3).

Traditionally, axillary dissection is used to obtain prognostic information in breast cancer; however, it is an invasive procedure that may adversely affect the quality of life (2,4).

Different imaging techniques such as magnetic resonance imaging, computed tomography and ultrasonography as well as and physical examination have not proven to be accurate in the detection of nodal metastasis (5–11).

Up to date used by conventional imaging modalities are shape, size, extracapsular spread and abnormal inner structures. The size is the most used parameter for the diagnosis, whereas the presence of central necrosis is the most accurate sign of malignity (12). Nevertheless several studies showed that these criteria are not enough to differentiate benign from malignant lymph nodes (13,14).

All these criteria remain questionable, and guidelines for the discrimination between non-metastatic and metastatic lymph nodes vary widely (6–8,15–17).

Diffusion-weighted MR imaging (DWI) analyzes water motion in tissues and any movements of the water protons leads to alteration of the signal intensity in DWI and ADC maps (12).

The purpose of our study was to assess the value of adding the DW-MRI including ADC measurement to the morphological criteria on increasing the detectability of metastatic lymph nodes in cancer breast patients.

2. Patients and methods

2.1. Study design and population

This study was prospectively conducted during the period from July 2013 to July 2015 at Diagnostic Radiology, Surgery and pathology departments, and included 52 breast cancer female patients referred to our institute for preoperative MRI evaluation. The study was approved by the local ethical committee, all patients were informed of the study aims and an informed written consent was obtained before participation.

We included recently diagnosed breast cancer patients defined as TNM stage I and II (18).

The Exclusion criteria were as follows: patients with carcinoma in situ (ductal or lobular; DCIS or LCIS) as they do not generally undergo axillary clearance surgery, previous surgical exploration of the axilla, biopsy or radiation therapy to axillary LNs.

From 52 included patients only 40 patients completed the study and the other 12 patients were further excluded due to patients unfit for surgery (3 patients), bad general condition interfere with completeness of MRI examination (4 patients), bad quality image from motion artifact (3 patients), and LN outside field of diffusion (2 patients). Patients’ age ranged between 29 and 65 years with mean age of 32 ± 7 and the affected side was left in 16 patients, right in 22 patients and bilateral affection in 2 cases.

All patients were subjected to MRI examination of the breast and axilla including all LNs levels (levels I, II and III), followed by axillary lymph node biopsy or surgical axillary clearance within two weeks of MRI examination (range from 2 to 15 days) by breast conservative surgery and axillary clearance.

2.2. MRI examination

Breast and axillary MRI examination was performed using a 1.5-T superconductive magnet (Intera Achiva Nova Dual system, Philips Healthcare, Best, the Netherlands). All patients were scanned with breast coil in the standard prone position.

MRI evaluation consisted of DWI and dynamic contrast enhanced MRI (DCE-MRI). The MR protocol is as follows:

- Initially coronal spectral selective attenuation inversion recovery (SPAIR) T2 weighted bilateral images of the entire breast were obtained with the following parameters: repetition time/echo time: 6000/140 ms, NEX: 2, matrix: 320 × 190 pixels, slice thickness: 5/1 mm.
- Then conventional breast MRI is performed:
  - Axial T1 weighted with fast spin echo sequence: repetition time/echo time: 467/9.9 ms, slice thickness 4/0 mm, matrix: 320 × 224, NEX: 1.
  - Sagittal T1 weighted fast spin echo images: repetition time/echo time: 617/15.5 ms, slice thickness 4/0 mm, matrix: 320 × 224, NEX: 1.
- Dynamic MR images were sequentially performed before 0, 90, 180 and 270 s after injection of 0.1–0.2 mmol/kg body weight of Gadopentetate dimeglumine. Axial fat suppressed T1 weighted (3D gradient echo) images were obtained with the following parameters: TR/TE: 5.8/2.8 ms, FOV: 35 × 35 cm, matrix: 320 × 320, slice thickness: 1.5 mm, NEX: 1.
• Subsequently Diffusion weighted images using single shot spin echo-echo planer imaging (SE-EPI) sequence in axial plane with spectral spatial fat suppression and parallel imaging (reduction factor = 2) were done. Sensitizing diffusion gradients were done with b0 & b1000 s/mm² with the following parameters: repetition time (TR): 4600–6800 ms, echo time (TE): 51 ms, field of view (FOV): 360x360 mm, flip angle: 90, Number of excitation (NEX): 2, matrix: 120x88 pixels, slice thickness: 4 mm and slice gap: 0 mm.

