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# ORIGINAL ARTICLE

# FROZEN SECTION EXAMINATION OF SENTINEL LYMPH NODE IN EARLY BREAST CANCER

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**Aim:** ***Sentinel lymph node biopsy (SLNB) is an alternative to axillary lymph node dissection (ALND) in patients with early breast cancer. Objective of this study is to determine feasibility, accuracy of frozen section (FS) in (SNLB) using different techniques.***
**Methods:** ***A review of 61 patients with breast cancer (stage I, II), undergoing SLNB in Department of Surgery, King Abdulaziz University and Bakhsh Hospitals during (December 2000 - 2005).SLNB was localized using methylene blue (n=27), lymphazorine (n=25), radioisotope (n=3) or combination of lymphazorine & radioisotope (n=4) and methylene blue & radioisotope (n=2). Overall results were analyzed. Sentinel lymph nodes (SLN), non sentinel lymph nodes (NSLN) were analyzed using haematoxylin–eosin; immunohistochemical staining and results were compared.***
**Results:** ***SLN identification rates were 100%. 77.0% of patients had stage I and 23.0% had stage II breast cancer. Positive SLN, NSLN, total axillary lymph node (TALN) were (19.7%, 18.0%, 23.0%) with false negative rate of SLN 3.3%. 77.00% of patients had breast conserving therapy while 23.0% had mastectomy. FS accuracy, sensitivity, specificity, positive and negative predictive values were (96.7%, 85.7%, 100.0%, 100.0%, 95.9%).Local breast recurrence rate was 3.3%.***
**Conclusion:** ***SLNB should be offered in patients with early breast cancers because of high detection rate, accurate staging and minimal morbidity. FS examination allowed synchronous ALND to be performed in patients with positive SLNB at our institution.***

**Keywords:** *axillary lymph node, breast histopathology, accuracy.*

## INTRODUCTION

Breast carcinoma is the most common cancer and the second leading cause of cancer related deaths among women.[1] Predictor of survival in breast cancer is the presence or absence of lymph node metastases.[2] Modern surgical techniques are able to offer two-thirds of women with breast cancer preservation of breast, with major morbidity related to side effects of axillary lymph node dissection such as paresthesia, hematoma, seroma, restricted shoulder motion, lymphedema. If these potentially debilitating side effects can be eliminated in those patients with node negative, then advance would be as significant as realization that breast cancer could be treated equally effectively with lumpectomy and radiation therapy as opposed to mastectomy.[1]

Sentinel lymph node biopsy (SLNB) is a minimally invasive technique, holds promise of becoming choice of nodal staging; particularly in early breast cancer patients.[3] It is based on hypothesis that lymphatic drainage from tumor reaches SLN first, before other regional nodes. Selective sampling of SLN could therefore accurately reflect nodal involvement, and more importantly, negative SLN might allow axillary dissection to be safely avoided.[4] Technical success of Sentinel lymph nodes (SLNB) in breast cancer ranges from 85-99%, improving with surgeon and team experiences.[5] Conversely, a number of patient and tumor related factors have been associated with failure to find sentinel nodes, such as older age, obesity, medial location of tumor, and diagnosis obtained by excisional biopsy.[6]

Two parameters defining adequacy of SLNB are SLN identification and false-negative rates. SLN identification rate is defined as proportion of patients in whom SLN is

identified and removed. False-negative rate is defined as proportion of patients with axillary nodal metastases who have negative SLNB. Successful SLNB is generally considered to be SLN identification rate > 90% and false-negative rate ≤ 5%.[7] Techniques for performing SLNB vary from institution to institution.Some advocate blue dye only,[8] others radioisotope only,[9] many demonstrated improved identification and lower false-negative rates using combination of blue dye and radioisotope.[10,11]

Aim of this study was to analyze clinical data of 61 patients with early breast cancer treated with SLNB using a radiolabeled tracer or/and blue dye for localizing SLN.Also to assess diagnostic accuracy, sensitivity, specificity, positive and negative predictive values of frozen section (FS) diagnosis of SLNB.

