Can Preoperative Axillary Ultrasound and Biopsy of Suspicious Lymph Nodes Be An Alternative To Sentinel Lymph Node Biopsy in Clinical Node Negative Early Breast Cancer?

ABSTRACT

Aim: The aim of this study was to assess the efficacy of pre-operative axillary ultrasonography (AUS) and pre-operative axillary fine-needle aspiration biopsy (FNAB) from suspicious lymph nodes in clinically node-negative breast cancer to compare with radiologically positive and sentinel lymph node biopsy (SLNB) positive involvement.

Method: Clinically node-negative early-stage breast cancer patients were included in the study. These patients under went pre-operative AUS examination, suspicious lymph nodes were evaluated with FNAB. AUS-FNAB results were compared with those of SLNB or of axillary dissection.

Results: Of 181 patients undergoing AUS, 32 were reported to have axillary metastasis, 25 suspicious and 124 benign nodes. The suspicious group underwent FNAB examination and metastasis was found in 9 of them. The sensitivity of AUS-FNAB was found to be 64.06%, specificity 100%, positive predictive value 100% and negative predictive value (NPV) 83.5%. False negativity rate (FN) of this method was 16,4%. Lymphovascular invasion and tumor size were found statistically significant factors for false negativity.

Conclusion: It was concluded that axillary AUS-FNAB with its high NPV, low FN rate, may be a clinical alternative to SLNB for early-stage breast cancer patients.

What's known?

Intraoperative frozen section sentinel lymph node biopsy (SLNB), which is a conventional method in patients with breast cancer, is still a widely used method for the evaluation of axilla in these patients.

What's new?

Recently, the trend in breast surgery is towards less invasive methods. SLNB can be evaluated with preoperative ultrasound-guided biopsy, which is also a less invasive method than SLNB. In our study, the false negativity rate with this method was determined as 16.4% in accordance with the literature, and it is an acceptable rate. The advantages of this method are that the patient is not injected with radioactive colloid and methylene, the duration of the operation is shortened because the frozen result is not expected, the need for additional surgery for SLNB is eliminated, and the condition of the preoperative axilla is known.

Keywords: Breast; Cancer; Axilla; Ultrasound; Biopsy

1. Introduction

Sentinel lymph node sampling is the standard procedure in clinically node-negative breast cancer patients, reducing morbidity without any negative impact on survival and regional local recurrence rates (1). However, sentinel lymph node biopsy (SLNB) has some disadvantages. It may produce additional morbidities such as seroma, sensory nerve damage, development of lymphedema and restriction of shoulder movement (2,3). Adequate evaluation of axillary lymph nodes (ALN) involvement by radiological methods prior to surgery may minimize possible morbidity due to invasive methods by extending multidisciplinary treatment options on a patient basis.

In a period when publications are reporting that axillar surgery is not considered therapeutic in clinical stage T1-T2 and that axillary lymph node dissection does not exert any effect on survival (4, 5) as in ACOSOG Z0011 trial (6) we follow-up these patients without axillary dissection even if SLNB results are positive. In the ongoing SOUND and INSEMA

studies (7,8), monitoring of the axillary region was evaluated in patients without clinical and radiological evidence of axillary metastasis.

At present, clinicians are more meticulous regarding pre-operative evaluation of axilla and investigation and assessment of non-invasive options is a widespread issue. Physical examination (PE) has 30% sensitivity, 95% specificity and 69% accuracy in detecting axillary metastasis.

The most valuable method for radiological evaluation of axillary lymph nodes is axillary ultrasound (AUS). (9,10). When axillary lymph nodes are evaluated together with AUS and PE, the sensitivity of the procedure increases to over 90% (11). In this context, imaging of axilla with AUS, which is a non-invasive method, as an alternative to SLNB has increasingly become standard procedure in the pre-operative evaluation of axilla. With AUS, regional lymph nodes can be evaluated in terms of their size and morphological characteristics. In early-stage breast cancer patients, at pre-operative staging, fine needle biopsy from suspicious lymph nodes apart from AUS increases the accuracy of the method. As AUS is a secure method with low cost, its employment is more common but, it has been stated that it is too operator dependent (12, 13).

The present study aims to compare the efficiency of pre-operative AUS in clinically node-negative breast cancer and that of pre-operative axillary biopsy in suspicious axillary lymph nodes with the efficiency of SLNB. Another aim of the study is to evaluate the consistency between preoperative imaging and SLNB and to identify the factors that affect false negativity.

