Sentinel lymph node biopsy versus observation in clinically and ultrasound node negative early stage breast cancer

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Abstract

Background: The gold standard for axillary staging in node-negative early-stage breast cancer is sentinel lymph node biopsy (SLNB). Axillary lymph node dissection (ALND), SLNB, and axillary radiotherapy have all been associated with axillary problems, but at a smaller incidence with SLNB alone than with ALND. The Z0011 trial demonstrated that there is no benefit from axillary dissection in the context of positive SLN.

Aim: Compare locoregional recurrence, disease free survival (DFS), and overall survival (OS) between SLNB and observation in patients with early stage clinically node negative breast cancer by palpation and preoperative ultrasonography.

Methodology: Candidates for Breast Conservative Surgery include 60 patients with clinically and radiologically node-negative early breast cancer, randomized to one of two groups: ***Study group (group A):*** 30 patients underwent BCS with no further axillary surgery. ***Control group (group B):*** 30 patients underwent BCS and SLNB. Follow up was done to detect the two years locoregional recurrence, DFS and OS.

Results: After a two-year follow-up, there was no discernible difference between the two arms in terms of axillary, local, or metastatic recurrence. Regarding post-operative arm edema, both arms significantly differ from one another.

Conclusion: Omission of axillary surgery in T_1 and some cases of T_2 N_0 breast cancer patients appears safe and applicable without affecting locoregional recurrence and axillary/nodal recurrence. Longer term follow-up is needed

Keywords: Early stage breast cancer, axillary dissection, arm edema, sentinel lymph node biopsy.

INTRODUCTION

The gold standard for axillary staging in node-negative early-stage breast cancer is sentinel lymph node biopsy (SLNB) (1).

Axillary lymph node dissection (ALND), SLNB, and axillary radiotherapy have all been associated with axillary problems and unfavorable side effects, but at a smaller extent with SLNB alone than with ALND. Although the majority of studies estimate a 3% to 7% incidence of lymphedema following SLNB compared to 5%–50% for ALND, the incidence of measured lymphedema has been reported to range from 0% to 22%. As a result, SLNB is linked to persistent postoperative problems. Despite being less of a burden than ALND, difficulties should nonetheless not be disregarded (2).

Giuliano et al. published the findings of the American College of Surgeons Oncology Group

(ACOSOG)-designed Z0011 Trial, which randomly assigned patients with 1-2 positive SLNs to have ALND or no further axillary surgery. They verified that, as had been suggested by prospective randomized clinical studies conducted before showed the development of SLNB, excision of lymph nodes did not have a curative goal. Additionally, the findings demonstrated that in the presence of SLN involvement, good local control may be attained by forgoing ALND (1% axillary relapse after 6.3 years of median follow up), and just one regional recurrence was noted in the SLND alone group with prolonged follow-up (after 9.3 years of median follow up).

The Z0011 trial demonstrated that there is no benefit to the patient's outcome when the axilla is dissected in the presence of positive SLN, indicating that the information gained by removing lymph nodes does not alter the patient's prognosis for the disease (3). Furthermore, adjuvant therapy is increasingly focused on the biological characteristics of the illness rather than the risk of recurrence; the prognostic information of axillary lymph node status has less of an influence on decision-making now than it did in the past. The type of adjuvant treatment did not differ between the two groups in the AMAROS trial, which randomly assigned patients with positive SLNs to receive either axillary clearance or axillary radiotherapy. This finding suggests that detailed information on axillary status will not change treatment recommendations (4).

Currently, three Randomized control trials (RCTs) are being conducted to investigate the potential of omitting SLNB in clinically node-negative breast cancer.

Sound Trial:

Patients who have breast cancer smaller than or equal to 2 cm, who are candidates for breast-conserving surgery, and who have either negative cytology of the single doubtful lymph node or negative ultrasound of the axilla will be eligible for randomization into two groups. Group 1 will receive SLNB, while group 2 will not receive any axillary surgical staging.

Distant disease-free survival is the trial's main outcome. The cumulative incidence of distant recurrences, the cumulative incidence of axillary recurrences, the DFS, and the overall survival will serve as secondary outcomes (OS).

Therefore, the hypotheses of this trial are that:

- Patients with small breast cancer do not have worse outcomes if they avoid axillary surgery.
- These patients' outcomes are not worsened by the lack of pathology information about the risk of recurrence provided by nodal status.
- Patients with a clinically meaningful nodal load can be identified by axillary pre-operative imaging (5).

