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Predictive value of fine needle aspiration biopsy of axillary lymph nodes in preoperative breast cancer staging

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ABSTRACT

Objective: Diagnosis of axillary nodal involvement is significant in the management of breast cancer as well as in predicting prognosis. In this prospective study, we evaluated the efficiency of US-guided fine needle aspiration biopsy (FNAB) in preoperative axillary staging of early breast cancer.

Material and Methods: Between January 2011 and July 2013, 46 women were prospectively enrolled in the study. Ultrasound guided-FNABs for axillary assessment were performed preoperatively. Cytology results were compared with histopathology reports to determine its sensitivity, specificity, negative and positive predictive value and accuracy.

Results: Nineteen cases that had malignant cytology on FNAB also had axillary involvement in axillary lymph node dissection (ALND) without any false-positive results. The sensitivity and specificity of US-guided FNAB were 63.3% and 100%, respectively. US-guided FNAB was accurate in predicting the status of the axilla in 76.1% of patients.

Conclusion: Although this technique is favorable due to its minimally invasive nature, it is not as effective as sentinel lymph node biopsy (SLNB) in terms of detecting axillary metastasis preoperatively. The low sensitivity and low accuracy rates decrease the usefulness of the technique. Therefore, it seems that US-guided FNAB alone could not replace SLNB. Nevertheless, combining some other molecular studies may be useful in increasing the technique's sensitivity. These issues should be determined by comprehensive clinical trials.

Keywords: Breast cancer, axillary ultrasound, axillary staging, axillary lymph node sampling, axillary fine-needle aspiration biopsy

INTRODUCTION

It is evident that breast surgery for breast cancer has changed largely and will be changing in the future as well in a dynamic fashion. Identifying the presence of axillary node metastasis in patients with invasive breast cancer is critical for determining prognosis and for deciding on appropriate treatment. The benefits of preoperative identification of axillary metastasis include allowing the surgeon to proceed directly to axillary lymph node dissection (ALND), to avoid an unnecessary sentinel lymph node biopsy (SLNB) as well as the requirement for a second surgical procedure involving the axillary nodes.

Thanks to both increase in awareness and advances in diagnostic techniques for breast cancer, patients are being detected at earlier stages. Axillary lymph node dissection is associated with more adverse consequences than benefit in women undergoing breast-conserving therapy who don't have palpable, suspicious lymph nodes, who have tumors 3.0 cm or smaller, and who have 3 or fewer positive nodes on sentinel node biopsy (1). Breast conserving surgery was found to be as safe as modified radical mastectomy in terms of disease free and total survival rate in early breast cancer (2).

Knowing the axillary involvement status preoperatively is of great significance. In recent years, breast-conserving surgery has been preferred over modified radical mastectomy while SLNB became the standard axillary staging procedure. However, SLNB also has complications. SLNB is a time-consuming, costly and invasive technique (3). Ultrasound (US)-guided axillary lymph node (LN) biopsy can be an appreciable alternative that would avoid the necessity of SLNB.

In this study, we aimed to evaluate the accuracy and sensitivity rates of US-guided fine needle aspiration biopsy (FNAB) in determining axillary lymph node involvement through comparing FNAB cytology and post-operative histopathologic data, and if this technique could replace SLNB.

MATERIAL AND METHODS

This study included 46 patients with breast cancer who were treated in our clinic between January 2011 and July 2013. Those patients who had stage I and II early breast cancer were enrolled prospectively and informed consents were obtained. The cases who fulfilled the criteria for malignancy in mammography

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and/or ultrasound or had palpable breast lump confirmed by tru-cut biopsy as invasive breast cancer constituted the study group.

Patient Selection Criteria
This study included clinically node-negative early breast cancer patients. Patients with a previous history of axillary-breast surgery and/or axillary-breast radiotherapy and those diagnosed with excisional biopsy were excluded. Patients who received neo-adjuvant chemotherapy were also excluded.

All patients' demographic properties, tumor characteristics (size, grade, estrogen, progesterone receptor status, HER-2 neu status), cytopathology results of FNAB and SLNB, and post-operative pathologic findings were prospectively recorded. The FNAB, SLNB, and ALND data were compared and evaluated along with patient and tumor characteristics.