## PATIENTS AND METHODS

A retrospective review of medical records of patients presenting to Department of Surgery, King Abdulaziz University and Bakhsh Hospitals with breast cancer were evaluated for enrollment into this study from (December 2000 to December 2005).Enrollment criteria includes: women who met our inclusion criteria of early breast cancer (AJCC 5th edition Stage T1 and T2, N0, N1, M0).[15]

Exclusion criteria were: 1) Multifocal /multicentric cancer. 2) Lymph node metastases on preoperative ultrasound. 3) Pregnant women. 4) Advanced breast cancer. 5) Previous breast biopsy and radiation.6) Allergic reactions to vital dyes.A total of 61 patients were enrolled in this study with their age ranged from (24-85 years).This study was approved by Ethical Committee to review the records of those patients.

Clinical factors assessed were: age at diagnosis, family history of breast cancer, tumor location. Pathological factors evaluated were: primary tumor size; histopathology of breast cancer, operation performed.

All patients had preoperative mammography; ultrasound scan of breast which was performed by radiologists specialized in breast cancer.SLN were identified using either methylene blue (n=27), lymphazorine dye (n=25), radioisotope (n=3), combination of lymphazorine dye & radioisotope (n=4) and methylene blue & radioisotope (n=2). On day of surgery radioactive albumin colloid (Nanocoll;GE Healthcare,Little Chalfont,England) is injected peritumoral SC (dose=20MPq) or 5 ml of 1% isosulfan blue dye (lymphazurin) US Surgical Corp., Norwalk, CT or 5 mL of 1% methylene blue dye (Micromedex) was injected intraparenchymally around either the tumor mass or around the biopsy cavity if a previous excision had been performed. The breast was then massaged for 5 minutes. In cases of lumpectomy with wide margin, a transverse incision was made just below hairline in axilla.[4] When modified radical mastectomy was planned,incision lines were marked and incision for SLNB was made through lateral part of these line.[7] The first 10 patients had both SLNB and axillary lymph node dissection (ALND) for establishement of SLNB technique and performed by one surgeon.Sentinel nodes were localized by careful dissection along blue-stained lymph vessels or guided by gamma detector (Navigator; USSC, Norwalk, CT).SLN was defined as any blue and/or 'hot' lymph node (specimen counts >10 Bq).All SLN were immediately sent for FS.Total number of SLN per patient were registered.

Frozen sections were stained with haematoxylin and eosin (H&E).The surgical team was subsequently notified of the result and If SLN positive for malignancy,then we proceed to level I and II axillary dissection.The SLN was fixed in 10% formalin,processed in the usual manner and embedded in paraffin.A single H&E-stained section of the SLN was cut from the paraffin block and examined.If initial review of the H&E-stained section was negative, a SLN protocol consisting of an additional 3 H&E stained levels,cut at 50-µm intervals,in conjunction with immunohistochemical stains for cytokeratin (AE1/AE3, Dako, Carpinteria, CA), was performed on the first of the 3 levels.

***Statistical analysis:*** Data were expressed as mean ± SD or percentage using SPSS version 12.Difference between parameters were done using Chi Square test.A $p<0.05$ was considered significant. Sensitivity, specificity, positive and negative predictive values, accuracy of FS was calculated with respect to histopathology.

## RESULTS

Table 1. Showed demographic and clinical characteristics of all patients.There was one (1.6%) male in the study, family history of breast cancer was positive in 7 (11.5%). SLN identification techniques were by methylene blue, lymphazorine, radioisotope, lymphazorine with radioisotope and methylene blue with radioisotope (44.3%, 41.0%, 4.9%, 6.6%, 3.3%). Breast tumor location were right, left, bilateral (55.7%, 42.6%, 1.6%) with site of tumor more in outer than inner quadrants (77.1 versus 22.9%). Operation was mostly Breast conservative therapy (BCT) in 47 (77.0%),modified radical mastectomy in 14 (23.0%),versus no ALND in 39 (63.9%) than ALND in 22 (36.1%) ($p<0.05$).Breast tumor diameter was ranged from (0.6-5.0; 1.99±0.94 cm) with most of patients (43) had tumor size 1-2 cm (70.5%). 2 (3.3%) patients had neoadjuvant chemotherapy then responded very well and tumor size decreased by 80% then they had BCT.

