

## Evaluation of Axillary Lymph Node Recurrence and Adverse Effects of Sentinel Lymph Node Biopsy with Single Technique Methylene Blue 1%: A Case Series in Indonesia

Dedy Hermansyah\* and Muhammad Al Anas

*Department of Surgery, Universitas Sumatera Utara, Indonesia*

Correspondence should be addressed to Dedy Hermansyah, Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

Received: May 21, 2023; Accepted: June 12, 2023; Published: June 17, 2023

### ABSTRACT

#### INTRODUCTION

Axillary Lymph Node Dissection (ALND) has been substituted as the standard minimally invasive method for axillary staging in clinically node-negative breast cancer by Sentinel Lymph Node Biopsy (SLNB). SLNB alone equals ALND in axillary staging, with lower related postoperative morbidity outcomes. Some worries persist about the complications and negative consequences of utilizing SLNB. In Indonesia, we presented a case series analyzing axillary lymph node recurrence and the adverse effects of SLNB.

#### METHODS

This case series is a retrospective study that included ten patients with clinically N0 breast cancer who received treatment at the Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara from April 2016 - April 2023 with the follow-up of axillary lymph node recurrence and the adverse effects such as paraesthesia, lymphedema, neuropathy, and stiffness. The Institutional Ethics Committee approved this study.

#### RESULTS

All the ten cases with clinically N0 breast cancer treated by a single experienced surgical oncologist, who received SLNB after follow-up ranging from 12 months - 60 months, showed all patients with clinically node-negative breast cancer with T1-T2 and various molecular subtypes had no complaint of paresthesia, pain, and lymph edema. The axillary lymph node recurrence was not found, and distant metastases were absent.

#### CONCLUSION

All ten cases with SLNB reported no complaint of paresthesia, pain, and lymph edema without the axillary lymph node recurrence and distant metastases, supporting the fact that SLNB is a safe procedure.

**Citation:** Dedy Hermansyah, Evaluation of Axillary Lymph Node Recurrence and Adverse Effects of Sentinel Lymph Node Biopsy with Single Technique Methylene Blue 1%: A Case Series in Indonesia. *Cancer Med J* 6(3): 23-29.

## **KEYWORDS**

Sentinel lymph node biopsy; Axillary lymph node recurrence; Adverse effects; Early-stage breast cancer

## **INTRODUCTION**

Unlike axillary lymph node dissection (ALND), sentinel lymph node biopsy (SLNB), a minimally invasive method, has been demonstrated to stage the axilla appropriately [1]. One of the most significant variables influencing the detection and false-negative rates of SLNB in breast cancer has been the mapping approach. Currently, the gold standard for identifying sentinel nodes (SNs) in early-stage breast cancer is a combination of lymphoscintigraphy, blue dye, and intraoperative gamma probe for SLNB [2,3].

However, SLNB for breast cancer has yet to gain popularity in Indonesia due to several reasons, including patient characteristics (the majority had the disease in an advanced stage), ambiguous recommendations, and a lack of facilities for radioisotope use because they are expensive and unavailable in most cancer centers. The fact that Indonesia has so many islands adds to the previously described concerns, making access to cancer facilities even more challenging [4]. All such factors contributed to the difficulty in the application of SLNB.

As the preferred minimally invasive technique for axillary staging in clinically node-negative (cN0) breast cancer, SLNB recently took the position of ALND. Regarding axillary staging, some significant clinical trials showed that SLNB alone is comparable to ALND with less postoperative morbidity. Additionally, in terms of disease-free survival (DFS), overall survival (OS), and regional recurrences (RR), SLNB alone showed equal effectiveness to upfront ALND. Nevertheless, even though several studies have confirmed these findings, some worries about the complications and negative consequences connected to using SLNB still exist [4].

According to earlier research, SLNB consequences include lymphedema, paresthesia, axillary seroma, wound infection, and brachial plexus injury (BPI). 25% of subjects after SLND alone had adverse surgical outcomes. Patients in the SLND group experienced increased paresthesias, seromas, and wound infections [4,5]. Hence, this study aims to evaluate the axillary lymph node recurrence and adverse effects of sentinel lymph node biopsy.

## **METHODS**

This case series is a retrospective study that included ten patients with clinically N0 breast cancer, including T1 and T2 disease, who received treatment at the Division of Surgical Oncology, Department of Surgery, Faculty of Medicine, Universitas Sumatera Utara from April 2016 - April 2023. An ultrasound-guided core biopsy of the breast tumor revealed malignancy. All patients had no prior history of ipsilateral breast surgery. Physical examination and ultrasound were used to establish the presence of N0 axillary lymph nodes prior to surgery. Patients with distant metastases discovered during the first staging workup and a history of blue dye allergy were excluded. This study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara. All patients were told about the SLNB surgery and gave their permission.