INSEMA (GBG75) Trial:

Patients scheduled for BCS and older than 18 years old with breast cancer less than 5 cm in diameter can be included in this experiment. Patients are first randomized in a 1:4 allocation to receive axillary SLNB or no axillary surgical intervention. In circumstances where there are less than four affected nodes, patients undergoing SLNB with positive SLNs are then randomly assigned (1:1) to either SLNB alone or completion axillary dissection (AD) (1 or 3 macro metastases). Patients will get complete AD if they have four or more macro metastatic SLNs (6).

BOOG 2013-08 Trial:

Adult women with unilateral invasive breast cancer who are cT1-2 N0 and are candidates for BCS are included, as are that receiving neoadjuvant chemotherapy. They are randomly assigned

to SLNB versus Observation following preoperative axillary US. Regional recurrence rate serves as the primary outcome. DFS, OS, number of delayed AD, axillary morbidity rate, quality of life, local recurrence rate, contralateral breast cancer, chest wall RT, cost-effectiveness, and local recurrence rate are secondary objectives (7).

Materials and methods

Between the first of March 2019 and the first of July 2021, this prospective randomized control trial on patients with early-stage breast cancer was carried out at Cairo University Hospitals, Faculty of Medicine, Cairo University.

The study involved 60 patients with early breast cancer who were node negative on imaging and clinical examination and were eligible for breast conserving surgery.

Inclusion criteria:

Patients who are 70 years old or more with Tumor size equal to or less than 2 cm (both clinically and radiologically) with no skin or chest wall invasion and no clinically or sonographically suspicious axillary lymph nodes.

Exclusion criteria:

Any contraindications of BCS (Multicentric and inflammatory breast cancer), locally advanced breast cancer, prior neoadjuvant chemotherapy and presence of distant metastasis.

Patient population:

Patients who presented to the breast clinic with suspicious breast lumps or screening-detected breast lesions underwent a triple assessment consisting of a clinical examination, sonomammography, and tru-cut biopsy; if breast cancer was found, a metastatic work-up (chest X-ray and abdominal ultrasound) was also completed, as well as Immunohistochemistry on the biopsy (ER and PR receptors, Her2-neu, and Ki67).

Following the presentation of the patient's data at the weekly multidisciplinary team (MDT) breast clinic, where experts in breast cancer management from the fields of surgical oncology, medical oncology, radiotherapy, radiology, and pathology discussed the findings of the investigations, patients who were classified as having clinically node-negative early stage breast cancer (tumor size of equal to or less than 2 cm) were randomly assigned to one of two groups:

Study group (group A): 30 patients underwent BCS with no further axillary surgery.

Control group (group B): 30 patients underwent BCS and SLNB.

Randomization A random sequence generator with random block size was used to create a randomized sequence in a 1:1 ratio. An independent individual, without any further involvement in the study, created concealed sequentially numbered, opaque envelopes. When patients were recruited, they were assigned a unique study-ID, and the corresponding randomization envelope was opened intraoperatively .

Group A (study group):

Technique of BCS: A curvilinear skin incision was performed according to the site and the size of the tumor and its relation to the nipple and the areola complex followed by elevation of skin flaps then excision of the tumor was done with adequate safety margin (1 cm). Cavitary margins were then taken and sent to the frozen section unit in the operating room to ensure adequate safety margins. Radio-opaque clips were then used to mark the site of the tumor for radiotherapy then mobilization of the glandular flaps was done to fill the defect followed by closure in layers.

No axillary surgery was performed in those patients.

Adjuvant systemic therapy and radiation therapy were completed according to the biological subtype and the final pathological staging.

Radiation Therapy: According to the protocol followed by the Department of Oncology, Faculty of Medicine, Cairo University.

All patients were given whole-breast hypofractionation (40 Gy in 15 fractions) that was typically delivered with tangentially oriented beams that treat the entire breast while minimizing dose to the underlying heart and lungs with no dedicated nodal field.

Follow up: was done by clinical examination and Mammo-sonography (Alternating with breast and axillary ultrasound) every 3 months in the first 6 months then every 6 months for 2 years to detect locoregional recurrence, DFS and OS in addition to the axillary/nodal recurrence rate and the post-operative wound complications and arm edema.

