REVIEW ARTICLE

SENTINEL NODE IMAGING AND BIOPSY IN BREAST CANCER

Nosheen Fatima,[1] Maseeh uz Zaman,[2] Unaiza Zaman,[3] Rabia Tahseen,[3] Areeba Zaman[3]

1 Department of Nuclear Medicine, Dr. Ziauddin Hospital, Karachi, Pakistan.
2 Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan.
3 Students MBBS, Dow Medical College, DUHS, Karachi, Pakistan.

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ABSTRACT

Involvement of axillary nodes in breast cancer is the major prognostic factor and axillary lymph node dissection (ALND) is the gold standard methodology. However, it is associated with considerably high morbidity like lymphedema and impaired functionality of ipsilateral arm. To address this issue, a less invasive sentinel node imaging and biopsy technique has been introduced and over the last two decades it has become standard of care in clinical and radiological negative axilla in breast cancer. In this review we will discuss historical background, breast lymphatics, techniques to detect nodes, strategies based on histopathological results and future trends for less invasive but more precise axillary nodal staging.

Key words: carcinoma breast, sentinel node biopsy, radiocolloid, blue dye, axillary reverse mapping

Breast cancer is the most frequent cancer diagnosed in women worldwide.[1] Axillary node status is one of the major prognostic factors in early-stage disease, and this information is important for tailoring the treatment.[2] Imaging techniques like ultrasound (US), computerized tomography (CT), mammogram and magnetic resonance imaging (MRI) have limited sensitivity for nodal metastasis.[3] Axillary lymph node dissection (ALND) is the traditional approach for nodal staging which involves dissection and removal of >10 of Berg level I and II axillary nodes.[2] However, incidence of axillary nodal metastasis has been documented in 10-30% patients with T1 lesions (≤ 2 cm primary tumor size) which reaches to 55-70% with tumor size >3 cm.[4] ALND, however, has significant short and long-term morbidity, the most significant being lymphedema. In recent years with earlier detection of breast cancer due to screening programs, most patients do not have nodal metastases at the time of diagnosis and are considered for breast conserving surgery. However, ALND in these patients carries greater surgical morbidity than the therapeutic procedure of the primary cancer.

Sentinel node biopsy (SNB) is a less invasive method of harvesting and checking for nodal involvement in patients with no clinical and radiological evidence of axillary nodes involvement.[5]

Historical Background: The term sentinel node was first coined by Cabanas in 1977 during his work upon penile cancers[6] and considered receiving direct lymphatic drainage from the primary tumor, and therefore is the first node or group of nodes to become involved when a tumor is metastasized. The second lined nodes are called echelon nodes. In 1992 this concept was revived by Morton who used vital dyes to detect the spread of malignant melanoma.[7] It was Giuliano and colleagues who adopted this technique for breast cancer.[8] The concept behind SLNB is that lymphatic metastases occur in an orderly manner and that the sentinel node status predicts the histological status of the regional lymph nodes. If the

Correspondence : Dr. Maseeh uz Zaman
Department of Radiology,
Aga Khan University Hospital,
Karachi, Pakistan
Tel: 34930051 - Ext.: 2020
Email: maseeh.uzzaman@aku.edu

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sentinel node(s) does not contain metastases, the draining nodal basin is highly unlikely to harbor metastases and completion axillary lymph nodal dissection (cALND) is not required.While patients with metastasis to a sentinel node would undergo either immediate or delayed completion cALND.

Lymphatic Drainage of Breast: Lymph from breast lobules flows into a sub-areolar plexus (Sappey's plexus) from which lymphatic drainage takes place through three main routes:[9]

1. Axillary or lateral pathway: fed by Sappey's Plexus, as well as by ducts satellite lymphatics and by most of parenchymal lymphatics and drain into pectoral group of axillary nodes.
2. Internal mammary pathway: starts from lateral and medial halves of the breast and passes through the pectoralis major; connections may lead across the median plane and hence to the contralateral breast.
3. Retromammary pathway: drains the posterior portion of the breast.

