



# Efficacy of Methylene Blue in Sentinel Lymph Node Biopsy for Early Breast Cancer

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## ABSTRACT

**Objective:** Sentinel lymph node biopsy is the recommended approach in the evaluation of axilla during breast cancer surgery. In this study, results of patients who underwent methylene blue sentinel lymph node biopsy were evaluated.

**Materials and Methods:** The study included 32 female patients with T1 and T2 tumors. 5 ml of 1% methylene blue was injected into the peritumoral area or around the cavity. The axillary sentinel lymph node was found and removed, and then axillary dissection was performed. The sentinel lymph node and axillary dissection specimen were histopathologically examined and the results were compared.

**Results:** The sentinel lymph node was found in 30 (94%) patients. Lymph node metastasis was not observed in 17 patients in both the sentinel lymph node and axilla. Two patients had metastasis in the axilla although this was not detected in sentinel lymph node. Eleven patients had metastasis both in the sentinel lymph node and in the axilla. The accuracy rate was 93%, and the false negativity rate was identified as 15%.

**Conclusion:** Sentinel lymph node biopsy by methylene blue is a method that can be applied with high accuracy. Methylene blue can be considered as an alternative to isosulphane blue in sentinel lymph node biopsy.

**Key words:** Breast cancer, sentinel lymph node, methylene blue

## Introduction

The evaluation of axillary lymph node metastases in breast cancer is important to determine prognosis, and to plan treatment after surgery. The standard approach recommended for the evaluation of axillary lymph node status is sentinel lymph node biopsy (1). Sentinel lymph node is the first lymph node receiving lymphatic drainage from a tumor. If there is a tumor spread to the lymph nodes, it will first be in the sentinel lymph node. Then it spreads to other lymph nodes. If there are not any metastases in sentinel lymph node it is assumed that there are no metastasis in other lymph nodes (2).

Giuliano and colleagues first applied sentinel lymph node biopsy in breast cancer in 1994 (3). They were able to find the sentinel lymph node in 114 of 174 patients (65.5%) and showed that the sentinel lymph node provided accurate information about axillary involvement in 109 (95.6%) patients. In subsequent studies, the false-negative rate was shown to be decreased to 0% (4).

In order to locate the sentinel lymph node, methylene blue, isosulphane blue and radioisotopes have been used. These methods may also be used in combination. Methylene blue is cheaper and more easily accessible than isosulphane blue and radioisotope applications. Its side effects are less serious than isosulphane blue. Studies have found similar efficacy as compared to other methods. In this study, we aimed to evaluate our results of sentinel lymph node biopsy (SLNB) with methylene blue in patients with early-stage breast cancer.

## Materials and Methods

The Akdeniz University Ethics Committee approved the study. Thirty-two women with T1 and T2 tumors and without clinical axillary lymph node metastases from Akdeniz University Faculty of Medicine, Department of General Surgery were included in the study. Pre-operative ultrasonographic evaluation of the breast and axilla and mammography were obtained in all patients. Core biopsy or excisional biopsy was performed for palpable tumors and wire-guided biopsy for non-palpable breast tumors for histopathological diagnosis.

Patients with clinically palpable axillary metastatic lymph nodes, patients with a history of previous axillary surgery, and patients who received breast radiotherapy were excluded.

Informed consent was obtained in all patients. Different surgeons performed the surgical procedures. A single person who would follow-up all patients was involved in the operation during sentinel lymph node biopsy. One % methylene blue was used to locate the sentinel lymph node. Five mL of sterile methylene blue was administered in the peritumoral area in four- quadrants, and if the patient underwent excisional biopsy the injections were applied into the parenchyma around the cavity in four quadrants. The tumor or excised tumor cavity was massaged for 5 minutes towards the axilla. Afterwards, either modified radical mastectomy or breast conserving surgery was performed as scheduled. During axillary dissection, the sentinel lymph nodes were found and removed. Then standard axillary dissection was completed. The extracted sentinel lymph nodes were evaluated with frozen section examination, then the sentinel lymph node and axillary dissection specimen were histopathologically evaluated and metastasis rates were compared.

**Results**

A total of 32 patients were included into the study. Patient’s age varied between 25-82 years (mean: 50). Twenty-eight (87.5%) patients underwent modified radical mastectomy, and 4 (12.5%) underwent breast conserving surgery. Tumor locations are shown in Table 1.

The sentinel lymph node was not found in two (6%) patients. In 30 patients, 1-2 (mean: 1.69) sentinel lymph nodes were removed. In 18 of these patients, only one sentinel lymph node was found. In 17 patients, metastasis was not detected in both sentinel lymph node and the axilla. Two patients had metastasis in the axilla, although it was not detected in the sentinel lymph node. Eleven patients had metastasis in both the sentinel lymph node and the axilla (Table 2). In our study the rates of accuracy, sensitivity, specificity, positive predictive value, negative predictive value and false negativity were calculated as 93%, 85%, 100%, 100%, 90% and 15%, respectively (Table 3).

When patients were evaluated according to tumor location, in the two patients who had false-negativity the tumor was located in the upper outer quadrant. Considering the number of sentinel lymph nodes removed, false-negativity was not an issue in patients with removal of 1 and 3 lymph nodes, whereas both of the false-negative sentinel lymph node patients had 2 lymph nodes removed. According to TNM stage, one N1 and one N3 patient had false-negative results. When evaluated according to tumor size, a patient with T1 and another with T2 stage had false negative findings.