2.3. Image analysis

All MR images were reviewed by two radiologists (prestudy radiological investigation was not included in the evaluation) on separate sessions. All LNs detected on MRI examination were examined at SPAIR T2WI as an anatomical reference, and CE-FS-T1WI was used to rule out any misidentification of blood vessels as lymph nodes and lastly at DWI. The ADC values were calculated for all examined axillary lymph nodes. To ensure accurate ADC values of the suspected lymph nodes, the ROI is placed on the maximum diameter covering nearly the whole LN, the area of the ROI in the selected LN ranged between 20 and 60 mm² with a mean of 35 mm².

Each lymph node was identified and numbered on the MR images and printed on film. Criteria to differentiate benign from malignant lymph nodes included size, the long to short axis (L/S) ratio, lost fatty hilum, and signal intensity on DWI and ADC values. A short-axis diameter >10 mm, a ratio of long to short axis diameter <1.5 and diffusion restriction were considered indicative of a metastasis (16).

The detected lymph nodes were classified according to the anatomical location levels: Level I lateral to the pectoralis minor muscle (lower axillary nodes); level II located beneath the pectoralis minor muscle (midaxillary nodes) and level III medial to the pectoralis minor muscle (apical axillary nodes) (16). All axillary LNs detected by MRI examination were subjected to biopsy or surgical resection, surgeon doing the operation attended the image analysis session to ensure that all LNs seen on DWI were subjected to surgical resection and a diagram of the selected lymph nodes was simulated and made available to the surgeon in the operating room. Biopsy of the selected LNs was done by a radiologist under ultrasound guidance in 25 cases.

2.4. Surgical evaluation

Axillary lymph node dissection was done for 15 cases. This dissection was started by removal of all areolar tissues in front of the axillary vein starting beneath the tendinous portion of the pectoralis minor muscle after its division and dissection.

<table>
<thead>
<tr>
<th>SI</th>
<th>Malignant</th>
<th>Benign</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>122</td>
<td>12</td>
<td>134</td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
<td>70</td>
<td>74</td>
</tr>
<tr>
<td>Total</td>
<td>126</td>
<td>82</td>
<td>208</td>
</tr>
</tbody>
</table>

Table 1 2 × 2 Contingency table between the detectability of a high-signal-intensity node on DWI and node metastasis.

Fig. 1 A 46 year old female patient: (a and b) axial CE-FS-T1WI demonstrates malignant RT breast mass and multiple enlarged RT axillary LNs displaying oval shape and obliterated fatty hilum. (c and d) DWI & color coded ADC map showing high SI & blue color, and ADC value measures $0.644 \times 10^{-3}$ mm²/s denoting restricted diffusion (histopathologically proved as metastatic).
is continued downwards and laterally and any palpable lymph node is removed.

2.5. Histopathological correlation

All samples were evaluated for evidence of cancer by a pathologist who was blinded to the MRI results. The excised lymph node was analyzed by serial sectioning of the whole node after formalin fixation and paraffin embedding. Every section of 200 mm was stained with hematoxylin eosin and by immunohistochemistry (IHC) using a monoclonal antibody to cytokeratin (KL1 Immunotech, France) for the detection of micrometastasis (<2 mm) and isolated tumor cells (0.2 mm).

