In early-stage breast cancer, sentinel lymph node biopsy can save unnecessary axillary dissection compared with fine-needle aspiration cytology for indeterminate axillary lymph nodes

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Introduction
The most prevalent female cancer is breast cancer. A significant prognostic factor and determinant of treatment is the state of axillary lymph nodes (LNs). Axillary LNs can be classified into pathological, indeterminate, and benign by ultrasonographic (US) assessment.
Aim
In early-stage breast cancer, the indeterminate axillary LNs are measured. This offers the full advantage of the available diagnostic instruments, fine-needle aspiration cytology (FNAC), and sentinel lymph node biopsy (SLNB) technique driven by US, and thus prevents excessive dissection of the axillary lymph node. In a step-wise sequence, suggestions are made for the treatment of indeterminate axillary LNs.
Patients and methods
This is a randomized, controlled sample that is prospective. Between October 2017 and October 2018, 60 female patients diagnosed with early-stage breast cancer with indeterminate axillary nodes were admitted to the breast cancer unit at Kasr Alainy University Hospital, Cairo University. Sensitivity, accuracy, positive predictive value, and negative predictive value of preoperative US-guided FNAC versus upfront frozen indeterminate node intraoperative SLNB were contrasted, and both findings were correlated to the final histo-guided FNAC.
Results
Sensitivity of SLNB was 83.33%, whereas sensitivity of the FNAC was 75%, with the negative predictive value of 83.33%, specificity of 83.3%, and positive predictive value of 75%.
Conclusion
FNAC is only moderately sensitive (75%), and inadequate sampling and being an operator dependent are potential limits of it. In addition, positive FNAC may cost the patient unnecessary axillary lymph node dissection.

Keywords:
early breast cancer, fine-needle aspiration cytology, sentinel node biopsy, indeterminate lymph nodes

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Introduction

Breast cancer is considered to be the commonest female malignancy in both the developing and the developed countries. After the introduction of the multidisciplinary team system, treatment of breast cancer has improved. As more advanced diagnostic devices and new therapeutic techniques become available, the relationship between diagnosis and therapy is increasingly becoming stronger. This raises new issues, such as the adequacy of axillary lymph node (LN) diagnostic preoperative staging for the implementation of particular therapeutic decisions [1].

For patients with breast carcinoma, axillary LN status is a significant prognostic factor and care determinant. In the preoperative assessment of breast cancer patients, ultrasonographic (US) breast and axilla tests are increasingly being used and can identify axillary LNs into pathological, indeterminate, and benign [2–4].

Through several years, axillary lymph node dissection (ALND) was the definite tool for treating metastases in LNs. Currently, there are many ways that are less invasive than ALND to assess the axillary LNs status such as US and fine-needle aspiration cytology (FNAC) using US. None of these methods, however, have been adequately effective in replacing the histological analysis [5].

Our analysis aims to determine the indeterminate axillary LNs before surgery and intraoperatively in early-stage breast cancer. This is to offer the patient the full advantage of the diagnostic, US-guided FNAC, and sentinel lymph node biopsy (SLNB) instruments available, and thereby prevent needless ALND and all its morbidities. Recommendations on how to deal in a step-wise pattern with indeterminate axillary LNs are provided.

Patients and methods

A randomized, supervised, prospective analysis was conducted. An informed consent was obtained from the participants of the study after approval of the ethical committee in Cairo University. During the period from October 2017 to October 2018, 60 female patients diagnosed with early-stage breast cancer (T1 and T2 N0 M0) with indeterminate axillary nodes were admitted to the breast surgery unit at Kasr Alainy University Hospital, Faculty of Medicine, Cairo University. Sensitivity, accuracy, and positive and negative predictive values of preoperative US-guided FNAC vs upfront intraoperative SLNB and frozen portion of indeterminate axillary LNs were evaluated and contrasted, and both findings were associated with the final results of the histopathological paraffin portion. The definition of indeterminate nodes is as follows: either diffuse cortical thickening 4 mm with central hilum or peripheral–focal-cortical thickening less than or equal to 3 mm by US and clinically no palpable nodes.

Inclusion criteria

Females patients with early-stage breast cancer of any age and pathology (T1 and T2 N0 M0) were included.