Furthermore, lymphatics may also reach sheath of the rectus abdominis, subperitoneal and subhepatic lymphatic plexuses. Usually axillary lymph nodes receive more than 75% of the lymph drained from the breast[9] (Fig. 1)

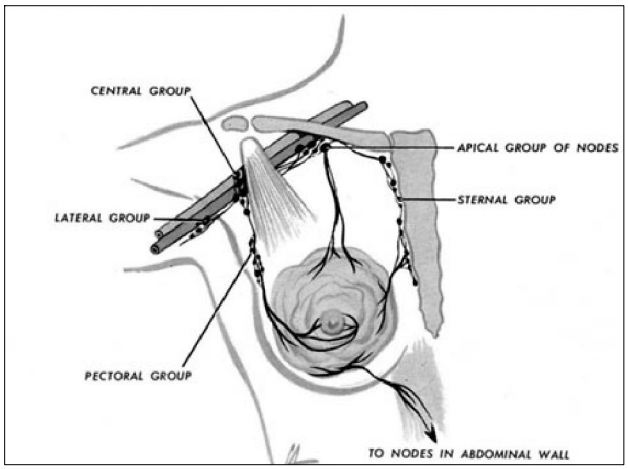

Figure 1: Sketch diagram showing lymphatic drainage of breast.

Indications of Sentinel Node Biopsy: On the basis of large body of data, SNB is indicated for smaller tumors (T1 and T2); multicentric tumors; ductal carcinoma in-situ (DCIS) when mastectomy or immediate reconstruction is planned; for older or obese patients; in male breast cancer; and prior excisional or diagnostic biopsy.[10]

Contraindications of Sentinel Node Biopsy: American Society of Clinical Oncology (ASCO) 2005[10] guidelines do not recommend SNB for large (T and T4), locally advanced invasive breast (LABC), inflammatory breast cancer (IBC), ductal carcinoma in- situ (DCIS) when breast-conserving surgery is to be done, prior non-oncologic breast or axillary surgery, presence of suspicious palpable axillary and pregnancy. However European Association of Nuclear Medicine (EANM) recommends the use of SNB in pregnant women due to potentially low fetal exposure to radiation. Other have suggested to use about 18 MBq (0.5 mCi) of radiocolloid and surgery on same day.[3]

Methods to Identify Sentinel Node(s): There are two ways to identify sentinel node(s) using either blue dye or radiocolloid or both.

a. **Blue Dye Injection:** Currently, the commonly used dyes are patent blue V (in Europe), isosulfan blue (in USA), and methylene blue. These dyes bind weakly to interstitial proteins, mostly albumin resulting in blue discoloration as they pass slowly through the sentinel node. Blue dye is injected intradermally over the primary tumor or subcutaneously in periareolar area, 10-20 min prior to surgery in a volume of 2-5 ml followed by gentle massage to enhance movement through lymphatics.[11] Care should be exercised to avoid injection into the dead space of a seroma. The injection should be performed after the patient is anaesthetized (general or local anesthesia) and washout starts after approximately 45 min. The advantage of blue dye technique is early visualization of "blue" lymphatic channels and nodes but has limitation of no information about drainage to internal mammary chain. There are reported incidences of allergic reaction in about

1% of cases and its use is contraindicated in pregnancy.[3]