Radiologic Technique and Criteria
Patients who were histopathologically diagnosed with breast cancer preoperatively were referred to the interventional radiology department for axillary lymph node FNAB. The FNABs were performed by one particular radiologist experienced in breast ultrasound before the surgical intervention, after evaluating the axillary lymph node status in gray-scale using 13.5 mHz linear probe and Hitachi Avius High Vision device.

The axillary LNs were inspected with regard to size, shape (round, ovoid), contour, central and cortical echogenicity in gray-scale ultrasound. The abnormal sonographic findings concerning lymph nodes were accepted as enlargement, rounding or circular configuration, irregularity and lobulation of contour, hypoechoic internal echo, greater than 3 mm of cortical thickness and absence of fatty hilum.

The most suspicious looking LNs were selected for FNAB. If there was more than one malignant looking LN then the largest one was chosen for aspiration. US-guided FNAB was performed a few times from the cortex by a 20-22 G syringe. The thickest or focally thickened part of the suspicious LNs was sampled. When all the axillary nodes looked normal, the biopsy was obtained from the subcapsular cortex of the largest node.

Pathologic Technique and Criteria
The aspirated material was smeared and fixed with 95% alcohol, and was stained using the Papanicolaou method. Cell-block and cytospin were also prepared. An experienced pathologist examined and classified the specimens into four groups: Malignant, benign, suspicious for malignancy and inadequate for assessment.

Surgical Technique
The patients with malignant FNAB underwent complete ALND at the time of definitive surgery. The patients with benign, suspicious or insufficient FNABs underwent SLNB using blue-dye and/or radiocolloid injection.

Twenty-three of the patients had a mastectomy, and the other 23 patients had breast-conserving surgery according to patient's needs and both the patient's and the surgeon's choice. Sentinel lymph node biopsy was performed in twenty-three cases peroperatively.

Statistical Analysis
The cytology findings of the FNABs were compared with the pathologic reports of SLNB and ALNDs. The FNAB diagnoses were compared with the histological diagnosis of either SLNB and/or ALND, and the sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV) and accuracy rates were calculated.

In the evaluation of US-FNAB accuracy, the presence of metastasis and atypical cytologic results were regarded as positive. Inadequate sampling on FNAB was considered as a negative result since patients with inadequate sampling also underwent SLNB as in negative cytology.

When evaluating the findings obtained in this study, statistical analyses were performed using Statistical Package for the Social Sciences program, version 17.0 (SPSS Inc; Chicago, IL, USA). The data was evaluated as a diagnostic screening test (sensitivity, specificity). Cohen Kappa analysis and chi-square test were used for comparison of quantitative data and intergroup comparisons, along with descriptive statistical methods (median, minimum, maximum value). The results were evaluated at 95% confidence interval and the significance was set at $p<0.05$.

RESULTS

Findings
Fine needle aspiration biopsy was applied to 46 cases to determine the requirement for an axillary surgical procedure and axillary staging. All of the patients, except one, were women with a median age of 54 years (29-71 years). The comparative data of these cases is shown in Table 1. The FNABs revealed 19 malignant and 23 benign results.

Three cases had inadequate samples, and one had findings suspicious for malignancy. Both SLNB and ALND showed malignant findings in the patient with cytology findings suspicious for malignancy.

None of the patients with inadequate axillary sampling had metastatic lymph nodes on axillary dissection (Table 2).

Statistical Analysis
Cytologic and histopathologic axillary findings are summarized in Table 2. As seen in this table there was no false positive result but six false negative results. Inadequate and suspicious FNAB results were considered as negative cytology for practical reasons; hence, 19 positive and 27 negative results were included in the assessment (Table 3).

