

# MORBIDITY OF SENTINEL LYMPH NODE BIOPSY (SLNB) ALONE VERSUS SLNB AND COMPLETION AXILLARY LYMPH NODE DISSECTION AFTER BREAST CANCER SURGERY- A PROSPECTIVE SINGLE CENTRE STUDY

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## ABSTRACT

### BACKGROUND

ALND after breast cancer surgery is associated with considerable morbidity. We hypothesised- 1) The morbidity in patients undergoing SLN biopsy only is significantly lower compared with those after SLN and completion ALND level I and II; and 2) The intermediate survival rates, local and axillary recurrence rates were significantly equivalent in both the groups.

### MATERIALS AND METHODS

Patients with early stage breast cancer (pT1 and pT2  $\leq$  3 cm, cN0) were included between April 2010 and April 2016 in this prospective single centre study. All patients underwent SLN biopsy. In all patients with SLN macrometastases and most patients with SLN micrometastases (43 of 68) or isolated tumour cells (11 of 19), a completion ALND was performed. Postoperative morbidity was assessed based on a standardised protocol.

### RESULTS

SLN biopsy alone was performed in 449 patients, whereas 210 patients underwent SLN and completion ALND. The median follow-ups were 31.0 and 29.5 months for the SLN and SLN and completion ALND groups, respectively. Intermediate-term follow-up information was available from 635 of 659 patients (96.4%) of enrolled patients. The following results were found in the SLN versus SLN and completion ALND group- Presence of lymphoedema (3.5% vs. 19.1%,  $P < 0.0001$ ), impaired shoulder range of motion (3.5% vs. 11.3%,  $P < 0.0001$ ), shoulder/arm pain (8.1% vs. 21.1%,  $P < 0.0001$ ) and numbness (10.9% vs. 37.7%,  $P < 0.0001$ ).

### CONCLUSION

The morbidity after SLN biopsy alone is not negligible, but significantly lower compared with ALND. The intermediate survival rates, local and axillary recurrence rates were equivalent in SLNB only and SLNB plus completion ALND groups.

### KEYWORDS

Sentinel Lymph Node Biopsy, Axillary Lymph Node Dissection, Morbidity Comparison, Prospective Study.

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### BACKGROUND

This is a prospective single centre study on 659 patients to assess the morbidity after Sentinel Lymph Node Biopsy (SLNB) compared with SLNB and completion Axillary Lymph Node Dissection (ALND). Many studies have proven that ALND after breast cancer surgery is associated with considerable morbidity. The main aim of the present study is to prove that- 1. The morbidity in patients undergoing SLNB only is significantly lower when compared to SLNB and completion ALND; 2.<sup>1</sup> The intermediate survival rates, local

and axillary recurrence rates were significantly equivalent in both the groups. Patients with early stage breast cancer (pT1 and pT2  $\leq$  3cm, cN0) were included in the time period between April 2010 and April 2016 in this study. All patients underwent SLN biopsy. In all patients with a positive SLN biopsy, a completion ALND was performed. Postoperative morbidity was assessed and compared based on a standardised protocol. SLN biopsy alone was performed in 449 patients, whereas 210 patients underwent SLNB and completion ALND. The median follow-ups were 31 and 29.5 months for the SLNB and SLNB and completion ALND groups, respectively. Intermediate term follow-up information was available in 635 of 659 patients (96.4%). These results clearly indicated a significantly lower incidence of morbidity in SLNB alone group when compared to SLNB and completion ALND group. They also showed an equivalent incidence of local and axillary tumour recurrence rates in both the groups. This study gives a compelling evidence to the fact that though the morbidity of SLNB alone is not negligible. It is comparatively less when compared to

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SLNB and completion ALND. The axillary lymph node status is one of the most important prognostic factors. The SLNB accurately reflects the status of remaining axillary lymph nodes in early stage breast cancer patients with a very low false-negative rate and most patients can be spared the considerable short and long-term sequelae of ALND.<sup>2</sup>

### Aims and Objectives

To assess the morbidity after Sentinel Lymph Node (SLN) biopsy compared with SLN and completion Axillary Lymph Node Dissection (ALND) in a prospective single center study.