b. **Radiocolloid Injection:** Radiolabeled colloids commonly used in SNB are Tc-99m Sulphur colloid (in USA), Tc-99m Nannocolloid (in Europe) and Tc-99m Antimony colloids (in Australia). The recommended specifications for these radio-colloids are (1) particle size: 100-200 nm as larger particles would fail to enter into lymphatic and smaller may quickly pass SN and enter in to second echelon nodes; (2) high specific activity as scavenger capacity of macrophages in SN is limited.[12] These colloids particles enter the lymphatic system and are trapped by mono-nuclear cells of SN and allow visualization of the sentinel node with a gamma camera prior to surgery and hand held gamma probe assisted intraoperative detection and harvesting of these hot nodes. Most of the injected radiocolloid remain at the injection site and about 1% of locally injected activity is taken up the sentinel node.[3] About 1 mCi (37 MBq) of radiocolloids are injected either peritumoral, intratumoral, periareolar or subareolar sites (Fig. 2). Peritumoral and intra-tumoral injection are more painful with delayed visualization of sentinel node but better chance of showing extra axillary drainage (i.e. internal mammary nodes). Visualization of internal mammary node is reported in 20% cases with positive biopsy in 17%[3] (Fig. 3) It is also important to know that in patients with a negative axilla, positive internal mammary biopsy is seen in 7.8%, whereas in patients with positive axilla, internal mammary biopsy is also positive in 41% cases.[3]

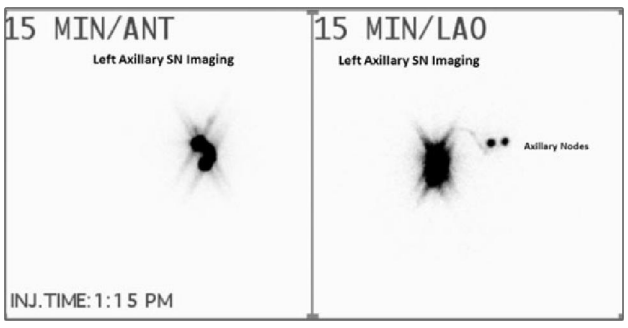

Figure 2A

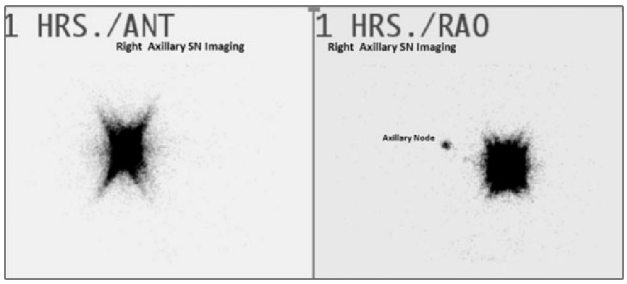

Figure 2B

Figure 2: (A) Left axillary sentinel node mapping shows two sentinel nodes with lymphatic channel in left axilla. (B) A solitary sentinel node seen in right axilla (large black spot is site of periareolar radiocolloid injection).

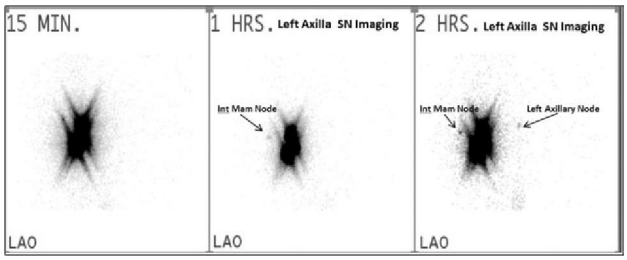

Figure 3: Left axillary sentinel node mapping showing an internal mammary node outlined at 1 hour image and left axillary sentinel node on 2 hour image (large black spot is periareolar site of radiocolloid injection).

c. **Dual (Blue Dye plus Radiocolloid) Mapping Technique:** Over the last 20 years, various groups have published their experience revealing a better identification rate for sentinel node with blue dye or radiocolloid. However, most of the centers do favor dual mapping technique due to proven higher identification rate and lower false negative rate.[13] However, it is recommended not to use same injection site for the radiocolloid and blue dye to further enhance the complementary information obtained by combining two mapping techniques.[13] (Fig. 4)

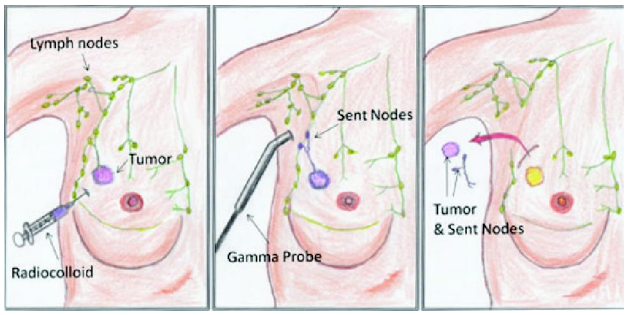

Figure 4: Sketch diagram showing sequence of dual mapping technique using radiocolloid and blue dye injection methods and excision during surgery.

