Differentiating between benign and malignant axillary lymph nodes in breast cancer patients using sono-elastography and diffusion-weighted MRI

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Purpose

Lymphatic metastasis is the most important prognostic factor in patients with breast cancer. Determination of nodal status is also critical for appropriate treatment planning. Lymph nodes can be detected and visualized by several imaging modalities including ultrasound (US), computed tomography (CT) and magnetic resonance imaging (MRI). However, the differentiation between benign and malignant lymph nodes remains challenging [1].

Ultrasound is the noninvasive most commonly used diagnostic tool in the assessment of the axilla. The dimensional and morphological criteria on which the US diagnosis of nodal metastases is based, however, are not completely reliable [2].

Sonoelastography is a method for visualizing the elasticity characteristics of a lesion. On the basis that malignant tissues tend to lose their elastic properties and become harder in consistency [3]. It has been reported to be helpful in the differential diagnosis of metastasis in cervical and inguinal lymph nodes [4]. Because Real-time elastography combines the penetration depth and resolution of ultrasound with high sensitivity to stiffness contrast, it can detect the superficial LNs, which elude palpation due to their small size or their deep location within the body [5]. Both qualitative; Elasticity score (ES) and semi-quantitative; strain ratio (SR) assessments are used for the interpretation of real-time elastography [6].

Diffusion-weighted imaging (DWI) is a MRI technique based on the imaging of the molecular mobility of water. With DWI qualitative and quantitative information about differences in diffusion capacities in benign and malignant tissues can be obtained [7]. The axillary lymph nodes are shown with marked high signal intensities in comparison to the adjacent muscle and surrounding normal vessels on DWI that makes it easy to identify [8]. Due to the different cellular density and extracellular diffusion, metastatic lymph nodes may be distinguishable from normal lymph nodes with ADC measurements [1].

*The purpose of this study was to evaluate the role of sonoelastography and DWI in differentiating between benign and malignant axillary lymph nodes.*
Methods and materials

This prospective study was performed during the period from July 2014 to July 2015 at Radiology Department, Mansoura University. It included 30 patients. Their age ranged from 26 to 57 years. Inclusion criteria were the presence of axillary lymph nodes with suspicious criteria or associated with suspicious breast lesion diagnosed by clinical examination and B mode ultrasound scan.

**B mode/ elastography scan** were performed using an ultrasound machine with embedded elastography module, equipped with 6.2~12 MHz linear array transducer.

The patient was placed in the supine position with elevation of affected arm and leaning to the other side.

For each enlarged axillary lymph node, B mode ultrasound images were first obtained. Shape represented by longitudinal to transverse diameter (L/T) ratio, size represented by transverse diameter (T) in mm, cortical thickness measured in mm and hilum state classified as preserved, compressed or faint of each axillary lymph node were evaluated and recorded. B mode score was used to sum up the 4 criteria.

After that, the system was switched into elastography mode to evaluate the stiffness of the lymph node.

Manual compression and decompression were applied using the probe with only light pressure, perpendicular to the skin. Elastogram appeared in the region of interest (ROI) to determine the elasticity of the target lymph node and the surrounding tissue represented by color scale that ranged from red (softest component) to green (intermediate stiffness) and blue (hardest component). Each lymph node was given an elasticity score.

1. **Qualitative assessment** of the elastograms, lymph node classification was performed on the basis of a 4-point scoring system (Fig. 1 on page 5) proposed by [9]:
   1. Absent or very small blue area
   2. Small, scattered blue areas, total blue area <45%
   3. Large blue area, total blue area ≥45%
   4. Blue area with or without a green rim

2. **Strain ratio (semi-quantitative assessment)** was obtained by comparing the absolute strain value of the lymph node cortex with that of surrounding subcutaneous fat
of highest strain. The strain ratio was calculated automatically by an embedded software program in the ultrasound unit.

**MRI** and **DWI** were performed using a 1.5 T machine. Patients lied in supine position and surface coil was applied in close contact with the axillary region. Image acquisition (axial and coronal T2, axial T2 SPAIR, DWI at b 0, 500,1000 and ADC maps) followed by image post-processing were performed.

(1) **Qualitative assessment:** Visual assessment of signal intensity in DW images at b 500 and 1000 and the corresponding ADC map images (Fig. 2 on page 5) was determined and classified as follows:

- Free diffusion; high or intermediate SI on DWI without decrease in SI on the corresponding ADC map,
- Partially restricted; high or intermediate SI on DWI with partial decrease or loss of SI on corresponding ADC map and
- Restricted; high or intermediate SI on DWI with total decrease or loss of SI on the corresponding ADC map.