The diagnostic power of FNAB as a screening tool for identifying metastatic lymph nodes was evaluated statistically. In terms of predicting axillary lymph node status, the sensitivity of axillary FNAB was 63.3%, with a positive predictive value of 100%, specificity of 100%, negative predictive value of 59.3%, and an accuracy rate of 76.1%. The consistency of axillary FNAB with final axillary histopathologic data was evaluated with Cohen Kappa analysis. In the comparison of the two procedures, a statistically significant and positive relationship was detected (Kappa: 4,155; $p<0.001$).

All nine patients who underwent SLNB as the only axillary procedure had negative results in final histopathology. The final

Table 1. Comparison of patient's demographic and histopathologic properties with final axillary histopathology results (n=46)

	Axilla (+)		Axilla (-)		
Properties	**n**	**%**	**n**	**%**	**p**
Age					0.367
≤50	9	32,1	9	50.0	
>50	19	67,9	9	50.0	
Axillary side					0.503
Right	15	53,6	7	38.9	
Left	13	46,4	11	61.1	
Menopausal status					0.367
Premenopausal	9	32,1	9	50.0	
Postmenopausal	19	67,9	9	50.0	
Family history					0.552
Negative	27	96,4	16	88.9	
Positive	1	3,6	2	11.1	
cT stage					0.948
I	14	50,0	8	44.4	
II	14	50,0	10	55.6	
cN stage					0.453
N0	22	78,6	16	88.9	
N+	6	21,4	2	11.1	
Clinical stage					0.300
I	13	46,4	7	38.9	
IIA	10	35,7	10	55.6	
IIB	5	17,9	1	5.5	
Histologic type					0.054
Invasive ductal carcinoma	28	100,0	15	83.3	
Other	0	0,0	3	16.7	
Surgery					0.131
BCT	11	39,2	12	66.6	
Mastectomy	17	60,8	6	33.4	
Axillary procedure					**<0.001***
SLNB	0	0,0	9	50.0	
ALND	17	60,7	6	33.3	
SLNB+ALND	11	39,3	3	16.7	
Estrogen receptor					1.000
Negative	6	21,4	4	22.2	
Positive	22	78,6	14	77.8	
Progesterone receptor					0.728
Negative	6	21,4	5	27.8	
Positive	22	78,6	13	72.2	
Hormone receptor					1.000
Negative	5	17,9	3	16.6	
Positive	23	82,1	15	83.4	
Cerb-B2					0.072
Negative	14	50,0	14	77.8	
Positive	14	50,0	4	22.2	
FNAB					
FNAB (+)	19	67,9	0	0.0	**<0.001***
FNAB (-)	6	21,4	17	94.4	
FNAB (Inadequate)	3	10.7	1	5.6	

Chi-square Test, *p<0.05. c: clinical; BCT: breast-conserving therapy; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; FNAB: fine needle aspiration biopsy

histopathology reports were positive in 92.9% and negative in 7.1% of 14 cases who underwent both SLNB and ALND. Within the 23 patients with only ALND, 73.9% had positive and 26.1% negative results in their final histopathology reports. According to these findings, the histopathologic axillary lymph node involvement showed statistically significant difference between different types of axillary surgery (p≤0.001).

All 19 patients who had positive FNABs were found to be positive in the final axillary histopathology. Twenty-seven cases had negative FNABs, 11 of which (29.6%) were found to have positive results in the final histopathology (p≤0.001).

While 28 of 43 cases (65.1%) with invasive ductal carcinoma as the histological type had positive lymph nodes in the final histopathology, none of the other histologic tumor types had a positive lymph node. The obtained data revealed that histopathologic axillary lymph node involvement rate had a statistically significant difference between different tumor types (p=0.054).