2.Material Method

2.1. Patient selection

Patients referring to General Surgery Clinics of University of Health Sciences Ankara Oncology Education and Research Hospital between 2016- 2017 and diagnosed with early-stage invasive breast cancer were included in the present study. After PE and mammography, breast and axillary ultrasonography were performed by experienced breast radiologists.

The exclusion criteria of the study were as follows: diagnosis of locally advanced breast cancer, palpable positive axillary lymph nodes, pure ductal carcinoma in situ, and negative axilla following neoadjuvant chemotherapy.

2.2. Axillary Ultrasonography

Axillary lymph nodes were classified as malignant, suspicious and benign. With patients in supine oblique position, AUS was performed on axillary region and lymph nodes at level-I and level-II were evaluated.

Lymph nodes were evaluated with grayscale ultrasonography in terms of size, longitudinal-transverse diameter (L/T) ratio, contour, echogenicity, the thickness of central fatty hilum and nodal cortex. When nodal cortex thickness is less than half of hilum diameter or is thinner than 3mm, it was considered normal. Lymph nodes that have at least one of the following suspicious findings for involvement were considered suspicious: L/T ratio smaller than 2 in lymph node, disappearance of typical ovoid configuration, asymmetrical thickening in nodal cortex, disappearance of echogenic fatty hilum or cortical indentation to hilum. Suspicious and malign lymph nodes were evaluated pathologically with fine needle aspiration biopsy (FNAB).

2.3. Surgical procedure and postoperative evaluation

Patients underwent breast-conserving surgery (BCS), oncoplastic surgery (OPS) or mastectomy. Suspicious and malign lymph nodes with AUS were evaluated with FNAB and

in patients with metastasis, axillary dissection was performed. These patients were discussed in the multidisciplinary tumor board and were not considered to receive neoadjuvant therapy.

In all patients SLNB was carried out with the combined method (Tc-99 labeled nano colloid + methylene blue staining). Removed sentinel lymph nodes were evaluated histopathologically with frozen technique intraoperatively. Lymph nodes in which macro-metastasis was detected were considered pathologically positive, and subsequently axillary dissection was carried out. In some of the patients undergoing BCS with positive sentinel lymph node, axillary dissection was not performed based upon the results of the ACOSOG Z011 study. When negative results were obtained in the frozen examination of the sentinel lymph node, axillary dissection was not performed.

The postoperative pathology reports of the patients were examined and the presence or absence of metastases in sentinel lymph node biopsy, the size of metastasis, the number of positive sentinel lymph nodes, the presence or absence of axillary metastasis, and extracapsular spread information were recorded.

The patient characteristics analyzed are as follows; age, weight, length and Body Mass Index (BMI) of patients, tumor location and size, its histological type and stage, estrogen receptor (ER) and progesterone receptor (PR) positivity, cerb2, Ki67 status and LVI. During analyses, patients were stratified into subgroups of age (≤ 50 and >50), BMI (< 20, 20-30, >30), tumor locations of the areola (upper outer quadrant (UOQ), lower outer quadrant (LOQ), lower internal quadrant (LIQ) and upper internal quadrant (UIQ)), tumor size (≤ 2 cm, 2-5 cm, ≥ 5cm); histopathological types (ductal, lobular and other pathology), and Ki67 value (≤15, 15-30, ≥30). For ER nuclear staining at the rate of over 10% and for PR over 5% was considered positive. Those who are HER-2/neu IHC 3+ or FISH positive were considered positive.

The results of postoperative pathology were compared with those of pre-operative AUS or AUS+FNAB and sensitivity, specificity, negative predictive value, positive predictive value and accuracy rate were calculated. Patients found to have axillary metastasis with postoperative pathological examination were divided into two groups, i.e., those whose pre-operative radiological AUS or AUS+FNAB results were positive (true positive) and those whose results were negative (false negative) and it was investigated whether there was any difference between two groups in terms of the number of positive lymph nodes in axilla.