Identification rate of SLN was 100%.For total number of removed SLN, NSLN, total axillary lymph node (TALN)

were 94, 164 and 258 while number of LN removed per patients were (1.54±1.30, 2.69±4.15 and 4.33±4.30 node/patient). Positive and negative pathological results for SLN, NSLN, TALN were (17 versus 77; 42 versus 122, 59 versus 199), meanwhile, number of patients with positive and negative results were (12 versus 49; 11 versus 50; 14 versus 47) Table 2.

Stages of Breast cancer were either I or II (77.0% versus 23.0%).Histopathological examination of breast cancer were invasive ductal carcinoma, ductal carcinoma in situ (DCIS), invasive lobular carcinoma, invasive tubulolobular pattern, invasive ductal carcinoma and DCIS (91.8%, 3.3%, 1.6%, 1.6%, 1.6%). Hospital stay duration, follow up ranged from (2-10; 4.10±1.52 days and 1-60; 18.34±15.44 months), 4 (6.6%) patients had non palpable breast lesion and on same day wire localization and wide margin was performed ,no drain inserted and discharged the same day. Recurrence rate in the breast was in 2 (3.3%), 1 (1.6%) patients followed for 5 years ,20 (32.8%) patients followed for 4 years ,15 (24.6) patients followed for 3 years ,10 (16.4%) patients followed for 2 years, 10 (16.4%) patients followed for 1 years , 5 (8.2%) patients followed for one mounth. No axillary recurrence. Table 3.

Table 4. Showed cross tabulation between SLN and NSLN frozen section results and SLN identification technique, operation type, ALND, cancer staging, histopathological results of breast cancer, recurrence rate. FS examination of SLNs showed 12 (19.7%) positive cases and 49 (80.3%) negative. Meanwhile, FS for NSLNs was positive 11 cases (18.1%) and negative for 50 (81.9%) cases, given false negative 2 (3.3%). Of 12 (19.7%) patients who had positive SLNs by frozen section, 9 (14.8%) cases showed positive NSLNs and 3 (4.9%) were negative Of 49 (80.3%) patients who had negative SLNs by frozen section, 2 (3.3%) cases had positive NSLNs and other 47 (77.0%) cases showed negative NSLNs. The 2 patients who were negative in FS and found positive in histopathology re-enter operation.

Frozen section of SLNB accuracy, sensitivity, specificity, positive and negative predictive values were (96.7%, 85.7%, 100.0%, 100.0%, 95.9%) Tables 5,6.

**Table 1. Demographic and clinical characteristics of patients.**

| Variables | Results (n=61) |
|---|---|
| **Age in years** | |
| Means ± SD | 47.84±14.70 |
| (Range) | (24.00-85.00) |
| **Sex (number, %)** | |
| male | 1 (1.6%) |
| female | 60 (98.4%) |
| **Family history (number, %)** | |
| positive | 7 (11.5%) |
| negative | 54 (88.5%) |
| **Sentinel lymph node technique (number, %)** | |
| Methylene blue | 27 (44.3%) |
| Lymphazorine dye | 25 (41.0%) |
| Radioisotope | 3 (4.9%) |
| Lymphazorine dye & radioisotope | 4 (6.6%) |
| Methylene blue & radioisotope | 2 (3.3%) |
| **Tumor location (number, %)** | |
| Right | 34 (55.7%) |
| Left | 26 (42.6%) |
| Bilateral | 1 (1.6%) |
| **Operation type (number, %)** | |
| Breast conservative therapy | 47 (77.0%) |
| Modified radical mastectomy | 14 (23.0%) |
| **Site of tumor (number of patients, %)** | |
| Outer quadrants | 47 (77.1%) |
| Inner or central quadrant | 14 (22.9%) |
| **Axillary lymph node dissection (number, %)** | |
| Yes | 22 (36.1%) |
| No | 39 (63.9%) |
| **Breast tumor diameter in cm** | |
| Means ± SD | 1.99±0.94 (0.6-5.0) |
| <1cm (number of patients, %) | 4 (6.6%) |
| 1-2 cm | 43 (70.5%) |
| 2.1-5 cm | 14 (23.0%) |