Exclusion criteria

The following were the exclusion criteria:

(1) Clinical and radiological (US) pathological axillary LNs (focal cortical thickening more than 3 mm, diffuse cortical thickening more than 4 mm or when there is lost or effaced hilum) and clinically palpable nodes.
(2) Locally advanced breast cancer (T3 and T4 with any N, M0).
(3) Metastatic breast cancer (any T and N with M1).
(4) Male breast cancer.

Methodology in details

(1) The 60 patients were divided into two groups. We used the even and odd method for randomization. Group 1 had the odd numbers (1, 3, 5, etc.), and group 2 had even numbers (2, 4, 6, etc.). The patients were randomized according to their presenting time.
(2) Both groups were carefully examined, and proper history was taken.
(3) Plan of management was put in the multidisciplinary team meeting.
(4) Group 1 was subjected to (after consent) sonar-guided FNAC before surgery. The results of cytology determined the next step of management.

After assessing the axillary LN status in gray scale using the 13.5-MHz linear probe and Hitachi Avius High Vision system, FNAC is conducted by a specific radiologist specialized in breast US before the surgical operation.

Fine-needle aspiration cytology technique

Using the Papanicolaou process and hematoxylin and eosin dye, the aspirated substance was smeared and fixed with 95% ethanol alcohol, and dyed. The specimens were analyzed and graded by an experienced pathologist into three groups: negative for malignancy, positive for malignancy, and insufficient for evaluation.

(1) Positive node: upfront axillary dissection.
(2) Negative and inconclusive nodes: sentinel node biopsy was collected and pathologically examined by frozen section technique. Accordingly, the following protocol was followed:
    (a) Negative nodes and positive nodes less than or equal to 2/3 or more, not matted, and no extracapsular extension: no further management to the axilla (ACOSOG Z0011 criteria).
    (b) Positive nodes more than or equal to three nodes, matted nodes, or gross extracapsular extension: proceeding to ALND.
(3) Group 2 was subjected to (after consent) upfront sentinel node biopsy and nodes will be collected and pathologically examined by frozen section technique. Accordingly, the following protocol was followed:
    (a) Negative nodes and positive nodes less than or equal to 2/3 or more: no further management to the axilla (ACOSOG Z0011 criteria).
    (b) Positive nodes more than or equal to three nodes, matted nodes, or gross extracapsular extension: proceeding to ALND.

Technique of sentinel lymph node biopsy

Injection of 3–5 ml of 1% methylene blue is used either retro-areolar. After 15 min, opening of axillary facia was done, with retrieval of approximately three LNs (the blue, nodes with blue lymphatics streaks, or the enlarged ones).

All specimens were sent to routine histopathology (paraffin section examination) to be compared with FNAC and frozen section of SLNB.

Statistical analysis

Data were collected through direct observations, as well as operative notes, admission log, operative notes, operation log, clinical records, pathology department log, outpatients' follow-up clinic records, and the weekly morbidity and mortality conference of the surgery department.

Numerical quantitative data were presented as mean, SD, and range values. Data were analyzed by applying independent Student *t* test for comparison of two groups' means.

Ordinal qualitative data were expressed as frequencies (*n*) and percentage (%) and analyzed by applying χ^2 test. Nonparametric tests (Mann–Whitney) were used for qualitative variable comparison.

Correlation analysis was done using Pearson correlation tests. The significance level was set at *P* value less than or equal to 0.05. Statistical analysis was performed with IBM SPSS Statistics (IBM SPSS Statistics for Windows, Version 23.0, IBM Corp., Armonk, NY: US), version 23 for Windows .

Results

Our study is a comparative prospective study in which we have randomized patients into two groups: group 1

Table 1 Demographic data

	FNAC group (*N*=30)	Upfront sentinel LN group (*N*=30)	*P* value
Age (years)	52.90±13.12	45.30±10.13	0.015
BMI (kg/m^2)	31.42±5.02	34.18±5.35	0.044
Marital status			
Married	30 (100.0)	24 (80.0)	0.010
Single	0	6 (20.0)	
Offspring			
None	0	6 (20.0)	
One child	3 (10.0)	3 (10.0)	
Two child	9 (30.0)	9 (30.0)	0.092
Three child	12 (40.0)	6 (20.0)	
Four child	6 (20.0)	6 (20.0)	
Family history (yes)	6 (20.0)	9 (30.0)	0.371

