# Ex-vivo assessment of sentinel lymph nodes in breast cancer with shear-wave elastography

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Aims and objectives

Axillary lymph node status is an important prognostic factor in early stage breast cancer. In the past, axillary lymph node dissection (ALND) has been routinely carried out in early stage breast cancer, since histological examination of lymph nodes offered the most accurate assessment for metastasis. Though ALND offered decreased local recurrence rates, it was also a major cause of morbidity due to lymphedema, nerve injury and shoulder dysfunction. Today, ALND is reserved for patients with clinically palpable axillary nodes or biopsy proven metastatic lymph nodes. Sentinel lymph node dissection (SLND) offers the advantage of determining axillary lymph node status with less morbidity than ALND, thus obviating the need for more extensive surgery and its associated morbidities. However if SLND is positive, then the patient needs to undergo further ALND with a second surgery. In order to avoid a second surgery and carry out ALND in the same session if SLND is positive, an on-site pathologist is necessary. Thus determining the status of sentinel lymph nodes by imaging prior to surgery offers the advantage of reserving the pathologist for lymph nodes that are more likely to be metastatic. Ultrasonography offers a non-invasive method for lymph node status, but its sensitivity ranges between 35% and 82% and its specificity between 73% and 97.9%. Sonoelastography offers complementary information to differentiate between metastatic and non-metastatic lymph nodes based on tissue stiffness levels.

Sonoelastography uses ultrasound waves to measure tissue stiffness (elasticity) with two different techniques; static (strain) and transient (shear wave, vibration). In static elastography, tissue compression by a transducer is applied and resultant tissue strain is formed as a tissue elasticity color map superimposed on real time B-mode sonogram. Static elastography has the disadvantage of having significant interobserver variability. Shear wave elastography (SWE) works by tracking transverse shear waves spreading laterally from the tissue and calculating the speed of propagation. SWE offers more reproducibility compared to static sonoelastography, but still can be affected by anatomical features and depth of target area. Since axillary space can hinder proper sonoelastographic evaluation because of anatomical barriers, in this study we decided to evaluate the use of SWE ex vivo to determine the stiffness differences between metastatic and non-metastatic lymph nodes. In addition, we measured B-mode sonographic features. The overall goal was to determine the B-mode and elastographic features that were significantly different between metastatic and non-metastatic lymph nodes.
Methods and materials

After obtaining institutional ethic review board approval, this prospective study was performed between March and July 2014. The patients were enrolled prospectively after obtaining informed consent. Patients included in the study had non-metastatic ductal carcinoma in-situ and no pathologic lymph node detected on axillary ultrasonography. After a multidisciplinary team consensus, patients underwent breast conserving mastectomy and sentinel node excision following lymphoscintigraphy by injection of a radioactive tracer (Technetium-99m). After surgical excision of sentinel lymph nodes, lymph nodes were labeled consecutively for sonographic and pathologic examinations. Lymph nodes were embedded in sonographic gel, with a 20 mm thick gel layer covering the lymph nodes. Air bubbles were minimized in order to avoid artifact in ultrasonographic imaging. B-mode and shear-wave elastographic (SWE) ultrasound examinations were performed using a 4-15 MHz linear transducer (Super-Sonic Imagine, Aix en Provence, France) Imaging was performed by an operator with a 5 year experience in breast imaging. B-mode sonographic features of lymph node size, long axis to short axis ratio, cortical thickness and hilum existence were evaluated. Minimum, maximum and mean elasticity values (in kPa) of hilar and cortical regions were obtained by real-time SWE imaging. In real-time SWE imaging, a color map is superimposed on B-mode imaging, so stiffness values can be seen on color map. For elasticity value measurement, region of interests (ROIs) of 2 mm in diameter were drawn in the stiffest areas based on the color map. Several images were acquired for a given lymph node, showing the elastographic and B mode images simultaneously.

Following sonographic examination, lymph nodes were fixated in formalin and send to pathology for hematoxylin and eosin staining. Further work-up with immunohistochemistry was carried out when necessary. The lymph nodes were examined for metastasis. Pathological results and imaging results were paired based on the initial labeling after surgery.

Statistical analysis:

Differences in mean values of all quantitative variables were assessed by Wilcoxon test (significance level at 0.05), between benign and metastatic lymph nodes. ROC analysis was carried out for all significant ultrasonographic and elastographic variables using the Statistical Package for Social Sciences (SPSS) (version 19.0 for Windows, SPSS Inc, Chicago, Illinois, USA) Based on ROC analysis, cut-off values were determined and sensitivity, specificity, positive predictive value, negative predictive value and accuracy levels were calculated.
Results