DISCUSSION

US-Guided FNAB as a Minimally Invasive Technique in Axillary Staging

Ultrasound-guided axillary FNAB has been carried out since 1997 (4, 5). US- guided FNAB emerged almost at the same time with SLNB, as an alternative technique. As it can be expected, through the technical development in ultrasound devices and introduction of high-resolution machines, the accuracy of FNAB has increased. It has been shown that lymph nodes

Table 2. Correlation between cytologic and histologic data

	Histology		
Cytology	**Benign**	**Malignant**	**n**
Inadequate	3/TN	1 /FN	4
Benign	18/TN	5 /FN	23
Malignant	0/FP	19 /TP	19
Total	21	25	46

TN: true negative; FN: false negative; FP: false positive; TP: true positive

Table 3. Correlation between FNAB results and axillary lymph node histopathology (n=46)

	Axillary histopathology				
Axillary FNAB	**Positive**	**Negative**	**Total**	**K[a]**	**p**
Positive	19	0	19	4.155	<0.001*
Negative	11	16	27		
Total	30	16	46		
Sensitivity		63.3%			
Specificity		100%			
Positive predictive value		100%			
Negative predictive value		59.3%			
Accuracy rate		76.1%			

[a]: Cohen Kappa analysis; *p<0.05. FNAB: fine needle aspiration biopsy

might be evaluated quite accurately with ultrasound (6). Many studies indicated that preoperative staging with axillary lymph node FNAB guides management rather correctly. Chang et al. (7) reported a considerably high positive and negative predictive value for US-FNAB as 98.7% and 81.8%, respectively.

If the preoperative axillary FNAB is positive then the decision for axillary dissection without SLNB can be straightforward. This technique also affects decisions on neoadjuvant chemotherapy, oncologic surgery and simultaneous reconstruction. Additionally, axillary lymph node sampling with US-FNAB performed before and after neo-adjuvant chemotherapy might be useful in the evaluation of treatment response (8).

Thanks to both comprehensive breast screening programs and the increased public awareness on breast cancer, the disease can be diagnosed at early stages in recent years. In such circumstances, a patient is less likely to have clinical or microscopic lymph node involvement on admission. Enlarged reactive LNs are another cause of clinically false positive evaluations. Size is not a useful criterion for distinguishing normal from abnormal axillary lymph nodes. Reactive or fatty lymph nodes may be large enough to be palpable and can be mistaken for metastatic disease (9).

Topal et al. (10) reported that the sensitivity of physical examination alone in axillary staging was 34-76%, and that of sonography was 36-92%. Nevertheless, Lumachi and colleagues suggested that by combining US with FNAB the specificity increased, the sensitivity remained unchanged, and a 100% specificity rate could be achieved in specialized breast centers (11). The ratio of false negative and false positive results on clinical examination is approximately equal to 1/3 (12). Similarly, the sensitivity rate was low while the specificity rate was pleasing in our study (Figure 1).

In a review published in JAMA, Rao et al. (1) advocated that axillary dissection was associated with more harm than benefit in women undergoing Breast Conserving Surgery (BCS) who do not have palpable, suspicious lymph nodes, have tumors 3.0 cm or smaller, and have 3 or fewer positive nodes on SLNB. In addition, the multi-disciplinary ACOSOG trial showed that completion of axillary dissection in clinical T1/T2, N0 tumors with a positive SLNB had no significant impact on local-regional recurrence and overall survival rates (13).

Factors Influencing Sensitivity and Specificity Rates

The number of involved lymph nodes is correlated with the sensitivity rate of US-FNAB. In case of involvement of two or more lymph nodes, the sensitivity increases from 47.1% to 80% (14). Deurloo et al. (15) suggested that the sensitivity and specificity rate of US-FNAB could be enhanced when lymph nodes with a cortical thickness of more than 2 mm were chosen for sampling.

The tumor size influences axillary lymph node involvement. As the tumor size grows, there is an increase in the number of involved nodes. The prognosis of small sized tumors that have axillary involvement is better than that of large ones (16). Especially, in primary breast cancer without axillary involvement, tumor location has prognostic value. Laterally localized tumors are more likely to metastasize to the axilla as compared to medially localized tumors. The tumor size means delayed diagnosis on the tumor dynamics. The tumors become more aggressive as they grow while more aggressive tumors grow faster.

