Assessment of accuracy of axillary sentinel lymph node biopsy in medially located breast cancer using methylene blue injection technique: our institute experience

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Background
Axillary lymph node status is the single most important prognostic factor in breast cancer. Sentinel lymph node biopsy (SLNB) can give an idea about the axillary nodal status, with a high rate of identification. Because the upper outer quadrant is the most common site for breast cancer, most studies of SLNB of the breast have been performed in patients with breast cancer mostly located in this quadrant of the breast, whereas the medial quadrants have much been less studied. In this study, we evaluate the axillary SLNB in medially located breast cancer only, using methylene blue injection technique, regarding identification rate, accuracy rate, and false negativity rate (FNR).
Patients and methods
The study included 42 female patients with medially located breast cancer and negative axilla, scheduled for modified radical mastectomy or conservative breast surgery. Overall, 4 milliliters of methylene blue 1% was injected in the peritumoral tissue. Sentinel lymph node(s) (SLN) and other axillary nodes were individually sent for pathological assessment.
Results
Average time taken from methylene blue injection until SLN(s) identification and dissection reached 45 min. SLN identification rate was 92.9% of the patients. The number of SLN removed per patient ranged from 1 to 3 nodes. The number of axillary lymph node removed during axillary lymph node dissection ranged from 10 to 22 nodes. Accuracy rate was 88.1%, and SLN FNR was 4.8%.
Conclusion
Axillary SLNB is highly valid in medially located breast cancer, with high identification and accuracy rates and low FNR.

Keywords:
breast cancer, lymphatic mapping, medial tumors, methylene blue, sentinel lymph node biopsy

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Introduction

Breast cancer is the commonest cancer among women worldwide, with an estimated 1.67 million new cases being diagnosed worldwide yearly [1]. Axillary lymph node status is the single most important prognostic factor in breast cancer in their early clinical stages [2]. Histopathological examination of axillary lymph nodes is still the most accurate method for assessing lymph node status. Until recently, this was routinely carried out through complete axillary lymph node dissection (ALND). The significance of a proper axillary dissection either for staging or local tumor control is well-established [3]. However, many women without metastasis were unnecessarily undergoing ALND. Thus, these patients are subjected to unnecessary morbid outcomes that are inherent to this surgical procedure. These complications include paresthesia and pain in the operated limb, weakness, edema of the limbs, and limited shoulder movement that hinders the daily activities [4]. The risk of developing lymphedema ranges from 8 to 37% and mainly depends on the extent of the axillary clearance. Undue handling of the axilla may cause major vessel thrombosis especially axillary vein [5].

In clinically node-negative patients (cN0 disease), sentinel lymph node biopsy (SLNB) gives an idea about the axillary nodal status with more than 90% identification rate (IR) and less than 10% false-negative rate (FNR) [2]. SLNB has widely replaced ALND in patients with early-stage breast cancer. In patients with negative SLNB, the possibility that other nonsentinel axillary nodes being negative is ~90–95% [4–6]. The use of blue dye and a radiocolloid (technetium-99m) in combination yields a lower

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FNR and non-IRs. The use of blue dye alone obviates the need for any additional equipment or procedures, although there is a risk of serious allergic reactions in 1–2% of cases. Proponents of a single modality approach have reported high success rates with each technique in isolation [7].

Earlier studies postulated that all breast lymph initially drains to the subareolar plexus and continues to the axillary lymph nodes [8,9]. Subsequent studies showed the presence of other routes for lymph drainage. It is now known that the drainage takes place through lateral and medial efferent lymphatic vessels that lead toward the axillary lymph nodes or the lymph nodes along the internal thoracic vessels [9]. However, previous studies have shown that sentinel lymph node (SLN) detected from intradermal injection of a radiotracer into upper medial quadrant of the breasts of healthy women is 100% located in the axillary lymph nodes [10].

