

Does The Tumor Location Affect The Accuracy of Sentinel Lymph Node Biopsy In Breast Cancer? A Single Institute Experience

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Abstract Background: Sentinel lymph node biopsy (SLNB) can give an idea about the nodal status with high accuracy. **Objective:** To assess the effect of breast cancer location on SLNB accuracy regarding identification rate (IR), accuracy rate and false negativity rate (FNR). **Methods:** Breast cancer patients with positive axilla who were scheduled for axillary lymph node dissection (ALND) were included. They were randomly allocated into two groups: Group I (G I) included patients with laterally located breast cancer while Group II (G II) included patients with medially located breast cancer. Four ml of Methylene blue (1%) was injected in the peritumoral tissue. SLNB was taken for histopathological examination while ALND was completed in all cases. SLN IR, FNR and accuracy rate were assessed in both groups. **Results:** This study included 104 female patients; 63 (60.6%) in GI whereas 41(39.4%) in GII. SLN identification was done successfully in 92% in G I and 87.8% in G II with no significant difference. In G I; Out of the 58 patients in whom SLN was identified; SLN was positive in 54 (93.1%) cases and negative in 4(6.9%) cases while in G II; SLN was positive in 31 out of 36 (86.1%) cases and negative in 5 (13.9%) cases with no significant difference regarding SLN accuracy or FNR. **Conclusion:** The tumor location doesn't affect axillary SLNB regarding identification rate, accuracy rate and false negativity rate. Methylene blue alone is still efficacious in SLNB lymphatic mapping especially in developing countries because of its low cost.

Keywords: Breast cancer, SLNB, identification rate, Accuracy rate, false negativity rate, Methylene blue lymphatic mapping

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1. Introduction

Axillary nodal status in breast cancer patients is a crucial prognostic factor in early clinical stages. Hence, axillary staging remains the standard of care for all breast cancer amenable to curative treatment. [1,2] Histopathological examination of axillary lymph nodes is still the most accurate method for assessing lymph node status which is routinely carried out by complete Axillary Lymph Node Dissection (ALND). [2,3] However, many women without metastasis undergo unnecessary lymphadenectomy and may suffer from its complications. [2,3] Sentinel Lymph Node (SLN) is the first lymph node traced by the radiocolloid or blue dye. The physiologic concept behind Sentinel Lymph Node Biopsy (SLNB) is based on the idea that tumor spreads via lymphatics in a sequential pattern. If there is no metastasis in the SLN; hence the risk of metastatic involvement of other lymph nodes is highly reduced. [4] In clinically node-negative patients, SLNB can give an idea about the axillary nodal status with an identification rate (IR) >90% and a false negativity rate

(FNR) <10%. [2] In a patient with negative SLNB; the possibility of the other nodes in the axilla being negative is about 90-95% so SLNB alone is now the standard staging procedure among all clinically node-negative (cN0) breast cancer patients. [2,3,4] The lowest FNR and non-identification rate of SLNB have been reported with the use of blue dye and a radiocolloid (technetium-99m) in combination. [4] Galimberti et al [5] has reported high success rates with each technique alone and concluded that the use of blue dye alone obviates the need for any additional equipment or procedures. Sappey postulated that all breast lymph would initially drain to the subareolar plexus and continue to the axillary lymph nodes based on results from mercury injections into lymphatic vessels. [6,7] Subsequent studies showed that Sappey was not completely right, since there are other routes for lymph drainage. [6,7] Drainage takes place through lateral and medial efferent lymphatic vessels directly towards the axillary or the internal thoracic lymph nodes. [7] Even when the parasternal lymph nodes are affected with metastasis; radical dissection of this lymph node group is not recommended since this procedure will not add any survival benefit. [8] Tassenoy et al [9] found SLN in the

axilla with 100% localization in the axillary lymph nodes following intradermal injection of radiotracer into medial quadrants of the breast in healthy women. On the other hand, other studies [9,10] showed that the tumors situated in the medial quadrants drain with a high frequency to the internal mammary chain and subclavicular lymph nodes. This debate may raise the doubt about accuracy of SLNB in medially located breast cancer. Most studies of lymphatic pathways of the breast cancer have concentrated on the upper lateral quadrant of the breast because of the high incidence of carcinoma at this site and the lymphatic drainage pathways of the medial half of the breast, however, has been less studied. [9] The current study aimed to assess the effect of breast cancer location either laterally or medially located on the accuracy of SLNB regarding SLN IR, FNR and accuracy rate.

2. Patients and Methods

All patients with pathologically proven breast cancer with positive axilla who were admitted to the department of Surgery, Medical Research Institute, Alexandria University, Egypt in the period between January 2019 and August 2019 and scheduled for ALND as a part of Modified Radical Mastectomy (MRM) or Conservative Breast Surgery (CBS) were included. Patients with centrally located breast cancer, previous breast and/or axillary surgery, multicentric breast cancer, patients with negative axilla and planned for SLNB, impaired renal functions and those received neoadjuvant chemotherapy (NAC) were excluded from the study. Informed Consent was taken from every patient to be included in the current study and approved by ethics committee of our institution.