Patients in the groups with and without radiological suspicion of axillary metastasis were compared in terms of tumor size, lymph vascular invasion (LVI), age, BMI, Ki67, tumor location, first biopsy results, pathology, grade, ER, PR and HER-2/neu

2.4. Statistical Analysis

In the evaluation of data, SPSS 16.0 program was used. Whether numerical data were distributed normally was evaluated with the Kolmogorov-Smirnov test. In descriptive statistics, numerical variables were expressed with mean, standard deviation, median and lowest and highest values and categorical data with number and percentage. In the evaluation of both numerical and categorical variables, whether there was any difference between axilla positive and negative groups was evaluated. To determine the differences between groups, in parametrically distributed numerical variables Student's t-test, and in categorical variables, chi-square or Fisher's exact test was used. In the comparison of the number of axillary lymph nodes, the Mann-Whitney U test was used. A P-value of <0.05 was considered statistically

significant. For variables influencing the false-negative rate, multiple logistic regression analysis was carried out, and odds ratios were given with their confidence interval.

3. Results

One hundred and eighty-one patients with clinically node negative were included in this study. Demographics, pathologic and clinic characteristics of patients were shown in Table 1.

According to the evaluation results of lymph nodes with AUS, 32 (17.7%) of the patients had axillary metastatic nodes, and 25 (13.8%) had suspicious nodes. In 124 patients (68.5%), there was no finding of metastasis.

Fifty-seven patients other than the benign cases, were evaluated with FNAB; 32 patients having axillary metastasis, which named AUS positive, was proved with FNAB and then with SLNB. Of the 25 patients reported to be suspicious according to AUS, 16 were found to be metastasis negative, while the remaining 9 were found to be positive with FNAB

In AUS or AUS+FNAB evaluation, 41(22.65%) out of 181 patients were reported to have positive axillary metastasis. Later than, SLNB was performed to the 25 suspicious AUS patients and of them 9 (which were positive in FNAB) were continued to be positive, while SNLB results for 16 patients (which were negative in FNAB) were negative in 13 patients and positive in 3 patients. Of 124 patients who were reported to be benign radiologically, axillary node metastasis was detected in 20 after SLNB. The flowchart of study was described in Figure 1.

Axilla was negative in 64.6% (n=117) and positive in 35.4% (n=64) of all 181 patients. Numbers of patients with/ without metastasis in axilla with AUS+FNA and SLNB methods and their comparison are given in Table 2. The false-negative rate of the test

according to these data is 16.4%. Data on the diagnostic power of the US+FNA test given in Table 3.

When 140 (77.3%) patients reported having negative results in AUS and AUS+FNAB evaluation were divided into two groups, i.e., 117 patients with negative pathological results (correct negative) and 23 positive patients (false negative), tumor size was found to be significantly higher in the positive group (p=0.003). There was no significant difference between the two groups with regard to age, BMI, Ki67, tumor location, first biopsy, pathology, grade, ER, PR, CerbB2 and accompanying DCIS. In false-negative patients, tumor size and LVI were found to be significant factors by multiple logistic regression analysis (Table 4).

4. Discussion

In the evaluation of lymph nodes by AUS, varying morphological criteria have been defined. Specificity and sensitivity vary according to these criteria. Based upon morphological criteria, lymph nodes meeting at least one of the criteria below are considered pathological: round shape (longitudinal/transverse diameter ratio below 2), disappearance of central fatty hilus, being hypoechoic and asymmetrical cortical thickening (cortex thickness asymmetrically 3 mm or over). In a systematic review, it was stated that AUS sensitivity was 49-87%, and it was between 26-76% when the size of the lymph node and morphological criteria are considered. Specificity was found to be 55-97% and 88-98%, based on size and morphological criteria, respectively (14). Therefore, morphological characteristics of lymph node rather than its size are more significant. While the size of the axillary lymph node was not considered significant by itself in determination of pathology, morphological changes were regarded as more valuable in the differentiation between malignant/benign (15). In AUS, color Doppler may be added to AUS. With this method, the blood supply of the lymph node

was evaluated in three groups—i.e., central, peripheral and lack of blood supply. Peripheral blood supply was evaluated as a malignant vascular pattern (16). Besides, strain elastography and shear wave elastography may also be carried out, but these methods are not adequate either for definitive diagnosis (17). Zhu et al. demonstrated that when cortical thickening of >3.5 mm is considered as cutoff, there was involvement in 3 or more lymph nodes (18).

Given these findings, lymph node size was not considered a criterium in our study using morphological criteria. In evaluation of 181 patients with clinically negative lymph nodes by AUS, axillary metastasis was found in 32 (17.7%) suspicious node in 25 (13.8%) while in 124 (68.5%) axilla was reported to be benign.