Many other studies on the localization of the SLN have shown that the tumors in the upper medial quadrant drain with a high frequency to the internal mammary chain and subclavicular lymph nodes [11]. This may raise the doubt about accuracy of SLNB identification in medially located breast cancer. Most studies of lymphatic pathways of the breast have been performed in patients with upper lateral quadrant tumors because of the high incidence of carcinoma at this site, and the lymphatic drainage pathways of the medial half of the breast, however, have been less studied [11]. This study aimed to assess the axillary SLNB in medially located breast cancer using methylene blue injection technique regarding IR, SLN FNR, and accuracy rate.

Patients and methods

This study included all patients with pathologically proven medially located [upper inner quadrant (UIQ) or lower inner quadrant (LIQ) breast cancers (clinically or radiologically proven)] negative axilla who were admitted to the Department of Surgery, Medical Research Institute, Alexandria University, Egypt, in the period between April 2018 and December 2018 and scheduled for modified radical mastectomy (MRM) or conservative breast surgery (CBS). ALND was performed for patients with positive SLNB results. All patients included in this study were subjected to complete history taking, medical history, and clinical and radiological examination of the breast and axilla. Negativity of the axilla was confirmed by both clinical examination and ultrasonography. Patients with multicentric breast cancer, patients with previous breast and/or axillary surgery, patients with impaired renal function, patients with advanced inoperable breast cancer, patients with positive axilla who planned for ALND, and patients who received neoadjuvant chemotherapy (NAC) were excluded from the study.

Technique

Patients were subjected to surgical procedure, that is, MRM or CBS. After the induction of anesthesia; 4 ml of methylene blue 1% was injected in the peritumoral tissue. Breast massaging was done for 5 min. The sentinel node (s) was taken after raising the upper flap during MRM or after lumpectomy during CBS. SLN dissection was completed in ~20–25 min. The nodes with blue staining were considered as sentinel nodes which were submitted to frozen sectioning and examined pathologically, whereas the surgical procedure was completed in positive SLNB cases by ALND.

SLN IR (the percentage of patients showing blue staining node(s) out of all patients included in the study), SLN FNR (the percentage of patients in whom SLN was identified but was pathologically negative), and accuracy rate (the percentage of patients in whom SLN was identified and was pathologically positive) were assessed. A written informed consent was taken from participants in this study according to the Declaration of Helsinki and approved by the Ethical Committee of Medical Research Institute.

Statistical analysis

Patients were studied using the descriptive statistics. Values related to SLNB technique in terms of IR, FNR, and accuracy rate were recorded. Fisher's exact test was done to determine the statistical; level of significance (*P* value) of 0.05 was used, below which the results were considered to be statistically significant.

Results

The study included 42 female patients with medially located (UIQ or LIQ) breast cancer with negative axilla who were scheduled for MRM or CBS. Table 1 shows the distribution of the studied patients according to clinicopathological characteristics and type of submitted surgery. Average time taken from methylene blue injection until SLN(s) identification and dissection was 45–50 min [5 min for breast massaging+20 min for raising the upper flap during MRM or lumpectomy during CBS +20–25 min for SLN(s) identification and dissection].

SLN identification was done successfully in 92.9% of the patient (39 of 42), and in the remaining 7.1% (three

Table 1 Clinicopathological characteristics and type of submitted surgery

Item	*N* (%)
Age	
Range (years)	37–61
Median	49
Menopausal status	
Premenopause	17
Postmenopause	25
Breast cancer side	
Right	19 (45.2)
Left	23 (54.8)
Breast cancer location	
UIQ	24 (57.1)
LIQ	18 (42.8)
Breast cancer stage	
Stage I	2 (4.8)
Stage II	29 (69)
Stage III	11 (26.2)
Type of submitted surgery	
MRM	27 (64.3)
Conservative breast surgery	15 (35.7)
Total	42 (100)

LIQ, lower inner quadrant; MRM, modified radical mastectomy; UIQ, upper inner quadrant.

