Pre-operative Diffusion-weighted Imaging (DWI) and Apparent Diffusion Coefficient (ADC) ratio in assessment of axillary lymph node status in patients with breast cancer: personal experience and literature review.

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Learning objectives

The DWI and ADC in pre-operative breast MRI might represent a valid diagnostic tool for differentiation of benign from metastatic axillary lymph nodes in patients with newly diagnosed breast cancer.

- Breast cancer is the most commonly diagnosed cancer among women throughout the world and its incidence continues to increase.

- The presence of axillary lymph node metastases in patients with breast cancer helps determine surgical and postsurgical management and remains the most important prognostic factor.

- The non-invasive differentiation between benign and malignant lymph nodes remains challenging; as a consequence the final diagnose of the metastatic nodes is currently based on pathologic analysis of tissue biopsy or axillary lymph node dissection, both of which are invasive procedures.

- The combination of DWI and ADC ratio seems to represent a promising and readily available non-invasive method in the differential diagnosis between metastatic and benign axillary lymph nodes in patients with breast cancer.
Background

The role of breast MRI in the assessment of axillary lymph nodes in breast cancer

The main goal for pre-operative imaging is to identify the presence of axillary metastases with a positive predictive value that is high enough to be useful to the surgeon in deciding when to proceed directly to ALND (axillary lymph node dissection).

ANATOMY OF AXILLARY REGION:

Familiarity with axillary anatomy is important, both to be able to thoroughly examine the axilla with ultrasonography (US), as well as to accurately identify the location of abnormal lymph nodes with any cross-sectional imaging modality (Figure 1).

Level I
- inferolateral to the pectoralis minor muscle
- within the axillary fat
- often seen near the axillary vein

Level II
- receive lymph from level I nodes
- located in the fat behind the pectoralis minor muscle
- also located between the pectoralis minor and pectoralis major muscle in an area called the Rotter space

Level III
- receive lymph from level II nodes
- represent the final step in lymph drainage through the axilla and drain into the subclavian lymphatic trunk and supraclavicular nodes, a path that ultimately leads to the thoracic duct

NORMAL LYMPH NODE MORPHOLOGY:

The normal axillary lymph node should be oval or bean shaped and should have smooth, well-defined margins. Normal lymph nodes range in size from few millimeters to about 1-2 cm long.
Each lymph node is surrounded by a continuous collagenous capsule and consists of two main regions: outer cortex and inner medulla. The collagenous capsule is only incomplete at the hilum where a single nodal artery enters the node and a single vein and a single efferent lymphatic vessel exit the node (Figure 2).

**METASTATIC LYMPH NODE MORPHOLOGY:**

Breast metastases generally enter the node through an afferent lymphatic vessel and then deposit in the subcapsular sinusoids. Metastatic deposits measuring less than 0.2 mm are called "isolated tumor cells", and deposits between 0.2 and 2.0 mm are called "micrometastases". This level of disease is not identifiable at imaging.

One model suggests that tumor cells spread in orderly fashion from the cortex into the deeper nodal parenchyma, proliferating along the medullary sinuses and then into the efferent lymphatics (Figure 3).

The growing metastasis coalesces and replaces normal nodal architecture, resulting then as focal cortical bulge or eccentric cortical thickening, which is detectable at imaging.

**GENERAL IMAGING FEATURES OF LYMPH NODE METASTASIS**

**US Evaluation**

- Diffuse, focal or eccentric cortical thickening, partial or complete obliteration of fatty hilum and nonhilar cortical blood flow (NHBF) on color Doppler imaging associated with tumor neovascularity. The above mentioned findings showed up to be more important than the size criteria in the identification of metastases and this is mainly because metastases can be also present in non-enlarged lymph nodes and thus not all enlarged nodes are malignant. Imaging findings are described in Table 1 and Figure 4.

