Axillary Ultrasound Examination in the Selection of Carcinoma of Breast Patients for Sentinel Node Biopsy - A Prospective Study

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ABSTRACT

Background: Axillary lymph node staging is the most significant factor in breast cancer staging. Axillary ultrasound is a simple, easy to use modality in detection of suspicious or abnormal lymph nodes in clinically negative axilla. AUS with FNAC in ultrasound suspicious cases increases the sensitivity of detection of abnormal or metastatic lymph nodes and it can be a good alternative for the costly, time taking sentinel node biopsy. The aim of our study is to determine the diagnostic accuracy of axillary ultrasound preoperatively associated when necessary with ultrasound guided fine needle aspiration cytology in invasive carcinoma of breast with clinically negative axilla, and so to find an alternative to sentinel node biopsy.

Material and methods: We evaluated 80 patients with carcinoma of breast from October 2013 to October 2015 coming to VSS Medical College Burla by doing there axillary ultrasound and in suspicious cases FNAC of the lymph node. Then the ultrasound negative and ultrasound positive but FNAC negative cases were taken up for sentinel node biopsy, and at last they all were correlated with final histopathology of axillary lymph nodes.

Result: Among the 32 patients with ultrasound suspicious lymph node histopathological alteration was seen in one or more lymph node (True Positive) in 62.5% cases (20/32) whereas in 37.5% (12/32) of cases it was false positive. In 48 patient with ultrasound of axilla showing normal or nonsuspicious lymph nodes, ultrasound could not detect the lymph nodes in 22.9% of cases (false negative) whereas the results were showing agreement in 77.1% of cases (True negative). The sensitivity, specificity, PPV, NPV and accuracy of axillary ultrasound alone was found to be 64.51%, 75%, 51%, 62.5%, 77.08% and 84.37% respectively and that of axillary ultrasound with FNAC was 75%, 100%, 100%, 70.58% and 84.37% respectively.

Conclusion: Axillary ultrasound with ultrasound guided FNAC is found to be a simple minimally invasive and easy to use alternative to sentinel node biopsy.

Key Words: Axillary ultrasound, sentinel lymph node biopsy, Fine needle aspiration cytology.

Introduction:

Axillary lymph node status is the single most significant prognostic indicator of carcinoma of breast1. It is essential for staging of the disease, to determine the patient’s survival and planning appropriate treatment option. Axillary lymph node status has been determined for years with the help of axillary lymph node dissection. But with common use of mammography screening programme and increased awareness, carcinoma of breast cases are diagnosed at an early stage. 30%-40% of diagnosed breast cancers do not exhibit lymph node metastasis in our scenario. Therefore axillary lymph node dissection in these cases is thought to be unjustified as it is associated with significant morbidity like lymphoedema and restriction of shoulder movement and so on. For these reasons in recent years sentinel node biopsy has met with general acceptance as an attempt to minimize over treatment of healthy axilla.

Sentinel lymph nodes are the first group of lymphatic basin draining the lymphatics from tumor. Although sentinel lymph node biopsy is a widely accepted procedure2. It carries some disadvantages such as increased cost of overall procedure because of need of preoperative lymphoscintigraphy, intra operative gamma probe use, prolonged operative time.
while waiting for frozen section result, non Sentinel lymph node skip metastasis (despite negative sentinel lymph node). A positive sentinel lymph node biopsy indicates axillary dissection. By contrast, more than half of breast cancer cases with positive sentinel lymph node biopsy have no node involvement beyond sentinel lymph node. Consequently new imaging methods for preoperative assessment and staging of lymph nodes in patients with breast cancer are gradually increasing.

Axillary ultrasound (AUS) is a simple, easy to use and potentially valuable technique for identifying axillary metastasis. Axillary ultrasound permits the visualization of lymph node size, shape, contour and changes in cortical morphology and feature that appears to be associated with the presence of axillary metastasis. However, sonographic signs of metastatic disease sometimes overlap with those of benign reactive changes limiting the liability of this modality alone to accurately stage the axilla. The addition of fine needle aspiration cytology has been shown to increase the specificity of nodal staging. Fine needle aspiration cytology is a minimally invasive intervention that establishes the cytological features of image (ultrasound) suspicious lymph nodes.

We can hypothesize that Ultrasound and Ultrasound guided fine needle aspiration cytology would yield important preoperative information about axillary lymph nodes in patients with invasive breast cancer. In this study we aimed to determine the effect of Ultrasound and Ultrasound guided fine needle aspiration cytology to preoperatively evaluate the axilla, evaluate the diagnostic accuracy of axillary ultrasound in association with ultrasound guided fine needle aspiration cytology in breast cancer patients.

