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Can Sentinel Node Biopsy Continue to Be a Diagnostic Tool for Radiologically Negative Axilla in Early Breast Cancer?

Anwar Mohamed Mostafa*, Nawel Hussein Matar, Ramadan Mahmoud Ali, Hassan Ashour
Department of Surgical Oncology, Faculty of Medicine, Zagazig University, Egypt
***Corresponding author:** Anwar Mohamed Mostafa, **Mobile:** (+20) 01014658188, **E-mail:** aboghena6616@gmail.com

ABSTRACT
Background: For staging of the axilla, axillary ultrasound (AUS) has been researched as a non-invasive substitute for sentinel lymph node biopsy (SLNB). **Objective:** The aim of the present study was to compare between accuracy of AUS and SLNB in assessment of the axillary nodal status in early breast cancer.
Patients and methods: A cross sectional study was conducted and included 60 female' patients with early breast cancer and carried out in General Surgery Department, Zagazig University Hospitals. All cases were arranged for accurate axillary ultrasound examination. Patients were postoperatively followed up for 6 months. **Results:** The most common quadrant to be affected is the upper outer quadrant (UOQ) seen in 32 patients of the studied group (53.3%). A total of 28 (46.7%) patients presented with T1 tumors and 32 patients presented with T2 tumors; with an overall incidence 53.3%. Only 4 patients underwent modified radical mastectomy with an overall incidence of 6.7%, and 44 patients underwent conservative breast surgery with overall incidence 73.3%**.** The number of excised lymph nodes (LNs) in study group ranged from 2 to 4. The level of excised LNs in study group ranged from level I and/or level II. Concerning the Validity of AUS finding; 73.3% of the studied women were negative SLN with Negative AUS LNs. **Conclusion:** The surgical procedure as sentinel LNs biopsy SLNB (by methylene blue MB) still has the upper hand as a diagnostic tool for axillary nodal status with more accuracy and sensitivity than radiological methods as axillary ultrasound AUS.
Keywords: Early Breast Cancer, Sentinel Node Biopsy, Axillary Ultrasound.

INTRODUCTION

One of the top 3 most prevalent cancers in the world, breast cancer is a serious health issue. It accounts for 25% of all cancer cases in women, making it the most prevalent. It is the leading cause of cancer death in less developed nations, ranking fifth among the most prevalent causes of cancer-related mortality globally [(1)].

One of the most significant prognostic indicators in breast cancer is the presence of axillary nodes. The therapy of breast cancer has undergone significant modifications over the past century, going from an era in which mastectomy or axillary lymph node dissection (ALND) was seldom performed to one in which modified radical mastectomy (MRM) was the standard of care. Less invasive surgical procedures also improve quality of life [(1)]. Identification and subsequent removal of the first node(s) to which the tumor drains its lymphatic fluid is known as a sentinel lymph node biopsy (SLNB). As a reliable substitute for ALND for staging patients with early breast cancer, SLNB has gained widespread acceptance [(2)].

The introduction of SLNB has led to a significant departure from ALND in the surgical management of the axilla for patients with early breast cancer, improving quality of life and lowering complication rates. SLNB also aims to spare the majority of patients the morbidities associated with dissecting all the axillary lymph nodes. The surgical technique of choice today for predicting the axillary status in clinically-negative breast cancer and preventing needless morbidity is SNLB [(3)].

SLNB became the norm of therapy for patients with clinically node-negative breast cancer because to the significant morbidity of ALND. However, SLNB is pricy, time-consuming, may result in morbidity, and can be worsened by seroma development, sensory nerve damage, lymphedema, and a restriction in shoulder range of motion. To prevent a second treatment, many centers depend on the availability of axillary imaging on sentinel lymph nodes [(4)].

We believe that alternatives to SLNB should be taken into account in a time when axillary surgery is no longer regarded as therapeutic in clinical T1-T2, N0 breast cancer and tumor biology as determined by biomarker profile and molecular profiling is more frequently used as the basis for adjuvant therapy decisions [(5)].