In this study, the sensitivity of AUS and FNAB in suspicious cases was found to be 64.1 % and specificity 100.0%. The positive predictive value of AUS-FNAB was 100.0%. Of 41 patients found to have metastasis with radiological evaluation, 100% was found to have metastasis after sentinel lymph node biopsy, corroborating radiological results. The negative predictive value of AUS was 83.0% and accuracy 87.3%. The results we obtained were superior to those reported in the literature;

In some publications, the axilla was evaluated only by ultrasound and the following results were found; Tucker et al: sensitivity 70%, NPV 84% and PPV 56 (19), Jackson et al: sensitivity 71%, specificity 83% and false negative rate 4% (20), Leenders et al: sensitivity 43.8%, specificity 80.7%, PPV 57.5%, NPV 70.7% (21), Feng et al: sensitivity 58.6-89.4%, PPV 79.6%, NPV 75.3% accuracy 76.6% (9).

In studies where axilla was evaluated with ultrasonography+ FNAB, the findings are more reliable: Diaz-ruiz et al: sensitivity of 77.5%, specificity 100%, PPV 100.0%, NPV 69.3% and accuracy 85.1% (22), Leenders et al: sensitivity 99%, PPV 99%, NPV 69%, false negative rate 28.1% (21), Rocha et al, sensitivity 79.4%, PPV 100%, NPV 69% (23), Feng et

al: sensitivity 52.4%, PPV 100%, NPV 74.8% accuracy 80.3% (9), Reyna et al: sensitivity 91%, specificity 95%, NPV 99% and PPV 71% (24). In this study our findings are; sensitivity: 64,1%, specificity: 100%, NPV: 83,6%, PPV: 100%, diagnostic accuracy: 87,3%, and false negativity rate: 16,4%.

In FNAB, investigation of various markers such as CEA, CA 15-3, Her 2; cytokeratin 19 fragments may further increase sensitivity (25). In the study of Tillman et al., carrying out pre-operative axillary staging with axillary ultrasonography and core biopsy of suspicious lymph node was found to be cost-effective (26).In the study of Harris et al., it was suggested that in ultrasonography, morphological characteristics were not efficient in the differentiation of N1/N2-3. However, it was also stated that AUS might be significant in demonstrating axillary lymph node involvement in tumors at the size of 2mm or smaller (27).In two different studies (18, 28), it was observed that obesity has no adverse impact on the efficiency of AUS. Likewise, in the present study, no negative effect of BMI on axillary AUS efficiency was demonstrated. In various studies, it was found that factors such as lobular histopathology, tumor size, palpability of tumor, multifocality, LVI, and tumor grade were influential on false-negative rates in axillary ultrasonography (29, 30). In addition, Zhu et al. found higher rates of false positivity in T1 tumors and hormone negative tumors (18). In the present study, the false-negative rate was found to be 16.4%, and histological subtype was not found to have any relation with false negativity or other parameters. Tumor size and LVI status were determined to be the factors influencing false negativity. Boland et al. reported that extracapsular spread and number of metastatic lymph nodes were higher in patients who were positive after AUS – FNAB, compared to cases found positive only with SLNB (31).The same findings were found in the study of Lloyd and Tandon (32, 33).

5. Conclusion

AUS can detect LN metastasis at a high rate in correlation with nodal tumor burden. This rate increases when FNAB is added to AUS. Pre-operative axillary staging makes it possible to refer patients with invasive breast cancer to pre-operative systemic treatment if necessary and to carry out direct axillary lymph node dissection without any need for intraoperative SLNB. The evaluation of axilla with pre-operative AUS and FNAB from the suspicious lymph node when necessary is a promising method for the status of the sentinel lymph node, as demonstrated in the present study. However, this method may miss metastatic LNs even at low rates, as shown in the present study. With the addition of new technological advances such as marker investigation from biopsy, AUS combined with FNAB may completely replace the SLNB procedure and may become the new gold standard.