### MATERIALS AND METHODS

Between April 2010 and April 2016, a total of 698 patients with early stage breast cancer were prospectively enrolled in the present single centre study. Inclusion criteria for the present study were- 1. Presence of palpable breast cancer; 2. Tumour size is equal to or less than 3 cm; 3. Absence of clinically palpable lymph nodes; 4. No prior history of breast cancer or other malignancies; 5. No neoadjuvant therapy; and 6. No pregnancy. 39 patients did not meet the inclusion criteria and were therefore excluded. Written informed consent was obtained from all the patients. Approval was obtained from all involved local ethic committees. The Government General Hospital, Kakinada, which is attached to Rangaraya Medical College was the centre, which participated in the study.

**Lymphatic Mapping and Operative Technique-** SLN mapping was done by using a combination of a radiocolloid and a vital blue dye. 99mTc-labelled nanocolloid at a dose of 70 mBq was injected peritumourally at 4 places, whereas at the injection site closest to the axilla, half of the dose was injected peritumourally and subdermally. The SLN were intraoperatively identified first by a handheld gamma probe. Up to 5 mL of isosulfan blue dye was injected in the same fashion as radioactive tracer 5 to 10 minutes prior to incision. Hot and blue lymph nodes were excised and labelled as SLN. Dissection was continued until all hot and blue nodes had been removed.

**Pathological Examination of Lymph Nodes-** Frozen sections were performed routinely intraoperatively. Lymph nodes larger than 5 cm in diameter were bisected, whereas lymph node less than or equal to 5 cm were not bisected, but completely subjected to frozen section analysis. The SLN were intraoperatively examined at 3 levels- 1. With haematoxylin and eosin stained sections at a cutting interval of 150 millimicrons; 2. The remaining tissue of SLN was formalin fixed and embedded in paraffin for histologic analysis; 3. The residual tissue was then examined using step sectioning at a cutting interval of 250 millimicrons and these step sections were stained with haematoxylin and eosin. If no carcinoma cells were detected, immunohistochemistry with cytokeratin antibody Lu-25 or CK-22 using a standard immunoperoxidase method was performed.

Macrometastases were defined as a diameter more than 2 mm. Micrometastases were defined based on a size exceeding 0.2 mm and less than or equal to 2 mm in diameter. Isolated tumour cells or tumour cell clusters were defined as measuring less than or equal to 0.2 mm in diameter.<sup>3</sup> All patients with SLN macrometastases in frozen sections underwent immediate completion ALND. If no macrometastases were found in frozen sections, but in final histopathology, patients underwent a delayed completion ALND. The decision to perform a completion ALND in patients with micrometastases and isolated tumour cells was left to individual surgeon's choice. No completion ALND was performed in women with tumour-free SLN.

**Postoperative follow-up-** The follow-up diagnostics included clinical examination of the breast and axilla every 3 months as well as annual mammography to detect local and axillary recurrences. Additional ultrasound of the breast was performed to clarify suspicious mammographic findings. A standardised study form was filled out- 1. Before surgery; 2. On day 3, postoperatively or prior to discharge, if patients were discharged earlier; and 3. During every follow-up examination in the outpatient clinic.

The patients were assessed at every follow-up for the presence or absence of subjective criteria and objective parameters. The subjective criteria included pain (arm, shoulder, breast and thorax), numbness and restrictions in daily activities due to scar or arm problems. The objective parameters included preoperative and postoperative measurements of- 1. Range of motion of shoulder in all directions according to neutral zero-crossing method; and 2. The circumference of both upper and forearm 15 cm above and 15 cm below olecranon process (to ensure measuring mid arm and mid forearm circumference). A deficit range of motion over 20° to standard values and in comparison to the unaffected side was considered abnormal. The diagnosis of lymphoedema was based on either subjective symptoms or objective findings and measurements. Symptoms like swelling and heaviness of the affected arm were considered diagnostic for lymphoedema as well as clinical findings such as indentation after skin impression or loss of skin folds. A 2 cm increase of the arm circumference compared with ipsilateral baseline assessments as measured 15 cm above and 15 cm below olecranon was considered abnormal. Difference in circumference of more than 2 cm to the measurement of contralateral arm were also considered abnormal.

