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Mini Review

# Sentinel lymph node biopsy in early breast cancer: A brief review

Sachin S Kadam[1,*], Tejaswini Kadam[2]

[1]Department of Surgical Oncology, Currae Cancer & Multispeciality Hospital, Mumbai, India

[2]Department of Ophthalmology , Conwest & Jain Superspeciality Eye Hospital, Mumbai, India

*Author for correspondence: Email: kool_sachin555@outlook.com

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## Abstract

In breast cancer, the status of the axillary lymph node decides the prognosis of the disease. Axillary lymph node dissection (ALND) was the traditional method to address the lymph node. Final histopathological examination is the confirmatory method to detect metastasis in axillary lymph node. As the tumor stage advances, the rate of metastasis in axillary lymph nodes increases, simultaneously. The positivity rate of axillary lymph nodes in early breast cancer is low as compared to locally advanced breast cancer. The role of Sentinel Lymph Node Biopsy (SLNB) has been emerged, established in early breast cancer and it is universally accepted by most of the medical centers, worldwide. SLNB is indicated in early breast cancer when there are clinically negative nodes by palpation and ultrasound examination. It is the procedure to stage the axilla and it has minimum morbidity as compared to ALND. ALND has been replaced by SLNB at many centers, worldwide. We have reviewed the potential SLNB research studies and prepared a brief review article.

**Keywords:** Sentinel lymph node, Early breast cancer, Axillary lymph node, Metastasis, Prognosis, Biopsy, Dissection, Pathologically positive

## Introduction

In breast cancer, traditionally, axillary lymph node dissection has been used as a procedure to remove axillary lymph nodes. In early breast cancer, sentinel lymph node biopsy has replaced axillary lymph node dissection in most of the patients. Thus, axillary lymph nodes decide the prognosis of breast cancer. Metastasis in axillary lymph nodes is defined accurately by histopathological examination. The rate of pathologically positive axillary lymph node decreases when there are clinically negative nodes by palpation and ultrasound examination. Sentinel Lymph Node Biopsy (SLNB) is the procedure of staging the axilla with minimal morbidity as compared to Axillary Lymph Node Dissection (ALND). Preoperative evaluation of axillary lymph nodes is very important as it decides whether patient will go for ALND or SLNB. Patient's with clinically positive axillary lymph nodes may undergo ALND and patients with clinically negative axillary lymph nodes may undergo SLNB.

### Indications of sentinel lymph node biopsy (SLNB)

All these indications are consistent with recommendations made by the American Society of Clinical Oncology in 2014 [1].

**Early breast cancer with clinically negative nodes:** Patient's with early breast cancer (T1 or T2) with clinically negative axillary lymph nodes are considered for SLNB as it has less morbidity than ALND [2]. Another indication is for patients whose axillary lymph nodes are turned out negative post fine needle aspiration or image guided core biopsy or detected abnormal lymph nodes.

**Ductal carcinoma in situ (DCIS) with planned mastectomy:** Whenever simple mastectomy has been planned for patients with DCIS, SLNB should be performed in all patients. As DCIS is non–invasive cancer, chances of axillary lymph node spread are very less. SLNB should be performed at same setting because if invasive cancer is found in post mastectomy specimen, SLNB will not be accurate for staging axillary lymph nodes in this scenario [3].

**DCIS with suspicious features:** It is a controversial indication [1]. Some of the centers recommend SLNB to patients undergoing breast-conserving surgery for DCIS with clinical suspicion of synchronous invasive cancer. Other recommends SLNB when DCIS is larger than 5 cm and DCIS with a palpable mass. Most of the women will not have any invasive disease in final specimen. The reported incidence of Invasive carcinoma in excised specimen is around 10-20% following a biopsy diagnosis of DCIS [4]. If invasive cancer is found after breast-conserving surgery performed for DCIS, SLNB can be performed as a second procedure to stage the axilla where disease stage and subsequent axillary management may change [5,6].

**Contraindications for sentinel lymph node biopsy (SLNB)**

**Clinically positive nodes:** Patients with clinically positive lymph nodes which have been proven pathologically as metastatic nodes are not the candidates for SLNB and they should be considered for ALND. Patients who have already received neo-adjuvant therapy needs re-evaluation for axillary lymph node staging.