Group B (Control group):

Technique of BCS: was the same as group A

Technique of SLNB:

Peritumeral or sub-areolar injection of 3-5 CCs 1% Methylene Blue dye was utilized in SLNB. A tiny axillary incision 2 cm below the hairline, an opening of the axillary fascia, and the extraction of roughly 3 LNs were performed after 15 minutes. We removed all the lymph nodes that were blue colored, swollen, or those had bluish lymphatic streaks before closing the wound without using a drain. The lymph nodes were then transported to the operating room's frozen section unit for detection of positive or negative SLN and management in accordance with ACOSOG Z0011 guidelines, where:

- No more ALND for patients with negative SLNB.
- No additional ALND for patients with ITCs, micro metastases, or macro metastases (1-2 positive out of 3–4 lymph nodes).
- ALND was conducted on patients who had three or more positive lymph nodes, matted lymph nodes, or lymph nodes with extra-capsular extension.

Then the SLNs were sent for paraffin analysis to confirm the frozen section results. Adjuvant systemic therapy and radiation therapy were completed according to the biological subtype and the final pathological staging.

Radiation therapy: follow the same protocol like group A.

Follow up: Detection of the two-year locoregional recurrence, DFS, and OS, as well as the axillary/nodal recurrence rate, post-operative wound complications, and arm edoema, was carried out similarly to group A every 3 months in the first 6 months, then every 6 months by clinical examination and Mammo-sonography (Alternating with breast and axillary ultrasound).

The institutional research and ethical committee examined the study protocol and approved it.

Statistical methods:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 26 (IBM Corp., Armonk, NY, USA). Data was summarized using mean, standard deviation, median, minimum and maximum in quantitative data and using frequency (count) and relative frequency (percentage) for categorical data. Comparisons between quantitative variables were

done using the non-parametric Mann-Whitney test. For comparison of paired measurements within each patient the non-parametric Friedman test and Wilcoxon signed rank test were used. For comparing categorical data, Chi square ($\chi 2$) test was performed. Exact test was used instead when the expected frequency is less than 5. P-values less than 0.05 were considered as statistically significant.

Results

Patients' characteristics:

Twenty eight patients of group A (93.3%) had invasive duct carcinoma (IDC), two patients (6.7%) had Invasive Lobular Carcinoma(ILC), while twenty-six patients (86.7%) were found to have IDC, one patient (3.3%) had ILC, one patient (3.3%) had mixed Duct and Lobular carcinoma, one patient (3.3%) had Paget's disease and one patient (3.3%) had Intracystic Papillary Carcinoma in group B (Table 1).

Regarding the grade, twenty-eight patients (93.3%) were grade II, and two patients (6.7%) were grade I in group A while twenty-two patients (75.9%) were grade II, six patients (20.7%) were grade I and one patient (3.4%) was grade III in group B (Table 1).

Table (1): Types and grades of the tumor in case and control groups

		Group A		Group B	
		Count	%	Count	%
Tumor Type	paget's	0	0.00%	1	3.30%
	IDC	28	93.30%	26	86.70%
	ILC	2	6.70%	1	3.30%
	Mixed	0	0.00%	1	3.30%
	Papillary	0	0.00%	1	3.30%
Tumor grade	I	2	6.70%	6	20.70%
	II	28	93.30%	22	75.90%
	III	0	0.00%	1	3.40%

Axillary/nodal recurrence:

There is no patient in both cases or control group that show axillary recurrence after two years of follow-up (0%) (**Table 2**).

Local recurrence:

No local in-breast recurrences could be detected (0%) in group A while there was a single case of local tumor bed recurrence (3.3%) which occurred 3 months after the operation in group B. By comparing both results of the cases and the control group, there is no significant difference between both groups regarding the local recurrence (p value = 1) (**Table 2**).

Metastatic recurrence:

There is one patient in group A (3.3%) that show metastatic bone recurrence 6 months after the operation, while in group B no patients showed metastatic recurrence after two years follow-up (0%). By comparing both results of the cases and the control group, there is no significant difference between both groups regarding the metastatic recurrence (p value = 1) (**Table 2**).

Arm edema:

After an average of 2 years follow-up, no patient in group A suffered from arm edema (0%) while in group B 9 patients (30%) suffered from grade I arm edema, 3 patients (10%) suffered from grade II arm edema and 18 patients (60%) did not suffer from arm edema. Two of the three patients with grade II arm edema underwent ALND and their edema still present after two years follow-up while the third patient underwent SLNB and her arm edema subsides after 6 months. By comparing the results of both groups, there is a significant difference between the cases and the control groups regarding the post-operative arm edema (p value = 0.009).