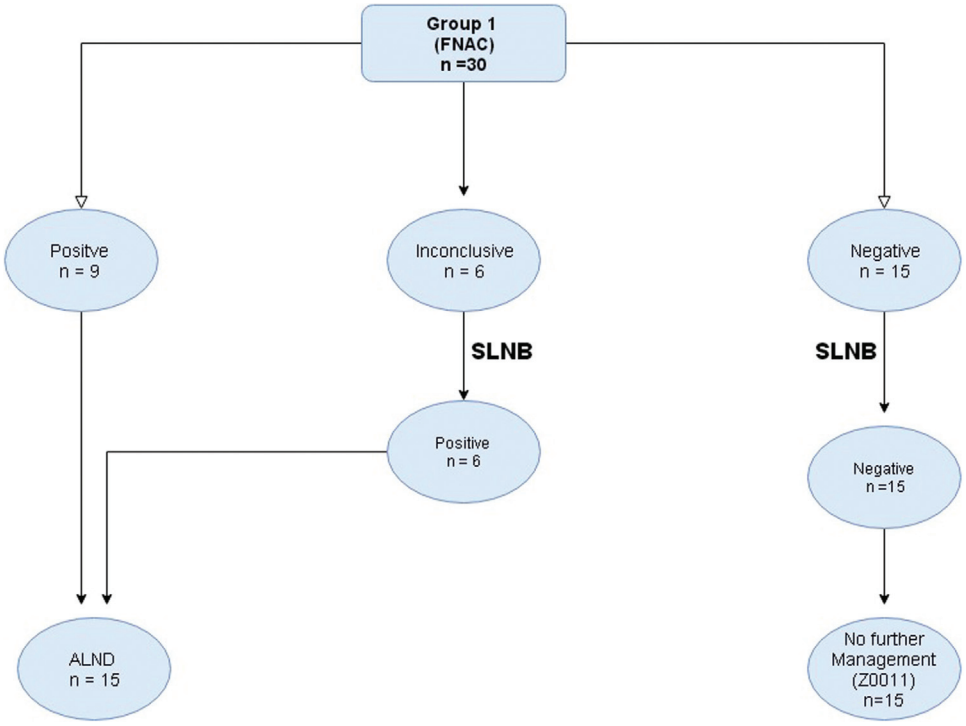
Data are expressed as mean±SD or *n* (%). FNAC, fine-needle aspiration cytology; LN, lymph node. *P* value more than 0.05=not significant. *P* value less than or equal to 0.05=significant.

Table 2 The clinical and radiological features of the studies groups

	FNAC group (*N*=30)	Upfront sentinel LN group (*N*=30)	*P* value
LN examination (radiological)			
Diffuse cortical thickness	15 (50.0)	24 (80.0)	0.015*
Focal cortical thickness	15 (50.0)	6 (20.0)	
Cortical thickness (mm)	2.84±1.11	3.50±0.76	0.010
LN examination (N0)	30 (100.0)	30 (100.0)	–
Tumor classification of the mass (T)			
T1	12 (40.0)	0	0.001
T2	18 (60.0)	30 (100.0)	
Breast examination			
LOQ	3 (10.0)	0	0.066
Retro-areolar	3 (10.0)	6 (20.0)	
UOQ	24 (80.0)	21 (70.0)	
Lower central	0	3 (10.0)	
Pathological type			
IDC	21 (70.0)	30 (100.0)	0.005
ILC	6 (20.0)	0	
ILC+IDC	3 (10.0)	0	

Data are expressed as mean±SD or *n* (%). FNAC, fine-needle aspiration cytology; LN, lymph node. *P* value more than 0.05=not significant. *P* value less than or equal to 0.05=significant.

Figure 1



FNAC group. FNAC, fine-needle aspiration cytology.

Table 3 Comparative statistics of operative and postoperative data

	FNAC group (*N*=30)	Upfront sentinel LN group (*N*=30)	*P* value
Grade (grade 2)	30 (100.0)	30 (100.0)	–
FNAC of axilla			
Inconclusive	6 (20.0)	0	0.001
Negative	15 (50.0)	0	
Positive	9 (30.0)	0	
Not done	0	30 (100.0)	
Frozen SLNB			
Negative	15 (50.0)	15 (50.0)	0.002
Positive	6 (20.0)	15 (50.0)	
Not done	9 (30.0)	0	
Paraffin sentinel			
Negative	15 (50.0)	12 (40.0)	0.001
Positive	6 (20.0)	18 (60.0)	
Not done	9 (30.0)	0	
Axillary dissection			
Positive	15 (50.0)	18 (60.0)	–
Not done	15 (50.0)	12 (40.0)	