**Locally advanced and inflammatory breast cancer:** Patients with locally advanced breast cancer and inflammatory breast cancer presents with larger tumor size which in turn results in higher rates of axillary lymph node metastasis [7,8]. In these patients, false negative rate is high as there are chances of partial obstruction or functional abnormality of subdermal lymphatics. Thus, expert panel guidelines and standard studies does not recommend SLNB for these patients and the recommendation is ALND [1,9,10]. Several studies contradict to the criteria of contraindication of SLNB if breast tumor size >5 cm. They have shown that SLNB can be accurate in patients with T3 tumors with clinically negative axilla [11,12]. Hence, tumor size >5 cm is not an absolute contraindication for SLNB provided ipsilateral axilla should be clinically negative.

**Neoadjuvant chemotherapy:** Neoadjuvant chemotherapy is the standard and accepted approach for women with inflammatory breast cancer, women with locally advanced breast cancer and who desire breast conserving surgery where it is an operable breast cancer. The indication of SLNB in these patients is still controversial and not universally accepted. It is still not yet proved in such patients whether it should be performed prior to or following the completion of neoadjuvant chemotherapy. The next question is whether we should go for SLNB or ALND, is still under evaluation.

**Recurrent breast cancer with previous axillary procedures and previous breast and axillary procedures for benign conditions:** Patients who had undergone excisional breast biopsies should be considered for SLNB [13,14]. Patients with extensive breast and axillary surgeries may have alteration or disruption of normal pattern of lymphatic drainage, which may increase the false negative rate of SLNB. In patients with recurrent breast cancer who had undergone surgery for breast cancer and axilla, the role of second SLNB has not been widely studied and the success rate of identifying a sentinel node may be lower with prior axillary surgery [15-17]. The recommendation in both these scenarios is to plan lymphoscintigraphy prior to SLNB.

**Male breast cancer:** The incidence and prevalence of male breast cancer is very less as compared to female breast cancer. Prospective data base is not available in male breast cancer proving the role of SLNB. Thus, the sensitivity and specificity of SLNB in male breast cancer is still under evaluation. The reason being it is an uncommon disease and most of the cases are treated with mastectomy instead of breast conserving surgery. If SLNB is performed in male breast cancer and which has shown positive nodes then, there is no literature support establishing the further treatment plan whether we should go for adjuvant radiation therapy or ALND [18].

**Pregnancy:** The role of SLNB in pregnant women is still unclear. The dye which are commonly used are isosulfan blue dye (Lymphazurin), methylene blue and radioactive colloid, out of which isosulfan blue has teratogenic effects on the developing fetus which is best avoided in women who are pregnant [19,20]. It is not yet clear whether pregnancy affects the lymphatic architecture of axilla. Hence, we can say pregnancy is a relative contraindication for SLNB.

**Significance and development of SLNB**

The SLNB technique has been demonstrated to be feasible, accurate, and less morbid than ALND. It is an established and accepted technique by most of the medical centers worldwide as the standard initial approach for patients with early-stage breast cancer. It utilizes the lymphatic mapping technique to locate and remove one or more (on average, three) axillary lymph nodes in patients with breast cancer [21]. The combination of isosulfan blue dye and radioactive colloid resulted in a significantly higher success rate with lower false negative rate as compared with using isosulfan blue dye alone. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, axillary recurrence was found 0.4 % after SLNB with ALND versus 0.7 % without ALND [21]. The Veronesi study demonstrated similar findings (0 % with ALND versus 0.8 % without ALND) [22]. The low axillary recurrence rates in these trials, even without ALND, were presumably due to the effects of adjuvant therapy (chemotherapy or radiotherapy) which may treat residual axillary disease burden. In patients who did not receive adjuvant therapy or ALND, the axillary recurrence rate was as high as 20 percent, as reported for the NSABP-04 trial [23]. SLNB is less morbid for patients than ALND. Several studies have shown that the risk of arm morbidity, particularly lymphedema, sensory loss, and shoulder abduction deficits, is significantly less for SLNB than ALND [24,25]. It is endorsed by multiple guidelines as an alternative to ALND for the diagnosis of axillary metastases in patients with clinically node-negative early breast cancer [26,27]. Sentinel node metastases are sub-divided into multiple groups like isolated tumor cell clusters, micrometastases, and macrometastases based upon the size of the largest tumor deposit present in the sentinel node.

**Isolated tumor cell clusters**

These are defined as small clusters of tumor cells not greater than 0.2 mm or non-confluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section [28]. According to the Tumor, Node, Metastasis (TNM) staging system, these are designated as pN0(i+). The prognosis of patients with isolated tumor cell clusters appear to similar as well as patients without any pathologic node involvement.