Sentinel Node Imaging: SN imaging is performed pre-operatively using either a single head or dual head gamma camera fitted with low energy high resolution collimator (LEHR). Imaging is recommended before surgery as it allows the visualization of extraaxillary drainage. Planar static images (less commonly dynamic images) are acquired at 10-15 min, 1 hour, 2-4 or 18-24 hours in anterior, lateral (with extended ipsilateral arm) and LAO 45 view (patient rotated not camera with ipsilateral arm over the head) SPECT/CT is not commonly used in sentinel imaging as it is time consuming, deliver more exposure due to additional CT exposure and expensive. However, based on published reports, current indications for SPECT/CT include non-visualization of SLN, obese patients or in patients with an unusual drainage pattern seen on planar imaging[14] (Fig. 5) There are two established protocols of SN scintigraphy:

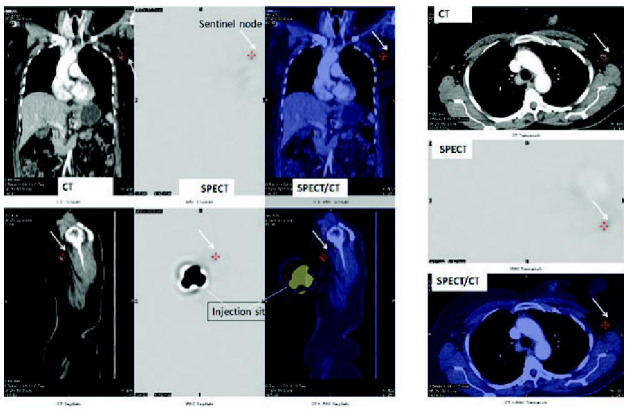

Figure 5: SPECT/CT showing better localization of solitary SN in left axilla after left periareolar injection of radiocolloid (CT image is used for anatomical mapping).

1-day protocol (same-day imaging and surgery) and a 2-day protocol (injection on day 1 and surgery on day 2), with no difference in clinical outcome.[3]

Harvesting Sentinel Node(s): At the end of SN imaging, technologist marks skin over the hot node(s) using a hot marker under gamma camera guidance. In the theater after the anesthesia, blue due is injected superficially followed by gentle massage to improvise the migration of dye. Axilla is scanned with a hand held gamma probe and incision is made over the site of maximal auditory signals. Gamma probe is inserted through the small incision into axilla to follow the direction of maximal auditory signal coming from the hot node seen on imaging. The criteria for a sentinel node are a blue node with lymphatic tract and a hot node with 5-10 times the background radioactivity or more than 10% of the activity of the hottest node (Fig. 6). After taking out sentinel node, axilla is searched with gamma probe for any residual hot node and with palpation to find an involved but cold and non-blue node. It is important to understand that differentiation between a sentinel node and secondary echelon node is difficult and a tumor may drain to >1 sentinel node.[3] Therefore, removal of only hottest blue node is likely to result in higher false negative rate (FNR, to be discussed below). Based on these facts it is recommended to harvest all hot and blue nodes or cold, non-blue palpable node as data have shown a FNR of 10% and 1% when 01 and 05 node(s) were removed respectively.[15,16]