One-stage axillary clearance and a reduction in the necessity for SLNB from 70% to 21% are both possible with preoperative ultrasound imaging of the axilla in individuals with clinically negative nodes [(4)].

For axilla staging, axillary ultrasound (AUS) has been researched as a noninvasive alternative to SLNB. Based on the morphological characteristics and size of the lymph nodes, AUS can detect illness in the axillary lymph nodes (ALN). Studies that have looked at the accuracy of AUS have found that it has good levels of sensitivity and specificity [(6)].

Axillary assessment is most frequently performed with ultrasound due to its accessibility and safety. High resolution transducers used in advanced ultrasound technology enable the detection of abnormal-appearing lymph nodes as well as detailed representations of nodal shape. It can be challenging and operator-specific to see how metastasis affects lymph node shape. The doctor can advise the patient to start with preoperative chemotherapy or to go straight to ALND and skip SLND if metastases are found using AUS prior to surgery [(7)]. Therefore, the current study aimed to compare between accuracy of AUS and SLNB in

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detection of the axillary nodal status in early breast cancer. Also, to find the choice of the minimal or less invasive technique to be used as a diagnostic tool for detection the axillary nodal malignancy in early breast cancer.

PATIENTS AND METHODS

A cross sectional study was carried out in the Department of General Surgery, Zagazig University Hospitals during the period from April 2022 to December 2022. The study included 60 female patients with early breast cancer.

Inclusion criteria: Patients with primary invasive breast cancer T1-T2 N0. Age ≥18 years old. No palpable lymph node metastasis by clinical examination preoperatively. Free AUS performed preoperatively.

Exclusion criteria: Patient with distant metastases, large tumor >5 cm, palpable axillary lymph nodes, radiologically-positive axillary lymph nodes affection preoperative by AUS examination, patients with known allergy to blue dye and patients lost during follow up were excluded.

All patients were subjected to full history taking and complete local examination included any breast mass assessing tenderness and hotness, site, size, shape, surface, number, consistency, edge and relation to underlying structures. Also, examination of ALN assessed number, size, shape, surface, consistency, fixation to each other and underlying structures. From the collected data TNM staging system was applied for proper selection of the patients.

I. Pre-operative investigations:

a. Laboratory investigations including CBC, bleeding profile, Liver and kidney function tests, Random blood sugar and Hepatitis markers were performed.

b. Radiological investigations:

- ***Mammography:*** It was possible to get oblique and cranio-caudal images of both breasts. It was carried out to assess the tumor's size, confirm the diagnosis, look for multicenter activity, rule out bilateral illness, and identify multicenterity.
- ***Breast ultrasonography:*** A diagnostic imaging method used in conjunction with mammography. In order to identify any pathology reported in the axillary lymph nodes, AUS was performed preoperatively in all instances.

c. Investigations to rule out metastasis: including Chest x-ray, Pelvi-abdominal U/S, and CT (abdomen and pelvis, chest).

d. ECG and medical fitness for surgery: for patients over 40 years.

II. Surgical Procedure: Under perfect aseptic circumstances in the operating theatre and while the patient was under general anesthesia, 5mL of diluted methylene blue dye (1% concentration) was administered intraparenchymally either around the tumor mass in certain cases or the biopsy cavity if the tumor had already been excised. Then, all SLNs were removed and sent for a pathologic analysis. Conservative breast surgery was done if the results of the histological investigation were negative, and a full ALND was done right away if they were positive for metastases. The tissue was subjected to immunohistochemistry (IHC) examination using industry-standard methods if permanent-section analysis does not indicate any metastases.

III. Post-operative Care: Every 6 hours, the vital signs of each patient were monitored, analgesia was administered, and the amount of the drain was measured for each patient. After 6 hours, patients were urged to get out of bed as soon as possible, and on the second post-operative day, oral intake and upper limb mobilisation were commenced. In the following 24 hours, hospital patients received their discharge.

