

The Role of Sentinel Lymph Node Biopsy in the Management of Breast Cancer

MM SAHA^a, MM HOSSAIN^b, S SAHA^c

Summary:

The sentinel lymph node (SLN) is defined as the first node(s) receiving lymphatic drainage from a primary tumour. A promising alternative to axillary lymph node dissection (ALND) is sentinel lymph node biopsy. SLN biopsy has been introduced as a technique to identify axillary lymph node most likely to contain tumour cells metastasizing from a primary carcinoma of breast. Several methods of identifying the SLN exists, including the use of radioactive tracer, lymphazurin dye or combination of the two via intraparenchymal and/or intradermal, peritumoral or periaerolar injection sites. Intraoperative evaluation of SLNs are done by performing FS (Frozen Section) on all the lymph nodes after serially sectioning them at 3-4mm intervals; at least 2 levels are cut of all the sentinel lymph nodes. In addition, touch preparation cytology (TP) smear may also be made for evaluation. The limitations of SLNB is that a proportion of patients who have metastasis limited to the SLN can be predicted when there is a combination of tumour

size <1.0cm, the absence of lymphovascular invasion and micrometastatic disease (<0.2cm) in SLN. However for patients with large breast cancer, the role of SLNB is controversial. Early studies of SLNB in large breast cancer patients demonstrated a high (8-18%) false negative rate, with the accuracy worsening with the increasing size. Excision of SLNs have an extremely low morbidity and a high degree of staging accuracy. A tumour-free SLN virtually excludes lymphatic involvement of the entire regional lymphatic basin. More than 50 observational studies of SLNB validated by a back up ALND demonstrate that SLNB is feasible, accurate and suitable for virtually all patients with operable clinically node negative disease. Sentinel lymph node biopsy not only provide prognostic information, but also aims to guide adjuvant therapy without the untoward side effects of complete axillary dissection.

Key words: Sentinel lymph node, Management, Breast Cancer.

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Introduction:

Breast cancer is the leading cause of death in women with over 3,00,000 deaths annually world wide¹. Axillary nodes status is the best single predictor of disease outcome in patient with early stage breast cancer. It has been shown that the presence of axillary node metastasis reduces the patient's survival by 28-40%² and the likelihood of treatment failure increases with the increase number of positive axillary nodes³. Furthermore the removal of axillary nodes also improves local and regional control, which leads to better over all survival. Axillary lymph node dissection (ALND) has been the only reliable method for

determining lymph node status⁴. However the clinical importance of axillary control and the extent of axillary surgery remain controversial issues. Previous studies on sentinel lymph node biopsy (SLNB) validated by a back up axillary lymph node dissection (ALND) confirm that SLNB is both feasible and accurate, reliably detecting axillary metastasis in 97% of all patients and 93% of node positive cases⁵.

The surgical management of invasive breast cancer has included complete removal of the tumour, with documentation of negative margins by either mastectomy or breast conserving surgery and synchronous complete axillary lymph node dissection (ALND). However the complication rate of ALND are reported to be 20-55%. This complications include lymphedema, sensory nerve damage, haemorrhage and post operative seroma formation as well as need for general anaesthesia⁶. In invasive breast carcinoma, axillary lymph node metastasis is seen in only 40% patients undergoing ALND⁷, and is even less in early breast cancer; therefore ALND is not needed in the

- a. Dr. Moni Mohan Saha, Professor & Director, Shaheed Sk Abu Naser Specialized Hospital, Khulna
- b. Dr. Md. Mokter Hossain, Assistant Professor, Department of Pathology, Khulna Medical College, Khulna
- c. Dr. Sukumar Saha, Junior Consultant, Shaheed Sk Abu Naser Specialized Hospital, Khulna.

Address of Correspondence: Dr. Moni Mohan Saha, Professor & Director, Shaheed Sk Abu Naser Specialized Hospital, Khulna.