(2) **Quantitative assessment:** mean ADC value was calculated by manually drawing regions of interest (ROI) in the most restricted (hypointense) portion of the selected LN on the ADC map. Multiple measurements were acquired and the mean value was calculated.

Finally, findings of B-mode ultrasound, elastography and DWI were compared with pathological results (reference standard) either cytological by FNAC or histological by core needle, excisional biopsy or axillary dissection according to the surgeon’s choice.

Standard statistical evaluation tools were used. Data were expressed as mean± standard deviation (SD) for quantitative parametric measures, in addition to median percentiles for quantitative non-parametric measures and both number and percentage for categorized data. For comparison between two independent mean groups for parametric data, T test was used, while, Chi-squared test was applied to study the association between each two variables or comparison between two independent groups as regards the categorized data. The probability of error (P value) at 0.05 and less was considered significant. ROC curves were constructed to obtain the best cutoff values and diagnostic validity test was done to calculate diagnostic performance.
Fig. 1: Elasticity scoring system for axillary lymph nodes

Fig. 2: Diagram shows patterns of axillary lymph node signal intensity observed on DW images and ADC maps for qualitative analysis. B = benign, M = malignant.

Results

Thirty patients with 30 Lymph nodes were evaluated of which 18 nodes were malignant and 12 nodes were benign.

**B-mode ultrasound criteria:**

There was a statistically significant difference in 3 criteria between benign and malignant nodes; transverse diameter \( (P =0.0004) \), cortical thickness \( (P =0.002) \) and hilum state \( (P =0.006) \) whereas L/T ratio showed insignificant difference \( (P = 0.14) \).

Cutoff values and their diagnostic performance are shown in (Table 1A).

Summation score >2 resulted in 77.78% sensitivity, 66.7% specificity and 73.3% accuracy in differentiating benign and malignant axillary nodes.

**Sonoelastography:**

- Score "3 or 4" was found in 16 out of 18 (88.8%) malignant nodes and score "1 or 2" was found in 10 out of 12 benign nodes (83.3%). The mean elasticity score (ES) in malignant nodes \( (3.33\pm 0.7) \) was significantly higher than that of benign nodes \( (1.83\pm 0.7) \) \( (P<0.0001) \).

**Elasticity score >2** was the best cutoff for malignancy, resulted in sensitivity, specificity and accuracy of 88.89%, 83.33% and 86.67% respectively.

- The mean SR of malignant nodes \( (8.26 \pm2.8) \) was significantly higher than that of benign ones \( (2.08 \pm1.8) \) \( (P<0.001) \).

**SR > 2.4** was the best cutoff value for malignancy, it resulted in sensitivity of 88.89%, specificity of 91.67%, accuracy of 90%, PPV of 94.1% and NPV of 84.6%.

Combination of both resulted in 88.89% sensitivity, 91.67% specificity, 93.33% accuracy, 94.4% PPV and 91.7% NPV for characterization of malignant nodes. (Table 1B)

**DWI:**

- All malignant lymph nodes showed partial or total restricted diffusion while 8 of 12 benign nodes (66.7%) showed free diffusion and 4 nodes (33.3%) showed partial or total restricted diffusion.
Partial or total restriction of diffusion in lymph nodes was significantly associated with malignancy (P value =0.0002) with 100% sensitivity, 66.7% specificity, 92.7% accuracy, 81.8% PPV and 100% NPV.

* ADC value in malignant nodes was significantly lower (0.7± 0.16 x 10^{-3} \text{ mm}^2/\text{s}) than in benign ones (1.4± 0.3 x 10^{-3} \text{ mm}^2/\text{s}) (P <0.0001).

ADC #1.0 was the best cutoff value that resulted in sensitivity, specificity, accuracy, PPV and NPV of 100%, 91.67%, 96.4%, 94.7% and 100% respectively.

Combined qualitative and quantitative assessment resulted in 100% sensitivity, 91.67% specificity, 96.4% accuracy, 94.7% PPV and 100% NPV. (Table 1C)

on comparing the three imaging modalities, the sensitivity, specificity and accuracy of DWI (100%, 91.67% and 96.4%) and US elastography (88.89%, 91.67% and 93.33%) were higher than those of B-mode ultrasound (77.78%, 66.7% and 73.3%) respectively.