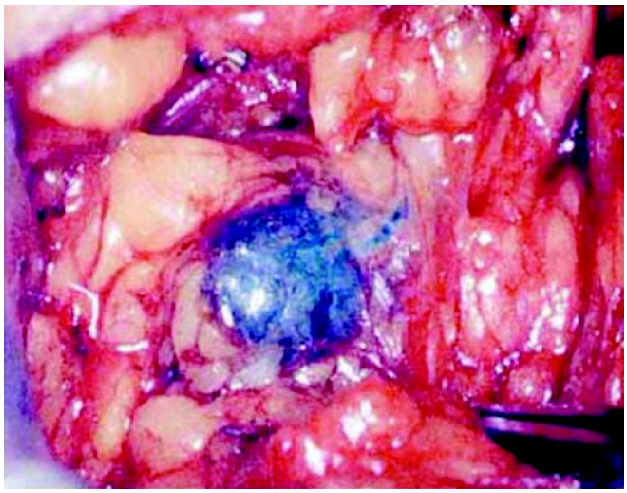

Figure 6: A blue sentinel node dissected in left axilla.

Management Strategies Based on Results: Practice of SN biopsy at a center is validated by its identification rate and false negative rate (FNR). Identification rate is defined as the proportion of patients in whom at least 1 sentinel node is found at operation. While false-negative rate is the proportion of ALND positive cases with a negative sentinel node at biopsy. According to ASCO 2005 guidelines, in order to abandon ALND, the multidisciplinary team must aim to achieve an identification rate of >85% and FNR <5%.[10] FNR is considered as the safety parameter and of SNB procedure and once technique is validated and adopted it becomes no more measureable. False negative results may be caused

by massive infiltration of sentinel node by tumor cell leading the diversion of flow to second echelon node. Another important cause of FNR is faulty preparation of radiocolloid resulting in small particles size with quick migration from first relay node to second echelon nodes.

Patients whom SN biopsy is positive for metastasis are subjected to ALND while those with a negative SN biopsy (on permanent section) do not require ALND.

Non-visualization of a sentinel node on imaging or after blue dye injection is disappointing on the part of surgeons and warrants surgical intervention (Fig. 7). This could be due to faulty technique or may be due to significant involvement of axillary nodes

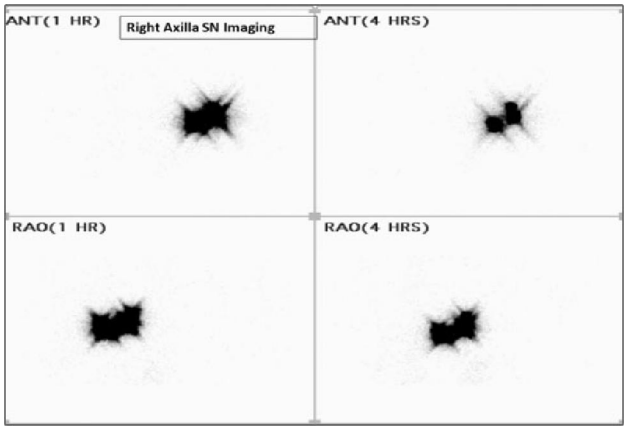

Figure 7: Non-visualization of sentinel node in right axilla or internal mammary region till 4 hour after radiocolloid injection ((large black spot is site of periareolar radiocolloid injection).

by cancer.[17] Published data have shown a higher incidence of positive axillary nodes in patients with non-visualization of node on imaging than patients with visualized nodes.[18] A second injection in case of negative imaging is not recommended due to reported high incidence of false negative rates.[3] In case of non-visualization of a SN (failed mapping), ASCO recommends ALND.[10]

Based histopathology results (classical staining or immunohistochemistry) metastases in a SN are divided into macrometastasis (> 2 mm), micrometastasis < 2 mm) and isolated tumor clusters (< 200 cells). There have been controversies regarding the prognostic importance of micrometastasis and isolated tumor cluster found in sentinel nodes biopsies. Practice based on considering micrometastasis and isolated cluster prognostically significant resulted in upstaging in 10% patients with breast cancers.[3] Results of some retrospective trials revealed disease free survival in patients with micrometastasis is not different than those with sentinel node negative patients. While other retrospective studies do favor a shorter survival in patients with micrometastasis. However, the ACOSOG Z0010 (American College of Surgeons Oncology Group trial Z0010)[19] and NSABP-32 (National Surgical Adjuvant Breast and Bowel Project trial B-32)[20] trials failed to demonstrate any reduction in overall survival in patients found to be SLN positive on immunohistochemistry (IHC) but not on hematoxylin and eosin (H&E) at five- and eight-year follow-up, respectively.