Follow up: Patients were monitored during their hospital stay, including the removal of sutures, and for the first 6 months following surgery, they were encouraged to visit an outpatient clinic once a week. Follow-up was done on any issues that may arise after surgery, such as wound infection, seroma, haematoma, and arm numbness. To determine if lymphedema had developed, serial measurements of the mid arm circumference of both arms were performed every week for the first post-operative month and then once a month for the next 6 months. When the amount of serous discharge at the injection site fell to less than 30 ml in 24 hours, the suction drain was withdrawn. This was done to monitor the area for any signs of infection and the permanence of the tattoo mark.

Ethical Consideration:

This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ANOVA was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS

The current study showed the patients' ages ranged from 26 to 65 years with mean age of 47 years. **Table 1** summarizes the clinical characteristics of the participants.

Table (1): Clinical characteristics distribution in studied patients.

Variables	(*n*=60)	
	No.	**%**
Age groups (in years)		
21-30	4	6.67%
31-40	12	20%
41-50	16	26.67%
51-60	20	33.33%
61-70	8	13.33%
Total	60	100%
The affected breast		
Right	36	60%
Left	24	40%
Total	60	100%
Size of the mass		
T1 (<2 cm)	28	46.7%
T2 (2-5 cm)	32	53.3%
Total	60	100%
Grade of Tumor:		
I	4	13.3%
II	40	66.7%
III	12	20%
Total	60	100%

The most common quadrant to be affected is the upper outer quadrant (UOQ) seen in 32 (53.3%) patients of the studied group **(Figure 1)**.

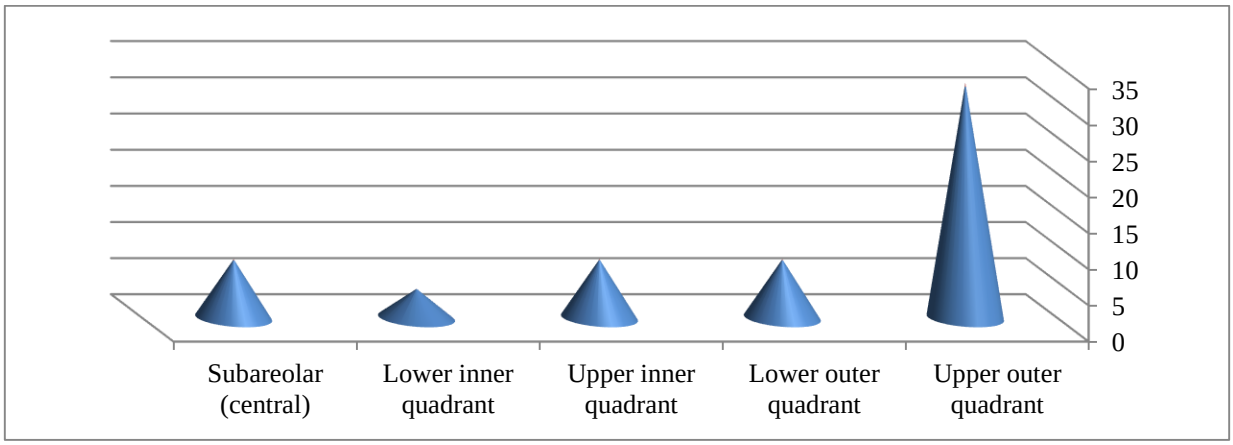

Figure (1): Site of breast quadrants affection in studied group.

Table 2 summarizes type of breast surgery after SLNB of participants.

Table (2): Type of breast surgery after SLNB in studied patients:

Type of surgery	(*n*=60)	
	No.	**%**
Modified radical mastectomy	4	6.7%
Quadrantectomy and axillary Clearance	8	13.3 %
Lumpectomy and axillary clearance	4	6.7%
Conservative breast surgery Without axillary clearance	44	73.3%
Total	**60**	**100%**

Table 3 summarizes the number and types of excised SLN during surgery of the participants.