The included patients were randomly allocated into two groups: Group I (G I) included patients with laterally located breast cancer [upper outer quadrant (UOQ) or lower outer quadrant (LOQ)] while Group II (G II) included patients with medially located breast cancer [upper inner quadrant (UIQ) or lower inner quadrant (LIQ)]. After the induction of anesthesia; four ml of Methylene blue of 1% concentration was injected in the Peritumoral tissue and breast massaging was done for 10

minutes. The sentinel node was identified after lumpectomy during CBS or raising the upper flap during MRM. The nodes with blue staining were considered as Sentinel nodes which were sent for histopathological study while the surgical procedure was being completed with ALND. SLN IR (The percentage of patients showing blue staining node(s) out of all patients included in the study), FNR (The percentage of patients in whom SLN identified but pathologically negative) and accuracy rate (The percentage of patients in whom SLN identified and pathologically positive) were assessed in both groups.

3. Statistical Analysis

Data were analyzed using the statistical package for social sciences (SPSS ver.20; SPSS Inc., Chicago, Illinois, USA). Quantitative data were described using the mean and SD, whereas qualitative data were described using the number and percent. For comparing quantitative variables between the two groups, we used the independent sample t-test. We used the Monte Carlo significance test if $>2 \times 2$ categories and more than 20% of the cells had an expected cell count less than 5. In all statistical tests, a level of significance of 0.05 was used; statistical significance was set at P less than 0.05.

4. Results

This study included 104 female patients who were allocated to one of the two groups: GI which included patients with laterally located breast cancer (UOQ or LOQ) and this group included 63(60.6%) patients whereas GII which included patients with medially located (UIQ or LIQ) breast cancer and this group included 41(39.4%) patients. On comparing the two groups, there was no statistically significant difference between them regarding patients' age (P = 0.196). The time taken from methylene blue injection until SLN(s) identification and retrieval ranged from 25-30 minutes in GI while in GII; it ranged from 30-35 minutes with no statistically significant difference between the two groups (P = 0.832). (Table 1).

Table 1. Clinicopathological Characteristics and type of submitted Surgery

Item	Group I n= 63 (60.6%)	Group II n= 41 (39.4%)	P-value		
Age					
• Range (Y)	36 -62	39 - 57	0.196		
• median	49	48			
Breast cancer Side					
• Right	28(44.4%)	19(46.3%)	0.621		
• Left	35(55.6%)	22(53.7%)			
Breast Cancer Location	UOQ 44 (69.8%)	LOQ 19 (30.2%)	UIQ 24 (58.5%)	LIQ 17 (41.5%)	0.09
Breast Cancer Stage					
• Stage II	46 (73%)		28(68.3%)		0.102
• Stage III	17(27%)		13(31.7%)		
Type of submitted Surgery					
• MRM	40(63.5%)		29(70.7. %)		0.064
• CBS	23(36.5%)		12(29.3%)		
Total	63(100%)		41(100%)		

UOQ: Upper Outer Quadrant, LOQ: lower Outer Quadrant, UIQ: Upper Inner quadrant, LIQ: lower Inner quadrant, MRM: Modified Radical Mastectomy, CBS: Conservative Breast Surgery, Monte Carlo test and t-test were done to determine the statistical significance and was found to be statistically significant (P <0.05).

Table 2. SLN identified, SLN Identification rate, SLN False Negativity rate and Accuracy rate

Parameter	Group I n= 63 (60.6%)	Group II n= 41 (39.4%)	P-value
SLN identified	58(92 %)	36(87.8%)	
• SLN with metastasis (Positive)	54(93.1%)	31(86.1%)	
• SLN without metastasis (Negative)	4(6.9%)	5(13.9%)	
SLN Not identified	5(8%)	5(12.2%)	
SLN IR(Identified)	92%	87.8%	0.092
SLN FNR (Identified & Negative)	6.9%	13.9%	0.071
Accuracy rate (Identified & Positive)	93.1%	86.1%	0.060

SLN; Sentinel Lymph Node, IR; Identification rate, FNR; False negativity rate. The Monte Carlo test and The t-test were done to determine the statistical significance and was found to be statistically significant ($P < 0.05$).

SLN identification was done successfully in 92% of the patients (58 out of 63) in G I while in G II; SLN was identified in 87.8% of the patients (36 out of 41) with no statistically significant difference between the two groups regarding SLN IR ($P = 0.092$). The number of SLN removed per patient ranges from 1 node to 3 nodes in both groups. The number of axillary lymph node removed during ALND ranged from 10 nodes to 22 nodes in G I while in G II; it ranged from 13 to 19 nodes with no statistically significant difference between the two groups ($P = 0.109$). In G I; Out of the 58 patients in whom SLN was identified; SLN was positive in 54 cases (93.1%) and negative in 4 cases (6.9%) while in G II; SLN was positive in 31 out of 36 cases (86.1%) and negative in 5 cases (13.9%) with no statistically significant difference between the two groups regarding SLNB accuracy rate ($P = 0.060$) or SLNB FNR ($P = 0.071$) as shown in Table 2.