**Table 1**

**Selected US Findings of Lymph Node Metastasis**

<table>
<thead>
<tr>
<th>US Findings</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse cortical thickening</td>
<td>Cortical thickness &gt; 3 mm, relatively nonspecific, can be seen in reactive nodes</td>
</tr>
</tbody>
</table>
Focal cortical bulge
Should be distinct, otherwise less specific; more specific if associated with another findings such as NHBF

Eccentric cortical thickening
Should be distinctly eccentric, otherwise less specific

Rounded hypoechoic node
High specificity in the setting of invasive cancer

Complete or partial effacement of the fatty hilum
High specificity in the setting of invasive cancer

NHBF on color Doppler images
Nonspecific unless combined with another finding, such as effacement of the fatty hilum

Complete or partial replacement of the node with an ill-defined or irregular mass
High specificity

Microcalcifications in the node
Should correlate with microcalcifications in the primary tumor


MRI

• One potential advantage that MR imaging has over US is that it gives a more global view of both axillae. This capability enhances the detection of potentially abnormal nodes (number, morphology and functional characteristics) and allows comparison of the axillae.
• It has been shown that the use of dedicated axillary MR imaging protocols improves the accuracy of MR imaging nodal staging.
• Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) are now widely used in routine clinical breast MRI.
• In our practice all patients are imaged in the prone position for both conventional and DW imaging to include as much of the axilla as is possible in the field of view, from the level of the suprasternal notch line down. We use axial orientation for bilateral dynamic breast MRI. Imaging findings are described in Table 2 and Figure 5.

Table 2

Specific MRI Lymph Node Findings Considered Suspicious

Irregular margins or apparent spiculation
Cortical nodularity or thickening
Replaced fatty hilum
Perinodal edema
Rim or heterogeneous enhancement

Fig. 1: Anatomy of axillary region.

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Fig. 2: Normal lymph node morphology. High-power photomicrograph (a) and schematic illustration (b) of normal nodal architecture. (Figure a. courtesy of Carla Di Loreto, MD, Institute of Pathology, Azienda ospedaliero-universitaria di Udine, Italy - Udine/IT)

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Fig. 3: Metastatic lymph node morphology. High-power photomicrograph (a) and schematic illustration (b) of normal lymphoid cells and metastatic cells mixed in a heterogeneous fashion. (Figure a. courtesy of Prof. Carla Di Loreto, MD and Enrico Pegolo, MD, Institute of Pathology, Azienda ospedaliero-universitaria di Udine, Italy - Udine/IT)

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**Fig. 4:** Selected US findings of lymph node metastasis. Diffuse cortical thickening (a), focal cortical bulge (b), rounded hypoechoic node (c), NHBF on color Doppler images (d) and microcalcifications in the node (e).

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**Fig. 5:** Specific MRI Lymph Node Findings Considered Suspicious. Irregular margins on MIP of Gd-enhanced T1 subtracted image (a), cortical nodularity on T1-weighted image (b) and replaced fatty hilum on T2-weighted STIR image (c).

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Findings and procedure details

The diagnostic accuracy of DWI and ADC in predicting axillary lymph nodes status

DWI - Diffusion weighted imaging (DWI) is a non-contrast MRI technique that can provide unique information about intercellular water motion (Figure 6). Every change in the movement of water protons produces a variation of signal intensity on DW images and, as a consequence, apparent diffusion coefficient (ADC) maps, being sensitive to certain parameters such as cell organization, cell density, microstructure and microcirculation.

Initial reports demonstrated that DW imaging may be a valuable tool for identifying and characterizing breast lesions and monitoring treatment response.

Because of its high sensitivity, DWI might find its utility also in detecting malignant axillary lymph nodes.

ADC - is calculated automatically and then displayed as a parametric map that reflects the degree of diffusion of water molecules through different tissues. Then, by use of a dedicated workstation, ADC measurements are recorded for a given region by drawing regions of interest (ROIs) on the ADC map. The mean ADC of metastatic lymph nodes shows up to be lower than that of benign nodes, as a result of more condensed cells and thus restricted water molecules diffusion (Figure 7).

**Case 1**: Invasive lobular carcinoma in 70-year-old woman with palpable left breast nodule. US-guided FNA confirmed the presence of metastatic disease in the left axilla (Figure 8).

**Case 2**: 37-year-old woman with history of previous bilateral breast reduction surgery (1983) and voluminous palpable mass of the left breast. Core needle biopsy was performed, yielding histology consistent with intermediate grade ductal carcinoma. (Figure 9).

**Case 3**: 69-year-old woman at high familial risk for breast cancer with palpable nodule of the left breast. Core needle biopsy was performed, yielding histology consistent with invasive ductal carcinoma. The patient underwent breast DCE MR examination for staging malignancy (Figure 10).