**Materials and Methods**

After approval from the institutional ethics committee, the study was conducted on patients of carcinoma of breast with clinically node negative axilla admitted in VSS Medical College Burla from October 2013 to October 2015. A total of 112 patients were selected of which 32 patients were excluded from the study; 22 as they were clinically node positive, 5 as they had taken neoadjuvant chemotherapy, 5 as they has been operated previously in the same breast.

So total 80 patients were scheduled for axillary ultrasound examination with a high resolution ultrasound (12MHz) by an experienced radiologist. In the ultrasound detailed shape, size, hilum, cortex of the axillary lymph nodes were evaluated. The criteria taken for suspicious lymph node in ultrasound are: Loss of hilum fat, cortical thickness >3mm and Lt/Wt ratio<1.5. If at least one of these criteria was observed the node was selected for Fine Needle Aspiration Cytology. If more than one abnormal lymph node was found the most suspicious one was selected. Ultrasound negative lymph node cases were scheduled for sentinel node biopsy.

Ultrasound guided fine needle aspiration cytology was done in all ultrasound suspicious cases. The cases which were showing signs of malignancy in FNAC were directly taken up for axillary node dissection during primary breast surgery, and the negative or inconclusive or indeterminate cases were scheduled for sentinel node biopsy.

Later all sentinel node positive and negative cases were taken up for final axillary dissection during primary breast surgery.

**Result**

Axillary ultrasound examination was performed in all 80 selected patients with clinically negative lymph node. Out of the 80 patients 48 patients (60%) show sonographically normal or nonsuspicious lymph nodes according to the criteria mentioned previously. Sentinel lymph node biopsy in these ultrasound negative cases was positive in 8 patients (16.66%). The definitive histopathological examination of the 48 cases confirmed negative result in 37 true negative cases (77.08%) and 8 cases showing false negative results.

The remaining 32 patients had sonographically suspicious lymph nodes; in particular, 26 cases (81.25%) showed loss of hilum fat, 15 cases (46.87%) showed Lt/Wt ratio>1.5, and 11 cases (34.37%) showed cortical thickening>3mm. There was concordance between the sonographic finding and final histopathological report in 20 of the 32 ultrasound suspicious lymph node cases (62.5% true positive) but discordant in the remaining 12 cases (37.5% false positive).

According to the numbers the sensitivity, specificity, positive predictive value, negative predictive value and accuracy of ultrasound examination of axilla alone were 64.51%, 73.91%, 62.5%, 75.55% and 70.129% respectively.

The ultrasound suspicious cases had undergone fine needle aspiration cytology. In 15 of the 32 ultrasound suspicious cases (46.87%) fine needle aspiration cytology showed positive result which were also in concordance with the final histopathological report. In 17 of the 32 patients (53.13%) fine needle aspiration cytology showed negative result. Sentinel node biopsy was performed in these 17 ultrasound positive and FNAC negative case, in which 4 cases (23.53%) showed positive result and 13
cases (76.47%) showed negative result. Of the 17 ultrasound suspicious and FNAC negative cases 12 cases (70.58%) were in concordance with final histopathology i.e. truly negative and 5 cases (29.42%) showed falsely negative.

Sixty five patients with negative ultrasound or positive ultrasound but negative FNAC underwent sentinel node biopsy. Final histopathological examination showed metastatic lymph node in 16(24.61%) of these 65 patients.

The sensitivity, specificity, PPV, NPV and accuracy of the ultrasound plus FNAC were 75%, 100%, 100%, 70.58%, 84.37% respectively.

Table 1: Showing Correlation of Axillary Ultrasound and Final Histopathology

<table>
<thead>
<tr>
<th>AUS</th>
<th>ALND</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>49</td>
</tr>
</tbody>
</table>

Table 2: Showing Correlation Between USG Guided Axillary Lymphnode FNAC & Final Histopathological Report

<table>
<thead>
<tr>
<th>FNAC</th>
<th>ALND</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Negative</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 3: Axillary Ultrasound Features

<table>
<thead>
<tr>
<th>Loss of Hilum fat</th>
<th>Cortical thickness&gt;3mm</th>
<th>L/W &lt; 1.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>26</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>83.8%</td>
<td>35.4%</td>
<td>51.6%</td>
</tr>
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</table>

Table 4: Showing Correlation Between SLNB and Final Histology in AUS Negative Patient

<table>
<thead>
<tr>
<th>SLNB (in AUS negative pt.)</th>
<th>ALND</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>37</td>
</tr>
</tbody>
</table>

Table 5: Showing Correlation Between The SLNB And Final Histopathology In Aus Positive And FNAC Negative.