Final diagnosis for all lymph nodes was made by correlation between magnetic resonance diffusion readings and histopathological sections which were performed in all cases.

2.6. Statistical analysis

Data obtained by MRI, surgery and histopathology were collected and compared. Statistical analyses were performed by using SPSS, Version 15.0.1, Inc. (Chicago, IL), 80% power of the study and 95% CI and level of significance 0.05.

The mean size, L/S ratio and the mean ADC values were compared among benign and metastatic axillary lymph nodes using Chi-square test, t test and Mann–Whitney U test. Sensitivity, specificity, accuracy, positive and negative predictive values of data obtained by MRI examination in differentiating axillary LNs were analyzed using the histopathological findings as the gold standard. The cutoff value of ADC to differentiate between benign and metastatic axillary lymph nodes was calculated using receiver-operating characteristic curve analysis.

When there is difference in numbers of lymph nodes counted on MR images and those were resected during surgery, nodes seen in MRI only were included in the statistical analysis.

3. Results

Among 464 surgically excised LNs, 208 LNs were coordinated radiologically and pathologically and included in the analysis (126 (60.5%) metastatic and 82 (39.5%) benign). All of those 208 lymph nodes were detected in all series of MRI examination with a median of 6 LNs/patient (ranged from 2 to 10). DW MRI revealed high signal intensity in 134 LNs (64.4%) and low signal in 74 (35.6%). There are 12 false positive
LNs (proved to be inflammatory at histopathology) and another four false negative LNs were seen of low signal at DWI MRI (3 staged as N0(i+) and one as N1mi at histopathology) (Figs. 3 and 4).

The $2 \times 2$ contingency table (Table 1) provided a sensitivity of 96%, a specificity of 85%, a PPV of 91%, an NPV of 94%, and an accuracy of 92%, with $P = 0.001$ when the detectability of metastatic lymph nodes using diffusion restriction as a criterion compared with histopathological examination.

The median of short axis diameter of the metastatic and non-metastatic lymph nodes was 9.5 and 7.5 with a range of 4.2–28.9 mm and 3.5–28.4 mm respectively, and the mean of the long/short axis ratio was lower for metastatic LN measuring $1.3 \pm 0.46$ (0.8–2.09) than the non-metastatic one measuring $1.6 \pm 0.5$ (1.05–2.9). No statistically significant difference detected between the metastatic and non-metastatic LNs regarding these two variables with $p = 0.87$ for short axis diameter and 0.82 for L/S ratio.

The preservation or absence of fatty hilum in metastatic and non-metastatic LNs was found statistically significant ($P = 0.001$). It was preserved in 52 (63.4%) non-metastatic LNs and 48 (38%) metastatic LNs and lost in 30 (36.6%) non-metastatic and 78 (62%) metastatic LNs, with 61.9% sensitivity, 63.4% specificity, 72.2% PPV, 52% NPV and 62.5% accuracy.

The mean ADC value was significantly lower for malignant than for benign LNs measuring $0.86 \pm 0.9 \times 10^{-3}$ mm$^2$/s (range of 0.13–2.28) and $1.53 \pm 0.6 \times 10^{-3}$ mm$^2$/s (range of 0.94–2.89) respectively ($P$ value = 0.01) (Figs. 1 and 2).

The AUC was 0.924 (95% confidence interval, 0.888–0.959). Using an ADC value of $1.09 \times 10^{-3}$ mm$^2$/s as a cutoff value for distinguishing metastatic from non-metastatic LNs had sensitivity of 94.5%, a specificity of 93.6%, PPV of 96%, NPV of 94.7% and accuracy of 95.6% (Fig. 5).

The degree of agreement between ADC value and high signal intensity of lymph nodes at DW MRI was highly significant ($k = 0.96$ and $P = 0.01$).