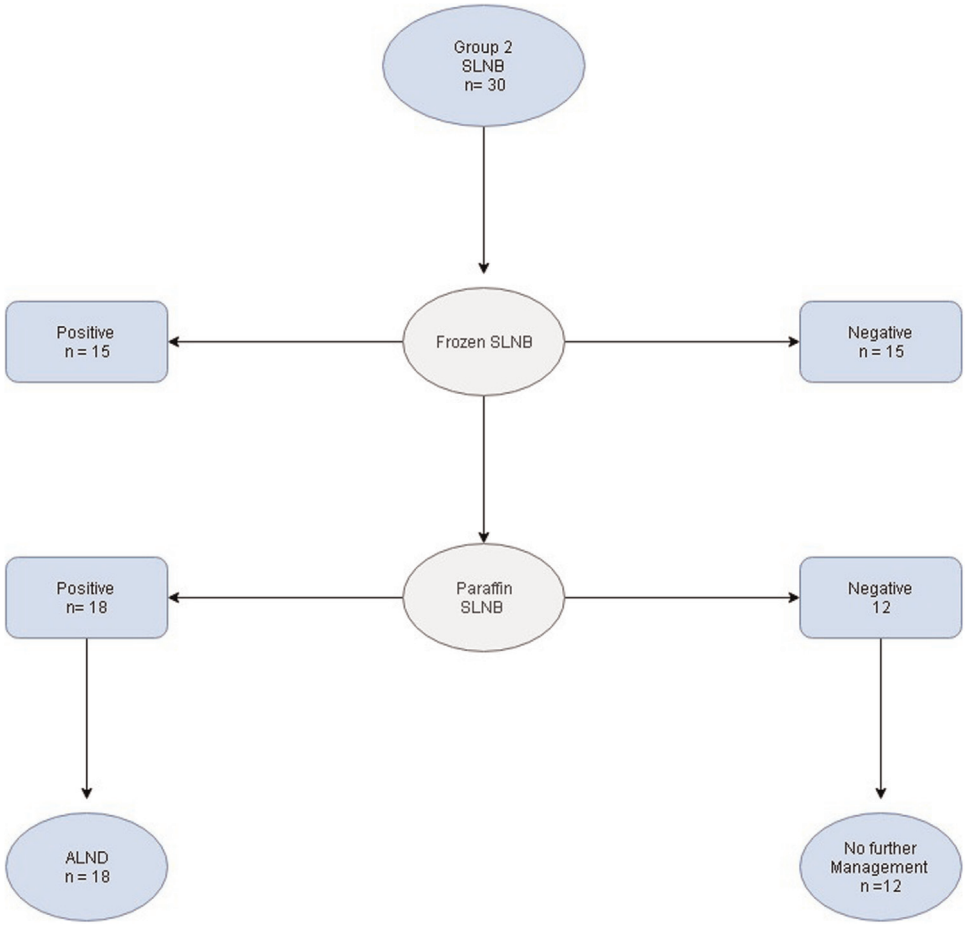
Data are expressed as *n* (%). FNAC, fine-needle aspiration cytology; LN, lymph node; SLNB, sentinel lymph node biopsy.

(patient who had preoperative FNAC) and group 2 (patients who had upfront SLNB). Tables 1 and 2 show comparative statistics of demographic data of both groups.

Among the 30 women who underwent preoperative FNAC, 15 (50%) of them were negative; thus, they underwent SLNB, whereas nine (30%) patients were positive and underwent ALND. However, six (20%) patients in the same group were found to be inconclusive and necessitated SLNB (Fig. 1 and Table 3).

In contrast, among the other 30 women who underwent upfront SLNB, 15 (50%) were positive and had ALND. The other 15 patients in the same group were negative by frozen SLNB; however, three of them were found to be positive, and they were subjected to ALND (Fig. 2 and Table 3).

Figure 2



Upfront SLNB group. SLNB, sentinel lymph node biopsy.

Table 4 Association between paraffin sentinel lymph node biopsy versus frozen in fine-needle aspiration cytology group

	Paraffin SLNB	
FNAC group (inconclusive and negative cytology)	Negative (*N*=15)	Positive (*N*=6)
Frozen SLNB		
Positive	0	6 (100.0)
Negative	15 (100.0)	0

Data are expressed as *n* (%). FNAC, fine-needle aspiration cytology; SLNB, sentinel lymph node biopsy.