Future Trends in Sentinel Biopsy in Breast Cancer:

1. **Axillary Reverse Mapping (ARM):** Various researchers have shown the presence of distinct and non-overlapping lymph nodes in axilla draining arm and breast. Based on this concept it was considered that selective removal of nodes draining the breast would minimize the risk of arm lymphedema. In Axillary Reverse Mapping (ARM) blue due is injected in the intermuscular groove over inner aspect of upper arm to identify blue nodes draining the arm and radiotracer is injected over breast to identifying hot axillary nodes draining breast (Fig. 8). Surgeon during axillary clearance excises only nodes draining the breast and sparing the arm draining blue nodes. Initial report have shown significant decline

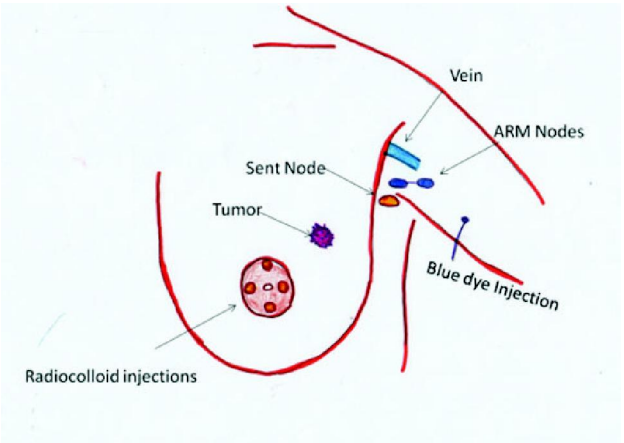

Figure 8: Sketch diagram showing sentinel node (hot) in axilla with periareolar injection of radiocolloid (yellow color) and ARM node (blue) in axilla after blue dye injection along medial aspect of upper arm.

in lymphedema incidence in patients with completion axillary clearance. However, some studies have shown 10-20% incidence of metastasis in ARM nodes.[21]

2. **Radioguided Occult Lesion Localization (ROLL):** This technique is used in patients with non-palpable breast lesion where under ultrasound guidance radiotracer is injected into tumor followed by gamma probed guided excision of non-palpable lesion with free margin.

3. **Sentinel Node and Occult Lesion Localization (SNOLL):** This is similar to ROLL but in addition to excision of non-palpable tumor, same radiotracer injection is used for excision of sentinel node as well.

4. **MRI Using Ultrasmall Paramagnetic Iron Oxide (-MRI-USPIO):** In this new technique USPOI (Ultra Small Paramagnetic Iron Oxide) is injected in periareolar region and on MRI the area of node not containing metastasis would enhance due to presence of iron oxide. Area of node harboring metastatic focus would not uptake iron oxide and would fail to enhance. This nonhomogenous enhancement of sentinel and echelon nodes on MRI provides evidence of presence and burden of nodal metastasis.[22]

5. **^{18}FDG PET/CT Imaging:** PET/CT is not recommended in early stage breast cancer patients as its sensitivity for detecting small nodal metastasis is low due to limited spatial resolution of PET scanner. So it cannot replace SNB.[23]

In last two decades lymphatic system of breast has been extensively studied and concept of sentinel node in breats cancer has been validated. Based on these facts, sentinel node biopsy has become a standard of care in patientswith early stage disease with clinical and radiological negative axilla. SNB has significantly reduced the unjustified axillary node dissection and its associated complication like lymphedema of upper arm. The major drawback of SNB is understaging due to false negative rate. However, with influx of more data and continuous research using newer techniques would further streng then its role in precise nodal staging of breast cancer.

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