**Case 4**: Invasive ductal carcinoma of the right breast in 65-year-old woman with palpable nodule of the right breast (Figure 11).
**Case 5**: Invasive lobular carcinoma in 70-year-old woman with palpable left breast nodule (Figure 12).

**Case 6**: 48-year-old patient with newly diagnosed right breast cancer - grade II invasive mucinous carcinoma (Figure 13).

**THE LITERATURE REVIEW**

There are few research articles published in the medical literature in English, which confirmed the usefulness of DWI in differentiating metastatic from non-metastatic lymph nodes, reporting a statistically significant difference (P < 0.01 or less) between the mean ADC value measured in the former and in the latter condition (Figure 14 - Table 3).

Adopting a threshold value of 1.09x10⁻³mm²/s DWI resulted in 94.7% sensitivity, 91.7% specificity, and 93.0% accuracy in the identification of metastasis in the series of lymph nodes (Figure 14 - Table 4).

On the other hand, Schipper et al. (Diagnostic Performance of Dedicated Axillary T2-and Diffusion-weighted MR Imaging for Nodal Staging in Breast Cancer. Radiology Dec 2014, 15:141167) showed in their study that the quantitative measurement of the mean ADC of each lymph node has low diagnostic performance (AUC, 0.54-0.58), with no statistically significant difference in mean ADC between lymph nodes with and those without macrometastasis. The diagnostic performance of dedicated axillary T2-and Diffusion-weighted MR imaging for nodal staging in patients with breast cancer is insufficient to replace sentinel lymph node biopsy in clinical practice.
**Fig. 6:** Schematic illustrates Brownian motion, the random motion of particles suspended in a fluid.

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Fig. 7: Axial DW MR image (a) demonstrates relatively high signal intensity of the right axillary lymph node due to low diffusivity. Corresponding axial ADC map (b) shows low "gray value". Images demonstrate an example of a histopathologically proven malignant lymph node.

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Fig. 8: US color Doppler image (a) of the axilla demonstrates an abnormal lymph node with complete effacement of the fatty hilum and echogenic calcifications. Axial T1- and T2-weighted STIR images (b, c) show disomogeneous signal intensity. DWI image (d) demonstrate the affected lymph node has high signal intensity and is dishomogeneously low on the ADC (e). In the ADC color map (f) a $0.988 \times 10^{-3}$mm$^2$/s ADC value was measured.

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Fig. 9: US gray-scale image (a) demonstrates diffuse cortical thickening of left axillary lymph node. Axial T1-weighted MR image (b) demonstrates an abnormal, lobulated axillary lymph node with slightly irregular margins. DWI image (c) shows high signal intensity of the same node and low on ADC (d), indicating the presence of restricted diffusion. In the ADC color map (e) a $0.674 \times 10^{-3} \text{mm}^2/\text{s}$ ADC value was measured. Histopathologic report yielded metastasis.

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Fig. 10: Axial maximum intensity projection image from a subtracted T1-weighted DCE MR imaging sequence (a) confirms the known left breast retroareolar mass (red arrow) and also reveals a right breast retroareolar lesion (white arrow) with associated abnormal enlarged, rounded and enhancing homolateral axillary lymph node (blue arrow). Subsequent biopsy of the right breast retroareolar mass yielded histology consistent of grade II invasive lobular carcinoma. Second-look US image (b) also demonstrates complete effacement of the fatty hilum of the affected lymph node, yielding histopathology consistent of metastasis. Axial DWI (c) and ADC map (d) of the same lymph node with ADC value of 0.515x10⁻³mm²/s (e).

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Fig. 11: Axillary gray-scale US image (a) depicts an abnormal node with a distinct focal cortical bulge that involves the higher pole, suspicious for metastatic disease. T1-weighted MR image (b) obtained without fat saturation confirmed an abnormal level I lymph node. DWI image (c) demonstrates the affected node with focal cortical bulge has high signal intensity and is low - 0.754x10^3mm²/s - on the ADC (d, e), indicating the presence of restricted diffusion. Histological analysis confirmed the presence of metastatic disease.