Combination of the included predictors has improved the detection of lymph node metastasis, as adding the presence of high signal intensity on DW MRI to the measured ADC values increased the sensitivity, specificity, PPV, NPV and accuracy, and this was also yielded when adding the lost fatty hilum to the high signal of the LNs on DW MRI alone, with more increase achieved when using these three variables in association; on the other hand, no changes in the results were noted when we used the size criteria in addition, as shown in Table 2.

The N staging of the 126 metastatic LNs was N1mi = 4, N1 = 110 and N2 = 12 LNs. There was negative correlation between the value of ADC and the histopathological N stage of the lymph nodes, which is statistically significant ($p = 0.001$). Also the sensitivity, specificity, PPV, NPV and accuracy of measuring ADC value in the diagnosis of metastatic LNs were increased with increased nodal staging (Table 3).
The histopathological examination of the metastatic LNs (n = 126) revealed the following: N1mi = 4, N1 = 110 and N2 = 12 LNs. There was negative correlation between the value of ADC and the degree of the nodal involvement, which is statistically significant (p = 0.001). Also the sensitivity, specificity, PPV, NPV and accuracy of measuring ADC value in the diagnosis of metastatic LNs were increased with increased nodal affection (Table 3).

4. Discussion

Worldwide, breast cancer is the commonest form of cancer in women (19,20).

Axillary lymph node metastasis is one of the main factors affecting the prognosis of patients with breast cancer, and the 5-year survival for breast cancer patients has been changed according to the nodal affection; for example, in node-negative disease it measures 82.8% compared with 73% in 1–3 positive nodes, 45.7% in 4–12 positive nodes, and 28.4% in cases with more than 13 positive nodes (10,21,22).

However, diagnosis of these nodes currently requires pathologic analysis of the tissue biopsy or dissection after surgery which considered the gold standard for diagnosis; unfortunately both of them are invasive procedures (23).

The investigators made extensive effort to develop a noninvasive technique that accurately preoperatively assesses both sentinel and distant axillary lymph nodes metastasis, aiming to reduce the time and the cost of diagnosis as well as the risk of complication to the patients due to unnecessary axillary sampling (24).

Traditionally the size based criteria have been used as indicators for metastasis considering a lymph node with short axis more than 10 mm is positive for malignancy (13,25); however, many authors had studied the relation between the lymph node size and metastasis, they concluded that no significant relation observed between the short axis diameter and metastasis (15,16,24,26–30), and they mentioned a low sensitivity ranged from 53% to 62%, also in the study of Obwegeser et al. (31). On 1276 axillary lymph nodes they found that 13.7% of lymph nodes with metastasis had short axis ranged from 5 to 9 mm, in agreement with those studies where we found no statistically significant difference in the short axis diameter or the L/S ratio between metastatic and benign nodes and we found an overlap in the diameter of the short axis and the L/S ratio between both groups (p value: 0.87 and 0.82 respectively).
In studies of Gupta et al. (32), and Ragheb et al. (33), they reported that S/L ratio was an effective indicator for metastatic nodes. This discrepancy may be explained by the inclusion of different anatomical and histological subtypes as in both studies they examined head and neck lymph nodes.

Small number of studies had examined the relation between loss of the fatty hilum in axillary LNs and metastasis. Mortellaro et al. (34), in their study concluded that there was a significant correlation between the loss of the fatty hilum of the axillary lymph nodes (on T2 STIR images) and positive metastatic nodes and they declared that this study was the first report of this relation. Also in the study of Kaur et al. (35), they examined the axillary lymph nodes using ultrasound and they described a sensitivity, specificity, PPV, NPV and accuracy of 70.45%, 83.3%, 91.61%, 53.5% and 74.69% respectively for the loss of the fatty hilum as a predictor for axillary nodal metastasis, and in our study we found that the relation between the loss of the fatty hilum and the metastatic involvement of the LNs was statistically significant, giving 61.9% sensitivity, 63.4% specificity, 72.2% PPV, 52% NPV and 62.5% accuracy which were less than those described by Kaur et al. (35), and this difference may be due to the usage of different imaging modalities in the two studies.