Table 2 Analysis of sentinel lymph node results

Parameters	*N* (%)
SLN investigated	42 (100)
SLN identified	39 (92.9)
SLN with metastasis (positive)	37 (88.1)
SLN without metastasis (negative)	2 (4.8)
SLN not identified	3 (7.1)
SLN identification rate (identified) (%)	92.9
SLN false negativity rate (identified and negative) (%)	4.8
Accuracy rate (identified and positive) (%)	88.1

SLN, sentinel lymph node. Fishers exact test was done to determine the statistical significance and was found to be statistically significant ($P<0.05$).

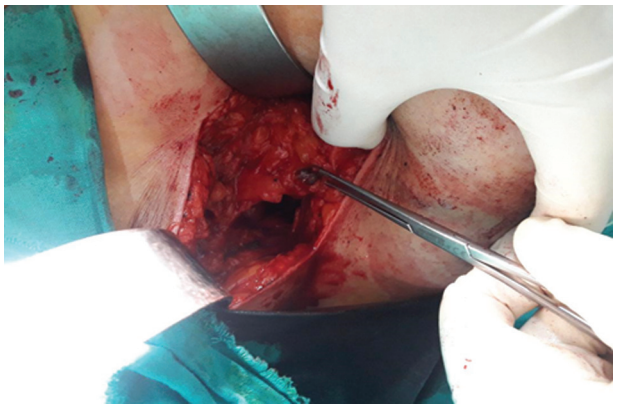
of 42), SLN identification could not be done. The number of SLN removed per patient ranged from 1 to 3 nodes (average 2.2). The number of axillary lymph node removed during ALND ranged from 10 to 22 nodes (average 12.7). Of 39 patients in whom the sentinel node was identified, malignancy was positive in 37 (94.9%) cases and negative for two (5.1%) cases.

The results are shown in Table 2. None of the patients in our study developed any operative or postoperative complications. Figure 1 shows a case from the studied patients in whom SLN was identified.

Discussion

The SLN is defined as the first nodes that drain the lymph from a particular organ before the subsequent

Figure 1



A 47-year-female patient with upper inner quadrant during axillary lymph node dissection; the instrument points to the blue stained sentinel lymph node.

nodes (non-SLNs). Thus, identification of SLN provides us an accurate clinical view into the regional basin. The physiologic concept behind SLN biopsy is based on the idea that metastatic cells spread through regional lymphatics in an orderly and reproducible manner. If there is no metastasis in the SLN, then the risk of other lymph nodes being involved with metastasis is highly remote [11]. SLNB alone has been established as the standard staging procedure among patients with clinically node-negative (cN0) breast cancer [12].

Several groups have studied lymphatic drainage pattern in patients with carcinoma of the breast. Although a high percentage of lymph drains toward the axilla, some drainage also occurs to internal mammary nodes or other extra-axillary sites [13]. Byrd *et al.* [14] found that the internal mammary chain was involved in 17% of the studied group. Based on quadrant location, central region was the most common followed by lower outer quadrant, LIQ, UIQ, and upper outer quadrant (29, 27, 25, 17, and 10%, respectively). This means that 42% of the studied group had medially located (UIQ or LIQ) breast cancers that drain also to internal mammary nodes or other extra-axillary sites which may affect axillary SLNB identification and accuracy. This assumption was supported by Uren *et al.* [15] who found that most patients with breast cancer (93%) have lymphatic drainage toward the axilla, but in 56%, drainage also occurred to lymph nodes outside the axilla [internal mammary chain (45%), supraclavicular (13%), and interpectoral and intramammary nodes (12%)]. Other several studies had confirmed the existence of drainage pathways other than the axilla [10–16].

Moreover, Colleoni *et al*. [17] concluded that women with tumors in the medial quadrants had the worst prognosis but were also less likely to be diagnosed with axillary node-positive tumors. Based on 250 breast lymphoscintigraphies among normal women, Vendrell-Torne *et al*. [18] 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.