The overall incidence of positive LN among the indeterminate LN in our study was 55% (33 cases of 60).

Sensitivity and specificity of the frozen sentinel assessment of the LN were found to be 83.33%, with positive predictive value and negative predictive value of 83.33%.

Sensitivity of the frozen sentinel assessment of the LN was found to be 83.33%, whereas the specificity was found to be 100%.

Accuracy of sentinel assessment of the LN is 80%.

Sensitivity of the FNAC in assessment of the indeterminate LN was found to be 75%. Inadequate (insufficient) sampling is another potential limit of FNAC (Tables 4 and 5).

Discussion

Several literature studies indicate that axillary US is a potentially useful tool for the diagnosis of axillary metastases. US allows the visualization of the scale, form, contour, and improvements in cortical anatomy and texture of the LN that tend to be consistent with the presence of axillary metastases. However, sometimes US does not effectively differentiate between malignant and benign reactive changes, which make it a limited tool to accurately stage the axilla; moreover, it is operator dependent. The sensitivity of US alone

Table 5 Association between paraffin sentinel lymph node biopsy versus frozen in upfront sentinel lymph node group

	Paraffin SLNB	
Upfront SLNB group	Negative (*N*=12)	Positive (*N*=18)
Frozen SLNB		
Positive	0	15 (83.3)
Negative	12 (100.0)	3 (16.7)

Data are expressed as *n* (%). SLNB, sentinel lymph node biopsy.

was 53.7%, specificity was 85.1%, and accuracy was 67.9% [6].

Since 1997, US-guided axillary FNAC has been carried out. As an alternative to SLNB, US-FNAC emerged. As can be predicted, the precision of the FNAC has improved with technological advances in US devices and the advent of high-resolution machines. Several studies have shown that preoperative staging of FNAC axillary LN directs treatment quite accurately [4,5].Van Wely and colleagues, demonstrated the accuracy of the US/FNAC to detect three or more positive LNs was 90.4%. Sensitivity, accuracy, positive predictive value, and negative predictive value were 89.0, 100, 54, and 100%, respectively [7]. Sensitivity, accuracy, positive predictive value, and negative predictive value of 83.7, 100, 100, and 74.6%, respectively, were shown by Castellano *et al.* [6].

In 2016, Akıncı *et al.* [8] observed that the US-led FNAC's sensitivity and specificity were 63.3 and 100%, respectively, with a negative predictive value of 59.3% and a positive predictive value of 100%.

Our study also differs in that we compared the results of negative FNAC with the results of SLNB, which showed that the cases that were negative by FNAC (*n*=15) were also negative by SLNB. However, it is important to mention that we had six (20%) cases were inconclusive by FNAC.

Conclusion

US-guided axillary LN FNAC has some benefits as well as drawbacks in women who have indeterminate nodes. There is absolutely no morbidity in FNAC. The treatment is simple, invasive to a minimum, and not painful. Therefore, preoperative staging of breast cancer is preferred. FNAC, on the contrary, is only mildly susceptible (75%), an approximation equivalent to that of some reported research. Another possible FNAC restriction that existed in 20% of cases in our sample is ineffective (insufficient) sampling. The indication of ALND is, however, still arguable in these circumstances. As for another downside, the US-guided axillary FNAC is a technique very reliant on the user.

In addition, there are important aspects in the clinical application of FNAC in management of indeterminate LNs in that some surgical oncologists would (reasonably) argue that the test does not identify all metastases in the axilla and it only gives an impression of single node, so there will be a lack of assessment of axillary LNs, especially the sentinel ones, which might change the decision of treatment regarding saving the patient unnecessary ALND if the patient was a eligible for ACOSOG Z0011 criteria (≤2/3 or more, not matted and with no extracapsular extension) and might avoid ALND.

Therefore, the knowledge of axillary LN involvement by SLNB is mandatory as it can spare patients unnecessary ALND with all morbidities.

Recommendations

Although the sensitivity of US-guided FNAC is not satisfactory, and the advent of the guidelines for ACOSOG Z0011 parameters in the treatment of SLNB in early breast cancer is not satisfactory, FNAC is therefore currently unable to replace SLNB in the category of indeterminate LNs. US-guided FNAC from borderline LNs can be tested by rigorous clinical trials as a minimally invasive procedure.

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Conflicts of interest

There are no conflicts of interest.

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