Diffusion-weighted technique is a functional magnetic resonance imaging that does not require contrast administration; it has been intensively investigated in both preclinical models and patients with cancer for lymph node assessment (36).

The potentiality in the identification of nodes on DWI was significantly higher than that on T2WI, and the axillary lymph nodes were shown with marked high signal intensity when compared with the adjacent muscle and surrounding normal vessels on DWI that made it easy to identify (37).

In the present study, high signal intensity of the axillary LNs on DWI was detected in 134 nodes (122 with and 12 without metastasis) while low signal intensity was detected in 74 LNs (4 with and 70 without metastasis), the presence of high signal on DWI in metastatic LNs was found to be statistically significant ($P$ value = 0.001), and this was in agreement with Perrone et al. (12) and Ismail et al. (38).

However, Wang et al. (24) in their study on rabbit models, found that both the metastatic and the inflammatory lymph nodes presented with high SI on DWI and that there was no statistical significant difference comparing the signal intensity on DWI between inflammatory and metastatic LNs; they concluded that visual assessment of DWI to differentiate metastatic from inflammatory axillary lymph nodes was difficult because both groups showed high signal intensities on DWI.

Measuring the ADC value yielded quantitative assessment of the water diffusivity in the tissue and (39) the larger the $b$-value is, the greater the degree of signal attenuation from the motion of water molecules is (39,40). In the study of Wang et al. (24), they use a high $b$-value of 800 s/mm$^2$, and they assumed that high $b$ value could evaluate water diffusion more exactly and eliminate the effects of capillary perfusion.

Also in our study, DWI was carried out at high $b$ value of 1000 s/mm$^2$ and the obtained ADC values were significantly lower for LNs with metastasis than those without metastasis, but there was an overlap between both groups. Many other previous studies had published the same results (12,24,38,41); Wang et al. (24) gave an explanation for this overlap as they found that not all malignant LNs were totally replaced by tumor cells, resulting in areas of metastasis with lower ADC and another areas without metastasis with higher ADC, and also the ROI of the ADC in a lymph node may be heterogeneous, containing metastatic and non-metastatic portions. On the other hand, in non-metastatic LNs diffusion of water molecules may be limited by inflammatory cell infiltration, reactive hyperplasia, or fibrous connective tissue proliferation which leads to decrease in ADC value.

We observed a wide variation in the mean and cutoff value of ADC between the different studies, and in the present one, we found that the mean ADC for metastatic and non metastatic LNs was $0.86 \pm 0.9 \times 10^{-3}$ mm$^2$/s and $1.53 \pm 0.6 \times 10^{-3}$ mm$^2$/s respectively and the cutoff value of

