Axillary lymph node ultrasound features that can predict malignancy in patients with primary invasive breast cancer

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Purpose

Axillary lymph node staging is one of the most important prognostic indicator of outcome in patients with breast cancer [1]. Currently, sentinel lymph node biopsy is used as an initial approach of the axilla in most patients with breast cancer [2]. With the development of adjuvant treatment studies have shown that depending on the tumor characteristics the approach of the axilla can be less invasive [3].

Ultrasound has been used as the primary imaging method to evaluate axillary lymph nodes in breast cancer in several studies, as it is an inexpensive method, which also allows biopsies. Many studies have been performed to correlate the sonographic findings of lymph nodes with metastatic involvement. It is now known that cortical thickening, obliteration of the fatty hilum and rounded shape are predictors of malignancy [4,5].

Ultrasound-guided axillary lymph node fine needle aspiration (FNA) showed in several studies adequate sensitivity and accuracy, excellent specificity and positive predictive value in lymph node metastasis detection in preoperative exams of patients with breast cancer [6-10]. As FNA is a fast examination and is well tolerated by patients, with limited adverse events, it is ideal as a screening method. Patients with preoperatively proven lymph node metastasis can go directly to axillary dissection or neoadjuvant therapy. While patients with negative lymph nodes cytology, are submitted to sentinel node biopsy.

It is known that the larger the size of the primary tumor, the more beneficial will the lymph node FNA be. For a larger tumor, the lymph node metastasis tends to be larger and more frequent [10, 11]. Koelliker and colleagues [11] have also shown that the fine needle aspiration in lymph nodes with normal morphology at ultrasound can increase the sensitivity of metastasis detection, particularly in patients with larger tumors.

The purpose of this study was to correlate the sonographic features of axillary lymph nodes in patients with primary invasive breast carcinoma with ultrasound-guided FNA results. Furthermore, we investigated the correlation between the sonographic features and the final pathology results from the sentinel lymphadenectomy or axillary lymph node dissection (ALND). Our goal was to evaluate nodal features that could predict metastatic involvement and also the role of axillary lymph node FNA in the staging of patients with breast cancer. Additionally we would like to assess whether depending on the tumor characteristics lymph nodes with normal ultrasound features could have metastatic involvement.
Methods and materials

· Study's design and patient selection:

This was a prospective study, approved by our institutional ethics committee in 12/2011, and included 182 patients referred to the Institute of Cancer of São Paulo with newly diagnosed primary invasive breast cancer from April 2012 to April 2014. After signing the informed consent form, all patients were submitted to ultrasound evaluation of the ipsilateral axilla and fine needle aspiration (FNA).

Exclusion criteria were as follow: patients with ductal carcinoma in situ, patients who had done neoadjuvant treatment before axillary evaluation and/or patients with previous history of breast cancer.

· Examination technique, axillary lymph node characterization and selection:

Radiologists with at least two years of experience in breast imaging evaluated the ipsilateral axilla with a high frequency transducer ultrasound machine. Patients were in supine position with hands under head. We evaluated axillary levels I, II and III in two orthogonal axes from the axilla base to the apex and from the posterior axillary line to the medial region of the pectoral muscles. Axillary levels were defined as: level I inferolateral to pectoralis minor, level II posterior to pectoralis minor and level III superomedial to pectoralis minor.

The radiologist decided which lymph node to biopsy according to the following criteria, in descending order of priority: lymph nodes with ultrasound suspicious characteristics, defined as those with cortical thickening equal or greater than 3 mm, any asymmetric or nodular cortical thickening, partial or complete fatty hilum obliteration, round morphology, presence of calcifications, espiculated or ill defined margins, regardless of cortical thickening.

In patients whose lymph nodes did not meet the suspicion criteria, lymph nodes located in the axilla base and closer to the breast were chosen, more common location of the sentinel lymph nodes. If lymph nodes were not found in that location, we performed FNA of the lymph node in axillary level I, closer to the axilla base.

· Fine needle aspiration technique:

After local asepsis, the thickest portion of the lymph node cortical was punctured with a 23G needle attached to a syringe of 10ml to obtain samples for cytological evaluation.

Were done one, two or three samples (syringes) separated for each node. The material was sent to cytological analysis.
· Statistical analysis:

Categorical data are presented as percentages and were tested using Pearson #2 test and Fisher exact test, if applicable. Continuous variables were tested for normality with the Kolmogorov-Smirnov test and are expressed as medians and interquartile ranges or as the mean±SD as applicable. We compared these variables using the Mann-Whitney U test.
Results

The mean age of the patients in the study group, 182 women, was 56 years (range 31-93 years). Relative to localization of the tumor, 81 were located in the right breast, 100 in the left breast and 1 tumor was bilateral, total 183 axillae included in the study. Out of these, 74 patients had surgery as the primary treatment and 72 had neoadjuvant treatment; after surgery, 19 patients are in palliative care, 11 died and 6 lost follow up in our institution. The primary cancer tumor mean size in the surgical specimen was 2.8 cm. There were 165 invasive carcinoma of no special type (invasive ductal carcinoma), 10 invasive lobular carcinoma, 2 metaplastic carcinoma, 4 mucinous carcinoma, 1 invasive micropapillary carcinoma and 1 secretory carcinoma.