**Micrometastases**

Micrometastatic nodal involvement is defined as a metastatic deposit >0.2 mm but ≤ 2.0 mm. If present, it is designated as pN1 in the American Joint Committee on Cancer (AJCC) staging system. Patients with pN1 breast cancer have a slightly worse prognosis compared with those with node-negative breast cancer [29].

**Macrometastases**

Macrometastatic involvement of the axillary nodes is defined by any tumor cell deposit >2.0 mm. The presence of macrometastases within the axillary nodes is a well-established independent prognostic factor. As the nodal involvement and tumor burden increases, the prognosis worsens.

**Extranodal extension**

Extranodal (extracapsular) extension is defined as invasive tumor cells or clusters that are present outside of the lymph node capsule and parenchyma.

**Occult metastatic disease**

Occult micrometastases refer to nodal metastases that are not seen on initial hematoxylin and eosin examination but are detected subsequently by additional levels or by immunohistochemical staining or reverse transcriptase polymerase chain reaction.

**Management of ipsilateral axilla after SLNB**

According to "Z-0011-eligible" criteria [30], there is no axillary intervention required after SLNB when-

- Clinically negative nodes based on an adequate clinical node evaluation, including imaging .
- A T1 or T2 (≤ 5 cm) primary breast cancer.
- Fewer than three metastatic sentinel lymph nodes on SLNB.
- Patients undergoing breast-conserving surgery followed by whole-breast irradiation.

A completion ALND is required for patients who have (2014 American Society of Clinical Oncology (ASCO) guidelines [1]).

- Three or more metastatic sentinel lymph nodes on SLNB.
- One or two metastatic sentinel lymph nodes on SLNB but who do not desire whole-breast irradiation

**No sentinel node metastasis**

No ALND in patients with early breast cancer who do not have nodal metastasis on SLNB, including those with isolated tumor cells present in the sentinel node(s).

**One or two sentinel node metastases**

There is evidence that ALND is not necessary in most women with early-stage breast cancer who have only one or two sentinel lymph node metastases and who will receive whole-breast irradiation as part of breast-conserving therapy. If, however, whole-breast irradiation is not planned, then ALND is indicated for such patients. Two randomized trials, the ACOSOG Z-0011 trial [30] and the International Breast Cancer Study Group 23-01 (IBCSG 23-01) trial, demonstrated that many of these patients with one or two metastatic sentinel nodes can safely avoid a completion axillary node dissection.

**Sentinel node metastasis with extra-nodal extension**

In the ACOSOG Z-0011 trial, patients who had gross extra-nodal extension were excluded from the trial. Thus, completion ALND is still considered the standard of care for patients with gross extra-nodal extension of sentinel node metastasis.

**Sentinel node metastasis with large tumor**

Patients with large tumors (eg, T3) with clinically negative axilla were excluded from the ACOSOG Z-0011 trial. Thus, completion ALND is still offered as the standard of care for any patient who has a large (>5 cm or T3) tumor with any positive sentinel nodes.

**Role of radiotherapy**

The recommendation is omitting of ALND in patients with one or two positive SLNs who plan to undergo whole-breast irradiation but not partial-breast irradiation . Reported in 2014, the After Mapping of the Axilla: Radiotherapy or Surgery (AMAROS) trial was a multi-institutional trial conducted by the European Organization for the Research and Treatment of Cancer (EORTC) [31]. The 10 year follow-up results of the AMAROS trial have been reported [32]. After 10 years, axillary recurrence remained low and comparable between the ALND group (7/744 patients; 0.93 percent) and the axillary radiotherapy group (11/681 patients; 1.82percent). Distant metastasis-free survival and overall survival rates were similar. This trial showed that axillary radiation is an acceptable alternative to ALND in patients who have positive sentinel node(s) but do not meet the Z0011 criteria.

## Conclusion

Sentinel Lymph Node Biopsy is the standard and established procedure to address the axillary lymph nodes in early breast cancer. It has replaced axillary lymph node dissection with minimum morbidity. However, there are several indications and contraindications which needs re-evaluation with the support of prospective data base study. In case of one or two sentinel lymph node metastasis, it is an institutional call and practice which decides further plan.

## Disclosures

**Conflicts of interest**

The authors declare that they have no conflict of interests.

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All authors have declared that no financial support was received from any organization for the submitted work.

**Financial relationships**

All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

**Other relationships**

All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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