<table>
<thead>
<tr>
<th>SLNB (in AUS positive &amp; FNAC negative pt.)</th>
<th>ALND</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Negative</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>5</td>
<td>12</td>
</tr>
</tbody>
</table>

**Discussion**

Axillary lymph node status is most important and significant factor for staging of carcinoma of breast and for proper planning of local and systemic management. Therefore for so many years surgeons depended on sentinel node biopsy for knowing the Axillary lymph node status in clinically negative axilla replacing complete ALND. Different trials and study have compared the morbidity between ALND and SLNB like that done by Purusottam et al. The SLNB group was found to have less seroma formation, less arm lymphhaedema, sensory deficit as compared to ALND group.

But the unenthusiastic side of SLNB is its increased cost, preoperative lymphoscintigraphy, intraoperative gamma probe, prolonged operative time while waiting for frozen section reports (when ALND done in one sitting), false negative
rate up to 20-30% etc. SLNB positive node required a delayed ALND at separate sitting in which scar tissue and edema obscure identification of neurovascular structures and leading to a higher complication rate.

So there was a search for an alternate objective method for so many years. Axillary ultrasound is found to be more effective. Other alternatives were also tried - like MRI. But in MRI there was no extra advantage regarding false negativity but its higher cost and physical restriction of patients decrease its use.\(^8\) F FDG-PET in combination with CT is also tried to determine the Axillary nodal status. But it shows similar accuracy with higher cost. So it remains a low priority compared to AUS.

Axillary ultrasound is a simple, noninvasive and easily applicable tool. It can assess the axillary lymph nodes preoperatively in breast cancer patient. The ultrasonographic parameters that are evaluated in Axillary ultrasound examination are the dimensions, shape, and morphology of the lymph nodes. A normal appearing lymph node is characterized by an elliptical shape, a thin and even hypo echoic cortex measuring 3 mm and hyper echoic hilum with blood vessels entering the hilum. Metastasis of lymph node mainly involves cortical, subcortical area and hilum region. The longitudinal diameter varies greatly among different lymph nodes. A large lymph node with diameter of about 2.5 cm may be seen in case of a reactive lymph node and even a small 5 mm lymph node may have micrometastasis. So only a single dimension may not be a determining factor for assessment of the metastasis.

The ratio between the longitudinal diameter and transverse diameter is more determining factor. This ratio is called as “Roundness Index” by Sakai et al.\(^5\) They demonstrated in their study that this ratio i.e. the L/T ratio is greater than 2 in approximately 80% of the histopathologically benign nodes and less than 2 in malignant lymph nodes. This ratio is also not absolutely specific. As regards to the hilum it is concerned it is normally central in location with respect to the lymph node but in suspicious or abnormal lymph node there occurs loss or effacement of fatty hilum. The normal cortex which is thin of around 3 mm in thickness and homogenous become thick irregularly and interrupted in places which is a sign of extra capsular spread and involvement of perinodal tissue or fat.

All the 80 women with invasive carcinoma of breast were evaluated by high resolution ultrasound. Ultrasound of the axilla showed abnormal echo-structure of the lymph node suspicious for metastasis in 32 patients (40%) and normal structure in 48 patients. This compares well with the findings of Van Rijkik et al (2006).\(^6\)

In the ultrasound positive group (32 patients) fine needle aspiration cytology (FNAC) of the lymph nodes was positive i.e. metastatic in 15 (46.8%) of the 32 patients. This compares favorably with findings of Van Rijk et al (2006). Axillary lymph nodes were also metastatic per final pathology in all 15 patients with positive fine needle aspiration cytology. On the other hand, lymph nodes were metastatic in 5 (21%) of the 17 negative fine needle aspiration cytology (FNAC) cases after sentinel lymph node biopsy (SLNB) and final pathology.

In the ultrasound negative group (48 patients) sentinel lymph node biopsy (SLNB) of axilla was positive in 8 of 48 patients (16%). This compared favorably with findings of Gurleyik G et al (2015) study (20%). Axillary lymph nodes were metastatic after final pathology in 11 (22%) of the patients with negative ultrasound.
65 patients with negative ultrasound or positive ultrasound but negative fine needle aspiration cytology (FNAC) underwent sentinel lymph node biopsy. Final pathology showed metastatic lymph nodes in 16 (24%) of the 65 patients.

In Axillary ultrasound lymph nodes were evaluated for specific ultrasound characteristics like loss of hilum fat, cortical thickening and L/W ratio <1.5. In the 32 patients in which ultrasound was suspicious Loss of hilum fat was seen in majority of the patients i.e. 26 out of 32 cases (83.8%); cortical thickening seen in 11 out of 32 (35.4%) cases and L/W < 1.5 seen in 16 out of 32 (50%) cases. Martha BM et al (2010) also found in their study that the sonographic feature most predictive of a positive USG result was the loss of fatty hilum which is concordance with our finding. Bedi et al (2008) suggested that hypoechoic cortex with focal cortical thickening is most predictive of malignancy.