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**Table 2** The sensitivity, specificity, PPV, NPV and accuracy of variables and its combination.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>Accuracy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High SI DW MRI</td>
<td>96.8</td>
<td>85.4</td>
<td>91</td>
<td>94.6</td>
<td>94.3</td>
</tr>
<tr>
<td>High signal with ADC value</td>
<td>98.4</td>
<td>95.2</td>
<td>96.9</td>
<td>97.5</td>
<td>97.4</td>
</tr>
<tr>
<td>Fatty hilum absence</td>
<td>55.6</td>
<td>52.4</td>
<td>64.2</td>
<td>43.4</td>
<td>54.3</td>
</tr>
<tr>
<td>Fatty hilum absence with High SI at DW-MRI</td>
<td>97</td>
<td>85</td>
<td>97.3</td>
<td>95</td>
<td>94.8</td>
</tr>
<tr>
<td>Fatty hilum absence with High SI at DW-MRI and ADC value</td>
<td>98.4</td>
<td>95</td>
<td>97</td>
<td>97.3</td>
<td>97.5</td>
</tr>
</tbody>
</table>
ADC for differentiating benign from malignant nodes was $1.09 \times 10^{-3} \text{mm}^2/\text{s}$, with a sensitivity of 94.6%, a specificity of 93.6%, PPV of 96%, NPV of 94.7% and accuracy of 95.6%, which is nearly the same as the results of Perrone et al. (12), who found that the mean ADC value for malignant lesions was $0.85 \times 10^{-3} \text{mm}^2/\text{s}$, and $1.448 \times 10^{-3} \text{mm}^2/\text{s}$ for benign ones while the cutoff value of ADC for differentiating benign from malignant nodes was $1.03 \times 10^{-3} \text{mm}^2/\text{s}$, with a sensitivity of 100% and a specificity of 92.9%. Also, İşıl et al. (42) used $1.22 \times 10^{-3} \text{mm}^2/\text{s}$ as the cutoff value of ADC, with a sensitivity of 75.6% and a specificity of 71.1%. And Ismail et al. (38) used the optimal $0.8 \times 10^{-3} \text{mm}^2/\text{s}$ as ADC cutoff value for distinguishing benign and malignant lymph nodes with recorded accuracy 96.7%, sensitivity 100%, specificity 87%, PPV 95.4% and NPV 100%. Also Wang’s et al. (24) results in their study on rabbit models showed that the ADC value of the axillary inflammatory lymph nodes $(0.9 \pm 0.14)$ was significantly higher than that of metastatic ones $(0.7 \pm 0.18)$. The researchers have been attributed this variation to that ADC value which had been affected by many factors, such as MRI acquisition parameters, the magnetic field, location, size and area of ROI, patient age as well as the body temperature (36).

In contrast to these results other publication described that the ADC value of metastatic LNs was significantly higher than that of non metastatic one $(1.43, 44)$; the difference between those studies and our one had been explained by the differences in the histological types; and also in the study of Kamitani et al. (1) they did not use a node by node basis to compare the DWI with histopathology results.

In this study we also examined the value of combination of various predictors on the detectability of axillary LNs metastasis, and we found that adding the high signal intensity of the LNs on DWI to the cutoff value of the ADC improves the sensitivity, specificity, PPV, NPV and accuracy of the test measuring 98.4%, 95.2%, 96.9%, 97.5%, and 97.4%. Also we observed increase in the examination sensitivity when using all of high signal on DWI, ADC cutoff value as well as loss of the fatty hilum in combination measuring 98.4%, 97.5%, 98.4%, 97.5%, and 98%, but the results were not better when we used the size criteria in addition, and this is in accordance with Kamitani et al. (1), who stated that the use of high signal intensity on DWI and the threshold ADC value in combination has increased the diagnostic accuracy for differentiating metastatic from benign lymph nodes. Also Kvistad et al. (45) in their study on dynamic contrast enhanced MRI in the pre-operative diagnosis of axillary LNs metastasis, concluded that their results were not better when the size and morphology of the lymph node were used as additional criteria.

In the present study we try to avoid the limitations mentioned in previous publications, as we examined the lymph nodes on node by node basis and not patient by patient basis; we included the patients blindly prior to operation or LN biopsy; and additionally we made a combined assessment of the criteria examined. However, we faced several other limitations. First: all included patients had breast cancer and this may lead to bias. Second: the low spatial resolution is more worse at high b values ($b = 1000 \text{s/mm}^2$), which was necessary to improve the sensitivity of DWI. The third limitation was as described previously that MRI has low sensitivity in detecting LNs less than 5 mm in diameter, reducing the detect-ability of the LNs in our study. MRI could detect only 44.8% of the surgically excised LNs.

In conclusion, no currently accurate MR criteria are established for the determination of axillary nodal metastasis in breast cancer patients. However, we found a high sensitivity when using DWI and ADC in the detection of metastatic LNs. Also, the combination of the cutoff value of ADC and lost fatty hila has increased the diagnostic accuracy for distinguishing metastatic from benign lymph nodes.

**Conflict of interest**

We have no conflict of interest to declare.

**References**

Value of MRI for predicting axillary metastasis