Table (3): Number and Types of excised SLN during surgery.

Variables	(*n*=60)	
	No.	**%**
No. of LNs		
2	12	20%
3	40	66.7%
4	8	13.3%
Level of SLN Excision		
Level I	51	85%
Level II	5	8.3%
Level I & II	4	6.7%
Total	**60**	**100%**

Regarding postoperative pathology, invasive duct carcinoma was the most common pathology diagnosed in 44 patients with an overall incidence 73.2% **(Table 4).**

Table (4): Postoperative pathology in studied group

Pathology	(*n*=60)	
	No.	%
Invasive duct carcinoma	44	73.2%
Invasive lobular carcinoma	4	6.7%
Mixed invasive duct and lobular carcinoma	4	6.7%
Mucinous carcinoma	4	6.7%
Duct hyperplasia with areas of low grade carcinoma	4	6.7%
Total	60	100%

Concerning the Validity of AUS finding; 73.3% of the studied women were negative SLN with Negative AUS LNs **(Table 5).**

Table (5): Validity of AUS finding in relation to blue SLNS finding :

Status of lymph nodes	(*n*=60)	
	No.	**%**
Negative SLN with Negative AUS LNs.	44	73.3%
positive SLN with Negative AUS LNs.	16	26.7%

Regarding post-operative complications; 6.7% was developed wound infection that responded conservatively in 3 patients with systemic antibiotics and repeated dressing, while the other patient needed secondary sutures after period of repeated dressing until the wound was clean under cover of systemic antibiotics according to culture and sensitivity examination from the wound. 4 patients developed wound hematoma due to blockage of the suction drain which responded to aspiration and compression under cover of antibiotics. No patient developed local recurrence at the mastectomy wound during a follow up period ranging from 4 to 6 months. Also, 4 patients (6.7%) developed ipsilateral upper limb lymphedema (the mid-arm circumference difference between both upper limbs was more than 2 cm) **(Table 6)**.

Table (6): The post-operative complications in studied patients.

Complications	(*n*=60)	
	No.	**%**
Wound infection	4	6.7%
Lymphedema of the ipsilateral arm	4	6.7%
Wound haematoma	4	6.6%
Local recurrence	0	0%
No complications	48	80%
Total	60	100%

The procedure of methylene blue dye injection was painful in the 1st 2 (3.4%) patients, this occurred when methylene blue was injected before anesthesia, so the injection was done after anesthesia in the following cases. 4 (6.7%) patients presented with prolonged tattooing at the injection site for more than 2 weeks but it completely disappeared at the end of the 2nd month. No patients presented with infection at the site of injection. No patient in the studied group developed any allergic reaction to methylene blue dye injection either locally or systematically. No patient developed local recurrence during a follow up period of up to 6 months **(Table 7)**.

Table (7): Complications of methylene blue.

Complications	No. of patients	Percentage
Pain	2	3.4%
Tattooing >2 weeks	4	6.7%
Injection site infection	0	0%
Allergy	0	0%
Total	6	10%

DISCUSSION

For all breast cancers, axillary staging continues to be the gold standard of care because it provides details necessary for customized surgical therapy. The axilla must be surgically probed since imaging approaches to detect axillary lymph nodes are not sensitive enough. ALND, however, can lead to lymphedema, nerve damage, shoulder dysfunction, and other short- and long-term consequences that impair functioning and lower quality of life [8].

Since the introduction of SLNB, surgical techniques for precisely staging the axilla in patients with early-stage breast cancer have grown less involved.

For axillary lymph node staging in clinically and radiologically node-negative breast cancer, SLNB has replaced ALND as the gold standard. SLNB staging can decrease surgical morbidity in terms of lymphedema and shoulder dysfunction without compromising prognostic data or diagnostic accuracy [9].

Based on the size and physical characteristics of the lymph nodes, AUS can detect illness in ALN. Studies that have looked at the accuracy of AUS have found that it has good levels of sensitivity and specificity [6].