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Fig. 12: Axial T1-weighted MR image (a) and axillary gray-scale US image (b) demonstrate the affected node with eccentric cortical thickening. On DWI image (c) the node shows slightly higher intensity and lower intensity on the ADC (d). In the ADC color map (e) a $0.953 \times 10^3 \text{mm}^2/\text{s}$ ADC value was measured.

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Fig. 13: US color Doppler image (a) of the right axilla showed a round and hypoechoic lymph node, with complete effacement of the fatty hilum and abnormal vascularity. Axial T2-weighted STIR image (b) demonstrates right axillary lymph node with rounded shape, thickened cortex and no perceptible fatty hilum. The affected node has high signal intensity on DWI image (c) and is slightly lower - $0.927 \times 10^3 \text{mm}^2/\text{s}$ - on the ADC (d, e).
### Table 3

<table>
<thead>
<tr>
<th>Author</th>
<th>Nº patients</th>
<th>Year</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td>Francesca Fornasa, et al.</td>
<td>215</td>
<td>2012</td>
<td>94.7%</td>
<td>91.7%</td>
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<tr>
<td>Anabel M. Scaranelo, et al.</td>
<td>74</td>
<td>2012</td>
<td>84%</td>
<td>77%</td>
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<tr>
<td>Ni He, et al.</td>
<td>136</td>
<td>2012</td>
<td>85.8%</td>
<td>84.6%</td>
</tr>
<tr>
<td>Ningbin Luo, et al.</td>
<td>36</td>
<td>2013</td>
<td>82.2%</td>
<td>82.3%</td>
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<tr>
<td>Eun Jeong Kim, et al.</td>
<td>252</td>
<td>2014</td>
<td>75.8%</td>
<td>83.9%</td>
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</table>

### Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Mean ADC metastatic lymph nodes</th>
<th>Mean ADC benign lymph nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Francesca Fornasa, et al.</td>
<td>2012</td>
<td>$0.878 \times 10^{-3}$ mm$^2$/s</td>
<td>$1.494 \times 10^{-3}$ mm$^2$/s</td>
</tr>
<tr>
<td>Anabel M. Scaranelo, et al.</td>
<td>2012</td>
<td>$0.673 \times 10^{-3}$ mm$^2$/s</td>
<td>$0.720 \times 10^{-3}$ mm$^2$/s</td>
</tr>
<tr>
<td>Isil Basara, et al.</td>
<td>2013</td>
<td>$1.00 \times 10^{-3}$ mm$^2$/s</td>
<td>$1.39 \times 10^{-3}$ mm$^2$/s</td>
</tr>
<tr>
<td>Ningbin Luo, et al.</td>
<td>2013</td>
<td>$0.787 \times 10^{-3}$ mm$^2$/s</td>
<td>$1.49 \times 10^{-3}$ mm$^2$/s</td>
</tr>
</tbody>
</table>

**Fig. 14**

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Conclusion

- In clinical practice, it is still difficult to discover the early metastasis involving axillary lymph nodes in patients with breast cancer.

- Given current estimates of diagnostic accuracy, an alternative strategy, where MRI is added to the current pathway before ALND/SLNB (sentinel lymph node biopsy), could be considered. This way, women at greatest risk (positive for nodal metastases by any of ultrasound, biopsy or USPIO-enhanced MRI) could be triaged for ALND, whilst those who are negative would still receive SLNB and benefit from the high specificity of this procedure. Fewer women would have to undergo two operations, namely SLNB followed by ALND where positive.

- Preliminary data indicate that the ADC ratio might be a reliable and accurate parameter to detect early metastatic axillary lymph nodes in breast cancer patients. Finally, ADC value of metastatic lymph nodes showed up to be lower than those of benign lymph nodes in patients with breast cancer. Furthermore, the ADC ratio, which is calculated between axillary lymph nodes with primary breast lesion, was significantly lower in metastatic lymph nodes when compared with benign lymph nodes (P<0.05).

- Not only metastasis, but also reactive hyperplasia or fibrotic proliferation, might affect diffusion. SLNB is currently the most accurate method to rule out small micrometastatic nodal disease in breast cancer. In the recent studies it is believed that the micrometastases remain beyond the morphologic resolution of any clinically available MR technology.

- Lymph node-specific contrast material-enhanced MR imaging could be of potential benefit, although there is a need for more studies and further research with standardised methods and criteria for classifying a node as positive before any changes to policy and practice should be considered.
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References