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Tables

Table 1: Demoghraphic, Pathologic and Clinic Features of All 181 Patients

FACTORS	*n (%)*	*FACTORS*	*n (%)*
Age (median;min-max)	51; 28 -79	**Tumor Size**	
BMI	27.84 ± 4.43	<2 cm	75 *(41.4%)*
Tumor Localization		2 – 5 cm	99 *(54.7%)*
Periareolar	13 *(7.2%)*	>5 cm	7 *(3.9%)*
UOQ	114 *(63.0%)*	**Breast Pathology**	
UIQ	20 *(11.0%)*	Invasive Ductal Carcinoma	148 *(81.8%)*
LIQ	14 *(7.7%)*	Invasize Lobular Carcinoma	14 *(7.7%)*
LOQ	20 *(11.0%)*	Other	19 *(10.5%)*
Breast Biopsy Method		**Tumor Grade**	
Tru-cut	146 *(80.7%)*	Grade 1	12 *(6.6%)*
Excisional Biopsy	35 *(19.3%)*	Grade 2	86 *(47.5%)*
Primary Tumor Excision		Grade 3	83 *(45.9%)*
Mastectomy	93 *(51.4%)*	**Hormone receptors**	
Breast conserving surgery	32 *(17.7%)*	ER	149 *(82.3%)*
Oncoplastic breast surgery	56 *(30.9%)*	PR	130 *(17.7%)*
		HER-2/neu	39 *(21.5%)*
Mean Ki67	33.2± 23,88		
LVI Positivity	38 *(21.0%)*		

**UIQ: Upper inner quadrant, UOQ: Upper outer quadrant, LIQ: Lower inner quadrant, LOQ: Lower outer quadrant*

Table 2. The Distribution of Axillary Metastasis Status After Radiological Evaluation and Pathological Evaluation

	Axillary Pathology (Gold Test)	
US-FNA	**Negative n (%)**	**Positive n (%)**
Negative	117 (83.6%)	23 (16.4%)
Positive	0 (0.0%)	41 (100.0%)
Total	117 (64.6%)	64 (35.4%)

Table 3. Sensitivity, Specificity, Positive and Negative Predictive Values of US-FNA Test

	%	95% Confidence Interval
Sensitivity	64.1	51.1-75.7
Specificity	100.0	96.9-100
Positive predictive value	100.0	97.0-100.0
Negative predictive value	83.6	78.6-87.6
Diagnostic accuracy	87.3	81.6-91.8

Table 4. Comparison of some characteristics between patients who were found to be negative with radiological evaluation and had positive and negative pathological results

	Without Axillary Metastasis (n=117)	**With Axillary Metastasis (n=23)**	**p value**
	Median (IQR) (min. – max.)	**Median (IQR) (min. – max.)**	
Age (years)	50 (18) (29-79)	52 (17) (36-75)	0.937***
	Mean±SD	**Mean±SD**	
BMI (kg/m$^{2)}$	27.62±4.36	28.13±3.85	0.604***
Tumor Size (mm)	21.7±11.57	29.91±13.86	0.003***
Ki67	31.05±23.84	32.13±26.06	0.847***
	n (%)	n (%)	
Tumor Localization			0.932*
Areola	8 (6.8%)	1 (4.3%)	
UOQ	71 (60.7%)	14 (60.9%)	
UIQ	15 (12.8%)	2 (8.7%)	
LIQ	11 (9.4%)	3 (13%)	
LOQ	12 (10.3%)	3 (13%)	
Diagnostic Biopsy			0.162**
FNAB / tru-cut	90 (76.9%)	21 (91.3%)	
Excisional	27 (23.1%)	2 (8.7%)	
Tumor Size			0.035*
0-2 cm	65 (55.6%)	6 (26.1%)	
2-5 cm	49 (41.9%)	16 (69.6%)	
>5cm	3 (2.6%)	1 (4.3%)	
Pathological classification			0.126*
Ductal	88 (75.2%)	20 (87.0%)	
Lobular	11 (9.4%)	3 (13.0%)	
Other	18 (15.4%)	0 (0%)	
Grade			0.703*

Grade 1	9 (7.7%)	2 (8.7%)	
Grade 2	62 (53%)	10 (43.5%)	
Grade 3	46 (39.3%)	11 (47.8%)	
ER			1.00**
Negative	22 (18.8%)	4 (17.4%)	
Positive	95 (81.2%)	19 (82.6%)	
PR			0.307*
Negative	38 (32.5%)	5 (21.7%)	
Positive	79 (67.5%)	18 (78.3%)	
HER-2			0.595*
Negative	97 (82.9%)	18 (78.3%)	
Positive	20 (17.1%)	5 (21.7%)	
LVI			0.014*
Negative	101 (86.3%)	15 (65.2%)	
Positive	16 (13.7%)	8 (34.8%)	
With DCIS			0.058**
Presence	45 (38.5%)	4 (17.4%)	
Absence	72 (61.5%)	19 (82.6%)	

** Pearson's chi-squared test, **Fisher's exact test, ***Student's t test*

Figure legands:

Figure 1. Flowchart of study algorithm