Table (2): Comparison between the group A and group B regarding axillary recurrence, local recurrence, metastatic recurrence and arm edema after 2 years follow-up

		Group A		Group B		P value
		Count	%	Count	%	
Axillary recurrence	Yes	0	0.0%	0	0.0%	------
	No	30	100.0%	30	100.0%	
local recurrence	Yes	0	0.0%	1	3.3%	1
	No	30	100.0%	29	96.7%	
Metastatic recurrence	Yes	1	3.3%	0	0.0%	1
	No	29	96.7%	30	100.0%	
Arm edema after 2 years follow up	Grade 4	0	0.0%	0	0.0%	0.009
	Grade 3	0	0.0%	0	0.0%	
	Grade 2	0	0.0%	3	10.0%	
	Grade 1	0	0.0%	9	30.0%	
	No	30	100.0%	18	60.0%	

Breast cancer biological subtypes:

All the 30 patients of group A (100%) were found to be ER positive, 24 patients (80%) were PR positive, 4 patients (13.3%) were Her2-neu positive and 6 patients (20%) with high proliferative index while in group B 27 patients (93.1%) were found to be ER positive, 22 patients (75.9%) were PR positive, 5 cases (17.2%) were Her2-neu positive and 8 patients (27.6%) with high proliferative index.

Regarding the luminal subtypes, 22 patients (73.3%) were luminal A, 4 patients (13.3%) were luminal B1 and 4 patients (13.3%) were luminal B2 in group A while 20 patients (69%) were luminal A, 3 patients (10.3%) were luminal B1, 4 patients (13.8%) were luminal B2, one patient (3.4%) was Her2 enriched and one patient (3.4%) was triple negative in group B **(Fig. 1)**

This means that there is no statistical difference between both groups in luminal subtypes.

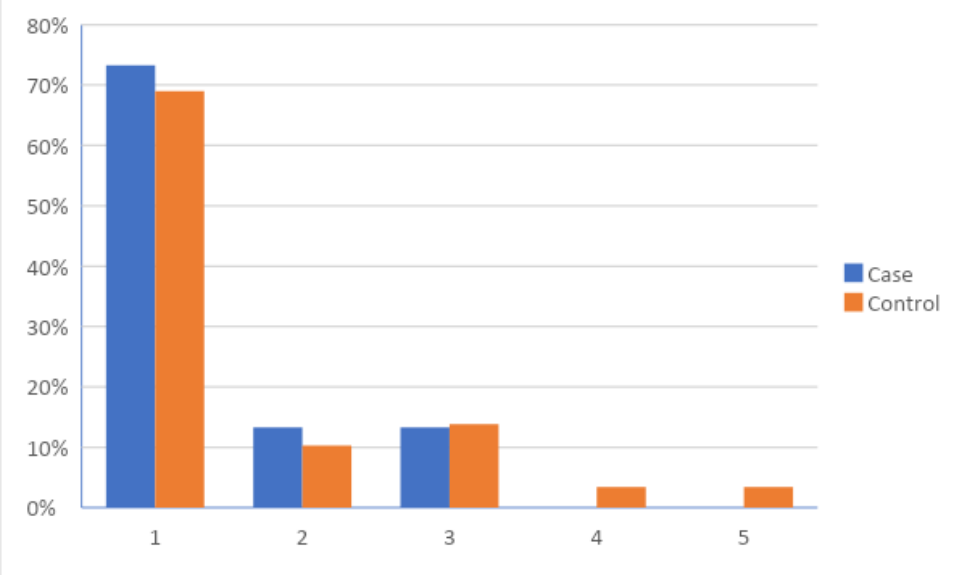

Fig. (1): Bar chart showing luminal subtypes in cases and control groups

Discussion

Our study compared locoregional recurrence, disease free survival, overall survival, axillary/nodal recurrence rate, and post-operative complications between SLNB and observation in patients with early stage clinically node negative breast cancer (clinically and sonographically).

The luminal subtypes in our patients were comparable to the other studies where in our study all patients of group A were hormone receptor positive and 13.3% were Her2neu positive while in group B 93 % were found to be hormone receptor positive and 17% were Her2neu positive.

This is consistent with the first findings of the INSEMA Trial, as reported by Reimer et al. Following the inclusion of 1001 patients, it was shown that 96.9% of the 1001 breast cancers were hormone receptor positive. Only 8.5% of tumours had Her2neu positivity, while only 5.4% of patients had the G3 tumour grade (6).