Patients were eligible for neoadjuvant treatment according to the severity criteria: patients with abnormal lymph nodes on ultrasound, or with positive FNA cytology result, or with palpable lymph nodes or with tumors above the stage T3. For analysis, we divided the study group in two: without neoadjuvant treatment (WONT) and with neoadjuvant treatment (WNT).

The mean age in the subgroup WONT was 58 years old and 78.6% of these patients were postmenopausal. In the subgroup WNT the mean age was 54 years old and 61.6% of these patients were postmenopausal (p=0.034). In the subgroup WONT most FNA cytology results were negative, most lymph nodes had normal cortical thickness and preserved fatty hilum. The lymph nodes were smaller and the tumor size at mammography, ultrasound and MRI were also smaller compared with the subgroup WNT. In the subgroup WONT we had 53.4% of breast conserving surgery versus 46.6% of mastectomy and in the subgroup WNT we had 70.4% of mastectomy versus 29.6% of breast conserving surgery (p=0.006). The feature distribution on these two subgroups are shown in Tables 1 and 2.

In the subgroup without neoadjuvant treatment (WONT), we correlated FNA cytology results with lymph node surgical pathology results and also the lymph nodes ultrasound features with lymph node pathology results. Considering that 9 of the 15 lymph nodes with inconclusive FNA results had normal appearance at ultrasound, we included FNA inconclusive results in FNA negative results. Also FNA suspect results were included in FNA positive results. Ultrasound-guided fine needle aspiration Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 39.3%, 92.6%, 81.2% and 65.5% in this subgroup (p=0.01). Ultrasound Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 72.7%, 53.6%, 55.8% and 70.9% (p=0.022) according with lymph node surgical pathology results, to differentiate normal and abnormal lymph nodes.

When we correlated lymph nodes ultrasound characteristics with metastatic involvement, in the subgroup without neoadjuvant treatment, features most associated with malignancy were diffuse cortical thickening and partial or complete fatty hilum obliteration.
as shown in Table 3; (Fig. 1-3). There was no statistical difference in size of lymph nodes, morphology, margins and palpability.

As we expected tumor size was bigger in patients with metastatic involvement of the axilla. Comparing in this subgroup without neoadjuvant treatment patients with metastatic lymph nodes had mean tumor size at mammography, MRI and surgical specimen of 3.4 cm, 4.6 cm and 3.2 cm respectively and patients without metastatic involvement had mean tumor size at mammography, MRI and surgical specimen of 2.3 cm, 3.0 cm and 2.3 cm respectively.

The subgroup with neoadjuvant treatment (WNT) was divided in two: with partial or negative response and with complete response [12]. There were 62 patients with partial / negative response and 10 patients with complete response. In the group with partial / negative response ultrasound-guided fine needle aspiration Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) were 64.8%, 55.2%, 64.8% and 55.2% (p=0.259). Ultrasound Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) in this group were 97.3%, 13.7%, 59.7% and 80.0% (p= 0.085), according with lymph node surgical pathology results, to differentiate normal and abnormal lymph nodes (Fig. 4,5). As we can see in these patients with neoadjuvant treatment there was no statistical difference (p>0.05). In the group with complete response it was not possible to calculate the values of FNA and ultrasound once all lymph nodes were negative at surgical pathology.

Finally, when we correlated ultrasound with FNA cytology results, ultrasound Sensitivity, Specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) to differentiate normal and abnormal lymph nodes were respectively 100%, 38%, 55% and 100% (p<<0.01), since all lymph nodes classified on ultrasound as normal (n=39) had negative (n=29) or inconclusive (n=10) FNA cytology results (Fig. 6,7).
### Table 1

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<table>
<thead>
<tr>
<th>Patients</th>
<th>Without Neoadjuvant Treatment (WONT)</th>
<th>With Neoadjuvant Treatment (WNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>FNA cytology results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>43</td>
<td>58,10%</td>
</tr>
<tr>
<td>Positive</td>
<td>13</td>
<td>17,60%</td>
</tr>
<tr>
<td>Suspect</td>
<td>3</td>
<td>4,10%</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>15</td>
<td>20,30%</td>
</tr>
<tr>
<td>Lymph Node Ultrasound Features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>31</td>
<td>41,90%</td>
</tr>
<tr>
<td>Abnormal</td>
<td>43</td>
<td>58,10%</td>
</tr>
<tr>
<td>Lymph Node Cortical Thickness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without Thickening</td>
<td>32</td>
<td>43,20%</td>
</tr>
<tr>
<td>Diffuse Thickening</td>
<td>20</td>
<td>27,00%</td>
</tr>
<tr>
<td>Asymmetric Thickening</td>
<td>21</td>
<td>28,40%</td>
</tr>
<tr>
<td>Focal / Nodular Thickening</td>
<td>1</td>
<td>1,40%</td>
</tr>
<tr>
<td>Fatty Hilum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preserved</td>
<td>59</td>
<td>79,70%</td>
</tr>
<tr>
<td>Partially Obliterated</td>
<td>10</td>
<td>13,50%</td>
</tr>
<tr>
<td>Complete Obliterated</td>
<td>5</td>
<td>6,80%</td>
</tr>
<tr>
<td>Type of Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast Conserving</td>
<td>39</td>
<td>53,40%</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>34</td>
<td>46,60%</td>
</tr>
</tbody>
</table>