### RESULTS

Between April 2010 and April 2016, SLN biopsies were performed in 659 patients meeting the inclusion criteria. The overall SLN identification rate was 98.3% (648 of 659). A median number of 2 SLNs were harvested per patient in both the groups. The SLNs were tumour free in 416 patients (416 of 659, 63.1%). Macrometastases were detected in 145 patients (145 of 659, 22.0%), micrometastases in 68 patients (68 of 659, 10.3%) and isolated tumour cells in 19 patients (19 of 659, 2.9%). All patients with SLN macrometastases and most patients with SLN

micrometastases and isolated tumour cells underwent completion ALND. SLNB and completion ALND was performed in 210 patients (210 of 659, 31.9%). Of those, 145 patients had SLN macrometastases, 43 patients had micrometastases, 11 patients had isolated tumour cells and in 11 patients, no SLN identification was possible. In the remaining 449 women (449 of 659, 68.1%), no further axillary surgery was performed. Based on frozen sections showing macrometastases (142 patients), micrometastases (7 patients) and in case of SLN identification failure (11 patients), an immediate completion ALND was performed in 160 patients (160 of 210, 76.2%). A delayed completion ALND was performed in 50 patients (50 of 210, 23.8%). Therefore, 7.6% (50 of 659) of the entire study population underwent delayed completion ALND.

**In-hospital morbidity and mortality-** A total of 651 (651 of 659, 98.8%) patients were evaluated. Eight patients were excluded due to incomplete datasheets. There was no reported morbidity in 66.2% and 35.8% in the SLNB group and in the SLNB and completion ALND group, respectively ( $p < 0.0001$ ). The following postoperative sequelae were significantly less frequent in SLNB only group compared with those having SLNB and completion ALND.<sup>1</sup> Shoulder range of motion (26.8% vs. 50.0%),<sup>2</sup> shoulder/arm pain (9.3% vs. 22.9%),<sup>3</sup> numbness (6.6% vs. 23.3%),<sup>4</sup> axillary pain (8.2% vs. 17.1%) and<sup>5</sup> seroma formation (all  $p$  values less than or equal to 0.001). Axillary seroma in the SLNB and completion ALND group required more often a puncture (13 of 16 cases, 81%) than the SLNB only group (2 of 8 cases, 25%). The wound infection rates were significantly lower in both the groups (0.9% vs. 2.9%,  $p = 0.08$ ), one patient died on the second day after SLNB and completion ALND due to MI.

### Intermediate Term Morbidity and Mortality-

Intermediate term follow-up information was collected for 635 of 659 patients (96.4%). The median range follow-up of patients undergoing SLNB and SLNB and completion ALND were 31.0 (11-62) and 29.5 (0-60) months, respectively. A total of 168 patients (168 of 431, 39.0%) and 140 patients (140 of 204, 68.6%) in the SLN and in the SLN and completion ALND group, respectively, suffered from at least one problem. Shoulder range of motion (3.5% vs. 11.3%), shoulder/arm pain (8.1% vs. 21.1%), painful scars (3.7% vs. 13.7%), numbness of the upper arm (10.9% vs. 37.7%) and lymphoedema (3.5% vs. 19.1%) were significantly less frequent in the SLN group compared with the SLN and completion ALND group (all  $P$  values  $\leq 0.0002$ ).

**Tumour recurrence-** After median (range) follow-up of 31.0 (11-62) and 29.5 (0-60) months, there was no statistical difference regarding breast or axillary tumour recurrences between patients undergoing SLN biopsy and those having SLN and completion ALND. Breast recurrence occurred in 0.9% and 2.5% in the SLN and SLN and completion ALND group, respectively ( $P = 0.155$ ). Axillary recurrences were detected in 1.2% (5 of 431) in the SLN and 1.5% (3 of 204) in the SLN and completion ALND group ( $P = 0.716$ ). All 8 patients with axillary recurrences were reoperated. Distant metastases occurred more frequently in

the SLN and completion ALND group compared with patients having SLN biopsy only ( $P = 0.034$ ). This can be explained by the fact that in the SLN and completion ALND group, the patients were mostly node positive.