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majority of the patients. Since ALND is also associated with significant morbidity. A promising alternative to ALND is sentinel node (SLN) biopsy for axillary staging of invasive breast cancer. Sentinel lymph node mapping is a minimally invasive procedure and is very effective and accurate method of evaluating the regional lymph nodes in breast cancer patients. It is noteworthy that a pathologically negative sentinel lymph node predicted the absence of metastasis. The remainder of regional lymph node basin with about a 98% degree of certainty⁸. The sentinel lymph node is defined as the first node(S) receiving lymphatic drainage from a primary tumour. It is therefore the node most likely to contain metastatic breast carcinoma. A tumour-free SLN virtually excludes lymphatic involvement of the entire regional lymphatic basin. Sentinel lymph node biopsy (SLNB) not only provides prognostic information but also aims to guide adjuvant therapy without the untoward side effects of complete axillary dissection. More than 50 observational studies of SLNB validated by a back up ALND demonstrate that SLNB is feasible, accurate and suitable for virtually all patients with operable, clinically node negative disease.

Historical perspective:

The concept of sentinel node was first described by Cabanas R in 1977 in the context of penile carcinoma⁹. In 1992 Morton and his colleagues reported a blue dye technique for lymphatic mapping and sentinel node biopsy in clinically node negative melanoma patients¹⁰ and later by Van der veen and colleagues with lympho scintigraphy to select melanoma patients for regional lymph node dissection¹¹. In the decade since the pioneering reports of Krag et al and Giuliano et al, SLNB has become a new standard of care for axillary lymph node staging in patients with breast carcinoma¹². Lymphatic mapping and SLNB are clearly changing the paradigm for the treatment of breast cancer.

Sentinel lymph node biopsy technique:

Sentinel lymph node biopsy is simple technique which uses subdermal or peritumoral injection of vital blue dye or radio-labelled colloid or both substances together to identify the first lymph node draining the primary tumour. Several methods of identifying the SLN exists, including the use of radioactive tracers, lymphazurin dye or combination of the two via intraparenchymal and /or intradermal, peritumoral or periaerolar injection

sites. In 1998 O'Hea et al¹³ reported their initial experience at Memorial Sloan-Kettering cancer centre that the blue dye and radioisotope were the complementary technique in SLN mapping biopsy in breast cancer patients, and that the overall success of this procedure was maximized when the two are used together(93%) as compared to when used alone(75 & 88% respectively) in SLND mapping in the breast cancer patients. With increasing experience of the breast surgical oncologists with this procedure over the last decade. SLNB is usually straight forward and a simple operation which has become standard of care for surgical management of breast cancer. Before the surgical resection of breast tumour(lumpectomy or mastectomy) blue dye and redioactive tracer is injected into the breast in a peritumoral, intradermal or periaerolar manner. Isotope counts are taken using a hand held-gamma probe for supraclavicular, infraclavicular, parasternal and axillary areas. More than a 95% of the time a hot spot is found in the ipsilateral axilla. An axillary incision is made the surgeon identifying all blue and /or hot nodes as well as palpable nodes. These are removed until the axillary background counts fall below a threshold value: defined as the background count; most authors report a median of two SLN per patient¹⁴. A success of 90-95% in finding the SLN and no more than 5-10% false negative results would seem reasonable targets for validation trials¹⁵. Results of identifying SLN using different technique are shown in Table-1. Intraparenchymal injection was the first technique described and is the most widely accepted. Recent data suggest that the intradermal technique is highly accurate and may increase the SLN identification rate. SLN localization was successful in 97% of cases with intradermal radioisotope injection and in 78% of those with intraparenchymal injection, a statistically significant difference¹⁶. Knox and Ley compare the intraparenchymal Vs intradermal injection of radioisotope for identification of SLN in breast cancer patients and reported that intradermal technique may increase SLN identification and is easy to use and has acceptable false negative rate (2%)¹⁷. The greater ease of SLN identification rate with intradermal injection may be due to the rich lymphatic network of skin overlying the breast as well as reduction in shine effect. Krag et al conducted multicenter validation study using radioactive tracer technique. The overall rate of identification of

hot spots was 93% with an accuracy of 97%, specificity 100% and sensitivity 89%¹⁸.