Only one expert breast surgeon participated in the study to eliminate bias during the SLNB evaluation using methylene blue 1%. The included surgeon had already received internal validation in doing SLNB, and the sentinel node detection rate for 60 patients with SLNB operations was 97.62%. Sentinel node metastasis was identified in 31.6% of patients, while macro metastases were reported in 31.58%. MBD has a sensitivity and specificity of 91.67% and 96.67%, respectively. The sentinel node's negative predictive value (NPV) for

predicting axillary metastasis was 96.67% (95% CI, 81-99%) [6].

All patients had breast-conserving surgery (BCS) or mastectomy for local treatment of the original tumor. Mastectomy was performed for individuals whose estimated defect size after wide excision exceeded 20% of the breast size when multicentricity was discovered, and the patient requested. 1.5 ml of 1% methylene blue was injected into the subareolar location, followed by a 5-minutes massage to allow the blue dye to enter the lymphatic pathways into the axillary area. Blue lymphatic channels were methodically traced down to the sentinel node using anatomical landmarks such as the region around the intercostobrachial nerve (intercostobrachial nodes) and medial pectoral bundle (medial pectoral nodes). We report

age, grade, molecular subtypes, and surgical therapy data. Furthermore, we present information on follow-up length, axillary lymph node recurrence, distant metastasis rates, and side effects such as paraesthesia, lymphedema, neuropathy, and stiffness.

## **RESULTS**

All ten clinically N0 breast cancer cases were treated in various healthcare centers in Medan, North Sumatra, Indonesia, by a single experienced surgical oncologist who received SLNB from April 2016 - April 2023. Table 1 shows each patient's clinical background, histopathological grading, molecular subtypes, and American Joint Committee on Cancer (AJCC) 8th edition staging. Table 2 shows the follow-up duration, the recurrence rate, and the adverse effect of SLNB.

Cases	Age	Grading	Molecular subtypes	Surgical Treatment
1	42-years-old	Grade 3	HER2-Positive	BCS + SLNB
2	49-years-old	Grade 1	Luminal A	MRM + SLNB
3	46-years-old	Grade 2	Luminal A	Skin-Sparing Mastectomy with Implant + SLNB
4	44-years-old	Grade 2	Luminal B	MRM + SLNB
5	51-years-old	Grade 2	HER2-Positive	MRM + SLNB
6	49-years-old	Grade 3	HER2-Positive	MRM + SLNB
7	48-years-old	Grade 2	Luminal B	MRM + SLNB
8	45-years-old	Grade 2	Luminal B	MRM + SLNB
9	34-years-old	Grade 1	Luminal A	MRM + SLNB
10	41-years-old	Grade 2	TNBC	Nipple-Sparing Mastectomy with Implant + SLNB

TNBC: Triple Negative Breast Cancer; MRM: Modified Radical Mastectomy; BCS: Breast-Conserving Surgery; SLNB: Sentinel Lymph Node Biopsy

**Table 1:** Patients' clinical background.

Table 1 showed that in every ten cases, with a mean age of 44.9 + 4.99 years old, the youngest of 34-years old, and the oldest was 51 years old. Three cases were reported with Grade 3 breast cancer, five with Grade 2 breast cancer, and two with Grade 1 breast cancer. Regarding molecular subtypes, three cases were reported with the Luminal A subtype, three cases were reported with the Luminal B

subtype, three patients reported with HER2-positive subtype, and one patient reported Triple Negative Breast Cancer. The surgical treatment for all ten cases ranges from Breast-Conserving Surgery with SLNB, Modified Radical Mastectomy with SLNB, Skin Sparing Mastectomy with Implant and SLNB, and Nipple Sparring Mastectomy with Implant and SLNB.

Case s	Follow-up Duration	Axillary Lymph Node Recurrence	Distant Metastases	Adverse Effect	Paraesthesia	Lymphedema	Neuropathy	Stiffness
1	24 months	Absent	Absent	-	-	-	-	-
2	60 months	Absent	Absent	-	-	-	-	-
3	48 months	Absent	Absent	-	-	-	-	-
4	15 months	Absent	Absent	-	-	-	-	-
5	28 months	Absent	Absent	-	-	-	-	-
6	36 months	Absent	Absent	-	-	-	-	-

7	12 months	Absent	Absent	-	-	-	-
8	12 months	Absent	Absent	-	-	-	-
9	60 months	Absent	Absent	-	-	-	-
10	60 months	Absent	Absent	-	-	-	-

**Table 2:** Patients’ recurrence rate and adverse effect of SLNB.

of paresthesia, pain, or lymph edema. The axillary lymph node recurrence was not found, and distance metastases were absent.