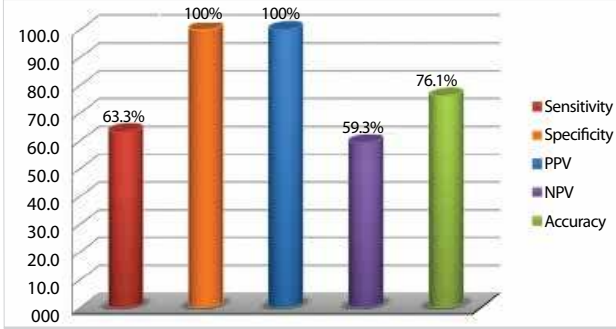

Figure 1. Diagnostic test results for fine needle aspiration biopsy
PPV: positive predictive value; NPV: negative predictive value

In our series, one patient had a sonographic negative axilla and was regarded as benign. The same patient's SLNB revealed negative findings for malignancy.

Even though FNAB is a less invasive, less expensive and rapid method for the evaluation of the axilla as compared to SLNB, the sensitivity of FNAB is not as high, and a negative result mandates SLNB. For this reason, the node positive group benefits most from axillary FNAB (17).

A review of the relevant literature, despite the methodologic differences in sampling and variability in patient populations, showed that unnecessary SLNBs were avoided in 1-28% of patients with preoperative axillary FNAB (18).

It is worth to consider that while the FNAB was negative in three cases and was positive in SLNB, none of them had metastatic lymph nodes in ALND.

The axillary lymph node FNAB produced false negative results in 19% of cases. It is difficult to explain all of them with micrometastasis. The biopsy should be repeated in case of non-diagnostic/insufficient cytology result since this group of patients has an extremely high proportion of positive nodes (19).

Various studies have reported the sensitivity and specificity rates of FNAB between 25-95% and 97-100%, respectively (8, 14, 20-30). False positive results has been reported around 1.4-1.6% (20, 23, 30), and false negative rates as 8-12% (15, 23, 24, 26, 29-31).

In our study, we found that the sensitivity and specificity of US-guided FNAB were 63.3% and 100%, respectively, with a negative predictive value of 59.3% and a positive predictive value of 100%.

The possible causes of false negative results may be the failure in imaging all the nodes, sampling error, micro-metastasis, mistakes in radiologic and pathologic assessment (30, 31).

Methods such as sampling more than one node, using immunohistochemical staining and imprint cytology have been proposed in order to increase sensitivity and accuracy in determining lymph node status with SLNB (32, 33).

In case of skip metastasis, it is clear that FNAB is more advantageous than SLNB. It is reported that metastatic disease could skip to level II nodes without involving level I nodes (34). With FNAB, not only the sentinel nodes but any lymph nodes that carry sonographic malignancy criteria can be sampled.

CONCLUSION

US-guided axillary lymph node FNAB has several advantages as well as disadvantages. The benefit of preoperative identification of axillary metastases is that it allows the surgeon to proceed directly to ALND, to avoid an unnecessary SLNB and a second surgical procedure involving the axillary nodes. Fine needle aspiration biopsy has almost no morbidity. The procedure is quick, minimally invasive and barely painful. Therefore, it is preferable in preoperative breast cancer staging.

Its false-negativity is especially detected in lymph nodes with partial involvement of micro-metastases or isolated tumor cells. However, the necessity of axillary dissection in such situations is also controversial. As for another disadvantage, US-guided axillary FNAB is a quite operator-dependent technique.

The sensitivity, specificity, negative and positive predictive value of axillary FNAB for assessment of axillary lymph node involvement in early breast cancer were determined in 46 breast cancer patients treated in January 2011-July 2013 in the General Surgery Clinic of Haseki Training and Research Hospital. We identified the sensitivity rate of axillary FNAB as 63.3%, positive predictive value of 100%, specificity of 100%, negative predictive value of 59.3% and accuracy of 76.1%.

Our sensitivity rate and negative predictive value of FNAB for axillary staging in early breast cancer was relatively lower than similar studies. The rates from specialized centers seem to be better. This study was the first experience in axillary staging with FNAB from our clinic with a limited number of cases. We think our study would be a modest contribution to the literature.

Since the sensitivity of US-guided FNAB is not satisfactory, FNAB cannot replace SLNB for the time being. As a minimally invasive technique, US-guided axillary lymph node FNAB should be evaluated by comprehensive clinical trials.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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