In our study, 60 cases were included, their ages ranged from 21 to 70 years with mean age of 45 years. This finding agree with **Cools-latigue and Meterissian** [10] who reported 60 cases, **Chen *et al.*** [11] who mentioned the range of 29- 65 years old with mean age 49 in their study.

In our study, 36 (60%) cases the mass was in the right breast, and 24 (40%) cases was in the left breast. This finding agree with **Ozdemir *et al.*** [12] who reported 66% of the patients presented with right breast mass and 34% of patients presented with left breast mass.

In our study, 32 (53.3%) cases presented with upper outer quadrant affection and 8 (13.3%) cases presented with lower outer quadrant affection. These finding was near to result of **Ozdemir *et al.*** [12] who reported 57% of cases with upper outer quadrant affection and 11% of cases with lower outer quadrant affection.

In the current study, 8 (13.3%) patients had upper inner quadrant presentations, 4 (3.3%) cases had lower inner quadrant presentations, and 8 (13.3%) cases had central masses. This conclusion was in agreement with that of **Ozdemir *et al.*** [12], who noted that 13% of cases had a central mass and that 15% of cases had upper inner quadrant affection, 4% had lower inner quadrant affection.

According to the tumor size T, all patients in our research had TNM staging of N0 M0, with 32 (53.3%) instances having T2 stage and 28 (46.7%) cases having T1 stage. This conclusion is in line with that of **Chen *et al.*** [11] who found that 51.7% of cases were in the T1N0M0 stage and 48.3% were in the T2N0M0 stage.

In our investigation, the SLNs were removed from Level I in 51 (85%) cases, Level II in 5 (8.3%) cases, and Level I and Level II in 4 (6.7%) cases. These results are consistent with those of **Nandu and Chaudhari** [13], who reported that 88% of level I instances, 5.7% of level II cases, and 6.3% of level I and level II cases .

In our investigation, invasive duct carcinoma was the pathology in 44 (73.2%) cases, invasive lobular carcinoma in 4 (6.7%) cases, combined invasive duct and lobular carcinoma in 4 (6.7%) cases, and other pathology in 8 (13.4%) instances. This conclusion is consistent with that of **Zhou *et al.*** [14] who found invasive ductal carcinoma in 86% of patients, invasive lobular carcinoma in 6% of cases, combined invasive ductal and lobular carcinoma in 14.9% of cases, and other pathology in 10.6% of cases.

In our study, according to primary tumor grading, 8 (13.3%) cases with grade I, 40 (66.7%) cases with grade II and 12 (20%) cases with grade III. Similarly, **Zhou *et al.*** [14] reported 13.9% of cases with grade I, 64% of cases with grade II and 22.1% of cases with grade III.

In our study, all the 60 cases were proven to be clinically and radiologically negative by both good axillary clinical examinations and good axillary ultrasonography AUS, but by SLNB intraoperative there were 16 cases proven to be positive for malignant metastasis of the primary breast tumor.

According to the current investigation, AUS demonstrated sensitivity of 69%, specificity of 100%, and accuracy of 61.7% in connection to blue SLNS findings in the study group. This research is consistent with the findings of **Cools-Lartigue and Meterissian** [10] who found AUS sensitivity of 75.9%, specificity of 99.8%, and accuracy of 64.6%.

The AUS had a 100% positive predictive value for SLNB by MB dye and a 75.47% negative predictive value for SLNB by MB, which was close to the values reported by **Cools-Lartigue and Meterissian** [10] who informed a 94.9% positive predictive value (PPV) and a 78.3% negative predictive value for AUS in relation to SLNB by MB technique.

CONCLUSION

The surgical procedure as sentinel LN biopsy SLNB (by methylene blue MB) still has the upper hand as a diagnostic tool for axillary nodal status with more accuracy and sensitivity than radiological methods as axillary ultrasound AUS.

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