Modified Radical Mastectomy and SLNB were performed. After 60 months of follow-up, the patient has no complaints of paresthesia, pain, or lymph edema. The axillary lymph node recurrence was not found, and distance metastases were absent.



**Figure 1:** The patient in Case 1 is a 42-year-old female diagnosed with invasive breast cancer of no special type of grade 2, HER2-positive subtype with T2N0M0.



**Figure 2:** The patient in Case 2 is a 49-year-old female diagnosed with invasive ductal cancer of grade 1, Luminal A subtype with T2N0M0.

Breast-conserving surgery and SLNB were performed. After a 24-months follow-up, the patient has no complaints



**Figure 3:** The patient in Case 3 is a 46-year-old female diagnosed with invasive ductal cancer of grade 2, Luminal A subtype with T2N0M0.

Skin-sparing mastectomy with implant and SLNB was performed. After 48 months of follow-up, the patient has no complaints of paresthesia, pain, or lymph edema. The axillary lymph node recurrence was not found; distance metastases were absent and showed no axillary lymph node recurrence or lymph edema after SLNB.



**Figure 4:** The patient in Case 9 is a 34-year-old female diagnosed with invasive ductal cancer of grade 1, Luminal A subtype with T2N0M0.

Modified Radical Mastectomy and SLNB were performed. After 60 months of follow-up, the patient has no complaints of paresthesia, pain, or lymph edema. The axillary lymph node recurrence was not found; distant metastases were absent and showed no axillary lymph node recurrence or lymph edema after SLNB.

## **DISCUSSION**

The gold-standard surgical technique for axillary lymph node staging in early-stage breast cancer is sentinel lymph node biopsy during upfront surgery. Survival and oncological outcomes are crucial when evaluating the efficacy of a novel therapy or procedure [6]. The study Z0011 findings supported that utilizing SLNB alone leads to fewer overall postoperative problems than combining SLNB plus ALND. Compared to 25% of individuals with SLNB, over 75% of those with ALND experienced complications. In contrast to SLNB with ALND, which necessitates more extensive dissection, most doctors would

hypothesize-and our data supports-that the less invasive nature of SLNB leads to fewer surgical sequelae, such as wound infection and seromas. At any follow-up period, axillary paresthesias were less likely to develop after SLN alone than after SLNB plus ALND. The intercostobrachial nerves are more likely to be disrupted by ALND than by SLNB alone, which is likely why adding ALND increased the number of axillary paresthesias [7].

Recent research has assessed the prognostic and therapeutic utility of SLNB and related problems. Their findings show that research designs can vary and that complication rates can range from 4.6% to 33%. Therefore, more convincing information about the actual frequency of problems and aftereffects linked to this procedure needs to be more convincing [8]. The accuracy of the SLNB method is between 65% and 100%, and there is false negativity of 0% to 14%, among other parameters that influence the unfavorable impact and axillary lymph node recurrence. Additionally, these percentages change depending on the surgeon's level of experience. Factors include using the technique in various ways, the length of the learning process, the comparatively low rate of lymph node existence when painted simply in blue, and the impact of previous biopsies [9].

According to research, SLNB offers more exact and accurate adjuvant therapy determination, shorter hospital stays, lower costs, and decreased comorbidities, including lymphedema, arm discomfort, and numbness associated with standard axillary dissection [10]. Patients' dissections did not result in any problems during the postoperative follow-up of the prior research. In early-stage breast tumors, SLNB has been used in place of standard ALND due to this breakthrough and the findings of investigations [11]. We performed SLNB in all our patients and detected SLNB stained in all patients.

A significant advance that will lessen the risks involved in the surgical dissection of the axillary area is using the SLNB method. Additionally, it has an axilla nodal involvement rate that is becoming more accurate. However, the SLNB procedure's accuracy varies from surgeon to surgeon, ranging from 65% to 100%, with a false negative rate between 0% and 14%. Additionally, patients using only dyes had a false negative rate of 9.1%, patients using only radiocolloids had a false positive rate of 10.9%, and patients utilizing a combination approach had a false negative rate of 6.7%. These two circumstances raised questions regarding the validity of SLNB since it was hypothesized that they would impact local recurrence and survival during long-term follow-up [12]. A prior study found that among 3548 patients with negative sentinel lymph node biopsy results, axillary recurrence was detected in fewer than 1% of cases (31 patients) during 4 years to 11 years of follow-up. Similarly, other studies have found no differences in overall survival, disease-free survival, or axillary recurrence between individuals with early-stage breast cancer who test negative for SLNB and those with standard axillary lymph node dissection. SLNB is dependable for this patient population [13].