**Table 2. Results of lymph nodes.**

| Variables | SLN | NSLN | TALN (SLN + NSLN) |
|---|---|---|---|
| **Identification rate of SLN** | | | |
| Yes | 61 (100%) | - | - |
| No | - | | |
| **Total number of lymph node removed** | | | |
| (number of lymph nodes, range) | 94 (1-8) | 164 (1-16) | 258 (1-17) |
| Number LN removed/patients (means±SD) | 1.54±1.30 | 2.69 ±4.15 | 4.23±4.30 |
| **Pathological results (number of lymph nodes, range)** | | | |
| Positive | 17 (1-3) | 42 (1-11) | 59 (1-12) |
| Negative | 77 (1-8) | 122 (1-16) | 199 (1-17) |
| Significance | **P<0.000** | **P<0.01** | **P<0.000** |
| **Patients number (number of lymph nodes, %)** | | | |
| Positive | 12 (19.7%) | 11 (18.0%) | 14 (23.0%) |
| Negative | 49 (80.3%) | 50 (82.0%) | 47 (77.0%) |
| significance | **P<0.000** | **P<0.000** | **P<0.000** |

SLN: Sentinel lymph node; NSLN: Non Sentinel lymph node; TALN: total axillary lymph node.

**Table 3. Results of breast cancer.**

| Variables | Number (%) |
|---|---|
| **Cancer staging** (number, %) | |
| 1st stage | 47 (77.0%) |
| 2nd stage | 14 (23.0%) |
| **Breast cancer histopathology** (number, %) | |
| Invasive ductal carcinoma | 56 (91.8%) |
| Ductal carcinoma in situ | 2 (3.3%) |
| Invasive lobular carcinoma | 1 (1.6%) |
| Invasive tubulolobular pattern | 1 (1.6%) |
| Invasive ductal carcinoma & DCIS | 1 (1.6%) |
| **Hospital stay in days** | |
| Means ± SD | 4.10±1.52 |
| (Range) | (2-10) |
| Recurrence rate (number, %) | |
| Yes | 2 (3.3%) |
| No | 59 (96.7%) |
| **Follow up** (months, means±SD, range) | 18.34±15.44 (1-60) |

**Table 4. Cross tabulation between results of sentinel lymph node (SLN) and non-sentinel lymph nodes (NSLN) frozen section and different studied parameters.**

| Variable | SLN Frozen section | | NSLN Frozen section | |
|---|---|---|---|---|
| | positive | negative | positive | negative |
| **SLN technique** (number, %) | | | | |
| Methylene blue | 8 (13.1%) | 19 (31.1%) | - | - |
| Lymphazorine dye | 3 (4.9%) | 22 (36.1%) | - | - |
| Radioisotope | 1 (1.6%) | 2 (3.3%) | - | - |
| Lymphazorine dye & radioisotope | - | 4 (6.6%) | - | - |
| Methylene blue & radioisotope | - | 2 (3.3%) | - | - |
| **SLN by frozen section** (number, %) | | | | |
| positive | 12 | - | 9 (14.8%) | 3 (4.9%) |
| negative | - | 49 | 2 (3.3%) | 47 (77.0%) |
| **Operation type** (number, %) | | | | |
| Breast conservative therapy (BCT) | 6 (9.8%) | 41 (67.2%) | 6 (9.8%) | 41 (67.2%) |
| Modified radical mastectomy | 6 (9.8%) | 8 (13.1%) | 5 (8.4%) | 9 (14.8%) |
| **Axillary lymph node dissection** (number, %) | | | | |
| Yes | 12 (19.7%) | 10 (16.4%) | 11 (18.0%) | 11 (18.0%) |
| No | - | 39 (63.9%) | - | 39 (63.9%) |
| **Cancer staging** (number, %) | | | | |
| 1st stage | 1 (1.6%) | 46 (75.4%) | - | 47 (77.0%) |
| 2nd stage | 11 (18.0%) | 3 (4.9%) | 11 (18.0%) | 3 (4.9%) |
| **Breast cancer histopathology** (number, %) | | | | |
| Invasive ductal carcinoma | 11 (18.0%) | 45 (73.8%) | 10 (16.4%) | 46 (75.4%) |
| Ductal carcinoma in situ (DCIS) | - | 2 (3.3%) | - | 2 (3.3%) |
| Invasive lobular carcinoma | - | 1 (1.6%) | - | 1 (1.6%) |
| Invasive tubulolobular pattern | - | 1 (1.6%) | - | 1 (1.6%) |
| Invasive ductal carcinoma & DCIS | 1 (1.6%) | - | 1 (1.6%) | - |
| **Recurrence rate** (number, %) | | | | |
| Yes | 1 (1.6%) | 1 (1.6%) | 1 (1.6%) | 1 (1.6%) |
| No | 10 (16.4%) | 49 (80.3%) | 10 (16.4%) | 49 (80.3%) |