Another study conducted by Martelli et al. in 2012 revealed that 89.1% of the axillary surgery group and 85.4% of the no-axillary surgery group were both hormone receptor positive (8).

According to some authors, the addition of radiocolloids to blue dye in SLNB does not increase identification rate to the extent that justifies its costs and limitations in use because in the ACOSOG Z0010 trial, the percent of failed SNB with blue dye was 1.4%, radiocolloid 2.3%, and the combination 1.2%. (9).

All of the patients in the control group underwent SLNB in our study using 1% Methylene Blue , which is highly effective as a single agent in SLNB in early stage breast cancer with a very high identification rate compared to patent blue and radiocolloids, has a low complication rate, is accessible and affordable, and is advised to be included in the breast surgeons' training programme. In our investigation, every surgical specimen had a lymph node identified (identification rate: 100%). Between 3 and 6 lymph nodes were seen, with a mean of 4.6.

Identification rates (IRs) for SLNB were shown to have grown with time, rising from 88% in 1992–2000 to 97% in 2007–2012. This increase in IR is probably attributable to the surgeons doing SLNB gaining more experience (10).

We advise using 1% Methylene Blue as a single agent in SLNB for early-stage breast cancer

based on these findings.

After a median follow-up of 24 months, we found that there is no patient in both group A and B that show axillary recurrence. We also found that no local in-breast recurrences could be detected (0%) in group A while there was a single case of local tumor bed recurrence (3.3%) in group B. Furthermore, there is one patient in group A (3.3%) that show metastatic bone recurrence while in group B no patients showed metastatic recurrence (0%).

This indicates that there is no discernible difference in the incidence of axillary/nodal, local, or metastatic recurrence between the two groups.

This is consistent with a 2012 study by Martelli et al. that revealed the crude 15-year crude cumulative incidence of ipsilateral breast tumor recurrence was 4% in the axillary dissection arm and 8.3% in the no axillary dissection arm. The incidence of distant metastases during a 15-year period was 9.6% in the arm without axillary dissection and 8.6% in the arm with axillary dissection (8).

This indicates that early stage clinically node negative breast cancer may be treated without SLNB without impacting locoregional recurrence, disease-free survival, or even overall survival.

The SOUND study, the INSEMA trial, and the BOOG trial are three more active trials that are using the identical strategy of skipping SLNB in early stage node negative breast cancer. We're awaiting the outcomes of these studies to see if they support or oppose the findings of our investigation.

The results of our study showed that there is significant difference between both groups regarding post-operative arm edema where all patients in group A did not suffer from any arm edema compared to only 60 % in group B. This indicates that omitting SLNB made the patients avoid the post-operative arm complications without affecting the locoregional recurrence.

This is in line with what Gentilini et al. reported in 2016 on an ancillary analysis that was planned and completed on the first 180 patients who enrolled in the SOUND trial to assess the effects of various surgical procedures on post-operative physical function and symptoms of the ipsilateral upper limb. They demonstrated that, compared to women who received either SLNB alone or no surgery of the axilla, 5 patients who underwent ALND reported substantially inferior arm physical function 1 week, 6 months, and 12 months following surgery. The physical function and symptoms of the ipsilateral upper limb were different in individuals who received SLNB, although these differences were only visible in the first week following surgery and disappeared at 6 and 12 months later (5).

The study limitation is number of patient may increase in further studies.

The major strengths of the study are the methodological robustness, which minimizes the risk of biases, including selection bias (randomization and concealment of allocation) and first study in Cairo university Hospital to study effect of omission SLND in early breast cancer.

Conclusion

The idea of omitting axillary surgery in T_1 and some cases of $T_2 N_0$ breast cancer patients appears safe and applicable as this eliminate post-operative arm complications and arm edema without affecting the locoregional recurrence and axillary/nodal recurrence. Pre-operative axillary ultrasound can accurately assess the axillary lymph node status and reliably rule out patients with positive or suspicious axillary lymph nodes from applying this protocol. However, longer term follow-up is needed.

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Declaration

Financial support and sponsorship**:** Nil.

Conflicts of interest**:** There are no conflicts of interest.

Ethical approval**:** The study was approved by the Institutional Ethics Committee

Abbreviations

ACOSOG	the American College of Surgeons Oncology Group
ALND	Axillary lymph node dissection
BCS	Breast Consevative Surgery
DFS	Disease free survival
IDC	Invasive duct carcinoma
OS	Overall survival
PAUS	Pre-operative axillary ultrasound
SLNB	Sentinel lymph node biopsy
IR	Identification rates

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