Out of 1,471 patients in whom Methylene Blue was injected, previous research notes that one patient experienced skin necrosis and 16 patients experienced bluish discoloration of the skin one week after surgery. Lymphedema rate and survival outcomes of SLNB-negative patients are also summarized. In the ALND group,

the lymphedema rate was 5.2%, whereas it was just 0.5% in the SLNB-alone group. Radiation treatment and lymphedema rates were substantially correlated. Breast conservation surgery (BCS) or mastectomy surgery was unrelated to lymphedema [14].

Prior studies likewise reported no differences in overall or disease-free survival after an average follow-up of 18 months between patients who received axillary dissection and those who underwent SLNB. Every one of our patients is monitored for recurrence and metastasis. There are several explanations for this variation, including the use of various application techniques, the length of the learning time, the relatively low rate of lymph node presence when painted with blue alone, and the impact of biopsies carried out prior to the SLNB treatment [15]. The location and dosage of blue dye injection are reportedly less significant than the surgical method used during SLNB and if the surgeon has enough knowledge in the field.

## **CONCLUSION**

All the ten cases with clinically N0 breast cancer treated by a single experienced surgical oncologist, who received SLNB after follow-ups ranging from 12 months - 5.5 years with clinically node-negative breast cancer with T1-T2 and various molecular subtypes had no complaint of paresthesia, pain, and lymph edema, without the axillary lymph node recurrence. This case series supports that SLNB is a safe procedure for early-stage breast cancer.

## **REFERENCES**

1. Verbelen H, Tjalma W, Meirte J, et al. (2019) Long-term morbidity after a negative sentinel node in breast cancer patients. *European Journal of Cancer Care* 28(5): e13077.
2. Li J, Chen X, Qi M, et al. (2018) Sentinel lymph node biopsy mapped with methylene blue dye alone in patients with breast cancer: A systematic review and meta-analysis. *PLoS One* 13(9): e0204364.
3. Dogan NU, Dogan S, Favero G, et al. (2019) The basics of sentinel lymph node biopsy: Anatomical and pathophysiological considerations and clinical aspects. *Journal of Oncology* 2019: 3415630.

4. National Institute of Health Research and Development (2013) Indonesian ministry of health. Basic health research; RISKESDAS 2013, Jakarta: 110-119.
5. Brahma B, Putri RI, Karsono R, et al. (2017) The predictive value of methylene blue dye as a single technique in breast cancer sentinel node biopsy: A study from Dharmais Cancer Hospital. *World Journal of Surgical Oncology* 15: 1-7.
6. Hermansyah D, Rahayu Y, Azrah A, et al. (2021) Accuracy of methylene blue test as single technique for sentinel lymph node biopsy in early stages breast cancer. *Asian Pacific Journal of Cancer Prevention* 22(9): 2765.
7. Lucci A, McCall LM, Beitsch PD, et al. (2007) Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *Journal of Clinical Oncology* 25(24): 3657-3663.
8. Espinosa-Pereiro CE, Gárate AZ, García-Doval I (2019) Complications and sequelae after sentinel lymph node biopsy in melanoma: A retrospective cohort study. *Actas Dermo-Sifiliográficas (English Edition)* 110(6): 482-489.
9. Chinnappan S, Chandra P, Kumar S, et al. (2022) Prediction of sentinel lymph node biopsy status in breast cancers with PET/CT negative axilla. *World Journal of Nuclear Medicine* 21(02): 120-126.
10. Devarakonda S, Thomas SS, Sen S, et al. (2021) Sentinel lymph node biopsy in early breast cancer using methylene blue dye alone: A safe, simple, and cost-effective procedure in resource-constrained settings. *Indian Journal of Surgical Oncology* 12: 210-217.
11. Giuliano AE, Ballman KV, McCall L, et al. (2017) Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: The ACOSOG Z0011 (Alliance) randomized clinical trial. *JAMA* 318(10): 918-926.
12. Pirhan Y (2021) Evaluation of axillary lymph node status after axillary dissection in patients with SLN negative or single SLN positive T1 and T2 breast cancer. *Annals of Medical Research* 28(1): 17-19.
13. Veronesi U, Galimberti V, Paganelli G, et al. (2009) Axillary metastases in breast cancer patients with negative sentinel nodes: A follow-up of 3548 cases. *European Journal of Cancer* 45(8): 1381-1388.
14. Agrawal SK, Sharma H, Priya N, et al. (2022) Diagnostic performance and survival outcome following sentinel lymph node biopsy in breast cancer patients from a tertiary cancer centre in India. *Ecancermedicalscience* 16: 1398.
15. Wibisana IGNG (2020) Sentinel lymph node biopsy for breast cancer using methylene blue: A new anatomical landmark involving intercostobrachial and medial pectoral nodes. *Medical Journal of Indonesia* 29(3): 298-304.