Intra-operative evaluation of sentinel lymph nodes:

Careful intraoperative palpation of the axilla is an essential component of SLN biopsy. Apart from the fact that the detection rate is approximately 80-90% in the largest series, the key problems are false negative and intraoperative examination of sentinel node. Routine frozen section (FS) examination appears to miss up to 30% of metastasis in sentinel nodes¹⁹. However the value of routine intraoperative SLN frozen section is controversial. If positive, FS has the obvious advantage of allowing an immediate axillary dissection and thereby avoiding the reoperation. On the other hand FS is costly, time consuming and subject to false negative results. Brogi et al in 2005 demonstrated that FS, touch preparation (TP) and cytological smear (CS) are equivalent for the intraoperative assessment of SLN in breast cancer (comparable sensitivities were 59%, 57%, 59% respectively)²⁰. Each method was more sensitive in detecting macrometastasis (>2mm tumour deposit, 96%, 93%, 93%) than micrometastasis (<2mm, 27%, 27%, 30% respectively). The added benefit of combining methods is small and the failure of intraoperative assessment is largely due to an inability to detect micrometastatic disease. A study by Krogerus et al²¹ compared the widely used method of intraoperative evaluation of SLN which is a modification of the method introduced by Veronesi et al²² including bisecting the lymph node in its long axis and examining serial sections to their own novel method. Krogerus's method included sectioning the lymph node into thin slices (1-1.5mm thick) perpendicular to the long axis and arranged on a prefrozen tissue-Tak, frozen section from two level were then examined. With this method, they found more and smaller metastasis compared to the widely used method and also the technique was less time consuming. Recently intraoperative evaluation of SLN includes performing FS (Frozen section) on all the lymph nodes after serially sectioning them at 3-4mm intervals; at least 2 levels are cut of all the sentinel lymph nodes. In addition touch preparation cytology (TP) smear may also be made for evaluation. However there exists a personal bias among pathologists in examining the cytology smears especially pathologists who are not practising cytopathologist. TP is an additional and complementary method to FS in the

intraoperative evaluation of SLN. The FS includes examining all lymph nodes bisecting them if they are more than 0.5cm in thickness and cutting at least two levels of each section. The sentinel node can be examined intra-operatively by frozen section or imprint cytology, both of which have a high specificity²³. Axillary node clearance can subsequently be performed if intra-operative examination of the node is positive for malignancy; thus avoiding the need for a second surgical procedure.

The introduction of SLNB has allowed focus examination of tumour biology within the sentinel node. The clinical role of immunohistochemistry (IHC) and polymerase chain reaction (PCR) in detecting micrometastatic disease remains however at an investigational stage²⁴.

Pathologic evaluation of sentinel lymph nodes on permanent sections (Role of serial sectioning (SS) and immunohistochemistry (IHC)):

while SLNB has clearly established its status and has become the new standard of care in axillary staging of breast cancer, there seems to be little consistency in the pathologic procedures used by different laboratories in their evaluation. Lymph nodes were marked as sentinel or non-sentinel. A preliminary frozen section was performed on the sentinel and non-SLNs at the Mayo clinic. If the SLN was negative for tumour, the lymph node was formalin fixed and paraffin embedded and at least four additional levels were examined. Two levels were stained with standard haematoxyline and eosin (H&E) and an additional level stained with cytokeratin antibody, together with negative control. The SLNs removed at the university of Pennsylvania were formalin fixed, paraffin embedded and evaluated with H&E and immunohistochemistry. All non-SLNs were evaluated with standard H&E sections. In all cases, the size of the SLN was measured using an oculometer. A micrometastasis was defined as a tumour deposit of <2.0mm. A metastasis >2.0 mm was considered to be a macrometastasis. If multiple tumour deposits were present in the SLN, the sum of the tumour deposits was used to classify the metastasis as micro –or macrometastasis. In cases in which there was more than one SLN positive for tumour, the patient was grouped according to the largest size of metastasis. Primary tumour or re-excision specimens were evaluated by routine histology. Various studies have shown that

SLNB with examination of multiple serial sections (SS) and immunohistochemistry (IHC) greatly improves the sensitivity for identifying nodal metastasis especially micrometastasis (<0.2cm). It has been suggested that these more comprehensive methods of pathologic examination will find axillary lymph node metastasis in 7-42% of patients with breast carcinoma initially diagnosed as lymph node negative and that missed metastasis may be prognostically significant²⁵. Vialo et al recommended sectioning the SLN entirely at close intervals²⁶.

As shown in Table-2, increasing the sectioning interval from 50 micrometer to 290 micrometer may miss as many as 17.7% of micrometastatic SLN.