Sensitivity of DWI 100% was higher than sensitivity of sonoelastography (88.89%) while specificity of sonoelastography was the same as DWI (91.67%). The accuracy of DWI (96.4%) was slightly higher than that of sonoelastography (93.33%). (Table 1D)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cutoff</th>
<th>AUC</th>
<th>95% CI</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<tbody>
<tr>
<td>T</td>
<td>&gt; 10 mm</td>
<td>0.829</td>
<td>0.681-0.976</td>
<td>77.8</td>
<td>66.7</td>
<td>73.3</td>
<td>77.8</td>
<td>66.7</td>
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<td>L/T</td>
<td>&gt; 1.8</td>
<td>0.685</td>
<td>0.475-0.895</td>
<td>77.8</td>
<td>75</td>
<td>76.7</td>
<td>82.4</td>
<td>69.2</td>
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<tr>
<td>Cortical thickness</td>
<td>&gt; 6 mm</td>
<td>0.819</td>
<td>0.667-0.972</td>
<td>77.8</td>
<td>66.7</td>
<td>73.3</td>
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<td>66.7</td>
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<tr>
<td>Hilum</td>
<td>Compressed or faint</td>
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<td>0.575-0.944</td>
<td>88.9</td>
<td>66.7</td>
<td>80</td>
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<tr>
<td>Total score</td>
<td>&gt; 2</td>
<td>0.856</td>
<td>0.720-0.993</td>
<td>77.78</td>
<td>66.7</td>
<td>73.3</td>
<td>77.8</td>
<td>66.7</td>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
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<td>88.89</td>
<td>91.67</td>
<td>90</td>
<td>94.1</td>
<td>84.6</td>
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<tr>
<td>ES + SR</td>
<td>ES &gt; 2 and SR &gt; 2.4</td>
<td></td>
<td></td>
<td>88.89</td>
<td>91.67</td>
<td>93.33</td>
<td>94.4</td>
<td>91.7</td>
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<th>Parameter</th>
<th>AUC</th>
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<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
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<td>DWI Partially restricted or restricted</td>
<td>0.833</td>
<td>0.694-0.973</td>
<td>100</td>
<td>66.67</td>
<td>92.9</td>
<td>81.8</td>
<td>100</td>
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<tr>
<td>ADC cutoff ≤ 1.0</td>
<td>0.944</td>
<td>0.835-1.000</td>
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<td>91.67</td>
<td>96.4</td>
<td>94.7</td>
<td>100</td>
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<tr>
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<td>91.67</td>
<td>96.4</td>
<td>94.7</td>
<td>100</td>
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<tr>
<th>Parameter</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>PPV (%)</th>
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<tr>
<td>UE</td>
<td>88.89</td>
<td>91.67</td>
<td>93.33</td>
<td>94.4</td>
<td>91.7</td>
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<td>91.67</td>
<td>96.4</td>
<td>94.7</td>
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</tbody>
</table>

**Table 1:** Cutoff values and diagnostic performance of (A) B mode criteria and score, (B) sonoelastography; elasticity score and SR, (C) DWI; visual assessment and ADC. (D) comparison between diagnostic performance of the three modalities

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Fig. 3: Female patient 37 years old with multiple suspicious breast lesions. Pathological examination revealed invasive ductal carcinoma (Malignant). (A) B mode ultrasound on right axilla showed enlarged axillary lymph node 12 x 8 mm, cortical thickness 4mm with preserved shape and hilum, score 1. (B) elastogram shows blue area on most of the lymph node area, score 4. (C) SR measured 2.5. (D)b500 and (E) b1000 DWI showed hyperintense signal of the right axillary node. (F) ADC map showed a hypointense signal over a small area of the node, partially restricted. (G) ADC value measured 1.0 x 10^-3 mm2/s

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Fig. 4: Female patient 36 years old with mastalgia and swollen breast. Pathological examination revealed non-specific lymphadenitis. (A) B mode ultrasound of the left axilla showed enlarged axillary lymph node 24 x 11 mm with oval shape, thickened cortex 8 mm and compressed hilum, score 3. (B) Elastogram showed blue area less than 45%, score 2. (C) SR measured 1.8. (D) b500 and (E) b1000 DW images showed hyperintense signal over the left axillary node. (F) ADC map showed persistence of the hyperintense signal, free diffusion. (G) ADC value measured 1.6 x 10^-3 mm^2/s

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Conclusion

Sonoelastography and DWI can significantly aid in improving characterization and differentiation between benign and malignant axillary nodes, thus reducing the unnecessary invasive biopsies and healthcare costs.

The sensitivity, specificity and accuracy of DWI (100%, 91.67% and 96.4%) and sonoelastography (88.89%, 91.67% and 93.33%) were higher than those of B-mode ultrasound (77.78%, 66.7% and 73.3%) respectively.
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