### Table 2

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<table>
<thead>
<tr>
<th>Patients</th>
<th>Without Neoadjuvant Treatment (WONT)</th>
<th>With Neoadjuvant Treatment (WNT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Lymph Node - Major Axis (cm)</td>
<td>1,7</td>
<td>0,8</td>
</tr>
<tr>
<td>Lymph Node - Minor Axis (cm)</td>
<td>0,7</td>
<td>0,4</td>
</tr>
<tr>
<td>Cortical Thickness (mm)</td>
<td>3</td>
<td>1,9</td>
</tr>
<tr>
<td>Tumor Size - Mamography (cm)</td>
<td>2,8</td>
<td>1,6</td>
</tr>
<tr>
<td>Tumor Size - Ultrasound (cm)</td>
<td>2,2</td>
<td>0,9</td>
</tr>
<tr>
<td>Tumor Size - MRI (cm)</td>
<td>3,7</td>
<td>2,4</td>
</tr>
</tbody>
</table>

*statistically significant
Fig. 1: 53-year-old, two irregular masses in the right breast with diagnosis of carcinoma. Ipsilateral axillary lymph node, level I, oval morphology, well-defined margins, with symmetric and diffuse cortical thickening (cortical thickness 4,6 mm), partial fatty hilum obliteration, measuring 1,4 x 0,8 cm.

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**Fig. 2:** Lymph node showed increased peripheral vascularization on color Doppler study.

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Fig. 3: FNA cytology result: positive (metastatic carcinoma). Right mastectomy: invasive carcinoma of no special type with focal areas of mucinous pattern, multifocal. Axillary lymph nodes dissection showed carcinoma metastasis in 13 lymph nodes of the 16 dissected.

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**Fig. 4:** 73-year-old, right breast invasive carcinoma affecting all breast. Ipsilateral axillary lymph node, level I, oval morphology, well-defined margins, with asymmetric cortical thickening (cortical thickness: 4.7mm), preserved fatty hilum, with 2.0 x 0.8 cm.

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Fig. 5: FNA cytology result: positive (metastatic carcinoma). She did neoadjuvant hormone therapy with partial response. Right mastectomy: residual lobular invasive carcinoma, measuring 7,0 x 4,0 cm. Axillary lymph nodes dissection: carcinoma metastasis in 10 of the 18 lymph nodes resected.

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**Fig. 6:** 62-year-old, left breast invasive breast tumor measuring 2.0 cm at MRI. Ipsilateral axillary lymph node, level I, with normal ultrasound features, oval morphology, well-defined margins, cortical thin (cortical thickness: 1.8 mm), preserved fatty hilum, with 1.1 x 0.6 cm.

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Fig. 7: FNA cytology result: negative (lymphoid tissue reaction). Left breast partial resection: 3.0 x 2.0 cm invasive lobular carcinoma. Sentinel lymph node biopsy: absence of metastasis in 2 dissected lymph nodes.

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Conclusion

In patients with newly diagnosed invasive breast cancer axillary ultrasound and ultrasound-guided FNA are a useful method of screening, helping to decide which is the better systemic and axillary approach. Depending on ultrasound and tumor characteristics we could spare FNA and direct the patient to sentinel lymphadenectomy or neoadjuvant treatment.

In our study, ultrasound-guided FNA brought no benefit in patients with axillary lymph nodes classified on ultrasound as normal, independently of tumor characteristics. All FNA cytology results were negative or inconclusive when the lymph nodes had normal appearance on ultrasound.

Lymph nodes ultrasound features most associated with malignancy were diffuse cortical thickening and partial or complete fatty hilum obliteration, in the subgroup without neoadjuvant treatment. In the subgroup with neoadjuvant treatment it was not possible to establish differences between the ultrasound characteristics of the lymph nodes that could predict metastatic involvement, probably because the vast majority of lymph nodes was abnormal. In this subgroup only eight patients had lymph nodes that were considered abnormal on ultrasound and of these only one patient had metastatic lymph nodes in surgical pathology.

In conclusion, our study showed that ultrasound is useful in differentiating lymph nodes with metastatic involvement in patients with primary invasive breast cancer. Patients with normal sonographic lymph nodes features could be spared from FNA and go straight to sentinel lymphadenectomy. Also, patients with T3 and T4 tumors and abnormal lymph nodes on ultrasound, that did not benefit from ultrasound-guided FNA in our study, could be directed to neoadjuvant treatment after abnormal ultrasound. The patients who benefited the most from FNA were the ones with stage T1 and T2 with abnormal sonographic lymph nodes features, since this population was candidate for sentinel lymphadenectomy.
References


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