**Discussion and Conclusions**

The axillary dissection applied in breast cancer surgery has complications such as lymphedema, pain, numbness, loss of sensation, limitation of

shoulder movement, seroma, nerve and vascular injuries (5). According to tumor size, axillary lymph node metastasis is not detected in 95-97% of T1, and 52-77% of T2 patients. Therefore, these patients will undergo unnecessary axillary dissection and face these complications. With the use of sentinel lymph node biopsy, unnecessary axillary dissection can be avoided in patients without lymph node metastasis (6).

There are two methods to perform sentinel lymph node biopsy. In the first method, isosulphane blue or methylene blue is injected. In the other method, radioactive material is injected first and the sentinel lymph node is found with a gamma probe. These two methods can be used in combination (5, 7).

Either isosulphane blue or methylene blue can be used as a dye in sentinel lymph node biopsy. Methylene blue is cheaper, more easily obtainable, and is a dye with fewer complications as compared to isosulphane blue. Considering our country, it gives the opportunity of performing SLNB even in clinics away from the city center. Hypersensitivity reactions which may also be fatal are reported at a rate of 0.6 to 2.5 % following isosulphane blue injection (8). Skin necrosis, fat necrosis, and fibrosis are among complications of methylene blue. However, in our study, no complications related to methylene blue was encountered. In studies conducted in our country isosulphane blue was often preferred (9-11). In the literature, there are many studies showing that methylene blue can be used safely and with high success as an alternative to isosulphane blue (12-15). Simmons and colleagues (16) have identified the sentinel lymph node in 104 of 112 patients by using methylene blue and reported that sentinel lymph node represented axillary status in 96.9% of patients. Bleesing et al. (17) compared isosulphane blue and methylene blue, and found the accuracy rate as 88.5 % with isosulphane blue and as 92.7% with methylene blue.

Core biopsy is the gold standard in the diagnosis of breast cancer, although there are physicians who prefer excisional biopsy. Some of our patients were referred to our clinic with a diagnosis and we chose to include the patients in whom excisional biopsy was previously performed into the study. The rate of modified radical mastectomy in our study seems

**Table 2. Comparison of SLNB results and axillary lymph node status**

|                     |       | Axillary metastasis |    |       |
|---------------------|-------|---------------------|----|-------|
|                     |       | Yes                 | No | Total |
| Sentinel Lymph Node | Yes   | 11                  | 0  | 11    |
|                     | No    | 2                   | 17 | 19    |
| Metastasis          | Total | 13                  | 17 | 30    |

SLNB: Sentinel lymph node biopsy

**Table 3. Sensitivity, specificity, negative predictive value, positive predictive value, accuracy rates**

|                           | n     | %   |
|---------------------------|-------|-----|
| Sensitivity               | 11/13 | 85  |
| Specificity               | 17/17 | 100 |
| Negative Predictive Value | 11/11 | 100 |
| Positive Predictive Value | 17/19 | 90  |
| Accuracy                  | 28/30 | 93  |

**Table 1. Tumor location**

|                      |          |
|----------------------|----------|
| Left breast          | 23 (72%) |
| Right breast         | 9 (18%)  |
| Upper outer quadrant | 24 (75%) |
| Upper inner quadrant | 5 (16%)  |
| Lower inner quadrant | 2 (6%)   |
| Central zone         | 1 (3%)   |

very high, especially considering that they were used for early stage breast cancer. This rate should have been much lower. The operative strategy is a joint decision by the patient and the surgeon. However, when looking at the results, it is believed that breast-conserving surgery should have been encouraged more. In our study, peritumoral injection of methylene blue was preferred. This application is a commonly used route in the use of methylene blue. Besides peritumoral area, the dye might also be injected intradermal, subdermal, or subareolar area. Similar success rates can be achieved by using different injection methods (18).

The spread of breast cancer is generally from level 1 to level 3. The rate of skip metastasis is about 2 to 4% (19). The false negative rate of sentinel lymph node is 0-10%. Especially in patients with tumors near the axilla and a history of previous axillary surgery, the false-negative rate is high (20). In our study, the two patients with false negative results had their tumor localized in the upper outer quadrant near the axilla.

During the learning process of sentinel lymph node biopsy, axillary dissection should be performed after identification of the sentinel lymph node. The results of sentinel node biopsy should be compared with axillary dissection results. At least 90% sentinel lymph node detection rate and less than 5% false-negative rate indicates that only sentinel lymph node biopsy without axillary dissection can be made. Tafra et al. (21) reported that 30 cases are adequate for the learning phase. In the ALMANAC study, it has been reported that at least 40 patients are required (22). In our first study of 30 cases, the sentinel lymph node detection rate was over 90% even though the false-negative rate was above 5%. We believe that as the number of patients increase, the false negativity rate will decrease to the desired level. These rates prove that we need to continue with axillary dissection after sentinel lymph node biopsy, and that we were unable to reach ideal results yet.

In conclusion, sentinel lymph node biopsy using methylene blue demonstrated axillary involvement with high accuracy. In patients scheduled for sentinel lymph node biopsy, use of methylene blue may be considered as an alternative to isosulphane blue.

**Ethics Committee Approval:** Ethics committee approval was received for this study from the ethics committee of Akdeniz University.

**Conflict of Interest:** No conflict of interest was declared by authors.

**Peer-review:** Externally peer-reviewed.

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

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