A total 66 sentinel lymph nodes obtained from 30 patients who underwent partial mastectomy and sentinel lymph node sampling were examined ex-vivo with ultrasound and elastography between March and July 2014. From the total of 64 sentinel lymph nodes removed, 55 were true sentinel lymph nodes and 9 were negative to methylene blue staining and non-radioactive. Among the sentinel lymph nodes, 12 were metastatic (% 18.8) and 52 were benign (% 81.2). B mode sonographic features of short axis length (mm), long to short axis ratio, cortical thickness (mm), cortical to hilar area ratio and elastographic values of cortical and hilar mean stiffness values (kPa) and their ratios with p-values are summarized in Table 1. Four of metastatic lymph nodes had no visible hilar fat, maximal cortical thickness in metastatic sentinel lymph node was 15 mm. B-mode features of short axis and cortical thickness were statistically significant. Mean short axes were 4.63 (mm) and 7.5 (mm) for benign and metastatic lymph nodes, respectively with a p-value of 0.002. Cortical thickness values were 1.6 (mm) and 4.4 (mm) for benign and metastatic lymph nodes, respectively with a p-value of 0.001. SWE features of cortical and hilar mean stiffness values (in kPa) were statistically significant. Cortical mean stiffness values were 10.7 (kPa) and 25.5 (kPa) for benign and metastatic lymph nodes, respectively with a p-value of 0.001. Hilar mean stiffness values were 7.5 (kPa) and 11.3 (kPa) for benign and metastatic lymph nodes, respectively with a p-value of 0.02.

Cut-off values were calculated based on the closest point of the ROC curves to the value 1 on left-upper graph. Cortical thickness of 2.05 mm, short axis diameter of 6.55 mm, cortical mean stiffness value of 14.75 kPA and hilar mean stiffness value of 9.35 kPA were calculated based on AUROCs. (Figure 1) Sensitivity, specificity, positive and negative predictive values and accuracy levels were calculated based on these cut-off values alone and in combination and are summarized in table 3. SWE feature of cortical mean stiffness offered the highest level of accuracy and specificity whereas short axis had the highest level of sensitivity and negative predictive value. In addition, accuracy levels were calculated when B-mode features and SWE features are used in combination and are summarized in table 4. Combining cortical thickness and cortical mean stiffness increases sensitivity and negative predictive value with a decrease in specificity and accuracy. Addition of short axis increases specificity up to %100 but sensitivity level decreases.
Table 1: Table 1 In vitro B mode sonographic and elasticity measurements in metastatic and non-metastatic sentinel lymph nodes. The values for short axis length, cortical thickness, cortical mean stiffness and hilar mean stiffness were statistically significantly different between metastatic and non-metastatic sentinel lymph nodes, with a p<0.05 for the Wilcoxon test.

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Table 2

Comparison of AUROCs for cortical thickness, short axis diameter and mean stiffness of cortex and hilum. Cortical thickness has the best power to predict metastasis status of sentinel lymph nodes, followed by cortical mean stiffness.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AUROC</th>
<th>SE</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical thickness</td>
<td>0.845</td>
<td>0.054</td>
<td>0.740-0.951</td>
</tr>
<tr>
<td>Cortical mean stiffness</td>
<td>0.824</td>
<td>0.072</td>
<td>0.682-0.965</td>
</tr>
<tr>
<td>Short axis</td>
<td>0.794</td>
<td>0.058</td>
<td>0.681-0.907</td>
</tr>
<tr>
<td>Hilar mean stiffness</td>
<td>0.759</td>
<td>0.094</td>
<td>0.574-0.943</td>
</tr>
</tbody>
</table>

Table 3: Table 2 Comparison of AUROCs for cortical thickness, short axis diameter and mean stiffness of cortex and hilum. Cortical thickness has the best power to predict metastasis status of sentinel lymph nodes, followed by cortical mean stiffness.

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### Table 3

Sensitivity, specificity, positive and negative predictive values according to B mode imaging and shear wave elastography cutoff values of cortical thickness of of 2.05 mm, short axis diameter of 6.55 mm and cortical mean stiffness value of 14.75 kPA

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortical thickness</td>
<td>75%</td>
<td>75%</td>
<td>41%</td>
<td>93%</td>
<td>75%</td>
</tr>
<tr>
<td>Cortical mean stiffness</td>
<td>75%</td>
<td>83%</td>
<td>50%</td>
<td>93%</td>
<td>81%</td>
</tr>
<tr>
<td>Short axis</td>
<td>83%</td>
<td>62%</td>
<td>33%</td>
<td>94%</td>
<td>66%</td>
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<tr>
<td>Hilar mean stiffness</td>
<td>33%</td>
<td>87%</td>
<td>50%</td>
<td>77%</td>
<td>72%</td>
</tr>
<tr>
<td>Cortical thickness and cortical mean stiffness</td>
<td>83%</td>
<td>67%</td>
<td>37%</td>
<td>95%</td>
<td>70%</td>
</tr>
<tr>
<td>Cortical thickness and cortical mean stiffness and short axis</td>
<td>34%</td>
<td>100%</td>
<td>100%</td>
<td>56%</td>
<td>64%</td>
</tr>
</tbody>
</table>

**Table 2:** Table 3 Sensitivity, specificity, positive and negative predictive values according to B mode imaging and shear wave elastography cutoff values of cortical thickness of of 2.05 mm, short axis diameter of 6.55 mm and cortical mean stiffness value of 14.75 kPA

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Fig. 1: AUROC. Cut-off values were calculated based on the closest point of the ROC curves to the value 1 on left-upper graph. Cortical thickness of 2.05 mm, short axis diameter of 6.55 mm, cortical mean stiffness value of 14.75 kPA and hilar mean stiffness value of 9.35 kPA were calculated based on AUROCs.
Conclusion

Combining B-mode features with SWE features increase specificity with a decrease in sensitivity. Since cortical mean stiffness offered the highest specificity, elastography can be utilized for cases with gray-zone ultrasonographic examination to decide for malignancy.