A study by Intra et al showed that examination of SLN by serial sectioning and IHC increases the detection rate of metastasis from, 9-33% in infiltrating carcinoma²⁷. A recent study at MD Anderson Cancer Centre by Chagger et al reported that 18% of initially node negative by H&E, sentinel nodes were converted to positive by additional examination of SS and performing IHC²⁸. This is supported by other studies in which addition of IHC using cytokeratin antibodies AE1/3 and Pan CK increased the sensitivity of SLNB and converted about 10% of otherwise lymph node negative patient to lymph node positive²⁹. Giuliano reported that 42.3% of SLN negative by H&E were positive by use of anti-cytokeratin antibodies, similar rates were reported by Reintgen and Krag et al³⁰.

Micrometastasis:

Lymph node metastasis in patient with breast carcinoma represent a broad spectrum of pathology findings ranging from gross disease, to H&E detected macrometastasis >2mm, to H&E and/or IHC detected micrometastasis <0.2mm, to single tumour cells found only by IHC. These gradations certainly reflect spectrum of prognostic significant³¹. At one extreme, in 2000, Rosser³² and Carter et al³³ suggested that the micrometastasis are not biologic metastasis at all but rather the benign transport of breast epithelium by preoperative manipulation of breast and are devoid of clinical significance.

Veronesi et al³⁴ data showed that the sentinel lymph node involved by microfoci (<0.2mm) of cancer cells are associated with a considerable rate of metastatic involvement in the remaining axillary lymph nodes. They believe that the presence of microfoci in the SLN is an indication to perform a total ALND. The Memorial Sloan-Kettering Cancer Center has developed a

nomogram to provide an accurate risk estimate using pathological characteristics of primary tumour such as tumour size, grade, presence of lymphovascular invasion, multifocality and estrogen receptor status together with SLN characteristics including size of metastasis, number of sentinel node positive and method of detection which may help in predicting non-sentinel node status after SLNB³⁵. This nomogram has been validated by study from MD Anderson Cancer Center³⁶.

Factors affecting SLN Status:

SLNB has false negative rate of 0% to 1.4% reported in many studies. As a result many medical centres are now using SLNB without a completion ALND in patients who have negative SLN. Bass et al³⁷ described the lymphatic mapping experience at the H.Lee Moffitt Cancer centre and Research Institute from 1994-1999 in 1, 147 breast cancer patients and reported 0.83% false negative rate of SLN. The risk of false negative results is low and may be further reduced if multicentric and multifocal tumours are excluded. Memorial Sloan-Kettering Cancer Center in 2000³⁸ identified histological features of SLN positive cancers that allowed for the prediction of non-SLN metastasis as shown in Table-3. According to their study the most accurate prediction of non SLN metastasis arose from the combination of three variables significant in univariate analysis: tumour size, lymphovascular invasion, and size of SLN metastasis. The proportion of patients who have metastasis limited to the SLN can be predicted when there is a combination of tumour size <1.0cm, the absence of lymphovascular invasion (LVI), and micrometastatic disease (<0.2cm) in SLN. It has been shown by other studies too that the tumour size is directly related to the probability of axillary lymph node involvement³⁹. For patients with large breast cancer, the role of SLNB is controversial. Early studies of SLNB in large breast cancer patients demonstrated a high (8-18%) false negative rate, with the accuracy worsening with the increasing size. Hill AD et al reported that the accuracy of SLNB appeared to diminish with the increasing size⁴⁰. The accuracy was 100% with T1a,b and decreased to 82% in T2,T3. This inaccuracy might be caused by alternate lymphatic drainage pathways, or by the increased prevalence of axillary metastasis in patient with large tumour. The tumour size and the size of SLN metastasis alone, as reported by other investigators may not be the only predictors of further residual disease in the axilla. The amount of disease harbored by all the SLN as a whole, reflected by the number of positive SLN and the ratio of positive SLN to total SLN(s), should also be considered as an

indication of the amount of further disease that may be present in the rest of axillary basin. The presence of more than one positive SLN and /or a ratio of positive SLN(s) to total SLN(s) greater than 0.5 should alert the clinician to a significant possibility of further disease in axillary basin in patients with a positive SLN⁴¹.