5. Discussion

Lymphatic drainage pattern in patients with breast cancer has been studied by several groups. (9-12) Although a high percentage of lymph drains towards the axilla; some drainage also occurs to internal mammary nodes or other extra-axillary sites. [11] Byrd et al [12] found that the internal mammary chain was involved in 17% patients with breast cancer and based on quadrant location of the carcinoma; thirty seven percent of laterally located (UOQ or LOQ) and 42 % of medially located (UIQ or LIQ) breast cancer drain also to internal mammary nodes or other extra-axillary sites which may affect axillary SLNB identification and accuracy. These results supported by Uren et al [13] who found most breast cancer patients (93%) have lymphatic drainage toward the axilla, but in 56% drainage occurred also to extra-axillary lymph nodes (internal mammary chain, supraclavicular, interpectoral and intramammary nodes). Other studies [7-14] confirmed the existence of drainage pathways other than to the axilla. Moreover; Kroman et al [10] concluded that women with tumors in the medial quadrants had the worst prognosis but were also the least likely to be diagnosed with axillary node positive tumors in comparison to laterally located breast cancer. Based on 250 breast lymphoscintigraphies among normal women; Vendrell-Torne et al [15] found that drainage from the lower medial quadrant in 30% of cases occurred exclusively to the internal mammary nodes, 56% drained to both the axilla and internal mammary nodes and 14% drained exclusively to the axilla. All of these previous

studies may give some doubt in the accuracy of axillary SLNB in medially located breast cancer and assume that the tumor location either laterally located or medially located may affect the accuracy of axillary SLNB but really the results of these studies are different from our sporadic observations in which we didn't find any differences between medially located and laterally located breast cancer regarding SLN identification rate and accuracy rate but still they are just observations which we can't propagate in our practice so we have conducted this study selecting our target population from patients with positive axilla who were already scheduled for ALND as a part of MRM or CBS. We excluded patients with negative axilla who were scheduled for SLNB to avoid the confounding factor as these cases may fall into the false negative group and subsequently to be exposed to unnecessary ALND. Some studies [3,4] concluded that several factors can affect the accuracy of the SLNB like previous excisional biopsy scars and NAC as lymphatic pathway may get fibrosed due to the effect of surgery or chemotherapy so we excluded patients with previous breast and/or axillary surgery and those who received NAC to avoid any possibility of lymphatic distortion which may affect the accuracy of our results. Also, we excluded patients with multicentric breast cancer to avoid any possibility of affection of lymphatic pathways by the presence of tumors outside the quadrant we aimed to study. Finally; we excluded patients with centrally located breast cancer to avoid selection bias as the tumor may be central but may also extend to another quadrant which may act as a confounding factor affecting our results. We used methylene blue because of its low cost and reduced risks of producing adverse effects; the main side effect was bluish discoloration over the site of injection. It didn't cause any life-threatening complications like acute renal shutdown or change in enteric circulation. This was the same rationale for which methylene blue has been used widely for lymphatic mapping by many studies. [16,17] In a cohort study, Simmons et al studied on 100 patients and demonstrated sentinel nodes in 93 subjects using methylene blue; and their results are equally efficacious as radio isotopes. [16,17] According to Paganelli et al [18,19], a subdermal injection is most suitable because of fast detection of the SLN and patient comfort and methylene blue when given intradermally produces severe skin reactions like Dermolysis and skin necrosis; hence it is usually given subcutaneously in the peritumoral tissue. [16,17] Ahmed et al [7] concluded that the use of a deep injection technique is associated with a higher rate of identification of sentinel nodes. We have used peritumoral

deep injection technique in the current study as the aim was to study lymphatic drainage of the tumor, so it seems logical, accordingly, to inject the tracer as close as possible to the tumor. One study concluded that the medial location of the tumor could be associated with non-identification of axillary SLN more than those located laterally. [20] In our results; SLN identification was done successfully in 92% of the patients (58 out of 63) in G I while in G II; SLN was identified in 87.8% of the patients (36 out of 41) with no statistically significant difference between the two groups regarding SLN IR which is not far from the findings of Tassenoy et al [9] who concluded that SLN was successfully identified in 91.9% regardless the site of the primary tumor; Moreover; they have used radio isotopes not blue dye and this supports our rationale in using methylene blue which was equally efficacious as radio isotopes for lymphatic mapping which was supported by many studies. [16,17]

6. Conclusion

The tumor location either laterally located or medially located breast cancer doesn't affect axillary SLNB regarding IR, FNR and accuracy rate so axillary SLNB is highly valid regardless the site of primary tumor. Methylene blue alone is still efficacious in SLNB lymphatic mapping especially in developing countries because of its low cost and minimal adverse effects. However, further multicentric studies with higher volume of cases over longer period are recommended for confirmation of our findings.

Conflict of Interest

The authors declare no conflict of interest or financial ties to conclude.

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