**Immediate Versus Delayed Completion ALND-** Follow-up information for women undergoing completion ALND were gathered for 204 patients (204 of 210, 97.1%). Of those, 155 patients (155 of 204, 76.0%) received an immediate and 49 patients (49 of 204, 24.0%) a delayed completion ALND. There were no statistically significant differences between these 2 groups neither with respect to overall postoperative morbidity (68.4% vs. 69.4%,  $P = 1.0$ ) nor regarding shoulder/arm pain (22.6% vs. 16.3%,  $P = 0.43$ ), numbness (35.5% vs. 44.9%,  $P = 0.24$ ), range of shoulder motion (11.6% vs. 10.2%,  $P = 1.0$ ) and lymphoedema (17.4% vs. 24.5%,  $P = 0.30$ ).

### DISCUSSION

The present prospective single centre investigation based on a large sample of breast cancer patients provides compelling evidence that postoperative morbidity after SLN procedure is significantly lower compared with SLN and completion ALND. Therefore, patients with negative SLN clearly benefit from omitting formal ALND. However, the morbidity after SLN biopsy is not negligible.<sup>4</sup>

ALND is associated with significant morbidity that negatively impacts quality of life. In a retrospective study including 390 breast cancer patients undergoing ALND, lymphoedema of the upper and forearm was found in 13.2% and 8.4%, respectively, after a median follow-up of 62 months. In the aforementioned investigation, numbness occurred in 28%, hypertrophic scars in 17% and shoulder pain in 15% of all patients.<sup>6</sup> Maunsell et al assessed 223 patients 3 months after ALND; they reported that 82% of patients suffered from at least one arm problem including swelling (24%), weakness (26%), limited arm movement (32%), stiffness (40%), pain (55%) and numbness (58%). Our results are in line with and confirm the prevalent occurrence of morbidity after ALND described in the literature.<sup>5</sup>

Lymphoedema represents one of the major factors contributing to postoperative morbidity as it may result in decreased range of motion, pain, weakness or stiffness of the affected extremity. The occurrence of lymphoedema after ALND has been reported in the literature between 5% and 25%.<sup>7,8</sup>

Although, there are generally accepted criteria to diagnose lymphoedema, a precise definition is lacking and no consensus exists of what constitutes lymphoedema.<sup>9</sup> This renders the interpretation of the literature regarding the presence of lymphoedema after breast cancer surgery difficult. Casley-Smith could show that circumferential measurements are highly correlated with the results of the more exact water displacement method. On the other hand, girth measurements do not always correlate with symptoms or quality of life.<sup>10</sup> A combination of symptom assessment and limb measurement as done in the present investigation

represents the most reliable clinical assessment to identify changes associated with post breast cancer surgery lymphoedema.<sup>11</sup>

In our patient sample, axillary recurrence occurred in 1.2% and 1.5% in the SLN and SLN and completion ALND groups, respectively. ALND provides excellent regional control with axillary recurrence rates ranging from 0% to 2%. However, the present prospective investigation provides compelling evidence that axillary recurrence rates in patients undergoing SLN biopsy only and in those having SLN and completion ALND did not significantly differ at a median follow-up of 30 months.

## CONCLUSION

Although, postoperative morbidity after SLN biopsy alone was significantly lower than after SLN and completion ALND in the present investigation, there were still 39% of patients in the former group who suffered from at least one problem. Because of the prospective design of our study and the use of a standardised protocol, we were able to assess the different morbidity parameters very accurately. Although, one would think that the removal of a median number of 2 axillary lymph nodes through a small incision should not lead to problems or complications, the present investigation provides compelling evidence that morbidity is not negligible occur even after SLN biopsy alone.<sup>12</sup>

A variety of prospective studies have compared postoperative morbidity after SLN biopsy and ALND, which show a clear advantage of the SLN technique for most of the variables and confirm the findings of our investigation.

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