Role of SLNB in patients undergoing Neoadjuvant chemotherapy:

The increasing use of neoadjuvant chemotherapy (CT) in patients with breast cancer has added to the challenge of axillary staging in these patients. It has been reported that SLNB performed prior to neoadjuvant CT eliminates any chemotherapeutic effects on the technical aspects of lymphatic mapping such as sclerosing of lymphatics in response to chemotherapy in the lymph nodes. Obtaining accurate axillary basin information prior to initiation of neoadjuvant chemotherapy may have therapeutic as well as prognostic implications. Jones et al recommended SLNB before neoadjuvant CT in clinically node negative patients at presentation⁴². Their sentinel node identification rates were significantly better when mapping is performed before neoadjuvant CT compared to after completion of CT (100% Vs 80.6%); failure to map correlated with clinically positive nodal disease at presentation and residual disease at ALND. Among patients who mapped successfully after CT, the false negative rate was found to be high (11%).

The role of SLNB in prophylactic mastectomy (PM):

Indications for prophylactic mastectomy range from lobular carcinoma-in situ (LCIS) to a genetic test showing BRCA 1 or 2 mutation, cosmesis and cancer phobia. Occult cancer has been found in upto 5% of PM cases. Dupont EL et al consequently considered the potential expansion of the use of SLN biopsy in these cases and reported that the non-specific technique of peri-aerolar injection of mapping agents appears to be accurate and sensitive for the identification of sentinel lymph node of patients under going PM⁴³. The lymph node mapping may eliminate the need for axillary dissection if the local disease is detected in the breast following prophylactic mastectomy.

Role of SLNB in clinically positive axillary nodes:

By current guidelines, clinically positive axillary nodes are a contraindication of SLNB; but clinical examination is falsely positive in a considerable proportion of patients with either moderately or highly suspicious findings and is by itself insufficient justification for axillary lymph node dissection. Its overall accuracy in various studies varies from 63-68%.

Follow up and survival analysis:

The follow up of patients after SLNB as for breast cancer patients in general, is for life. The rate of isolated axillary relapse after a negative SLNB is comparable to that after a conventional ALND 1% or less⁴⁴. The long-term sequel of SLNB remains to be defined, especially the incidence of axillary recurrence. Previous studies also showed quiet infrequent (0% to 2.1% at follow up of 40-180 months) local recurrence after ALND. Given the low rate of local recurrence after ALND; many studies reported comparably good results in patients with a negative SLNB and no ALND with axillary local recurrence ranging from 0% to 1.4% at 14 to 46 months of follow up⁴⁵.

Although SLNB has recently been incorporated into TNM classification, the optimal histopathological work up of SLNs is currently not standardized. Validation trial done in 2005 on survival analysis following SLNB demonstrated its accuracy in staging early breast cancer. It was reported that patients with a positive SLNB result had a significant lower, five year disease free survival rate than patients with a negative SLNB result. This correlated well with established stage II & III survival information. In conclusion, SLNB is a successful method of staging breast cancer and should be part of the standard of care in this disease.

In summary, SLNB has become the standard of care in the surgical management of a large subset of breast cancer patients. With increasing experience of surgeons and by developing standard protocols by pathologists for handling and processing of these lymph nodes the false negative rates have gone down, sensitivity of identifying micrometastasis has improved greatly, which has made this procedure in the treatment of choice.

Table-I

Sentinel Lymph Node Biopsy Using Different Techniques Weiser et al³

Method	SLN found (%)	Sensitivity	Accuracy
Isotope	92	93	97
Blue dye	78	91	97
Isotope+blue dye	89	97	99

Table-II*Relation of Sectioning Interval with Missed SLN Micrometastasis²³*

Sectioning interval(mm)	Missed micro-metastasis(%)	No. with non sentinel lymph node metastasis
110	5.3	1
170	8.8	0
230	12.4	2
290	17.7	3

Table-III*Correlation of Primary Tumor Size, Lympho-vascular Invasion (LVI) and SLN Meastasis Size with Non SLN Metastasis³*

Number of Predictive Factors Present Tumor Size: <1.0cm, LVI negative, SLN metastases <0.2 cm	Sentinel Lymph Node Only Positive (% cases)
3	100
2	74
1	66
0	43

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