**Table 5. Statistical formulas.**

| Outcome measure | Formula |
|---|---|
| Positive predictive value | TP/TP+FP |
| Negative predictive value | TN/TN+FN |
| Sensitivity | TP/TP+ FN |
| Specificity | TN/TN+FP |
| Accuracy | TP+TN/TP+TN+FP+FN |

TP, true positive; TN, true negative; FP, false positive; FN, false negative.

**Table 6. Results of frozen section of Sentinel lymph node in breast cancer patients.**

| Results | Frozen section (n=61) |
|---|---|
| True positive (number) | 12 |
| True negative (number) | 47 |
| False positive (number) | 0 |
| False negative (number) | 2 |
| Sensitivity (%) | 85.7% |
| Specificity (%) | 100.0% |
| Positive predictive value (%) | 100.0% |
| Negative predictive value (%) | 95.9% |
| Accuracy (%) | 96.7% |

## DISCUSSION

Axillary nodal status is considered to be essential in determining patient's prognosis and treatment. Regional control is thought to be important in patients with positive axillary nodes.While ALND can achieve both goals, it is equally well recognized as the most morbid part of breast cancer surgery. SLNB is accurate in staging axilla and has minimal morbidity.[3]

Acceptance of BCT as an alternative to mastectomy came only in 1990s, number of studies showed that BCT resulted in overall survival rates that were similar to mastectomy.[12] It was also established by then that adjuvant radiation therapy to conserved breast was necessary to achieve acceptable rates of local recurrence. BCT is routinely practiced and its long term efficacy is proven.[13] In this study, 77.0% had BCT while 23.0% had mastectomy, 36.1% patients had ALND, 19.7% showed positive SLNB by frozen section while others 16.4% performed both SLNB and ALND performed in the beginning to establish the technique by one surgeon.

Sentinel lymph node biopsy is now accepted as an alternative to axillary dissection for staging axilla in early breast cancer patients.[14] However, in approximately 6% of patients with SLNs, remaining axillary nodes harbor metastases.Therefore, long-term efficacy of SLNB alone in controlling axillary disease in such patients needs to be established.This technique requires attention to details in planning surgery and meticulous surgical dissection. .[15] Multidisciplinary cooperation among team of surgeons, pathologist, nuclear medicine specialists is essential to the success of this enterprise.[14] A significant benefit of SLNB is that by virtue of limited tissue disruption, avoids axillary dissection morbidity.This improves diagnostic accuracy of axillary nodal metastases because efforts of pathologist are focused on limited volume of tissue.[15]