These studies may give some doubt about the accuracy of axillary SLNB in medially located breast cancers. The results of these studies are different from our study in which we detected axillary SLNB in medially located tumors with accuracy rate, IR, and FNR that did not differ from rates described for laterally or centrally located breast cancers in other studies.

In this study, we have selected our target population from patients with medially located (UIQ or LIQ) breast cancer with negative axilla who were scheduled for MRM or CBS. Patients with positive axilla who were already scheduled for ALND were not included. We also excluded patients with multicentric breast cancer to avoid any possibility of affection of lymphatic pathways by the presence of tumors outside UIQ or LIQ. Some studies concluded that several factors can affect the accuracy of the SLNB like previous excisional biopsy scars and NAC, as lymphatic pathway may get fibrosed owing to the effect of chemotherapy [5,6]. For this reason, 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.

We used methylene blue because of its low cost, easier-to-use benefit, and reduced risks of adverse effects; the main adverse effect was bluish discoloration over the site of injection. It did not 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 [19,20]. In a cohort study, Asoglu *et al*. [19] studied 266 patients and demonstrated sentinel nodes in 251 subjects using methylene blue, with a success rate of 94.3%. Recently, several studies reported that blue dye alone was sufficient for identifying SLNs in breast cancer [20–22]. Thus, the use of methylene blue alone as a mapping method is a feasible method and may expand the use of SLNB in developing countries.

In a comparative study, Cody [23] concluded that the results of sentinel node biopsy by using blue dye, radioisotope, or a combination of both were comparable, and the IRs were 81, 92 and 93%, respectively, whereas the FNRs were 9, 7, and 5%, respectively. Gipponi *et al*. [24] found that the sentinel node detection rate increased from 73.8% with blue dye alone, to 94.1% with radiotracer alone, up to 98.7% with a combination of blue dye and radiotracer.

According to Kaklamanos *et al*. [25], a subdermal injection is most suitable because of fast detection of the SLN and patient comfort, but when methylene blue is given intradermal, it produces severe skin reactions like dermolysis and skin necrosis. Therefore, it is usually given subcutaneously or in the peritumoral tissue. Ahmed *et al*. [9] concluded that the use of a deep injection technique is associated with a higher rate of identification sentinel nodes. We have used peritumoral injection technique in the current study, as the aim was to study lymphatic drainage from the tumor, so accordingly, to inject the dye as close as possible to the tumor.Opposite to our results, one study concluded that the medial location of the tumor could be associated with nonidentification of SLN [26]. Our results concluded that SLN identification was done successfully in 92.9% of the patient (39 of 42). Moreover, accuracy rate was 88.1%. Tassenoy *et al*. [11] concluded that SLN was successfully identified in 91.9%, which is not far from our findings in spite of using radio isotopes and not blue dye, and this supports our rationale in using methylene blue for lymphatic mapping. Moreover, our results matched with the results of meta-analysis study done by Kim *et al*. [13], where the overall IR was 96%, ranging from 41 to 100%, and the FNR ranged from 0 to 29%, averaging 7.3% overall, and they also found no significant difference between FNRs in studies using blue dye alone and studies using radioisotope tracer.

Conclusion and recommendations

(1) Axillary SLNB is highly valid in medially located breast cancer with high identification and accuracy rates and low FNR.
(2) Dual technique (radiocolloid and blue dye) for SLNB identification is still highly recommended for more accuracy.
(3) Methylene blue alone is efficacious in SLNB lymphatic mapping especially in developing countries because of its low cost and reduced risks of producing adverse effects.

(4) We recommend further multicenter studies with inclusion of larger number of cases for confirmation of our finding.
(5) For comparison, involvement of tumors in other locations of the breast and the use radiocolloid are required.

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Conflicts of interest
There are no conflicts of interest.

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