On correlating the tumor size with ultrasound characteristics and ultrasound guided fine needle aspiration cytology; we found that ultrasound guided fine needle aspiration cytology positivity increased steadily with increase in tumor size. Tumor with T1 (1-2cm) size show ultrasound guided Fine needle aspiration positivity 55%, 73% in T2 (2-5cm) and 93% positivity in T3 (>5cm) size tumors. The ability of ultrasound to detect more suspicious lymph nodes increases with increasing tumor size with 16% in T1 and increase to 29% in T2 category & 69% in T3 category. Martha BM et al (2010) also found that the sensitivity of ultrasound guided fine needle aspiration to detect metastatic disease in axilla increased with increasing primary tumor size.

Based on the statistical measures the sensitivity and specificity of ultrasound alone was 64.51% and 75.51%. Previous studies of ultrasound performance have reported sensitivity values of 34-71% and specificity of 74-96% (H Wang So et al 2013). For majority (48/80) of our patients with invasive breast cancer our axillary ultrasound images were not suspicious for metastasis. In 23% of these 48 patients positive (final) pathology results were discordant due to negative ultrasound images. Ultrasound negative cases require intra operative sentinel lymph node biopsy (SLNB) to prove lymph node involvement. Ultrasounds alone produce a high false negative rate in determining axillary node metastasis. The presence of small metastatic deposits and the extent of nodal metastases were independent factors for false negative ultrasound (Fung AD et al10, Stachs A et al11.)

Ultrasound showed structurally abnormal lymph nodes in 64.5% (20/32) of our patients with positive final pathology. Khout et al12, reported a rate of 61.2% and Stachs et al reported a rate of 47.6% in addition ultrasound guided fine needle aspiration cytology was negative in majority of our patients (17/32, 53%) with suspicious image. We found a false negative rates of ultrasound guided fine needle aspiration cytology (FNAC) of 29.41% (5/17) after final pathology. False negative rates of fine needle aspiration cytology (FNAC) have been reported by Diepstraten et al13 as 25% and Leenders et al14 as 31%. Small metastasis has been reported as most common cause of false negative results. (Fung AD et al, 2014, Stachs A et al)

Sentinel lymph node biopsy (SLNB) done in 17 cases of ultrasound suspicious but fine needle aspiration cytology (FNAC) negative cases of which 4 cases showed sentinel lymph node positive and 13 cases showed sentinel lymph node negative. Of the 4 cases 75% i.e. 3 cases show true positive on final histology but 1 case show false positive. It may be due to the involvement of sentinel lymph node only with no involvement of other axillary lymph nodes. Of the 13 cases (out of 17) with sentinel lymph node negative final axillary lymph node dissection pathology report showed 11 case of truly negative but 2 cases (15%) with false negative. It may be due to skipping of sentinel lymph node by tumor cells and metastasis directly to axillary lymph nodes. In Axillary ultrasound negative cases also sentinel lymph node biopsy done and in that case also there is 87.5% true positive and 12.5% false positive and 10% false negative and 90% true negative found. It compared favorably with findings of Ibrahim Zada et al15 study.

Thirty one of our 80 patients (38.75%) had metastatic lymph nodes at final histology. In 25 out of 31 cases (48%), the presence of metastatic nodes was preoperatively determined by ultrasound guided fine needle aspiration cytology. In Khout’s et al study 49 of 219 patients (21.5%) had metastatic nodes at which 22 patients (45%) were preoperatively diagnosed by fine needle aspiration cytology. Ultrasound guided fine needle aspiration cytology positivity allow patients to be directly go to axillary lymph node dissection thereby avoiding potentially unnecessary sentinel lymph node biopsy. In other words, pre operative, identification of axillary metastasis allow the surgeon to proceed directly to axillary lymph node dissection. Both Ultrasound positive and fine needle aspiration cytology positive were employed in 18% of our breast cancer patients who proceeded directly to axillary lymph node dissection.
This rate represents 16% of the 10,934 patients with breast cancer included in a meta analysis conducted by Houssami and Tan.

So axillary ultrasound and selective ultrasound guided fine needle aspiration cytology is not only a rapid but also a hassle free procedure of staging the axilla preoperatively. Only those patients who showed benign or indeterminate features of lymph nodes on ultrasound and had negative ultrasound guided fine needle aspiration of suspicious lymph node will require sentinel lymph node biopsy as a staging procedure. Rest of the patient who showed definite features of lymph nodes involvement on ultrasound and positive ultrasound guided fine needle aspiration cytology may undergo axillary lymph node dissection as a part of primary breast surgery for carcinoma of breast, thus saving time and avoiding the morbidities associated with sentinel lymph node biopsy.

To conclude, in the coming years ultrasound examination of axillary lymph nodes is going to emerge as an optimum method for knowing axillary nodal status.

**REFERENCE**