Controversy remains regarding various technical aspects of SLNB.Some authors advocate a single technique,using either blue dye alone or isotope alone,[16] while others maintain that a combination approach to identify SLN is preferable.[17] In this study, either only methylene blue dye, lymphazorine dye, radioisotope alone or combination of lymphazorine dye & radioisotope or methylene blue dye & radioisotope were used.Methods described in this study had proven valid in detecting axillary SLN (detection rate of 100%) and in staging of axilla (false-negative rate 3.3%), The false negative patients underwent axillary lymph node dissection level 1 and level 11.These results are fully acceptable when compared with international results.[18,19] Current consensus is that false-negative rate of up to 5% is acceptable.[20] False-negative SLNB in practice would result in leaving behind of positive NSLN.This could potentially be detrimental to overall survival either directly through uncontrolled regional recurrence, or indirectly through inappropriate selection of adjuvant systemic treatment.[20]

Namwongprom et al.[20] used radioisotope-guided SLN identification and biopsy prior to axillary clearance. Their SLN identification and false negative rates were 91.4% and 30.8%. Giuliano et al.[8] and Kern[21] used only blue dye for detecting SLNs, and reported identification rate to be 93.5% and 98%. They proposed that subareolar injection resulted in superior detection by blue dye. Discrepancy between our results and others using blue dye as sole guide for SLN localization could be explained by different

surgical approaches, also long delay after blue dye injection might be responsible for loss of dye intensity in some SLN in other studies.[3]Some studies had demonstrated improved identification rates, lower false-negative rates using combination of blue dye and radioisotope.[10] In a consensus conference published in 2002, panel recommended use of both radio-colloid and blue dye together for surgeons less experienced in SLNB.[11]Nos et al.[22] demonstrated improved false negative rate, but corresponding drop in SLN identification rates, with blue dye alone where SLNs were confirmed blue before complete histopathological analysis. An advantage of blue dye alone technique is that need for expensive equipment is reduced, and logistical problems involved in lymphoscintigraphy are avoided.

In this study, sensitivity, specificity, positive, negative predictive values, accuracy of frozen section in detection of SLNB were 85.7%, 100.0%, 100.0%, 95.9%, 96.7%. Only 2 cases (3.3%) showed negative SLNB proven to have positive NSLN. Meanwhile, 63.9% of patients with negative SLNB did not have ALND and so protected from ALND complications.In this respect, Veronesi et al,[23] reported sensitivity and false negative results of FS in SLNB were 64% and 24%. Their high false negative results were due to micrometastasis of disease.In this respect, Krag et al.[6] reported sensitivity, accuracy, negative predictive value of SLNs to predict ALN status was 88.6%, 96.8%, 95.7%. Mikhitarian et al.[24]reported sensitivity, accuracy, negative predictive value, false negative rate, specificity and positive predictive values of pathological analysis of SLNB to predict ALNs pathological status were 84.1%, 94.7%, 92.6%, 15.9%, 100%, 100%.Many investigators have proposed that if SLNs are examined more thoroughly with additional histopathologic sections and supplementary examination by immunohistochemistry with anticytokeratin antibodies or cytokeratin reverse transcriptase polymerase chain reaction, more micrometastases would be detected and improve sensitivity.[25]

Recurrence rate of breast cancer in this study was 3.3% in breast with no axillary recurrence, where one of patient was SLNB negative and other was positive and had ALND, local recurrence developed after one year mainly due to failure of taking the radiotherapy after lumpectomy. In this respect, Veronesi et al.[26] report findings from 953 patients with early breast cancer who underwent SLNB but not axillary dissection where no involvement of SLN was seen. After 7 years follow-up, three patients (0.3%) developed disease recurrence in axilla. All three patients underwent ALND and were well at time of follow-up, 5-year overall survival rate of whole series was 98%. Results of Veronesi et al,[26] together with those reported previously, dissipate fears that axillary SLNB policy would result in higher rate of subsequent axillary metastases with all of associated problems.

In Conclusion Sentinel lymph node biopsy is a reliable and minimally invasive procedure, representing a new standard of care for patients with clinically node-negative breast cancer.Frozen section examination is simple and rapid methods for detecting nodal metastases using haematoxylin and eosin (H&E) stain only.However, these methods are less sensitive for detection of micrometastatic disease.Despite these limitations. This approach represents a potential emotional and time benefit for patient by eliminating need for a second hospitalization for delayed ALND.

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